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Fifteen-year survival of invasive epithelial ovarian cancer in women with BRCA1/2 mutations – the National Israeli Study of Ovarian Cancer

Ofer Lavie [a,b], Angela Chetrit [c], Ilya Novikov [d], Siegal Sadetzki [c,e,*], , for the National Israeli Study of Ovarian Cancer [1]

[a] Gyneco-oncology Unit, Department of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel
[b] Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel
[c] Cancer & Radiation Epidemiology Unit, Gertner Institute for Epidemiology & Health Policy Research, Chaim Sheba Medical Center, Tel Hashomer, Israel
[d] Biostatistics Unit, Gertner Institute for Epidemiology & Health Policy Research, Chaim Sheba Medical Center, Tel Hashomer, Israel
[e] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

HIGHLIGHTS

- Women with Invasive EOC carriers of BRCA1/2 mutation have lower 5, 10, and 15 years all-cause mortality than non-carriers.
- In the first 5 years, being a carrier was associated with a 26% reduction in mortality compared to non-carriers.
- For women who survived 5 years and more, being a BRCA carrier was not associated with better survival in the subsequent years.
- These results may have implications for the clinical management of BRCA carrier patients and for predicting their prognosis.

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ABSTRACT

Objective. Compare 5, 10 and 15 year survival in invasive epithelial ovarian cancer, between patients with and without BRCA1/2 germ line mutation in a nonselective group of patients diagnosed during 1994–99.

Methods. The analysis was based on 779 Jewish patients: 229 carriers to the Ashkenazi Jewish founder mutations in BRCA1 (185delAG; 5382insC) and BRCA2 (6174delT); and 550 non-carriers. Clinical characteristics were abstracted from the patients' medical records and vital status was updated through the National Population Registry up to 11/2015. The Kaplan-Meier method, log-rank tests, and Cox-regression model were used for survival analyses.

Results. By the end of the follow-up period, (range 1–20 years), 629 (80.7%) deaths occurred. While considerably higher survival was observed during the first 5 years from diagnosis among carriers compared to non-carriers (46.7% vs. 36.2%, $p = 0.0004$), the survival rates at 15 years were 22.3% vs. 21.8% respectively ($p = 0.04$). The age-adjusted hazard ratio for all-cause mortality of carriers versus non-carriers was 0.74 (95%CI 0.60–0.91) in the first 5 years. For women who survived 5 and 10 years, the age-adjusted hazard ratios for mortality during 5 additional years, of carriers compared to non-carriers, were 1.38 (95%CI 0.93–2.04) and 1.08 (95% CI 0.61–1.92), respectively.

Conclusion. The results of this study, with up to 20 years follow-up, support studies with shorter follow-up that suggested that the advantage in survival observed among BRCA1/2 carriers during the first 5 years decreases over time. Clinically, this may have implications for follow-up and therapy, especially of new agents that are particularly effective in BRCA carriers.

* Corresponding author at: Cancer & Radiation Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer 5262000, Israel.
E-mail address: siegals@gertner.health.gov.il (S. Sadetzki).

[1] Shmuel Anderman, MD; Marco Altaras, MD; Shaul Anteby, MD; Jack Atad, MD; Amiram Avni, MD; Amiran Bar-Am, MD; Dan Beck, MD; Uzi Beller, MD; Gilad Ben-Baruch, MD; Yehuda Ben-David, MD; Haim Biran, MD; Moshe Ben Ami, MD; Angela Chetrit, MSc; Shulamit Cohan, MD; Ram Dgani MD; Yehudit Fishler, CTR; Ami Fishman, MD; Eitan Friedman, MD; Ofer Gemer, MD; Ruth Gershoni, MD; Walter Gottlieb, MD; Reuvit Halperin, MD; Galit Hirsh-Yechezkel, PhD; David Idelman, MD; Rafael Katan, MD; Yuri Kopilovic, MD; Efrat Lahad, MD; Liat Lerner Geva, MD; Hanoch Levavi, MD; Albert Levit, MD; Tally Levy, MD; Beatriz Lifschiz-Mercer, MD; Flora Lubin, MSc, RD; Zohar Liviatan, MD; Jacob Markovich, MD (deceased); Joseph Menzcer, MD (deceased); Baruch Modan, MD (Chairman, deceased); Hedva Nitzan, RN, MPH; Moshe Oettinger, MD; Tamar Peretz, MD; Benjamin Piura, MD; Shulamit Rizel, MD; Siegal Sadetzki, MD; Adi Shani, MD; David Schneider, MD; Michael Shtark, MD; Mariana Shteiner, MD; Zion Tal, MD; Chaim Yaffe, MD; Ilana Yanai, MD; Shifra Zohar, MD; and Ahuva Zoltan, RN, BA.

