# Risk factors and prognostic factors in patients with double primary cancer: Epithelial ovarian cancer and breast cancer

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**Summary**

*Background and Objective:* The most important known risk factor for ovarian cancer is the BRCA1-2 mutation, which is clinically often manifested through a positive family history of cancer of the breast and/or ovary. Whether other risk factors and prognostic factors in women with a positive family history of cancer of the breast and/or ovary and/or with BRCA1-2 mutation are important remains to be elucidated. Recent studies have shown that in the double primary breast and ovarian cancer (DPBOC), BRCA1-2 mutation is present in at least 86% of cases. Therefore, the group of patients with DPBOC, especially with epithelial ovarian cancer and breast cancer, is the most suitable for such an analysis. The aim of this study was to verify the hypothesis that, in this group, some other risk factors, in addition to a specific family history of cancer, as well as unfavourable pathomorphological prognostic factors, are more expressed than in a control group of patients with sporadic epithelial ovarian cancer only.

*Methods:* We compared the study group of 31 patients with DPBOC (epithelial ovarian cancer) to a control group of 62 patients with a single, sporadic epithelial ovarian cancer and negative specific family history. The data were obtained from the Cancer Registry of Slovenia and from clinical records. For every patient, we filled-in a protocol and analysed the data, comparing other risk factors in addition to specific family history and prognostic, clinical, and pathomorphological factors. Statistical analysis was performed using descriptive statistics, chi-square test and t-test. Multivariate analysis was also planned, but the necessary conditions were not met.

*Results:* In the study group, we found a higher percentage of positive non-specific family histories than in the control group, but the difference was not statistically significant. No difference in procreative risk factors was observed between the groups. There was a higher percentage of borderline significance of women from the study group that developed ovarian cancer between 45 and 59 years of age. In the study group, ovarian cancer was significantly more often found at Stage I, although the groups did not differ in detection procedures. Also, we did not find any differences in the distribution of tumour grades or histologic tumour types.

*Conclusion:* The results did not confirm our hypothesis, yet they indicated some differences between the groups regarding the risk factors for ovarian cancer. Regarding the prognostic factors, we even found a significantly higher percentage of Stage I epithelial ovarian cancer in the study group, with no difference in the mode of detection. Considering the results that are not typical of BRCA-related cancer (what double primary cancer of the ovary and breast is supposed to be) and previous reports, we find it more likely that the patients with BRCA1-2 mutations represent only a subgroup within the group of patients with double primary breast and ovarian cancer.

*Key words:* Ovarian cancer; Breast cancer; BRCA1-2; Double primary cancer; Risk factors; Prognostic factors.

## Introduction

Among risk factors for epithelial ovarian cancer, besides being a woman, the most important is genetic predisposition due to germinal BRCA1 or BRCA2 gene mutation. This mutation is often expressed in a positive family history of ovarian cancer and/or breast cancer [1], but it can also be expressed in a form of double primary cancer, namely epithelial ovarian cancer and breast cancer. The results of the first investigations of BRCA1-2 status in patients with double primary cancer of the breast and ovary (DPCBO) confirmed previous mathematical calculations [2] and demonstrated the presence of BRCA1-2 mutation in 86-87.5% of these patients [3, 4]. Considering that the presently available methods of gene analysis can offer us data about coding sequences of BRCA1-2 only and that they may overlook big deletions and splicing variants [5, 6], some authors conclude that, in DPCBO, the presence of BRCA1-2 mutation could be 100% [3].

Occurrence of DPCBO in a certain patient can, according to these reports, be used as an indirect genetic information or a surrogate measure for genetic predisposition.

The importance of other risk factors for the occurrence of ovarian cancer and/or breast cancer in the presence of BRCA1-2 mutations remains to be elucidated [7]. The existing reports on the role of procreative factors are controversial [8-12]. The reports on clinical and pathomorphologic characteristics of BRCA-related ovarian cancer nearly unanimously show that such a cancer is more aggressive than sporadic types.

