Gynecology and Obstetrics Clinical Medicine 1 (2021) 19–24

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

BRCA1/2 mutations and survival of high-grade endometrioid endometrial cancer

Yibo Dai, Jingyuan Wang, Luyang Zhao, Zhiqi Wang *

Department of Obstetrics and Gynecology, Peking University People's Hospital, Beijing, China

ARTICLE INFO

Keywords:
Endometrial cancer
BRCA1/2
Mutations
Survival
Recurrence

ABSTRACT

Background: BRCA1/2 mutations have been shown to be associated with the development of many solid tumors including endometrial cancer (EC). The objectives of this study are to analyze the association between *BRCA1/2* mutational status and clinicopathological characteristics as well as outcomes in EC patients.

Methods: 510 eligible EC patients from the Cancer Genome Atlas database were included in the study. The association between clinicopathological characteristics and different *BRCA1/2* mutational status was compared and analyzed. Analyses of the impact of *BRCA* mutations on survival in EC patients was conducted using Kaplan-Meier survival analyses and Cox regressions. In order to control confounding bias between groups, propensity score matching method was used.

Results: Among the eligible patients, 11 (2.2%) harbored *BRCA1* mutation, 43 (8.4%) harbored *BRCA2* mutation, and 36 (7.1%) harbored both. Body mass index, rates of hypertension history, proportion of non-endometrioid histology and rates of positive peritoneal cytology were lower in patients with *BRCA1/2* mutations compared with the group of wild-type counterpart ($p = 0.020$, 0.048, 0.001 and 0.012, respectively). Patients with *BRCA1/2* mutations showed longer overall (OS) and recurrence-free survival (RFS) (in Kaplan-Meier analyses, $p < 0.001$ and $p = 0.004$, respectively; in Cox regressions, $p = 0.001$ and 0.007, respectively). Further analyses showed that the impact of *BRCA* mutations on survival was significant only in patients with high-grade endometrioid EC. Based on the cohorts generated after propensity score matching, in high-grade endometrioid EC patients, the influence of *BRCA1/2* mutations remained significant on OS, but not on RFS ($p = 0.003$ and 0.057 in Kaplan-Meier analyses, $p = 0.020$ and 0.071 in Cox regressions).

Conclusion: BRCA1/2 mutations are associated with better survival in patients with high grade endometrioid EC, indicating the value of *BRCA* testing in EC clinical management.

1. Introduction

Endometrial cancer (EC) is one of the most common gynecological cancers both in China and in western countries,[1–3] causing increasingly higher health-economic burdens. During the past decades, efforts have been made in prognostic prediction of EC. Dr. Bohkman, in 1983, proposed a dualistic classification model of EC based on patients' pathological and metabolic features,[4] which, however, was later on found to be still limited in accuracy.[5] Recently, genomic studies have provided new insights into better understanding of tumor development, leading to more reliable survival prediction and the possibility of designing new treatment strategies. In 2013, the Cancer Genome Atlas (TCGA) research network proposed molecular classifications of EC based on multi-omics data.[6] Since then, many researchers tried to establish simplified EC prognostic model for better clinical feasibility, exemplified by the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) model,[7] and the integrated molecular and clinicopathological risk profile based on the PORTEC trial data.[8] And several key molecular changes

* Corresponding author. Department of Obstetrics and Gynecology, Peking University People's Hospital, No. 11, Xizhimen South Street, Xicheng District, Beijing, 100044, China.
E-mail address: wangzqnet@sina.com (Z. Wang).

Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2020.10.006

Available online 8 December 2020

were identified for their vital clinical significance, such as the mutations of *POLE*, *TP53*, *CTNNB1*, etc.[6,9–11]

Another gene, *BRCA1/2*, is now generally recognized by the gynecologic oncology community as a vital biomarker in ovarian cancer treatment for suggesting potential efficacy of poly ADP-ribose polymerase (PARP) inhibitors treatment,[12] and germline mutations of *BRCA1/2* were proved to be associated with hereditary breast and ovarian cancer (HBOC) syndrome.[13] Nevertheless, evidences regarding the role of *BRCA1/2* in endometrial cancer were relatively limited. A recent study proved that loss-of-heterozygosity in EC patients with germline *BRCA* mutations was associated with unfavorable clinicopathological features,[14] indicating the possible role of *BRCA* mutation in EC carcinogenesis. But until recently, most studies focused only on germline, instead of somatic, *BRCA* mutations, and detailed survival data of EC patients with *BRCA* mutations were still lacking.

