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Comparative Histopathological Analysis of Ovarian Tumors with an Emphasis on High-Grade Serous Carcinoma Prevalence

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ABSTRACT

Background: Ovarian cancer is the world's second most frequent gynecologic malignancy, accounting for the fifth leading cause of cancer-related death among women in developed countries. Ovarian tumors present with diverse histopathological diagnoses. **Objective:** To determine the prevalence and histological examination of various forms of ovarian malignancies. **Study Design:** A descriptive cross-sectional study. **Settings:** Pathology Department of Hayatabad Medical Complex, Peshawar, Pakistan. **Duration:** 01 January to 31 December, 2023. **Methods:** 146 ovarian tumor specimens were collected over one year. All confirmed histopathological cases of ovarian tumors were selected in the study. The collected data was analyzed through SPSS-26. The Chi-square test was applied to find the significant associations between categorical parameters. **Results:** Among the 146 specimens, high-grade serous carcinoma (HGSC) was frequently observed, accounting for 31.5% of cases, followed by clear cell carcinoma (4.1%), mucinous carcinoma (4.1%), and endometrioid carcinoma (4.1%). Geographic analysis revealed significant variations in HGSC prevalence, with Peshawar showing the highest number of HGSC cases 28.2% (n=22/7). A statistically significant association has been determined between geographic location and HGSC diagnosis (p=0.006). **Conclusion:** It is concluded that the HGSC was the most prevalent ovarian tumor case in Khyber Pakhtunkhwa, with significant geographic variations. Enhancing awareness, early detection, and standardized diagnostic practices are essential to improve patient outcomes.

Keywords: *Endometrioid Carcinoma, High-grade Serous Carcinoma, HGSC, Mucinous Carcinoma, Ovarian tumor.*

INTRODUCTION

Ovarian cancer ranks as the second most prevalent gynecologic malignancy worldwide and holds the highest mortality rate among gynecologic cancers in the United States and Europe.[1] Fifth (5th) among developed-world women's major causes of death, ovarian cancer is the sixth (6th) most prevalent cancer among American women.[2-4] The lifetime risk for a female to develop an ovarian tumor is around 6.0-7.0%, with a 1.5% chance of developing ovarian cancer and a 1.0% risk of mortality from ovarian cancer.[5] Ovarian cancer is rare in children, accounting for less than 5.0% of cases. Benign ovarian tumors constitute 75-80% of all ovarian tumors, with 55.0-65.0% occurring in females under 40 years of age.[5] Ovarian cancers comprise diverse diseases characterized by unique precursor lesions, histology, causes, developmental origins, and distinct mutational profiles.[1] The complexity of ovarian cancer involves a multitude of factors, complicated biological processes, and unpredictable outcomes. Unlike other female cancers that often have early warning signs, ovarian cancer usually

manifests with non-specific symptoms, which frequently results in late-stage diagnosis.[2,4]

70% to 80% of all ovarian cancer fatalities are caused by high-grade serous ovarian carcinoma (HGSC), the most common and severe histological type of the disease. The high prevalence and mortality rate are primarily due to the challenges of early diagnosis and the tendency for recurrence, largely because of resistance to chemotherapeutic agents.[6] According to the latest World Health Organization (WHO) classification, serous tumors are frequently observed in the female genital tract.[7] The WHO classification has significantly influenced the categorization and language of serous tumors.[8] Traditionally, ovarian tumors were diagnosed using a three-tier grading system based on their biological behavior: benign, borderline, and malignant.[8] This approach was based on three parameters: architectural pattern, cytological atypia, and mitotic numbers.[9]

Risk factors for HGSC include being under 45 years of age, a family history of ovarian tumors, early menarche and late menopause, nulliparity, not breastfeeding, not using oral hormonal contraceptives, use of estrogen-based menopausal replacement therapy, diabetes, obesity, and cigarette smoking.[10,11] According to the Ovarian Tumor Tissue Analysis (OTTA) consortium, twelve participating studies reported that high-grade serous carcinoma (HGSC) accounted for about 59.3% of all cases of ovarian tumors.[12] In India, a study found that about 90% of ovarian cancers are epithelial ovarian carcinomas, with HGSC making up 70% and LGSC about 5%.[13] In Pakistan, a study reported that HGSC have a prevalence of 51.7%.[2] Early-stage HGSC frequently eludes detection with methods designed to identify ovarian masses. Another key screening approach involves evaluating serum biomarkers closely associated with tumor types.[14] A recent prevalence screening involving 410,000 women did not show that HGSC could be detected at an early stage; the majority of cases identified were at an advanced stage.[14,15]

