doi:10.25143/prom-rsu_2010-08_dts

RĪGAS STRADIŅA UNIVERSITĀTE

ESF
EIROPAS SOCIĀLAIS FONDS

RĪGA STRADIŅŠ UNIVERSITY

DEPARTMENT OF SURGERY

Andrejs Vanags

POPULATION SCREENING FOR HEREDITARY CANCER IN VALKA DISTRICT

Synopsis of doctoral thesis

Supervisors
Rector of Riga Stradins University and Head of the Department of surgery
Professor Jānis Gardovskis
Head of Department of Pathology, Riga Stradins University
Assistant Professor Ilze Štrumfa

Riga, 2010

RĪGAS STRADIŅA UNIVERSITĀTE

ESF
EIROPAS SOCIĀLAIS FONDS

RĪGA STRADIŅŠ UNIVERSITY

DEPARTMENT OF SURGERY

Andrejs Vanags

POPULATION SCREENING FOR HEREDITARY CANCER IN VALKA DISTRICT

Synopsis of doctoral thesis

Supervisors
Rector of Riga Stradins University and Head of the Department of surgery
Professor Jānis Gardovskis
Head of Department of Pathology, Riga Stradins University
Assistant Professor Ilze Štrumfa

Riga, 2010

Doctor's dissertation was carried out in:
Rīga Stradiņš University;
Paula Stradiņš Clinical University hospital

Supervisors:
Professor, *Dr. habil. med.* **Jānis Gardovskis**
Assistant professor, *Dr.med.* **Ilze Štrumfa**

Scientific counsellors:
Professor Uldis Teibe
Dr.med. Arvīds Irmejs

Official reviewers:

Professor, *Dr. habil. med.* **Aigars Pētersons**

Professor, *Dr. habil. med.* **Jan Lubinski**

Professor, *Dr. habil. med.* **Andres Metspalu**

The doctoral thesis is available in RSU library and in RSU homepage: www.rsu.lv

Doctorate Council of Surgery will take place on 15th December, 2010

Rīga Stradiņš University Hippocrates auditory
Riga, Dzirciema Street 16

Head of Doctorate Council of Surgery:
Professor *Dr. habil. med.* **Romans Lācis**

Secretary of the doctorate council:
Professor *Dr. habil. med.* **Andrejs Skaģers**

CONTENT

LIST OF ABBREVIATIONS

BRCA – breast cancer (gene)

CDH1 – E-cadherine (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 haematological tumour

FLC – familial lung cancer

FPan – familial pancreatic cancer

HBC – hereditary breast cancer

HBOC – hereditary breast-ovarian cancer

HEC – hereditary endometrial cancer

HNPCC – hereditary nonpolyposis colorectal cancer

HOC – hereditary ovarian cancer

HPC – hereditary prostate cancer

HSC – hereditary stomach cancer

PCR – polymerase chain reaction

s – suspected (hereditary or familial cancer syndrome)

INTRODUCTION

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 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.

Objectives:

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, the course and the burden of index cancer in all the revealed hereditary cancer syndromes;
4. to identify the frequency of the *BRCA1* gene founder mutations in population;
5. to analyse the role of family size in the hereditary cancer diagnostics.

Working hypotheses:

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 mutations 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.

Scientific and practical novelty

The performed work represents the first population screening for hereditary cancer in Latvia and one of the few in world medical science. Population screening provides novel data about the full spectrum, frequency and clinical course of hereditary malignancies. 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.

Personal input

The author was personally involved in all stages of the population screening 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.

Financial support
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. Encouragement was received by ESF project Nr. 2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009.

The structure of the Thesis
The Thesis is written in English. The work has classical structure containing introduction, literature review, description of materials and methods, results, discussion, conclusion, practical recommendations, list of references and annexes. The Thesis is written on 218 pages; 47 tables and 81 figures are included. There are 253 references.

MATERIALS 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 1) holding 24323 adult inhabitants and 22 registered family physicians.

Figure 1. A map of Latvia with districts and largest settlements. Valka district in the northeast of Latvia is depicted by the ring.

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. Additional information about radiation therapy, chemotherapy and extent of operation also was collected.
The hereditary cancer syndromes were sought for according to the international hereditary cancer assessment criteria. The corresponding persons were invited for consultation. During it, hereditary cancer syndrome entity was explained to them, written prophylactic recommendations were given and 6 ml of 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.

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 district adult 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 1.

Table 1. 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 nationalities	459	2.46 (2.25 – 2.70)

Abbreviation in the 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. The participants of the study were asked if his / her relatives (father, mother, grandparents, siblings, children, grandchildren 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 verify 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 2.

Table 2. The applied diagnostic criteria of hereditary cancer

Hereditary syndrome	Diagnostic criteria
Definitive hereditary non-polyposis colorectal cancer (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 (sHNPCC)	• 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 AND One of those patients is first degree relative to other two or second degree relative through male

Suspected hereditary breast cancer, variety 1 (sHBC1)	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 (sHBC2)	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 AND One of those patients is first degree relative to other two or second degree relative through male
Suspected hereditary ovarian cancer (sHOC)	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 AND One of those patients is first degree relative to other two or second degree relative through male
Suspected hereditary breast/ovarian cancer, variety 1 (sHBOC1)	Breast and ovarian cancer in the same individual at any age
Suspected hereditary breast/ovarian cancer, variety 2 (sHBOC2)	Two breast or ovarian cancers among first degree relatives (or second through male) at any age
Cancer family aggregation (CFA)	At least 3 first degree blood relatives with non-concordant 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 (sHEC)	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 (sFEC1)	Two first degree relatives with endometrial cancer at any age
Suspected familial endometrial cancer, variety 2 (sFEC2)	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 (sFLC)	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 (sHSC)	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 (sHPC)	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 (sFBtT)	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 (sFHemT)	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 (sFBlaC)	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 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 or ovarian cancer case was mentioned in family cancer history, *BRCA1* founder mutations 5382insC, 300T/G, 4153delA were searched for 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 for 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 2.

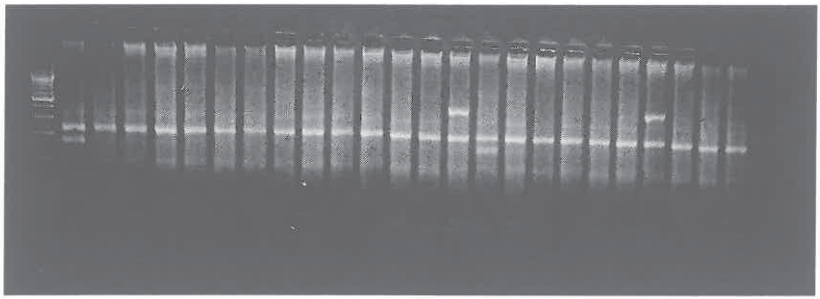


Figure 2. The distribution of the amplification products in 3% agarose gel. Position 1- marker GeneRuler 100 bp DNA Ladder. Positions 2 and 16: test DNA carrying *BRCA1* gene mutation 5382insC in exon 20. Positions 15 and 22: test DNA carrying *BRCA1* gene mutation 4153delA in exon 11. Positions 3-14, 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 diagnostic criteria of hereditary/familial cancer syndromes, 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 (*Confidence Iinterval Analysis*) software.
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.
The cancer burden reflecting the frequency of cancer among blood relatives 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. The 95% confidence interval for single proportion, for differences between two proportions and for means was calculated as well. The confidence interval calculations were performed 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 to (A+B)/C.

No contraindications are observed for this approach. When none observed events is present, both r and p are 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

$D - \sqrt{(p_1 - l_1)^2 + (u_2 - p_2)^2}$ 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; $\mathrm{SE}_{(\bar{x})}$ – 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

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

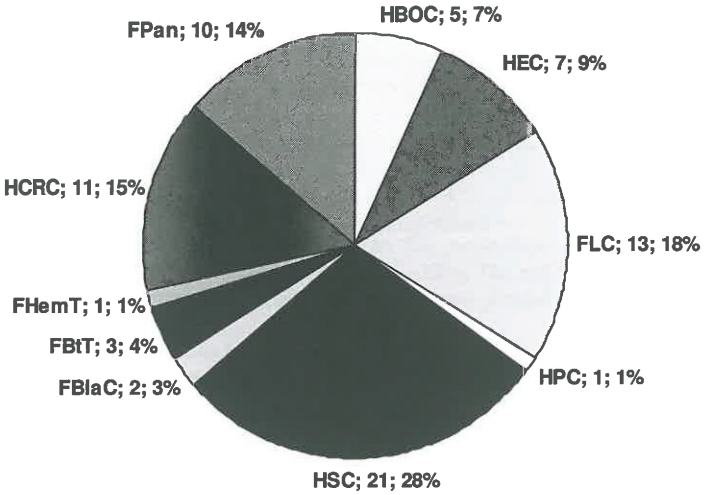
$t_{1-\alpha/2}$ is the t distribution of $n_1 + n_2 - 2$.

RESULTS

Clinical results

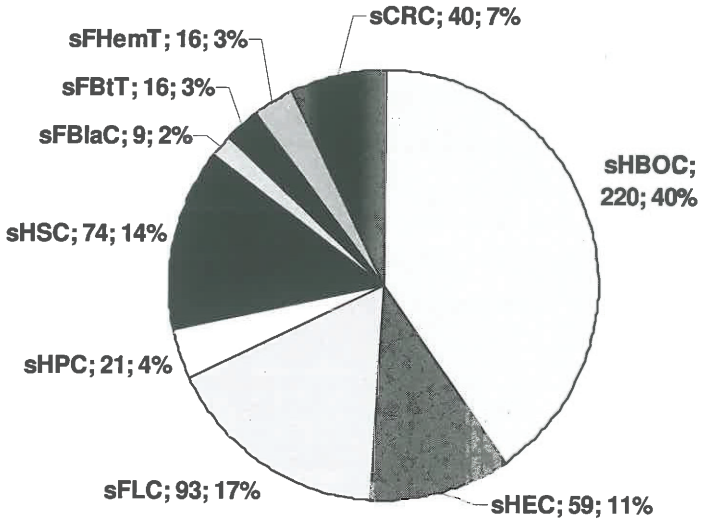
Analysing 18642 family cancer histories, at least one cancer case was identified in 11508 (61.72%) cases. There were 7132 (38.27%) cases with negative family cancer history. The increased risk group comprised 885 persons as they fulfilled the clinical diagnostic criteria of hereditary cancer syndromes.

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%), suspected 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%), suspected 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%), suspected 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%), suspected 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%), suspected 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%), suspected 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%), suspected 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%), suspected 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 suspected familial brain tumour in 16 cases (0.09%; 95% CI = 0.05 – 0.14%). The structure of hereditary cancer is depicted in Figure 3.



A.

The applied abbreviations:
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.

