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Clinical and statistical analysis of ovarian cancer incidence rate and identification of a subgroup of patients with BRCA1/2 mutations in the russian federation

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Abstract:

The study aimed to analyze prevalence and incidence of ovarian cancer (OC) in the Russian female population taking into account genotyping for BRCA1/2-status; to develop a clinical and statistical model for predicting prevalence of hereditary OC; to assess the need for screening programmes to identify hypothetic patients (I/II-degree relatives of OC patients). The authors performed information search and analysis of data on prevalence and incidence of OC in Russia, including data on patients with BRCA1/2 mutations, and on clinical recommendations concerning the disease state. It was shown that the number of patients with BRCA1/2 mutations who are newly diagnosed with OC at an early stage could equal 326-486, and the number of patients with advanced cancer – 1197-1437. At present 13 206-14 329 women of the total number of patients with confirmed OC have BRCA1/2 mutations. About 1683–1762 female relatives of these patients will be identified as BRCA1/2 mutation carriers, and 673–705 individuals will develop OC during their lifetime. The survival rate in the "screening group" is 2.4 times higher compared to the group, who have not been screened. BRCA1/2 mutations screening in all OC patients regardless of family history is advisable for both medical and economic reasons. Objectives. The objectives of the study were: to analyze prevalence and incidence of ovarian cancer in the Russian female population taking into account genotyping for BRCA1/2-status; to develop a clinical and statistical model for predicting prevalence of hereditary ovarian cancer with due regard to the disease stage. Materials and methods. The authors of the study performed information search and analysis of the data on prevalence and incidence of ovarian cancer in the Russian Federation, including data on patients with BRCA1/2 mutations. Results. Taking into account the probabilities integrated into the statistical model it was shown that the number of patients with BRCA1/2 mutations who are newly diagnosed with ovarian cancer at an early disease stage could equal 326-486 people, and the number of patients with advanced cancer – 1197-1437 people. If we look at the whole population of patients with confirmed ovarian cancer who are registered at the cancer centres of the Russian Federation, the number of patients with BRCA1/2 mutations equals 13 206-14 329 people at present. 1683–1762 female relatives of these patients will be identified as BRCA1/2 mutation carriers, and 673–705 individuals will develop ovarian cancer during their lifetime. Conclusions. The identification of patients with BRCA1/2- associated cancer and female relatives with BRCA mutations will help lessen the burden on the state budget in the social service sector, as well as on the healthcare budget thanks to the optimization of the existing treatment regimens.

Keywords: hereditary ovarian cancer, BRCA1/2 mutations, incidence.

INTRODUCTION

The overall cancer burden profile in women is dominated by tumours of reproductive organs (39.2%), with malignant genital tumours accounting for 18.3% of all tumours in women. Ovarian cancer (OC) was diagnosed in 13 543 women in Russia in 2015 and ranked eighth in the overall cancer incidence rate (4.4%) and third among gynaecological tumours (after uterine corpus cancer and cervical cancer) [1]. Although the annual incidence rate is rather negligible and accounts for less than 1%, note should be taken of the survival rate in this population. During the first year after diagnosis, the mortality rate is 22.7%, and the annual mortality rate is 6.3% [2]. This may be attributed to difficulties in diagnosing advanced cancer, especially at the so-called "early" stages. Different authors demonstrate that detailed examination reveals retroperitoneal lymph nodes metastases of various localization in patients with I-II OC stages (which could be considered early stages from the perspective of clinical pharmacology) in 30% cases. This being the case, the FIGO and TNM classifications that have already undergone several modifications, are rather tentative [3]. A significant number of malignant ovarian tumours are known to be hereditary. It has been demonstrated that inactivating mutations of BRCA1/2 genes lead to almost 60% lifetime risk of OC development [4]. Hereditary OC tumour syndromes became the subject of intensive research at the beginning of 1990s. The first gene associated with this disease – BRCA1 (BReast CAncer1) – was discovered in 1990 [5], and the second gene, BRCA2 [6], was discovered 4 years later. BRCA1 and BRCA2 code for different proteins, but both gene products play a key role in maintaining the integrity of the genome, particularly in DNA repair processes [7]. Keeping in mind a relatively high prevalence of BRCA1/2 mutations in patients with OC, it is necessary to match the financial resources required (expected) to provide specialized cancer care and the number of patients with these mutations. Therefore, it is important to be able to predict OC incidence both in the overall population and in the target population of patients with BRCA1/2 mutations.

The objectives of the study were: to analyze prevalence and incidence of OC in the Russian female population taking into account genotyping for BRCA1/2-status; to develop a clinical and statistical model for predicting prevalence of hereditary OC with due regard to the disease stage; to assess the need for introduction of screening programmes which would help identify hypothetic patients (first or second degree female relatives of patients with OC), who are considered to be at risk of developing OC and are subject to mandatory screening.

MATERIALS AND METHODS

At the first stage the authors of the study performed information search and analysis of the data on prevalence and incidence of OC in the Russian Federation, including data on patients with BRCA1/2 mutations, and on clinical recommendations pertaining to the disease state and outcomes in different clinical groups.

