ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2023, Volume 12, Number 2: 1650-1654
P-ISSN.2089-1180, E-ISSN: 2302-2914

BRCA 1 and 2 somatic mutation in high grade serous epithelial ovarian cancer in Indonesian women that was operated on Dr. Soetomo General Hospital, Surabaya in 2019-2021

Jonathan Kevin Djuanda[1], Brahmana Askandar Tjokroprawiro[1*], Grace Ariani[2]

ABSTRACT

Background: Ovarian cancer remains as major problem worldwide. BRCA1 and BRCA2 play a unique role in deoxyribonucleic acid (DNA) damage repair, especially in homologous recombination repair. There are no data on the prevalence of BRCA1 and BRCA2 somatic mutations in the Indonesian population. This study aimed to determine the incidence of BRCA1 and BRCA2 somatic mutations among a cohort of patients with high-grade serous epithelial ovarian cancer, and assess its correlation with clinical characteristics of the cohort.

Methods: This was an analytical observational study of 26 patients admitted to our hospital from 2019 to 2021. Pathological specimens were obtained from the patients and examined for BRCA1 and BRCA2 somatic mutations. Data on clinical characteristics were collected from medical records. Statistical analysis was performed to determine the relationship between BRCA mutation status and clinical characteristics, including age, stage, menopausal status, parity, family history of malignancy, and patient outcomes.

Results: Twenty-six patients with high-grade serous epithelial ovarian cancer were included in the study. Six patients (27% of 22 patients) had BRCA1 and BRCA2 somatic mutations, four did not pass the quality control test, and the remaining tested negative for these mutations. Most patients were over 50 years of age (73%). Additionally, 84% of patients were diagnosed at stage III, and only one patient had a family history of malignancy. At the end of the study, most patients (65%) had died. Statistical analysis showed no significant differences between the clinical characteristics of the groups.

Conclusion: The incidence of BRCA1 and BRCA2 somatic mutations among patients with high-grade serous epithelial ovarian cancer at our hospital during 2019–2021 was 27%. There were no significant differences in the clinical characteristics of those with and without mutations, hence NGS screening following diagnosis establishment may be beneficial in further management plans.

Keywords: Epithelial ovarian cancer, BRCA somatic mutation, clinical characteristics, prevalence.
Cite This Article: Djuanda, J.K., Tjokroprawiro, B.A., Ariani, G. 2023. BRCA 1 and 2 somatic mutation in high grade serous epithelial ovarian cancer in Indonesian women that was operated on Dr. Soetomo General Hospital, Surabaya in 2019-2021. *Bali Medical Journal* 12(2): 1650-1654. DOI: 10.15562/bmj.v12i2.4504

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Airlangga University/ Dr. Soetomo Academic Hospital, Surabaya Indonesia;
[2]Department of Anatomical Pathology, Faculty of Medicine, Airlangga University/Dr. Soetomo Academic Hospital, Surabaya Indonesia;

*Corresponding author:
Brahmana Askandar Tjokroprawiro;
Department of Obstetrics and Gynecology, Faculty of Medicine, Airlangga University/ Dr. Soetomo Academic Hospital, Surabaya, Indonesia;
brahmanaaskandar@fk.unair.ac.id

Received: 2023-04-28
Accepted: 2023-05-03
Published: 2023-05-23

INTRODUCTION

Ovarian cancer is ranked seventh in terms of prevalence among all cancer types in Asia. In 2012, the total number of ovarian cancer cases in Indonesia ranked fifth among all countries worldwide. In Indonesia, ovarian cancer is the third most common cancer type among women.[1] Among the known heritable risk factors, ovarian cancer is mostly associated with mutations in the BRCA1 and BRCA2 genes. These two genes contribute to 60–80% of all inherited breast cancers and 15–22% of all ovarian cancers. BRCA1 and BRCA2 mutations are found in germ and somatic cells. BRCA somatic mutations occur in 5–7% of all ovarian cancers. BRCA1 and BRCA2 mutations are more commonly found in high-grade serous ovarian cancers. In general, 10–15% of patients with epithelial ovarian cancer have germline mutations of BRCA1 and BRCA2, with the prevalence being higher in patients with high-grade serous ovarian cancer (20–25%). Based on histopathological results, epithelial ovarian cancer accounted for the highest proportion of ovarian cancer subtypes. Moreover, 70% of epithelial ovarian cancer cases were of the high-grade serous type, and the highest proportion of BRCA1 and BRCA2 somatic mutations was also of this subtype.[2,3]

