Research article

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Pathogenic or likely-pathogenic *BRCA* variants in Vietnamese ovarian carcinoma: a retrospective analysis of prevalence and pathological insights

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Abstract

Background: Ovarian cancer is a leading cause of gynecological cancer mortality worldwide, with high-grade serous carcinoma being the most aggressive subtype. Pathogenic variants of the *BRCA1* and *BRCA2* genes play an important role in the pathogenesis of the disease. Although detailed documentation exists for *BRCA* variants in specific demographics, knowledge about these variants in Vietnamese patients is still insufficient. This study was conducted to address that knowledge gap.

Methods: We performed a retrospective observational study at the Ho Chi Minh City Oncology Hospital. The study comprised 84 Vietnamese women diagnosed with ovarian carcinoma, who underwent next-generation sequencing for the *BRCA1* and *BRCA2* genes from August 2022 to April 2024. Clinical information, such as age at diagnosis and FIGO stage, was documented. Following the 2020 World Health Organization (WHO) Classification of Female Genital Tumors guidelines, we examined histopathological slides and employed additional immunohistochemical staining when necessary to categorize the tumors into specific subtypes of ovarian carcinoma.

Results: Our cohort's mean age was 54.5 years (range 18–78), and the majority presented at an advanced stage (60.7% at FIGO IIIC). High-grade serous carcinoma represented 81.5% of the cases. 27.4% (23/84) of the tumors harbored pathogenic or likely pathogenic *BRCA* variants. We discovered these variants solely in high-grade serous carcinoma, resulting in a statistically significant association ($p = 0.02$). We noted several recurrent variants, including *BRCA1* c.4997dupA, *BRCA1* c.5251C>T, and *BRCA2* c.1813delA, highlighting possible founder effects or variants specific to the population.

Conclusion: This study reports a 27.4% prevalence of pathogenic *BRCA* variants within a cohort of Vietnamese ovarian carcinoma patients. All the pathogenic variants were found within the high-grade serous carcinoma subtype. Our findings emphasize the critical role of *BRCA* mutations in ovarian cancer pathogenesis, especially in high-grade serous carcinoma.

Keywords: Ovarian carcinoma, *BRCA1/2* pathogenic variants, high-grade serous carcinoma, next-generation sequencing, Vietnamese population.

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1. INTRODUCTION

Ovarian cancer is one of the most lethal malignancies affecting women worldwide [1]. It is responsible for approximately 295,000 new cases and 184,000 deaths annually globally [2]. Among them, high-grade serous carcinoma is the most prevalent [2]. Despite advancements in surgical techniques and chemotherapeutic interventions, the five-year survival rate of patients with advanced-stage ovarian cancer remains poor [3].

BRCA1 and *BRCA2* are critical genes for homologous recombination repair, a DNA repair pathway that ensures genomic stability [4]. Pathogenic variants of *BRCA* are associated with a significantly increased lifetime risk of developing ovarian cancer [5]. In addition to their role in cancer risk, pathogenic variants of *BRCA* have profound implications for treatment. Poly (ADP-ribose) polymerase (PARP) inhibitors are therapies that exploit the DNA repair deficiencies in tumors with pathogenic variants of *BRCA* to induce synthetic lethality [6].

While the clinical significance of *BRCA* variants is well established, knowledge of the prevalence and spectrum of these mutations varies across populations. Studies have identified population-specific variants, including founder variants, in groups such as Ashkenazi Jews, North African, and Greek populations [7-9]. However, the Vietnamese population remains underrepresented in global studies. In Vietnam, we recorded over 1,200 new cases of ovarian cancer and approximately 1,000 deaths by the disease annually [10]. Despite this burden, few studies have characterized the prevalence and types of pathogenic *BRCA* variants in our population.