Population groups. The study population included adult Russians (18+ years) who were diagnosed with OC. The overall study population was divided into groups depending on the OC stage (I–II, III, IV). The information search included the analysis of clinical and statistical data on incidence and prevalence of OC and took account of the BRCA1/2-status. The clinical and statistical model was developed using the method of modeling

Table 1 Trends of OC prevalence and incidence in Russia

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Prevalence (people)	80908	83827	86319	89505	92200	94304	97476	102814	106494	110307	114256	118346	122583
Incidence (people)	12609	12761	12843	13093	12960	12935	13262	13634	12900/ 13100	12900/ 13100	12900/ 13100	12900/ 13100	12900/ 13100

kinetics behind the patient flow. Probabilities of events were determined based on clinical and epidemiological trials results, international recommendations, expert estimations, etc. It was assumed that the prevalence of BRCA1/2 mutations in patients with OC was 10% at early stages and 15% at advanced stages [8, 9].

RESULTS

The first step was to analyse annual statistical reports on prevalence, incidence and mortality rates in patient groups with OC over the period from 2004 until 2014. The number of patients with newly diagnosed OC rose from 12 082 to 13 634 in the period from 2004 until 2014 [1]. It was determined that the annual increase in OC incidence was 0.86%, however over the last three years (from 2012 until 2014) the identification of patients with malignant ovarian tumours was at the level of 12 900–13 200 and did not show a trend towards significant increase. At the same time, the prevalence increases by 3.58% annually. And 60.9% of patients are diagnosed with OC at the moment when they already have III and IV disease stages. As we have stated earlier, one-year mortality rate during the first year after diagnosis equals 23%, while overall mortality stands at 6.3% [2]. If we presume that the increase in the disease prevalence remains constant in the coming years and is equal to 3.58% a year, the number of patients with OC registered in cancer centres will total 109 068 in 2016 and 121 206 in 2019. Since the prevalence rate is increasing rapidly, the predicted disease incidence in 2017 will be about 12 600-13 100 cases. This is not likely to change significantly by 2019 (Tables 1-5).

The clinical and statistical analysis of OC incidence and prevalence took account of BRCA1/2 mutations. The next step of the study was to predict the number of patients with malignant tumours of female reproductive organs accompanied by BRCA1/2 mutations. We used the data on OC prevalence and incidence in the population concerned to predict the number of patients with both early and advanced OC and BRCA1/2 mutations by 2019. Taking into account the probabilities integrated into the model, it was shown that the number of patients with BRCA1/2 mutations who are newly diagnosed OC and at an early disease stage could equal 326-486, and the number of patients with advanced cancer – 1197-1437. If we look at the whole population of patients with confirmed ovarian cancer who are registered at the cancer centres of the Russian Federation, the number of patients with BRCA1/2 mutations equals 13 206-14 329 people at the present moment (Tables 3, 5).

Table 2 Prediction of the number of patients with newly diagnosed OC across disease stages (in percentage and absolute terms)

I	II	III	IV
24,9%	12,2%	40,4%	20,5%
3262	1598	5292	2686

Table 3 Incidence of OC and *BRCA*1/2 mutations

	Early with *BRCAm*	Early without *BRCAm*	Advanced with *BRCAm*	Advanced without *BRCAm*
Var. 1 (people)	486	4374	1197	6782
Var. 2 (people)	326	2936	1436	8140

Table 4 Forecast for incidence of OC and *BRCA*1/2 mutations (in % and absolute values)

I	II	III	IV
24,9%	12,2%	40,4%	20,5%
26517	12992	43024	21831

Table 5 Prevalence of OC and *BRCA*1/2 mutations

	Early *BRCAm*	Early without *BRCAm*	Advanced *BRCAm*	Advanced without *BRCAm*
Var. 1 (people)	3814	34 330	9392	53 222
Var. 2 (people)	2652	23 866	11 677	66 171

The study also included the analysis of the need for introduction of BRCA1/2 mutations screening programmes for the female relatives of patients with OC and BRCA1/2 mutations. When predicting the number of hypothetic patients who need BRCA1/2 mutations screening it was assumed that the patients with OC have three female relatives of I-II degree. Taking into account the probabilities integrated into the model, the risk of developing BRCA1/2-associated OC (with regard to the current life expectancy in the female population of 76.5 years) is 0.4 and correlates with the age of potential patients (Tables 8, 9). It should be noted that the probability of BRCA1/2 mutations inheritance is 0.5. Thus, if the number of patients with BRCA1/2 mutations and a newly diagnosed OC at an early stage makes 326-486 cases, and newly diagnosed OC at an advanced stage – 1197-1437 cases (ideally all patients should undergo screening), the number of potential patients (first or second degree female relatives) who need the screening will make 3365-3525 cases. According to expert assessments about 1683–1762 female relatives of these patients will be identified as BRCA1/2 mutation carriers, and 673–705 individuals will develop ovarian cancer during their lifetime (the risk of this subtype of ovarian cancer is 0.4). Thus, total screening of all patients with OC and their first and second degree female relatives will help identify a significant number of "potential" patients.

