

Ovarian cancer in Latvia is highly attributable to recurrent mutations in the *BRCA1* gene

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Abstract

Most hereditary ovarian cancers are associated with germline mutations in the *BRCA1* and *BRCA2* genes. The aim of this study was to estimate the role of *BRCA1* mutations in ovarian cancer in Latvia and to determine the mutation profile and frequency of founder mutations in ovarian cancer patients. The analysis of the entire *BRCA1* gene was carried out in 34 ovarian cancer patients by SSCP/HD analysis and automatic sequencing of the variants detected. The screening for founder mutations was performed in 75 ovarian cancer patients recruited for the Project “Genome database of Latvian population” and in 86 consecutive ovarian cancer patients treated at the Latvian Oncology Centre. Six of seven pathogenic mutation carriers identified by the analysis of the entire *BRCA1* gene were carriers of founder mutations. A high proportion of *BRCA1* mutation carriers was revealed also by the screening for recurrent mutations. Altogether 44 mutation carriers in 195 ovarian cancer patients were identified in our study. The high frequency (24.6 %) of two founder mutations in Latvian ovarian cancer patients allow us to suggest that testing for these mutations should be offered to all women with ovarian cancer diagnosed before the age of 65 years.

Key words: *BRCA1* gene, founder mutations, genetic testing, Latvian population, ovarian cancer.

Introduction

Despite significant advances in therapy over the past 30 years, ovarian cancer remains the most deadly gynaecological cancer with over 100,000 deaths worldwide. Most women with ovarian cancer still develop recurrent disease and die within five years. Minimal symptoms in the early stages of the disease and the concealed position of the ovaries in the abdomen mean that only 30 % of patients are diagnosed with early-stage disease. Treating patients at an early stage of the disease remains the most important factor in successful treatment.

It has been noted that ovarian cancer tends to cluster in some families and significant impact of genetic factors in ovarian cancer development have been detected. The discovery of the breast/ovarian cancer susceptibility genes *BRCA1* (Miki et al. 1994) and *BRCA2* (Wooster et al. 1995) facilitated detection of individuals predisposed to cancer. These tumour suppressor genes are involved in many important cellular processes, including DNA damage recognition, DNA repair, chromatin remodelling and control of transcription. Inactivating germline mutations in *BRCA1* and *BRCA2* genes account

for highly penetrant cancer predisposition, mostly limited to carcinomas of breast and ovaries. Inherited mutations in the genes predisposing to cancer are considered now as most important risk factors. The characteristic features of hereditary cancer cases are earlier onset of disease and recurrence of cancer with high probability.

The mutation prevalence and spectrum in the *BRCA1* gene have been assessed in different populations (Risch et al. 2001; Sarantaus et al. 2001; Meindl 2002; Menkiszak et al. 2003) and the screening for identification of individuals with elevated risk of cancer is widely used in clinics of all developed countries. The nature of germline mutations depends on the ethnicity of population. Recurrent mutations has been identified in the Ashkenazi Jewish population, and another recurrent mutation was identified in the Icelandic population (Liede, Narod 2002). Similarly, founder effects have been observed in Eastern European populations (Gayther et al. 1997; Csokay et al. 1999; Gorski et al. 2000; Oszurek et al. 2001). A high prevalence of recurrent mutations facilitates the identification of the risk individuals. Early diagnosis of cancer is associated strongly with better survival of patients. Screening procedures has been shown to reduce breast cancer mortality by approximately 35 % (Vainio, Bianchini 2002), and even more in ovarian cancer patients.

The lifetime risk of ovarian carcinoma has been estimated to be ~60 % in *BRCA1* mutation carriers (Easton et al. 1995) and ~30 % in *BRCA2* mutation carriers (Ford et al. 1998).

