Risk of ovarian cancer in breast cancer patients- prognostic factors and time interval

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Abstract

Breast cancer is the most common malignancy diagnosed in women accounting for 23% of all malignancies worldwide. Epithelial ovarian cancer is the most lethal gynecologic cancer leading to 47% of all deaths from cancers of female genital tract. Women with a history of breast cancer have a two fold higher risk of developing a subsequent ovarian cancer.

Patients and methods: Among 770 patients with cancer breast diagnosed between 1998 to 2005, ten patients developed ovarian cancer.

Analysis of various predisposing factors was done retrospectively. These factors included age at first diagnosis, histopathologic subtype, family history and time to diagnosis of secondary ovarian cancer.

Results: Mean age at diagnosis of breast cancer was 43 years (range 34-50). During a mean follow up of 54 months, 10 cases of secondary ovarian cancer were recorded in the study cohort of 770 women with breast cancer. Mean time to ovarian cancer diagnosis was 6 years. Positive family history was recorded in 25% of the patients whose relatives had either breast or ovarian cancer.

Conclusion: In our interim analysis, it was founded that the development of secondary cancer in the study group was higher among younger patients (<40 years) as well as patients with positive family history. Close medical surveillance, and perhaps even prophylactic oophorectomy, might be justified in high-risk group.

Introduction

Breast cancer is the most common malignancy diagnosed in women accounting for 23% of all malignancies worldwide 1. Epithelial ovarian cancer is the most lethal gynecologic cancer leading to 47% of all deaths from cancers of female genital tract 2.

Women with a history of breast cancer have a two fold higher risk of developing a subsequent ovarian cancer 3. This risk seems to be highest among or even confined to women who are younger than 50 years at diagnosis of breast cancer4. Particularly the high rate of primary ovarian cancer is found in breast cancer patients with mutations in the high penetrance genes BRCA1 or BRCA2, which are associated with hereditary breast cancer and ovarian cancer5,6. Such women experience almost 50% cumulative risk of developing ovarian cancer by the age of 70 years 7.

To estimate the risk of subsequent ovarian cancer in clinical setting, use of information such as age at onset of breast cancer, and presence of family history would be more practical than mutation screening8, especially if not present in many centers. Moreover, mutation in BRCA1 or BRCA2 are present in small numbers in all patients with breast cancer and ovarian cancer, and they seem to account for only a limited fraction of all breast cancers with a genetic component9,10 The average interval between the diagnosis of the two primaries is unknown.11

Patients and Methods

In this study, we explored a large population of breast cancer patients diagnosed between 1998 and 2005 in the department of clinical oncology private section, Cairo University, Aswan oncology institute and health insurance patients. We analyzed cases that developed secondary ovarian cancer as regards age at first diagnosis, stage and histology of each cancer type at diagnosis. Special emphasis was directed to the age at diagnosis of breast cancer, pathology and time interval to develop secondary ovarian cancer as well as the presence of family history (first-degree relative such as mother, sister, daughter or father or brother or close relative as grandparent, aunt or uncle, nephew or niece). Patients with a time interval less than 12 months between the two diagnoses were excluded to reduce the likelihood of including patients with a metastatic primary tumor 4.

Study outcome included overall survival and time to progression, each measured from the time of definitive surgery. The duration of overall survival was the interval between diagnosis and death. Data were censored at the last follow-up of patients.

Statistical method

Kaplan Meier method was used for estimating overall survival, and relapse free survival. P-value is considered significant at 0.05 level. Numerical data were described in terms of means and medians for central tendency and standard deviation and range, minimum and maximum for dispersion.

Results

Among the study group, 770 women with breast cancer presented to department of clinical oncology private section, Cairo University Aswan oncology institute and health insurance between 1998 and 2005, 10 patients developed secondary ovarian cancer. The demographics of the studied population are presented in table 1. The mean age at breast cancer diagnosis was 43 years (range 34-50) during a mean follow up of 54 months.

