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BRCA1/2 status and clinicopathologic characteristics of patients with double primary breast and ovarian cancer

M. CVELBAR[1,2], M. HOCEVAR[1], G. VIDMAR[3,4], E. TEUGELS[5]

[1]Institute of Oncology Ljubljana, Slovenia, e-mail: mirjam.cvelbar@guest.ames.si; [2]Community Health Center Novo mesto; [3]Institute for Rehabilitation, Republic of Slovenia; [4]University of Ljubljana, Faculty of Medicine, Institute of Biostatistics and Biomedical Informatics; [5]Laboratory of Molecular Oncology, Department of Medical Oncology, Oncologisch Centrum UZ Brussel

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The aim of the study was to analyse the results of BRCA1/2 testing in a group of patients with double primary breast and ovarian cancer (DPBOC) in Slovenia. Additionally, the family history and the clinicopathologic characteristics of BRCA1/2 mutation positive and negative patients with DPBOC were analysed, comparing them to a group of untested patients with DPBOC. For these groups of patients, survival analysis was also performed. From the 52 patients who were invited to genetic counselling and testing, 20 responded positively (38% compliance). BRCA1/2 mutations were found in 60% (12/20): 45% BRCA1 and 15% BRCA2 (9 and 3 patients, respectively). There was significantly higher grade of ovarian cancer and significantly higher rate of multiple primary breast cancer in BRCA1/2 positive group. Additionaly, there was a trend towards higher rate of first-degree family history of breast cancer, a trend towards higher stage of ovarian cancer, and a trend towards breast cancer being the first cancer in BRCA1/2 positive group. According to survival analysis, the tested group was not a representative sample of the larger untested group (of 51 patients), so we estimate that the rate of BRCA1/2 mutations in DPBOC patients is probably less than 60%.

Key words: breast cancer, ovarian cancer, BRCA1 gene, BRCA2 gene, double primary cancer.

Breast and ovarian cancer are related to nowadays recognisable germinal BRCA1 or BRCA2 mutations in 3-15% of the cases [1, 2]). When both cancers occur in the same patient, in a synchronic or metachronic way, the probability of BRCA1 and BRCA2 (BRCA1/2) germinal mutation is much higher. Early calculations [3] and some genetic studies in small series of patients [4, 5] were indicating that the rate of BRCA1/2 mutations in a case of double primary breast and ovarian cancer (DPBOC) could be close to 100%. These results were not confirmed by a study preceding the present one [6], but the results were indicating rather that BRCA1/2 mutation positive patients are only a subgroup within DPBOC group of patients, like some other authors had been suggesting [7,8].

Fishman demonstrated the presence of BRCA1/2 mutations in 57% of the DPBOC patients [9] and Schorge in 62% of the families with DPBOC [4]. The differences between positive and negative tested patients in terms of family history and in terms of clinical and pathologic characteristics of the tumors have not been analysed.

The aim of the present study was to analyse the results of BRCA1/2 testing in Slovenian DPBOC patients, as well as the results of the mutation probability calculations according to the BRCAPRO model. Additionally, the aim was to analyse the family history and the clinicopathologic characteristics of BRCA1/2 mutation positive patients with DPBOC in comparison with the BRCA1/2 mutation negative ones, and of the whole tested group in comparison with a bigger group of untested patients with DPBOC. The last scope was to perform survival analysis.

Our hypotheses were that:

1. There are two subgroups of patients with DPBOC: a subgroup of BRCA1/2 mutation positive patients and a subgroup of BRCA1/2 mutation negative patients;
2. The subgroups of BRCA1/2 positive and BRCA1/2 negative patients with DPBOC differ with regard to the family history and clinicopathologic characteristics. We hoped to find phenotipical characteristics of BRCA1/2 positive and BRCA1/2 negative DPBOC;
3. The group of tested patients with DPBOC does not differ markedly from the population of untested patients with DPBOC and therefore the rate of BRCA1/2 mutations in the tested group could also serve as a surogate measure of the prevalence of BRCA1/2 mutations in the whole population of the patients with DPBOC in Slovenia.

Patients and methods

According to the Cancer Registry of the Republic Slovenia, 167 DPBOC cases occurred in Slovenia in the period from 1976 to 2005.

