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Profile of Somatic BRCA1/2 Mutations in High Grade Serous Ovarian Carcinoma

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ABSTRACT

Ovarian cancer ranks as the third most prevalent cancer among women, with 70% of these cases classified as high-grade serous ovarian carcinoma (HGSOC). This type is marked by significant genomic instability and the presence of somatic loss-of-function mutations in the BRCA1/2 genes. It is advisable to conduct BRCA testing for patients diagnosed with HGSOC due to its critical role in genetic counseling for both patients and their families, as well as its implications for treatment options. The objective of this study was to analyze the profile of somatic mutations in BRCA1/2 within cases of HGSOC. This research employed a descriptive observational design and a retrospective methodology. The sample consisted of data regarding somatic BRCA1/2 mutation results from HGSOC diagnoses obtained from surgical specimens at the Anatomic Pathology Laboratory of Dr. Soetomo General Academic Hospital in Surabaya in 2022. A total of 11 cases were analyzed. The data collected encompassed the distribution of somatic BRCA1/2 mutations, histopathological diagnoses, age demographics, parity status, and T-stage classification. Out of the 11 cases, 4 exhibited positive BRCA mutations: 1 case had a mutation in BRCA1, while 3 cases showed mutations in BRCA2. The highest rate of somatic BRCA1/2 mutations was observed in the age group of 50-59 years (45.45%). When examining parity, the majority of cases (54.54%) were found in individuals with no previous pregnancies (0 parity). In terms of T-stage distribution, most HGSOC cases were classified at the T3 stage (72.72%). Overall, the incidence of somatic BRCA1/2 mutations in HGSOC at our hospital in 2022 was recorded at 36.36%.

Keywords: cancer; ovarian cancer; somatic BRCA mutation; high grade serous ovarian carcinoma; profile.

INTRODUCTION

Ovarian cancer is associated with a poor survival rate. Based on data from the Global Cancer Incidence, Mortality, and Prevalence (Globocan) 2020, there were 313,959 new ovarian cancer cases globally, resulting in 207,252 deaths among women [1]. In Indonesia, it was the third leading cause of cancer-related deaths in women in 2022, with 15,130 new cases and 9,673 fatalities reported [2]. According to WHO (2020), approximately 70% of ovarian cancers are classified as high-grade serous ovarian carcinoma (HGSOC), a particularly aggressive form [3]. Due to its asymptomatic nature and lack of effective screening tools, around 80% of HGSOC cases are diagnosed at advanced stages (FIGO stage III or IV). The overall five-year survival rate is below 30% [4]. While initial treatments often show success, about 70% of patients experience recurrence within three years [5].

BRCA1/2 mutations play a critical role in understanding the biology, prognosis, and treatment of HGSOC, which is the most aggressive and common subtype of epithelial ovarian cancer. These mutations are strongly linked to hereditary breast and gynecological cancers, especially ovarian cancer (Hereditary Breast and Ovarian Cancer or HBOC). Germline BRCA1/2 mutations (gBRCAms) are estimated to account for roughly 5% of breast cancers and 15-18% of ovarian cancers. Additionally, another 5-7% of ovarian cancers exhibit pathogenic somatic BRCA1/2 mutations (sBRCAms) [6].

This retrospective study investigates the profile of somatic BRCA1/2 mutations in HGSOC cases treated at Dr. Soetomo General Hospital in 2022.

METHODS

The research utilized a descriptive observational design with a retrospective methodology.

This investigation examined data from 11 instances of high-grade serous ovarian carcinoma (HGSOC), concentrating on somatic mutations in BRCA1/2. Surgical specimens were obtained from Dr. Soetomo General Academic Hospital in Surabaya in 2022.

The criteria for inclusion mandated that histopathological findings corresponded to the characteristics of HGSOC, as determined by diagnoses from the Anatomical Pathology Laboratory at Dr. Soetomo General Academic Hospital within that timeframe; somatic BRCA1/2 mutations were analyzed in these specimens. Cases diagnosed with an additional malignancy were excluded from the analysis. Data was collected from archived records, encompassing the distribution of somatic BRCA1/2 mutation cases, histopathological diagnoses, age demographics, parity, and T stage.

The study was carried out with the approval and supervision of the Ethics Committee at Dr. Soetomo General Academic Hospital (registration number 2943/120/4/VI/2024).

RESULT

In 2022, research conducted at Dr. Soetomo General Academic Hospital in Surabaya identified 11 cases of high-grade serous ovarian cancer (HGSOC) with somatic BRCA1/2 mutations, representing 39.28% of all cases. Among these, four cases tested positive for BRCA mutations, including one with a BRCA1 mutation and three with BRCA2 mutations. The remaining seven cases (63.63%) were negative for BRCA1/2 mutations. Table 1 provides details on the characteristics of the somatic BRCA1/2 mutations.

The patients' ages ranged from 38 to 62 years, with an average age of 51 years. The highest incidence was observed in the 50–59 age group.

