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**Original Research Article**

# Frequencies, clinicopathological features, and risk factors of type I and type II endometrial cancer; a retrospective observational study at a tertiary care hospital in Pakistan

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## ABSTRACT

**Background:** Endometrial cancer (EC) is the most common gynecological malignancy worldwide. The death rates for EC have increased by more than 100% over the past 2 decades. EC is subdivided into two types based on distinct histological and clinical features: type I and type II. Our study aims to determine the risk factors and clinicopathological features of both type I and type II EC and draw a comparison between the two types based on frequency, risk factors and clinicopathological features.
**Methods:** It was a retrospective observational study including patients of a single tertiary care center. The study included Patients diagnosed, treated, and followed up for type I and type II endometrial cancer at the study center over the past 19 years from 1st January 2000 to 31st December 2018. All the patients with metastatic endometrial cancer were excluded from the study. SPSS version 26 was used for statistical analysis.
**Results:** A total of 376 patients were included in this study. Among these 343 (91.7) patients had endometroid adenocarcinoma (Type I) and 32 (8.3) had serous and clear cell tumor (type II). Type I EC had a mean age of 57.56 (SD±10.42) while patients with type II EC presented with a mean age of64.97 (SD±6.59). Hypertension and Diabetes were the most common comorbid in EC patients. HRT prior to EC was found to have an association with risk of EC. Compared to patients who were on HRT, patients who were not on HRT prior to diagnosis of EC had 80% less chance of developing endometrial cancer. (Confidence interval: 0.056-0.114, p=0.016).
**Conclusions:** In summary our study demonstrates that both sub types of endometrial cancer have many risk factors that are similar to each other. Despite the difference between the population of both subgroups we were able to prove associations between risk factors and endometrial cancer. However further research is needed at provincial and national level with larger and relatively comparable sample sizes for both subgroups to recognize risk factors and numerically associate them to EC for Pakistani population.

**Keywords:** Cancer, Endometrial, Type I, Type II, Pakistan

## INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries and the fourth most common cancer in women after breast, lung and colorectal cancers.[1] The death rates from EC have increased by more than 100% over the past two decades, with type II EC accounting for up to 40% of the death cases.[2] EC is subdivided into two types based on distinct histological and clinical features. The majority of EC are classified as type I which accounts for more than 70% of the cases.[3] Type I tumors- also known as endometrioid

adenocarcinomas- are usually low-grade tumors associated with unopposed estrogen stimulation and present with a good prognosis and a low risk of relapse or metastasis.[4] Type II tumors, on the other hand, although less common but account for majority of EC related deaths. Type II cancers are not estrogen dependent and develop independently of the endometrial hyperplasia pathway.[5] These are more likely to be high grade and of papillary serous or clear cell histologic type with the poor prognosis as well as a higher risk of relapse or metastasis.[4]

While research on type I EC is extensive and these have been associated with a number of risk factors involving exposure to estrogen, the etiology for the more aggressive type II EC remains unknown. General risk factors for EC include increasing age, long-term exposure to unopposed estrogens, residence in North America or Europe, high concentrations of estrogens postmenopausal, metabolic syndrome (obesity, diabetes), years of menstruation, nulliparity, history of breast cancer, long-term use of tamoxifen, HNPCC family syndrome, hormone-replacement therapy with less than 12-14 days of progestogens and first-degree relative with EC.[2,6,7] However, EC nulliparity, oral contraceptive use, cigarette smoking, use of tamoxifen, age at menarche, and diabetes were associated with an increased risk of type II EC in premenopausal women.[8]