BRCA1 and BRCA2 play a unique role in deoxyribonucleic acid (DNA) damage repair, especially in homologous recombination repair. BRCA1 is part of a larger molecule that examines DNA for the presence or absence of double-strand break damage. Meanwhile, BRCA2 is directly related to the DNA repair process by assisting the RAD51 complex in attaching to the site of damage and initiating gene repair. Defects or damage

to BRCA1 and BRCA2 disrupts this DNA repair process, converting it to an error-prone mechanism, whereby cells with defective DNA accumulate.[4]

In Indonesia, no data to date have described the prevalence of BRCA1 and BRCA2 mutations, both somatic and germline, among ovarian cancer cases. Currently, germline and somatic BRCA mutations are widely studied for the development of treatments, such as targeted therapy using PARP inhibitors. This study aimed to determine the incidence of BRCA1 and BRCA2 somatic mutations among a cohort of patients with high-grade serous epithelial ovarian cancer, and assess its correlation with clinical characteristics of the cohort. This study is expected to provide baseline data that can play an important role in developing management plans for patients with ovarian cancer in the future.

METHODS

This was an analytical observational study with a cross-sectional design that used secondary data or medical records of patients diagnosed with high-grade serous epithelial ovarian cancer who underwent surgery and histopathological examination at our hospital from January 2019 to December 2021. This study was conducted under the approval and supervision of the Ethics Committee of Dr. Soetomo hospital (registration no. 1144/104/4/XII/2021).

Clinical characteristics were assessed, including age, cancer stage, surgery performed, and pathological characteristics (histopathological type, tumor grade, chemotherapy administered, and family history of malignancy). The selection of patients for this study was based on the medical records of patients indicating a diagnosis of high-grade serous epithelial ovarian cancer and a surgical intervention with histopathological examination and meeting the inclusion criteria. Data on clinical characteristics and patient and family medical histories were collected and then analyzed to determine the association effect between BRCA1 and BRCA2 somatic mutation status and clinical characteristics, disease course, and family history of malignancy.

The analysis of the BRCA mutation began with the selection of the tumor sample. All of our eligible samples underwent a confirmatory examination to evaluate the high grade serous ovarian cancer histopathology as well as to determine the percentage of viable tumor area. Our institution keeps the pathology sample in a Formalin Fixed Paraffin Embedded (FFPE) material to preserve the tissue as well as the genetic materials. The FFPE blocks were sent to a specialized laboratory in which the tumor DNA will be extracted via the Next Gene Sequencing (NGS) method. After sequencing is completed, the DNA sequence and variant are analysed and any mutation detected are reported.

Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Data were tabulated descriptively using percentage and mean with standard deviation or median. Statistical analysis with Chi-Square and Mann-Whitney equation were performed. Statistical significance was set at $p < 0.05$.

RESULTS

There were 26 patients diagnosed with high-grade serous epithelial ovarian cancer who underwent surgery at our institution. All histopathological examinations were also performed at our institution. There were eight patients in 2019, six in 2020, and 12 in 2021. Most patients were over 50 years old, with an average age of 54 years. The youngest patient was 36 years old and the oldest was 71 years old; 73% of the patients were multiparous and 27% were nulliparous.

Most patients were diagnosed with FIGO stage III disease (n = 22, 84.6%) through surgical staging. Eighteen patients received chemotherapy (69.2%), whereas the remaining did not (30.8%). Almost none of the patients had a family history of malignancy. Among patients with documented first-to-third-degree family relations (25 patients, 96.2%), only one patient (3.8%) had a history of breast cancer in their siblings. Most patients had died at the time of data collection (17 patients, 65.4%), while nine patients were still undergoing treatment or routine monitoring.

All 26 samples were subjected to NGS to detect any BRCA1 and BRCA2 mutations. From the NGS examination, six positive cases of BRCA mutation (23.1%) were obtained, with four invalid cases (15.4%) due to failure of the quality control test in the laboratory where the NGS was conducted. The remaining 16 patients had negative results. Five patients had a BRCA1 mutation (83%) and one patient had a BRCA2 mutation (17%). All invalid cases were from the oldest sample (year 2019) and thus, time-related sample degradation was suspected to be the main cause of the invalid results.