Our study aims to address the critical knowledge gap regarding pathogenic *BRCA* variants in Vietnamese ovarian carcinoma patients. Specifically, we seek to determine the prevalence of pathogenic *BRCA* variants, identify the specific variant types, analyze their distribution across histological subtypes, and examine correlations between pathogenic *BRCA* variants and clinical features (including age and stage). By achieving these objectives, we aim to establish a foundational understanding of the genetic landscape of pathogenic *BRCA* variants in Vietnamese ovarian cancer patients being treated at Ho Chi Minh City Oncology Hospital.

2. MATERIALS AND METHODS

Our research involves a retrospective, observational case series examination. We incorporated cases that underwent next-generation sequencing for *BRCA* genes at Ho Chi Minh City Oncology Hospital, a leading oncology facility in Vietnam, from August 2022 to April 2024. A total of 84 cases of ovarian carcinoma were considered. Clinical data, including age at diagnosis and International Federation of Gynecology and Obstetrics (FIGO) stage, was gathered from patient records to enhance the analysis.

2.1 Next-generation Sequencing Workflow at the Hospital

Genomic DNA was isolated from formalin-fixed, paraffin-embedded (FFPE) neoplastic tissues utilizing the GeneReadTM DNA FFPE Kit (Qiagen). Next-generation sequencing was conducted on the Illumina MiSeqDx platform employing the BRCAaccuTestTM Plus, which specifically targets the *BRCA1* and *BRCA2* genes. The sequencing data underwent processing and analysis through NGeneAnalySysTM Software, with the variants being categorized in accordance with the guidelines set forth by the American College of Medical Genetics and Genomics. The *BRCA* variants were categorized based on the guidelines established by the American College of Medical Genetics and Genomics into these classifications: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign variants. In this study, cases identified with pathogenic or likely pathogenic

variants were combined into the pathogenic category, whereas cases with benign or likely benign variants were sorted into the benign group.

2.2 Histotype Confirmation

Histopathological slides containing tumor specimens from these cases were collected for examination. For those slides that were faded or challenging to evaluate, new slides were created from the corresponding formalin-fixed, paraffin-embedded blocks. We analyzed a total of 259 tumor slides from these cases, with an average of 3.1 slides per case (ranging from 1 to 9 slides). We then applied the criteria outlined by the 2020 WHO Classifications of Female Genital Tumors [2] to categorize the tumors into specific histopathological subtypes. In instances of ambiguous or overlapping characteristics, further immunohistochemistry testing was conducted to ensure precise classification. We utilized the immunohistochemical algorithm for ovarian typing suggested by Köbel et al. to assist in the diagnostic process. This comprehensive approach ensured that each tumor was accurately classified.

2.3 Ethical Consideration

This research received approval from the Ethics Committee of Ho Chi Minh City Medicine and Pharmacy University, with the approval number IRB-VN01002. Since this investigation made use of archived genetic data and formalin-fixed, paraffin-embedded tissue specimens without direct patient interaction, obtaining informed consent was unnecessary. The privacy of patient information was preserved throughout the course of the study, and all data were anonymized for analysis to protect confidentiality.

2.4 Statistical Analysis

Statistical analyses were conducted using R software (version 4.4.2), with a significance threshold set at $p < 0.05$. Continuous variables, such as patient age, were summarized as means with standard deviations (for normally distributed data) or medians with ranges (for non-normally distributed data). Categorical variables, including histological subtypes and *BRCA* variant status, were reported as frequencies and percentages.

Comparative analyses were performed to explore associations between *BRCA* variant status and clinical or pathological characteristics. For categorical variables, such as histological subtype and tumor stage, Chi-square tests or Fisher's exact tests were applied, depending on the data distribution. Continuous variables, such as age, were analyzed using t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data. For the purpose of the study, cases with variants of uncertain significance (VUS) were excluded from statistical analyses due to the inability to definitively classify them as pathogenic or benign.

3. RESULTS

Our study cohort consisted of 84 Vietnamese women diagnosed with ovarian carcinoma. The mean age of the patients was 54.5 years, with a range of 18 to 78 years. Of these, 45 patients (53.6%) were aged 55 years or younger, while 39 patients (46.4.1%) were older than 55 years.