## Patients and Methods

We planned our study as a retrospective case-control study. The study group consisted of 31 patients with DPCBO, registered in Slovenia in the period 1989-2001, in whom the ovarian cancer was epithelial; borderline cases were also included.

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Tumours were either synchronous (both tumours detected within 12 months) or heterochronous (tumours detected within an interval of more than 12 months) and the first site detected was either the ovary or breast.

The control group comprised 62 patients with ovarian epithelial cancer who were first treated in 1998 at the Institute of Oncology in Ljubljana or at the Department of Gynaecology and Obstetrics of the University Medical Centre in Ljubljana, and who did not have any other registered primary cancer before, simultaneously, or later. Other exclusion criteria were positive and uncertain family histories of breast and/or ovarian cancer in the first or in the second generation. In this way, we reduced to a minimum the possibility of having some patients with BRCA1-2 germinal mutations in the control group. We also excluded cases with primary peritoneal cancer because it is another pathohistologic entity, even though the newest reports show that this entity makes up part of the syndrome of familiar breast and ovarian cancer related to BRCA1-2 mutation.

We prepared a protocol and gathered, for each patient, the data on risk factors and prognostic factors (family history, procreative history, clinical and pathohistologic characteristics of the tumours). The data were retrieved from the Cancer Registry of Slovenia and from clinical records.

The data were processed by univariate and bivariate analysis with chi-square and t-tests, whereas the conditions to perform multivariate analysis were not met.

Table 1. — *Procreative risk factors for ovarian cancer in the group of patients with double primary cancer of the ovary (epithelial) and breast and for the control group with epithelial ovarian cancer only.*

| | Group 1 (no.) | mean/% | Group 2 (no.) | mean/% | p |
|---|---|---|---|---|---|
| Age at menarche (yrs) | 28 | 13.93 | 53 | 14.23 | p (t) = 0.511 |
| Age at menopause (yrs) | 21 | 49.52 | 40 | 49.45 | p (t) = 0.963 |
| Age at 1st delivery (yrs) | 12 | 22.1 | 21 | 23.1 | p (t) = 0.383 |
| Length of lactation[x] (months) | 20 | 4.55 | 33 | 3.76 | p (t) = 0.694 |
| Nuliparity (frequency) | 7/31 | 22.6% | 18/62 | 29.0% | p ($\chi^2$) = 0.508 |
| Hormone replacement therapy (frequency)[xx] | 1/13 | 7.7% | 1/38 | 2.6% | p ($\chi^2$) = 0.417 |
| No. of deliveries | 31 | 1.7 | 62 | 1.6 | p ($\chi^2$) = 0.873* |
| No. of abortions[xxx] | 28 | 0.5 | 54 | 0.55 | p ($\chi^2$) = 0.925** |

Group 1 = study group of patients with double primary cancer of the ovary (epithelial) and breast.
Group 2 = control group of patients with sporadic ovarian epithelial cancer only.
[x] cumulative;
[xx] before ovary cancer detection;
[xxx] spontaneous and induced together;
* based on contingency table with 4 categories;
** based on contingency table with 3 categories.

## Results

In the study group with DPBOC, a higher percentage of positive non-specific family histories was found than in the control group (50% vs 31%), but the difference was not statistically significant (p = 0.106).

Mean age at menarche, first delivery, and menopause did not differ significantly between the two groups (Table 1). Neither was there any statistically significant difference obtained in comparing these same data by age categories.

Similarly, no statistically significant difference was found when comparing mean number of deliveries, mean duration of lactation, mean number of abortions, frequency of nulliparity, and frequency of hormone replacement therapy before the detection of ovarian cancer (Table 1). The analysis of some additional risk factors was not possible because too many data were missing.

Within the complex of clinical and pathomorphological prognostic factors, a difference of borderline significance was found regarding the age at the detection of tumour (p = 0.053). The percentage of patients aged between 45-59 years was higher in the study group with DPCBO (Table 2). As regards the data on the site of the first primary cancer in these patients, ovarian cancer was the first or synchronous cancer in 61% of cases (Figure 1).