From 2002 to 2005 all living patients with DPBOC (52) were invited for a genetic counselling session at the Cancer Genetic Clinic of the Institute of Oncology in Ljubljana. A BRCA1/2 genetic screen was offered to the patients who responded positively (20, 38.5%) and all agreed to provide a blood sample for this purpose.

All the breast and ovarian cancers of the tested patients had epithelial origin (carcinomas). Six DPBOC patients developed bilateral breast cancer and one patient developed double primary ipsilateral breast cancer. One patient developed gastric cancer before breast and ovarian cancer while another patient had a uterine (endometrial) primary cancer synchronically with ovarian cancer.

The screen was carried out by the Laboratory of Molecular Oncology at the Vrije Universiteit Brussel. Briefly, the mutation analysis was performed on genomic DNA extracted blood samples. The large exons (exon 11 of BRCA1, exons 10 & 11 of BRCA2) were analysed using the protein truncation test (PTT, 10) while the remaining small exons as well as the 5' and 3' regions of the large exons were screened by denaturing gradient gel electrophoresis (DGGE, 11). Mutations were further characterized by sequence analysis. Large deletions or duplications in BRCA1 were revealed by multiplex ligation-dependent probe amplification (MLPA, Ingeny probes P002 & P087).

While performing genetic counselling and genetic testing, and handling the genetic data, we respected their particular nature, in accordance with the European Convention on Human Rights and Biomedicine (Oviedo Convention) and in accordance with 25 recommendations of the European Commision on ethical, juridic and social implications of genetic testing.

We analysed the family history of the tested patients, as well as clinical and pathologic characteristics of ovarian and breast cancers. The data for that purpose were obtained from the patients' clinical records.

As a control group we analysed a larger group of untested patients with DPBOC, where both cancers were epithelial ones (carcinomas). As for the ovarian cancer, we included also patients with borderline epithelial tumours. We excluded those with germinal cancers of the ovaries and other non-epithelial cancers like lymphoma of the ovary. We also excluded patients with peritoneal form of the ovarian cancer, pseudomyxoma, undifferentiated adenocarcinomas of the ovary, metastatic cancers of the ovary and/or of the breast and also patients with DPBOC whose clinical data were missing in a part that could not be filled in by a wider investigation of the case. As for the breast cancer, we included patients with invasive and/or in situ carcinoma. Using all these criteria, 51 patients with DPBOC were included into the control group.

In both the tested and untested group we analysed and compared the following parameters: total oncologic family history of first and second degree (any cancer cases of any type), family history of breast cancer at first degree, age at the diagnosis of the first cancer, frequency of breast cancer that developed as a first cancer, occurence of double primary breast cancers (bilateral or ipsilateral), hystologic type of ovarian cancer, stage of the ovarian cancer, and grade of the ovarian cancer. We compared the mean value of BRCAPRO mutation probability calculation in BRCA1/2 positive and BRCA1/2 negative groups. Additionally, we compared the survival of tested and untested groups and of BRCA1/2 positive v. BRCA1/2 negative groups.

We performed descriptive statistical analysis and bivariate analysis with exact tests (Fisher's for categorical variables and Mann-Whitney for numeric variables). Survival analysis was performed using Kaplan-Meier method and exact log-rank test. Statistical analyses were conducted using SPSS for Windows 14.0.2 (SPSS Inc., Chicago, IL, USA).

Results

Among the 20 tested patients with DPBOC there were 9 patients (45%) found to be BRCA1 mutation positive and 3 patients (15%) found to be BRCA2 mutation positive. Cumulatively, 60% of the tested patients with DPBOC were found to be BRCA1/2 mutation positive.

Two BRCA1 mutations in the tested group appeared twice, without any known family links: 1806C>T and 235G>A. The other BRCA1 mutations were 300T>G, 300T>A, deletion 962del4 (962delCTCA) and a big deletion of the exons 5 to 7. Among BRCA2 mutations, one case of the slovenian founder mutation IVS16-2A>G was found. The other two BRCA2 mutations were 3493C>T and insertion 5579insA.

Regarding mutation probability calculations according to BRCAPRO model, the analysis revealed a significantly higher estimated probability in the subgroup of BRCA1/2 mutation positive patients (Table 1, Figure 1).

Regarding the total family history, we did not find significant differences between the groups of the tested and the untested patients and between the subgroups of BRCA1/2 positive and BRCA1/2 negative patients. Regarding positive family history of breast cancer in first-degree relative(s), we found a trend towards higher rate among BRCA1/2 positive patients compared to BRCA1/2 negative ones (Table 2).