All the clinical characteristics were analyzed statistically, and none of them showed significant differences between those with the mutations and those without (all *p* values were > 0.05) (Table 1).

DISCUSSION

This is the first study conducted in an Indonesian institution to assess the incidence of BRCA1 and BRCA2 somatic mutations among high-grade serous ovarian cancer patients. This study revealed six BRCA1 and BRCA2 somatic mutation cases among 22 valid cases from which genetic material was extracted (mutation rate, 27%).

Moschetta et al. reported that somatic BRCA mutations were found in 5–7% of all ovarian cancer cases, with the highest prevalence found in high-grade serous ovarian cancer.[5] Among ovarian cancer cases with BRCA germline mutations, 15–20% of somatic mutations may coexist (one case of BRCA somatic mutation for every 4–5 patients with BRCA germline mutations). Hereditary factors are responsible for approximately 4–5% of cases of ovarian cancer, although several studies have reported that this hereditary mutation rate can reach 20% among ovarian cancer cases.[6,7] However, the proportion of somatic BRCA mutations varies, ranging from 10–30% of all BRCA mutations in patients with high-grade serous ovarian cancer, regardless of their germline BRCA mutation status.[8] The studies mentioned above included epithelial ovarian cancer cases in general and were not limited to high-grade serous epithelial ovarian cancer cases, as in our study.

The mutation rate of 27% obtained in our study was higher than that obtained in several previous studies on BRCA somatic

Table 1. Patient clinical characteristics and bivariate analysis of each characteristic.

Clinical Characteristics	sBRCA negative	sBRCA positive	QC Failure	*p*
Age, n (%)				0.585
<40 years old	2 (7)	0 (0)	0 (0)	
41-50 years old	4 (14)	0 (0)	1 (4)	
51-60 years old	8 (28)	2 (7)	3 (12)	
>60 years old	2 (7)	4 (14)	0 (0)	
Menopausal status, n (%)				0.166
Pre-menopause	11 (42)	6 (23)	3 (12)	
Menopause	5 (19)	0 (0)	1 (4)	
Parity, n (%)				0.107
Nulliparous	6 (23)	0 (0)	1 (4)	
Multiparous	10 (10)	6 (23)	3 (12)	
Ca-125 levels, median (min-max)	764.4 (49.6-3258)	836.5 (338.5-2271.5)	761.95 (51.1-1654)	0.302
FIGO stage on diagnosis, n (%)				0.281
I	2 (7)	0 (0)	0 (0)	
II	1 (4)	0 (0)	0 (0)	
III	12 (46)	6 (23)	4 (14)	
IV	1 (4)	0 (0)	0 (0)	
Chemotherapy administration, n (%)				0.267
Yes	12 (46)	3 (12)	3 (12)	
No	4 (14)	3 (12)	1 (4)	
Family history of malignancy, n (%)				0.273
Present	0 (0)	1 (4)	0 (0)	
None	16 (62)	5 (19)	4 (14)	
Patient's current outcome, n (%)				0.523
Alive	7 (26)	2 (7)	0 (0)	
Deceased	9 (35)	4 (14)	4 (14)	

sBRCA: Somatic BRCA mutation; QC: Quality control

mutations.[3,5,8] However, there has been no specified limit for the normal range of BRCA somatic mutations. In addition, many other studies have used different populations.[3,5,9] In this study, we used a population that has been reported to have the highest rates of BRCA1 and BRCA2 somatic mutations, namely, patients with high-grade serous epithelial ovarian cancer. Kim et al. conducted a study on a group of patients with high-grade serous epithelial ovarian cancer and reported a mutation rate of 39.8%.[9] Turashvili et al. reported a different result, with 7% somatic mutations in cases of high-grade serous ovarian cancer.[3] A review of the literature showed that studies examining the incidence of BRCA somatic mutations only in high-grade serous ovarian cancer cases are still relatively rare; many studies have been conducted involving the entire spectrum of epithelial ovarian cancers and not only high-grade serous types. Many studies have also shown conflicting results, as in case of Turashvili et al. and Kim et al.[3,9]

