An Epidemiological Assessment of Endometrial Carcinoma Including Demographics and Histopathological Correlation, from a Tertiary Care Teaching Hospital in South India

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ABSTRACT

BACKGROUND

Endometrial cancer (EC) is also the second most common gynaecologic malignancy in developing countries, with an incidence of 5.9 per 100,000 women. Due to the multiple modifiable factors, a better understanding of the prognostic indicators can lead to early detection and treatment. The purpose of this study was to evaluate the frequency and the distribution of various risk factors, epidemiological factors, and histological patterns of patients diagnosed with endometrial carcinoma in a tertiary teaching hospital in south India and compare them with similar studies. The compiled findings of 60 consecutive cases that presented to our tertiary care teaching hospital in Kerala, south India, over one-and-a-half-year period were studied.

METHODS

This study was essentially an ex post facto retrospective study done on 60 patients for one and half years. Retrospective data collection and compilation were done with previously prepared structured questionnaires in patients with histologically proven endometrial carcinoma. All cases were subjected to hysterectomy with post-surgical histopathology correlation. A study of the risk factors, general epidemiological characteristics, endometrial biopsy findings, and post-surgical histopathology was done.

RESULTS

The mean age at presentation was 59.83 years. The mean age of menarche was 13.72 years, and menopause was 49.42 years. The majority of patients were married, multiparous, and presented with bleeding per vaginum (77 %). 61.7 % of the patients had a history of hypertension, 31.7 % had a history of hypothyroidism, and 43.3 % had a history of diabetes mellitus in the study population. The most common histopathological type by endometrial biopsy and histopathological correlation was endometrioid adenocarcinoma (88.3 %).

CONCLUSIONS

Postmenopausal age group, with early menarche and late menopause, high body mass index (BMI), thickened endometrium on ultrasound, and atrophic uterus were some of the features associated with endometrial carcinoma. The most common histological subtype was found to be endometrioid carcinoma

KEYWORDS

Endometrial Carcinoma, Risk Factors, Prognostic Indicators

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BACKGROUND

Endometrial cancer is the sixth most common malignancy among females in developed countries and the fourth most common cancer in women. However, it is the second most common gynaecologic malignancy in developing countries, with 5.9 per 100,000 women. In India, the incidence is 4.3 per 100,000 women. Every year about 7400 new cases are registered in the UK and 88 068 in the European Union.[1] Due to earlier diagnosis and treatment advances in the West, the overall mortality of endometrial cancer has decreased by 28 % over the last two decades.[2] With peak incidence between ages 55 and 65, more than 90 % of cases occur in women older than 50, with a median age of 63. The peak age at presentation for endometrial carcinoma was approximately sixty years.

Risk factors include long-lasting endogenous or exogenous hypoestrogenism (polycystic ovary, anovulation, nulliparity), hypertension, diabetes mellitus, and obesity (body mass index > 30 increases risk from three to four-fold). Recently tamoxifen, a chemotherapeutic and chemo preventive agent for women with breast cancer and those at risk for breast cancer, respectively, has also been found to be associated with an increased risk of developing endometrial cancer.[3,4] In addition, up to 5% of endometrial cancers are associated with Lynch syndrome type II (known as hereditary nonpolyposis colorectal carcinoma syndrome); those with this syndrome have a lifetime risk of developing endometrial cancers of 30 % – 60 %.

On the contrary, oral contraceptive pill use increased age at menarche, and high parity was associated with a decreased risk. There is growing evidence that the use of combined oral contraceptives decreases the risk of endometrial neoplasia, reducing its incidence in premenopausal and perimenopausal women.

