

RESEARCH ARTICLE

Editorial Process: Submission:05/24/2025 Acceptance:11/19/2025 Published:11/22/2025

Prevalence of *BRCA1/2* Mutation in High-Grade Non-Mucinous Ovarian Carcinoma

Maria Angeline Christianto^{1*}, Grace Ariani^{1,2}

Abstract

Objective: Ovarian cancer is the third most common cancer among women with the most common subtype being high-grade ovarian carcinoma (90%), characterized by high genomic instability and somatic loss-of-function variants in *BRCA1/2* genes. BRCA testing in patients with Epithelial Ovarian Cancer (EOC) is recommended because of its role in genome counseling, as well as enabling therapeutics. This study aimed to determine the prevalence of somatic *BRCA1/2* mutations in high-grade (non-mucinous) ovarian carcinoma cases. **Methods:** This research was a descriptive observational study with a retrospective approach. The sample used data from somatic *BRCA1/2* mutation results with a diagnosis of high-grade non-mucinous ovarian carcinoma from surgery specimens at the Anatomic Pathology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, during 2019-2022. The total number of samples was 49 cases. The collected data includes the distribution of somatic *BRCA1/2* mutation cases, histopathological diagnoses, age groups, and T stage. **Result:** Among 49 cases, 9 cases had positive *BRCA* mutations, with 6 cases positive for *BRCA1* mutations and 3 cases positive for *BRCA2* mutations, all in HGSOE. No somatic *BRCA1/2* mutations were detected in Endometrioid Ovarian Cancer (EOC) and Ovarian Clear Cell Carcinoma (OCCC). The highest somatic *BRCA1/2* mutation rate occurred in the 50-59 age group. The distribution of cases based on T stage showed that most high-grade (non-mucinous) ovarian carcinomas were at T3 stage (61.22%), particularly in HGSOE (17.86% of *BRCA1* and 10.71% of *BRCA2* mutation cases). **Conclusion:** The occurrence of somatic *BRCA1/2* mutations in high-grade non-mucinous ovarian carcinoma at our hospital from 2019-2022 was 18.37%, all in HGSOE.

Keywords: BRCA somatic mutation- ovarian clear cell carcinoma- endometrioid ovarian carcinoma- high grade serous

Asian Pac J Cancer Prev, 26 (11), 4179-4183

Introduction

Ovarian cancer is associated with a poor prognosis and low survival rate. According to the Global Cancer Incidence, Mortality, and Prevalence (Globocan) 2020, there were 313.959 cases of ovarian cancer worldwide, leading to 207.252 deaths among women [1]. In Indonesia, ovarian cancer was the third leading cause of cancer-related death among women in 2022, with 15.130 new cases and 9.673 deaths reported [2]. Approximately 60% of ovarian cancer patients are diagnosed at an advanced stage, largely due to the lack of symptoms and the absence of effective screening markers. The overall 5-year survival rate is less than 30% [3]. Although initial treatments are often effective, 70% of patients experience a relapse within three years [4].

Epithelial ovarian cancer (EOC) accounts for about 95% of ovarian cancer cases, including endometrioid, mucinous, clear cell, and serous carcinoma (both high-grade and low-grade) [5]. EOC often exhibits significant genomic instability, frequently involving the loss of function

in the TP53 gene and other genes associated with the homologous recombination repair pathway, such as *BRCA1* and *BRCA2* [6].

BRCA1 and *BRCA2* mutations can be categorized as either germline or somatic. These mutations are strongly associated with hereditary breast and gynecological cancers, particularly ovarian cancer (Hereditary Breast and Ovarian Cancer / HBOC). Germline *BRCA1/2* mutations (gBRCAms) are believed to account for about 5% of breast cancers and 15-18% of ovarian cancers, with an additional 5-7% of ovarian cancers exhibiting pathogenic somatic *BRCA1/2* mutations (sBRCAms) [7]. The loss of germline function in *BRCA1/2* genes significantly increases the risk of developing breast cancer (by 60-85%) and ovarian cancer (by 15-40%). Germline mutations in *BRCA1* and *BRCA2* have been found in 18% of women diagnosed with epithelial ovarian cancer (EOC), with somatic mutations identified in another 7%. BRCA testing is recommended for EOC patients due to its critical role in genomic counselling and therapeutic decision-making for patients and their families [7].

