doi:10.25143/prom-rsu_2010-08_dt

RĪGAS STRADIŅA UNIVERSITĀTE

Riga Stradiņš University

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POPULATION SCREENING FOR HEREDITARY CANCER IN VALKA DISTRICT

For obtaining the degree of a Doctor of Medicine

Speciality – surgery

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Riga, 2010

CONTENT

LIST OF ABBREVIATIONS

APC – adenomatous polyposis coli (gene)

BRCA – breast cancer (gene)

CDH1 – E-cadherin (gene)

CFA – cancer family aggregation

CI – confidence interval

DNA – deoxyribonucleic acid

EU – European Union

FAP – familial adenomatous polyposis

FBlaC – familial urinary bladder cancer

FBtT – familial brain tumour

FCC – familial colorectal cancer

FCC1 – familial colorectal cancer, variety 1

FCC2 – familial colorectal cancer, variety 2

FEC – familial endometrial cancer

FHemT – familial malignant haematological tumour

FLC – familial lung cancer

FPan – familial pancreatic cancer

HBC – hereditary breast cancer

HBOC – hereditary breast - ovarian cancer

HEC – hereditary endometrial cancer

MLH1 – human mutL homologue 1 (gene)

MSH2 – human mutS homologue 2 (gene)

MSH6 – human mutS homologue 6 (gene)

HNPCC – hereditary non-polyposis colorectal cancer

HOC – hereditary ovarian cancer

HPC – hereditary prostate cancer

PMS1 – human postmeiotic segregation 1 (gene)

PMS2 – human postmeiotic segregation 2 (gene)

HSC – hereditary stomach cancer

MMR – mismatch repair

NHL – non-Hodgkin's lymphoma

OR – odds ratio

PCR – polymerase chain reaction

RR – relative risk

SD – standard deviation

Susp. - suspected

SIR – standardized incidence ratio

BACKGROUND

Significant development in cancer research has resulted not only in expanding knowledge of cancer biology but also in improved treatment results. The number of cancer death cases in the European Union (EU) has decreased by 9% between 1985 and 2000. However, oncologic diseases remain an important cause of mortality and morbidity. In the year 2000, there were 1.12 million death from cancer recorded in the EU (Boyle and Ferlay, 2005). In order to lessen cancer mortality, early diagnostics or prevention strategies have demonstrated significant efficiency (Eccles, 2004). At present, it is estimated that 5 – 10% of tumours might have hereditary basis – an inherited gene mutation (Daly, 2004; Irmejs *et al.*, 2007). The cancer risk for a healthy person can rise significantly, if this person carries a pathogenic mutation with high penetrance (Olopade and Pichert, 2001). Besides the elevated risk of disease, hereditary cancers frequently arise early in life, resulting in loss of economically active persons. In order to prevent hereditary cancer or at least to diagnose it early, follow-up programs could be offered to persons subjected to increased hereditary cancer risk. However, this necessitates well-planned strategy in order to find out the target patients.

The best known approach in order to identify hereditary background of a cancer is careful analysis of the family oncologic history of a patient undergoing tumour treatment (Irmejs *et al.*, 2007; Federico *et al.*, 1999). This approach within the frames of the presented study further is designated in brief as hospital screening. In the result of hospital screening, the healthy family members gain a possibility to estimate their own cancer risk and undergo appropriate diagnostic procedures. Besides that, population-based hospital screening provides an insight into the importance of the problem in the local population.

Individual testing can be offered to the persons inquiring about their own cancer risk. Such programs can lead to optimal result for the patient, including the early diagnostics and/or psychological support. However, no significant, analysable scientific data can be obtained in this way.

The third alternative for the diagnostics of hereditary cancer is the population screening – strategy that targets the whole adult population within a region in order to find out families with increased cancer risk. The benefits of such approach include revealing of persons at risk before the tumour development. Also, all possible hereditary cancer syndromes can be diagnosed independently of the predominant location. However, the population screening demands time and experienced personnel as well as financial input.

The methods of finding out the hereditary basis of the cancer include analysis of family history as well as molecular tests in order to reveal pathogenic high-penetrance mutations. The family history can be subjected to various biases like denial of serious problems, lack of sufficient knowledge, poor compliance, inability to express the information correctly and others. The molecular genetic testing brings objective data but can be impeded by sensitivity restrictions and presence of new or unknown mutation. Thus, absolute efficiency of any

screening program cannot be expected. In order to plan and focus the medical resources, the expedience of different approaches should be evaluated in order to create an optimal strategy for the diagnostics of hereditary cancer risk. It should be emphasized that the question is also of major significance in the medical science as justified data are necessary for any scientific evaluations like risk or penetrance estimates.

Goal: to analyse the role of population screening in the diagnostic pathway of hereditary cancer.

In order to achieve this goal, the following **objectives** were set:

1. to evaluate usability of population screening in hereditary cancer diagnostics;
2. to determine the full spectrum of hereditary cancer by the population screening in Valka district;
3. to estimate the clinical frequency, the age structure and the course and the burden of index cancer in all the revealed hereditary cancer syndromes;
4. to identify the frequency of the *BRCA1* founder mutations in population and to compare with acquired data in high risk group;
5. to analyse the role of family size in the hereditary cancer diagnostics.

Working hypothesis:

1. Population screening is a useful identification method of hereditary cancer revealing the whole spectrum of hereditary and familial cancer.
2. Family cancer history is an effective selection tool to identify pedigrees with high cancer burden.
3. Western type of population structure with small family size has an impact on the diagnostics of hereditary cancer. This effect must be considered elaborating the diagnostic strategy of hereditary cancer.
4. Frequency of mutation does not show the prevalence of hereditary cancer. Combined approach is necessary in hereditary cancer diagnostics incorporating clinical and molecular data.
5. The population screening identifies an additional group of persons to whom surveillance can be offered. In addition, the surveillance schedule can be adjusted by population screening data.

Organizational and laboratory basis

The pilot project of the population screening was carried out within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co-financed by European Union Interreg IIIB Neighbourhood program. The following group of Valka district

family physicians participated in the Interreg project: Maruta Bindre (Smiltene), Lilita Ezerina (Smiltene), Juris Ezerins (Smiltene), Elvira Freiberga (Grundzale), Alla Grinberga (Palsmane), Sanita Jansone (Varini), Alda Karklina (Karki), Maija Klavina (Smiltene), Ritma Klavina (Valka), Marianna Kire (Valka), Valdis Kiris (Valka), Zane Lukina (Smiltene), Inga Natra (Valka), Maris Natra (Valka), Liga Putrina (Valka), Olga Ribkina (Seda), Anna Sakare (Evele), Ilona Uzbeka (Valka), Inese Verselo (Trikata), Sniedze Viksna (Smiltene), Maija Zalite (Strenci), Liga Ziemele (Smiltene). The clinical diagnostics and patient consultations were performed in the Hereditary Cancer Institute, Riga Stradiņš University. The molecular tests were performed in the Hereditary Cancer Institute and the University of Tartu, Estonia.

Scientific novelty

The performed work represents the first population screening for hereditary cancer in Latvia. In addition, only few studies in the whole world are devoted to the hereditary cancer diagnostics by population screening. Population screening provides novel data about the full spectrum and frequency of hereditary malignancies allowing evaluating the structure of hereditary cancer. The hereditary cancer structure highlights the future directions for hereditary cancer research.

Practical diagnostic novelty

Evidence-based population screening and surveillance protocols are elaborated for general use in collaboration with family doctors in order to identify the families with increased cancer burden and to provide the hereditary cancer prophylaxis. The data about the frequency and structure of hereditary cancer in Latvia allow planning health care resources and targeted cancer screening.

Personal input

The author was personally involved in all stages of the Interreg project, including the project design, the patient consultations and the clinical diagnostics. The literature studies, data analysis and description were performed by the author personally.

Ethical concerns

All patients provided informed consent for participation in the study approved by Central Medical Ethics Commission of Latvia and Commission of Ethics, Riga Stradiņš University.

LITERATURE REVIEW

Hereditary cancer – the entity of the syndrome

Definition

Somatic genetic changes are frequent in tissues of malignant tumours. These genetic defects are local to the affected tissues and acquired in the result of environmental carcinogenic insults. In contrast, a proportion of cancers, probably different in accordance to the affected organ (Trimbath and Giardiello, 2002; Guillem *et al*, 2006; Rubin *et al*., 1998; Reedy *et al*., 2002; Pal *et al*., 2005), have inherited genetic basis – an inherited mutation that increases the risk of cancer development during some life period. Hereditary cancer (or tumour, in wider sense) can be defined as a tumour developing in a person who carries an inherited gene mutation bearing increased tumour risk.

The history of hereditary cancer concept can be followed as far back as to the year 1865. It was started by a French surgeon Paul Broca who described his wife's pedigree showing breast cancer in 4 generations (Garber and Offit, 2005). At present, several syndromes are described clinically and mutation analysis has become a widespread tool in clinical diagnostics as well as in research. Although the progress is tremendous it is probably not as efficient as the advances in the appendicitis surgery over similar time period since the operation by R.Fitz, 1886. At present, ongoing search for new mutations is a desired target for scientific studies. The possibility to incorporate the acquired knowledge in diagnostic algorithm to benefit the people who are at imminent risk is another methodological target.

Evidence of the hereditary nature in a subgroup of cancer

The role of heredity in carcinogenesis was substantiated initially by observations of striking familial aggregation of tumour cases as noted above (Garber and Offit, 2005). The case reports were followed by large-scale epidemiologic studies. Discovery of gene mutations correlating with the cancer risk at least in part of the families bearing increased cancer load confirmed the hypothesis of the hereditary nature in a subgroup of cancer implying that in these cases a single gene mutation is responsible for the increased cancer risk (Hall *et al*., 1990; Narod *et al*., 1991; Wooster *et al*., 1994).

Familial tumour risks have been detected for all major sites of cancer as well as for tumours of different histogenesis: oesophageal (standardized incidence ratio, SIR, 3.95; 95% confidence interval, CI = 1.57 – 8.18), gastric (SIR, 2.05; 95% CI = 1.56 – 2.65), large bowel (SIR, 1.95; 95% CI = 1.79 – 2.13), liver (SIR, 1.66; 95% CI = 1.13 – 2.36), pancreatic (SIR, 1.70; 95% CI = 1.17 – 2.39), lung (SIR, 1.83; 95% CI = 1.63 – 2.06), breast (SIR, 1.67; 95% CI = 1.58 – 1.76), renal (SIR, 1.82; 95% CI = 1.38 – 2.36) and urinary bladder cancer (SIR, 1.66; 95% CI = 1.35 – 2.01), melanoma (SIR, 2.43; 95% CI = 2.06 – 2.84), non-Hodgkin's lymphoma (SIR, 1.86; 95% CI = 1.45 – 2.35), Hodgkin's lymphoma (SIR, 3.95; 95% CI = 1.69 – 7.82), myeloma (SIR, 3.31; 95% CI = 2.05 – 5.07), leukaemia (SIR, 1.80; 95% CI = 1.34 – 2.36). These data were obtained in a study that was based on the identification of

concordantly affected blood relatives (Hemminki and Li, 2004) therefore the SIRs could be possibly reduced due to the study design that did not account for non-concordant risk-affecting cancer.

Familial aggregation of cancer cases can be explained by genetic influences as well as by shared environmental effects. The genetic quota can be assessed directly by mutation analysis if available (i.e., known mutation with proved significance is present in the kindred and the means for genetic analysis are available). Alternatively, epidemiologic analysis can be done, evaluating the cancer incidence among blood relatives in contrast to spouses (Hemminki and Li, 2004). Evaluation of siblings in accordance to the age difference may give a clue to shared early childhood effects (Hemminki and Li, 2004) thus separating this effect from genetic influences. The effect of familial transmission of risk behaviour can be evaluated (Bermejo and Hemminki, 2005). The presence of environmental risk factors can be directly detected during the evaluation of the affected persons.

In the previously mentioned study by Hemminki and Li, 2004 spouse effects were found only for gastric and lung cancer and melanoma but the relevant SIRs did not exceed 1.24. Shared early childhood effects were suggested for testicular tumours, melanoma, endocrine tumours and leukaemia with a suggestion that sun exposure could be related to melanoma occurrence and childhood infections – to leukaemia (Hemminki and Li, 2004). Thus, for most tumours there is an evidence of familial risk factors not limited to shared environment.

Mode of inheritance

Studying directly the behaviour of well-described mutations, autosomal dominant mode of inheritance is suggested for the best-known hereditary cancer syndromes, namely, hereditary non-polyposis colorectal cancer (HNPCC) and hereditary breast – ovarian cancer (Hall *et al.*, 1990; Narod *et al.*, 1991; Wooster *et al.*, 1994). The mode of inheritance has been studied by epidemiologic analysis exploring the hypothesis that occurrence of cancer in parents and offspring may be due to dominant mutation whereas cancer affecting only siblings may indicate a recessive mutation (Hemminki and Li, 2004). Dominant inheritance was found in this way for most of cancers whereas recessive mode was suggested for renal, prostate and testicular cancer. In male-specific locations X-linked recessive condition could not be excluded. The low number of known recessive cancer syndromes in humans as opposed to experimental animals has raised the concern of observation bias (Hemminki and Li, 2004) therefore further developments might be expected. Segregation analysis is another way to explore the mode of inheritance.

Methods of hereditary cancer diagnostics

The presence of the genetic risk can be evaluated by the family history. The features that lead to a suspicion of genetic predisposition include unusually young age at onset of cancer, multiple cancers in one individual or multiple blood relatives with cancer at the same or related sites. Single occurrence of tumour even in unusually young age in a family with

multiple aged and healthy blood relatives in both lines is less likely to be due to inherited factors than presence of multiple affected relatives in the family with young average age of tumour development (Eccles, 2004). The suggestion to check the family history data provided by patient seems reasonable. However, high accuracy of reporting cancers, reaching 83% for first-degree relatives, has been described previously (Love *et al.*, 1985). Other studies have also accepted the family history data as provided by probands (Lin *et al.*, 2006). Comparing the error rate by patients and physicians, significantly higher rate was found in the physician assessment although involving different level of action and responsibility (Sweet *et al.*, 2002). In general, the family history is the starting point in the identification of hereditary cancer. However, as the diagnosis of hereditary cancer syndrome implies serious examinations, concerns and prophylaxis, objective risk estimates are desired. If known for the considered cancer syndrome, genetic investigations for the underlying mutation are preferred by the geneticists. Therefore the clinical selection criteria are utilised to select cases with the highest likelihood of detecting a mutation in order to limit the total costs of genetic investigations (Eccles, 2004). Nevertheless, mutation analysis is not straightforward. It is estimated that even the most sensitive techniques might have less than 90% sensitivity for all possible mutations (Eccles, 2004). For some genes, at least 5 – 10% of mutations are large deletions involving one or more whole exons. Such genetic changes cannot be diagnosed by any technique that relies on the comparison of the wild-type allele with the mutant allele. Mutation analysis is facilitated by the presence of frequent founder mutations; however, founder mutations are not present in all ethnic groups or all tumour locations. The following problems can be faced during genetic testing: unique mutation, previously unknown mutation in an undiscovered gene, no living affected individual, genetic variation of unknown significance. Thus, risk estimate by clinical history is still valuable both from scientific and practical point of view.

Treatment possibilities

Clinical interventions have been formulated for mutation carriers within affected families. The primary interventions for mutation carriers of highly penetrant syndromes are surgical (Guillem *et al.*, 2006). Although for some familial cancer syndromes prophylactic surgery is still developing and for others seems impossible, ASCO/SSO (American Society of Clinical Oncology and Society of Surgical Oncology) guidelines by consensus statement are available for several locations. These guidelines include modern surgical approaches, clinical and genetic indications for surgery, timing and efficacy of prophylactic operations (Guillem *et al.*, 2006).

Specific hereditary cancer syndromes and the relevant genetic background

Hereditary breast – ovarian cancer

The description of a kindred affected by breast cancer in 4 generations was the beginning of the hereditary breast-ovarian cancer concept (Garber and Offit, 2005). Nowadays, the clinical observations have been extended to large-scale epidemiological research. Population-based studies have confirmed that breast and ovarian cancer has genetic predisposition as evidenced by the role of family history. The SIR for breast cancer constitute 1.67 (95% CI = 1.58 – 1.76) if a relative is affected by breast cancer (Hemminki and Li, 2004).

The largest burden of the inherited predisposition to the breast and ovarian cancer is explained by mutations in 2 genes – *BRCA1* on the long arm of chromosome 17 (Hall *et al.*, 1990; Narod *et al.*, 1991), and *BRCA2* on 13q (Wooster *et al.*, 1994). These mutations were discovered quite recently, in the time span between 1990 and 1994. *BRCA* mutations mostly result in protein truncation. However, missense mutations replacing only 1 amino acid may segregate together with cancer development (Guillem *et al*, 2006). The population frequency of *BRCA* mutations is estimated to be less than 1:500 except for Ashkenazi Jews with a carrier frequency of 1:40 (Szabo and King, 1997). However, BRCA mutations are not found in 16% (95% CI = 6 – 28 %) of families with at least 4 cases of breast cancer (Ford *et al.*, 1998).

BRCA mutations are not uniformly found in early-onset breast cancer patients with positive family history (Shih *et al.*, 2002). In contrast, most of the hereditary ovarian cancer is attributable to *BRCA1* and *BRCA2* mutations. These mutations account for 10% of ovarian cancer cases, and MMR gene mutations (HNPCC) – for 1%. The lifetime risk of ovarian cancer is 1.5% in the general population, 5 – 12% in HNPCC syndrome, 10 – 20% in BRCA2 mutation carriers and 20 – 40% in *BRCA1* mutation carriers (Whittemore *et al.*, 1997; Struewing *et al.*, 1997; Ford *et al.*, 1998; Risch *et al.*, 2001; Guillem *et al*, 2006). Fallopian tube cancer risk is increased more than 100-fold in *BRCA1* mutations carriers (Brose *et al.*, 2001). The mean age of ovarian cancer development is approximately 40 years but prognosis is more favourable than in sporadic cases (Offit and Kauf, 2006), possibly because 20% of the hereditary ovarian cancer cases are associated with synchronous endometrial cancer (Guillem *et al.*, 2006) facilitating the clinical diagnostics.

The breast may also be involved by the rare and aggressive Li-Fraumeni syndrome, caused by germline *TP53* mutation and manifesting by soft tissue sarcomas, breast cancer and other early-onset malignancies (Li and Fraumeni, 1969). Cowden syndrome is caused by *PTEN* mutations and affects breast and thyroid (Liaw *et al.*, 1997).

The breast cancer risk in *ATM* mutation carriers is 5 times greater than in the population (Swift *et al.*, 1990). The lifetime risk of breast cancer is 56 – 87% in *BRCA1* and *BRCA2* mutation carriers and 30 – 50% in Cowden syndrome (Guillem *et al.*, 2006; Srivastava *et al.*, 2001).

Prophylactic surgery can be considered in carriers of a pathogenic mutation with high penetrance. If genetic testing has not yielded positive findings but is considered not informative because of the family history and results of tests in other family members, surgical prophylaxis is also acceptable. It is generally suggested that prophylactic operations should not be performed in the absence of genetic testing as true negative result would place the female at the average population risk level (Guillem *et al.*, 2006). Modern surgical approaches for breast cancer (Figure 1) prophylaxis include total bilateral mastectomy without axillary lymph node dissection, skin-sparing total mastectomy, subcutaneous s. nipple-sparing mastectomy and areolar-sparing mastectomy. The risk reduction of at least 90% can be achieved by mastectomy or skin-sparing mastectomy (Guillem *et al.*, 2006; Meijers-Heijboer *et al.*, 2001; Carlson *et al.*, 1997). Few cancer cases have been observed after nipple-sparing mastectomy (Rebbeck *et al.*, 2004) in accordance to the fact that some breast tissue is preserved in this case and may undergo malignant change. However, cosmetic effects might be better. Loss of nipple sensation can be problematic in younger women (Guillem *et al.*, 2006).

Risk of breast cancer can also be reduced performing prophylactic salpingo-oophorectomy that decreases the risk of breast cancer for 50% (Kauf *et al.*, 2002; Rebbeck, 2000; Rebbeck *et al.*, 2004). It has been suggested that the agreement rate for this operation via laparoscopic approach may be higher than for mastectomy due to cosmetic and/or psychological reasons (Guillem *et al.*, 2006).

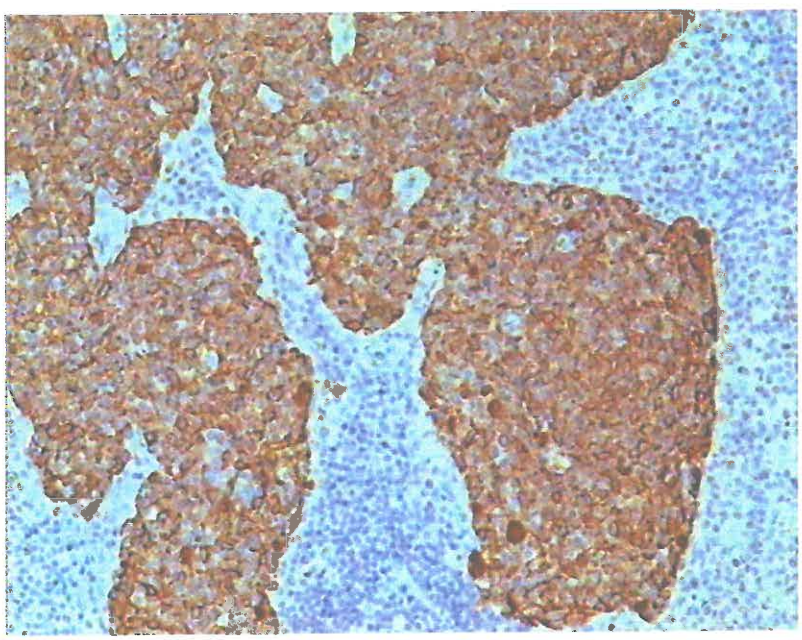


Figure 1. Hereditary medullary breast cancer. Anti – cytokeratin AE1/ AE3, immunoperoxidase, original magnification 100x. Microphotograph by A. Vanags

Tamoxifen can be advised for prophylaxis with 30 – 40% risk reduction as observed in mutation carriers after first breast cancer (Narod *et al.*, 2000) although this might seem contrasting with the usual triple-negative immunophenotype in *BRCA1* mutation related breast cancer. Prospective validation of prevention in mutation carriers is desired (Guillem *et al.*, 2006). As life-long treatment is expected, complications should be considered.

There are no uniform consensus statements for the breast cancer surveillance in mutation carriers although the general principles are clarified. Mammography and ultrasonography is recommended as well as MRI showing higher sensitivity although lower specifity (Brekelmans *et al.*, 2001; Kriege *et al.*, 2003). However, failure of surveillance may occur even within 1 year (Guillem *et al.*, 2006).

Ovarian cancer is known for the lack of recognizable premalignant process that limits the options for screening. Early diagnostics also is not successful therefore late diagnosis is frequent and resulting mortality is high (Guillem *et al.*, 2006). Therefore risk-reducing salpingo-oophorectomy appears attractive both for an individual and on population level. In Western countries performing prophylactic salpingo-oophorectomy on the basis of strong family history is replaced by the operation indications by genetic findings. Occult cancer can be found as frequently as 12% (Lu *et al.*, 2000; Colgan *et al.*, 2001; Powell *et al.*, 2005). Pelvic cytology may help to reveal occult cancer (Paley *et al.*, 2001). Estrogen replacement therapy after ovarectomy is questionable as it can ameliorate the menopausal symptoms but risk of breast cancer might increase. Simultaneous hysterectomy can be suggested for other indications, MMR mutation or possible tamoxifen treatment that implies increased endometrial cancer risk (Guillem *et al.*, 2006). The prophylactic salpingo-oophorectomy reduces ovarian cancer risk for 75 – 96% (Kauf *et al.*, 2002; Rebbeck *et al.*, 2004). Alternatively, periodic screening with CA-125 and transvaginal sonography can be advised although the efficacy is not known (Guillem *et al.*, 2006).

BRCA mutations – the prototype of the genetic basis of autosomally dominantly transmitted hereditary cancer

Testing for mutations in *BRCA1* and *BRCA2* genes has become an accepted practice in many diagnostic clinical genetics units (Eccles, 2004). At least several hundred germline mutations are identified in *BRCA1* and *BRCA2* genes in patients from hereditary breast or ovarian cancer families (Bergman *et al.*, 2001). Some of the mutations are recurrent in patients belonging to specific ethnic group or residing in definite geographic territory. The recurrent mutations are called founder mutations bearing in mind the idea that these could originate from a single ancestor. Knowledge about founder mutations is of diagnostic importance as this helps to design efficient and economically optimal mutational screening. *BRCA1* and *BRCA2* are large genes, therefore complete testing of the coding regions is significantly more time-consuming and expensive than search for founder mutations known to predominate in

the specific ethnic group. The frequency of *BRCA1* founder mutations in hereditary breast ovarian cancer patients from geographically and historically homogeneous population can be as high as 33% of all mutations in *BRCA1* and *BRCA2*, as reported from southern Italy for 5083del19 (Baudi *et al.*, 2001) or even 67 – 77%, as reported from Sweden for 3171ins5 (Einbeigi *et al.*, 2001; Bergman *et al.*, 2001).

The presence of founder mutations in Latvian population is suggested by three facts. First, the age characteristics of Latvian hereditary breast and ovarian cancers might give rise to the hypothesis of strong founder effect in the population. Secondly, analysis of selected Latvian breast and ovarian cancer cases has shown the presence of founder mutations. Thirdly, the Eastern European populations frequently are characterized by founder effects that might be related to the density of historical events rather than coincidence. These statements will be shortly discussed further.

An interesting observation is made by Norwegian group of scientists (Borg *et al.*, 1999), namely, the founder mutation carriers have later onset of the disease. This finding is confirmed also by other groups (Levy-Lahad *et al.*, 1997; Malander *et al.*, 2004; Capalbo *et al.*, 2006). Hypothetically one can expect presence of founder mutation in a population with higher age of cancer diagnostics in hereditary breast-ovarian cancer patients. In patients with early onset of disease, presence of a rare mutation is more probable, as founder mutation would be lost during previous centuries, e.g. in 50 generations (Bergman *et al.*, 2001), if it would cause deadly disease during child-bearing, breastfeeding or nursing age. According to this, description of hereditary breast cancers in Latvia by Gardovskis, 2008 suggests the presence of founder mutations.

By *BRCA1* gene analysis in a selected group of breast and ovarian cancer patients form Latvia, 5382insC was found in 8/75 breast cancer patients and constituted 8/15 (53.3%) mutations, but 4154delA was found in 4/75 patients and constituted 4/15 mutations. One 300T>G mutation also was present in this group. In ovarian cancer patients, 5382insC was found in 4 patients, representing 4/6 mutations. Single cases of 4154delA and 300T>G were also found in the ovarian cancer group. Although the recruitment of patients was done by combined criteria (Tikhomirova *et al.*, 2005), these data justified the presence of founder mutations in Latvian population.

The frequency of *BRCA1* mutations 5382insC and 4154delA in patients with diagnosis of hereditary breast and ovarian cancer in Latvia is 36% (Gardovskis, 2008). Thus, it is justified to include these mutations in the genetic analysis as founder mutations; however, the burden of other mutations also may be significant and search for these mutations should be performed. Attention to the clinical diagnosis of hereditary breast and ovarian cancer must be paid as in many cases the family history remains the only present clue to the diagnosis.

The geographic context of the mutations 5382insC and 4154delA is following (see also Table 1 and Table 2).

In Poland, recurrent mutations were very common, accounting for 94% of detected mutations. *BRCA1* mutations 5382insC, C61G and 4153delA represented 51%, 20% and 11% of all identified *BRCA1* and *BRCA2* mutations in 66 hereditary breast and ovarian cancer families; *BRCA1* mutations were found in 34/66 families (Górsky *et al.*, 2000). In later large scale study, the high rate of founder mutations in Polish hereditary breast and ovarian cancer patients was confirmed – 97.5% families with mutations had recurrent mutation, and 91.0% – one of the founder mutations. By entire sequencing of *BRCA1* and *BRCA2*, mutation was detected in 66% of breast and 63% of breast – ovarian cancer families (Górsky *et al.*, 2004). In another group of 63 families, strong founder effect was confirmed, but the relative frequencies of mutations were as follows: 5382insC, 67%; 300T>G, 33% and 4153delA, 0% (Janiszewska *et al.*, 2003). The breast cancer risk in the carriers of founder mutations is influenced by other genetic (Jakubowska *et al.*, 2007) and environmental / lifestyle (Gronwald, Byrski *et al.*, 2006) factors.

Lithuanian population is characterized by high incidence of *BRCA1* 4153delA mutation in hereditary breast – ovarian cancer families (Gronwald *et al.*, 2005). In total, one of three founder mutations (4153delA, 5382insC and C16G) was found in 9/13 families with definitive hereditary breast or breast – ovarian cancer. 4153delA accounted for 56%, 5382insC – for 33% and C16G – for 11% of the detected mutations (Gronwald *et al.*, 2005). In Russia, 5382insC predominated (94%) as described by Loginova *et al.*, 2003. These data suggest that 4153delA is characteristic for Lithuanian population with the diagnostic consequences. Similarly, 5382insC can be "mapped" to the European part of Russia and Eastern Europe although it is highly characteristic also for Ashkenazi Jews.

No data are available for Estonia, another neighbouring country in Latvia with ethnically different population and language. In Finland, northern neighbour of Estonia, 21 different *BRCA1* mutations have been identified, and 14 of them are considered to be founder mutations. However, such high number of proposed founder mutations limits the economic efficiency and rate of genetic testing. Among non-selected ovarian cancer patients, 13/233 (5.6%) had *BRCA* mutations, and 26% of Finnish ovarian carcinoma families were found to be mutation positive (Sarantaus, Auranen *et al.*, 2001; Sarantaus, Vahteristo *et al.*, 2001). Large deletion has been detected in 1/61 idex patients from families affected by breast and/or ovarian cancer (Pylkäs *et al.*, 2008)

Sweden is an example of genetically contrasting population. The frequency of *BRCA1* mutation 3171ins5 was 67-77% of all mutations in *BRCA1* and *BRCA2* in the western Sweden (Einbeigi *et al.*, 2001; Bergman *et al.*, 2001). The role of 3171ins5 together with 4 other *BRCA1* gene mutations and 1 *BRCA2* gene mutation has been estimated as 75% of all *BRCA1/2* mutations in the western Sweden (Einbeigi *et al.*, 2007). Southern Swedish population was characterized by founder mutations 2595delA (5/15 mutation-bearing breast

and ovarian cancer families), C1806T (3/15 families), 3171ins5 also denoted as 3166ins5 (3/15 families), 1201del11 (2/15 families) as reported by Johannsson *et al.*, 1996.

Two founder mutations, 1675delA and 1135insA, accounted for almost one third of all familial breast and ovarian cancers and for more than half of *BRCA1* mutations in Norway (Borg *et al.*, 1999).

In Denmark, most mutations were identified only in single family. The most frequent recurrent *BRCA1* mutations were 2594delC (16%), 3438G>T (9%), 5382insC (8%), 3829delT (5%) as described by Thomassen *et al.*, 2008. The West Denmark was characterized by presence of mutations that have been described in other Scandinavian countries while the mutation spectrum in East Denmark is closer to the mutations reported from Baltic countries; Ashkenazi mutations also have been found. Thus, full screening of *BRCA* genes was recommended for Danish hereditary breast and ovarian cancer families (Thomassen *et al.*, 2008).

The population frequency of three founder mutations, namely *BRCA1* 185delAG, 5382insC and *BRCA2* 6174delT, in Ashkenazi Jews is approximately 2% (Levy-Lahad *et al.*, 1997). The frequency of *BRCA1* mutation 5382insC in Ashkenazi Jews is estimated as 0.2-0.3%, e.g., 0.25% in Australian Jewish population. The frequency of this mutation is constant in different Jewish communities despite different history of migration and opportunity for changes in allele frequency (Bahar *et al.*, 2001). The founder mutation is found in 59% (25/42) of high-risk Ashkenazi families with at least 2 ovarian cancer cases within family, but its frequency is high also in non-selected ovarian cancers – 39% (7/18) in those with minimal or negative family history (Levy-Lahad *et al.*, 1997).

In France, 22 mutations of *BRCA1* gene were found in high risk families with breast and/or ovarian cancer (Peyrat *et al.*, 1998). In French Canadian, *BRCA1* and *BRCA2* mutations were found in 40% of families with hereditary breast and/or ovarian cancer (Tonin, 2006); 84% of families carried one of eight founder mutations. Among these, there were 3 *BRCA1* mutations, namely 2953delGTA+C, 3875delGTCT and 446C-->T.

In Iceland, the founder mutation was found in *BRCA2* gene, namely, 999del5 (Thorlacius *et al.*, 1996). Mutation 4184del4 was reported from Great Britain (Gayther *et al.*, 1995). In Holland, 2804delAA, 2312del5, 1411insT and C2457T have been reported (Peelen *et al.*, 1997; Petrij-Bosch *et al.*, 1997).

Table 1. Geographic distribution of *BRCA1* mutation 5382insC

Country or ethnic group	% from *BRCA1* mutations	Reference
Poland	53 – 67%	Górski *et al.*, 2000 Janiszewska *et al.*, 2003
Lithuania	33%	Gronwald *et al.*, 2005

Russia	94%	Loginova *et al.*, 2003
Finland	6.7%	Vehmanen *et al.*, 1997
Sweden	Not found	Johannsson *et al.*, 1996
Denmark	8%	Thomassen *et al.*, 2008
Ashkenazi Jews	75.4%	Moslehi *et al.*, 2000
Italy	Occasional	Capalbo *et al.*, 2006 Montagna *et al.*, 2003

Table 2. Geographic distribution of *BRCA1* mutation 4153delA.

Country	% from *BRCA1* mutations	Reference
Poland	11%	Górski *et al.*, 2000
Lithuania	56%	Gronwald *et al.*, 2005
Russia	Frequent	Gayther *et al.*, 1997
Finland	Not found	Vehmanen *et al.*, 1997
Sweden	Not found	Johannsson *et al.*, 1996

The data about the geographic distribution of *BRCA1* mutations 5382insC and 4153delA is separately presented in the Tables 1-2. It can be seen that the frequency of these mutations in neighbouring countries is high enough to initiate search for them in Latvian population. However, the structure of *BRCA* mutations in Latvia remains an intriguing question as the known founder mutations are more characteristic in Eastern European countries. Gene drift from northern countries could bring different impact, and the local factors remain to be analysed. In the present situation, clinical data regain major importance both in clinical and scientific analysis.

Hereditary colorectal cancer

Colorectal cancer is a frequent cause of oncological morbidity and mortality. It is the second most common cancer in Europe (13.0%) almost matching the frequency of lung cancer, the most widespread malignancy (13.2%). In European Union countries colorectal cancer is the most frequent tumour. Colorectal cancer is also the second most common cause of cancer death in Europe (Boyle and Ferlay, 2005). It is estimated that 80% of colorectal cancer cases are related to environmental factors thus representing sporadic disease. In 20% of colorectal cancer patients, genetic background exists. However, the discovered genetic mutations related to high lifetime risk of colorectal cancer account only for 5 – 6% of colorectal cancer cases (Trimbath and Giardiello, 2002). The two main hereditary cancer syndromes involving the large bowel are familial adenomatous polyposis, responsible for 1% of the annual colorectal

cancer burden, and hereditary non-polyposis colorectal cancer that accounts for 2 – 3% of colorectal cancer cases (Guillem *et al.*, 2006).

Hereditary non-polyposis colorectal cancer (HNPCC)

HNPCC is caused by germline mutation in any of the DNA mismatch repair genes (MMR) and is characterised by early-onset colorectal cancer, mostly in proximal location; an increased risk of metachronous colorectal tumours and a characteristic, wide spectrum of benign and malignant extracolonic tumours (Guillem *et al.*, 2006). This syndrome comprises 2 – 3% of colorectal cancers (Koornstra *et al.*, 2009).

The history of HNPCC concept began in 1966 when Lynch *et al.* described the family aggregation of colorectal, gastric and endometrial cancers under the term "cancer family syndrome". Later the syndrome was designated Lynch syndrome or HNPCC. The diagnostic criteria of HNPCC are following. Set of criteria called Amsterdam Criteria I request the presence of all the subsequent facts: 1) at least three relatives affected by histologically verified colorectal cancer and one of the patients is a first-degree relative of the other two. Familial adenomatous polyposis must be excluded; 2) colorectal cancer involving 2 or more generations; 3) at least one colorectal cancer case diagnosed before the age of 50. The other set of criteria, known as Amsterdam Criteria II, allows using the presence of certain extracolonic cancers for the diagnosis of HNPCC syndrome: 1) at least three relatives with histologically verified HNPCC-associated cancer, one of whom is a first-degree relative of the other two. Familial adenomatous polyposis must be excluded; 2) colorectal cancer diagnosed in 2 or more generations; 3) at least one HNPCC-related cancer diagnosed before the age of 50. The HNPCC-related tumours in the diagnostic context include endometrial cancer, cancer of the small intestine and of renal pelvis or ureter (Trimbath and Giardiello, 2002). However, awareness exists that not all HNPCC cases can be diagnosed by these criteria (Guillem *et al.*, 2006).

The published frequency of HNPCC varies widely, from 1% to 13% of colorectal cancers (Trimbath and Giardiello, 2002). The cause of HNPCC is a mutation in mismatch repair genes with autosomal dominant mode of inheritance. The mismatch repair genes include *MSH2* (human mutS homologue 2) and *MSH6* (human mutS homologue 6), both on chromosome 2p16 (Fishel *et al.*, 1993; Leach *et al.*, 1993; Akiyama *et al.*, 1997; Miyaki *et al.*, 1997); *MLH1* (human mutL homologue 1) on chromosome 3p21 (Papadopoulos *et al.*, 1994; Bronner *et al.*, 1994); *PMS1* (human postmeiotic segregation 1) on chromosome 2q31 and *PMS2* (human postmeiotic segregation 2) on chromosome 7q11 (Nicolaides *et al.*, 1994). Germline mutations of *MSH2* and *MLH1* account for more than 95% of mutations in HNPCC families (Liu *et al.*, 1996). MMR mutations are detected in 60% of Amsterdam criteria fulfilling families (Lynch and de la Chapelle, 2003).

The lifetime risk of colorectal cancer (Figure 2) in HNPCC-related mutation carriers is 80%, and the average age of diagnosis is 44 years (Lynch, Shaw *et al.*, 1996). HNPCC-related

colorectal cancer is characterised by more frequent occurrence in the right side of colon (Lynch, Shaw *et al.*, 1996), certain histological features, high rate of microsatellite instability, improved survival but high risk of metachronous colorectal cancer. The rate of right colonic tumours is 60 – 80% in HNPCC vs. 23 – 32% of sporadic colorectal cancers (Lynch, Shaw *et al.*, 1996). Histologically, HNPCC-related colorectal cancers are characterised by high grade, mucinous component and more marked host response (Trimbath and Giardiello, 2002). The risk of colorectal cancer in 10 years after surgical resection is 45% (Trimbath and Giardiello, 2002).

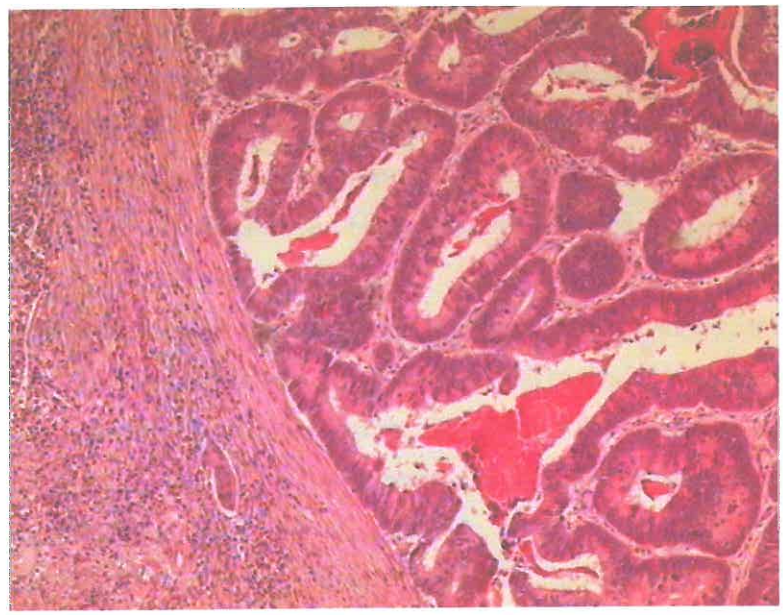


Figure 2. Cancer of the large bowel. Haematoxylin – eosin, original magnification 100x. Microphotograph by A. Vanags

HNPCC is associated with elevated risk of extracolonic tumours, including endometrial, gastric, small intestinal, pancreatic, biliary tree, ovarian cancer, transitional cell carcinoma and brain tumours (Watson and Lynch, 1993; Koornstra *et al.*, 2009). The cumulative risk of extracolonic tumour is 47.4% (95% CI = 43.9 – 50.85) for females and 26.5% (95% CI = 22.6 – 30.4%) for males at the age of 70 years, considering proven and obligate mutation carriers and their first degree-relatives (Barrow *et al*, 2009). Males have significantly higher risks of gastric (Barrow *et al.*, 2009) and urologic (Watson *et al.*, 2008) cancer. Gastric cancer has lifetime risk of 5.8% to the age of 70 years with the greatest risk within interval 50 - 65 years and low risk before the age of 50 years (Watson *et al.*, 2008). Other groups have reported higher lifetime risk – 12% in Korea (Park *et al.*, 2000), 13% in Finland (Aarnio *et al.*, 1999) and even 18% by Hampel *et al.*, 2005.

The risk of endometrial cancer is as high as 39% by the age of 70 (Trimbath and Giardiello, 2002). Slightly higher risk estimate of 43% is also described (Hampel *et al.*, 2005).

The risk of ovarian cancer is 6.7 – 9% by the age of 70 (Watson *et al.*, 2008; Trimbath and Giardiello, 2002). It is higher in *MSH2* mutation carriers. The highest risk period for ovarian cancer is from age 40 to 55 years, but 8 / 72 of ovarian cancers were diagnosed even before the age of 35 years (Watson *et al.*, 2008).

The lifetime risk of urologic cancer is 8.4% (95% CI = 6.6 – 10.8). The risk of urothelial cancer in HNPCC is 1.6 times higher in males than in females and 7 times higher in *MSH2* than in *MLH1* family members (Watson *et al.*, 2008).

Breast cancer occurs in HNPCC kindreds at the same risk as in general population (Watson *et al.*, 2008). The lifetime risk of brain tumours is estimated to be 2%; these neoplasms frequently occur in young patients and have dismal prognosis. Twenty-six percent of brain tumours develop before 25 years of age, the lethality is 90%; and almost one forth of death cases occurs before the age of 25 years (Watson *et al.*, 2008). The relative risk of small intestinal cancer as well as cancer of the biliary tree is increased in comparison to general population (Trimbath and Giardiello, 2002).

Analysing cancers developing in mismatch repair gene mutation carriers, the frequency of high-level microsatellite instability was different according to the location: high (96 – 100%) in ureteric, gastric and colorectal cancer, intermediate (60 – 63%) in endometrial cancers and cancer of urinary bladder, low (0 – 25%) in renal cancer and brain tumours (Gylling *et al.*, 2008) suggesting different pathways of carcinogenesis.

The management of HNPCC include screening and eligible treatment, optimized for the presence of mutation and the associated risk. No childhood measures are necessary in contrast to FAP (Trimbath and Giardiello, 2002). The screening includes search for colorectal and endometrial cancer in combinations with screening for other malignancies if indicated by family cancer history (Guillem *at al.*, 2006). First-degree relatives of affected individuals should undergo colonoscopy every 1-2 years starting between 20 and 30 years and annually after 40 years of age. Alternatively, it is also suggested to start colonoscopies at the age 25 and perform it once per 1-2 years. For mutation carriers it is advised to start annual colonoscopies at the age of 25 or 5 years before the age of diagnosis of the youngest case in the family, whichever comes first. Annual screening for endometrial cancer should be started at age 25-35 and include endometrial aspiration or transvaginal ultrasound (Trimbath and Giardiello, 2002). Endometrial cancer is the only extracolonic tumour location for which there is evidence of surveillance benefit as diagnostics of tumours in early stage can be achieved (Koornstra *et al.*, 2009). However, gynaecological screening including clinical examination, transvaginal ultrasound imaging, hysteroscopy and endometrial biopsy has not resulted in decreased malignancy rate (Barrow *et al.*, 2009). Preventive measures for ovarian cancer should be used beginning at the age of 40. Early oophorectomy could be considered, probably in *MSH2* mutation carriers (Watson *et al.*, 2008). Prophylactic gynaecologic surgery is suggested to be the best preventive option in females who have completed childbearing

plans (Manchada *et al.*, 2009). Surveillance has been recommended for urinary tract and gastric cancer if these tumours are present in the kindred (Koornstra *et al.*, 2009). Alternatively, surveillance for urothelial cancer is recommended for carriers of *MSH2* mutations after age of 50. Ultrasonography and urine cytology can be used to screen for urinary tract cancer (Guillem *et al.*, 2006). Regular gastric surveillance is suggested by some (Goecke *et al.*, 2006) but rejected by other scientists (Watson *et al.*, 2008). It seems reasonable to recommend annual esophagogastroduodenoscopy for those patients whose pedigrees are marked by presence of gastric cancer cases (Guillem *et al.*, 2006).

Prophylactic total colectomy with ileorectal anastomosis can be considered in patients for whom endoscopic surveillance is not possible or who refuse to undergo it (Guillem *et al.*, 2006; Scaife and Rodriguez-Bigas, 2003). Performing colorectal cancer surgery, risk of synchronous and metachronous cancer must be taken into account (Trimbath and Giardiello, 2002). If cancer is present, partial colectomy carries higher cancer risk than total colectomy with ileorectal anastomosis (Guillem *et al.*, 2006); the risk can be as high as 12% in 10-12 years (Rodriguez-Bigas *et al.*, 1997; Lee *et al.*, 2001). If the first tumour is a rectal cancer, total proctocolectomy can also be considered as the risk of proximal metachronous cancer is 17 – 45% (Lee *et al.*, 2001; Vasen *et al.*, 1995; Guillem *et al.*, 2006). Prophylactic hysterectomy and bilateral salpingooophorectomy should be considered after completing childbirth, especially during colorectal surgery. There is no evidence of the efficacy of chemoprotection (Koornstra *et al.*, 2009).

Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant disorder caused by germline mutation in the tumour suppressor *APC* gene on chromosome 5q12. The principal manifestation of this syndrome is the development of numerous (at least 100) colorectal adenomas beginning from teenage years. At the age of 35 years, 95% of FAP patients have developed adenomas. Due to malignisation in accordance with the adenoma-carcinoma sequence, the lifetime risk of colorectal cancer approaches 100% with the average age of cancer diagnosis at 34.5 – 43 years (Trimbath and Giardiello, 2002; Petersen *et al.*, 1990; Jarvinen, 1985). A wide spectrum of benign extracolonic manifestations is possible as well as extracolonic malignancies including hepatoblastoma, small intestinal, biliary and pancreatic tumours, thyroid malignancies, brain tumours. Attenuated FAP (Spirio *et al.*, 1993) is characterised by lower number of adenomas (20-100) and subsequently, later cancer development (Giardiello *et al.*, 1997).

FAP can be caused by any of more than 300 mutations described in *APC* (Laurent – Puig *et al*, 1998). These mutations include insertions, deletions and nonsense mutations resulting in frameshift or premature stop codons that, in turn, truncate the APC protein. Approximately 10% of FAP patients share one mutation – the deletion of AAAAG in codon 1309 (Trimbath

and Giardiello, 2002). Genotype – phenotype correlations are described, but are confounded by the significant variability.

An unusual variant of *APC* mutation has been described in 6% of Ashkenazi Jews. A missense mutation I1307K implies twofold lifetime risk of colorectal cancer. The biochemical basis is the replacement of thymine by adenine that in the surrounding adenine-rich sequence results in long adenine chain. During DNA replication, this site becomes prone to somatic mutations (Laken *et al.*, 1997; Rozen *et al.*, 1999).

The management of FAP patients include timely diagnostics, follow-up by optimal schedule in order to detect some less frequent ominous manifestations and prophylaxis of colorectal cancer. It has been suggested to diagnose FAP as early as at the age of 10-12 years (Trimbath and Giardiello, 2002), optimally by genetic testing of first-degree relatives of FAP patients (Winaver *et al.*, 1997), alternatively by yearly sigmoidoscopy (colonoscopy if attenuated FAP is suggested) decreasing the frequency of endoscopy with each decade if negative. Full colonoscopy is suggested after the diagnosis has been established. The timing of surgery depends on the severity of the initial manifestations. If the polyposis around puberty is mild it has been suggested to perform prophylactic surgery in mid teens, but severe polyposis, severe dysplasia, tubulovillous architecture, multiple adenomas larger than 5 mm and such symptoms as bleeding, diarrhoea, anaemia and failure to thrive are indications to consider early surgical treatment (Guillem *et al.*, 2006; Church and Simmang, 2003). In cases with small adenomas and strong family history of abdominal desmoid disease the colectomy could be delayed (Guillem *et al.*, 2006). The surgical approaches include total proctocolectomy with permanent ileostomy, total colectomy with ileorectal anastomosis and proctocolectomy with ileal pouch – anal anastomosis. Total proctocolectomy with permanent ileostomy is indicated for patients with poor sphincter function or tumour invasion in sphincter as well as in case of mesenteric desmoid. The colectomy is associated with high rectal cancer risk of 4 – 8% in 10 years and 26 – 32% in 25 years (Vasen, Luijt *et al.*, 1996; Bertario *et al.*, 2000). It is not recommended for patients having severe rectal polyposis with more than 20 adenomas, marked colonic polyposis with more than 1000 adenomas, adenoma larger then 3 cm or an adenoma with severe dysplasia (Church and Simmang, 2003; Debinski *et al.*, 1996; Church *et al.*, 2001; Guillem *et al.*, 2006; Sarre *et al.*, 1987). Endoscopic surveillance is recommended at 6 – 12 month intervals after the surgery. The functional outcome after total colectomy with ileorectal anastomosis and proctocolectomy with ileal pouch – anal anastomosis has been matter of discussions (Guillem *et al.*, 2006).

Hepatoblastoma is a childhood tumour that is curable by early surgery but may cause death if not treated properly. As the risk of hepatoblastoma is 1:150 in *APC* mutation carriers and 1:300 in their children, screening with serum alpha-fetoprotein levels and liver imaging is advised in children of FAP patients from infancy to 5 years of age (Trimbath and Giardiello, 2002).

Prophylactic use of COX-2 inhibitors is under research. Non-steroidal anti-inflammatory drugs sulindac, rofecoxib, celecoxib, exisulid reduce the polyp number and size in FAP patients but rectal cancer can develop even on background of seemingly successive polyp control (Guillem *et al.*, 2006). The compliance and adverse effects also remain questionable issues. It is recommended to consider these medications in particular situations like refusal from colectomy or necessity to reduce polyp number in order to facilitate endoscopic control of them and to postpone the scarring to such a degree that cancels any efforts of polyp fulguration or polypectomy.

Even if hepatoblastoma has been avoided or treated in the childhood and colorectal cancer risk is controlled, death of FAP patient can be caused by desmoids or cancer in the duodenal area.

Desmoids occur in 12 – 17% of FAP patients (Church and Simmang, 2003; Soravia *et al.*, 2000). These tumours frequently are intraabdominal and occur after abdominal surgery suggesting they are triggered by surgical intervention (Clark *et al.*, 1999; Soravia *et al.*, 2000; Penna *et al.*, 1993). Surgical treatment may be difficult. Tamoxifen can be used if the tumour is slowly growing or mildly symptomatic (Tsukada *et al.*, 1992; Bus *et al.*, 1999), vinblastine and methotrexate can be used in more aggressive cases (Azzarelli *et al.*, 2001; Skapek *et al.*, 1998) but doxorubicin and dacarbazine can be used for rapidly growing tumour (Lynch *et al.*, 1994; Poritz *et al.*, 2001).

The rate of duodenal adenomas in FAP patients is 80 – 90% with a risk of malignancy 3 – 5%. The surveillance includes upper gastrointestinal endoscopy beginning from the age of 25 – 30 years. Endoscopic removal, pancreas-preserving duodenectomy or pancreaticoduodenectomy are among the treatment options. It seems that COX-2 inhibitors are even less effective in order to control duodenal polyposis (Guillem *et al.*, 2006).

Other hereditary/familial colorectal cancer syndromes

CRAC gene is mapped to 15q14-22 (Tomlinson *et al.*, 1999). *MYH* gene mutations bring an increased colorectal cancer risk in a recessive mode, presenting mostly as attenuated polyposis (Sampson *et al.*, 2003). Testing for *MYH* gene mutations is advised in patients with at least 15 colorectal adenomas and family history suggesting recessive mode of inheritance (Sieber *et al.*, 2003). Familial colorectal cancer can be diagnosed clinically as the aggregation of 3 cancer cases in the same location among blood relatives is considered a high risk cluster (Hampel *et al.*, 2004); however, if the pedigree corresponds to the diagnostic criteria of HNPCC, this more specific diagnosis should be used.

Hereditary endometrial cancer

Part of the hereditary endometrial cancer (Figure 3) burden is due to HNPCC. The risk of endometrial cancer in HNPCC pedigrees is 20 – 60%, and in some studies it is estimated as equal to the risk of colorectal cancer (Manchada *et al.*, 2009) or possibly exceeding the risk of

colorectal cancer in women (Aarnio *et al.*, 1995; Dunlop *et al.*, 1997; Quehenberger *at al.*, 2005). Three to five percent of endometrial cancers are associated with mutations in MMR genes (Guillem *et al*, 2006). HNPCC-associated endometrial cancers typically develop before menopause in contrast to sporadic cases (Watson *et al.*, 1994; Vasen *et al.*, 1994; Brown *et al.*, 2001) and are characterized by favourable prognosis (Vasen *et al.*, 1994; Boks *et al.*, 2002). Surveillance should be started early, in the age interval of 25 – 35 years or 10 years before the youngest diagnosed tumour case in the family (Brown *et al.*, 2001). Transvaginal ultrasonography or endometrial biopsy are recommended for the surveillance; however, the efficacy of transvaginal ultrasonography has been doubted (Dove-Edwin *et al.*, 2002) and also it has been questioned whether endometrial biopsy offers diagnostic and survival advantage over curettage due to bleeding (Guillem *et al*, 2006). Prophylactic surgery decreases the risk of cancer significantly (Schmeler *et al.*, 2006) but the statistic survival benefit is affected by the beneficial prognosis of HNPCC-related endometrial cancer (Offit and Kauf, 2006). Hysterectomy can be combined by colectomy. Performing prophylactic hysterectomy, the possible presence of occult, non-bleeding endometrial cancer should be considered in order to perform the operation in accordance to oncological practice and staging. Preoperative endometrial biopsy and/or frozen section should be used for this purpose. Risk-reducing salpingo-oophorectomy should be considered due to elevated ovarian cancer risk and the availability of estrogen replacement therapy that is not contraindicated in HNPCC (Guillem *et al.*, 2006).

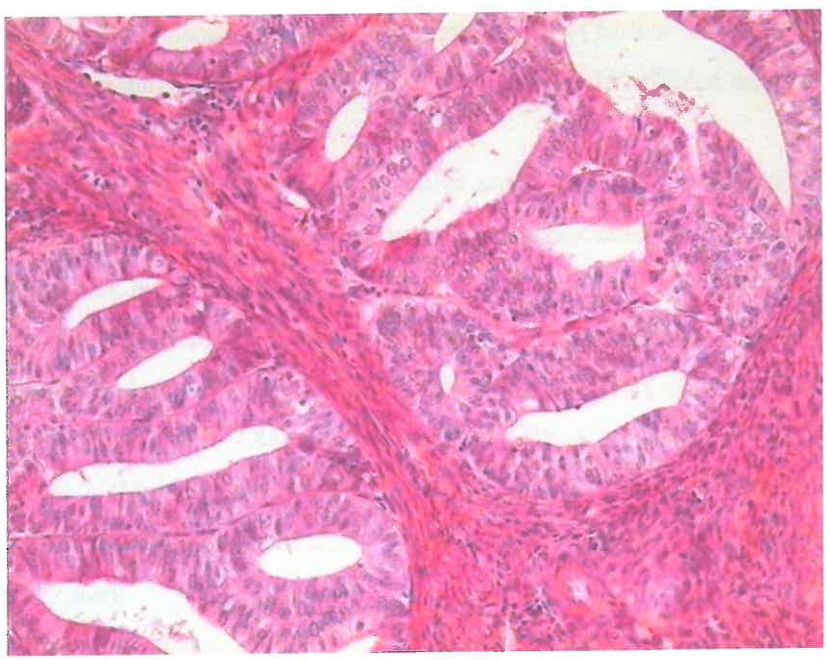


Figure 3. Endometrial cancer. Haematoxylin-eosin, original magnification 100x. Microphotograph by A. Vanags

Hereditary factors in lung cancer

Lung cancer is the most common cancer in the world (Parkin *et al.*, 2005) and the leading cause of cancer death in Europe (Boyle and Ferlay, 2005) and the whole world (Nitadori *et al.*, 2006) due to its frequent occurrence and grave prognosis implying 5-year-survival of 15% in the case of best available treatment (Molina *et al.*, 2008). Tobacco smoking is the main risk factor of the lung cancer causing approximately 90% of the lung cancer cases. Lot of scientific efforts has been applied to the analysis of tobacco-initiated lung carcinogenesis. Diminishing of the smoking frequency in the population is an effective measure in the limitation of lung cancer causing concentration of organizational and informative efforts in this direction. Thus, studies of the hereditary factors in lung cancer run behind similar research concerning tumours in other locations although the first records suggesting the familial clustering of lung cancer date back to the middle of the previous century (Tokuhata *et al.*, 1963). Up to 2005, 31 case – control studies and 17 cohort studies have been published on this field (Matakidou, Eisen and Houlston, 2005).

Epidemiologic evidence about lung cancer in relatives

Many (10/28) of the case – control studies have been devoted to the analysis of lung cancer in females (Matakidou, Eisen and Houlston, 2005). Thus, multivariate analysis of the family history of women with lung cancer showed that family history of lung cancer in a first-degree relative significantly increased the risk of lung cancer with odds ratio (OR) 1.61 (Rachtan *et al.*, 2008). Similar results were obtained in the United Kingdom by Matakidou *et al.*, 2005: the risk of lung cancer in female was significantly increased (OR, 1.49, 95% CI = 1.13 – 1.96) if a first-degree relative was affected by lung cancer and was further increased having higher numbers of affected relatives (OR for persons having 2 or more affected relatives, 2.68, 95% CI = 1.29 – 5.55).

A large scale population-based prospective cohort study has been conducted in Japan over time period of 13 years in order to analyse the possible association between lung cancer risk and family history of lung cancer. It was found that the risk of lung cancer was higher in persons who had family history of lung cancer in first-degree relative The association was stronger in females and non-smokers, reaching the following levels of hazard ratio: in general group, 1.95 (95% CI = 1.31 – 2.88); in females 2.65 (95% CI = 1.40 – 5.01); in males 1.69 (95% CI = 1.03 – 2.78); in non-smokers 2.48 (95% CI = 1.27 – 4.84); in smokers 1.73 (95% CI = 0.99 – 3.00). The risk of lung cancer was not influenced by general family cancer history (Nitadori *et al.*, 2006).

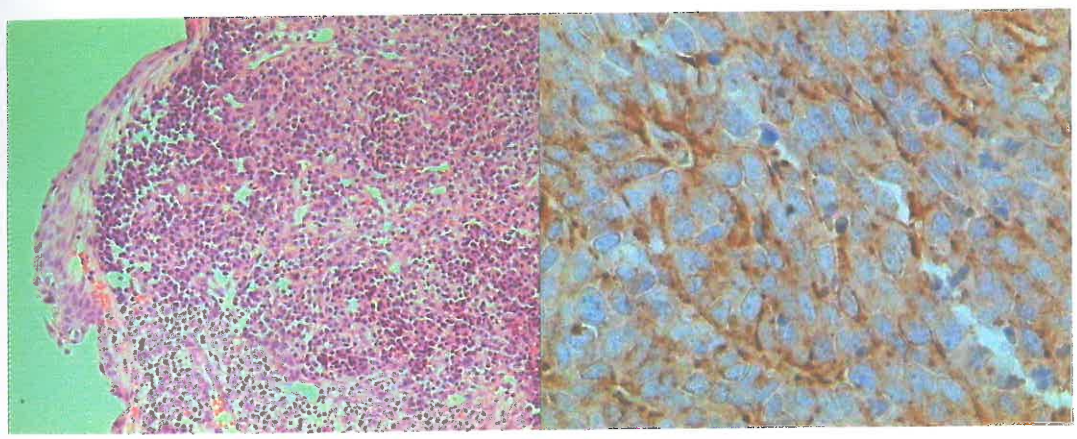
In Icelandic population, increased relative risk of lung cancer in the kinship of lung cancer patients was demonstrated by Jonsson *et al.*, 2004.

Hemminki and Li, 2005 have reported higher lung cancer risk in sibling (2.15) than in the offspring (1.77) of affected parents. In contrast, the odds ratios associated with lung cancer in

father, mother and siblings, were 1.41, 2.14 and 1.53, respectively, in the study performed by Gao *et al.*, 2009, in USA.

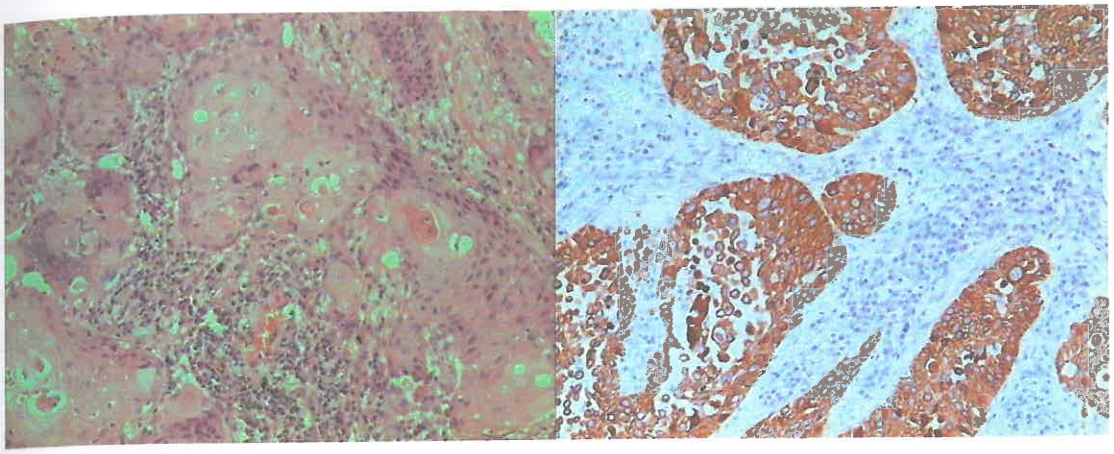
Family history and histology

The family history would have more practical value if it would help to evaluate the risk of potentially treatable tumour. Small cell cancer (Figure 4) usually is subjected to chemotherapy and irradiation; the role of surgery is limited and the prognosis is dismal in most cases. In contrast, the prognosis of lung cancer is relatively better if non-small cell cancer (Figure 5) is revealed in early stage and treated surgically (International Early Lung Cancer Action Program Investigators, 2006). Taking into account the different approaches in treatment, it would be important to know the possible association between family history and the type of lung tumour if such correlation exists.

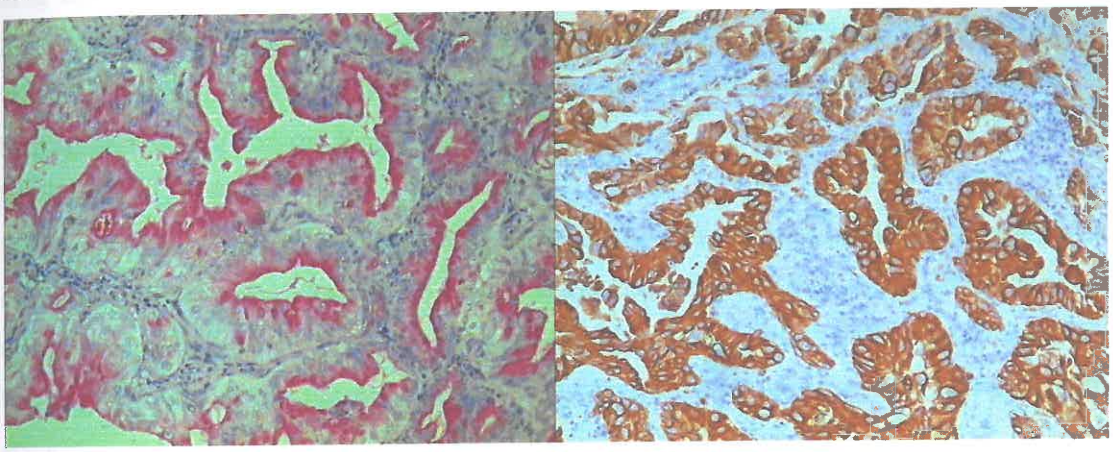


A. B.

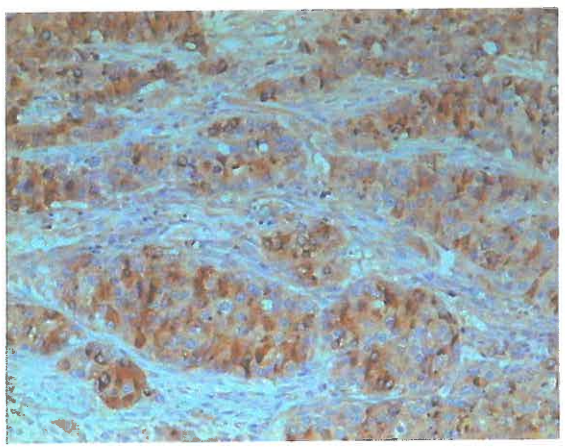
Figure 4. Small cell lung cancer. A, haematoxylin-eosin stain, original magnification 100x; B, anti-chromogranin A by immunoperoxidase, original magnification 400x. Microphotographs by A. Vanags



A. B.



C. D.



E.

Figure 5. Non-small cell lung cancer. A, squamous cell cancer, haematoxylin-eosin stain; B, anti-high molecular weight cytokeratin in squamous cell cancer by immunoperoxidase; C, adenocarcinoma, mucicarmin stain; D, anti-cytokeratin 7 in adenocarcinoma by immunoperoxidase; E, large cell neuroendocrine carcinoma, anti-chromogranin A by immunoperoxidase. A-E, original magnification 100x. Microphotographs by A. Vanags

The association between family history and lung tumour was the strongest for squamous cell cancer in Japanese group (Nitadori *et al.*, 2006) and USA patients (Ambrosone *et al.*, 1993).

However, the data were somewhat controversial in the USA group. Squamous cell cancer was most strongly associated with positive family history in the whole group of patients as well as in such subgroups as patients younger than 57 years, non-smokers and persons with lower level of smoking, as well as in women. Nevertheless, large cell cancer and small cell carcinoma also showed association with the family history in the whole group and among non-smokers and less smoking subjects, respectively (Ambrosone *et al.*, 1993). Statistically insignificant trend to the highest family-size-adjusted mean number of lung cancer per family was found in small cell cancer (Sellers *et al.*, 1992). In contrast, using the data from the Swedish Family – Cancer Database and Swedish Cancer Registry in order to compare the lung cancer rate in persons with parental family history to those without positive family history, the risk was highest for adenocarcinoma and large cell carcinoma (Li and Hemminki, 2004; Li and Hemminki, 2003). Adenocarcinoma showed stronger association with familial background among non-smoking USA females (Wu *et al.*, 1996). No association was found by Ganti *et al.*, 2009.

It is possible that different mutations in geographically distant regions manifest themselves as different tumour types. Changes in classification and morphological diagnostic criteria of different morphological types also can influence the results. Thus, further research of the histological type of familial lung cancer would be necessary as these data represent both scientific and practical value. However, most studies have reported association between family history and non-small cell lung cancer, amenable to surgical treatment (Molina *et al.*, 2008).

Familial background and prognosis

Positive family history has been associated with a trend towards slightly lower survival in lung cancer patients (Ganti *et al*, 2009) although few data were available. The survival from lung cancer was found to correlate between blood relatives but not in spouses (Lindström *et al.*, 2009). The development of second lung cancer may be stronger influenced by genetic factors (Li and Hemminki, 2005).

Genetic background of familial lung cancer

There are different hypotheses about the mode of lung cancer inheritance. Highly penetrant recessive gene (Li and Hemminki, 2005) as well as autosomal dominant mode of inheritance (Sellers *et al.*, 1990) are suspected by different groups of scientists. The first opinion is based on the observation that siblings of lung cancer patients have higher risk than the offspring (2.15 and 1.77, respectively). The autosomal dominant inheritance implying rare gene was suggested by segregation analysis. Segregation at this locus was considered to account for 69% of the cumulative incidence until the age of 50 years, 47% – until 60 years, 22% – until 70 years (Sellers *et al.*, 1990).

By finding no clinical evidence of link between Li – Fraumeni syndrome, familial retinoblastoma, familial melanoma and families with aggregation of lung cancer it was

concluded that mutations of *p53*, *Rb*, *p16* and mismatch repair genes play no significant hereditary role in lung cancer although are frequent in lung cancer tissues (Tomizawa *et al.*, 1998).

The possible genetic loci of familial lung cancer susceptibility are described in chromosome 6q 23-25 (You *et al.*, 2009; Bailey-Wilson *et al.*, 2004), 15q24-25.1 (Liu *et al.*, 2008) and chromosome 12 (Schwartz and Ruckdeschel, 2006). Significant association has been found between lung cancer susceptibility and 3 single nucleotide polymorphisms in the first intron of the RGS17 gene. Accumulation of the transcripts of this gene was shown in lung cancer tissues (You *et al.*, 2009). Thus, 6q23-35 seems to be the major susceptibility locus of familial lung cancer.

A family with multiple cases of non-small cell lung cancer and germline mutation of the *T790M* drug resistance mutation in EGFR is reported (Bell *et al.*, 2005).

Familial lung cancer and other malignancies

The initially mapped susceptibility locus 6q23-25 corresponds to genomic region that is deleted not only in lung cancers but in other malignancies (Bailey-Wilson *et al.*, 2004). Comparing Japanese patients who had lung cancer with the group of patients who had lung cancer in the setting of multiple primary malignancies, not only clinical differences like advanced age and early stage of lung tumour but also differences in family history were found. The patients with multiple primary malignancies had more family members affected by other malignant tumours except for smoking-related tumours (Haraguchi *et al.*, 2007). The authors attributed this association of tumours to hereditary factors. Thus, evidence has been published that lung cancer can be associated with other tumours on genetic basis and these patients might differ in later age of lung malignancy. In Poland, a common variant of *CDKN2A* with alanine to threonine substitution (A148T) was found to be common in melanoma, lung cancer and colorectal cancer patients (Debniak *et al.*, 2006). In Sweden, association between lung, rectal, cervical, renal and urinary bladder cancers was found (Li and Hemminki, 2003). An increased risk of any cancer (relative risk, RR, 1.25; 95% CI = 1.05 – 1.50) in the kindred of lung cancer patients was found by Gorlova *et al.*, 2007. The breast cancer risk was increased in female relatives of lung cancer patients (Gorlova *et al.*, 2007). Increased risk of vocal cord, oesophageal, colorectal and pancreatic cancers among the relatives of lung cancer patients was described by McDuffie HH, 1991.

Interaction of hereditary and environmental factors in familial lung cancer

In familial clustering of lung cancer, two main mechanisms could be proposed. The familial aggregation could be caused either by genetic, hereditary factors or by shared exposure to tobacco smoke by heritability of lifestyle and passive smoking. Synergistic influence of smoking and hereditary factors has been observed (Rachtan *et al.*, 2008). It was shown by Gorlova *et al.*, 2007 that smoking increases the risk of lung cancer in those already affected by increased risk because of family cancer history. If the risk of early-onset lung cancer

among the relatives of lung cancer patients was estimated as 1.44 (95% CI = 1.05 – 1.97), than in smoking relatives the risk increased to 5.52 (95% CI = 1.19 – 25.51). However, smoking alone is not sufficient explanation for familial clustering of lung cancer cases. The mapping of genetic susceptibility locus proves the presence of heritable genetic factor. Finally, epidemiologic analysis has demonstrated that heritability of smoking alone cannot explain the increased risk of lung cancer in the affected families (Bermejo and Hemminki, 2005).

Substantiation of the diagnostic criteria

Although there is an expanding body of evidence suggesting the role of hereditary factors in the lung cancer development, the term "hereditary lung cancer" still is not used widely, and the diagnostic criteria are not well-defined. It was suggested by Wood *et al.*, 2000 that presence of at least 2 first-degree relatives with lung cancer in family, one of which is diagnosed before the age of 55, should reveal the autosomal dominant hereditary lung cancer. However, these criteria were found to be too stringent by the same scientific group.

There was an attempt to identify hereditary lung cancer by criteria that are analogous to Amsterdam criteria of HNPCC. However, in a cohort of 1068 families identified by a proband having lung cancer, no family corresponded to all three criteria (Tomizawa *et al.*, 1998). It seems these criteria are not helpful in identification of the persons at risk; but the existence of family-based risk group has been shown by epidemiologic studies. In the meta-analysis of 28 case – control studies, published between 1963 – 2005, it was found by Athena Matakidou *et al.*, that the pooled relative risk of lung cancer in a person having a relative affected by lung cancer is 1.82 (95% CI = 1.58 – 2.10). The pooled RR of 4 meta-analysed cohort studies was 2.01 (95% CI = 1.62 – 2.50). The pooled RR of case-control and cohort studies was 1.84 (95% CI = 1.64 – 2.05) (Matakidou, Eisen and Houlston, 2005).

Earlier onset is well-known trait of inherited tumour. Occasionally, lung cancer has been reported in very young patients with family history of lung cancer but absence of Li-Fraumeni syndrome (Tajiri *et al.*, 1999). In several studies of familial lung cancer, cases with earlier onset of the tumour have been analysed. It is evident from the meta-analysis (Matakidou, Eisen and Houlston, 2005) that age limit is a controversial diagnostic variable as similar RR values are achieved with very different cut-off levels (Table 3).

Table 3. Evaluation of age as a diagnostic criterion in the familial lung cancer

Age limit	Type of the study	Authors	RR (95% CI)
64	Cohort	Goldgar *et al.*, 1994	2.53 (0.8 – 8.00)
60	Case – control	Matakidou *et al.*, 2005	2.02 (1.22 – 3.34)
60	Case – control	Schwartz *et al.*, 1996 Wu *et al.*, 2004	4.39 (1.33 – 14.42)[1]

		Matakidou *et al.*, 2005	
60	Cohort	Jonsson *et al.*, 2004 Li and Hemminki, 2005	2.22 (1.08 – 4.57)[1]
55	Case – control	Osann, 1991 Wu *et al.*, 1996 Etzel *et al.*, 2003	1.10 (0.73 – 1.65)[1]
55	Case – control	Rachtan *et al.*, 2008	2.48, p=0.0001
50	Case – control	Tsugane *et al.*, 1987 Bromen *et al.*, 2000	1.68 (0.28 – 10.12)[1]
50	Case – control	Gorlova *et al.*, 2007	1.44 (1.05 – 1.97)
45	Case – control	Kreuzer *et al.*, 1998	2.60 (1.10 – 6.15)

Abbreviation in table: RR, relative risk

[1] Pooled by Matakidou, Eisen and Houlston, 2005

The case – control studies provided evidence that higher number of affected relatives is associated with a trend towards higher risk of lung cancer: relative risk is estimated as 1.57 (95% CI = 1.34 - 1.84) if 1 relative is affected and as 2.52 (95% CI = 1.72 – 3.70) if at least 2 relatives are affected (Matakidou, Eisen and Houlston, 2005).

In summary, hereditary factors are likely to act in the development of lung cancer. The risk of tumour determined by genetic factors increases the risk caused by smoking and retain importance upon smoking cessation programs. The exact genetic defect comprising the hereditary risk of lung cancer is under investigation, but the most probable candidate region is 6q23-25. Hypothetically, other regions and genes may be involved. It is likely that several genetic syndromes of hereditary lung cancer exist, probably one of these involving lungs and other – specifically involving several organs. The hereditary / familial lung cancer in the scientific viewpoint offers also unique possibility to study interaction between genetic and environmental factors as the most frequent cause of lung cancer is well described.

