Effect of BRCA1 and BRCA2 mutations on endometrial carcinoma survival rates

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Abstract

Background: To evaluate Effect of BRCA1 and BRCA2 mutations on endometrial carcinoma survival rates.

Methods : Data were collected from The Cancer Genome Atlas endometrial cancer database for pathogenic mutations in BRCA1 (58) and BRCA2 (77), coexisting BRCA1 /2 mutations (40), and non-mutations (461). Clinicopathological features and survival rates were compared. Survival time was analyzed using combined data and Cox proportional hazard models, with BRCA1 and BRCA2 as time-varying covariates.

Results: Patients with BRCA1 mutations presented with higher risk disease (endometrioid endometrial carcinoma grade 3 and uterine serous carcinoma) than non-carriers and BRCA2 mutation carriers (p = 0.005 non carriers vs BRCA1 mutation carriers, p = 0.008 BRCA1 mutation carriers vs BRCA2 mutation carriers). BRCA1 and BRCA2 mutation carriers tended to have more endometrioid endometrial carcinoma grade 3 than non-carrier group. Overall survival (OS) rates were higher for all patients with BRCA1 and BRCA2 mutations than non-carriers. Patients with BRCA2 mutations had the most favorable progression-free survival (PFS), followed by patients with BRCA1 and BRCA2 co-mutations, and then BRCA1 alteration carriers (p = 0.011). BRCA1/2 non-carriers had the worst PFS and OS.

Conclusions: Patients with BRCA1 mutations presented with higher risk disease than non-carriers and BRCA2 mutation carriers. BRCA1 and BRCA2 mutation carriers had more favorable OS and PFS than non- BRCA mutation carriers in patients with endometrioid endometrial carcinoma and uterine serous carcinoma.

Background

Endometrial cancer is the most common gynecologic malignancy in advanced countries [1]. The incidence of endometrial cancer increased 0.7% per year from 1999 to 2015, according to data from the National Cancer Institute's Surveillance, Epidemiology and End Results program. The mortality of endometrial cancer grew 1% per year from 1999 to 2015, based on analyses from the Centers for Disease Control and Prevention [2]. Two types of endometrial cancer are classified by clinicohistological features and genetic characteristics. Type 1 endometrial carcinoma is associated with hyperestrogenism and favorable prognosis [3, 4]. Histologic features of the cancer tissue are more likely to present endometrial gland-like carcinoma. Genetic features are related to *PTEN* and *POLE* [5, 6]. Type 2 endometrial carcinoma is more aggressive than type 1 and is more likely to be associated with *BRCA1*, *BRCA2* and *TP53* [5, 6]. Clear cell, serous carcinoma, and mixed carcinoma are classified as type 2 endometrial carcinomas. Germline *BRCA1* and *BRCA2* are well-known risk factors of both ovarian and breast cancer and are identified in 6-15% of females with epithelial ovarian carcinoma [7-9]. A multinational cohort study of patients with 11,847 *BRCA1* mutations revealed a distinct increased risk of uterine carcinoma (HR 2.65, 95% CI 1.69-4.16) [10]. However, a prospective study found that the significantly increased risk

was associated with *BRCA1/2* deficiencies in patients taking tamoxifen [11]. Some data identified an increased risk of uterine serous carcinoma in patients with *BRCA* mutations [12-14]. *BRCA1/2* mutations are related to homologous recombination, DNA repair, chromatin remodeling, cell cycle checkpoint surveillance, and transcriptional regulation [15]. The clinicopathological features of *BRCA1/2* mutations carriers differ from features of non-carriers in epithelial ovarian cancer. Patients with *BRCA1* mutations tend to have more aggressive histology [15], higher grade [16], and more advanced stage than non-carriers [16, 17]. Less data was available in *BRCA2* mutated epithelial ovarian cancers and uterine serous carcinomas due to lower prevalence [15, 17, 18]. One small cohort identified that prognosis was similar in *BRCA* mutated uterine serous carcinoma and non-carriers [17]. Another study found that g*BRCA1* and g*BRCA2* mutation carriers were associated with favorable 5-year overall survival in epithelial ovarian cancer [19]. Some studies revealed that *BRCA1* and *BRCA2* mutation carriers had better prognosis than non-carriers [16, 18, 20], whereas others failed to find differences [21, 22]. One study reported that *BRCA2* mutation carriers have more favorable outcomes than non-carriers [23]. Less data is available for prognosis of patients with endometrial carcinomas based on *BRCA1* and *BRCA2* mutations status [17].