The majority of patients were diagnosed at advanced stages of the disease. Based on the FIGO staging system, 60.7% (n = 51) of cases were classified as stage IIIC, and 17.9% (n = 15) as stage IVB. A smaller proportion of patients were at stage IIIB (10.7%, n = 5) and stage IIIA (2.4%, n = 2). Early-stage cases were rare, with 4.8% (n = 4) at stage IC and only 3.6% (n = 3) at stage IIB.

Our study cohort was predominantly comprised of individuals diagnosed with high-grade serous carcinoma, which constituted 81.5% (n=71) of the examined cases. This finding is in accordance with the worldwide incidence of high-grade serous carcinoma, which is acknowledged as the most prevalent histological subtype of ovarian carcinoma.

Other histological subtypes were represented in lesser frequencies, including endometrioid carcinoma (7.1%, n=6), , clear cell carcinoma (3.6%, n=3), mucinous carcinoma (2.4%, n=2), low-grade serous carcinoma (1.2%, n=1), and carcinosarcoma (1.2%, n=1). Representative images of these histological subtypes are shown in Image 1.

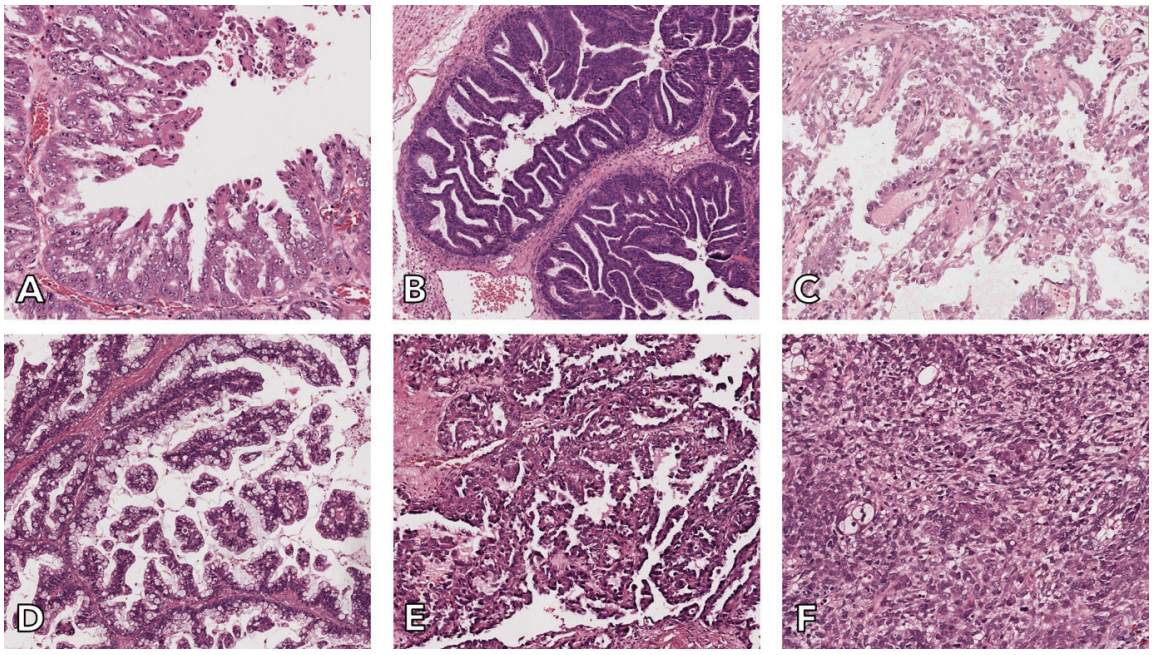

Image 1. Representative histological subtypes of ovarian carcinoma in the cohort: A. High-grade serous carcinoma (hematoxylin-eosin - H&E, 200x); B. Endometrioid carcinoma (H&E, 100x); C. Clear cell carcinoma (H&E, 100x); D. Mucinous carcinoma (H&E, 100x); E. Low-grade serous carcinoma (H&E, 100x); F. Carcinosarcoma (H&E, 200x).