As the search for the exact genetic marker for hereditary / familial lung cancer is still under way, the risk identification depends on clinical criteria. There is no sufficient evidence to choose a definitive age limit as a diagnostic criterion of hereditary / familial lung cancer. The published data suggest that the number of affected relatives might be associated with the risk of lung cancer and thus can be used as a criterion in risk estimates (Hampel *et al.*, 2004).

Hereditary / familial gastric cancer

Gastric cancer is the second most common cause of cancer-related death in the world but its incidence is variable between different regions (Parkin *et al.*, 2001). Diet and *Helicobacter pylori* are well-known environmental risk factors (Imsland *et al.*, 2002). Similarly to the lung

cancer, environmental factors influence the cancer risk significantly but there is an expanding body of evidence suggesting an important role of hereditary factors. The reports suggesting familial clustering of gastric cancer stem back to 1913 and the studies of hereditary gastric cancer are going on.

By the location of tumour, cardiac and distal gastric cancer can be distinguished. The distal cancer, involving corpus or antrum, is related to chronic *Helicobacter pylori* infection. The rate of this cancer type is decreasing in the developed countries. The cancer of the cardia is either stable or increasing in frequency and is either unrelated or inversely related to *Helicobacter pylori* infection.

There are several morphological classifications of gastric cancer (Rosai, 1996). The Lauren classification (Lauren, 1965) is one of these, distinguishing diffuse and intestinal type of gastric cancer and allowing grouping into indeterminate type the tumours that show solid architecture without glandular differentiation or mixing of the 2 principal types. Although this classification has several morphological weaknesses it is useful in defining clinicopathological types and has been used in epidemiologic studies. The intestinal cancer is associated with environmental factors (Lynch *et al.*, 2008). The incidence of this type is decreasing while the incidence of diffuse type is estimated as either stable or increasing (Crew and Neugut, 2006).

Evidence of the family history as a risk factor of gastric carcinoma

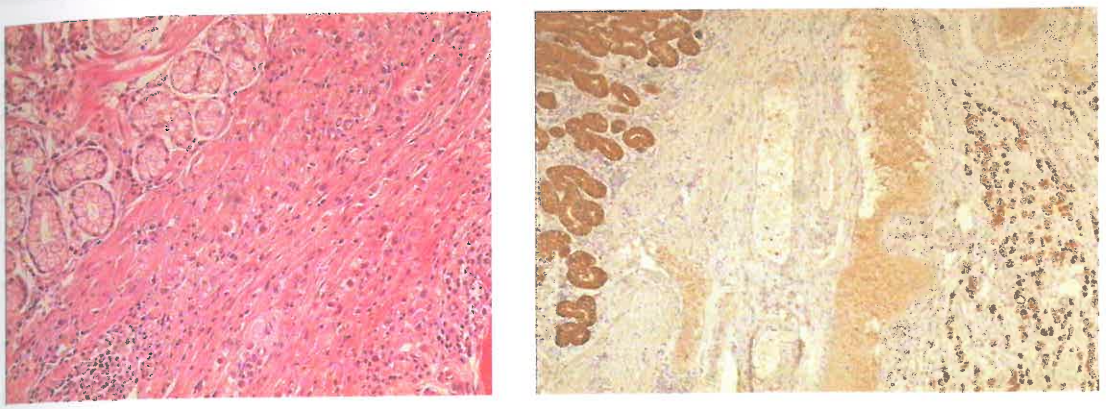
Positive family cancer history is a risk factor for developing gastric cancer. In Icelandic patients, the relative risk of gastric cancer was 2.2 (95% CI = 1.6 – 3.0) and 1.3 (95% CI = 1.0 – 1.7) for first and second degree relatives of male probands with gastric cancer and 1.6 (95% CI = 1.2 – 2.6) and 1.4 (95% CI = 0.9 – 2.0) for first and second degree relatives of female probands with gastric cancer (Imsland *et al.*, 2002). The probands were selected by being younger than 60 years in the moment of cancer diagnostics, and the risk for relatives was even higher if the disease developed before 50 years of age. Interestingly, the relative risk was not markedly different in dependence on the cancer type (intestinal or diffuse type of gastric cancer) in probands. The role of family cancer history has been confirmed by other groups (Kawasaki *et al.*, 2007; Kondo *et al.*, 2003). Association of gastric cancer with colorectal and lung cancer is also described (Kawasaki *et al.*, 2007).

Familial clustering is shown in approximately 10% of gastric cancer patients, and in 3% of gastric cancer cases autosomal dominant mode of inheritance with high penetrance is present (Cisco *et al.*, 2008).

Hereditary diffuse gastric cancer

Familial gastric cancer is a complex syndrome. The analysis of hereditary background started with diffuse gastric cancer (Figure 6) by demonstrating autosomal dominant mode of

inheritance and showing the molecular basis – germline truncating mutations in *E-cadherin/CDH1*, located on chromosome 16q22 (Kaurah *et al.*, 2007).



A. B.

Figure 6. Diffuse gastric cancer. A, tissue structure. Note the rounded antral mucous glands in the upper left part of the figure and the faintly discernible cancer infiltration in the submucosa. Haematoxylin – eosin, original magnification 100x. B, submucosal growth pattern as highlighted by immunohistochemical visualization of cytokeratin AE1/AE3. Smoothly contoured benign glands are present in the left part of the figure. Immunoperoxidase, original magnification 50x. Microphotograph by A. Vanags

The mutations were first described in three Maori pedigrees with early-onset diffuse gastric cancer (Guilford *et al.*, 1998). Later *E-cadherin/CDH1* inactivating germline mutations were also shown in a proportion of European families with aggregation of diffuse but not intestinal gastric cancer (Caldas *et al.*, 1999). Initially, truncating mutations that are distributed throughout the gene were considered characteristic for hereditary diffuse gastric cancer in contrast to either missense mutations or exon skipping in sporadic cancers (Caldas *et al.*, 1999). Later, it was discovered that *CDH1* mutations in hereditary gastric cancer included point mutations, small deletions and insertions along the entire coding sequence (Brooks-Wilson *et al.*, 2004). *CDH1* germline mutations C1003T, 70G→T, 2195G>A, 1792C→T and other splicing and missense mutations are described in hereditary diffuse gastric cancer family (Lynch *et al.*, 2008; Kaurah *et al.*, 2007). Founder mutations are rare, described in the original Maori families as well as in group of families originating from Newfoundland. Recurrent mutations are due to both independent mutational events and common ancestry (Kaurah *et al.*, 2007).

Studying 6 single cases of diffuse gastric cancer in a person younger than 35 years; 26 families with at least 2 gastric cancer cases and 1 case diagnosed as diffuse gastric cancer before the age of 50 years, 5 families with at least 3 cases of gastric cancer at any age and 1 family with 2 cases of diffuse gastric cancer, both diagnosed in persons older than 50 years of

age, germline *CDH1* mutations were found in 14 families with at least 2 gastric cancer cases and 1 case diagnosed as diffuse gastric cancer in a person younger than 50 years and in the family with 2 cases of diffuse gastric cancer, both diagnosed in persons older than 50 years of age (Kaurah *et al.*, 2007). Using the diagnostic criterion of 2 gastric cancer cases per kindred in combination with at least 1 diffuse gastric cancer diagnosed before the age of 50 years, *CDH1* mutations are found in 53.1% families (Kaurah *et al.*, 2007; Brooks-Wilson, 2004; Suriano *et al.*, 2005). It has been estimated by another group that *CDH1* mutations are identified in 30-50% of hereditary diffuse gastric cancer patients (Cisco *et al.*, 2008).

The penetrance of *CDH1* gene mutations determines the lifetime risk of gastric cancer and confers also the risk for lobular breast carcinoma in females. The lifetime risk for gastric cancer was estimated as 70% by Lynch *et al.*, 2008. In contrast, the cumulative risk of gastric cancer by the age of 75 years was estimated to be 40% (95% CI = 12 – 91% for males and 63% (95% CI = 19 – 99%) for females by Kaurah *et al.*, 2007. Another group reported that the cumulative risk of gastric cancer by the age of 80 years was 67% (95% CI = 39 – 99%) for males and 83% (95% CI = 58 – 99%) for females (Pharoah *et al.*, 2001).

The risk for lobular breast carcinoma in *CDH1* gene mutation carrying females was found to be 40% (Lynch *et al.*, 2008). Close to the previous result, the risk of breast cancer in female mutation carriers was assessed to be 39% (95% CI = 12 – 84%) by Pharoah *et al.*, 2001. The cumulative risk of female breast cancer by the age of 75 years was estimated to be 52% (29 – 94%) among the carriers of Newfoundland founder mutation (Kaurah *et al.*, 2007).

At present, hereditary diffuse gastric cancer is defined clinically as any family that fits one of the following criteria: either two or more documented cases of diffuse gastric cancer (Figure 6) in first or second degree relatives with at least one tumour diagnosed before the age of 50 or at least three documented cases of diffuse gastric cancer in first or second degree relatives independently of the age of onset (Caldas *et al.*, 1999). It was suggested that 25% of such families will have inactivating *CDH1* germline mutations. The rate of mutations is 30 – 50% in well-defined families from low incidence areas (Lynch *et al.*, 2008; Lynch *et al.*, 2005; Suriano *et al.*, 2003; Kaurah *et al.*, 2007).

Familial intestinal gastric cancer

Gastric cancer can be part of HNPCC, Li-Fraumeni syndrome, FAP, Peutz-Jeghers syndrome (Caldas *et al.*, 1999). It has been shown by Finnish study that gastric cancer is a part of HNPCC syndrome (Aarnio *et al.*, 1999). Intestinal type (Figure 7) is dominating in these families but may be unrelated to *Helicobacter pylori* infection.

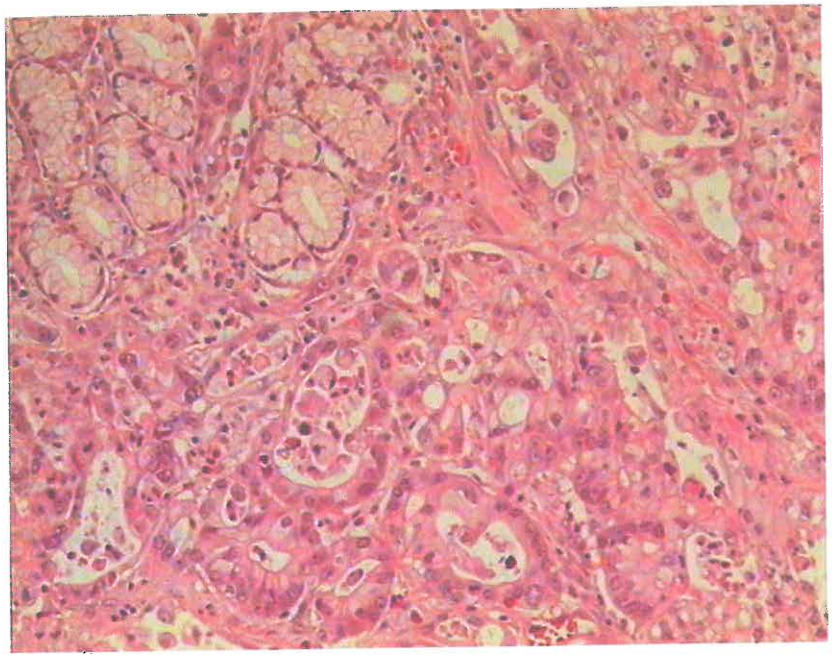


Figure 7. Intestinal type of gastric cancer: tissue structure composed by malignant glands. Haematoxylin-eosin, original magnification 100x. Microphotograph by A. Vanags

The diagnostic criteria of familial intestinal gastric cancer are adjusted to the incidence of gastric cancer in the corresponding population. In countries with high rate, the criteria must be analogous to the diagnostic criteria of HNPCC: 1) at least three relatives should have intestinal gastric cancer and one of them should be first degree relative of the other two; 2) at least two successive generations must be affected, 3) in one of the patients gastric cancer should be diagnosed before the age of 50. In contrast, in countries with low incidence of gastric cancer, the criteria should be following: 1) two or more documented cases of intestinal gastric cancer in first or second degree relatives with at least one tumour diagnosed before the age of 50 or 2) at least three documented cases of intestinal gastric cancer in relatives at any age.

Gastric cancer in other hereditary cancer syndromes

Gastric cancer can be a manifestation of HNPCC, Li-Fraumeni, FAP or Peutz-Jeghers syndrome. These syndromes are diagnosed by the corresponding criteria.

Follow-up and prophylaxis

If the kindred corresponds to the diagnostic criteria of hereditary diffuse gastric cancer, genetic testing should be advised involving diagnostic testing, namely, search for the mutation in an affected patient, and genetic testing of the healthy family members. The mutation carriers have 70% lifetime risk of diffuse gastric cancer (Caldas *et al.*, 1999), known for its propensity to submucosal spread, marked difficulties in early endoscopic diagnostics and dismal prognosis in advanced stages. Therefore an option of prophylactic gastrectomy can be considered taking into account that the average age of clinically detectable gastric

cancer development in hereditary diffuse gastric cancer kindred is 38 years (Caldas *et al.*, 1999; Lynch *et al.*, 2008). The age range is wide, from 16 to 82 years (Lynch *et al.*, 2008). The earliest lethality is recorded at 16 – 20 years (Guilford *et al*, 1998; Kaurah *et al.*, 2007) therefore the prophylactic gastrectomy might be suggested even in 20 – 30 year-old males. In females, the impact of gastrectomy on pregnancy should be considered (Kaurah *et al.*, 2007). It is suggested to carry out the prophylactic gastrectomy 5 years earlier than the youngest age of gastric cancer diagnosis in the family (Cisco *et al.*, 2008). It has been estimated that the prophylactic gastrectomy might carry 1 – 2% mortality, 10 – 20% major acute morbidity and inevitable late morbidity as weight loss, dumping syndrome, diarrhoea. As the prophylactic operations would be performed in young and healthy adults, the expected mortality and rate of complications might be lower as after curative gastrectomy for gastric tumour in an elderly person (Caldas *et al.*, 1999)

In the stomachs removed by prophylactic gastrectomy, foci of diffuse cancer are frequent (as shown in figure 5C). The rate of such operations that in fact are curative not prophylactic is between 76.5 – 100% (Lynch *et al.*, 2008; Fitzgerald and Caldas, 2002).

The published agreement rate for prophylactic gastrectomy is between 45% (23/51) and 68% (17/25) (Kaurah *et al.*, 2007; Lynch *et al.*, 2008). If the prophylactic gastrectomy is not acceptable, frequent surveillance gastroscopy with the best accessory techniques should be offered and combined by rigorous biopsies from any suspicious lesion. The gastroscopy should be performed once or twice per year (Caldas *et al.*, 1999; Cisco *et al.*, 2008). At least 15 random mucosal biopsies must be provided for pathology (Lynch *et al.*, 2008). However, insufficient efficacy of chromoendoscopy, endoscopic ultrasound, random biopsies and PET-CT has been demonstrated in *CDH1* mutation carriers (Lynch *et al.*, 2008). MRI for breast cancer diagnosis is advocated (Cisco *et al.*, 2008; Cisco and Norton, 2008).

Other hereditary/familial tumour syndromes

Familial renal, prostate and urinary bladder cancer

Significant role of genetic contribution in renal carcinomas has been suggested (Gudbjartsson *et al.*, 2002). Increased risk of renal cancer (Figure 8) is shown in the offspring of renal cancer patients. Having a sibling affected by kidney cancer also increase the risk of kidney cancer. The following standardized incidence ratios were found by Hemminki and Li, 2004: 1.92 (95% CI = 1.33 – 2.69) if parent had renal cancer and 3.94 (95% CI = 2.46 – 5.97) if a sibling had renal cancer. As the SIR ratio was 2.05 at significance level $p = 0.01$, recessive mode of inheritance was proposed. If recessive genes determine the renal cancer risk, autosomal recessive mode of transmission is probable as no gender effect was found (Hemminki and Li, 2004).

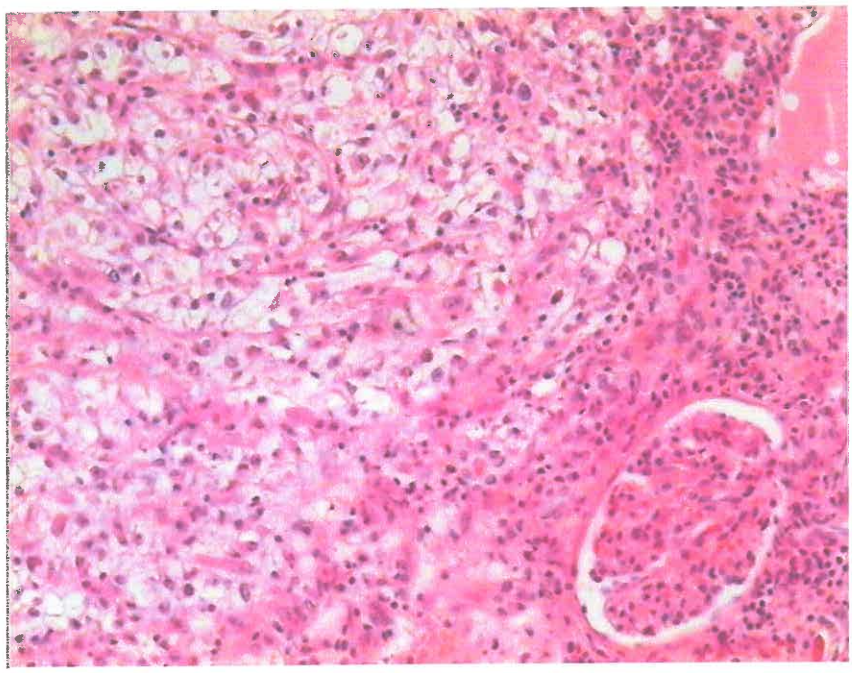
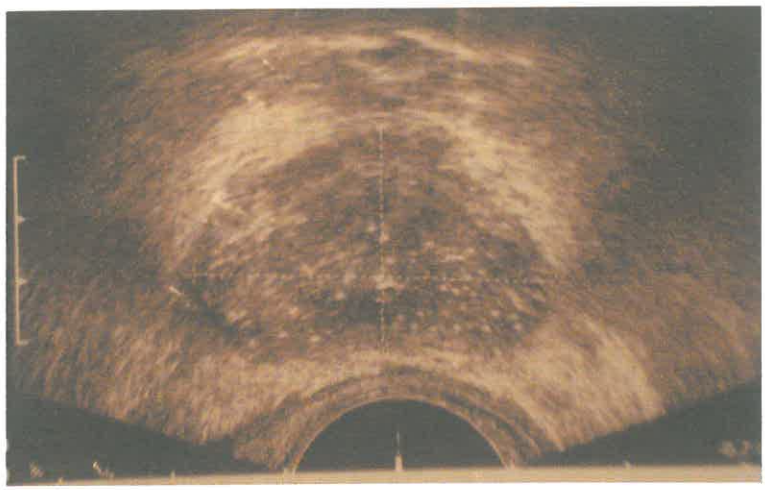
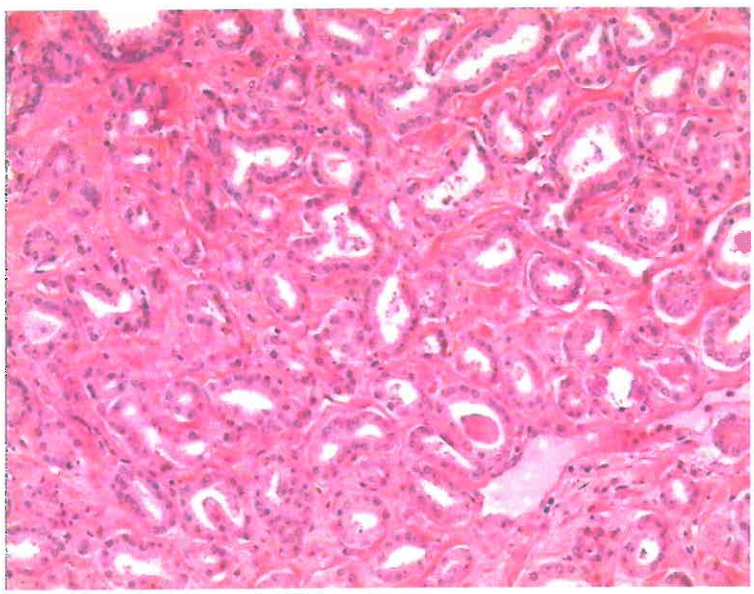


Figure 8. Renal cancer. Morphological structure of clear cell renal cancer, invading the kidney tissue. Note the residual glomerulus. Haematoxylin-eosin, original magnification 100x. Microphotograph by A. Vanags

Familial clustering of prostate cancer (Figure 9) has been demonstrated. Among the offspring of prostate cancer patients, the standardized incidence ratio is 2.55 (95% CI = 2.22 – 2.92) but among siblings of prostate cancer patients – 3.58 (95% CI = 3.07 – 4.17). Strong genetic contribution to prostate cancer was found by twin studies (Lichtenstein *et al.*, 2000). Recessive inheritance of prostate cancer has been suggested (Hemminki and Li, 2004) basing on the observation that affected sibling confers higher risk than affected parent (SIR ratio of 1.41; p = 0.00). X-linked locus has been suggested by linkage studies (Xu *et al.*, 1998). Segregation analysis also points towards either X-linked or recessive inheritance (Cui *et al.*, 2001).



A.



B.

Figure 9. Prostatic cancer. A, calcinated structure of prostate cancer detected by transrectal ultrasound. B, Tissue structure, haematoxylin – eosin, original magnification 100x. Microphotograph by A. Vanags

For urinary bladder cancer, familial risk can be considered with the observation that standardized incidence ratio for this tumour is 1.89 (95% CI = 1.38 – 2.53) if a parent has had urinary cancer. No increased incidence was observed if a sibling has had bladder cancer (Hemminki and Li, 2004). As in other hereditary cancer syndromes, early age at cancer onset in probands and aggregation of cases within families are features consistent with a hereditary aetiology (Lin *et al.*, 2006). Statistically significantly higher incidence of bladder cancer has been observed among the relatives of urinary cancer patients if compared to relatives of controls (Kramer *et al.*, 1991). The relative risk identified in this study was 1.9 (95% CI = 1.1

– 2.7). In a later study, similarly increased relative risk of 1.8 (95% CI = 1.3 – 2.7) was found after adjustment for age, gender and smoking history of the relatives (Aben *et al.*, 2002). However, in twin study environmental factors were found more important contributing to 69% in contrast to 31% of genetic contribution (Lichtenstein *et al.*, 2000). It has been suggested that family history alone does not contribute to the elevated bladder cancer risk but in the combination with current smoker status it confers significantly elevated risk thus helping to identify the cases for whom either intensive efforts to quit smoking or increased surveillance should be advised (Lin *et al.*, 2006). The risk in smoker is increased by having affected young first-degree blood relative. Notably, family history of bladder cancer in smokers conferred 2.5-fold increased risk of superficial urothelial bladder cancer but the RR was not significant in the invasive subgroup (Lin *et al.*, 2006) with serious prognosis. Thus, there is evidence that, using family history as a risk identification tool; treatable cases can be identified upon proper surveillance. It should be noted that family history alone was not identified as a significant risk factor for urinary bladder cancer by Lin *et al.*, 2006, but the same study also failed to demonstrate smoking as a significant risk factor in the absence of positive family history. Thus, it is possible that higher power study would demonstrate both factors as significant. Joint effect of family history, early onset (before the age of 45 years) and smoking is suggested also by Kantor *et al.*, 1985. Different age was chosen as the border for early onset cases in different studies (Table 4).

Table 4. Age of cancer diagnostics as a criterion of increased familial urinary bladder risk

Age, years	Epidemiologic evidence by age limit	Reference
45	Relative risk 2.7 (95% CI = 0.8 – 8.9)	Kantor *et al.*, 1985
45	Familial risk 7.26 (95% CI = 2.6 – 14.2)	Plna and Hemminki, 2001
60	Hazard ratio 2.5 (95% CI = 2.0 – 4.0)	Aben *et al.*, 2002
60	Familial relative risk 5.07 (95% CI = 0.97 – 12.5)	Goldgar *et al.*, 1994
65	4.43 (95% CI = 1.44 – 13.60)	Lin *et al.*, 2006

Abbreviation in table: CI, confidence interval

Familial pancreatic cancer

Risk for pancreatic cancer is increased from 1.70 (95% CI = 1.17 – 2.39) to 1.73 (95% CI = 1.13 – 2.54; for adenocarcinoma thus excluding pancreatic endocrine tumours) in the offspring of pancreatic cancer patients (Hemminki and Li, 2004; Hemminki and Li, 2003) thus showing an evidence of hereditary factor in pancreatic cancer development. The population-attributable proportion of familial pancreatic cancer has been estimated to be 1.1% (Hemminki and Li, 2003).

The selection criteria for familial pancreatic cancer include presence of pancreatic cancer (Figure 10) or pancreatic cancer and melanoma (Figure 11) in at least 2 first-degree relatives (Rieder *et al.*, 2002).

Pancreatic cancer shows kindred association with other malignancies. Pancreatic cancer has been associated with lung, rectal or endometrial cancer or melanoma in the parents (Hemminki and Li, 2003). On the background of general low pancreatic SIR 1.73 (95% CI = 1.13 – 2.54) by family anamnesis of pancreatic cancer, high SIRS were observed for parental lung cancer in specific groups. SIR was 10.01 and 7.96 among offspring diagnosed with pancreatic cancer before the age of 50 years if the parents had squamous cell cancer and adenocarcinoma of the lung before the age of 60 years (Hemminki and Li, 2003). In German national case collection of familial pancreatic cancer, 11/21 families were affected by pancreatic cancer only, but cases of malignant melanoma (in 5 families), breast cancer (in 3 families), prostate (in 2 families), colon (in 2 families) and lung cancer (in 2 families) were also observed. In contrast, strong association between pancreatic and lung cancer has been observed by other explorers (Hemminki and Li, 2003). The difference might be either due to different mutations or due to different study approach: association with lung cancer was observed studying probands with pancreatic cancer while relatively lower rate of lung cancer was observed in families that were selected by history of pancreatic cancer or melanoma (as shown in Figure 10).

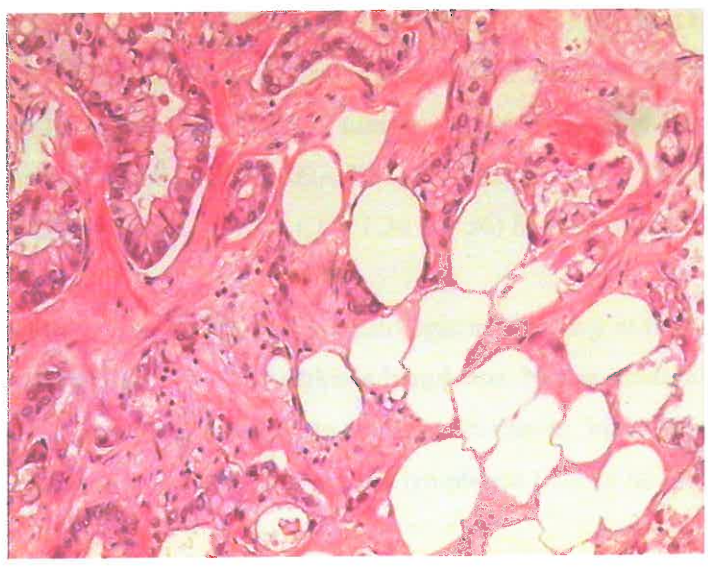


Figure 10. Pancreatic cancer invading peripancreatic adipose tissue. Haematoxylin – eosin, original magnification 100x. Microphotograph by A. Vanags

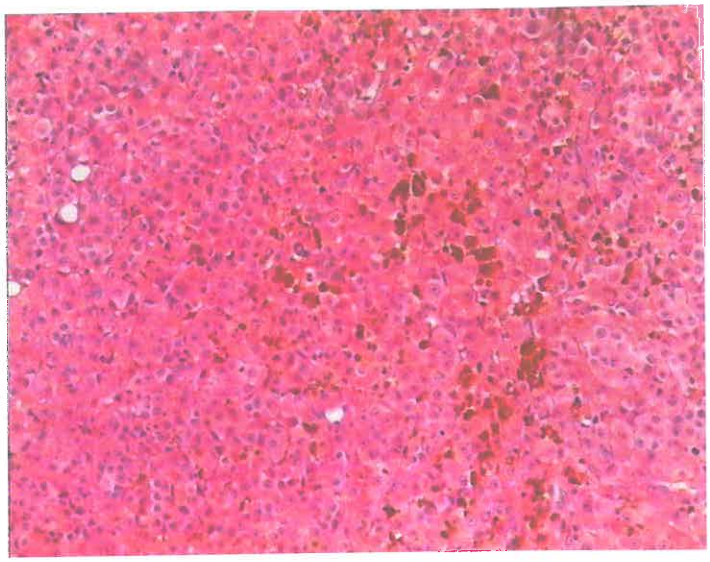


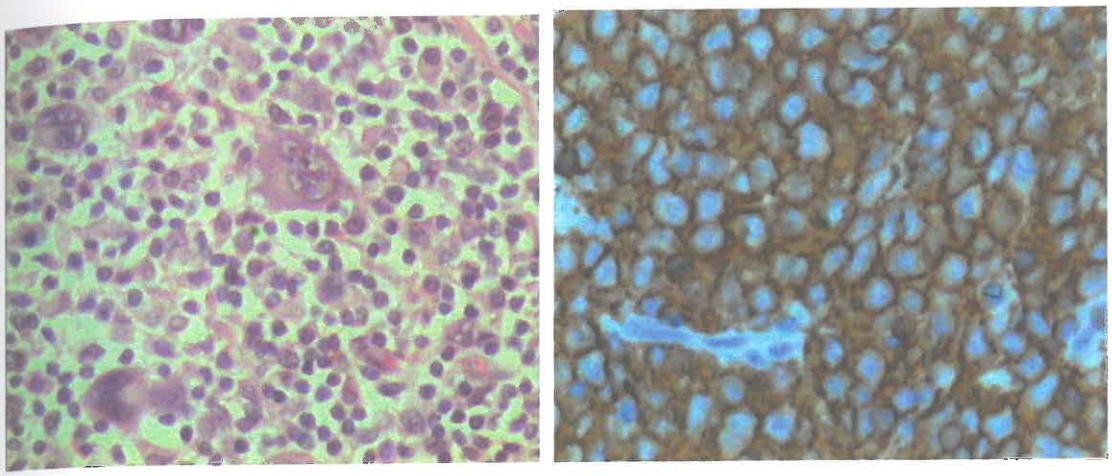
Figure 11. Melanoma showing cellular atypia as well as presence of melanin. Haematoxylin – eosin, original magnification 100x. Microphotograph by A. Vanags

The genetic background can include mutations in *BRCA2* or *CDKN2A*, as suggested by presence of breast cancer and melanoma in familial pancreatic cancer families (Rieder *et al.*, 2002).

Hereditary haematological malignancies

Increased risk by occurrence of concordant tumour in first-degree relatives has been described for all major types of haematological malignancies. The standardized incidence ratio in offspring of parents having the same type of tumour is 1.86 (95% CI = 1.45 – 2.35) for non-Hodgkin's lymphoma, 3.95 (95% CI = 1.69 – 7.82) for Hodgkin's lymphoma, 3.31 (95% CI = 2.05 – 5.07) for myeloma and 1.80 (95% CI = 1.34 – 2.36) for leukaemia (Hemminki and Li, 2004).

The history of lymphoma (Figure 12) and haematologic malignancy in first degree relatives is associated with increased risk of non-Hodgkin's lymphoma. No associations were found with lung, breast, prostate, colorectal, liver, stomach, thyroid cancer, brain tumours or myeloma suggesting specific familial risk of non-Hodgkin's lymphoma (Zhu *et al.*, 1998).



A. B.

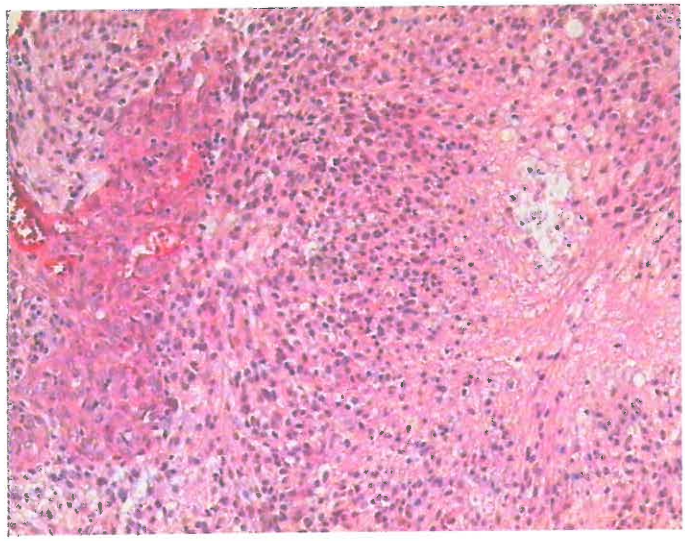
Figure 12. Lymphoma: A, Hodgkin's lymphoma, haematoxylin – eosin, original magnification 400x; B, non-Hodgkin's lymphoma , anti-CD20, immunoperoxidase, original magnification 400x. Microphotographs by A. Vanags

Familial brain tumours

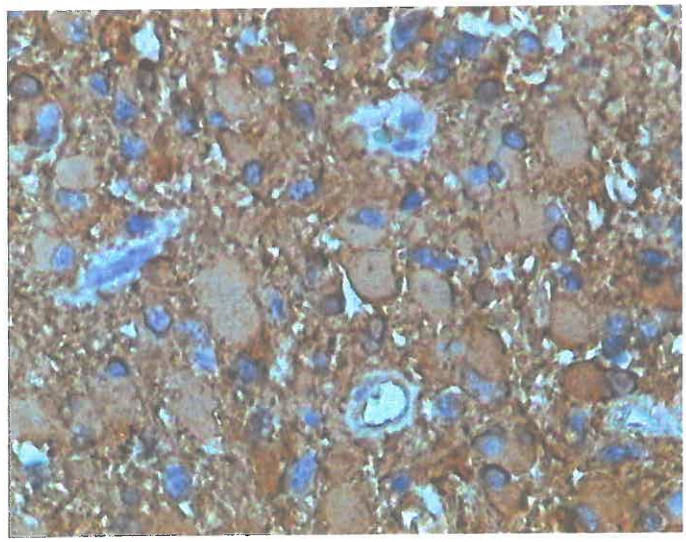
Tumours of the nervous system are among the malignancies analysed for familial risk. It was shown by Hemminki and Li, 2004 that SIR for concordant tumour is increased in offspring if parents are affected but no spouse correlation exists. The magnitude of SIR in the offspring of affected parents was estimated to be 1.78 (95% CI = 1.45 – 2.17). The risks conferred by affected parent or affected sibling were almost equal (Hemminki and Li, 2004). Thus, there is evidence that familial factors describe risk of nervous system and brain tumours. This can be explained at least partially by Lynch syndrome (Vasen *et al.*, 1996; Watson *et al.*, 2008) also characterised by elevated risk of brain tumours.

The clinical course of brain tumours frequently is fulminant: 26% of diagnoses are made before the age of 25; the mortality reaches 90% and 23% of deaths occur before the age of 25 years (Watson *et al.*, 2008). Glioblastoma, depicted in the Figure 13, is an example of an aggressive primary brain tumour. In addition, no pre-tumourous process is known for central nervous system malignancies and no preventive measures are available thus limiting the possibilities of early diagnostics.

The aggressive course even influence the risk estimates as the affected mutation carriers are less likely to undergo mutation analysis or leave children thus limiting the availability of genetic diagnostics and scientific studies (Watson *et al.*, 2008).



A.



B.

Figure 13. Glioblastoma. A, Presence of necrosis and microvascular proliferation in this brain tumour substantiates the diagnosis of glioblastoma, grade IV. Haematoxylin – eosin, original magnification 100x. B, Presence of gemistocytes in glial tumour. Anti-glial fibrillary acidic protein, immunoperoxidase, original magnification 400x. Microphotograph by A. Vanags

Cancer family aggregation

For all cancer sites, increased risk of concordant tumour has been observed with standardized incidence ratio 1.88 (95% CI = 1.80 – 1.96) if a parent has been affected and 2.07 (95% CI = 1.97 – 2.19) if a sibling has been affected (Hemminki and Li, 2004). However, associations between non-concordant tumours are well known: thus, breast and ovarian cancer can present in the same families forming hereditary breast-ovarian cancer syndrome associated with *BRCA* mutations. HNPCC is another example of non-concordant cancer associations as the syndrome is characterised by increased risk of extra-colonic malignancies.

Family history of cancer has been evaluated for cancer mortality risk in female. Besides the risk associations within the same site, it was found that breast cancer is a risk factor for ovarian cancer mortality with relative risk estimate of 1.6; stomach cancer is a risk factor for ovarian cancer mortality with relative risk estimate of 1.5; and uterine cancer is a risk factor for pancreatic cancer mortality with a relative risk of 1.6 (Poole *et al.*, 1999). The association between breast and ovarian cancer can be explained by *BRCA* mutations. Although ovarian cancer occurs in hereditary diffuse gastric cancer families and endometrial and pancreatic cancer occurs within HNPCC kindreds, is it not known, if these, statistically proven associations can be explained with these syndromes. It is possible that inherited cancer-susceptibility genes increase the risk for cancer at many sites; in fact, the known ones act in this way. Low-penetrance multi-organ influencing genes may manifest themselves as cancer family aggregation that would be difficult to recognize. An example of genetic basis of such association can be the following. A common variant of *CDKN2A*, characterized by alanine to threonine substitution, has been associated with melanoma and lung cancer (Debniak *et al.*, 2006). Alternatively, it is possible, that there are other high penetrance genes participating in the hereditary cancer syndromes.

Approaches of identification of hereditary cancer cases

In general, hereditary cancer can be identified either on individual consultation, or on the basis of an affected proband undergoing oncological treatment. Family history and molecular examination are the main diagnostic tools. The hospital based design stidying families with random probands is shown to yield accurate estimate of relative risk but the population based approach with mutation carrier probands provides penetrance estimates (Choi *et al.*, 2008).

Population screening for hereditary disorders

Genetic screening is an attractive option in the age of genomic medicine (Guttmacher and Collins, 2003). However, the disease criteria for meaningful population genetic risk screening are following. The disorder should be common and serious. There must be a manageable number of predominant mutations implying that these mutations are known. These mutations should have a high penetrance, and the natural history should be defined and consistent. Effective preventive or surveillance interventions must be available. The mutation detection must be relatively inexpensive. The screening test must be acceptable to the population. There must be available resources for patient education and consulting (Grody, 2003). Considering these criteria, population molecular genetic screening for autosomal dominant cancer syndromes has been discouraged (Grody, 2003), as the penetrance of 50 – 85% as for *BRCA* mutations was considered too low. The rarity and heterogeneity of mutations is another obstacle. Genetic testing is considered appropriate only in the high-risk group.

As the genetic investigation in the population level faces problems in the practical application, hypothetically another option still remains – namely, population screening by clinical criteria. This design should include genetic investigation in high-risk families.

The present experience in the population screening for hereditary cancer

The experience in population screening for hereditary cancer is scant. The largest screening has been carried out in the West Pomeranian Region, Poland, 2001-2002, by the application of questionnaires. More than 1 million of questionnaires were collected by family doctors and nurses and evaluated by specialists in genetics and oncology. Two percent of families were suspected for having any cancer family syndrome. After additional consultation, clinical and molecular examination, high risk was identified in 10 525 families. The most frequently diagnosed syndromes were following: hereditary breast – ovarian cancer syndrome in 4121 families, HNPCC in 568 families, FAP in 22 families, late onset hereditary colorectal cancer in 459 families, hereditary stomach cancer in 1250 families, hereditary renal cancer in 565 families, hereditary laryngeal cancer in 206 families, hereditary prostate cancer in 170 families, neurofibromatosis (NF1) in 66 families, von Hippel Lindau disease (VHL) in 36 families, retinoblastoma in 4 families, Peutz Jeghers syndrome in 3 families, juvenile polyposis in 2 families, familial lung cancer in 242 families, familial leukaemia/lymphoma in 77 families, familial liver cancer in 68 families, familial cervical cancer in 30 families, familial pancreatic cancer in 73 families, familial melanoma in 44 families, familial urinary bladder cancer in 19 families as well as unspecified cancer family aggregations – 3319 families (Gronwald, Raczynski *et al.*, 2006).

Population-based study of the prevalence of family history of cancer was performed in USA, surveying approximately 36 000 households (Ramsey *et al.*, 2006). In the result, information about the presence of cancer in the family history was collected. The investigators estimated that 7.74% of the respondents had a relative with breast cancer, 7.10% - with lung cancer, 4.96% - with colorectal cancer, 4.68% - with prostate cancer and 1.97% - with ovarian cancer. The conclusion was made that an important fraction of persons in USA have a relative affected by cancer and thus should undergo earlier or more aggressive screening.

MATERIAL AND METHODS

The study design

The investigation was designed as population screening within the frames of the project "The development of hereditary cancer prophylaxis in Estonia and Latvia" co-financed by European Union Interreg IIIB Neighbourhood programme. The population screening for hereditary cancer was carried out in the Valka district - a territorial unit in the northeast of Latvia (Figure 14).

Figure 14. Map of Latvia with mentioned districts (in uppercase) and the largest settlements. Note the highlighted Valka district in the northeast of Latvia.

The Valka district is holding 24323 adult inhabitants and 22 registered family physicians. For the distribution of family physicians praxes (listed in Table 5) in Valka district see Figure 15.

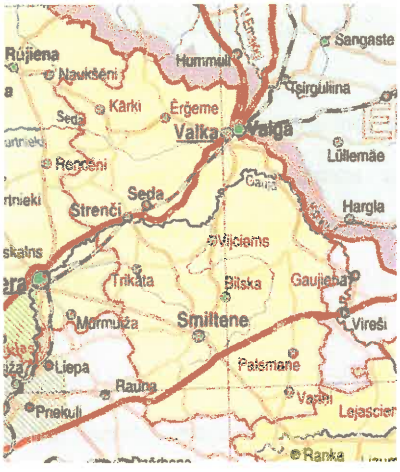


Figure 15. Map of Valka district with mentioned towns and civil parishes

Table 5. Group of Valka district family physicians within the INTERREG project

	Name, surname	Place of practice
1.	Liga Putrina	Valka
2.	Maruta Bindre	Smiltene
3.	Lilita Ezerina	Smiltene
4.	Juris Ezerins	Smiltene
5.	Elvira Freiberga	Grundzale
6.	Alla Grinberga	Palsmane
7.	Sanita Jansone	Varini
8.	Alda Karklina	Karki
9.	Maija Klavina	Smiltene
10.	Ritma Klavina	Valka
11.	Marianna Kire	Valka
12.	Valdis Kiris	Valka
13.	Zane Lukina	Smiltene
14.	Inga Natra	Valka
15.	Maris Natra	Valka
16.	Olga Ribkina	Seda
17.	Anna Sakare	Evele
18.	Ilona Uzbeka	Valka
19.	Inese Verselo	Trikata
20.	Sniedze Viksna	Smiltene
21.	Maija Zalite	Strenci
22.	Liga Ziemele	Smiltene

Adult persons voluntarily filled out questionnaire concerning family cancer history. The data about presence and localisation of tumours in kinsmen, as well as about the age in the time of the diagnosis were collected.

The hereditary cancer syndromes were sought for according to the International hereditary cancer assessment criteria and the corresponding persons were invited for consultation. During it, hereditary cancer syndrome entity was explained to them, written prophylactic recommendations were given and venous blood samples were proposed to take.

BRCA1 gene was examined for entity of mutations 5382insC, 300T/G, 4153delA, if at least one breast or ovary cancer case were established in the family. If there were 3 or more breast and/or ovarian cancer cases in the family, multiplex PCR was applied for *BRCA1/BRCA2* genes.

The project was accepted by the Central Commitee of Medical Ethics (Annex 1).

The study group

From 09/2005 to 06/2007 in collaboration with 22 family physicians, 18642 family cancer histories were collected from adult inhabitants of Valka district representing 76.6% of the Valka population. The criteria for participation in this study were the following.

Inclusion criteria

Registered place of residence within Valka district

Adult age

Agreement to participate to this study

Exclusion criteria

Registered place of residence outside Valka district

Age less than 18

Refusal to participate in this study

No recruitment restrictions were applied for upper age level, gender, ethnicity, presence or absence of cancer, cancer stage and other diagnoses. Written informed consent was obtained from all patients. The interview took 45 minutes to complete.

Among the responders, there were 10438 women (55.98%) and 7904 men (42.39%). The ethnic characteristics of the group are displayed in the Table 6.

Table 6. Ethnicity of the respondents in the study group.

Nationality	Absolute number	Proportion, % (95% CI, %)
Latvians	14887	79.86 (79.3 – 80.4)
Russians	2201	11.81 (11.40 – 12.30)
Byelorussians	395	2.12 (1.92 – 2.34)
Ukrainians	312	1.67 (1.50 – 1.87)
Polacks	171	0.92 (0.79 – 1.07)
Estonians	120	0.64 (0.54 – 0.77)
Lithuanians	97	0.52 (0.43 – 0.63)
Others and unknown nationality	459	2.46 (2.25 – 2.70)

Abbreviation in table: CI, confidence interval.

BRCA1 gene founder mutations 5382insC, 300T/G, 4153delA were searched for in 588 cases.

METHODS

The cancer family history

In order to obtain the family cancer history all patients filled in the questionnaire (included as Annex 2). The participants of the study were asked if his / her relatives (father, mother, grandparents, siblings, children, grandchildren, aunts, uncles and other blood relatives) have had any tumour. If any positive answers were given the participants were asked about the localisation of the tumour. The data about the age of patient at the time of tumour diagnosis were obtained. If the patient has died because of the tumour the death age was ascertained as well. Additional questions were asked about the treatment modalities (e.g. radiation therapy and chemotherapy, extent of operation) of affected persons in order to identify the presence of malignant tumour and to specify its location.

Clinical diagnostics

The filled forms of family cancer history were sent to Hereditary Cancer Institute located at Paul Stradins Clinical University Hospital. Analysis of filled forms was performed to identify any hereditary cancer syndrome as described in Table 7.

Table 7. The applied diagnostic criteria of hereditary cancer.

Hereditary syndrome	Diagnostic criteria
Definitive HNPCC	Amsterdam II criteria: • At least 3 relatives affected by HNPCC associated cancer (colorectal, endometrial, small bowel, ureteric, renal pelvis); at least one should be first-degree relative of the other two AND • At least two successive generations should be affected AND • At least one cancer should be diagnosed before age 50 AND • Familial adenomatous polyposis (FAP) should be excluded
Suspected HNPCC (HNPCC susp.)	• At least 2 first degree relatives with HNPCC associated cancer (colorectal, endometrial, small bowel, ureteric, renal pelvis) AND • At least one cancer should be diagnosed before age 50
Familial colorectal cancer, variety 1 (FCC1)	Colorectal cancer in at least 2 first degree relatives after the age of 50. HNPCC and FAP should be excluded

Familial colorectal cancer, variety 2 (FCC2)	Colorectal cancer in at least 2 second degree relatives at any age. HNPCC and FAP should be excluded
Definitive hereditary breast cancer (HBC)	At least 3 breast cancer patients in family at any age One of those patients is first degree relative to other two or second degree relative through male
Suspected hereditary breast cancer, variety 1 (HBC susp.1)	At least one of the following criteria: 1) Breast cancer diagnosed under the age of 40; 2) Medullary or atypical medullary breast cancer; 3) Male breast cancer; 4) Bilateral breast cancer, one of them diagnosed under the age of 50.
Suspected hereditary breast cancer, variety 2 (HBC susp.2)	Two breast cancers among first degree relatives (or second through male) at any age
Definitive hereditary ovarian cancer (HOC)	At least 3 ovarian cancer cases in family at any age One of those patients is first degree relative to other two or second degree relative through male
Suspected hereditary ovarian cancer (HOC susp.)	Two ovarian cancer cases among first degree relatives
Definitive hereditary breast/ovarian cancer (HBOC)	At least 3 breast/ovarian cancer patients in family at any age One of those patients is first degree relative to other two or second degree relative through male
Suspected hereditary breast/ovarian cancer, variety 1 (HBOC susp.1)	Breast and ovarian cancer in the same individual at any age
Suspected hereditary breast/ovarian cancer, variety 2 (HBOC susp.2)	Two breast or ovarian cancers among first degree relatives (or second through male) at any age One breast cancer diagnosed under the age of 50 and one ovarian cancer diagnosed at any age among first degree relatives (or second through male relatives)
Cancer family aggregation (CFA)	At least 3 first degree blood relatives with malignancy of any localisation
Definitive hereditary endometrial cancer (HEC)	At least 3 first degree relatives with endometrial cancer and at least one of them diagnosed before age of 50
Suspected hereditary endometrial cancer (HEC susp.)	Two first degree relatives with endometrial cancer and at least one of them diagnosed before age of 50

Familial endometrial cancer (FEC)	At least 3 first degree relatives with endometrial cancer at any age
Suspected familial endometrial cancer, variety 1 (FEC susp.1)	At least 2 first degree relatives with endometrial cancer at any age
Suspected familial endometrial cancer, variety 2 (FEC susp.2)	At least 2 second degree relatives with endometrial cancer at any age
Familial lung cancer (FLC)	At least 3 first degree relatives with lung cancer at any age
Suspected familial lung cancer (FLC susp.)	Two first degree relatives with lung cancer at any age
Hereditary stomach cancer (HSC)	At least 3 first degree relatives with stomach cancer at any age
Suspected hereditary stomach cancer (HSC susp.)	Two first degree relatives with stomach cancer at any age
Hereditary prostate cancer (HPC)	At least 3 blood relatives with prostate cancer at any age OR 2 blood relatives with prostate cancer diagnosed before age of 55 in both of them
Suspected hereditary prostate cancer (HPC susp.)	Two blood relatives with prostate cancer at any age OR Case of prostate cancer diagnosed before age of 55
Familial brain tumour (FBtT)	At least 3 first degree relatives with brain tumour at any age
Suspected familial brain tumour (FBtT susp.)	Two first degree relatives with brain tumour at any age
Familial malignant haematological tumour (FHemT)	At least 3 first degree relatives with malignant haematological tumour at any age
Suspected familial malignant haematological tumour (FHemT susp.)	Two first degree relatives with malignant haematological tumour at any age
Familial pancreatic tumour (FPan)	At least 2 first-degree relatives with pancreatic tumour or melanoma at any age
Familial urinary bladder cancer (FBlaC)	At least 3 first degree relatives with urinary bladder cancer at any age
Suspected familial urinary bladder cancer (FBlaC susp.)	Two first degree relatives with urinary bladder cancer at any age

All cases corresponding to the diagnostic criteria of any hereditary cancer syndrome, according to international diagnostic criteria, were invited for additional medical consultation. The diagnosis was updated according to additional data presented by participants. Written preventive recommendations were given as well.

Molecular diagnostics

Molecular examination was offered to the adult participants of the study possessing reasonably high risk of mutation. For this purpose the participants whose family cancer history corresponded to the requirements of hereditary cancer syndromes (see Table 7) underwent extended discussion to check if the additional data confirmed the initial clinical diagnosis of hereditary cancer syndrome. The participant was invited to submit a venous blood sample of 6 ml in order to isolate DNA.

If at least one breast cancer case was mentioned in family cancer history, *BRCA1* mutations 5382insC, 300T/G, 4153delA were searched for. The presence of the founder mutations in *BRCA1* gene 300T>G, 4154delA and 5382insC was identified by multiplex PCR with subsequent restriction analysis and gel separation of the of reaction products. The analysis was based on specific amplification of particular gene fragments. After the PCR and restriction amplification the products were subjected to separation and visualisation in agarose gel. The following reagents were used: 10mM dNTP mixture (Fermentas, Vilnius, Lithuania), Taq polymerase (5 units per microliter), Taq polymerase buffer and 25 mM $MgCl_2$ (Fermentas), enzyme Eco471 (AvaII), agarose (Fermentas), TBE buffer Bio-Rad, DNS marker geneRuler 100bp DNA Ladder (Fermentas), primers, distilled water. The equipment consisted of Thermocycler TGradient / TProfessional (Biometra), Electroforesis camera HU-20 (Scie-plus), the dynamo EPS 310 (Amersham Pharmacia Biotech), automated micropipettes, and digital documentation system (Canon/Syngene).

For the analysis, 2 microliters of the test DNA (100 – 200 nanograms) were placed into PCR tube. The PCR mixture for 10 reactions was made of following components:

Taq polymerase buffer	25.0 microliters
25 mM $MgCl_2$	15.0 microliters
10mM dNTP	2.5 microliters
Primers (6)	10.0 microliters per primer
Taq polymerase	0.6 microliters
Distilled water	126.9 microliters

By micropipette, 2 microliters of test DNA in the PCR tube were stirred with 23 microliters of the prepared PCR mixture in ice bath. After that, PCR tubes were placed into PCR-cycler and subjected to the following program:

94 °C	10 minutes		
94 °C	25 seconds		
68 °C	25 seconds	-1.3 °C	x10
72 °C	35 seconds		
94 °C	25 seconds		
55 °C	40 seconds		x35
72 °C	40 seconds		
72 °C	7 minutes		
4 °C			

While the amplification reaction was proceeding, the agarose gel was prepared by boiling 12 g agarose in 40 mL 0.5% TBE buffer in microwave oven while the agarose dissolved completely. In the result, translucent solution was obtained and cooled in room temperature until 50°C. After that the agarose solution was filled into the gel form. The gelatinization was carried out at room temperature for 30 – 45 minutes. The gel was placed into the electrophoresis tank containing 0.5% TBE.

The amplified specimens were divided into 2 parts. One part was transferred to agarose gel. The amplification products were separated at 120 V 40 minutes.

The other part is mixed with 8 microliters of the following restriction mixture:

Restriction buffer	20 microliters
Enzyme Eco471	5 microliters
Distilled water	55 microliters

The restriction mixture was incubated at 37 °C for 12 – 20 hours in the incubator TDB-120. After that, the amplification and restriction products were separated in agarose gel as described above. The distribution of the amplification products in the agarose gel were visualized in CVM20 transilluminator and fixed by digital camera. The typical interpretation of the PCR amplification product distribution is shown in the Figure 16.

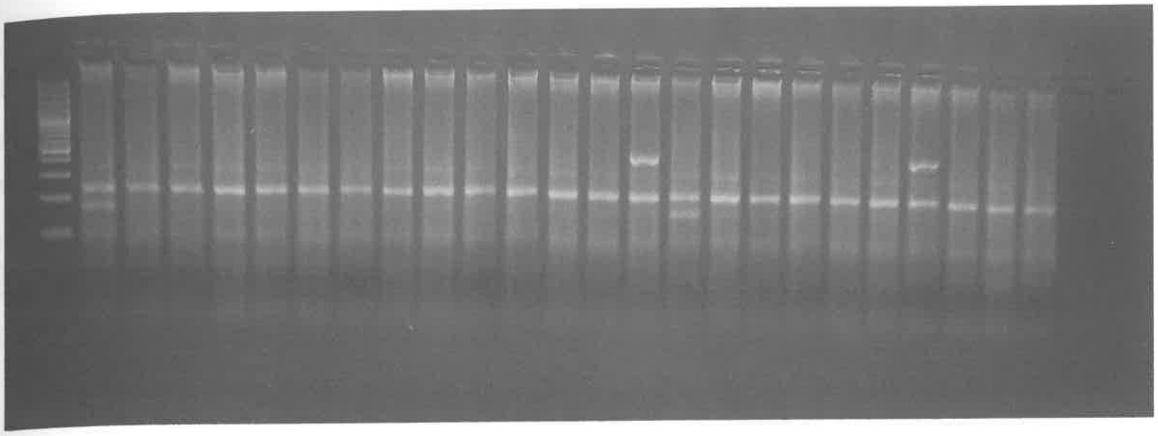


Figure 16. The distribution of the amplification products in 3% agarose gel. Position 1- marker GeneRuler 100 bp DNA Ladder. Positions 2 and 16: test DNA carrying *BRCA1* gene mutation 5382insC in exon 20. Positions 15 and 22: test DNA carrying *BRCA1* gene mutation 4153delA in exon 11. Positions 3-14, 17-21 and 23-25: test DNA not displaying *BRCA1* gene founder mutations.

The algorithm of data analysis

The following approach to analysis was undertaken. After the respective cases were diagnosed by clinical hereditary/familial cancer syndrome, the population frequency was calculated as the ratio between the number of diagnosed cases and the studied group. In order to characterise the course of malignant tumour, the data about the age of tumour diagnostics, age of tumour-related death and survival of the affected persons were retrieved from the questionnaires and subjected to descriptive statistical analysis using CIA software. Re-evaluation of the data characterising the affected persons was performed after detailed analysis of the relationships between different pedigrees. Additional data obtained during consultations were applied in order to identify inter-related families. In this way, the possibility to include any person repeatedly in the analysis due to several kindred relationships was eliminated. After re-evaluation, the descriptive calculations were repeated.

The frequency of cancer was calculated in a descriptive approach as the ratio between affected persons and the whole number of blood relatives in the affected blood line. In cases when the diagnosis was substantiated on peculiar characteristics of a single case in accordance with the criteria provided in the Methods section, the number of relatives was counted in the whole kindred.

Methods of statistical analysis

In the present study descriptive statistic was used as well 95% confidence interval for single proportion, for differences between two proportions and for means was calculated. The confidence interval calculations were made by CIA (DOS programme Confidence Interval Analysis) software.

Confidence interval for single proportion

Recommended method, called Wilson`s method, was applied for calculation of single proportion.

According to Altman and co-authors (Altman *et al.*, 2005), if r is the observed number of subjects with some feature in a sample of size n, then the estimated proportion who have the feature is $p = r/n$. The proportion without the feature is $q = 1-p$. Then the calculations of the three quantities were used subsequently:

$$A = 2r + z^2;$$

$$B = z\sqrt{z^2 + 4rq}\ ;$$

$$C = 2(n+z^2),$$

where z is $z_{1-\alpha/2}$, from the standard normal distribution.

After evaluation of the instant quantities the confidence interval for the population proportion is shown as:

$$(A - B)/C \text{ to } (A+B)/C.$$

No contraindications are observed for this approach.

When none observed events is present, r and p are both zero, and the recommended confidence interval is 0 to $z^2/(n+z^2)$. When $r=n$ so that $p=1$, the interval expresses as $n/(n+z^2)$ to 1. No negative values were accepted for confidence interval. As proved by Altman *et al.*, 2005 the Wilson's method can be applied in the research analysis of small groups and small or large proportions approaching 0 or 1, respectively.

Confidence interval for differences between two proportions

The confidence interval for differences between two proportions was calculated by Newcombe's method as described by Altman et al., 2005. The following method also is suitable for any data. The difference between two population proportions is estimated as

$$D = p_1 - p_2,$$

where D is the difference between the observed proportions in the two samples.

Calculation of l_2 and u_2 representing the lower and upper limits that define the $100(1-\alpha)\%$ confidence interval for the first sample as well as evaluation of l_2 and u_2 the lower and upper limits for the second sample was used.

The $100(1-\alpha)\%$ confidence interval for the population difference in proportions is calculated as

$$D - \sqrt{(p_1 - l_1)^2 + (u_2 - p_2)^2} \text{ to } D + \sqrt{(p_2 - l_2)^2 + (u_1 - p_1)^2}\ .$$

D is not generally at the midpoint of the interval.

Confidence interval for the mean

The confidence interval for a population mean was calculated by the following formula:

$$\bar{x} - [t_{1-\alpha/2} \times \mathrm{SE}(\bar{x})] \quad \text{to} \quad \bar{x} + [t_{1-\alpha/2} \times \mathrm{SE}(\bar{x})]$$

$t_{1-\alpha/2}$ - corresponding value from the t distribution with $n-1$ degrees of freedom associated with a probability of $100(1 - \alpha)\%$; $\bar{x}$ – mean; $\mathrm{SE}_{(x)}$ – standard error; n – sample size. Values of t can be found from statistical textbooks (Altman *et al.*, 2005).

The standard error is computed as

$$\mathrm{SE} = \mathrm{SD}/\sqrt{n}$$

Confidence interval for the difference between means

The confidence interval for the difference between two population means is calculated subsequently. If the mean values of two samples are x_1 and x_2, s_1 and s_2 are standard deviations and n_1 and n_2 are the sample sizes, than the standard deviation is calculated as

$$s = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}.$$

If the difference between the means is

$$d = \bar{x}_1 - \bar{x}_2$$

the standard error of the difference between two samples is given by

$$\mathrm{SE}(d) = s \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}.$$

Hence confidence interval for the difference of the two populations means

$$d - [t_{1-\alpha/2} \times \mathrm{SE}(d)] \quad \text{to} \quad d + [t_{1-\alpha/2} \times \mathrm{SE}(d)],$$

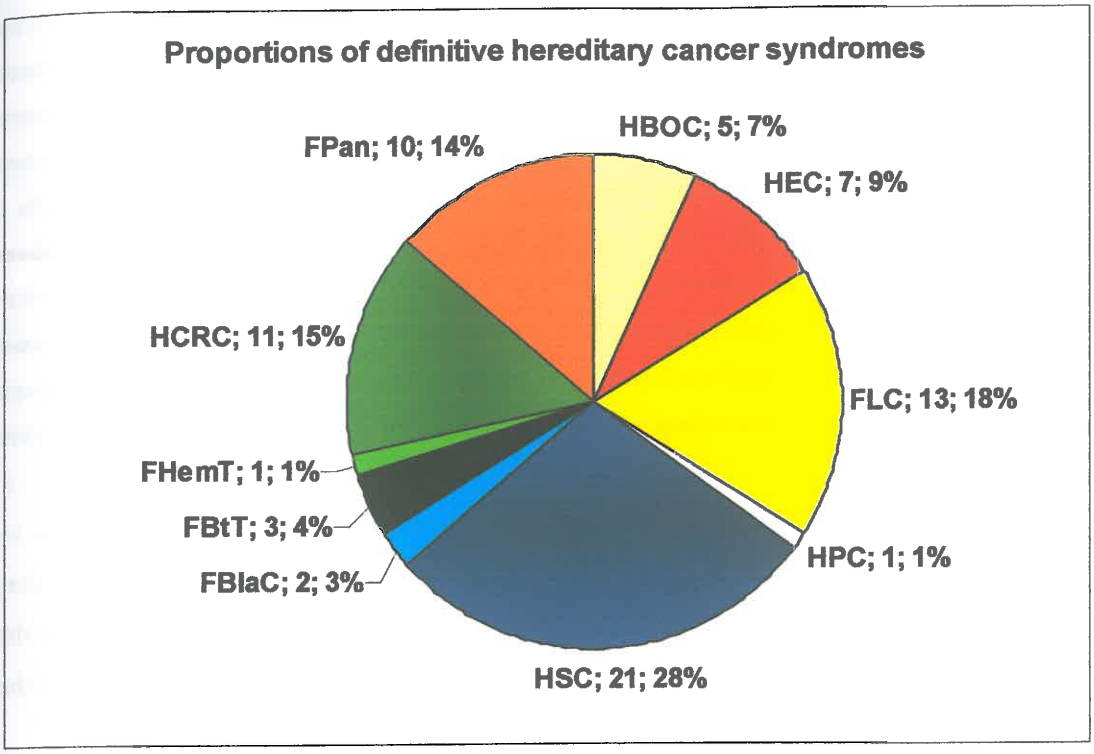
$t_{1-\alpha/2}$ is the t distribution of $n_1 + n_2 - 2$.

RESULTS

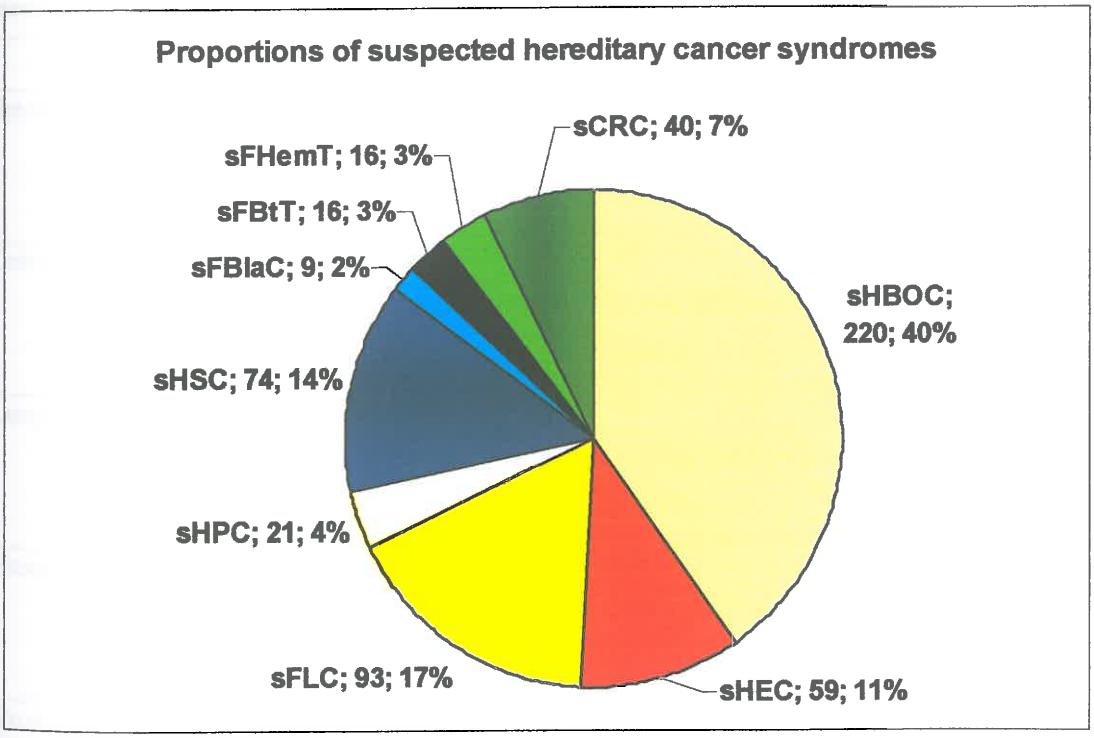
CLINICAL RESULTS

Analysing 18642 family cancer histories, at least one cancer case was identified in 11508 (61.72%) cases. There were 7132 (38.27%) cases with negative family cancer history. The increased risk group comprised 885 persons as they fulfilled the clinical diagnostic criteria of hereditary cancer syndromes. 928 persons underwent consultation due to clinically verified presence of or suspicion of hereditary cancer syndrome or due to presence of at least one case of breast and/ or ovary cancer in the family cancer history.

In the result of the population screening, the following hereditary cancer syndromes were detected: hereditary breast and/or ovarian cancer in 5 cases (0.03%; 95% CI = 0.01 – 0.06%), suspicion of hereditary breast and/or ovarian cancer in 220 cases (1.18%; 95% CI = 1.04 – 1.35%), hereditary colorectal cancer in 11 cases (0.06%; 95% CI = 0.03 – 0.10%), suspicion of hereditary colorectal cancer in 40 cases (0.22%; 95% CI = 0.16 – 0.29%), family cancer aggregation in 469 cases (2.52%; 95% CI = 2.30 – 2.75%), hereditary and familial endometrial cancer in 7 cases (0.04%; 95% CI = 0.02 – 0.08%), suspicion of hereditary and familial endometrial cancer in 59 cases (0.32%; 95% CI = 0.25 – 0.41%), hereditary stomach cancer in 21 cases (0.11%; 95% CI = 0.07 – 0.17%), suspicion of hereditary stomach cancer in 74 cases (0.40%; 95% CI = 0.32 – 0.50%), familial lung cancer in 13 cases (0.07%; 95% CI = 0.04 – 0.12%), suspicion of familial lung cancer in 93 cases (0.50%; 95% CI = 0.41 – 0.61%), hereditary prostate cancer in 1 case (0.005%; 95% CI = 0.001 – 0.03%), suspicion of hereditary prostate cancer in 21 cases (0.11%; 95% CI = 0.07 – 0.17%), familial pancreatic cancer in 10 cases (0.05%; 95% CI = 0.03 – 0.10%), familial cancer of urinary bladder in 2 cases (0.01%; 95% CI = 0.003 – 0.04%), suspicion of familial cancer of urinary bladder in 9 cases (0.05%; 95% CI = 0.03 – 0.09%), familial haematological tumour in 1 case (0.005%; 95% CI = 0.001 – 0.03%), suspicion of familial haematological tumour in 16 cases (0.09%; 95% CI = 0.05 – 0.14%), familial brain tumour in 3 cases (0.02%; 95% CI = 0.005 – 0.05%) and suspicion of familial brain tumour in 16 cases (0.09%; 95% CI = 0.05 – 0.14%). The structure of hereditary cancer is depicted in Figure 17.



A.



B.

Figure 17. The reciprocal proportions of specific hereditary cancer syndromes: A, in the definitive group; B, in the suspected group.

Abbreviations in Figure 17:

A: HBOC, hereditary breast and/or ovarian cancer syndromes; HEC, hereditary and familial endometrial cancer syndrome; FLC, familial lung cancer syndrome; HPC, hereditary prostate

cancer syndrome; HSC, hereditary stomach cancer syndrome; FBlaC, familial urinary bladder cancer syndrome, FBtT, familial brain tumour syndrome; FHemT, familial haematological tumour syndrome; HCRC, hereditary colorectal cancer syndromes; FPan, familial pancreatic cancer syndrome.

B: sHBOC, suspected hereditary breast and/or ovarian cancer syndromes; sHEC, suspected hereditary and familial endometrial cancer syndrome; sFLC, suspected familial lung cancer syndrome; sHPC, suspected hereditary prostate cancer syndrome; sHSC, suspected hereditary stomach cancer syndrome; sFBlaC, suspected familial urinary bladder cancer syndrome; sFBtT, suspected familial brain tumour syndrome, sFHemT, suspected familial haematological tumour syndrome; sHCRC, suspected hereditary colorectal cancer syndromes

For some tumour locations, the proportion of definitive and suspected hereditary cancer syndrome among all definitive or suspected hereditary cancer syndromes, respectively, is not statistically different. As shown in Table 8, this is true in case of hereditary colorectal, endometrial and prostate cancer. In contrast, for some tumours the difference is significant.

Table 8. Analysis of the proportions of definitive and suspected hereditary cancer syndromes by tumour location.

Syndrome	Definitive	Suspected	p
Breast-ovarian	5 6.8% [95% CI = 2.9 – 14.9%]	220 40.1% [95% CI = 36.1 – 44.3%]	$p \leq 0.05$
Colorectal	11 14.9% [95% CI = 8.5 – 24.7%]	40 7.3% [95% CI = 5.4 – 9.8%]	$p > 0.05$
Lung	13 17.6% [95% CI = 10.6 – 27.8%]	93 17.0% [95% CI = 14.1 - 20.3%]	$p > 0.05$
Stomach	21 28.4% [95% CI = 19.4 – 39.5%]	74 13.5% [95% CI = 10.9 – 16.6%]	$p \leq 0.05$
Prostate	1 1.4% [95% CI = 0.2 – 7.3%]	21 3.8% [95% CI = 2.5 – 5.8%]	$p > 0.05$
Endometrium	7 9.5% [95% CI = 4.7 – 18.3%]	59 10.8% [95% CI = 8.4 – 13.6%]	$p > 0.05$

Urinary bladder	2 2.7% [95% CI = 0.7 – 9.3%]	9 1.6% [95% CI = 0.9 – 3.1%]	$p > 0.05$
Haematological tumours	1 1.4% [95% CI = 0.2 – 7.3%]	16 2.9% [95% CI = 1.8 – 4.7%]	$p > 0.05$
Pancreas	10 13.5% [95% CI = 7.5 – 23.1%]	0 by criteria	$p \leq 0.05$
Brain	3 4.1% [95% CI = 1.4 – 11.3]	16 2.9% [95% CI = 1.8 – 4.7%]	$p > 0.05$
Total	74	548	

Abbreviation in table: CI, confidence interval

Thus, in case of hereditary breast – ovarian cancer, the proportion of suspected combined HBOC among suspected hereditary cancer cases is significantly higher than the proportion of definitive combined HBOC among the definitive hereditary cancer cases (Figure 18). The reverse is true for hereditary stomach cancer. This might suggest either differences in penetrance or different stringency of diagnostic criteria.

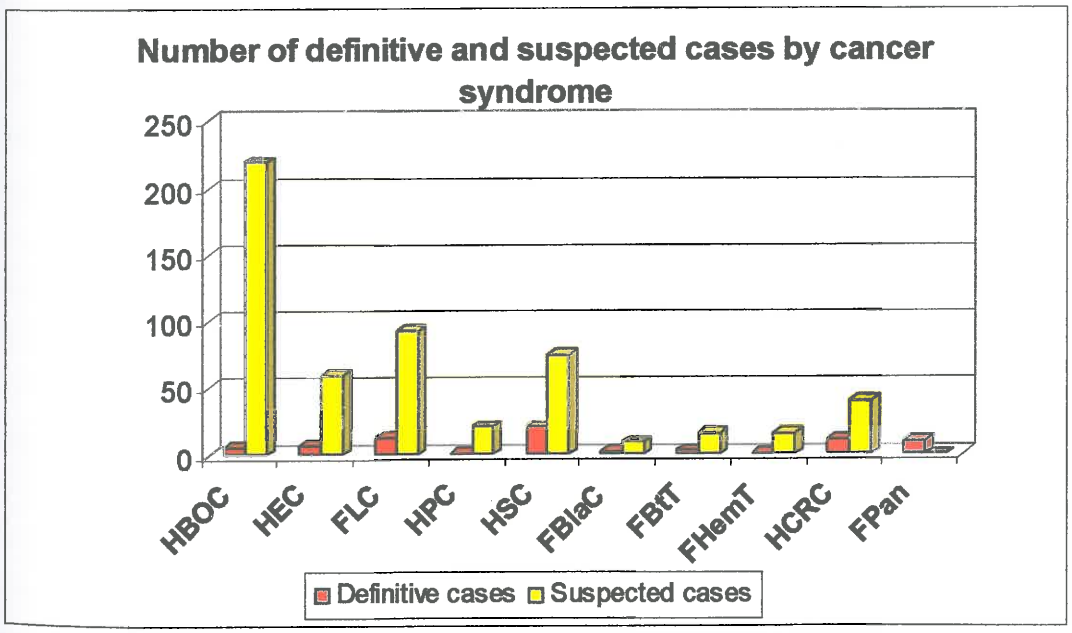


Figure 18. Number of definitive and suspected cancer cases by syndrome.

Abbreviations in figure: HBOC, hereditary breast and/or ovarian cancer syndromes; HEC, hereditary and familial endometrial cancer syndrome; FLC, familial lung cancer syndrome; HPC, hereditary prostate cancer syndrome; HSC, hereditary stomach cancer syndrome; FBlaC,

familial urinary bladder cancer syndrome, FBtT, familial brain tumour syndrome; FHemT, familial haematological tumour syndrome; HCRC, hereditary colorectal cancer syndromes; FPan, familial pancreatic cancer syndrome.

Hereditary breast and ovarian cancer syndromes

Due to the shared genetic basis of the hereditary breast and ovarian cancer, the data about malignancies in these locations were analysed in conjunction. During the population screening, definitive hereditary breast and ovarian cancer syndromes were identified in 5 cases. Among them, there were 2 cases of HBC, 2 cases of HBOC and 1 case of HOC syndrome.

Hereditary breast cancer syndrome was diagnosed in 2 probands. In one of the families, there was a case of breast cancer in proband's mother at the age of 45 years. Her 2 sisters had had breast cancer as well. All the 3 affected persons died at the age interval 50 – 55 years. No other cancer cases were present in the pedigree. The other kindred (Figure 19) was characterised by the presence of breast cancer in proband's mother who was affected at the age of 40 years and died 13 years later as well as in her 2 sisters both affected at the age of 60 years (Figure 20). A case of endometrial cancer was diagnosed in another sister of proband's mother.