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1. Introduction

Epithelial ovarian cancer (EOC) is the fifth most common cause of cancer deaths in women in the western world [1]. The standard first line treatment is a combination of debulking surgery and taxane and platinum chemotherapy [2]. However, despite these treatments, the prognosis of EOC patients is poor, with an overall 5-year survival rate ranging from 30% to 50%. About 75% of the patients are diagnosed with advanced-stage disease (stage III to IV), and among these patients, the 5-year survival rate is around 30% [1,3,4].

Substantial heterogeneity exists among patients with ovarian cancer, in prognosis and in response to both chemotherapies and targeted therapies [5–7]. The identification of biomarkers that are prognostic or predictive of clinical benefit would facilitate evidence-based selection of particular agents or dosages for optimal treatment of individual patients. Specifically, BRCA1 and BRCA2 (BRCA1/2) mutations are a well-investigated risk factor that may be used as a prognostic factor. Several studies have shown that ovarian cancer patients with BRCA mutations present a superior response to platinum-based chemotherapy compared to non-carriers [6–8]. Yet, whether or not this translates into a long-term survival advantage is unclear. In addition, the status of BRCA mutations has implications for maintenance and treatment of recurrences with PARP inhibitors [9–11].

We previously reported [12] an improved survival among patients who are BRCA1/2 mutation carriers compared with non-carrier women after a median follow-up of 2.5 years. The 3-year survival rates were 65.8% among carriers compared with 51.9% among non-carriers ($P < 0.001$) [12]. A later analysis of the same cohort (median follow up of 6.2 years) suggested a significantly longer median survival for carriers compared with the non-carriers (53.7 vs 37.9 months; respectively; $P = 0.002$ [13]).

A pooled analysis of 26 observational studies on the survival of women with ovarian cancer, which included data from 1213 EOC cases with pathogenic germline mutations in BRCA1 ($n = 909$) or BRCA2 ($n = 304$) and from 2666 non-carriers suggested an improved 5-year overall survival among the carriers [6].

A cohort study of 1626 women with ovarian cancer in the US and Canada, with a mean 6.9 years follow-up reported a lower annual mortality rate in women carrying inherited BRCA1 or BRCA2 mutations, yet in years 3 to 10, mortality rates were higher for carriers than for non-carriers [14]. Recently, Kotsopoulos J et al. [15] also suggested that despite the short-term survival advantage observed among BRCA mutation carriers, which is likely due to higher initial sensitivity to chemotherapy, BRCA mutation status does not confer a benefit for long-term (10 years) survival.

In summary, while most studies nowadays agree upon an overall advantage in survival for ovarian cancer patients carrying the germline BRCA mutations compared to non-carriers, at up to 5 years following the diagnosis, it is not clear if this advantage remains after longer periods. Moreover, to date, no study has explored the very long (>10 years) survival of carriers.

The aim of the present study was to compare 5, 10 and 15 year survival rates between invasive EOC patients with and without BRCA1/2 germline mutation among a non-selective group of Jewish patients, controlling for demographic and clinically known prognostic factors.

2. Patients and methods

This follow up is based on a nationwide case-control study conducted in Israel between 1994 and 1999, which aimed to examine environmental and genetic risk factors for EOC [16].

The study design was detailed in previous publications [12,13,16]. In short, the study population comprised all incident pathologically confirmed Jewish women with EOC who were diagnosed in all-gynecologic departments in Israel.

Data on possible risk factors were collected by an interview and since 1996, when genetic tests for BRCA1/2 mutations became available, blood samples were collected for DNA extraction. Analysis of the founder mutations in BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT), were performed using standard laboratory methods [16,17].

Of 1226 women with invasive EOC who were eligible to participate in the study, 1036 (84.5%) were successfully interviewed. Of them 779 were tested for BRCA1/2 mutations and followed for vital status updated to November 2015 through the Israel Population Registry.

