Original article

Role of Reproductive Factors on the Risk of Endometrial Cancer in Nineveh Province, Iraq: A Case-Control Study

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ABSTRACT

Background: Endometrial cancer (EC) is the sixth most common cancer worldwide. This study aimed to evaluate the associations between reproductive risk factors and EC in Nineveh Province, north Iraq, due to limited research.

Methods: The study was conducted from September 2024 to the end of the year, using a case-control design. It included 100 cases of histologically diagnosed EC from 2022 to 2024 and 200 age-matched controls admitted to hospitals in the same catchment area for non-neoplastic and non-gynecological conditions. Informed consent was obtained before the interviews. The association between risk factors and EC development was measured using odds ratios (OR) and 95% confidence intervals (CI), with P-values ≤ 0.05 considered statistically significant.

Results: The study found that nulliparous women were present in 12/94 (12.77%) cases and 10/194 (5.15%) controls, with a risk nearly three times significantly higher than that of parous women (OR, 2.69; 95% CI, 1.12–6.48, P = 0.032). The mean number of children in cases (5.16 ± 2.45) was significantly lower (P = 0.001) than that in controls (6.51 ± 2.66), and the mean age at first birth was significantly higher in cases (23.13 ± 5.50, P = 0.001). However, there was no significant difference in the age at menarche and menopause between the cases and controls.

Conclusion: Parity and first-age delivery differed significantly among study participants. However, the age of menarche and menopause is not associated with increased EC risk.

Keywords:

Endometrial cancer, Reproductive factors, Parity, Age at first birth, Age at menarche, Age at menopause.

INTRODUCTION

Endometrial cancer, is a type of cancer that affects the endometrium, which is the lining of the uterus. Cancer of the endometrium is a common gynecological cancer affecting women worldwide,[1] particularly those experiencing menopause, and it is the sixth most common malignancy in women.[2,3] The number of EC cases, percentage, and crude incidence rate among Iraqi women by primary site and gender in 2023 were 1302, 5.2%, and 6.07/100,000, respectively.[4]

The endometrium's structure varies in response to the menstrual cycle, and unopposed estrogen exposure increases this risk.[5] Individual differences in unopposed estrogen exposure may be linked to reproductive characteristics like parity, age at menarche, menopause, and delivery age.

Numerous studies have found that early menarche and late menopause[5,9] are risk factors for EC. Women with a menarche age of 17 years or older had a 45% [95% CI 0.36–0.83] reduced risk compared to those aged 12 years or younger. A link existed between lifetime menstrual years and EC risk, with a 1.9% increase for each additional year. Additionally, individuals with menstrual periods lasting until age 55 or beyond have a 5-fold higher risk of EC [95% CI = 2.48–10.69] compared to those who went through menopause before the age of 45.[9]

Endometrial carcinoma is increasingly prevalent in nulliparous women.[2,10,11] Childlessness is associated with an increased risk of type I and type II EC.[10] Hormonal changes during pregnancy may have immunological advantages and influence the incidence of EC,[12] reducing the risk of the disease by 10.9% for each additional child.[13]

The risk of developing EC decreases with increasing age at the time of her first live birth.[14,15] A study by Sugawara et al.,[16] found that a woman's risk of developing EC decreased with age at the time of her first live birth. Multivariate hazard ratios were 0.79 for women aged 23-25 at first birth and 0.53 for those aged 26 and above, respectively, compared to those aged 22 years or less at first delivery. However, some studies suggest older age at

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first childbirth increases the risk of EC,[17] while others find no association between the maternal age at first birth.[18]

The present study aimed to identify the reproductive risk factors associated with EC in Nineveh Province over the past three years, as no previous research has been conducted in this area.

