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Prevalence and Histopathological Findings of Endometrioid Carcinoma and Associated Risk Factors: A Cross-Sectional Study

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ABSTRACT

Ovarian cancer ranks as the seventh most frequently diagnosed malignancy among women worldwide. Endometrioid carcinoma, a type of proliferative endometrial tumor, accounts for approximately 15% of epithelial ovarian cancers, making it the third most common subtype. **Objective:** To investigate the relationship between Endometrioid Carcinoma and potential risk factors, including demographic, reproductive, and lifestyle factors. **Methods:** A cross-sectional study was conducted at Hayatabad Medical Complex's Department of Pathology from January 1 to December 31, 2023. The study analyzed 139 ovarian tumor specimens confirmed through histopathology. Statistical analysis using SPSS version 26 identified significant associations between variables using Chi-square tests and logistic regression, with a significance level of $p < 0.05$. **Results:** A total of 139 ovarian specimens with the patient's mean age (45.34 years) with the highest prevalence of endometrioid carcinoma observed in women aged 40-49 and 60 years and above. The prevalence of endometrioid carcinoma was about 14.4% (n=20). A significant association was identified between parity and endometrioid carcinoma (p-value = <0.001). Menopausal status also showed a significant association, with postmenopausal women having a higher prevalence of endometrioid carcinoma. Logistic regression analysis indicated that age was a significant predictor of endometrioid carcinoma (p-value = 0.028).**Conclusions:** Significant association between nullipara and premenopausal women with endometrioid carcinoma, emphasizing the importance of considering parity and menopausal status as a risk factor for endometrioid carcinoma.

INTRODUCTION

The second most common gynecologic cancer worldwide, ovarian cancer is the worst in both Europe and the United States [1]. It ranks as the seventh most commonly diagnosed cancer among women worldwide and the tenth in China [2]. In Western and Asian nations, the frequency of ovarian tumors varies; in women of reproductive age, two-thirds of cases occur. Ovarian cancer in children is extremely uncommon, affecting fewer than 5% of cases [3]. Of all ovarian tumors, 75-80% are benign ones, and 55-65% of them are seen in women under 40 years [4]. Most ovarian cancers arise from the epithelial cells of the ovary and are classified by the WHO into five major histological types based on epithelial characteristics. Historically, ovarian tumors have been classified into three categories: benign, borderline (or "carcinoma of low malignant potential"), and malignant, using criteria such as architectural pattern, cytological atypia, and mitotic counts [5]. With a frequency of 15%, endometrioid carcinoma is the third most common epithelial ovarian cancer subtype, after serous and mucinous cystadenocarcinomas, and is characterized by its proliferative growth in the endometrium [6]. Typically

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appearing a cystic mass with hemorrhagic, serous, or mucinous components, endometrioid carcinoma's ultrasound appearance closely resembles that of an endometrioma, characterized by a low-level echo-filled, thick-walled cystic structure [7]. This carcinoma represents a subset of primary epithelial ovarian tumors, making up approximately 10% to 15% of ovarian malignancies [8]. Patients with endometriosis may develop endometrioid carcinomas, especially if their endometriomas are larger than 10 cm, grow more quickly, or have solid, solid-cystic regions or papillary outgrowths, which are signs of cancer [9, 10]. The prevalence of endometrioid carcinoma varies globally; a study in China reported a prevalence of about 9.5%, while another study found a prevalence of approximately 11% [11, 12]. In Pakistan, the reported prevalence of endometrioid carcinoma varies, with one study documenting a rate of 24.2% and another reporting a prevalence of 7.6% [13, 14]. Women with Endometrioid Carcinoma (EC) may be asymptomatic, while others might experience symptoms related to their pelvic mass [15]. Both endometrioid and clear cell ovarian cancers share similar associations, with increased risks linked to endometriosis, Hormone Replacement Therapy (HRT), and advancing age, and decreased risks associated with tubal ligation [2]. Ovarian cancer often presents with non-specific symptoms, which can lead to late-stage detection. Endometrioid carcinoma has several established risk factors, including advancing age, hormone replacement therapy, high dietary fat intake, family history, genetic predisposition, and nulliparity(never having given birth). Nevertheless, additional research is necessary to ascertain the possible contributions of other risk factors, such as obesity, talc powder use, fertility drugs, infertility, radiation exposure, and in vitro fertilization, to the development of endometrioid carcinoma, as their effects are still unknown [14, 16]. MRI imaging of endometrioid carcinoma identifies two main types: solid and cystic, with cystic types having various subtypes. Endometrial thickening may also be visible in imaging studies [17]. According to their solid development pattern, endometrioid carcinomas are categorized into three categories by the International Federation of Gynecology and Obstetrics (FIGO) system: Grade 1 has less than 5% solid architecture, Grade 2 has 6-50% solid architecture, and Grade 3 has more than 50% solid architecture [18]. The rationale for this study is to address the rising incidence of endometrioid carcinoma in Khyber Pakhtunkhwa, where data on its prevalence and associated risk factors are limited. The objective of the study was to assess the prevalence and risk factors of endometrioid carcinoma in this region to help improve patient outcomes and reduce the burden of ovarian tumors.