Regarding the age at the diagnosis of the first cancer and regarding the age at the diagnosis of the ovarian cancer, there were no significant differences between the groups nor between

Table 1. BRCAPRO calculation of BRCA1-2 mutation probability in patients with DPBOC

Group	Minimum	Maximum	Median	Mean	Std. Deviation
BRCA+	0,007	1,000	0,945	0,643	0,433
BRCA-	0,004	0,740	0,052	0,137	0,247
Total	0,004	1,000	0,171	0,441	0,443

exact Mann-Whitney test: p = 0,005

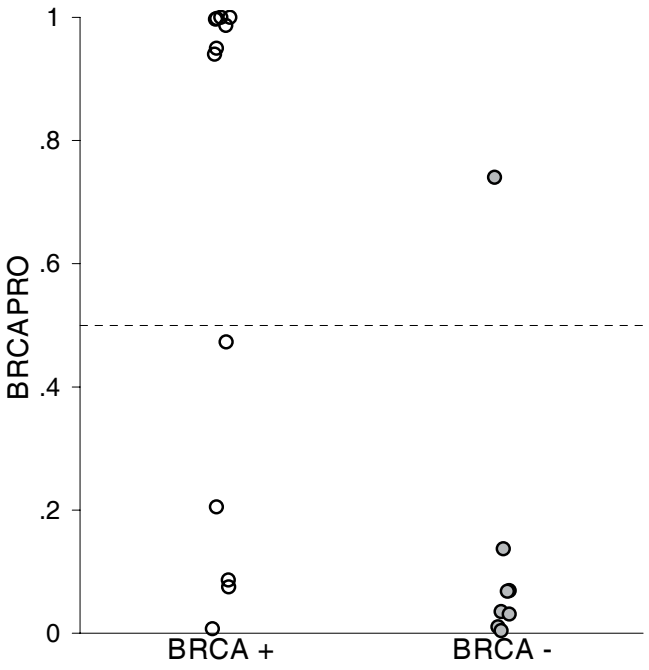

Figure 1. Distribution of BRCAPRO values in BRCA positive and BRCA negative group (shown with jittered dot-plot. One value in the BRCA- group exceeds 50%, and five values in the BRCA+ group are below 50%.)

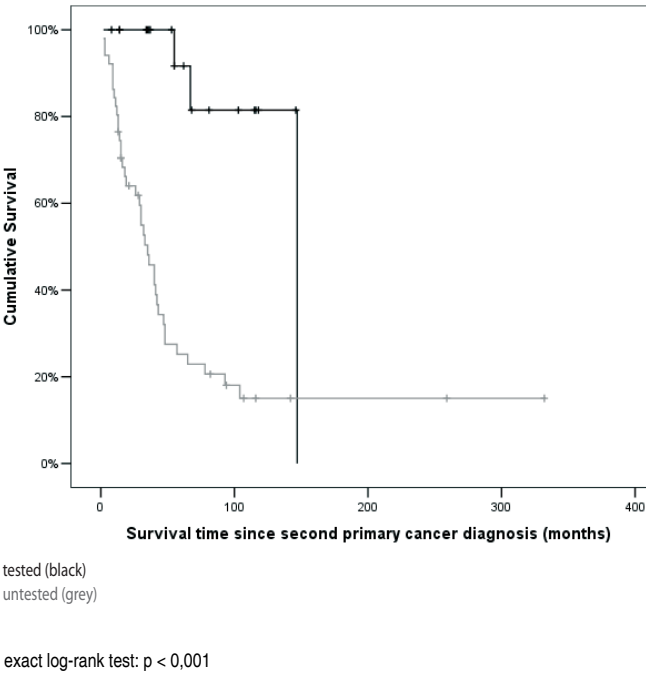

Figure 2. Survival time of tested and untested patients with DPBOC

the subgroups. There were neither significant differences regarding the sequence of the ovarian cancer, the stage of the ovarian cancer, or histology type of the ovarian cancer.

Regarding the grade of the ovarian cancer, there were no significant differences between the tested and untested group, but among the tested patients, there was a significantly higher rate of high-grade ovarian cancer in BRCA1/2 positive subgroup (Table 3).