SUBJECTS AND METHODS

Study Design: The methodology employed in the current study was a retrospective case-control design to achieve the objectives delineated in this research. To explore the potential association between exposure to a specific reproductive risk factor and the occurrence of EC, a group of women diagnosed with EC (cases) was compared to a group of women without such a diagnosis (controls). The ratios of cases and controls exposed to specific risk variables to those who were not exposed were then carefully analyzed.

Study setting: The current study was conducted from September 2024 to the end of that year at the Oncology and Nuclear Medicine Hospital, its departments (Ibn-Sinna Teaching Hospital and Medical Research and Care Center), and Al-Salam Teaching Hospital in Nineveh Province, northern Iraq.

Recruitment criteria: The cases included adult women diagnosed histologically with EC irrespective of clinical staging or metastasis, who attended the Oncology and Nuclear Medicine Hospital and its departments from 2022 to 2024. The controls included adult women visiting hospitals in the same catchment area for non-neoplastic and non-gynecological issues. These women do not exhibit suspicious symptoms, such as irregular vaginal bleeding, discharge, or pelvic pain, and have no prior malignancies anywhere in the body. Patients with secondary EC were excluded. Furthermore, women with suspected EC symptoms and a personal history of any other malignancy were excluded from the control group. Overall, those who did not agree to participate were excluded from the study.

Data collection: The cases were identified and selected from the medical records of the Oncology and Nuclear Medicine Hospital and its departments. The information gathered from medical records included age, height and weight, phone number, and year of diagnosis. They were then contacted via phone, and informed consent was obtained. Those who provided consent were interviewed over the phone to answer other required questions of the predefined structured questionnaire. Responses to the questionnaire were used to collect data regarding controls during direct interviews with them.

Demographic parameters (such as age, educational level, occupation, ethnicity, marital status, body mass index (BMI), and smoking status) and reproductive history (such as age at menarche and menopause, parity, and age at first childbirth) were included in the questionnaire and considered as independent variables. BMI was determined using the formula: [weight (kg) / height (m)]^2. The questionnaire was translated from English to Arabic to make data collection easier.

Sampling technique and sample size determination: In the current study, cases and controls were individually matched based on age (± 5 years) and were selected using convenience sampling. The formula for unmatched case-control studies was used to estimate the sample size, providing a conservative approximation, as there was no prior information on the percentage of discordant pairs (i.e., pairs where the exposure status differed between the matched case and control):

$n = ((Z_{1-\alpha/2} + Z_{1-\beta})^2.(P_0 (1 - P_0)+P_1 (1 - P_1)/(P_1 - P_0)^2)$

$Z_{1-\alpha/2}$ = 1.96: standard normal deviate for 95% confidence level,

$Z_{1-\beta}$ = 0.84: standard normal deviate for 80% power,

P_1: The estimated proportion of exposure among the cases (based on previous studies)

P_0: The estimated proportion of exposure among the controls (based on previous studies)

$n = ((1.96 + 0.84)^2.(0.20(1 - 0.20) + 0.20)+0.38(1 - 0.38)/(0.38 - 0.20)^2)$

$n = \sim 96$

The predicted minimum sample size was 192 (96 cases and 96 controls). To increase statistical power and account for probable data loss, researchers used a 1:2 matching ratio, resulting in a final sample size of 100 cases and 200 age-matched control subjects.

Statistical Analysis: Data coding, tabulation, and analysis were performed using Microsoft Excel 2013, Med-Calc, and SPSS statistical software. Descriptive statistics included mean ± standard deviation (SD) for measurable variables and frequencies and percentages for categorical variables.

An independent t-test of the two means was used to compare the quantitative parameters. Chi-square test was used to compare categorical variables. OR and 95% CI were used to measure the association between the risk factors and the development of EC. P-values ≤ 0.05 were considered statistically significant throughout the data analysis.

Ethical Considerations: The Scientific and Ethical Research Committee/Nineveh Health Directorate approved this study on September 16, 2024 (Research ID: 2024144). The study procedures followed the ethical criteria outlined in the Declaration of Helsinki.