¹Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. ²Medical Staff of Anatomical Pathology Laboratory, Dr Soetomo General Academic Hospital, Surabaya, Indonesia. *For Correspondence: mariaangelinezhou@gmail.com

We aimed to examine the prevalence of somatic *BRCA1* and *BRCA2* mutations in high-grade non-mucinous ovarian carcinoma cases operated on at Dr. Soetomo General Academic Hospital between 2019 and 2022.

Materials and Methods

This descriptive observational study with a retrospective approach, analyzed 49 cases of high-grade non-mucinous ovarian carcinoma that underwent surgical treatment and histopathological evaluation at the Dr. Soetomo General Academic Hospital in Surabaya between 2019 and 2022, and were tested for *BRCA1/2* mutations.

The inclusion criteria required histopathological findings that matched the characteristics of high-grade non-mucinous ovarian carcinoma, including serous carcinoma (HGSOC), endometrioid carcinoma (EnOC), and clear cell carcinoma (OCCC), diagnosed at the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital during that period; somatic *BRCA1/2* mutations were tested in these samples. Cases with an additional malignancy diagnosis were excluded from the study. Data were gathered from archival records and the collected data includes the distribution of somatic *BRCA1/2* mutation cases, histopathological diagnoses, age groups, and T stage.

Results

Prevalence s*BRCA1/2* mutations

Between 2019-2022, 49 cases of high-grade non-mucinous ovarian carcinoma underwent surgical treatment and histopathological examination at the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, with *BRCA1/2* mutation testing. Out of the 49 cases tested for *BRCA1/2* mutations, 4 were invalid due to failure in the quality control test at the laboratory where the NGS (Next Generation Sequencing) was performed. Among the 45 successfully tested cases, 20% tested positive for mutations, with

BRCA1 mutations observed in 6 cases (13.33%) and *BRCA2* mutations in 3 cases (6.67%). The study found 36 cases of somatic *BRCA1/2* mutations in high-grade serous ovarian carcinoma (HGSOC), with positive results in 18.75% for *BRCA1* and 9.37% for *BRCA2*, while 63.88% were negative (Figure 1). No somatic *BRCA1/2* mutations were found in endometrioid ovarian carcinoma (EnOC) or ovarian clear cell carcinoma (OCCC) (Table 1, Figures 2, 3).

Distribution cases based on age

Patients' ages ranged from 36-72 years, with an average of 52 years. The highest incidence was in the 50-59 age group. The highest number of positive *BRCA1/2* mutations in HGSOC was found in patients 50-59 age group. For EnOC and OCCC, patients with BRCA mutations were found predominantly in the 40-49 age group (Table 1).

Distribution cases based on T stages

The distribution of pT stages for high-grade (non-mucinous) ovarian carcinoma with somatic *BRCA1/2* mutations was as follows: pT3 (61.22%), pT1 (22.45%), and pT2 (16.33%). For HGSOC, the most frequent pT stage was pT3, occurring in 17.86% of *BRCA1*-mutated and 10.71% of *BRCA2*-mutated cases. pT3 was also the most common stage among negative *BRCA1/2* mutation cases (64.29%). In OCCC with *BRCA* mutations, pT2 was the most common stage (50%), followed by pT1 (40%) and pT3 (10%). For EnOC, pT1 was the most prevalent stage (66.66%), with pT3 at 33.33% (Table 1).

Discussion

From 2019 to 2022, 49 cases of somatic *BRCA1* and *BRCA2* mutations were identified in high-grade (non-mucinous) ovarian carcinoma cases treated surgically at Dr. Soetomo General Academic Hospital, Surabaya.