The applied abbreviations:

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

Figure 3. The reciprocal proportions of specific hereditary cancer syndromes: A, in the definitive group; B, in the suspected group.

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 3, this is true in case of hereditary colorectal, endometrial and prostate cancer. In contrast, for some tumours the difference is statistically significant.

Table 3. 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 the Table: CI, confidence interval

Hereditary breast and ovarian cancer syndromes

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 (Figure 4). 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.

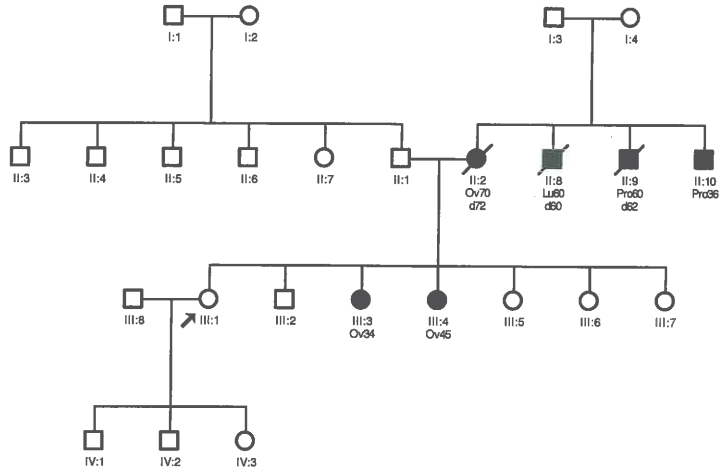


Figure 4. Pedigree affected by hereditary ovarian cancer.
Abbreviations in the Figure: Ov, ovarian cancer; Lu, lung cancer; Pro, prostate cancer; d, dead. The age of tumour diagnostics is shown as the number following the abbreviation of diagnosis, and the death age is shown as the number following the abbreviation "d". The proband is indicated by an arrow.

In total, 220 cases of suspected hereditary breast and ovarian cancer syndrome were found (Figure 5). 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. Proband's health status is reflected in Table 4.

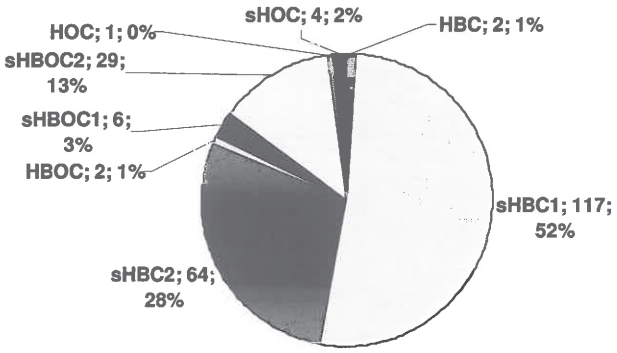


Figure 5. The relative yield of different hereditary breast and/or ovarian cancer syndromes in the diagnostics of definitive and suspected hereditary breast and/or ovarian cancer syndrome.

Abbreviations in the Figure: 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.

Table 4 Proband's health status in suspected hereditary breast and/or ovarian cancer syndrome families

Syndrome	Total number	Affected probands[1]	Proportion, % (95% CI)
sHBC1	117	5	4.3 (95% CI = 1.8 – 9.6%)
sHBC2	64	12	18.8 (95% CI = 11.1 – 30.0%)
sHBOC1	6	0	0 (95% CI = 0 – 39.0%)
sHBOC2	29	6	20.7% (95% CI = 9.8 – 38.4%)
sHOC	4	0	0 (95% CI = 0 – 49.0%)

[1] by breast and/or ovarian cancer

Abbreviations in the Table: CI, confidence interval; sHBC1, suspected hereditary breast cancer syndrome, variety 1; sHBC2, suspected hereditary breast cancer syndrome, variety 2; sHBOC1, suspected hereditary breast – ovarian cancer syndrome, variety 1; sHBOC2, suspected hereditary breast – ovarian cancer syndrome, variety 2; sHOC, 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 5.

Table 5. 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
sHBC1	34	25	21	12	15	6	3
sHBC2	15	6	9	15	11	8	0
HBOC	0	0	1	0	1	0	0
sHBOC1	2	1	2	0	0	0	1
sHBOC2	8	3	7	3	5	0	3
HOC	0	0	1	0	0	0	0
sHOC	1	1	1	0	1	0	0

Abbreviations in the Table: ≥ more than or equals to; 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.

Comparison of proband's health status by suspected hereditary breast and ovarian cancer syndromes is reflected in Table 6.

Table 6. Comparison of proband's health status by suspected hereditary breast and ovarian cancer syndromes

Syndrome	Data: number of affected probands/whole number of probands, relative number of affected probands, % [95% confidence interval, %]		
	Variety 1	Variety 2	Difference
sHBC	5 / 117 4.3 [1.8 – 9.6]	12 / 64 18.8 [11.1 – 30.0]	$p \leq 0.05$
sHBOC	0 / 6 0 [0 – 39.0]	6 / 29 20.7 [9.8 – 38.4]	$p > 0.05$
Combined	5 / 123 4.1 [1.7 – 9.2]	18 / 93 19.4 [12.6 – 28.5]	$p \leq 0.05$

Abbreviations in the Table: sHBC, suspected hereditary breast cancer; sHBOC, suspected hereditary breast – ovarian cancer.

The syndromes differed between themselves in the cancer frequency among female blood relatives. The data are summarized in the Table 7. There is statistically significant difference in breast cancer frequency among sHBC1 and sHBC2.

Table 7. Cancer burden among female blood relatives in suspected hereditary breast and/or ovarian cancer syndromes

Syndrome	Frequency of the index cancers		
	Frequency, %	95% CI	
		Lower	Upper
sHBC1	16.3	13.8	19.1
sHBC2	32.3	27.5	36.4
sHBOC1	19.3	9.2	36.3
sHBOC2	30.8	25.0	37.3
sHOC	36.4	19.7	57.0

Abbreviations in the Table: CI, confidence interval; sHBC1, suspected hereditary breast cancer syndrome, variety 1; sHBC2, suspected hereditary breast cancer syndrome, variety 2; sHBOC, suspected hereditary breast – ovarian cancer syndrome, variety 1; sHBOC, suspected hereditary breast – ovarian cancer syndrome, variety 2; sHOC, suspected hereditary ovarian cancer syndrome.

The characteristics of the disease course in the affected persons in hereditary breast and/or ovarian cancer pedigrees were analysed as shown in Table 8 and Table 9.

Table 8. The cancer course 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
	Survival	0 – 13	4.5	6.1	4	0 – 14.2
sHBC1	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
	Survival	0 – 53	7.5	10.6	61	4.8 – 10.2
sHBC2	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
	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
	Survival	0 – 13	4.8	4.9	5	0 – 10.9
sHBOC1	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
	Survival	0 – 19	5.7	7.3	6	0 – 13.4
sHBOC2	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
	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	-
	Survival	2	2	-	1	-
sHOC	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
	Survival	0 – 10	3	3.2	8	0.3 – 5.7

Abbreviations in the Table: SD, standard deviation; CIM, confidence interval for the mean; HBC, suspected hereditary breast cancer; sHBC1, suspected hereditary breast cancer, variety 1; sHBC2, suspected hereditary breast cancer, variety 2; HBOC,

hereditary breast – ovarian cancer; sHBOC1, suspected hereditary breast – ovarian cancer, variety 1; sHBOC2, suspected hereditary breast – ovarian cancer, variety 2; HOC, hereditary ovarian cancer; sHOC, suspected hereditary ovarian cancer.

Table 9. 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
sHBC1	117	17	24	5	15	15	41
sHBC2	126	14	18	10	10	26	48
HBOC	7	1	3	0	1	0	2
sHBOC1	6	1	1	0	1	0	3
sHBOC2	59	8	10	5	8	11	17
HOC	3	0	1	0	0	0	2
sHOC	7	2	4	1	0	0	0

Abbreviations in the Table: ND, no data available; >, larger than; HBC, hereditary breast cancer; sHBC1, suspected hereditary breast cancer, variety 1; sHBC2, suspected hereditary breast cancer, variety 2; HBOC, hereditary breast – ovarian cancer; sHBOC1, suspected hereditary breast – ovarian cancer, variety 1; sHBOC2, suspected hereditary breast – ovarian cancer, variety 2; HOC, hereditary ovarian cancer; sHOC, suspected hereditary ovarian cancer.

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 6) involving the large bowel.
Age distribution of probands is reflected in Table 10.

Table 10. 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
sHNPCC	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 the Table: ≥, more than or equals to; HNPCC, hereditary non-polyposis colorectal cancer; sHNPCC, suspected hereditary non-polyposis colorectal cancer; FCC1, familial colorectal cancer, variety 1; FCC2, familial colorectal cancer, variety 2.

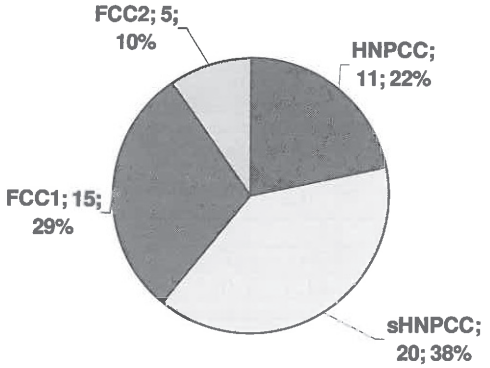


Figure 6. The relative distribution of hereditary colorectal cancer syndromes. Abbreviations in the Figure: HNPCC, definitive hereditary non-polyposis colorectal cancer syndrome; sHNPCC, suspected hereditary non-polyposis colorectal cancer syndrome; FCC1, familial colorectal cancer syndrome, variety 1; FCC2, familial colorectal cancer syndrome, variety 2.

HNPCC syndrome was diagnosed in 11 probands. These families presented with cancer history compatible with the Amsterdam criteria (Figure 7).

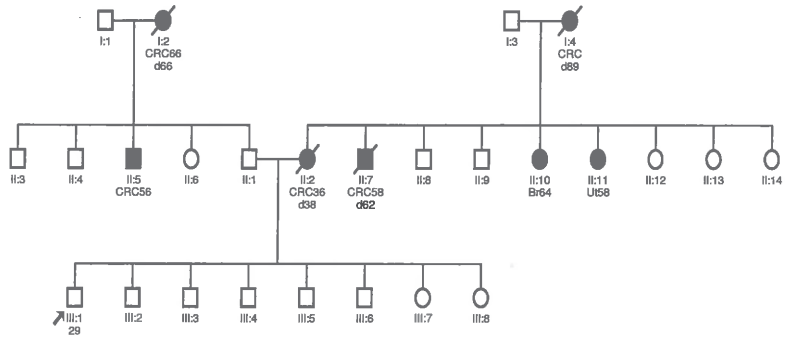


Figure 7. Pedigree corresponding to the diagnostic criteria of HNPCC. Two generations are affected.
Abbreviations in the Figure: CRC, colorectal cancer; Br, breast cancer; Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

In order to characterize the clinical features of hereditary colorectal cancer the data about the age of cancer diagnostics, cancer related death age (Table 11), first year lethality, course of the disease, cancer burden as well as proband's health status were analysed.

