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 gBRCA1 and gBRCA2 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

| Variable                  | Noncarrier group (n = 461) | BRCA1 mutation carriers (n = 58) | BRCA2 mutation carriers (n = 77) | $p$  |
|---------------------------|----------------------------|---------------------------------|---------------------------------|------|
| **Histology**             |                            |                                 |                                 |      |
| EEC G1                    | 76/461 (16.5)              | 5/58 (8.6)                      | 13/77 (16.9)                    | 0.129|
| EEC G2                    | 107/461 (23.2)             | 7/58 (12.1)                     | 17/77 (22.1)                    | 0.063|
| EEC G3                    | 139/461 (30.1)             | 31/58 (53.4)                    | 37/77 (48.1)                    | <0.001|
| USC                       | 139/461 (30.1)             | 15/58 (25.9)                    | 10/77 (12.9)                    | 0.545|
| High riskc                | 278/461 (60.3)             | 46/58 (79.3)                    | 47/77 (61.0)                    | 0.005|
| **Age**                   |                            |                                 |                                 |      |
| Mean ± SD                 | 64.4 ± 10.7                | 61.1 ± 12.7                     | 59.9 ± 12.0                     | 0.036|
| > 70 y                    | 145/461 (31.5)             | 11/58 (19.6)                    | 13/77 (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|
| >= 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|
| 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|
| < 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|
| 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.
c 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) | OS (months) | p    |
|-------------------|--------------|-------------|------|
|                   | Mean ± SD (95% CI) | Mean ± SD (95% CI) |      |
| Noncarriers       | 102.8 ± 3.8 (95.3-110.3) | 121.9 ± 8.6 (105.1-138.8) | 0.011 |
| 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 ≥ 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 carci orn and grade (Multivariate Cox proportional hazards model).

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

Declinations
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 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
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.
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.