Table 1: Correlation between various clinical and pathological variables in patients with cancer breast and secondary ovarian cancer

Variables	Breast cancer		Ovarian cancer	
	Number	%	Number	%
Age				
34-44	7	70%	4	40%
>44-50	3	30%	6	60%
Mean age	43		48	
Stage				
I, II	8	80%	3	30%
III, IV	2	20%	7	70%
Histology				
Ductal	9	90%		
Lobular	1	10%		
Serous			6	60%
Mucinous			1	10%
Endometroid			2	20%
Clear cell			1	10%
Grade				
Grade I,II	3	30%	4	40%
Grade III	7	70%	6	60%
Family history	3	30%	1	10%

Eighty percent of primary breast cancer patients were stage I-II, 90% were invasive duct carcinoma with 70% being high grade. The histology of ovarian cancer was mostly serous 60%, 20% endometroid and 10% mucinous as well as clear cell. Estrogen Receptor (ER) and Progesterone Receptor (PR) were available in 80% of cases of breast cancer. We found that ER+/PR+ tumors were documented in 5 cases of breast cancer who developed ovarian cancer (62.5%). Among 3280 relatives, 7 cases of breast or ovarian cancer were documented. The pathological characteristics of the study population are presented in table 2.

Table 2: Time interval between diagnosis and survival times in months

Variables	Months	P value
Time interval between diagnosis		
Mean	60	
Median	36	
Range	24- 128	
Survival times		
Breast cancer DFS	61	
Ovarian cancer DFS	39	0.013
Breast cancer OS	115	
Ovarian cancer OS	42	0.019
Combined breast and ovarian cancer OS	115	

Disease free survival (DFS), Overall survival (OS)

Mean time interval to ovarian cancer diagnosis was 60 months with a median of 36 months ranging from 24 to 128 months. The overall survival of breast cancer was 115 months compared to 42 months in those developing secondary ovarian cancer. The overall survival of both groups was 115 months. The progression free survival of primary breast cancer was 61 months versus 39 months for the secondary ovarian.

Table 3: Relation between different variables and secondary ovarian cancer

Variable	Number	%	P value
Age			
34-44	7	70%	
>44-50	3	30%	0.06
Stage			
I, II	8	80%	
III, IV	2	20%	0.01
Histology			
Ductal	9	90%	
Lobular	1	10%	0.001
Grade			
Grade I,II	3	30%	
Grade III	7	70%	0.06

Discussion

In our study two-fold increased risk of primary ovarian cancer in women with primary breast cancer was reported. Women without a family history of breast or ovarian cancer, this high risk seemed confined to patients diagnosed at young age.

Our most interesting finding, however, was the increased risk in women with early-onset breast cancer, and those with family history of breast cancer or ovarian cancer. Also noteworthy is the finding that patients with family history, especially if an ovarian cancer is present, have a higher risk of ovarian cancer. This risk is present for postmenopausal women, and seems to be constant over time.

In a study done by Bergfeldt, et al, the Mean age at breast-cancer diagnosis was 48 years (range 11–66 years). During a mean follow-up of 6 years, 122 cases of ovarian cancer were recorded in the study cohort of 30 552 women with breast cancer. Mean time to ovarian cancer diagnosis was 7 years (SD=5·9). Among 146 162 relatives, 3689 cases of breast or ovarian cancer were documented. Patients without any family history of breast or ovarian cancer had a 60% increased risk overall, but the excess risk seemed confined to premenopausal ages, and was three-fold in women younger than 40 years (3·3, 2·2–4·9). A family history of breast or ovarian cancer in a close relative was associated with a four-fold (4·3,

2·9–6·0) increased risk of ovarian cancer, and in women diagnosed before the age of 40 years, the risk was seven-fold (7·3, 3·1–14·3). In patients older than 40 years at diagnosis, the SIRs were smaller but remained raised11.

In our study the mean age of patients at the diagnosis of breast cancer was 43 years, with a range of (34-50) years. The mean time to ovarian cancer diagnosis was 5 years with a range of (2- 10.6) years. Increased risk was found in women with primary breast cancer at the age range of 34-44 years (70%).
Our results expand the knowledge of an association between breast cancer and the risk of subsequent ovarian cancer. . Euhus et al, reported that diagnosis at a young age has been noted as a minor risk factor, and patients with breast cancer who have mutations in BRCA1 or BRCA2 have increased risk 12. Although such mutations are rare (present in <5% of all breast cancer cases), hereditary factors might account for close to 25% of breast-cancer13-15. The average cumulative risks in BRCA1-mutation carriers by age 70 years were 65% for breast cancer and 39% for ovarian cancer16. Therefore, our study lends support to theories of a connection between as yet unknown genes and cancer susceptibility. A reasonable proxy for unknown genetic risk factors might be a family history of breast or ovarian cancer.