Based on our estimated mutation rate of 27%, the provision of targeted therapies, such as PARP inhibitors (ex. olaparib) could benefit these patients; therefore, in the future, NGS examination to determine the status of BRCA somatic mutations in patients with ovarian cancer may have therapeutic potential. The administration of PARP inhibitor therapy to ovarian cancer patients with BRCA somatic mutations may prolong their life expectancy and the period of disease-free survival.[10]

While there are no studies examining the impact of somatic BRCA mutations on menopausal status or vice versa, a study conducted by Lin et al found that germline BRCA1 and BRCA2 mutations are associated with an earlier incidence of menopause. This effect was thought to be caused by damage to the DNA repair mechanism, which increases the rate of ovum damage, ultimately leading to primary ovarian insufficiency.[11,12] Although we did not examine BRCA germline mutations in our study, none of our patients had a history of early menopause.

Most patients in our study were multiparous, with only seven patients being nulliparous (27%). Our statistical analysis did not show a significant correlation of parity status with BRCA somatic mutation (p = 0.107); this is most likely due to our small sample size. Ovarian cancer pathogenesis is related to repeated damage to the ovarian surface epithelium caused by the cyclical ovulation process.[13] If the patient does not conceive, the menstrual process will continue without interruption. Thus, the risk of ovarian epithelial damage and defects in the repair process is higher, making higher parity a protective risk factor for the incidence of epithelial ovarian cancer. Higher parity was found to be protective against breast and ovarian cancer risks in patients with BRCA1 and BRCA2 germline mutations.[14,15]

Regarding family history of malignancy, we only found one patient with a history of breast cancer in the first-degree family and none in the other 25 patients. Thus, family

history also did not have a statistically significant association with *BRCA* somatic mutations (p = 0.273). Notably, BRCA1 and BRCA2 somatic mutations are not directly associated with a family history of cancer. However, patients without germline BRCA mutations can also have spontaneous BRCA1 and BRCA2 somatic mutations in ovarian tumor cells.

Paik et al. reported that of the 298 cases examined for somatic and germline BRCA mutations, 89 positive results were obtained, with 64 patients having BRCA1 germline mutations, 14 having BRCA2 germline mutations, and 11 having somatic BRCA mutations.[16] It was noted that in the group of patients with germline mutations, more than 20% had a history of other malignancies in their immediate family (primarily breast and ovarian malignancies). However, in the group with positive somatic mutations, only one patient had a family history of breast cancer, a similar proportion as observed in our results. This is most likely because BRCA somatic mutations in ovarian cancer are not related to heredity, and therefore are not associated with an increased risk in the family. However, in our study, we did not examine germline mutation status, which may have a varying proportion of cases with a family history of malignancy.

Mortality was observed in 13 patients from the group with negative BRCA somatic mutations (13 of 20; 65%) and four with positive BRCA somatic mutations (four of six patients; 66.7%). The statistical analysis between the outcomes of patients with BRCA1 and BRCA2 somatic mutation status also did not yield significant results (p = 0.523).

One of the limitations of this study is the small sample size, which may limit any inferences made regarding the proportions of mutations and characteristics of ovarian cancer patients in the general population. However, one study conducted by Kim et al. reported that ovarian cancer patients with BRCA germline mutations had a longer period of progression-free survival than those who did not have a BRCA germline mutation. Kim et al. did not discuss the status of somatic mutations; however, interestingly, the results of Kim's study may be expected since high-grade serous ovarian cancer cases generally have a good therapeutic response to platinum-based chemotherapy.[9] Different results were reported by Shi et al from a study in China, in which they found no relationship between survival rates and germline mutation status of BRCA1 and BRCA2 in patients with ovarian cancer. However, Shi et al enrolled all ovarian cancer patients and not only those with the high-grade serous type. Shi et al also reported that postoperative residues have a significant effect on the survival of patients with ovarian cancer.[17] Another studies also evaluated prognostic factor for ovarian cancer.[18-20] This can be a consideration for further research to determine the factors involved in the survival of ovarian cancer patients with BRCA mutations. When conditions allow, it is important to examine both somatic and germline mutations in patients with high-grade serous epithelial ovarian cancer to help determine the therapeutic steps and educate patients and families regarding the risk of malignancy in the future.[21]

CONCLUSION

In conclusion, there was no significant relationship between the clinical characteristics of the patients and the somatic mutation status of BRCA1 and BRCA2 in our cohort. Hence, no clinical characteristics can be used as a basis for clinicians to suspect the presence of these somatic mutations without performing NGS.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

ETHICAL CONSIDERATION

This study was conducted under the approval and supervision of the Ethics Committee of Dr. Soetomo hospital (registration no. 1144/104/4/XII/2021).