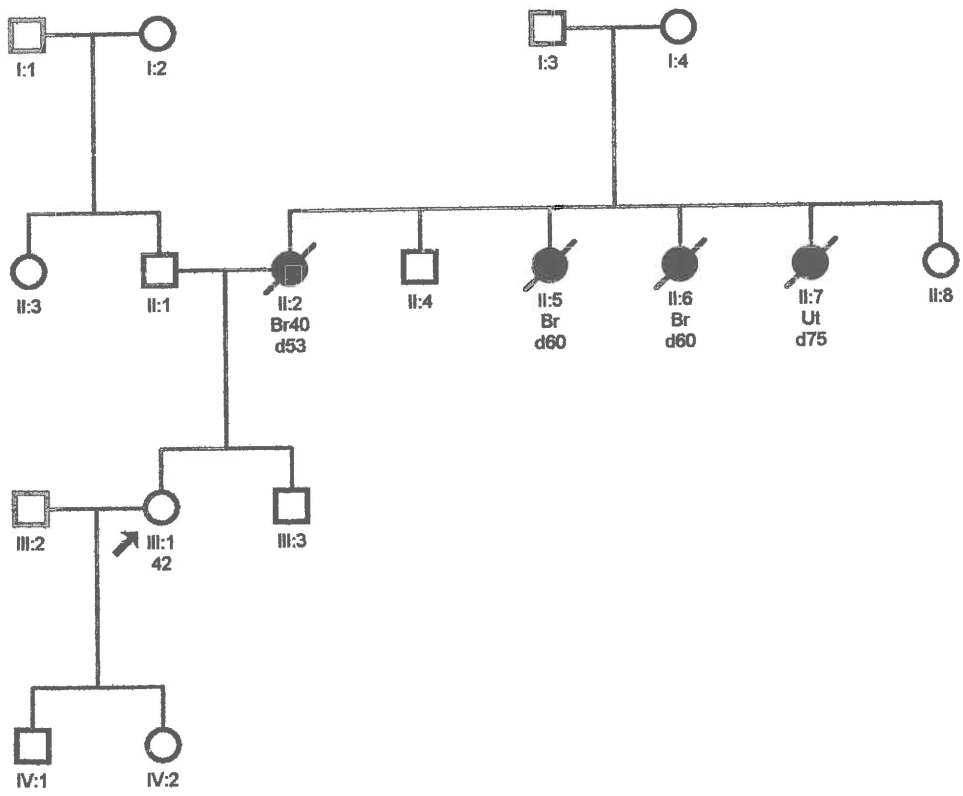


Figure 19. Pedigree corresponding to the diagnostic criteria of definitive hereditary breast cancer (MAK77). Abbreviations in the figure: Br, breast cancer; Ut, endometrial cancer; d, dead. The

age of tumour diagnostics is shown as the number following the abbreviation of diagnosis, and the death age is shown as the number following the abbreviation "d". The proband is indicated by an arrow.

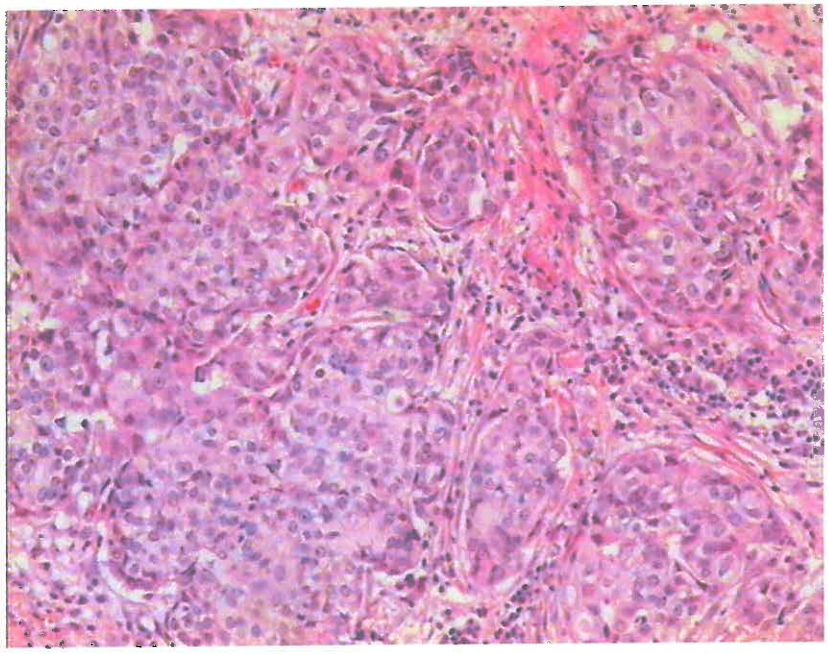


Figure 20. High-grade ductal breast cancer. Haematoxylin – eosin, original magnification 100x. Microphotograph by A. Vanags

Two cases of hereditary breast - ovarian cancer syndrome were found. One of these probands was oncologically healthy female aged 40. Her mother had had breast cancer at the age of 60. Ovarian cancer was diagnosed in mother's sister at the age of 53, and bilateral breast cancer was present in the grandmother from mother side, diagnosed at the age of 72 and 82 years. Cases of haematological malignancy, not further specified, lung cancer (probably unrelated to the affected line) and colorectal cancer were reported in the kindred as well (see Figure 21). Another proband, diagnosed with HBOC syndrome, was 62-year-old female who have had breast cancer at the age of 40. Her mother has died at the age of 59 within 1 year after ovarian cancer was diagnosed. Grandmother of the proband (through mother) had had breast cancer at the age of 67 (see Figure 22).

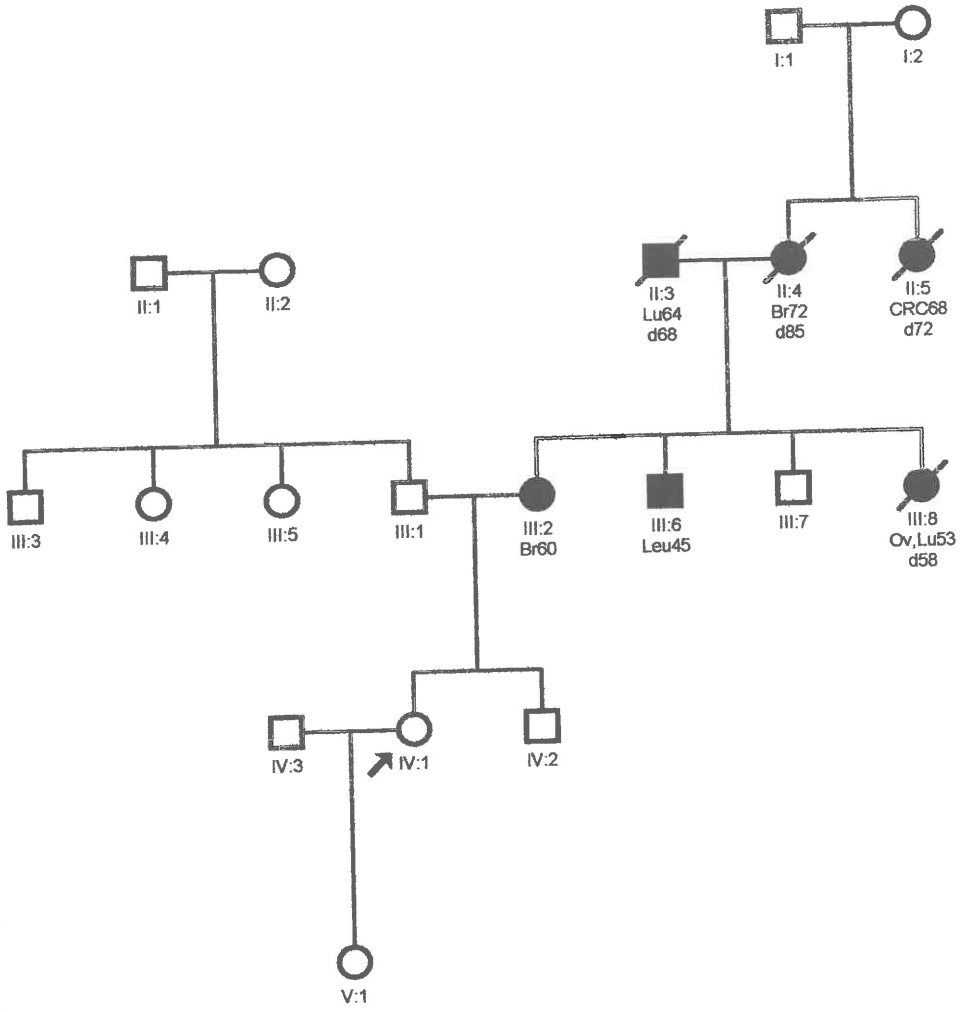


Figure 21. Pedigree showing definitive hereditary breast – ovarian cancer syndrome. Abbreviations in the figure: Lu, lung cancer; Br, breast cancer; CRC, colorectal cancer; Leu, haematological malignancy; Ov, ovarian cancer; d, dead. The age of tumour diagnostics is shown as the number following the abbreviation of diagnosis, and the death age is shown as the number following the abbreviation "d". The proband is indicated by an arrow.

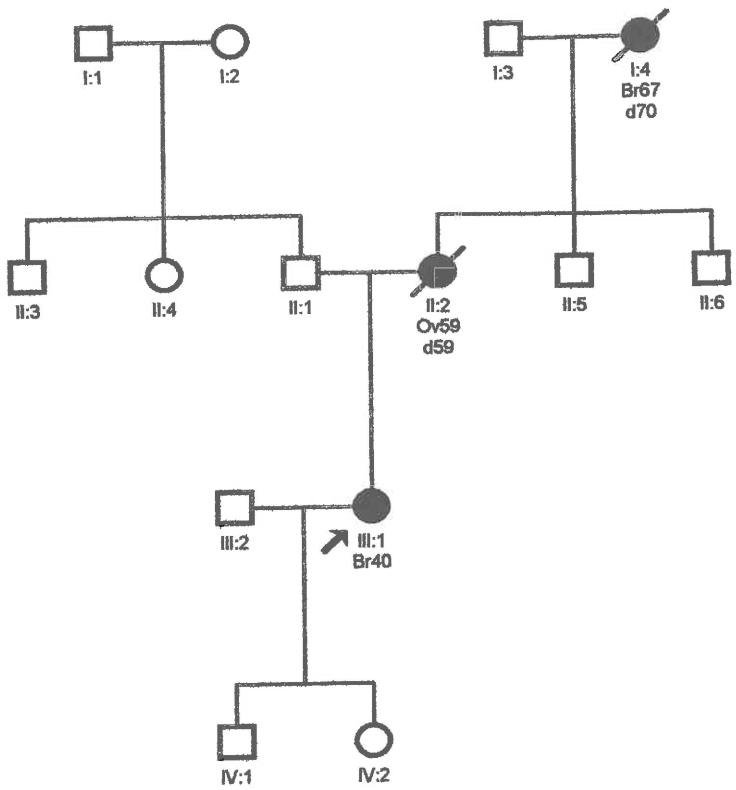


Figure 22. Definitive hereditary breast – ovarian cancer manifesting itself in 3 generations. Abbreviations in the figure: Br, breast cancer; Ov, ovarian cancer; d, dead. The age of tumour diagnostics is shown as the number following the abbreviation of diagnosis, and the death age is shown as the number following the abbreviation "d". The proband is indicated by an arrow.

Hereditary ovarian cancer syndrome was diagnosed in oncologically healthy 42-year-old female. Ovarian cancer was diagnosed in two of her sisters at the age of 34 and 45 as well as in her mother. A case of lung cancer was also present in the kindred (see Figure 23), and 2 additional cases of prostate cancer were detected suggesting possible *BRCA2* mutation.

In summary, 3/5 of the definitive hereditary breast and ovarian cancer syndromes were diagnosed in probands younger than 50 years. One of the probands had had early-onset breast cancer but others (4/5) were healthy.

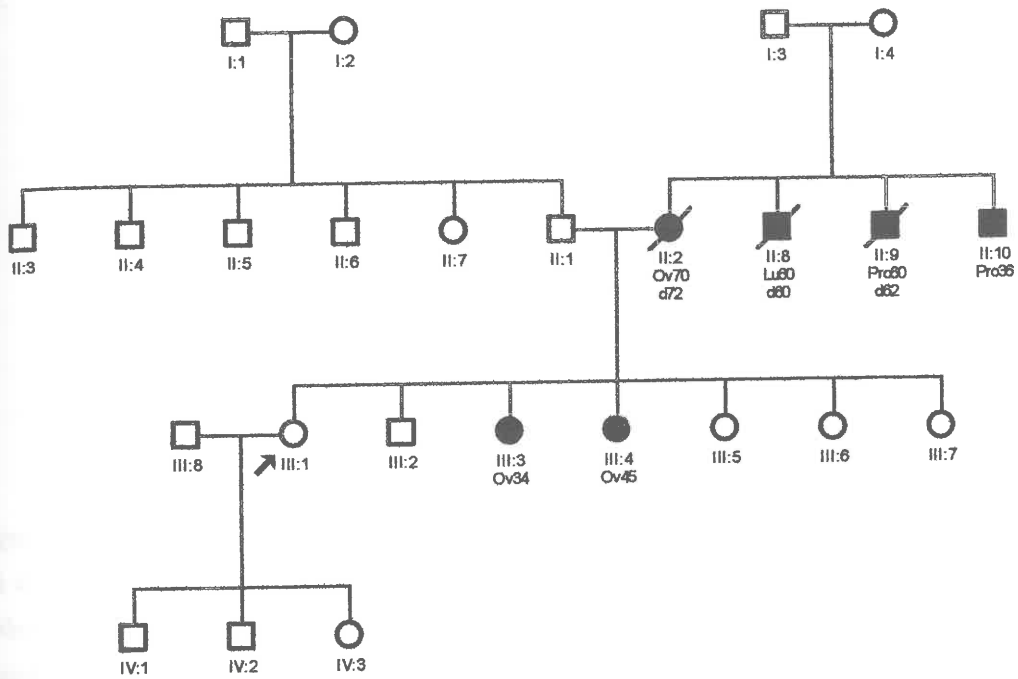


Figure 23. Pedigree affected by hereditary ovarian cancer. Abbreviations in the figure: Ov, ovarian cancer; Lu, lung cancer; Pro, prostate cancer; d, dead. The age of tumour diagnostics is shown as the number following the abbreviation of diagnosis, and the death age is shown as the number following the abbreviation "d". The proband is indicated by an arrow.

Significantly higher number of suspected hereditary breast and ovarian cancer syndrome cases was identified. In total, 220 cases of suspected hereditary breast and ovarian cancer syndrome were found (Figure 24). Among these, there were 117 (53.3%; 95% CI = 46.6 – 59.7%) cases of suspected hereditary breast cancer syndrome, variety 1, and 64 cases (29.1%; 95% CI = 23.5 – 35.4%) of suspected hereditary breast cancer syndrome, variety 2; 6 cases (2.7%; 95% CI = 1.3 – 5.8%) of suspected hereditary breast-ovarian cancer syndrome, variety 1, and 29 cases (13.1%; 95% CI = 9.3 – 18.3%) of suspected hereditary breast-ovarian cancer syndrome, variety 2, as well as 4 cases (1.8%; 95% CI = 0.7 – 4.6%) of suspected hereditary ovarian cancer syndrome.

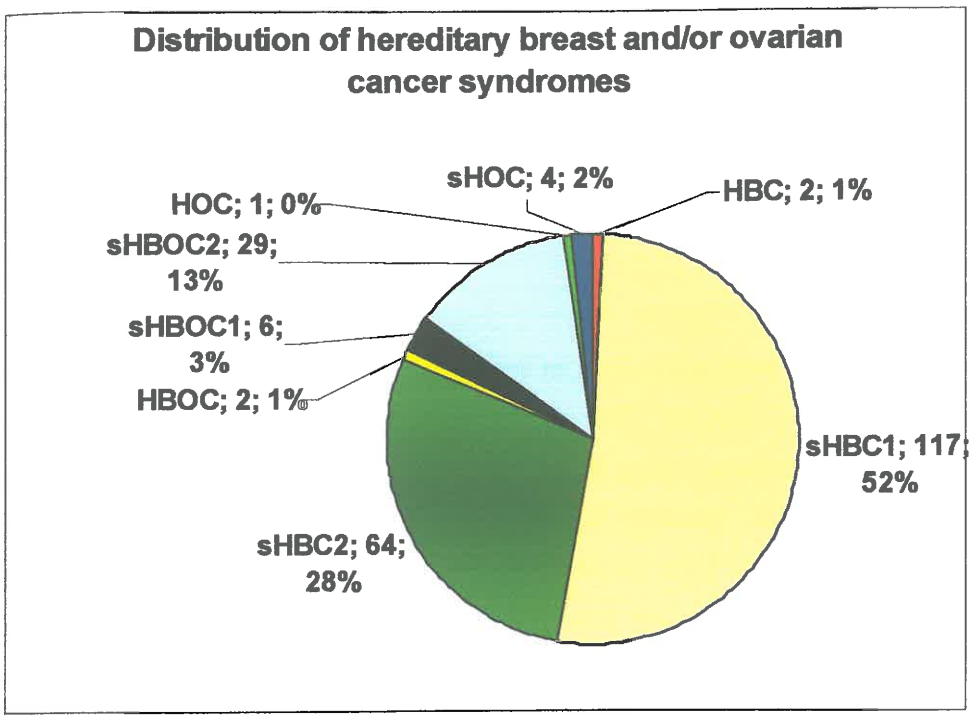


Figure 24. The relative input of different hereditary breast and/or ovarian cancer syndromes in the diagnostics of definitive and suspected hereditary breast and/or ovarian cancer syndrome. Abbreviations in the figure 24: HBC, hereditary breast cancer syndrome; sHBC1, suspected hereditary breast cancer syndrome, variety 1; sHBC2, suspected hereditary breast cancer syndrome, variety 2; HBOC, hereditary breast – ovarian cancer syndrome; sHBOC1, suspected hereditary breast – ovarian cancer syndrome, variety 1; sHBOC2, suspected hereditary breast – ovarian cancer syndrome, variety 2; HOC, hereditary ovarian cancer syndrome; sHOC, suspected hereditary ovarian cancer syndrome.

Among the suspected hereditary breast and ovarian cancer syndromes, breast-related syndromes had the highest diagnostic yield (Figure 25).

In the 117 HBC susp.1 pedigrees, 126 breast cancers in 124 persons were reported among 1440 blood relatives corresponding to the frequency 8.6% (95% CI = 7.3 – 10.2%). Four of the affected persons were males, but 120 – females. The breast cancer burden in females was 120 / 734 (16.3%; 95% CI = 13.8 – 19.1%) female blood relatives. Although these pedigrees were identified by the diagnostic criteria of HBC susp.1, additional cases of breast cancer were occasionally observed therefore there were 2 affected generations in 4 families, but 1 – in the other 113 pedigrees. No ovarian cancer was present in these families in accordance with the diagnostic criteria. The total burden of malignant tumours in these families was 235 tumours, affecting 221 persons.

The age of probands diagnosed with HBC susp.1 syndrome was 18 – 83 years (mean, 42.4 years; standard deviation 17.7 years; 95% CI for the mean 39.3 – 45.5 years). Among the probands diagnosed with HBC susp.1 syndrome, 5 (4.0%; 95% CI = 1.7 – 9.1) were affected by breast cancer themselves at the age 37, 39, 39, 45 and 49 years. In addition, head-and-neck cancer was diagnosed in 1 proband at the age of 60 years and endometrial cancer – in another, at the age of 63 years.

In the 64 HBC susp.2 pedigrees, 136 breast cancers in 134 persons were reported among 781 blood relatives corresponding to the frequency 17.2% (95% CI = 14.7 – 20.0%). No male breast cancer cases were reported in this group. The breast cancer burden in females was 134 / 415 (32.3%; 95% CI = 28.0 – 36.9%) female blood relatives. There were 2 affected generations in 46 (71.9%; 95% CI = 59.9 – 81.4%) families, but 1 – in the other 18 (28.1%; 95% CI = 18.6 – 40.1%) pedigrees. No ovarian cancer was present in these families in accordance with the diagnostic criteria. The total burden of malignant tumours in these families was 189 tumours, affecting 177 persons.

The age of probands diagnosed with HBC susp.2 syndrome was 18 – 79 years (mean, 47.5 years; standard deviation 17.5 years; 95% CI for the mean, 44.5 – 50.5 years). Among the probands diagnosed with HBC susp.2, 12 (18.8%; 95% CI = 11.1 – 30.0%) were affected by breast cancer, diagnosed at the age 28 – 69 years. In addition, 2 probands were affected by endometrial cancer. One of the endometrial cancer cases affected proband who had had breast cancer 18 years before the development of the second tumour. Another case of endometrial cancer developed at the age of 42 years.

Six probands were diagnosed with HBOC susp.1 syndrome. In all cases, the family history was remarkable for the occurrence of breast cancer and ovarian cancer in single person. Thus, there were 6 patients affected by index cancers, 6 cases of breast cancer and 6 cases of ovarian cancer among 58 blood relatives, including 31 females. The frequencies of breast cancer and ovarian cancer was 10.3 % (95% CI = 4.8 – 20.8%) among all blood relatives and 19.3% (95% CI = 9.2 – 36.3%) among female blood relatives. Considering the total cancer burden, 21 malignant tumours were reported in 14 affected people. All the probands were oncologically healthy.

The HBOC susp.2 syndrome was found in 29 probands. In these families, comprising 352 blood relatives including 211 females, the total burden of index cancers was 18.5% (95% CI = 14.8 – 22.9%) among all blood relatives and 30.8% (95% CI = 25.0 – 37.3%) among female blood relatives. The total amount of malignant tumours was 121 tumours in 108 persons.

Among the probands, diagnosed with HBOC susp.2, six were affected by cancer themselves (20.7%; 95% CI = 9.8 – 38.4%). Three probands were diagnosed with ovarian cancer at the age of 56, 61 and 78 years. Unilateral breast cancer was diagnosed in 1 proband at the age of 48 years, bilateral breast cancer - in another proband at the age 75 years. In 1 proband, breast and ovarian cancers were diagnosed at the age of 45 years.

Suspected HOC syndrome was diagnosed in 4 oncologically healthy persons. In these families, there were 8 cases of ovarian cancer in 8 patients. In general, 10 cancer cases have been diagnosed affecting 8 persons among 38 blood relatives. There were 22 female blood relatives in these pedigrees. Thus, the total burden of ovarian cancer was 21.1% (95% CI = 11.1 – 36.3%) among all blood relatives and 36.4% (95% CI = 19.7 – 57.0%) among female blood relatives.

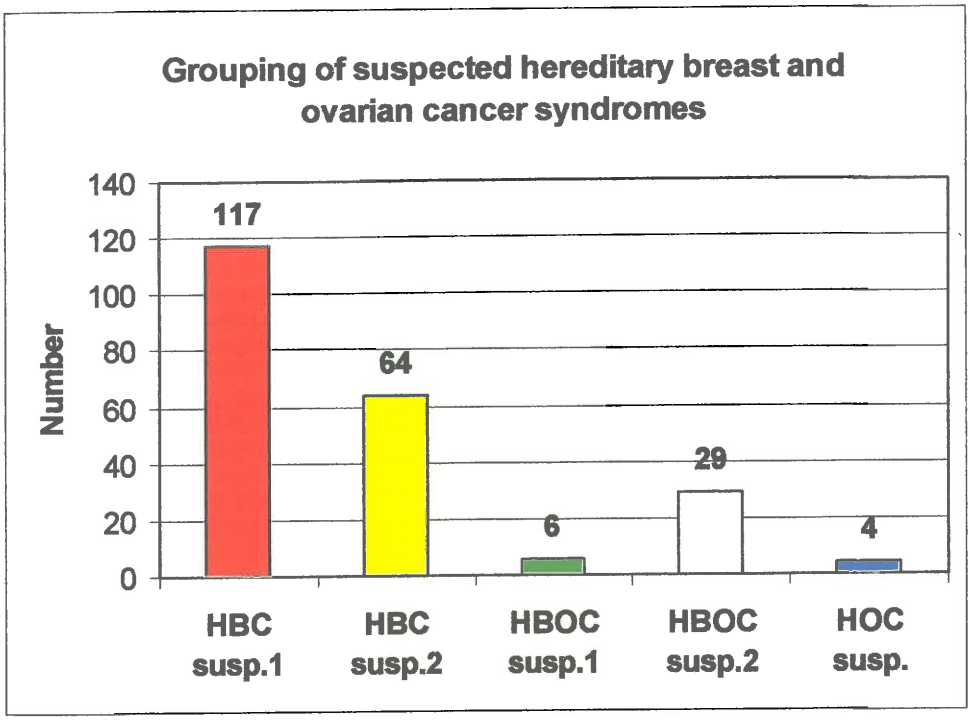


Figure 25. The grouping of suspected hereditary breast and ovarian cancer syndromes.
Abbreviations in the figure: HBC susp.1, suspected hereditary breast cancer syndrome, variety 1; HBC susp.2, suspected hereditary breast cancer syndrome, variety 2; HBOC susp.1, suspected hereditary breast – ovarian cancer syndrome, variety 1; HBOC susp.2, suspected hereditary breast – ovarian cancer syndrome, variety 2; HOC susp., suspected hereditary ovarian cancer syndrome.

The age structure of probands diagnosed with definitive or suspected hereditary breast – ovarian cancer syndromes was analysed. The data are presented in Table 9.

Table 9. Age distribution in probands with diagnosis of definitive and suspected hereditary breast ovarian cancer syndromes.

Diagnosis	Age, years						
	18-29	30-39	40-49	50-59	60-69	70-79	≥ 80
HBC	0	0	1	1	0	0	0
HBC susp.1	34	25	21	12	15	6	3
HBC susp.2	15	6	9	15	11	8	0
HBOC	0	0	1	0	1	0	0
HBOC susp.1	2	1	2	0	0	0	1
HBOC susp.2	8	3	7	3	5	0	3
HOC	0	0	1	0	0	0	0
HOC susp.	1	1	1	0	1	0	0

Abbreviations in table: ≥ more than or equals to; HBC, hereditary breast cancer syndrome; HBC susp.1, suspected hereditary breast cancer syndrome, variety 1; HBC susp.2, suspected hereditary breast cancer syndrome, variety 2; HBOC, hereditary breast-ovarian cancer syndrome; HBOC susp.1, suspected hereditary breast-ovarian cancer syndrome, variety 1; HBOC susp.2, suspected hereditary breast-ovarian cancer syndrome, variety 2; HOC, hereditary ovarian cancer syndrome; HOC susp.2, suspected hereditary ovarian cancer syndrome, variety 2.

Suspected hereditary breast cancer syndrome, variety 1, was more frequently detected in younger age groups. Suspected hereditary breast cancer syndrome, variety 2, was more frequently detected in middle age groups with a peak in the interval 50 – 59 years (Figure 26). No correlation with proband's age was detected for suspected HBOC and suspected HOC syndromes.

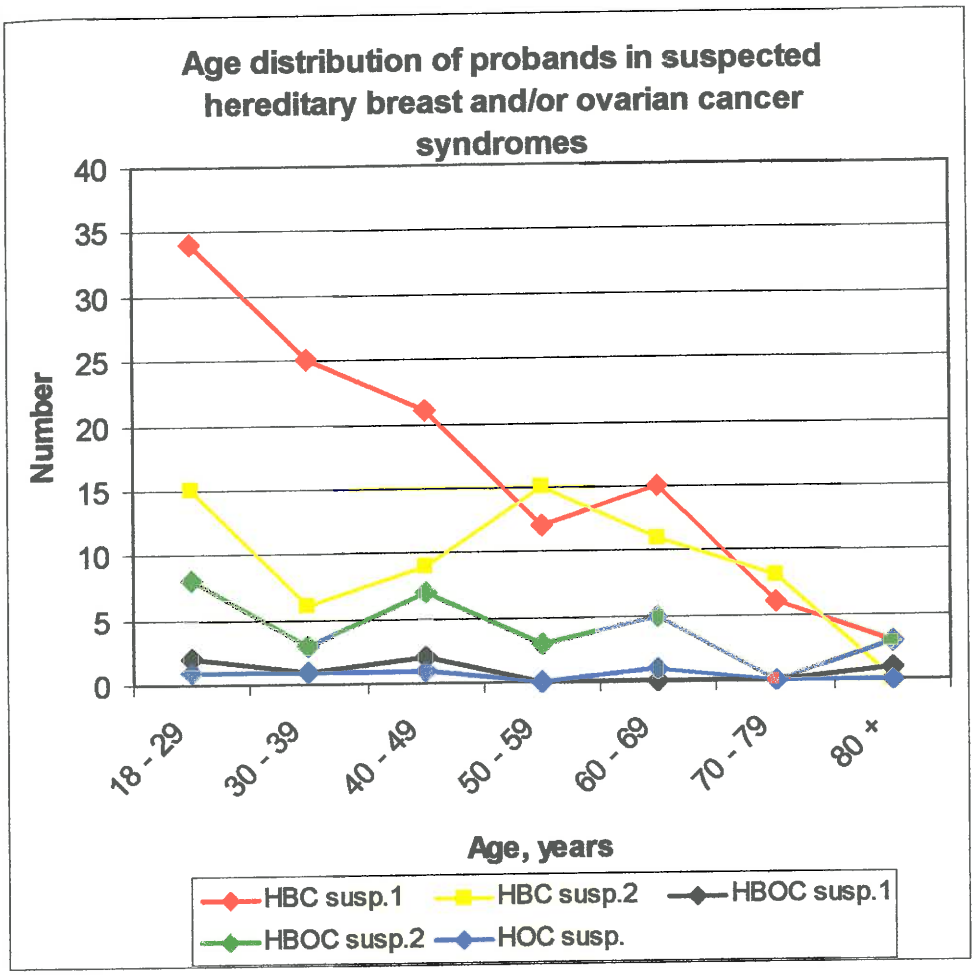


Figure 26. The age distribution of hereditary breast and ovarian syndrome cases.

The proband's health status in respect to oncological diseases was summarized in the Table 10.

Table 10. Proband's health status in suspected hereditary breast and/or ovarian cancer syndrome families.

Syndrome	Total number	Affected probands[1]	Proportion, % (95% CI)
HBC susp.1	117	5	4.3 (95% CI = 1.8 – 9.6%)
HBC susp.2	64	12	18.8 (95% CI = 11.1 – 30.0%)
HBOC susp.1	6	0	0 (95% CI = 0 – 39.0%)
HBOC susp.2	29	6	20.7% (95% CI = 9.8 – 38.4%)
HOC susp.	4	0	0 (95% CI = 0 – 49.0%)

[1] by breast and/or ovarian cancer

Abbreviations in table: CI, confidence interval; HBC susp.1, suspected hereditary breast cancer syndrome, variety 1; HBC susp.2, suspected hereditary breast cancer syndrome, variety 2; HBOC susp.1, suspected hereditary breast – ovarian cancer syndrome, variety 1;

HBOC susp.2, suspected hereditary breast – ovarian cancer syndrome, variety 2; HOC susp., suspected hereditary ovarian cancer syndrome.

The occurrence of malignant tumours is more frequent in probands belonging to HBC susp.2, than in probands belonging to HBC susp.1, group. Similar although statistically not significant trend was observed for suspected breast-ovarian cancer subtypes (see Table 11). Combining HBC and HBOC, more frequent occurrence of malignant tumours in probands belonging to variety 2 was confirmed as statistically significant.

Table 11. Comparison of proband's health status by suspected hereditary breast and ovarian cancer syndromes.

Syndrome	Variety 1	Variety 2	Difference
Susp. HBC	5 / 117 4.3% 95% CI = 1.8 – 9.6%	12 / 64 18.8 95% CI = 11.1 – 30.0%	$p \leq 0.05$
Susp. HBOC	0 / 6 0% 95% CI = 0 – 39.0%	6 / 29 20.7% 95% CI = 9.8 – 38.4%	$p > 0.05$
Combined	5 / 123 4.1% 95% CI = 1.7 – 9.2%	18 / 93 19.4% 95% CI = 12.6 – 28.5%	$p \leq 0.05$

Abbreviations in table: susp.HBC, suspected hereditary breast cancer; susp.HBOC, suspected hereditary breast – ovarian cancer; CI, confidence interval.

The syndromes differed between themselves in the cancer frequency among female blood relatives. The data are summarized in the Table 12. There is statistically significant difference in breast cancer frequency among HBC susp.1 and HBC susp.2.

Table 12. Cancer frequency among female blood relatives in suspected hereditary breast and/or ovarian cancer syndromes

Syndrome	Frequency of the index cancers		
	Frequency, %	95% CI	
		Lower	Upper
HBC susp.1	16.3	13.8	19.1
HBC susp.2	32.3	27.5	36.4
HBOC susp.1	19.3	9.2	36.3
HBOC susp.2	30.8	25.0	37.3

HOC susp.	36.4	19.7	57.0

Abbreviations in the table: CI, confidence interval; HBC susp.1, suspected hereditary breast cancer syndrome, variety 1; HBC susp.2, suspected hereditary breast cancer syndrome, variety 2; HBOC susp.1, suspected hereditary breast – ovarian cancer syndrome, variety 1; HBOC susp.2, suspected hereditary breast – ovarian cancer syndrome, variety 2; HOC susp., suspected hereditary ovarian cancer syndrome.

In order to characterise the course of the hereditary breast and / or ovarian cancer, data about all tumour-affected persons were retrieved and analysed. The age of cancer diagnosis and tumour – related death was analysed. The survival time was analysed if the patient died from tumour. The age of definite cancer manifestation was detected as age of tumour diagnostics if known, or age of tumour-related death. Re-evaluation of the pedigrees was performed in order to exclude from the calculations those persons who were reported by several proband due to kindred relationships between families. The results are presented in Tables 13 and 14.

Table 13. The characteristics of the disease course in the affected persons in hereditary breast and/or ovarian cancer pedigrees

Syndrome	Parameter	Range, years	Mean, years	SD, years	Count	95% CIM
HBC	Age of diagnosis	40 – 55	47.5	6.5	4	37.1 – 57.8
	Age of death	50 – 60	54.7	4.5	6	50.0 – 59.4
	Age of manifestation	40 – 60	51.7	8.2	6	43.1 – 60.3
	Survival	0 – 13	4.5	6.1	4	0 – 14.2
HBC susp.1	Age of diagnosis	20 – 70	38.0	8.9	104	36.2 – 39.7
	Age of death	26 – 78	44.7	12.9	73	41.7 – 47.7
	Age of manifestation	20 – 70	38.3	9.0	116	36.6 – 40.0
	Survival	0 – 53	7.5	10.6	61	4.8 – 10.2
HBC susp.2	Age of diagnosis	25 – 82	51.8	14.4	102	48.9 – 54.6
	Age of death	25 – 66	60.9	17.1	66	56.7 – 65.1
	Age of manifestation	25 – 88	52.7	14.9	116	50.0 – 55.4
	Survival	0 – 46	8.1	10.4	52	5.2 – 11.0
HBOC	Age of diagnosis	34 – 82	61.0	15.2	7	46.9 – 75.0
	Age of death	58 – 85	71.4	13.3	5	54.9 – 87.9
	Age of manifestation	34 – 82	61.0	15.3	7	46.8 – 75.1
	Survival	0 – 13	4.8	4.9	5	0 – 10.9
HBOC susp.1	Age of diagnosis	40 – 60	48.8	7.2	12	44.2 – 53.3
	Age of death	47 – 69	54.3	11.4	6	42.3 – 66.3

	Age of manifestation	40 – 60	48.8	7.2	12	44.2 – 53.4
	Survival	0 – 19	5.7	7.3	6	0 – 13.4
HBOC susp.2	Age of diagnosis	18 – 86	56.6	17.4	53	51.8 – 61.4
	Age of death	23 – 87	66.1	16.8	47	61.2 – 71.0
	Age of manifestation	18 – 86	58.2	17.2	63	53.9 – 62.5
	Survival	0 – 36	7.1	9.6	37	3.9 – 10.3
HOC	Age of diagnosis	34 – 70	49.7	18.4	3	4.0 – 95.4
	Age of death	72	72	-	1	-
	Age of manifestation	34 – 70	49.7	18.4	3	4.0 – 95.4
	Survival	2	2	-	1	-
HOC susp.	Age of diagnosis	45 – 70	54.2	9.3	8	46.4 – 61.9
	Age of death	47 – 72	57.2	8.5	8	50.1 – 64.3
	Age of manifestation	45 – 70	54.2	9.3	8	46.4 – 62.0
	Survival	0 – 10	3	3.2	8	0.3 – 5.7

Abbreviations in table: Abbreviations in table: HBC, suspected hereditary breast cancer; HBC susp.1, suspected hereditary breast cancer, variety 1; HBC susp.2, suspected hereditary breast cancer, variety 2; HBOC, hereditary breast – ovarian cancer; HBOC susp.1, suspected hereditary breast – ovarian cancer, variety 1; HBOC susp.2, suspected hereditary breast – ovarian cancer, variety 2; HOC, hereditary ovarian cancer; HOC susp., suspected hereditary ovarian cancer; SD, standard deviation; CIM, confidence interval for the mean.

Table 14. The distribution of the survival of affected persons in different hereditary breast and ovarian cancer syndromes.

Syndrome	Total number	Survival, years				ND	Alive
		0-1	2-5	6-10	> 10		
HBC	6	2	1	0	1	2	0
HBC1	117	17	24	5	15	15	41
HBC2	126	14	18	10	10	26	48
HBOC	7	1	3	0	1	0	2
HBOC1	6	1	1	0	1	0	3
HBOC2	59	8	10	5	8	11	17
HOC	3	0	1	0	0	0	2
HOC susp.	7	2	4	1	0	0	0

Abbreviations in table: ND, no data available; >, larger than; HBC, hereditary breast cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast cancer, variety 2; HBOC, hereditary breast – ovarian cancer; HBOC1, suspected hereditary

breast – ovarian cancer, variety 1; HBOC2, suspected hereditary breast – ovarian cancer, variety 2; HOC, hereditary ovarian cancer; HOC susp., suspected hereditary ovarian cancer.

Due to hypothetic possibility of incomplete information about hereditary breast and/or ovarian cancer in the family, the information about single cases of breast and ovarian cancer cases in kindred was collected and analysed as well offering the probands also the possibility to undergo additional consultations and genetic testing for *BRCA* mutations. There were 840 probands reporting a single case of breast cancer in the family, not complying with the diagnostic criteria of suspected hereditary breast cancer, variety 1 and 82 probands reporting a single case of ovarian cancer in the family.

Hereditary colorectal cancer

During the population screening, 51 probands were diagnosed with different hereditary cancer syndromes (Figure 27) involving the large bowel.

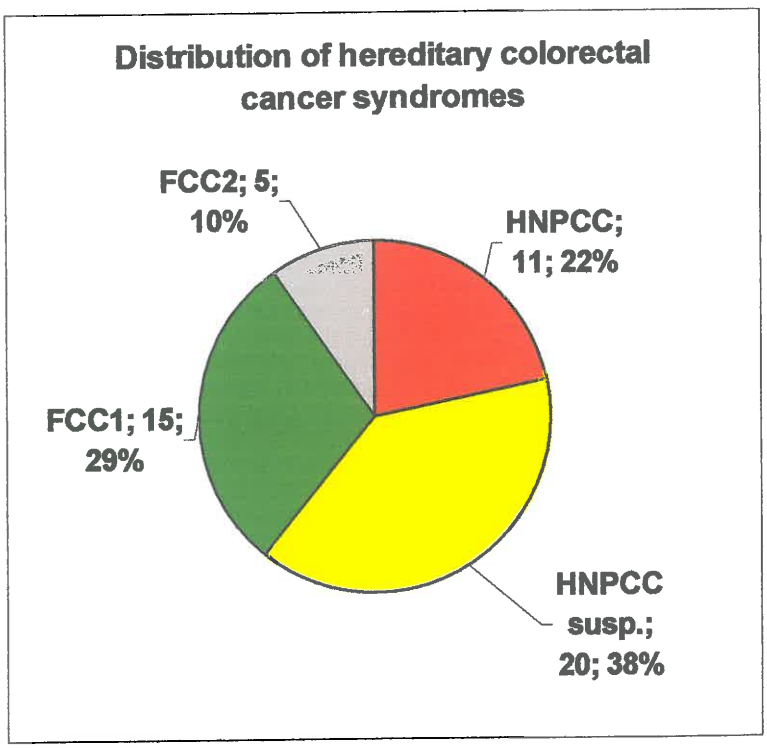
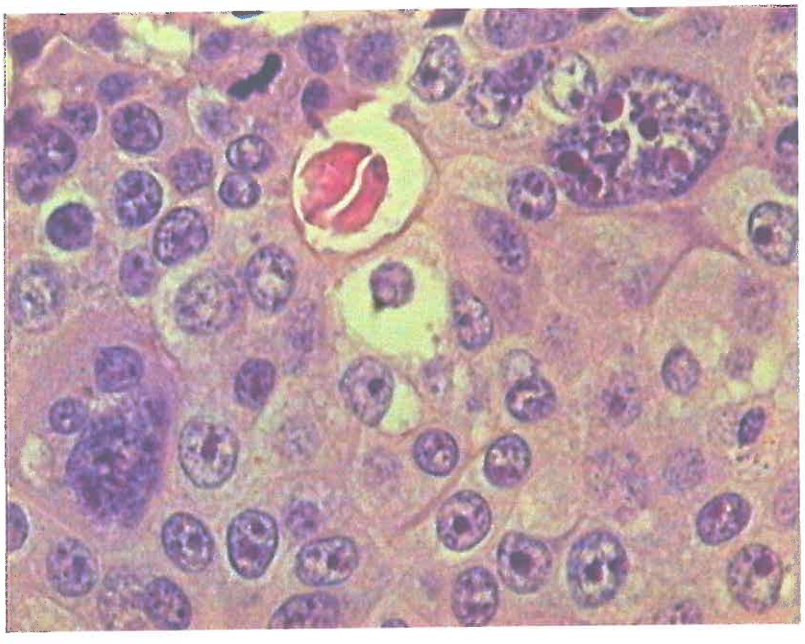


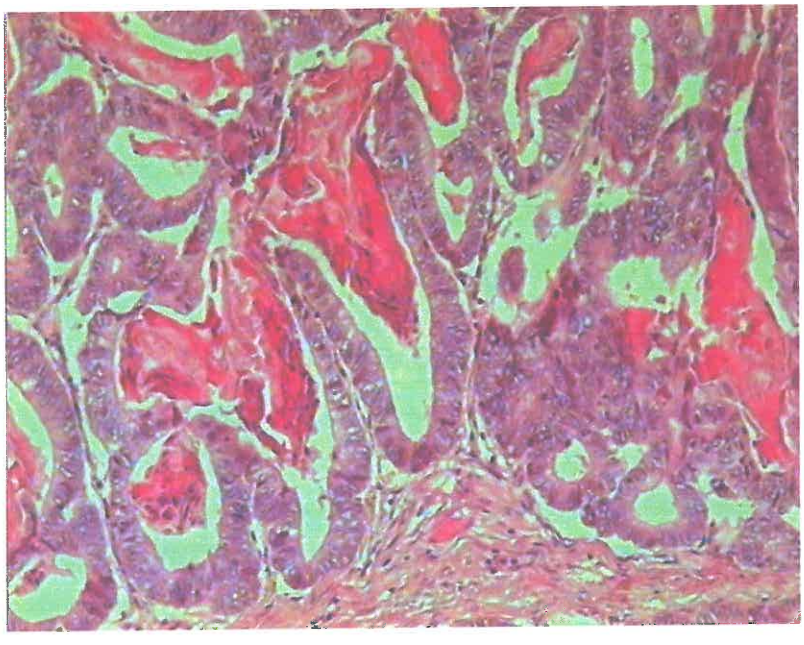
Figure 27. The relative distribution of hereditary colorectal cancer syndromes. Abbreviations in the figure: HNPCC, definitive hereditary non-polyposis colorectal cancer syndrome; HNPCC susp., suspected hereditary non-polyposis colorectal cancer syndrome; FCC1, familial colorectal cancer syndrome, variety 1; FCC2, familial colorectal cancer syndrome, variety 2.

Hereditary non-polyposis colorectal cancer syndrome was detected in 11 probands, among them 9 (81.8%; 95% CI = 52.3 – 94.9%) persons were younger than 50 years. There were 7

females and 3 males in this group. Nine probands (81.8%; 95% CI = 52.3 – 94.9%) were oncologically healthy. Colorectal cancer in a 49-year-old male was diagnosed shortly before the population screening. Another case of colorectal cancer (Figure 28) was diagnosed during the follow-up of the screened group – it was discovered in 61-year-old female, 4 years after she underwent the screening.



A.



B.

Figure 28. Hereditary high-grade colorectal carcinoma. Haematoxylin – eosin. A, original magnification 400x; B, original magnification 100x. Microphotographs by A. Vanags

Suspected HNPCC syndrome was observed in 20 probands. Among them 9 (45.0%; 95% CI = 25.8 – 65.8%) persons were in the age group 18 – 49. There were 18 (90.0%; 95% CI = 69.9 – 97.2%) females and 2 (10.0%; 95% CI = 2.8 – 30.1%) males in this group. Colorectal cancer has been diagnosed in 1 (5%; 95% CI = 0.9 – 23.6%) female proband 3 years before the population screening at the age of 68 years. In addition, breast cancer has been diagnosed in another proband.

No cases of familial adenomatous polyposis were revealed during the population screening. Familial colorectal cancer syndrome was revealed in 20 cases, with the peak at age of 60 – 69 (Figure 29). One of these probands, a 76-year-old male, had had colorectal cancer 4 years prior to the population screening, at the age of 72 years. There were 17 (89.5%; 95% CI = 68.6 – 97.1%) females and 2 (10.5%; 95% CI = 2.9 – 31.4%) males in this group of probands. The FCC group comprised 15 cases of FCC1 and 5 cases of FCC2 syndrome.

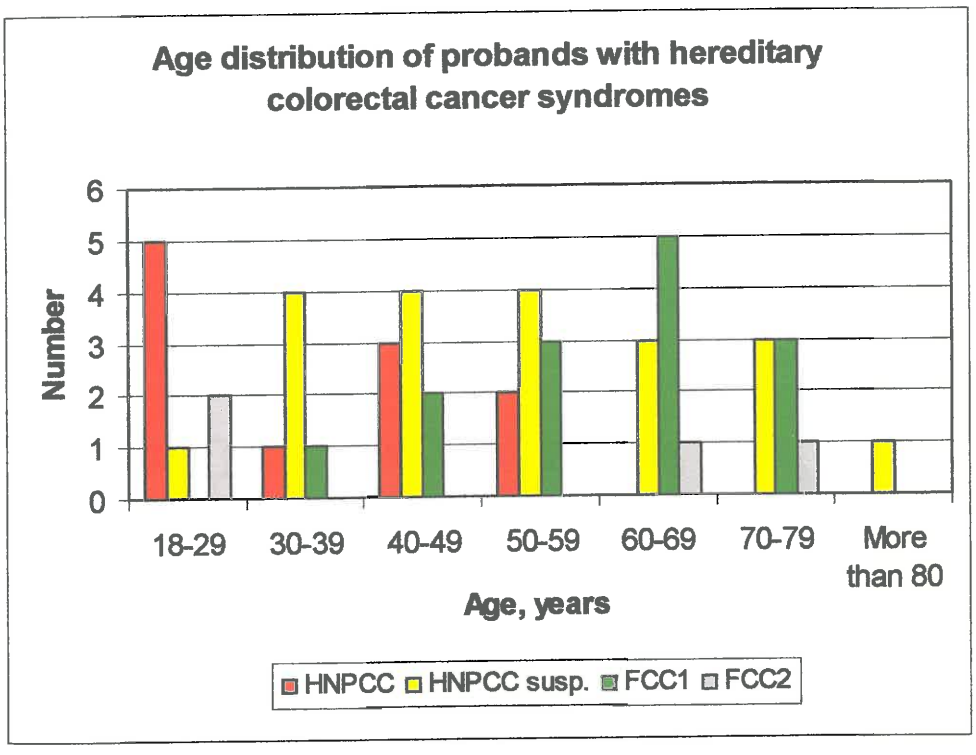


Figure 29. Age distribution of probands diagnosed with hereditary colorectal cancer syndromes. Abbreviations in figure: HNPCC, hereditary non-polyposis colorectal cancer; HNPCC susp., suspected hereditary non-polyposis colorectal cancer; FCC1, familial colorectal cancer, variety 1; FCC2, familial colorectal cancer, variety 2.

The age distribution of probands suggests elimination of HNPCC probands with advancing age (Table 15). In contrast, the chance to be diagnosed with FCC increases with age as the older relatives enter the risk group.

Table 15. Age distribution of probands with hereditary colorectal cancer syndromes

Diagnosis	Analysable number	18-29	30-39	40-49	50-59	60-69	70-79	≥ 80
HNPCC	11	5	1	3	2	0	0	0
HNPCC susp.	20	1	4	4	4	3	3	1
FCC1 and 2	18	2	1	2	3	6	4	0
FCC1	13	0	1	2	3	5	2	0
FCC2	5	2	0	0	0	1	2	0

Abbreviations in table: HNPCC, hereditary non-polyposis colorectal cancer; HNPCC susp., suspected hereditary non-polyposis colorectal cancer; FCC1, familial colorectal cancer, variety 1; FCC2, familial colorectal cancer, variety 2; ≥, more than or equals to.

HNPCC

As already noted, HNPCC syndrome was diagnosed in 11 probands. These families presented with cancer history compatible with the Amsterdam criteria (Figure 30).

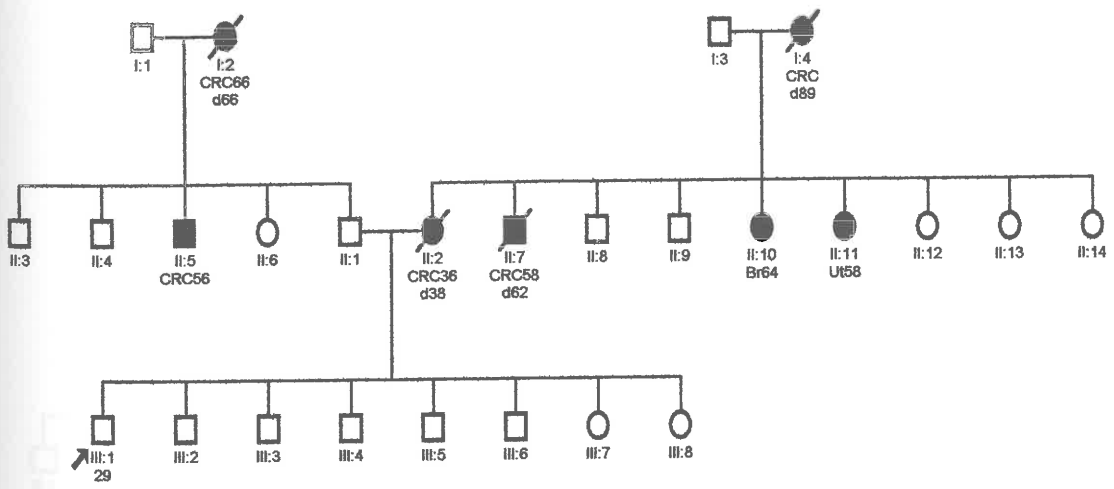


Figure 30. Pedigree corresponding to the diagnostic criteria of HNPCC. Early-onset colorectal cancer has been diagnosed in proband's mother. Her brother and mother have been affected by colorectal cancer as well, and her sister had had endometrial cancer. Two generations are affected. Interestingly, the pedigree shows also 2 late-onset cases of colorectal cancer in the paternal line that should be considered separately.

Abbreviations in the figure: CRC, colorectal cancer; Br, breast cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

The data about cancer-affected persons in HNPCC pedigrees were collected (see annex 3-6) and analysed. Among the affected persons in HNPCC families, there were 30 / 44 (68.2%; 95% CI = 53.4 – 80.0%) females and 14 / 44 (31.8%; 95% CI = 20.0 – 46.6%) males.

The age of cancer diagnostics was 30 – 77 years (mean 54.2 years; SD 11.6 years; 95% CI for the mean, 50.2 – 58.2 years). The data about the age of cancer diagnostics were available at 34 cases. Among the patients who were affected by HNPCC-related cancer, 21 were alive. Among dead affected patients, the death occurred at the age of 28 – 89 years (mean 61.7 years; SD 15.6 years; 95% CI for the mean, 54.2 – 69.2 years). Exact death age was reported for 19 patients. Considering the dead patients, survival was found to be 0 – 16 years (mean 2.6 years; SD 4.4 years; 95% CI for the mean, 0 – 5.2 years). The data about survival were available about 13 patients. The age of definite tumour manifestation was estimated in 40 cases and was 28 – 89 years (mean; 55.6; SD 14.2 years; 95% CI for the mean, 51.1 – 60.1 years).

There were 23 cases of colorectal cancer and 19 cases of endometrial cancer in HNPCC pedigrees as well as single cases of cancer in the small intestine and renal pelvis, respectively. Interestingly, endometrial cancer was the dominant manifestation of the hereditary cancer syndrome in some pedigrees (Figure 31).

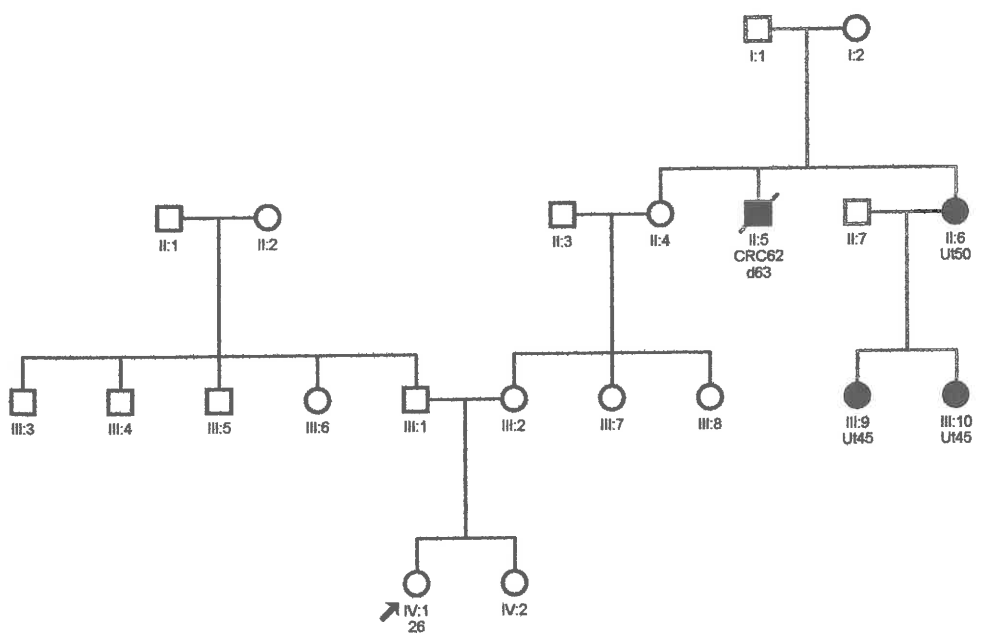


Figure 31. HNPCC kindred with predominance of endometrial cancer (MK1620).

Abbreviations in the figure: CRC, colorectal cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Analysing the patients with colorectal cancer in HNPCC pedigrees, the age of tumour diagnostics was 36 – 77 years (mean 59.3 years; SD, 10.6 years; 95% CI for the mean, 53.8 – 64.8 years). The data about the time of tumour diagnostics were available in 17 people, excluding the youngest patient. Seven patients were alive at the time of population screening, but the others affected by colorectal cancer had died at the age 28 – 89 (mean 61.5 years; SD 15.5 years; 95% CI for the mean, 52.9 – 70.0 years). The data about the death age were available for 15 persons. The survival, evaluating the dead persons, was estimated 0 – 6 years (mean 1.7 years; SD 1.9 years; 95% CI for the mean, 0.6 – 2.7 years). The age of definite colorectal cancer manifestation was estimated for 22 patients and was 28 – 89 years (mean 60.0 years; SD, 14.5 years; 95% CI for the mean, 53.6 – 66.4 years). Among the 23 patients affected by colorectal cancer, there were 14 males and 9 females.

The endometrial cancer was diagnosed at the age 30 – 65 years (mean 48.4 years; SD 10.4 years; 95% CI for the mean, 43.4 – 53.4 years). Most of the patients affected by endometrial cancer were alive at the time when population screening was carried out (Figure 32). The 2 remaining patients died at the age 37 and 72 years; the death occurred 1 and 16 years after the initial diagnosis, respectively.

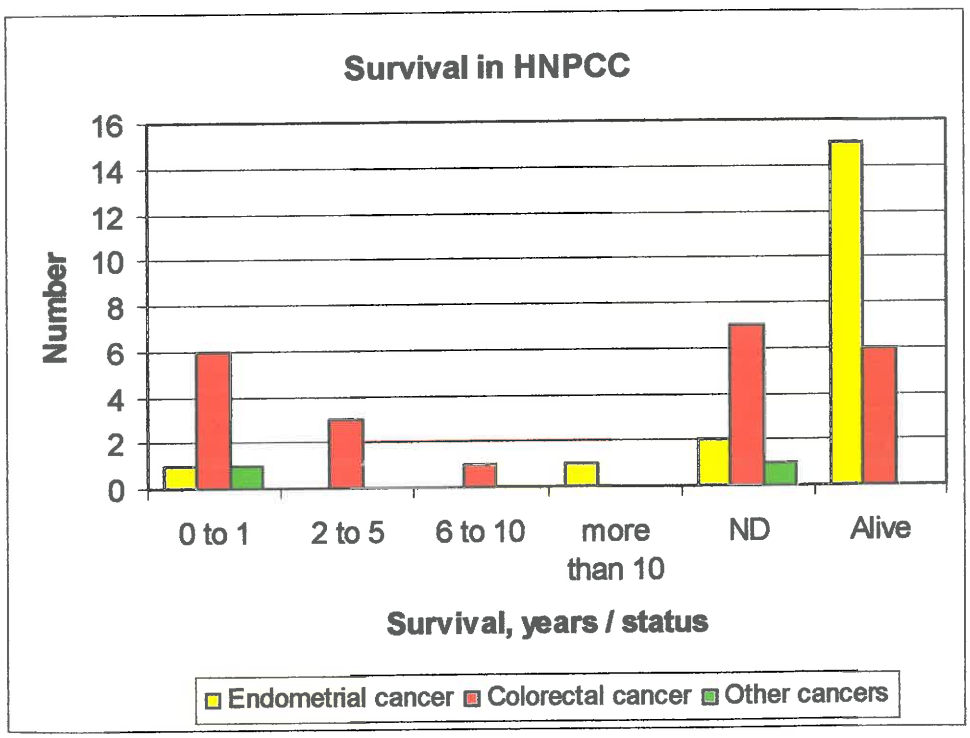


Figure 32. Distribution of survival in-between cancer affected patients with HNPCC pedigrees. Abbreviation in figure: ND, no data available.

In order to evaluate the cancer burden in HNPCC pedigrees, data about presence and location of various HNPCC-related tumours were retrieved. The number of blood relatives in the affected branch was determined for each kindred. In HNPCC families, 44 / 146 (30.1%; 95%

CI = 23.3 – 38.0%) persons were affected by HNPCC-related cancers. The frequency of colorectal cancer among blood relatives was 23 / 146 (15.8%; 95% CI = 10.7 – 22.5%), of endometrial cancer – 19 / 146 (13.0 %; 95% CI = 8.5 – 19.4%) among blood relatives or 19 / 85 (22.4%; 95% CI = 14.8 – 32.3%) among female blood relatives.

Suspected HNPCC

In suspected HNPCC pedigrees, 42 persons were affected by HNPCC-related cancer. Among them, there were 26 / 42 (61.9%; 95% CI = 46.8 – 75.0%) females and 16 / 42 (38.1%; 95% CI = 25.0 – 53.2%) males.

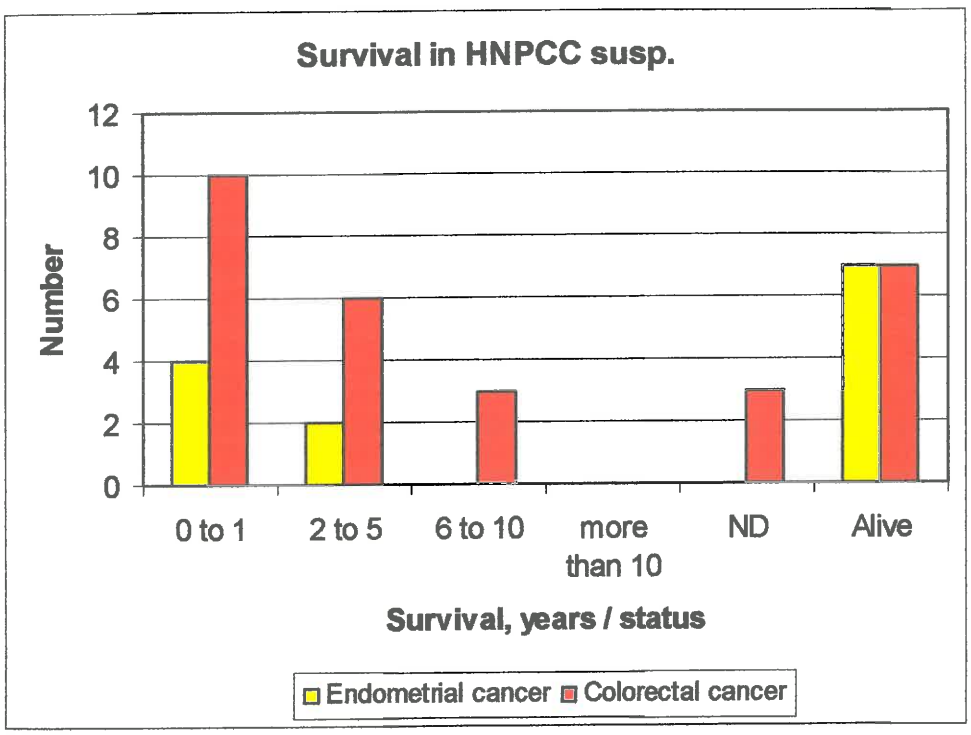


Figure 33. Distribution of survival in cancer-affected patients within suspected HNPCC families.

In the suspected HNPCC pedigrees, the age of tumour diagnostics was 27 – 82 years (mean 53.7 years; SD, 14.3 years; 95% CI for the mean, 49.1 – 58.3 years). The data about the age of tumour diagnostics were available in 39 cases. Fourteen persons were alive at the time of population screening. The death of the others occurred at the age 28 – 88 years (mean 55.5 years; SD 15.6 years; 95% CI for the mean, 49.5 – 61.5 years). The exact death age was reported in 28 cases. The survival was 0 – 10 years (mean 2.3 years; SD 2.8; 95% CI for the mean, 1.1 – 3.5 years). Survival data were available for 25 persons as 14 were alive and data were insufficient in 3 cases (Figure 33). The age of definite tumour manifestation was estimated in 42 cases and was 27 – 82 years (mean 53.4 years; SD 14.1 years; 95% CI for the mean, 49.0 – 57.8 years).

Among the persons affected by colorectal cancer within the suspected HNPCC syndrome, the age of tumour diagnostics was 28 – 82 year (mean 55.2 years; SD 15.2 years; 95% CI for the mean, 49.1 – 61.3 years). The data about the age of tumour diagnostics were available at 26 cases. Seven affected persons were alive. The death age was 32 – 88 years (mean 56.7 years; SD, 15.4 years; 95% CI for the mean, 49.9 – 63.5 years). The exact death age was reported by the probands in 22 cases. The survival was 0 – 10 years (mean 2.5 years; SD 3.0; 95% CI for the mean, 1.2 – 3.8 years). Survival data were available in 19 cases. The age of definite tumour manifestation was estimated in 29 cases and was 28 – 82 years (mean 54.7 years; SD 14.7 years; 95% CI for the mean, 49.1 – 60.3 years).

Among the females from suspected HNPCC pedigrees who were affected by endometrial cancer, the age of tumour diagnostics was 27 – 72 years (mean 50.5 years; SD 12.4 years; 95% CI for the mean, 43.0 – 58.0 years). The age of tumour diagnostics was determined in 13 cases. Seven patients were alive. The death of the remaining occurred at the age of 28 – 73 years (mean, 51.2 years; SD 17.2 years; 95% CI for the mean, 33.1 – 69.3 years). The death age was established in 6 cases. The survival was 0 – 5 years (mean 1.5; SD 1.9 years; 95% CI for the mean, 0 – 3.5 years) when applicable (6 cases).

Analysing suspected HNPCC pedigrees in order to determine the cancer burden, 41 / 265 (15.5%; 95% CI = 11.6 – 20.3%) persons were affected by HNPCC-related cancers. One kindred was excluded from this specific evaluation due to incomplete data set on the number of relatives in the affected line. The frequency of colorectal cancer among blood relatives was 28 / 265 (10.6%; 95% CI = 7.4 – 14.8%), of endometrial cancer – 13 / 265 (4.9%; 95% CI = 2.9 – 8.2%) among blood relatives or 13 / 135 (9.6%; 95% CI = 5.7 – 15.8%) among female blood relatives.

Synopsis about the cancer course in definitive and suspected HNPCC

Analysing the whole group of HNPCC pedigrees, the following data were obtained.

The diagnosis was established at the age 27 – 82 years (mean 53.9 years; SD, 13.0; 95% CI for the mean, 50.9 – 56.9 years). The exact age of diagnosis was known in 73 cases. The death occurred at the age 28 – 89 years (mean 58.0 years; SD 15.8; 95% CI for the mean, 53.4 – 62.6 years). The death age was reported exactly in 47 cases. The survival (see also figure 33) was 0 – 16 years (mean 2.4 years; SD, 3.4; 95% CI for the mean, 1.3 – 3.5 years). The age of tumour manifestation was estimated in 82 cases. It was 27 – 89 years (mean, 54.6 years; SD 14.1 years; 95% CI for the mean, 51.5 – 57.7 years).

Considering colorectal cancer, the tumour was diagnosed at the age 28 - 82 years (mean 56.8 years; SD, 13.6; 95% CI for the mean, 52.6 – 60.9 years). The age of tumour diagnostics was known in 43 cases. The death occurred at the age 28 – 89 (mean 58.7 years; SD 15.4; 95% CI for the mean, 53.6 – 63.8 years). The survival of the dead persons has been 0 – 10 years (mean 2.2 years; SD, 2.7; 95% CI for the mean, 1.2 – 3.2 years). The age of tumour

manifestation was 28 – 89 years (mean, 57.0 years; SD 14.7 years; 95% CI for the mean 52.9 – 61.1 years). The data about the age of tumour diagnostics, definite tumour manifestation, patient's death and survival were available at 43, 51, 37 and 29 cases, respectively.

In the endometrial cancer subgroup, the tumour was diagnosed at the age 27 – 72 years (mean 49.4 years; SD 11.2; 95% CI for the mean, 45.1 – 53.7 years). If the patient died, the death age was 28 – 73 years (mean 52.0 years, SD 17.3 years; 95% CI for the mean, 37.5 – 66.5 years), but survival – 0 – 16 years (mean 3.2 years; SD, 5.4; 95% CI for the mean, 0 – 7.7 years). The data about the age of tumour manifestation, patient's death age and survival were reported in 29, 8 and 8 cases, respectively. Age of definite tumour manifestation was equal with the age of tumour diagnostics. The survival data of the affected persons from definitive and suspected HNPCC families are depicted in Figure 34.

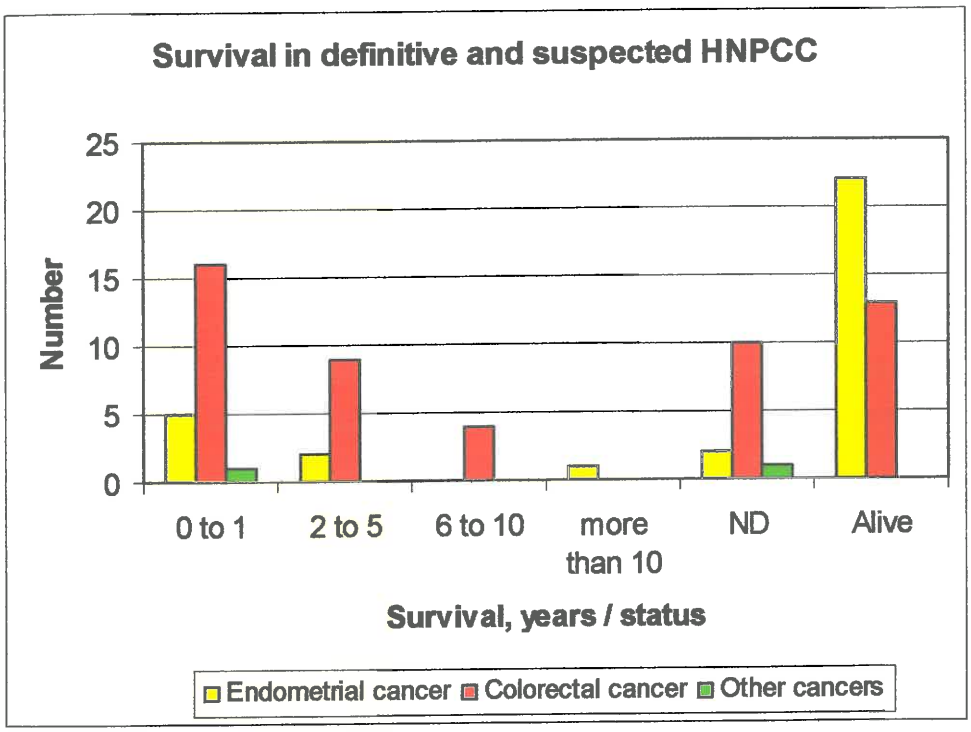


Figure 34. Distribution of survival of cancer-affected patients in definitive and suspected HNPCC. Abbreviation in the figure: ND, no data available.

The following evidence of genetic anticipation was found. The mean age of cancer diagnostics in the oldest affected generation was 61.4 years (SD 12.8; 95% CI for the mean 56.4 – 66.4 years) but in the next generation – 49.8 years (SD 13.7; 95% CI for the mean 44.9 – 54.7 years).

FCC

In FCC families, 41 cases of colorectal cancer were identified (Figure 35 and 36).

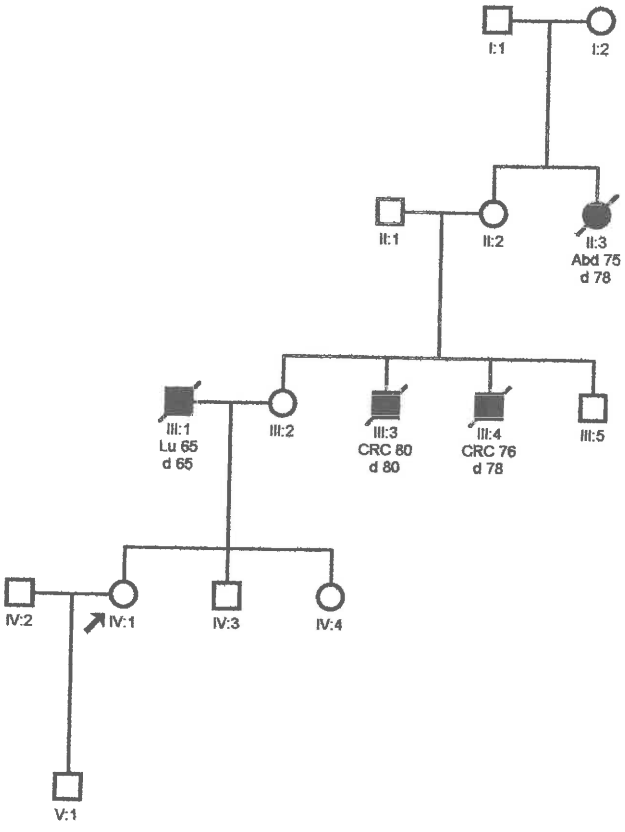


Figure 35. Pedigree of familial colorectal cancer, variety 1. Abbreviations in the figure: Abd, malignant tumour in the abdominal cavity, not further specified; Lu, lung cancer; CRC, colorectal cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Among the persons (Annex 7) who were affected by late-onset familial colorectal cancer there were 18 (43.9%; 95% CI = 30.0 – 59.0) males and 23 (56.1%; 95% CI = 41.0 – 70.1%) females. The cancer was diagnosed at the age 41 – 89 years (mean 72.0 years; SD 12.8 years; 95% CI for the mean 67.3 – 76.7 years). Five patients were alive at the time when population screening was carried out. The death ensured at the age 52 – 90 years (mean 76.3 years; SD 8.9 years; 95% CI for the mean, 73.1 – 79.5 years). The survival was 0 – 8 years (mean 2.2 years; SD 2.0 years; 95% CI for the mean 1.3 – 3.1 years). The distribution of survival is depicted in figure 36. The age of definitive tumour manifestation, known in 37 cases, was 41 – 89 years (mean, 72.2 years; SD 11.8 years; 95% CI for the mean, 68.3 – 76.1 years).

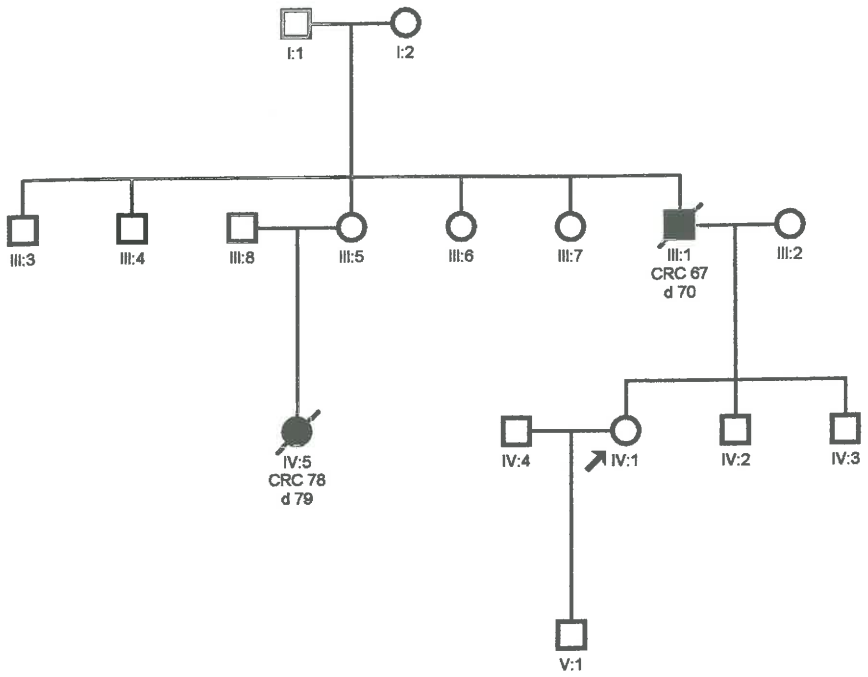


Figure 36. Pedigree of familial colorectal cancer, variety 2. Abbreviations in the figure: CRC, colorectal cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

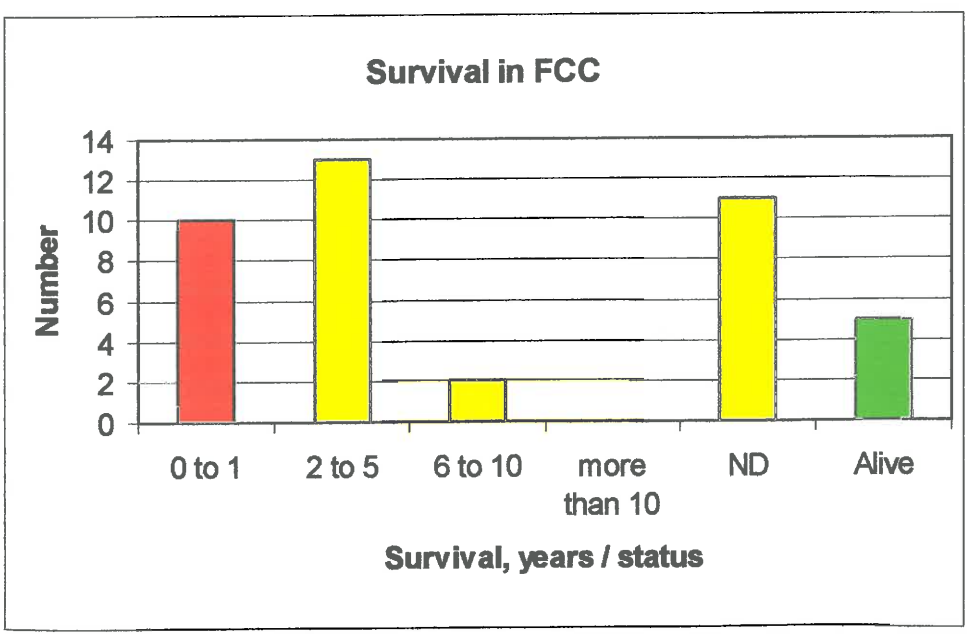


Figure 37. Distribution of survival in familial colorectal cancer group. Abbreviation in the figure: ND, no data available.

The frequency of colorectal cancer in FCC pedigrees (Annex 8) was 41 / 241 or 17.0% (95% CI = 12.8 – 22.3%).

