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Association of BRCA 1 and BRCA 2 Mutational Status on Prognosis of Early-Stage Serous Epithelial Ovarian Cancer

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Abstract

Research Question: To study if live birth rates are influenced by uterine size and/or presence of congenital uterine abnormalities (CUA) diagnosed by Three-dimensional ultrasound (3D-US) on the day of embryo transfer (ET).

Design: A total of 244 oocyte recipients under hormonal replacement therapy for endometrial preparation were included and a 3D-US was performed before the blastocyst transfer.

We analysed the relationship between type of uterus, endometrial thickness and volume, interostial distance (IOD) and transverse diameter (TD) with live birth rate (LBR).

Results: 3D-US could be performed in 236 patients. In 16.5% of the cases a uterine anomaly, either congenital or acquired, was seen by the 3D-US but not previously diagnosed by 2D-US. Endometrial volume, thickness and TD were significantly higher in normal uterus than in CUA ($p<0.05$).

LBR was 49.5% in normal uterus whereas it was 35.3% in CUA ($p=0.14$), with a miscarriage rate of 18.2% and 31.8%, respectively ($p=0.12$). In CUA, there was a significant relationship between the likelihood of live birth and endometrial volume (OR:2.76: 95%CI: 1.14-6.69), $p=0.025$.

Conclusions: An unsuspected finding was present in 16.5% of the cases. CUA showed a significantly lower endometrial volume, thickness and TD when compared with normal uterus. There was a significant relationship between the likelihood of live birth and endometrial volume on the day of ET in patients with CUA, but not in normal uteri. Patients with CUA showed a decreased, albeit not significant, probability of live birth and an increase in the miscarriage rate.

Keywords: Gynecologic malignancy; Ovarian cancer; High-grade serous carcinoma; BRCA 1 & 2 germline mutation; Clinical outcome; Survival outcome.

Introduction

The deadliest gynecologic disease, ovarian cancer was responsible for 313,959 new cases and 207,252 cancer-related deaths worldwide in 2020 [1]. Additionally, the rate of ovarian cancer has been steadily rising in our nation. Since 1990, Bangladesh's ovarian cancer death rate per 100,000 persons has risen by 40.3%, or 1.8% year, on average. According to Hyman et al. (2012), the incidence of ovarian cancer in Bangladesh was estimated to be 3132 in 2015 [2]. There are various histological subtypes of ovarian cancer, with