Clinical characteristics were abstracted from medical records and original surgery and pathology reports. During the study period, all patients were treated by debulking surgery, followed by a platinum-based combination chemotherapeutic regimen.

2.1. Statistical analysis

The Chi-square test was used for comparison of categorical variables and the unpaired *t*-test for continuous variables between the groups of mutation carriers and non-carriers. Survival time was defined as starting from the date of ovarian cancer diagnosis referring to the date of a histo-pathological diagnosis to the date of death or date of last follow-up, whichever occurred first. Survival for carriers and non-carriers was assessed using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

Five, 10 and 15 year survival rates, median survival time, and 95% confidence intervals (CIs), were presented for the study population by mutation status and by demographic and clinical factors known to influence survival including age, stage, morphology, and grade. A Cox proportional hazard regression model was performed to evaluate the effects of BRCA1/2 mutation status and clinical characteristics on survival. In addition, age adjusted hazard ratios (HRs) and 95% CI of being a BRCA1/2 carrier versus non-carrier were provided for 5–10 year and 10–15 year follow-up periods for women who survived 5 and 10 years after diagnosis, respectively, for the total group, and stratified by selected clinical characteristics.

The study received the approval of the institutional review board of Sheba medical center and the Israel Ministry of Health. Informed consent for the genetic analysis was obtained from all study subjects.

3. Results

The distribution of the study population by selected clinical characteristics and BRCA carrier status is presented in Table 1. Of the 779 women (median age at diagnosis = 60 years, ranging from 23 to 87 years) with a diagnosis of invasive EOC, 229 (29.3%) had BRCA1 and/or BRCA2 mutations and 550 (70.6%) women were defined as non-carriers of the three common Ashkenazi mutations.

A comparison between the carriers and non-carriers indicated a significantly younger mean age at diagnosis among the BRCA carrier group (57.3 ± 10.6 vs 60.0 ± 12.5 years, respectively $p = 0.002$). In addition, statistically significant differences in stage distribution ($p = 0.02$), tumor grade ($p < 0.001$), morphology (differentiation between serous and non-serous tumors) ($p = 0.001$) were documented between the study groups. Of the total study population, 605 (77.7%) were of Ashkenazi origin and 174 (22.3%) were classified as non-Ashkenazi. As expected, the percent of ovarian cancer patients from Ashkenazi origin was significantly higher among the carrier than the non-carrier group (93% vs 71% respectively, $p < 0.001$) (Table 1).

By the end of the follow-up period, (range 1–20 years), 629 (80.7%) deaths from all causes occurred. Of the 779 women diagnosed with invasive EOC, 306 (39.3%) were alive at 5 years following the diagnosis, 202 (25.9%) were alive at 10 years follow-up and 171 (22%) were alive at 15 years follow-up. The median survival of ovarian cancer for the total study population was 42 months (95%CI 38.6–46.3), independent of the BRCA status. In each follow up period, higher stage, grade

Table 1
Distribution of the study population by selected clinical characteristics and BRCA1/2 carrier status.

	Total N = 779		BRCA1/2 carriers N = 229	Non-carriers N = 550	P
	n	%	%	%	
Stage					0.02
I	111	14.3	8.7	16.6	
II	51	6.6	8.3	5.8	
III	527	67.7	71.6	66.0	
IV	71	9.0	7.9	9.6	
Unstageable	19	2.4	3.5	2.0	
Grade[a]					<0.001
I–II Well/moderate	169	27.0	15.6	32.0	
III–IV Poor/anaplastic	458	73.0	84.4	68.0	
Morphology					0.001
Serous	445	57.1	61.1	55.5	
Non-serous	291	37.4	31.3	44.1	
Mucinous	43	5.5	7.6	0.4	
Age at diagnosis, years					0.001
<50	189	24.3	26.6	23.3	
50–59	199	25.5	33.6	22.2	
60–69	216	27.7	24.0	29.3	
70+	175	22.5	15.7	25.3	
Origin					<0.001
Ashkenaz	605	77.7	93.0	71.3	
Non-Ashkenaz	174	22.3	7.0	28.7	

[a] 152 patients had grade unknown.

Table 2
Five, 10 and 15 Year survival (%) by BRCA1/2 carrier status and clinical characteristics.

