Epidemiologic, Clinical, and Molecular Characteristics of Hereditary Prostate Cancer in Latvia

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Key words: *hereditary prostate cancer; BRCA1; NBS1.*

Summary. *Background and Objective. Prostate cancer is one of the most commonly diagnosed malignancy affecting men in Latvia. The aim of this study was to evaluate the epidemiological features and molecular basis of hereditary prostate cancer in Latvia.*

Material and Methods. A total of 1217 newly diagnosed prostate cancer patients were recruited in our study. Data were analyzed according to clinical diagnostic criteria for hereditary prostate cancer. Molecular testing for the founder mutation 657del5 of the NBS1 gene was performed for the first 280 prostate cancer patients and 173 control cases, and for the founder mutations 300T/G, 4153delA, and 5382insC of the BRCA1 gene for 112 prostate cancer patients with a history of breast or ovarian cancer in their families.

Results. Of the 1217 families, 14 (1.2%; 95% CI, 0.7%–1.9%) matched clinical diagnostic criteria for definitive hereditary prostate cancer, and of the 1217 families, 196 (16.1%; 95% CI, 14.1%–18.3%) for suspected hereditary prostate cancer. The founder mutation of the NBS1 gene was detected in 1 (0.4%, 95% CI, 0.1%–2.0%) of the 280 cases in the prostate cancer group and in 1 (0.6%; 95% CI, 0.1%–3.2%) of the 173 cases in the control group. The mutation 5382insC of the BRCA1 gene was detected in 2 (1.8%; 95% CI, 0.5%–6.3%) of the 112 cases analyzed in the prostate cancer group. No other BRCA1 founder mutations were detected.

Conclusions. Our study did not reveal predisposition genes for hereditary prostate cancer as the founder mutations of the BRCA1 and NBS1 genes are rarely detected in Latvia, but showed the importance of evaluation risk individually as a positive family history of cancer was associated with the earlier onset of prostate cancer.

Introduction

Prostate cancer is one of the most commonly diagnosed cancers among men worldwide with a significant difference in incidence rates among the world's geographic regions; during the past 15 years, it has become an important concern of public health (1). The highest incidence has been reported in the Scandinavian countries, with an intermediate incidence being reported in the United States and the United Kingdom and the lowest being in the Far East, especially in China and Japan (2). In the United States and Sweden, prostate cancer is the most common cancer of all malignancies, ahead of lung cancer (3). In 2008, around 338 000 men were diagnosed with prostate cancer in Europe (4). The lowest European incidence rates are in Southern and Eastern Europe, and the highest rates are found in Northern and Western Europe (Fig. 1). Prostate cancer is the second most commonly diagnosed malignancy in men after lung cancer in Latvia (Fig. 2).

The prevalence and incidence rates for prostate cancer in Latvia are increasing year by year: from 1813 cases in 2000 to 4850 cases in 2010 and from 522 cases in 2000 to 855 cases in 2010, respectively (Fig. 3). Despite a wide range of diagnostic measures and aggressive treatment, the mortality rate from prostate cancer has not changed significantly and is one of the major causes of death among men in Latvia.

Progression of prostate cancer is a complex interaction of molecular, environmental, and possibly social factors (5). Family cancer history is an important screening tool for identification of high-risk patients groups with inherited cancer. It is important to differentiate molecular and environmental risk factors affecting the progression of prostate cancer, and family cancer history is a helpful tool that captures some of these risk aspects (6). Although environment, diet, lifestyle, sex hormones, and genetic predisposition of individuals are all risk factors for prostate cancer, a positive family history of prostate cancer is the most important clinical risk factor. According to a Nordic study of twins, hereditary factors play a much greater role in the etiology of prostate cancer than in that of any other malignancy (7).

Many studies on several alleles indicate the conferring of dominantly inherited susceptibility for prostate cancer with high penetrance, causing multiple cases of prostate cancer in a family. However,