Studies conducted to assess the global prevalence of EC in pre- and post-menopausal women provide compelling evidence that indicate a general rising trend. From 1990-2017 there were 153 countries that showed increasing trends for EC across 195 countries.[9] Studies among the European countries show that EC is less common among the pre-menopausal women and its incidence and mortality continues to decline throughout the Europe especially in Western and Southern European countries at a rate 0f 2-4% per annum. Studies carried out in Asian region have also shown a rising incidence of EC (10.40%) in the region between 1990-2017.[9] A study conducted in China (n=1746) showed that 41.7% of participants were diagnosed before menopause and 58.3% were diagnosed after menopause. The prevalence of EC was higher in post-menopausal women than pre-menopausal women. The study also showed that out of total cases 17.6% (n=307) were type 2 EC and among these 69% were diagnosed among post-menopausal women.[10] Locally very few studies have been conducted in Pakistan to indicate the prevalence and risk factors of type I and II EC among pre- and post-menopausal women based on evidence. However few studies can be found that give a rough estimate. A study was carried out in Lahore which found that 28.4% (n=42) of the ECs were among the post-menopausal women (age=51-60) and 14% of the total cases are type II.[11] Another study in the Karachi (n=16,351) indicated that the EC was the third most common cancer (2.49%) among females in the Pakistan.[12]

As is evident from previous papers there is more literature on type I EC than type II. Despite all the findings, there is still no clear etiology or well-known risk factor behind type II EC. There is also a lack of sufficient literature comparing the clinicopathological features and risk factors of type I and II ECs: especially amongst the Pakistani population. Distinguishing behind the two types is extremely important because they have different etiology, characteristics, and treatment.[13,14] Our study aims to determine the risk factors and clinicopathological features of both type I and type II EC and draw a comparison between the two types based on frequency, risk factors and clinicopathological features.

## METHODS

### *Data source, study design and population*

This study was conducted at the department of obstetrics and gynecology at the Aga Khan University Hospital, Karachi, Pakistan. It was a retrospective observational study including patients of a single tertiary care center. The study included Patients diagnosed, treated, and followed up for type I and type II endometrial cancer at the Department of Obstetrics and Gynecology at the Aga Khan University Hospital, Karachi, Pakistan over the past 19 years from 1st January 2000 to 31st December 2018. All the patients with metastatic endometrial cancer were excluded from the study. The data was collected from the patient files.

### *Measures and outcomes*

Patient characteristics that were recorded on a predesigned questionnaire included: age, body mass index, parity, history of smoking, hypertension, and diabetes. Other than this, family history of cancers, intake of hormones, tamoxifen usage, radiotherapy, and history of polycystic ovarian syndrome (PCOS) was also recorded. Histologically, endometroid adenocarcinoma and mucinous adenocarcinoma were recorded as type 1 endometrial carcinoma while clear cell and papillary serous carcinoma were categorized as type 2 endometrial carcinoma.

### *Statistical analysis*

Data from the Performa was entered to SPSS version 26 where statistical analysis was conducted. Continuous parametric data was represented as means and standard deviation, while continuous nonparametric data was represented as median and Interquartile range. Categorical data was be represented as frequencies and proportions. Associations between categorical covariates were assessed by using chi square/Fisher's exact value tests, while the t test and Mann Whitney U test were used to assess group differences for continuous variables. A two-sided $p \leq 0.05$ will be considered statistically significant.

### *Ethical considerations*

The Ethical exemption was obtained from the institutional review board of the institute on 31-03-2021 before initiating the study, (Reference ID: 2021-6042-16988).

## RESULTS

### *Frequency of type I and type II endometrial cancer*

A total of 397 patients with endometrial cancer (EC) presented to Aga Khan university hospital between January 2000 to December 2018. Twenty-one patients were lost to follow up, therefore these were excluded, and 376 patients were included in this study. Patients were divided into two categories: patients with type I EC and patients with type II EC. Among the patients included in this study three hundred and forty-three patients had endometroid adenocarcinoma (Type I) and 32 had serous and clear cell tumor (type II). Type I tumors accounted for 91.7% of the total EC cases while 8.3% were type II tumors.