Early molecular changes has been analysed in ovaries removed prophylactically from *BRCA1* mutation carriers who are at significant risk for ovarian cancer development, and a higher rate of potentially premalignant lesions was revealed compared to controls (Werness et al. 1999). However, contrary results have been published as well (Stratton et al. 1999). Phenotypic differences have been detected in ovarian surface epithelium in women from families with a cancer history and in women with no cancer in their family, and more data are needed to understand better the difference between hereditary and sporadic cancers to tailor better the therapeutic and prophylactic procedures to individual patients.

The diagnosis of hereditary breast/ovarian cancer syndrome indicates that the development of ovarian cancer several years after breast cancer may represent the common case and that the knowledge about the genetic basis of disease may be very useful for appropriate management of cancer patients.

Nearly 300 women are diagnosed with ovarian cancer in Latvia annually and a high mortality of women with ovarian cancer is associated with late diagnosis of disease (approximately 70 % of them are diagnosed at stages III - IV).

The aim of our study was to estimate the hereditary fraction of ovarian cancer in the Latvian population, to characterise the mutation spectrum of *BRCA1* gene in ovarian cancer patients and to assess the possibilities and criteria for identification of women with elevated risk of ovarian cancer.

Materials and methods

Permission for the study of hereditary ovarian cancer was obtained from the Central Ethics Committee of Latvia.

Ovarian cancer patients were recruited at the Latvian Oncology Center (LOC). The

criteria for including patients in mutation analysis of the entire *BRCA1* gene were the following:

- (i) agreement of the patient to participate in *BRCA1* gene testing,
- (ii) diagnosis of ovarian cancer before the age of 55 years,
- (iii) breast and/or ovarian cancer in the family and the diagnosis of ovarian cancer before the age of 61 years.

Three recurrent mutations were screened in ovarian cancer patients recruited for the National project “Genome database of Latvian population”. Information concerning the personal and family history of cancer was obtained from questionnaires filled by the patients. Screening for 4154delA and 5382insC mutations in consecutive ovarian cancer patients treated at LOC was carried out also.

The DNA was isolated from blood by standard phenol-chloroform procedure and from blood of consecutive ovarian cancer patients by a non-enzymatic salting out procedure.

Oligonucleotide PCR primers for exons 2 - 10 and 12 - 24 were used according to Friedman et al. (1994) and according to sequences available in the BIC (Breast cancer information core) database (<http://research.nhgri.nih.gov/projects/bic>) for exon 11.

Amplification reactions for all coding exons including flanking intronic sequences of the *BRCA1* gene (40 different fragments – 220 - 350 bp) were performed using the reagent kit (Fermentas, Lithuania) and the PTC 100 (MJ Research Inc., USA) thermocycler.

Amplified DNA fragments were analysed for mutations by SSCP (single strand conformation polymorphism) and/or HD (heteroduplex) analysis. Gels were visualised by silver staining.

The analysis of recurrent mutations was carried out by two or three loadings of samples on each gel with appropriate intervals. A positive control was included in each loading.

The DNA was reamplified if variant bands were detected, and the PCR product was directly sequenced using the ABI 3100 PRISM Genetic Analyser (Applied Biosystems, USA). The sequencing reactions were performed using an Amersham Exo (exonuclease I) and SAP (shrimp alkaline phosphatase) pre-sequencing kit and a BigDye Terminator Cycle Sequencing Kit.

Results and discussion

The analysis of the entire *BRCA1* gene was carried out in 34 ovarian cancer patients to characterise the mutation profile in ovarian cancer patients in the Latvian population.

Seven carriers of four different deleterious mutations (5382insC, 4154delA, 300T>G and 962del4) were detected by the analysis of the entire *BRCA1* gene (Table 1). The 962del4 mutation was reported earlier in Austria and Germany (Meindl et al. 2002), but it was not detected in our previous studies of breast cancer patients (Csokay et al. 1999; Tihomirova et al., unpublished data).

Missense mutations of uncertain clinical significance were detected as well: 162A>G (novel, not registered in the BIC database), 1186A>G and 4158A>G. Several common polymorphisms were observed in this study: 3232A>G, 3634A>G, 3667A>G, 4227T>C, 5272+66G>A and others (in exons 8, 9, 12, 17).