The study involved the analysis of demographic characteristics of patients with OC and BRCA1/2 mutations, and justification of screening programmes aimed at identification of BRCA1/2 mutations in I-II degree female relatives of patients with OC. It was determined that the average age of patients with BRCA1/2-associated OC is 52 years which is below the retirement age for women in the Russian Federation (Law 166-FZ "On public pensions" of 15.12.2001). No differences in age characteristics were observed in comparison with the overall population of patients with OC (Table 6). At the same time, some differences were observed in patients distribution across disease stages: 67% of BRCA1/2-negative and 81% of BRCA1/2-positive patients have III-IV stages of the disease (Table 10). The fact that advanced cancer is more frequent in patients with BRCA1/2 mutations is attributable to poor efficacy of existing screening programmes, and therefore the identification of BRCA1/2 mutations in female relatives of patients with confirmed OC will help improve diagnosis of the disease at early (I–II) stages. An

additional clinical and statistical model was developed in order to assess potential impact of the screening programmes (procedures) on clinical outcomes in the patient population concerned. Two strategies were analysed: 1) no screening of I-II degree female relatives of patients with OC, 2) mandatory screening of I-II degree female relatives of patients with OC. It was assumed that none of the screened women had malignant tumours at the time of screening. If BRCA1/2 mutations were discovered (in the previous periods), potential patients had to undergo screening every six months, which makes it possible to diagnose the disease at the initial stage. According to the developed model, the probability of OC development in the group of female relatives was 0.4. The number of patients with confirmed OC and BRCA1/2 mutations was 100 (this number of patients is hypothetical and was chosen to facilitate the calculations). Thus, 200 first or second degree female relatives were screened for BRCA1/2 mutations during the previous periods as part of the 2nd strategy. It was taken into account that screening for BRCA1/2-status is a routine practice, which has long been used in Russian specialized cancer centres.

It was determined that out of 200 first or second degree female relatives in both groups under analysis – 100 will be BRCA1/2 mutation carriers, and 40 will be diagnosed with OC. However, when performing modeling, significant differences were observed both in disease stages and in patients survival rates. In the first group 2.4 patients will have I stage of the disease, 5.2 – II stage, and 32.4 – IV stage at the moment of establishing diagnosis (Table 10). In the second group all patients will be diagnosed with cancer at the earliest stage (I) according to the probabilities integrated into the model. After that the five-year survival rate (Table 7) was determined: 14.8 patients will survive five years in the first group, and 36 patients – in the second group. Thus, the survival rate in the "screening group" is 2.4 times higher compared to the first group.

Table 6 Age distribution of patients with *BRCA*-associated OC

Age	*BRCA*-associated (%)	Without *BRCA* mutations (%)
Under 40	11	11
41–50	31	31
51–60	30	31
61 and older	29	27

Table 7 Five-year survival rate of OC patients with *BRCA*1/2 mutations across disease stages

Disease stage	Five-year survival rate
I	90%
IA	94%
IB	92%
IC	85%
II	70%
IIA	78%
IIB	73%
III	39%
IIIA	59%
IIIB	52%
IIIC	39%
IV	17%

Table 8 Risk of OC development in female carriers of *BRCA*1 mutation

Age	25	30	35	40	45	50	55	60	65	70	75	80
OC risk (%)	0	1	2	4	8	15	20	27	33	38	43	48

Table 9 Risk of OC development in female carriers of *BRCA*2 mutation

Age	25	30	35	40	45	50	55	60	65	70	75	80
OC risk (%)		0	0	0	0	1	3	5	7	9	11	12

Table 10 Distribution of patients with *BRCA*-associated OC and of patients with OC not accompanied by *BRCA* mutations across disease stages

Stage	*BRCA*-negative (%)	*BRCA*-positive (%)
I	18	6
II	15	13
III–IV	67	81

CONCLUSIONS

Thus, BRCA1/2 mutations screening in all patients with confirmed OC (regardless of their family history) is advisable for both medical and economic reasons. The average age of BRCA1/2-associated cancer patients is 52 years, and 41% of the analysed population are younger than 50, i.e. the majority of patients are of working age, which suggests that the screening has socio-economic importance for the country [10]. Therefore, the screening of all patients newly diagnosed with OC for BRCA1/2 mutations should become mandatory. The next important step is initiating screening programmes for first and second degree female relatives of patients with confirmed BRCA1/2-positive status. The combination of the mentioned procedures will make it possible to improve treatment regimens, reduce the mortality rate, assess predisposition to reproductive organ tumours in female relatives of OC patients and, thus, offer the possibility of diagnosing the disease at early stages. It is worthwhile mentioning that 60.9% of patients are diagnosed with OC when they already have III and IV disease stages which results in significant disability (II disability group) when the patient needs constant nursing care. The identification of a subgroup of patients with BRCA1/2-associated cancer and female relatives with BRCA mutations will help lessen the burden on the state budget in the social service sector, as well as on the healthcare budget at different levels thanks to the optimization of the existing treatment regimens.

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