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over 90% of primary ovarian tumors being serous ovarian cancer (SOC) [3]. Historically, invasive SOC has been divided into four categories based on histologic appearance: serous, mucinous, endometrioid, and clear cell types. The most common kind of ovarian cancer, known as high-grade serous ovarian carcinoma (HGSOC), has a dismal prognosis [4]. Hereditary susceptibility is thought to be responsible for 5–14% of ovarian cancer cases, and mutations in the BRCA 1 and BRCA 2 genes provide a significant risk. Since their main roles are to maintain genomic stability and control cell growth, BRCA1 and BRCA2 are regarded as tumour suppressor genes implicated in homologous recombination (HR)-mediated DNA double strand break repair, which is also involved in cellular proliferation and chromosomal stability [5]. The genes BRCA1 and BRCA2 have been found to be causal in 65–75% of hereditary SOC cases. According to Lheureux et al. (2019), there is a significant correlation between high-grade SOC subtype vulnerability and harmful mutations in BRCA 1 and BRCA 2 [6]. Following their initial identification, mutations in the BRCA1 and BRCA2 genes have come to be understood as both a prognostic factor and a predictor of ovarian cancer susceptibility [7]. In women diagnosed with ovarian cancer, the frequency of germline mutations in BRCA 1 and BRCA 2 varies from 3% to 27% [8]. A family history of breast or ovarian cancer is the strongest known risk factor for ovarian cancer. According to a large prospective cohort research, carriers of BRCA 1 and BRCA 2 had a cumulative risk of 44% and 17%, respectively, of ovarian cancer until the age of 80. Among epithelial ovarian malignancies, high-grade serous ovarian cancer (HGSOC) is the most common and deadly type. In comparison to patients without a mutation, BRCA germline mutations were found to significantly improve overall survival in a sizable, pooled analysis of 26 observational studies. The mean 5-year overall survival for carriers of the BRCA 1 and BRCA 2 mutations was 44% and 52%, respectively, compared to 36% for non-carriers. Comparably, other studies have also shown that carriers of BRCA mutations have increased survival rates. Better prognosis due to chemo-sensitivity, response to PARP therapy and better survival rate [9]. There is proof that patients with ovarian cancer who have germline BRCA mutations have a better prognosis than those who do not. BRCA mutant patients survived longer than non-BRCA patients (77 versus 29 months), according to the first study that examined patient outcomes after receiving a BRCA mutation in 1996 (Rubin et al., 1996). Subsequent research has verified that these patients respond more favorably to platinum therapy than do those without BRCA mutations. It appears that those who carry the BRCA mutation are more susceptible to the advantages of intraperitoneal chemotherapy [10]. The precise impact of germ line BRCA1 and BRCA 2 mutations on the prognosis of ovarian cancer remains unclear to this day. Despite inconsistent results from other studies, a number of studies found that patients with germline BRCA mutations had a better prognosis, most likely as a result of their high response rate to platinum-based chemotherapy [11]. According to a Hyman study, patients with BRCA 2 mutations had a better prognosis than those with BRCA 1 mutations. The examination of the precise link between the survival outcomes and germline BRCA 1 and BRCA 2 mutations is hampered by the study population's variability and ethnicity [12]. In addition, BRCA 1 is a large gene whose protein product contains three representative domains that are regularly and frequently altered in cancer patients [13]. Regretfully, there is currently little information in our nation about the prognosis of serous ovarian cancer in relation to the presence or absence of BRCA mutations. Thus, the purpose of this research is to evaluate the impact of BRCA mutational status on prognosis in patients with serous epithelial ovarian cancer, with particular attention to the differences in clinical features between carriers and non-carriers of the mutation.

Methodology

The longitudinal cohort study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) & NICRH Dhaka. Study period was from May 2020 to December 2021. A total 32 women with histopathologically confirmed early stage (FIGO stage I to II) serous epithelial ovarian cancer were included in the study. Participants were divided into two groups according to their mutation status; patients with BRCA mutation were Exposed Group and those without BRCA mutation as Unexposed Group. Patients who matched the inclusion and exclusion criteria were approached for participation in the study. Patients who were not willing to give consent were excluded. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

Result

Table I shows that, maximum study subjects 12(75.0%) were in ≤45 years age group in exposed group and 14(87.5%) were in >45 years age group in unexposed group. Mean age of the study subjects was 37.33±3.55 and 42.43±4.22 years in exposed and unexposed group respectively.

Table 1: Distribution of the patients according to age (n = 32).

Age (years)	Exposed Group (n=16)	Unexposed Group (n=16)
≤45	12(75.0)	2(12.5)
>45	4(25.0)	14(87.5)
Mean ± SD	37.33±3.55	42.43±4.22

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Table II shows that, majority of the patients 11 (68.8%) and 12 (75.0%) were literate and 5 (31.3%) and 4 (25.0%) were illiterate in exposed and unexposed group respectively

Table 3 shows that, 6 (37.5%) respondent of exposed group and 5 (31.3%) of unexposed group had family history of breast / ovarian cancer.

Table 4 shows that, majority respondents of Unexposed group 12 (75.0%) underwent Primary Debulking Surgery as primary treatment modality, whereas 9 (56.2%) exposed group did not receive Primary Debulking Surgery

Table 5 shows that, majority respondents of exposed group 9 (56.2%) received neo adjuvant chemotherapy and interval debulking surgery, whereas 3 (18.8%) respondents of unexposed group received Neoadjuvant chemotherapy and interval debulking surgery

Table 6 shows that, 2 (12.5%) respondent of Exposed group and 5 (31.3%) of Unexposed group showed recurrence of disease. Though disease recurrence was less in Exposed group.

Table 2: Distribution of the patients according to educational status (n = 32).

Education	Exposed Group (n=16)	Unexposed Group (n=16)
Illiterate	5 (31.3)	4 (25.0)
Literate	11 (68.8)	12 (75.0)

Table 3: Distribution of the patients according to family history of breast / ovarian cancer (n = 32).