METHODS

This one-year descriptive cross-sectional study was conducted from January 1, 2023, to December 31, 2023, at the Department of Pathology, Hayatabad Medical Complex, Peshawar, Pakistan. A non-probability convenience sampling technique was employed, and a sample size of 139 was calculated using OpenEpi, based on an anticipated frequency of endometrioid carcinoma of approximately 10%, a 95% confidence interval, and a 5% margin of error [19]. The study included tumor specimens from patients who underwent surgical procedures such as cystectomy, oophorectomy, salpingo-oophorectomy, and total abdominal hysterectomy with or without salpingo-oophorectomy, with histopathologically confirmed ovarian tumors. Exclusion criteria encompassed patients with two or more synchronous ovarian tumors, incomplete or insufficient histopathological data, and specimens of non-ovarian origin or not meeting the study's diagnostic criteria. Data were collected prospectively from medical records and pathology archives. Tumor specimens obtained from surgical procedures, whether performed at Hayatabad Medical Complex or elsewhere, were processed in the Department of Pathology. Demographic and clinical information including patient age, gender, parity, and presenting symptoms was documented on a pre-designed proforma. Histopathological analysis involved tumor classification following the World Health Organization (WHO) classification system for ovarian tumors [19]. Tumor sections were stained using Hematoxylin and Eosin (H&E) for the assessment of tumor type, presence of necrosis, lymphovascular invasion, and cellular atypia. Ethical approval was obtained from the Institutional Review Board of Hayatabad Medical Complex Peshawar (Ref. No: HMC-QAD-F-00970). Informed consent was obtained in writing from all participants before data collection. To ensure confidentiality, participant data were coded, and access to personal information was restricted to authorized research personnel only. Data analysis was conducted using SPSS version 26.0, with descriptive statistics to summarize baseline data, chi-square tests to examine categorical variable associations, and logistic regression analysis to identify potential correlations between risk factors and endometrioid carcinoma. The chi-square test was chosen to compare categorical variables, while logistic regression was used to analyze relationships between predictor variables and disease occurrence. A significance level of $p < 0.05$ was set for all tests.

RESULTS

The participants were between the ages of 13 and 85, with a mean age of 45.34 ± 17.311 years. The age of the study participants was categorized into six distinct age groups. The majority of participants were either in the 40 to 49 years' age group, representing 25.2% (n=35) of the sample, or in the 60 years and above category, which constituted

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25.9% (n=36) of the participants. A smaller portion of the participants were under 20 years' old (13.7%, n=19), followed by those in the 30 to 39 years' group (12.9%, n=18). The 50 to 59 years' group accounted for 15.1% (n=21), while the 20 to 29 years' group had about 7.2% (n=10), as shown in figure 1.

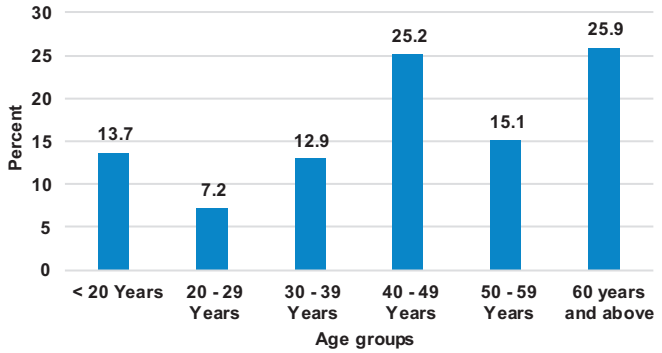

Figure 1: Age Distribution of the study Participants

The specimens analyzed in the study were diverse, with the majority being a uterus with adnexa, accounting for 43.2% (n=60) of the total. This was followed by total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH BSO) specimens, which were about 13.7% (n=19) of the total samples. Ovarian specimens were also significant, with 9.4% (n=13) comprising ovaries alone and 8.6% (n=12) being ovarian cysts. Smaller proportions included pelvic masses (6.5%, n=9), ovaries with fallopian tubes (4.3%, n=6), uterus with adnexa and appendix (3.6%, n=5), and uterus with adnexa and peritoneum (3.6%, n=5). Specimens such as cystectomy (2.9%, n=4), ovary NOS (2.9%, n=4), oophorectomy (0.7%, n=1), and abdominal mass (0.7%, n=1) were also less frequently examined (Figure 2).