Early-stage symptoms are sometimes vague or diffuse, the majority of patients have advanced-stage ovarian cancer when they first arrive. Advanced ovarian cancer is often treated with cytoreductive surgery and taxane-platinum-based chemotherapy. Most individuals will eventually experience a relapse of the disease despite obtaining the ideal initial treatment.[1] Widespread *TP53* mutations, chromosomal instability (CIN), numerous copy number abnormalities, and notable genomic variability between and within patients are characteristics of ovarian HGSC. This intricacy has made it difficult to establish successful precision medicine techniques. Clinically, almost all patients eventually relapse despite the remarkable response rates to first-line platinum-taxane therapy. With every treatment, the chance of responding to more platinum-based chemotherapy decreases, and most patients eventually acquire deadly resistance to chemotherapy.[6] The study's primary objective was to carry out a comparative histopathological analysis of ovarian tumors in Khyber Pakhtunkhwa, Pakistan, focusing on the prevalence of HGSC. The study aim was to determine the prevalence of various type of ovarian tumors and to characterize the histopathological features of these tumors.

METHODS

This descriptive cross-sectional study was carried out in the Department of Pathology of Hayatabad Medical Complex, Peshawar, Pakistan, over one year, from 01 January to 31 December 2023 after approval from hospital institutional review and ethical board vide letter No. 1021/HEC/B&PSC/2022 on dated 21/12/2022.

The study enrolled all consecutive cases of histopathological ovarian tumors reported during this period. Those who had their specimens processed after being operated on elsewhere. Specimens from all surgical procedures, including Ovarian, were included. Patients with histopathologically confirmed ovarian tumors, patients whose tumors were removed through any surgical procedure including with or without salpingo-oophorectomy, total abdominal hysterectomy, salpingo-oophorectomy, oophorectomy, cystectomy, and tumor specimens processed. Patients with two or more synchronous ovarian tumors, incomplete or insufficient histopathological data, and specimens with non-ovarian origin or those not meeting the study's diagnostic criteria were excluded from the study. The WHO classification system for ovarian tumors was used for tumor classification.[17] We acquired informed consent from each individual. During the whole study, full adherence to data confidentiality was maintained.

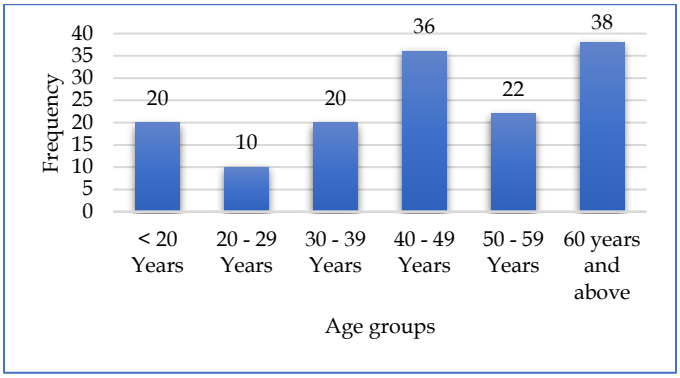
The data was analyzed in version 26 of the Statistical Package for Social Sciences. Descriptive statistics were used to summarize demographic traits like age. We computed rates and percentages for the various histological subtypes of ovarian cancers. The prevalence of each histological type was shown to be significantly correlated with the participant's age and geographic location, as determined by the Chi-square test. To determine whether there was a significant correlation between the participants' ages and high-grade serous carcinoma, regression analysis was used. A statistically significant p-value was defined as one less than 0.05.