Ovarian cancer was found significantly more often in Stage I in the study group with DPBOC with respect to the control group (p = 0.039; Table 2). At the same time the two groups did not differ significantly in the diagnostic modalities of detection (trouble-induced investigations, preventive care or follow-up procedures, etc.) (Table 3). Neither was there any significant difference in pathohistological tumour types and in tumour grades, including borderline tumours (Table 2).

Table 2. — *Clinical and pathomorphologic prognostic factors in the group of patients with double primary cancer of the ovary (epithelial) and breast and in the control group with epithelial ovarian cancer only.*

| | Group 1 (no.) | % | Group 2 (no.) | % | p ($\chi^2$) |
|---|---|---|---|---|---|
| *Age* | | | | | |
| ≤ 44 | 2 | 6.5 | 13 | 21.0 | p = 0.053 |
| 45-59 | 16 | 51.6 | 18 | 29.0 | |
| ≥ 60 | 13 | 41.9 | 31 | 50.0 | |
| *Stage* | | | | | |
| I | 11 | 38 | 11 | 18 | p = 0.039* |
| II | 1 | 3 | 9 | 14 | |
| III | 14 | 48 | 32 | 52 | |
| IV | 3 | 10 | 10 | 16 | |
| *Pathohistologic type* | | | | | |
| serous | 21 | 75.0 | 44 | 75.9 | p = 0.333 |
| mucinous | 2 | 7.1 | 3 | 5.2 | |
| endometrioid | 1 | 3.6 | 7 | 12.1 | |
| clearcell | 1 | 3.6 | 0 | 0 | |
| mixed | 2 | 7.1 | 4 | 6.8 | |
| undifferentiated | 1 | 3.6 | 0 | 0 | |
| *Grade* | | | | | |
| borderline | 6 | 20.7 | 12 | 20.7 | p = 0.929 |
| grade 1 | 2 | 6.9 | 5 | 8.6 | |
| grade 2 | 7 | 24.1 | 11 | 19.0 | |
| grade 3 | 14 | 48.3 | 30 | 51.7 | |

Group 1 = study group of patients with double primary cancer of the ovary (epithelial) and breast.
Group 2 = control group of patients with sporadic ovarian epithelial cancer only.
* based on contingency table with 2 categories (Stage I, Stage II-IV).

Table 3. — *Diagnostic modality of detection for ovarian cancer in the group of patients with double primary cancer of the ovary (epithelial) and breast and in the control group with epithelial ovarian cancer only.*

| | Group 1 (no.) | % | Group 2 (no.) | % | p ($\chi^2$) |
|---|---|---|---|---|---|
| Problems | 22 | 79 | 49 | 85 | 0.783 |
| Preventive | 3 | 11 | 4 | 7 | |
| By chance | 1 | 4 | 3 | 5 | |
| Other | 2 | 7 | 2 | 3 | |
| Total | 28 | 100 | 58 | 100 | |

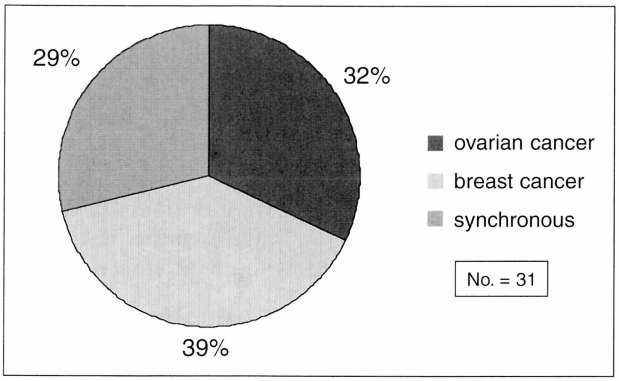


Figure 1. — Site of the first primary cancer in patients with DPBOC.