FUNDING

None.

AUTHOR CONTRIBUTION

All of the authors contributed to the study from the conceptual framework, data gathering, and analysis until the study's results were interpreted upon publication.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317:2402-2416.
3. Turashvili G, Lazaro C, Ying S, Charames G, Wong A, Hamilton K, et al. Tumor BRCA testing in high grade serous carcinoma: mutation rates and optimal tissue requirements. Cancers. 2020;12(11):3468.
4. Sullivan MR, Bernstein KA. Rad-iCal new insights into rad51 regulation. Genes (Basel). 2018;9(12):629.
5. Moschetta M, George A, Kaye SB, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. Ann Oncol. 2016;27:1449-1455.
6. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. J Clin Oncol. 2020;38:1222-1245.
7. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381:2416-2428.
8. Eoh KJ, Kim HM, Lee JY, Kim S, Kim SW, Kim YT, et al. Mutation landscape of germline and somatic BRCA1/2 in patients with high-grade serous ovarian cancer. BMC Cancer. 2020;20:204.
9. Kim SI, Lee M, Kim HS, Chung HH, Kim JW, Park NH, et al. Effect of BRCA mutational status on survival outcome in advanced-stage high-grade serous ovarian cancer. J Ovarian Res. 2019;12:40.
10. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495-2505.
11. Lin WT, Beattie M, Chen LM, Oktay K, Crawford SL, Gold EB, et al. Comparison of age at natural menopause in BRCA1/2mutation carriers with a non-clinic-based sample of women in northern california. Cancer. 2013;119:1652-1659.
12. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: A possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol. 2010;28:240-244.
13. Levanon K, Ng V, Piao HY, Zhang Y, Chang MC, Roh MH, et al. Primary ex vivo cultures of human fallopian tube epithelium as a model for serous ovarian carcinogenesis. Oncogene. 2010;29:1103-1113.
14. Milne RL, Osorio A, Ramón y Cajal T, Baiget M, Lasa A, Diaz-Rubio E, et al. Parity and the risk of breast and ovarian cancer in BRCA1 and

BRCA2 mutation carriers. Breast Cancer Res Treat. 2010;119:221-232.
15. Clavel-Chapelon F, E3N-EPIC Group. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. Br J Cancer. 2002;86:723-727.
16. Paik ES, Heo EJ, Choi CH, Kim JH, Kim JW, Kim YM, et al. Prevalence and clinical characterization of BRCA1 and BRCA2 mutations in Korean patients with epithelial ovarian cancer. Cancer Sci. 2021;112:5055-5067.
17. Shi T, Wang P, Tang W, Jiang R, Yin S, Shi D, et al. Survival benefit of germline BRCA mutation is associated with residual disease in ovarian cancer. Cell Physiol Biochem. 2018;47:2088-2096.
18. Prakosa T, Mudigdo A, Purwanto B, Wasita B, Cilmiaty R, Widianingsih V. A cross-sectional study: The correlation of pro-angiogenic factors expression level and epithelial ovarian cancer staging. Bali Med J. 2020;9(1):125-128.
19. Prabowo A, Tjokroprawiro BA, Utomo B. Correlation between clinicopathological factors and clinical outcomes of recurrent epithelial ovarian cancer at a tertiary hospital in Surabaya, Indonesia. Bali Med J. 2022;11(2):807-812.
20. Dewi IGASM, Susraini AAAN, Ekawati NP. HER2/neu and Ki-67 as prognostic factors in serous type ovarian carcinoma. Bali Med J. 2020;9(2):567-571.
21. Gori S, Barberis M, Bella MA, Buttitta F, Capoluongo E, Carrera P, et al. Recommendations for the implementation of BRCA testing in ovarian cancer patients and their relatives. Crit Rev Oncol Hematol. 2019;140:67-72.