Based on high throughput sequencing technology, TCGA is a pioneering project aiming at systemically revealing the genomic information of various cancer types, and also paving the way for further investigations about the association between genetic alterations and cancer survival outcome. Because of its open access to all qualified researchers, this database has become one of the most important sources for genomic study and has generated tremendous new data in the field of cancer research.

In this study, based on TCGA data, we compared the clinicopathological characteristics of patients with *BRCA1/2* mutations and those with wild-type *BRCA* genes, and the survival influence of *BRCA1/2* mutations were also analyzed.

2. Methods

2.1. Data sources and patient selection

In this study, genetic and clinicopathological data of patients from TCGA Uterine Corpus Endometrial Carcinoma (UCEC) project were downloaded from the UCSC-Xena[15] and cBioPortal online platform.[16,17] There were totally 548 patients in this cohort. 5 patients with colorectal cancer history and another 33 patients without genetic information were excluded. Finally, 510 eligible patients were included in this study for further analyses. The Institutional Review Board of Peking University People's Hospital considered the protocol for exemption from review since all data and analyses were based on deidentified patient information from a public database.

2.2. Term definitions

The definitions of all clinicopathological characteristics in this study were according to those described in the Common Data Element (CDE) Browser 5.3.5 (https://cdebrowser.nci.nih.gov). The stage of each case was determined based on the American Joint Committee on Cancer (AJCC) staging system, and the system version used was according to the time of making diagnosis. For tumor grade, G1, G2 and G3 were used to describe tumors with well, moderately, and poorly or undifferentiated cancer cells, respectively, which was in accordance with the FIGO grading system,[18] and high-grade indicated tumors classified in G3 group. Tumors with serous and mixed serous and endometrioid histology were categorized as non-endometrioid type. In the study, data about *BRCA1/2* somatic mutations were analyzed, which included the presence of all missense and truncating mutations. The patients were categorized into different subgroups according to *BRCA1/2* mutational status.

2.3. Follow-up and outcome measures

The median follow-up time was 30.47 months (interquartile range: 17.43–52.76 months) for all eligible patients, 29.33 months (interquartile range: 17.07–49.47 months) for patients with wild-type *BRCA* genes, and 40.67 months (interquartile range: 22.88–72.55 months) for patients with *BRCA* mutations. Overall survival (OS) and recurrence-free survival (RFS), as two endpoints used in this study, were definited from the time of initial disease diagnosis to the time when death or disease recurrence occurred, respectively. Patients without any endpoint event were censored at their last follow-up in survival analyses.

2.4. Statistical analyses

In this study, χ^2 test and Fisher's exact test were used for comparing categorical variables. To analyze the survival influence of *BRCA* mutation, Kaplan-Meier survival analyses (log rank test) and univariate Cox proportional hazard models were used. Patient stratifications were performed according to the clinicopathological features and further survival analyses were conducted based on certain patient subgroups. In order to control possible confounding bias caused by differences in baseline characteristics, propensity score matching (PSM) was conducted. In the PSM analysis of high-grade endometrioid EC cohort, matching variables included body mass index (BMI) and hypertension history, with clipper width being 0.02 and matching ratio being 1:1. Kaplan-Meier survival analyses and Cox regressions based on balanced cohorts after PSM were conducted. In all Cox regression models, the proportional hazard hypothesis was verified using time-dependent covariate method. All statistical analyses were performed with Statistics Package for the Social Sciences (SPSS) software (version 22.0; IBM Corporation, Armonk, NY, USA). All p values used in the study were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