Analysing proband's health status, in 4/51 cases (7.8%; 95% CI = 3.1 – 24.9%) malignant tumour was diagnosed.

Knowledge of the age of cancer diagnostics (Table 11) facilitates to focus the planning of well-timed surveillance and preventive measures.

Table 11. Age of tumour manifestation in hereditary and familial colorectal cancer syndromes

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
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
sHNPCC	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)

Abbreviations in the Table: CIM, confidence interval for the mean; HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; NA, not applicable; sHNPCC, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer.

The cancer-affected HNPCC patients were characterized by low survival rate. Endometrial cancer patients had better survival (Table 12).

Table 12. The course of the malignant tumours within hereditary and familial colorectal cancer syndromes

Syndrome	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
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 (NA)	17/19	89,5 (68,6-97,1)
sHNPCC	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)

Abbreviations in the Table: N, number; Fr., frequency; CI, confidence interval; HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer; Ut, endometrial cancer; sHNPCC, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; NA, not applicable.

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 13.

Table 13. Cancer burden in hereditary and familial colorectal cancer syndromes

Syndrome	Tumour location	Frequency, %	95% CI, %
HNPCC	Index cancer	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]
sHNPCC	Index cancer	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	Kolorektāls vēzis	17,0	12,8 – 22,3

[1] in female

Abbreviations in the Table: CI, confidence interval; HNPCC, hereditary non-polyposis colorectal cancer; sHNPCC, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer.

In most hereditary colorectal cancer groups the family size was significantly different from the family size of group without diagnostic findings. The respective data are reflected in Table 14.

Table 14. Characteristics of the reported family size in respect to hereditary or familial colorectal cancer syndrome

Diagnosis	Number of the blood relatives			
	Interval	Mean	SD	95% CIM
HNPCC	7 – 26	13,3	5,4	9,6 – 17,0
sHNPCC	6 – 22	13,9	5,2	11,4 – 16,4
FCC	3 – 19	12,0	3,8	10,2 – 13,8
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; HNPCC, hereditary non-polyposis colorectal cancer; sHNPCC, suspected hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer.

Hereditary endometrial cancer syndromes

Hereditary endometrial cancer syndromes were detected in 66 probands. The distribution of different hereditary endometrial cancer syndromes was following (Figure 8).

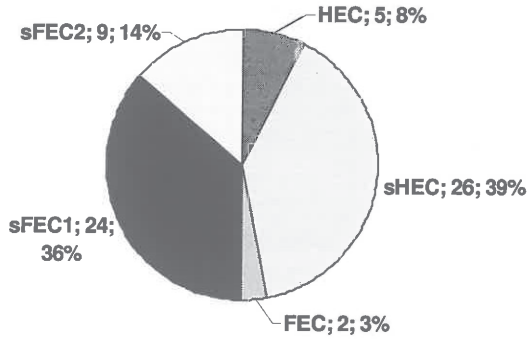


Figure 8. Distribution of definitive and suspected hereditary and familial endometrial cancer syndromes.
Abbreviations in the Figure: HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; sFEC1, suspected familial endometrial cancer, variety 1; sFEC2, suspected familial endometrial cancer, variety 2.

The definitive hereditary endometrial cancer syndrome (Figure 9) was mostly diagnosed in probands younger than 50 years (4/5). All probands diagnosed with hereditary endometrial cancer syndrome were healthy themselves (Table 15).

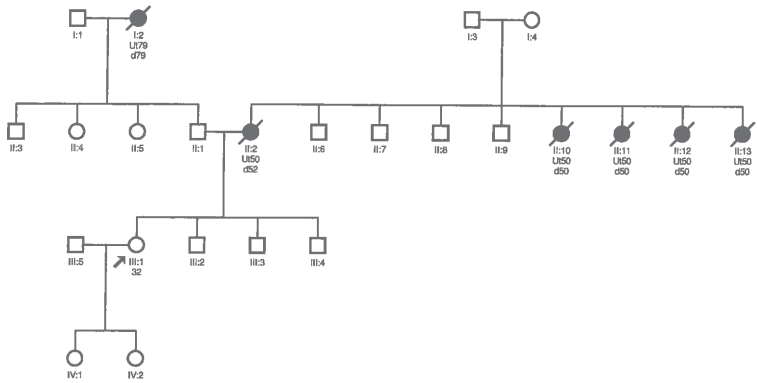


Figure 9. Pedigree of a family affected by hereditary endometrial cancer.
Abbreviations in the figure: Ut, endometrial cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Table 15. Proband's health status in hereditary and familial endometrial cancer

Syndrome	Affected probands	
	Number	Frequency, % (95% CI, %)
HEC	0 / 5	0 (0 – 43.3)
sHEC	4 / 24	16.7 (6.7 – 35.8)
FEC	0 / 2	0 (0 – 65.8)
FEC1	3 / 18	16.7 (5.8 – 39.2)
FEC2	1 / 7	14.3 (2.6 – 51.3)
Total	8 / 56	14.3 (7.4 – 25.7)

Abbreviations in the Table: CI, confidence interval; HEC, hereditary endometrial cancer, sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, familial endometrial cancer, variety 1; FEC2, familial endometrial cancer, variety 2.

The population frequencies of hereditary and familial endometrial cancer syndromes were determined by clinical data (Table 16).

Table 16. The population frequency of different hereditary and familial endometrial cancer syndromes

Syndrome	Number	Population frequency	95% CI, %
HEC	5	0,027	0,011 – 0,063
sHEC	26	0,139	0,095 – 0,204
FEC / FEC1	26	0,139	0,095 – 0,204
FEC2	9	0,048	0,025 – 0,092

Abbreviations in the Table: CI, confidence interval; HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2.

The identified pedigrees of hereditary and familial endometrial cancer syndromes also were characterised by generally high frequency of malignant tumours among the blood relatives as shown in Table 17.

Table 17. Endometrial cancer frequency in hereditary and familial endometrial cancer syndromes

Syndrome	Tumour location	Frequency, %	95% CI, %
HEC	Endometrial cancer[1]	41,5[1]	27,8 – 56,6[1]
sHEC	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]

[1] in female

Abbreviations in the Table: CI, confidence interval; HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial

cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2

The syndromes were characterised also by the age of tumour diagnostics and tumour-related death as shown in Table 18. The mean age was below 50 years of age in sHEC group suggesting marked trend towards tumour occurrence in young persons. The youngest cases have been affected in FEC2.

Table 18. The age of tumour manifestation in hereditary and familial endometrial cancer syndromes

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HEC	40 – 75	52,1 (47,2 – 57,0)	44 – 76	57,7 (49,6 – 65,8)
sHEC	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)

Abbreviations in the Table: CIM, confidence interval for the mean; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2

The course of hereditary endometrial cancer was characterized by the first year lethality, survival time and number of affected persons by endometrial cancer being alive during the population screening (Table 19).

Table 19. The course of the malignant tumours within hereditary and familial cancer syndromes

Syndrom e	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
HEC	7/17	41.2 (21.6-64.0)	6,1 (0-13.9)	5/17	29.4 (13.3-53.1)
sHEC	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)

Abbreviations in the Table: N, number; Fr., frequency; CI, confidence interval; HEC, hereditary endometrial cancer; sHEC, suspected hereditary endometrial cancer; FEC, familial endometrial cancer; FEC1, suspected familial endometrial cancer, variety 1; FEC2, suspected familial endometrial cancer, variety 2.

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 endometrial cancers was calculated for each location (Table 20). It is one of the most significant findings as it highlights the importance of hereditary cancer concept by identifying groups of risk.

Table 20. Population-attributable fraction of endometrial cancer

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Endometrial	16,5	14,5 – 18,9	3,8	2,9 – 5,1

Abbreviation in the Table: CI, confidence interval.

Familial lung cancer syndromes

During the population screening, the first pedigrees with familial lung cancer in Latvia were identified (Figure 10). Familial lung cancer syndrome was diagnosed in 13 probands. Suspected familial lung cancer syndrome was diagnosed in 93 probands. In all cases, the probands were oncologically healthy themselves (Table 21).

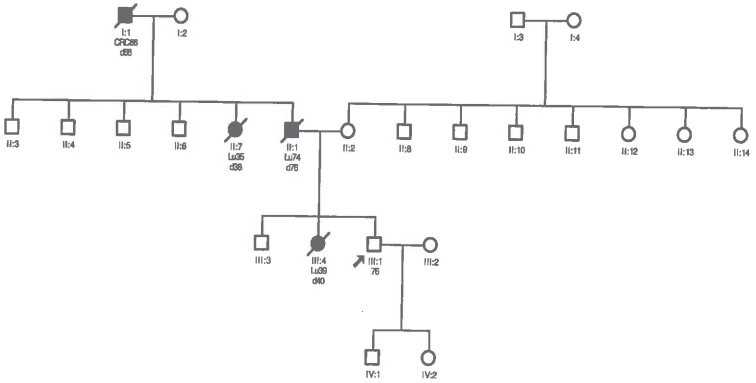


Figure 10. Pedigree of a family affected by familial lung cancer.
Abbreviations in the Figure: CRC, colorectal cancer; Lu, lung cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Table 21. Proband's health status within familial lung cancer syndromes

Syndrome	Affected probands	
	Number	Frequency,% (95% CI,%)
FLC d/s	0/106	0 (0 – 3.5)

Abbreviations in the Table: CI, confidence interval; FLC, familial lung cancer; d, definitive; s, suspected.

The population frequencies of familial lung cancer syndromes were determined clinically (Table 22).

Table 22. The population frequency of familial lung cancer syndromes

Syndrome	Number	Population frequency,%	95% CI, %
FLC	13	0.070	0.041 – 0.119
sFLC	93	0.499	0.407 – 0.611

Abbreviations in the Table: CI, confidence interval; FLC, familial lung cancer; sFLC, suspected familial lung cancer.

The identified pedigrees of familial lung cancer syndromes were characterised by high cancer burden in blood relatives (Table 23).

Table 23. Cancer burden in familial lung cancer syndromes

Syndrome	Tumour location	Frequency, %	95% CI, %
FLC	Lung cancer	25.5	19.3 – 32.8
sFLC	Lung cancer	17.2	15.0 – 19.7

Abbreviations in the Table: CI, confidence interval; FLC, familial lung cancer; sFLC, suspected familial lung cancer.