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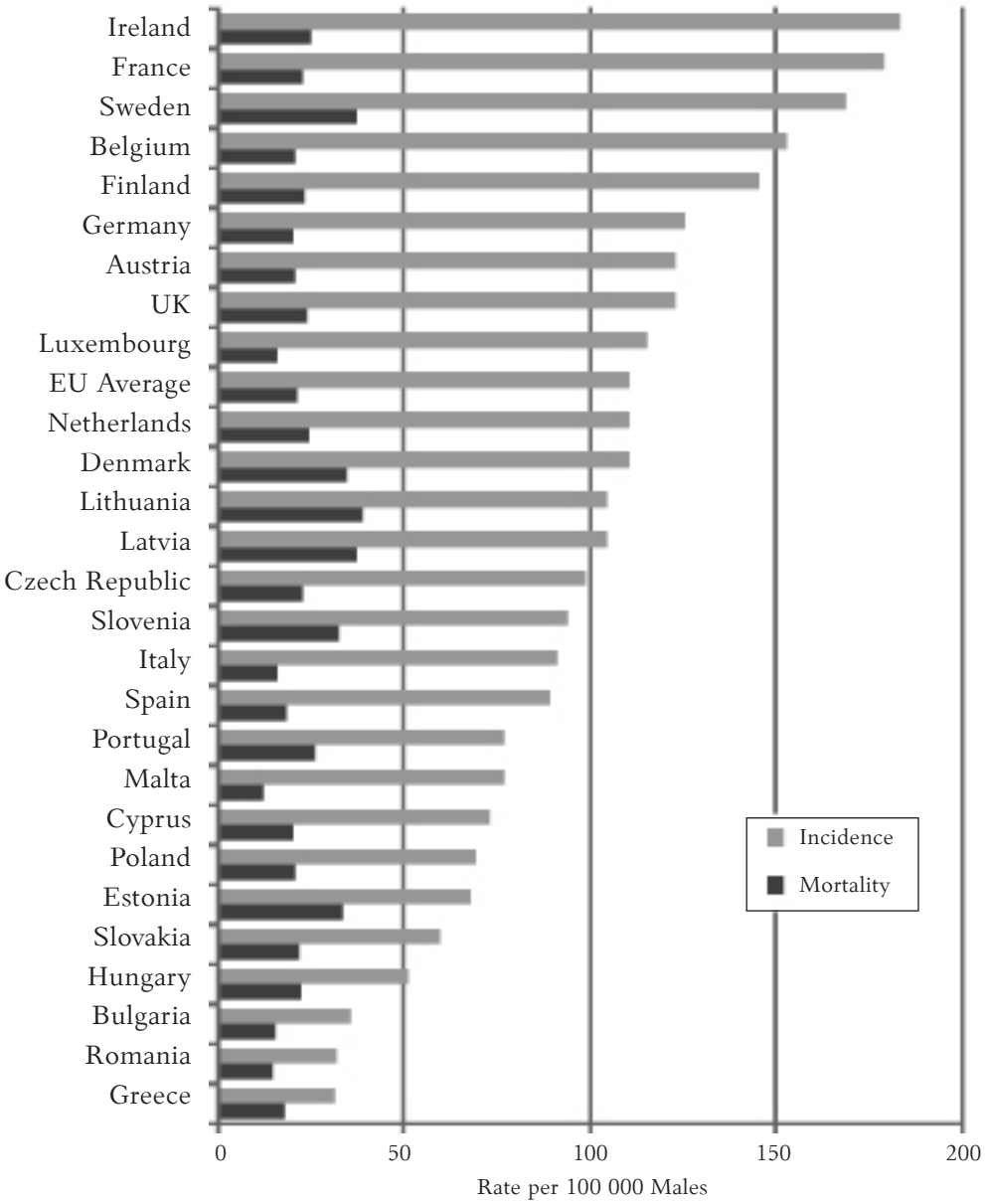

Fig. 1. Age-standardized prostate cancer incidence and mortality rate by country (year 2008 estimates)

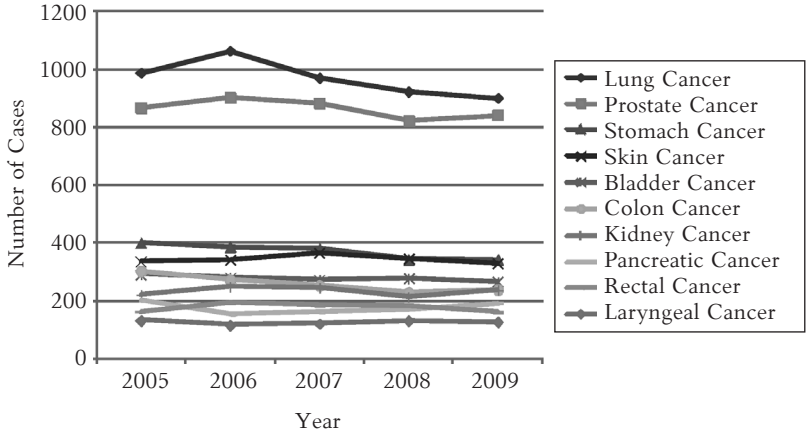

Fig. 2. Ten most common malignancies among men during 2005–2009
Source: Latvian Centre of Health Economics Data, 2009.