Among 510 eligible patients, a total of 90 (17.6%) had *BRCA1/2* mutations, with 11 (2.2%) harboring *BRCA1* mutation, 43 (8.4%) harboring *BRCA2* mutation, and 36 (7.1%) harboring both. Compared with patients with wild-type *BRCA* genes, the patient group with *BRCA1/2* mutations as a whole had lower BMI ($p = 0.020$), fewer cases with hypertension history ($p = 0.048$), more tumors with endometrioid histology ($p = 0.001$), and lower rates of positive peritoneal cytology ($p = 0.012$) (Table 1). In the group with *BRCA1* mutations, more advanced age patients ($p = 0.040$), patients with higher BMI ($p = 0.025$) and higher frequency of residual disease after primary surgery ($p = 0.024$) were observed, compared with patients with *BRCA2* or both gene mutations. Besides, significant statistic differences were also observed among the 3 groups regarding tumor grade and rates of lymph node metastasis ($p < 0.001$ and $p = 0.017$, respectively), as more patients with low-grade tumors and lower rates of lymph node metastasis were noted in the group with *BRCA2* mutations (Table 2).

In Kaplan-Meier survival analyses, *BRCA* wild-type group showed significantly shorter OS and RFS compared with the group with *BRCA* mutations ($p < 0.001$ and $p = 0.004$, respectively) (Fig. 1). The results were further validated by Cox proportional hazard models ($p = 0.001$ for OS and $p = 0.007$ for RFS) (Table S1). When patients were classified according to stage, grade and histology, there were remained statistical significance in the impact of *BRCA* mutations on OS and RFS in patients with high grade tumors or endometrioid type (in high-grade cohort, $p = 0.001$ and 0.006 for OS and RFS; in endometrioid EC cohort, $p = 0.012$ and 0.036 for OS and RFS), while in low-grade or non-endometrioid EC patients, *BRCA* mutation could not bring additional survival benefits (Table S1).

Cross-classification of EC patients by grade and histology was conducted. Both Kaplan-Meier survival analyses and Cox regressions showed that the survival influence of *BRCA* mutations were only significant in high-grade endometrioid EC patients ($p = 0.001$ and 0.012 for OS and RFS in Kaplan-Meier analyses, $p = 0.010$ and 0.018 for OS and RFS in Cox regressions) (Table 3 and Fig. 2). In order to further validate the results and minimize the confounding, PSM was conducted in high-grade endometrioid EC patients, and two groups with comparable baseline clinicopathological characteristics were generated (Table S2). In the cohorts after PSM, *BRCA* mutations still significantly influenced patients'

Table 1
Clinicopathological characteristics of patients with different *BRCA1/2* mutational status[a] No. (%).

Characteristic	*BRCA1/2* mutational status		*P* Value[b]
	Wild type (n = 420)	Mutant type (n = 90)	
Age≥65y			0.073
No	218 (52.0)	55 (62.5)	
Yes	201 (48.0)	33 (37.5)	
BMI≥28 kg/m^2,			**0.020**
No	114 (28.7)	35 (41.7)	
Yes	283 (71.3)	49 (58.3)	
Diabetes history			0.382
No	239 (72.9)	50 (78.1)	
Yes	89 (27.1)	14 (21.9)	
Hypertension history			**0.048**
No	133 (38.2)	37 (50.7)	
Yes	215 (61.8)	36 (49.3)	
AJCC stage			0.107
Early (stage I-II)	296 (70.5)	71 (78.9)	
Advanced (stage III-IV)	124 (29.5)	19 (21.1)	
Grade			0.771
Low (grade 1–2)	175 (41.7)	36 (40.0)	
High (grade 3)	245 (58.3)	54 (60.0)	
Histology,			**0.001**
Endometrioid type	304 (72.4)	80 (88.9)	
Non-endometrioid type	116 (27.6)	10 (11.1)	
Lymph node metastasis			0.150
No	279 (80.4)	69 (87.3)	
Yes	68 (19.6)	10 (12.7)	
Depth of myometrial invasion			0.974
<50%	202 (55.5)	44 (55.7)	
≥50%	162 (44.5)	35 (44.3)	
Peritoneal cytology			**0.012**
Negative	265 (83.9)	65 (95.6)	
Positive	51 (16.1)	3 (4.4)	
Residual disease			0.938
No	289 (82.6)	60 (82.2)	
Yes	61 (17.4)	13 (17.8)	
Radiation therapy use			0.960
No	223 (56.0)	49 (56.3)	
Yes	175 (44.0)	38 (43.7)	
Chemotherapy use			0.099
No	112 (56.3)	32 (69.6)	
Yes	87 (43.7)	14 (30.4)	
Molecular targeted therapy use			0.221
No	188 (66.0)	48 (73.8)	
Yes	97 (34.0)	17 (26.2)	

Abbreviations: BMI, body mass index; AJCC, American Joint Committee on Cancer.
[a] For some characteristics, the values do not sum to heading totals because of missing data.
[b] χ^2 test.

