Overall survival in BRCA-associated ovarian cancer: case-control study of an Italian series

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Summary

About 10% of all ovarian cancers are due to BRCA 1 and/or BRCA 2 mutations. Some studies have shown that patients belonging to this group have a better survival compared to sporadic groups but data are still inconclusive. The aim of this study was to investigate overall survival in patients with ovarian cancer and germ-line mutations in the BRCA1/2 genes in comparison to high-risk patients, defined as patients with ovarian cancer and a strong family history of breast and ovarian cancer, but who tested negative for the BRCA mutation. We collected all the clinical features and did follow-up. The two groups showed similar characteristics concerning age at diagnosis, histological type and stage. Grade 3 was more frequent in the BRCA group. Survival data did not show any advantage for the BRCA mutated group.

Key words: BRCA1; BRCA2; Ovarian cancer.

Introduction

Ovarian cancer is the most common cause of mortality of tumors from gynecologic origin and is often diagnosed after patients have already progressed to advanced disease stage because of their nonspecific initial symptoms [1]. The standard of therapy for advanced stages is optimal surgery with minimal residual disease (radical hysterectomy, bilateral annessiectomy, appendectomy, omentectomy and lymphadenectomy), followed by chemotherapy with a platinum and taxane combination is the best goal for survival [2].

Epidemiologic data and molecular analysis show that about 10% of all epithelial ovarian cancers are associated with inherited mutations in BRCA1 and/or BRCA2 genes [3]. Hereditary and sporadic ovarian tumors show similar characteristics such as histopathologic type distribution and high-grade frequency; furthermore, the diagnosis is often made at an advanced stage (III and IV) in both cases [3].

In sporadic ovarian cancer Stage III-IV the median 5-year survival is 30% [2].

Estimated risk of developing ovarian cancer in a lifetime in women harboring BRCA1/BRCA2 mutations is about 30-40% for BRCA1 and 15-25% for BRCA2 [4].

Several studies have shown improved survival in BRCA-associated ovarian cancer but a few others suggest a poorer clinical outcome, therefore data are still inconclusive. Interestingly, some investigators have hypothesized that this difference might be due to a different responsiveness to chemotherapeutic agents. The objectivies of the present study were to evaluate the overall survival of ovarian cancer patients and to investgate long-term survival of BRCA1/BRCA2 mutation carriers and non carriers as compared to high-risk breast and ovarian cancer [4].

Revised manuscript accepted for publication July 30, 2010

Patients and Methods

The study was conducted by reviewing patient charts from the Oncology Institute of Veneto and Oncology-Gynecology Department of Mirano, Venice, Italy. All data were abstracted from medical records and original surgery and pathology reports; also information on the patient's vital status was updated through the charts. Since this was a retrospective study, patients enrolled covered a period of 15 years. Some patients were tested almost ten years after their ovarian cancer was diagnosed. Patients were subdivided in two groups: BRCA-related ovarian cancer patients and high-risk breast/ovarian cancer patients, who tested as non carriers for the BRCA mutation. A total of 88 patients affected by epithelial ovarian cancer were included in the study. Forty-eight tested positive for a deleterious mutation in the BRCA 1 and/or 2 gene (34 BRCA1 and 14 BRCA2) and 40 patients were selected as a control group. To complete the genetic testing for the patients already recruited, all patients were approached by their gynecologist/oncologist and, after giving informed consent to participate in the study, blood samples were collected. Genetic mutation assessment was performed at the Oncology Section of the Department of Oncology, University of Padua, Italy.

Analysis were performed with standard laboratory methods. A multiplex polymerase chain reaction was designed to amplify the exons containing the mutations with the use of fluorescence-labeled primers in a single reaction. Samples available for testing included peripheral blood.

Patient characteristics

Data abstracted from charts were collected according to the World Health Organization (WHO) and the stage by TNM classification. For each patient, age at diagnosis, tumor histological type, TNM stage and follow-up were recorded. All patients were treated by the best debulking surgery possible for the stage of disease, followed by a platinum-based chemotherapy regimen.

Different platinum-chemotherapy regimens were considered: carboplatin and taxol (which is the standard chemotherapy for ovarian cancer), cisplatinum (DDP), carboplatin as a single

agent, cisplatinum plus taxol, cisplatinum plus cyclophosphamide plus epirubicin (PEC), cisplatinum plus cyclophosphamide, carboplatin plus taxol plus epirubicin (TEC), and carboplatin plus mitoxantrone.