The guidelines from the Society of Gynecologic Oncology (SGO) and the American Society of Clinical Oncology (ASCO) recommend offering germline genetic

Table 1. Characteristics of Somatic *BRCA1/2* Mutation in High Grade (Non Mucinous) Ovarian Carcinoma Patients

Clinical Characteristics	sBRCA negative	sBRCA positive	QC failure
Age, n (%)			
30-39 years old	3 (6.12)	0 (0)	0 (0)
40-49 years old	13 (26.53)	2 (4.08)	1 (2.04)
50-59 years old	12 (24.5)	4 (8.16)	3 (6.12)
60-69 years old	6 (12.25)	3 (6.12)	0 (0)
70-79 years old	2 (4.08)	0 (0)	0 (0)
Histology type, n (%)			
High-grade serous ovarian carcinoma	23 (46.94)	9 (18.37)	4 (8.16)
Endometrioid ovarian carcinoma	3 (6.12)	0 (0)	0 (0)
Clear cell ovarian carcinoma	10 (20.41)	0 (0)	0 (0)
pT Stage, n (%)			
1	10 (20.41)	1 (2.04)	0 (0)
2	6 (12.25)	0 (0)	2 (4.08)
3	20 (40.81)	8 (16.33)	2 (4.08)

sBRCA, Somatic BRCA mutation; QC, Quality control

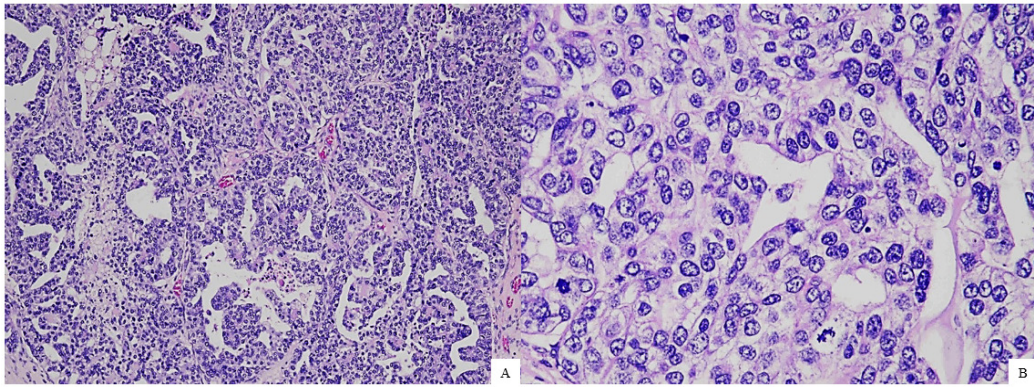


Figure 1. High-Grade Serous Ovarian Carcinoma. A. 100x magnification. B. 400x magnification.

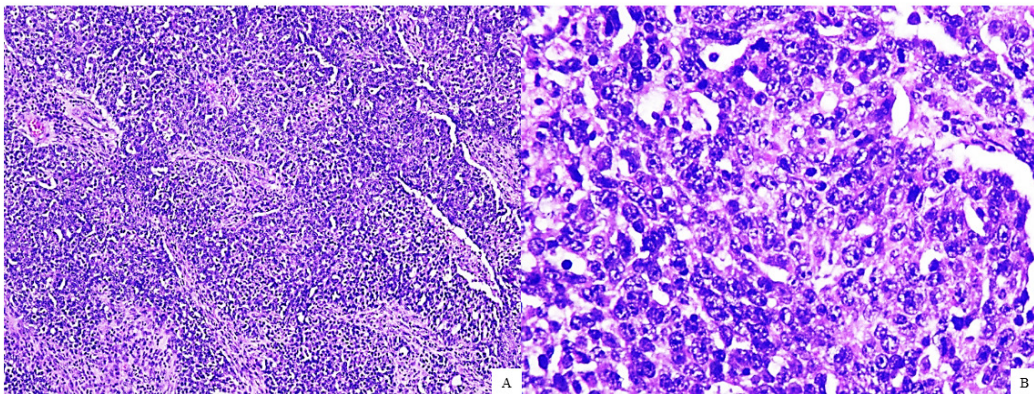


Figure 2. Endometrioid Ovarian Carcinoma. A. 100x magnification. B. 400x magnification.