Table 1: Distribution of study subjects according to socio-demographic variables.

Parameters	Cases, No. (%)	Controls No. (%)
Age (years) [Mean ± SD]	59.00 ± 11.00	58.86 ± 10.68
BMI (Kg/m²) [Mean ± SD]	33.39 ± 7.13	30.56 ± 6.67
Occupation		
Housewife	86 (86.0)	191 (95.5)
Currently employee	3 (3.0)	5 (2.5)
Previously employee	11 (11.0)	4 (2.0)
Education		
Illiterate	33 (33.0)	106 (53.0)
Primary schools	38 (38.0)	67 (33.50)
Secondary schools	25 (25.0)	24 (12.0)
University+	4 (4.0)	3 (1.5)
Ethnicity		
Arab	82 (82.0)	174 (87.0)
Kurd	3 (3.0)	10 (5.0)
Turkmen	7 (7.0)	9 (4.5)
Shabak	8 (8.0)	7 (3.5)
Marital status		
Married	54 (54.0)	117 (58.5)
Single	6 (6.0)	6 (3.00)
Widow	35 (35.0)	72 (36.0)
Divorced	5 (5.0)	5 (2.5)
Active smoking		
Current	2 (2.0)	13 (6.5)
Former	8 (8.0)	18 (9.0)
Non-smoker	90 (90.0)	169 (84.5)
Passive smoking		
Yes	64 (64.0)	128 (64.0)
No	36 (36.0)	72 (36.0)

RESULTS

Table 1 illustrates the study sample's socio-demographic characteristics. There were no age differences between the cases and controls, reflecting successful age-individual matching. The mean BMI was (33.39 ± 7.13) for cases and (30.56 ± 6.67) for controls. Regarding women's education, 71 (71%) cases and 173 (86.5%) controls were illiterate or had only primary school education, whereas 29 (29%) cases and 27 (13.5%) controls had secondary and higher education, respectively.

Housewives represented 86% (86/100) of cases and 95.5% (191/200) of controls, whereas currently and previously employees constituted 14% (14/100) of cases and 4.5% (9/200) of controls, respectively. Regarding marital status, 54 (54%) cases and 117 (58.5%) controls were married, six (6%) cases and six (3%) controls were single, and 40 (40%) cases and 77 (38.5%) controls were widowed or divorced at the time of the interview.

Arabs represented 82% (82/100) of the cases and 87% (174/200) of the controls, whereas 18% (18/100) of the cases and 13% (26/200) of the controls were from other ethnic groups. Ninety percent (90/100) of the patients were non-smokers compared to 84.5% (169/200) of the controls. The passive smoking percentage was equal in both groups. Table 2 shows the relationship between reproductive factors and risk of EC in the study groups. The ages at menarche and menopause were similar between the patients and their relatives. Women experiencing menarche at younger ages (<12 years) had a slightly statistically insignificant higher risk compared to those who had menarche between 12-15 years of age (OR, 1.19; CI, 0.50–2.84). Menarche after 15 years of age was associated with a reduced risk of EC (OR, 0.66; CI, 0.21–2.12). The risk was approximately 1.5 times higher among women who had menopause at late ages (≥55 years) than among women who had menopause at less than 55 years, with statistically insignificant differences among the study sample. Nulliparous women were present in 12/94 (12.77%) cases and 10/194 (5.15%) controls, with a risk nearly three times significantly higher than that of parous women (OR, 2.69; 95% CI, 1.12–6.48). Compared to 25.26% (49/194) of the controls, 37.23% (35/94) of the cases in the study group had fewer than five live births. There were statistically significant differences in the number of children between women with EC and the controls (p = 0.001). Compared to mothers with five or more children, women with a history of nulliparity and parity of fewer than five children had an EC risk that was approximately three and two times greater (OR, 3.45; 95% CI, 1.40–8.50; OR, 2.05; 95% CI,

Table 2: The relationship between reproductive factors and endometrial cancer in the study sampled groups.