Extra-colonic, extra-endometrial cancers in hereditary and familial colorectal cancer syndromes

Data about cancer in other locations were retrieved and analysed. In HNPCC pedigrees, only 3/11 (27.3%; 95% CI = 9.7 – 56.6%) families reported presence of cancers, not included in the diagnostic criteria (i.e., colorectal, endometrial, small intestinal and renal pelvis cancer). Single cases of brain tumour (0.7%; 95% CI = 0.1 – 0.3%), breast cancer, lung cancer and head-and-neck cancer were reported. In 1 case, proband reported malignancy located in the abdominal cavity but not further specified. In suspected HNPCC, 22 additional cancers were present in 14/20 (41.2%; 95% CI = 26.3 – 57.8%) pedigrees. These included 4 cases of breast cancer (4/135 of female blood relatives; 3.0%; 95% CI = 1.2 – 7.4%), 4 cases of prostate cancer, 2 cases of lung cancer, 2 cases of pancreatic cancer, 2 cases of brain tumours (2/265; 0.8%; 95% CI = 0.2 – 2.7%) as well as isolated cases of head-and-neck cancer, urinary bladder cancer, melanoma, Wilms tumour, gastric cancer (1/265; 0.4%; 95% CI = 0.1 – 2.1%), renal cancer, cancer of the vulva and ovarian cancer (1/135 female blood relatives; 0.7%; 0.1 – 4.1%).

In FCC, 14 additional tumours were present in 10/20 (33.3%; 95% CI = 19.2 – 51.2%) families. There were 3 cases of sarcoma, 2 cases of prostate cancer, 2 cases of brain tumours (both in the same kindred), 2 cases of gastric cancer as well as single cases of lung cancer, haematological malignancy, breast cancer. In 2 cases, the location of cancer was unknown to the proband.

Hereditary endometrial cancer syndromes

Hereditary endometrial cancer syndromes were detected in 66 probands. The distribution of different hereditary endometrial cancer syndromes was following (Figure 38). Hereditary endometrial cancer syndrome was diagnosed in 5 cases. There were 2 cases of familial endometrial cancer syndrome. Suspicion of the respective conditions was diagnosed in 59 cases. Among these, there were 26 persons with suspected hereditary endometrial cancer, 24 persons with suspected familial endometrial cancer variety 1, and 9 persons with suspected familial endometrial cancer, variety 2.

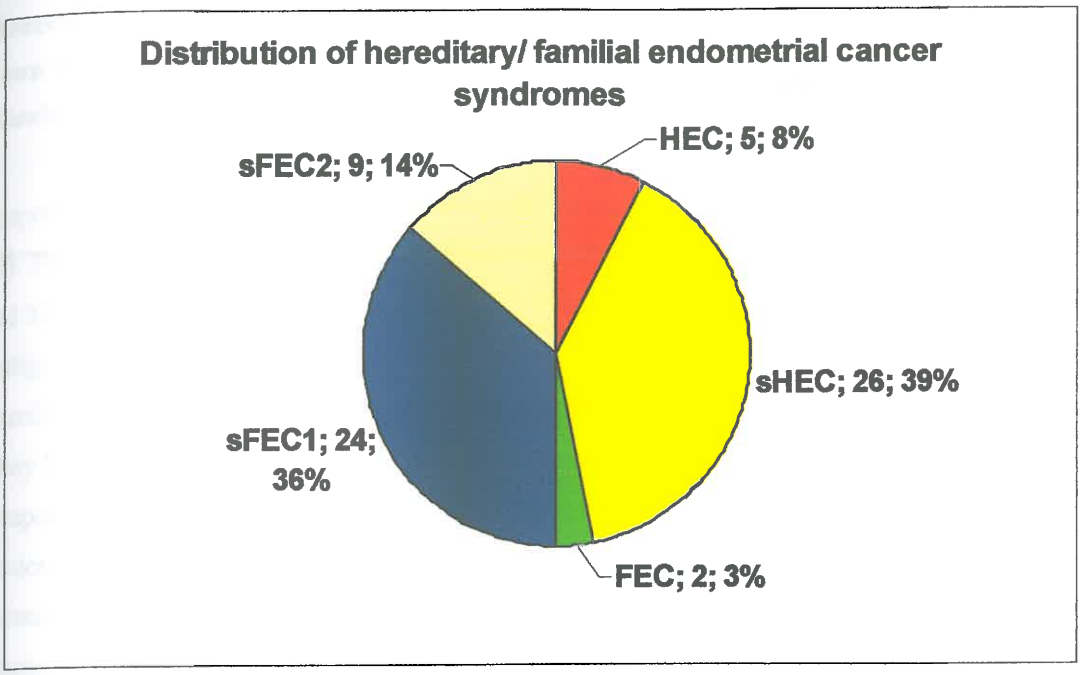


Figure 38. Distribution of definitive and suspected hereditary and familial endometrial cancer syndromes.

Abbreviations in the Figure 38: HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; sFEC1, suspected familial endometrial cancer, variety 1; sFEC2, suspected familial endometrial cancer, variety 2.

The definitive hereditary endometrial cancer syndrome (Figure 39) was mostly diagnosed in probands younger than 50 years (4/5). All probands diagnosed with hereditary endometrial cancer syndrome were healthy themselves.

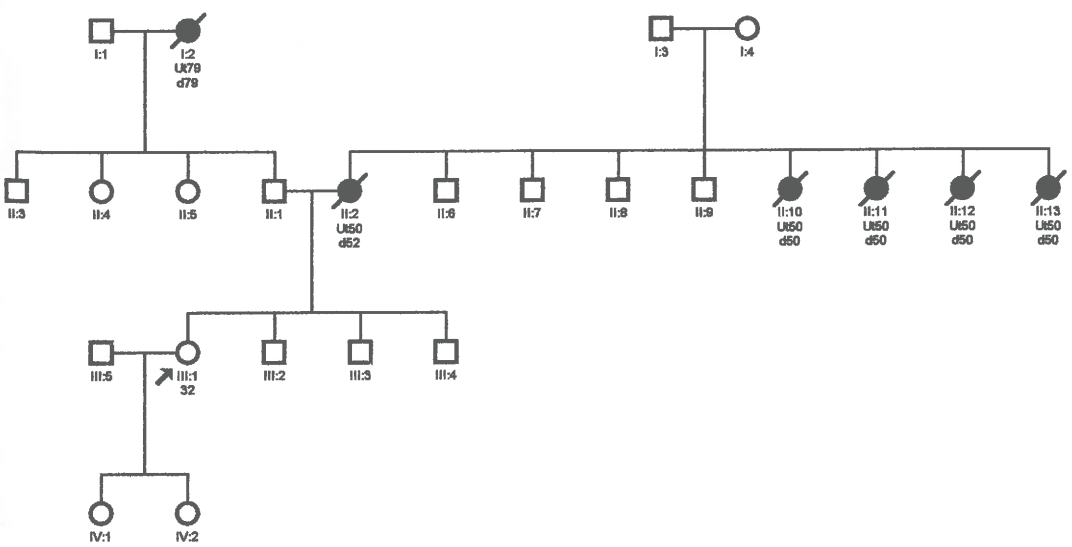


Figure 39. Pedigree of a family affected by hereditary endometrial cancer. Endometrial cancer has been diagnosed in proband's mother. It has also caused premature death of 4 sisters of proband's mother.

Abbreviations in the figure: Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Suspected hereditary endometrial cancer syndrome was diagnosed in all age groups (Figure 40). Four probands had had endometrial cancer themselves, occurring at the age 45; 55; 60 and 37 years. The tumour has been treated 40; 3; 14 and 22 years ago, respectively. No other malignant tumours were present in the probands.

Familial endometrial cancer syndrome was diagnosed in 2 females, aged 54 and 36 years. They had no history of malignant tumours themselves.

Suspected familial endometrial cancer syndrome, variety 1, was diagnosed in all age groups. Endometrial cancer was diagnosed in three persons at the age 53, 65 and 56 years. The tumour was treated 9, 18 and 5 years ago, respectively. In addition, breast cancer has been diagnosed in another proband 10 years ago, at the age of 37 years.

Suspected familial endometrial cancer syndrome, variety 2, was diagnosed in all age groups (Figure 40). One proband had had endometrial cancer herself, occurring at the age 42 years. The tumour has been treated 14 years ago. In addition, another proband had had gastric cancer at the age 71 year, 7 years ago.

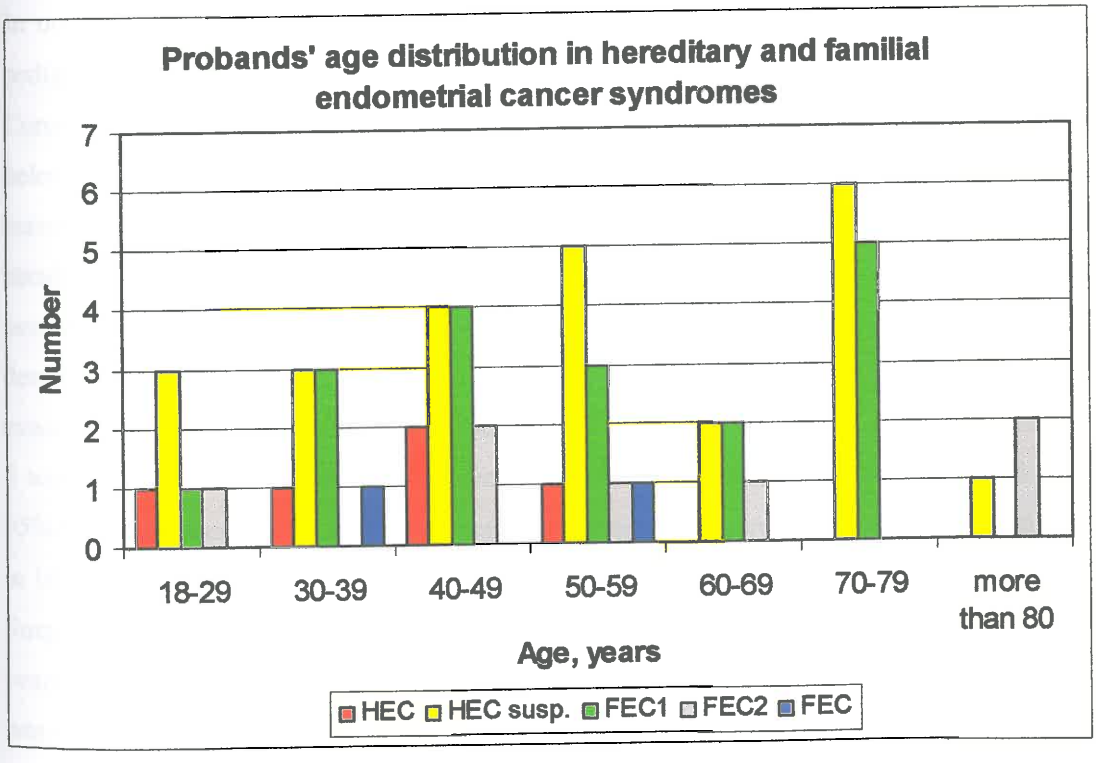


Figure 40. The age distribution of probands having definitive and suspected hereditary endometrial cancer syndrome.

Abbreviations in figure: HEC, hereditary endometrial cancer syndrome; HEC susp., suspected hereditary endometrial cancer syndrome; FEC1, suspected familial endometrial cancer syndrome, variety 1; FEC2, suspected familial endometrial cancer syndrome, variety 2; FEC, familial endometrial cancer syndrome.

The age distribution of probands having definitive or suspected hereditary endometrial cancer syndromes is presented in Figure 40 (see also Annex 9) and the oncological health status of probands is shown in Table 16.

Table 16. Oncological health status in probands with hereditary endometrial cancer syndromes.

	HEC	HEC susp.	FEC	FEC susp.1	FEC susp.2
Malignant tumour present	0 / 5	4 / 24	0 / 2	4 / 18	2 / 7
Endometrial cancer present	0 / 5	4 / 24	0 / 2	3 / 18	1 / 7

Abbreviations in table: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC susp.1, suspected familial endometrial cancer, variety 1; FEC susp.2, suspected familial endometrial cancer, variety 2

In order to characterize the course of endometrial cancer in hereditary endometrial cancer pedigrees, the data about affected persons were retrieved (Annex 10).

Consequentially, the data about the age of endometrial cancer diagnostics in persons belonging to hereditary endometrial cancer pedigrees were available in 16 cases. Definitive hereditary endometrial cancer was diagnosed at the age of 40 – 75 years (mean 52.1 years; standard deviation 9.2 years; 95% CI for the mean, 47.2 – 57.0 years). Among the affected persons, 5 were alive, but 11 died at the age 44 – 76 years (mean 57.7 years; standard deviation 12.0 years; 95% CI for the mean, 49.6 – 65.8 years). In addition, no data about the exact death age were available about 1 person. The survival was calculated for 11 persons, as 5 were alive. The survival was 0 – 34 years (mean 6.1 years; standard deviation 11.6 years; 95% CI for the mean, 0 – 13.9 years). The age of definite tumour manifestation was estimated in 16 cases but did not add information in comparison to the age of tumour diagnostics.

Suspected hereditary endometrial cancer was diagnosed at the age 30 – 81 year (mean 48.5 years; standard deviation 14.1 years; 44.4 – 52.6 years). The exact age of cancer diagnostics was reported in 48 cases. Among the affected persons, 37 died at the age 35 – 87 years (mean 58.7 years, standard deviation 15.2 years; 95% CI for the mean, 53.6 – 63.8 years). The survival was known for 33 persons and it ranged 0 – 44 years (mean 9.7 years; standard deviation 13.0 years; 95% CI for the mean, 5.1 – 14.3 years). The age of definite tumour

manifestation was estimated in 52 cases and was 30 – 82 years (mean 49.2 years; standard deviation 14.4 years; 95% CI for the mean, 45.2 – 53.2 years).

In the combined group of FEC and FEC susp.1, the endometrial cancer was diagnosed at the age 52 – 90 years (mean 66.7 years; standard deviation 9.4 years; 95% CI for the mean, 63.5 – 69.9 years). The exact age of cancer diagnostics was reported in 36 cases. Among the affected persons, 37 died at the age 54 – 91 years (mean 72.4 years, standard deviation 8.9 years; 69.4 – 75.4 years). The survival was known for 23 persons and it ranged 0 – 34 years (mean 4.7 years; standard deviation 8.3 years; 95% CI for the mean, 1.1 – 8.3 years). The age of definite tumour manifestation was estimated in 50 cases and was 52 – 90 years (mean 68.2 years; standard deviation 9.2 years; 95% CI for the mean, 65.6 – 70.8 years).

In FEC susp.2 families the endometrial cancer was diagnosed at the age 26 – 82 years (mean 57.6 years; standard deviation 15.9 years; 95% CI for the mean, 49.9 – 65.3 years). The exact age of cancer diagnostics was reported in 19 cases. Among the affected persons, 17 died at the age 26 – 83 years (mean 63.3 years, standard deviation 16.8 years; 54.7 – 71.9 years). The survival was known for 14 persons and it ranged 0 – 10 years (mean 2.8 years; standard deviation 3.5 years; 95% CI for the mean, 0.8 – 4.8 years). The age of definite tumour manifestation was estimated in 22 cases and was 26 – 82 years (mean 57.8 years; standard deviation 15.9 years; 95% CI for the mean, 50.8 – 64.8 years). The survival of the affected females by hereditary or familial endometrial cancer is presented in Table 17.

Table 17. The survival of the females affected by hereditary or familial endometrial cancer.

Diagnosis	0-1	2-5	6-10	11-15	More than 15	ND	Alive	Total
HEC	7	2	0	0	2	1	5	17
HEC susp.	8	13	5	0	7	8	15	56
FEC and FEC1	14	5	2	1	2	16	14	54
FEC2	10	1	3	0	0	3	5	22
Total	39	21	10	1	11	28	39	149

Abbreviations in table: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer syndrome; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; ND, no data available.

The distribution of survival is depicted in Figure 41. Although the first year lethality was 39 / 149 (26.2%; 95% CI = 19.8 – 33.8%), equally significant number of affected persons (39 / 149) was alive at the time when population screening was carried out. There was a weak trend

towards shorter survival if the tumour developed at older age (Figure 42). Thus, there is no evidence of more deleterious hereditary endometrial cancer course in younger affected patients.

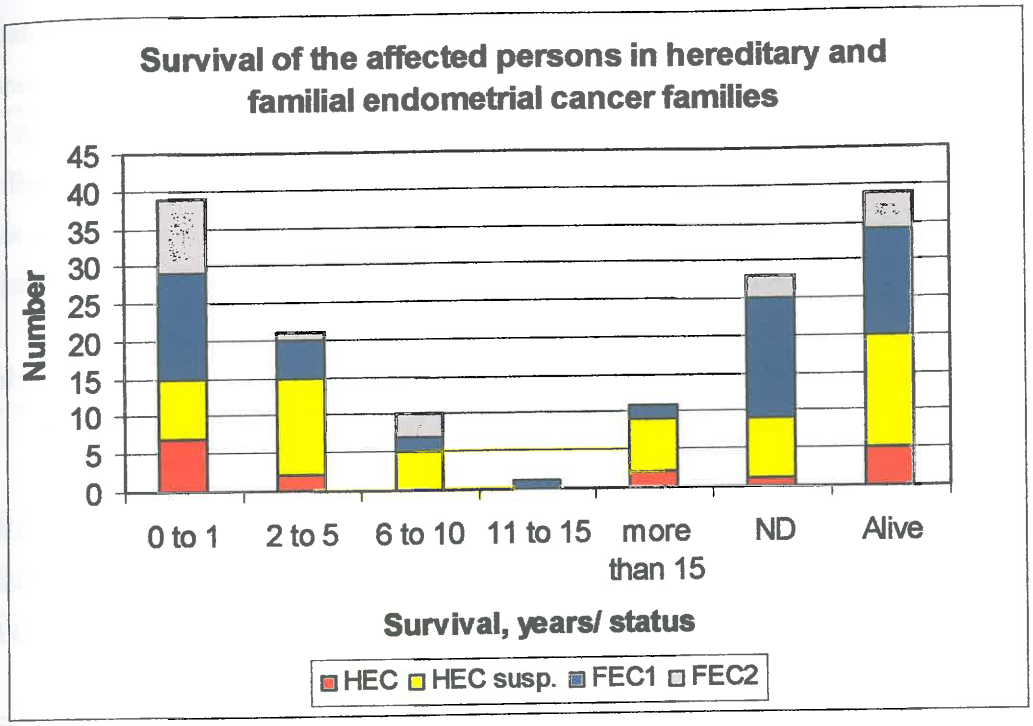


Figure 41. Distribution of survival in females affected by hereditary or suspected hereditary endometrial cancer.

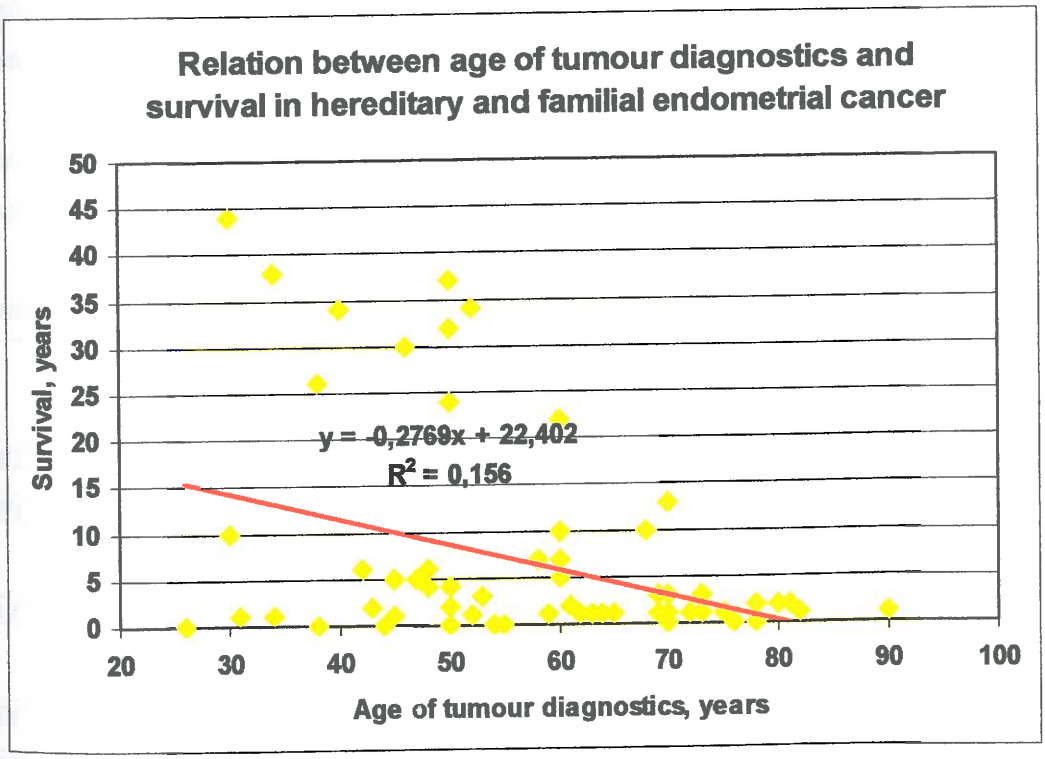


Figure 42. Correlation between the age of definitive or suspected hereditary endometrial cancer diagnostics and the survival.

To estimate the frequency of endometrial cancer development among the females of definitive or suspected hereditary endometrial cancer pedigrees, the number of affected women as well as total number of females in the affected blood line was established for each kindred (Annex 11). The frequency of endometrial cancer in different hereditary endometrial cancer syndromes is reflected in Table 18. There is a trend towards higher tumour frequency in definitive hereditary endometrial cancer in comparison to the other syndromes but the difference does not gain statistical significance. Although number of cancer cases per kindred was not high (2 – 5 cases), the total frequency of endometrial cancer among female blood relatives in the affected lines was as high as 32.2% (95% CI = 28.1 – 36.6%).

Table 18. Endometrial cancer frequency in different hereditary endometrial cancer syndromes

Diagnosis	Number of affected persons/blood relatives	Incidence, %	95% CI, %
HEC	17 / 41	41.5	27.8 – 56.6
HEC susp.	56 / 174	32.2	25.7 – 39.4
FEC and FEC susp. 1	54 / 180	30.0	23.8 – 37.1
FEC susp. 2	22 / 68	32.4	22.4 – 44.2
Total	149 / 463	32.2	28.1 – 36.6

Abbreviations in table: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC susp., suspected familial endometrial cancer; CI, confidence interval.

The different hereditary endometrial cancer syndromes were compared as shown in Tables 19 and 20.

Table 19. The frequency of different hereditary endometrial cancer syndromes

Diagnosis	Number	Relative frequency	95% CI of relative frequency
HEC	5 / 66	7.6%	3.3 – 16.5%
HEC susp.	26 / 66	39.4%	28.5 – 51.5%
FEC and FEC susp.1	26 / 66	39.4%	28.5 – 51.5%
FEC susp. 2	9 / 66	13.6%	7.3 – 23.9%

Abbreviations in table: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC susp. 1, suspected familial

endometrial cancer, variety 1; FEC susp. 2, suspected familial endometrial cancer, variety 2; CI, confidence interval

Table 20. Characteristics of different hereditary endometrial cancer syndromes

Diagnosis	Age of tumour diagnostics, years	Age of death, years	Survival, years
HEC, interval	40–75	44-76	0-34
Mean	52.1	57.7	6.1
SD	SD 9.2	12.0	11.6
HEC susp., interval	30-81	30-87	0-44
Mean	48.5	58.7	9.7
SD	14.1	15.2	13.0
FEC and FEC susp.1, interval	52-90	54-91	0-34
Mean	66.2	72.4	4.7
SD	9.2	8.9	8.3
FEC susp. 2, interval	26-82	26-83	0-10
Mean	57.6	63.3	2.8
SD	15.9	16.8	3.5

Abbreviations in table: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC susp. 1, suspected familial endometrial cancer, variety 1; FEC susp. 2, suspected familial endometrial cancer, variety 2; SD, standard deviation; CI, confidence interval.

Interesting data were obtained about the presence of other, extra-endometrial cancers in the hereditary and familial endometrial cancer pedigrees. Among the 5 families, affected by HEC, only 1 was characterised by the presence of other cancers in the same blood line as the endometrial cancers. Isolated cases of breast cancer, lung cancer and laryngeal cancer were observed.

In the suspected HEC families, 46 extra-endometrial cancers were reported in 16/26 families. There were 13 cases of gastric cancer, 9 cases of brain tumour, 9 cases of breast cancer, 2 cases of renal cancer, 2 cases of lung cancer and single cases of haematological tumour, non-melanoma skin cancer, ovarian cancer. In 4 cases, the location was unknown to the proband, in 3 cases the tumour was described as gynaecological malignancy but in 1 case – as abdominal malignancy. The frequency of gastric cancer in suspected HEC group was 13 / 320 (4.1%; 95% CI = 2.4 – 6.8%), the frequency of brain tumours – 9 / 320 (2.8%; 95% CI = 1.5 – 5.3%). The frequency of breast cancer in females was 9 / 174 (5.2%; 95% CI = 2.7 – 9.5%).

In the combined FEC/FEC1 group, 27 extra-endometrial cancers were reported in 13/26 families comprising 284 blood relatives in the affected lines. There were 6 cases of gastric cancer, 7 cases of urinary bladder cancer, 4 cases of lung cancer, 4 cases of breast cancer and single cases of prostate, ovarian and colorectal cancer. In 1 case, the location of tumours was ascribed to the abdomen but in 2 cases the location of malignant tumour was unknown to the proband.

In FEC2 group, extra-endometrial cancers were present in all families. There were 12 cases of gastric cancer, 3 cases of pancreatic cancer, 2 cases of breast cancer, 2 cases of prostate cancer and single cases of lung cancer, colorectal cancer and haematological malignancy. Liver was affected in 3 cases. The frequency of gastric cancer was 12 / 110 (10.9%; 95% CI = 6.3 – 18.1%).

Familial lung cancer syndromes

During the population screening, the first pedigrees with familial lung cancer (Figure 43) in Latvia were identified. Several of these families demonstrated high number of the relevant tumours, as will be shown further.

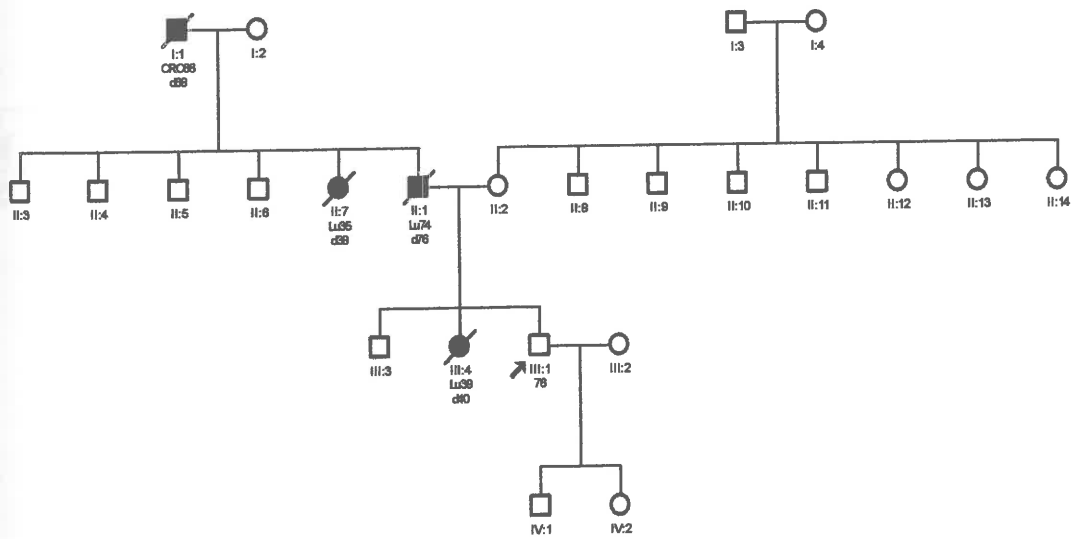


Figure 43. Pedigree of a family affected by familial lung cancer.
Abbreviations in the figure: CRC, colorectal cancer; Lu, lung cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Familial lung cancer syndrome (Figures 43 – 45) was diagnosed in 13 probands. Among them, there was oncologically healthy 44-year-old female, whose grandfather from paternal side as well as 3 brothers of father had had lung cancer. Another proband was 49-year-old

female, whose kindred demonstrated 5 cases of lung cancer. Hereditary lung cancer syndrome was diagnosed also in 55-year-old male who's father and 3 brothers of the father had had lung cancer. Seventy six-year-old male had a history of lung cancer in his sister as well as in father and father's sister (Figure 43). Fifty two-year-old male presented family history of lung cancer in his mother, her father and brother; three other malignant tumours also were present in the kindred. Sixty three-year-old male had a history of lung cancer in 2 brothers and father of his mother. Forty four-year-old male presented lung cancer history in his father as well as in 2 brothers of his father.

Several young people were diagnosed with familial lung cancer syndrome as well. Nineteen-year-old proband, 26 and 21-year-old males had identical histories of lung cancer in father, sister and brother of the maternal grandfather. Familial lung cancer syndrome was diagnosed also in 20-year-old female, whose father and two his brothers had developed lung cancer. Forty three-year-old male had similar family cancer history. Thirty-year-old male had a history of lung cancer in his paternal grandfather, his sister and father as well as 2 other cancer cases among blood relatives.

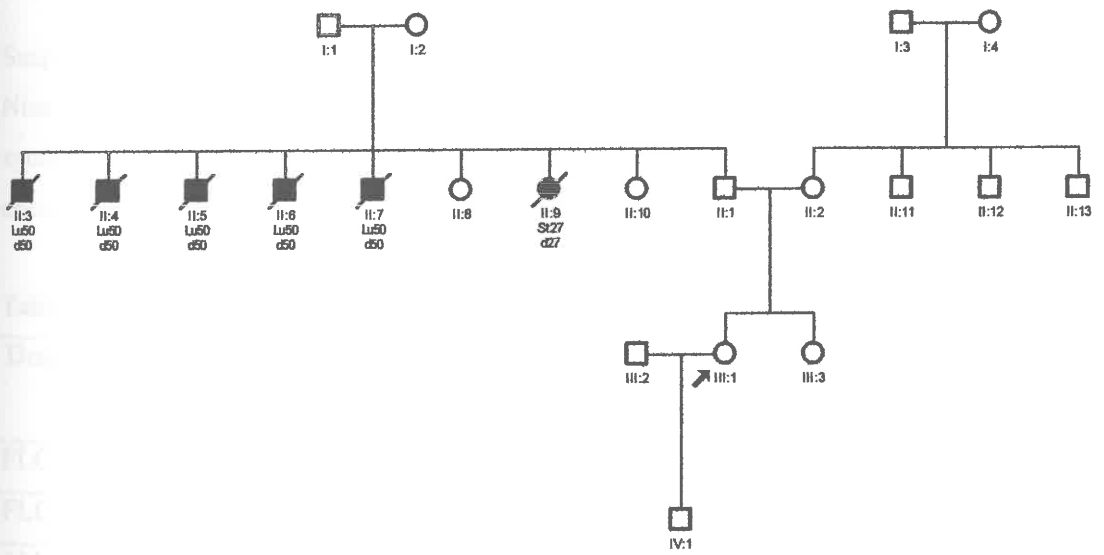


Figure 44. Familial lung cancer presenting as multiple cases of lung cancer in a single generation. Abbreviations in the figure: Lu, lung cancer; St, gastric cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

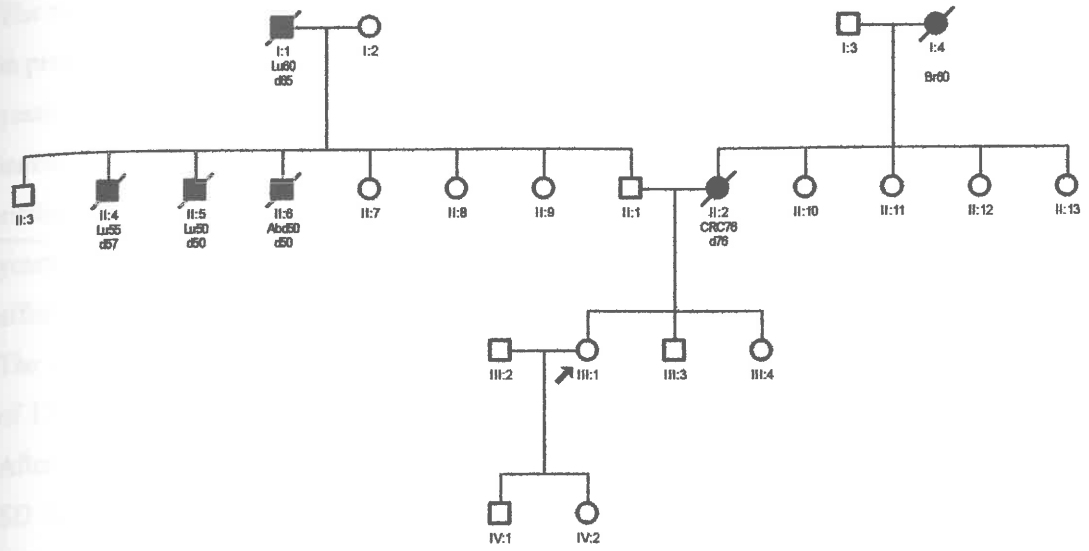


Figure 45. Familial lung cancer affecting 2 generations. Abbreviations in the figure: Lu, lung cancer; Abd, cancer in the abdominal cavity, not further specified; CRC, colorectal cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Suspected familial lung cancer syndrome was diagnosed in 93 probands.

Nine of the probands diagnosed with FLC syndrome and 57 probands with suspected FLC syndrome were younger than 50 years (see Table 21). In all cases, the probands were oncologically healthy themselves.

Table 21. Age distribution of probands with familial lung cancer syndrome

Diagnosis	Total number	Age, years						
		18-29	30-39	40-49	50-59	60-69	70-79	≥ 80
FLC	13	4	1	4	2	1	1	0
FLC susp.	93	15	18	24	13	13	5	5

Abbreviations in table: FLC, familial lung cancer; FLC susp., suspected familial lung cancer, ≥, greater than or equal to.

In order to characterise the familial lung cancer syndrome, the data about tumour-affected persons within these families were analysed (Annex 12). The 106 probands reported 232 persons, affected by lung cancer. Among these, there were 48 females (20.7%; 95% CI = 16.0 – 26.4%) and 184 males (79.3%; 95% CI = 73.6 – 84.0%).

After re-evaluation, 208 affected persons were recognised. Among them, there were 41 female (19.7%; 95% CI = 14.9 – 25.6%) and 167 males (80.3%; 95% CI = 74.4 – 85.1%).

The time of lung cancer diagnosis as well as survival was following. In general, lung cancer in persons belonging to the familial lung cancer pedigrees was diagnosed at the age of 18 – 90 years, mean 57.6 years (SD, 12.1 years; 95% CI for the mean 55.7 – 59.5 years). This analysis included 163 persons whose exact age of diagnosis was reported by the proband. The re-evaluated mean age of lung cancer diagnosis was 57.9 years (interval 18 – 90 years, SD 12.3 years; 95% CI for the mean 55.9 – 59.9 years), based on the analysis of data about 148 affected persons from 95 pedigrees.

The 213 affected persons whose exact death age was reported by the proband died at the age of 13 – 90 years (mean 59.7 years, SD 12.2 years, 95% CI for the mean 58.1 – 61.3 years). After re-evaluation, the mean death age was estimated as 60.3 years (interval, 13 – 90 years; SD 12.3 years; 95% CI for the mean 58.5 – 62.1 years), based on the analysis of data about 191 affected persons.

Using re-evaluated data, the age of definite manifestation of the tumour was also evaluated including data about the age of diagnostics if available or death age. This parameter was available for analysis in 196 cases. The mean age of the definite manifestation of the tumour varied widely from 13 to 90 years (mean 58.8 years, SD 12.8 years, 95% CI for the mean 57.0 – 60.6 years).

Survival data were available about 159 affected persons, as several probands did not know the length of the disease in their older relatives. Thus, the average survival after the establishment of lung cancer diagnosis was 1.9 years (SD 5.3 years; 95% CI for the mean 1.1 – 2.7 years; interval, 0 – 59 years). After re-evaluation, the mean survival was estimated 2.0 years (interval 0 – 59 years; SD 5.5 years; 95% CI for the mean 1.1 – 2.9 years), based on the analysis of data about 144 affected persons from 95 families.

In FLC pedigrees, the mean age of lung cancer diagnostics was 56.0 years (SD 8.4 years; 95% CI for the mean 53.0 – 59.0 years; interval, 35 – 78 years); the mean age of tumour manifestation was 56.4 years (SD 9.5 years; 95% CI for the mean 53.4 – 59.4 years; interval, 35 – 79 years). The death of the affected persons occurred at the mean age of 57.1 years (SD 9.5 years; 95% CI for the mean 54.1 – 60.1 years; interval, 36 – 79 years). The survival was 0.9 years (SD 1.5 years; 95% CI for the mean 0.4 – 1.4 years; interval, 0 – 5 years). In FLC susp. pedigrees, the mean age of lung cancer diagnostics was 58.5 years (SD 13.2 years; 95% CI for the mean 56.1 – 60.9 years; interval, 18 – 90 years); the mean age of tumour manifestation was 59.5 years (SD 13.4 years; 95% CI for the mean 57.4 – 61.6 years; interval, 13 – 90 years). The death of the affected persons occurred at the mean age of 61.2 years (SD 12.9 years; 95% CI for the mean 59.1 – 63.3 years; interval, 13 – 90 years). The mean survival was 2.4 years (SD 6.2 years; 95% CI for the mean 1.2 – 3.6 years; interval, 0 – 59 years).

As shown in Figure 46, a large segment of the affected persons dies within the first year after diagnosis. The first year lethality constitutes 90/147, 61.2%; 95% CI = 53.2 – 68.7%

considering the persons about whom full data set is available. Alternatively, the data provides an evidence that at least 90/208; 43.3%, 95% CI = 36.7 – 50.1% of the persons affected by hereditary lung cancer die within first year after diagnosis. Only 3 of the affected persons were alive at the time of population screening.

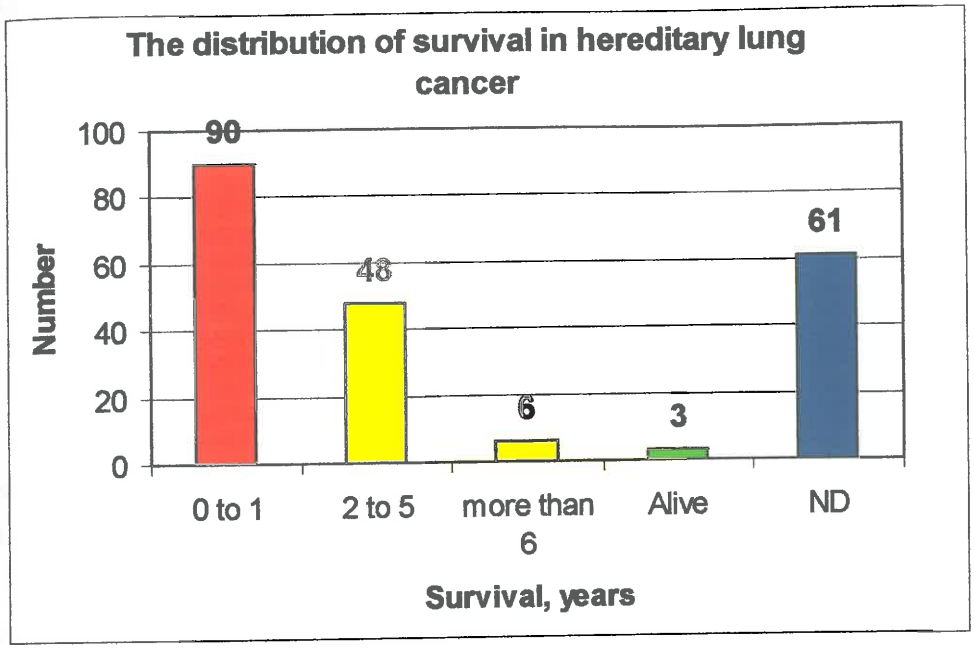


Figure 46. Survival of lung cancer patients in familial lung cancer families. Abbreviation in figure: ND, no data available

The age of lung cancer diagnostics (Figure 47) as well as the survival after the establishment of diagnosis shows differences between the kindreds. Several kindreds were selected for demonstration of these differences. Thus, kindred SNV-1366 is characterised by trend towards later cancer development. The kindreds IN-092 and IV-869 demonstrate clustering of the youngest patients. Interval of disease onset at 50-60 years is characteristic for kindreds LEZ-655 and SJ-172. Both kindreds SNV-1366 and OR-323 are characterised by very dense age clustering of the cases (by the age of tumour diagnostics) and very short survival. Variability of the underlying genetic changes could be suspected on the basis of these data.

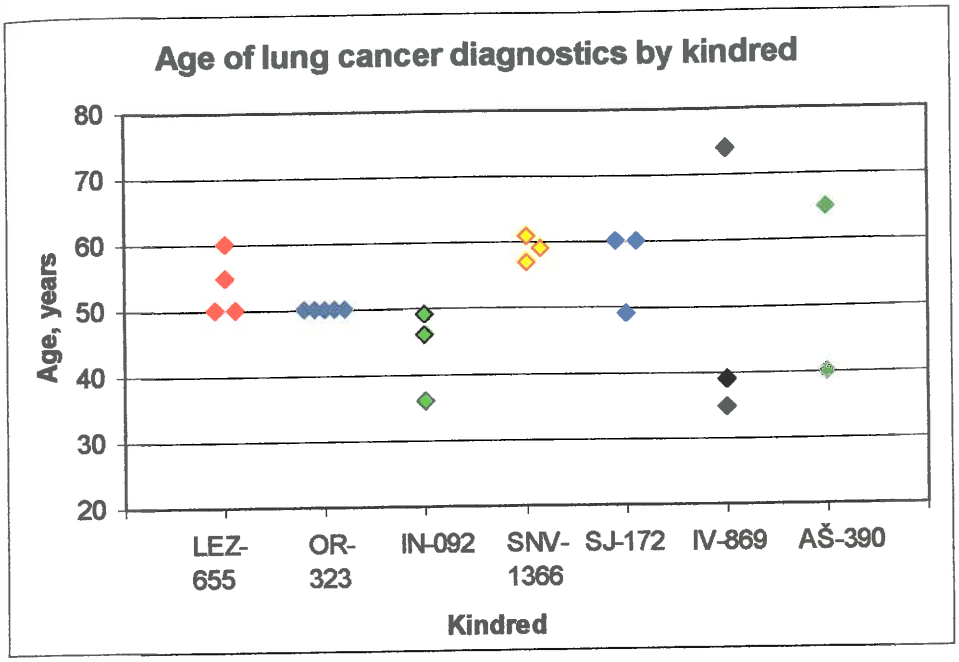


Figure 47. Age of lung cancer diagnostics in the affected persons from definitive and suspected familial lung cancer kindreds.

The number of affected persons in their blood relatives was determined for each kindred (Annex 13). In summary, 230 / 1249 persons in those blood lines that were diagnosed as familial lung cancer had developed the malignancy, corresponding to the frequency of 18.4% (95% CI = 16.4 – 20.7%). The rate of lung cancer was 43 / 169 (25.4%; CI = 19.5 – 32.5%) in definitive FLC kindreds and 187 / 1080 (17.3%; 95% CI = 15.2 – 19.7%) in suspected FLC kindreds. After re-evaluation of the relationships between kindreds, the risk of lung cancer was 40 / 157 (25.5%; 95% CI = 19.3 – 32.8%) in FLC kindreds and 168 / 977 (17.2%; 95% CI = 15.0 – 19.7%) in FLC susp. kindreds.

Further analysis disclosed that the rate of lung cancer was 78 / 505 (15.4%; 95% CI = 12.6 – 18.9%) in those FLC susp.kindreds that were affected by lung cancer in one generation but 109 / 575 (19%; 95% CI = 16.0 – 22.4%) in those FLC susp.kindreds that were affected by lung cancer in two generations. After reevaluation of the relationships between kindreds, the risk of lung cancer was 18 / 63 (28.6%; 95% CI = 18.9 – 40.7%) in FLC kindreds affected in single generation; 22 / 94 (23.4%; 95% CI = 16.0 – 32.9%) in FLC kindreds affected in two generations; 68 / 441 (15.4%; 95% CI = 12.3 – 19.1%) in FLC susp. kindreds affected in single generation and 100 / 536 (18.7%; 95% CI = 15.6 – 22.2%) in FLC susp. kindreds affected in two generations.

If the kindreds were grouped into early-onset and late-onset groups by occurrence or absence of at least 1 cancer case at or before the age of 50 years, the following data were obtained. Among reevaluated affected persons, the rate of lung cancer was 22 / 80 (27.5%; 95% CI = 18.9 – 38.1%) in FLC kindreds having early-onset cases and 18 / 77 (23.4%; 95% CI = 15.3 –

34.0%) in FLC kindreds having only late-onset cases. The rate of lung cancer was 70 / 395 (17.7%; 95% CI = 14.3 – 21.8%) in early-onset FLC susp. and 98 /582 (16.8%; 95% CI = 14.0 – 20.1%) in late-onset FLC kindreds.

Among the early onset FLC kindreds, 4 kindreds were affected in 1 generation and 2 – in 2 generations. Among the late onset FLC kindreds, 1 kindred was affected in 1 generation and 5 - in 2 generations. Analysing the early-onset FLC susp. kindreds, 14 were affected in a single generations but 20 in 2 generations. Similarly, among late-onset FLC susp. kindreds, there were 20 kindreds affected in a single generation and 39 – in 2 generations.

Within the FLC group, the frequency of lung cancer was 15 / 48 (31.3%; 95% CI = 19.9 – 45.3%) in early-onset, single-generation kindreds; 7 / 32 (21.9%; 95% CI = 11.0 – 38.8%) in early-onset, two-generation kindreds; 3 / 15 (20.0%; 95% CI = 7.0 – 45.2%) in late-onset, single-generation kindreds and 15 / 62 (24.2%; 95% CI = 15.2 – 36.2%) in late-onset, two-generation kindreds.

Within the FLC susp. group, the frequency of lung cancer was 28 /181 (15.5%; 95% CI = 10.9 – 21.4%) in early-onset, single-generation kindreds; 42 / 214 (19.6%; 95% CI = 14.9 – 25.5%) in early-onset, two-generation kindreds; 40 / 260 (15.4%; 95% CI = 11.5 – 20.3%) in late-onset, single-generation kindreds and 58 / 322 (18.0%; 95% CI = 14.2 – 22.6%) in late-onset, two-generation kindreds.

In early-onset, two-generation FLC kindreds the frequency of lung cancer was 7 / 32 (21.9%; 95% CI = 11.0 – 38.8%). Combining the early-onset, single-generation FLC kindreds with early-onset, single-generation FLC susp. kindreds and early-onset, two-generation FLC susp. kindreds, the frequency of lung cancer was 85 / 443 (19.2%; 95% CI = 15.8 – 23.1%).

Association between familial lung cancer and occurence of other malignancies was also studied (Annex 14). In general, no other tumours were found in 54 pedigrees. Among the other kindreds, 11 cases of endometrial cancer, 10 cases of breast cancer, 8 cases of colorectal cancer, 8 cases of haematologic malignancies, 6 cases of stomach cancer, 1 case of duodenal malignancy, 4 cases of ovarian cancer, 3 cases of pancreatic cancer, 2 cases of renal cancer, 2 cases of head and neck cancer were observed among 537 blood relatives of these families or 1134 persons in the whole re-evaluated group. In 5 persons, bones were affected, invariably – spine. Liver was affected in 3 cases, brain – in 1 case. In 4 cases the location of cancer was unknown for the proband, in 1 case the malignancy was described as malignant gynaecological tumour.

The following evidence of genetic anticipation was found. Forty six pedigrees affected in 2 generations and characterised by exact data about tumour manifestation in both generations were identified. The mean age of tumour manifestation in the oldest generation (49 affected persons) was 64.3 years (interval, 35 – 90 years; standard deviation 11.9 years; 95% CI for

the mean 60.9 – 67.7 years). The mean age of tumour manifestation in the youngest generation (53 affected persons) was 55.7 years (interval, 13 – 79 years; standard deviation 12.8 years; 95% CI for the mean 52.2 – 59.2 years). Thus, the age of affected person differs by generation. However, the difference showed wide interval: from -18 to 40 years, mean 11.2, standard deviation 13.4.

Low frequency of spouse correlation was found. Full data set was available about 218 spouse couples. In 81 of these families, 1 of the married persons was affected by lung cancer but only in 2 cases (2/81; 2.5%; 95% CI = 0.7 – 8.6%) the spouse of the affected person also had lung cancer.

The age of tumour manifestation correlated between different relatives from the same kindred (Figure 48).

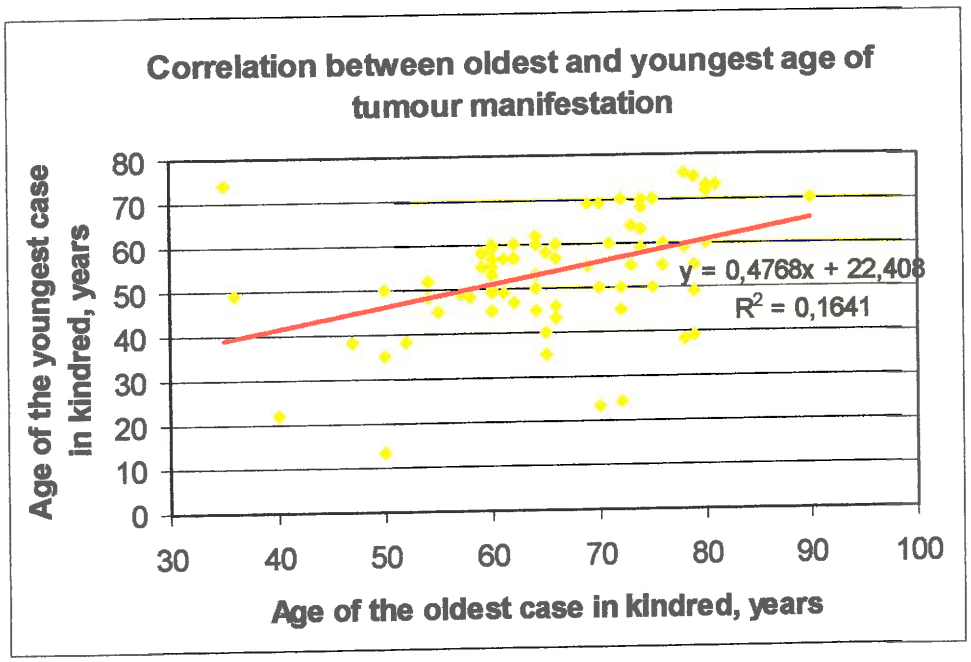


Figure 48. Correlation between the age of tumour manifestation in the oldest and youngest affected person in a kindred.

Hereditary and familial stomach cancer

Hereditary stomach cancer syndrome (Figure 49) was observed in 21 cases. This is the first documented evidence of hereditary stomach cancer in Latvia. In addition, 74 kindreds of suspected hereditary stomach cancer were diagnosed. The age distribution of these probands is reflected in Table 22.

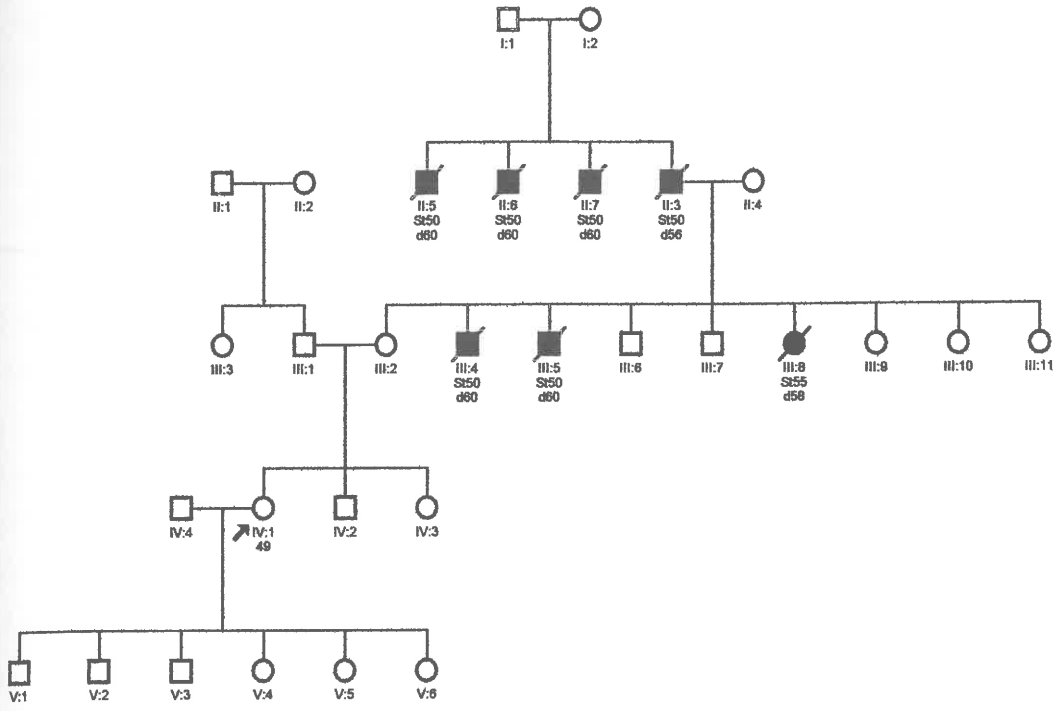


Figure 49. Hereditary stomach cancer manifesting itself in multiple affected persons in 2 generations.

Abbreviations in the figure: St, gastric cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Table 22. Age distribution of probands affected by hereditary stomach cancer syndrome

Diagnosis	Analysable number	18-29	30-39	40-49	50-59	60-69	70-79	More than 80
HSC	21	0	0	7	2	6	5	1
HSC susp.	74	3	7	19	13	13	16	3

Abbreviations in table: HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer.

The age distribution of probands diagnosed with definitive and suspected hereditary and familial gastric cancer syndrome, shows plateau in the middle age group (Figure 50).

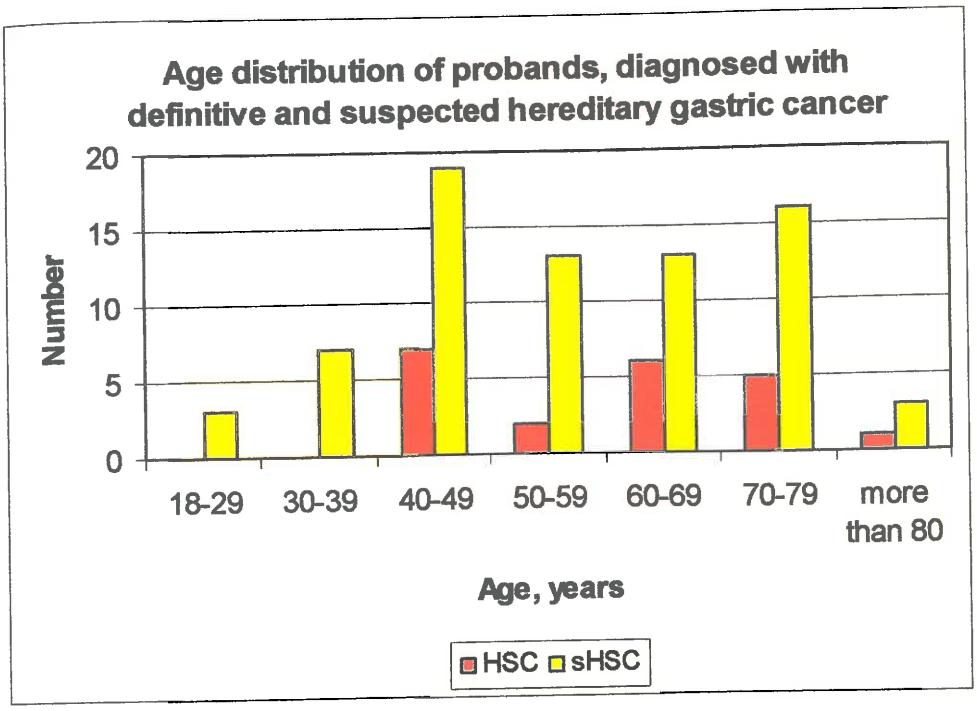


Figure 50. The age distribution of probands diagnosed with definitive and suspected hereditary stomach cancer syndrome. Abbreviations in the Figure 50: HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer syndrome.

The probands mostly were oncologically healthy themselves. Gastric cancer was diagnosed in 1 proband – a 74 years old female. However, another proband, a 58 years old female, had a history of breast cancer at the age of 41. It has to be noted that breast cancer does not belong to the diagnostic criteria of hereditary stomach cancer syndrome.

Among the 74 cases of suspected hereditary stomach cancer syndrome, 6 probands were affected by cancer in different locations. However, no cases of gastric cancer were observed. Endometrial cancer was diagnosed in 2 probands at the age of 53 and 63 years, respectively. Thirty nine-year-old male had history of urinary bladder cancer at the age of 33 years. Seventy nine-year-old female had had ovarian cancer at the age of 77 years. Prostate cancer was revealed in 74-year-old male. Another male was diagnosed with colorectal cancer at the age of 75 years during the follow up.

In order to characterize the course of the definitive and suspected hereditary stomach cancer in Valka population, the data about affected persons were retrieved. There were 225 affected persons in 95 pedigrees (Annex 15). Among the patients, there were 126 (57.5%; 95% CI = 50.9 – 63.9%) males and 93 (42.5%; 95% CI = 36.1 – 49.1%) females. The stomach cancer was diagnosed at the age 30 – 95 years with the mean 60.9 years (SD, 11.8; 95% CI for the mean 58.9 – 62.9 years). The death of the patient had ensured at the age of 30 – 96 years

(mean, 63.0 years; SD, 12.3; 95% CI for the mean 61.2 – 64.8 years). The survival after the diagnosis was highly variable, ranging from less than 1 year to 20 years, mean 2.5 years (SD, 3.7; 95% CI for the mean 1.9 – 3.1 years). The exact age of diagnosis and death was reported by proband in 138 and 187 cases, respectively. Twelve affected persons (5.4%; 95% CI = 3.1 – 9.2%) were alive at the time the population screening was carried out. It was possible to calculate the exact survival in 129 cases. The age of definite tumour manifestation was 30 – 95 years (mean, 61.3; SD 12.0; 95% CI for the mean 59.6 – 63.0 years). It was possible to determine this parameter in 196 cases.

In hereditary stomach cancer families, the mean age of tumour diagnostics, reported exactly for 39 persons, was 56.9 years (interval, 30 – 83 years; SD 10.7; 95% CI for the mean 53.4 – 60.3 years). The death of those affected patients who died of the gastric cancer occurred at the mean age of 58.3 years (interval, 30 – 90 years; SD, 12.2; 95% CI for the mean 55.3 – 61.3 years). The death age was reported by the probands exactly for 66 patients. The mean survival, calculated for 35 patients, was 2.6 years (interval, 0 – 20; SD 4.1; 95% CI for the mean 1.2 – 4.0 years). The mean age of tumour manifestation, established in 70 cases, was 57.4 years (interval, 30 – 83 years; SD 11.7; 95% CI for the mean 54.6 – 60.2 years). There were 26 females and 45 males among the affected persons.

Analysing suspected hereditary stomach cancer kindreds, the mean age of tumour diagnostics, reported exactly in 99 cases, was 62.5 years (interval, 34 – 95 years; SD 11.8; 95% CI for the mean 60.1 – 64.8 years). The death of the affected patients occurred at the mean age of 65.6 years (interval, 37 – 96 years; SD, 11.6; 95% CI for the mean 63.4 – 67.6 years). The death age was known exactly in 121 cases. The mean survival, calculated for 94 cases, was 2.4 years (interval, 0 – 20 years; SD 3.5; 95% CI for the mean 1.7 – 3.1 years). The mean age of definite tumour manifestation was 63.4 years (interval, 34 – 95 years; SD 11.6 years; 95% CI for the mean 61.3 – 65.5 years). It was possible to evaluate this parameter in 124 cases. There were 67 females and 81 male among the affected persons.

In order to determine the tumour frequency in the affected blood lines, number of the relevant cancer cases and relatives were determined for each kindred (Annex 16). In general, there were 225 cases of stomach cancer among 1235 persons corresponding to the frequency 18.2% (95% CI = 16.2 – 20.5%). In hereditary stomach cancer kindreds the stomach cancer frequency was 76 / 302 (25.2%; 95% CI = 20.6 – 30.4%) but in suspected hereditary stomach cancer kindreds – 149 / 933 (16.0%; 95% CI = 13.8 – 18.5%).

Among hereditary stomach cancer pedigrees, there were no other cancer cases in 8 / 21 families. The cancer frequency in this subgroup was 29 / 106 (27.4%; 95% CI = 19.8 –

36.5%). In the remaining HSC families, the following cancers were reported: 9 endometrial cancer cases, 4 lung cancer cases, 3 breast cancer cases, 3 colorectal cancer cases and single cases of unspecified gynaecological, pancreatic, laryngeal and urinary bladder cancer as well as a single case of a haematologic malignant tumour. In isolated cases, the malignant tumour was found in the brain or liver (Annex 17).

Among suspected hereditary stomach cancer pedigrees, no other cancer cases were present in 23 / 74 families. The cancer frequency in this subgroup was 46 / 244 (18.9%; 95% CI = 14.4 – 24.2%). In the remaining HSC families, the following cancers were reported: 12 endometrial and 2 cervical cancer cases, 11 lung cancer cases, 7 colorectal cancer cases, 6 breast cancer cases, 6 cases of renal cancer, 5 cases of urinary bladder cancer, 3 ovarian cancer cases, 3 cases of unspecified gynaecologic cancer, 3 cases of pancreatic cancer, 2 cases of prostatic cancer, 2 cases of head and neck cancer and single cases of oesophageal and thyroid cancer. There were 8 cases of brain tumour and 4 cases of haematologic malignancy. In 6 cases, the malignant tumour was found in the liver, but in 5 cases – in the abdominal cavity. In 9 cases, the location of cancer in the affected person was not known to the proband. Combining all families affected by stomach cancer only vs. other families, the rate of stomach cancer was 75 / 350 (21.4%; 95% CI = 17.5 – 26.0%) vs. 150 / 885 (16.9%; 95% CI = 14.6 – 19.6%).

The spouse correlation was also analysed. Full data set, describing the presence and exact location of malignant tumours in both persons was obtained about 191 spouse couples belonging to the definitive and suspected HSC kindreds. Among these couples, at least 1 case of gastric cancer was present in 83 families but there were only 3 cases of gastric cancer in both spouses (Figure 51). Thus, spouse correlation for gastric cancer was low: 3.6%, 95% CI = 1.2 – 10.1%.

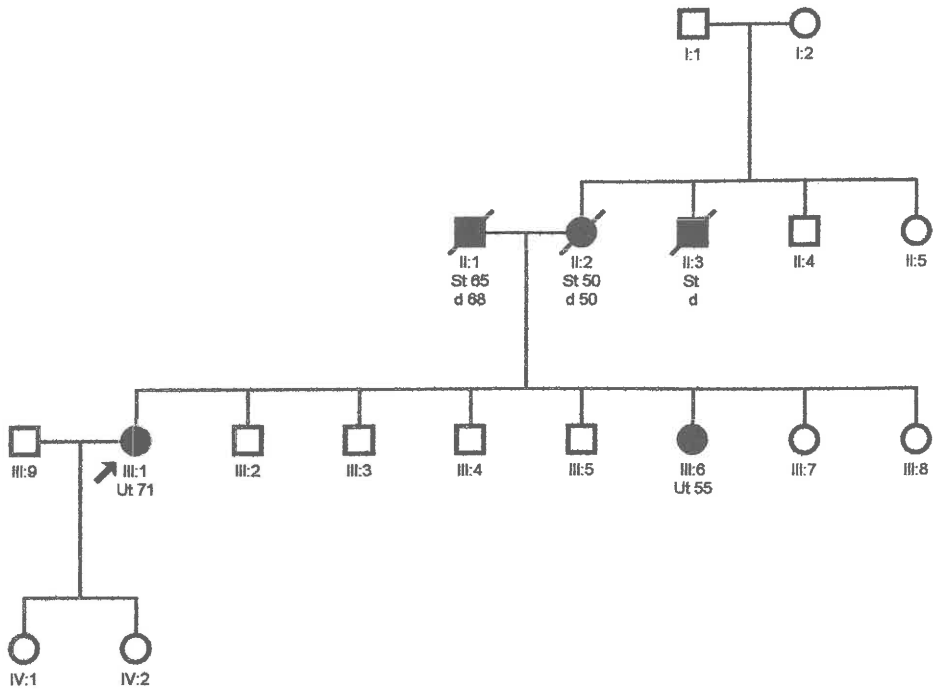


Figure 51. A rare case of spouse correlation in a suspected hereditary stomach cancer pedigree (OR-118). There are 2 cases of gastric cancer (II:2 and II:4) among the blood relatives. The third case (II:1) represents spouse correlation and cannot be attributed to the genetic background. Abbreviations in the figure: St, gastric cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Hereditary prostate cancer

Hereditary prostate cancer syndromes were diagnosed in 22 probands. One of them, 74-year-old male, had hereditary prostate cancer as prostate cancer was diagnosed in the proband himself, his brother and father's brother thus fulfilling the criterion of prostate cancer in three blood relatives at any age. It must be noted that this kindred (Figure 52) has one of the largest number of male relatives among all kindreds (see Table 22) considered in relation to hereditary prostate cancer. Thus, an additional evidence of the kindred size importance is obtained.

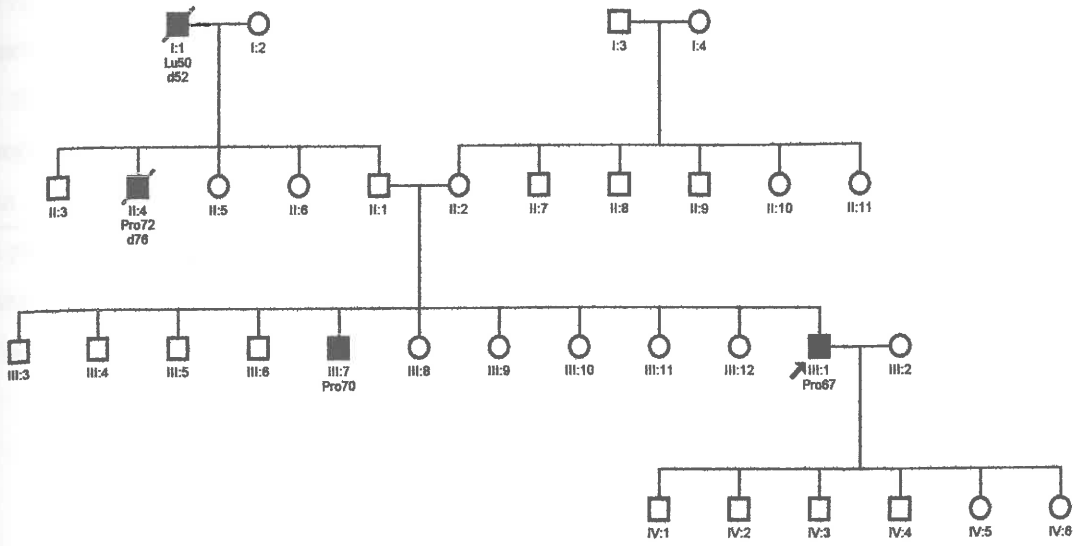


Figure 52. Pedigree of a family affected by hereditary prostate cancer (EF319).
Abbreviations in the figure: Lu, lung cancer; Pro, prostate cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

In 21 persons, suspected hereditary prostate cancer syndrome was diagnosed. The age distribution of these probands is reflected in the Table 23.

Table 23. Age distribution of probands with hereditary prostate cancer syndromes

Diagnosis	Analysable number	18-29	30-39	40-49	50-59	60-69	70-79	≥ 80
HPC	1	0	0	0	0	0	1	0
HPC susp.	21	1	5	5	5	3	2	0

Abbreviations in table: HPC, hereditary prostate cancer; HPC susp., suspected hereditary prostate cancer; ≥, more than or equal to.

Prostate cancer was present in the proband having diagnosis of definitive hereditary prostate cancer as well as in 4 probands having diagnosis of suspected hereditary prostate cancer.

In order to characterize the tumour course, the data about all affected persons were retrieved (Annex 18). The age of prostate cancer diagnosis, reported exactly for 28 persons, was 35 – 75 years (mean 57.7 years; SD 11.3 years; 95% CI for the mean 53.3 – 62.1 years). Among the affected persons, a significant group (14/34) was alive (Figure 53). Survival data were not available about 6 persons. The other 14 affected persons died 0 – 24 years after diagnosis (mean, 4.5 years; SD 6.9 years; 95% CI for the mean 0.5 – 8.5 years). The death occurred at

the age 37 – 80 years (mean, 60.7; SD 11.8 years; 95% CI for the mean 55.0 – 66.4 years). Exact age of death was reported in 19 cases.

As the data about the age of diagnosis and age of death were incomplete but mutually complementary, the age of definite tumour manifestation was determined on the basis of these data. This parameter was defined as age of tumour diagnostics if available, or age at which the patient died of tumour if the age of diagnostics was not known. The age of definite tumour manifestation was determined in 33 cases. It was 35 – 75 years (mean, 57.4 years; SD, 10.9; 95% CI for the mean 53.5 – 61.3 years).

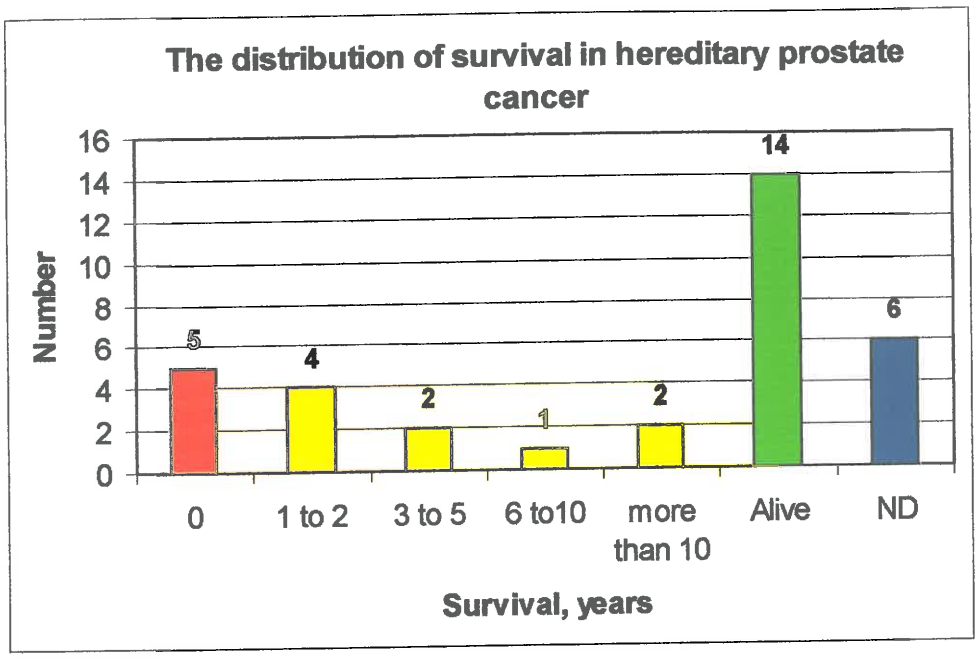


Figure 53. The distribution of survival in hereditary prostate cancer. Abbreviation in the figure: ND, no data available.

The number of affected persons and male blood relatives in the affected line of each kindred was determined (Annex 19). In general, prostate cancer has been diagnosed in 37/167 (22.2%, 95% CI = 16.5 – 29.0%) persons. Among them, there were 3/14 (21.4%; 95% CI = 7.6 – 47.6%) affected males in the HPC kindred and 34/153 (22.2%; 95% CI = 16.4 – 29.4%) males in HPC susp. kindreds.

Data about other cancers in HPC kindreds were retrieved (Annex 20). There was a single case of lung cancer in the HPC kindred. No other cancers were present in 12 HPC susp. pedigrees, but 9 families reported presence of other malignant tumours. Among these, there were 8 cases of endometrial cancer and 4 cases of ovarian cancer. Single cases of colorectal, gastric, pancreatic, lung cancers as well as a haematologic neoplasm were reported. In 2 persons, malignant tumour of small intestine was present. Brain was affected by tumour in 2 persons.

Other syndromes: familial clustering of urinary bladder, familial pancreatic cancer, familial haematologic malignancies, familial brain tumours

Familial clustering of urinary bladder cancer

In the result of population screening, 11 persons were diagnosed with familial bladder cancer syndrome. Among them, there were 2 probands with the diagnosis of definitive familial bladder cancer syndrome and 9 probands with the diagnosis of suspected hereditary urinary bladder cancer syndrome. In the families, affected by definitive familial bladder cancer, 3 cases of index cancer were reported among first-degree relatives while there were 2 cases of urinary bladder cancer in the families affected by suspected urinary bladder cancer. In all cases, 2 generations were affected (Figure 54).

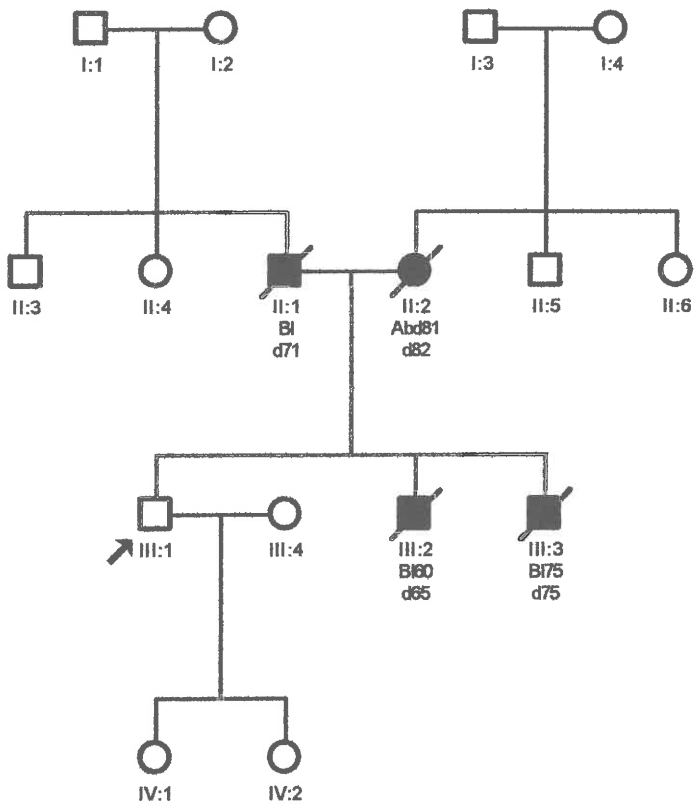


Figure 54. Pedigree of a family affected by familial cancer of urinary bladder.
Abbreviations in the figure: Bl, urinary bladder cancer; Abd, malignant tumour in the abdominal cavity, not further specified; d, dead. The age of cancer diagnostics is shown by number following the diagnosis whenever reported, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

In total, 24 cases of urinary bladder cancer were reported among 123 blood relatives belonging to these kindreds corresponding to the frequency of bladder cancer of 24/123 (19.5%; 95% CI = 72.1 – 79.7%). After re-evaluation of the relationships between the kindreds and exclusion of those affected and healthy persons that were related to several

probands, the frequency of urinary bladder cancer was estimated as 18 / 79 (22.8%; 95% CI = 14.9 – 33.2%).

The exact age of tumour diagnostics was reported by the probands in 22 cases (Annex 21). It was 60 – 87 years (mean 71.8 years; SD, 7.3 years; 95% CI for the mean 68.6 – 75.0 years). The death age was known to the probands in 19 cases. The death of the affected persons occurred at the age of 65 – 92 years (mean 75.9 years; SD, 7.9 years; 95% CI for the mean 72.1 – 79.7 years). Five of the reported patients were alive at the time of population screening. The survival, reported for 17 persons, was 0 – 19 years (mean 4.1 years; SD, 4.6 years; 95% CI for the mean 1.7 – 6.5 years). The age of definitive tumour manifestation, estimated in 24 cases, was 60 – 87 years (mean 71.7 years; SD, 7.0 years; 95% CI for the mean 68.7 – 74.7 years). There were 6 / 24 (25%; 95% CI = 12.0 – 44.9%) females and 18 / 24 (75%; 95% CI = 55.1 – 88.0%) males reported as affected by bladder cancer.

After the re-evaluation of the kindreds, these data changed slightly. The exact age of tumour diagnostics was known in 16 cases. It was 60 – 87 years (mean, 70.7 years; SD, 7.5 years; 95% CI for the mean 66.7 – 74.7 years). The death age, known in 15 cases, was 65 – 92 years (mean, 75.7 years; SD, 7.4 years; 95% CI for the mean 71.6 – 79.8 years). Three of the affected persons were alive at the time of population screening. The survival, known for 13 persons, was 0 – 19 years (mean, 4.8 years; SD, 4.9 years; 95% CI for the mean 1.8 – 7.8 years). The age of definitive tumour manifestation, estimated in 28 cases, was 60 – 87 years (mean, 70.8 years; SD, 7.0 years; 95% CI for the mean 67.3 – 74.3 years). There were 5 / 18 (27.8%; 95% CI = 12.5 – 50.9%) females and 13 / 18 (72.2%; 95% CI = 49.1 – 87.5%) males among the affected persons.