## Discussion

According to the results, the study group with DPBOC and the control group with sporadic ovarian cancer alone do not differ statistically significantly in any of the eight analysed procreative risk factors. The absence of a statistically significant difference regarding procreative risk factors could mean that it is a genetic factor that is decisive in the development of DPBOC or even of multiple primary cancer, which we also encountered in several patients of our study group. On the basis of the already mentioned mathematical modelling and clinical studies, we supposed that the decisive genetic factor could be BRCA1-2 mutation. However, the penetration of such a mutation is never 100% and, according to the latest studies, it is even lower than estimated before, ranging from a minimum of 11% to a maximum of 65% [13]. Therefore, there must be some other influential factors that modify the risk and can be genetic and/or epigenetic [14]. While reflecting on the fact that no epigenetic risk modifiers considered as characteristic for the study group with DPBOC were found in our study, we should take into account a limitation of our study, i.e. the small number of the patients included due to two basic causes: low incidence of DPBOC in general and the small size of the Slovenian population. Because of these limitations, it is possible that some differences that were indicated but did not reach statistical significance (e.g., the percentage of nulliparous or the percentage of multiparous patients) may be of importance for the identification of risk modifiers.

It is also possible that, due to scarce and conflicting data on hormonal risk modifiers for BRCA1-2-related ovarian cancer [9, 12], the role of procreative factors, e.g., the number of deliveries is small. On the other hand, the decisive factor may be – also in the case of ovarian and breast cancer – a non-specific hormonal factor, namely an excessive production of corticosteroids and their effect on the cell level in stressful situations, as is becoming evident from the studies of basic oncogenesis [15]. This factor was not included in our study due to its limitation set by our retrospective approach, but we did obtain some indicative data from the medical records on difficult family situations of the patients that developed DPBOC.

A second limitation of our study could be the nonhomogeneity of the study group regarding the site of the first of the two primary cancers, which is again the consequence of the already mentioned causes of low incidence and small population. Only ten out of 31 patients developed ovarian cancer as the first primary cancer with no synchronous breast cancer – too few to form a study group on its own. However, according to the reports [16], the influence of earlier radiotherapy for breast cancer on the development of subsequent ovarian cancer is negligible; therefore, it was not considered as a disturbing factor in the risk factor analyses of our study group.

The analysis of clinical and pathomorphological prognostic factors showed two statistically significant differences: a higher percentage of patients aged between 45-59 years at the detection of ovarian cancer in the study group with DPBOC and a higher percentage of Stage I ovarian cancer in the same group. There was no statistically significant difference regarding (i) mean age at the detection of ovarian cancer, (ii) distribution of various diagnostic modalities at detection, (iii) distribution of various pathohistological tumour types, and (iv) distribution of grades of tumour differentiation. These results are in contrast with the results of the studies on BRCA1-2-related ovarian cancer. The mean age at the detection of ovarian cancer in our study was found to be 58 years for both groups, while Rubin, in his first study on BRCA1-2-related ovarian cancer, reported a lower mean age at the detection of ovarian cancer in BRCA1 mutation carriers than in the control group [17]. The percentage of serous type ovarian cancer, which, according to six studies of BRCA1-2 related tumours, ranged between 81-94% [7]; in our study group it amounted to 75% and was practically not different from the control group result of 76%. A similar result was obtained by Johannsson *et al.* in their study of BRCA1-related ovarian cancer [18]. Our results of tumour grade distribution are also in contrast with the data from the studies on BRCA1-2-related ovarian cancer, where the percentage of low-malignant tumours was low, while mid- or high-grade ovarian cancers prevailed considerably [7]. In the studies of BRCA1-2-related ovarian cancer, Stage III-IV ovarian cancer ranged from 70-100%; in our study group with DPBOC, Stage I ovarian cancer was statistically significantly more frequent, while Stage III-IV disease was found in 58%.

Greater similarity can be found in comparing our results to the results of those studies that analysed ovarian cancer in patients with DPBOC without or before determining BRCA1-2 status. In their study from 1996, Suris-Swartz *et al.* [19] reported the same mean age of 56 years in both the study and control group, 60% of serous tumours in the study group (vs 36% in the control group) and a significantly higher portion of early Stage I-II disease in the study group (53% vs 22%). Fishmann *et al.* in 1998 [20] reported that the mean age of patients with double primary cancer, one of which was ovarian cancer and the other breast, endometrial or another cancer, was the late 50s for the detection of ovarian cancer and did not differ from the control group with a single primary

epithelial ovarian cancer. He also reported that all secondary primary ovarian cancers were found from following the symptoms reported by patients themselves and that 87% were already in an advanced stage of disease.