	Carriers			Non-carriers			P for carriers vs. non-carriers		
	5y	10y	15y	5y	10y	15y	5y	10y	15y
Total	46.7	28.0	22.3	36.2	25.1	21.8	<0.001	0.01	0.04
Stage									
I–II	82.1	64.1	51.3	75.6	67.5	62.6	0.4	0.8	0.4
III–IV	39.0	20.3	16.5	25.2	13.0	10.3	<0.001	<0.001	<0.001
Grade									
Well/Moderate	56.7	26.7	26.7	49.6	38.8	35.3	0.4	0.6	0.7
Poor/anaplastic	46.3	27.8	21.0	32.1	19.3	16.2	0.001	0.001	0.003
Morphology									
Serous	45.0	25.7	20.7	32.1	20.0	16.7	0.002	0.02	0.02
Non-serous[a]	50.0	31.8	25.0	39.4	29.1	25.1	0.02	0.11	0.2
Age at onset									
<50	47.5	24.6	19.7	51.5	43.7	39.8	0.8	0.08	0.05
50–59	55.8	32.5	26.0	47.5	34.4	31.1	0.10	0.5	0.7
60+	38.5	26.4	20.9	25.0	13.3	10.3	0.004	0.001	0.002
Origin									
Ashkenaz	46.5	28.2	22.5	34.7	23.7	20.9	<0.001	0.008	0.02
Non-Ashkenaz	50.0	25.0	18.7	39.9	28.5	24.0	0.3	0.6	0.7

[a] Excluding mucinous.

and age at diagnosis were significantly and negatively associated with survival. No significant differences in median survival were observed between women from Ashkenazi and non-Ashkenazi ancestry (42.2 vs 41.2 months, p = 0.6) (not presented in Tables).

Significant differences in survival rates were shown between carriers and non-carriers. The rates were: 46.7% vs 36.2% for surviving the first 5 years (p < 0.001), 28% vs 25.1% for 10 year survival (p = 0.01) and 22.3% vs 21.8% for 15 year survival (p = 0.04), respectively (Table 2). These differences in 5-year, 10-year and 15-year survival between carriers and non-carriers were found to be statistically significant for stages – III–IV, poor/anaplastic grading, serous morphology, later age at diagnosis (age 60 years and over) and Ashkenazi origin.

Fig. 1 presents the survival curves of the BRCA1/2 carriers and the non-carriers. While a clear advantage in survival for the carriers is shown at the beginning of the follow-up, the gap between the groups disappeared after 10 years follow-up.

A multivariate analysis suggested that patients with BRCA1/2 mutation have a lower all-cause mortality than non-carriers (HR 0.68, 95%CI 0.54–0.84, 0.75, 95%CI 0.62–0.61, and 0.78, 95%CI 0.65–0.94) for 5, 10, and 15 years respectively, controlling for the above mentioned clinical characteristics (Table 3). This model shows that age at diagnosis and stage remained independent factors affecting survival. No association between Ashkenazi origin and morphology type and survival was found in the adjusted model.

Table 4 shows the impact of being a carrier on survival for each 5 years following the diagnosis, i.e. in the first 5 years following the diagnosis, in the next 5 years for those who survived the first 5 years and the subsequent 5 years for women who survived at least 10 years after the diagnosis. In the first 5 years, being a carrier was associated with a 26% reduction in mortality compared to non-carriers, (age-adjusted HR 0.74 (95%CI 0.60–0.91)). This advantage in survival was not shown for women who survived at least 5 and 10 years; the HRs for mortality during 5 additional years was 1.38 (95%CI 0.93–2.04) and 1.08 (95%CI 0.61–1.92), respectively. Controlling for stage, morphology and Ashkenazi origin did not affect the results. In other words, after surviving the first 5 years following the diagnosis, being a BRCA carrier did not provide any survival protection for EOC patients. Similar patterns were shown when the analysis was stratified by selected factors associated with survival.

4. Discussion

The goal of the current study was to compare long term (10 and 15 year) survival of BRCA carriers and non-carriers in a non-selective group of patients with EOC (including 229 carriers of BRCA1/2 mutations and 550 non-carriers). The results support recent publications that suggested better short-term survival for patients who are carriers of the BRCA1/2 mutations but no advantage after a long follow-up. Our results show that while indeed better survival among carriers is evident up to 15 years following the diagnosis, the advantage in survival observed among the carriers is driven by the first 5 years and decreases over time. For women who survived 5 years and more, being a BRCA carrier was no longer a marker for better survival in the subsequent years.