testing for women with non-mucinous ovarian carcinoma, specifically *BRCA1/2* analysis, irrespective of clinical characteristics, age at diagnosis, or family history of cancer [8–10]. *BRCA1/2* testing plays a critical role in refining molecular diagnosis, guiding targeted therapeutic strategies, and facilitating access to oncogenetic counseling as part of preventive care. The *BRCA1/2* mutation status serves not only as a prognostic biomarker associated with patient survival but also as a predictive marker for chemotherapy response and sensitivity or resistance to PARP inhibitors in cases of sporadic ovarian carcinoma [4, 11].

Out of 45 cases examined for somatic *BRCA1/2* mutations, 20% were positive, with 6 (13.33%) for *BRCA1* and 3 (6.67%) for *BRCA2*, consistent with previous studies reporting a 16–40% prevalence [12–14]. An elevated risk

of hereditary breast and ovarian cancers was found in *BRCA* mutation, especially high-grade serous ovarian carcinoma, which was the most common type associated with these mutations [7].

Patients with *BRCA* mutations have a higher risk of hereditary breast and ovarian cancers, contributing to 5% of breast cancers, 15–18% of ovarian cancers, and an additional 5–7% of somatic *BRCA1/2* mutations. These carriers also face increased risks for cancers of the fallopian tubes and peritoneum. Although high-grade serous ovarian carcinoma is the most common diagnosis in these patients, they may also develop endometrioid or clear cell ovarian carcinomas at rates similar to the general population [7].

Between 2019 and 2022, 36 HGSOC cases with somatic *BRCA* mutations were recorded at Dr. Soetomo

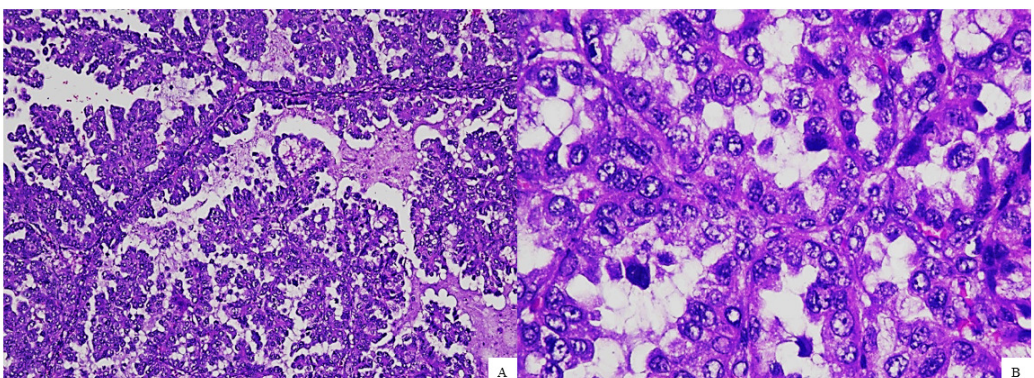


Figure 3. Ovarian Clear Cell Carcinoma. A. 100x magnification. B. 400x magnification.

Hospital. Among the 32 valid tests, 6 (18.75%) showed *BRCA1* mutations and 3 (9.37%) had *BRCA2* mutations, while 23 cases (63.88%) tested negative. Four cases (11.11%) produced invalid results. Prior studies by Manchana et al. [15] and Paik et al. [16] similarly reported that BRCA mutations were found only in HGSOc cases. Azribi et al. [17] reported positive somatic *BRCA1/2* mutations in 10/39 (25.64%) cases, with negative somatic *BRCA1/2* mutations in 29/39 (74.36%) cases. Ji et al. [18] identified *BRCA1/2* mutations in 25 (21.7%) cases, *BRCA1* in 19 (16.5%) cases, and *BRCA2* in 6 (5.2%) cases. Invalid results (4 cases) may be due to failed quality control tests before NGS. Factors like cold ischemic time, fixative, fixation time (minimum and maximum), processing, and storage could affect molecular integrity and test results [4].