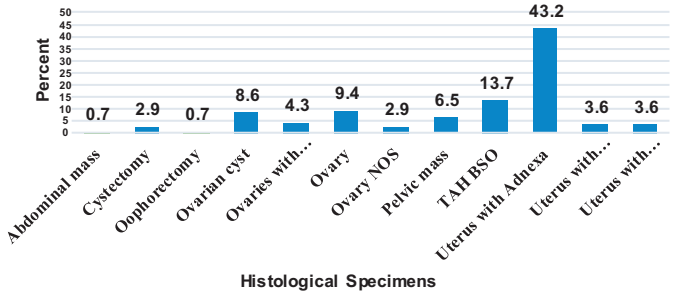

Figure 2: Frequency of Different Histological Specimens

The parity data showed that among the 63 participants with available information, 28.6% (n=18) were nulliparous, while the majority (71.4%, n=45) were multiparous. Regarding menopause status, data was available for 38 participants. Of these, 18.8% (n=6) were in the premenopausal stage, and 81.2% (n=32) were postmenopausal. When examining the prevalence of endometrioid carcinoma, 14.4% (n=20) of the total sample was diagnosed with endometrioid carcinoma, as illustrated in figure 3. The study examined various diagnoses among the participants, with Papillary Serous Adenocarcinoma being the most common, accounting for 20.1% (n=28) of the cases. Serous Carcinoma was also prevalent, accounting for 16.5% (n=23) of the cases. Mucinous Adenocarcinoma was diagnosed in 12.2% (n=17) of the participants, while Clear Cell Carcinoma and Brenner Tumor were identified in 9.4% (n=13) and 7.2% (n=10) of cases, respectively. Other diagnoses included Granulosa Cell Tumor (7.2%, n=10), Sclerosing Stromal Tumor (5.8%, n=8), and Yolk Sac Tumor (2.2%, n=3). Less frequent diagnoses, each representing less than 1% of the cases, included Dysgerminoma (n=1), Low-grade Appendiceal Mucinous Neoplasm (n=1), Malignant Spindle Cell Tumor (n=1), Mixed Mullerian Tumor (n=1), and Mucinous Adenocarcinoma with Omental Implants (n=1) while Mixed Germ Cell Tumor was about 1.4% (n=2)(Figure 3).

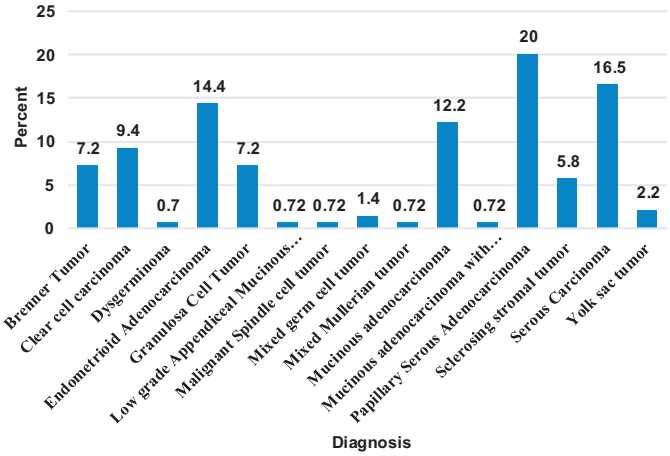

Figure 3: Prevalence of Different Histological Tumors Diagnosed

The histological examination of the endometrioid carcinoma reveals an enlarged uterus with a thickened endometrium on gross examination. Tumors typically present as polypoid or exophytic masses within the uterine cavity. Solid, whitish, and friable ovarian masses were observed in approximately 70% of cases as shown in table 1, indicating a common presentation. Partially cystic and solid tumors were seen in about 55% of patients, with the cystic areas often containing papillary growths in around 35% of cases. Hemorrhagic foci within the tumor were found in approximately 45% of cases. Multiple cysts containing haemorrhagic fluid and necrosis were found in about 25% of patients, while cystic cavities filled with thick, mucoid material were reported in 25% of cases. Additionally, amber-colored fluid within cystic parts was observed in about 15% of specimens, often accompanied by papillary projections. Multiple papillary growths within the uterine cavity were found in approximately 30% of endometrioid carcinoma cases.