### *Patient characteristics*

The demographic and tumor characteristics of the patients have been summarized in Table 1. The overall mean age of the patients presenting to the study center was 57.17 years (SD±10.34). Among these patients presenting with type I EC had a mean age of 57.56 (SD±10.42) while patients with type II EC presented with a mean age of 64.97 (SD±6.59). Overall median BMI of patients was 30 (IQR±9.53). When grouped separately the patients with type I EC had a higher median BMI (30.22) while type II patients had a lower median BMI of 27.89. The median age of menarche for patients in both sub types was 12 years (IQR±13). Patients in both cancer sub types were multiparous with type I subgroup having a median parity of 3.0 while type II EC patients having a median parity of 4.0.

Hypertension was the most common presenting comorbid among the patients. It was present in 188 (54.8%) patients with type I EC, while 20 (62.5%) patients from type II subgroup also had hypertension. Diabetes was second most common comorbid. The 136 (39.7%) patients from type I group had diabetes and 10 (31.2%) from type II group. A family history of previous cancers was seen among 55 (16.2%) type I EC patients while 6 (19.4%) patients with type II EC had a family history. PCOS was also seen in 2 (0.6%) patients with type I EC while none of the patients with type II EC had a history of PCOS. Six patients from type I group had a history of smoking while none of the patients from type II group were smokers. Four (1.2%) Patients were on hormonal replacement therapy (HRT) prior to diagnosis of EC in type I group while 3 (9.7%) patients were on HRT in type II group. Adjuvant radiation was given to 154 (44.89%) patients in type I EC group while 16 (50.0%) patients in type II EC group received radiation therapy prior to EC diagnosis. 16 out 343 type I EC patients died of disease while 3 type II patients died due to EC.

### *Factors associated with type I and Type II endometrial cancer*

Chi-Square test was performed to determine the association of factors associated with incidence of type I or type II cancer. The only variable that was found to have an association with the incidence of endometrial cancer was whether the patient was on HRT prior to the diagnosis of endometrial cancer. Compared to patients who were on HRT, patients who were not on HRT prior to diagnosis of EC had 80% less chance of developing the endometrial cancer (CI: 0.056-0.114, p=0.016) (Table 2).

**Table 1: Demographic and tumor characteristics of patients (n=376).**

| Variables | N (%) | Mean (SD) | Median (IQR) |
|---|---|---|---|
| **Age (years)** | | 57.17(10.34) | - |
| **BMI (kg/m$^2$)** | | | 30 (9.53) |
| **Parity** | | | 3 (4) |
| **Age of menarche (years)** | | | 12 (13) |
| **Type of cancer** | | | |
| Endometroid adenocarcinoma | 343 (91.7) | | |
| Serous papillary | 19 (5.1) | | |
| Clear cell | 13 (3.2) | | |
| **OCP use** | | | |
| No | 370 (98.4) | | |
| Yes | 1 (0.3) | | |
| **Hypertension** | | | |
| No | 167 (44.4) | | |
| Yes | 209 (55.6) | | |
| **Diabetes** | | | |
| No | 230 (61.2) | | |
| Yes | 146 (38.8) | | |

Continued.

| Variables | N (%) | Mean (SD) | Median (IQR) |
|---|---|---|---|
| **Family history** | | | |
| No | 311 (82.7) | | |
| Yes | 6 1 (16.2) | | |
| **HRT** | | | |
| No | 358 (95.2) | | |
| Yes | 7 (1.9) | | |
| **PCOS** | | | |
| No | 374 (99.5) | | |
| Yes | 2 (0.5) | | |
| **Tamoxifen** | | | |
| No | 361 (96.0) | | |
| Yes | 11 (2.9) | | |
| **Smoking** | | | |
| No | 366 (97.3) | | |
| Yes | 6 (1.6) | | |
| **Grade** | | | |
| 1 | 135 (35.9) | | |
| 2 | 169 (44.9) | | |
| 3 | 59 (15.7) | | |
| **Stage** | | | |
| 0 | 2 (0.5) | | |
| 1 | 178 (47.3) | | |
| 2 | 109 (29.0) | | |
| 3 | 31 (8.2) | | |
| 4 | 31 (8.2) | | |
| 5 | 9 (2.4) | | |
| **Radiation** | | | |
| No | 200 (53.2) | | |
| Yes | 170 (45.2) | | |
| **Status** | | | |
| Alive | 313 (83.2) | | |
| Dead | 19 (5.1) | | |
| Unknown | 39 (10.4) | | |