Childhood cases have been reported in sFLC. However, the mean age of lung cancer diagnostics exceeded 55 years of age (Table 24).

Table 24. Age of lung cancer manifestation in familial lung cancer syndromes

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
FLC	35 – 78	56.0 (53.0 – 59.0)	36 – 79	57.1 (54.1 – 60.1)
sFLC	18 – 90	58.5 (56.1 – 60.9)	13 – 90	61.2 (59.1 – 63.3)
Total	18 – 90	57.9 (55.9 – 59.9)	13 – 90	61.2 (58.5 – 62.1)

Abbreviations in the Table: CIM, confidence interval for the mean; FLC, familial lung cancer; sFLC, suspected familial lung cancer.

The first year lethality in both syndromes groups was high (Table 25) showing an evidence of aggressive tumour. Familial lung cancer syndromes were characterized by low survival. Only 3 affected persons were alive during the population screening.

Table 25. Course of the disease in familial lung cancer syndromes

Syndrome	First year lethality		Survival,years (95% CI)	Alive	
	Count	Frequency, % (95% CI)		Count	Frequency, % (95% CI,%)
Whole group (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)

Abbreviations in the Table: CI, confidence interval; FLC, familial lung cancer; d/s, definitive and suspected.

Lung cancer is characterized by high population-attributable fraction like other hereditary cancer syndromes exceeding 10% borderline (Table 26).

Table 26. Population-attributable fraction of FLC in Valka district

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Lung	12.9	11.5 – 14.6	2.4	1.8 – 3.2

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

Hereditary stomach cancer

Hereditary stomach cancer syndrome (Figure 11) 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.

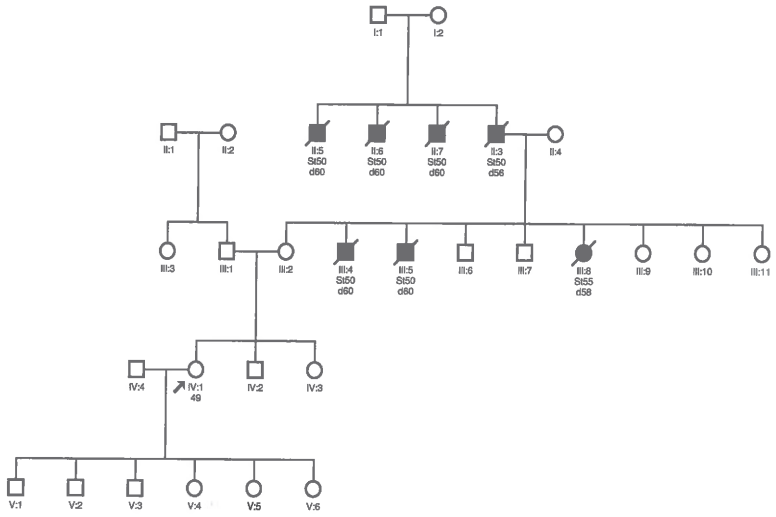


Figure 11. Hereditary stomach cancer manifesting itself in multiple affected persons in 2 generations.
Abbreviations in the Figure: St, gastric cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

The total population frequency of hereditary stomach cancer in Valka district was 0.51% (Table 27)

Table 27. The population frequency of hereditary stomach cancer in Valka district population

Syndrome	Number	Population frequency	95% CI, %
HSC	21	0,113	0,074 – 0,172
sHSC.	74	0,397	0,316 – 0,498

Abbreviations in the Table: CI, confidence interval; HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer

Population screening allows identifying hereditary stomach cancer in oncologically healthy persons. Only one proband had stomach cancer corresponding to the frequency 1.1% (95% CI = 0.2 – 5.7%).

The cancer burden among blood relatives in hereditary stomach cancer pedigrees was high showing also statistically significant difference between HSC and sHSC (Table 28).

Table 28. The gastric cancer burden in hereditary stomach cancer syndromes

Syndrome	Frequency, %	95% CI, %
HSC	25.2	20.6 – 30.4
sHSC	16.0	13.8 – 18.5

Abbreviations in the Table: CI, confidence interval; HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer.

The mean age of stomach cancer diagnostics was over 55 years of age. However, isolated stomach cancer cases were identified in persons younger than 35 years of age (Table 29).

Table 29. The age of tumour manifestation in hereditary stomach cancer syndromes

Syndrome	Age of diagnosis, years		Age of death, years	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HSC	30 – 83	56.9 (53.4 – 66.3)	30 – 90	58.3 (55.3 – 61.3)
sHSC	34 – 95	62.5 (60.1 – 64.8)	37 – 96	65.6 (63.4 – 67.6)

Abbreviations in the Table: CIM, confidence interval for the mean; HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer.

The first-year lethality was high in this group like in familial lung and familial pancreatic cancer, but survival was very low and did not exceed 3 years (Table 30). During the population screening only 5.3 % of cancer-affected persons in HSC and 5.4% of affected persons in sHSC group were alive.

Table 30. The course of the disease in hereditary stomach cancer syndromes

Syndrome	First-year lethality		Survival, years	Alive	
	N	Fr., % (95% CI)	(95% CI)	N	Fr., % (95% CI)
HSC	17/76	22.4 (14.5-32.9)	2.6 (1.2-4.0)	4/76	5.3 (2.1-12.8)
sHSC	54/149	36.2 (28.9-44.2)	2.4 (1.7-3.1)	8/149	5.4 (2.7-10.2)

Abbreviations in the Table: N, number; Fr., frequency; CI, confidence interval; HSC, hereditary stomach cancer; sHSC, suspected hereditary stomach cancer.

Familial stomach cancer was characterized by population-attributed fraction of hereditary cancer exceeding 10% (Table 31).

Table 31. Population-attributable fraction of hereditary and familial stomach cancer

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Stomach cancer	13.8	12.2 – 15.6	4.7	3.8 – 5.9

Abbreviation in the Table: CI, confidence interval.

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. Thus, spouse correlation for gastric cancer was low: 3.6%, 95% CI = 1.2 – 10.1%.

Hereditary prostate cancer

The hereditary prostate cancer syndrome was diagnosed in one person. In addition, 21 persons were diagnosed with suspected hereditary prostate cancer syndrome (Figure 12).

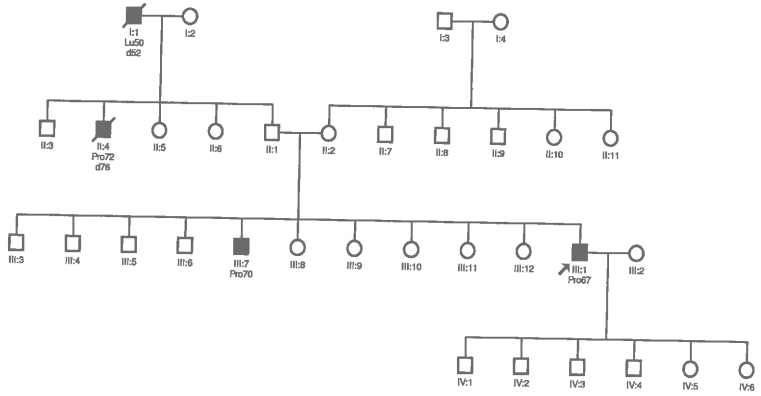


Figure 12. Pedigree of a family affected by hereditary prostate cancer.
Abbreviations in the Figure: Lu, lung cancer; Pro, prostate cancer; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

After evaluating health status of probands, only part of inspected probands had malignant tumour themselves. Persons diagnosed with HPC/sHPC syndrome mostly were oncologically healthy. However, the instant syndrome had one of the highest

proportion of oncologically affected probands among various hereditary cancer syndromes, namely 5/22, corresponding to the frequency 22.7% (95% CI = 10.1 – 43.4%)

The population frequencies in clinical hereditary and suspected hereditary prostate cancer syndromes were 0.005% and 0.113% correspondingly from total population of Valka district (Table 32).

Table 32. The population frequency of hereditary prostate cancer syndromes

Syndrome	Number	Population frequency	95% CI, %
HPC	1	0.005	0.001 – 0.030
sHPC	21	0.113	0.074 – 0.172

Abbreviations in the Table: CI, confidence interval; HPC, hereditary prostate cancer; sHPC, suspected hereditary prostate cancer.

Prostate cancer burden in HPC/sHPC pedigrees significantly exceeds the cumulative incidence of the instant tumour in European Union (Table 33). Every fifth male relative had prostate cancer.

Table 33. Burden of prostate cancer in hereditary prostate cancer syndromes

Syndrome	Cancer burden, %	95% CI, %
HPC	21.4	7.6 – 47.6
sHPC	22.2	16.4 – 29.4

Abbreviations in the Table: CI, confidence interval; HPC, hereditary prostate cancer; sHPC, suspected hereditary prostate cancer.

In both groups the age of diagnostics and age of death was above 50 years (Table 34). The survival data are presented in the Table 35.

Table 34. The age of prostate cancer manifestation in hereditary prostate cancer groups

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
HPC d/s	35 – 75	57.7 (53.3 – 62.1)	37 – 80	60.7 (55.0 – 66.4)

Abbreviations in the Table: CIM, confidence interval for the mean; HPC, hereditary prostate cancer; d, definitive; s, suspected.

Table 35. The cancer course within hereditary prostate cancer syndromes

Syndrome	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
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)

Abbreviations in the Table: N, number; Fr., frequency; CI, confidence interval; HPC, hereditary prostate cancer; d, definitive syndrome; s, suspected syndrome.

Although hereditary prostate cancer constitutes only a small part of all prostate cancer cases, the total HPC/sHPC group reaches 7.4% (Table 36).

Table 36. Population-attributable fraction of hereditary prostate cancer syndromes

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Prostate	7.4	5.4 – 10.1	0.6	0.2 – 1.8

Abbreviation in the Table: CI, confidence interval.

Familial 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 (Figure 13).

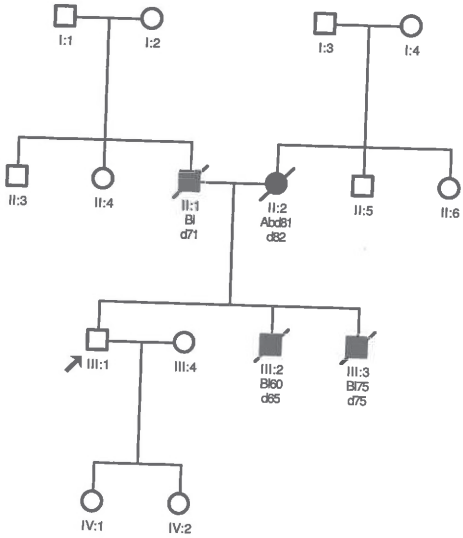


Figure 13. Pedigree of a family affected by familial cancer of urinary bladder. Abbreviations in the figure: Bl, urinary bladder cancer; Abd, malignant tumour in the abdominal cavity, not further specified; d, dead. The age of cancer diagnostics is shown by number following the diagnosis whenever reported, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

At the time of population screening none of the probands diagnosed with familial urinary bladder cancer was affected by the index cancer (Table 37)

Table 37. Proband's health status in familial urinary bladder cancer syndrome

Syndrome	Affected probands	
	Number	Frequency,% (95% CI,%)
FBlaC d/s	0/11	0 (0 – 25.9)

Abbreviations in the Table: CI, confidence interval; FBlaC, familial urinary bladder cancer; d, definitive syndrome; s, suspected syndrome.