In our study the pathology of the majority of breast cancer patients was found to be infiltrating ductal carcinoma (90%). While in ovarian cancer patients papillary serous adenocarcinoma (60%) was found to be more than the other types. This goes with various studies done that revealed the pathology of the breast cancers was found to be infiltrating ductal carcinoma (63%). And showing that invasive ductal carcinoma is the most common pathology in both familial and sporadic breast carcinoma16. On the other hand, the ovarian cancer pathology was more varied. They found papillary serous adenocarcinoma (53%) to be the most frequent type of ovarian cancer histology. This finding is also not unexpected as previous studies have shown that familial ovarian cancer has a higher proportion of serous adenocarcinoma compared to non-familial tumors17, 18.

There is limited data on the reciprocal time interval between metachronous primary breast and ovarian carcinomas. Time interval of women with breast cancer ranged from 48 to 84 months, with a mean of 58 months in many studies9,19. However, many of these studies are limited by small sample sizes obtained from single academic institutions, and it is non significant. In our study the time interval ranged from 24-128 months with a mean of 60 months.

Moreover, we found that the most independent prognostic variables were age at diagnosis and presence of familial history of breast or ovarian cancers.

Therefore we recommend close follow up using radiological (CT chest, abdomino-pelvic) and laboratory investigations (CA125, CA15-3) for detection of early signs of ovarian cancer especially in young patients and those with a positive family history.

Conclusion

In our study, there was an increased risk of secondary ovarian cancer in young patients with breast cancer and those with family history of the disease. Future directions should include searching for gene mutations in this subgroup of patients to determine patients at risk in an earlier stage of disease. Close medical surveillance, and perhaps even prophylactic oophorectomy, might be justified in high risk group.

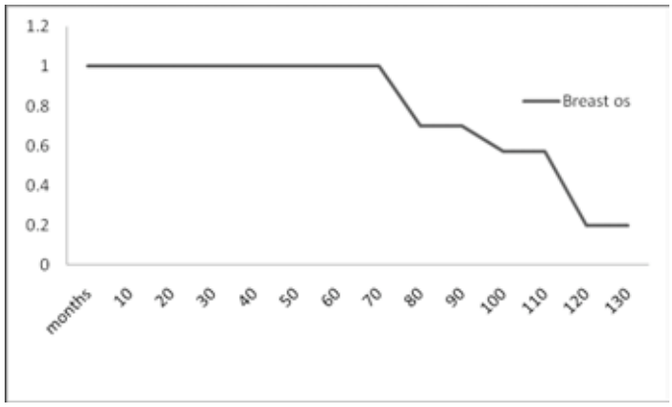

Fig 1: Kaplan–Meier analysis of overall survival (OS) for breast cancer

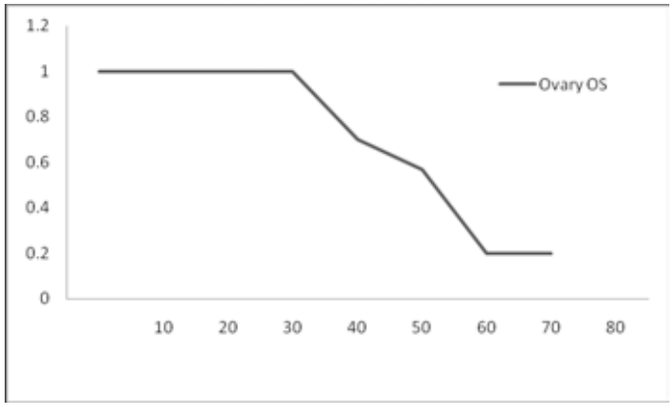

Fig 2: Kaplan–Meier analysis of overall survival (OS) for ovarian cancer

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