The mechanism of impact of *BRCA1/2* mutations on prognosis of cancers is unclear. The literature hypothesizes that favorable prognosis of patients with *BRCA1/2* mutations may be caused by good response to platinum-based chemotherapy regimens [18, 24]. This hypothesis is consistent with vitro studies that demonstrated that *BRCA1* and *BRCA2* mutated cells have a good response to agents, such as platinum-based regimens that induce double-strand DNA breaks [25].

From The Cancer Genome Atlas (TCGA) dataset, we aimed to obtain evidence of the effect of *BRCA* mutations on prognosis of endometrioid endometrial carcinoma and uterine serous carcinoma. Since limited data are available for patients with endometrial cancer with *BRCA1* and *BRCA2* mutations, these results may provide evidence on the biology of *BRCA1/2* mutations, the clinical management of mutation carriers, and the potential impact of clinical trial designs, especially regimens targeting *BRCA1/2* mutations, such as poly (ADP-ribose)-polymerase (PARP) inhibitors [26].

Methods

Study Design

The data was obtained from The Cancer Genome Atlas endometrial cancer database (provisional and Pancancer Atlas), which involved 27 U.S. institutions between 1988 and 2014, and was used for this study because of its large sample size and user-friendly data structure [http://www.cbioportal.org]. All study participants had been diagnosed as endometrial carcinoma. The retrospective cohort was generated from 529 patients from the Pancancer Atlas database and 548 patients from the provisional database. After excluding duplicate patients from both databases (n = 441), the final cohort comprised 636 patients. Somatic and germline BRCA1 and BRCA2 mutations were not separated. We obtained clinical, demographic, molecular, and pathology information from these patients. Patients were stratified into four groups according to BRCA1 and BRCA2 mutation status: BRCA1 mutation, BRCA2 mutation,

coexisting BRCA1 and BRCA2 mutation, and non-carriers. Variables recorded for each case were as follows: histology (endometroid endometrial carcinoma and uterine serous carcinoma included), age at diagnosis (≥70, 50-69, <50 years old), mean age at diagnosis, myometrial invasion (≥50% or <50% myometrial invasion), lymph node involvement, and International Federation of Gynecology and Obstetrics (FIGO) stage (2009 version). Overall survival (OS) was defined as the interval from the date of initial surgical resection to the date of death or last contact. Progression-free survival (PFS) was defined as the interval from the date of diagnosis or surgical resection to the date of recurrence, death, or censored last contact.

Statistical Analysis

Statistical analysis was performed using Mann-Whitney tests for continuous variables, and chi-square analysis and Fisher's exact test for categorical variables. The Student's t-test was used to analyze body mass index and age of onset. OS and PFS were analyzed using the Kaplan-Meier method and the log-rank tests starting at the date of diagnosis. Analyses of risk factors were performed using multivariate Cox proportional hazards models. For all tests, statistical significance was less than 0.05 ($p < 0.05$, exact 2-tailed). All calculations were performed using SPSS software (Version 23, IBM, USA).

Results

The study included 636 endometrial cancer cases with pathogenic mutations in *BRCA1* (58), *BRCA2* (77), both *BRCA1* and *BRCA2* (40), and non-carriers (461). Data were available on 100% for age of onset, 83% for body mass index, 100% for tumor stage, 100% for myometrial invasion, 97% for lymph node involvement, 95.5% for overall survival and 93.1% for progression-free interval. Each patient received appropriate therapy by current National Comprehensive Cancer Network (NCCN) guideline. Patients with *BRCA1* mutations presented with higher risk disease (endometrioid grade 3 endometrial carcinoma and uterine serous carcinoma) than non-carrier group and *BRCA2* mutation carriers ($p = 0.005$, non-carrier group vs *BRCA1* mutation carriers; $p = 0.008$, *BRCA1* mutation carriers vs *BRCA2* mutation carriers). More patients with *BRCA1* and *BRCA2* mutation occurred in grade 3 endometrioid endometrial carcinomas than non-carrier group. There were fewer patients with *BRCA2* and *BRCA1* mutation than non-carrier group in uterine serous carcinomas (Table 1). *BRCA1* mutations and *BRCA2* mutations carriers were