The population frequency of familial urinary bladder cancer was as small as 0.064% (Table 38)

Table 38. Frequency of familial urinary bladder cancer syndrome in Valka district

Syndrome	Probands	Population frequency	95% CI, %
FBlaC d/s	11	0.064	0.037 – 0.112

Abbreviations in the Table: CI, confidence interval; FBlaC, familial urinary bladder cancer; d/s, definitive and suspected syndrome.

The identified pedigrees were characterized by high cancer burden reaching 22.8% of blood relatives in the affected line (95% CI = 14.9 – 33.2%). FBlaC was marked for late occurrence (Table 39). The first year lethality and survival is presented in Table 40.

Table 39. Age of cancer manifestation in familial urinary bladder cancer syndromes

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
FBlaC	60 – 87	70.7 (66.7 – 74.7)	65 – 92	75.7 (71.6 – 79.8)

Abbreviations in the Table: CI, confidence interval; FBlaC, familial urinary bladder cancer

Table 40. The course of familial urinary bladder cancer

Syndrom	First-year lethality		Survival, years	Alive	
e	N	Fr., % (95% CI)	(95% CI)	N	Fr., % (95% CI)
FBlaC d/s	3/18	16. (5.8-39.2)	4.8 (1.7-6.5)	3/18	16.7 (5.8-39.2)

Abbreviations in the Table: CI, confidence interval; FBlaC, familial urinary bladder cancer; d/s, definitive and suspected syndrome.

Population-attributable fraction was close to 10% (Table 41).

Table 41. Population-attributable fraction in familial urinary bladder cancer

Origin of the tumour	Hereditary cases		Definitive hereditary cases	
	Fraction, %	95% CI, %	Fraction, %	95% CI, %
Urinary bladder	9.6	6.6 – 13.9	2.4	1.1 – 5.2

Abbreviations in the Table: CI, confidence interval.

Familial pancreatic cancer

Using the clinical diagnostic criteria of familial pancreatic cancer, 10 probands were diagnosed with familial pancreatic cancer syndrome (Figure 14). Only one proband was affected by pancreatic cancer himself. The corresponding frequency of probands affected by index tumours thus was 10% (95% CI = 1.8 – 40.4%).

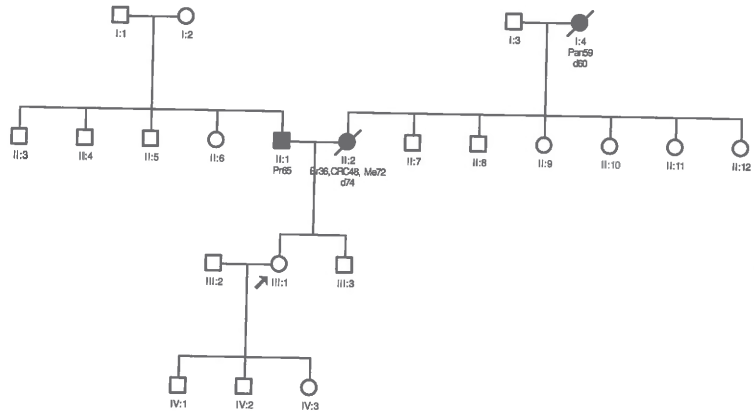


Figure 14. Kindred showing presence of pancreatic cancer and melanoma in two first-degree blood relatives.
Abbreviations in the figure: Pan, pancreatic cancer; Pr, prostate cancer; Br, breast cancer; CRC, colorectal cancer, Me, melanoma; d, dead. The age of cancer diagnostics is shown by number following the diagnosis, and the age of death is shown by the number, following the abbreviation "d". The proband is indicated by an arrow.

Familial pancreatic cancer was characterized by rare occurence (Table 42) but high index tumour burden of 14.7% (95% CI = 9.1 – 22.9%)

Table 42. Frequency of familial pancreatic cancer in Valka district population

Syndrome	Probands	Population frequency	95% CI, %
FPan	10	0.054	0.029 – 0.099

Abbreviations in the Table: CI, confidence interval; FPan, familial pancreatic cancer.

FPan was characterized by occurrence in aged persons (Table 43) and very low survival (Table 44).

Table 43. Age of cancer manifestation in familial pancreatic cancer syndromes

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
FPan	51 – 72	61.6 (57.3 – 65.9)	51 – 83	63.4 (58.2 – 68.6)

Abbreviations in the Table: CI, confidence interval; FPan, familial pancreatic cancer.

Table 44. The course of the malignant tumours within familial pancreatic cancer syndrome

Syndrome	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
FPan	15/21	71.4 (50.0-86.2)	1.1 (0.2-1.4)	1/21	4.8 (0.8-22.7)

Abbreviations in the Table: CI, confidence interval; FPan, familial pancreatic cancer.

Familial pancreatic cancer group comprised 6.3% of all pancreatic cancer cases (95% CI = 4.1 – 9.6%).

Other hereditary cancer syndromes

No evidence of dominant inheritance in renal and testicular cancers was found. During population screening, familial haematologic tumour syndrome was discovered in 17 families (Figure 15) and familial brain tumour syndrome was discovered in 19 families.

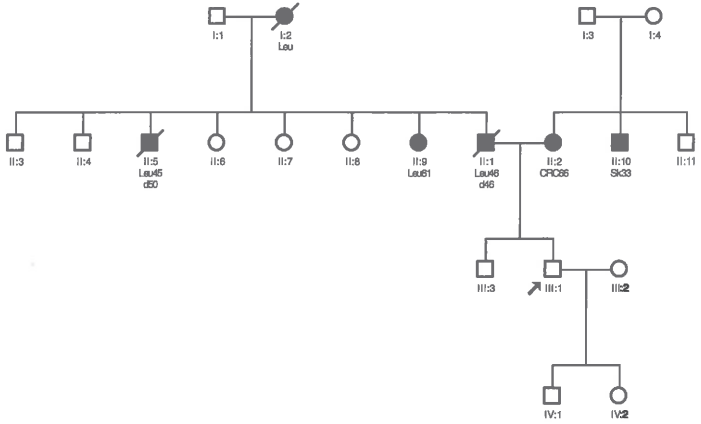


Figure 15. Pedigree of a family affected by familial aggregation of haematologic tumours.

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 familial haematologic tumour syndrome or familial brain tumour syndrome was identified mostly in healthy persons (Table 45).

Table 45. Health status of probands diagnosed with familial haematologic or brain tumour syndrome

Syndrome	Affected probands	
	Number	Frequency (95% CI)
FHemT d/s	1/17	5.9% (1.0 – 27.0%)
FBtT d/s	0/19	0% (0 – 16.8%)

Abbreviations in the Table: CI, confidence interval; FHemT, familial haematological tumour syndrome; FBtT, familial brain tumour syndrome; d, definitive syndrome; s, suspected syndrome.

Syndromes mentioned above were not frequent in Valka district (Table 46), possibly due to very low survival and fast elimination of syndrome-related affected persons.

Table 46. The population frequency of the familial haematologic or brain tumour syndrome

Syndrome	Probands	Population frequency	95% CI, %
FHemT d/s	17	0.091	0.057 – 0.146
FBtT	3	0.016	0.005 – 0.047
sFBtT	16	0.086	0.053 – 0.139

Abbreviations in the Table: CI, confidence interval; FHemT, familial haematological tumour syndrome; d/s, definitive and suspected syndrome; FBtT, familial brain tumour syndrome; sFBtT, suspected familial brain tumour syndrome.

The identified pedigrees of the respective familial cancer syndromes, namely, FHem T and FBtT, were characterised by high frequency of the index malignancies among the blood relatives as shown in Table 47.

Table 47. The index tumour burden in blood relatives of the affected kindreds

Syndrome	Tumour type	Frequency, %	95% CI, %
FHemT d/s	Malignant haematologic tumour	16.3	12.1 – 21.2
FBtT	Brain tumour	32.3	18.6 – 49.9
sFBtT	Brain tumour	14.4	10.4 – 19.5

Abbreviations in the Table: CI, confidence interval; FHemT, familial haematological tumour syndrome; d/s, definitive and suspected syndrome; FBtT, familial brain tumour syndrome; sFBtT, suspected familial brain tumour syndrome.

Childhood cases have been reported in FBtT and FHemT (Table 48). However, the mean age of tumour manifestation was slightly less than 50 years of age.

Table 48. The age of tumour manifestation in the familial haematologic or brain tumour syndrome

Syndrome	Age of diagnosis		Age of death	
	Interval	Mean (95% CIM)	Interval	Mean (95% CIM)
FHemT	3 – 88	47.5 (38.9 – 56.1)	4 – 86	49.8 (40.5 – 59.1)
FBtT	2 – 77	43.9 (35.0 – 52.8)	2 – 77	47.8 (39.7 – 55.9)

Abbreviations in the Table: CI, confidence interval; FHemT, familial haematological tumour syndrome; FBtT, familial brain tumour syndrome.

Survival parameters indicated fast progression of the familial haematological and brain tumours (Table 49). During the population screening only 7.7% and 18.9% of affected persons were alive in FHemT and in FBtTof respectively.

Table 49. The course of the malignant tumours within the familial haematologic or brain tumour syndrome

Syndrome	First-year lethality		Survival, years (95% CI)	Alive	
	N	Fr., % (95% CI)		N	Fr., % (95% CI)
FHemT	11/37	29.7 (17.5-45.8)	1.9 (1.1-2.7)	7/37	18.9 (9.5-34.2)
FBtT	16/26	61.5 (42.5-77.6)	1.5 (0.3-2.7)	2/26	7.7 (2.1-24.1)

Abbreviations in the Table: CI, confidence interval; FHemT, familial haematological tumour syndrome; FBtT, familial brain tumour syndrome.

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

The reported family size in the joint group of definitive hereditary cancer syndrome, suspected hereditary cancer, CFA and group of patients whose family cancer history was undiagnostic of any oncological syndrome was compared as shown in Table 50. 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 50. 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 among 588 (1.70%) blood samples examined by multiplex PCR (Table 51). In 8 cases the *BRCA1* gene mutation was 5382insC, in 2 – 4153delA.

Table 51. 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%)
Total	588	10 1,7% (95% TI = 0,9 – 3,1%)

Abbreviations in the Table: CI, confidence interval.