Presenting as postmenopausal bleeding, the disease occurs most frequently in white women (90 %). Although endometrial carcinoma presents as postmenopausal bleeding (PMB), only 10 % of women with PMB will eventually have cancer. Another common symptom is vaginal discharge due to pyometra. Ninety percent of these women present with abnormal vaginal bleeding, and 75 % present with stage 1 disease.[5] Prognostic factors, which influence the treatment algorithm in endometrial carcinoma include grade of tumour, histological type, depth of myometrial invasion, cervical involvement, and lymphadenopathy.[6,7]

Histopathological examination of hysterectomy specimens revealed that 20% to 43 % of patients with atypical endometrial hyperplasia biopsy also harboured EC.[8,9] Atypical endometrial hyperplasia is considered as a precancerous state, with more than 25 % of patients progressing to endometrial carcinoma.[10-12]

The rate of unanticipated endometrial carcinoma during a hysterectomy to treat benign conditions is generally relatively low.[11] Some scoring systems have been developed for the prediction of endometrial carcinoma, like Angioli et al. "risk of endometrial malignancy (REM) score",[12] classifies patients with endometrial abnormalities into high or low risk groups using serum markers, ultrasound, and clinical features. The score encompassed parameters like patient's age, sonographic endometrial thickness (ET) measurement, and blood HE4 & CA125 levels.[12]

Routine mass screening of the population for endometrium is impractical and not cost-effective due to the low prevalence of the precursor disease. It is crucial to promptly evaluate individuals past their fourth decade of life if there is abnormal vaginal bleeding**.** 20 – 25 % of cases of endometrial carcinoma are diagnosed in premenopausal women. But only 1 – 5 % are found in women younger than 40 years of age.[12-15] Although EC is less common under the age of 35 years, it is not absent. Thus, in high-risk patients younger than 35 years, endometrial evaluation might be required.[16]

In peri and postmenopausal patients, endometrial carcinoma is the most common gynaecologic malignancy, and it is found that 85 – 95 % of women harbouring endometrial carcinoma present with postmenopausal bleeding.[17,18] The risk of endometrial carcinoma in a 50-year-old woman with postmenopausal bleeding is 9 %. It rises to 16 % for a woman in her sixties, 28 % for a woman in her seventies, and even up to 60 % for a woman in her eighties.[19] The majority of patients with postmenopausal bleeding have atrophic changes of the vagina or endometrium.[19]

Only the United States guidelines "recommend either the use of TVS or outpatient endometrial sampling as the first important step in diagnosing women with postmenopausal bleeding."[17] The policy was based on similar sensitivities and cost-effectiveness for detecting endometrial carcinoma for endometrial thickness ≥ 5 mm and endometrial biopsy sampling when 'sufficient' tissue was obtained.[15,17] In most recent guidelines, the first step is transvaginal ultrasound (TVS), based on the procedure's high sensitivity and non-invasive character.

The preoperative evaluation includes chest X-ray, clinical and gynaecological examination, a transvaginal ultrasound, blood counts, liver, and renal function profiles. Computed tomography (CT) scan for investigating the presence of extrapelvic disease is not routinely recommended. Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best non-invasive tool to stage the disease.

The study's objective is to study the frequency and the distribution of the various risk factors, epidemiological factors, and histological patterns of patients diagnosed with endometrial carcinoma in a tertiary teaching hospital in south India and compare them with similar studies.

METHODS

An ex-post-facto cross-sectional research design was adopted for the study that was essentially a descriptive investigation which was done on a sample of 60 patients with consecutive cases of uterine bleeding diagnosed with endometrial carcinoma over one and half years from June 2018 to December 2019 at Department of Obstetrics and Gynaecology, Sree Avittom Thirunal Hospital, Government Medical College, Thiruvananthapuram. Retrospective data collection and compilation were done with previously

prepared structured questionnaires in patients presenting to the gynaecological department with histologically proven endometrial carcinoma. The cases were subjected to hysterectomy with post-surgical histopathology correlation. Various parameters were assessed, including demographics, clinical findings, and histopathological correlation

Inclusion Criteria

1. Patients with histologically proven endometrial carcinoma by endometrial biopsy (fractional curettage/dilatation and curettage).
2. Patients having post-surgical histopathology report.

Exclusion Criteria

1. Those who refused surgery or/and have a medical contraindication for surgery.
2. Those patients where surgery is not the primary modality of treatment including cases of advanced endometrial carcinoma.

Data Collection Tool

Semi-structured data collection proforma.