Family history of breast / ovarian cancer	Exposed Group (n=16)	Unexposed Group (n=16)
Yes	6 (37.5)	5 (31.3)
No	10 (62.5)	11 (68.8)

Table 4: Distribution of the patients according to Primary Debulking Surgery (n = 32).

Primary Debulking Surgery	Exposed Group (n=16)	Unexposed Group (n=16)
Yes	7 (43.8)	12 (75.0)
No	9 (56.2)	4 (25.0)

Table 5: Distribution of the patients according to Neoadjuvant Chemotherapy and Interval Debulking Surgery (n = 32).

Neoadjuvant Chemotherapy and Interval Debulking Surgery	Exposed Group (n=16)	Unexposed Group (n=16)
Yes	9 (56.2)	3 (18.8)
No	7 (43.8)	13 (81.2)

Table 7 shows that, 2 (12.5%) respondents of Exposed group and 4 (25.0%) of Unexposed group showed platinum sensitive recurrence.

Table 8 shows that, Mean time of recurrence for Exposed group and for Unexposed group was 11.34±2.63 and 9.33±3.34 months respectively. Mean progression free survival for Exposed group and for Unexposed group was 13.35±2.24 and 11.18±2.54 months respectively. Mean treatment free interval (TFI) for Exposed group and for Unexposed group was 11.17±2.16 and 9.24±2.07 months respectively.

Table 9 shows that, One-year overall survival for Exposed group was more 15 (93.8%) and for Unexposed group was 14 (87.5%)

Table 6: Distribution of the patients according to status of recurrence of disease after treatment (n = 32).

Status of recurrence	Exposed Group (n=16)	Unexposed Group (n=16)
Yes	2 (12.5)	5 (31.3)
No	14 (87.5)	11 (68.8)

Table 7: Distribution of the patients according to types of recurrence (n = 32).

Types of recurrence	Exposed Group (n=16)	Unexposed Group (n=16)
Platinum Sensitive	2 (12.5)	4 (25.0)
Platinum Resistant	0 (0)	2(12.5)
No	14 (87.5)	10 (62.5)

Table 8: Distribution of the patients according to Time of recurrence, Progression free survival and Treatment free interval (n = 32).

Types of recurrence	Exposed Group (n=16)	Unexposed Group (n=16)
Time of recurrence (months)	11.34±2.63	9.33±3.34
Progression free survival (months)	13.35±2.24	11.18±2.54
Treatment free interval (months)	11.17±2.16	9.24±2.07

Table 9: Distribution of the patients according to one-year overall survival (n = 32).

One-year overall survival	Exposed Group (n=16)	Unexposed Group (n=16)
Present	15 (93.8)	14 (87.5)
Absent	1 (6.2)	2 (12.5)