DISCUSSION

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.

Hereditary breast cancer

Breast cancer is the most frequent malignant tumour in women with approximately thousand of new cases in Latvia. 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). 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. Comparison of hospital and population screening is shown in Table 52 and Table 53.

Table 52. Prevalence of breast hereditary cancer syndromes by population screening

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

[1]among female; [2]among male

Abbreviation in the Table: CI, confidence interval.

Table 53. 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 the 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.

In the diagnostics of suspected hereditary breast cancer the population screening shows statistically insignificant trend towards greater yield.

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 28 per ten thousands, value that is intermediate between the data about definitive and suspected hereditary breast cancer obtained for Latvian population.

Hereditary 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). 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).

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).
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 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 showed higher yield of definitive hereditary cancer syndrome diagnostics.
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.

Hereditary 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 05.05.2009).

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 sHEC, 4 cases of FEC and 46 cases of sFEC have been observed in a hospital group comprising 672 endometrial cancer patients (Svampane *et al.*, 2009). These numbers correspond to the following frequencies: HEC by hospital screening, 0.9% (95% CI = 0.4 – 1.9%), sHEC by hospital screening, 2.8% (95%CI = 1.8 – 4.4%), FEC by hospital screening, 0.6% (95% CI = 0.2 – 1.5%), sFEC 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 by hospital screening, the frequency of endometrial cancer having definite hereditary basis can be expected to be 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.

Hereditary 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%]. The total burden of hereditary breast and/or ovarian cancer by population and hospital screening is shown in Table 54.

Table 54. 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 population screening	3 [1.0 – 8.4][1]
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.

Comparison with other population screenings for hereditary cancer

The largest and exclusive 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 district and Poland is shown in the Figure 16. 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.

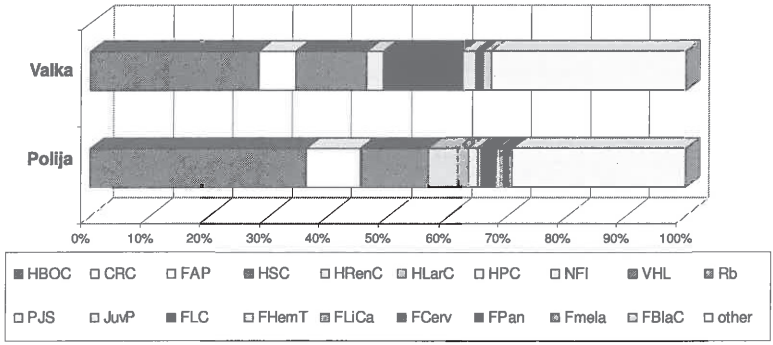


Figure 16. Population structure of hereditary and familial cancer aggregation in the Valka district and the West Pomeranian region of Poland.
Abbreviations in the Figure: HBOC, hereditary breast and/or ovarian cancer syndrome; CRC, hereditary non-polyposis colorectal cancer syndromes; FAP, familial adenomatous 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 estimates of the total hereditary cancer burden in Latvian population were calculated (Table 55). 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.
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 55. 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.

PUBLICATIONS AND REPORTS ON DOCTOR'S DISSERTATION ISSUE

Pubmed publications

1. A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M.Bitina, I.Melbarde-Gorkusa, **A.Vanags**, *G.Kurzawski*, *J.Suchy*, *B.Gorski*, J.Gardovskis. *Clinical, molecular and geographical features of hereditary breast / ovarian cancer in Latvia. Hereditary Cancer in Clinical Practice*, 2005; 3(2):71-76.
2. A.Irmejs, E.Miklasevics, V.Boroschenko, A.Gardovskis, **A.Vanags**, I.Melbarde-Gorkusa, M.Bitina, *J.Suchy*, J.Gardovskis. *Pilot study on low penetrance breast and colorectal cancer predisposition markers in Latvia. Hereditary Cancer in Clinical Practice*, 2006; 4(1):48-51.
3. A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M.Bitina, I.Melbarde-Gorkusa, **A.Vanags**, J.Gardovskis. *Update on hereditary breast* – ovarian cancer in Latvia. *Proceedings of the XXXV World Congress of the International College of Surgeons*, 2006:191-195.
4. V.Borošenko, A.Irmejs, I.Melbārde-Gorkuša, A.Gardovskis, M.Pavārs, **A.Vanags**, G.Trofimovičs, E.Miklaševičs, J.Gardovskis. *Initial results of colorectal polyposis research in Latvia. Anticancer Research*, 2009; 29:711-716.
5. A.Vanags, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Ābolinš, U.Teibe, G.Trofimovičs, E.Miklaševičs, J.Gardovskis. *Population screening for hereditary and familial cancer syndromes in Valka district of Latvia. Hereditary Cancer in Clinical Practice*, 2010; 8; http://www.hccpjournal.com/content/8/1/8, doi:10.1186/1897-4287-8-8

Publications in peer-reviewed medical and scientific journals of Latvia

1. A.Irmejs, E.Miklasevics, V.Borosenko, A.Gardovskis, **A.Vanags**, I.Melbarde – Gorkusa, M.Bitina, J.Suchy, J. Gardovskis. *Pilot study on the moderate penetrance breast and colorectal cancer predisposition markers in Latvia. Acta Chirurgica Latviensis*, 2005(5):3-5.
2. **A.Vanags**, A.Irmejs, V.Borošenko, A.Gardovskis, E.Miklaševičs, J.Gardovskis. [*The first results of the population screening for hereditary cancer and clinical and molecular examination of high-risk group*] [*Article in Latvian*] Pārmantotā vēža populācijas skrīninga analīzes un paaugstināta riska grupas klīniski molekulāro īpatnību izpētes pirmie rezultāti. Riga Stradiņš University. *Collection of scientific papers*, 2006. Riga, RSU, 2007:163-166.
3. V.Borosenko, A.Irmejs, E.Miklasevics, A.Gardovskis, **A.Vanags**, I.Melbārde-Gorkuša, M.Bitiņa, J.Suchy, J.Gardovskis. [*The clinical manifestations and molecular characteristics of intermediate penetrance mutations predisposing to colorectal cancer*] [*Article in Latvian*] Vidējas penetrances pakāpes kolorektālo vēzi predisponējošo gēnu mutāciju klīniskās izpausmes un molekulārās īpatnības Latvijā. Riga Stradiņš University. *Collection of scientific papers* 2006. Riga, RSU, 2007: 149-151.
4. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M. Bitiņa. [*The clinical, molecular and geographical peculiarities of hereditary breast-ovarian cancer in Latvia*]. [*Article in Latvian*] Pārmantota krūts un olnīcu vēža klīniskās, molekulārās un ģeogrāfiskās īpatnības Latvijā. Riga Stradiņš University. *Collection of scientific papers* 2006. Riga, RSU, 2007:152-155.

5. V.Borosenko, A.Irmejs, **A.Vanags**, I.Melbarde-Gorkusa, A.Abele, A.Gardovskis, M.Pavars, W.Friedl, J.Gardovskis. *First results of colorectal polyposis research in Latvia. Acta Chirurgica Latviensis*, 2007 (7):3-6.
6. **A.Vanags**, A.Irmejs, E.Miklasevics, A.Gardovskis, V.Borosenko, J.Gardovskis. [*The population screening for hereditary cancer in Valka district*] [*Article in Latvian*] Pārmantota vēža populācijas skrīnings Valkas rajonā. Riga Stradiņš University. *Collection of scientific papers* 2007. Riga, RSU, 2008: 156-159.
7. **A.Vanags**, A.Irmejs, E.Miklasevics, I.Strumfa, J.Gardovskis.*Identification of BRCA1 gene mutation-bearing kindred: the possibilities of a new diagnostic approach to cancer prevention. Acta Chirurgica Latviensis*, 2008 (8):87-89.
8. **A.Vanags**, M.Pavars, P.Prieditis, I.Strumfa, A.Irmejs, J.Gardovskis. *Biliary cystadenocarcinoma: a case study of a rare tumour. Acta Chirurgica Latviensis*, 2008 (8):90-93.
9. V.Borosenko, A.Irmejs, **A.Vanags**, I.Melbarde-Gorkusa, A.Abele, A.Gardovskis, M.Pavars, M.Bitina, *W.Friedl*, J.Gardovskis. *First results of colorectal polyposis research in Latvia.* Riga Stradiņš University. *Collection of Scientific Papers 2007*, RSU, Riga, Latvia, 2008: 46-49.
10. A.Gardovskis, A.Irmejs, E.Miklashevics, **A.Vanags**, I.Melbarde-Gorkusha, V.Boroshenko, M.Bitina, J.Gardovskis. *Hereditary breast and ovarian cancer hospital based screening in Latvia.* Riga Stradiņš University. *Collection of scientific papers* 2007; RSU, Riga, Latvia, 2008; 39-41.
11. **A.Vanags**, A. Irmejs, V.Borosenko, A. Gardovskis, E.Miklasevics, J.Gardovskis. *Comparison of the expedience of population and hospital screening in hereditary cancer detection.* Riga Stradiņš University. *Collection of scientific papers* 2008
12. *Epidemiological, clinical, molecular features and early detection strategy of most frequent hereditary cancers in Latvia.* J.Gardovskis, I.Štrumfa, E.Miklaševičs, A.Irmejs, G.Trofimovičs, E.Vjaters, V.Borošenko, I.Melbārde-Gorkuša, A.Gardovskis, **A.Vanags**, A.Ābele, S.Subatniece, M.Bitiņa, L.Švampāne, J.Žestkova, D.Bērziņa, K.Aksenoka, V.Boka, A.Puķītis, A.Stāka, L.Tihomirova. *Proceedings of the Latvian Academy of sciences*, 2009; Sect.B, Vol.63:131-140.
13. *Biliary cystic tumours with mesenchymal stroma.* **A.Vanags**, M.Pavars, P.Prieditis, I.Strumfa, A.Irmejs, J.Gardovskis. *Acta Chirurgica Latviensis*, 2009; 9:95-99.
14. *The first evidence of familial lung cancer in Latvia by population screening for hereditary cancer.* **A.Vanags**, J.Grushina, I.Strumfa, J.Gardovskis. *Acta Chirurgica Latviensis*, 2009; 9:3-9.

Abstracts

1. A.Irmejs, A.Gardovskis, V.Borosenko, M. Bitina, **A.Vanags**, I.Melbarde – Gorkusa, G.Kurzawski, J.Suchy, B.Gorski, J.Gardovskis. *Hereditary breast – ovarian cancer in Latvia.* 4th *Congress of Baltic Association of Surgeons, Abstracts Volume*, 2004, p. 29
2. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, M.Bitiņa, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko. [*The clinical, molecular and geographical peculiarities of hereditary breast-ovarian cancer in Latvia*] [*Abstract in Latvian*] Pārmantota krūts – olnīcu vēža klīniskās, molekulārās un

ģeogrāfiskās īpatnības Latvijā. The Proceedings of the 3rd Congress of the Surgeons of Latvia, 2005, p. 61.