We recorded pathogenic *BRCA* variants in 23 out of 84 ovarian carcinoma cases, yielding an overall prevalence of 27.4% of the studied population. Among the pathogenic variants, *BRCA1* variants were slightly more common than *BRCA2* variants, accounting for 12 cases and 11 cases, respectively. Table 1 summarizes the variants and their prevalence recorded in our study.

Table 1. Summary of Pathogenic *BRCA* Variants and Their Prevalence in the Study Cohort

Gene	Variant	Frequency
BRCA1	c.1999C>T	1/23
BRCA1	c.3034delA	1/23
BRCA1	c.4258C>T	1/23
BRCA1	c.4997dupA	2/23
BRCA1	c.509_510insTG	1/23
BRCA1	c.3995delG	1/23
BRCA1	c.1016del	1/23
BRCA1	c.1961delA	1/23
BRCA1	c.5251C>T	2/23
BRCA1	c.5335delC	1/23
BRCA2	c.4478_4481delAAAG	1/23
BRCA2	c.1813delA	3/23
BRCA2	c.7976+1G>A	1/23
BRCA2	c.1813delA	1/23
BRCA2	c.8810_8813delATGA	1/23
BRCA2	c.8702delG	1/23
BRCA2	c.5782G>T	1/23
BRCA2	c.4431delT	1/23
BRCA2	c.196C>T	1/23

Patients who possess pathogenic variants in the *BRCA* gene tend to receive their diagnoses at a somewhat older age when compared to individuals who do not have these specific genetic variants, indicating a notable difference in the age

of onset for these conditions. The median age at which individuals with pathogenic variants were diagnosed stood at 57.5 years, and this figure came with a range of variations spanning 8.8 years, whereas the tumors with benign variants presented with a median diagnosis age of 51.9 years, accompanied by a broader range of 11.5 years (Figure 1). In the subgroup of patients who were identified as having pathogenic variants, those with pathogenic *BRCA1* variants exhibited a median diagnosis age of 57.5 years, whereas their counterparts with pathogenic *BRCA2* variants were diagnosed at a slightly older age, with a median age of 58 years when they received their diagnosis. Upon careful analysis, we discovered that there was no statistically significant difference observable in the ages at which these different groups received their diagnoses.