associated with having a younger age at the time of diagnosis than noncarriers (p = 0.036, *BRCA1* mutation carriers vs non carriers; p = 0.001, *BRCA2* mutation carriers vs non carriers). Compared to patients with *BRCA1* mutations, body mass index was higher in non-carriers. No significant differences were identified between *BRCA1* and *BRCA2* mutation carriers for mean age at diagnosis (p = 0.559). We failed to detect any differences in body mass index between *BRCA2* mutation carriers and *BRCA* non-carriers (p = 0.120), and between *BRCA1* carriers and *BRCA2* carriers (p = 0.148). No significant differences were found in depth for myometrial invasion or lymph node involvement among *BRCA1* mutation, *BRCA2* mutation, and *BRCA1/2* mutation carriers (p > 0.05, Table 1). There were no differences identified in stage among *BRCA* mutated carriers and non-carriers (p > 0.05, Table 1). This study did not include patients with coexisting *BRCA1* and *BRCA2* mutations because of the limited number of cases.

Table 1

Clinicopathologic characteristics of endometrial carcinoma based on *BRCA* mutation status. [a, b]

Variable	Noncarrier group (n = 461)	*BRCA1* mutation carriers (n = 58)	*BRCA2* mutation carriers (n = 77)	*P*[1]	*P*[2]	*P*[3]
Histology						
EEC G1	76/461 (16.5)	5/58 (8.6)	13/77 (16.9)	0.129	>0.99	0.205
EEC G2	107/461 (23.2)	7/58 (12.1)	17/77 (22.1)	0.063	0.885	0.173
EEC G3	139/461 (30.1)	31/58 (53.4)	37/77 (48.1)	<0.001	0.003	0.603
USC	139/461 (30.1)	15/58 (25.9)	10/77 (12.9)	0.545	0.002	0.074
High risk[c]	278/461 (60.3)	46/58 (79.3)	47/77 (61.0)	0.005	>0.99	0.008
Age						
Mean ± SD	64.4 ± 10.7	61.1 ± 12.7	59.9 ± 12.0	0.036	0.001	0.559
>70 y	145/460 (31.5)	11/56 (19.6)	13/75 (17.3)			
50-70 y	279/460 (60.7)	37/56 (66.1)	52/75 (69.3)			
<50 y	36/460 (7.8)	8/56 (14.3)	10/75 (13.3)			
Missing	1/461 (0.2)	2/58 (3.4)	2/77 (1.3)			
Myometrial invasion						
<50%	247/452 (54.6)	29/58 (50.0)	44/75 (58.7)	0.571	0.668	0.256
>=50%	205/452 (45.4)	29/58 (50.0)	31/75 (41.3)			
Missing	9/461 (2.0)	0	2/77 (1.3)			
Lymph node invasion						

Positive	69/397 (17.4)	9/49 (18.4)	11/71 (15.4)	1.000	0.847	0.704
Negative	328/397 (82.6)	40/49 (81.7)	60/71 (84.5)			
No LND (<=stage II)	44/461 (9.5)	5/58 (8.6)	5/77 (6.5)			
No LND (>stage II)	20/461 (4.3)	4/58 (6.9)	1/77 (1.3)			
BMI						
Mean ± SD	34.3 ± 17.4	29.8 ± 7.6	31.2 ± 8.7	0.034	0.120	0.148
<25	78/433 (18.0)	16/55 (29.1)	24/73 (32.5)			
25-30	91/433 (21.0)	13/55 (23.6)	14/73 (17.5)			
>30	264/433 (61.0)	26/55 (47.3)	35/73 (50.0)			
Missing	28/461 (6.1)	3/58 (5.6)	4/77 (6.5)			
FIGO stage						
I-II	327/461 (70.9)	39/58 (67.2)	59/77 (76.6)	0.647	0.420	0.156
III-IV	134/461 (29.1)	19/58 (32.8)	18/77 (23.4)			

Abbreviations: EEC, endometrioid endometrial carcinoma; USC, uterine serous carcinoma; LND, lymphadenectomy

P[1], non-carriers VS *BRCA1* carriers; *P*[2], non-carriers VS *BRCA2* carriers;

P[3], *BRCA1* carriers VS *BRCA2* carriers

[a] Values are given as mean ± SD or number/number (percentage) unless indicated otherwise.

[b] Only available data included, denominators represent patients with

available information.

[e] Endometroid endometrial carcinoma and uterine serous carcinoma.