Table 2
Clinicopathological characteristics of patients with *BRCA* mutations[a] No. (%).

Characteristic	*BRCA1* mutation (n = 11)	*BRCA2* mutation (n = 43)	*BRCA1* and *BRCA2* mutation (n = 36)	*P* Value[b]
Age≥65y				**0.040**
No	3 (30.0)	26 (60.5)	26 (74.3)	
Yes	7 (70.0)	17 (39.5)	9 (25.7)	
BMI≥28 kg/m^2				**0.025**
No	1 (11.1)	15 (35.7)	19 (57.6)	
Yes	8 (88.9)	27 (64.3)	14 (42.4)	
Diabetes history				0.911
No	5 (71.4)	24 (77.4)	21 (80.8)	
Yes	2 (28.6)	7 (22.6)	5 (19.2)	
Hypertension history				0.162
No	2 (25.0)	16 (47.1)	19 (61.3)	
Yes	6 (75.0)	18 (52.9)	12 (38.7)	
AJCC stage				0.087
Early (stage I-II)	8 (72.7)	38 (88.4)	25 (69.4)	
Advanced (stage III-IV)	3 (27.3)	5 (11.6)	11 (30.6)	
Grade				**<0.001**
Low (G1 - 2)	3 (27.3)	26 (60.5)	7 (19.4)	
High (G3)	8 (72.7)	17 (39.5)	29 (80.6)	
Histology				0.181
Endometrioid type	8 (72.7)	40 (93.0)	32 (88.9)	
Non-endometrioid type	3 (27.3)	3 (7.0)	4 (11.1)	
Lymph node metastasis				**0.017**
No	7 (77.8)	38 (97.4)	24 (77.4)	
Yes	2 (22.2)	1 (2.6)	7 (22.6)	
Depth of myometrial invasion				0.462
<50%	3 (42.9)	25 (62.5)	16 (50.0)	
≥50%	4 (57.1)	15 (37.5)	16 (50.0)	
Peritoneal cytology				0.713
Negative	7 (100.0)	31 (96.9)	27 (93.1)	
Positive	0	1 (3.1)	2 (6.9)	
Residual disease				**0.024**
No	4 (57.1)	26 (76.5)	30 (93.8)	
Yes	3 (42.9)	8 (23.5)	2 (6.3)	
Radiation therapy use				0.904
No	5 (55.6)	25 (59.5)	19 (52.8)	
Yes	4 (44.4)	17 (40.5)	17 (47.2)	
Chemotherapy use				0.731
No	3 (60.0)	14 (66.7)	15 (75.0)	
Yes	2 (40.0)	7 (33.3)	5 (25.0)	
Molecular targeted therapy use				0.256
No	4 (80.0)	27 (81.8)	17 (63.0)	
Yes	1 (20.0)	6 (18.2)	10 (37.0)	

Abbreviations: BMI, body mass index; AJCC, American Joint Committee on Cancer.
[a] For some characteristics, the values do not sum to heading totals because of missing data.
[b] Fisher's exact test.

OS (p = 0.003 in Kaplan-Meier analysis), with *BRCA* mutant group showing better survival outcome, while the difference in RFS between the two groups was not significant (p = 0.057 in Kaplan-Meier analysis) (Fig. 2). This result was also validated by Cox regressions after PSM (for OS, hazard ratio [HR] = 0.082, 95% confidence interval [CI] 0.010–0.676, p = 0.020; for RFS, HR = 0.303, 95% CI 0.083–1.106, p = 0.071) (data not shown in tables and figures).