This finding is in line with the emerging literature indicating that BRCA related ovarian cancer is not associated with a superior long-term prognosis as was initially thought.

In a study of 6556 epithelial ovarian cancer cases identified from 27 studies, the 10-year survival estimates were 25% (95%CI, 22%–28%) for women with BRCA1 mutations, 35% (95%CI, 30%–41%) for women with BRCA2 mutations (p < 0.001), and 30% (95%CI, 28%–31%) for non-carriers [18].

In an investigation of 1421 patients with EOC of whom 109 (7.7%) had BRCA1 mutations and 68 (4.8%) had BRCA2 mutations, mortality rates were 43% for non-carriers, 57% for BRCA1 mutation carriers and 69% for BRCA2 mutation carriers 10 years following the diagnosis [15]. Among women with stage III/IV serous cancers and no residual disease, the 10-year actuarial survival was 42% for non-carriers and 29% for mutation carriers (p = 0.40). The authors suggested that despite a short-term survival advantage among BRCA mutation carriers, likely due to higher initial sensitivity to chemotherapy, BRCA mutation status does not confer a benefit for long-term mortality. In addition, the authors suggested that the diminishing survival advantage with time from diagnosis may be attributed to the higher rate of complete debulking among non-carriers (39%) compared to carriers (19%), which reflects tumor biology and is strongly associated with improved outcome.

In contrast to these studies, a meta-analysis of 34 studies (7986 patients) concluded that ovarian cancer patients with BRCA1 or BRCA2 mutations have a survival advantage compared to non-carriers (HR = 0.69, 95%CI 0.61–0.79) [19]. However, this advantage was documented in a follow up of 3 to 10 years, with no data concerning the survival over 10 years.

The authors of the above mentioned studies estimated the overall survival by calculating the numbers of deaths from the initiation of

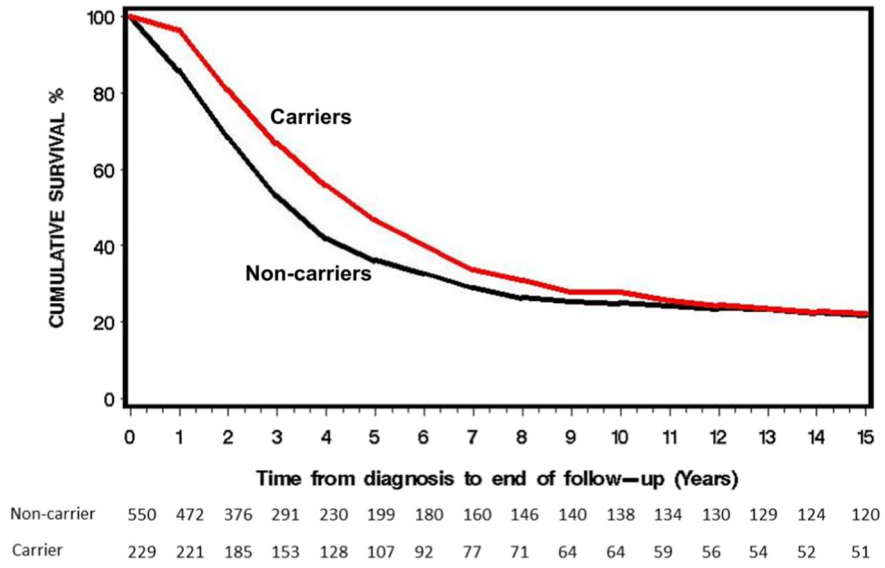

Fig. 1. Survival of epithelial invasive ovarian cancer patients by BRCA mutation status.

the study, thus wrongly assuming that the HRs for mortality comparing carriers to non-carriers are constant over time. However, most mortality of EOC patients appear in the first 5 years [4]. Our results suggest that the advantage in survival of carriers seen after 5 years is driven by the first 5 years; while an analysis of those who survived 5 years and more shows no advantage.