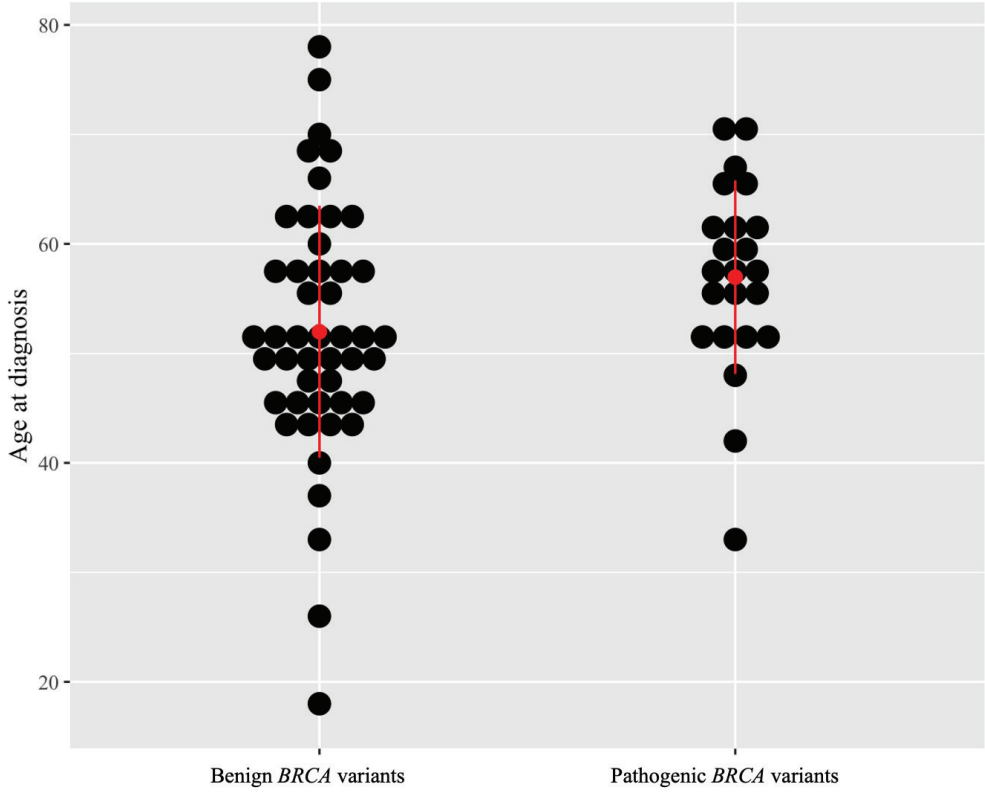

Figure 1. Dot Plot Showing Age Distribution of Cases with Pathogenic and Benign BRCA Variants

All instances involving pathogenic variants within the *BRCA* genes were identified and classified at FIGO stage IIIC or IVB (Figure 2). In contrast, the patients who did not possess these specific variants exhibited a much broader and more diverse range of diagnoses, spanning from FIGO stage I all the way up to stage IV. Similarly, when we examined the age at which these patients were diagnosed, we observed a lack of statistical significance in the distribution of FIGO stages between the two distinct groups, which strongly suggests that the mere presence of *BRCA* variants may not have a notable impact on the stage at which patients ultimately present with their illness.

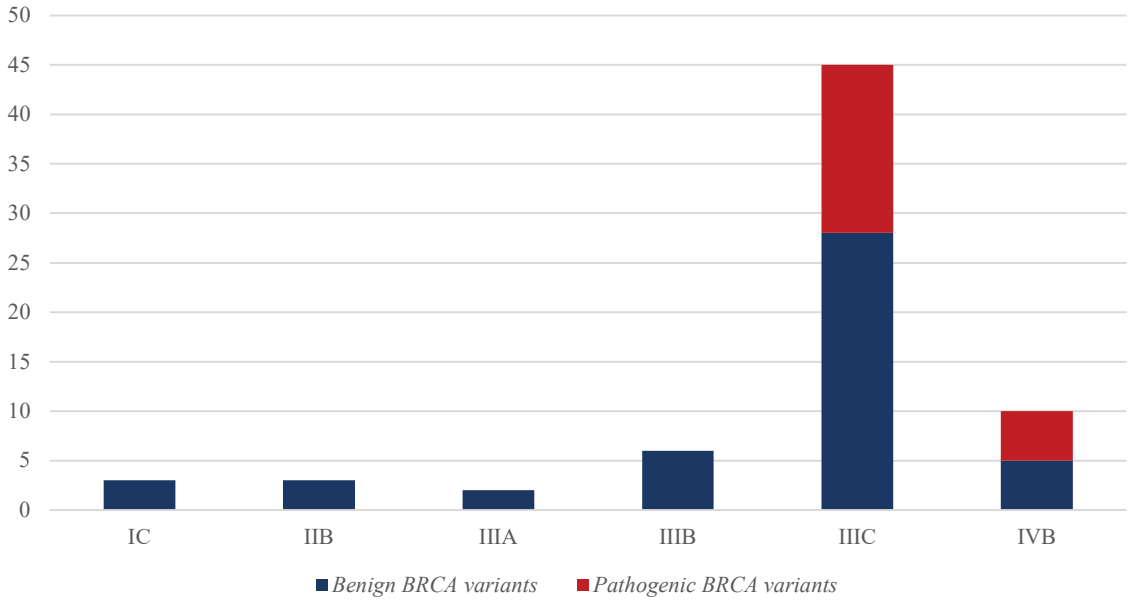

Figure 2. Column Chart Showing the Distribution of Pathogenic and Benign *BRCA* Variant Cases Across FIGO Stages

All cases with pathogenic variants were high-grade serous carcinoma, demonstrating a significant contrast with other ovarian carcinoma subtypes, none of which harbored these variants. This highlights the strong relationship between the presence of pathogenic *BRCA* variants and the development of this aggressive subtype. Our analysis comparing high-grade serous carcinoma to the group of other subtypes recorded a statistical significance with p = 0.02 using Fisher's Exact Test, underscoring the link between pathogenic *BRCA* variants and high-grade serous carcinoma.