Patients with *BRCA1* and/or *BRCA2* mutation had more favorable OS ($p < 0.001$, Figure 1) and PFS ($p = 0.008$, Figure 2) than non-carriers (Table 2). Patients with *BRCA2* mutations had the longest PFS,

followed by patients with *BRCA1/2* mutations, and then *BRCA1* mutations. *BRCA1/2* non-carriers had the worst PFS.

Table 2
Comparison of PFS and OS of patients based on *BRCA* mutation status

Variable	PFS (months) Mean ± SD (95% CI)	*p*	OS (months) Mean ± SD (95% CI)	*p*
Noncarriers	102.8 ± 3.8 (95.3-110.3)	0.011	121.9 ± 8.6 (105.1-138.8)	<0.001
BRCA1 mutation	191.2 ± 12.3 (167.2-215.3)		189.9 ± 21.0 (148.9-231.0)	
BRCA2 mutation	207.5 ± 6.9 (194.1-221.0)		180.1 ± 31.6 (118.3-242.0)	
BRCA1/2 mutation	202.3 ± 10.8 (181.1-223.4)		176.0 ± 31.2 (114.8-237.1)	
Abbreviations: PFS, progression free survival; OS, overall survival				

Independent factors associated with better prognosis in all endometrial adenocarcinomas were *BRCA1/2* mutation, <50% myometrial invasion, and lymph node-negative status (Table 3). Compared to noncarriers, the hazard ratio was 0.29 (95% CI, 0.10-0.78; p = 0.015) for carriers of *BRCA1*, 0.17 (95% CI, 0.05-0.54; p = 0.003) for *BRCA2,* and 0.29 (95% CI, 0.05-0.59; p = 0.037) for *BRCA1/2*. We noticed a significant increased risk in ³ 50% myometrial invasion (HR, 2.87; 95% CI, 1.65-5.00; $p < 0.001$). Compared to lymph node-positive status, the hazard ratio of lymph node negative was 0.18 (95% CI, 0.05-0.59; $p = 0.005$).

Table 3
Relative risk of overall survival (OS) and progression-free interval (PFS) in patients with endometrial carcinoma in relation to histology and grade (Multivariate Cox proportional hazards model).

	All patients (*N* = 565)			
	OS (414/565)		PFS (396/565)	
Variable name	HR [95% CI]	P	HR [95% CI]	P
Myometrial invasion ³ 50% vs. <50%	2.87 [1.65–5.00]	<0.001	2.60 [1.23–5.38]	0.010
BRCA1/2 mutation vs. *BRCA* noncarriers	0.29 [0.09–0.93]	0.037	N/A	N/A
BRCA1 mutation vs. *BRCA* noncarriers	0.29 [0.10–0.78]	0.015	N/A	N/A
BRCA2 mutation vs. *BRCA* noncarriers	0.17 [0.05–0.54]	0.003	N/A	N/A
Lymph node – vs. lymph node +	0.18 [0.05–0.60]	0.005	N/A	N/A

Discussion

To the best of our knowledge, this study was the first to investigate the effect of *BRCA* mutations on the prognosis of endometrioid endometrial carcinoma. Patients with *BRCA1* mutations presented with higher risk disease than non-carrier group and *BRCA2* mutation carriers [17]. Among endometrioid endometrial carcinoma group, there were more patients with *BRCA1* or *BRCA2* mutation than non-carrier group in our study. Patients with *BRCA1* and *BRCA2* mutations had more favorable outcomes than noncarriers in endometrial carcinoma, which differ from the results of previous studies. There were no significant differences identified in prognosis of uterine serous carcinoma between *BRCA* mutation carriers and noncarriers [17]. In addition, our findings differ from the analysis of ovarian cancer data from the Cancer Genome Atlas project, and another study that found that patients with *BRCA2* mutation had more favorable prognosis than *BRCA2* non-carriers [19, 23]. The survival advantage of patients with *BRCA1/2* could be associated with intrinsic biological differences, response to therapeutic regimes, or both. The hazard ratios (HR) compared to non-carriers were 0.29 for *BRCA1* mutation carriers, 0.17 for *BRCA2* mutation carriers, and 0.29 for *BRCA1/2* mutation carriers. These findings differ from the hazard ratios for *BRCA1* carriers compared to non-carriers reported by Yang et al. (multivariate adjusted HR= 0.76) and other analysis (multivariate adjusted HR= 0.73) among patients with ovarian cancer [19, 23]. The reason for these differences could be that we did not separate germline and somatic *BRCA* mutations in this study. The survival differences between *BRCA2* mutation carriers and non-carriers are attenuated and may even be reversed for *BRCA1* mutation carriers in the long run [27, 28].