No somatic *BRCA1/2* mutations were found in endometrioid ovarian carcinoma or ovarian clear cell carcinoma. Similar results were found in the study by Azribi et al. [17], where no somatic *BRCA1/2* mutations were found in endometrioid ovarian carcinoma and ovarian clear cell carcinoma. The studies by Manchana et al. [15] and Paik et al. [16] also found similar results to this study, where all positive BRCA mutations were found in patients with HGSOc and not in EnOC. This trend aligns with Wang et al. [19], who stated that BRCA mutation carriers are more frequently found in HGSOc. Zhao et al. [20] found negative *BRCA1/2* mutations in OCCc.

In the present study, patient ages ranged from 36 to 72 years, with a mean age of 52. The highest incidence of ovarian carcinoma, particularly high-grade serous ovarian carcinoma (HGSOc) and *BRCA1/2* mutations, occurred in the 50-59 age group. In contrast, BRCA mutations in endometrioid ovarian carcinoma (EnOC) and ovarian clear cell carcinoma (OCCc) were most frequently observed in patients aged 40-49. These findings align with previous studies. Richau et al. [6] and Paik et al. [16] reported median ages of 57 and 53 years, respectively, for ovarian carcinoma cases [6,16]. Similarly, studies by Finch et al. [21] and Alsop et al. [22] found the highest incidence of *BRCA1* mutations in the 50-59 age range, with *BRCA1/2* mutations most common between ages 51-60. *BRCA1* carriers face a rising ovarian cancer risk with age, from 1.5% before 40 to 10-21% by age 50, while *BRCA2* carriers have a lower risk under 50 years (3-5%) [21, 23].

Additional studies support these trends: Paik et al. [16] reported a median age of 54 for somatic BRCA mutations; Plaskocinska et al. [24] found *BRCA1/2* mutations in 12% of HGSOc patients under 70, but only 1% over 70. Chen et al. [25] noted EnOC was most prevalent in patients ≤50 years, while Iida et al. [26] reported the highest OCCc incidence in the 40-49 age group.

The distribution of T stages aligns with findings by Azribi et al. [17], that T3 is the most common stage in ovarian cancer with BRCA mutations. Diagnosis in the late stage often happens because asymptomatic. As it were around a quarter of ovarian cancer cases are recognized early. Liu et al. [27] similarly reported that T3 was the predominant stage in high-grade serous ovarian carcinoma (40.81%).

In ovarian clear cell carcinoma with BRCA mutations, T2 was the most common stage (50%), followed by T1 (40%) and T3 (10%). In contrast, T1 has been identified as the most common stage in ovarian clear cell carcinoma (37.80%), with T3 and T2 being less frequent. The discrepancy between Liu et al. [27] and this study may stem from differences in sample sizes, with one study analyzing 3,003 cases compared to 10 in this study.

For endometrioid ovarian carcinoma, the most common T stage was T1 (66.66%), followed by T3 (33.33%). This study also contrasts with Assem et al. (2018), where T2 was the most frequent stage in endometrioid ovarian carcinoma (46.7%), followed by T1 and T3 at lower frequencies.³⁰ The difference may be attributed to the smaller sample size in this study (3 cases) compared to Assem et al. [28] (2018) with 30 cases.

In conclusions, the occurrence of somatic *BRCA1/2* mutations in high-grade (non-mucinous) ovarian carcinoma at our hospital from 2019-2022 was 18.37%, all in high-grade serous ovarian carcinoma. The highest mutation rate was observed in the 50-59 year age group, with stage T3 being the most prevalent.