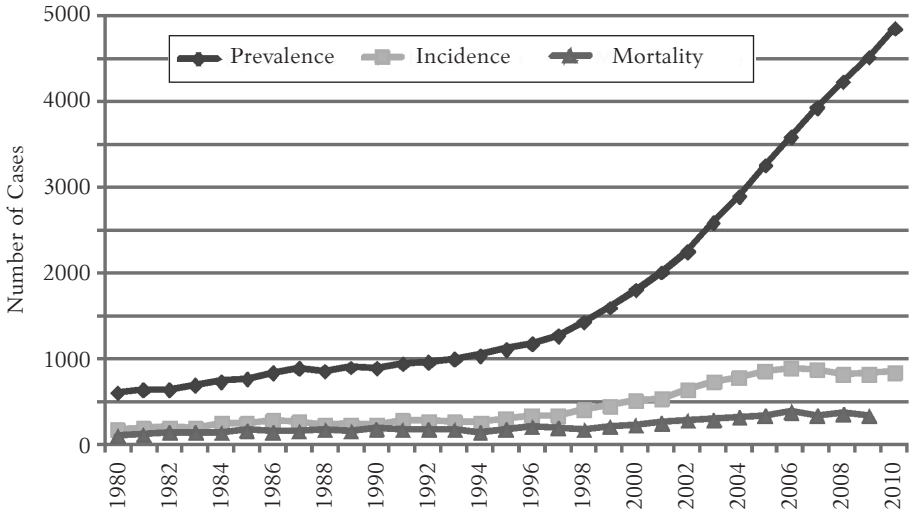

Fig. 3. Prostate cancer prevalence, incidence, and mortality rates in absolute numbers
Source: Latvian Centre of Health Economics Data, 2010.

the genes involved in predisposition to hereditary prostate cancer have not been identified. This may be due to the fact that several genes with small-to-moderate effect are involved in carcinogenesis. Epidemiologically prostate cancer can be divided into hereditary and sporadic forms (8), but it is not possible to distinguish these two groups at the molecular level. Although possible inherited prostate cancer susceptibility genes, such as *BRCA1*, *BRCA2*, *ELAC2*, *RNASEL*, *MSR1*, *NBS1*, and *CHEK2*, have been identified in some families, the proportion of cases of hereditary prostate cancer attributable to germ line mutations in these loci is small (9–12). Many studies have not proven the role of these genes in hereditary prostate cancer (13). Mutations of these candidate genes have also been identified in sporadic prostate cancer. Because prostate cancer is a common cancer, it may be difficult to distinguish the clustering of sporadic prostate cancers within families from true hereditary prostate cancer.

Genome research is a complex and time-consuming process. Revealing the most frequent mutations in the Latvian population could considerably improve the presymptomatic diagnosis of prostate cancer. As no detailed studies have been done in Latvia, the aim of the present study was to evaluate the epidemiological features and molecular basis of hereditary prostate cancer in Latvia, and to consider the clinical implications of our findings.

Material and Methods

This was a prospective study involving 1217 patients with newly diagnosed prostate cancer from all regions of Latvia identified at the largest oncology hospitals. All patients for our study were selected and identified from November 2003 to March 2011. All patients were enrolled in the study regardless of TNM stage, Gleason's score, ethnicity, or health status.

Data on clinical characteristics including age at diagnosis, individual nationality, and family cancer history were collected using a standardized questionnaire previously tested in hospital- and population-based screening (14, 15). Prostate cancer patients were asked if their blood relatives had had any malignancy. Further, information on cancer localization, age of cancer diagnosis, and age at death, if applicable, was collected. Completed questionnaires were analyzed separately depending on positive (at least one malignancy of any localization among blood relatives) or negative (no malignancy among blood relatives) data of family cancer history. Table 1 summarizes the characteristics of patients with prostate cancer by age groups in association with a family history of prostate cancer. Family cancer histories matching hereditary cancer syndrome were analyzed according to the clinical diagnostic criteria of hereditary prostate cancer (Table 2). All patients were invited for additional consultation and were offered molecular diagnostics. If patients agreed, peripheral venous blood samples were collected. Molecular examination was performed for the first 280 prostate cancer patients and 173 control cases for the founder mutation 657del5 of the *NBS1* gene and 68 prostate cancer patients for the founder mutations 300T/G, 4153delA, and 5382insC of the *BRCA1* gene if any case of breast or ovarian cancer was observed in their family. Blood samples of the control group were collected from the clamped distal part of the umbilical cord in consecutive anonymous newborns.