The exact mechanism driving the association between BRCA mutation and survival is not yet known. The improved primary platinum sensitivity associated with germline homologous recombination mutations is consistent with in vitro data that cells with defective homologous recombination are more sensitive to agents that include double strand DNA breaks [20–22]. Since BRCA1/2 gene products play a pivotal role in DNA repair mechanisms [21–23], most studies suggested that the ovarian cancer survival advantage observed among carriers could be mediated through their improved response to platinum-based agents. Accordingly, the reduced potential of BRCA-associated cancer cells to repair platinum-induced double stranded DNA breaks may explain the increased sensitivity to chemotherapy and a short-term advantage in overall survival [23].

The above model has led to the development of Poly (ADP-Ribose) polymerase enzyme (PARP) inhibitors, drugs that target the DNA repair defect of BRCA-associated tumors [22,23]. The upshot is that inhibition of PARP in a cell with deficiency of the BRCA proteins results in substantially better cellular sensitivity to platinum-based chemotherapy compared to a cell with normal levels of the BRCA protein [21,22,24].

Table 3
Factors associated with survival of invasive epithelial ovarian cancer patients – Cox proportional hazards models.

Factor	5 year survival (N = 760; Events = 459)		10 year survival (N = 760; Events = 561)		15 year survival (N = 760; Events = 590)	
	HR	95%CI	HR	95%CI	HR	95%CI
BRCA status						
Carrier vs. non-carrier	0.68	0.54–0.84	0.75	0.62–0.91	0.78	0.65–0.94
Age at diagnosis						
Continuous	1.02	1.02–1.03	1.03	1.02–1.03	1.03	1.02–1.03
Origin						
Ashkenazi vs. non-Ashkenazi	1.06	0.84–1.33	1.06	0.86–1.30	1.06	0.87–1.29
Stage						
–III–IV vs. –I–II	4.52	3.22–6.33	4.51	3.40–6.0	4.13	3.17–5.36

The explanation for the current results suggests that EOC recurrences during 10 and 15 years may tend to be platinum-resistant tumors, and thus the BRCA mutations no longer have an advantage in the second and third lines of chemotherapy treatment. These results may explain similar or even worse long-term prognosis of EOC with the BRCA mutation after the recurrence of the disease.

The primary strength of our analysis is its presentation of a long follow up period of up to 20 years, which assessed not only the overall survival but also the segmented survival for each period. This enabled characterizing both the short-and long-term effects of BRCA mutations on survival of EOC patients. In addition, our cohort is of a relatively homogenous population of Jewish women tested for the three founder mutations that are relatively prevalent in this ethnic group. It includes consecutive EOC patients, who were all treated similarly by debulking surgery followed by carboplatinum (AUC 6) and Taxol (175 mg/m^2) chemotherapy. These consistent clinical variables that impact survival diminish the possibility of an existing confounder that might bias the results. Also, mortality data were derived from the population registry, which has a close to 100% completeness rate.

In addition to the standard survival analyses expressed by survival rates of time from diagnosis, we explored the survival of those who remained alive after 5 and 10 years. This approach enabled distinguishing the overall survival advantage seen among carriers from the effect of the mutation in each time period. Our results indicated that the overall benefit in survival seen among carriers disappears over time.

Among the limitations of our study are the analysis of only the three founder mutations in BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) that were known in the era of the initiation of the cohort collection (1994). However these mutations compromise 92–94% of the BRCA1/2 germ line mutations responsible for the inherited ovarian cancer in our population suggesting that this limitation does not affect dramatically the progression free survival (PFS) or the overall survival (OS) of the long term follow up of our current cohort.

Other disadvantages are the limited sample size which does not enable differentiating survival between BRCA1 and BRCA2 carriers, the lack of controlling for some possible confounders or modifiers such as other genes that may affect prognosis, and the lack of clinical data and treatments beyond the first line of chemotherapy. Unfortunately, cause of death was not available for this study; consequently we only performed all-cause mortality analyses. However, data from cases of ovarian cancer within the Women's Health Initiative showed that 91.3% deaths were specific to ovarian cancer during a follow-up of

Table 4
Age adjusted Hazard Ratios and 95% CI of being BRCA1/2 carrier versus non-carrier among invasive epithelial ovarian cancer patients stratified by selected clinical characteristics.