Increase the number of *BRCA1/2* mutation tests in endometrioid ovarian carcinoma and ovarian clear cell carcinoma cases to achieve a more balanced case distribution. Additional research is necessary to explore menopause status, parity, CA-125 levels, family medical history, and treatment to aid in future prognosis and management. Further studies are needed to understand the relationship between *BRCA1/2* mutation status, age, and T stage to aid in future prognosis and management.

Author Contribution Statement

All authors contributed to the conception and design of the study. Maria Angeline Christianto was responsible for data collection, analysis, interpretation, and manuscript writing. Grace Ariani developed the concept and critically revised the manuscript for important intellectual content, reviewed the text and manuscript writing, and approved the final version. All authors read and approved the final manuscript.

Acknowledgements

Ethical Declaration

Approval from the Research Ethical Committee of Dr. Soetomo General Academic Hospital, dated June 13th, 2023, with number 2943/120/4/VI/2024, was obtained.

Conflict of Interest

No potential conflict of interest was reported by the authors.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-49. <https://doi.org/10.3322/caac.21660>.

2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2024.
3. Guo T, Dong X, Xie S, Zhang L, Zeng P, Zhang L. Cellular mechanism of gene mutations and potential therapeutic targets in ovarian cancer. *Cancer Manag Res*. 2021;13:3081-100. <https://doi.org/10.2147/cmar.S292992>.
4. Grafodatskaya D, O'Rielly DD, Bedard K, Butcher DT, Howlett CJ, Lytwyn A, et al. Practice guidelines for brca1/2 tumour testing in ovarian cancer. *J Med Genet*. 2022;59(8):727-36. <https://doi.org/10.1136/jmedgenet-2021-108238>.
5. Arora T, Mullangi S, Vadakekut ES, Lekkala MR. Epithelial ovarian cancer. *InStatPearls*;2024.
6. Richau CS, Scherer NM, Matta BP, de Armas EM, de Barros Moreira FC, Bergmann A, et al. Brca1, brca2, and tp53 germline and somatic variants and clinicopathological characteristics of brazilian patients with epithelial ovarian cancer. *Cancer Med*. 2024;13(3):e6729. <https://doi.org/10.1002/cam4.6729>.
7. Sánchez-Lorenzo L, Salas-Benito D, Villamayor J, Patiño-García A, González-Martín A. The brca gene in epithelial ovarian cancer. *Cancers (Basel)*. 2022;14(5). <https://doi.org/10.3390/cancers14051235>.
8. Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of gynecologic oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2015;136(1):3-7. <https://doi.org/10.1016/j.ygyno.2014.09.009>.
9. 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(11):1222-45. <https://doi.org/10.1200/jco.19.02960>.
10. Randall LM, Pothuri B, Swisher EM, Diaz JP, Buchanan A, Witkop CT, et al. Multi-disciplinary summit on genetics services for women with gynecologic cancers: A society of gynecologic oncology white paper. *Gynecol Oncol*. 2017;146(2):217-24. <https://doi.org/10.1016/j.ygyno.2017.06.002>.
11. Prevalence and penetrance of brca1 and brca2 mutations in a population-based series of breast cancer cases. Anglian breast cancer study group. *Br J Cancer*. 2000;83(10):1301-8. <https://doi.org/10.1054/bjoc.2000.1407>.
12. Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, 2nd, et al. Somatic mutations in brca1 and brca2 could expand the number of patients that benefit from poly (adp ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol*. 2010;28(22):3570-6. <https://doi.org/10.1200/jco.2009.27.2997>.
