High Incidence of Mutations in *BRCA1 and BRCA2* Genes in Ovarian Cancer

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 144, No. 7, pp. 93-95, July, 2007
Original article submitted March 14, 2007

The incidence of mutations in the *BRCA1* and *BRCA2* genes in the studied sampling of 74 patients with ovarian cancer was 19%. The incidence of mutations in the Russian sampling of patients, formed without consideration for the family history, is one of the highest in European countries. Retrospective analysis showed that 9% patients carrying mutation had no family history of ovarian or breast cancer. The majority of mutations (86%) were detected in *BRCA1* gene, where 5382insC mutation predominated (58%). These data suggest the possibility and advisability of screening for mutations in the *BRCA1/2* genes in patients with ovarian cancer, particularly because this population includes patients without family history of ovarian and/or breast cancer.

Key Words: *BRCA1 and BRCA2 genes; mutations; ovarian cancer*

Ovarian cancer (OC) is a prevalent tumor disease, a leading cause of mortality among patients with tumors of the reproductive organs [13]. The main cause of high mortality of patients with OC is late detection of the disease. An effective approach promoting early detection of OC is evaluation of the hereditary predisposition to the disease. Hereditary form of OC is observed mainly within familial mammary and ovarian cancer syndrome. Familial cancer of the ovaries alone is much rarer. Hereditary predisposition in these syndromes is linked with mutations in the *BRCA1* and *BRCA2* genes. The risk of OC in the presence of mutation in the *BRCA1* gene is 40-50%, in mutations in the *BRCA2* gene 20-30% [4]. The highest percentage of hereditary breast cancer (BC) and/or OC is linked with mutations in the *BRCA1* gene. In familial OC, the incidence of mutations in the *BRCA1* gene is significantly higher than the incidence of mutations in this gene in familial BC [2].

High incidence of mutations in familial OC stimulated studies of samplings of OC patients not selected by familial history. High incidence of mutations in the *BRCA1* and *BRCA2* genes was detected in some populations. The highest incidence of mutations in these genes was detected in the population of the Ashkenazi Jews: almost half (47%) patients in a sampling not selected by family history had mutations in one of these genes [5]. However, the incidence of mutations in the *BRCA1/2* genes was different in samplings from different populations, varying from 3 to 40%. Familial accumulation of OC or BC was not observed in all probands with mutations. The incidence of familial cases varied within a wide range for samplings of patients from different populations: from 57 to 94% [1].

These data indicate the importance of the search for hereditary mutations in the *BRCA1/2* genes in OC patients not selected by the family history. The data on these studies are important for understanding the formation and prevalence of mutations in

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different populations, relationship between the genotype and clinical manifestations, and for practical diagnosis.

We studied mutations in the *BRCA1* and *BRCA2* genes in Russian patients with OC.

MATERIALS AND METHODS

The choice of patients was based on OC diagnosis. The sampling was formed without preliminary analysis of the family history of the disease and included 74 patients with OC. The presence of family history was cleared out retrospectively in women with detected mutations in the *BRCA1* and *BRCA2* genes.

Peripheral blood lymphocyte DNA was isolated using incubation in a medium with proteinase K and sodium dodecylsulfate (0.5%; 3-h incubation at 55°C) with subsequent phenol-chloroform extraction. PCR and conformation-sensitive gel electrophoresis were carried out [2]. Fragments of DNA with electrophoretically detected structural variations were sequenced by two complementary chains of the DNA fragment.

All exons with adjacent intron fragments were studied for *BRCA1* gene, exon 11 for *BRCA2* gene (this exon occupies about one half of the entire encoding part of *BRCA2* gene and includes the area of predominant accumulation of mutations in OC [7]).

RESULTS

Study of the primary structure of all encoding sites of *BRCA1* gene in 74 patients with OC revealed mutations in 12 (16%) patients. The incidence of mutations in *BRCA1* gene in Russian patients with OC in our study is most close to the incidence in Poland (12.7%) [9]. The incidence of mutations in *BRCA1* gene in patients examined in other countries was lower. The incidence of this mutation in other countries with European population varied from 7.4% (Sweden [10]) to 10% (Czechia [15]). The lowest (2.7%) incidence of mutations was observed in Korea [8]. On the other hand, the incidence of mutations in *BRCA1* gene in Russia is almost 2-fold lower than the incidence of mutations in the same gene in Ashkenazi Jews (30%) [5], the highest among the studied samplings of patients from other populations.