4. Discussion

In recent years, researches designed to better understand the significance of *BRCA* mutations are changing clinical practice, especially in the domain of ovarian cancer treatment. There were success in several key clinical trials, including SOLO-1[19], PAOLA,[20] PRIMA,[21] etc., which facilitated the National Comprehensive Cancer Network (NCCN) recommendation of PARP inhibitors as first-line maintenance therapy in epithelial ovarian cancer, and also urged the delivery of *BRCA* testing as a common practice.[22] In EC, however, we have limited understanding of *BRCA* mutational status since few research evidences supporting related clinical applications. In this study, we have proved the role of *BRCA* mutations in predicting EC patients' survival. Our results demonstrate that high-grade endometrioid EC patients with *BRCA1/2* mutations have longer survival than those with wild-type *BRCA*, though the time to recurrence is not significantly affected.

Previous work suggested that patients with germline *BRCA1* mutations were linked to an increased risk of developing serous or serous-like EC.[23] A recent study carried out by de Jonge et al.[14] further proved that ECs developed in the context of germline *BRCA* mutation and subsequent loss-of-heterozygosity were more commonly of non-endometrioid type.

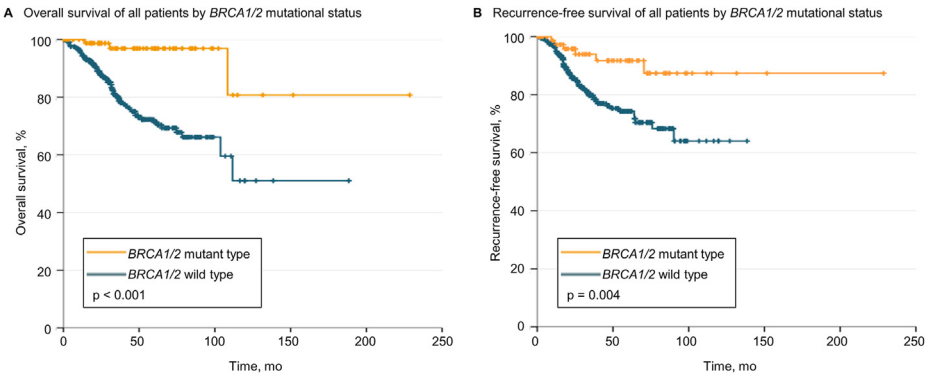

Fig. 1. Overall and recurrence-free survival of EC patients by *BRCA1/2* mutational status.

Table 3
Survival influence of *BRCA* mutation in different cohorts.[a].

Patient cohort	OS			RFS		
	Kaplan-Meier survival analysis	Cox regression		Kaplan-Meier survival analysis	Cox regression	
	P Value[b]	HR (95% CI)	*P* Value	*P* Value[b]	HR (95% CI)	*P* Value
Low-grade endometrioid type	0.116	0.038 (0.000–23.783)	0.319	0.254	0.327 (0.043–2.473)	0.279
High-grade endometrioid type	0.001	0.073 (0.010–0.537)	0.010	0.012	0.278 (0.096–0.806)	0.018
High-grade non-endometrioid type	0.110	0.328 (0.078–1.378)	0.128	0.229	0.313 (0.042–2.314)	0.255

Abbreviations: OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.
[a] Survival analyses could not be conducted in low-grade non-endometrioid type since only 2 cases were included in this group.
[b] Log rank test.