We presume that resistance to platinum-based treatment was more likely to occur in endometrial carcinoma with *BRCA2* mutations than with *BRCA1* mutations, leading to reverse prognosis. The mechanism of resistance to platinum-based treatment in *BRCA1* and *BRCA2* carriers was associated with homologous recombination restoration that occurs by inactivation of the p53-binding protein1 (53BP1), which is important in maintaining the balance between homologous recombination and non-homologous end joining, and is transferred to non-homologous end joining in *BRCA1*-mutant cells [29]. One study reported that *BRCA1*/2 mutations are associated with favorable prognosis in short-term surveillance, but this advantage attenuates over time, and homologous recombination was reversed through induction by platinum-based treatment in *BRCA1* carriers [27]. Newer agents, especially those effective in *BRCA1/2* mutation carriers, like PARP inhibitors, are required for treatment of both primary and relapsed cancers with *BRCA1/2* mutations and should be investigated in clinical trials for analysis of long-term survival.

We saw no differences in lymph node involvement among *BRCA1*- or *BRCA2*-mutated tumors and non-carriers in this study. These results differed from ovarian cancer, in which significant differences were found between patients with *BRCA* mutations and non-carriers; however, *BRCA1*- and *BRCA2*-related tumors were similar to each other [19]. Our findings contrast with results of breast cancer, in which substantial differences were revealed between *BRCA1*- and *BRCA2*-associated disease [30, 31]. We noticed higher grade histology in endometrial cancers with *BRCA1* and *BRCA2* alterations, which is similar to the result of ovarian cancer [15, 16]. Our results revealed that fewer *BRCA2* and *BRCA1* mutations occurred in uterine serous carcinomas than non-carrier group. *BRCA1* mutations occurred more

frequently than non-mutations in higher risk disease (endometroid endometrial carcinomas and uterine serous carcinomas). Some data showed an increased risk of uterine serous carcinoma in patients with *BRCA* mutation [12-14]. *BRCA1* carriers and non-carriers presented no significant differences in advanced disease in our study, which is similar to the result of previous studies [17]. However, less data is available for *BRCA2*-mutated epithelial ovarian cancer or endometrial carcinoma due to a lower prevalence [15, 18].

Data showed that women with *BRCA* mutated recurrent or advanced ovarian cancer responded to olaparib if they failed multiple prior lines of chemotherapy [32, 33]. PARP inhibitors, such as niraparib, rucaparib, and olaparib, are Food and Drug Administration-approved anti-cancer drugs administered after failure of two or three prior lines of treatment in patients with *BRCA*-mutated recurrent ovarian cancer. For now, there are no clinical trials available for endometrial carcinoma with *BRCA* mutations using PARP inhibitors. The findings of our study may suggest potential management of patients with *BRCA*-mutated endometrial carcinoma. Patients could receive individual management if they were stratified based on *BRCA* mutation status. In addition, our study revealed that *BRCA1*- and/or *BRCA2*-mutated endometrial carcinomas had better prognosis than non-carriers, even in high-grade or advanced-stage disease. In the future, our findings could be used for counseling patients on their prognosis.

This study had several limitations, including its retrospective nature and small sample size. Some clinical information, such as family history, was missing. Further studies are necessary to identify differences between prognosis of endometrial carcinomas and germline or somatic *BRCA* mutations in larger cohorts.

Conclusions

Patients with *BRCA1* mutations presented with higher risk endometrial carcinoma than non-carrier group or *BRCA2* mutation carriers. *BRCA1* or *BRCA2* mutation carriers tended to have more grade 3 endometrioid endometrial carcinoma than non-carrier group. *BRCA1* and *BRCA2* mutation carriers have more favorable overall survival and progression-free survival among patients with endometrial carcinoma. Independent factors associated with more favorable prognosis for all endometrial adenocarcinomas included *BRCA1/2* mutation, <50% myometrial invasion, and negative lymph node status.