Family history was detected for 11 probands of 12 patients with mutation in *BRCA1* gene. Other cases with OC and/or BC, in addition to the proband, were recorded in 10 (91%) families. In Poland, the percentage of familial cases in the presence of *BRCA1* gene mutations was somewhat lower (72%) [9]. More than 90% familial cases among probands with mutations were recorded in Sweden [10], similar results were obtained in Canada, where the sampling of OC patients included women of different ethnic groups [14]. In USA in a study of a sampling from patients of predominantly European origin the percentage of familial cases among patients with *BRCA1* gene mutations was only 65% [12]. These data indicate differences between the populations by the incidence of mutations in the *BRCA1* gene and by their relationship with family history of OC.

The 5382insC mutation predominated (58%) among mutations in the *BRCA1* gene (Fig. 1). High incidence of this mutation was observed previously in studies of samplings of patients with familial BC and OC [1-3]. The remaining part of the spectrum included 4 mutations. The spectrum characteristics in our study are in general close to those for a sampling of patients with familial BC [1]. Hence, the same set of mutations forms predisposition to OC and BC. This fact suggests that genotypical characteristics other than position of the mutation in the gene are essential for cancer location in the presence of mutations in *BRCA1* gene. Our data suggest that interactions between *BRCA1* gene and another gene are essential for cancer location [3].

Two missense mutations were detected in *BRCA2* gene: K1690N and K1888R (2/74, 3%). A significant percent of missense mutations in the *BRCA2* gene spectrum is characteristic of OC sampling not selected by family history and of other populations. For example, in Poland almost all detected changes in the structure of *BRCA2* gene (3.9%) were missense variants [9]. In the sampling studied in the USA, missense variants in the *BRCA2* gene accounted for 61% [12]. Though precise significance of these variants is as a rule unknown, there are good grounds to regard them as the risk alleles [6,9].

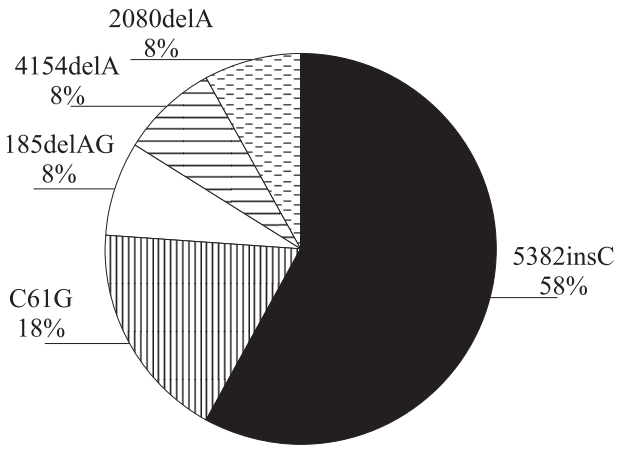

Fig. 1. Spectrum of mutations in the *BRCA1* gene.

Hence, mutations in the *BRCA1* and *BRCA2* genes were for the first time studied in Russian patients with OC not selected by family history of this disease. The overal incidence of mutations in *BRCA1* and *BRCA2* genes was 19%. This incidence of mutations in the Russian sampling is one of the highest in European countries. The major part of mutations is located in *BRCA1* gene. The spectrum of this gene includes just several mutations, the 5382insC mutation predominating.

The severity of consequences of untimely detection of OC and the significance of preventive measures in this disease suggest screening studies as an effective measure. This screening will detect patients without family history of OC/BC, but with mutation determining predisposition to OC/BC, which can be inherited. Presymptomatic genetic testing can be recommended for members of families with accumulation of cancer of these two locations, detected by screening, with the aim of further preventive measures. In addition, information about the presence of a mutation is essential for predicting the development and for the treatment of OC [9].

The study was partially supported by the Russian Foundation for Basic Research (grant No. 07-04-01602).

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