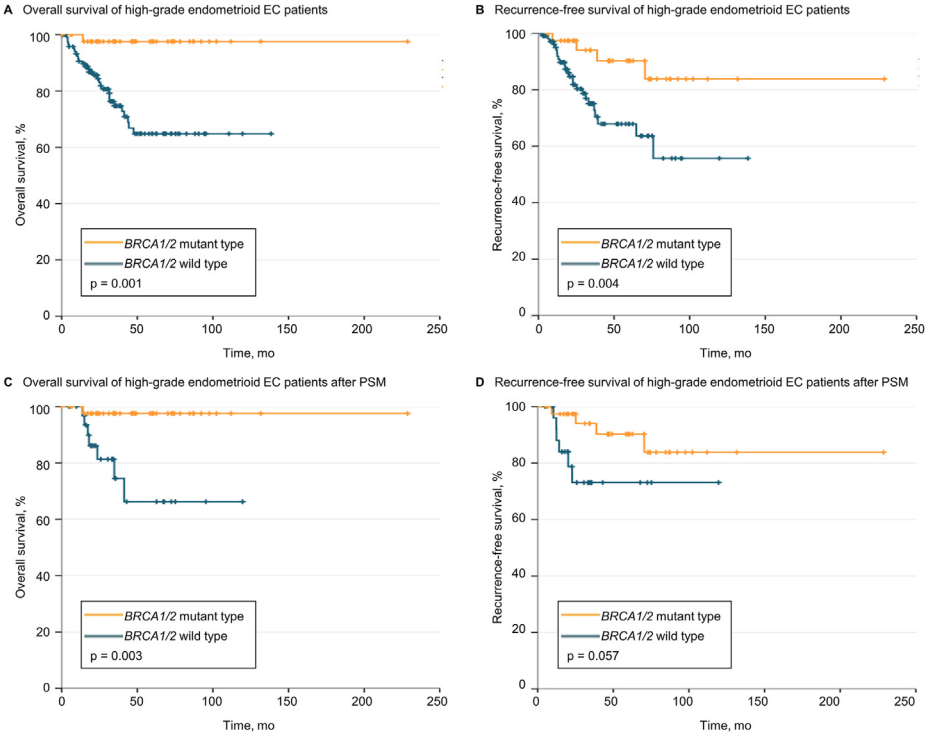

Fig. 2. Survival of high-grade endometrioid EC patients before and after PSM. Abbreviations: EC, endometrial cancer; PSM, propensity score matching.

Our study, however, showed that in EC cohort with *BRCA1/2* somatic mutations, there were significantly more endometrioid cases (88.9% vs. 72.4%, p = 0.001). In addition, the distribution of histological types was similar among patients with *BRCA1*, *BRCA2* or both mutations (p = 0.181). These results suggested the possible differences in tumorigenesis-related mechanisms after germline or somatic *BRCA* mutations. Besides, based on the study results of de Jonge et al.,[14] ECs with germline *BRCA* mutation and loss-of-heterozygosity showed more adverse prognostic factors compared with those without loss-of-heterozygosity, indicating unfavorable survival. But in another recent study by Kadan et al.,[24] serous ECs with *BRCA* mutations showed similar survival with *BRCA* wild-type ones, which was in accordance with

our data (p = 0.115 and 0.226 for OS and RFS in non-endometrioid EC).

According to previous studies, *BRCA1/2* mutations were associated with homologous recombination defects and increased mutation burden in the genome.[25] And higher tumor mutation burden was proved to be associated with better survival outcome in multiple cancer types from direct and indirect evidences.[6,26–28] These results might partly explain why high-grade endometrioid EC patients with *BRCA* mutations exhibited better survival than *BRCA* wild-type ones. While for non-endometrioid type EC, more invasive biological behavior endowed it generally poor survival compared with endometrioid ones, in which context, the positive survival impact of *BRCA* mutation might be not prominent enough to show a statistically significant effect. But still, more studies were needed to validate the above proposed mechanism.

In our study, detailed clinicopathological features of patients with distinct *BRCA* mutational status were compared, and stratification of patients according to clinicopathological features was performed. But there were also several limitations. Firstly, as a retrospective study, the capacity of controlling inter-group confounders was limited, though statistical method, such as PSM, was used. Besides, though the rates of receiving radio-, chemo- and molecular targeted therapies were basically comparable between the groups, detailed information about adjuvant therapy use was lacking in TCGA database. Secondly, in the study, since the number of patients with *BRCA1* mutations was limited, we did not manage to compare the survival influence of *BRCA1* and *BRCA2* mutations and discuss their roles separately. Larger cohorts may be helpful for more detailed comparison and better robustness of the results. Thirdly, since germline and somatic *BRCA* mutations may be distinct in their prognostic roles, it is better to set another cohort of germline *BRCA* mutant patients for further comparisons, which was not achieved in our study.

Currently, the trend toward individualized tumor management based on both clinicopathological features and molecular profiles is coming to the mainstream of clinical practice in gynecologic oncology treatment, and gene testing is getting increasing impact in revealing certain prognostic features and suggesting specific treatment modalities. One example is the currently ongoing PORTEC-4a trial, which combined EC patients' molecular and clinicopathological features in the clinical-decision system for choosing radiation therapy mode.[29] Our results about *BRCA* mutation provide another promising biomarker for prognostic prediction in the subgroup of high-grade endometrioid EC patients, and might be helpful for future molecular profile based immuno- and targeted therapy strategy planning. Nonetheless, further studies are needed in the future to fully validate the clinical significance of different *BRCA* mutation types, and more genetic researches might be helpful for better understanding the underlying mechanisms so as to better guide clinical practice.