13. McAlpine JN, Porter H, Köbel M, Nelson BH, Prentice LM, Kalloger SE, et al. Brca1 and brca2 mutations correlate with tp53 abnormalities and presence of immune cell infiltrates in ovarian high-grade serous carcinoma. *Mod Pathol*. 2012;25(5):740-50. <https://doi.org/10.1038/modpathol.2011.211>.
14. Maffiini A, Simbolo M, Parisi A, Rusev B, Luchini C, Cataldo I, et al. Brca somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing. *Oncotarget*. 2016;7(2):1076-83. <https://doi.org/10.18632/oncotarget.6834>.
15. Manchana T, Phoolcharoen N, Tantbirojn P. Brca mutation in high grade epithelial ovarian cancers. *Gynecol Oncol Rep*. 2019;29:102-5. <https://doi.org/10.1016/j.gore.2019.07.007>.
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(12):5055-67. <https://doi.org/10.1111/cas.15166>.
17. Azribi F, Abdou E, Dawoud E, Ashour M, Kamal A, Al Sayed M, et al. Prevalence of brca1 and brca2 pathogenic sequence variants in ovarian cancer patients in the gulf region: The predict study. *BMC Cancer*. 2021;21(1):1350. <https://doi.org/10.1186/s12885-021-09094-8>.
18. Ji G, Yao Q, Bao L, Zhang J, Bai Q, Zhu X, et al. Germline and tumor brca1/2 mutations in chinese high grade serous ovarian cancer patients. *Ann Transl Med*. 2021;9(6):453. <https://doi.org/10.21037/atm-20-6827>.
19. Wang Y, Li N, Ren Y, Zhao J. Association of brca1/2 mutations with prognosis and surgical cytoreduction outcomes in ovarian cancer patients: An updated meta-analysis. *J Obstet Gynaecol Res*. 2022;48(9):2270-84. <https://doi.org/10.1111/jog.15326>.
20. Zhao Q, Yang J, Li L, Cao D, Yu M, Shen K. Germline and somatic mutations in homologous recombination genes among chinese ovarian cancer patients detected using next-generation sequencing. *J Gynecol Oncol*. 2017;28(4):e39. <https://doi.org/10.3802/jgo.2017.28.e39>.
21. Finch AP, Lubinski J, Möller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a brca1 or brca2 mutation. *J Clin Oncol*. 2014;32(15):1547-53. <https://doi.org/10.1200/jco.2013.53.2820>.
22. Alsop K, Fereday S, Meldrum C, DeFazio A, Arora C, George J, et al. Brca mutation frequency and patterns of treatment response in brca mutation-positive women with ovarian cancer: A report from the australian ovarian cancer study group. *J Clin Oncol*. 2012;30:2654-63. <https://doi.org/10.1200/JCO.2011.39.8545>.
23. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in brca1 and brca2. *Science*. 2003;302(5645):643-6. <https://doi.org/10.1126/science.1088759>.
24. Plaskocinska I, Shipman H, Drummond J, Thompson E, Buchanan V, Newcombe B, et al. New paradigms for brca1/brca2 testing in women with ovarian cancer: Results of the genetic testing in epithelial ovarian cancer (gteoc) study. *J Med Genet*. 2016;53(10):655-61. <https://doi.org/10.1136/jmedgenet-2016-103902>.
25. Chen S, Lu H, Jiang S, Li M, Weng H, Zhu J, et al. An analysis of clinical characteristics and prognosis of endometrioid ovarian cancer based on the seer database and two centers in china. *BMC Cancer*. 2023;23(1):608. <https://doi.org/10.1186/s12885-023-11048-1>.
26. Iida Y, Okamoto A, Hollis RL, Gourley C, Herrington CS. Clear cell carcinoma of the ovary: A clinical and molecular perspective. *Int J Gynecol Cancer*. 2021;31(4):605-16. <https://doi.org/10.1136/ijgc-2020-001656>.
27. Liu T, Gao Y, Li S, Xu S. Exploration and prognostic analysis of two types of high-risk ovarian cancers: Clear cell vs. Serous carcinoma: A population-based study. *J Ovarian Res*. 2024;17(1):119. <https://doi.org/10.1186/s13048-024-01435-y>.
28. Assem H, Rambau PF, Lee S, Ogilvie T, Sienko A, Kelemen LE, et al. High-grade endometrioid carcinoma of the ovary: A clinicopathologic study of 30 cases. *Am J Surg Pathol*. 2018;42(4):534-44. <https://doi.org/10.1097/pas.0000000000001016>.



This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.