Primary and Metastatic Ovarian Cancer in Patients with Prior Breast Carcinoma. Pre-operative Markers and Treatment Results

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Abstract. *Background: The pre-operative diagnosis of primary and metastatic malignant ovarian tumors in patients treated for breast cancer is difficult. The objective of this study was to analyze and compare the characteristics and outcome of women with a history of breast cancer in order to identify pre-operative markers useful in differential diagnosis and the role of surgery in their management. Materials and Methods: The medical records of 36 patients with a history of breast cancer, who had been operated on either for primary or metastatic cancer between 1987 and 2003, were reviewed retrospectively. Results: Twenty-seven patients had been diagnosed with primary epithelial ovarian cancer (POC) and nine had metastatic disease (MOC), resulting in a 3:1 ratio. The median age of breast and ovarian cancer diagnosis was 45 and 56 years, respectively, and the median interval was 8 years. The serum CA 125 level was elevated in the majority of cases, in 70% of the POC group and 56% of the MOC, but the median level was higher, though not statistically significant, in the former. Serum CA 15-3 levels were elevated >100 U/ml in 89% of patients with MOC (p=0.0002). BrCA mutation risk, as calculated with the BRCAPRO software program, was 41.8% and 9% in primary and metastatic tumors, respectively (p=0.0477). Ovarian spread was not the only site of metastatic breast cancer in 55.5% of the MOC group, compared to 11% of the POC patients Disease was disseminated in the abdominal cavity at the time of diagnosis in both groups, however, 78% of patients had unilateral tumors in the POC group and bilateral disease in the MOC (p=0.0133). Cytoreduction to less than 2 cm tumor diameter was feasible in 67% of primary and 44% of metastatic neoplasms. In the follow-up period (12-204 months), the median survival was 10 months for patients with metastatic disease, compared to 33 months for those with primary tumors (p<0.05). Conclusion: Small bilateral ovarian enlargements and minor serum elevation of CA 125 titers in patients with initial Stage IV breast cancer, suffering from multiple metastatic disease, are likely to illustrate MOC. Unilateral ovarian mass and high serum levels of CA 125 in apparently disease-free patients with a positive family history and high prevelance of BRCA mutations are suggestive of primary tumors. Optimal cytoreduction was feasible in both groups, but survival was longer in patients with primary tumors (p<0.05).*

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Breast cancer is the most common malignancy in women, with approximately 1,200,000 new cases diagnosed annually worldwide and is one of the leading causes of death among women (1).

Population screening with mammography has increased the numbers of breast cancer diagnosed in younger patients at an early stage and has contributed to improved survival from the disease. As a subsequence, there is a higher risk that these patients may develop another primary malignant tumor, including that of the ovaries.

The estimated risk of developing primary ovarian cancer is approximately double for all patients with prior breast cancer. The relative risk (RR) can be even higher, RR=17 (3.5-50) in *BRCA 1* or *2* mutation carriers (2). Furthermore, metastatic breast cancer to the ovaries is also not uncommon and represents 6-27.8% of all ovarian malignant tumors (3, 4). It is important to note that improved survival has been reported in ovarian cancer patients with *BRCA 1*

mutations, while abdominal metastasis of breast cancer carries a dismal prognosis (5-8). A pre-operative workup has not been able, to date, to differentiate primary ovarian cancer from metastatic breast cancer to the ovaries. Therefore, gynecological oncologists are often challenged regarding the choice of the appropriate treatment planning for women with a history of breast cancer presenting with an adnexal mass suspicious of malignancy. Furthermore, at the present time, there are no clear guidelines regarding the role of surgical cytoreduction in metastatic breast cancer to the ovaries.

The objective of this study was to analyze and compare the characteristics and outcome of 36 patients with a history of breast cancer, who had been operated on either for primary or metastatic ovarian cancer, in order to identify pre-operative markers useful in differential diagnosis, as well as the role of surgery in their management.

Materials and Methods

During the study period (1987-2003), 36 patients with prior invasive breast cancer underwent laparotomy for primary ovarian cancer (POC) or metastatic breast cancer to the ovaries (MOC). Individual medical records for both ovarian and breast cancer were retrospectively reviewed for patient and disease characteristics. Data on patient age at diagnosis of breast cancer, stage and histological type, site and outcome of extra-ovarian metastatic breast cancer, family history of breast or ovarian cancer, lymph node status, *BRCA* mutation status, time-interval to ovarian tumor exploration, pre-operative CA 125 and CA 15-3 serum levels, presence of ascites, type and extent of abdominal surgery, histology of the adnexal mass and overall survival were recorded. The histological slides were reviewed at a combined Gynecology Service–Pathology conference, before being included in the data base.