**Table 2: Factors associated with occurrence of type I and type II endometrial cancer.**

| Variables | Type I (n=343) | Type II (n=32) | P value |
|---|---|---|---|
| **Age (years)** | 57.56 (10.42) | 64.97 (6.59) | <0.001 |
| **BMI (Kg/m$^2$)** | 30.22 (9.62) | 27.89 (9.23) | 0.061 |
| **Parity** | 3 (4.0) | 4 (3.75) | 0.212 |
| **Age of menarche (years)** | 12 (13.0) | 12 (13.0) | 0.748 |
| **OCP use** | | | |
| No | 338 (99.7) | 31 (100) | 1.000* |
| Yes | 1 (0.3) | 1 (0) | |
| **Hypertension** | | | |
| No | 155 (45.2) | 12 (37.5) | 0.403 |
| Yes | 188 (54.8) | 20 (62.5) | |
| **Diabetes** | | | |
| No | 207 (60.3) | 22 (68.8) | 0.351 |
| Yes | 136 (39.7) | 10 (31.2) | |
| **Family history** | | | |
| No | 285 (83.8) | 20 (80.6) | 0.648 |
| Yes | 55 (16.2) | 6 (19.4) | |
| **HRT** | | | |
| No | 329 (98.8) | 28 (90.3) | 0.016 |
| Yes | 4 (1.2) | 3 (9.7) | |

Continued.

| Variables | Type I (n=343) | Type II (n=32) | P value |
|---|---|---|---|
| **PCOS** | | | |
| No | 341 (99.4) | 32 (100) | 1.000* |
| Yes | 2 (0.6) | 0 (0) | |
| **Tamoxifen** | | | |
| No | 330 (97.1) | 30 (96.8) | 1.000* |
| Yes | 10 (2.9) | 1 (3.2) | |
| **Smoking** | | | |
| No | 334(98.2) | 31 (100) | 1.000* |
| Yes | 6 (1.8) | 0 (0) | |

*Fishers test applied.

## DISCUSSION

Endometrial cancer is the most common gynecological malignancy worldwide. The death rates for EC have increased by more than 100% over the past 2 decades.[14,15] Endometrial adenocarcinoma is the most common type and accounts for more than 70% of the cases while papillary serous and clear cell carcinomas are less common and account for only 10% of EC.[4,16]

In our study the mean age of the patients presenting with type I EC was 57.56 (SD±10.42). It is consistent with the median age of 60 for type I patients found in a study conducted in United states at a tertiary care center.[2] The mean age for type II patients in our study was 64.97 (SD±6.59) which is also consistent with the mean age found in previous studies, for instance the mean age of 66.5 years found in a systemic review conducted in Australia.[17] The minute difference between the mean ages of this study and the previous studies is probably because of the difference in sample size of the studies.

The median BMI for type I EC patients was found to be 30.22 in this study and 27.89 for type II EC patients. We were not able to find any association between BMI and risk of endometrial cancer. Our results are consistent with a study conducted in Sweden which states that it found no correlation between obesity and increased endometrial cancer risk.[18] However the results of our study are in contradiction with the general observations worldwide which associate BMI as a risk factor for type I cancer.[8] This contradiction may have arisen because of very small sample size and very a smaller number of type II EC patients in our sample. This probably influenced the results.

Diabetes in this study was present in 136 (39.7) people with type I EC and in 10 (31.2) people with type II EC, with a p=0.351. It was found in this study that the incidence of diabetes is high among patients with type I endometrial cancer. Previous studies also support this, a meta-analysis conducted by Friberg in Sweden showed a relationship between diabetes and increased risk of endometrial cancer.[19] The analysis of this study showed that hypertension is quite prevalent in both EC groups. Type I EC group had 188 (54.8) patients with hypertension and type II group had 20 (62.5) patients with a p=0.403. The high incidence of the hypertension indicates it maybe a risk factor for EC and the previous studies conducted worldwide also support this, a meta-analysis by Aune in Norway indicates an increased risk of EC in hypertensive patients.[20] The insignificance of p value in this current study maybe due to a small sample size of the study.