Among cases without pathogenic variants, we identified 17 cases to have VUS. These VUS cases highlight the importance of further research in understanding the clinical implications of these genetic alterations. We summarize the number of each type of variants according to ovarian carcinoma subtypes in Table 2.

Table 2. Distribution of *BRCA* Variants Across Ovarian Carcinoma Subtypes

Ovarian carcinoma subtypes		*BRCA* variants			
		Pathogenic	VUS	Benign	
High-grade serous carcinoma		23	14	35	
Group of other subtypes	Endometrioid carcinoma	0	2	4	p = 0.02
	Clear cell carcinoma	0	0	3	
	Mucinous carcinoma	0	0	2	
	Low-grade serous carcinoma	0	0	1	
	Carcinosarcoma	0	1	0	

4. DISCUSSION

4.1 Cohort Characteristics

The subjects examined in our investigation exhibit an age at diagnosis that ranges from 18 to 78 years, with a calculated mean age of 54.5 years. This mean age is slightly lower than the median age of 60 to 65 years commonly observed in other populations worldwide [11].

60.7% of the cases were identified at stage IIIC, underscoring the aggressive characteristics of the disease, which is frequently diagnosed at advanced stages due to its asymptomatic early development [12]. The majority of our cohort consisted of patients diagnosed with high-grade serous carcinoma, which constituted 81.5% of the cases. Our observation is consistent with global data, where high-grade serous carcinoma is the most prevalent subtype, accounting for approximately 70% of all ovarian carcinoma cases [13]. In summary, the cohort in our study is representative of global ovarian carcinoma populations, with a slightly younger mean age, a high proportion of advanced-stage diagnoses (60.7% at stage IIIC), and a predominance of high-grade serous carcinoma (81.5%), consistent with the global prevalence of this aggressive subtype.

4.2 Pathogenic *BRCA* Variants Recorded in Our Cohort

For *BRCA1*, the majority of variants detected were frameshift mutations, including c.3034delA, c.3995delG, c.4997dupA, c.509_510insTG, c.1016del, and c.1961delA. These mutations are predicted to severely disrupt protein function, contributing to homologous recombination deficiency. Among these, c.4997dupA and c.5251C>T had the highest recurrence in our study, appearing in two cases each (9.1% of mutation-positive cases). These findings are consistent with previous research, such as the study by Le Nguyen Trong Nhan et al., which reported c.4997dupA as the most frequently observed *BRCA1* mutation in Vietnamese patients with breast or ovarian cancer (2/12 pathogenic cases) [14]. Similarly, c.5251C>T has been identified as a recurrent variant in Vietnam. Studies by Tran Van Thuan et al. [15] and Hoang Anh Vu et al. [16] highlighted c.5251C>T as a frequent pathogenic variant in *BRCA1*, further supporting its role as a recurrent mutation in the Vietnamese population. Hoang Anh Vu et al. reported this mutation in 4 out of 8 pathogenic *BRCA1* cases, underscoring its significance in ovarian cancer genetics in Vietnam.

For *BRCA2*, frameshift mutations also dominated, including c.4478_4481delAAAG, c.8810_8813delATGA, c.8702delG, c.4431delT, and c.1813delA. Among these, c.1813delA was the most frequent, observed in three cases (27.3% of mutation-positive cases). Interestingly, while c.1813delA has limited documentation in Vietnamese populations, it has been reported as a common variant in the Tohoku region of Japan [17], suggesting potential geographic or ethnic specificity. Additional *BRCA2* variants included a splice-site mutation (c.7976+1G>A), a nonsense mutation (c.5782G>T), and a missense mutation (c.196C>T), further diversifying the mutational spectrum.