Parity distribution revealed that the majority of cases (54.54%) occurred in patients with no prior childbirths (0 parity).

Regarding pT stages, HGSOC cases with somatic BRCA1/2 mutations were distributed as follows: pT3 accounted for 72.72%, including three cases (37.5%) with positive BRCA2 mutations, while pT1 comprised 27.28%, including one case (33.33%) with a positive BRCA1 mutation. Among negative BRCA1/2 mutation cases, pT3 was also the most prevalent stage (63.63%).

TABLE 1: Characteristics of Somatic BRCA1/2 Mutations in HGSOC Patients.

Clinical Characteristics	sBRCA negative	sBRCA positive	
		sBRCA1	sBRCA2
Age, n (%)			
30-39 years old	1 (9,09)	0	0
40-49 years old	3 (27,27)	0	1 (9,09)
50-59 years old	3 (27,27)	1 (9,09)	1 (9,09)
60-69 years old	0	0	1 (9,09)
Parity, n (%)			
0	4 (36,36)	0	2 (18,18)
1	2 (18,18)	0	0
2	0	1 (9,09)	0
3	0	0	1 (9,09)
Histology type, n (%)			
High-grade serous ovarian carcinoma	7 (63,63)	1 (9,09)	3 (27,27)
pT Stage, n (%)			
1	2 (18,18)	1 (9,09)	0
2	0	0	0
3	5 (45,45)	0	3 (27,27)

sBRCA: Somatic BRCA mutation.

DISCUSSION

In 2022, 11 cases of somatic BRCA1/2 mutations were identified among patients undergoing surgery at Dr. Soetomo General Academic Hospital in Surabaya. These cases accounted for 39.28% of all high-grade serous ovarian carcinoma (HGSOC) cases treated surgically and analyzed in the hospital's Anatomical Pathology Laboratory during that period.

BRCA1/2 mutations play a crucial role in understanding the biology, prognosis, and treatment of HGSOC, the most prevalent and aggressive form of epithelial ovarian cancer.

These tumor suppressor genes are essential for genomic stability via homologous recombination, a DNA repair process that addresses double-strand breaks. Mutations in BRCA1 or BRCA2 disrupt this mechanism, leading to increased genomic instability. This deficiency not only drives HGSOC development but also renders such tumors highly responsive to treatments like platinum-based chemotherapy and PARP inhibitors [7–9].

Of the 11 cases, 4 tested positive for BRCA mutations—1 for BRCA1 and 3 for BRCA2—while the remaining 7 cases (63.63%) were negative.

These findings are consistent with previous studies highlighting a significant prevalence of such mutations in HGSOC patients [10, 11]. Women who possess BRCA1/2 mutations are at a significantly higher risk of developing ovarian cancer. The lifetime risk for those with a BRCA1 mutation is estimated to be between 40-60%, whereas for BRCA2 mutation carriers, it ranges from 11-27%. These results highlight the importance of conducting genetic testing for BRCA mutations in all HGSOC patients, irrespective of their family history, given the mutation prevalence of 15-25% and the implications for targeted therapies [7–9].

When examining the distribution of cases by the number of pregnancies, it was noted that the highest proportion (54.54%) occurred in women with no children. It was particularly striking that nulliparous women were at a greater risk for developing HGSOC compared to those who had given birth, which underscores the protective role that having children plays against ovarian cancer [12, 13].

The ages of the patients ranged from 38 to 62 years, with an average age of 51. The highest incidence was observed in the 50-59 age group, which aligns with existing studies that report increased mutation rates in this demographic [14–16]. For individuals carrying the BRCA1 mutation, the incidence of ovarian cancer is approximately 1.5% for those under 40 years old, rising to between 10-21% by age 50. In contrast, those with the BRCA2 mutation face a risk of less than 3-5% by age 50 [16, 17].

In terms of T-stage distribution, most HGSOC cases with somatic BRCA1/2 mutations were classified as T3 stage (72.72%), which corresponds with the late-stage diagnoses frequently encountered in ovarian cancer due to often subtle or absent symptoms [4]. This observation is consistent with research indicating that T3 is the most prevalent stage among ovarian cancers associated with BRCA mutations [10].

CONCLUSION

In 2022, a notable percentage of high-grade serous ovarian carcinoma (HGSOC) cases at Dr. Soetomo General Academic Hospital were associated with somatic BRCA1/2 mutations, with 39.28% of patients exhibiting these genetic alterations. The highest mutation prevalence was observed in individuals aged 50-59, while the majority of cases involved patients with no prior parity. Additionally, the T3 stage emerged as the most frequently diagnosed stage.

Genetic testing for BRCA mutations should be implemented for all HGSOC patients, irrespective of their family medical history, due to its relevance for targeted treatments. Further studies are needed to investigate factors such as menopausal status, CA-125 levels, familial health history, and treatment approaches to enhance prognosis and management strategies.

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