Statistical analysis

Univariate survival analysis was performed using the Kaplan-Meier method for estimating survival functions and the log-rank test to compare them. All tests were two-tailed and the significance level was set at 5%. Differences in proportion were assessed by means of the chi square test.

Results

Patient survival and other clinical characteristics of the tumors were compared in patients with BRCA1 or BRCA2 mutations and those without mutations.

The clinical features of a total of 88 patients affected by ovarian cancer were analyzed: 48 were associated with a germ-line mutation on BRCA1 or BRCA2 genes and 40 were classified as affected by high-risk ovarian cancer. Median age at diagnosis was 51 years old for inherited ovarian cancer and 54.5 years for the non carrier group. Among BRCA mutation carriers ten out of 34 who carried BRCA1 mutations were diagnosed before age 45, whereas no women who carried BRCA2 mutations were diagnosed at age < 45. Seven ovarian cancers out of 40 in the high-risk group were diagnosed before 45 years. Histological features were found to be similar in both groups: 37 (77.1%) were serous ovarian cancers, seven (14.6%) endometrioid and four (8.3%) anaplastic in the BRCA1/BRCA2 carrier group while 36 (90%) were found to be serous ovarian cancer, two (5%) endometrioid, one (2.5%) clear cell and one (2.5%) anaplastic in the non carrier group.

Tumor grade was G3 in 75% of BRCA 1 and 2 groups and 32.5% in the non carrier group (chi square test p = 0.0196). Grade 1 and 2 was found in 25% of the BRCA 1 and BRCA2 groups and 67.5% in the non carrier group (chi square test p = 0.0133). Advanced stage of disease at the time of diagnosis (Stage III-IV) was found to be 72.9% for patients carrying a deleterious mutation and 43.7% for the non carrier group. Comparison of survival between the two groups for advanced stage did not show any difference (Table 1).

Table 1. — *Patient characteristics*.

Variables	BRCA	Familial cancer
Total	48	40
Stage		
I	9	13
II	4	6
III	28	17
IV	7	4
Grade		
1-2	12 (25%)	27 (67.5%)
3	36 (75%)	13 (32.5%)
First breast cancer diagnosis	7	7
Median age	51 y	54,5 y
Histologic type		
SP: serous papillary	37	36
Non SP	11	4

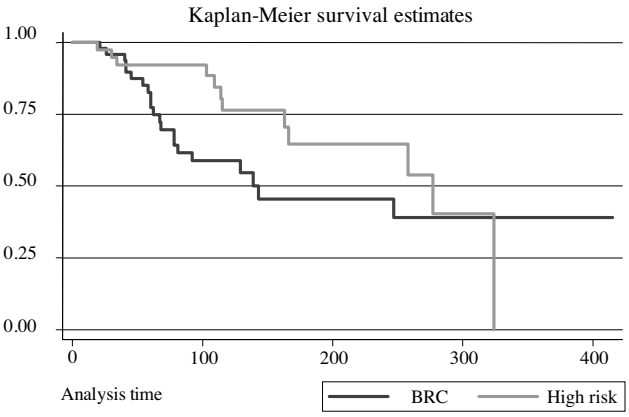

Figure 1. — Median overall survival for the two groups.

Seven women with BRCA1/BRCA2 and seven non carriers had a previous breast cancer diagnosed almost five years before ovarian cancer, and only one patient had first ovarian cancer and then breast cancer, and she is still alive. Treatment at any stage of disease was with a platinum-based chemotherapy regimen. Eight different chemotherapy regimens, as reported in patients and methods, were considered for the treatment of the ovarian cancer. All regimens were platinum-containing therapy and were distributed over 15 years of the patients' accrual.

Despite the advanced stage of disease, median survival from diagnosis for the women with inherited mutations was about 145 months while that for the high-risk group was 280 months. This difference was not statistically significant; the log-rank test for equality of survivor functions ($pr > chi^2 = 0.1352$) is shown in Figure 1.

Discussion

In this retrospective study the clinical features and survival of two groups of ovarian cancer patients were investigated. We wanted to demonstrate if there were any differences in survival between BRCA-positive ovarian cancer patients and a group of high-risk patients tested as non carriers of the BRCA mutations.

To our knowledge there are almost 12 studies comparing survival between the BRCA and sporadic or high-risk ovarian cancer patients; six showed a statistically significant improved survival for BRCA carriers and another six showed no statistically significant difference (Table 2) [6-17].