Table 1: Histopathological Findings of the Endometroid Carcinoma Cases

Histopathological Findings	Percentage (%)
Ovarian Masses (Solid, Whitish, Friable)	70%
Partially Cystic Solid Tumors	55%
Cystic Areas with Papillary Growth	35%
Hemorrhagic Foci	45%

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Cysts with Hemorrhagic Fluid and Necrosis	25%
Cysts with Thick Mucoid Material	25%
Cysts with Amber-colored Fluid	15%
Multiple Papillary Growth	30%

The study assessed the association between endometrioid carcinoma and age, parity, and menopause status using Chi-square tests and Logistic Regression analysis. While there was no significant association between age group and endometrioid carcinoma using Pearson Chi-Square ($p = 0.103$). However, the likelihood ratio test showed a significant association ($p = 0.021$), and linear-by-linear association test revealed a significant trend, with increasing likelihood of endometrioid carcinoma with age ($p = 0.009$). The age groups 40—49 years and above 60 years (20% cases each), both showed higher occurrence of endometroid carcinomas as shown in table 2.

Table 2: Correlation of Age, Parity and Menopausal Status with Endometrioid Carcinoma

Variables		Endometrioid Carcinoma N (%)			
		No	Yes	Total	p-Value
Age Groups	<20Years	19 (100%)	0 (0%)	19 (100%)	0.035
	20 - 29 Years	10 (100%)	0 (0%)	10 (100%)	
	30 - 39 Years	17 (94%)	1 (6%)	18 (100%)	
	40 - 49 Years	28 (80%)	7 (20%)	35 (100%)	
	50 - 59 Years	16 (76%)	5 (24%)	21 (100%)	
	60 Years and above	29 (80.5%)	7 (19.5%)	36 (100%)	
Parity	Nulliparity	9 (50%)	9 (50%)	18 (100%)	<0.001
	Multiparity	43 (95.5%)	2 (4.5%)	45 (100%)	
Menopausal Status	Premenopausal Women	2 (33.3%)	4 (66.7%)	6 (100%)	0.009
	Postmenopausal Women	22 (84.6%)	4 (15.4%)	26 (100%)	

The results showed a strong association between nulliparity (having no children) and endometrioid carcinoma, with 9 out of 18 nulliparous individuals diagnosed with the condition (p-value = 0.000), a significantly lower prevalence of endometrioid carcinoma among multiparous individuals (those who have had children), a significant relationship between premenopausal status and endometrioid carcinoma, with 4 out of 6 premenopausal women diagnosed with the condition (p-value = 0.009), and a lower prevalence of endometrioid carcinoma among postmenopausal women, and histopathological changes were also observed (Figure 4).

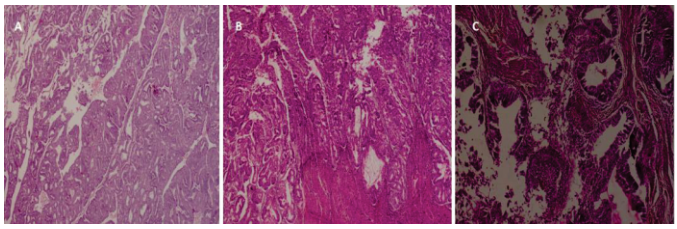

Figure 4: Histologic Features of Endometrioid Carcinoma

A) Confluent back-to-back glands (10x power view of Endometroid Carcinoma)
B) FIGO grade 1 tumor with less than 5% solid component (20x power view of Endometroid Carcinoma)
C) Glands lined by pleomorphic hyper chromatic cells (40x power view of Endometroid Carcinoma)

The multivariate regression analysis was conducted to assess the effects of age group, parity, and menopausal status on the occurrence of Endometrioid Carcinoma (EC). The dependent variable, EC, was observed in two categories: "Yes" (30.8%) and "No" (69.2%). The model fitting criteria indicated a significant improvement over the intercept-only model (Chi-Square=32.097, df=6, $p<0.001$), as presented in Table 3. This suggests that the predictors collectively contribute to distinguishing between the presence and absence of EC. The pseudo-R-square values—Cox and Snell (0.709), Nagelkerke (1.000), and McFadden (1.000)—indicate a strong model fit. Likelihood ratio tests revealed significant effects for parity ($p = 0.006$), age group ($p < 0.001$), and menopausal status ($p = 0.017$).