Regarding the breast cancer, we did not find differences between the groups or between the subgroups in the sequence of this cancer and in the temporal relationship of breast and ovarian cancer. However, we found a significantly higher rate of double primary breast cancer in the group of tested patients with DPBOC compared to the untested group, as well as a significantly higher rate of double primary breast cancer in the subgroup of BRCA1/2 positive patients compared to BRCA1/2 negative one. Additionally, we found that all the tested patients with double primary breast cancer were BRCA1/2 positive (Table 4).

Survival analysis revealed significantly longer survival of the tested patients in comparison with the untested ones. Within the tested patients, however, there was no significant difference between BRCA1/2 positive and BRCA1/2 negative subgroup (Figures 2, 3).

Table 2. Family history in tested and non-tested patients with DPBOC, in BRCA mutation positive and negative

		Tested N=20	Non-tested N=51	p (Fisher's exact test)	BRCA+ N=12	BRCA- N=8	p (Fisher's exact test)
Family history	Positive	14	23	0,195	9	5	0,642
(of any cancer at 1st or 2nd degree)	Uncertainly positive	0	4		0	0	
	Negative	6	24		3	3	
Family history of 1st-degree breast cancer	Positive	7	5	0,029	6	1	0,157
	Uncertainly positive	0	1		0	0	
	Negative	13	45		6	7	

Table 3. The ovarian cancer characteristics in tested and non-tested patients with DPBOC, and in BRCA mutation positive and negative ones

		Tested N=20	Non-tested N=51	p	BRCA+ N=12	BRCA- N=08	p
Age at 1st cancer	mean	52,0	52,4	0,878 (t test)	49,6	55,5	0,173 (t test)
Age at the ovarian cancer	mean	59,1	56,5	0,286 (t test)	58,8	59,6	0,801 (t test)
Sequence of the ovarian cancer	first	6	22	0,131 (exact χ^2)	3	3	0,240 (exact χ^2)
	second	9	20		6	3	
	third	3	2		3	0	
	paralel to 1st	1	7		0	1	
	paralel to 2nd	1	0		0	1	
Stage of the ovarian cancer	first	9	13	0,299 (exact χ^2)	3	6	0,133 (exact χ^2)
	second	1	8		1	0	
	third	7	24		6	1	
	fourth	3	5		2	1	
Hystology Type of the Ovarian cancer	serous	11	34	0,735 (exact χ^2)	8	3	0,332 (exact χ^2)
	mucinous	2	3		0	2	
	endometrioid	3	5		2	2	
	clearcell	0	1		0	0	
	transitional	0	1		0	0	
	mixed	3	2		1	2	
	dedifferentiated	1	2		1	0	
Grade of the Ovarian cancer	borderline	3	5	0,979 (exact χ^2)	0	3	0,001 (exact χ^2)
	first	3	6		0	3	
	second	3	9		2	1	
	third	10	25		9	1	
	dedifferentiated	1	1		1	0	

Table 4. Breast cancer characteristics in tested and non-tested patients with DPBOC, and in BRCA mutation positive and negative ones

		Tested N=20	Non-tested N=51	p	BRCA+ N=12	BRCA- N=8	p
Sequence of the breast cancer	first	12	29	0,839 (exact χ^2)	9	3	0,213 (exact χ^2)
	second	6	18		2	4	
	third	0	1		0	0	
	paralel to 1st	2	2		1	1	
	2nd and 3rd or 3rd and 4th	0	1		0	0	
Temporal relationship of breast cancer (BC) and ovarian cancer (OC)	First BC, then OC after>1year	12	24	0,594 (exact χ^2)	9	3	0,235 (exact χ^2)
	First OC, then BC after>1year	5	19		2	3	
	Both BC and OC in <1year	3	8		1	2	
Occurrence of double breast cancer	yes	7	2	0,001 (exact χ^2)	7	0	0,015 (Fisher's exact test)
	no	13	48		5	8	
	uncertain	0	1		0	0	