The bridge between the studies of DPBOC and the studies of BRCA1-2-related ovarian cancer is represented by another Fishmann *et al.* study [21], where they at first performed an analysis of clinical and pathohistologic parameters in the group with DPBOC. Their results were similar to those obtained by Suris-Swartz *et al.* They then determined BRCA1-2 status in all the patients of the group. In spite of the fact that all the patients were Ashkenazi Jews and a higher incidence was already expected because of the ethnic factor, BRCA1-2 mutations were found only in 57.1% of patients.

Some of the subsequent studies [3, 4] indeed showed much higher frequencies of BRCA1-2 mutations and Shih *et al.* [3], taking into account the data of the Danish study by Petrij-Bosch *et al.* [22], reporting that 25% of BRCA1-2 mutations were found within the non-coding sequences which were not attainable by standard gene analysis techniques, made a conclusion that the presence of BRCA1-2 mutations could be 100% in patients with DPBOC [3]. It was on this conclusion that we grounded our study as well as the elaboration of inclusion/exclusion criteria for both the study group and the control group. However the results of our study speak in favour of a previous hypothesis by Suris-Swartz *et al.* that patients with BRCA1-2 mutations are only a subgroup within a group of DPBOC patients. This hypothesis was also confirmed by some preliminary data of BRCA1-2 gene testing of our patients: only one out of four was found to be a mutation carrier.

According to the conclusions of Suris-Swartz *et al.*, the subgroup with BRCA1-2 mutations could be represented by those patients who developed breast cancer first and also before the age 50. Our preliminary results do not confirm such a conclusion. Nonetheless, according to our results the subgroup with BRCA1-2 mutations could represent only a small part of the patients with DPBOC; otherwise its influence in our study would have been greater in terms of the differences in clinical and pathomorphological prognostic factors for ovarian cancer between the study group and the control group.

Fishmann *et al.* [20] also reported that patients with multiple primary cancer more frequently had a positive family history of some kind of cancer. This same phenomenon was observed in our study, too, though the difference did not reach the level of statistical significance ($p = 0106$). Furthermore, Bergfeldt *et al.* in 2001 reported [23] that any kind of cancer detected in close relatives increased the risk for secondary primary cancer of the breast after the first one of the ovary. We believe these findings may influence clinical risk assessment and thereby also the intensity of follow-up of each individual patient after the completed treatment of the first primary cancer of the breast or ovary because it seems that patients with a positive family history of some kind of cancer are at a greater risk of developing DPBOC even if they are not carriers of the BRCA1-2 mutation.

## Conclusion

The results did not confirm the hypothesis that in patients with DPBOC (epithelial), other risk factors, besides specific family history and some prognostic factors, are more expressed; yet they indicated some differences between the groups regarding the risk factors. As regards the prognostic factors, we even found a significantly higher percentage of Stage I epithelial ovarian cancer in the DPBOC group, with no difference in diagnostic modality of detection.

Therefore, our results did not confirm the hypothesis supported by some recent studies on small series, on which we also based our present study, that nearly all patients with DPBOC are carriers of the BRCA1-2 mutation. From genetically supported studies, BRCA1-2-related cancers are actually known to be more aggressive. According to our results, it is more probable that patients with BRCA1-2 mutations are only a subgroup within the group of patients with DPBOC, as has also been suggested in some other studies. Our preliminary results of BRCA1-2 testing are also indicative of this.

Yet, considering the relatively small number of patients included in our study, our results may serve as a rough estimation only. While low incidence of DPBOC represents an important limitation to the investigations anywhere in the world, we are additionally confronted with the limitation of the small size of the Slovenian population. It will therefore be very useful to establish an international collaboration of research centres in order to obtain greater series and thereby also more reliable data.

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