Statistical data analysis was carried out with the CIA (DOS program Confidence Interval Analysis)

Table 1. Characteristics of Prostate Cancer Cases by Age Groups in Association With Family Cancer History at Age of Diagnosis

Age Group, Years	No. of Cases	Family Cancer History	
		Positive	Negative
		n (%)	n (%)
⩽44	1	1 (100.0)	0 (0.0)
45–49	17	13 (76.5)	4 23.5
50–54	70	61 (87.1)	9 (12.9)
55–59	160	98 (61.3)	62 (38.8)
60–64	275	154 (56.0)	121 (44.0)
65–69	318	144 (45.3)	174 (54.7)
70–74	212	106 (50.0)	106 (50.0)
75–79	119	47 (39.5)	72 (60.5)
80–84	33	11 (33.3)	22 (66.7)
⩾ 85	12	5 (41.7)	7 (58.3)
Total	1217	640 (52.6)	577 (47.4)

Table 2. Clinical Diagnostic Criteria of Hereditary Prostate Cancer

Definitive Hereditary Prostate Cancer	Suspected Hereditary Prostate Cancer
1) At least 3 blood relatives with prostate cancer at any age or	1) Two blood relatives with prostate cancer at any age or
2) Two blood relatives with prostate cancer diagnosed before the age of 55 years in both of them	2) A case of prostate cancer diagnosed before the age of 55 years

software (16). The study was approved by the Drug and Pharmaceutical Product Research Ethics Committee of Latvia. Written informed consent was obtained from all the patients.

Results

In total, 1217 family cancer histories were analyzed; 640 families (52.6%; 95% CI, 49.8% to 55.4%) were found to have a positive family history of cancer, and 577 families (47.4%; 95% CI, 44.6% to 50.2%) had no family cancer history. Our series showed the relationship between family cancer history and age at the onset of prostate cancer: individuals with a positive family history of cancer were younger at the onset of prostate cancer than individuals with a negative family history of cancer (Fig. 4).

Of the 1217 families, 14 (1.2%; 95% CI, 0.7% to 1.9%) matched the definitive clinical diagnostic criteria of hereditary prostate cancer, and of the 1217 families, 196 (16.1%; 95%, CI, 14.1% to 18.3%) matched suspected clinical diagnostic criteria of hereditary prostate cancer. In our study, the median age at diagnosis was 64.1 years (range, 51–74 years) in the definitive hereditary prostate cancer group and 58.5 years (range, 42–85 years) in the suspected hereditary prostate cancer group. At least 1 other cancer was found among blood relatives in 9 (64.3%; 95% CI, 38.8% to 83.7%) of the 14 family cancer histories of the definitive hereditary prostate cancer group and in 87 (44.4%; 95% CI, 37.6% to 51.4%) of the 196 family cancer histories of the suspected hereditary prostate cancer group. A more detailed summary of characteristics of the most frequently diagnosed malignancies among blood relatives is provided in Figs. 5 and 6.

Equally, a founder mutation of the *NBS1* gene was detected in 1 (0.4%; 95% CI, 0.1% to 2.0%) of the 280 cases in the prostate cancer group and in 1 (0.6%; 95% CI, 0.1% to 3.2%) of the 173 cases in the control group. The individual from the prostate cancer group was a 68-year-old male with a negative family history of cancer. As the control group data were anonymous, no data concerning family cancer history were available.