In the definitive familial bladder cancer kindreds, no other tumours were present. However, 10/11 of the families affected by suspected hereditary bladder cancer syndrome were characterised by the presence of malignant tumours in other locations, too (Annex 22). There were 13 malignant tumours in other locations, arising among these blood relatives, corresponding to the total frequency of malignant tumours 31 / 79 (39.2%; 95% CI = 29.2 – 50.3%). Among these tumours, there were 5 cases of gastric cancer, 2 cases of lung cancer, 2 cases of uterine cancer as well as single cases of colorectal cancer and haematologic malignant tumour. In one case, liver was affected, and in another case, gynaecologic tumour was reported by the proband.

Familial haematologic malignancies

During population screening, aggregation of haematologic tumours was discovered in 17 families (Figure 55). One proband was diagnosed with familial haematologic tumour syndrome as there were 4 cases of the relevant tumours among first-degree relatives in 2 generations. Suspected familial haematologic tumours were diagnosed in 14 pedigrees showing at least 2 cases of the respective malignancies among first-degree relatives in each

kindred and in 2 kindreds showing 2 cases of the respective malignancies among second-degree relatives in each kindred. Two generations were affected in 11 / 16 (68.8%; 44.4 – 85.8%) of the FHemT susp. families. Among the affected persons, there were 18 / 37 (48.6%; 33.4 – 64.1%) females and 19 / 37 (51.4%; 95% CI = 35.9 – 66.5%) males.

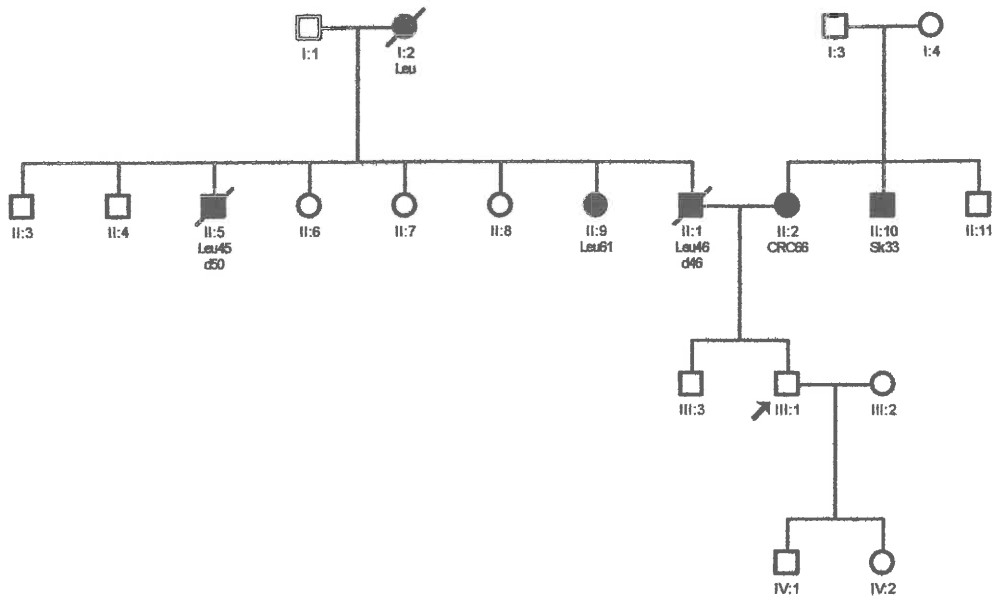


Figure 55. Pedigree of a family affected by familial aggregation of haematologic tumours. Abbreviations in the figure: Leu, haematological malignant tumour, CRC, colorectal cancer; Sk, non-melanoma skin cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

The age of diagnostics was known in 29 cases (Annex 23). The tumours affected persons in wide age range 3 - 88 years (mean, 47.5 years; SD, 22.6 years; 95% CI for the mean 38.9 – 56.1%).

The age distribution of the affected persons (Figure 56) shows trend towards clustering of the cases in three age intervals: the largest group consists of aged people, 60 – 69 years old; another peak occurs in the age interval 30 – 39 years, and there are also affected children, younger than 5 years (Figure 57).

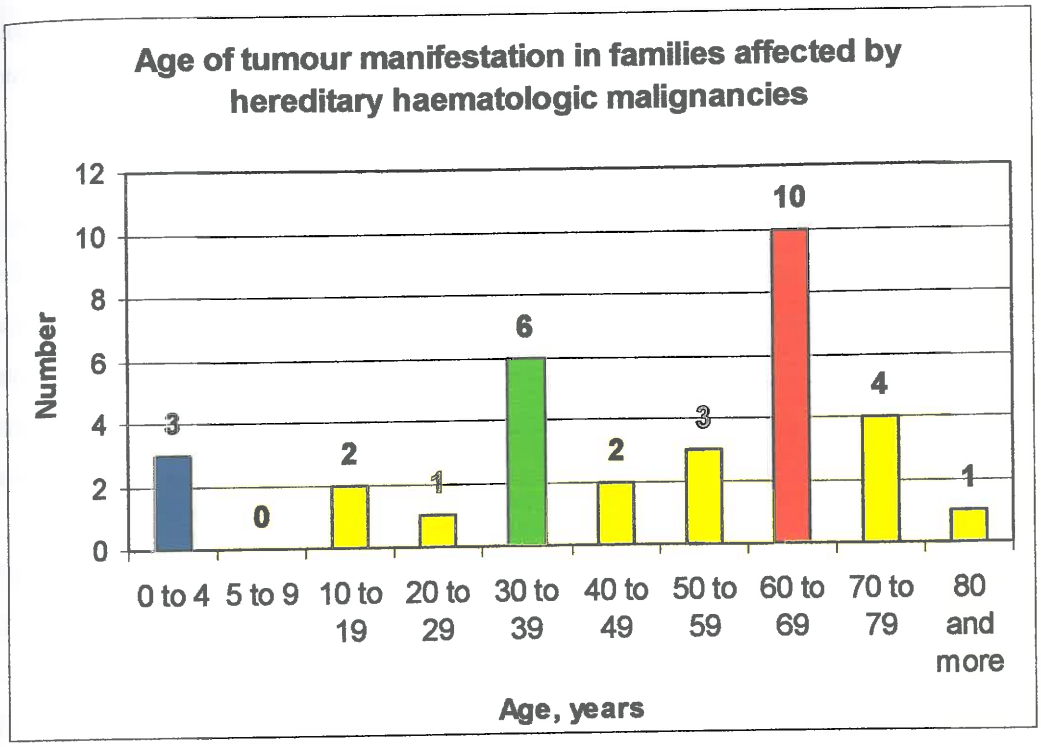


Figure 56. The age distribution of the definite tumour manifestation in the families affected by familial clustering of haematologic malignancies.

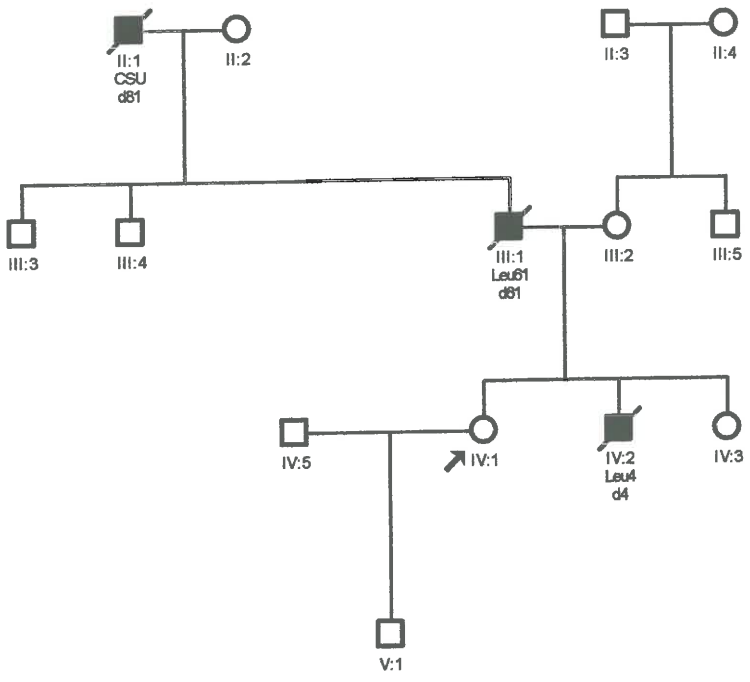


Figure 57. Pedigree showing family affected by haematologic tumours in 2 first-degree relatives. Note the different age of tumour diagnostics and the presence of single case in a child.

Abbreviations in the figure: Leu, haematological malignant tumour, CSU, malignant tumour, not further specified; d, dead. The age of cancer diagnostics is shown by number following the

diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Seven affected persons were alive at the time of population screening. The death age was known for 26 persons and was within the range 4 – 86 years (mean 49.8 years; SD, 23.1 years; 95% CI for the mean 40.5 – 59.1 years). The survival was known for 23 dead persons and ranged from 0 to 6 years (mean, 1.9 years; SD 1.8 years; 95% CI for the mean 1.1 – 2.7 years). The age of definite tumour manifestation was estimated in 26 cases and was 3 – 88 years (mean 47.9 years; SD, 22.3 years; 95% CI for the mean 38.9 – 56.9 years).

The burden of the haematologic malignancies was 37 / 227 persons (16.3%; 95% CI = 12.1 – 21.7%).

No other malignant tumours were present in 8 / 17 families. In the other 9 families, 15 other malignant tumours were reported, including 4 cases of endometrial cancer, 2 cases of colorectal cancer and single cases of gastric cancer, skin cancer and melanoma. In 3 cases the tumour affected brain, in 2 cases – liver, but in 1 case, the location of tumour was unknown to the proband (Annex 24).

Familial pancreatic cancer

Using the clinical diagnostic criteria of familial pancreatic cancer, 10 probands were diagnosed with familial pancreatic cancer syndrome. In 2 families, a case of melanoma was diagnosed in combination with pancreatic cancer in another blood relative of the proband who was first-degree relative of the melanoma-affected person (Figure 58). In the other families the diagnosis was based on the presence of 2 cases of pancreatic cancer in first-degree relatives (Figure 59).

The total load of index cancer in these families was 21 / 138 (15.2%; 95% CI = 10.2 – 22.1%) blood relatives, including 2 cases of melanoma and 19 cases of pancreatic cancer. Mostly there were 2 cases of pancreatic cancer in these pedigrees. Three cases were observed in a single family affected by pancreatic cancer in two lines After re-evaluation of the kinship links between the kindreds and exclusion of those presons who were blood relatives to several probands, the rate of index cancer was estimated as 15 / 102 (14.7%; 95% CI = 9.1 – 22.9%), including 2 cases of melanoma and 13 cases of pancreatic cancer.

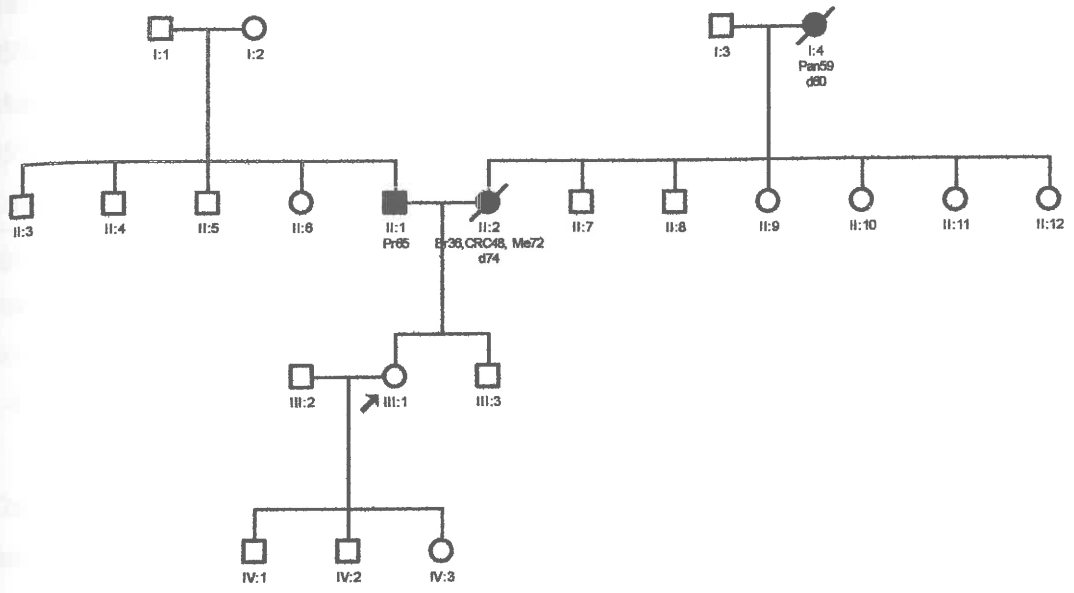


Figure 58. Kindred showing presence of pancreatic cancer and melanoma in two first-degree blood relatives.

Abbreviations in the figure: Pan, pancreatic cancer; Pr, prostate cancer; Br, breast cancer; CRC, colorectal cancer, Me, melanoma; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

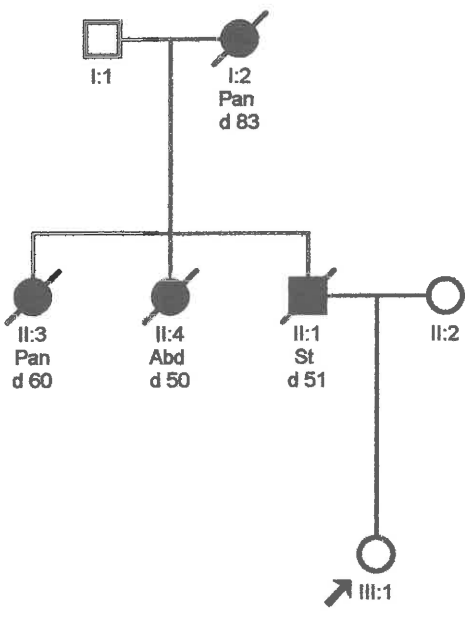


Figure 59. Kindred showing presence of pancreatic cancer in two first-degree blood relatives.

Abbreviations in the figure: Pan, pancreatic cancer; Abd, malignant tumour in the abdominal cavity, not further specified; St, gastric cancer; Ut, endometrial cancer; Lym, lymphoma; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

The index tumours were diagnosed at the age 50 – 72 years (mean, 58.2 years; SD 7.7 years; 95% CI for the mean 54.5 – 61.9 years); the exact age of diagnosis was known in 19 cases (Annex 25). The death occurred at the age 51 – 83 years (mean, 59.7 years; SD, 9.4 years; 95% CI for the mean 55.3 – 64.1 years); the exact death age was known in 20 cases. Combining the data about the age of patient at the time of tumour diagnostics and death, the age of definite tumour manifestation was estimated in 21 cases as 50 – 83 years (mean, 59.5 years; SD 9.1 year; 95% CI for the mean 55.4 – 63.6 years). The survival was known in 18 cases. It ranged from 0 to 5 years (mean 0.8 years; SD 1.3 years; 95% CI for the mean 0.2 – 1.4 years).

The possible relations between the families were re-evaluated in order to exclude the cases that were included in the analysis repeatedly due to kinship to several probands. After the re-evaluation, the age of the index tumour diagnostics was estimated to be 51 – 72 years (mean 61.6 years; SD 7.1 years; 95% CI for the mean 57.3 – 65.9 years. The data about 13 cases were available). The death age in this group was known in 14 cases and ranged 51 – 83 years (mean 63.4 years; SD 9.0 years; 95% CI for the mean 58.2 – 68.6 years). The survival, known in 12 cases, was 0 – 5 years (mean 1.1 years; SD 1.4 years; 95% CI for the mean 0.2 – 2.0 years). The age of definite tumour manifestation was estimated in 15 cases. It ranged from 51 to 83 years (mean 62.9 years; SD 8.6 years; 95% CI for the mean 58.1 – 67.7 years).

The pancreatic cancer cases in familial pancreatic cancer kindreds were diagnosed at the age 50 – 72 years (mean 56.8 years; SD 6.8 years; 95% CI for the mean 53.3 – 60.3 years); the exact age of dianosis was known in 17 cases. The death occurred at the age 51 – 83 years (mean 58.9 years; SD, 9.1 years; 95% CI for the mean 54.5 – 63.3 years); the exact death age was known in 19 cases. Combining the data about the age of patient at the time of tumour diagnostics and death, the age of definite tumour manifestation was estimated in 19 cases as 50 – 83 years (mean 58.3 years; SD 8.8 year; 95% CI for the mean 54.1 – 62.5 years). The survival was known in 17 cases (Figure 60). It ranged from 0 to 5 years (mean 0.7 years; SD 1.3 years; 95% CI for the mean 0.03 – 1.4 years). Melanoma was present in 2 females. One of them was diagnosed with the tumour at the age of 69 years and was alive; the other was diagnosed at the age of 72 years and died 2 years later.

After re-evaluation of the data, the characteristics of pancreatic cancer course in the familial pancreatic cancer pedigrees changed only slightly. The age of the cancer diagnostics was estimated to be 51 – 72 years (mean 60.0 years; SD 6.4 years; 95% CI for the mean 55.7 – 64.3 years. The data about 11 cases were available). The death age in this group was known in 13 cases and ranged 51 – 83 years (mean 62.6 years; SD 8.8 years; 57.3 – 67.9 years). The survival, known in 11 cases, was 0 – 5 years (mean 1.0 years; SD 1.5 years; 95% CI for the

mean 0 – 2.0 years). The age of definite tumour manifestation was estimated in 13 cases. It ranged from 51 to 83 years (mean 61.8 years; SD 8.7 years; 95% CI for the mean 56.5 – 67.1 years).

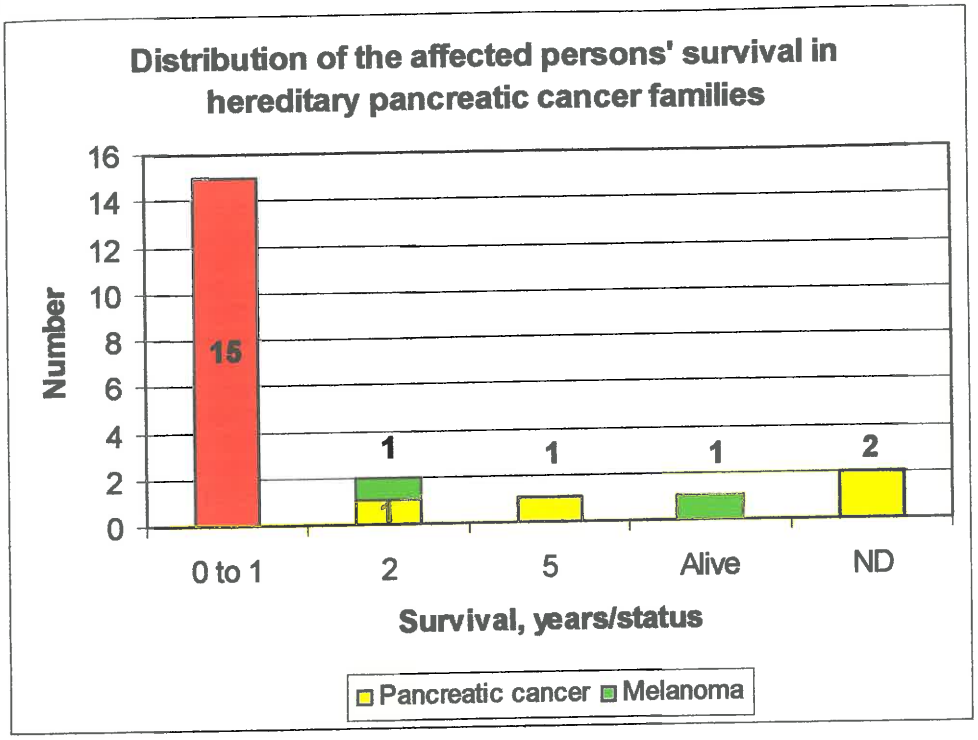


Figure 60. The distribution of the survival in familial pancreatic cancer. Abbreviation in the figure: ND, no data available.

Among the familial pancreatic cancer pedigrees, no other cancer cases were present in 5 families, including 1 cluster of 4 partially related families and 1 unrelated kindred. In the other 4 unrelated families other malignant tumours also were reported (Figure 61) including 2 cases of endometrial cancer and single cases of gastric cancer, haematologic malignant tumour, breast cancer and brain tumour. In 2 cases the tumour was located in the abdominal cavity but the exact location of it was unknown to the proband (Annex 26).

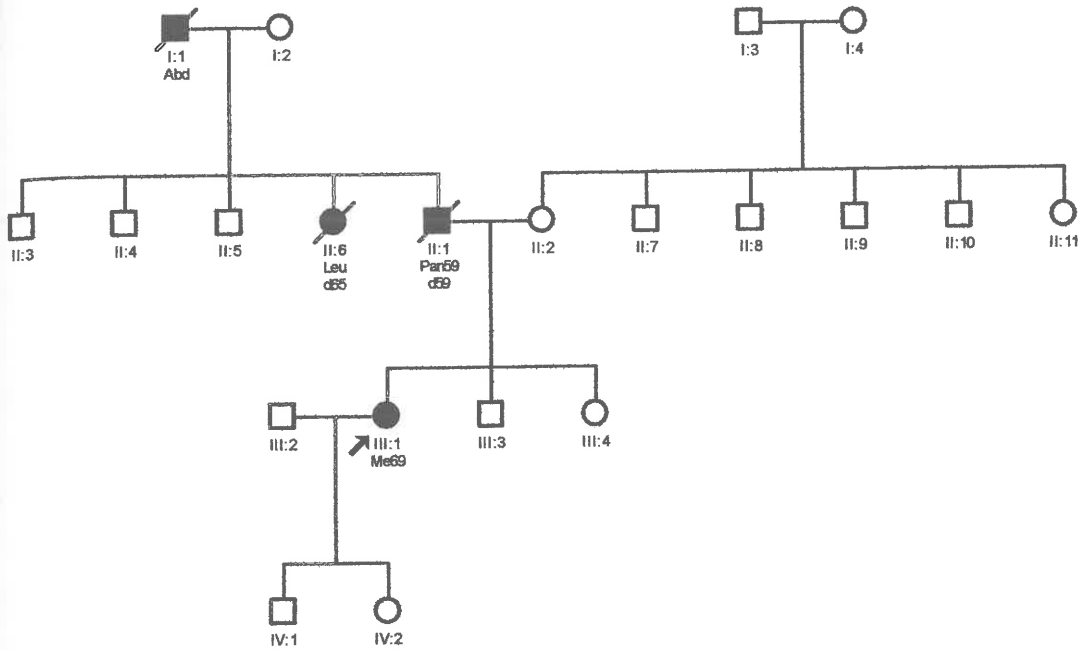


Figure 61. Pedigree affected by familial pancreatic cancer and other malignant tumours.
Abbreviations in the figure: Abd, malignant tumour in the abdominal cavity, not further specified; Leu, malignant haematological tumour; Pan, pancreatic cancer; Me, melanoma; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Familial brain tumours

Nineteen probands with the diagnosis of familial brain tumour syndrome were discovered. The burden of brain tumours in this group was 43 / 260 (16.5%; 95% CI = 12.5 – 21.5%) persons.

Definitive familial brain tumour syndrome was found in 3 families, characterised by the presence of at least 3 cases of brain tumours among first-degree relatives (Figure 62). Four respective tumours were reported in single kindred. These families were characterised also by the absence of other malignant tumours. The burden of brain tumours was 10 / 31 (32.3%; 95% CI = 18.6 – 49.9%) relatives.

Sixteen probands were characterised by presence of at least 2 cases of brain tumours among blood relatives (Figure 62). The burden of brain tumours (Annex 27) in these families was 33 / 229 (14.4%; 95% CI = 10.4 – 19.5%) persons. In 7 families, only brain tumours were reported, but in 9 other families, other malignant tumours also were present (Figure 63).

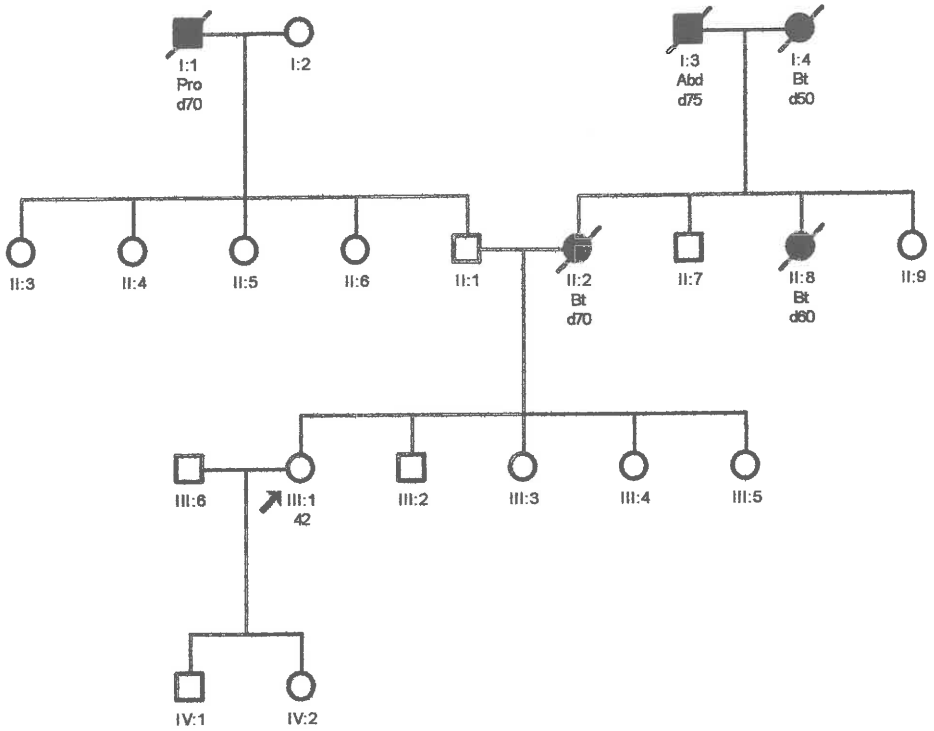


Figure 62. Kindred corresponding to the criteria of definitive familial brain tumour.

Abbreviations in the figure: Pro, prostate cancer; Abd, malignant tumour in the abdominal cavity, not further specified; Bt, brain tumour; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

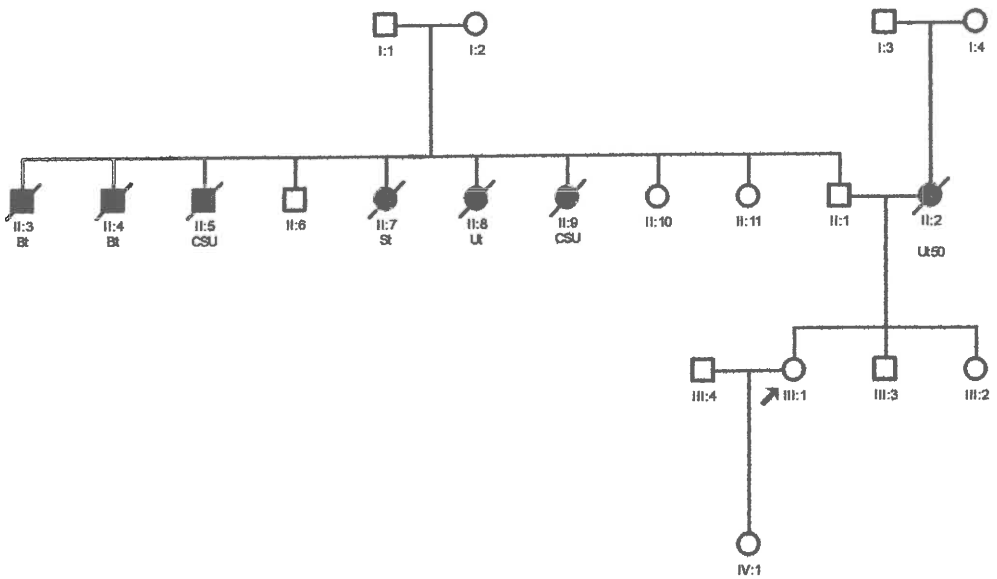


Figure 63. Suspected familial brain tumour in the background of multiple malignant tumours in blood relatives.

Abbreviations in the figure: Bt, brain tumour; CSU, malignant tumour, not further specified; St, gastric cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by

number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Among the other malignancies reported in suspected familial brain tumour kindreds, there were 5 cases of gastric cancer, 5 cases of endometrial cancer, 2 cases of colorectal cancer, 3 cases of haematological malignant tumours; single cases of prostatic and breast cancers. In 4 cases, the primary location of malignant tumour was unknown to the proband (Annex 27).
The exact age of tumour diagnostics (Annex 28), reported by the probands about 26 patients, was 2 – 77 years (mean 43.9 years, SD 22.0 years; 95% CI for the mean 35.0 – 52.8 years). Two of the affected persons were alive at the time of population screening. The death of the others occurred at the age 2 – 77 years (mean, 47.8 years; SD 22.0 years; 95% CI for the mean 39.7 – 55.9 years). The age of definite tumour manifestation was estimated in 35 cases and was 2 – 77 years (mean, 46.5 years; SD, 20.9 years; 39.3 – 53.7 years). The distribution of this parameter is shown in figure 63, revealing 2 peaks: marked in the middle age, grouping around the age interval 50 – 59 years, and less marked, at childhood (Figure 65).

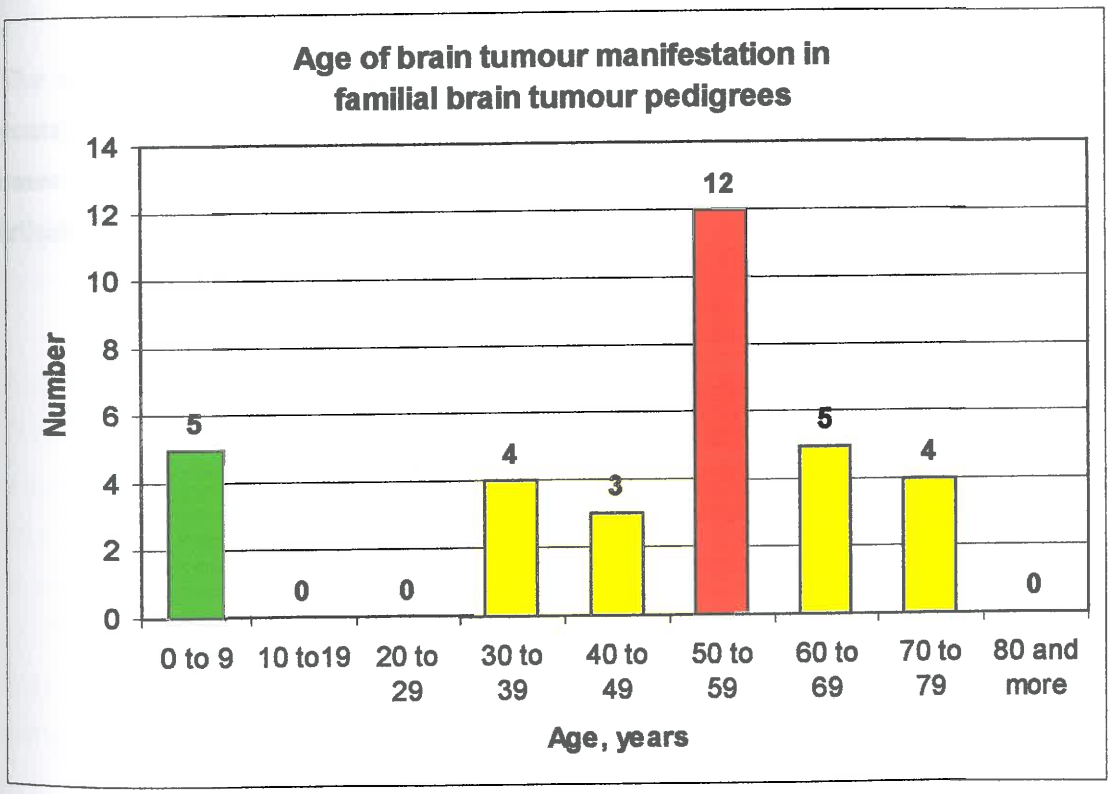


Figure 64. Distribution chart showing the age of definite brain tumour manifestation in definite and suspected familial brain tumour families.

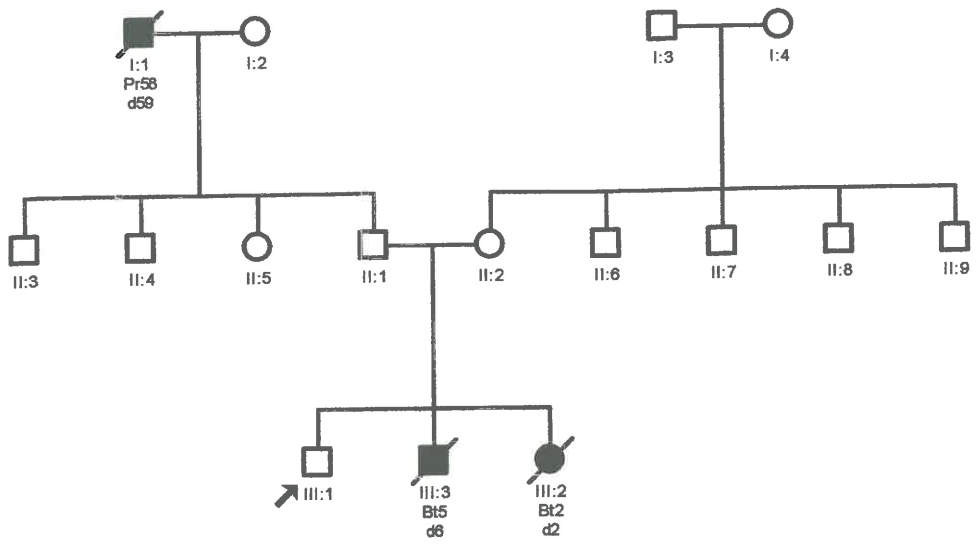


Figure 65. Kindred characterised by occurrence of brain tumours in children.
Abbreviations in the figure: Pr, prostate cancer; Bt, brain tumour; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

The survival of the persons affected by familial brain tumour was 0 – 10 years (mean 1.5 years; SD 2.8 years; 95% CI for the mean 0.3 – 2.7 years). The survival was known in 24 cases. The distribution of the survival is shown in Figure 66, revealing high first-year lethality.

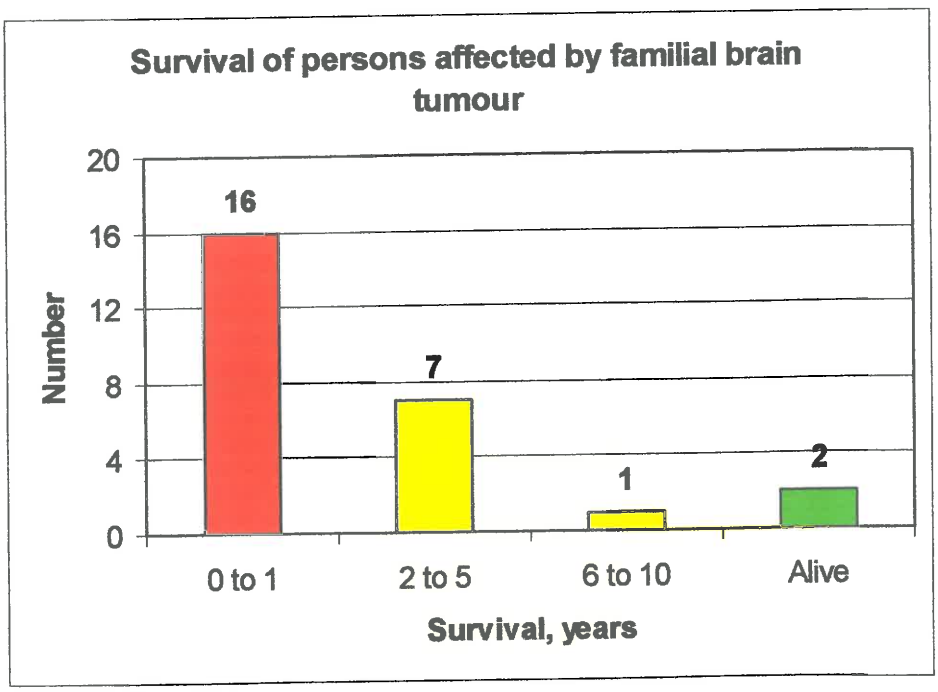


Figure 66. Survival of persons affected by definitive or suspected familial brain tumour.

Cancer family aggregation

Cancer family aggregation, defined as occurrence of non-concordant malignant tumours in 3 or more first-degree blood relatives, represented a common hereditary cancer syndrome (see Figure 67), diagnosed in 469 probands.

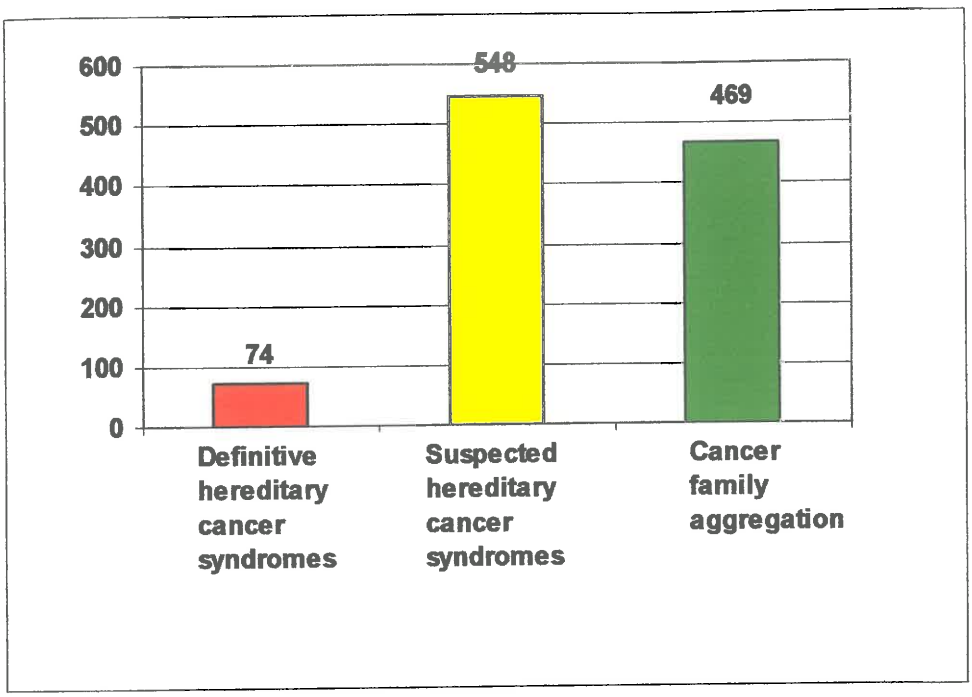


Figure 67. The proportions of definitive and suspected hereditary cancer syndromes and cancer family aggregation.

Among them, 206 probands had combined type of family cancer history allowing making diagnosis of some hereditary cancer syndrome by location. However, if the family cancer load could not be explained by single more specific hereditary cancer syndrome and diagnosis of cancer family aggregation was justified (Figure 68), combined diagnoses were issued in order to ensure the most complete surveillance. Two hundred sixty three probands had the diagnosis of CFA only, designated futher as pure CFA. The scientific analysis was performed for both data sets in order to characterise the syndrome and to test the clinical hypothesis of optimal surveillance approach.

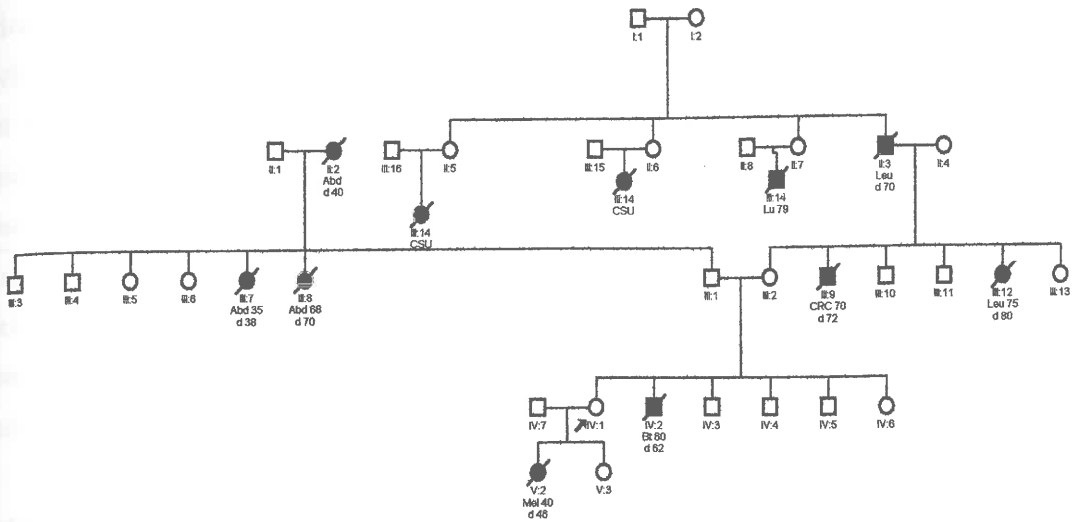


Figure 68. Kindred corresponding to the criteria of cancer family aggregation (CFA). The diagnosis of CFA is substantiated by occurrence of haematological malignant tumour in father in combination with colorectal cancer in his son and another case of haematological malignant tumour in his daughter. Additional cases of different malignant tumours are present in blood relatives. A cluster of unspecified malignant tumour in abdominal cavity in 3 female blood relatives from the opposite side also corresponds to the CFA although is not required for diagnosis.

Abbreviations in the figure: Abd, malignant tumour in the abdominal cavity, not further specified; CSU, cancer of unspecified primary site; Lu, lung cancer; Leu, haematological malignant tumour; CRC, colorectal cancer; Bt, brain tumour; Mel, melanoma; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

There was female predominance among the probands. Only 155 males were present in the group of 469 probands diagnosed with CFA. The age of probands was 18 – 93 years (mean, 50.6 years; SD 17.1 years; 95% CI for the mean, 49.0 – 52.2 years). The exact age was known for 466 probands.

The number of persons affected by malignant tumour ranged from 3 to 11 (mean, 3.9; SD, 1.2; 95% CI for the mean, 3.8 – 4.0). In total, there were 1807 affected persons in these 469 kindreds. As several persons were affected by multiple malignant tumours, 1839 malignant neoplasms were reported in these families.

Among these 1839 malignant tumours, there were 260 cases of gastric cancer, 217 cases of lung cancer, 170 cases of endometrial cancer, 157 cases of breast cancer, 108 cases of colorectal cancer, 88 cases of haematologic malignant tumours, 66 cases of brain tumours, 49 cases of prostate cancer, 41 cases of pancreatic cancer, 41 cases of renal cancer, 38 cases of

urinary bladder cancer, 35 cases of ovarian cancer, 9 cases of melanoma and 23 cases of non-melanoma skin cancer, 8 cases of uterine cervix cancer. In several cases, the probands could not report the exact location of cancer in a relative. Thus, in 40 cases the tumour was described as gynaecologic malignant process. In 71 cases, the location of tumour was described as abdominal. Liver has been affected in 48 patients. In 132 cases, the location of tumour was completely unknown to the proband. The statistic evaluation of these data is included in the table 23. The distribution of malignant tumours in the CFA group was compared with the distribution of malignant tumours in the Latvian population as shown in Table 24.

Table 24. The number and distribution of malignant tumours by location in the CFA group in comparison with the Latvian population

Location	CFA	Population, 2006	Conclusion
Stomach	260 14.1% (95% CI = 12.6 – 15.8%)	591 / 9102 6.5% (95% CI = 6.0 – 7.0%)	Difference statistically significant
Lung	217 11.8% (95% CI = 10.4 – 13.4%)	1070 11.8% (95% CI = 11.1 – 12.4%)	Difference not significant
Corpus uteri	170 9.2% (95% CI = 8.0 – 10.7%)	371 4.1 (95% CI = 3.7 – 4.5%)	Difference statistically significant
Breast	157 8.5% (95% CI = 7.3 – 9.9%)	1022 11.2 (95% CI = 10.6 – 11.9%)	Difference statistically significant
Colorectal	108 5.9% (95% CI = 4.9 – 7.0%)	943 10.3 (95% CI = 9.8 – 11.0%)	Difference statistically significant
Haematological	88 4.8% (95% CI = 3.9 – 5.9%)	400 4.4% (95% CI = 4.0 – 4.8%)	Difference not significant
Brain	66 3.6% (95% CI = 2.8 – 4.5%)	ND	
Prostate	49 2.7% (95% CI = 2.0 – 3.5%)	782 8.6% (95% CI = 8.0 – 9.2%)	Difference statistically significant

Pancreas	41 2.2% (95% CI = 1.6 – 3.0%)	286 3.1% (95% CI = 2.8 – 3.5%)	Difference not significant
Kidney	41 2.2% (95% CI = 1.6 – 3.0%)	388 4.3% (95% CI = 3.9 – 4.7%)	Difference statistically significant
Urinary bladder	38 2.1% (95% CI = 1.5 – 2.8%)	355 3.9% (95% CI = 3.5 – 4.3%)	Difference statistically significant
Ovary	35 1.9% (95% CI = 1.4 – 2.6%)	275 3.0% (95% CI = 2.7 – 3.4%)	Difference statistically significant
Uterine cervix	8 0.4% (95% CI = 0.2 – 0.9%)	219 2.4% (95% CI = 2.1 – 2.7%)	Difference statistically significant
Melanoma	9 0.5% (95% CI = 0.3 – 0.9%)	ND	
Total	1839	9102	

Abbreviation in the table: CI, confidence interval; ND, no data available.

The affected persons in the CFA families were characterised by age and sex distribution as shown in Table 25.

Table 25. Age and sex distribution of the affected persons in CFA families by tumour location

Location	Number[1]	Males	Age interval	Mean age	SD	Cases[2]	95% CIM
Stomach	260	139	17 – 91	61.7	13.0	237	60.0 – 63.4
Lung	217	171	18 – 88	61.4	12.1	201	59.7 – 63.1
Ut	170	NA	18 – 83	57.0	15.3	160	54.6 – 59.4
Breast	157	0	18 – 86	55.6	15.1	148	53.1 – 58.1
CRC	108	48	17 – 88	65.2	12.1	101	62.8 – 67.6
Haemat	88	35	4 – 90	52.5	20.3	81	48.0 – 57.0
Brain	66	34	2 – 83	53.9	16.0	53	49.5 – 58.3
Prostate	49	49	35 – 81	65.4	11.9	46	61.9 – 68.9
Pan	41	16	21 – 83	62.9	10.9	39	59.4 – 66.4
Kidney	41	26	2 – 80	61.0	15.8	40	55.9 – 66.0

Bla	38	21	34 – 87	66.7	12.9	35	62.3 – 71.1
Ovary	35	NA	25 – 79	54.0	13.3	31	49.1 – 58.9
Cx	8	NA	31 – 83	41.4	17.5	8	26.8 – 56.0
Gyn	40	NA	20 – 84	55.6	15.0	31	50.1 – 61.1
Liver	48	25	22 – 82	59.1	14.0	44	54.8 – 63.4

[1] Total number of malignant tumours in the specified location

[2] Number of cases characterised by exactly reported age of tumour manifestation

Abbreviations in table: Ut, endometrial cancer; CRC, colorectal cancer; Pan, pancreatic cancer; Bla, urinary blader; Cx, uterine cervical cancer; SD, standard deviation; NA, not applicable; Gyn, gynaecologic malignancy.

Comparing the tumours reported by CFA probands and occuring in the whole population of Latvia, 2006, differences in the relative distribution of malignant tumours (Table 24) were observed as shown in the Figure 69. The malignant tumours in CFA group and Latvian population were also ranged as shown in Figure 70. The following trends were observed.

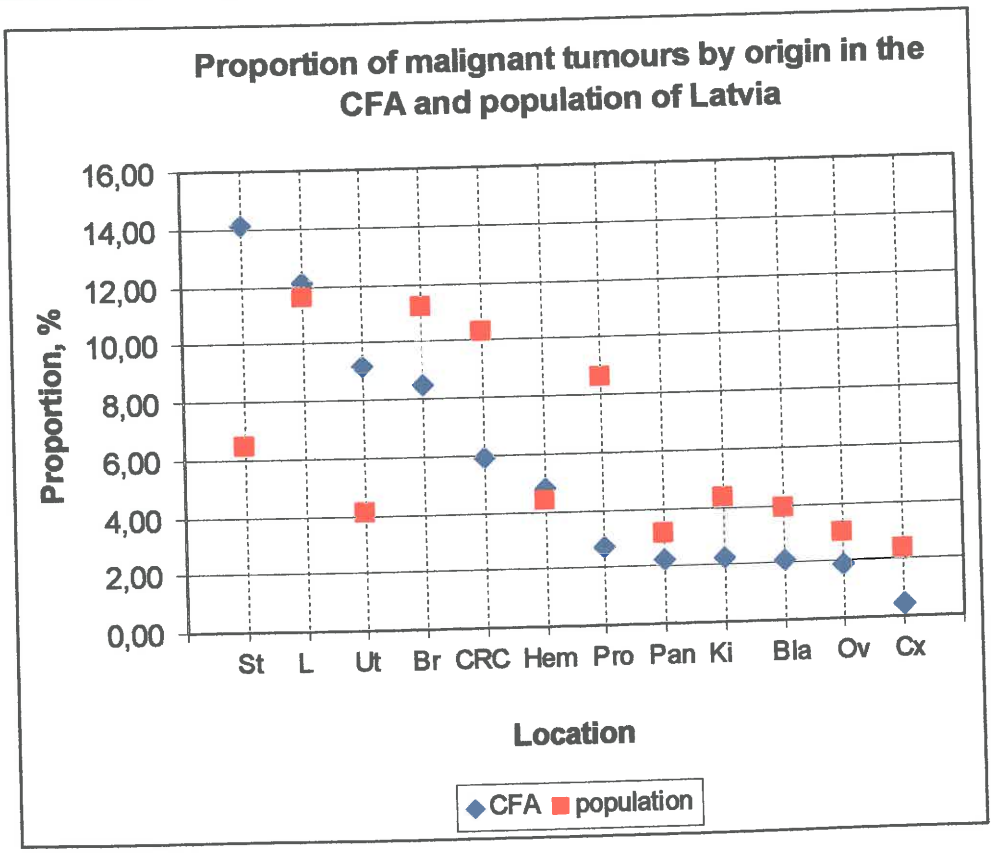


Figure 69. The different proportions of malignant tumours in the CFA group and in the population of Latvia, 2006.

Abbreviations in the figure: St, stomach; L, lung; Ut, endometrium; Br, breast; CRC, colorectal cancer; Hem, haematological tumour; Pro, prostate; Pan, pancreas; Ki, kidney; Bla, urinary bladder; Ov, ovary; Cx, cervix uteri.

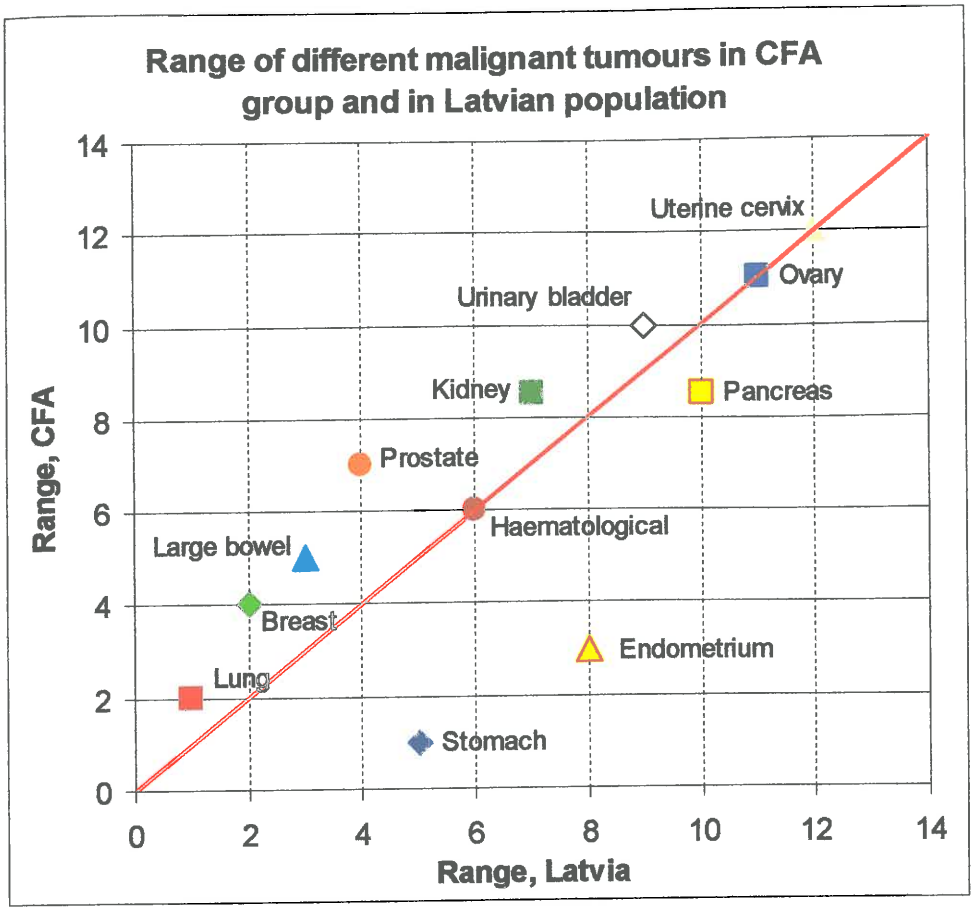


Figure 70. The relation between the ranges of different malignant tumours reported in the CFA group and in the whole population of Latvia (2006).

Thus, the range of gastric cancer and endometrial cancer was higher in CFA group. The more frequent occurrence of these tumours does not seem to be related to coincidence by chance only and hypothetically could be attributed to genetic differences between CFA group and the general population. Extracolonic Lynch syndrome cannot be excluded. On the other hand, breast and ovarian cancers as well as colorectal, prostate, renal and urinary bladder cancer were less frequently reported in CFA group than in Latvian population. This can be explained by the diagnostic criteria, identifying other, more specific hereditary cancer syndromes.

In the pure CFA group, there were 923 affected persons. As several persons had multiple malignant tumours, 947 malignant neoplasms were reported in these families. These malignant tumours included 97 cases of gastric cancer, 96 cases of lung cancer, 76 cases of endometrial cancer, 57 cases of breast cancer, 57 cases of colorectal cancer, 47 cases of haematologic malignant tumours, 22 cases of brain tumours, 29 cases of prostate cancer, 22 cases of pancreatic cancer, 23 cases of renal cancer, 20 cases of urinary bladder cancer, 10 cases of ovarian cancer, 4 cases of melanoma and 21 cases of non-melanoma skin cancer, 6 cases of uterine cervix cancer. In several cases, the probands could not report the exact

location of cancer in a relative. Thus, in 29 cases the tumour was described as gynaecologic malignant process. In 58 cases, the location of tumour was described as abdominal. Liver has been affected in 24 patients. In 94 cases, the location of tumour was completely unknown to the proband. The distribution of tumours in this group was compared to the whole CFA group and population of Latvia as shown in Table 26.

Table 26. The number and distribution of malignant tumours by location in the pure CFA group in comparison with total CFA group and Latvian population

Location	CFA	Pure CFA	Population, 2006
Stomach	260 14.1% (95% CI = 12.6 – 15.8%)	97 10.2% (95% CI = 8.5 – 12.3%)	591 6.5% (95% CI = 6.0 – 7.0%)
Lung	217 11.8% (95% CI = 10.4 – 13.4%)	96 10.1% (95% CI = 8.4 – 12.2%)	1070 11.8% (95% CI = 11.1 – 12.4%)
Corpus uteri	170 9.2% (95% CI = 8.0 – 10.7%)	76 8.0% (95% CI =6.5 – 9.9%)	371 4.1 (95% CI = 3.7 – 4.5%)
Breast	157 8.5% (95% CI = 7.3 – 9.9%)	57 6.0% (95% CI = 4.7 – 7.7%)	1022 11.2 (95% CI = 10.6 – 11.9%)
Colorectal	108 5.9% (95% CI = 4.9 – 7.0%)	57 6.0% (95% CI = 4.7 – 7.7%)	943 10.3 (95% CI = 9.8 – 11.0%)
Haematologic	88 4.8% (95% CI = 3.9 – 5.9%)	47 5.0% (95% CI =3.8 – 6.5%)	400 4.4% (95% CI = 4.0 – 4.8%)
Brain	66 3.6% (95% CI = 2.8 – 4.5%)	22 2.3% (95% CI = 1.5 – 3.5%)	ND
Prostate	49 2.7% (95% CI = 2.0 – 3.5%)	29 3.1 (95% CI = 2.1 – 4.4%)	782 8.6% (95% CI = 8.0 – 9.2%)
Pancreas	41 2.2% (95% CI = 1.6 – 3.0%)	22 2.3% (95% CI = 1.5 – 3.5%)	286 3.1% (95% CI = 2.8 – 3.5%)

Kidney	41 2.2% (95% CI = 1.6 – 3.0%)	23 2.4% (95% CI = 1.6 – 3.6%)	388 4.3% (95% CI = 3.9 – 4.7%)
Urinary bladder	38 2.1% (95% CI = 1.5 – 2.8%)	20 2.1% (95% CI = 1.4 – 3.2%)	355 3.9% (95% CI = 3.5 – 4.3%)
Ovary	35 1.9% (95% CI = 1.4 – 2.6%)	10 1.1% (95% CI = 0.6 – 1.9%)	275 3.0% (95% CI = 2.7 – 3.4%)
Uterine cervix	8 0.4% (95% CI = 0.2 – 0.9%)	6 0.6% (95% CI = 0.3 – 1.4%)	219 2.4% (95% CI = 2.1 – 2.7%)
Melanoma	9 0.5% (95% CI = 0.3 – 0.9%)	4 0.4% (95% CI = 0.2 – 1.1%)	ND
Total	1839	947	9102

Abbreviations in table: CI, confidence interval; ND, no data available

The affected persons in the pure CFA families were also characterised by age and sex distribution as shown in Table 27.

Table 27. Age and sex distribution of the affected persons in CFA families by tumour location

Location	Number	Males	Age interval	Mean age	SD	Cases	95% CIM
Stomach	97	51	35 – 91	62.1	13.3	90	59.3 – 64.9
Lung	96	74	25 – 88	63.7	11.4	88	61.3 – 66.1
Ut	76	NA	30 – 82	58.0	15.0	71	54.4 – 61.6
Breast	57	0	40 – 82	58.1	11.1	51	55.0 – 61.2
CRC	57	24	44 – 85	66.2	10.0	54	63.5 – 68.9
Hemat	47	16	4 – 78	53.4	18.1	43	47.8 – 59.0
Brain	22	13	20 – 83	55.6	15.3	18	48.0 – 63.2
Prostate	29	29	57 – 81	69.3	8.2	26	66.0 – 72.6
Pan	22	8	21 – 77	60.8	12.1	21	55.3 – 66.3
Kidney	23	13	2 – 77	55.5	17.0	23	48.1 – 62.9
Bla	20	10	42 – 82	62.4	12.0	17	56.2 – 68.6
Ovary	10	NA	44 – 73	58.4	12.6	7	46.7 – 70.1
Cx	6	NA	31 – 83	43.7	20.1	6	22.6 – 64.8

Gyn	29	NA	20 – 72	52.8	12.9	22	47.1 – 58.5
Li	24	14	35 – 82	64.3	11.7	23	59.2 – 69.4

Abbreviations in table: SD, standard deviation, NA, not applicable; Ut, endometrial cancer; CRC, colorectal cancer; Hemat, malignant haematological tumour; Pan, pancreatic cancer; Bla, urinary bladder cancer; Cx, uterine cervical cancer; Gyn, gynaecologic malignant tumour; Li, malignant tumour in the liver

The ranges of different malignant tumours in the pure CFA group were compared with the general CFA group and the population of Latvia as shown in Figure 71. In general, the same trends were observed allowing cautious interpretation.

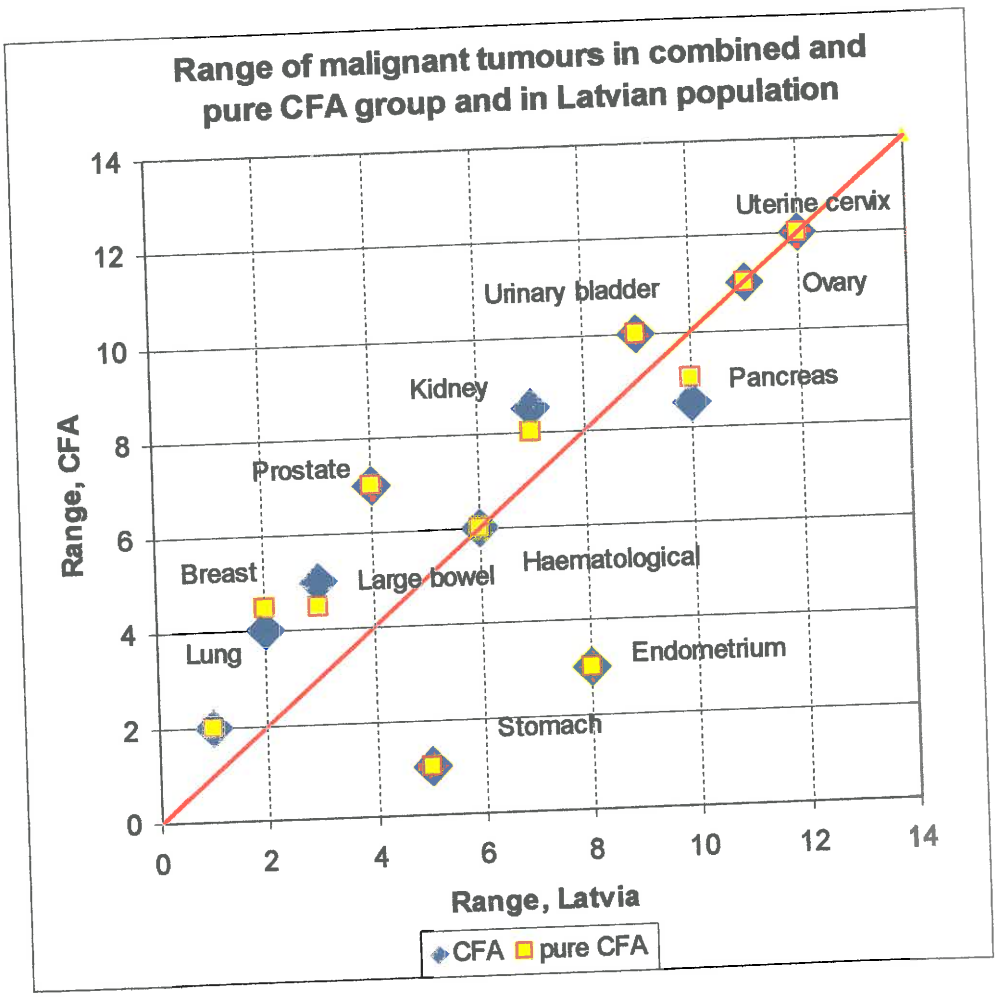


Figure 71. The relation between the ranges of different malignant tumours reported in the general and pure CFA groups and in the whole population of Latvia (2006).

Other findings

Among other findings of the population screening, there were 3 kindreds showing 2 cases of renal cancer. In only one kindred, first-degree relatives were affected in 2 generations (Figure 72). In the other kindreds, first-degree or second-degree relatives were affected in a single generation (Figure 73).

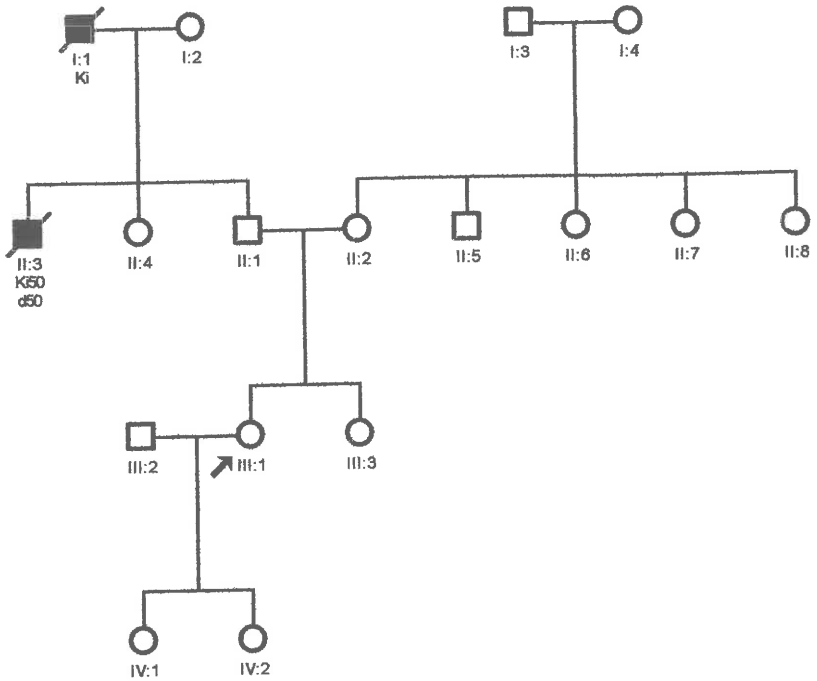


Figure 72. Pedigree showing renal cancer in 2 first-degree relatives in 2 generations. The pedigree hypothetically could correspond to dominant mode of transmission.

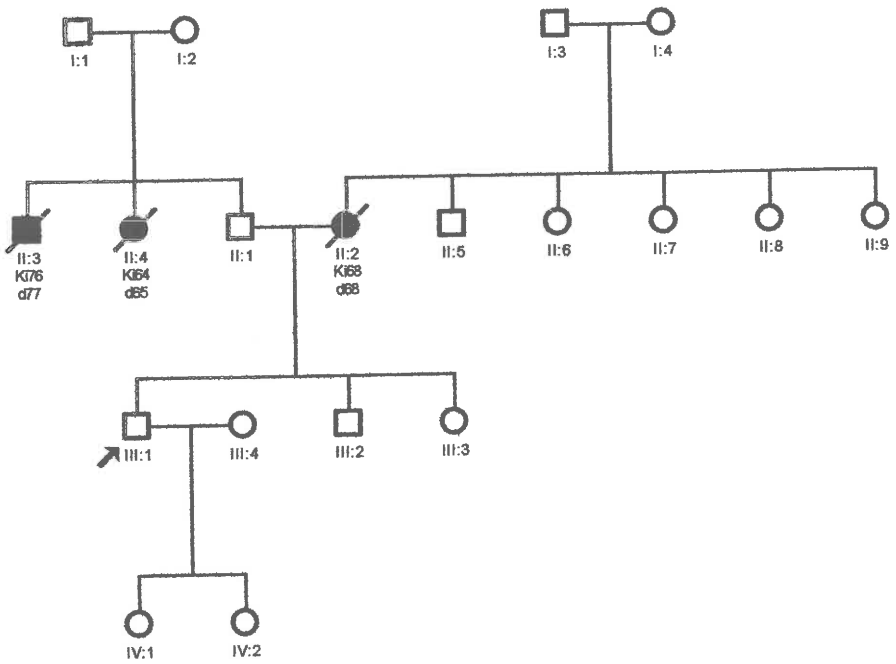


Figure 73. Kidney cancer in 2 first-degree relatives in a single generation. The pedigree hypothetically could correspond to recessive mode of transmission.

Several associations of tumours not corresponding to the criteria of any specific familial tumour syndrome were found (Annex 29). Two cases of melanoma were present in first-degree relatives in a single family. There were also cases of renal cancer and gastric cancer but no case of pancreatic cancer. There were 2 cases of adrenal tumour in first-degree blood relatives affecting single generation of 1 family; a case of lung cancer also was present. Three probands reported 2 cases of thyroid cancer in first-degree relatives in 2 generations; no other cancers were found among blood relatives. Five probands reported 2 cases of cancer of the uterine cervix in first degree relatives in 2 generations. Again, no other cancers were found among blood relatives. Two probands reported 2 cases of laryngeal cancer in first-degree relatives in 2 generations.

Size of the families diagnosed with the hereditary and familial cancer syndromes

The size of family was analysed using the most frequent hereditary cancer models as hereditary non-polyposis colorectal cancer, hereditary and familial gastric cancer, familial lung cancer, hereditary and familial endometrial cancer, hereditary prostate cancer. The data are presented in the Tables 28 and 29. Data characterising the syndromes affecting both sexes are included in the Table 28, but syndromes manifesting themselves in one sex only are characterised in Table 29.

Table 28. Characteristics of the reported family size in respect to hereditary or familial cancer syndrome

Diagnosis	Number of the blood relatives			
	Interval	Mean	SD	95% CIM
HNPCC	7 – 26	13.3	5.4	9.6 – 17.0
HNPCC susp.	6 – 22	13.9	5.2	11.4 – 16.4
FCC	3 – 19	12.0	3.8	10.2 – 13.8
HSC	7 – 29	14.4	6.4	11.5 – 17.3
HSC susp.	4 – 24	12.8	4.3	11.8 – 13.8
FLC	11 – 17	13.0	1.8	11.9 – 14.1
FLC susp.	5 – 29	11.7	4.1	10.8 – 12.6
HB/OC	10 – 16	12.2	2.5	9.1 – 15.3
HBC1	4 – 47	12.3	5.4	11.3 – 13.3
HBC2	5 – 37	12.2	5.7	10.8 – 13.6
HBOC1	7 – 13	9.7	2.0	7.7 – 11.7
HBOC2	5 – 22	12.1	4.7	10.3 – 13.9

Abbreviations in the table: SD, standard deviation; CIM, confidence interval for the mean; HNPCC, hereditary non-polyposis colorectal cancer; HNPCC susp., suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; FLC, familial lung cancer; FLC susp., suspected familial lung cancer; HB/OC , hereditary breast and/or ovarian cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast cancer, variety 2; HBOC1 suspected hereditary breast -ovarian cancer, variety 1; HBOC2, suspected hereditary breast-ovarian cancer, variety 2

Table 29. Characteristics of the reported family size in respect to hereditary or familial cancer syndrome in syndromes limited to one affected sex

Diagnosis	Number of the blood relatives			
	Interval	Mean	SD	95% CIM
HPC	3 – 16	7.3	4.4	5.3 – 9.3
HPC def.	14	14	ND	ND
HPC susp.	3 – 16	7.0	4.2	5.0 – 9.0
HEC	6 – 10	8.2	1.5	6.4 – 9.0
HEC susp.	3 – 13	6.7	2.6	5.7 – 7.7
FEC1	3 – 13	6.9	2.3	5.9 – 7.9
FEC	4 – 9	6.5	3.5	ND
FEC and FEC1	3 – 13	6.9	2.4	5.9 – 7.9
FEC2	4 – 12	7.6	2.8	5.4 – 9.8
HOC susp.	4 – 8	5.5	2.4	1.7 – 9.3

Abbreviations in the table: SD, standard deviation; CIM, confidence interval for the mean; HPC, the joint group of definitive and suspected hereditary prostate cancer; HPC def., definitive hereditary prostate cancer; ND, no data available; HPC susp., suspected hereditary prostate cancer; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; HOC susp., suspected hereditary ovarian cancer.

The reported family size in the joint group of definitive hereditary cancer syndrome groups, suspected hereditary cancer groups, CFA and group of patients whose family cancer history was undiagnostic of any oncological syndrome was compared as shown in Table 30. There was statistically significant difference between the size of family diagnosed with a definitive or suspected hereditary cancer syndrome and families with non-diagnostic findings.

Table 30. Comparison of the reported family size in hereditary or familial cancer syndromes and other status of family cancer history

Group	The number of blood relatives			
	Interval	Mean	SD	95% CIM
Definitive	7 – 29	13.6	4.9	12.2 – 15.0
Suspected	3 – 47	12.2	4.8	11.7 – 12.7
CFA	6 – 22	11.4	3.6	10.5 – 12.3
Not diagnostic	4 – 25	9.5	3.8	8.9 – 10.1

Abbreviations in the table: SD, standard deviation; CIM, confidence interval for the mean; CFA, cancer family aggregation

MOLECULAR RESULTS

Taking into account the clinical data, 588 blood samples were subjected to *BRCA1* testing for the presence of mutations 300T/G, 4153delA and 5382insC. Among these, 10 mutation carriers in 7 families were discovered (1.70%) of blood samples examined by multiplex PCR (Table 31). In 8 cases the *BRCA1* gene mutation was 5382insC, in 2 – 4153delA.

Table 31. Relation between the presence of *BRCA1* mutation and clinical data

Hereditary cancer syndromes	Tested persons	*BRCA1* mutation
Hereditary breast – ovary cancer	5	0 0% (95% CI = 0 – 43.5%)
Suspicion of hereditary breast – ovarian cancer	153	2 1.3% (95% CI = 0.4 – 4.6%)
Single case of index cancer in the kindred	430	8 1.9% (95% CI = 0.9 – 3.6%)

Characteristics of mutation carriers

The persons affected by mutations did not always show typical family history. Thus, *BRCA1* gene mutation 4153delA was found in oncologically healthy 28-year-old male whose family history causes suspicion of family cancer aggregation (Figure 74) as well as in 46-year old female with ovary cancer and family history corresponding to hereditary ovarian cancer (Figure 75). *BRCA1* gene mutation 5382insC was found in 18 year old oncologically healthy female and her 22-year-old brother whose family history causes suspicion of hereditary breast ovarian cancer (Figure 76). The same mutation was found in 3 oncologically healthy sisters in the age of 21, 18 and 26 years (Figure 77). Sixty-five-year old female with history of breast

cancer at the age of 52 and no other cancer cases in the family history also was subjected to this mutation (Figure 78). The *BRCA1* gene mutation 5382insC was also found in 57-year-old female with a history of breast cancer in the age of 56. There was another cancer case in her first-degree relative (Figure 79). Forty-one-year-old male was a carrier of this mutation; there was a case of ovary cancer in his family history (Figure 80).