Table S1
Cox proportional hazard models for the survival influence of *BRCA* mutation

Patient cohort	OS		RFS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All patients	0.133 (0.042–0.422)	0.001	0.317 (0.137–0.731)	0.007
Early stage	0.099 (0.013–0.720)	0.022	0.199 (0.048–0.825)	0.026
Advanced stage	0.168 (0.041–0.697)	0.014	0.405 (0.140–1.165)	0.094
Low-grade	0.038 (0.000–23.300)	0.318	0.319 (0.042–2.409)	0.268
High-grade	0.129 (0.041–0.413)	0.001	0.272 (0.108–0.685)	0.006
Endometrioid type	0.078 (0.011–0.566)	0.012	0.369 (0.145–0.935)	0.036
Non-endometrioid type	0.316 (0.075–1.326)	0.115	0.291 (0.039–2.150)	0.226

Abbreviations: OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

Table S2
Clinicopathological characteristics of high grade endometrioid endometrial cancer patients before and after PSM[a],No. (%)

Characteristic	Cohort before PSM			Cohort after PSM		
	BRCA wild type (n = 130)	*BRCA* mutant type (n = 45)	*P* Value	*BRCA* wild type (n = 420)	*BRCA* mutant type (n = 90)	*P* Value
Age≥65y			0.064			0.894
No	63 (48.8)	28 (65.1)		21 (63.6)	28 (65.1)	
Yes	66 (51.2)	15 (34.9)		12 (36.4)	15 (34.9)	
BMI≥28 kg/m^2			**0.005**			0.897
No	32 (26.2)	20 (50.0)		16 (48.5)	20 (50.0)	
Yes	90 (73.8)	20 (50.0)		17 (51.5)	20 (50.0)	
Diabetes history			0.174			0.456
No	60 (65.9)	23 (79.3)		22 (71.0)	23 (79.3)	
Yes	31 (34.1)	6 (20.7)		9 (29.0)	6 (20.7)	
Hypertension history			**0.007**			0.945
No	31 (31.6)	21 (56.8)		19 (57.6)	21 (56.8)	
Yes	67 (68.4)	16 (43.2)		14 (42.4)	16 (43.2)	
AJCC stage			0.538			0.564
Early (stage I-II)	92 (70.8)	34 (75.6)		23 (69.7)	34 (75.6)	
Advanced (stage III-IV)	38 (29.2)	11 (24.4)		10 (30.3)	11 (24.4)	
Lymph node metastasis			0.733			0.406
No	95 (80.5)	34 (82.9)		24 (75.0)	34 (82.9)	
Yes	23 (19.5)	7 (17.1)		8 (25.0)	7 (17.1)	
Depth of myometrial invasion			0.238			0.344
<50%	53 (51.0)	16 (40.0)		13 (52.0)	16 (40.0)	
≥50%	51 (49.0)	24 (60.0)		12 (48.0)	24 (60.0)	
Peritoneal cytology			0.506[b]			0.626[b]
Negative	78 (88.6)	33 (94.3)		19 (90.5)	33 (94.3)	

(*continued on next page*)

Table S2 (*continued*)

Characteristic	Cohort before PSM			Cohort after PSM		
	BRCA wild type (n = 130)	*BRCA* mutant type (n = 45)	*P* Value	*BRCA* wild type (n = 420)	*BRCA* mutant type (n = 90)	*P* Value
Positive	10 (11.4)	2 (5.7)		2 (9.5)	2 (5.7)	
Residual disease			0.614			0.872
No	78 (76.5)	29 (80.6)		23 (82.1)	29 (80.6)	
Yes	24 (23.5)	7 (19.4)		5 (17.9)	7 (19.4)	
Radiation therapy use			0.695			0.927
No	59 (50.0)	20 (46.5)		15 (45.5)	20 (46.5)	
Yes	59 (50.0)	23 (53.5)		18 (54.5)	23 (53.5)	
Chemotherapy use			0.749			0.384
No	47 (68.1)	20 (71.4)		10 (58.8)	20 (71.4)	
Yes	22 (31.9)	8 (28.6)		7 (41.2)	8 (28.6)	
Molecular targeted therapy use			0.811			0.523
No	45 (60.8)	19 (63.3)		12 (54.5)	19 (63.3)	
Yes	29 (39.2)	11 (36.7)		10 (45.5)	11 (36.7)	