Abbreviations

FIGO: International Federation of Gynecology and Obstetrics

OS: Overall survival

PFS: Progression-free survival

PARP: poly (ADP-ribose)-polymerase

TCGA: The Cancer Genome Atlas

Declatations

Authors contributions

AW analyzed and interpreted the data and was a major contributor in writing the manuscript; AW and RH interpreted the data; ZZ and ZZ abstracted the data; AW designed the work; AW designed the work and interpreted the data. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhangjiagang Hospital TCM Affiliated to Nanjing University of Chinese Medicine (committee's reference number: 2018-1071). Because all patients involved in TCGA were publicly published. The Ethics Committee approved this consent procedure.

Availability of data and materials

All data and materials were from TCGA which was published publicly.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

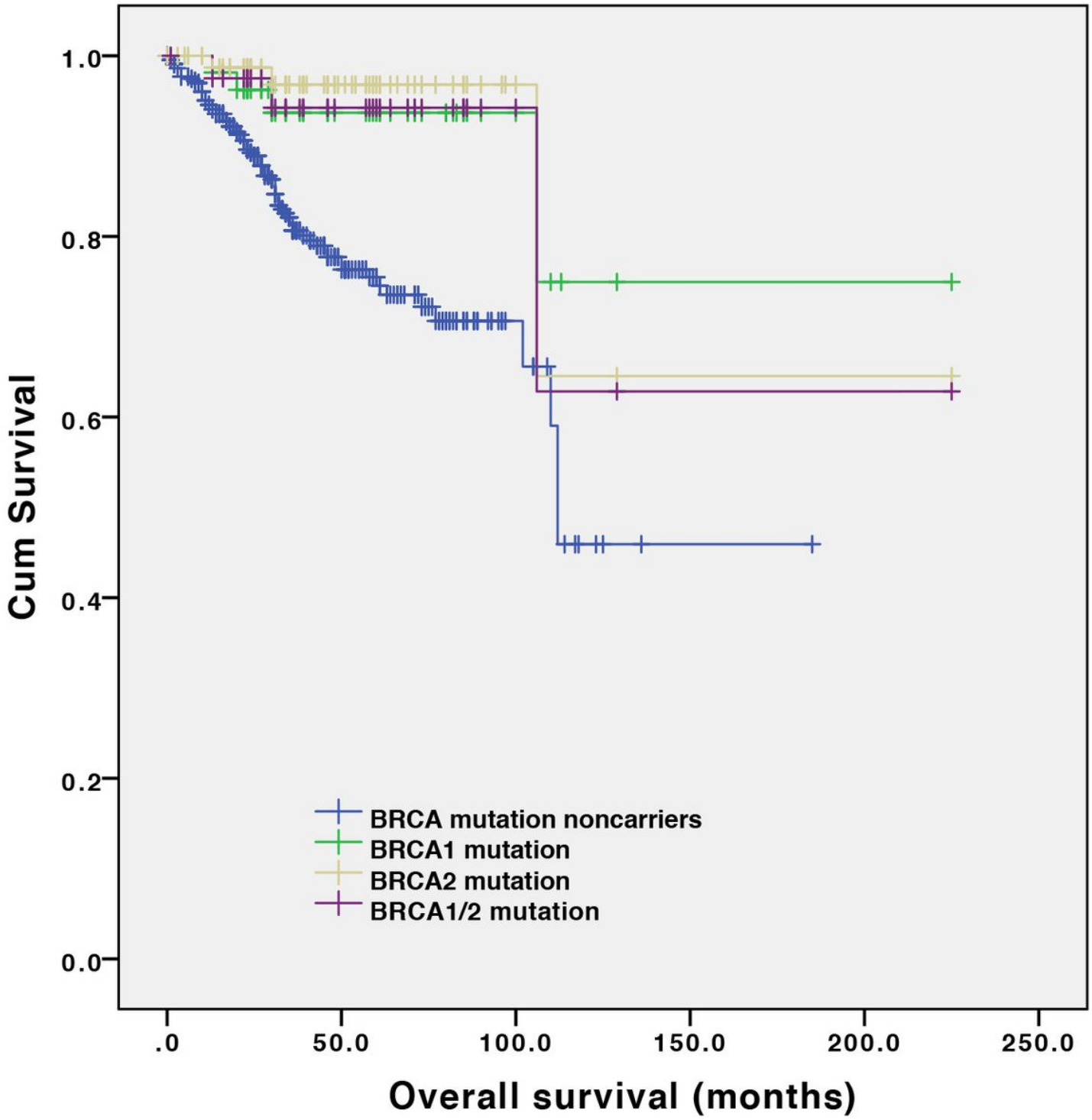

Figure 1

Overall survival from endometrial carcinoma based on BRCA mutation status Legend: Overall survival (OS) rates were higher for all patients with BRCA1 or BRCA2 mutations than non-carriers.