For the purpose of this study the clinical presentation of the abdominal disease was divided into symptom-related and asymptomatic, diagnosed during routine follow-up tests.

A positive family history was established if the patient had one first-degree relative with either breast or ovarian cancer. The risk of *BRCA 1* or *BRCA 2* mutations was calculated using the BRCAPRO software (9, 10).

Patients in the study were analyzed in two groups: a) double primary breast and ovarian cancer (POC) and b) metastatic breast cancer to the ovaries (MOC). Comparisons and statistical analysis between the two groups were performed using the Chi-square test for a given characteristic. The results were considered statistically significant if the p value was <0.05.

The potential risk of *BRCA 1* and *BRCA 2* mutations was calculated in each individual case by using the BRCAPRO software, a computer program which implements a statistical model for calculating an individual's probability of carrying a deleterious *BRCA 1* or *2* mutation, neither or both on the basis of the personal cancer status and the history of breast and ovarian cancer among first- and second-degree relatives. The model implements the autosomal dominant Mendelian characteristics of the genes and incorporates prevalence and penetrance on the basis of the published results.

Table I. *Patient characteristics.*

Characteristics	POC	MOC	p value
Median age at BC diagnosis	49 (34-74)	42 (30-57)	
Median age at OC diagnosis	58 (39-81)	54 (39-73)	
BC-OC interval <5 yrs	8 (30%)	3 (44%)	NS (p=0.9998)
BC-OC interval >5 yrs	19 (70%)	6 (56%)	
Family history positive BC-OC	8 (30%)	1 (11%)	NS (p=0.8724)
No family history BC-OC	19 (70%)	8 (89%)	
Mean *BRCA 1-2* mutation risk	41.8% (50-94%)	9% (0.6%-69%)	
Mutation risk >20%	19 (70%)	1(11.11%)	p=0.04
Mutation risk <20%	8 (30%)	8 (88.88%)	

POC = primary ovarian cancer.
MOC = metastatic breast cancer to the ovaries.
BC = breast cancer.
OC = ovarian cancer.

The survival probability data were computed using the Kaplan-Meier method and differences in survival between patient groups were calculated using the log-rank test.

Statistical analysis was performed with STATA Version 8.0 (11).

Results

Twenty-seven patients were diagnosed with POC and nine had MOC. Three patients from group 1 and one patient from group 2 had a diagnosis of bilateral breast cancer, either synchronous or metachronous. The median age at diagnosis of breast cancer and ovarian tumor was 49 and 58 years in the POC group and 42 and 54 years in the MOC, respectively (Table I) . The mean interval between the events was 8.5 years (range, 0-25) and 10.3 years, respectively (range, 2-20). In 96% of the patients in group 1 (n=26) the breast cancer diagnosis preceded that of ovarian cancer by more than a year.

A family history of breast cancer or ovarian cancer in a first-degree relative was reported in 30% of the patients with POC compared to 11% among the patients with MOC (Table I). The *BRCA* mutation risk in patients with POC ranged between 50%-94% and the mean *BRCA* mutation risk was 41.8%. Over 70% of all patients with POC had an estimated *BRCA* mutation risk of at least 20%. The risk in MOC patients ranged between 0.6%-69%, with a mean risk of 9%. Over 70% of all patients had an estimated *BRCA* mutation risk of less than 1.6%.

Infiltrating ductal carcinoma was the intitial diagnosis in 13 patients (48%) in group 1 and in six patients (66.6%) in group 2. One patient from group 1 had a myeloid histology and one from group 2 had a mixed type (ductal and lobular). The remaining histological reports on breast cancer were unknown (Table II).