Method of Study

After taking informed consent, the patient's name, age, and details were recorded on a proforma. We retrospectively studied the risk factors and other general epidemiological characteristics of patients who presented with biopsy proven endometrial carcinoma, including age, parity, menarche, menopause, BMI, marital status, endometrial thickness in ultrasound, presenting complaints, use of hormone replacement therapy (HRT)/tamoxifen, family history of hypertension, diabetes mellitus, presence of hypothyroidism, poly cystic ovarian syndrome (PCOS), fibroids pap smear findings and endometrial biopsy findings. Stage 1 and stage 2 patients were subjected to hysterectomy. They were followed for histopathological correlation of the type and revised 2009 FIGO grading.

Ethical Consideration

1. Informed written consent was obtained from the participants.
2. Data collection and compilation was done on the semi-structured data collection proforma
3. Confidentiality was maintained throughout the study period.
4. Expenses: Participants did not bear any additional expenses as part of this study.

Analysis of Data

Data was analysed after entry into Microsoft Excel sheet. Qualitative variables were analysed as proportions, whereas analysis was performed using simple mean and standard deviation for quantitative variables. In both cases, analysis was done using statistical package for social science (SPSS) version 16.

RESULTS

Age	
Mean	59.83
Median	59.00
Mode	58
Standard deviation	8.846
Range	41
Minimum	39
Maximum	80

Table 1. Age-Wise Distribution

The mean age is 59.83 years with a standard deviation of 8.846. The age ranged from 39 - 80 years. The median age was 59 years, and the mode was 58 years.

Menopause	
Mean	49.42
Median	50.00
Mode	50[a]
Standard deviation	5.153
Range	63
a. Multiple modes exist. The smallest value is shown	

Table 2. Distribution According to Menopause

Distribution according to the age of menopause - In the study population, the mean age of menopause is 49.42 years, with a standard deviation of 5.153. The median age for menopause is 50 years, and mode is 50 years. Tables 1 to 3 shows the distribution.

BMI	
Mean	24.63
Median	25.00
Mode	24[a]
Standard deviation	3.268
Range	21
a. Multiple modes exist. The smallest value is shown	

Table 3. Distribution According to Body Mass Index (BMI)

In the study population, the mean body mass index was 24.63 years with a standard deviation of 3.26. The median for BMI was 25 and mode 24.

Tables 1 to 3 show the distribution. Not the number of patients. Tables 4 to 7 show the percentage or the number of patients in a particular group**.** So total number of patients will be reflected in these table.

Complaints	Frequency	Percent
Bleeding PV	46	76.7
Discharge PV	11	18.3
Asymptomatic	1	1.7
Pain abdomen	2	3.3
Total	60	100.0

Table 4. Distribution According to Presenting Complaints

In the study population, majority of patients (76.7 %) had bleeding per vaginum as the presenting complaint, followed by discharge per vaginum in 18.3 % of women, asymptomatic in 1.7 % and pain abdomen in 3.3 %

Pap Smear	Frequency	Percent
NILM	31	51.7
Atypical cells	11	18.3
Inflammatory cells	18	30.0
Total	**60**	**100.0**

Table 5. Distribution of Pap Smear

Maximum patients (51.7 %) were negative for intraepithelial lesion or malignancy (NILM). Inflammatory cells were found in 30 % of the cases, and the remaining 18.3 % of patients had atypical cells in the PAP smears

Endometrial Biopsy	Frequency	Percent
Endometrioid adenocarcinoma	46	76.7
Clear cell carcinoma	7	11.7
Papillary variant	5	8.3
Villoglandular type	1	1.7
Spindle cell variant	1	1.7
Total	**60**	**100.0**

Table 6. Distribution According to Endometrial Biopsy Findings

The majority of the patients in the study population had endometrioid adenocarcinoma (76.7 %) on endometrial biopsy. 11.7 % had clear cell carcinoma while 8.3 % of patients had papillary variant. 1.7 % of patients had villoglandular type and spindle cell variant