	≤5y survival (N = 779; Events = 473)			5-10y survival[a] (N = 306; Events = 104)			>10y survival[b] (N = 202; Events = 52)		
	HR	95%CI	P	HR	95% CI	P	HR	95% CI	P
Total	0.74	0.60–0.91	0.005	1.38	0.93–2.04	0.11	1.08	0.61–1.92	0.79
Stage									
I–II	0.74	0.32–1.69	0.5	2.12	0.81–5.58	0.13	1.44	0.59–3.55	0.4
III–IV	0.68	0.54–0.84	0.01	1.01	0.65–1.56	0.97	0.78	0.36–1.68	0.52
Grade									
Poor/anaplastic	0.66	0.51–0.85	0.01	1.06	0.66–1.71	0.81	1.35	0.66–2.78	0.41
Morphology									
Serous	0.72	0.55–0.94	0.01	1.20	0.73–1.97	0.47	0.77	0.34–1.71	0.51
Origin									
Ashkenaz	0.74	0.59–0.92	0.007	1.31	0.85–2.02	0.22	1.09	0.58–2.05	0.78

[a] For women who survived 5 years after diagnosis
[b] For women who survived 10 years after diagnosis.

17 years [25]. In addition, Candido-dos Reis et al. [18] analyzed the effect of germline mutations in BRCA1 and BRCA2 on 10-years overall mortality of women diagnosed with ovarian cancer based on a large population of 5060 non-carriers, 1058 BRCA1 carriers and 438 BRCA2 carriers. They also restricted the analysis to a subset of 3075 cases for whom cause of death was available and reported that the findings of ovarian cancer specific mortality were broadly similar to the results for all-cause mortality suggesting that differences in non-ovarian cancer mortality do not account for the time dependent effect for BRCA1 and BRCA2 carriers.

In addition, the prognostic role of somatic mutations that may be present in approximately 5–10% of all ovarian cancers [20,26,27] and the tumor genotype transformations that can explain a different response to chemotherapy resulting in a different survival subgroup of EOC patients with nongermline BRCA mutations [28] was beyond the scope of our study.

Our results may have implications for the clinical management of patients carrying a BRCA mutation and for predicting their prognosis. From the therapeutic point of view, in addition to the performance of germline mutation for EOC patients, we should reevaluate and explore the option of performing somatic mutations for all EOC patients, in the hope that in the near future the use of the PARP DNA repair pathway inhibition [28,29] as maintenance therapy will equilibrate or, hopefully will significantly improve the overall survivors of BRCA germline carriers and specific tumors with somatic BRCA mutations.

Moreover, studies specific to long-term survivors should focus on gene expression analyses in order to elucidate relationship between clinical outcomes in EOC patients and potential causative genetic alterations.

Recently, the SOLO1 study [30] estimated a PFS of 52 months for ovarian cancer BRCA carriers receiving PARP inhibitors (Olaparib) as first line therapy as compared to at least 19 months in the ovarian cancer BRCA carriers receiving placebo. Given the long-term prognostic effect of BRCA status and the possibility for personalized treatments in carriers and non-carriers, the next step should be to evaluate the OS during a long term follow up of BRCA carriers receiving PARP inhibitors and to evaluate how this knowledge can be used to optimize treatments, testing targeted therapy and performing phase III studies aiming to evaluate prolongation of the adjuvant or maintenance PARP inhibitor therapy with or without other biological agents in BRCA carriers. In summary, relatively little data are available on the very long-term survival of women with BRCA-associated EOC.

With up to 20 years follow-up of ovarian cancer patients with a BRCA mutation, this study suggests that despite a short-term (5 year) survival advantage among these patients, which is likely due to higher initial sensitivity to chemotherapy, BRCA mutation status does not confer a benefit for long-term survival. Longer follow up and larger studies that include comprehensive genomic germline and somatic screening of BRCA1 and BRCA2 in primary EOCs are needed to determine if alterations at the germline, somatic, and other genetic expressions influence the very long-term prognosis of EOC. While long-term survival is an improvement on the most common outcome of ovarian cancer, a cure should remain the goal.

A conflict of interest statement

The authors declare no conflict of interest.

An author contribution section

OL - Ofer Lavie, AC - Angela Chetrit, IN - Ilya Novikov, SS - Siegal Sadetzki.

OL designed the study.

SS, AC were involved in the data collection.

The data analysis and data interpretation were done by OL, AC, IN and SS.

The first draft of the article was written by OL and AC.

All authors made critical review of the article and approved the version to be published.

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