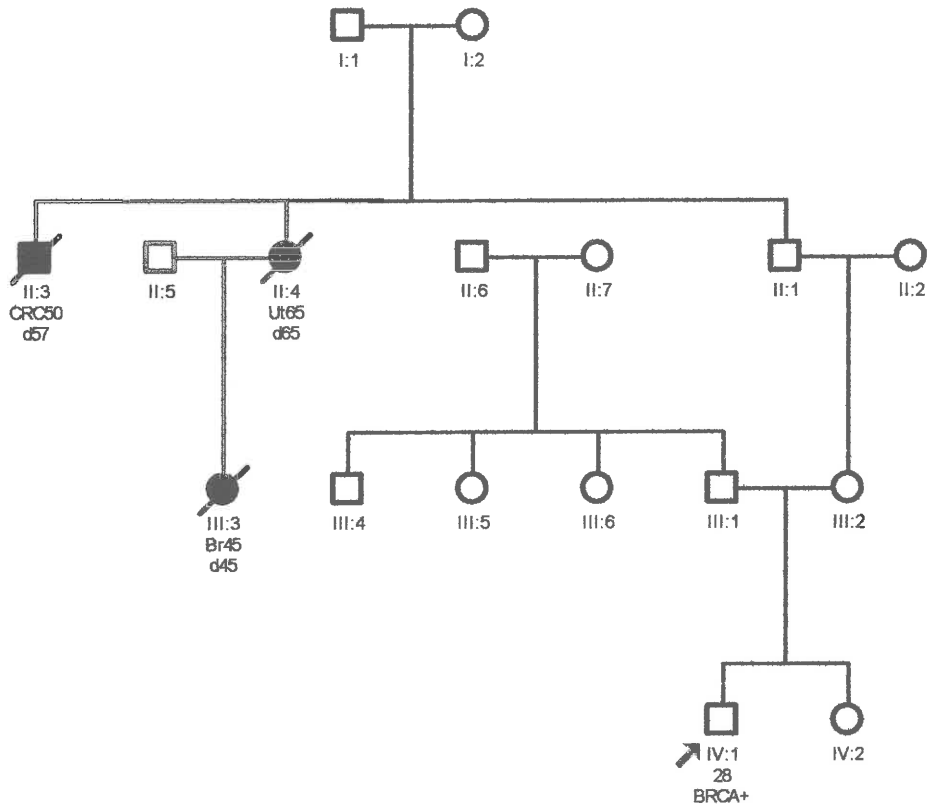


Figure 73. Mutation of *BRCA1* in family with family cancer aggregation. Abbreviations in the figure: CRC, colorectal cancer; Ut, endometrial cancer; Br, breast cancer; d, dead; BRCA+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

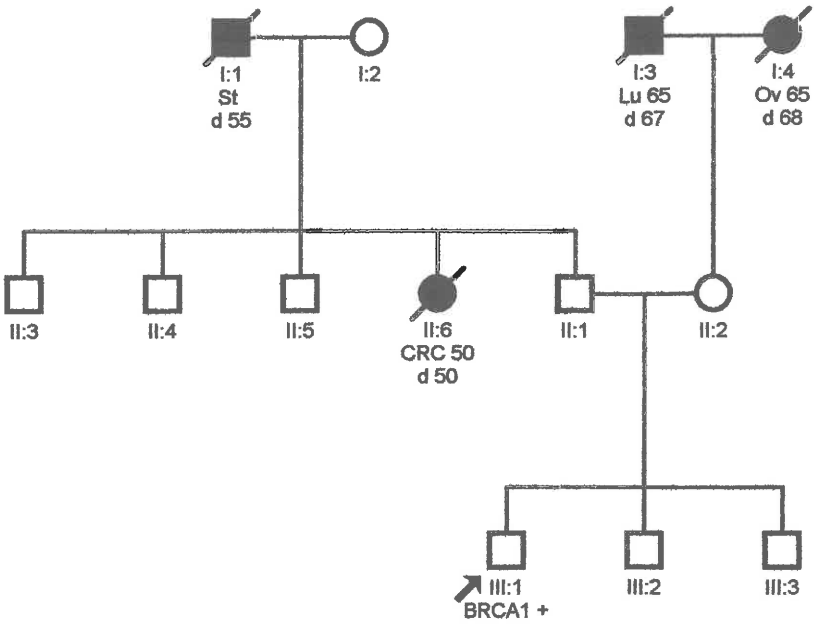


Figure 74. Mutation of *BRCA1* in a family with several cases of malignant tumours in different blood lines. Abbreviations in the figure: St, stomach cancer; Lu, lung cancer; Ov, ovarian cancer; CRC, colorectal cancer; d, dead; BRCA1+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

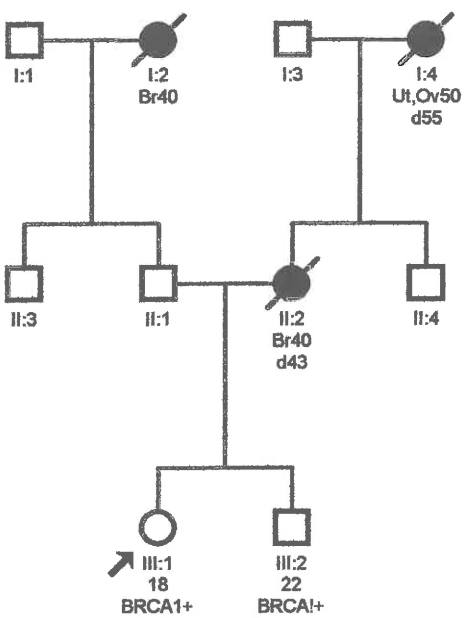


Figure 75. Mutation of *BRCA1* in a family with suspected hereditary breast ovarian cancer. Abbreviations in the figure: Br, breast cancer; Ut, endometrial cancer; Ov, ovarian cancer; d, dead; BRCA1+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

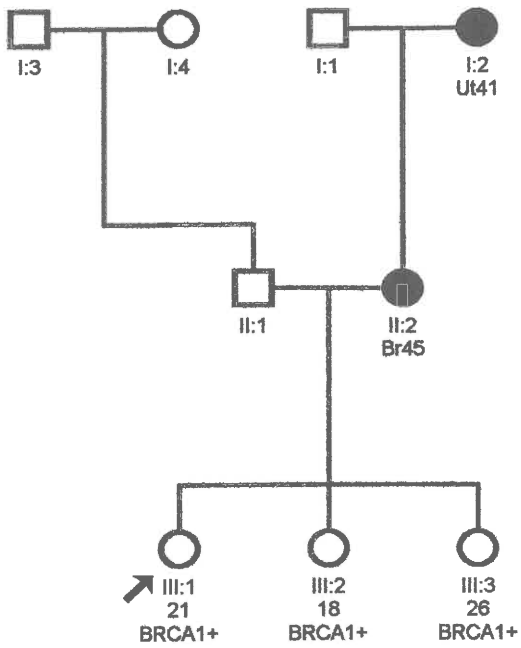


Figure 76. Mutation of *BRCA1* in three oncologically healthy first degree relatives. Abbreviations in the figure: Ut, endometrial cancer; Br, breast cancer; BRCA1+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis. The proband is indicated by an arrow.

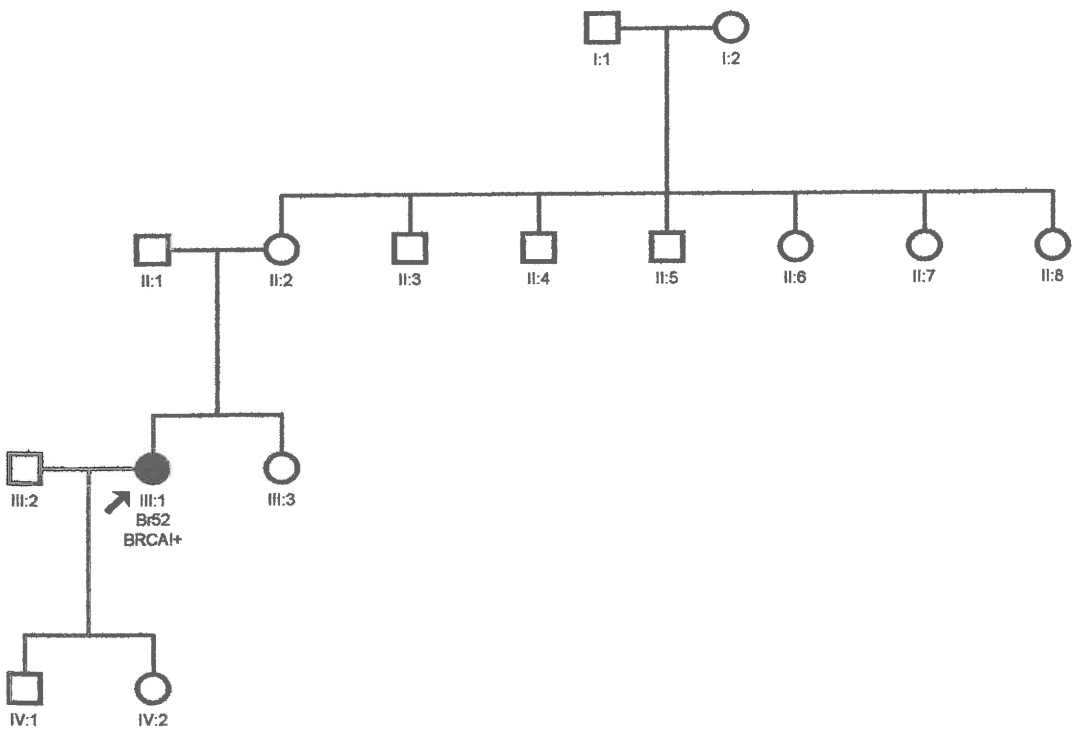


Figure 77. Mutation of *BRCA1* in a family with single case of breast cancer. Abbreviations in the figure: Br, breast cancer; BRCA!+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis. The proband is indicated by an arrow.

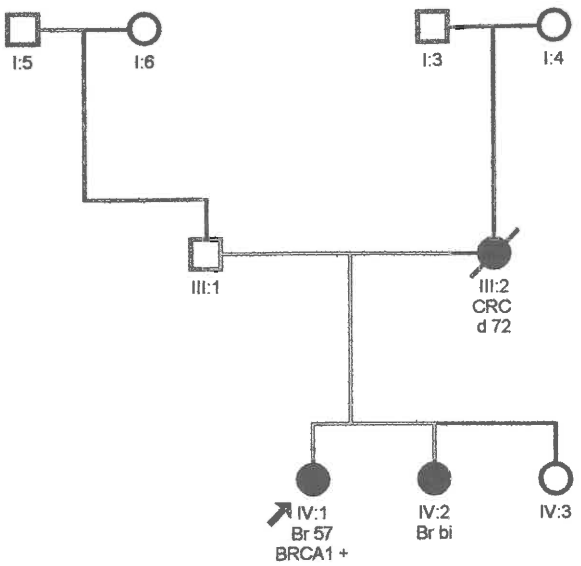


Figure 78. The *BRCA1* gene mutation in a breast cancer patient. Abbreviations in the figure: CRC, colorectal cancer; Br, breast cancer; d, dead; BRCA1+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

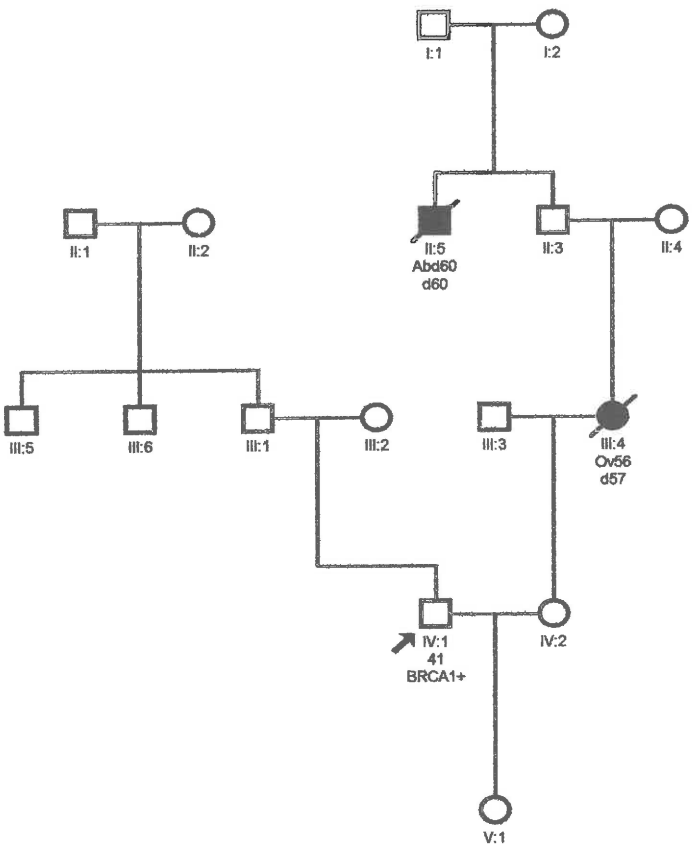


Figure 79. *BRCA1* gene mutation in a male carrier. Abbreviations in the figure: Abd, malignant tumour in the abdominal cavity, not further specified; Ov, ovarian cancer; d, dead; BRCA1+, mutation in *BRCA1* gene present. The age of cancer diagnostics is shown by number following

the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Comparison of different hereditary and familial cancer syndromes

In the summary of the population screening, the different hereditary and familial cancer syndromes were compared between themselves in order to assess the whole picture of the hereditary cancer spectrum in Latvia.

The identified pedigrees of hereditary and familial cancer syndromes were characterised by generally high frequency of malignant tumours among the blood relatives as shown in Table 32. Statistically significant diference of the cancer frequency between the definitive and suspected groups was found in case of HNPCC for index cancers and endometrial cancer, HSC for gastric cancer. In contrast, the frequency of colorectal cancer in HNPCC, HNPCC susp. and FCC was almost identical. Similarly, HEC, HEC susp., FEC and FEC susp. showed close frequencies of endometrial cancer.

Table 32. Comparison of different hereditary and familial cancer syndromes by frequency of index cancers in blood relatives of the affected kindreds

Syndrome	Tumour location	Frequency, %	95% CI, %
HBC susp.1	Breast	8.6	7.2 – 10.2
	Breast[1]	16.3[1]	13.8 – 19.1[1]
HBC susp.2	Breast	17.4	14.9 – 20.2
	Breast[1]	31.8[1]	27.5 – 36.4[1]
HBOC susp.1	Breast and ovary	10.3	4.8 – 20.8
	Breast and ovary[1]	19.3[1]	9.2 – 36.3[1]
HBOC susp.2	Breast and ovary	18.5	14.8 – 22.9
	Breast and ovary[1]	30.8[1]	25.0 – 37.3[1]
HOC susp.	Ovary	21.1	11.1 – 36.3
	Ovary[1]	36.4[1]	19.7 – 57.0[11]
HNPCC	Index cancers	30.1	23.3 – 38.0
	Colorectal cancer	15.8	10.7 – 22.5
	Endometrial cancer	13.0	8.5 – 19.4
	Endometrial cancer[1]	14.8[1]	4.5 – 32.3[1]
HNPCC susp.	Index cancers	15.5	11.6 – 20.3
	Colorectal cancer	10.6	7.4 – 14.8
	Endometrial cancer	4.9	2.9 – 8.2
	Endometrial cancer[1]	9.6	5.7 – 15.8[1]

FCC	Colorectal cancer	17.0	12.8 – 22.3
HEC	Endometrial cancer[1]	41.5[1]	27.8 – 56.6[1]
HEC susp.	Endometrial cancer[1]	32.2[1]	25.7 – 39.4[1]
FEC / FEC1	Endometrial cancer[1]	30.0[1]	23.8 – 37.1[1]
FEC2	Endometrial cancer[1]	32.4[1]	22.4 – 44.2[1]
FLC	Lung cancer	25.5	19.3 – 32.8
FLC susp.	Lung cancer	17.2	15.0 – 19.7
HSC	Gastric cancer	25.2	20.6 – 30.4
HSC susp.	Gastric cancer	16.0	13.8 – 18.5
HPC	Prostate cancer[2]	21.4[2]	7.6 – 47.6[2]
HPC susp.	Prostate cancer[2]	22.2[2]	16.4 – 29.4[2]
FBlaC d/s	Urinary bladder cancer	22.8	14.9 – 33.2
FHemT d/s	Malignant haematologic tumour	16.3	12.1 – 21.2
FPan	Index cancers	14.7	9.1 – 22.9
FBtT	Brain tumour	32.3	18.6 – 49.9
FBtT susp.	Brain tumour	14.4	10.4 – 19.5

[1] in female

[2] in male

Abbreviations in table: CI, confidence interval; HBC susp.1, suspected hereditary breast cancer, variety 1; HBC susp.2, suspected hereditary breast cancer, variety 2; HBOC susp.1, suspected hereditary breast ovarian cancer, variety 1; HBOC susp.2, suspected hereditary breast ovarian cancer, variety 2; HOC susp., suspected hereditary ovarian cancer; HNPCC, hereditary non-polyposis colorectal cancer; HNPCC susp., suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; FLC, familial lung cancer; FLC susp., suspected familial lung cancer; HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; HPC, hereditary prostate cancer; HPC susp., suspected hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; d/s, definitive and suspected; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour; FBtT susp., suspected familial brain tumour.

The population frequencies of clinical syndromes (Table 33) were determined in order to characterize the expedience of the corresponding clinical criteria. These data were applied to

estimate the hypothetical load of hereditary cancer in Latvian population as will be shown in discussion.

Table 33. Comparison of different hereditary and familial cancer sydromes by population frequency

Syndrome	Number	Population frequency	95% CI, %
HBC susp.1	117	0.628	0.524 – 0.752
HBC susp.2	64	0.343	0.269 – 0.438
HBOC susp.1	6	0.032	0.015 – 0.070
HBOC susp.2	29	0.156	0.108 – 0.223
HOC susp.	4	0.021	0.008 – 0.055
HNPCC	11	0.059	0.033 – 0.106
HNPCC susp.	20	0.107	0.069 – 0.166
FCC	20	0.107	0.069 – 0.166
HEC	5	0.027	0.011 – 0.063
HEC susp.	26	0.139	0.095 – 0.204
FEC / FEC1	26	0.139	0.095 – 0.204
FEC2	9	0.048	0.025 – 0.092
FLC	13	0.070	0.041 – 0.119
FLC susp.	93	0.499	0.407 – 0.611
HSC	21	0.113	0.074 – 0.172
HSC susp.	74	0.397	0.316 – 0.498
HPC	1	0.005	0.001 – 0.030
HPC susp.	21	0.113	0.074 – 0.172
FBlaC d/s	12	0.064	0.037 – 0.112
FHemT d/s	17	0.091	0.057 – 0.146
FPan	10	0.054	0.029 – 0.099
FBtT	3	0.016	0.005 – 0.047
FBtT susp.	16	0.086	0.053 – 0.139

Abbreviations in table: CI, confidence interval; HBC susp.1, suspected hereditary breast cancer, variety 1; HBC susp.2, suspected hereditary breast cancer, variety 2; HBOC susp.1, suspected hereditary breast ovarian cancer, variety 1; HBOC susp.2, suspected hereditary breast ovarian cancer, variety 2; HOC susp., suspected hereditary ovarian cancer; HNPCC, hereditary non-polyposis colorectal cancer; HNPCC susp., suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial

endometrial cancer, variety 2; FLC, familial lung cancer; FLC susp., suspected familial lung cancer; HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; HPC, hereditary prostate cancer; HPC susp., suspected hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; d/s, definitive and suspected; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour; FBtT susp., suspected familial brain tumour.

The syndromes were characterised also by the age of tumour disgnostics and tumour-related death as shown in Table 34. HBC susp.1 was characterised by the lowest mean age of tumour diagnostics that can be at least partially explained by the stringency of diagnostic criteria. The mean age was below 50 years of age in HBC, HBC susp.1, HBOC susp.1, HOC, FHemT, FBtT, endometrial cancer group within HNPCC and HEC susp., suggesting marked trend towards tumour occurrence in young persons. Childhood cases have been reported in FBtT, FHemT and FLC. The youngest cases have been affected early in all groups, even in syndromes like FCC of FEC2 that were not limited by the age in the diagnostic criteria. FBlaC was the only exception, occurring only in aged persons.

Table 34. Comparison of different hereditary and familial cancer syndromes by age of tumour manifestation

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HBC	40 – 55	47.5 (37.1 – 57.8)	50 – 60	54.7 (50.0 – 59.4)
HBC1	20 – 70	38.0 (36.2 – 39.7)	26 – 78	44.7 (41.7 – 47.7)
HBC2	25 – 82	51.8 (48.9 – 54.6)	25 – 66	60.9 (56.7 – 65.1)
HBOC	34 – 82	61.0 (46.9 – 75.0)	58 – 85	71.4 (54.9 – 87.9)
HBOC1	40 – 60	48.8 (44.2 – 53.3)	47 – 69	54.3 (42.3 – 66.3)
HBOC2	18 – 86	56.6 (51.8 – 61.4)	23 – 87	66.1 (61.2 – 71.0)
HOC	34 – 70	49.7 (4.0 – 95.4)	72	72
HOC susp.	45 – 70	54.2 (46.4 – 61.9)	47 – 72	57.2 (50.1 – 64.3)
HNPCC	30 -77	54.2 (50.2 – 58.2)	28 – 89	61.7 (54.2 – 69.2)
CRC	36 – 77	59.3 (53.8 – 64.8)	28 – 89	61.5 (52.9 – 70.0)
Ut	30 – 65	48.4 (43.4 – 53.4)	37 – 72	NA
HNPCCs	27 – 82	53.7 (49.1 – 58.3)	28 – 88	55.5 (49.5 – 61.5)
CRC	28 – 82	55.2 (49.1 – 61.3)	32 – 88	56.7 (49.9 – 63.5)
Ut	27 – 72	50.5 (43.0 – 58.0)	28 – 73	51.2 (33.1 – 69.3)
FCC.	41 – 89	72.0 (67.3 – 76.7)	52 – 90	76.3 (73.1 – 79.5)
HEC	40 – 75	52.1 (47.2 – 57.0)	44 – 76	57.7 (49.6 – 65.8)

HEC susp.	30 – 81	48.5 (44.4 – 52.6)	35 – 87	58.7 (53.6 – 63.8)
FEC/ FEC1	52 – 90	66.2 (63.5 – 69.9)	54 – 91	72.4 (69.4 – 75.4)
FEC2	26 – 82	57.6 (49.9 – 65.3)	26 – 83	63.3 (54.7 – 71.9)
FLC d/s	18 – 90	57.9 (55.9 – 59.9)	13 – 90	61.2 (58.5 – 62.1)
HSC	30 – 83	56.9 (53.4 – 66.3)	30 – 90	58.3 (55.3 – 61.3)
HSC susp.	34 – 95	62.5 (60.1 – 64.8)	37 – 96	65.6 (63.4 – 67.6)
HPC d/s.	35 – 75	57.7 (53.3 – 62.1)	37 – 80	60.7 (55.0 – 66.4)
FBlaC	60 – 87	70.7 (66.7 – 74.7)	65 – 92	75.7 (71.6 – 79.8)
FHemT	3 – 88	47.5 (38.9 – 56.1)	4 – 86	49.8 (40.5 – 59.1)
FPan	51 – 72	61.6 (57.3 – 65.9)	51 – 83	63.4 (58.2 – 68.6)
FBtT d/s.	2 – 77	43.9 (35.0 – 52.8)	2 – 77	47.8 (39.7 – 55.9)

Abbreviations in table: CIM, confidence interval for the mean; HBC, hereditary breast cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast cancer, variety 2; HBOC, hereditary breast ovarian cancer; HBOC1, suspected hereditary breast ovarian cancer, variety 1; HBOC2, suspected hereditary breast ovarian cancer, variety 2; HOC, hereditary ovarian cancer; HOC susp., suspected hereditary ovarian cancer; HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; NA, not applicable; HNPCCs, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; FLC, familial lung cancer; d/s, definitive and suspected; HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; HPC, hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour.

In order to test for the earlier occurrence of hereditary cancers in Valka population, the proportion of cases occurring before the age of 50 years was compared in the hereditary group and in the studied Valka population (Table 35). The proportion of cases occurring before the age of 50 was statistically significantly higher in the hereditary group for colorectal, endometrial, breast, lung cancer and haematological tumours.

Table 35. The proportion of early-onset cancer cases by location in the hereditary group in comparison with the whole studied Valka population

Location	Hereditary cancers		Valka population		p< 0.05[1]
	N	Prop. (95% CI)	N	Prop. (95% CI)	
Colorectal	19 / 92	20.6 (13.6-30.0)	43 / 777	5.8 (4.3-7.7)	Yes

Endometrial	51 / 181	28.2 (22.1-35.1)	158/1094	15.1(13.1-17.5)	Yes
Breast	170/ 310	54.8 (49.3-60.3)	279/1364	21.8(19.7-24.2)	Yes
Ovarian	16 / 51	31.4 (20.3-45.0)	39 / 156	27.1 (20.5-34.9)	No
Lung	35 / 232	15.0 (11.1-20.3)	147/1795	8.3 (7.1-9.6)	Yes
Stomach	20 / 225	8.9 (5. 8-13.3)	162/1615	10.2 (8.8-11.8)	No
Pancreas	0 / 21	0 (0-15.5)	19 / 302	6.3 (4.1-9.6)	No
Prostate	4 / 37	10.8 (4.3-24.7)	12 / 499	2.6 (1.5-4.4)	No
Haematologic	13 / 37	35.1 (21.8-51.2)	115 / 687	16.9 (14.3-19.9)	Yes
Bladder	0 / 24	0 (0-13.8)	11 / 249	4.6 (2.6-8.1)	No
Brain	10 / 43	23.3 (13.1-37.3)	14 / 96	14.9 (9.1-23.5)	No

[1]Difference statistically significant at $p<0.05$

Abbreviations in table: N, number; Prop., proportion; CI, confidence interval.

Using the data about the total number of cancers reported in the kindred by all recruited persons and the number of cancers in the families affected by definitive and suspected hereditary cancer syndrome, the fraction of familial or hereditary cancers was calculated for each location (Table 36). Only the index cancers were encountered. All syndromes that include cancer of particular location as a diagnostic criterion were encountered.

These fractions are among the most significant findings of the population screening as they highlight the importance of the hereditary cancer concept in the practical identification of risk groups and in the oncologic research. Ovarian cancer is characterized by the highest PAF in accordance with the well-known role and high frequency of *BRCA* mutations in ovarian cancers. However, all the most frequent cancer locations are characterized by PAF of hereditary cancer exceeding 10%.

Table 36. Population-attributable fraction

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Colorectal	11.8	9.8 – 14.3	3.0	2.0 – 4.4
Endometrial	16.5	14.5 – 18.9	3.8	2.9 – 5.1
Breast	25.0	22.7 – 27.4	0.8	0.4 – 1.4
Ovarian	35.4	28.1 – 43.5	3.5	1.5 – 7.9
Lung	12.9	11.5 – 14.6	2.4	1.8 – 3.2
Stomach	13.8	12.2 – 15.6	4.7	3.8 – 5.9
Pancreas	6.3	4.1 – 9.6	6.3	4.1 – 9.6
Melanoma	20.0	8.1 – 41.6	10.0	2.8 – 30.1
Prostate	7.4	5.4 – 10.1	0.6	0.2 – 1.8

Haematologic	5.4	3.9 – 7.3	0.6	0.2 – 1.5
Kidney	1.5	0.7 – 3.2	0	0 – 0.1
Urinary bladder	9.6	6.6 – 13.9	2.4	1.1 – 5.2

Abbreviation in the table: CI, confidence interval.

The data about proband's health status were summarized in Table 37

Table 37. Proband's health status

Syndrome	Affected probands	
	Number	Frequency (95% CI)
HB/OC	1/5	20% (3.6 – 62.4%)
HBC1	5/117	4.3% (1.8 – 9.6%)
HBC2	12/64	18.8% (11.1 – 30.0%)
HBOC1	0/6	0% (0 – 39.0%)
HBOC2	6/29	20.7% (9.8 – 38.4%)
HOC susp.	0/4	0% (0 – 49.0%)
HNPCC d/s, FCC	4/51	7.8% (3.1 – 24.9%)
HEC, FEC d/s	8/56	14.3% (7.4 – 25.7%)
FLC d/s	0/106	0% (0 – 3.5%)
HSC d/s	1/95	1.1% (0.2 – 5.7%)
HPC d/s	5/22	22.7% (10.1 – 43.4%)
FBlaC d/s	0/11	0% (0 – 25.9%)
FHemT d/s	1/17	5.9% (1.0 – 27.0%)
FPan d/s	1/10	10% (1.8 – 40.4%)
FBtT d/s	0/19	0% (0 – 16.8%)

Abbreviations in table: CI, confidence interval; HB/OC, hereditary breast and/or ovarian cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast cancer, variety 2; HBOC1, suspected hereditary breast ovarian cancer, variety 1; HBOC2, suspected hereditary breast ovarian cancer, variety 2; HOC susp., suspected hereditary ovarian cancer; HNPCC, hereditary non-polyposis colorectal cancer; d/s, definitive and suspected; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; FEC, familial endometrial cancer; FLC, familial lung cancer; HSC, hereditary stomach cancer; HPC, hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour.

The course of malignant tumours was characterized by first-years lethality, survival and frequency of the affected persons who were alive at the time of population screening (Table 38).

Table 38. The course of the malignant tumours within hereditary and familial cancer syndromes

Syndrome	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
HBC	2/6	33.3 (9.7-70.0)	4.5 (0-14.2)	0/6	0 (0-39.0)
HBOC	1/7	14.3 (2.6-51.3)	4.8 (0-10.9)	2/7	28.6 (8.2-64.1)
HOC	0/3	0 (0-56.2)	2.0	2/3	66.7 (20.8-93.9)
HBC1	17/117	14.5 (9.3-22.0)	7.5 (4.8-10.2)	41/117	35.0 (27.0-44.0)
HBC2	14/126	11.1 (6.7-17.8)	8.1 (5.2-11.0)	48/126	38.1 (30.1- 46.8)
HBOC1	1/6	16.7 (3.0-56.3)	5.7 (0-13.4)	3/6	50.0 (18.8- 81.2)
HBOC2	8/59	13.6 (7.0-24.5)	7.1 (3.9-10.3)	17/59	28.8 (18.8-41.4)
HOCs	2/7	28.6 (8.2-64.1)	3.0 (0.3-5.7)	0/7	0 (0-35.4)
HNPCC	8/44	18.2 (9.5-32.0)	2.6 (0-5.2)	23/44	52.3 (37.9-66.2)
CRC	6/23	26.1 (12.5-46.5)	1.7 (0.6-2.7)	6/23	26.1 (12.5-46.5)
Ut	1/19	5.3 (0.9-24.6)	8.5	17/19	89.5 (68.6-97.1)
HNPCCs	14/42	25.0 (15.5-37.7)	2.3 (1.1-3.5)	14/42	33.3 (21.0-48.4)
CRC	10/29	34.5 (19.9-52.6)	2.5 (1.2-3.8)	7/29	24.1 (12.2-42.1)
Ut	4/13	30.8 (12.7-57.6)	1.5 (0-3.5)	7/13	53.8 (29.1-76.8)
FCC	10/41	24.4 (13.8-39.3)	2.2 (1.3-3.1)	5/41	12.2 (5.3-25.5)
HEC	7/17	41.2 (21.6-64.0)	6.1 (0-13.9)	5/17	29.4 (13.3-53.1)
HECs	8/56	14.3 (7.4-25.7)	9.7 (5.1-14.3)	15/56	26.8 (17.0-39.6)
FEC/FEC1	14/54	25.9 (16.1-38.9)	4.7 (1.1-8.3)	14/54	25.9 (16.1-38.9)
FEC2	10/22	45.4 (26.9-65.3)	2.8 (0.8-4.8)	5/22	22.7 (10.1-43.4)
FLC d/s	90/208	43.3 (36.7-50.0)	2.0 (1.1-2.9)	3/208	1.4 (0.5-4.2)
HSC	17/76	22.4 (14.5-32.9)	2.6 (1.2-4.0)	4/76	5.3 (2.1-12.8)
HSCs	54/149	36.2 (28.9-44.2)	2.4 (1.7-3.1)	8/149	5.4 (2.7-10.2)
HPC d/s	5/34	14.7 (6.4-30.1)	4.5 (0.5-8.5)	14/34	41.2 (26.4-57.8)
FBlaC d/s	3/18	16.7 (5.8-39.2)	4.8 (1.7-6.5)	3/18	16.7 (5.8-39.2)
FHemT	11/37	29.7 (17.5-45.8)	1.9 (1.1-2.7)	7/37	18.9 (9.5-34.2)
FPan	15/21	71.4 (50.0-86.2)	1.1 (0.2-1.4)	1/21	4.8 (0.8-22.7)
FBtT d/s	16/26	61.5 (42.5-77.6)	1.5 (0.3-2.7)	2/26	7.7 (2.1-24.1)

Abbreviations in table: N, number; Fr., frequency; CI, confidence interval; HBC, hereditary breast cancer; HBOC, hereditary breast ovarian cancer; HOC, hereditary ovarian cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast

cancer, variety 2; HBOC1, suspected hereditary breast ovarian cancer, variety 1; HBOC2, suspected hereditary breast ovarian cancer, variety 2; HOC susp., suspected hereditary ovarian cancer; HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; HNPCCs, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; HECs, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; FLC, familial lung cancer; d/s, definitive and suspected; HSC, hereditary stomach cancer; HSCs, suspected hereditary stomach cancer; HPC, hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour.

The national composition was studied in several groups by data reported by the proband itself. The results are reflected in Table 39. In general, the national stucture was homogeneous, however, several important exceptions were found. The frequency of Latvians in the *BRCA1*-mutation positive group was lower than in Valka population. This diference was statistically significant, as shown by non-overlapping confidence intervals representing 79.3 – 80.4% for the investigated population and 10.8 – 60.3% for the mutation carriers. The mutation carriers reported affiliation to Russian (40% 95% CI = 16.8 – 68.7%) and Ukrainian (30%; 95% CI = 10.8 – 60.3%) nationalities significantly more frequently than it was found in the Valka population (11.4 – 12.3% and 1.50 – 1.87%, respectively). In the HNPCC group, the frequency of Latvians (28. 0 – 78.7%) was sugnificantly lower than in population on the expense of significantly increased frequency of reported Russian nationality: 11.4 – 12.3% in the studied Valka population *versus* 21.3 – 72.0% in HNPCC group. In the suspected FLC group the frequency of reported Latvian nationality (71.0%, 95% CI = 61.1 – 79.2%) is lower than in the screened Valka population.

Table 39. The national composition of studied subgroups

Syndrome	Total	Latvian	Li	Ru	Ukr	Po	Byel	Est	Oth
HBC	2	2	0	0	0	0	0	0	0
HBOC	2	2	0	0	0	0	0	0	0
HOC	1	0	1	0	0	0	0	0	0
HBC1	117	98	2	12	1	3	1	0	0
HBC2	64	57	0	6	0	0	0	0	1
HBOC1	6	6	0	0	0	0	0	0	0
HBOC2	29	22	6	0	0	1	0	0	0
HNPCC	11	6	5	0	0	0	0	0	0

HNPCCs	20	15	0	2	1	1	0	0	1
FCC	20	19	0	1	0	0	0	0	0
HEC	5	4	0	1	0	0	0	0	0
HECs	26	23	0	2	0	0	0	0	1
FEC	2	2	0	0	0	0	0	0	0
FEC1	26	18	1	4	0	0	1	0	0
FEC2	9	9	0	0	0	0	0	0	0
FLC	13	10	0	2	0	0	1	0	0
FLCs	93	66	0	22	0	1	2	2	0
HSC	21	19	0	1	0	0	0	0	1
HSCs	74	62	1	9	0	0	0	2	0
HPC	1	1	0	0	0	0	0	0	0
HPCs	21	18	1	2	0	0	0	0	0
FBlaC	2	2	0	0	0	0	0	0	0
FBlaCs	9	5	0	3	0	0	1	0	0
FHemT	1	1	0	0	0	0	0	0	0
FHemTs	16	15	0	1	0	0	0	0	0
FPan	10	10	0	0	0	0	0	0	0
FBtT	3	3	0	0	0	0	0	0	0
FBtTs	16	13	0	3	0	0	0	0	0
BRCA	10	3	0	4	3	0	0	0	0
Total	18642	14887	97	2201	312	171	395	120	459

Abbreviations in table: Li, Lithuanian; Ru, Russian; Ukr, Ukrainian; Po, Polack; Byel, Byelorussian; Est, Estonian; Oth, others and unknown nationality; HBC, hereditary breast cancer; HBOC, hereditary breast-ovarian cancer; HOC, hereditary ovarian cancer; HBC1, suspected hereditary breast cancer, variety 1; HBC2, suspected hereditary breast cancer, variety 2; HBOC1, suspected hereditary breast-ovarian cancer, variety 1; HBOC2, suspected hereditary breast-ovarian cancer, variety 2; HNPCC, hereditary non-polyposis colorectal cancer; HNPCCs, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; HEC, hereditary endometrial cancer; HECs, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2; FLC, familial lung cancer; s, suspected; HSC, hereditary stomach cancer; HPC, hereditary prostate cancer; FBlaC, familial cancer of urinary bladder; FHemT, familial aggregation of haematological tumours; FPan, familial pancreatic cancer; FBtT, familial brain tumour; *BRCA*, *BRCA1* mutation carriers.

DISCUSSION OF THE RESULTS

Principles of the setup of population screening

Population screening for hereditary cancer is a possibility to identify healthy persons at higher cancer risk thus giving input in the early diagnostics and prevention of cancer. Performance of the prophylactic measures in this group can be recommended to improve the results of cancer care.

In contrast to more widespread population-based hereditary cancer identification programs based on the examination of cancer patient, population screening is aimed primarily at risk identification of healthy persons before any tumour development (Grody, 2003). As shown by our results, this can be successfully achieved before the tumour development in a proband having diagnosis of definitive hereditary cancer syndrome or, adding genetic search for specific mutations, before definite clinical diagnosis of fully developed hereditary cancer syndrome in the kindred.

Besides that, knowledge about the genetic characteristics of the population such as frequency of particular gene damage and frequency of specific mutations will also provide a valuable tool for future screening programs aiming at reduced cancer burden in the population by timely diagnostics of hereditary cancer cases. The characteristic of population might also serve as basis for a future insight in cancerogenesis by co-analysing local genetic and environmental factors.

The population screening programs for hereditary cancer still are in the stage of development as Pubmed search brought almost no results of similar trials. Therefore our experience might be valuable for other centres planning and setting up programs with similar goals. Taking into account the above mentioned reasons, we carried out the population screening for hereditary cancer in Valka district.

In our experience, population screening for hereditary cancer is easily manageable. The compliance of population during screening program was sufficiently high – 76.6% of the adult population voluntarily took part in the screening program. This is in accordance with previously published experience from the population screening in West Pomerania region, Poland, mentioning participation rate 74.0% (1 258 401/1 700 000) of population or 87% of individuals who were insured in the West Pomeranian Regional Health Foundation (Gronwald, Raczynski *et al.*, 2006). Thus, there is evidence that accurate management will result in appropriate public response. Although well-informed individual is able to complete the questionnaire without assistance, we found useful to involve family doctors in this process as we agree with Eccles, 2004 that the family history should be taken and evaluated properly in order to exclude misunderstanding of diagnoses or even manifestation of Munchausen's syndrome.

Comparison of the expedience of population and hospital screening in hereditary cancer detection in several hereditary cancer models

Breast cancer

Breast cancer is the most frequent malignant tumour in women with approximately thousand of new cases in Latvia. This is a major challenge for the practice and science of oncology considering the still significant mortality, on the one hand, and the positive trends on the other – the possibilities of timely diagnostics, screening, expanding possibilities to apply individualised oncological treatment and growing understanding about biology, including the genetic basis.

Taking into account the above mentioned facts, breast cancer was selected as the first model in order to compare the expedience of population screening and hospital screening for hereditary cancer.

The hospital screening data are described by Gardovskis, 2008. In brief, the hospital screening for hereditary breast cancer syndromes was carried out in the largest oncology hospitals of Latvia, namely the Oncology Centre of Latvia, beginning from 11/2005, as well as Oncology Hospital of Liepaja, P.Stradin's Clinical University Hospital and Oncology Hospital of Daugavpils beginning from 01/2004 and lasting until 06/2007. Cases were considered consecutive, if at least 70% of newly diagnosed patients were involved in the study from the particular hospital in the given period of time. Similarly to the population screening, no patient selection was performed; all adult inhabitants of Valka district as well as all patients treated for the described diagnoses in the above mentioned oncology hospitals within the respective time period were invited for discussion in order to collect family cancer anamnesis. By this approach, among 1011 consecutive hospital breast cancer cases, there were 10 cases of HBC, 6 cases of HBOC, 147 cases of suspected hereditary breast cancer (including 61 case of HBC susp.1 and 86 cases of HBC susp.2) and 11 cases of HBOC susp., corresponding to clinical frequency of hereditary cancer syndromes involving breast: HBC, 0.99% [95% CI = 0.5 – 1.8%]; HBOC, 0.59% [95% CI = 0.3 – 1.3%]; HBC susp., 14.54% [95% CI = 12.5 – 16.8%]; and HBOC susp., 1.09% [95% CI = 0.6 – 1.9%].

In European Union, there were 370100 new cases of breast cancer in 2004 constituting 12.8% of all malignant tumours (Boyle and Ferlay, 2005). It has an estimated cumulative risk (age 0 – 74 years) of 7.79% (Boyle and Ferlay, 2005). Using this value and the clinical frequencies of breast cancer having definitive and suspected hereditary basis among all breast cancers 1.58% [95% CI = 1.0 – 2.6%] and 15.62% [95% CI = 13.5 – 18.0%], as detected by hospital screening, prevalence of breast cancer with definitive hereditary basis in Latvian females can be expected to be 12.3 per ten thousands with the interval 7.79 – 20.3 per 10000 as based on 95% confidence interval of the corresponding relative value. Similarly, prevalence of breast cancer with suspected

hereditary basis in Latvian females can be expected to be 121.7 or within interval 105.2 – 140.2 per ten thousands (Table 40).

Table 40. Prevalence of hereditary breast cancer syndromes by hospital screening data

Diagnosis	Number of cases[1]	Relative frequency among cancer cases, % [95% CI]	Prevalence among female per ten thousands
Hereditary breast cancer	10	0.99 [0.5 - 1.8]	7.7 [3.9 - 14.0]
Hereditary breast-ovarian cancer	6	0.59 [0.3 - 1.3]	4.6 [2.3 - 10.1]
Hereditary breast and breast-ovarian cancer	16	1.58 [1.0 – 2.6]	12.3 [7.79 – 20.3]
Suspected hereditary breast cancer	147	14.54 [12.5 – 16.8]	113.3 [97.4 - 130.9]
Suspected hereditary breast-ovarian cancer	11	1.09 [0.6 – 1.9]	8.5 [4.7 - 14.8]
Suspected hereditary breast and breast-ovarian cancer	158	15.62 [13.5 – 18.0]	121.7 [105.2-140.2]
Total hereditary breast-ovarian cancer syndromes	172	17.01 [14.8 – 19.5]	132.5 [115.3 - 151.9]
Total	1011		

[1]By Gardovskis, 2008

Abbreviation in table: CI, confidence interval

In the result of population screening, the prevalence of definitive hereditary breast cancer syndromes is estimated 2.9 or within interval 1 – 8.4 per ten thousands as based on 95% CI of the corresponding relative value. The prevalence of suspected hereditary breast cancer syndromes in the result of population screening is estimated as 149 within interval 128 – 175 per ten thousands females (Table 41). The prevalence for males was calculated separately and is also presented in the table 41.

Table 41. Prevalence of breast hereditary cancer syndromes by population screening

Diagnosis	Number	Sex	Prevalence, per ten thousands [95% CI]
Hereditary breast and breast-ovarian cancer syndrome	3	F	2.9 [1 – 8.4][1]
	1	M	1.3 [0.2 – 7.2][2]
Suspected hereditary breast and breast-ovarian cancer syndrome	156	F	149 [128 – 175][1]
	67	M	85 [67 – 107][2]

[1]among female; [2]among male

Abbreviation in table: CI, confidence interval.

There is a trend towards higher yield of definitive hereditary breast cancer syndromes by hospital screening although the difference is not statistically significant at 95% probability level. This trend could be explained by the fact that in hospital screening the proband already has the disease thus adding one case of cancer to the kindred in comparison with the situation before the proband's illness. An additional cancer case in kindred can convert the diagnosis of suspected hereditary breast cancer into definitive. The same trend is reflected by the proportion of definitive hereditary breast cancer among all breast cancer cases with hereditary or suspected hereditary basis: 16 / 174 [9.2%, CI = 5.7 – 14.4%] among hospital cases in contrast to 4 / 220 [1.8%; CI = 0.7 – 4.6%] in the population screening. This difference is statistically significant at $p<0.05$ level. It might show the part of hereditary cancer cases that can be really prevented or at least diagnosed early by appropriate means in the result of population screening.

In the diagnostics of suspected hereditary breast cancer the population screening shows statistically insignificant trend towards greater yield, resulting in the prevalence of suspected hereditary breast cancer in females 149 (interval, based on 95% CI of the corresponding relative values 128 – 175) per ten thousands. However, additional cases of hereditary breast ovarian cancer syndrome were revealed among males – population group that was not reached through the hospital screening. This group demands additional efforts in order to explain the meaning of such diagnosis in men.

Taking into account the difficulties that embarrass both hospital and population screening, the frequency of suspected HBOC might be interpreted as more reliable characteristics of the hereditary cancer syndrome burden in local population.

These values can be compared to Telemark screening (Stormorken *et al.*, 2006), where prevalence for being at risk for definitive hereditary breast and breast-ovarian cancer was estimated as 2.8 per thousand equivalent to prevalence 28 per ten thousands, value that is

intermediate between the data about definitive and suspected hereditary breast cancer obtained for Latvian population.

The trend towards higher yield of population screening in the model of breast cancer can be confirmed also by the following estimates. Among 10642 females during their lifetime, 829 cases of breast cancer can be expected. Taking into account the rate of definitive hereditary breast cancer 1.58% [CI = 1.0 – 2.6%] and of suspected hereditary breast cancer 15.62% [CI = 13.5 – 18.0%] as estimated by hospital screening, there could be 13 (interval, based on 95% CI of the corresponding relative values 8.3 – 21.6%) patients with the diagnosis of hereditary breast cancer and 130 (interval, based on 95% CI of the corresponding relative values 111.9 – 149.2%) cases of suspected hereditary breast cancer. The population screening has disclosed only 3 female patients with definitive hereditary breast cancer syndromes, but 156 cases of suspected hereditary breast cancer syndromes.

Colorectal cancer

Colorectal cancer in Europe remains the second most common incident form of cancer with 376400 new cases in 2004 that constitutes 13% of all cancer cases (Boyle and Ferlay, 2005). Taking into account the high incidence and mortality of colorectal cancer that define this malignancy as an important medical problem (Boyle and Ferlay, 2005) and also the well-described role of heredity in the development of colorectal cancer (Lynch *et al.*, 1993; Lynch and de la Chapelle, 2003; Trimbath and Giardiello, 2002; Irmejs *et al.*, 2007), this location was selected as another model to study the expedience of hospital and population screening.

In the colorectal cancer hospital group, 1 [0.14%; 95% CI = 0.00 – 0.80%] case of definitive colorectal cancer was diagnosed along with 13 [1.85%; 95% CI = 1.1-3.1%] cases of suspected HNPCC and 20 [2.8%; 95% CI = 1.9 – 4.4%] cases of FCC among 702 consecutive cases (Irmejs *et al.*, 2007).

The cumulative risk (age 0 – 74 years) of colorectal cancer is estimated as 4.53% in EU men and 2.70% in women (Boyle and Ferlay, 2005). In a group of 18642 persons with gender composition analogous to Valka, 282 cases can be expected among 10438 females and 358 cases among 7904 males, resulting in 640 cases when reaching the upper age limit. Based on the local hospital screening data, 0.14% [95% CI = 0 – 0.80%] or 1 [95% CI = 0 – 5] case of definitive hereditary HNPCC can be expected among them as well as 30 [22 – 42] cases of hereditary colorectal cancer syndromes with lower risk. The population screening has disclosed 11 definitive cases of HNPCC syndrome and 40 syndromes of lower risk. Thus, in this model the population screening has shown higher yield of definitive hereditary cancer syndrome diagnostics. The yield of

suspected hereditary cancer syndrome also has been high, approaching closely the highest confidence level of the hospital screening. It has to be emphasized that the possibility to diagnose any hereditary cancer syndrome is not directly dependant on the age of the proband as the age of proband (in contrast to the age of the affected persons) is not included in limiting diagnostic criteria. The presence of cancer in proband itself also is not mandatory for diagnosing any hereditary cancer syndrome.

The frequency of definitive hereditary colorectal cancer in Latvia by hospital screening data is less than reported from Sweden, Denmark, Finland, Italy, USA and Israel, where the incidence of definitive hereditary colorectal cancer by Amsterdam criteria is between 0.5-1.5% of all newly diagnosed colorectal cancer cases, but is close to the frequency of 0.3% reported by scientists from the United Kingdom (Evans *et al.*, 1997; Olsson *et* Lindblom, 2003; Katballe *et al.*, 2002; Mecklin *et al.*, 1995; Cornaggia *et al.*, 2000; Peel *et al.*, 2000; Foulkes *et al.*, 2002). The group of Raedle *et al.* has reported frequency 3.2% of hereditary colorectal cancers among all colorectal cancers in German population (Raedle *et al.*, 2002); although the study group is small, the difference between German and Latvian data reaches statistical significance (Irmejs *et al.*, 2007). Thus, hospital screening yields lower number of definitive colorectal cancer than in other Western type societies. Hypothetically, lower frequency of definitive hereditary colorectal cancer in any particular country can be explained by ethnic differences as well as by frequency of factors causing sporadic colorectal cancer. Alternatively, it may be hypothesised that the trend towards higher frequency of hereditary colorectal cancer as revealed by population screening is more in line with other European data and thus can be considered true.

The following frequencies of suspected HNPCC are reported from other European countries: 1.4% in Great Britain (Evans *et al.*, 1997), 1.7% in Finland (Mecklin *et al.*, 1995), 6.84% in Poland (Kladny *et al.*, 2003), 4.6% in Italy (de Leon *et al.*, 1999). Thus, the frequency of suspected hereditary colorectal cancer by hospital screening data is within the "European interval" signalling that the true incidence of hereditary colorectal cancer in Latvia might be not lower than in other European countries. This hypothesis is confirmed by population screening data showing higher burden of definitive and suspected colorectal cancer.

It is possible to conclude that population screening discloses more patients at risk and also brings more information about the real burden of hereditary colorectal cancer in Latvia despite the fact that population screening faces the same problems as the hospital screening in Latvia – incomplete medical information about malignant tumours in previous generations due to several historical reasons.

Endometrial cancer

The endometrial cancer remains an important cause of female oncological morbidity. In the year 2006, there have been 372 new incident cases corresponding to 7.9% of malignant tumours in female and 4.0% of the whole malignant tumour burden in the Latvian population (Databases of the Central Statistics Board, accessed 09.11.2009). The cumulative incidence (age 0 – 74 years) of endometrial cancer in EU women is 1.50% (Boyle and Ferlay, 2005).

By hospital screening, 6 cases of HEC, 19 cases of HEC susp., 4 cases of FEC and 46 cases of FEC susp. have been observed in a hospital group comprising 672 endometrial cancer patients (Svampane *et al.*, accepted for publication in RSU Collection of Scientific Papers, 2009). These numbers correspond to the following frequencies: HEC by hospital screening, 0.9% (95% CI = 0.4 – 1.9%), HEC susp. by hospital screening, 2.8% (95%CI = 1.8 – 4.4%), FEC by hospital screening, 0.6% (95% CI = 0.2 – 1.5%), FEC susp. by hospital screening, 6.8% (95% CI = 5.2 – 9.0%).

Taking into account the cumulative risk of endometrial cancer and the frequency of definitive and suspected hereditary and familial endometrial cancer in the population, the frequency of endometrial cancer having definite hereditary basis can be estimated as 2.3 (interval, based on 95% CI of the corresponding relative values, 1.2 – 4.1) per 10 thousands. The hereditary basis of endometrial cancer could be suspected in further 14.6 (interval, based on 95% CI of the corresponding relative values, 11.6 – 18.2) cases per 10 thousands.

By population screening, the frequency of definitive hereditary cancer syndromes selectively involving endometrium, was 7 (interval, based on 95% CI of the corresponding relative values, 3.2 – 13.8), but the frequency of lower-risk syndromes – 49 (interval, based on 95% CI of the corresponding relative values, 37.2 – 64.2) per 10 thousands. Thus, higher yield of persons at risk is discovered by population screening. The difference is statistically significant in the case of suspected hereditary and familial endometrial cancer.

Ovarian cancer

The cumulative risk (0-74 years) of ovarian cancer in European Union, 2004 was estimated 1.21% (Boyle and Ferlay, 2005). In the result of the hospital screening (Gardovskis, 2008), the relative frequency of definitive hereditary ovarian and breast ovarian cancer presenting as ovarian cancer is determined as 3.7% [95% CI = 2.0 – 6.9%] and the relative frequency of suspected hereditary ovarian cancer and breast ovarian cancer presenting as ovarian cancer is calculated as 7.8% [95% CI = 5.1 – 11.9%]. This corresponds to the prevalence of hereditary ovarian cancer 4.5 per 10 thousand females with the interval 2.4 – 8.3 per 10000 as based on 95% confidence

interval of the corresponding relative value (see also Table 42) The prevalence of suspected hereditary ovarian cancer can be estimated as 9.4 per 10000 with the interval 6.2 – 14.4 per 10000 as based on 95% confidence interval of the corresponding relative value.

The total burden of hereditary breast and/or ovarian cancer by population and hospital screening is shown in Table 43.

Table 42. Yield of hereditary ovarian cancer syndromes by hospital screening

Diagnosis	Number of cases	Relative frequency among cancer cases, % [95% CI]	Prevalence among female per ten thousands
Hereditary ovarian cancer	1	0.4 [0.1 – 2.3]	0.5 [0.1 – 2.8]
Hereditary breast-ovarian cancer, presenting as ovarian cancer in the proband	8	3.3 [1.7 – 6.4]	4 [2.1 – 7.7]
Suspected hereditary ovarian cancer	4	1.6 [0.6 – 4.2]	1.9 [0.7 – 5.1]
Suspected hereditary breast-ovarian cancer, presenting as ovarian cancer in the proband	15	6.2 [3.8 – 9.9]	7.5 [4.6 – 12.0]
Definitive and suspected hereditary ovarian and breast ovarian cancer, presenting as ovarian cancer in the proband	28	11.5 [8.1 – 16.1]	13.9 [9.8 – 19.5]
Total	243		

Table 43. Total burden of hereditary breast and/or ovarian cancer by population and hospital screening.

Diagnosis	Prevalence among female per ten thousands
Hereditary ovarian and breast - ovarian cancer syndromes, presenting as ovarian cancer in the proband	4.5 [2.4 – 8.3][1]
Suspected hereditary ovarian and/or breast-ovarian cancer, presenting as ovarian cancer in the proband	9.4 [6.2 – 14.4][1]
Hereditary ovarian and breast-ovarian cancer syndromes by	3 [1.0 – 8.4][1]

population screening	
Suspected hereditary ovarian and breast-ovarian cancer syndromes by population screening	28 [19.4 – 39.9][1]

[1]the numbers in brackets describe the interval based on 95% CI of the corresponding relative value

It can be concluded that population screening allows to identify significantly higher number of suspected hereditary breast-ovarian cancer syndromes. No difference was found for the definitive syndromes.

Other cancer locations

There was no possibility to carry out similar comparative analysis of the hospital and population screening for hereditary and familial gastric cancer, familial lung cancer, familial haematological malignancies, and familial brain tumours as the population screening has brought the first scientific evidence of the existence and role of these familial cancer syndromes in Latvian population. More research, including the studies of hospital-based cases, should be focused in these directions, especially considering the most frequent syndromes as familial lung cancer or syndromes allowing prophylactic intervention as gastric cancer.

Family size as a hypothetic limiting factor in the diagnostics of hereditary and familial cancer syndromes

The diagnosis of familial or hereditary cancer syndromes in most cases requires defined number of index cancer cases. Occasionally, the properties of a single cancer case might draw attention in the genetic context, e.g., hereditary nature of breast cancer can be suspected if the patient is young. If the most frequent mutations are known, molecular workup of such cases occasionally could reveal the presence of the mutation and thus prove the hereditary nature of the given case. However, such cases are rare (Eccles, 2004). Also, the diagnostics of such situation requires constellation of several prerequisites: well-studied syndrome allowing suspicion of the diagnosis by a particular characteristics; known mutation and availability of the genetic testing allowing the exact diagnostics. Low output should be expected as a rule.

In many situations, the genetic analysis is not straightforward for several reasons including incomplete data about the characteristics of the hereditary cases and the clinical differences between the hereditary and sporadic cases; incomplete information about the mutations or even about the mutated gene, as well as a plenty of technical and economic reasons. In these cases,

clinical diagnostics gain the utmost importance. Mostly, 3 cases of particular cancer should be present in first-degree relatives to diagnose the hereditary cancer syndrome with certainty and 2 – to suspect the hereditary cancer.

Thus, if proband is a true carrier of oncogenic inherited mutation, but has no information about the relatives (e.g., an adopted child) the diagnosis of hereditary cancer syndrome or hereditary cancer is not possible.

If the proband is a true carrier of oncogenic inherited mutation and can report only the health status of the parents, diagnosis of suspected hereditary cancer becomes possible when the proband develops disease assuming penetrance of 100%, sufficient lifespan and proper diagnostics in mutation carriers. However, such a nuclear family cannot provide history in order to diagnose definitive hereditary cancer syndrome. Also, diagnosis of suspected hereditary cancer would not become evident before the development of the disease in the proband.

If the information about grandparents is added to the previously described scenario, definitive hereditary cancer syndrome can be diagnosed if the proband is affected but otherwise diagnosis of suspected hereditary cancer syndrome should attract attention to the increased risk of a particular tumour in the proband.

Finally, adding 1 more affected first-degree relative to the previous family history would lead to the diagnosis of hereditary cancer syndrome in the proband already before the disease. The summary of these considerations is shown in the Table 44.

Table 44. Minimal requirements of family size for several diagnostic conclusions

Description of the family	All[1]	Line[2]	Possible conclusions
Proband only	1	1	Cancer risk prediction by family history not possible Diagnostics of definitive or suspected hereditary cancer or syndrome by clinical means not possible Molecular investigation for a mutation possible but may be limited due to lack of indications
Proband and his/her parents	3	2	Cancer risk prediction by family history cannot be based on the diagnosis of definitive or suspected hereditary cancer syndrome Diagnostics of suspected hereditary cancer or

			syndrome not possible before proband's illness Suspected hereditary cancer can be diagnosed if proband becomes affected Diagnostics of definitive hereditary cancer or syndrome not possible
Proband, his/her parents and grandparents	7	3	Suspected hereditary cancer syndrome can be diagnosed if proband is healthy Increased risk of cancer in the proband can be identified Definitive hereditary cancer can be diagnosed if proband is affected
Proband, his/her parents and grandparents, an additional first-degree relative	8	4	Definitive hereditary cancer syndrome can be diagnosed if proband is healthy Increased risk of cancer in the proband can be identified

[1]Number of reported blood relatives of the proband

[2]Number of blood relatives in the affected line

The results of the population screening are in agreement with these theoretical considerations: the lowest number of blood relatives in families diagnosed with definitive hereditary cancer syndrome is 7, but the lowest number of blood relatives in families diagnosed with suspected hereditary cancer syndrome is 3, corresponding exactly to the theoretical lowest number of blood relatives necessary for this diagnosis.

These findings are encouraging in the light of the following theoretical analysis of the family size. Although, as will be discussed further, small family size can limit the possibility to reveal the true hereditary nature of a tumour, the Valka population screening study has been successful in the identification of cancer risk in such small families. Thus, the population screening has shown that the diagnosis can be reached before the tumour develops, even if the families has the theoretically lowest diagnostically informative number of blood relatives.

The following theoretical considerations are devoted to the possibility to diagnose true hereditary cancer in families of different size.

The possibility to reveal a really existing mutation depends on the size of the kindred. If we assume that a female, carrying *BRCA* mutation and having *BRCA*-related cancer, becomes a foundress of a hypothetical kindred with only one child in each of next two generations, the

probability that her only child will be a daughter carrying mutation and developing disease with the highest penetrance for breast cancer is not greater than 0.5x0.5x0.87 that equals 0.22. Taking into account the next generation, the probability of the third tumour in this kindred drops until 0.05. The other possibilities of non-penetrant mutation in female offspring or having male offspring with even lower penetrance still exist but do not allow the clue to clinical diagnosis. Thus, the chance to diagnose clinically this kindred with a real mutation drops until 5%. In contrast, if there are 3 children in each generation, the probability of having at least one daughter is $1\text{-}0.5^3$ equals 0.875; the probability of having manifested mutation in female is 0.38 and the probability of having third female in the next generation with a clinically manifested mutation is already 0.15, almost three times greater than upon previously assumed conditions.

In the same kindred, hereditary cancer could be diagnosed also, if two daughters of the foundress become affected by breast cancer. The probability that 2 of 3 children are female equals to the probability of having 1 son, namely, $3x0.5^3 = 0.375$. The probability of them to be affected might be estimated as $0.375x (0.5x0.87)^2 = 0.07$. Thus, the probability to diagnose this kindred through 3 affected females in 3 generations is 0.15 and in 2 generations – 0.07, resulting in probability of independent events 0.22.

In the same kindred, after we have postulated that at least one offspring is a female with mutation related tumour that might occur with a probability of 0.38, the other two according to the present hypothetical situation might be males. The probability that at least one of these children carries a mutation is $1 - 0.5^2$, the possibility that the male carrier has at least one daughter who is also a carrier of mutation and clinically overt disease, is 0.75x0.5x0.875x0.5x0.87=0.14. In total, the chance to diagnose the real hereditary cancer in this pedigree by clinical means is at least 0.36.

Several conclusions can be suggested. It might be emphasized that size of family can restrict the clinical diagnostics of hereditary cancers significantly. In a Western type society, it might be recommended to employ genetic testing more widely, not limiting it only to persons with hereditary cancer syndrome or suspicions of hereditary cancer syndrome. The evidence of finding 7 *BRCA* mutations in people without such diagnosis serves as a proof of this recommendation. The adherence to strict clinical guidelines can be medically justified in populations with predominantly large families with beneficial economical effect for the population screening. Clinical selection criteria are also useful to select cases with the highest likelihood of detecting a mutation in order to limit the cost of testing (Eccles, 2004). The conclusion is in accordance with literature data and in fact explains why some criteria have been found to be too stringent.

On the contrary, in the result of the population screening no significantly different number of blood relatives in the affected line was found in the families diagnosed with hereditary cancer syndrome (mean 13.6; 95% CIM = 12.2 – 15.0), suspected hereditary cancer syndrome (mean 12.2; 95% CIM = 11.7 – 12.7) or CFA (mean 11.4; 95% CIM = 10.5 – 12.3). In contrast, the families with no hereditary / suspected hereditary cancer syndrome diagnosis were significantly smaller (mean 9.5; 95% CIM = 8.9 – 10.1). Thus, an evidence of family size as a factor influencing the clinical diagnostics of hereditary cancer is obtained in accordance with the theoretical considerations. However, the family size did not preclude successful diagnostics of the described cases. Hypothetically, the real number of hereditary cancer cases in the population could be even higher if part remains undiagnosed due to the family size. Further studies are indicated.

Interestingly, according to the family size there is no justification to expect more complete manifestation of suspected hereditary cancer syndrome or CFA in larger families if presence of the same mutations with the same penetrance is considered in the corresponding definitive and suspected syndrome. However, theoretically mutations with lower penetrance and possibly different clinical course could be responsible for lower number of affected persons in families of the same size.

Hereditary and familial tumour syndromes by location

In contrast to hospital screening (Irmejs, 2004; Irmejs *et al.*, 2007; Gardovskis, 2008; Gardovskis *et al.*, 2005), the population screening allows to analyse the whole spectrum of hereditary cancers.

Hereditary breast – ovarian cancer

The hereditary breast – ovarian cancer is already studied in Latvia on hospital basis (Gardovskis, 2008). The population screening repeatedly confirmed the importance of the syndrome. Applying the population screening, the hereditary breast – ovarian cancer research in Latvia was also extended by the establishment of the population frequencies of the given syndromes, the possibilities of surveillance and early diagnostics.

The population frequency of definitive hereditary breast and ovarian cancer syndromes is 0.03% (95% CI = 0.01 – 0.06%) and of the corresponding suspected syndromes 1.18% (95% CI = 1.04 – 1.35 %). The suspected hereditary breast and ovarian cancer syndromes form the largest group among the suspected hereditary cancer syndromes, constituting 40.1% (95% CI = 36.1 – 44.3%). In contrast, the definitive syndromes form only 6.8% (95% CI = 2.9 – 14.9%), and the difference is statistically significant. The hereditary breast cancer is one of the best known hereditary tumour

syndromes therefore detailed diagnostic criteria are available. It is possible that part of the less known tumour syndromes are diagnosed if the syndrome is marked as in case of definitive hereditary cancer but the corresponding cases with either incomplete kindred data or less pronounced manifestations corresponding to the level of suspicion for hereditary cancer syndrome may be missed. The comparatively low rate of definitive hereditary breast cancer can also be explained by the study design as was explained at the comparative analysis of hospital and population screening for hereditary breast cancer.

The identified families corresponded to the diagnostic criteria of definitive or suspected hereditary breast-ovarian cancer. Increased risk of breast and/ or ovarian cancer in such pedigrees is described in other populations (Hampel *et al.*, 2004). The data obtained by Valka population screening confirmed the increased risk of breast-ovarian cancer in the respective Valka families by showing increased frequency of breast and ovarian cancer among blood relatives. The frequency of index cancers in all the suspected syndromes exceed the cumulative frequency in EU females (Boyle and Ferlay, 2005), thus surveillance is indicated in all these cases. The criteria of the suspected hereditary breast – ovarian cancer syndrome had the highest yield. The results of the Valka population screening has substantiated the application of the clinical diagnostic criteria of definitive and suspected hereditary breast cancer. Dissemination of this knowledge for practical use should be encouraged.

The frequency of breast cancer among blood relatives in HBC susp.1 was statistically significantly lower than in HBC susp.2 paralleling the published views that occurrence of single early cancer case is less valid indicator of hereditary nature of cancer in the particular kindred (Eccles, 2004). However, as HBC susp.1 is the most frequent syndrome in the whole group of definitive and suspected hereditary breast and ovarian cancer, it still retains high diagnostic significance. Suspected hereditary breast cancer syndrome, variety 1, was also more frequently detected in younger age groups and had low rate of affected probands – thus, the syndrome represents a frequent entity that can be diagnosed in young and healthy persons that would benefit from the surveillance.

Hypothetically, in a young (aged 18 – 39) female from a hereditary breast cancer kindred and small nuclear family, the possibility to diagnose the hereditary status depends on the application of HBC susp.1 criteria, as the risk of illness in the proband itself is low during this age period, the data about mother's health status are available but the information about previous generation might be lost. In contrast, when a similar proband would reach higher age and thus move into age group 30 – 59 years, the risk of breast cancer in her generation becomes significant. If the proband or her sister would develop cancer, the kindred would correspond to the diagnostic

criteria of HBC susp.2. This is confirmed by the presented data, showing higher proportion of breast cancer among HBC susp.2 probands and age distribution that corresponds to this hypothesis: predominance of young probands in HBC susp.1 and peak of occurrence of susp.HBC2 in the age group 50 – 59.

Although the number of cases in the HBOC susp.1, HBOC susp.2 and HOC susp. groups is low, there is a trend towards more frequent occurrence of cancer in two-case families. This might be explained by different stringency of diagnostic criteria.

The reverse is true for HBC susp.1 and HBC susp.2, pointing towards relatively high numbers of clinically fulminant breast cancers in Valka district – occurring in females younger than 40 years or in male or early and bilaterally. As described in literature, these traits are characteristic for hereditary cancers therefore can be used as diagnostic criteria (Gardovskis *et al.*, 2005; Hampel *et al.*, 2004). However, fulminant course of hereditary breast cancer is not characteristic for population with high proportion of founder mutations (Borg *et al.*, 1999). Thus, the proportion HBC susp.1 : HBC susp.2 provides an indirect evidence of such genetic background that cannot be limited to *BRCA* founder mutations.

The mean age of the cancer diagnostics was within the economically active range for all the syndromes; although the 95% CIs in case of several syndromes extended above 60 years. Comparing the mean age of cancer diagnostics by the hospital screening (Gardovskis, 2008) and the population screening, in case of HBC and HBOC no statistically significant difference was observed as the mean age by hospital screening (50.2 and 47.2 years, respectively) was within the 95% CI by the population screening (37.1 – 57.8 years and 46.9 – 75.0 years, respectively). In contrast, the mean age of cancer diagnostics by hospital screening (Gardovskis, 2008) in case of HBC susp. 1 and HBC susp.2 (40.5 and 59.3 years, respectively) was higher than the upper limit of the 95% CI by population screening (36.2 – 39.7 and 48.9 – 54.6 years, respectively).

The high frequency of breast and ovarian cancer among the females of the affected blood lines, the age structure of the probands as well as their oncologic health status demonstrates the need for surveillance as will be discussed further.

Hereditary non-polyposis colorectal cancer syndrome and other hereditary/ familial colorectal cancer syndromes

Hereditary non-polyposis colorectal cancer is well-substantiated in the international medical literature devoted to its diagnostic criteria, molecular basis, risk evaluation and possibilities of intervention (Trimbath and Giardiello, 2002; Guillem *et al.*, 2006; Lynch, Shaw *et al.*, 1996). It

has also been studied in Latvian population on hospital patient basis (Irmejs, 2004; Irmejs *et al.*, 2007).

During the Valka district population screening, both HNPCC families and pedigrees affected by other hereditary colorectal cancer syndromes (HNPCC susp., FCC1, FCC2) were diagnosed. The population frequency of these groups was identified to be 0.06% (95% CI = 0.03 – 0.10%) in case of HNPCC and 0.22% (0.16 – 0.29%) in case of suspected hereditary and familial colorectal cancer syndromes. In a hypothetic population of 2 294 590 persons that equals in size the population of Latvia in 2006 (Data bases of the Central Statistics Board, accessed 09.11.2009) but would be identical to Valka population in the age structure, gender and national composition, these frequencies would correspond to 1377 (interval, based on the 95% CI of the relative value, 688 – 2295) persons diagnosed with HNPCC syndrome and 5048 (interval, based on the 95% CI of the relative value, 3671 – 6654) persons diagnosed with suspected hereditary colorectal cancer syndromes. The population estimates have not been described previously.

In order to estimate the magnitude of cancer risk in these pedigrees, the frequency of colorectal and endometrial cancer among blood relatives in the affected branch was analysed. The real tumour risk for mutation carriers is definitely greater as there was no possibility to exclude non-carriers by clinical means. However, parameter that can be evaluated on clinical basis is easy and cheap for general medical use, and can give insight in the importance of the problem.

The frequency of colorectal cancer among blood relatives of the affected line in HNPCC families was 15.8% (95% CI = 10.7 – 22.5%), in suspected HNPCC families - 11.3% (8.0 – 15.9%), in FCC families - 17.0% (12.8 – 22.3%). These values exceed significantly the described cumulative incidence (0 – 74 years) of colorectal cancer in EU that constitutes 4.53% in males and 2.70% in females (Boyle and Ferlay, 2005). Although there is a trend towards higher frequency of colorectal cancer in HNPCC and FCC syndromes in comparison with HNPCC susp., the difference is not statistically significant. Two important conclusions can be inferred from these data – the high frequency of colorectal cancer prompts prophylactic follow-up of persons belonging to the affected blood line. The surveillance for colorectal cancer should be equally intense for all the mentioned syndromes as the colorectal cancer frequency shows no statistically significant differences among the syndromes.

The frequency of colorectal cancer in the evaluated families is lower than the described 80% lifetime risk in mutation carriers (Lynch, Shaw *et al.*, 1996) due to the above mentioned reasons.

In the presented study, the incidence of definitive or suspected HNPCC syndromes was higher than of FCC syndromes but FCC still constitutes 39.2% of hereditary or familial colorectal cancer syndromes pointing towards diagnostic significance of FCC criteria. As similar data are published

in the result of hospital screening for hereditary colorectal cancer in Latvia (Irmejs *et al.*, 2007), this might be suggested as a general conclusion for the whole population.

In the previously noted hypothetical population, the identified population frequencies of hereditary and familial colorectal cancer syndromes and frequencies of colorectal cancer in these pedigrees would correspond to 891 colorectal cancer cases that could be prevented or at least identified early by population screening combined by the recommended follow-up as will be discussed further.

The frequency of HNPCC among the definitive hereditary cancer syndromes was 14.9% (95% CI = 8.5 – 24.7%). The frequency of other hereditary colorectal cancer syndromes in the suspected hereditary cancer group was 7.3% (95% CI = 5.4 – 9.8%). The frequency of colorectal cancer among all malignant tumours diagnosed in the Latvian population in 2006 is not statistically different, constituting 943 / 9102 cases (10.3%; 95% CI = 9.8 – 11.0%) in general population; 481 / 4418 (10.9 %; 95% CI = 10.0 – 11.8%) in males and 462 / 4684 (9.9 %; 95% CI = 9.0 – 10.8%) in females by the year 2006. Thus, as so far these data could point towards relative stable proportion of hereditary and sporadic cancers, possibly limited by the evolution.

Probands' age structure revealed that significant proportion of probands (45%; 95% CI = 32.3 – 58.6%) diagnosed with hereditary cancer syndromes are younger than 50 years of age. In addition, the younger age is more frequent in proband diagnosed with HNPCC and thus subjected to higher cancer risk. Thus, the age structure of probands is well-suited for timely initiation of surveillance. In addition, the age distribution of probands suggests elimination of HNPCC probands with advancing age. In contrast, the chance to be diagnosed with FCC increases with age as the older relatives enter the risk group.

The probands mostly were oncologically healthy themselves (81.8%; 95% CI = 52.3 – 94.9% in HNPCC; 95%; 95% CI = 76.4 – 99.1% in susp. HNPCC and 95%; 95% CI = 76.4 – 99.1% in FCC groups) – a finding that also suggests the possibility to reveal the persons at risk timely.

Female predominance was found among probands in all groups (63.6%; 95% CI = 35.4 – 84.8%) in HNPCC group, 90%; 95% CI = 69.9 – 97.2% in susp. HNPCC, 85%; 95% CI = 63.9 – 94.8% in FCC) reaching 82.4% (95% CI = 69.7 – 90.4%) in general, contrasting with 56.0% (55.3 – 56.7%) in the screened population. It is possible that males are deleted from the study group by the disease thus diminishing the possibility to identify them as probands.

The youngest cases died from colorectal cancer in early age, namely, 28 years. This early occurrence corresponds to the literature data about HNPCC (Lynch *et al.*, 2004) including even description of colorectal cancer in 19 years old patient.

The mean age of colorectal cancer diagnostics (59.3 (95% CI = 53.8 – 64.8) years in HNPCC, 55.2 (95% CI = 49.1 – 61.3) years in susp. HNPCC and 56.8 (95% CI = 52.6 – 60.9) years in the whole group of definitive and suspected HNPCC) was slightly larger than the result of 44 years published by Lynch, Shaw *et al.*, 1996. However, relatively young persons at the economically active age are affected. Once the person is affected by hereditary colorectal cancer, the prognosis is serious as reflected by low survival. The death also occurs prematurely: at the mean age of 61.5 (95% CI = 52.9 – 70.0) years in HNPCC, 56.7 (95% CI = 49.9 – 63.5) years in suspected HNPCC and 58.7 (95% CI = 53.6 – 63.8) years in the whole group of definitive and suspected HNPCC. Occasionally, colorectal cancer has caused death of the patients as early as 28 years of age. This also emphasizes the need to identify the persons at risk properly and to provide adequate follow-up possibilities.

Onset of hereditary colorectal cancer after the age of 50 is also well-known phenomenon that is described even in known mutation carriers (Lynch *et al.*, 2004). Thus, surveillance measures in risk persons should not be cancelled at this age as both the obtained data and literature publications suggest permanent cancer risk.

The age of colorectal cancer diagnostics in FCC families was higher (mean, 72.0 years; 95% CI = 67.3 – 76.7 years) as predicted by the diagnostic criteria. However, the frequency of colorectal cancer among blood relatives in these pedigrees was not lower.

The frequency of endometrial cancer among females was significant: 22.4% (95% CI = 14.8 – 32.3%) among female blood relatives in HNPCC families and 9.6% (95% CI = 5.7 – 15.8%) in susp. HNPCC families. It exceeds the cumulative incidence (0 – 74 years) in the EU estimated as 1.5% (Boyle and Ferlay, 2005). There is a trend towards lower endometrial cancer risk in susp. HNPCC families. Although the difference is not statistically significant, further studies in larger group would be necessary to gain more information in larger group. The difference seems to be more marked than in case of colorectal cancer that could be explained by diverse mutations.

The endometrial cancer was diagnosed at the mean age 48.4 (95% CI = 43.4 – 53.4) years in HNPCC families, 50.5 (95% CI = 43.0 – 58.0) years in the susp. HNPCC families and 49.4 (95% CI = 45.1 – 53.7) years in the whole group of definitive and suspected HNPCC. The youngest case was diagnosed with the endometrial cancer at the age of 27 years. Thus, again, females were affected by endometrial cancer at the economically active age. The affected women mostly were alive at the time when population screening was carried out: 17/19 (89.5%; 95% CI = 68.6 – 97.1%) in HNPCC, 7/13 (53.8%; 95% CI = 29.1 – 76.8%) in suspected HNPCC and 24/32 (75%; 95% CI = 57.9 – 86.7%) in the whole group of definitive and suspected HNPCC. The proportion of living persons in the groups of colorectal and endometrial cancer groups was significantly

different. Thus, the prognosis is probably better than in case of colorectal cancer; however, the high frequency suggests the need for surveillance. The beneficial prognosis of endometrial cancer in the setting of HNPCC is in agreement with the published data (Vasen *et al.*, 1994; Boks *et al.*, 2002).

Although cancers in locations other than colorectal, endometrial, small intestinal and renal pelvis were noted, the frequency was low and no dominant location was observed. Among unusual findings, 2 cases of childhood CNS tumours in a single FCC pedigree and several sarcomas in different FCC families were recorded.

In conclusion, blood relatives of the HNPCC, susp. HNPCC and FCC pedigrees are subjected to increased cancer risk that can be approximated by the clinical evaluation of cancer family history at low cost. The course of cancer is unfavourable; considering the two frequent locations, colorectal cancer has worse prognosis than endometrial cancer. In order to prevent cancer development and to prevent the economic loss caused by death or by durable disability of economically active persons, surveillance should be offered in order to start active treatment at precancerous conditions or the cancer at early stage.