RESULTS

There were 146 female participants in the research, ages ranging from 13 to 85, with a mean age of 45.44 ±17.52 years. The following was the distribution of ages: 13.7% of the population was under 20, 6.8% was between 20 and

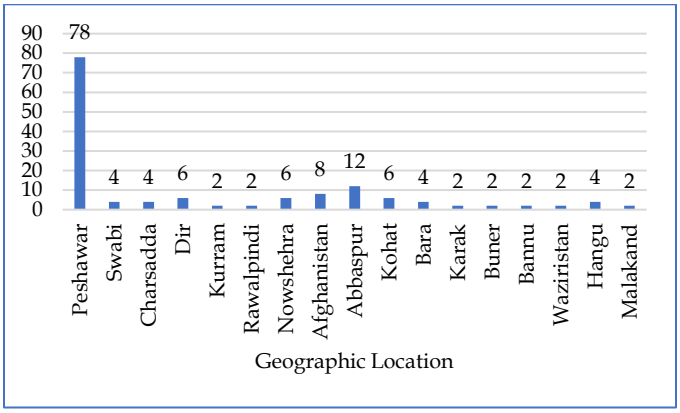
29 years old, 13.7% was between 30 and 39 years old, 24.7% was between 40 and 49 years old, 15.1% was between 50 and 59 years old, and 26.0% was over 60.

Figure 1: Frequency of different Age groups



The study participants came from various districts, with the majority from Peshawar, accounting for 53.4%. Other districts and regions included Swabi (2.7%), Charsadda (2.7%), Dir (4.1%), Kurram (1.4%), Rawalpindi (1.4%), Nowshehra (4.1%), Afghanistan (5.5%), Abbaspur (8.2%), Kohat (4.1%), Bara (2.7%), Karak (1.4%), Buner (1.4%), Bannu (1.4%), Waziristan (1.4%), Hangu (2.7%), and Malakand (1.4%).

Figure 2: Geographic location of the participants



Type and Gross Examination of Specimens

The specimens collected in the study were categorized into various types, described in Table 1. The most common specimen was Uterus with Adnexa, which accounted for 35.6% of the total. Other common specimens included total abdominal hysterectomy with Bilateral salpingo-oophorectomy (TAH BSO) about 12.3% and pelvic mass (6.8%). Less frequent specimens were abdominal mass, adnexa, adnexa with peritoneum, left adnexa, left ovary, oophorectomy, and uterus with left adnexa, each accounting for 1.4%. The specimens received and examined are of varying type and presentation. The notable findings are as follows: 1) Uterus with Bilateral Ovaries and Fallopian Tubes: This was the most frequently received specimen type, accounting for approximately 35.6% (n=52) of the total specimens. These specimens were often received in formalin. 2) Uterus with Attached or Separate Adnexa: A significant number of specimens (approximately 17.8%, n=26) consisted of the uterus with either attached or separate ovaries and fallopian tubes. Some of these specimens included additional pieces such as omental tissue or peritoneum. 3) Ovarian and Cystic Masses: Specimens included ovarian masses or cysts, some already opened or ruptured, accounting for about 10.3% (n=15). The sizes of these masses varied, with the largest measuring up to 16x14x10 cm. 4) Hemorrhagic cysts or Multicystic ovaries were received in approximately 4.8% (n=7) of the specimens, with some measuring collectively up to 11x9x7 cm. 5) Multiple Detached Pieces: Some specimens (about 6.8%, n=10) were received as multiple detached pieces, including cystic masses, friable and spongy tissues, or nodular pieces. For instance, one specimen collectively consisted of multiple gray-brown pieces of crispy and spongy tissue measuring 18x14x7 cm. 6) Complex Specimens: Certain specimens (about 8.2%, n=12) were more complex and received in multiple containers with different types of tissues, including ovarian tissue, peritoneal tissue, and omentum. There were also specimens described as consisting of piece-meal ovarian tumors and segments of the gut. 7) Other Specific Specimens: Specific notable specimens included an atrophic uterus with one side matted ovary and fallopian tube (1.4%, n=2), a uterus with both sides of fallopian tube and ovaries (approximately 4.8%, n=7), and a uterus with both detached ovarian masses (1.4%, n=2). Specimens sometimes included additional components such as appendices or mesentery pieces, making up about 4.1% (n=6) of the total specimens. The gross examination revealed a diverse range of specimens primarily involving the uterus, ovaries, and fallopian tubes, often with additional tissues such as omentum and peritoneum.