4.3 Predominance of *BRCA* Variants in High-Grade Serous Ovarian Carcinoma

The predominance of pathogenic *BRCA* variants in high-grade serous carcinoma is consistent with previous studies that highlighted the critical role of *BRCA* gene mutations in the development of this aggressive form of ovarian cancer [18-20]. *BRCA* genes are essential in DNA damage repair through homologous recombination. This impairment in DNA repair mechanisms leads to genomic instability, which is a hallmark of cancer progression and contributes to the aggressive nature of high-grade serous ovarian carcinoma.

Globally, studies have reported that approximately 20 to 25% of high-grade serous carcinoma cases harbor *BRCA1* or *BRCA2* mutations [18, 21]. In our cohort, we observe a similar prevalence, with 19% of all high-grade serous carcinoma cases harboring pathogenic *BRCA* variants.

Among the research conducted on *BRCA* variants in the Vietnamese demographic, the

study by Hoang Anh Vu et al. [16] stands out as one of the limited investigations that explored the association between these mutations and subtypes of ovarian carcinoma. Their data revealed that *BRCA* mutation were confined to serous and endometrioid carcinomas, aligning with our results that pathogenic *BRCA* variants were exclusively identified in high-grade serous carcinoma. However, their research depended on pre-existing diagnoses to identify subtypes. A notable advantage of our study is the thorough re-examination of histological slides, categorizing subtypes in accordance with the latest WHO Classification of Female Genital Tumors. Moreover, we employed immunohistochemistry as necessary, particularly in instances with scant tumor tissue or poorly differentiated characteristics, to guarantee accurate subtype classification (as illustrated in Image 2).