Hereditary and familial endometrial cancer

In the result of population screening, the presence of different hereditary and familial endometrial cancer syndromes was confirmed and the frequency of the corresponding syndromes was determined. Definitive hereditary endometrial cancer syndrome was identified, but the diagnostic criteria of suspected hereditary endometrial cancer syndrome and suspected familial endometrial cancer syndrome had the highest yield.

The frequency of endometrial cancer among female blood relatives belonging to the families affected by hereditary of familial endometrial cancer was high. In the whole group, the endometrial cancer frequency is 32.2% (95% CI = 28.1 – 36.6%) exceeding the cumulative incidence (0 – 74 years) in the EU estimated as 1.5% (Boyle and Ferlay, 2005). In HEC, the endometrial cancer frequency was as high as 41.5% (95% CI = 27.8 – 56.6%). Thus, the cancer risk in females belonging to these pedigrees is elevated. Probably even higher risk can be expected in mutation carriers as the present analysis included all blood relatives of the affected sex in the affected blood lines.

The endometrial cancer frequency was elevated in all syndromes. No statistically significant differences were observed. The frequency of endometrial cancer in HNPCC families also was not statistically significantly different although trend towards higher cancer frequency in hereditary

and familial endometrial cancer families was observed. The frequency of endometrial cancer in HNPCC susp. families was significantly lower.

For practical means, the higher endometrial cancer frequency in hereditary and familial endometrial cancer families substantiates the need for surveillance that should be identical for all these syndromes.

The surveillance would be especially desirable as prophylactic operations could be possible under appropriate circumstances, therapeutic intervention is possible and the prognosis is not dismal although serious. In other words, the follow-up would provide a possibility to diagnose more or less manageable condition.

The endometrial cancer has developed in economically active females: in HEC group, the mean age of endometrial cancer diagnostics is 52.1 years (95% CI = 47.2 – 57.0 years), in HEC susp., 48.5 years (95% CI = 44.4 – 52.6 years), in FEC and FEC1 66.2 years (95% CI = 63.1 – 69.3 years) and in FEC2 57.6 years (95% CI = 49.9 – 65.3 years). The age of tumour development is significantly higher in FEC/FEC1 group in comparison with HEC and HEC susp. as a result of the diagnostic criteria helping to identify a subgroup, developing cancer in later age but still subjected to high cancer frequency in the affected blood line. The youngest patients were 40, 30 and 26 years old in HEC, susp.HEC and FEC2 groups, respectively.

The percentage of affected persons who were alive at the time of population screening was statistically significantly lower than in case of endometrial cancer in combined HNPCC: 39/149 (26.2%; 95% CI = 19.8 – 33.8%) vs. 22/32 (68.8%; 95% CI = 51.4 – 82.0%). Thus, the course of isolated hereditary and familial endometrial cancer could be less beneficial than in the case of HNPCC-associated endometrial cancer (Vasen *et al.*, 1994; Boks *et al.*, 2002).

Although probands diagnosed with hereditary and endometrial cancer syndromes belonged to all age groups, the age peak was before the age of 59. Additional peak was observed in the age group 70-79 years for suspected HEC and FEC1. A subgroup of the probands was already affected by endometrial cancer. The affected persons constituted 14.3% (95% CI = 7.4 – 25.7%) of the probands. Thus, the rate of endometrial cancer in probands was less than in the whole group of definitive and suspected hereditary and familial endometrial cancer. Together with the age distribution revealing proband who are even younger than the youngest diagnosed hereditary endometrial cancer case, these data suggest that part of risk persons can be identified sufficiently early to initiate the surveillance measures.

The data about extra-endometrial cancers in hereditary and familial endometrial cancer pedigrees were interesting. High frequency of gastric cancer was revealed in suspected HEC and FEC2, namely, 4.1% (95% CI = 2.4 – 6.8%) and 10.9% (6.3 – 18.1%). These frequencies exceed the

cumulative incidence (age 0 – 74 years) of gastric cancer in EU that corresponds to 1.62% in males and 0.68% in females (Boyle and Ferlay, 2005). The frequency of brain tumours in suspected HEC also was elevated, reaching 2.8% (95% CI = 1.5 – 5.3%). The cumulative incidence of brain tumours in EU represents 0.68% in males and 0.49% in females (Boyle and Ferlay, 2005). As endometrial, gastric and brain tumours can occur in Lynch syndrome, an unusual manifestation of it can be suspected. Otherwise, the association between hereditary and familial endometrial cancer and mismatch repair genes is controversial but probable as some differences between HEC/FEC and HNPCC are observed that theoretically could be due to different mutations.

Hereditary and familial stomach cancer

In the result of the Valka district population screening, the first pedigrees of definitive and suspected hereditary and familial stomach cancer were identified. Hence, the population screening brought the first documented evidence of hereditary and stomach cancer in Latvia, adding it to the scientific proficiency in the studies of gastric cancer in Latvia.

Hereditary stomach cancer was the most frequent definitive hereditary cancer syndrome in Valka population. Among the suspected hereditary cancer syndromes, hereditary and familial stomach cancer was the third most common syndrome. The frequency of definitive hereditary stomach cancer syndrome in Valka population was 0.11% but of the suspected syndrome - 0.4%. In the same hypothetic population as previously noted, this would be equivalent to 2524 probands affected by definitive hereditary stomach cancer syndrome and 9178 probands affected by suspected hereditary stomach cancer syndrome.

The frequency of gastric cancer in the identified families was determined as the ratio between the numbers of gastric cancer cases and of blood relatives in the affected line. It was 25.2% (95% CI = 20.6 – 30.4%) in hereditary stomach cancer families, but 16.0% (95% CI = 13.8 – 18.5%) in suspected hereditary stomach cancer kindreds. In hereditary stomach cancer model, it became possible to identify the difference between definitive and suspected hereditary cancer syndromes in the aspect of cancer frequency among blood relatives. This confirms the model of risk stratification into high risk group identified by the presence of at least 3 affected first-degree blood relatives, and moderate risk-group, characterised by the presence of concordant cancer in 2 first-degree blood relatives.

The frequency of gastric cancer was significantly lower than the lifetime risk for gastric cancer in *CDH1* mutation carriers (Lynch *et al.*, 2008; Pharoah *et al.*, 2001). The difference is caused by the methodology as there was no possibility to convey mutational analysis and therefore all the

blood relatives were included in the estimates. It has to be noted that the estimates of gastric cancer risk by Kaurah *et al.*, 2007 show CI overlap with the frequency of gastric cancer in Valka pedigrees.

The frequency of gastric cancer both in definitive and suspected hereditary stomach cancer pedigrees exceeds the cumulative risk (0 – 74 years) in EU constituting 1.62% in males and 0.68% in females (Boyle and Ferlay, 2005). Accordingly, surveillance should be offered to both groups.

The high frequency of gastric cancer in the identified families confirms the practical value of the applied criteria for the identification of risk group. The family-shared risk might be explained not only by hereditary factors but also by shared environmental factors. Even independently of the underlying explanation the applied criteria allow to detect risk group. However, the low spouse correlation points towards high importance of the genetic background in the identified group.

Taking into account the frequency of gastric cancer in the affected blood lines by population screening data in combination with the frequency of these syndromes in the population, 2104 cases of gastric cancer in the previously noted hypothetic population could be related to the hereditary factors.

The earliest cases of gastric cancer in the identified at-risk-families were diagnosed early – at 30 years and 34 years, respectively, in the definitive and suspected hereditary gastric cancer groups. However, significantly earlier cancer development (at 16 – 20 years) has been described in literature (Lynch *et al.*, 2008; Kaurah *et al.*, 2007; Guilford *et al.*, 1998). Therefore the surveillance should be started early in both groups.

The frequency of gastric cancer does not differ significantly in dependence on the presence of other cancers in the pedigree. Thus, these data do not influence the surveillance for gastric cancer.

The most frequent extra-gastric cancer in these families was endometrial cancer with the frequency among blood relatives 6.0% (95% CI = 4.0 – 9.0%) and frequency among female blood relatives 10.7% (95% CI = 7.1 – 16.1%). The frequency of endometrial cancer in female blood relatives in these pedigrees thus exceeds the cumulative frequency (0 – 74 years) of endometrial cancer in EU females – 2.43% (Boyle and Ferlay, 2005).

The clinical diagnostics of hereditary stomach cancer is embarrassed by the variety of diagnostic criteria. In particular, the familial intestinal cancer should be diagnosed by criteria that are analogous to the Amsterdam criteria: at least 3 relatives should have intestinal gastric cancer and one of them should be first degree relative of the other two; at least 2 successive generations must be affected and in one of the patients gastric cancer should be diagnosed before the age of 50. In contrast, the hereditary diffuse gastric cancer is diagnosed on the basis of at least 2 cases of

diffuse gastric cancer in first or second degree relatives with at least 1 tumour diagnosed before the age of 50 or at least 3 documented cases of diffuse gastric cancer in first or second degree relatives independently of the age of onset (Caldas *et al.*, 1999). As the incidence of diffuse gastric cancer is stable, the criteria are not dependant on the total incidence of gastric cancer in the country (Crew and Neugut, 2006). Thus, the criteria for both types of hereditary or familial gastric cancer differs by the number of affected relatives, the degree of kinship, the presence or absence of age limit. However, in Latvian population the information about the cancer type in older relatives cannot be obtained due to several reasons; such information also is too specific to be obtained from the probands. Therefore the criteria were based on the assumption that 3 cases of concordant cancer among the blood relatives points towards high risk of this tumour and 2 cases – towards moderate risk (Hampel *et al.*, 2004). The high frequency of gastric cancer in the identified families as well as difference in cancer frequency among definitive and suspected stomach cancer groups shows the appropriateness of these criteria. The criteria based on the number of affected persons should be recommended for general use.

There was a strong trend towards earlier age of tumour diagnostics in the definitive hereditary stomach cancer group than in the suspected group. The differences in the death age and age of tumour manifestation were statistically significant confirming earlier tumour manifestation and earlier death in the definitive group.

The age distribution of the probands showed wide plateau at the age interval 30 – 70 years. As the mean age of hereditary stomach cancer diagnostics was 56.9 years and the mean age of suspected hereditary cancer diagnostics was 62.5 years, at least part of the probands were younger and thus surveillance would be started at proper time.

The oncologic health status of probands also was appropriate for the surveillance as only 1 proband has gastric cancer herself. However, the seemingly beneficial health status of probands might partially be attributable to the rapid course of gastric cancer eliminating the affected persons from the population and decreasing their chance to be included in the population screening as probands. The course of the tumour has been aggressive – only 5.4% (95% CI = 3.1 – 9.2%) of the affected persons were alive at the time of population screening. The mean survival was only 2.5 years.

There is targeted determination to employ the surveillance for hereditary stomach cancer. The frequency of gastric cancer in the affected families is high. It is known from the published evidence that the course of disease is unfavourable due to frequently delayed diagnostics, tendency develop widespread metastases in the abdominal cavity and by haematogeneous spread, limited possibilities of surgical treatment due to this dissemination and resistance to other

oncologic treatment options. The theoretical considerations are confirmed by the presented data suggesting poor survival. Any possibility to prevent disease like this would be useful. The surveillance includes a possibility to diagnose the tumour early. This option is embarrassed by difficulties in case of diffuse tumour growth, but surgical prophylaxis could become an effective solution of this problem. Thus, population screening has identified hereditary and familial stomach cancer as an important, previously unrecognised problem in Latvian population that can be approached by surveillance and surgery.

The population-attributable fraction of definitive and suspected hereditary stomach cancer in Valka population was 13.9% (95% CI = 12.3 – 15.7%) and of definitive stomach cancer – 4.4% (95% CI = 3.5 – 5.5%). These values slightly exceed the published estimates (Cisco *et al.*, 2008) describing familial clustering in 10% of gastric cancer patients and autosomal dominant mode of inheritance in 3% of patients. The high frequency of gastric cancer in the identified families indirectly confirm the expedience of the used criteria therefore the higher finding could be considered true for Valka population. It is possible that higher proportion of hereditary cancer in a particular location can be expected in population subjected to general high frequency of this cancer as the environmental carcinogenic factors lessen the influence of the evolutionary pressure striving to eliminate the carriers of harmful mutations.

Familial lung cancer

The published data suggest the existence of the hereditary background in the development in lung cancer. The epidemiological evidence of familial clustering is substantiated by mathematical models that help to evaluate the input of genetic and behavioural factors. The final proof will be brought by genetic research moving towards the identification of the genes and mutations responsible for lung cancer susceptibility.

In the result of population screening a group of familial lung cancer syndrome was identified including 13 pedigrees of definitive and 93 – of suspected familial lung cancer syndrome with total frequency in Valka population 0.6% (95% CI = 0.5 – 0.7%). The frequency of lung cancer cases among blood relatives in this group is high reaching 25.5% (95% CI = 19.3 – 32.8%) in FLC and 17.2% (95% CI = 15.0 – 19.7%) in FLC susp. This exceeds significantly the EU cumulative risk of lung cancer (age 0 – 74 years) estimated as 6.5% in men and 1.6% in women (Boyle and Ferlay, 2005) taking into account also the fact that lung cancer incidence in Latvia is close to the EU average (Kaiser and Gommer, 2007). Thus, the applied criteria are useful in order to identify high-risk group of practical size. It should be noted that at the present phase of medical

science development the familial lung cancer concept is still under research. However, within the frames of the presented survey it has already shown its practical merit.

As shown by the results, the population screening identifies the persons-at-risk at sufficiently early age to provide screening programs. Although lung cancer carries a grave prognosis, better treatment results can be expected if non-small cell cancer is identified at early stage. The screening should ensure early diagnostics, and the literature data mostly suggest development of non-small cell lung cancer in familial lung cancer families. Thus, the population screening as a cancer prevention tool and the biology of familial lung cancer fits together in order to provide the best assistance for the risk group. Additionally, the identified group could be a target of educational efforts aiming at smoking cessation. It could be reasonable to propose that these people after receiving adequate information may develop high motivation for healthy life style.

The identified probands were oncologically healthy. However, this cannot be interpreted as risk-lowering factor as, firstly, the probands are mostly young; secondly, lung cancer once already developed would rapidly eliminate the affected person from screening. The last assumption is based on the survival data in the presented group showing first-year lethality 61.2% (95% CI = 53.2 – 68.7 %). Only 3 affected people were alive at the time of population screening.

The age of cancer onset varied widely. The youngest case in Valka group died at the age 13 years. Although this would be an unusually early onset of lung cancer in general, it is in accordance with literature data describing primary squamous cell carcinoma in 11-year-old boy with substantial family history of cancer (Tajiri *et al.*, 1999). Further investigation of such cases would be necessary; however, it was beyond the scope of population screening. However, the mean age of cancer diagnostics was 57.6 years (95% CI = 55.7 – 59.5 years) and of definite tumour manifestation – 58.8 years (95% CI = 57.0 – 60.6%). Thus, very early onset is not a rule. Adding the age of tumour onset to the analysis, no significant differences in cancer frequency were observed. Thus, the presented findings are in agreement with the published evidence (Matakidou, Eisen and Houlston, 2005) that age is not useful diagnostic criterion in the clinical evaluation of familial lung cancer families.

A trend towards higher rate of lung cancer in definitive familial lung cancer families than in suspected cases was detected. This is in agreement with the published data suggesting increased frequency with higher number of affected relatives (Matakidou *et al.*, 2005). Although the trend did not reach 95% probability level, it initiated the search for additional factors that might help to evaluate the risk more exactly. The number of affected generations was found to be important. The frequency of lung cancer was significantly lower in FLC susp. families affected in single generation in comparison to FLC families affected in single generation or the whole FLC group.

Complexity was added by the observation that FLC families that are affected in single generation show trend to even higher cancer frequency than FLC families affected in 2 generations. Further analysis in larger group would be necessary. If the trend would be confirmed, complex genetic background could be suspected. This would be in accordance with the medical literature (Li and Hemminki, 2005; Sellers *et al.*, 1990). Genetic heterogeneity could also be further suspected on the basis of our data, namely, the clinical differences between families and the correlation between the age of tumour manifestation in the oldest and the youngest affected person from the same kindred.

In our group, similarly to the published findings (Nitadori *et al.*, 2006), the frequency of lung cancer in the familial lung cancer families was not influenced by general family cancer history. However, further studies would be necessary in order to evaluate possible specific links between lung cancer and malignant tumours by other locations.

Low rate of spouse correlation was found. This could be evaluated as indirect evidence of the role of genetic background rather than shared environmental factors in the family clustering of lung cancer.

In conclusion, the population screening has brought the first evidence of familial lung cancer in Latvia. The diagnostic criteria based on the number of lung cancer cases among blood relatives allow identifying high-risk group at early age, before the development of cancer. Thus, population screening is an effective tool in identification of risk group and initiation of protective measures. Familial lung cancer syndrome can be diagnosed by use of simple questionnaire. Number of cases in the pedigree is the most important criterion. The diagnostic role of early cancer development and higher number of affected generations should be further investigated.

Familial aggregation of haematological malignancies

The population screening has brought the following evidence of familial haematological malignancies. The frequency of inherited haematological malignancies in Valka district pedigrees was high both in the definitive FHem group 30.8% (95% CI = 12.7 – 57.6%) as well in the suspected FHem group 15.4% (95% CI = 11.2 – 20.9%). It is in contrast to the estimated cumulative incidence in EU in 2006 that was 2.7% and 1.75% in males and in females, respectively (Boyle and Ferlay, 2005). Thus, detection of inherited tumours is necessary option and surveillance programme should be considered as the treatment possibilities are reasonable.

The affected persons in Valka district trend towards clustering of tumours into 3 groups according to the detected peaks of the tumour manifestation age in the population screening: children younger than 5 years of age, middle-aged persons 30 – 39 years of age as well as older persons 60

– 69 years of age. However, the tumour manifestation was in wide diapason 3 – 88 years. During the population screening some families demonstrated course complying with genetic anticipation, that is also documented in some reports of familial leukemia (Horwitz *et al.*, 1996; Segel and Lichtman, 2004) and non-Hodgkin's lymphoma (Wiernik *et al.*, 2001) as well as in multiple myeloma (Deshpande *et al.*, 1998). In some published studies increased risk of haematological malignancy in relatives were observed (Negri *et al.*, 2006; Pottern *et al.*, 1991) and the risk of haematopoietic malignancies increases within the number of family members affected by the instant tumours (Wang *et al.*, 2007). The total burden of haematological tumours in the Valka district population screening was 16.3% (95% CI = 12.1 – 21.7%) in families confirming to the criteria of definitive FHem and suspected FHem that is according to the mentioned above statement.

The mean age of death in Valka screening group was established as 49.8 years (SD 23.1 years) with the mean survival 1.9 years as it confirmed to the other studies where the age-adjusted risk of dead was established as high as the relatives have diagnosed haematopoietic malignancies below the age of 50 (Negri *et al.*, 2006).

In summary, family history studies, like signed Valka district population screening, have brought the evidence for a familial genesis in haematological tumours (Linet and Pottern, 1992). Some times it is difficult to prepare the firm conclusions due to given opacities in the reliability of registration rates of cancer histories. Further studies are necessary to validate obtained results in major number of cases.

Familial brain tumours

The published data suggests the existence of hereditary basis in the development of brain tumours. In the result of population screening in Valka district a group of familial brain tumour syndrome were detected – 3 pedigrees of definitive familial brain tumour syndrome as well as 16 pedigrees with suspected familial brain tumour.

The frequency of familial brain tumours among blood relatives was high reaching 32.3% (95% CI = 18.6 – 49.9%) in definitive familial brain tumour (FBtC) and in suspected FBtC 14.4% (95% CI = 10.4 – 19.5 %) that relevantly exceeds the EU cumulative incidence of brain tumours (age 0 – 74) estimated as 0.68 % in men and 0.49 in women (Boyle and Ferlay, 2005). Therefore, the used criteria possibly could be applicable to reveal high-risk group in practical size.

At the present stage, the familial brain cancer development is still under the research. However, in practice some published studies shows the grave prognosis and the clinical course of instant tumours often are fulminant (Watson *et al.*, 2008). Early onset of the brain tumours in

combination with high mortality rate limits the availability of early diagnostics as well as genetic investigations often are unavailable due to the early onset of the disease with low survival time in teen age that excludes them from the most scientific studies.

The survival data in presented group revealed high first year lethality 61.5% (95% CI = 42.5 – 77.6%). Only two affected persons were alive during the time of population screening and the youngest case in Valka district died at 2 years of age. In overall, the mean age of death was 47.8 years. Along the leukemia, brain tumours represent the big part of tumours in children under the 15 years of age (Kaatsch *et al.*, 2001). This is also true in the presented study showing the slightly elevated number of cases at the age under the 9 years. However, the mean age of cancer diagnostics was 59.7 years (95% CI = 58.2-61.2 %) in definitive HBtC and 41.8 years (95% CI = 32.0 - 51.5 %) in suspected HBtC with the highest peak of age of tumour manifestation showing the 50-59 years.

In summary, primary brain tumours represents heterogeneous group of diseases (glioblastoma, astrocytoma, meningioma, ependymoma etc.) mostly with grave prognosis. Therefore, improved registration and, possibly, the surveillance are essential to characterise homogeneous subgroups of brain tumours. There is no published punctual tactics in revealing of high risk persons. Magnetic resonance imaging (MRI) of brain in asymptomatic individuals in adult is not recommended (Komotar *et al.*, 2008). Although, the detection of the symptomatic recurrence in paediatric brain tumours also is not recommended (Torres *et al.*, 1994).

Hereditary and familial cancers of the urinary system and male reproductive organs

Although significant role of genetic contribution in renal carcinomas has been suggested by Gudbjartsson *et al.*, 2002, Valka population screening did not disclose any pedigree with at least three cases of renal cancer that could correspond to high risk. There were only 3 pedigrees showing 2 cases of renal cancer. One family was affected in 2 generations, suggesting dominant mode of transmission; recessive mode could be hypothesised for the other families showing affected first- or second- generation relatives in a single generation.

No familial aggregation of testicular cancers was observed. Possibly this could be explained by the fact that germinal cell tumours arise early in life and previously had serious prognosis thus eliminating the affected persons from the reproduction.

The population screening brought the first evidence of hereditary urinary bladder cancer in Latvia. The frequency of urinary bladder cancer in these pedigrees was as high as 22.8% (95% CI = 14.9 – 33.2%). In contrast, the cumulative frequency of urinary bladder cancer in EU is 2.82% in males and 0.52% in females (Boyle and Ferlay, 2005). The affected persons were relatively

old: the mean age of cancer diagnostics was 70.7 years and the youngest case was diagnosed at the age of 60 years. Thus, familial bladder cancer in Latvia mostly affects the persons at the age of retirement. The observed cases in Valka population also are older than most (Kantor *et al.*, 1985; Plna and Hemminki, 2001; Aben *et al.*, 2002; Goldgar *et al.*, 1994) but not all (Lin *et al.*, 2006) of the described groups. Several age limits are considered as additional diagnostic criteria of hereditary bladder cancer. Most of these described limits are within the frames 45 – 60 years and thus seem not applicable in Latvia as all our identified cases are older.

The survival of the affected persons was variable. Some of the affected persons died within the year of diagnosis suggesting aggressive or neglected disease. Others survived as long as 19 years. Probably at least part of the cases were of low malignancy, possibly superficial similarly to the findings of Lin *et al.*, 2006. These should be identified by surveillance and treated properly.

The most frequent cancer in another location was gastric cancer. The frequency of it was 4.1% (95% CI = 1.7 – 0.9%) in the whole group of definitive and suspected familial urinary bladder cancer and 6.3% (95% CI = 2.7 – 14.0%) in the subgroup of families showing mixed cancer history with presence of cancers other than urinary bladder cancer. It is interesting that the families of definitive bladder cancer were free of other cancers in the family history. Although the number of affected families is far too low to draw any conclusion, an underlying genetic heterogeneity can be suspected.

Hereditary prostate cancer was found with low frequency. It was characterised by early manifestation as shown by relatively low mean age of tumour diagnostics. The youngest affected case was only 35 years old. Thus, the surveillance for prostate cancer in these families should be initiated earlier than in the population. There was relatively high proportion of affected probands and relatively high proportion of living persons among the affected patients. The frequency of prostate cancer among male relatives was 22.2% (95% CI = 16.5 – 29.0%) in contrast to the cumulative frequency 5.91% in EU males, aged 0 – 74 years (Boyle and Ferlay, 2005).

Familial pancreatic cancer

One mostly accepted definition of familial pancreatic cancer is the presence of two or more pancreatic cancer cases in mutually the first degree relatives (Windsor, 2007). Kindreds must not be a part of another familial cancer syndrome.

During the population screening carried out in Valka district the following evidence of familial pancreatic cancer was established. Although pancreatic cancer is not among the most frequent cancer types diagnosed in population, composing only 3.1% (95% CI = 2.8 – 3.5%) of the total cancer burden in Latvian population in 2006, the population screening revealed 10 probands

corresponding to FPan syndrome. The rate of FPan constituted 14% (95% CI = 7.5 – 23.1%) of all revealed definitive hereditary cancer syndrome types exceeding even the rate of HBOC and several other hereditary and familial cancer syndromes. The population attributable fraction of familial pancreatic cancer in Valka district in the presented study was 6.3% (95% CI = 4.1 – 9.6%) corresponding to the 7 – 10% level as reported by Lynch, Smyrk *et al.*, 1996; Lynch *et al*, 1990. In more recent studies, lower levels are described by Hemminki and Li, 2003; Bartsch *et al.*, 2004, ranging from 1.1 – 3.5%. The lower prevalence of familial pancreatic cancer has been attributed to strict diagnostic criteria (Windsor, 2007). However, presence of 2 pancreatic cancer cases in first-degree relatives as in Valka population screening is the same requirement as emplyed by Hemminki and Li, 2003. Thus, the data from Valka population screening are more in line with Pezzilli, 2007. The different prevalence can be a reality in genetically different populations. As part of familial pancreatic cancer burden can be attributed to *BRCA2* mutations, the variable proportions of *BRCA1*: *BRCA2* mutations can also influence the rate of familial pancreatic cancer.

The frequency of confirmed pancreatic cancer in the familial pancreatic cancer pedigrees was identified as 15.2% (95% CI=10.2 – 22.1%) that greatly exceeds the cumulative incidence (0 – 74 years) in EU estimated as 0.88% and 0.55% in males and females, respectively (Boyle and Ferlay, 2005). Thus, the pancreatic cancer risk in the families fulfilling the criteria of FPan is significantly elevated. The mean age of tumour diagnostics in instant group was 60.0 (95% CI=55.7 – 64.3%) – contains economically active population group.

In the families corresponding to the criteria of familial pancreatic cancer, the characteristics of pancreatic cancer course was the following: death age ranged in 51-83 years (mean, 62.6 years; standard deviation 8.8 years) with the survival rate 0-5 years (mean, 1.0 years; standard deviation 1.5 years). The short mean survival and low 5-year survival rate in Valka district 5.9% (1.0-27.0%) could be due to the biological properties of pancreatic cancer, namely, the rapid spread into peripancreatic tissues precluding radical surgery. However, delayed diagnostics could also enhance the limitations of radical treatment possibilities. It has to be noted that 5-year-survival from pancreatic cancer in Valka district is in accordance with the described overall 5-year survival rate, estimated as less than 5% (Konner *et al.*, 2002). Thus, the most reasonable approach to better treatment results in case of pancreatic cancer could be the surveillance aiming at early diagnostics.

Follow-up of risk persons

According to the literature data follow-up of female, which family cancer history corresponds to the criteria of hereditary breast cancer, includes breast self-examination annually (Olopade and Pichert, 2001). Annual mammography still remains the gold standard of follow-up (Cortesi *et al.*, 2006), recommended from 25 years of age. Clinical and US evaluation of breast twice per year also is suggested for this purpose as well additional fine needle aspiration or core biopsy if suggested by clinical indications in US control. Clinical investigations mentioned above are recommended to start from 25-30 years of age (Olopade and Pichert, 2001). In *BRCA* mutation carriers, breast tumours tend to be of high grade and lack calcifications thus decreasing sensitivity of mammography therefore magnetic resonance imaging is considered for screening (Eccles, 2004). Mutation carrying males may also be at risk for the breast cancer and their risk for prostate cancer rises up to 16 % (Struewing *et al.*, 1997) in contrast to the cumulative risk of 5.91% in EU males aged 0 – 74 years (Boyle and Ferlay, 2005). The relative risk for prostate cancer in *BRCA1* mutation carrier males is estimated as 3.33 (Ford *et al.*, 1994). Elevated relative risk of colon cancer constituting 4.11 is also described by some authors (Ford *et al.*, 1994) but denied by other scientific groups (Struewing *et al.*, 1997).

Surveillance for ovarian cancer includes pelvic, ultrasound examination and serum testing for tumour markers, e. g. CA125. However, due to lack of recognisable precancerous changes in the ovaries none of methods have been shown to detect ovarian cancer in early stage than in symptomatic patients (Eccles, 2004). According to the Modena group recommendations serum tumour markers testing as well as transvaginal US examination is recommended to start from 25 years of age.

Our data provide the evidence that in all definite or suspected hereditary breast – ovarian cancer syndromes the frequency of index cancers among female blood relatives exceed the respective cumulative frequencies in EU females. Thus, surveillance for these cancers is indicated in all these syndromes. Although the frequency of cancer development is different in various syndromes, e.g. HBC susp. 1 and HBC susp.2, the frequencies does not characterize the biological properties of cancer, such as growth rate, therefore intensity of follow-up cannot be lowered in syndromes characterised by lower frequency of affected female blood relatives. The same surveillance schedule thus should be initiated in all syndromes.

According to this literature data and results of the present study the following schedule is recommended – annual breast self-examination, clinical and US examination twice per year from 25 years as well as mammography and MRI examination every year from 25 years age, if clinically hereditary breast-ovarian cancer is established. Transvaginal US examination and

serum testing for tumour markers CA125 is advised from 35 years of age. Colonoscopy and prostate cancer screening is advised according to the symptoms.

The presented study revealed that the mean age of tumour diagnostics and 95% confidence interval for the mean age are the following: HBOC, mean 61.0 years, 95% CI = 46.9 – 75.0 years; HBC, mean 47.5 years, 95% CI = 37.1 – 57.8 years; HBC susp. 1, mean 38.0 years; 95% CI = 36.2 – 39.7 and HBC susp. 2, mean 51.8 years, 95% CI = 48.9 – 54.6 years; HBOC susp. 1, mean 48.8 years, 95% CI = 44.2 – 53.3; and HBOC susp. 2, mean 56.6 years, 95% CI = 51.8 – 61.4 years and HOC susp., mean 54.2 years, 95% CI = 46.4 – 61.9 years. HOC group is not analysable due to much lower number of cancer cases and wide dispersion of age.

That means in 95% of all hereditary breast-ovarian cancer syndrome cases clinical tumour manifestation is expected after 35 years of age. The follow-up should be started earlier as it must ensure early, possibly preclinical diagnostics. The starting point at 25 years would correspond to this and also would allow diagnosing several earliest cases.

The life time risk of colorectal cancer in MMR gene mutation carriers belonging to HNPCC pedigrees reaches 80% (Lynch, Shaw *et al*, 1996). HNPCC is characterised by early age at onset of colorectal cancer (Lynch *et al*, 2004): the mean age of diagnosis is approximately 44 years (Lynch, Shaw *et al.*, 1996). Although Valka patients show greater mean age of tumour diagnostics, the affected persons still are young. In addition, data of performed study may suggest age-dependent elimination of HNPCC probands in contrast to FCC probands.

Due to early cancer development, the surveillance in HNPCC and in suspected HNPCC should include colonoscopy every 1-2 years beginning from 20-25 years and annually after 40 years of age (Trimbath and Giardiello, 2002). The data of the present study might validate the offered recommendation plan, accounting also for early diagnostics and genetic anticipation. In FCC probands colonoscopy should be started from 35 years of age as the youngest case of FCC was 41 years old. Thus, the follow-up is recommended to start 5 years before the youngest case.

According to the literature data the risk of extracolonic tumours, e.g. endometrial cancer and ovarian cancer, could be in high range. The surveillance therefore should include endometrial aspiration or transvaginal ultrasound, and it is recommended for females beginning from 25-35 years of age (Guillem *et al*, 2006; Trimbath and Giardiello, 2002). The frequency of endometrial cancer among female blood relatives in the presented study is as high as 22.4%, 95% CI = 14.8 – 32.3%. Therefore proposed surveillance mentioned above is advised in the result of the performed research.

By literature data, kidney ultrasound as well as urine cytology each 1-2 years should be considered for pedigrees with predilection by urinary tumours (Guillem *et al.*, 2006). Within the

frames of the Valka population screening only 1 case of renal pelvis tumour in HNPCC kindred was revealed. Thus, due to the rarity of renal pelvis cancer in HNPCC, this surveillance option could not be recommended for general use in HNPCC group but can be an additional option.

Breast cancer risk in HNPCC related cases is described as similar in general population (Watson *et al.*, 2008). The results of Valka population screening suggest similar conclusion as the frequency of breast cancer among female blood relatives in HNPCC and suspected HNPCC families is lower than the cumulative risk of incident breast cancer in EU women estimated as 7.79 by Boyle and Ferlay, 2005. Therefore surveillance for breast cancer is not recommended as a part of HNPCC-related person follow-up.

The risk of ovarian cancer in HNPCC families is estimated as 6.7-9% by the age of 70 and it is higher in mutation carriers (Trimbath and Giardiello, 2002; Watson *et al.*, 2008). However, the Valka population screening data do not substantiate surveillance for ovarian cancer as the frequency is low and does not exceed the cumulative incidence in EU women (Boyle and Ferlay, 2005). Besides that, ovarian cancer is known for lack of recognisable premalignant process or early diagnostic manifestations thus limiting the efficiency of any surveillance. The literature data, however, could be helpful in estimating the extent of preventive operation.

Frequency of brain tumours in HNPCC families has been a matter of dispute (Aarnio *et al.*, 1999; Watson *et al.*, 2008; Vasen *et al.*, 1996). The Valka population screening data reveal frequency of brain tumours (0.7%; 95% CI = 0.1 – 3.8%), that is very close to the cumulative risk for brain tumour – 0.68 and 0.49 for male and for female respectively (Boyle and Ferlay, 2005). Taking into account this finding and the limited possibilities of early treatment, surveillance for brain tumour cannot be justified.

Although lung cancer cases have been observed in HNPCC and suspected HNPCC pedigrees from Valka district, the frequency of lung cancer (0.7%; 95% CI = 0.1 – 3.8% in HNPCC) is lower than the cumulative incidence in EU constituting 6.47 and 1.64 for male and for female correspondingly (Boyle and Ferlay, 2005). Thus, specific surveillance cannot be justified.

The cumulative risk of incident endometrial cancer in EU women estimated as 1.5 by Boyle and Ferlay, 2005. The frequency was significantly higher in whole hereditary endometrial cancer groups: in HEC, 41.5% (95% CI = 27.8 – 56.6%), in suspected HEC 32.2% (95% CI = 25.7 – 39.4%), in FEC 46.2% (95% CI = 23.2 – 70.9%), in FEC1 28.7% (95% CI = 22.4 – 36.0%) and in FEC2 32.2% (95% CI = 28.1 – 36.6%), thus, substantiated necessity of strong surveillance programme.

In the whole hereditary endometrial cancer syndrome groups the lowest observed border of the 95% confidence interval of the mean age was 44.4 years. Thus, starting the surveillance at the age

of 35 would be appropriate in at least 95% of affected females. However, the youngest cases, belonging to FEC2 and suspected HEC groups, respectively, were diagnosed at 26 and 30 years of age. Therefore, it would be possible to consider the beginning of surveillance at the age of 25.

In some reports no current guidelines are offered for early detection of lung cancer. Inadequate beneficial evidence in asymptomatic patients is reported (US Preventive Services Task Force, 2004). The American Cancer Society does not support screening for at-risk persons (Smith *et al.*, 2001). In contrast, screening benefit has been reported by the International Early Lung Cancer Action Program, 2006.

The cumulative risk of incident lung cancer in EU estimated as 6.47 and 1.64 in males and females respectively (Boyle and Ferlay, 2005). The frequency was significantly higher in FLC, 25.5% (95% CI = 19.3 – 32.8%) and in suspected FLC 17.2% (95% CI = 15.0 – 19.7%).

The mean age of lung cancer diagnostics in both groups was: in FLC 56.0 (53 – 59) years of age, in suspected FLC 58.4 (56.0 – 60.8) years of age. However, clustering of younger lung cancer cases also could be revealed in family cancer history. Thus, the surveillance should be started either at 45 years or 10 years before the younger case of lung cancer in family, whatever comes first, and should consist of lung X-ray. Taking into account the high first-year lethality in Valka group that might suggest rapid course, the screening should be performed twice a year.

Smoking relatives has an increased risk of lung cancer (Gorlova *et al*, 2007). Cessation of smoking also should be strongly recommended for high risk persons.

Both HSC and suspected HSC in Valka district were characterised by remarkable frequency of gastric cancer: HSC, 25.2% (95% CI=20.6-30.4%), in suspected HSC, 16.0% (95% CI=13.8-18.5%) which is higher than the cumulative risk of stomach cancer in EU: in females, 0.68 % and in males 1.62%. Therefore, surveillance and /or prevention programme is strongly indicated. However, the design of such programme necessitates the starting point and the regularity of health checks.

The mean age of cancer diagnostics was: in HSC 56.9 (53.4 – 60.3) years of age, in suspected HSC 62.5 (58.4 – 66.6) years of age that represents part of the published interval ranging from 16 to 82 years of age (Lynch *et al.*, 2008). Therefore the surveillance programme should be started either at the age of 40 years or 10 years before the youngest gastric cancer case in family, whatever comes first.

Practically, it is important to distinguish between cases that correspond to the criteria of hereditary diffuse stomach cancer (HDSC) and familial intestinal stomach cancer (FISC). If the kindred fulfilled the criteria of hereditary diffuse gastric cancer, *E-cadherin* gene (*CDH1*) evaluation must be offered for due to described frequency of *CDH1* gene mutation in HDSC that

ranges 30-50% (Cisco *et al*, 2008). HDSC is characterised by tendency to submucosal extension, by dismal prognosis as well as by marked difficulties in early endoscopic detection. Hence, prophylactic gastrectomy can be considered as a gold standard, 5 years earlier than the youngest age of gastric tumour diagnosis in the family (Cisco *et al.*, 2008) in proved *CDH1* mutation carriers.

Evaluation of *CDH1* gene mutations is not available in Latvia at present time. In the absence of appropriate genetic testing, preventive gastrectomies also have not been performed. Thus, frequent chromendoscopy surveillance combined with biopsies from any suspicious positions can only be recommended. The endoscopy should be performed biannually (Caldas *et al.*, 1999; Cisco *et al.*, 2008). At least 15 mucosal biopsies must be provided for histological evaluation (Lynch *et al.*, 2008). Magnetic resonance imaging of mammary gland is recommended in HDSC cases due to 20 – 40% risk of breast cancer (Cisco *et al.*, 2008).

If family cancer history corresponded to the criteria of familial intestinal cancer gastroscopy should be suggested with random biopsies from suspected lesion once or twice per year (Caldas *et al.*, 1999).

In conclusion, taking into account the possible high number of HSC cases in Latvia, the prognosis and intervention possibilities as well as psychological and compliance considerations, it would be of utmost importance to set up the *CDH1* gene mutation analysis in combination with subsequent surgical prophylaxis. The minimal recommendations for the present situation include clinical evaluation of family history and surveillance by chromendoscopy. This approach has also the economic and practical benefit as no distinction between hereditary diffuse and familial intestinal gastric cancer is necessary that may prove to be difficult in the absence of complete ancient medical documentation.

Population - attributable fraction of prostate cancer in Valka district is 7.4% (5.4-10.1%), moderately high, with mean age of detection 72.0 (67.0-76.9) years of age in HPC group, in suspected HPC 56.8 (52.8-60.8) years of age. Taking into account to the moderately high risk of prostate cancer the surveillance programme should be also recommended in HPC and in suspected HPC. According to the published data the surveillance is advised to begin 5 years from the youngest prostate cancer case in family history or from 45 years of age. Prostate specific antigen (PSA) as well as transrectal ultrasound guided biopsy of prostate, in case of increased level of PSA, is recommended.

The following frequency of urinary bladder cancer was revealed in selected families from Valka district: in HBlaC, 31.6% (95% CI = 15.4 – 54.0%), in suspected HBlaC 20.0% (95% CI = 11.8 – 31.8%) in contrast to published data of incident urinary bladder cancer frequency estimated in EU

as 2.82% and 0.52% (Boyle and Ferlay, 2005). Thus, surveillance also is recommended by urine cytology, beginning from 50 years of age and continuing annually.

Once familial pancreatic cancer syndrome is established there is a choice to undergo surveillance like endoscopic US, MRI or computed tomography. However, there is no acceptable screening protocol (Windsor, 2007). Prophylactic pancreatectomy is not recommended in asymptomatic individuals belonging to familial pancreatic cancer high-risk families (Rieder *et al.*, 2004) due to insufficient data of efficiency as well as severe morbidity of offered procedure.

The frequency of affected persons among blood relatives in the definitive and suspected familial brain tumour and hematologic tumour families is high. However, in contrast to the previously discussed types of inherited tumours, no reasonable surveillance program is available.

Hereditary and familial cancer – the overview

Several studies of hereditary cancer have been carried out in Latvia (Irmejs, 2004; Irmejs *et al.*, 2007; Gardovskis, 2008; Gardovskis *et al.*, 2005), focusing on specific cancer locations. The population screening provides the data about the whole spectrum of hereditary cancers providing not only practically important data but a possibility to compare the role of heredity by cancer location.

As shown in the Table 45, all hereditary cancer syndromes are characterised by high frequency of the respective cancers among the blood relatives. These frequencies exceed the cumulative frequencies in EU. The difference is least marked for HBOC susp.1 and HPC although still statistically significant.

Table 45. Comparison between frequency of index cancers in blood relatives of the affected kindreds and the cumulative risk in EU

Syndrome	Tumour location	Frequency, %	95% confidence interval, %	Cumulative risk
HBC susp.1	Breast[1]	16.3[1]	13.8 – 19.1[1]	7.79%[1]
HBC susp.2	Breast[1]	31.8[1]	27.5 – 36.4[1]	7.79%[1]
HBOC susp.1	Breast and ovary[1]	19.3[1]	9.2 – 36.3[1]	9.00%
HBOC susp.2	Breast and ovary[1]	30.8[1]	25.0 – 37.3[1]	9.00%
HOC susp.	Ovary[1]	36.4[1]	19.7 – 57.0[11]	1.21%
HNPCC	Colorectal cancer	15.8	10.7 – 22.5	Male 4.53%

				Female 2.70%
	Endometrial cancer[1]	14.8[1]	4.5 – 32.3[1]	1.50%
HNPCC susp.	Colorectal cancer	11.3	8.0 – 15.9	Male 4.53% Female 2.70%
	Endometrial cancer[1]	9.6	5.7 – 15.8	1.50%
FCC	Colorectal cancer	17.0	12.8 – 22.3	Male 4.53% Female 2.70%
HEC	Endometrial cancer[1]	41.5[1]	27.8 – 56.6[1]	1.50%[1]
HEC susp.	Endometrial cancer[1]	32.2[1]	25.7 – 39.4[1]	1.50%[1]
FEC / FEC1	Endometrial cancer[1]	30.0[1]	23.8 – 37.1[1]	1.50%[1]
FEC2	Endometrial cancer[1]	32.4[1]	22.4 – 44.2[1]	1.50%[1]
FLC	Lung cancer	25.5	19.3 – 32.8	Male 6.47% Female 1.64%
FLC susp.	Lung cancer	17.2	15.0 – 19.7	Male 6.47% Female 1.64%
HSC	Gastric cancer	25.2	20.6 – 30.4	Male 1.62% Female 0.68%
HSC susp.	Gastric cancer	16.0	13.8 – 18.5	Male 1.62% Female 0.68%
HPC	Prostate cancer[2]	21.4[2]	7.6 – 47.6[2]	5.91%[2]
HPC susp.	Prostate cancer[2]	22.2[2]	16.4 – 29.4[2]	5.91%[2]
FBlaC	Urinary bladder cancer	22.8	14.9 – 33.2	Male 2.82% Female 0.52%
FHemT	Malignant haematologic tumour	16.3	12.1 – 21.2	Male 2.7% Female 1.75%
FPan	Index cancers	14.7	9.1 – 22.9	Male 0.88% Female 0.55%
FBtT	Brain tumour	32.3	18.6 – 49.9	Male 0.68% Female 0.49%
FBtT susp.	Brain tumour	14.4	10.4 – 19.5	Male 0.68% Female 0.49%

Abbreviations in table: HBC susp.1, suspected hereditary breast cancer syndrome, variety 1; HBC susp.2, suspected hereditary breast cancer syndrome, variety 2; HBOC susp.1, suspected

hereditary breast - ovarian cancer syndrome, variety 1; HBOC susp.2, suspected hereditary breast - ovarian cancer syndrome, variety 2; HOC susp., suspected hereditary ovarian cancer syndrome; HNPCC, hereditary non-polyposis colorectal cancer syndrome; HNPCC susp., suspected hereditary non-polyposis colorectal cancer syndrome; FCC, familial colorectal cancer syndrome; HEC, hereditary endometrial cancer syndrome; HEC susp., suspected hereditary endometrial cancer syndrome; FEC, familial endometrial cancer syndrome; FEC susp. 1, suspected familial endometrial cancer syndrome, variety 1; FEC susp. 2, suspected familial endometrial cancer syndrome, variety 2; FLC, familial lung cancer syndrome; FLC susp., suspected familial lung cancer syndrome; HSC, hereditary stomach cancer syndrome; HSC susp., suspected hereditary stomach cancer syndrome; HPC, hereditary prostate cancer syndrome; HPC susp., suspected hereditary prostate cancer syndrome; FBlaC, familial urinary bladder cancer syndrome; FHemT, familial haematologic tumour syndrome; FBtT, familial brain tumour syndrome; FBtT susp., suspected familial brain tumour syndrome.

Analysing the population screening data, it has to be noted that CFA was found to be the most common syndrome involving clustering of several malignant tumours among first-degree blood relatives. It has been estimated that CFA is not attributable to smaller family size that could potentially limit the possibility to reveal a true hereditary cancer syndrome. Further studies are desirable.

Evaluation of molecular diagnostics possibilities

During the population screening in Valka district only 10 (1.7%; 95% CI = 0.9 – 3.1% of the molecularly screened group or 0.05%; 95% CI = 0.03 – 0.1% of the screened Valka population) *BRCA1* gene mutations were revealed in 7 families. The total yield of molecular diagnostics thus was low.

Any population screening must correspond to the criteria for genetic risk screening (Guttmacher *et al.*, 2003, Grody, 2003). According to this, the candidate diseases must be common and serious with high penetrance. Well-defined history with manageable number of predominant mutations also must be present. The screening test must be cheap, acceptable to whole population and effective surveillance must be feasible.

In contrast to recessive gene carrier screening, when carriers are asymptomatic and often have no family history of the disorder and mutation rates are high, e.g., cystic fibrosis, in autosomal dominant diseases, e.g., hereditary breast or/and ovarian cancer, HNPCC etc., the mutations have

significantly lower frequency and often can be detected in person suffering from cancer (Grody, 2003).

The autosomal dominant transmission of the best known hereditary cancer syndromes associated with the prototypic mutations is one factor that explains why the mutation rate in Valka population screening was very low.

An additional explanation is associated with the study design. The frequency of *BRCA1* gene mutations according to the literature data is 1/500 – 1/800 in general population (Ford *et al.*, 1995; Peto *et al.*, 1996). According to this 23 mutation carriers must be expected among 18642 persons who were screened by clinical diagnostics in Valka district. However, in order to fulfil the assumption of the economic efficacy of the screening test, only founder mutations were searched for and testing was offered only to the probands who reported at least single case of breast and ovarian cancer case in the family. Part of *BRCA* mutations could be missed by these limits. However, even more interesting explanation exists, namely – the *BRCA1* founder mutations have been detected in a group of persons, reporting statistically significantly different national composition than the whole studied group and belonging to nations that are not frequent in Valka district. Taking into account the high frequency of clinically identified syndromes in ethnically homogeneous population, it can be concluded that the tested founder mutations are not characteristic for that nationality that is dominant in Valka district.

The third explanation of low number of mutations is searching of founder mutations which are characteristic for Eastern Europe population - ex20(5382insC), ex5(300T/G), ex11.17(4153delA). Although these mutations have been detected in the population of Latvia (Tikhomirova *et al.*, 2005), there is no evidence that these comprise the bulk of Latvian mutations. In fact, the low rate of identified *BRCA* mutations in Valka population by searching for these East European founder mutations point towards presence of other mutations that might include either other founder mutations characteristic for Latvians, or Scandinavian founder mutations or non-recurrent mutations, or large deletions. The full sequencing of *BRCA1/BRCA2* gene is necessary either to detect unique *BRCA* mutations or to reveal founder mutations which are typical for Latvian population. However, the costs of full *BRCA1/BRCA2* gene sequencing could be an expensive. Therefore, according to the published recommendations instant screening would not be useful for population screening (Grody, 2003). It can be concluded that clinical diagnostics of hereditary cancer fits better the demands of population screening but molecular diagnostics is suitable in selected cases, probably on hospital basis. If *BRCA* mutation structure in Latvia will be elucidated and will be characterized by strong founder effects, targeted molecular tests can be employed in the further screening.

The population screening for disease-causing mutations (Grody, 2003; Guttmacher and Collins, 2003) becomes rational if it corresponds to certain criteria. The disease must be common and serious, with high penetrance and manageable number of predominant mutations. The test must be cheap, acceptable to whole population and an effective surveillance must be feasible (Grody, 2003). It was shown earlier that *BRCA1* gene founder mutations 4153delA and 5382insC are common in Latvia (Gardovskis et al., 2005; Tikhomirova et al., 2005).

In order to fulfil the assumption of the economic efficacy of the screening test, only founder mutations in the *BRCA1* gene were searched for and testing was offered only to the persons who reported at least one case of breast and/or ovarian cancer in the family. Part of the *BRCA1* mutations may be missed by this approach. However, in this way we found 10 mutation carriers in 7 families that correspond to 2663 clinically screened persons per one mutation-bearing family. This value is comparable with data obtained by Gronwald *et al.*, 2006 who reported 438 mutation-bearing families corresponding to 2873 clinically screened persons per one mutation-bearing family.

The number of *BRCA1* mutations exceeds the one of probands diagnosed by clinical criteria for hereditary breast-ovarian cancer, group 1. None of the *BRCA1* mutation carriers was identified by group 1 clinical diagnostic criteria and 8 of them reported only isolated cases of index cancer among blood relatives. Thus, clinical criteria revealed less than half of high-risk persons. The finding of the *BRCA1* mutations in individuals with no significant family history may be explained by paternal inheritance, lack of knowledge of the family cancer history or small family size. In this study, the inheritance through male was ascertained by criteria. The significance of the family size was demonstrated by higher number of blood relatives in group 1 and 2 in comparison to non-diagnostic family histories.

Comparison with other population screenings for hereditary cancer

The largest and almost only population screening for hereditary cancer was performed in the West Pomeranian region of Poland (Gronwald, Raczynski *et al.*, 2006). The comparison between the relative yield of different hereditary and familial cancer syndromes in Valka and Poland is shown in the Figure 81. Although the data by Gronwald, Raczynski *et al.* characterize families, but Valka data - probands, relative comparison could give some insight in the structure of hereditary cancer population structure. The dominance of breast – ovarian cancer as the most frequent hereditary cancer syndrome is even more marked in Pomerania. CFA shows almost the same frequency. Familial lung cancer is relatively more frequent in Valka. Although familial haematologic malignancies and familial bladder cancer are rare, the syndromes are comparatively

more frequent in Valka. HSC is characterized by relatively high frequency in both groups. In general, the analogy between both data sets confirms the validity of findings.

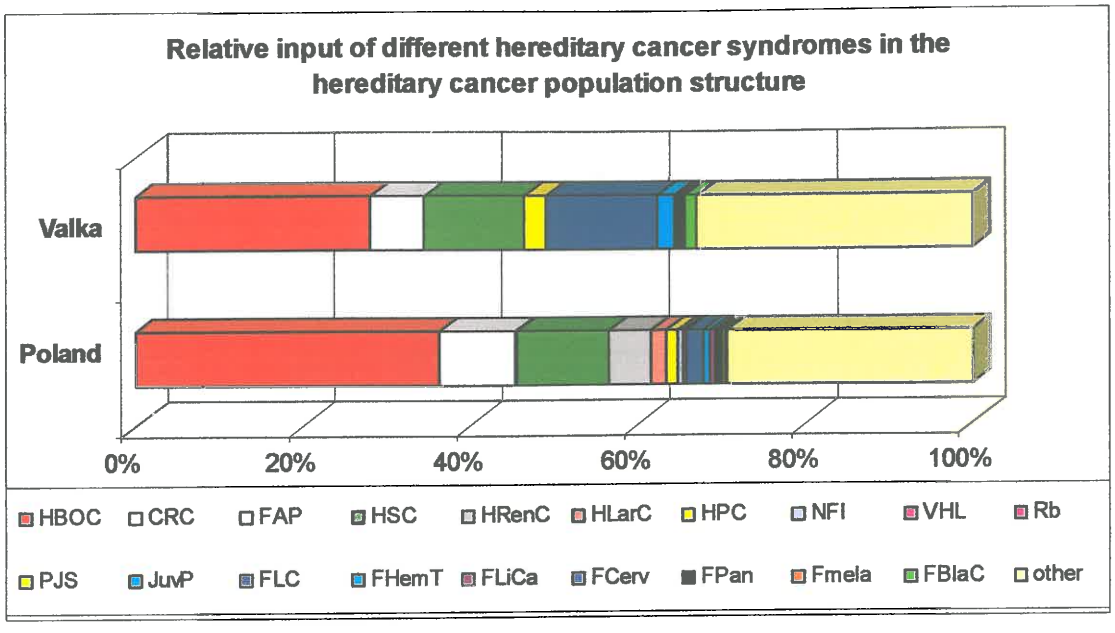


Figure 81. Population structure of hereditary and familial cancer aggregation in the Valka district and the West Pomeranian region of Poland.

Abbreviations in the figure: HBOC, hereditary breast and/or ovarian cancer syndrome; CRC, hereditary non-polyposis colorectal cancer syndromes; FAP, familial adenomatous polyposis; HSC, hereditary stomach cancer; HRenC, hereditary renal cancer; HLarC, hereditary laryngeal cancer; HPC; hereditary prostate cancer; NFI, neurofibromatosis; VHL, von Hippel Lindau syndrome; Rb, familial retinoblastoma; PJS, Peutz Jegher syndrome; JuvP, juvenile polyposis; FLC, familial lung cancer; FHemT, familial haematological tumour; FLiCa, familial liver cancer; FCerv; familial cervical cancer; FPan; familial pancreatic cancer; Fmela, familial melanoma, FBlaC, familial cancer of urinary bladder.

The hypothetic impact of population screening for hereditary cancer on the oncologic situation of Latvia

Using the population-attributable fraction, the impact of hereditary cancer diagnostics on the yearly cancer burden in Latvia was approximated as shown in the Table 46. The evaluation represent only rough calculation as the population of Latvia cannot be considered identical to

Valka population by national structure and possibly by distribution of other factors influencing the cancer risk. However, this estimate still characterizes the possible practical gain of hereditary cancer population screening.

Table 46. Impact of hereditary cancer diagnostics on the yearly cancer burden by population attributable fraction

Localization	Cases per year	FH, %	FH, 95% CI	HC per year	FDH, %	FDH, 95% CI	DHC per year
CRC	943	11.8	9.8 – 14.3	111 92 – 135	3.0	2.0 – 4.4	28 19 – 41
Endometrial	372	16.5	14.5 – 18.9	61 54 – 70	3.8	2.9 – 5.1	14 11 – 19
Breast	1022	25.0	22.7 – 27.4	256 232 – 280	0.8	0.4 – 1.4	8 4 – 14
Ovarian	275	35.4	28.1 – 43.5	97 77 – 120	3.5	1.5 – 7.9	10 4 – 22
Lung	1070	12.9	11.5 – 14.6	138 123–156	2.4	1.8 – 3.2	26 19 – 34
Stomach	591	13.8	12.2 – 15.6	82 72 – 92	4.7	3.8 – 5.9	28 22 – 35
Pancreas	286	6.3	4.1 – 9.6	18 12 – 27	6.3	4.1 – 9.6	18 12 – 27
Prostate	782	7.4	5.4 – 10.1	58 42 – 79	0.6	0.2 – 1.8	5 2 – 14
Haematologic	400	5.4	3.9 – 7.3	22 16 – 29	0.6	0.2 – 1.5	2 1 – 6
Kidney	388	1.5	0.7 – 3.2	6 3 – 12	0	0 – 0.1	0 0 – 0
Urinary bladder	355	9.6	6.6 – 13.9	34 23 – 49	2.4	1.1 – 5.2	9 4 – 18

Abbreviations in the table: FH, fraction of hereditary cases; FDH, fraction of definitive hereditary cases; HC, hereditary cases; DHC, definitive hereditary cases.

The estimates of the total hereditary cancer burden in Latvian population are shown in the Table 47. These estimates were obtained by cancer frequency among blood relatives and the frequency of different syndromes in the population. These data are not limited by a single year but represent the total number of risk persons that might develop the tumour in some period of their life.

Table 47. Estimates of the hereditary cancer burden in Latvian population

Tumour location	Result	Interval
Breast	3042	1999 – 4758
Ovary	490	196 – 1335
Endometrial cancer	1699	786 – 3764
CRC	891	477 – 1960
Endometrial	1699	786 – 3764
Lung cancer	2379	1582 – 3658
Gastric cancer	2111	1351 – 3314
Prostate cancer	264	124 – 655
Urinary bladder cancer	335	127 – 853
Malignant haematologic tumour	340	158 – 710
Pancreatic cancer	157	51 – 468
Melanoma	25	3 – 157
Brain tumour	403	147 – 1160

Clinical population screening by the relaxed criteria of suspected syndromes can be highly recommended as it yields high number of persons to whom further surveillance should be advised. This is a practical advantage of population screening for hereditary cancer.

CONCLUSIONS

1. Population screening is a useful tool for the identification of reasonable number of persons belonging to families with high frequency of malignant tumours. Another benefit of the population screening is the possibility to identify mostly oncologically healthy persons belonging to hereditary and familial cancer families so that appropriate surveillance can be offered. The age structure and health status of diagnosed probands are well-suited for further surveillance. The population screening in collaboration with family doctors is easy manageable as characterised by high compliance (76.6%).
2. The population screening discloses the full spectrum and clinical frequency of hereditary cancers in the analysed population. It has brought the first scientific evidence of familial lung cancer, hereditary and familial gastric cancer, familial cancer of urinary bladder, familial aggregation of haematological malignant tumours and familial brain tumours in Latvia. Although an evidence of family size as an influencing factor in the diagnostics of familial and hereditary cancer was obtained, the size of families did not preclude the clinical diagnostics.
3. By clinical criteria, 0.40% of the screened population were identified as definitive hereditary cancer syndrome group and additional 2.94% - as suspected group. *BRCA1* gene founder mutation was revealed in 1.70% of molecularly tested persons.
4. The hereditary breast-ovarian cancer was the most frequent syndrome among hereditary and familial cancer syndromes. The diagnostic criteria of the suspected syndromes had the highest yield.
5. The hereditary stomach cancer represents the most common definitive hereditary cancer syndrome and the third most common suspected hereditary cancer syndrome. The characteristics of the syndrome urges to its proper recognition.
6. The population screening revealed familial lung cancer as a second most common hereditary tumour. The number of affected relatives is the most important criterion in the identification of pedigrees showing high frequency of lung cancer. Familial lung cancer is characterized by low spouse correlation and genetic anticipation.
7. No evidence of dominant inheritance in renal and testicular cancers was found. Familial aggregation of urinary bladder was marked by late age of cancer diagnostics. Familial haematological and brain tumour syndromes were characterized with presence of childhood cases.
8. The verified clinical criteria ensure the highest diagnostic yield and thus should be the basis of population screening for hereditary cancer. Molecular examination yield additional data.

PRACTICAL RECOMMENDATIONS

1. Population screening can be recommended as a general tool in the whole country. Alternatively, in tight economic situation the tested clinical diagnostic criteria can be recommended for population-based use by family doctors and clinicians. Surveillance program is elaborated during the course of the presented work.
2. The follow-up of definitive HB/OC and suspected HB/OC should include breast self-examination, clinical and ultrasound examination from 25 years of age twice per year, mammography and MRI examination annually from 25 years of age, transvaginal examination and serum testing for tumour marker, CA125 from 35 years of age. *BRCA1* gene mutation careers should undergo the same follow-up schedule as in HB/OC. Surgical prophylaxis could be considered including some modification of bilateral mastectomy and salpingoophorectomy.
3. HNPCC/suspected HNPCC follow-up should include colonoscopy every two years from 25 years of age and annually after 35 years of age in HNPCC/suspected HNPCC/FCC1/FCC2. Transvaginal ultrasound from 25 years of age should be included in cases of HNPCC and in suspected HNPCC. In female matching the criteria of hereditary and familial endometrial cancer syndrome it would be reasonable to start the surveillance programme at the age of 25 by the transvaginal ultrasound annually. Prophylactic hysterectomy is recommended to HEC syndrome patients with proved MMR gene mutation.
4. In familial lung cancer the surveillance should be started at 45 years of age consisting of X-ray twice per year. Cessation of smoking is strongly recommended for FLC persons.
5. In hereditary diffuse stomach cancer *E-cadherin* gene (*CDH1*) evaluation should be set up as prophylactic gastrectomy can be recommended to *CDH1* gene mutation carriers. Biannual chromendoscopy surveillance combined with at least 15 biopsies is indicated in hereditary stomach cancer syndrome from 45 years of age.
6. The practical logistics of population screening for hereditary cancer should involve medical team, including family doctors, clinical hereditary cancer specialists and geneticians. Molecular examination should be offered as widely as possible.

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ANNEX 1. The decision of the Central Committee of Medical Ethics

Kopija

Centrālā medicīnas ētikas komiteja

Rīgā, Baznīcas ielā 25, LV1010 tel. 7043721 fax7043751

28.septembrī 2005.g. A-38

Lēmums Nr.38

Centrālā medicīnas ētikas komiteja 2005.gada 28. septembrī izskatīja VAS P.Stradiņa KUS iesniegto pieteikuma projektu „Pārmantotā vēža populācijas skrīninga un aprūpes pilotprojekts" atbilstību bioētikas normām.

Pamatojoties uz Centrālā medicīnas ētikas komitejas 2005. gada 28.septembra sēdes protokola Nr. 7 punktu 4, tiek izsniegts atzinums, ka VAS P.Stradiņa KUS iesniegtais pieteikuma projekts„Pārmantotā vēža populācijas skrīninga un aprūpes pilotprojekts" atbilst bioētikas normām ar noteikumu, ka atbilstoši Latvijas likumdošanai uz Igauniju analīzes izmeklējumiem var tikt sūtītas ar Centrālās medicīnas ētikas komitejas atļauju tikai tajos gadījumos, ja Latvijā tās nav iespējams veikt.

Centrālās medicīnas ētikas komitejas
Priekšsēdētāja vietn. A.Lejnieks

L.Rudze,7043776

ANNEX 2. CANCER FAMILY HISTORY

Paula Stradiņa klīniskā universitātes slimnīca, Pārmantotā vēža konsultatīvais kabinets
Rīga, Pilsoņu 13, LV 1002, tālr. 7069974

Ģimenes onkoloģiskās anamnēzes anketa

VĀRDS, UZVĀRDS:			
PERSONAS KODS:		KONTAKTTĀLRUNIS:	
ADRESE:			
PACIENTA KODS:			

Projekta *Pārmantotā vēža profilakses pasākumu attīstība Igaunijā un Latvijā* ietvaros sadarbībā ar Valkas rajona ģimenes ārstiem tiek veikts pilot-projekts, kura mērķis ir konstatēt ģimenes, kurās vairākās paaudzēs ir sastopami audzēji, piedāvāt šo ģimeņu locekļiem mūsdienīgas izmeklēšanas iespējas, kas ļauj konstatēt augsta riska pacientus jau daudzus gadus pirms slimības pazīmju parādīšanās, un ievērojami uzlabot audzēju ārstēšanas efektivitāti. Projektu īsteno Paula Stradiņa klīniskā universitātes slimnīca sadarbībā ar Igaunijas Genoma projekta fondu, Tartu universitātes slimnīcas Onkoloģijas klīniku un to daļēji finansē Eiropas Savienība (Eiropas Reģionālās attīstības fonds) Interreg III B Kaimiņattiecību programmus ietvaros.

Informācija, kas tiek sniegta ir konfidenciāla un bez pacienta piekrišanas netiks izpausta! Gadījumā, ja būs dati par to, ka pacientam ir paaugstināts risks saslimt ar ļaundabīgiem audzējiem, tiks piedāvāta speciālista bezmaksas konsultācija ģimenes ārsta praksē.

Piekrītu piedalīties_____
Pacienta paraksts, atšifrējums (vārds, uzvārds)

Griezuma vieta

ĢIMENES ĀRSTA VĀRDS, UZVĀRDS:	

PACIENTA VECĀKU TAUTĪBA:	Mātes: Tēva:	PACIENTA VECUMS (pilni gadi):		PACIENTA DZIMUMS:	S ī V ī	**PACIENTA KODS:**	
ONKOLOĢISKĀ DIAGNOZE: *(ja vesels, ievilkt svītru)*			TNM STADIJA:			KURĀ GADĀ DIAGNOZE NOTEIKTA:	

Radinieki	Personu skaits	Vai kādam no radiniekiem ir bijis kāds audzējs? *(ierakstīt "JĀ", "NĒ" vai "NAV ZINĀMS")*	Audzēja lokalizācija *(orgāna vai ķermeņa daļas nosaukums)*	Cik gadu vecumā audzējs konstatēts?	Ja miris, tad cik gadu vecumā?
Brāļi					
Māsas					
Dēli					
Meitas					
Mazbērni					
TĒVS					
- Tēva brāļi					
- Tēva māsas					
- Tēva tēvs					
- Tēva māte					
MĀTE					
- Mātes brāļi					
- Mātes māsas					
- Mātes tēvs					
- Mātes māte					
CITI ASINSRADINIEKI					

Paldies par sadarbību!

ANNEX 3. The clinical characteristics of tumours in hereditary non-polyposis colorectal cancer kindreds

Kindred	Nationality of proband	Sex of the affected persons	Location of cancer	Age of cancer diagnostics	Age of death	Survival
IU-514	Latvian	F	Endometrial	65	Alive	Alive
IU-514	Latvian	F	Endometrial	65	Alive	Alive
IU-514	Latvian	F	CRC	55	Alive	Alive
IU-514	Latvian	F	CRC	61	Alive	Alive
MĶ-1620	Russian	F	Endometrial	50	Alive	Alive
MĶ-1620	Russian	M	CRC	62	63	1
MĶ-1620	Russian	F	Endometrial	45	Alive	Alive
MĶ-1620	Russian	F	Endometrial	45	Alive	Alive
MĶ-1619	Russian	F	Endometrial	50	Alive	Alive
MĶ-1619	Russian	M	CRC	62	63	1
MĶ-1619	Russian	F	Endometrial	45	Alive	Alive
MĶ-1619	Russian	F	Endometrial	45	Alive	Alive
MĶ-929	Russian	M	CRC	61	61	0
MĶ-929	Russian	F	Endometrial	50	Alive	Alive
MĶ-929	Russian	F	Endometrial	30	Alive	Alive
MB-610	Latvian	F	Endometrial	55	Alive	Alive
MB-610	Latvian	F	CRC	75	Alive	Alive
MB-610	Latvian	F	CRC	70	76	6
MB-610	Latvian	F	CRC	ND	85	ND
MB-610	Latvian	F	Endometrial	ND	ND	ND
MB-610	Latvian	F	Endometrial	ND	ND	ND
SNV-399	Latvian	M	CRC	56	Alive	Alive
SNV-399	Latvian	F	CRC	66	66	0
SNV-399	Latvian	F	CRC	36	38	2
SNV-399	Latvian	M	CRC	58	62	4
SNV-399	Latvian	F	Endometrial	58	Alive	Alive
SNV-399	Latvian	F	CRC	ND	89	ND
MĶ-54	Russian	M	CRC	60	61	1

MĶ-54	Russian	M	CRC	60	62	2
MĶ-54	Russian	F	Endometrial	36	37	1
MĶ-54	Russian	F	Small intestine	60	60	0
MB-138	Latvian	M	CRC	49	Alive	Alive
MB-138	Latvian	F	Endometrial	56	72	16
MB-138	Latvian	F	Renal pelvis	ND	80	ND
MN-898	Latvian	M	CRC	ND	59	ND
MN-898	Latvian	F	Endometrial	ND	Alive	Alive
MN-898	Latvian	M	CRC	ND	50	ND
MN-898	Latvian	F	CRC	ND	28	ND
MB-219	Latvian	M	CRC	77	Alive	Alive
MB-219	Latvian	M	CRC	ND	ND	ND
MB-219	Latvian	M	CRC	40	ND	ND
MĶ-930	Russian	F	Endometrial	30	Alive	Alive
MĶ-930	Russian	F	Endometrial	50	Alive	Alive
MĶ-930	Russian	M	CRC	60	60	0

Abbreviations in table: F, female; M, male; CRC, colorectal cancer; ND, no data available.

ANNEX 4. Cancer burden in hereditary non-polyposis colorectal cancer kindreds

Kindred	Affected by HNPCC-related cancer	Affected by colorectal cancer	Blood relatives	Affected by endometrial cancer	Females among blood relatives
IU-514	4	2	18	2	9
MĶ-1620	4	1	11	3	9
MĶ-1619	4	1	11	3	9
MĶ-929	3	1	9	2	14
MB-610	6	3	18	3	11
SNV-399	6	5	26	1	11
MĶ-54	4	2	9	1	4
MB-138	3	1	13	1	3
MN-898	4	3	12	1	6
MB-219	3	3	12	0	4
MĶ-930	3	1	7	2	5

Abbreviation in table: HNPCC, hereditary non-polyposis colorectal cancer

ANNEX 5. Characteristics of tumour course in suspected HNPCC kindreds

Kindred	Nationality of proband	Sex of the affected persons	Location of cancer	Age of cancer diagnostics	Age of death	Survival
SNV-532	Latvian	F	Endometrial	51	Alive	Alive
SNV-532	Latvian	M	CRC	ND	60	ND
SNV-532	Latvian	F	CRC	ND	38	ND
MĶ-1179	Latvian	F	Endometrial	42	Alive	Alive
MĶ-1179	Latvian	M	CRC	59	Alive	Alive
MĶ-1179	Latvian	F	CRC	28	Alive	Alive
MN-1234	Russian	M	CRC	54	54	0
MN-1234	Russian	F	Endometrial	50	Alive	Alive
LEZ-1473	Latvian	F	Endometrial	42	47	5
LEZ-1473	Latvian	F	CRC	81	82	1
MN-1281	Latvian	M	CRC	49	Alive	Alive
MN-1281	Latvian	F	Endometrial	72	73	1
MZ-395	Latvian	F	CRC	68	Alive	Alive
MZ-395	Latvian	M	CRC	49	59	10
IV-47	Latvian	F	CRC	42	43	1
IV-47	Latvian	F	CRC	66	67	1
LEZ-197	Latvian	M	CRC	49	52	3
LEZ-197	Latvian	F	Endometrial	59	Alive	Alive
VĶ-521	Polish	F	CRC	47	Alive	Alive
VĶ-521	Polish	F	CRC	71	72	1
MN-310	Latvian	F	CRC	39	40	1
MN-310	Latvian	F	Endometrial	62	Alive	Alive
LEZ-264	Ukrainian	M	CRC	62	64	2
LEZ-264	Ukrainian	F	CRC	45	49	4
MZ-315	Latvian	F	CRC	69	Alive	Alive
MZ-315	Latvian	M	CRC	49	59	10
MZ-502	Latvian	M	CRC	30	32	2
MZ-502	Latvian	M	CRC	38	40	2
AŠ-324	Latvian	F	Endometrial	69	69	0

AŠ-324	Latvian	F	CRC	38	38	0
SNV-366	Latvian	M	CRC	ND	53	ND
SNV-366	Latvian	F	Endometrial	45	Alive	Alive
SNV-477	Latvian	F	Endometrial	27	28	1
SNV-477	Latvian	M	CRC	73	76	3
RK-1	ND	F	CRC	72	73	1
RK-1	ND	F	Endometrial	40	40	0
MĶ-901	Russian	M	CRC	46	46	0
MĶ-901	Russian	M	CRC	63	63	0
LEZ-489	Latvian	F	Endometrial	48	50	2
LEZ-489	Latvian	M	CRC	82	88	6
SNV-501	Latvian	M	CRC	67	Alive	Alive
SNV-501	Latvian	F	Endometrial	50	Alive	Alive

Abbreviations in table: HNPCC, hereditary non-polyposis colorectal cancer; M, male; F, female; CRC, colorectal cancer; ND, no data available.

ANNEX 6. Cancer load and size of kindred in families affected by suspected hereditary non-polyposis colorectal cancer.

Kindred	Affected by HNPCC-related cancer	Affected by colorectal cancer	Blood relatives	Affected by endometrial cancer	Females among blood relatives
MĶ-1179	3	2	11	1	6
SNV-532	3	2	11	1	7
MN-1234	2	1	13	1	6
LEZ-1473	2	1	10	1	6
MN-1281	2	1	15	1	4
MZ-395	2	2	17	0	7
IV-47	2	2	17	0	10
LEZ-197	2	1	28	1	11
VĶ-521	2	2	17	0	6
MN-310	2	1	7	1	5
LEZ-264	2	2	18	0	9
MZ-315	2	2	8	0	5
MZ-502	2	2	11	0	8
AŠ-324	2	1	16	1	7
SNV-366	2	1	21	1	10
SNV-477	2	1	13	1	10
RK-1	3	1	13	2	9
MĶ-901	2	2	6	0	3
LEZ-489	2	1	ND	1	ND
SNV-501	2	1	13	1	6

Abbreviations in table: HNPCC, hereditary non-polyposis colorectal cancer syndrome; ND, no data available.

ANNEX 7. Characteristics of tumour course in familial colorectal cancer kindreds

Kindred	Nationality of proband	Sex of the affected persons	Age of cancer diagnostics	Age of death	Survival
MN-941	Latvian	M	ND	ND	ND
MN-941	Latvian	F	ND	76	ND
LEZ-765	Latvian	M	78	80	2
LEZ-765	Latvian	M	81	81	0
SNV-960	Latvian	F	89	89	0
SNV-960	Latvian	F	ND	ND	ND
SNV-429	Latvian	M	72	Alive	Alive
SNV-429	Latvian	F	52	52	0
SNV-498	Latvian	M	80	80	0
SNV-498	Latvian	M	76	78	2
SNV-497	Latvian	F	88	88	0
SNV-497	Latvian	F	80	82	2
MZ-49	Latvian	F	72	80	8
MZ-49	Latvian	F	ND	70	ND
MN-862	Latvian	F	67	69	2
MN-862	Latvian	F	75	78	3
LZ-117	Latvian	F	ND	80	ND
LZ-117	Latvian	F	ND	75	ND
EF-4	Latvian	F	73	75	ND
EF-4	Latvian	M	62	63	1
IV-809	Latvian	M	ND	65	ND
IV-809	Latvian	F	75	80	5
AK-146	Latvian	F	60	62	2
AK-146	Latvian	M	ND	74	ND
AK-146	Latvian	F	61	62	1
MN-118	Russian	M	70	73	3
MN-118	Russian	M	75	79	4
MN-976	Latvian	F	85	88	3
MN-976	Latvian	F	86	89	3

VĶ-842	Latvian	M	67	70	3
VĶ-842	Latvian	F	78	79	1
MB-6	Latvian	F	89	90	1
MB-6	Latvian	F	80	82	2
LEZ-1507	Latvian	F	66	72	6
LEZ-1507	Latvian	M	79	Alive	Alive
LP-219	Latvian	M	46	Alive	Alive
LP-219	Latvian	M	ND	ND	ND
LP-220	Latvian	M	46	Alive	Alive
LP-220	Latvian	M	ND	ND	ND
MZ-143	Latvian	M	41	Alive	Alive
MZ-143	Latvian	F	82	82	0

Abbreviations in table: M, male; F, female: ND, no data available.

ANNEX 8. Cancer load and size of kindred in families affected by familial colorectal cancer.