For example Zweemer *et al*. showed a five-year survival of 47% for non carriers with respect to 40% for carriers [12]. Ramus *et al*. showed 52-month median survival for BRCA 1 and 49 for BRCA2 with respect to 35 months for non carrier consecutive patients (p = 0.5) [13]. Moreover Buller *et al*. [14] and Kringen *et al*. [15] showed similar data with no statistical significance in survival in the two groups of patients. In our study the different distribution of patient characteristics as no G1 and a high number of G3 in 75% of the hereditary ovarian can-

Table 2. — *BRCA-ovarian cancer median survival*.

References/year	BRCA-ovarian cancers Median survival	Sporadic cancer Median survival
Pharoah *et al*. 1999	20.6 (BRCA1), 16 (BRCA2) months	19.5 months
Aida *et al*. 1998	91.43 months of DF interval	40.92 months of DF interval
Boyd *et al*. 2000	40 months	25 months
Cass *et al*. 2003	91 months	54 months
Johannsson *et al*. 1998	30% of BRCA1 cases at 5 years	45% control cases at 5 years
Ben David *et al*. 2002	53.4 months	37.8 months
Zweemer *et al*. 2001	40% 5-years	46% 5-years
Ramus *et al*. 2001	52 months BRCA1 49 months BRCA2	35 months
Buller *et al*. 2002	4,5 years	4.6 years
Kringen *et al*. 2005	33% BRCA1 5-years	23% 5-years
Pal *et al*. 2007	27% BRCA1 4-years 87% BRCA2 4-years	12% 4-years
Chetrit *et al*. 2008	53.7 months	37.9 months

DF = disease-free.

cer patients showed a statistically significant difference with respect to the high-risk group ($p = 0.0196$) even if it did not correlate with a worse survival. In Chetrit *et al.'s* study grade of tumor was found to have a significant difference in survival between the two groups. The population was homogeneous and selected in the same polulation with the attempt to avoid bias [17].

In our retrospective study the small sample size of cases did not allow for a good differentiation between the influence of BRCA1 and BRCA2 on survival. To understand those non statistically significant results we may have to consider some bias in the accrual of patients and the small number of patients could be the reason for low statistical power.

Other studies on clinical characteristics of patients with hereditary *vs* sporadic ovarian cancer have suggested two possible mechanisms for improved survival of BRCA group carriers: 1) potential indolent clinical behavior due to a lower rate of mitotic index despite a more aggressive phenotype, or 2) a more favorable response to chemotherapy.

Different functions of BRCA genes can enhance those hypotheses such as maintaining chromosome stability, regulating cellular proliferation and DNA repair; in particular, the proteins encoded by the BRCA genes are involved in homology-directed repair of DNA double strand breaks [18-20].

Taniguchi *et al*. suggest a molecular mechanism for understanding genetic instability in ovarian cancer cells through the involvement of Fanconi proteins.

Fanconi protein protect cells against cell death and genotoxicity induced by cross-linking agents and work together with BRCA1 and BRCA2 proteins in the DNA repair pathway as well. Hypomorphic BRCA2 mutations lead to a type of Fanconi anemia (FANC-RRCA pathway) in which BRCA2 fails to bind to RAD51 in response to genotoxic agents. Such an inactivation of the FANC-BRCA pathway can give rise to cells sensitive to DNA cross-linking agents such as cisplatin [21].

Tailored chemotherapy for BRCA 1 and BRCA2 ovarian cancer based on their higher sensitivity to double breaking DNA-strand agents can be a way to improve their survival. In this study it does not seem that the platinum-containing regimen changed survival in the BRCA group considering their lack of BRCA1 and BRCA2 function.

Another explanation of why there was no difference in survival between the two groups could be that in the high-risk group there were some possible confounders or modifiers such as other genes involved in the impact on prognosis.

Conclusion

Several studies as well as ours have investigated survival in BRCA-related ovarian cancer. Our study did not find any improvment in survival for hereditary ovarian cancer patients with respect to high-risk cases. To our knowledge, today randomized studies show that prophylactic surgery is the only treatment to reduce ovarian cancer risk in BRCA-mutated women [22]. Our future goal will be to define recomendations for treatment and prevention of ovarian cancer in our region and to study the side-effects of early menopause in women submitted to prophylactic surgery.

Acknowledgement

We thank Emma D'Andrea for BRCA analysis.

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