Abbreviations: PSM, propensity score matching; BMI, body mass index; AJCC, American Joint Committee on Cancer.

[a] For some characteristics, the values do not sum to heading totals because of missing data.

[b] Fisher's exact test, all other comparisons are by χ^2 test.

Funding

This work was supported by the National Natural Science Foundation of China (81972426 and 81874108), Special Projects for Strengthening Basic Research of Peking University (BMU2018JC005), National Key Technology R&D Program of China (2019YFC1005200 and 2019YFC1005201).

Declaration of competing interest

No conflict of interest was reported from the authors.

Acknowledgements

The results of this study are based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *Ca - Cancer J Clin*. 2020;70:7–30.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Canc*. 2018;103:356–387.
3. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. *Chin J Canc Res*. 2018;30:1–12.
4. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol*. 1983;15:10–17.
5. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. *Lancet Oncol*. 2014;15:e268–e278.
6. The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497:67–73.
7. Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. *Cancer*. 2017;123:802–813.
8. Stelloo E, Nout RA, Osse EM, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. *Clin Canc Res*. 2016;22:4215–4224.
9. Church DN, Stelloo E, Nout RA, et al. Prognostic significance of POLE proofreading mutations in endometrial cancer. *J Natl Cancer Inst*. 2014;107:402.
10. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular-based classification for endometrial cancers. *Br J Canc*. 2015;113:299–310.
11. Kurnit KC, Kim GN, Fellman BM, et al. CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. *Mod Pathol*. 2017;30:1032–1041.
12. Faraoni I, Graziani G. Role of BRCA mutations in cancer treatment with poly(ADP-ribose) polymerase (PARP) inhibitors. *Cancers*. 2018;10:487.
13. Nielsen FC, Van Overeem Hansen T, Sørensen CS. Hereditary breast and ovarian cancer: new genes in confined pathways. *Nat Rev Canc*. 2016;16:599–612.
14. de Jonge MM, Ritterhouse LL, de Kroon CD, et al. Germline BRCA-associated endometrial carcinoma is a distinct clinicopathologic entity. *Clin Canc Res*. 2019;25:7517–7526.
15. Goldman M, Craft B, Hastie M, et al. The UCSC Xena platform for public and private cancer genomics data visualization and interpretation. *bioRxiv*. 2019:326470.
16. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data: figure.1. *Canc Discov*. 2012;2:401–404.
17. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal*. 2013;6:pl1–pl.
18. Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. *Int J Gynaecol Obstet*. 2006;95:S105–S143.
19. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379:2495–2505.
20. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med*. 2019;381:2416–2428.
21. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381:2391–2402.
22. George A, Kaye S, Banerjee S. Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer. *Nat Rev Clin Oncol*. 2017;14:284–296.
23. Shu CA, Pike MC, Jotwani AR, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. *JAMA Oncol*. 2016;2:1434–1440.
24. Kadan Y, Raviv O, Segev Y, et al. Impact of BRCA mutations on outcomes among patients with serous endometrial cancer. *Int J Gynaecol Obstet*. 2018;142:91–96.
25. Riaz N, Blecua P, Lim RS, et al. Pan-cancer analysis of bi-allelic alterations in homologous recombination DNA repair genes. *Nat Commun*. 2017;8:857.
26. Wang Z, Zhao J, Wang G, et al. Comutations in DNA damage response pathways serve as potential biomarkers for immune checkpoint blockade. *Canc Res*. 2018;78:6486.
27. Network TCGAR. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513:202–209.
28. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet*. 2019;51:202–206.
29. Wortman BG, Bosse T, Nout RA, et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial. *Gynecol Oncol*. 2018;151:69–75.