Kindred	Diagnosis	Affected by colorectal cancer	Blood relatives
MN-941	FCC2	2	14
LEZ-765	FCC1	2	15
SNV-960	FCC1	2	19
SNV-429	FCC1	2	18
SNV-498	FCC1	2	11
SNV-497	FCC1	2	12
MZ-49	FCC1	2	9
MN-862	FCC1	2	10
LZ-117	FCC1	2	9
EF-4	FCC1	2	14
IV-809	FCC1	2	12
AK-146	FCC1	3	12
MN-118	FCC1	2	14
MN-976	FCC1	2	15
VĶ-842	FCC2	2	15
MB-6	FCC1	2	9
LEZ-1507	FCC1	2	3
LP-219	FCC2	2	8
LP-220	FCC2	2	8
MN-0941	FCC2	2	13
MN-0118	FCC2	2	14
MZ-143	FCC2	2	15

Abbreviations in table: FCC1, familial colorectal cancer, variety 1; FCC2, familial colorectal cancer, variety 2.

ANNEX 9. Age distribution of probands with hereditary endometrial cancer syndromes

Diagnosis	Analysable number	18-29	30-39	40-49	50-59	60-69	70-79	More than 80
HEC	5	1	1	2	1	0	0	0
HEC susp.	26	4	3	4	6	2	6	1
FEC	2	0	1	0	1	0	0	0
FEC susp.1	24	2	5	5	3	4	5	0
FEC susp.2	9	2	0	2	1	1	1	2

Abbreviations: HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; FEC susp.1, suspected familial endometrial cancer, variety 1; FEC susp.2, suspected familial endometrial cancer, variety 2; susp., suspected hereditary endometrial cancer syndromes

ANNEX 10. The characteristics of endometrial cancer course in definitive and suspected hereditary endometrial cancer kindreds

Kindred	Diagnosis	Nationality of the proband	Age of the tumour diagnostics, years	Age of death, years	Survival, years
MAK-471	FEC	Latvian	60	82	22
MAK-471	FEC	Latvian	70	83	13
MAK-471	FEC	Latvian	78	Alive	Alive
ZL-1063	FEC	Latvian	60	86	7
ZL-1063	FEC	Latvian	ND	80	ND
ZL-1063	FEC	Latvian	ND	65	ND
AK-316	FEC susp.1	Latvian	80	Alive	Alive
AK-316	FEC susp.1	Latvian	78	80	2
IU-225	FEC susp.1	Latvian	62	63	1
IU-225	FEC susp.1	Latvian	78	78	0
JE-259	FEC susp.1	Latvian	65	66	1
JE-259	FEC susp.1	Latvian	ND	85	ND
JE-556	FEC susp.1	Latvian	70	Alive	Alive
JE-556	FEC susp.1	Latvian	80	82	2
LEZ-1222	FEC susp.1	Lithuanian	54	54	0
LEZ-1222	FEC susp.1	Lithuanian	59	60	1
LZ-789	FEC susp.1	Latvian	ND	ND	ND
LZ-789	FEC susp.1	Latvian	ND	ND	ND
MB-749	FEC susp.1	Latvian	70	70	0
MB-749	FEC susp.1	Latvian	80	ND	ND
MB-876	FEC susp.1	Latvian	60	Alive	Alive
MB-876	FEC susp.1	Latvian	70	70	0
MB-877	FEC susp.1	Latvian	60	Alive	Alive
MB-877	FEC susp.1	Latvian	70	70	0
MĶ-1325	FEC susp.1	Russian	ND	70	ND
MĶ-1325	FEC susp.1	Russian	ND	76	ND
MĶ-1326	FEC susp.1	Russian	ND	70	ND

MĶ-1326	FEC susp.1	Russian	ND	76	ND
MĶ-1327	FEC susp.1	Russian	ND	70	ND
MĶ-1327	FEC susp.1	Russian	ND	76	ND
MĶ-1587	FEC susp.1	Latvian	73	74	1
MĶ-1587	FEC susp.1	Latvian	69	70	1
MĶ-270	FEC susp.1	Latvian	59	Alive	Alive
MĶ-270	FEC susp.1	Latvian	60	70	10
MN-0305	FEC susp.1	Latvian	ND	Alive	Alive
MN-0305	FEC susp.1	Latvian	ND	Alive	Alive
MN-0362	FEC susp.1	Latvian	56	Alive	Alive
MN-0362	FEC susp.1	Latvian	70	73	3
MN-1294	FEC susp.1	Latvian	70	71	1
MN-1294	FEC susp.1	Latvian	70	73	3
MZ-181	FEC susp.1	Latvian	65	Alive	Alive
MZ-181	FEC susp.1	Latvian	90	91	1
MZ-636	FEC susp.1	Latvian	60	Alive	Alive
MZ-636	FEC susp.1	Latvian	ND	77	ND
OR-118	FEC susp.1	Russian	53	Alive	Alive
OR-118	FEC susp.1	Russian	55	Alive	Alive
SJ-210	FEC susp.1	Byelorussian	ND	60	ND
SJ-210	FEC susp.1	Byelorussian	ND	60	ND
SNV-357	FEC susp.1	Latvian	ND	65	ND
SNV-357	FEC susp.1	Latvian	ND	78	ND
SNV-830	FEC susp.1	Latvian	63	Alive	Alive
SNV-830	FEC susp.1	Latvian	55	55	0
SNV-943	FEC susp.1	Latvian	60	65	5
SNV-943	FEC susp.1	Latvian	52	86	34
AG-112	FEC susp.2	Latvian	42	Alive	Alive
AG-112	FEC susp.2	Latvian	60	70	10
AŠ-31	FEC susp.2	Latvian	63	64	1
AŠ-31	FEC susp.2	Latvian	69	70	1
AŠ-31	FEC susp.2	Latvian	82	83	1
AŠ-31	FEC susp.2	Latvian	69	70	1

AŠ-395	FEC susp.2	Latvian	ND	80	ND
AŠ-395	FEC susp.2	Latvian	58	65	7
AŠ-487	FEC susp.2	Latvian	69	70	1
AŠ-487	FEC susp.2	Latvian	82	83	1
AŠ-487	FEC susp.2	Latvian	69	70	1
AŠ-487	FEC susp.2	Latvian	63	64	1
LEZ-308	FEC susp.2	Latvian	50	Alive	Alive
LEZ-308	FEC susp.2	Latvian	31	32	1
LEZ-33	FEC susp.2	Latvian	60	Alive	Alive
LEZ-33	FEC susp.2	Latvian	68	78	10
MB-30	FEC susp.2	Latvian	ND	56	ND
MB-30	FEC susp.2	Latvian	ND	40	ND
VĶ-972	FEC susp.2	Latvian	37	Alive	Alive
VĶ-972	FEC susp.2	Latvian	53	56	3
ZL-998	FEC susp.2	Latvian	44	Alive	Alive
ZL-998	FEC susp.2	Latvian	26	26	0
MAK-302	HEC	Latvian	45	50	5
MAK-302	HEC	Latvian	64	65	1
MAK-302	HEC	Latvian	ND	ND	ND
MN-0110	HEC	Russian	50	74	24
MN-0110	HEC	Russian	40	74	34
MN-0110	HEC	Russian	45	Alive	Alive
SNV-1477	HEC	Latvian	50	52	2
SNV-1477	HEC	Latvian	50	50	0
SNV-1477	HEC	Latvian	50	50	0
SNV-1477	HEC	Latvian	50	50	0
SNV-1477	HEC	Latvian	50	50	0
SNV-257	HEC	Latvian	57	Alive	Alive
SNV-257	HEC	Latvian	44	44	0
SNV-257	HEC	Latvian	75	76	1
SNV-613	HEC	Latvian	63	Alive	Alive
SNV-613	HEC	Latvian	43	Alive	Alive
SNV-613	HEC	Latvian	58	Alive	Alive

AG-9	HEC susp.	Latvian	48	54	6
AG-9	HEC susp.	Latvian	52	53	1
AK-188	HEC susp.	Latvian	45	46	1
AK-188	HEC susp.	Latvian	ND	55	ND
AK-384	HEC susp.	Latvian	ND	44	ND
AK-384	HEC susp.	Latvian	ND	82	ND
AŠ-106	HEC susp.	Latvian	81	83	2
AŠ-106	HEC susp.	Latvian	38	38	0
IV-1004	HEC susp.	Latvian	45	46	1
IV-1004	HEC susp.	Latvian	45	Alive	Alive
LEZ-912	HEC susp.	Latvian	47	52	5
LEZ-912	HEC susp.	Latvian	69	72	3
MB-13	HEC susp.	Latvian	50	82	32
MB-13	HEC susp.	Latvian	48	52	4
MB-21	HEC susp.	Latvian	30	Alive	Alive
MB-21	HEC susp.	Latvian	30	74	44
MN-0403	HEC susp.	Latvian	42	48	6
MN-0403	HEC susp.	Latvian	73	76	3
MN-0471	HEC susp.	ND	35	Alive	Alive
MN-0471	HEC susp.	ND	ND	ND	ND
MN-0471	HEC susp.	ND	50	54	4
MN-0472	HEC susp.	Latvian	37	Alive	Alive
MN-0472	HEC susp.	Latvian	ND	ND	ND
MN-0472	HEC susp.	Latvian	50	54	4
MN-0686	HEC susp.	Latvian	70	Alive	Alive
MN-0686	HEC susp.	Latvian	43	45	2
MN-0687	HEC susp.	Latvian	70	Alive	Alive
MN-0687	HEC susp.	Latvian	43	45	2
MN-0960	HEC susp.	Latvian	46	76	30
MN-0960	HEC susp.	Latvian	ND	ND	ND
MN-0993	HEC susp.	Russian	50	54	4
MN-0993	HEC susp.	Russian	ND	ND	ND
MZ-40	HEC susp.	Latvian	50	50	0

MZ-40	HEC susp.	Latvian	40	Alive	Alive
SNV-1338	HEC susp.	Latvian	55	Alive	Alive
SNV-1338	HEC susp.	Latvian	34	72	38
SNV-191	HEC susp.	Latvian	ND	45	ND
SNV-191	HEC susp.	Latvian	60	Alive	Alive
SNV-191	HEC susp.	Latvian	80	82	2
VĶ-1038	HEC susp.	Latvian	53	56	3
VĶ-1038	HEC susp.	Latvian	37	Alive	Alive
VĶ-1382	HEC susp.	Russian	38	64	26
VĶ-1382	HEC susp.	Russian	72	73	1
VĶ-1383	HEC susp.	Latvian	38	64	26
VĶ-1383	HEC susp.	Latvian	76	76	0
VĶ-818	HEC susp.	Latvian	40	Alive	Alive
VĶ-818	HEC susp.	Latvian	65	Alive	Alive
VĶ-818	HEC susp.	Latvian	50	87	37
VĶ-983	HEC susp.	Latvian	30	40	10
VĶ-983	HEC susp.	Latvian	40	Alive	Alive
VĶ-984	HEC susp.	Latvian	30	40	10
VĶ-984	HEC susp.	Latvian	40	Alive	Alive
VĶ-985	HEC susp.	Latvian	40	Alive	Alive
VĶ-985	HEC susp.	Latvian	30	40	10
ZL-1019	HEC susp.	Latvian	61	63	2
ZL-1019	HEC susp.	Latvian	34	35	1

Abbreviations in table: FEC, familial endometrial cancer; FEC susp.1, suspected familial endometrial cancer, variety 1; FEC susp.2, suspected familial endometrial cancer, variety 2; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; ND, no data available.

ANNEX 11. Endometrial cancer burden and number of female blood relatives in hereditary endometrial cancer kindreds

Kindred	Diagnosis	Affected	Total number
MAK-471	FEC	3	9
ZL-1063	FEC	3	4
AK-316	FEC susp.1	2	6
IU-225	FEC susp.1	2	4
JE-259	FEC susp.1	2	8
JE-556	FEC susp.1	2	5
LEZ-1222	FEC susp.1	2	11
LZ-789	FEC susp.1	2	5
MB-749	FEC susp.1	2	7
MB-876	FEC susp.1	2	4
MB-877	FEC susp.1	2	7
MĶ-1325	FEC susp.1	2	7
MĶ-1326	FEC susp.1	2	8
MĶ-1327	FEC susp.1	2	8
MĶ-1587	FEC susp.1	2	3
MĶ-270	FEC susp.1	2	5
MN-0305	FEC susp.1	2	6
MN-0362	FEC susp.1	2	7
MN-1294	FEC susp.1	2	6
MZ-181	FEC susp.1	2	8
MZ-636	FEC susp.1	2	4
OR-118	FEC susp.1	2	9
SJ-210	FEC susp.1	2	8
SNV-357	FEC susp.1	2	9
SNV-830	FEC susp.1	2	9
SNV-943	FEC susp.1	2	13
AG-112	FEC susp.2	2	5
AŠ-31	FEC susp.2	4	6
AŠ-395	FEC susp.2	2	5
AŠ-487	FEC susp.2	4	9

LEZ-308	FEC susp.2	2	11
LEZ-33	FEC susp.2	2	4
MB-30	FEC susp.2	2	12
VĶ-972	FEC susp.2	2	9
ZL-998	FEC susp.2	2	7
MAK-302	HEC	3	8
MN-0110	HEC	3	6
SNV-1477	HEC	5	9
SNV-257	HEC	3	8
SNV-613	HEC	3	10
AG-9	HEC susp.	2	6
AK-188	HEC susp.	2	4
AK-384	HEC susp.	2	4
AŠ-106	HEC susp.	2	6
IV-1004	HEC susp.	2	7
LEZ-912	HEC susp.	2	7
MB-13	HEC susp.	2	11
MB-21	HEC susp.	2	8
MN-0403	HEC susp.	2	10
MN-0471	HEC susp.	3	9
MN-0472	HEC susp.	3	10
MN-0686	HEC susp.	2	4
MN-0687	HEC susp.	2	5
MN-0960	HEC susp.	2	8
MN-0993	HEC susp.	2	3
MZ-40	HEC susp.	2	13
SNV-1338	HEC susp.	2	4
SNV-191	HEC susp.	3	6
VĶ-1038	HEC susp.	2	9
VĶ-1382	HEC susp.	2	3
VĶ-1383	HEC susp.	2	4
VĶ-818	HEC susp.	3	7
VĶ-983	HEC susp.	2	6

VK-984	HEC susp.	2	6
VK-985	HEC susp.	2	7
ZL-1019	HEC susp.	2	7

Abbreviations in table: FEC, familial endometrial cancer; FEC susp.1, suspected familial endometrial cancer, variety 1; FEC susp.2, suspected familial endometrial cancer, variety 2; HEC, hereditary endometrial cancer; HEC susp., suspected hereditary endometrial cancer; ND, no data available.

ANNEX 12. The characteristics of lung tumour course in definitive and suspected familial lung cancer kindreds

Kindred	Nationality of proband	Sex of affected persons	Age of tumour diagnostics	Age of death	Survival, years
LEZ-655	Latvian	M	60	65	5
LEZ-655	Latvian	M	55	57	2
LEZ-655	Latvian	M	50	50	0
LEZ-655	Latvian	M	50	50	0
OR-323	Byelorussian	M	50	50	0
OR-323	Byelorussian	M	50	50	0
OR-323	Byelorussian	M	50	50	0
OR-323	Byelorussian	M	50	50	0
OR-323	Byelorussian	M	50	50	0
IN-092	Latvian	M	49	53	4
IN-092	Latvian	M	ND	36	ND
IN-092	Latvian	M	ND	46	ND
SNV-1366	Latvian	F	57	57	0
SNV-1366	Latvian	M	59	59	0
SNV-1366	Latvian	M	61	61	0
SJ-172	Latvian	M	49	54	5
SJ-172	Latvian	M	ND	60	ND
SJ-172	Latvian	M	ND	60	ND
IV-869	Latvian	F	39	40	1
IV-869	Latvian	M	74	76	2
IV-869	Latvian	F	35	38	3
AŠ-390	Latvian	F	40	50	10
AŠ-390	Latvian	M	65	70	5
AG-43	Latvian	M	ND	80	ND
AG-43	Latvian	M	ND	60	ND
AG-66	Latvian	M	59	62	3
AG-66	Latvian	M	ND	60	ND
SNV-308	Latvian	M	72	72	0

SNV-308	Latvian	M	80	82	2
LEZ-552	Latvian	F	50	52	2
LEZ-552	Latvian	M	72	73	1
JE-499	Latvian	M	62	62	0
JE-499	Latvian	F	57	57	0
JE-499	Latvian	M	58	58	0
JE-500	Latvian	M	62	62	0
JE-500	Latvian	F	57	57	0
JE-500	Latvian	M	58	58	0
LZ-815	Latvian	M	59	60	1
LZ-815	Latvian	F	57	57	0
LZ-815	Latvian	M	62	62	0
LZ-816	Latvian	M	59	60	1
LZ-816	Latvian	F	57	57	0
MB-450	Latvian	M	60	60	0
MB-450	Latvian	F	55	55	0
LEZ-1418	Latvian	M	60	60	0
LEZ-1418	Latvian	M	49	49	0
LZ-438	Polish	M	ND	64	ND
LZ-438	Polish	M	ND	60	ND
SJ-274	Latvian	F	55	55	0
SJ-274	Latvian	M	60	60	0
LEZ-257	Latvian	M	69	70	1
LEZ-257	Latvian	M	55	60	5
AŠ-372	Estonian	M	45	45	0
AŠ-372	Estonian	M	ND	ND	ND
ZL-786	Latvian	M	66	66	0
ZL-786	Latvian	M	ND	60	ND
MN-1206	Russian	M	67	69	2
MN-1206	Russian	M	59	62	3
MN-1206	Russian	M	78	79	1
VĶ-1171	Russian	M	60	61	1
VĶ-1171	Russian	M	50	50	0

VĶ-1171	Russian	M	55	55	0
VĶ-1171	Russian	M	60	60	0
MĶ-1289	Latvian	M	60	66	6
MĶ-1289	Latvian	M	60	60	0
AK-68	Latvian	M	66	74	12
AK-68	Latvian	M	46	47	1
IU-340	Latvian	M	ND	ND	0
IU-340	Latvian	F	ND	74	ND
MB-749	Latvian	M	40	40	0
MB-749	Latvian	F	38	ND	ND
MB-749	Latvian	F	ND	78	ND
MZ-529	Latvian	M	69	69	0
MZ-529	Latvian	M	69	71	2
EF-75	Latvian	F	58	65	7
EF-75	Latvian	F	ND	ND	ND
ZL-473	Latvian	M	74	74	0
ZL-473	Latvian	F	ND	68	ND
ZL-197	Latvian	M	45	47	2
ZL-197	Latvian	M	64	66	2
MĶ-254	Latvian	M	50	50	0
MĶ-254	Latvian	M	70	70	0
MĶ-814	Russian	M	73	73	0
MĶ-814	Russian	M	80	80	0
LZ-900	Latvian	M	ND	72	ND
LZ-900	Latvian	F	ND	24	ND
MN-60	Latvian	M	79	79	0
MN-60	Latvian	M	75	78	3
JE-326	Latvian	M	60	60	0
JE-326	Latvian	F	57	57	0
JE-326	Latvian	M	59	59	0
LEZ-759	Latvian	M	70	75	5
LEZ-759	Latvian	F	23	24	1
MAK-30	Latvian	M	ND	55	ND

MAK-30	Latvian	M	ND	79	ND
MAK-30	Latvian	M	ND	70	ND
AG-334	Latvian	M	65	ND	ND
AG-334	Latvian	M	ND	ND	ND
RK-125	Latvian	M	ND	ND	ND
RK-125	Latvian	F	ND	ND	ND
EF-346	Latvian	M	18	21	3
EF-346	Latvian	F	ND	ND	ND
LZ-464	Russian	M	54	54	0
LZ-464	Russian	M	ND	48	ND
LZ-463	Russian	M	54	54	0
LZ-463	Russian	M	ND	48	ND
LZ-462	Russian	M	54	54	0
LZ-462	Russian	M	ND	48	ND
LZ-465	Russian	M	54	54	0
LZ-465	Russian	M	ND	48	ND
MĶ-917	Latvian	F	57	58	1
MĶ-917	Latvian	M	66	68	2
MN-1304	Latvian	M	64	68	4
MN-1304	Latvian	F	53	58	5
MĶ-875	Latvian	F	57	58	1
MĶ-875	Latvian	M	66	68	2
MB-600	Latvian	M	59	60	1
MB-600	Latvian	M	ND	74	ND
MĶ-989	Russian	M	37	37	0
MĶ-989	Russian	M	63	65	0
MĶ-989	Russian	M	35	35	0
MĶ-990	Russian	M	37	37	0
MĶ-990	Russian	M	35	35	0
MĶ-990	Russian	M	65	65	0
MN-1087	Latvian	M	49	51	2
MN-1087	Latvian	F	61	63	2
OR-269	Russian	F	ND	74	ND

OR-269	Russian	F	ND	70	ND
MĶ-821	Russian	M	73	73	0
MĶ-821	Russian	M	81	81	0
AK-219	Latvian	M	ND	ND	ND
AK-219	Latvian	M	ND	ND	ND
AK-637	Latvian	M	64	69	5
AK-637	Latvian	M	50	55	5
AŠ-309	Latvian	M	39	40	1
AŠ-309	Latvian	M	79	80	1
AŠ-243	Latvian	M	22	81	59
AŠ-243	Latvian	M	40	63	23
AŠ-36	Latvian	M	43	48	5
AŠ-36	Latvian	M	66	67	1
EF-315	Latvian	M	70	73	3
EF-315	Latvian	M	72	74	2
IV-0072	Latvian	M	49	51	2
IV-0072	Latvian	M	79	80	1
IV-0683	Latvian	F	ND	50	ND
IV-0683	Latvian	M	ND	ND	ND
IV-0681	Latvian	M	ND	ND	ND
IV-0681	Latvian	F	ND	50	ND
IV-0682	Latvian	M	ND	ND	ND
IV-0682	Latvian	F	ND	50	ND
JE-229	Byelorussian	F	53	54	1
JE-229	Byelorussian	F	ND	60	ND
LEZ-27	Latvian	M	74	74	0
LEZ-27	Latvian	M	63	63	0
JE-214	Latvian	M	70	70	0
JE-214	Latvian	F	90	90	0
LEZ-1188	Latvian	M	38	41	3
LEZ-1188	Latvian	M	47	49	2
LEZ-456	Russian	M	47	52	5
LEZ-456	Russian	M	62	64	2

LZ-139	Latvian	M	ND	78	ND
LZ-139	Latvian	M	ND	76	ND
LZ-437	Latvian	M	ND	64	ND
LZ-437	Latvian	M	ND	60	ND
LZ-485	Latvian	M	ND	70	ND
LZ-485	Latvian	F	ND	75	ND
LZ-644	Estonian	M	ND	76	ND
LZ-644	Estonian	M	ND	60	ND
LZ-677	Latvian	M	ND	50	ND
LZ-677	Latvian	M	ND	60	ND
MB-919	Latvian	M	38	38	0
MB-919	Latvian	M	52	52	0
MB-823	Latvian	F	64	Alive	Alive
MB-823	Latvian	F	73	73	0
MĶ-432	Latvian	M	45	46	4
MĶ-432	Latvian	M	ND	ND	ND
MĶ-954	Russian	M	35	40	5
MĶ-954	Russian	M	50	50	0
MĶ-830	Latvian	F	ND	60	ND
MĶ-830	Latvian	F	ND	55	ND
MĶ-1728	Russian	M	62	63	1
MĶ-1728	Russian	M	60	60	0
MĶ-1670	Latvian	M	60	61	1
MĶ-1670	Latvian	F	80	81	1
MĶ-1184	Latvian	M	ND	50	ND
MĶ-1184	Latvian	M	ND	75	ND
MN-0903	Russian	M	ND	73	ND
MN-0903	Russian	M	55	56	1
MZ-749	Latvian	M	69	69	0
MZ-749	Latvian	M	70	70	0
MZ-707	Latvian	F	ND	59	ND
MZ-707	Latvian	M	ND	58	ND
OR-321	Latvian	M	45	50	5

OR-321	Latvian	F	55	55	0
OR-322	Latvian	M	45	50	5
OR-322	Latvian	F	55	55	0
OR-277	Russian	F	ND	74	ND
OR-277	Russian	F	ND	70	ND
OR-275	Russian	F	ND	74	ND
OR-275	Russian	F	ND	70	ND
OR-110	Russian	M	62	62	0
OR-110	Russian	M	64	64	2
OR-100	Russian	M	62	62	0
OR-100	Russian	M	64	64	0
SNV-595	Latvian	M	58	60	2
SNV-595	Latvian	M	65	70	5
SNV-553	Latvian	M	72	72	0
SNV-553	Latvian	M	ND	ND	ND
SNV-1382	Latvian	M	54	55	1
SNV-1382	Latvian	M	52	52	0
SNV-1112	Latvian	M	59	59	0
SNV-1112	Latvian	M	55	55	0
SNV-1043	Latvian	M	ND	13	ND
SNV-1043	Latvian	M	ND	50	ND
VĶ-946	Latvian	M	55	55	0
VĶ-946	Latvian	M	76	78	2
VĶ-696	Russian	M	48	50	2
VĶ-696	Russian	F	58	60	2
VĶ-539	Byelorussian	M	57	57	0
VĶ-539	Byelorussian	M	49	49	0
VĶ-1370	Latvian	M	ND	45	ND
VĶ-1370	Latvian	M	72	Alive	Alive
VĶ-1132	Latvian	M	71	71	0
VĶ-1132	Latvian	M	60	62	2
VĶ-1108	Russian	M	45	50	5
VĶ-1108	Russian	M	60	63	3

VĶ-1052	Russian	M	59	60	1
VĶ-1052	Russian	M	55	Alive	Alive
VĶ-1083	Russian	M	ND	64	ND
VĶ-1083	Russian	M	ND	62	ND
VĶ-1107	Russian	M	45	50	5
VĶ-1107	Russian	M	60	63	3

Abbreviations in table: M, male; F, female; ND, no data available.

ANNEX 13. Number of affected persons and blood relatives in the considered blood line from definitive and suspected familial lung cancer kindreds

Kindred	Diagnosis	Cases of lung cancer	Affected generations	Blood relatives in the affected line
IN-092	FLC	3	1	11
IV-869	FLC	3	2	17
JE-326	FLC	3	2	12
JE-499	FLC	3	2	12
JE-500	FLC	3	2	12
LEZ-655	FLC	4	2	15
LZ-815	FLC	3	2	13
MAK-30	FLC	3	2	12
MN-1206	FLC	3	1	15
OR-323	FLC	5	1	12
SJ-172	FLC	3	1	14
SNV-1366	FLC	3	2	13
VĶ-1171	FLC	4	1	11
AG-334	FLC susp.	2	2	17
AG-43	FLC susp.	2	1	21
AG-66	FLC susp.	2	2	14
AK-219	FLC susp.	2	1	13
AK-637	FLC susp.	2	1	12
AK-68	FLC susp.	2	1	17
AŠ-243	FLC susp.	2	1	18
AŠ-309	FLC susp.	2	2	10
AŠ-36	FLC susp.	2	2	13
AŠ-372	FLC susp.	2	2	18
AŠ-390	FLC susp.	2	2	7
EF-315	FLC susp.	2	2	18
EF-346	FLC susp.	2	1	ND
EF-75	FLC susp.	2	2	7
IU-340	FLC susp.	2	1	14
IV-0072	FLC susp.	2	2	8

IV-0681	FLC susp.	2	1	9
IV-0682	FLC susp.	2	1	9
IV-0683	FLC susp.	2	1	9
JE-214	FLC susp.	2	2	15
JE-229	FLC susp.	2	2	8
LEZ-1188	FLC susp.	2	2	10
LEZ-1418	FLC susp.	2	1	12
LEZ-257	FLC susp.	2	1	14
LEZ-27	FLC susp.	2	2	16
LEZ-456	FLC susp.	2	1	15
LEZ-552	FLC susp.	2	2	10
LEZ-759	FLC susp.	2	1	12
LZ-139	FLC susp.	2	2	13
LZ-437	FLC susp.	2	1	8
LZ-438	FLC susp.	2	1	13
LZ-462	FLC susp.	2	1	10
LZ-463	FLC susp.	2	1	10
LZ-464	FLC susp.	2	1	12
LZ-465	FLC susp.	2	1	11
LZ-485	FLC susp.	2	2	7
LZ-644	FLC susp.	2	1	17
LZ-677	FLC susp.	2	2	8
LZ-816	FLC susp.	2	2	13
LZ-900	FLC susp.	2	1	8
MB-450	FLC susp.	2	1	11
MB-600	FLC susp.	2	2	9
MB-749	FLC susp.	3	2	17
MB-823	FLC susp.	2	2	13
MB-919	FLC susp.	2	2	8
MĶ-1289	FLC susp.	2	2	10
MĶ-1670	FLC susp.	2	2	9
MĶ-1728	FLC susp.	2	2	9
MĶ-254	FLC susp.	2	2	18

MĶ-432	FLC susp.	2	2	8
MĶ-814	FLC susp.	2	2	12
MĶ-821	FLC susp.	2	2	10
MĶ-830	FLC susp.	2	1	9
MĶ-875	FLC susp.	2	2	13
MĶ-917	FLC susp.	2	2	10
MĶ-954	FLC susp.	2	2	8
MĶ-989	FLC susp.	3	2	8
MĶ-990	FLC susp.	3	2	11
MN-0903	FLC susp.	2	2	15
MN-1087	FLC susp.	2	1	15
MN-1184	FLC susp.	2	2	5
MN-1304	FLC susp.	2	2	10
MN-60	FLC susp.	2	2	9
MZ-529	FLC susp.	2	1	29
MZ-707	FLC susp.	2	1	8
MZ-749	FLC susp.	2	1	15
OR-100	FLC susp.	2	2	10
OR-110	FLC susp.	2	2	8
OR-269	FLC susp.	2	2	12
OR-275	FLC susp.	2	2	10
OR-277	FLC susp.	2	2	10
OR-321	FLC susp.	2	1	25
OR-322	FLC susp.	2	1	14
RK-125	FLC susp.	2	1	16
SJ-274	FLC susp.	2	2	11
SNV-1043	FLC susp.	2	2	10
SNV-1112	FLC susp.	2	1	11
SNV-1382	FLC susp.	2	1	13
SNV-308	FLC susp.	2	1	18
SNV-553	FLC susp.	2	1	6
SNV-595	FLC susp.	2	2	8
VĶ-1052	FLC susp.	2	1	7

VĶ-1083	FLC susp.	2	2	8
VĶ-1107	FLC susp.	2	2	10
VĶ-1108	FLC susp.	2	2	10
VĶ-1132	FLC susp.	2	1	11
VĶ-1370	FLC susp.	2	1	14
VĶ-539	FLC susp.	2	2	9
VĶ-696	FLC susp.	2	2	16
VĶ-946	FLC susp.	2	2	6
ZL-197	FLC susp.	2	1	13
ZL-473	FLC susp.	2	1	6
ZL-786	FLC susp.	2	2	13

Abbreviations in table: FLC, familial lung cancer; FLC susp., suspected familial lung cancer.

ANNEX 14. Association of familial lung cancer with other malignant tumours

Kindred	Cases of lung cancer	Other cancers	Blood relatives in the affected line
AG-334	2	Uterus	17
AG-43	2	Pancreas, stomach	21
AG-66	2	Uterus	14
AK-219	2	None	13
AK-637	2	None	12
AK-68	2	CSU	17
AŠ-243	2	None	18
AŠ-309	2	None	10
AŠ-36	2	None	13
AŠ-372	2	Uterus	18
AŠ-390	2	None	7
EF-315	2	None	18
EF-346	2	Uterus, stomach, liver	ND
EF-75	2	Gynaecological	7
IN-092	3	None	11
IU-340	2	Uterus, CSU	14
IV-0072	2	None	8
IV-0681	2	None	9
IV-0682	2	None	9
IV-0683	2	None	9
IV-869	3	CRC	17
JE-214	2	None	15
JE-229	2	None	8
JE-326	3	Bone – spine	12
JE-499	3	Bones – spine	12
JE-500	3	Bones – spine	12
LEZ-1188	2	None	10
LEZ-1418	2	CRC	12
LEZ-257	2	Duodenum	14
LEZ-27	2	None	16

LEZ-456	2	None	15
LEZ-552	2	HN, kidney	10
LEZ-655	4	None	15
LEZ-759	2	Stomach	12
LZ-139	2	None	13
LZ-437	2	Leu	8
LZ-438	2	Leu	13
LZ-462	2	Ov, breast	10
LZ-463	2	Ov, breast	10
LZ-464	2	Ov, breast	12
LZ-465	2	Ov, breast	11
LZ-485	2	None	7
LZ-644	2	None	17
LZ-677	2	None	8
LZ-815	3	Bones – spine	13
LZ-816	2	Bones – spine	13
LZ-900	2	None	8
MAK-30	3	CRC	12
MB-450	2	Bones – spine	11
MB-600	2	None	9
MB-749	3	2 uterus, CSU	17
MB-823	2	None	13
MB-919	2	None	8
MĶ-1289	2	Breast, brain	10
MĶ-1670	2	None	9
MĶ-1728	2	None	9
MĶ-254	2	CRC	18
MĶ-432	2	None	8
MĶ-814	2	Liver, Leu	12
MĶ-821	2	Liver, Leu	10
MĶ-830	2	None	9
MĶ-875	2	Leu, Ov, breast, uterus, CRC	13
MĶ-917	2	Leu, Ov, uterus, 2 breast, CRC	10

MĶ-954	2	None	8
MĶ-989	3	None	7
MĶ-990	3	None	11
MN-0903	2	None	15
MN-1087	2	Stomach, CRC	15
MN-1184	2	None	5
MN-1206	3	Uterus	15
MN-1304	2	2 breast, Leu, Ov, CRC	10
MN-60	2	None	9
MZ-529	2	Leu, Stomach	29
MZ-707	2	None	8
MZ-749	2	None	15
OR-100	2	None	10
OR-110	2	None	8
OR-269	2	None	12
OR-275	2	None	10
OR-277	2	None	10
OR-321	2	None	25
OR-322	2	None	14
OR-323	5	Stomach	12
RK-125	2	Breast, HN	16
SJ-172	3	None	14
SJ-274	2	Breast	11
SNV-1043	2	None	10
SNV-1112	2	None	11
SNV-1366	3	Bones – spine	13
SNV-1382	2	None	13
SNV-308	2	Kidney, pancreas	18
SNV-553	2	None	6
SNV-595	2	None	8
VĶ-1052	2	None	7
VĶ-1083	2	None	8
VĶ-1107	2	None	10

VĶ-1108	2	None	10
VĶ-1132	2	None	11
VĶ-1171	4	CSU	11
VĶ-1370	2	None	14
VĶ-539	2	None	9
VĶ-696	2	None	16
VĶ-946	2	None	6
ZL-197	2	Uterus	13
ZL-473	2	Breast	6
ZL-786	2	Pancreas	13

Abbreviations in table: CSU, malignant tumour of unknown location (by family history only); CRC, colorectal cancer; HN, malignant tumour of head and neck; Ov, ovarian cancer; Leu, malignant haematologic tumour.

ANNEX 15. The characteristics of affected persons from definitive and suspected hereditary stomach cancer families.

Kindred	Diagnosis	Nationality by the proband	Sex of the affected persons	Age of tumour diagnostics, years	Age of death, years	Survival, years
LZ-922	HSC	Latvian	F	ND	64	ND
LZ-922	HSC	Latvian	M	ND	70	ND
LZ-922	HSC	Latvian	F	ND	70	ND
VĶ-1412	HSC susp.	Latvian	M	ND	ND	ND
VĶ-1412	HSC susp.	Latvian	M	ND	53	ND
AK-336	HSC	Latvian	M	50	52	2
AK-336	HSC	Latvian	ND	ND	50	ND
AK-336	HSC	Latvian	ND	ND	50	ND
AK-336	HSC	Latvian	ND	ND	50	ND
MN-1162	HSC	Latvian	M	ND	74	ND
MN-1162	HSC	Latvian	M	ND	70	ND
MN-1162	HSC	Latvian	F	70	90	20
RK-107	HSC	Latvian	M	50	60	10
RK-107	HSC	Latvian	M	50	60	10
RK-107	HSC	Latvian	F	55	58	3
RK-107	HSC	Latvian	M	50	56	6
RK-107	HSC	Latvian	M	ND	50	ND
RK-107	HSC	Latvian	M	ND	50	ND
RK-107	HSC	Latvian	M	50	60	10
IU-319	HSC	Russian	M	ND	43	ND
IU-319	HSC	Russian	M	ND	43	ND
IU-319	HSC	Russian	M	ND	50	ND
IU-065	HSC	Latvian	M	ND	43	ND
IU-065	HSC	Latvian	M	ND	43	ND
IU-065	HSC	Latvian	F	ND	60	ND
MĶ-22	HSC	Latvian	F	58	59	1
MĶ-22	HSC	Latvian	M	65	70	5

MĶ-22	HSC	Latvian	M	54	54	0
ZL-936	HSC susp.	Latvian	F	95	96	1
ZL-936	HSC susp.	Latvian	F	59	60	1
MĶ-1672	HSC susp.	Latvian	F	67	68	1
MĶ-1672	HSC susp.	Latvian	F	65	67	2
VĶ-1216	HSC	Latvian	F	38	40	2
VĶ-1216	HSC	Latvian	F	72	Alive	Alive
VĶ-1216	HSC	Latvian	F	ND	72	ND
MB-30	HSC	Latvian	M	ND	50	ND
MB-30	HSC	Latvian	ND	ND	60	ND
MB-30	HSC	Latvian	F	58	Alive	Alive
MB-30	HSC	Latvian	M	ND	54	ND
MB-30	HSC	Latvian	M	ND	70	ND
LEZ-1222	HSC susp.	Lithuanian	F	60	60	0
LEZ-1222	HSC susp.	Lithuanian	F	56	56	0
MZ-40	HSC	Latvian	M	30	30	0
MZ-40	HSC	Latvian	M	60	60	0
MZ-40	HSC	Latvian	F	50	50	0
MZ-40	HSC	Latvian	F	50	50	0
MZ-40	HSC	Latvian	F	50	50	0
OR-118	HSC susp.	Russian	F	50	50	0
OR-118	HSC susp.	Russian	M	ND	ND	ND
SNV-830	HSC susp.	Latvian	M	50	60	10
SNV-830	HSC susp.	Latvian	M	50	60	10
VĶ-172	HSC	Latvian	F	46	48	2
VĶ-172	HSC	Latvian	F	64	66	2
VĶ-172	HSC	Latvian	F	83	85	2
VĶ-173	HSC susp.	Latvian	F	46	48	2
VĶ-173	HSC susp.	Latvian	F	64	66	2
AŠ-94	HSC susp.	Latvian	M	68	69	1
AŠ-94	HSC susp.	Latvian	M	69	69	0
ZL-72	HSC susp.	Latvian	M	57	Alive	Alive
ZL-72	HSC susp.	Latvian	F	64	68	4

ZL-103	HSC	Latvian	M	51	54	3
ZL-103	HSC	Latvian	M	ND	ND	ND
ZL-103	HSC	Latvian	M	ND	ND	ND
ZL-103	HSC	Latvian	F	ND	70	ND
ZL-103	HSC	Latvian	M	68	68	0
IV-483	HSC susp.	Russian	M	48	49	1
IV-483	HSC susp.	Russian	M	ND	66	ND
IV-482	HSC susp.	Russian	M	48	49	1
IV-482	HSC susp.	Russian	M	65	66	1
IV-902	HSC susp.	Latvian	F	56	57	1
IV-902	HSC susp.	Latvian	M	77	80	3
VĶ-778	HSC susp.	Latvian	F	70	90	20
VĶ-778	HSC susp.	Latvian	F	74	80	6
SNV-888	HSC susp.	Latvian	F	82	86	4
SNV-888	HSC susp.	Latvian	M	82	84	2
AK-753	HSC susp.	Latvian	M	60	72	12
AK-753	HSC susp.	Latvian	M	60	69	9
MB-886	HSC susp.	Latvian	M	60	66	6
MB-886	HSC susp.	Latvian	M	75	80	5
LEZ-1426	HSC susp.	Latvian	F	65	Alive	Alive
LEZ-1426	HSC susp.	Latvian	M	55	56	1
AK-181	HSC susp.	Latvian	M	54	55	1
AK-181	HSC susp.	Latvian	F	75	75	0
MN-1059	HSC susp.	Latvian	F	69	70	1
MN-1059	HSC susp.	Latvian	F	63	70	7
MN-1060	HSC susp.	Russian	M	47	47	0
MN-1060	HSC susp.	Russian	F	57	60	3
AK-312	HSC susp.	Latvian	M	49	49	0
AK-312	HSC susp.	Latvian	F	74	74	0
AK-334	HSC susp.	Latvian	M	ND	54	ND
AK-334	HSC susp.	Latvian	F	ND	76	ND
MB-739	HSC susp.	Latvian	F	40	46	6
MB-739	HSC susp.	Latvian	F	ND	78	ND

MZ-786	HSC susp.	Latvian	M	45	45	0
MZ-786	HSC susp.	Latvian	F	77	79	2
VĶ-1112	HSC	Latvian	M	70	72	2
VĶ-1112	HSC	Latvian	F	ND	85	ND
VĶ-1112	HSC	Latvian	M	60	62	2
VĶ-1112	HSC	Latvian	F	74	Alive	Alive
OR-36	HSC susp.	Russian	F	71	72	1
OR-36	HSC susp.	Russian	F	80	80	0
MB-208	HSC	Latvian	M	ND	54	ND
MB-208	HSC	Latvian	M	ND	60	ND
MB-208	HSC	Latvian	M	59	Alive	Alive
IU-275	HSC susp.	Latvian	F	51	Alive	Alive
IU-275	HSC susp.	Latvian	M	ND	ND	ND
EF-78	HSC susp.	Latvian	M	79	80	1
EF-78	HSC susp.	Latvian	M	75	75	0
EF-76	HSC susp.	Latvian	M	80	80	0
EF-76	HSC susp.	Latvian	M	74	75	1
EF-94	HSC susp.	Latvian	M	75	75	0
EF-94	HSC susp.	Latvian	M	ND	80	ND
MAK-39	HSC susp.	Latvian	M	80	80	0
MAK-39	HSC susp.	Latvian	M	ND	80	ND
LZ-443	HSC susp.	Latvian	M	52	Alive	Alive
LZ-443	HSC susp.	Latvian	F	55	65	10
LEZ-307	HSC susp.	Latvian	M	48	54	6
LEZ-307	HSC susp.	Latvian	F	60	70	10
LEZ-602	HSC susp.	Latvian	M	64	66	2
LEZ-602	HSC susp.	Latvian	M	70	72	2
MB-3	HSC susp.	Latvian	F	72	72	0
MB-3	HSC susp.	Latvian	M	79	79	0
AG-11	HSC	Latvian	F	ND	70	ND
AG-11	HSC	Latvian	F	ND	70	ND
AG-11	HSC	Latvian	M	ND	82	ND
MZ-546	HSC susp.	Latvian	M	ND	51	ND

MZ-546	HSC susp.	Latvian	M	ND	70	ND
MĶ-1425	HSC susp.	Estonian	F	34	37	3
MĶ-1425	HSC susp.	Estonian	F	ND	ND	ND
MĶ-1044	HSC	Latvian	M	70	70	0
MĶ-1044	HSC	Latvian	F	60	60	0
MĶ-1044	HSC	Latvian	M	50	50	0
MĶ-844	HSC susp.	Russian	M	51	51	0
MĶ-844	HSC susp.	Russian	F	60	66	6
MN-524	HSC susp.	Latvian	F	57	58	1
MN-524	HSC susp.	Latvian	F	55	56	1
MN-571	HSC	Latvian	M	ND	ND	ND
MN-571	HSC	Latvian	M	58	60	2
MN-571	HSC	Latvian	M	69	70	1
MN-403	HSC susp.	Latvian	M	45	48	3
MN-403	HSC susp.	Latvian	F	50	51	1
MN-382	HSC	Latvian	M	58	60	2
MN-382	HSC	Latvian	F	60	62	2
MN-382	HSC	Latvian	F	54	55	1
IV-761	HSC susp.	Latvian	M	70	70	0
IV-761	HSC susp.	Latvian	M	ND	70	ND
IV-797	HSC susp.	Latvian	F	ND	72	ND
IV-797	HSC susp.	Latvian	F	ND	70	ND
VĶ-972	HSC	Latvian	M	41	42	1
VĶ-972	HSC	Latvian	M	62	62	0
VĶ-972	HSC	Latvian	F	ND	ND	ND
MĶ-508	HSC susp.	Latvian	M	54	57	3
MĶ-508	HSC susp.	Latvian	F	ND	ND	ND
MĶ-50	HSC susp.	Latvian	M	65	65	0
MĶ-50	HSC susp.	Latvian	M	75	75	0
MN-16	HSC susp.	Latvian	M	40	42	2
MN-16	HSC susp.	Latvian	M	43	43	0
MĶ-1125	HSC susp.	Latvian	M	56	56	0
MĶ-1125	HSC susp.	Latvian	M	76	76	0

AŠ-230	HSC susp.	Latvian	M	68	70	2
AŠ-230	HSC susp.	Latvian	M	68	68	0
MĶ-924	HSC susp.	Latvian	F	60	60	0
MĶ-924	HSC susp.	Latvian	F	60	60	0
SNV-947	HSC susp.	Latvian	M	70	70	0
SNV-947	HSC susp.	Latvian	F	ND	50	ND
MN-0198	HSC susp.	Latvian	F	65	72	7
MN-0198	HSC susp.	Latvian	F	ND	ND	ND
JE-227	HSC susp.	Latvian	M	70	70	0
JE-227	HSC susp.	Latvian	F	45	45	0
VĶ-1038	HSC	Latvian	M	41	42	1
VĶ-1038	HSC	Latvian	M	62	62	0
VĶ-1038	HSC	Latvian	F	Nd	ND	ND
MN-0118	HSC susp.	Russian	F	68	70	2
MN-0118	HSC susp.	Russian	F	63	67	4
MN-0941	HSC susp.	Latvian	F	ND	ND	ND
MN-0941	HSC susp.	Latvian	M	ND	60	ND
LEZ-308	HSC susp.	Latvian	M	ND	65	ND
LEZ-308	HSC susp.	Latvian	M	ND	60	ND
AG-291	HSC susp.	Latvian	M	ND	55	ND
AG-291	HSC susp.	Latvian	M	ND	Alive	Alive
AG-592	HSC susp.	Latvian	M	ND	ND	ND
AG-592	HSC susp.	Latvian	M	ND	ND	ND
AK-247	HSC susp.	Estonian	F	ND	ND	ND
AK-247	HSC susp.	Estonian	F	ND	ND	ND
EF-17	HSC susp.	Latvian	F	72	75	3
EF-17	HSC susp.	Latvian	F	ND	ND	ND
IN-036	HSC	Gypsy	M	ND	41	ND
IN-036	HSC	Gypsy	M	ND	41	ND
IN-036	HSC	Gypsy	M	ND	41	ND
IV-1088	HSC susp.	Russian	M	64	64	0
IV-1088	HSC susp.	Russian	F	67	68	1
LEZ-510	HSC susp.	Latvian	F	63	64	1

LEZ-510	HSC susp.	Latvian	F	70	80	10
LZ-968	HSC susp.	Latvian	F	ND	80	ND
LZ-968	HSC susp.	Latvian	F	ND	67	ND
MB-233	HSC susp.	Latvian	M	62	Alive	Alive
MB-233	HSC susp,	Latvian	M	70	70	0
MB-40	HSC susp.	Latvian	F	46	46	0
MB-40	HSC susp.	Latvian	M	ND	71	ND
MB-87	HSC susp.	Latvian	M	50	50	0
MB-87	HSC susp.	Latvian	M	ND	50	ND
MĶ-692	HSC susp.	Russian	M	40	50	10
MĶ-692	HSC susp.	Russian	M	ND	ND	ND
MN-0706	HSC susp.	Latvian	M	ND	ND	ND
MN-0706	HSC susp.	Latvian	F	ND	79	ND
MN-0073	HSC susp.	Latvian	M	ND	Alive	Alive
MN-0073	HSC susp.	Latvian	F	81	82	1
MN-0833	HSC susp.	Latvian	M	ND	ND	ND
MN-0833	HSC susp.	Latvian	M	ND	ND	ND
MZ-471	HSC susp.	Latvian	F	61	61	0
MZ-471	HSC susp.	Latvian	F	ND	68	ND
SNV-324	HSC susp.	Latvian	F	79	80	1
SNV-324	HSC susp.	Latvian	F	ND	ND	ND
SNV-1277	HSC susp.	Latvian	F	ND	60	ND
SNV-1277	HSC susp.	Latvian	M	ND	80	ND
ZL-479	HSC susp.	Latvian	M	60	62	2
ZL-479	HSC susp.	Latvian	M	ND	70	ND
VĶ-1413	HSC susp.	Latvian	M	ND	ND	ND
VĶ-1413	HSC susp.	Latvian	M	ND	ND	ND
MĶ-815	HSC susp.	Latvian	M	ND	Alive	Alive
MĶ-815	HSC susp.	Latvian	F	70	70	0

Abbreviations in table: HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; M, male; F, female; ND, no data available.

ANNEX 16. The stomach cancer burden in suspected and definitive HSC families

Kindred	Diagnosis	Affected	Affected generations	Relatives in blood line
AG-11	HSC	3	2	23
AK-336	HSC	4	2	15
IN-036	HSC	3	1	15
IU-065	HSC	3	1	7
IU-319	HSC	3	2	26
LZ-922	HSC	3	1	8
MB-208	HSC	3	2	11
MB-30	HSC	6	3	21
MĶ-1044	HSC	3	2	12
MĶ-22	HSC	3	2	9
MN-1162	HSC	3	1	10
MN-571	HSC	3	2	14
MZ-40	HSC	5	1	19
RK-107	HSC	7	2	29
VĶ-1112	HSC	4	2	18
VĶ-1216	HSC	3	2	9
VĶ-172	HSC	3	2	8
VĶ-173	HSC	3	2	8
VĶ-972	HSC	3	2	12
ZL-103	HSC	5	2	10
AG-291	HSC susp.	2	2	10
AG-592	HSC susp.	2	2	9
AK-181	HSC susp.	2	2	10
AK-247	HSC susp.	2	1	18
AK-312	HSC susp.	2	2	12
AK-334	HSC susp.	2	2	17
AK-753	HSC susp.	2	2	22
AŠ-230	HSC susp.	2	2	11
AŠ-94	HSC susp.	2	2	20
EF-17	HSC susp.	2	1	6
EF-76	HSC susp.	2	2	11

EF-78	HSC susp.	2	2	12
EF-94	HSC susp.	2	2	19
IU-275	HSC susp.	2	2	22
IV-1088	HSC susp.	2	1	14
IV-482	HSC susp.	2	2	10
IV-483	HSC susp.	2	2	13
IV-761	HSC susp.	2	2	14
IV-797	HSC susp.	2	2	12
IV-902	HSC susp.	2	2	13
JE-227	HSC susp.	2	2	7
LEZ-1222	HSC susp.	2	1	17
LEZ-1426	HSC susp.	2	2	17
LEZ-307	HSC susp.	2	2	13
LEZ-308	HSC susp.	2	1	13
LEZ-510	HSC susp.	2	1	16
LEZ-602	HSC susp.	2	2	7
LZ-443	HSC susp.	2	2	12
LZ-968	HSC susp.	2	2	9
MAK-39	HSC susp.	2	1	12
MB-233	HSC susp.	2	2	11
MB-3	HSC susp.	2	2	10
MB-40	HSC susp.	2	2	10
MB-739	HSC susp.	2	2	12
MB-87	HSC susp.	2	2	12
MB-886	HSC susp.	2	2	11
MĶ-1125	HSC susp.	2	2	7
MĶ-1425	HSC susp.	2	1	19
MĶ-1672	HSC susp.	2	2	18
MĶ-50	HSC susp.	2	2	10
MĶ-508	HSC susp.	2	2	11
MĶ-692	HSC susp.	2	1	17
MĶ-815	HSC susp.	2	2	5
MĶ-844	HSC susp.	2	2	8

MK-924	HSC susp.	2	1	14
MN-0043	HSC susp.	2	2	4
MN-0118	HSC susp.	2	2	14
MN-0198	HSC susp.	2	2	11
MN-0706	HSC susp.	2	1	13
MN-0833	HSC susp.	2	1	6
MN-0941	HSC susp.	2	2	15
MN-1059	HSC susp.	2	2	14
MN-1060	HSC susp.	2	2	7
MN-16	HSC susp.	2	1	20
MN-382	HSC susp.	3	2	8
MN-403	HSC susp.	2	1	16
MN-524	HSC susp.	2	2	13
MZ-471	HSC susp.	2	2	9
MZ-546	HSC susp.	2	2	13
MZ-786	HSC susp.	2	2	24
OR-118	HSC susp.	2	1	19
OR-36	HSC susp.	2	2	12
SNV-1277	HSC susp.	2	2	12
SNV-324	HSC susp.	2	2	11
SNV-830	HSC susp.	2	1	15
SNV-888	HSC susp.	2	1	8
SNV-947	HSC susp.	2	1	13
VK-1038	HSC susp.	3	2	18
VK-1412	HSC susp.	2	2	10
VK-1413	HSC susp.	2	2	8
VK-778	HSC susp.	2	1	21
ZL-479	HSC susp.	2	1	15
ZL-72	HSC susp.	2	2	15
ZL-936	HSC susp.	2	2	14

Abbreviations in table: HSC, hereditary stomach cancer; HSC susp., suspected hereditary stomach cancer; ND, no data available.

ANNEX 17. Other tumours in the hereditary stomach cancer kindreds

Kindred	Affected by stomach cancer	Other cancers	Total in blood line	Females in blood line
LZ-922	3	Leu	8	3
VĶ-1412	2	None[1]	10	2
AK-336	4	None	15	5
MN-1162	3	None[1]	10	5
RK-107	7	None	29	6
IU-319	3	Breast	26	2
IU-065	3	None	7	5
MĶ-22	3	CRC	9	4
ZL-936	2	None[1]	14	8
MĶ-1672	2	Breast, liver	18	11
VĶ-1216	3	None	10	6
MB-30	6	Lung, Pan, 2 Ut, CRC	21	ND
LEZ-1222	2	2 Ut, breast	17	12
MZ-40	5	Brain, 2 Ut	19	13
OR-118	2	2 Ut	19	9
SNV-830	2	2 Ut	15	9
VĶ-172	3	Bl, lung	8	4
VĶ-173	3	Bl, lung	8	4
AŠ-94	2	2 brain	20	6
ZL-72	2	Leu, kidney	15	4
ZL-103	5	CRC	10	3
IV-483	2	Gyn, liver	13	8
IV-482	2	Gyn	10	6
IV-902	2	Cx, liver	13	6
VĶ-778	2	2HN, Gyn	21	11
SNV-888	2	Abd, CSU	8	3
AK-753	2	Prostate	22	3
MB-886	2	2 Bl	11	6
LEZ-1426	2	CRC, breast, lung	17	8

AK-181	2	Breast	10	5
MN-1059	2	Lung	14	11
MN-1060	2	Oesophagus	7	2
AK-312	2	CSU	12	5
AK-334	2	Liver	17	8
MB-739	2	Prostate, CRC	12	3
MZ-786	2	Leu	24	7
VK-1112	4	Liver, larynx	18	4
OR-36	2	Kidney	12	6
MB-208	3	Lung	11	2
IU-275	2	Lung, CSU	22	7
EF-78	2	Kidney, Thy	12	3
EF-76	2	Abd, Kidney, brain	11	4
EF-94	2	Kidney, Abd	19	6
MAK-39	2	CSU	12	2
LZ-443	2	2 lung, Abd, CSU	12	5
LEZ-307	2	Bl, Leu	13	4
LEZ-602	2	Brain, lung	7	ND
MB-3	2	None	10	3
AG-11	3	Gyn	23	11
MZ-546	2	Liver	13	4
MAK-37	2	None	12	ND
MK-1425	2	Bl, Abd	19	6
MK-1044	3	None	12	3
MK-844	2	Lung, Ut	8	3
MN-524	2	Brain	13	6
MN-571	3	Ut, lung	14	6
MN-403	2	2 brain, 2 ut	16	10
MN-382	3	None	8	6
IV-761	2	CSU, Pan, Ut	14	3
IV-797	2	Pan	12	7
VK-972	3	2 Ut, breast	12	9
MK-508	2	2 CSU, CRC	11	5

MĶ-50	2	Ovary	10	3
MN-16	2	Lung, kidney, Pan	20	8
MĶ-1125	2	Ovary	7	1
AŠ-230	2	Brain, CSU	11	6
MĶ-924	2	Cx	14	5
SNV-947	2	Lung	13	8
MN-0198	2	Ovary	11	8
JE-227	2	None	7	3
VĶ-1038	3	2Ut, breast	18	9
MN-0118	2	2 CRC, Lung	14	4
MN-0941	2	None	15	10
LEZ-308	2	2 Ut, Leu	13	8
AG-291	2	None	10	4
AG-592	2	None	9	3
AK-247	2	None	18	8
EF-17	2	None	6	3
IN-036	3	None	15	5
IV-1088	2	None	14	7
LEZ-510	2	None	16	9
LZ-968	2	None	9	6
MB-233	2	None	11	6
MB-40	2	None	10	3
MB-87	2	None	12	4
MĶ-692	2	None	17	7
MN-0706	2	None	13	4
MN-0043	2	None	4	2
MN-0833	2	None	6	2
MZ-471	2	None	9	5
SNV-324	2	None	11	8
SNV-1277	2	Breast	12	3
ZL-479	2	None	15	5
VĶ-1413	2	None	8	1
MĶ-815	2	None	5	3

[1] in the considered blood line

Abbreviations in the table: Leu, haematological malignant tumour; CRC, colorectal cancer; Pan, pancreatic cancer; Ut, endometrial cancer; Bl, cancer of the urinary bladder; Gyn, malignant gynaecological tumour, not further specified; Cx, cancer of the uterine cervix; HN, cancer of the head and neck; Abd, malignant tumour in the abdominal cavity, not further specified; CSU, cancer of unknown primary location (by family cancer history only); Thy, thyroid cancer; ND, no data available.

ANNEX 18. Tumour course in the affected persons belonging to the definitive and suspected prostate cancer kindreds

Kindred	Nationality of proband	Age of tumour diagnostics	Age of death	Survival
LEZ-172	Latvian	55	Alive	Alive
LEZ-172	Latvian	65	70	5
SNV-630	Latvian	35	Alive	Alive
SNV-630	Latvian	67	Alive	Alive
ZL-724	Latvian	55	Alive	Alive
MĶ-1131	Russian	53	Alive	Alive
IN-075	Latvian	58	Alive	Alive
IN-075	Latvian	73	75	2
EF-319	Latvian	74	Alive	Alive
EF-319	Latvian	72	76	2
EF-319	Latvian	70	Alive	Alive
LEZ-197	Latvian	62	Alive	Alive
LEZ-197	Latvian	52	Alive	Alive
AŠ-324	Latvian	ND	ND	ND
AŠ-324	Latvian	66	66	0
VĶ-635	Latvian	50	74	24
VĶ-635	Latvian	ND	56	ND
MN-0120	Lithuanian	62	62	0
MN-0120	Lithuanian	36	Alive	Alive
MN-0350	Latvian	35	37	2
LE-556	Latvian	52	52	0
MĶ-760	Latvian	48	54	6
MĶ-821	Latvian	50	50	0
MN-0110	Russian	53	68	15
MN-0110	Russian	55	Alive	Alive
JE-556	Latvian	52	52	0
EF-304	Latvian	69	Alive	Alive
EF-304	Latvian	56	58	2
EF-307	Latvian	69	Alive	Alive

EF-307	Latvian	56	58	2
EF-320	Latvian	69	Alive	Alive
EF-320	Latvian	56	58	2
IV-0823	Latvian	65	Alive	Alive
IV-0823	Latvian	75	80	5
MZ-436	Latvian	ND	61	ND
MZ-436	Latvian	ND	63	ND
MZ-612	Latvian	ND	40	ND
MZ-612	Latvian	ND	60	ND

Abbreviation in table: ND, no data available.

ANNEX 19. Number of affected persons and blood relatives in the definitive and suspected prostate cancer kindreds

Kindred	Diagnosis	Affected persons	Number of male blood relatives in the affected line[1]
LEZ-172	HPC susp.	2	5
SNV-630	HPC susp.	2	4
ZL-724	HPC susp.	1	6
MĶ-1131	HPC susp.	1	6
IN-075	HPC susp.	2	4
EF-319	HPC	3	14
LEZ-197	HPC susp.	2	16
AŠ-324	HPC susp.	2	5
VĶ-635	HPC susp.	2	6
MN-0120	HPC susp.	2	7
MN-0350	HPC susp.	1	6
LE-556	HPC susp.	1	0
MĶ-760	HPC susp.	1	8
MĶ-821	HPC susp.	1	3
MN-0110	HPC susp. in 2 branches	2	4
JE-556	HPC susp.	1	5
EF-304	HPC susp.	2	14
EF-307	HPC susp.	2	16
EF-320	HPC susp.	2	13
IV-0823	HPC susp.	2	3
MZ-436	HPC susp.	2	3
MZ-612	HPC susp.	2	5
		22	153

[1] The whole kindred was considered if the diagnosis of suspected hereditary prostate cancer was based on the age of prostate cancer development in a single person

Abbreviations in table: HPC, hereditary prostate cancer; HPC susp., suspected hereditary prostate cancer; ND, no data available.

ANNEX 20. Other cancers in HPC kindreds

Kindred	Diagnosis	Other tumours
LEZ-172	HPC susp.	None
SNV-630	HPC susp.	None
ZL-724	HPC susp.	None
MĶ-1131	HPC susp.	None
IN-075	HPC susp.	None
EF-319	HPC	Lung
LEZ-197	HPC susp.	CRC, pancreas, uterus
AŠ-324	HPC susp.	None
VĶ-635	HPC susp.	Leu
MN-0120	HPC susp.	3 ovary, lung
MN-0350	HPC susp.	Brain, uterus
LE-556	HPC susp.	Uterus
MĶ-760	HPC susp.	Ovary, stomach
MĶ-821	HPC susp.	None
MN-0110	HPC susp. double	3 uterus, duodenum
JE-556	HPC susp.	2 uterus, brain
EF-304	HPC susp.	None
EF-307	HPC susp.	None
EF-320	HPC susp.	None
IV-0823	HPC susp.	None
MZ-436	HPC susp.	None
MZ-612	HPC susp.	Small intestine

Abbreviations in table: HPC, hereditary prostate cancer; HPC susp., suspected hereditary prostate cancer; CRC, colorectal cancer; Leu, haematologic malignant tumour

ANNEX 21. Course of familial urinary bladder cancer

Kindred	Diagnosis	Nationality of proband	Sex of affected persons	Age of tumour diagnostics	Age of death	Survival, years
VĶ-879	FBlaC	Latvian	M	60	65	5
			M	75	75	0
			M	ND	71	ND
VĶ-884	FBlaC	Latvian	M	60	65	5
			M	75	75	0
			M	ND	71	ND
LEZ-307	FBlaC susp	Latvian	F	71	76	5
			M	67	72	5
LZ-655	FBlaC susp.	Latvian	F	66	66	0
			M	87	92	5
LZ-656	FBlac susp.	Latvian	F	66	Alive	Alive
			M	87	92	5
MB-886	FBlaC susp.	Latvian	F	75	77	2
			M	65	74	9
MĶ-1325	FBlaC susp.	Russian	M	74	Alive	Alive
			M	73	74	1
MĶ-1326	FBlaC susp.	Russian	M	74	Alive	Alive
			M	73	74	1
MĶ-1327	FBlaC susp.	Russian	M	74	Alive	Alive
			M	73	74	1
MN-60	FBlaC susp.	Latvian	F	75	78	3
			F	80	84	4
VĶ-1482	FBlaC susp.	Byelorussian	M	61	Alive	Alive
			M	68	87	19

Abbreviations in table: FBlaC, familial bladder cancer; FBlaC susp., suspicion of familial bladder cancer; M, male; F, female; ND, no data available.

ANNEX 22. Other malignant tumours in familial bladder cancer kindreds

Kindred	Index cancer, cases	Affected generations	Other cancers	Relatives[1]
LEZ-307	2	2	2 stomach, Leu[2]	11
LZ-656	2	2	Lung, Gyn, Leu, Li	16
MB-886	2	2	2 stomach	11
MĶ-1325	2	2	2 uterus; breast[2], Li[2] stomach[2]	12
MĶ-1326	2	2	2 uterus, breast[2], Li[2], stomach[2]	12
MĶ-1327	2	2	2 uterus, breast[2], Li[2], stomach[2]	16
MN-60	2	2	Lung, CRC, stomach	10
VĶ-879	3	2	None	9
VĶ-884	3	2	None	10
LZ-655	2	2	Leu, lung, Gyn, Li	10
VĶ-1482	2	2	None	6

[1]blood relatives in the affected line; [2] in another blood line of the same kindred

Abbreviations in table: Leu; haematologic malignancy; Gyn, unspecified gynaecologic cancer; Li, liver; CRC, colorectal cancer

ANNEX 23. The course of the tumour in families affected by aggregation of haematologic tumours

Kindred	Diagnosis	Nationality of proband	Sex of affected persons	Age of tumour diagnostics, years	Age of death, years	Survival, years
VĶ-1252	FHemT	Latvian	M	46	46	0
VĶ-1252	FHemT	Latvian	M	45	50	5
VĶ-1252	FHemT	Latvian	F	61	Alive	Alive
VĶ-1252	FHemT	Latvian	F	ND	ND	ND
LEZ-710	FHemT susp.	Latvian	F	77	80	3
LEZ-710	FHemT susp.	Latvian	F	62	62	0
LEZ-1172	FHemT susp.	Latvian	M	17	18	1
LEZ-1172	FHemT susp.	Latvian	F	33	34	1
MAK-297	FHemT susp.2	Latvian	M	18	19	1
MAK-297	FHemT susp.2	Latvian	F	34	35	1
SNV-301	FHemT susp.	Latvian	M	4	4	0
SNV-301	FHemT susp.	Latvian	M	61	61	0
VĶ-768	FHemT susp.	Latvian	F	75	80	5
VĶ-768	FHemT susp.	Latvian	M	ND	70	ND
MĶ-1213	FHemT susp.2	Latvian	F	36	Alive	Alive
MĶ-1213	FHemT susp.2	Latvian	M	3	Alive	Alive
AG-378	FHemT susp.	Latvian	F	4	4	0
AG-378	FHemT susp.	Latvian	M	ND	ND	ND
AG-378	FHemT susp.	Latvian	M	ND	ND	ND
AG-462	FHemT susp.	Latvian	F	ND	Alive	Alive
AG-462	FHemT susp.	Latvian	F	ND	27	ND
MZ-64	FHemT susp.	Russian	M	63	65	2
MZ-64	FHemT susp.	Russian	F	88	90	2
SNV-477	FHemT susp.	Latvian	F	61	Alive	Alive
SNV-477	FHemT susp.	Latvian	F	65	67	2
AG-143	FHemT susp.	Latvian	M	35	36	1
AG-143	FHemT susp.	Latvian	M	ND	ND	ND
LEZ-389	FHemT susp.	Latvian	M	34	36	2

LEZ-389	FHemT susp.	Latvian	M	54	60	6
MB-394	FHemT susp.	Latvian	M	50	52	2
MB-394	FHemT susp.	Latvian	F	38	40	2
MĶ-47	FHemT susp.	Latvian	F	62	Alive	Alive
MĶ-47	FHemT susp.	Latvian	M	ND	60	ND
MĶ-1651	FHemT susp.	Latvian	M	58	63	5
MĶ-1651	FHemT susp.	Latvian	F	61	Alive	Alive
SNV-60	FHemT susp.	Latvian	M	62	63	1
SNV-60	FHemT susp.	Latvian	F	70	72	2

Abbreviations in table: FHemT, familial haematologic tumour aggregation; FHemT susp., suspicion of familial haematologic tumour aggregation; M, male; F, female; ND, no data available.

ANNEX 24. Other malignant tumours in kindreds affected by familial haematologic tumour aggregation

Kindred	Diagnosis	Cases of index cancer	Affected generations	Other cancers	Blood relatives in the affected line
VĶ-1252	FHemT	4	2	CRC[1]	13
AG-143	FHemT susp.	2	2	None	13
AG-378	FHemT susp.	3	2	None	16
AG-462	FHemT susp.	2	2	Liver	8
LEZ-1172	FHemT susp.	2	2	Bt, uterus	12
LEZ-389	FHemT susp.	2	1	None	17
LEZ-710	FHemT susp.	2	1	CRC, liver	14
MB-394	FHemT susp.	2	2	None	13
MĶ-1651	FHemT susp.	2	1	None	8
MĶ-47	FHemT susp.	2	1	None	22
MZ-64	FHemT susp.	2	2	Uterus	18
SNV-301	FHemT susp.	2	2	CSU	8
SNV-477	FHemT susp. HNPCC susp.[1]	2	2	Uterus	7
SNV-60	FHemT susp.	2	2	None	11
VĶ-768	FHemT susp.	2	2	CRC, mela, stomach, Bt	21
MAK-297	FHemT susp.2	2	1	Uterus, Bt	11
MĶ-1213	FHemT susp.2	2	2	Skin	15
		37	17		227

[1]in another blood line

Abbreviations in table: HHemT, familial haematologic tumour aggregation; HHemT susp., suspicion of familial haematologic tumour aggregation; CRC, colorectal cancer; Bt, brain tumour; Mela, melanoma.

ANNEX 25. The course of the tumour in families affected by familial pancreatic cancer

Kindred	Diagnosis	Nationality of proband	Sex of affected persons	Age of tumour diagnostics	Age of death	Survival, years
AG-338	FPan	Latvian	F	ND	60	ND
AG-338	FPan	Latvian	F	ND	83	ND
LEZ-33	FPan	Latvian	M	56	57	1
LEZ-33	FPan	Latvian	M	56	57	1
LEZ-33	FPan	Latvian	F	65	65	0
LP-322	FPan	Latvian	M	62	63	1
LP-322	FPan	Latvian	M	65	67	2
MĶ-426	FPan	Latvian	M	51	51	0
MĶ-426	FPan	Latvian	M	51	51	0
MĶ-436	FPan	Latvian	M	50	51	1
MĶ-436	FPan	Latvian	M	51	51	0
MĶ-437	FPan	Latvian	M	51	51	0
MĶ-437	FPan	Latvian	M	51	51	0
MĶ-438	FPan	Latvian	M	51	51	0
MĶ-438	FPan	Latvian	M	51	51	0
SNV-138	FPan	Latvian	F	69 (melanoma)	Alive	Alive
SNV-138	FPan	Latvian	M	59	59	0
SNV-197	FPan	Latvian	F	72 (melanoma)	74	2
SNV-197	FPan	Latvian	F	59	60	1
ZL-292	FPan	Latvian	M	64	69	5
ZL-292	FPan	Latvian	F	72	72	0

Abbreviations in table: M, male; F, female; ND, no data available

ANNEX 26. Other malignant tumours in familial pancreatic cancer kindreds

Kindred	Cases of index cancer	Affected generations	Other cancers	Blood relatives in the affected line
AG-338	2	2	Stomach, Abd	20
LEZ-33	3	2	2 uterus	19
LP-322	2	2	None	8
MĶ-426	2	2	None	9
MĶ-436	2	2	None	21
MĶ-437	2	2	None	8
MĶ-438	2	2	None	7
SNV-138	2	2	Leu, Abd	15
SNV-197	2	2	Breast	13
ZL-292	2	2	Brain	18
	21			138

Abbreviations in table: Leu, haematologic malignant tumour; Abd, malignant tumour in the abdominal cavity.

ANNEX 27. Burden of malignant tumours in families affected by familial brain tumour

Kindred	Diagnosis	Cases of index cancer	Other cancers	Blood relatives in the affected line
JE-186	FBtT	4	None	12
LZ-549	FBtT	3	None	12
VĶ-901	FBtT	3	None	7
MN-472	FBtT susp	2	Stomach, 2 uterus, 3 CSU	15
IV-0439	FBtT susp.	2	None	19
IV-0607	FBtT susp.	2	None	14
IV-0613	FBtT susp.	2	None	14
IV-0614	FBtT susp.	2	None	14
MAK-295	FBtT susp.	2	Uterus, Leu	11
MAK-297	FBtT susp.	3	Uterus, 2 leu	11
MN-403	FBtT susp.	2	2 stomach, 2 uterus	16
MN-471	FBtT susp.	2	3 uterus, 1 stomach, 2 CSU	15
MZ-143	FBtT susp.	2	2 CRC	23
MZ-294	FBtT susp.	2	Prostate	8
MZ-472	FBtT susp.	2	Breast, CSU	12
MZ-789	FBtT susp.	2	None	15
SJ-218	FBtT susp.	2	None	14
AŠ-94	FBtT susp.2	2	2 stomach	19
MB-644	FBtTsusp.	2	None	9

Abbreviations in table: FBtT, familial aggregation of brain tumours; FBtT susp., suspected familial aggregation of brain tumours; FBtT susp.2, suspected familial aggregation of brain tumours, variety 2; CSU, cancer of unknown location; CRC, colorectal cancer.

ANNEX 28. The characteristics of familial brain tumour course

Kindred	Diagnosis	Nationality of proband	Sex of affected persons	Age of tumour diagnostics	Age of death	Survival, years
JE-186	FBtT	Latvian	M	60	65	5
JE-186	FBtT	Latvian	M	ND	ND	ND
JE-186	FBtT	Latvian	F	ND	ND	ND
JE-186	FBtT	Latvian	F	ND	ND	ND
LZ-549	FBtT	Latvian	F	ND	62	ND
LZ-549	FBtT	Latvian	F	ND	50	ND
LZ-549	FbtT	Latvian	F	ND	60	ND
MN-403	FBtT susp.	Latvian	M	54	56	2
			F	53	56	3
MN-471	FBtT susp.	ND	M	ND	ND	ND
			M	ND	ND	ND
MN-472	FBtT susp.	Latvian	M	ND	ND	ND
			M	ND	ND	ND
MZ-472	FBtT susp.	Latvian	F	ND	73	ND
			F	ND	71	ND
VĶ-901	FBtT	Latvian	M	59	59	0
			M	60	62	2
			M	ND	ND	ND
SJ-218	FBtT susp.	Latvian	M	60	60	0
			M	60	60	0
MZ-294	FBtT susp.	Latvian	M	5	6	1
			F	2	2	0
AŠ-94	FBtT susp.2	Latvian	F	41	41	0
			F	2	2.5	0.5
MAK-297	FBtT susp.	Latvian	F	48	Alive	Alive
			F	34	35	1
			F	77	77	0
MAK-295	FBtT susp.	Latvian	F	48	Alive	Alive
			F	34	35	1

IV-0439	FBtT susp.	Russian	M	51	52	1
			F	53	63	10
IV-0613	FBtT susp.	Latvian	M	53	54	1
			F	58	60	2
IV-0614	FBtT susp.	Russian	M	53	54	1
			F	58	60	2
IV-0607	FBtT susp.	Russian	M	53	54	1
			F	58	60	2
MZ-143	FBtT susp.	Latvian	M	5	5	0
			F	2	2	0
MZ-789	FBtT susp.	Latvian	F	ND	30	ND
			F	ND	50	ND
MZ-644	FBtT susp.	Latvian	M	ND	31	ND
			F	ND	70	ND

Abbreviations in table: FBtT, familial aggregation of brain tumours; FBtT susp., suspected familial aggregation of brain tumours; FBtT susp.2, suspected familial aggregation of brain tumours, variety 2; M, male; F, female; ND, no data available.

ANNEX 29. Selected associations of tumours not corresponding to the criteria of any specific familial tumour syndrome

Kindred	Diagnosis	Description	Other cancers
AŠ-149	FKiC susp.	2 cases of renal cancer in first degree blood relatives in 2 generations	None
IV-0326	FKiC susp.	2 cases of renal cancer in first degree blood relatives in 1 generation	None
MN-0256	CFA	2 cases of renal cancer in second degree blood relatives in 1 generation	Colorectal, stomach
AK-803	CFA	2 cases of melanoma in the setting of CFA	Kidney, stomach
SJ-164	None	2 cases of adrenal tumour in first-degree blood relatives in 1 generation	Lung
LZ-529 LZ-528 LZ-527	None	2 cases of thyroid cancer in first degree relatives in 2 generations	None
IV-1163 IV-1164 IV-1165 IV-1166 IV-1167	None	2 cases of cancer of the uterine cervix in first degree relatives in 2 generations	None
MB-385	CFA	2 cases of laryngeal cancer in first degree relatives in 2 generations	Bones, stomach
SNV-807	None	2 cases of laryngeal cancer in first degree relatives in 2 generations	None

Abbreviations in table: FKiC susp., suspicion of familial renal cancer; CFA, cancer family aggregation.