Seventy-five ovarian cancer patients were screened for three recurrent mutations prevalent amongst breast cancer patients in Latvia and detected also by the analysis of the entire *BRCA1* gene in ovarian cancer patients. One 300T>G mutation carrier, six

Table 1. *BRCA1* gene mutation analysis in ovarian cancer patients from Latvia (number of carriers detected). *, pathogenic mutations: 5382insC, 4154delA, 300T>G, 962del4

	No. of patients	Age range (average age)	No. of pathogenic mutation carriers*
Analysis of the entire gene	34	20 - 61 (43.5)	7
Screening for three mutations (5382insC, 415delA, 300T>G)	75	24 - 71 (50.3)	18
Screening for two mutations (5382insC, 4154delA)	86	34 - 81 (60.7)	19

4154delA and eleven 5382insC mutation carriers were identified (Table 1).

A high proportion of mutation carriers (19 of 86) was detected by the screening for two recurrent mutations in the group of consecutive ovarian cancer patients (Table 1), in spite of the fact that such criteria as early onset of the disease or positive family history of cancer were not applied in this patient group.

The analysis of family history data given by patients included in this study allows us to characterise the most prevalent cancer sites in families of *BRCA1* mutation carriers identified (Table 2).

The *BRCA1* mutation spectrum in Latvian ovarian cancer patients differs insignificantly from that in breast cancer patients. Three pathogenic founder mutations (5382insC, 4154delA and 300T>G) detected in our studies of breast cancer patients were found in ovarian cancer patients approximately in the same proportions and women with founder mutations make up 86 % of mutation carriers identified.

Apart from protein-truncating recurrent mutations, the analysis of the entire *BRCA1* gene resulted in detection of the unique *BRCA1* frameshift mutation 962del4 and the unique missense mutation 162A>G in ovarian cancer patients of Latvian ethnicity. Two known missense mutations (1186A>G and 4158A>G) with unclear significance and several common polymorphisms were identified as well. 962del4, 4154delA and 5382insC are pathogenic protein-truncating mutations.

The 300T>G missense mutation leads to substitution of cysteine to glycine in an important RING-finger domain of *brca1* protein and its strong pathogenic nature was proved unambiguously. In contrast to other Eastern European countries (Hungary, Poland) and Germany (Neuhausen 2000) the frequency of this mutation in Latvia is significantly lower. This fact was confirmed by the additional screening in another 100 breast/ovarian cancer patients with early onset of disease and a family history of cancer in most of them (unpublished).

The frequencies of pathogenic mutation carriers were similar in all patient groups tested: 20.6 % of mutation carriers were identified by the analysis of the entire *BRCA1* gene in 34 patients, 24.0 % mutation carriers by screening for three mutations in patients who donated blood for the Genome Database of the Latvian population, and 22.1 % by screening for two mutations in consecutive ovarian cancer patients (Table 1). Mutation analysis of the entire *BRCA1* gene is laborious because of the large size of the gene and the diversity of mutations detected. The results of our study indicate that the screening for

Table 2. Cancer sites reported in families of *BRCA1* mutation carriers

Cancer site	Number of cases
Breast	12
Ovary	10
Colon, rectum	9
Uterus	6
Lung	6
Kidney	2
Prostate	2
Stomach	2
Melanoma	1
Liver	1
Pancreas	1
Cervix	1
Neuroblastoma	1
Other	5

only two mutations (5382insC and 4154delA) allows easy identification of the majority of women with high risk of breast and ovarian cancer.

Studies of consecutive ovarian cancer patients unselected for age or family history provide useful information regarding the contribution of germline *BRCA1/2* mutations to ovarian cancer occurrence in a population. These studies have been performed in many populations with founder *BRCA1* or/and *BRCA2* mutations.