Of the 112 samples analyzed in the prostate cancer group, 2 cases (1.8%; 95% CI, 0.5% to 6.3%) of 5382insC mutation of the *BRCA1* gene were iden-

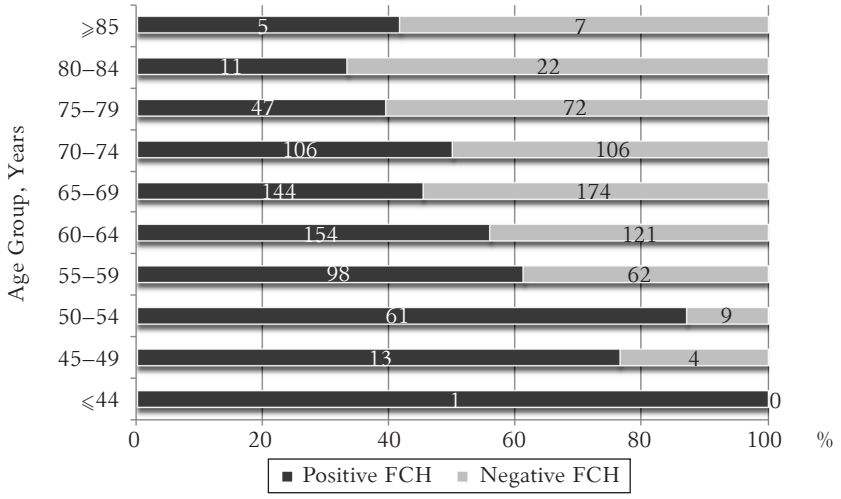

Fig. 4. Percentage distribution of cases with positive and negative family cancer history (FCH) by age at the onset of prostate cancer

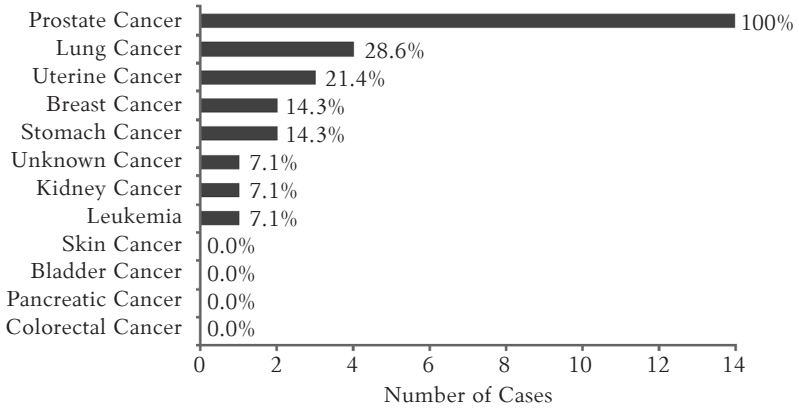

Fig. 5. Percentage distribution of the most frequently diagnosed malignancies among blood relatives in the definitive hereditary prostate cancer group

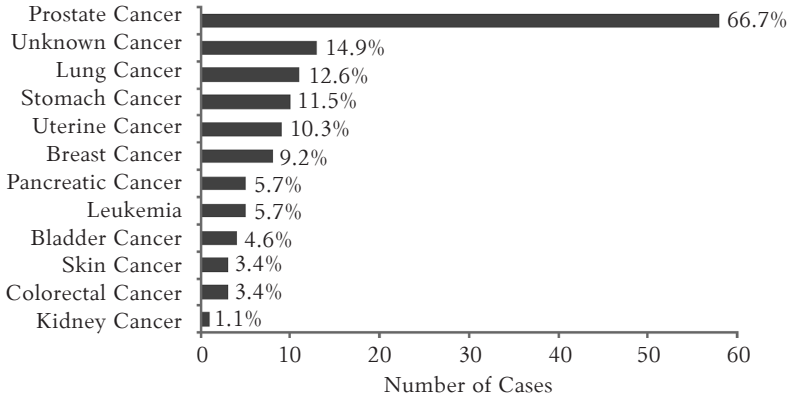

Fig. 6. Percentage distribution of the most frequently diagnosed malignancies among blood relatives in the suspected hereditary prostate cancer group

tified. The first individual was a 66-year-old male with a positive family history of cancer (2 sisters with breast cancer and father's brother with gastric cancer). The second individual was a 70-year-old male from the family matching the clinical diagnostic criteria of hereditary breast cancer. No other *BRCA1* founder mutations were detected.

Discussion

Although it is thought that 5% to 10% of prostate cancer cases are hereditary (17), our study revealed a relatively low proportion of families with definitive inheritance and high proportion of families with suspected inheritance (1.3% vs. 14.1%). As clinical definition of hereditary prostate cancer is based on the data of family cancer history, any missing part of information is critical. Therefore, any family with no other malignancies among relatives should be carefully evaluated and considered as incomplete as data could be missing due to loss of contact during wartime, deportation, and migration in the middle of the 20th century in Latvia.