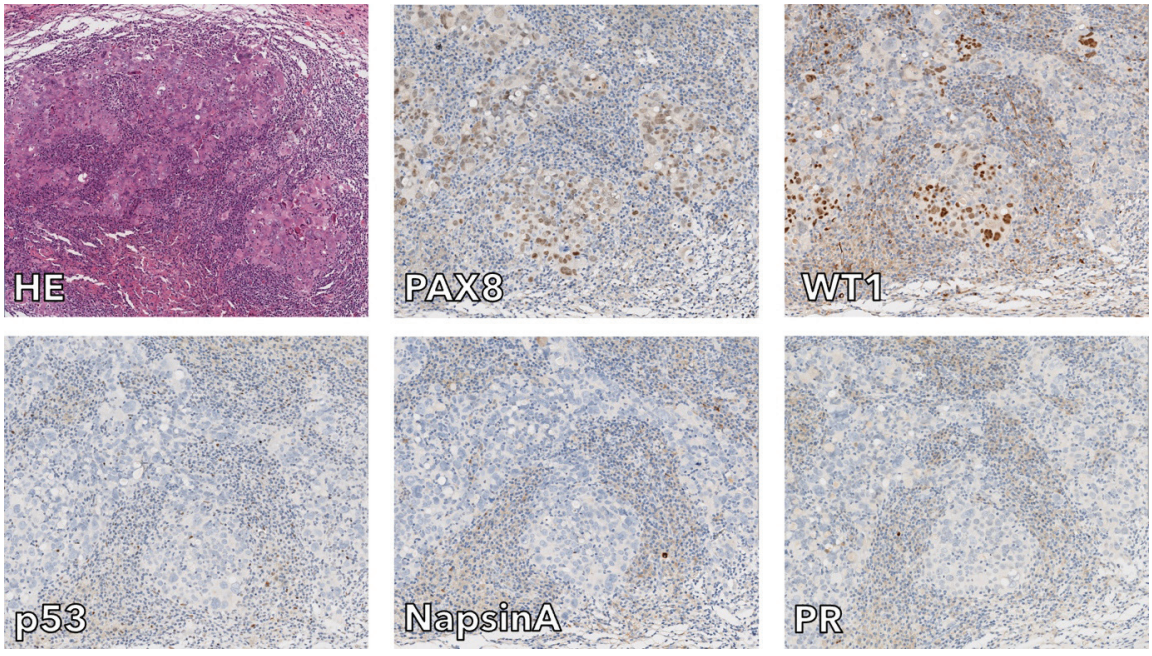

Image 2. Application of Immunohistochemistry in Classifying a Case with Scant, Poorly Differentiated Tumor Cells: H&E (40x) reveals limited tumor morphology; immunohistochemistry confirms the diagnosis: PAX8 (100x) and WT1 (100x) are positive, indicating Müllerian and serous origin; p53 (100x) shows aberrant null staining, consistent with TP53 mutation seen in high-grade serous carcinoma; NapsinA (100x) and PR (100x) are negative, ruling out clear cell carcinoma and endometrioid carcinoma. Final diagnosis: High-grade serous carcinoma.

4.4 Application of the Results

Our findings emphasize the importance of *BRCA* genetic testing in Vietnamese ovarian cancer patients, particularly those with high-grade serous carcinoma, where all pathogenic *BRCA* variants were detected. This supports integrating *BRCA* screening into clinical practice for risk assessment, genetic counseling, and personalized treatment using PARP inhibitors.

The discovery of recurrent *BRCA* variants suggests potential founder mutations, warranting further studies and the establishment of a Vietnamese *BRCA* variant database to enhance diagnostic accuracy. Additionally, our study highlights the utility of immunohistochemistry in tumor classification, particularly in cases with scant or poorly differentiated tumor cells, reinforcing the role of immunohistochemistry as an essential adjunct tool in pathology practice.

Overall, these findings contribute to better genetic screening, treatment personalization, and improved ovarian cancer management in Vietnam.

4.5 Limitations and Future Directions

Our study is not without limitations. The relatively small sample size may restrict the generalizability of our findings. Expanding the cohort to include more diverse and larger populations would provide a more comprehensive understanding of variant prevalence and patterns.

Additionally, the number of slides per case (from 1 to 9 slides) was limited, even with the use of immunohistochemistry for tumor classification. This could impact the accuracy of histological subtyping, particularly in cases with scant tumor tissue.

Furthermore, our study was conducted at a tertiary oncology hospital (Ho Chi Minh City Oncology Hospital), where the majority of tumors were diagnosed at advanced stages. This may introduce selection bias and limit the applicability of our findings to early-stage ovarian carcinoma cases.

Another limitation is the lack of germline testing, preventing us from determining whether the identified *BRCA* variants were inherited or somatic. The absence of Sanger sequencing confirmation also poses a challenge in ensuring the accuracy of next-generation sequencing results.

Lastly, our study is a retrospective case series, which inherently lacks control groups and prospective validation. Future studies should aim for larger, prospective, and multi-institutional designs to further validate and expand upon our findings.

5. CONCLUSION

In conclusion, this study sheds light on the prevalence and spectrum of pathogenic *BRCA* variants in Vietnamese women diagnosed with ovarian carcinoma, particularly high-grade serous carcinoma. Our findings indicate that 27.4% of the studied cohort harbored pathogenic *BRCA* variants, all of which were observed in high-grade serous carcinoma. The results underscore the critical role of *BRCA* gene mutations in the pathogenesis of high-grade serous ovarian cancer, aligning with global observations that suggest a significant association between these genetic alterations and the aggressive nature of this malignancy. However, limitations such as small sample size, retrospective design, and lack of germline testing and Sanger sequencing may affect generalizability. Despite these constraints, our study highlights the need for genetic testing in ovarian cancer management and calls for larger, multi-center studies to refine understanding and improve patient outcomes in Vietnam.

6. ABBREVIATION LIST

BRCA: Breast Cancer gene
FFPE: Formalin-Fixed Paraffin-Embedded
FIGO: International Federation of Gynecology and Obstetrics
H&E: Hematoxylin and Eosin
VUS: Variant of Uncertain Significance
WHO: World Health Organization

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