The proportion of the two founder mutations in unselected ovarian cancer patients in our population (22.1 %) is lower than the frequency of founder mutations in the Israel Ashkenazi Jewish population (29.0 %; Modan et al. 2001), but higher than in Polish (13.5 %; Menkiszak et al. 2003), Finnish (8.6 %; Sarantaus et al. 2001), Hungarian (11.0 %; Van Der Looji et al. 2000) and French Canadian (8.1 %; Tonin et al. 1999) populations.

The proportion of ovarian cancer cases diagnosed in different age groups is shown in Fig. 1A and the proportion of *BRCA1* mutation carriers identified in the same age groups are shown in the Fig. 1B. These figures show that the major proportion of mutation carriers among ovarian cancer patients can be identified by the screening of women diagnosed before 65 years.

The data concerning cancer history in the family reported by *BRCA1* mutation carriers (Table 2) show that, apart from breast and ovarian cancer in the family (the main criterion used for genetic testing of hereditary cancer), other cancer sites were reported as well. Colorectal, uterine and lung cancers are reported more frequently. Thus, the presence of other cancers in the family history is very important information for genetic counselling and important criterion to offer *BRCA1* testing in these families.

It has been suggested that ovarian cancer risk depends on the localisation of mutation in the *BRCA1* gene (Gayther et al. 1995). Mutations in the 3'-end of the *BRCA1* gene are more strongly associated with breast cancer and mutations in the middle of the gene

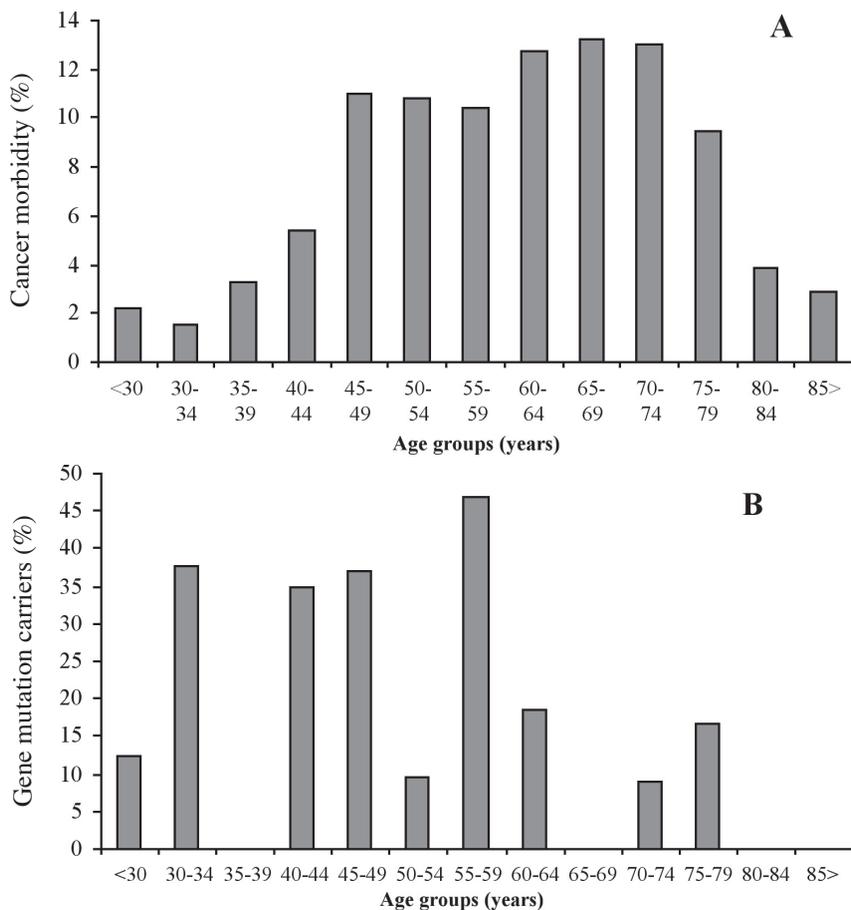


Fig. 1. Ovarian cancer patients and *BRCA1* mutation carriers in different age groups. A, Ovarian cancer morbidity (%) in Latvia by age (average in 1999 - 2003). B, *BRCA1* gene mutation carriers (%) amongst ovarian cancer patients by age.