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Discussion

One of the most prevalent forms of cancer in women is ovarian cancer, which also happens to be the leading cause of death from gynecological cancer and one of the most common causes of deadly cancer in women overall. Most patients come with advanced-stage disease since the symptoms are generally ambiguous, making early detection difficult [14]. Surgery and chemotherapy are typically used in the treatment of ovarian cancer. It is commonly known that hereditary mutations in BRCA1 and BRCA2 increase the risk of ovarian cancer. Despite the widespread belief that germ-line BRCA mutations cause between 5.0% and 10.0% of ovarian cancer cases, new research indicates that this number is likely underestimated. In line with the age-specific penetrance of BRCA1 versus BRCA2 carriers, BRCA1 carriers had epithelial ovarian cancer (EOC) at an earlier age than BRCA2 carriers. The cross-sectional observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total 32 women with histopathologically confirmed early stage (FIGO stage I to II) serous epithelial ovarian cancer were included in the study. In this study, maximum study subjects 12(75.0%) were in ≤45 years age group in exposed group and 14(87.5%) were in >45 years age group in unexposed group. Mean age of the study subjects was 37.33±3.55 and 42.43±4.22 years in exposed and unexposed group respectively. Another study shows the risk of ovarian cancer increases in women who have ovulated more over their lifetime. This includes those who have never had children, those who begin ovulation at a younger age or reach menopause at an older age [15]. Ovarian cancer is most commonly diagnosed after menopause [16]. In this present study it was observed that age belonged to ≤45 years was significantly ($p<0.05$) more common in BRCA1 & 2 mutation group between two groups, however educational status was almost alike between two groups, no statistical significant difference was observed between two groups. Neff et al. (2017) study found convincing evidence of an age discrepancy for onset of disease between BRCA1/2, with BRCA1 patients having an increased risk after age 40 and BRCA2 patients after age 50 years, which is comparable with the current study [10]. National Comprehensive Cancer Network (NCCN) and Society of Gynecologic Oncology (SGO) recommend consideration of salpingo-oophorectomy (RRSO) following completion of childbearing and after 35 years in women with known BRCA mutation. This is based on the relative increase in risk of a gynecologic malignancy in a BRCA1 carrier after 40 years. Kim et al. 2019 study observed that 60.8% patients belonged to age ≥50 years in BRCA mutation and 75.3% in BRCA non mutated group ($p>0.05$), which is higher age ranged with the current study [8]. Similarly, Shi et al. (2018) study also higher age ranged ages at diagnosis between pathogenic mutation carriers and non-carriers. Shi et al. (2018) study showed there were no significant ($p>0.05$) differences in mean ages at diagnosis between pathogenic mutation and non-mutation group. The higher age ranged obtained by the above authors maybe due to geographical variations, racial, ethnic differences and genetic causes may have significant influence on their study subjects. Majority of the patients 11 (68.8%) and 12 (75.0%) were literate and 5 (31.3%) and 4 (25.0%) were illiterate in exposed and unexposed group respectively. Alberg et al. (2016) study findings suggested that ovarian cancer risk may be inversely associated with socioeconomic status, higher levels of education were inversely associated with ovarian cancer risk and individuals with the highest income level had a non-significantly lower risk than did those with the lowest income level.

In this present study, about 6 (37.5%) respondent of exposed group and 5 (31.3%) of unexposed group had family history of breast / ovarian cancer. In another study it was observed that 36.36% respondent of Exposed group and 25% of Unexposed group showed positive family history of breast and ovarian cancer. Positive family history of breast/ovarian cancer was significantly ($p=0.031$) associated with BRCA1 & BRCA 2 mutation group. Shi et al. (2018) study reported that patients who had family or personal history of Hereditary Breast and Ovarian Cancer (HBOC) related tumors had a significantly ($p<0.001$) increased rate of pathogenic gBRCA1/2 mutations, which support with the present study. In last decade, recommendations for BRCA testing and genetic counseling have further expanded to any individual who is diagnosed with an invasive ovarian cancer, even in the absence of a family history (Society of Gynecologic Oncology, 2015 and National Comprehensive Cancer Network, 2017) [17, 18]. On the others hand, according to Bolton et al. 2012 cases from BRCA 1/BRCA 2 non-mutated families could carry germline mutations in genes in the same pathway as BRCA1/BRCA2 or in different pathways that produce similar clinical features [19].

In this study majority respondents of Unexposed group 12 (75.0%) underwent Primary Debulking Surgery as primary treatment modality, whereas 9 (56.2%) exposed group did not receive Primary Debulking Surgery. Majority respondents of exposed group 9 (56.2%) received neo adjuvant chemotherapy and interval debulking surgery, whereas 3 (18.8%) respondents of unexposed group received Neoadjuvant chemotherapy and interval debulking surgery. Shi et al. (2018) study obtained that the effect of gBRCA1/2 mutations might be superior on the initial response to chemotherapy, particularly in those with incomplete cytoreduction, leading to a better survival. Majority respondents of Unexposed group (75%) received Primary Debulking Surgery whether majority respondents of exposed group (54.55%) received Neo adjuvant chemotherapy and interval debulking surgery. Significant difference was not found between groups regarding type of treatment. Kim et al. (2019) study observed