Histological Type	Frequency	Percent
Endometrioid adenocarcinoma	53	88.3
Papillary variant	2	3.3
Clear cell carcinoma	1	1.7
Serous intraepithelial carcinoma	2	3.3
Villoglandular type	1	1.7
Spindle cell variant	1	1.7
Total	**60**	**100.0**

Table 7. Distribution of Histological Type

Distribution of histological type - 86.3 % was endometroid adenocarcinoma, 3.3 % were papillary variant, 1.7 % were clear cell carcinoma, 3.3 % were serous intraepithelial carcinoma, villoglandular and spindle cell variant were 1.7 %

DISCUSSION

In our study, the mean age at presentation was 59.83 years. The age of the patients in our study ranged from 39 - 80 years with a standard deviation of 8.846. The maximum number of patients was 58 years. The minimum age was 39 years and the maximum age was 80 years. In a similar Indian study conducted by Srivastava et al. 22 patients (61 %) were between the age group of 41 and 60 years at the time of diagnosis, followed by 10 patients (28 %) whose age was more than 60 years. The mean age at presentation in their study was 52.77 ± 9.8 years.[20] In another study by Yoney et al. the median age of the patients was 53, ranging between 31 and 77. There were 58 patients (23.6 %) under the age of 60 and 188 patients (76.4 %) over the age of 60.[21] In both these studies, the mean age at presentation was lower than in our study. In another study by Anderson et al. the mean age at presentation was 63, higher than our study.[22]

The mean age of menarche was 13.72 with a standard deviation of 1. 175. The maximum number of patients had menarche at the age of 14, the maximum age was 16 years, and the minimum age was 10 years. Factors that decrease the risk for endometrial cancer include late age at menarche. In a study by Brinton et al. they have found a statistically significant relationship between early age at menarche (< 12 years) and endometrial carcinoma.[23]

The mean age of menopause was 49.42 years with a standard deviation of 5.153 years. The maximum age was 63 years and the minimum age was 40 years. In a retrospective study by Srivastava et al. majority of patients (72 %) attained menopause at the time of presentation, and (28 %) presented at a perimenopausal state with some menstrual irregularity.[20]

The present study's mean body mass index was 24.63 with a standard deviation of 3. 268. The maximum number of patients had a BMI of 24, and the range is 21. High body mass index is a high-risk factor for type I endometrial carcinoma and has been linked to elevated oestrogen levels, particularly in postmenopausal women, where adipose tissue is the leading site of oestrogen production from androgen precursors. In a study by Weiderpass et al. overweight women (recent BMI 28 – 29.99) had a 50 % increase in risk for endometrial cancer. Obese women (current BMI 30 – 33.99) had a 3-fold increased risk, and markedly obese women (recent BMI ≥ 34) had a 6-fold increased risk.[24]

Among the study participants, the mean endometrial thickness in ultrasound was 14.3 mm with a standard deviation of 5.4 mm.

The majority of the patients (98 %) were married in our study, and the majority of patients were multiparous (95 %). Factors that decrease the risk for endometrial cancer include early age at first birth and last pregnancy at a later age, more children and a more extended breastfeeding period. In a study by Henderson et al. increasing parity was strongly associated with decreased risk of endometrial carcinoma relative risk of 0.12 for parity 3 compared to nulliparous women.[25] In a study by Lambe et al. nulliparous women were at a higher risk of endometrial cancer with an odds ratio of 1.38.[26]

The majority of patients presented with bleeding per vaginum (77 %) followed by discharge per vaginum (18 %), 2% were asymptomatic, and the remaining 3 % presented with pain abdomen. Similar findings were also obtained in another Indian study by Srivastava et al. where 72 % of patients presented with postmenopausal bleeding per vaginum.[20]

In the study by Zandrino et al. the presenting symptoms were abnormal postmenopausal bleeding in 80 % of patients, mucinous vaginal discharge in 10 % of patients, and intermenstrual dysfunctional bleeding in 10 % of patients.[27] Most patients (96.7 %) had no history of any HRT/Tamoxifen usage in the study population. According to million women study published in Lancet, oestrogens and tibolone have a statistically significant risk of endometrial cancer. In a population-based study by Chen et al. the incidence of endometrial cancer was 0.388 % in patients with tamoxifen treatment.