localised between 2401 and 4191 result in a higher proportion of ovarian cancer (Risch et al. 2001; Thompson et al. 2002). However, other genetic or environmental factors may function as modifiers of the risk of ovarian cancer (Phelan et al. 1996; Narod 2002). Our data indicate that a high proportion of mutations in the 3'-end of the gene can be detected among ovarian cancer patients. The screening for the most prevalent recurrent mutations resulted in detection of 17 carriers of the 4154delA mutation and 24 carriers of the 5382insC mutation and only two carriers of the 300T>G mutation were identified. Our results indicate that at least the specific mutation 5382insC localised in the 3'-end of the gene may be associated with ovarian cancer in a high proportion of cases.

If the recurrent mutations are not detected in a patient with early onset of disease and a strong family history of cancer, the analysis of entire *BRCA1* gene should be offered. An example of this strategy is the identification of the 962del14 mutation carrier. One ovarian cancer patient diagnosed at the age of 40 years had breast cancer at age of 36

and a positive family history of other cancers (colorectal and renal cancer). Recurrent mutations were not detected and the patient was involved in the analysis of the entire *BRCA1* gene. A protein-truncating mutation in the 5'-end of the exon 11 was detected.

Altogether 44 *BRCA1* pathogenic mutation carriers were identified in our study. The *BRCA1* gene mutations were implicated in a large proportion of ovarian cancer incidence in Latvia. The screening for specific mutation in their families would allow to identify unaffected relatives who are at elevated risk of cancer. Special surveillance programme favouring diagnostics at an early stage of disease then should be offered to *BRCA1* mutation carriers.

The results of this study are useful for genetic counselling and genetic testing in the Latvian population. Further studies would be useful to estimate the risk of disease and possibilities of prevention of cancer in healthy mutation carriers.

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Olnīcu vēzis Latvijā ir bieži saistīts ar mutācijām *BRCA1* gēnā

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Kopsavilkums

Iedzimto olnīcu vēzi raksturo agrīna saslimšana un bieža slimības atkārtšanās. Ir zināma tā saistība ar iedzimtām mutācijām krūts un olnīcu vēzi predisponējošos gēnos *BRCA1* un *BRCA2*. Darba mērķis bija novērtēt *BRCA1* gēna mutāciju nozīmi olnīcu vēža etioloģijā sievietēm Latvijā un raksturot Latvijā izplatīto mutāciju spektru. Pētījums veikts ar AML ētikas komisijas atļauju. 34 olnīcu vēža slimniecēm ar vēzi ģimenē vai agrīnu saslimšanu (vidējais vecums 43 g.) tika veikta pilna *BRCA1* gēna testēšana, izmantojot vienpavediena DNS konformācijas polimorfismu un DNS heterodupleksu analīzi un atrasto ģenētisko variantu automatisko DNS sekvenēšanu. Izplatīto mutāciju skrīnings tika veikts dažādās pacientu grupās (161 sievietei). Kopumā, analizējot 195 slimnieču DNS, noteiktas 44 patogēno mutāciju nesējas, no tām divas mutācijas (5382insC un 4154delA) 41 slimnieci. Divu *BRCA1* gēna mutāciju bieža sastopamība (21 %) olnīcu vēža slimniecēm Latvijā dod iespēju viegli identificēt lielāko daļu to ģimeņu, kurās tiek pārmantota vēzi predisponējoša mutācija. Tālāka vienas konkrētas mutācijas testēšana veselajām radniecēm šajās ģimenēs ļauj viegli identificēt lielāko daļu riska personu, kurām draud saslimšana ar krūts vai olnīcu vēzi.