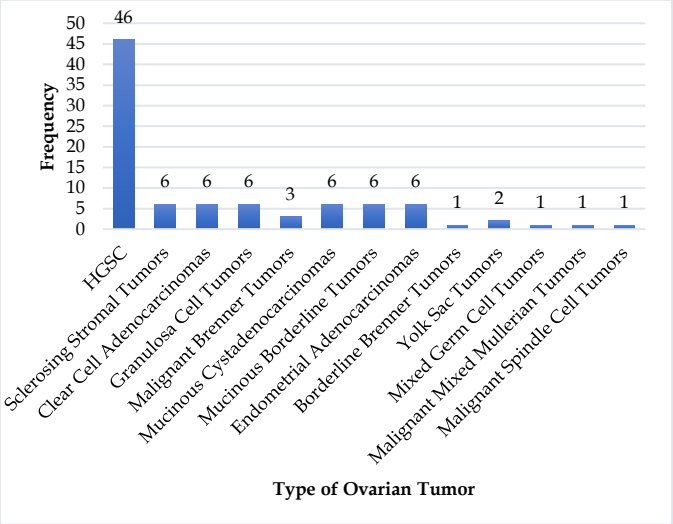
Table 1: Different types of histological specimens

Specimen Type	Frequency % (n)
Uterus with Ovary and Fallopian Tube	35.6% (52)
Uterus with Attached or Separate Adnexa	17.8% (26)
Ovarian and Cystic Masses	10.3% (15)
Hemorrhagic Cysts or Multicystic Ovaries	4.8% (7)
Multiple Detached Pieces	6.8% (10)
Complex Specimens (containing peritoneum and omentum)	8.2% (12)
Atrophic Uterus with Matted Ovary and Fallopian Tube	1.4% (2)
TAH-BSO	4.8% (7)
Uterus with both Ovaries	1.4% (2)
Other Specific Specimens	8.9% (13)
Total	100.0% (146)

Prevalence of Different Ovarian Tumors

Our study of 146 ovarian tumor specimens observed diverse histopathological diagnoses. Serous borderline tumors were present in 9 cases (6.2%), while sclerosing stromal tumors were identified in 6 cases (4.1%). Papillary serous adenocarcinomas and clear cell adenocarcinomas were each found in 7 cases (4.8%) and 6 cases (4.1%), respectively. Granulosa cell tumors were diagnosed in 6 cases (4.1%), and papillary serous cystadenocarcinomas also appeared in 7 cases (4.8%). Malignant Brenner tumors were relatively rare, with only 3 cases (2.1%). Additionally, mucinous cystadenocarcinomas and mucinous borderline tumors were both identified in 6 cases each (4.1%). Endometrial adenocarcinomas were observed in 6 cases (4.1%), and serous carcinomas were found in 4 cases (2.7%). Borderline Brenner tumors were identified in 1 case (0.7%). Other less common diagnoses included yolk sac tumors in 2 cases (1.4%), mixed germ cell tumors in 1 case (0.7%), malignant mixed Mullerian tumors in 1 case (0.7%), and malignant spindle cell tumors in 1 case (0.7%).

Figure 3: Frequency of different ovarian tumors



Among the 146 samples, 46 cases (31.5%) were identified as High-Grade Serous Carcinoma (HGSC) within the sample population, making it a significant finding in the overall distribution of ovarian tumors. This includes 9 cases of Papillary Serous Adenocarcinoma, 6 cases of Serous Carcinoma, 16 cases of Papillary Serous Carcinoma, 2 cases of Serous adenocarcinoma, and 13 cases of Papillary Serous Cystadenocarcinoma.