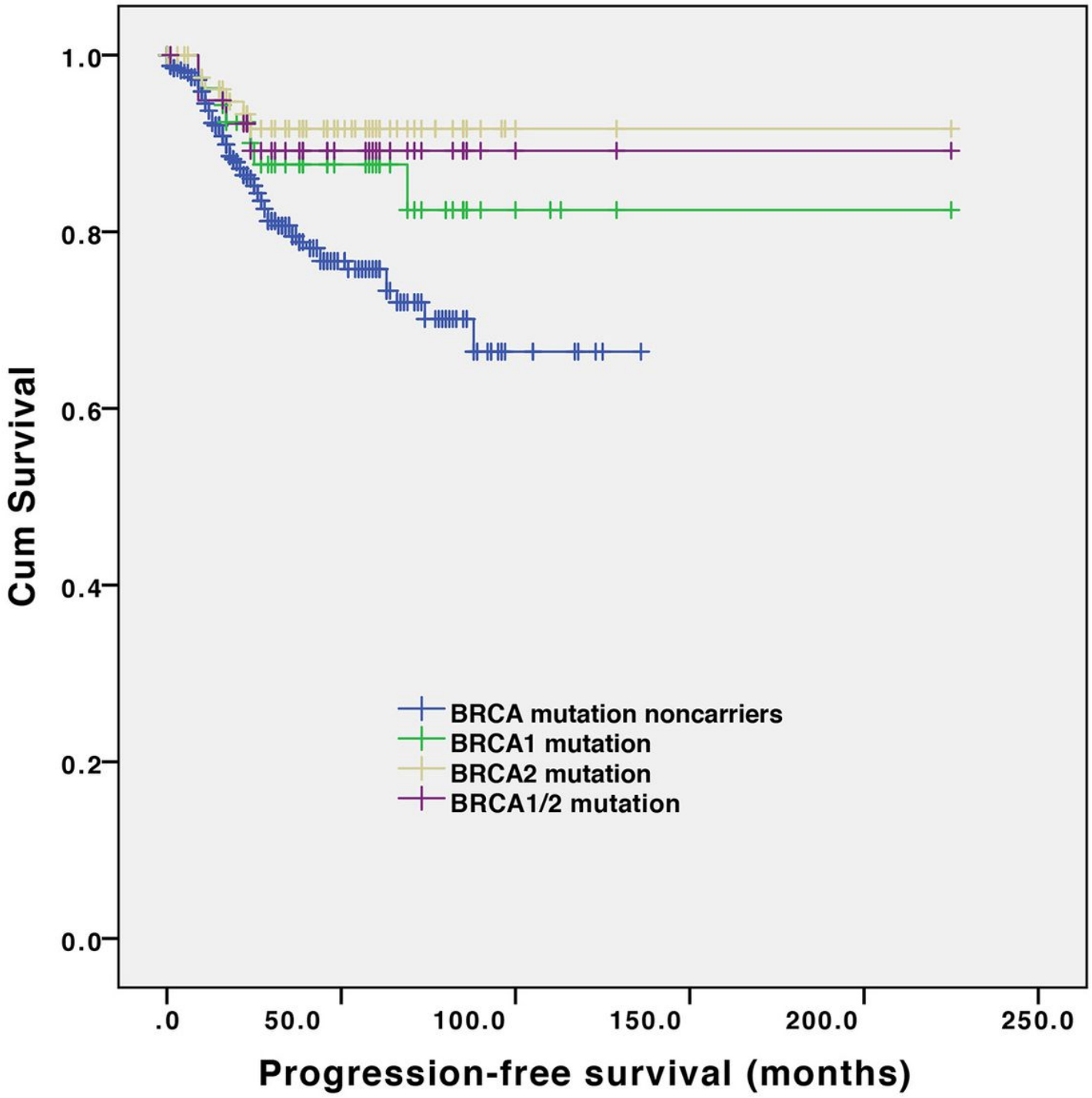

Figure 2

Progression-free survival from endometrial carcinoma based on BRCA mutation status Legend: Patients with BRCA2 mutations had the most favorable progression-free survival (PFS), followed by patients with BRCA1 and BRCA2 co-mutations and BRCA1 alteration carriers. BRCA1/2 non-carriers had the worst PFS.