Studies conducted previously found cigarette smoking to reduce the risk of endometrial cancer, especially in post-menopausal women, it has been reported in a meta-analysis by Bin Wang in China.[21] However, in this present study on 6 (1.8) patients reported a history of smoking in type I EC group and none were reported in type II EC group. This is most probably because of the negative social stigma associated with smoking in Pakistani society hence women in Pakistan refrain from disclosing their smoking history. As a result of this we were not able to record any finding that could associate smoking with reduced EC risk.

Family History of previous malignancies was reported by 55 (16.2) people in type I sub type and 6 (19.4) patients in type II EC group. Uterine and Colon cancer were the most reported malignancies in family history for both subtypes. The p=0.648. Studies show that a history of colon cancer or uterine cancer in first degree relatives increase the chances of endometrial cancer in the patient. A meta-analysis by Aung Ko Win associated Colon cancer in first degree relative to increased risk of EC in patients.[22] Similarly, Linda Cook associated uterine cancer with increased risk if EC.[23] Our study does show an increased incidence of EC in patients with family history of colon and uterine cancer however the p value was found to be insignificant which again maybe due to sample size restriction and can be improved by increasing the study population.

HRT has been associated with increased risk of EC in previous studies. Rieck in 2009 showed that the use of Tamoxifen increases the risk of EC.[24] It was also proven by a study that use of tamoxifen for breast cancer can increase the risk of EC in future for the same patient.[25] Similarly, a metanalysis showed that long-term use of estrogen increases the risk of EC and this risk remains for a long time even after discontinuing HRT.[26] In our current study 4 (1.2) patients in type I group reported HRT prior

to EC diagnosis and 3 (9.7) patients in type II group reported it. The p=0.016. Our results are consistent with the previous studies and conclude that patients on HRT had an 80% more chance of devolving EC than patients who were not on HRT previously.

PCOS was reported by only 2 (0.6) patients in type I EC patients while no patient in type II EC group reported a history of PCOS. In our study we were not able to prove any co relation of PCOS history with increased risk of endometrial cancer as very few patients reported it. The literature regarding this goes both ways, some studies report PCOS not to be a risk factor for EC while some report an association. Our results are in line with some previous studies as they also report no correlation between PCOS and EC. A meta-analysis by Patricia Ellis reviewed that PCOS has no relation with increased risk of EC.[27] Another study by Hardiman reported that although obesity, hyperinsulinemia and anovulation are all related to both PCOS and EC but the evidence any correlation between PCOS and EC is still inconclusive.[28] However on the other hand Haoula reported that women with history of PCOS are three times more likely to develop endometrial cancer as compared to women with no PCOS history.[29]

### *Limitations*

This study has a few limitations which include its style which was retrospective in nature hence data for a few variables could not be recorded as it was missing from files and patients had to excluded. Although the study was conducted in a well-established tertiary care Centre of the country, still the study population was not representative of the national population as Pakistan is an LMIC and a large percentage of the population here mostly go to public hospitals which are cheaper hence patients presenting to our study center were limited. Moreover, the population in both subgroups of the study had a large difference hence it was difficult to formulate an association for some variables.

## CONCLUSION

In summary our study demonstrates that both sub types of endometrial cancer have many risk factors that are similar to each other. Our study particularly exhibited an association between HRT and risk of endometrial cancer. Despite the difference between the population of both subgroups we were able to prove associations between risk factors and endometrial cancer. However, studies on a provincial and national level are needed which include public hospitals too and have a bigger sample size where both the groups have relatively comparable population, so better analysis can be done to numerically prove the associations of some risk factors with endometrial cancer for the Pakistani population. This will eventually help the clinicians in Pakistan to better counsel and give early intervention to patients with proven risk factors for endometrial cancer.

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