Table II. *Breast disease characteristics.*

Characteristics	POC	MOC	*p* value
BC lymph node positive status	9 (33%)	7 (77.7%)	NS ($p=0.2487$)
Ductal BC	13 (48%)	6 (66.6%)	
Myeloid BC	1	-	
Ductal-lobular BC	-	1	
N/A breast histology	13	2	
CA 15-3 >100 U/ml	2 (8%)	8(88.8%)	$p=0.0002$
History of TMX therapy	20 (74%)	6 (66.6%)	
Extra-ovarian metastasis	3 (11%)	5 (55.5%)	NS ($p=0.10$)
Stage IV	4 (15%)	6 (66.6%)	NS ($p=0.06$)

POC = primary ovarian cancer.
MOC = metastatic breast cancer to the ovaries.
BC = breast cancer.
TMX = Tamoxifen.
NS = Not significant.
N/A = Non available.

Table III. *Ovarian cancer characteristics.*

Characteristics	POC	MOC	*p* value
Presentation /symptom-related	20 (74%)	6 (67%)	NS ($p=0.9960$)
Presentation/ routine follow-up	7 (26%)	3 (33%)	
Ascites	10 (37%)	7 (77,7)	NS ($p=0.3431$)
CA 125 >80 U/ml	19 (70%)	4 (44%)	NS ($p=0.74$)
FIGO stage III-IV	22 (81%)	8 (89%)	NS ($p=0.99$)
Serous histology	18 (66.5%)	metastatic	
Endometrioid histology	4 (15%)	metastatic	
Histology N/A	5(18.5%)	metastatic	
Unilateral	21(78%)	1 (22%)	
Bilateral	6 (22%)	8 (78%)	$p=0.01$
Optimal cytoreduction	18 (67%)	4 (44%)	NS ($p=0.84$)
Median survival	33 months	10 months	$p<0.05$

POC = primary ovarian cancer.
MOC = metastatic breast cancer to the ovaries.
NS = No significant.
N/A = Non available.

Axillary lymph nodes were positive in nine patients (33%) with POC and in seven patients (77.7%) with MOC. The majority of patients in group 1 had early-stage breast cancer when the diagnosis was made, while the 66.6% in the MOC group had stage IV (Table II).

Tamoxifen was widely used before the 1990's for post-menopausal patients with breast cancer who had positive estrogen receptor proteins. Twenty patients (74%) with POC and six (67%) with MOC in our study had received tamoxifen therapy (Table II).

There were no other obvious metastatic disease sites, apart from the abdomen, at the time of the second operation. However, metastases of breast cancer outside the pelvis and abdomen (bone, liver, skin metastasis) were noted in three patients (11%) of the POC group and in five patients (56%) of the MOC group sometime prior to ovarian tumor diagnosis (Table II).

Eight patients (88.8%) with MOC and two (8%) with POC had higher serum levels of CA 15-3 (>100 U/ml). The median serum level of CA15-3 for patients with MOC was 120 (50-300 U/ml) and for those with POC was 25 U/ml (Table II).

Ovarian tumors were diagnosed in 20 patients (74%) with POC following an investigation of their symptoms (vaginal bleeding, ascites, abdominal girth, pelvic pain), while in seven patients (26%) the diagnosis was made as a consequence of follow-up examination. Ascites was present in ten patients (37%) with POC (Table III). Six patients (67%) with MOC had symptoms and three (33%) were asymptomatic. Ascites was present in seven patients (77.7%) with MOC.

Nineteen patients (70%) with POC and four (44%) with MOC had serum CA 125 levels higher than 80 U/ml (Table III). The median level of serum CA 125 for patients with POC was 2470 U/ml (range 50-12790) and for MOC, 846 U/ml (range 11-5472).

Patients with either POC or MOC (81% and 89%, respectively) were likely to present with disseminated abdominal disease corresponding to FIGO stages III and IV (Table III).

The analysis of ovarian histopathology in the group 1 patients revealed that 66.66% were serous cystadenocarcinomas.

Primary ovarian tumors were more often unilateral (78%), while bilateral tumors were usually encountered in metastatic disease ($p=0.01$) (Table III). Eighteen patients with POC (67%) and four patients with MOC (44%) had undergone optimal cytoreduction (max. tumor diameter <2 cm).

In the follow-up period of 12-204 months, the median survival was shorter in the MOC group, reaching 10 months, compared to 33 months for patients with POC ($p<0.05$) (Table III).