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that nearly two third (62.7%) patients received primary debulking surgery (PDS) in BRCA mutation and 61.0% in BRCA non-mutation type, which also not significant (p=0.378) between two groups in terms type of treatment. In contrary to Shi et al. (2018) study findings, Hyman stated that there was no correlation between the BRCA mutation status and the rate of optimal debulking surgery [2], which might be affected by various ethnics and different sample size. Narod, (2016) study mentioned that survival is maximized when residual disease is minimized after complete cytoreduction and chemotherapy [20]. Moreover, Ren et al. 2015 found that neoadjuvant chemotherapy was independently associated with OS, which was consistent with previous retrospective study [21]. Petrillo et al. (2017) reported that in the subgroup of BRCA1/BRCA2 non-mutation carriers, patients with neoadjuvant chemotherapy had a worse PFS than those with primary debulking surgery, but no significant difference was found in BRCA1/BRCA2 mutation carriers, nor in the estimation of OS [22].

About 2 (12.5%) respondent of Exposed group and 5 (31.3%) of Unexposed group showed recurrence of disease. Though disease recurrence was less in Exposed group. About 2 (12.5%) respondents of Exposed group and 4 (25.0%) of Unexposed group showed platinum sensitive recurrence. Regarding the status of recurrence of disease after treatment in another study it was observed that majority respondents of both groups did not show any recurrence of disease. In this study, 18.18% respondent of Exposed group type and 25% of Unexposed group showed platinum sensitive recurrence. It was observed that there was no significant difference between two groups in terms of types of recurrence (p=0.231). This study suggest that women are routinely referred for genetic counseling and genetic testing either during or soon after their primary systemic therapy is completed so that this information is available in a timely fashion for inclusion in decisions about subsequent treatment strategies in the event of a relapse (Pal et al. 2007). Kim et al. (2019) study observed that the proportions of platinum-sensitive recurrence (PSR) were 80.6% and. 63.8% in BRCA1 & BRCA2 mutation group and BRCA 1 & BRCA 2 non mutation group respectively and showed not significant (p=0.099) between two groups [8]. Mean time of recurrence for Exposed group and for Unexposed group was 11.34±2.63 and 9.33±3.34 months respectively. Mean progression free survival for Exposed group and for Unexposed group was 13.35±2.24 and 11.18±2.54 months respectively. Mean treatment free interval (TFI) for Exposed group and for Unexposed group was 11.17±2.16 and 9.24±2.07 months respectively. One-year overall survival for Exposed group was more 15 (93.8%) and for Unexposed group was 14 (87.5%). In another study, Mean time of recurrence for Exposed group and for Unexposed group was 10.34±2.73 and 8.33±3.44 months respectively. Independent sample t test showed the difference was not statistically significant (p=0.556). In this current study it was observed that Mean progression free survival for Exposed group and for Unexposed group was 12.35±2.23 and 10.18±2.56 months respectively. Independent sample t test showed the difference was statistically significant (p=0.030). Kim et al. (2019) obtained in their study that patients in the BRCA mutation group had significantly (p<0.001) longer (median, 21.7 vs. 15.4 months) progression-free survival (PFS) than those in the non-mutated BRCA group. Mean treatment free interval (TFI) for Exposed group and for Unexposed group was 12.17±2.18 and 10.24±2.09 months respectively. Independent sample t test showed the difference was statistically significant (p=0.013). Kim et al. (2019) study showed that the median treatment free interval was longer in the patients with BRCA mutations (12.3 months vs. 9.0 months, P=0.002), which support with the present study [8].

Conclusion

The purpose of this study was to determine if the prognosis of early-stage serous epithelial ovarian cancer was influenced by the mutational status of BRCA 1 and BRCA 2. Major patients in both groups lived for a year, despite the lack of statistical significance in the outcome. The group with BRCA 1 and BRCA 2 mutations had considerably longer treatment-free intervals and progression-free survival than the non-mutated group.

Limitations

The study population was enrolled Bangabandhu Sheikh Mujib Medical University (BSMMU) & NICRH, Dhaka, Bangladesh so that the results of the study may not be reflect the exact picture of the entire country.

Declaration

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Conflict of interest: None declared.

Ethical approval

The study was approved by the ethical committee of Bangabandhu Sheikh Mujib Medical University (BSMMU)

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