95 % of patients in our study had no family history of endometrial carcinoma and colon cancer. A first- or second-degree family history of uterine cancer was modestly associated with a statistically significant risk for endometrial carcinoma in a study by Cook et al.[28] In a study by Meyer et al. the cumulative lifetime risk of endometrial cancer for women with Lynch syndrome is 40 % to 60 %, which equals or exceeds their risk of colorectal cancer.[29]

61.7 % of the patients had a history of hypertension, 31.7 % had hypothyroidism, and 43.3 % had a history of diabetes mellitus in the study population. Weiderpass et al.

found that hypertension increases the risk of endometrial cancer among obese women.[24] In a survey by Brinton et al. uterine cancers were related to previous thyroid diseases with a significant risk.[23]

In a population-based prospective cohort study by Emilie et al. women with diabetes and high BMI had a > 6-fold increased risk of endometrial cancer. A meta-analysis by Friberg et al. found that diabetes had statistically significant association with increased risk of endometrial cancer with a relative risk of 2.1.[30]

33.3 % of the patients had a history of fibroids in the uterus in our study. In a survey by Wise in black women, uterine leiomyoma history was associated with a 42 % greater incidence of endometrial cancer.[31] Among the study subjects, 20 % of the patients had a history of polycystic ovarian syndrome.

Polycystic ovarian syndrome, a condition characterized by ovarian hyperandrogenism, chronic anovulation, and progesterone deficiency, has also been associated with an increased risk for ovarian and endometrial cancer.

Balen et al. found that in women with chronic anovulation, the excess risk of endometrial cancer was identified to be 3.

In a study by Dumesic et al. women with PCOS have a 2.7-fold increased risk of developing endometrial cancer.[32]

In the study population, on examination, most of the patients (56.7 %) had atrophic uterus. 23.3 % of the patients had a bulky uterus, and the uterus was normal-sized in the remaining patients.

When PAP smear was done, the maximum number of patients (51.7 %) showed negative for intraepithelial lesion and malignancy (NILM). Inflammatory cells were found in 30 % of the cases, and the remaining 18.3 % of patients had atypical cells in the PAP smears.

In our study, the most common histological type in endometrial biopsy with 46 out of 60 patients (76.7 %) having endometrioid adenocarcinoma. 7 out of 60 patients (11.7 %) had clear cell carcinoma while five patients (8.3 %) had papillary variant.

One patient each (1.7 %) had villoglandular type and spindle cell variant. Post-surgical histopathology report showed endometrioid adenocarcinoma in 53 patients (88.3 %), papillary variant in two patients (3.3 %), clear cell carcinoma in one case (1.7 %), serous intraepithelial carcinoma in two patients (3.3 %), villoglandular type in one case (1.7 %) and spindle cell variant in one case (1.7 %). It was also noted that 36 out of 60 patients (60 %) had grade 1 disease, while 19 out of 60 (31.7 %) patients had grade 2 and 5 out of 60 (8.3 %) had grade 3 disease.

In the Indian study by Srivastava et al. the most common histopathology of endometrial carcinoma was endometrioid adenocarcinoma (20 patients, 75 %), 48 % were grade I, 37 % was grade II, and 14.8 % were grade III.

It was followed by papillary adenocarcinoma, i.e. 22 %, and adenosquamous carcinoma (3 %).[20] A study by Yoney et al. also stated that most of the cases had endometrioid adenocarcinoma histology (227 patients, 92.3 %), out of which 51 (61.4 %) subjects had grade 1 disease.[21]

CONCLUSIONS

Postmenopausal age group, with early menarche and late menopause, high BMI, thickened endometrium on ultrasound, and atrophic uterus were some of the features associated with endometrial carcinoma. The most common histological subtype was found to be endometrioid carcinoma.

Limitations of the Study

Our study has taken only the early stages of endometrial carcinoma i.e., stage 1 and stage 2, followed by hysterectomy for histopathological correlation. Advanced stages where surgery was not the treatment of choice were not studied.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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