Discussion

Gynecological oncologists, mainly those practicing in cancer centers, are at times faced with the dilemma of surgically exploring or systemically treating patients with a history of breast cancer, presenting with an adnexal mass suspicious of malignancy (12). In order to reach a decision, the high incidence of a second primary ovarian cancer (RR=2) and the favorable prognosis of the disease in the context of a hereditary syndrome must be considered. On the other hand, visceral metastases of breast cancer behave more aggressively than bone or liver

metastatic tumors and the role of surgery in their treatment has been poorly studied (13, 14).

Curtin *et al.* reported 121 patients with prior breast cancer who presented with an ovarian tumor. The authors noted a 50% incidence of malignancy and a 3:1 ratio of POC to MOC. A number of publications have supported these findings as well as our own data (POC:MOC ratio = 3:1) which are also in accordance (15).

The mean age of breast and ovarian cancer diagnosis in the literature is in the range of 47-50 and 55-60 years, respectively (12, 15-18). The corresponding figures in our material were similar for patients in the POC group, *i.e.,* 49 and 58 years. However, the median age of women in the MOC group was younger, at 42 and 54 years (Table I). Currently, available data are limited regarding the time-interval between the two events for women who develop dual primary cancers of the breast and the ovaries. In a study by Olawaiye *et al.*, the time-interval between the diagnosis of breast and ovarian carcinoma was 4 years and disease was diagnosed at an early stage I-II (65%) (3). In our study, the majority of patients with POC had early stage breast cancer and the median interval was 8.5 years.

The time-interval between the initial breast cancer diagnosis and metastatic ovarian cancer has been reported to be from 60-104 months. It is postulated that longer time-intervals have a favorable influence on survival, probably reflecting a less aggressive tumor biology or more enthusiastic surgical effort (12, 16). In an older study, the interval was rather short (median of 11.5 months). This difference can be attributed to the fact that, in this series, most metastases (76%) were incidentally found at the time of oophorectomy, performed for hormonal castration, as opposed to other reports where the surgery had been motivated by a pelvic mass (17) .

The mean time-interval between breast cancer diagnosis and metastatic ovarian disease was long in this study (10.3 years), and was even more pronounced than in the POC group. One possible explanation could be the reluctance to operate on small pelvic tumors diagnosed early after breast cancer treatment. Furthermore, a more detailed look at the data suggests that many of this group of patients were submitted to multiple and prolonged therapeutic schemas for metastatic disease, mostly to the bones (Table I).

Invasive ductal carcinomas and stage IV disease have been reported to account for intra-abdominal dissemination (12). Ductal histology is also more common in patients with prior breast cancer who subsequently develop familial or sporadic ovarian cancer (3). In our small series, the majority of patients with MOC had initial stage IV breast cancer, while ductal carcinoma was the most common histological type encountered in both groups ($p=0.0600$) (Table II).

A substantial number of patients with MOC in the literature (45%) (2, 12) , as well as in our material (55.5%), had been treated for metastatic disease in sites other than the ovaries, prior to surgical exploration. The corresponding figure in the POC group of 11% was significantly lower ($p=0.1026$).

It has been estimated that 88% of women with both breast and ovarian cancer carry *BRCA 1* mutations (19), compared to less than 5 % for all ovarian cancer patients (20, 21). The 88% estimate was obtained from women attending high-risk clinics and, thus, may be somewhat higher than in a sample from the general population. Various authors have reported that the actual incidence of *BRCA 1* mutations in patients with both breast and ovarian cancer is over 50% (18, 22-24).

A significantly higher percentage of patients with POC *versus* MOC reported having a first-degree family member with either one of these cancers ($p=0.8724$). Indirect evidence, using the BRCAPRO software program, suggested that breast cancer mutation risk was higher in the POC group 41.8%, compared to the MOC group 9% ($p=0.0477$). The risk was even more pronounced if patients had a history of bilateral breast cancer before the age of 50, when applying the BRCAPRO statistical model (Table I).

Patients treated for breast cancer are expected to be under close follow-up. Approximately 50% of published cases were asymptomatic and diagnosed at the time of routine check up. A high percentage of patients in both groups reported herein (74% and 67%, respectively), were investigated for symptom complaints, mostly abdominal pain, that resulted in ovarian tumor identification ($p=0.9960$). This could be attributed to the long disease-free interval observed in both groups and the prolongation of the follow-up visits.