Comparative Histopathological Analysis of Different Ovarian Tumors

The histological characteristics of each specimen according to the type of tumor were examined, and the following features were noticed: Serous Borderline Tumors were characterized by their papillary formations with a thin, delicate stroma and minimal cytological atypia. These tumors often exhibited a low mitotic rate and a predominantly cystic appearance with papillary projections. Sclerosing Stromal Tumors were noted for their dense stromal fibrosis and sparse cellularity. These tumors showed a well-circumscribed stromal component with minimal epithelial growth and low mitotic activity. Papillary Serous Adenocarcinomas displayed high-grade features, including significant stromal invasion, prominent nuclear atypia, and frequent mitotic figures. The papillary structures were often accompanied by extensive necrosis and hemorrhage. Clear Cell Adenocarcinomas were distinguished by clear cytoplasm, solid nests or trabecular patterns, and a high degree of nuclear atypia. These tumors frequently showed cystic areas filled with clear or yellowish fluid. Granulosa Cell Tumors exhibited small, uniform cells arranged in trabecular or follicular patterns with occasional Call-Exner bodies. These tumors often demonstrated low mitotic activity and mild nuclear atypia. Extensive papillary projections, significant stromal invasion, and high mitotic activity marked Papillary Serous Cystadenocarcinomas. The presence of necrosis and Hemorrhagic areas was common. Malignant Brenner Tumors displayed invasive patterns with areas of necrosis and hemorrhage. The epithelial cells were atypical and infiltrated surrounding tissues. Benign Brenner Tumors showed non-invasive transitional epithelium with a smooth appearance and minimal stroma. Mucinous Cystadenocarcinomas showed cystic structures filled with mucinous material, often with extensive stromal invasion and high mitotic activity. A variable mixture of solid and cystic areas characterized these tumors. Endometrioid Adenocarcinomas were recognized by their complex glandular architecture, marked nuclear atypia, and areas of endometrial-like stroma. These tumors often exhibited high mitotic activity and focal necrosis. Histologic characteristics such as Schiller-Duval bodies, high mitotic rates, and extensive necrosis were identified in Yolk Sac Tumors. The tumors were predominantly solid with prominent vascularity. Mixed Germ Cell Tumors contain a combination of germ cell elements, including embryonal carcinoma and teratoma components, with diverse histological features such as necrosis and varying degrees of differentiation.

Association of HGSC with Demographic Characteristics of Participants

The distribution of HGSC cases was fairly even across different age groups, with the most cases observed in individuals aged 40 to 49 (13 cases), followed by those aged 30 to 39 (9 cases). The fewest cases were noted in individuals aged 20 to 29, with only 2 cases. The chi-square test resulted in a Pearson chi-square value of 3.951 and a p-value of 0.556, indicating no significant statistical link between the age group and the prevalence of HGSC

in this sample. Furthermore, linear regression analysis examining the relationship between age and HGSC revealed no significant association, with a p-value of 0.627 (Table 2).

Analyzing High-Grade Serous Carcinoma (HGSC) cases across different districts reveals significant geographic variation. Out of a total of 146 cases, 45 are diagnosed with HGSC. The chi-square test results indicated a statistically significant association between district and HGSC diagnosis, with a Pearson Chi-Square value of 33.621 and a p-value of 0.006. For instance, Peshawar has the highest number of HGSC cases (22 out of 78), while districts such as Afghanistan, Bara, and Karak report no HGSC cases. Other districts, like Charsadda and Buner, show a higher proportion of HGSC cases relative to their total number of cases. The chi-square test revealed no linear trend in HGSC cases across districts, but the overall chi-square test suggests that geographic factors might influence HGSC diagnosis rates.

Table 2: Comparative analysis of HGSC in different Age groups and Geographic locations

Parameter		High-Grade Serous Carcinoma		
		No	Yes	p-value
Age groups	< 20 Years	14	6	0.556
	20—29 Years	8	2	
	30—39 Years	11	9	
	40—49 Years	23	13	
	50—59 Years	16	6	
	60 years and above	29	9	
Geographic Location	Peshawar	56	22	0.006
	Swabi	2	2	
	Charsadda	0	4	
	Dir	2	4	
	Kurram	1	1	
	Nowshehra	4	2	
	Abbaspur	8	4	
	Kohat	4	2	
	Buner	0	2	
	Waziristan	0	2	
	Hangu	4	0	
	Other	24	0	