Except for younger age at diagnosis, no phenotypic features have been clearly associated with hereditary prostate cancer (18). Our data did not reveal a significant difference in the median age at diagnosis of prostate cancer comparing the definitive and suspected hereditary prostate cancer groups.

The molecular pathology of prostate cancer is complex; not only multiple genes are involved in its pathogenesis, but additional environmental factors as well (5). The *BRCA1*, *BRCA2*, *NBS1*, and *CHEK2* genes have been only recently identified as possible prostate cancer susceptibility genes. *ELAC2* was the first hereditary prostate cancer susceptibility gene identified, and subsequent studies have not confirmed the evidence for its role in prostate cancer (19). Therefore, it is not possible to comment on the importance of these genes in hereditary prostate cancer until additional confirmatory studies have been performed.

A study from southern Sweden (n=356) revealed that 15% of patients with prostate cancer had at least 1 case of prostate cancer among their brothers or fathers. Based on the family history, 3.1% were classified as having hereditary prostate cancer. Fur-

thermore, this proportion was significantly higher among patients diagnosed before the age of 60 years than among older patients (7.1% vs. 2.2%) (20).

A systematic genealogy study from France (n=691) confirmed the data of earlier studies, revealing a 3.6% prevalence of hereditary forms of prostate cancer. Analysis of the results according to the age at diagnosis of prostate cancer showed a higher incidence of hereditary forms occurring at younger age, i.e., before the age of 65 years. Similarly, the study confirmed the earlier onset of prostate cancer in patients with a genetic predisposition (21).

Both positive and negative studies have been published showing the increased risk of prostate cancer in *BRCA1* and *BRCA2* mutation carriers (22–24). To establish the influence of the *BRCA1* gene, 1793 men with prostate cancer and 4570 controls were genotyped for founder mutations (C61G, 4153delA, and 5382insC) in Poland. The results showed a higher frequency of the 4153delA mutation in prostate cancer cases (0.22%) than controls (0.04%). Data suggest that the 5382insC mutation is unlikely to be pathogenic for prostate cancer in the Polish population as it was more frequently present in the control population than in the prostate cancer group (25). In our study, of the 68 individuals analyzed, only 1 case was found to carry the mutation 5382insC in the *BRCA1* gene. This may be explained by the high proportion of the Slavic population in Latvia. Although there are data confirming a more aggressive prostate cancer phenotype for *BRCA1* and *BRCA2* mutation carriers, it was not considered for analysis in our study as the number of cases was limited (26, 27).

A recent study has reported that *BRCA2* carriers with prostate cancer have a poorer survival rate than noncarrier with prostate cancer. In this study, the survival rate of men with the *BRCA2* mutation and prostate cancer (n=182) was compared with that of men with the *BRCA1* mutation and prostate cancer (n=119). The median survival rate from diagnosis was 4.0 years for men with the *BRCA2* mutation and 8.0 years for men with the *BRCA1* mutation, with a highly significant difference (28).

The frequency of the *NBS1* gene mutation in the German population is 1 per 866 people (29). In comparison, a remarkably high carrier frequency of the 657del5 mutation in the *NBS1* gene was detected in the Slavic populations: 1 per 154 in the Czech Republic, 1 per 190 in Poland, and 1 per 182 in Ukraine (30). Our data failed to support the involvement of the *NBS1* gene in our prostate cancer cases, as no statistically significant difference between the prostate cancer and control groups was detected in Latvia (1 per 280 vs. 1 per 173). This supports previous studies and confirms geographical and racial differences among populations.

Conclusions

Increased incidence rates for prostate cancer in Latvia may be the result of improved detection and better awareness of the disease rather than a true increase in the prevalence of the disease. Our study did not reveal predisposition genes for hereditary prostate cancer as the founder mutations of the *BRCA1* and *NBS1* genes are rarely detected in Latvia. We observed a insignificant difference in the frequency of *BRACA1* and *NBS1* founder mutations between prostate cancer and the control group; this may be explained by geographical differences and the relatively high proportion of mixed ethnic groups in Latvia. Our epidemiological series show a lower incidence of hereditary prostate cancer in Latvia compared with the data from other populations. The main reason affecting this may be an incomplete family cancer history due to the loss of contact with relatives.

This emphasizes the importance of evaluation of family cancer history as individuals with a positive family history of cancer (at least one malignancy of any localization among blood relatives) have an earlier onset of prostate cancer than individuals with a negative family history of cancer (no malignancy cases among blood relatives).

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Statement of Conflict of Interest

The authors state no conflict of interest.

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