3. A.Irmejs, **A.Vanags**, V.Borosenko, A.Gardovskis, E.Miklasevics, J. Gardovskis. *First results of hereditary cancer population screening in Latvia. Familial cancer*, 2006, 61.
4. V.Borosenko, A.Irmejs, E.Miklasevics, A.Gardovskis, **A.Vanags**, I.Melbārde-Gorkuša, M.Bitina, J.Suchy, J.Gardovskis. *Pilot study on the moderate penetrance breast and colorectal cancer predisposition markers in Latvia. Familial cancer*, 2006, 52.
5. A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M, Bitina, I.Melbarde-Gorkusa, **A.Vanags**, G.Kurzawski, J.Suchy, B.Gorski, J.Gardovskis. *Clinical, molecular and geographical features of hereditary breast – ovarian cancer in Latvia. Familial cancer*, 2006, 56.
6. A.Irmejs, **A.Vanags**, V.Borosenko, A.Gardovskis, E.Miklasevics, J.Gardovskis. *First results of hereditary cancer population screening in Latvia. Cancer and genetics*, 2006, 24.
7. E.Miklasevics, V.Borosenko, A.Irmejs, A.Gardovskis, **A.Vanags**, I.Melbarde-Gorkusa, M.Bitina, J.Gardovskis. *First results on the moderate penetrance breast and colorectal cancer predisposition markers in Latvia. Cancer and genetics*, 2006, 33.
8. A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M.Bitina, I.Melbarde-Gorkusa, **A.Vanags**, J.Gardovskis. *Update on hereditary breast – ovarian cancer in Latvia. Cancer and genetics*, 2006, 19.
9. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The clinical, molecular and geographical characteristics of hereditary breast – ovarian cancer in Latvia*] [*Abstract in Latvian*] Pārmantota krūts un olnīcu vēža klīniskās, molekulārās un ģeogrāfiskās īpatnības Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2006, p. 107.
10. A.Irmejs, E.Miklaševičs, V.Borošenko, A.Gardovskis, **A.Vanags**, I.Melbārde-Gorkuša, M.Bitiņa, J.Gardovskis. [*The first data about intermediate penetrance mutations predisposing to colorectal and breast cancer in Latvia*] [*Abstract in Latvian*] Pirmie rezultāti par vidējas penetrances pakāpes resnās, taisnās zarnas un krūts vēzi predisponējošo gēnu mutāciju īpatnībām Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2006, p. 108.
11. **A.Vanags**, A.Irmejs, V.Borošenko, A.Gardovskis, E.Miklaševičs, J.Gardovskis. [*The up-to-dated results of the population screening for hereditary cancer*] [*Abstract in Latvian*] Jaunākie pārmantota vēža populācijas skrīninga rezultāti. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2007, p. 192.
12. **A. Vanags**, A.Irmejs, V.Borošenko, A.Gardovskis, E.Miklaševičs, I.Melbārde – Gorkuša, J.Gardovskis. [*The characteristics of hereditary cancer risk group in population*] [*Abstract in Latvian*] Pārmantotā vēža paaugstinātā riska grupas raksturojums populācijā. The Proceedings of the 4th Congress of the Surgeons of Latvia, 2007, pp. 36. -37.
13. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The hospital screening for hereditary breast – ovarian cancer in Latvia*] [*Abstract in Latvian*] Pārmantotā krūts –

olnīcu vēža hospitālais skrīnings Latvijā. The Proceedings of the 4th Congress of the Surgeons of Latvia, 2007, pp. 28.-29.

14. V.Borošenko, A.Irmejs, A.Gardovskis, **A.Vanags**, E.Miklaševičs, I.Melbārde – Gorkuša, M, Bitiņa, J.Gardovskis. [*The hospital and population screening for hereditary colorectal cancer in Latvia*] [*Abstract in Latvian*] Pārmantota kolorektāla vēža hospitālais un populācijas skrīnings Latvijā. The Proceedings of the 4th Congress of the Surgeons of Latvia, 2007, pp. 34.-35.
15. V. Borošenko, A.Irmejs, A.Gardovskis, **A.Vanags**, E.Miklaševičs, I.Melbārde-Gorkuša, M.Bitiņa, J.Gardovskis. [*The novel data in hereditary colorectal cancer screening in Latvia*] [*Abstract in Latvian*] Jaunākie dati par pārmantota kolorektālā vēža skrīningu Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2007, p. 190.
16. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The novel data about the clinical and molecular characteristics of hereditary breast-ovarian cancer in Latvia*] [*Abstract in Latvian*] Jaunākie dati par pārmantotā krūts un olnīcu vēža klīniskajām un molekulārajām īpatnībām Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2007, p. 189.
17. **A.Vanags**, A.Irmejs, E.Miklaševičs, A.Gardovskis, V.Borošenko, J.Gardovskis. *Population screening for hereditary cancer in Valka region: final results.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2008, p.157.
18. V.Borošenko, A.Irmejs, I.Melbārde-Gorkuša, A.Gardovskis, **A.Vanags**, M.Pavārs, E.Miklaševics, *W.Friedl*, J.Gardovskis. *First results on polyposis research in Latvia.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2008, p.163.
19. A. Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The clinical, epidemiological and molecular characteristics of hereditary breast – ovarian cancer in Latvia*] [*Abstract in Latvian*] Pārmantotā krūts – olnīcu vēža klīniskais, epidemioloģiskais un molekulārais raksturojums Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2008, p.156.
20. A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The hospital screening for hereditary breast and ovarian cancer in ovarian cancer patients*] [*Abstract in Latvian*] Pārmantotā krūts un olnīcu vēža hospitālais skrīnings olnīcu vēža pacientēm Latvijā. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2009, p. 171.
21. V.Borosenko, A.Irmejs, I.Melbarde-Gorkusa, A.Gardovskis, M.Pavars, L.Svampane, **A.Vanags**, I.Strumfa, E.Miklasevics, G.Trofimovics, J.Gardovskis. *Initial results of colorectal cancer determined low penetrance genes research in Latvia.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2009, p. 175.
22. **A.Vanags**, I.Strumfa, A.Irmejs, E.Miklasevics, J.Gardovskis. *Population screening for hereditary cancer: a novel, effective tool in early cancer diagnostics. International Surgical Week ISW 2009 / the 43th World Congress of the International Society of Surgery*, (06.-10.09.2009., Adelaide, Austrālija), *Abstract Book*, 305.
23. **A.Vanags**, M.Pavars, I.Strumfa, J.Gardovskis. *Prolonged clinical course of two surgically treated cystic pancreatobiliary tumours with mesenchymal*

stroma. International Surgical Week ISW 2009 / the 43th World Congress of the International Society of Surgery, (06.-10.09.2009., Adelaide, Austrālija), *Abstract Book*, 256.

24. I.Štrumfa, I.Melbārde-Gorkuša, **A.Vanags**, E.Miklaševičs, A.Āboliņš, J.Gardovskis. [*The morphological and immunophenotypical traits of breast cancer as an indicator for BRCA1 gene mutation*] [*Abstract in Latvian*] Krūts vēža morfoloģijas un imūnfenotipa īpatnības kā norāde uz *BRCA1* gēna mutāciju. The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2010 (18.-19.03.2010.). Riga, RSU, 2010, p. 276.
25. **A.Vanags**, E.Miklasevics, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *The ethnic distribution of BRCA1 founder mutations 4154delA and 5382 insC in Valka population.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2010 (18.-19.03.2010.). Riga, RSU, 2010, p. 277.
26. **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *Screening for hereditary colorectal cancer in regional population.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2010 (18.-19.03.2010.). Riga, RSU, 2010, p. 278.
27. **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *The first evidence of familial urinary bladder cancer in Latvia.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2010 (18.-19.03.2010.). Riga, RSU, 2010, p. 279.
28. **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *Familial pancreatic cancer by population screening in Valka district.* The Proceedings of the Scientific Conference of Rīga Stradiņš university, 2010 (18.-19.03.2010.). Riga, RSU, 2010, p. 280.
29. **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *The clinical characteristics of familial lung cancer (FLC) by population screening. 2nd European Lung Cancer Conference* (29.-30.04.2010.), Abstract N.127P.
30. **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Āboliņš, G.Trofimovičs, J.Gardovskis. *The first evidence of familial brain tumours in Latvia. Acta Chirurgica Latviensis*, 2010, *Suppl.* 10/1:10-11.
31. **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Āboliņš, G.Trofimovičs, J.Gardovskis. *The characteristics of the hereditary and familial gastric cancer in Latvia by population screening. Acta Chirurgica Latviensis*, 2010, *Suppl.* 10/1:17.
32. I.Štrumfa, **A.Vanags**, A.Āboliņš, G.Volanska, J.Gardovskis. *The diagnostic protocols in surgical oncological pathology. Acta Chirurgica Latviensis*, 2010, *Suppl.* 10/1:80-81.
33. **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Āboliņš, G.Trofimovičs, J.Gardovskis. *The frequency of index cancer in hereditary cancer pedigrees. Acta Chirurgica Latviensis*, 2010, *Suppl.* 10/1:82-83.
34. **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Āboliņš, G.Trofimovičs, J.Gardovskis. *The full spectrum of hereditary and familial cancer by population screening in Valka district. Acta Chirurgica Latviensis*, 2010, *Suppl.* 10/1:84.