Delay in diagnosis, as well as tumor biology, could be responsible for the extensive dissemination of the disease in the abdomen at the time of surgical exploration mentioned by other authors and found in over 80% of the population in this study. Considering the difficulty of intra-operative frozen-section diagnosis and the paucity of solid data to support maximal surgical cytoreduction in MOC, surgery was carried out with caution at all times. Nevertheless, cytoreduction to less than 2 cm and maximum tumor diameter was achieved in 67% of patients with advanced, stages III and IV POC ($p=0.8437$). Radical surgery was not feasible in 56% of our patients with MOC, compared to 32% in a large series from a specialized center (16).

Bilateral nodular or infiltrating disease in small-sized ovaries (78%) and the presence of ascites (77.7%) were more frequent ($p=0.0133$) in MOC and could be considered as clinically suggestive of metastatic disease (Table III). Billaterality, as a characteristic feature of metastatic ovarian tumors, has been identified in 59-75% of cases in other, larger series, as well (17, 25, 26) .

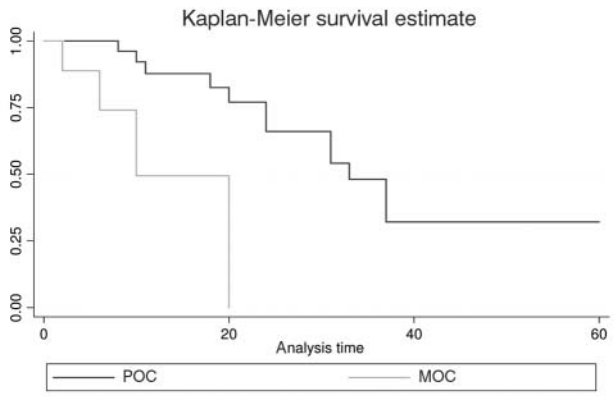

Figure 1. *Survival using the Kaplan-Meier curves, in patients with a history of breast cancer, presenting with POC and MOC.*

The peritoneal dissemination of primary or metastatic tumors is known to indiscriminately elevate the serum CA 125 levels. Therefore, the primary or metastatic nature of an adnexal mass canot be based on the positivity of this marker (25) ($p=0.7419$). However, higher serum CA 125 levels (>80 U/ml) and lower levels (CA 15-3 <100 U/ml) of breast cancer antigen levels were detected in patients with primary tumors, as opposed to metastatic disease ($p=0.0002$).

Serous papillary adenocarcinomas were the most frequent histological type of POC (44%) Previous studies have shown that this morphology is more often found in familial ovarian cancer, compared to sporadic disease (5).

The ovarian cancer death rate among 824 women with a history of breast cancer was significantly lower than that of a cohort of 25,637 women with ovarian cancer only, according to the recent SEER, USA study (27). Other authors agree that survival is improved and is in the range of 77-79 months *versus* 29-30 months, respectively (6, 7, 14). Patients with MOC have a poor prognosis, as shown by their short median survival, in this, as well as in other reports in the literature (11, 16). The survival in the POC group was 33 months, longer than in patients with MOC ($p<0.05$) (Figure 1), but nevertheless lower than corresponding figures in the literature (6, 7, 14).

The pre-operative diagnosis of POC compared to MOC remains difficult. The intra-operative identification of MOC may be suspected by disease spread and confirmed by frozen section, but it is the surgeon's responsibility to proceed with aggressive tumor resection or not. Published data suggest that there may be a role for maximal surgical effort, even in metastatic ovarian cancer from the breast, and that the residual tumor volume may be of prognostic significance. However, the survival advantage conferred by this methodology remains to be determined and guidelines are not clearly defined (3, 16, 28-29).

Conclusion

Small bilateral ovarian tumors, presenting in an initial stage IV breast cancer patient with metastatic disease, low elevation of CA 125 titers (<80 U/ml), higher levels of serum breast cancer antigens (>100 U/ml) and low *BRCA* mutation probability (<20%) outline a subgroup of patients more likely to suffer from metastatic disease with short-term survival. On the other hand, unilateral ovarian mass, limited extra-ovarian metastases prior to abdominal exploration, a high prevelance of *BRCA* mutations (>20%), bilateral breast cancer, high levels of CA 125 (>80 U/ml) and low levels CA 15-3 (<100 U/ml) in the serum define those patients with POC that benefit from radical tumor resection.

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