DISCUSSION

The findings of our study provide a comprehensive overview of the histopathological diagnosis of 146 ovarian tumor specimens. Our findings revealed that HGSC accounts for 31.5% of the cases, aligning with but slightly lower than the 68% reported by Mie et al. and the 71.3% reported by Zhou *et al.*, In contrast it is higher than the 29.8% of serous carcinoma reported by Ahmad et al.[6,18,19] Similarly, our study found clear cell carcinoma in 4.1% of cases, which is considerably lower than the 12% reported by Mie et al. and 11.1% reported by Zhou et al. Furthermore, we identified mucinous carcinoma in 4.1% of cases and endometrioid carcinoma also in 4.1%, compared to 3% and 11% reported by Mie *et al.*, respectively, and compared to 8.1% and 9.5% reported by Zhou *et al.*, respectively.[6,18] Ahmad *et al.*, also reported a higher prevalence of endometrioid carcinoma, about 24.2%, mucinous carcinoma, about 8.1%, and clear cell carcinoma, about 6.4, which is higher than our findings.[19]

While Wentzensen *et al.*, reported 73.7% serous, 13.2% endometrioid, 7.2% mucinous, and 5.9% clear cell carcinomas in their analysis of the Ovarian Cancer Cohort Consortium. In contrast, our study found a prevalence of 31.5% HGSC, 4.1% clear cell carcinoma, 4.1% mucinous carcinoma, and 4.1% endometrioid carcinoma.[20] Our findings were also lower than those reported by Mushtaq *et al.*, who found 55.9% of cases to be serous carcinoma and 38.9% to be clear cell carcinoma.[21]

We observed granulosa cell tumors in 4.1% of cases, whereas Ahmad et al. reported an 8.1% prevalence. In our study, yolk sac tumors accounted for 1.4% and malignant mixed germ cell tumors for 0.7%, compared to 5.2% and 0.4%, respectively, as Ahmad et al. reported. Runa *et al.*, reported that germ cell tumors comprised 42.2% of ovarian tumors, with serous tumors accounting for 35.4%.[5] In contrast, our study found a significantly lower prevalence of germ cell tumors at 0.7%, and serous tumors constituted 31.5% of the total cases. Kanwal et al. reported a 57.1% prevalence of HGSC, which is significantly higher than our finding of 31.5%.[2] This variation could be due to differences in sample size, geographical factors, or diagnostic practices.

Our study found that HGSC had the highest prevalence among all ovarian tumors. However, the prevalence of HGSC in our study was slightly lower compared to the figures reported in other studies. Our study results found no significant association between the age group and HGSC prevalence, which is in contrast to the study by Mallen *et al.*, and Ali *et al.*, who reported a significant association between ovarian cancers and the age of the participants.[1,4] On the other side, prostatic adenocarcinoma is one of the most common carcinoma in male.[22]

Possible reasons for this discrepancy include differences in sample size and demographics and geographic and ethnic variations. Our study identified a significant association between HGSC and geographic location; in contrast, there is a lack of previous studies exploring geographic variations in HGSC prevalence. There are several potential causes for the variation in HGSC prevalence between districts, including regional genetic predispositions, variations in healthcare availability, and environmental exposures. The observed geographic distribution, with Peshawar having the highest number

of HGSC cases (28.2, n=22), suggests that local factors may play a role in the development and diagnosis.

CONCLUSION

This study findings highlight the prevalence of HGSC (31.5%), followed by other tumor types such as clear cell carcinoma, mucinous carcinoma, and endometrioid carcinoma. Despite sample size limitations and potential selection bias, our study contributes to understanding ovarian tumor epidemiology in the region. It underscores the need for larger and prospective studies to provide a comprehensive understanding of ovarian tumors. Awareness, early detection, and standardized diagnostic practices can improve patient outcomes and contribute to a better understanding of ovarian tumors.

LIMITATIONS

Our findings demonstrate some similarities with previously reported data while highlighting the differences. Our study's relatively lower prevalence of HGSC and germ cell tumors underscores the potential influence of regional and methodological factors. Our study may have some limitations, such as the sample size of 146 ovarian tumor specimens not representing the entire population, and results could not be generalized to the entire population. Our study is retrospective, relying on previously collected data, which may introduce selection bias and impact the accuracy of histopathological diagnosis.

SUGGESTIONS / RECOMMENDATIONS

To overcome these limitations, we recommend further studies involving larger sample sizes and multiple centers encompassing different regions and populations. Prospective studies with standardized diagnostic criteria and techniques would also enhance the reliability and comparability of results. Additionally, molecular and genetic analysis can provide deeper insights into the etiology and uncover the region-specific risk factors.

CONFLICT OF INTEREST / DISCLOSURE

The authors have no conflict of interest.

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