Presentations in the congresses and conferences

1) A.Irmejs, A.Gardovskis, V.Borosenko, M. Bitina, **A.Vanags**, I.Melbarde – Gorkusa, G.Kurzawski, J.Suchy, B.Gorski, J.Gardovskis. *Hereditary breast – ovarian cancer in Latvia. 4th Congress of Baltic Association of Surgeons,* 2004, Riga, Latvia.
2) A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, M.Bitiņa, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko. [*The clinical, molecular and geographical peculiarities of hereditary breast-ovarian cancer in Latvia*] P*presentation in Latvian*] Pārmantota krūts – olnīcu vēža klīniskās, molekulārās un ģeogrāfiskās īpatnības Latvijā. The 3rd Congress of the Surgeons of Latvia, 20.05.2005., Riga, Latvia.
3) A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The clinical, molecular and geographical characteristics of hereditary breast – ovarian cancer in Latvia*] [*Presentation in Latvian*] Pārmantota krūts un olnīcu vēža klīniskās, molekulārās un ģeogrāfiskās īpatnības Latvijā. The Scientific Conference of Rīga Stradiņš university, 03.03.2006., Riga, Latvija.
4) A.Irmejs, E.Miklaševičs, V.Borošenko, A.Gardovskis, **A.Vanags**, I.Melbārde-Gorkuša, M.Bitiņa, J.Gardovskis. [*The first data about intermediate penetrance mutations predisposing to colorectal and breast cancer in Latvia*] [*Presentationt in Latvian*] Pirmie rezultāti par vidējas penetrances pakāpes resnās, taisnās zarnas un krūts vēzi predisponējošo gēnu mutāciju īpatnībām Latvijā. The Scientific Conference of Rīga Stradiņš university, 03.03.2006., Rīga, Latvija.
5) A.Irmejs, **A.Vanags**, V.Borosenko, A.Gardovskis, E.Miklasevics, J. Gardovskis. *First results of hereditary cancer population screening in Latvia. Familial cancer conference*, 15.-16.06.2006, Madrid, Spain.
6) V.Borosenko, A.Irmejs, E.Miklasevics, A.Gardovskis, **A.Vanags**, I.Melbārde-Gorkuša, M.Bitina, J.Suchy, J.Gardovskis. *Pilot study on the moderate penetrance breast and colorectal cancer predisposition markers in Latvia. Familial cancer conference*, 15.-16.06.2006, Madrid, Spain.
7) A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M, Bitina, I.Melbarde-Gorkusa, **A.Vanags**, G.Kurzawski, J.Suchy, B.Gorski, J.Gardovskis. *Clinical, molecular and geographical features of hereditary breast – ovarian cancer in Latvia. Familial cancer conference*, 15.-16.06.2006, Madrid, Spain.
8) A.Irmejs, **A.Vanags**, V.Borosenko, A.Gardovskis, E.Miklasevics, J.Gardovskis. *First results of hereditary cancer population screening in Latvia. Eric K.Fernstrom Foundation. Cancer and Genetics. Eric K Fernstrom symposium Cancer and Genetics*, 07.-09.09.2006., Lund, Sweden.
9) E.Miklasevics, V.Borosenko, A.Irmejs, A.Gardovskis, **A.Vanags**, I.Melbarde-Gorkusa, M.Bitina, J.Gardovskis. *First results on the moderate penetrance breast and colorectal cancer predisposition markers in Latvia. Eric K.Fernstrom Foundation. Cancer and Genetics. Eric K Fernstrom symposium Cancer and genetics*, 07.-09.09.2006., Lund, Sweden.
10) A.Gardovskis, A.Irmejs, E.Miklasevics, V.Borosenko, M.Bitina, I.Melbarde-Gorkusa, **A.Vanags**, J.Gardovskis. *Update on hereditary breast – ovarian cancer in Latvia. Eric K.Fernstrom Foundation. Cancer and Genetics. Eric K Fernstrom symposium Cancer and genetics*, 07.-09.09.2006., Lund, Sweden.
11) **A.Vanags,** A.Irmejs, V.Borošenko, A.Gardovskis, E.Miklaševičs, J.Gardovskis. [*The up-to-dated results of the population screening for hereditary cancer*] [*Presentation in Latvian*] Jaunākie pārmantota vēža populācijas skrīninga rezultāti. The Scientific Conference of Rīga Stradiņš university, 29.-30.03.2007., Riga, Latvia.

12) V. Borošenko, A.Irmejs, A.Gardovskis, **A.Vanags**, E.Miklaševičs, I.Melbārde-Gorkuša, M.Bitiņa, J.Gardovskis. [*The novel data in hereditary colorectal cancer screening in Latvia*] [*Presentation in Latvian*] Jaunākie dati par pārmantota kolorektālā vēža skrīningu Latvijā. The Scientific Conference of Rīga Stradiņš university, 29.-30. 03.2007., Riga, Latvia.
13) A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The novel data about the clinical and molecular characteristics of hereditary breast-ovarian cancer in Latvia*] [*Presentation in Latvian*] Jaunākie dati par pārmantotā krūts un olnīcu vēža klīniskajām un molekulārajām īpatnībām Latvijā. The Scientific Conference of Rīga Stradiņš university, 29.-30.03.2007., Riga, Latvia.
14) **A. Vanags**, A.Irmejs, V.Borošenko, A.Gardovskis, E.Miklaševičs, I.Melbārde – Gorkuša, J.Gardovskis. . [*The characteristics of hereditary cancer risk group in population*] [*Presentation in Latvian*] Pārmantotā vēža paaugstinātā riska grupas raksturojums populācijā. The 4th Congress of the Surgeons of Latvia, 31.05.-01.06.2007., Riga, Latvia.
15) A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde – Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The hospital screening for hereditary breast – ovarian cancer in Latvia*] [*Presentation in Latvian*] Pārmantotā krūts – olnīcu vēža hospitālais skrīnings Latvijā. The 4th Congress of the Surgeons of Latvia, 31.05.-01.06.2007., Riga, Latvia.
16) V.Borošenko, A.Irmejs, A.Gardovskis, **A.Vanags**, E.Miklaševičs, I.Melbārde – Gorkuša, M, Bitiņa, J.Gardovskis. [*The hospital and population screening for hereditary colorectal cancer in Latvia*] [*Presentation in Latvian*] Pārmantota kolorektāla vēža hospitālais un populācijas skrīnings Latvijā. The 4th Congress of the Surgeons of Latvia, 31.05.-01.06.2007., Riga, Latvia.
17) **A.Vanags**, A.Irmejs, E.Miklaševičs, A.Gardovskis, V.Borošenko, J.Gardovskis. *Population screening for hereditary cancer in Valka region: final results.* The Scientific Conference of Rīga Stradiņš university, 13.-14.03.2008., Riga, Latvia.
18) V.Borošenko, A.Irmejs, I.Melbārde-Gorkuša, A.Gardovskis, **A.Vanags**, M.Pavārs, E.Miklaševics, W.Friedl, J.Gardovskis. *First results on polyposis research in Latvia.* The Scientific Conference of Rīga Stradiņš university, 13.-14.03.2008., Riga, Latvia.
19) A. Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The clinical, epidemiological and molecular characteristics of hereditary breast – ovarian cancer in Latvia*] [*Presentation in Latvian*] Pārmantotā krūts – olnīcu vēža klīniskais, epidemioloģiskais un molekulārais raksturojums Latvijā. The Scientific Conference of Rīga Stradiņš university, 13.-14.03.2008., Riga, Latvia.
20) A.Gardovskis, A.Irmejs, E.Miklaševičs, **A.Vanags**, I.Melbārde-Gorkuša, J.Gardovskis, V.Borošenko, M.Bitiņa. [*The hospital screening for hereditary breast and ovarian cancer in ovarian cancer patients*] [*Presentation in Latvian*] Pārmantotā krūts un olnīcu vēža hospitālais skrīnings olnīcu vēža pacientēm Latvijā. The Scientific Conference of Rīga Stradiņš university, 02.-03.04.2009., Riga, Latvia.
21) V.Borosenko, A.Irmejs, I.Melbarde-Gorkusa, A.Gardovskis, M.Pavars, L.Svampane, **A.Vanags**, I.Strumfa, E.Miklasevics, G.Trofimovics, J.Gardovskis. *Initial results of colorectal cancer determined low penetrance genes research in Latvia.* The Scientific Conference of Rīga Stradiņš university, 02.-03.04.2009., Riga, Latvia.
22) **A.Vanags**, I.Strumfa, A.Irmejs, E.Miklasevics, J.Gardovskis. *Population screening for hereditary cancer: a novel, effective tool in early cancer diagnostics. International*

Surgical Week ISW 2009 / the 43th World Congress of the International Society of Surgery, Adelaide, Australia, 06.-10.09.2009.

23) **A.Vanags**, M.Pavars, I.Strumfa, J.Gardovskis. *Prolonged clinical course of two surgically treated cystic pancreatobiliary tumours with mesenchymal stroma. International Surgical Week ISW 2009 / the 43th World Congress of the International Society of Surgery*, Adelaide, Australia, 06.-10.09.2009.

24) I.Štrumfa, I.Melbārde-Gorkuša, **A.Vanags**, E.Miklaševičs, A.Ābolinš, J.Gardovskis. [*The morphological and immunophenotypical traits of breast cancer as an indicator for BRCA1 gene mutation*] [*Presentation in Latvian*] Krūts vēža morfoloģijas un imūnfenotipa īpatnības kā norāde uz *BRCA1* gēna mutāciju. The Scientific Conference of Rīga Stradiņš university, 18.-19.03.2010., Riga, Latvia.

25) *The ethnic distribution of BRCA1 founder mutations 4154delA and 5382 insC in Valka population.* **A.Vanags**, E.Miklasevics, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. The Scientific Conference of Rīga Stradiņš university, 18.-19.03.2010., Riga, Latvia.

26) *Screening for hereditary colorectal cancer in regional population.* **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. The Scientific Conference of Rīga Stradiņš university, 18.-19.03.2010., Riga, Latvia.

27) *The first evidence of familial urinary bladder cancer in Latvia.* **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. The Scientific Conference of Rīga Stradiņš university, 18.-19.03.2010., Riga, Latvia.

28) *Familial pancreatic cancer by population screening in Valka district.* **A.Vanags**, I.Strumfa, A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. The Scientific Conference of Rīga Stradiņš university, 18.-19.03.2010., Riga, Latvia.

29) *The clinical characteristics of familial lung cancer (FLC) by population screening.* A.Vanags, **I.Strumfa,** A.Gardovskis, V.Borosenko, A.Abolins, G.Trofimovics, J.Gardovskis. *2nd European Lung Cancer Conference* (29.-30.04.2010.),Nr.127P, Geneva, Switzerland.

30) *The first evidence of familial brain tumours in Latvia.* **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Ābolinš, G.Trofimovičs, J.Gardovskis. *5th Baltic Congress of Oncology,* 14.-15.05.2010., Riga, Latvija.

31) *The characteristics of the hereditary and familial gastric cancer in Latvia by population screening.* **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Ābolinš, G.Trofimovičs, J.Gardovskis. *5th Baltic Congress of Oncology,* 14.-15.05.2010., Riga, Latvija.

32) *The diagnostic protocols in surgical oncological pathology.* I.Štrumfa, **A.Vanags**, A.Ābolinš, G.Volanska, J.Gardovskis. *5th Baltic Congress of Oncology,* 14.-15.05.2010., Riga, Latvija.

33) *The frequency of index cancer in hereditary cancer pedigrees.* **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Ābolinš, G.Trofimovičs, J.Gardovskis. *5th Baltic Congress of Oncolog),* 14.-15.05.2010., Riga, Latvija.

34) *The full spectrum of hereditary and familial cancer by population screening in Valka district.* **A.Vanags**, I.Štrumfa, A.Gardovskis, V.Borošenko, A.Ābolinš, G.Trofimovičs, J.Gardovskis. *5th Baltic Congress of Oncology,* 14.-15.05.2010., Riga, Latvija.