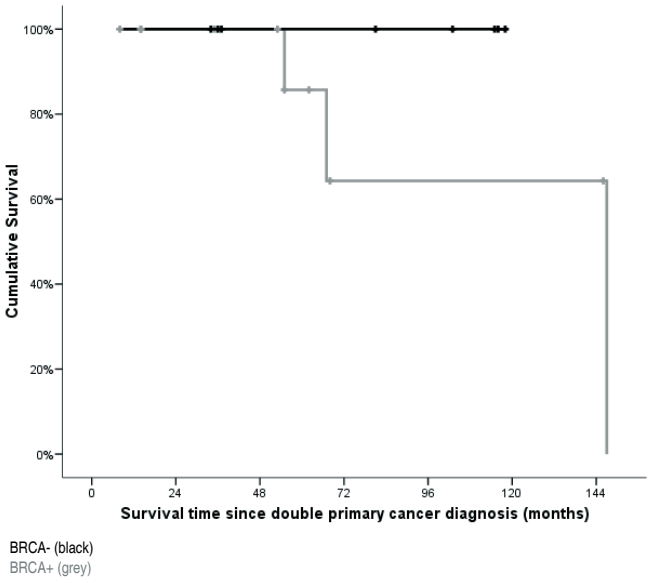

Figure 3. Survival time of BRCA1/2 positive and BRCA1/2 negative patients with DPBOC

Discussion

The observed 60% rate of the germinal BRCA1/2 mutations in the tested group of the patients with DPBOC is in accordance with a previous study (6) and in accordance with the results of some other studies (4,8), but it is in divergence with other studies on this topics (3, 4, 5). The reliability limitation of the present study is in the small number of the patients included, which is due both to the low incidence of DPBOC in general and to the small size of the Slovenian population (two million inhabitants).

Among the observed 12 mutations, there were three BRCA2 mutations and among them only one case of the Slovenian founder (12) mutation (IVS16-2A>G). This fact is, however, not surprising, because the founder mutation had been previously observed only in the families with multiple breast cancer cases, but with no ovarian cancer cases (12). Only recently it was found that ovarian cancer can be an expression of Slovenian founder mutation as well (13).

Among BRCA1 mutations, the most frequent Slovenian BRCA1 mutation (1806C>T) (14) was present twice and the third and the fourth most frequent ones (300T>G, 300T>A) were present once each. Another BRCA1 mutation twice observed 235G>A in our study has not yet been reported in the Slovenian families.

The fact that with both of the twice present BRCA1 mutations, one patient developed multiple primary breast cancer (MPBC) and the other did not, indicates the multiple-grade process of cancerogenesis in BRCA mutation positive patients as well, like other studies have revealed (15).

Genomic rearrangements were found in our study in three patients; they were in the form of two different deletions within BRCA1 gene. One deletion was 962delCTCA (962del4), which was found twice, and the other was big deletion of the exons 5 to 7. With one fourth (3/12) of BRCA1/2 mutations being rearrangements, our results do not confirm the suggestion that DPBOC would represent a specific phenotype with high probability of detecting inherited rearrangements in BRCA1 (16).

In the group of BRCA1/2 mutation positive patients, there was a marginally significant trend of higher rate of first-degree positive family history of breast cancer. This trend, which should presumably be provable with a larger sample, is consistent with higher penetrance of BRCA1/2 mutations in comparison with other mutations related to breast cancer (CHEK2, TP53, additional unknown susceptibility genes with various degrees of penetrance) (17), therefore indicating the importance of family history. Nevertheless, since BRCA1/2 mutation penetrance is not 100% (according to our results it is less than 75%, because 25% of BRCA positive patients had no cancer in the family), even completely negative family history does not exclude the possibility of BRCA1/2 germinal mutation.

Ovarian epithelial cancer was of significantly higher grade in the group of BRCA1/2 positive patients, just as we expected and in accordance with presumably more agressive BRCA1/2 linked cancers. The expected higher stage of ovarian cancer at the diagnosis was observed as a marginally significant trend. Higher rate of serous histologic type, which would be in accordance with some previous reports (18, 19), was not found. Nevertheless, there are other studies that did not find significant differences in clinicopathologic characteristics of BRCA1/2-linked and BRCA1/2-unlinked epithelial ovarial cancer (20, 21). In any case, we are aware of the limited reliability of our finding due to the small size of our study group.