Table 3: Binary Logistic Regression Analysis of Endometroid Carcinoma with Age

Model Summary: Dependent Variable (EC) Independent Variable (Age) Covariates (Parity and Menopausal Status)					
Model Fit					
Chi-Square	df	p-Value	-2 Log Likelihood	Cox and Snell R Square	Nagelkerke R Square
32.097	6	0.001	106.088	0.709	1.000
Variables in the Equation					
Predictor	B	S.E.	Wald	df	p-Value	Exp (B) (Odds Ratio)
Age	0.033	0.016	4.429	1	0.001	1.033
Parity	37.894	13324	0.00	1	0.006	1.174
Menopausal Status	-1.749	13626	0.00	1	0.017	1.092

DISCUSSION

This study focused on the prevalence and risk factors associated with endometrioid carcinoma, enrolling 139 ovarian cancer specimens. This study found a prevalence of endometrioid carcinoma of 14.4%, which is consistent with findings from Zhou *et al.* (11%) and Wentzensen et al. (13.2%), although it is somewhat higher than the 9.5% prevalence reported by Mei *et al.* [11, 12, 20]. Mei *et al.* also noted a higher prevalence of 24.2%, while Kanwal *et al.* reported a lower prevalence of 7.6% in a comparable setting [12, 14]. These variations may reflect regional differences and methodological factors, highlighting the importance of locally focused data for accurate assessment. When examining the distribution of ovarian carcinoma subtypes, this study revealed a pattern that diverged from prior research. For instance, Wentzensen *et al.* reported that serous carcinoma constituted 73.7% of cases in their analysis, followed by mucinous (7.2%) and

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clear cell carcinomas (5.9%) [20]. Similarly, Saeed *et al.* found that serous carcinoma was the most common subtype, at 55.9%, while clear cell carcinoma accounted for 38.9% [21]. In contrast, our study observed a markedly lower prevalence of serous carcinoma (16.5%) but higher occurrences of mucinous adenocarcinoma (12.2%) and clear cell carcinoma (9.4%). Additionally, granulosa cell tumors accounted for 7.2% of cases, close to the 8.1% prevalence found by Ahmad et al. but lower than the 14.4% reported by Kanwal *et al.* [13, 14]. Germ cell tumors, including yolk sac and mixed germ cell tumors, comprised 3.6% of cases in this study, which is lower than the 11% prevalence observed by Kanwal *et al.* [14]. For mucinous carcinoma, Ahmad *et al.* reported a prevalence of 8.1%, aligning with our study's finding of 12.2% [13]. However, the prevalence of clear cell carcinoma in this study was 9.4%, which is higher than Ahmad *et al.* 6.4% and Kanwal *et al.* 3.4% [13, 14]. Such differences in subtype distribution underscore the need for further investigation into potential geographic or genetic factors influencing these rates. The analysis also identified several demographic factors associated with endometrioid carcinoma. Age showed a weak but statistically significant correlation, which aligns with findings from Ali *et al.* [16]. Parity emerged as a significant variable; nulliparous women demonstrated a notably higher risk of developing endometrioid carcinoma than parous women, consistent with findings from Ali *et al.* and Reid *et al.*, who reported that parous women had a 30–60% lower risk of endometrioid carcinoma than nulliparous women [16, 19]. Additionally, this study showed a substantial association between menopausal status and endometrioid carcinoma, with premenopausal women having higher risk, a finding in line with Ali *et al.* report of nulliparity and late menopause as significant risk factors [16]. Our study identified several associations, rather than causal factors, between endometrioid carcinoma and risk factors such as age, parity, and menopausal status, contributing valuable insights to regional ovarian cancer research. Given that these associations are less frequently explored in local literature, further studies are warranted to investigate the impact of these factors in diverse populations and enhance understanding of the disease's etiology. There were a few limitations in this study to consider. The study has limitations that may affect the generalizability and profundity of the findings. Specifically, the cross-sectional methodology and relatively small sample size mean that the data cannot be used to demonstrate a causal relationship between the development of endometrioid carcinoma and the identified risk variables. Larger, multi-center investigations should be conducted in the future to confirm these results and investigate additional possible risk factors.

CONCLUSIONS

This study identified a higher prevalence of endometrioid carcinoma in the region and explored its association with demographic factors such as age, parity, and menopausal status. While age showed a significant association with the condition, nulliparous and premenopausal women were significantly more likely to develop endometrioid carcinoma compared to multiparous and postmenopausal women. These findings underscore the importance of considering parity and menopausal status as potential risk factors. This study highlights associations rather than causative links, given the study's descriptive and cross-sectional design. Further research is needed to explore the underlying mechanisms and causative pathways.

Authors Contribution

Conceptualization: PK
Methodology: PK
Formal analysis: SNP, MJ, SA, FAB, PK
Writing, review and editing: SNP, MJ, SA, FAB, PK, NB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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