Multiple primary breast cancer (MPBC), which was present in 7 out of 12 BRCA1/2 positive patients, is known to be more frequently present in carriers of BRCA1/2 mutation than in non-carriers (22). In most of the cases, MPBC is presented as contralateral breast cancer (CBC), which is but one of the forms of MPBC, especially in the actual era of conservative breast cancer surgery. According to the published data, BRCA1 carriers have an estimated cumulative risk of contralateral new primary breast cancer of 48% by age 50 years and 64% by age 70 years (23). Another study showed that for BRCA1/2 germinal mutation carriers who were diagnosed with their first primary breast cancer before age 49 years and who did not undergo oophorectomy or receive treatment with tamoxifen, the 10-year risk of contralateral breast cancer was 43.4% for BRCA1 carriers and 34.6% for BRCA2 carriers (24). In comparison, according to the study of Shahedi, women with hereditary/familial BRCA1/2 negative breast cancer who were diagnosed before age 50 years had a cumulative probability of developing CBC of nearly 40% after 15 years (23).

Interpretation of our results regarding MPBC is of very limited range, because the subgroup of MPBC is still small

(6 contralateral and 1 ipsilateral cancer) and it is not possible to analyse subgroups according to the age at the diagnosis of the first breast cancer, according to the family history and according to hormonal factors, which in our patients are even more complex than usually (e.g., previous ovarian cancer with oophorectomy, synchronic ovarian cancer or later ovarian cancer with oophorectomy; eventual hormone replacement therapy after oophorectomy; different types of hormone therapy of breast cancer; and other previous exogenic – like hormone contraceptives – or endogenic hormonal factors – like the age at menarche, number, period and type of pregnancies, breast-feeding and age at menopause for some patients). Hence, the most notable result remains that all of the 7 patients with DPBOC and MPBC were found to be carriers of BRCA1/2 mutation.

As expected, the BRCAPRO mutation probability calculation predicted well the majority of BRCA1/2 positive patients with DPBOC. This confirms that precise and correct ascertainment of the family history is still the basis of a good clinical practice in cases of breast cancer and ovarian cancer. The sole occurence of DPBOC at BRCAPRO model is still not an indicator of higher BRCA1/2 mutation probability, because the lowest estimate for a patient with DPBOC was only 0.004. At the same time, BRCAPRO model predicted very well all BRCA1/2 positive patients with DPBOC plus MPBC, because for all the 7 such cases the estimated probability was more than 0.90, even though 2 such patients had comletely negative family history.

Regarding our third hypothesis, there are two facts emerging from the study – namely that the tested patients had a marginally higher rate of positive first-degree family history for breast cancer and they had significantly higher rate of MPBC besides ovarian cancer – indicating more BRCA1/2 mutations among tested patients than among untested patients with DPBOC. This means that the tested group is not representative of the whole DPBOC patients group in Slovenia. However, it confirms our previous observations and our first hypothesis that BRCA1/2 positive patients are only a subgroup in the group of patients with DPBOC, and it indicates that BRCA1/2 mutation rate in the whole DPBOC group in Slovenia is most probably even lower than in the tested group, therefore bellow 60%.

The results of the survival analysis, which show a significantly longer survival in the group of the tested patients in comparison to the group of the untested ones, are another indicator that the tested group of DPBOC patients is not a representative sample of the whole DPBOC patients group in Slovenia.

The absence of a significant difference in the survival time of BRCA1/2 positive v. BRCA1/2 negative DPBOC patients is in accordance with previous reports (25) and can be explained by the fact that BRCA1/2 mutation in spite of more frequently present negative prognostic factors means also higher sensitivity of the epithelial cancers for chemotherapeutics and consecutively equal or better survival of BRCA1/2 positive patients compared to theBRCA1/2 negative ones.

Conclusions

1. The tested group of the patients with DPBOC has a 60% (45 % BRCA1 and 15% BRCA2) BRCA1/2 mutation cariers rate.
2. The observed differences between BRCA1/2 positive and BRCA1/2 negative subgroup of patients with DPBOC are:
   - a trend towards higher rate of first-degree family-history of breast cancer in BRCA1/2 positive group;
   - significantly higher grade of ovarian cancer in BRCA1/2 positive group;
   - a trend towards higher stage of ovarian cancer in BRCA1/2 positive group;
   - significantly higher rate of MPBC in BRCA1/2 positive group;
   - a trend towards breast cancer as the first cancer in BRCA1/2 positive group.
3. The rate of BRCA1/2 mutations in the whole population of the patients with DPBOC in Slovenia is probably lower than the rate in the tested group, thus probably less than 60%.

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