Reproductive factors	Cases No. (%)	Controls No. (%)	OR	95% CI	p-value
Age of menarche in years					
12<	9 (9.0)	15 (7.5)	1.19	0.50 ; 2.84	0.660
≥16	4 (4.0)	12 (6.0)	0.66	0.21 ; 2.12	0.592
12-15[a]	87 (87.0)	173 (86.5)	1.00		
Total	100 (100)	200 (100.0)			
Mean ± SD	12.89 ± 1.39	12.84 ± 1.29			0.740
Age of menopause in years					
≥55	12 (18.46)	21 (13.29)	1.48	0.68 ; 3.21	0.323
55<	53 (81.54)	137 (86.71)			
Total	65[c] (100)	158[c] (100)			
Mean ± SD	49.63 ± 5.03	49.42 ± 4.65			0.776
Parity					
Nulliparous	12 (12.77)	10 (5.15)	2.69	1.12 ; 6.48	0.032[b]
Parous	82 (87.23)	184 (94.85)			
No. of live births					
0	12 (12.77)	10 (5.15)	3.45	1.40 ; 8.50	0.005[b]
1-4	35 (37.23)	49 (25.26)	2.05	`1.19 ; 3.54	0.009[b]
≥5[a]	47 (50.0)	135 (69.59)	1.00		
Total	94[d] (100)	194[d] (100)			
Mean ± SD	5.16 ± 2.45	6.51 ± 2.66			0.001[b]
Age at 1st birth in years					
≥30	10 (12.1)	13 (7.07)	1.83	0.77 ; 4.36	0.169
30<	72 (87.8)	171 (92.93)			
Total	82[e] (100)	184[e] (100)			
Mean ± SD	23.13 ± 5.60	20.53 ± 5.16			0.001[b]

a) Reference group, **b)** Statistically significant, **c)** Premenopausal participants were excluded, **d)** Single participants were excluded, **e)** Single and nulliparous participants were excluded.

1.19–3.54), respectively. The patients' mean age at first birth was significantly higher (23.13 ± 5.60) than that of the controls (20.53 ± 5.16) (p= 0.001). Nonetheless, there was an insignificant difference among the sampled group for the precise age of thirty, above and below.

DISCUSSION

Nulliparity, parity of fewer than five children, and age at first delivery were statistically different between the cases and controls in this study. These findings are consistent with some prior studies that compared parous and nulliparous women and discovered that parous women had a lower risk of EC. A systematic review of high-quality articles published from 2000 to April 2024 by Salehiniya et al.,[2] found that nulliparity increased the risk of EC globally. Similarly, in a pooled cohort analysis of 13 prospective cohort studies conducted between 1963 and 2014 in the Asia Cohort Consortium, Katagiri et al.,[5] discovered that Asian women who had more deliveries were significantly less likely to develop EC. Conversely, in a study by Cho et al.,[19], having multiple births increased the risk of EC. Nonetheless, some studies have indicated no link between parity and the risk of EC.[20] Cultural diversity is considerable in various countries. In Iraq, traditional culture encourages newly married couples to start a family soon after marriage. Couples experiencing subfertility are urged to address infertility issues promptly. Consequently, they often undergo multiple infertility treatments, which may increase their exposure to medications and elevate the risk of EC.

Furthermore, the current study found evidence of a strong association between increasing age at first childbirth and EC risk. This finding aligns with some older studies[17,21] but contrasts with and contradicts the majority of reports indicating that increasing maternal age at first birth is either associated with a reduced risk of EC[14,15,22,23] or not associated with any risk at all.[5,24] Determining the impact of childbearing factors can be challenging due to their various overlapping influences. The extent to which these components have been modeled differs across studies.

Our study did not associate the age of menarche and menopause with the risk of EC. This is compatible with the Mexican case-control study by Salazar et al.[21]; however, several studies have reported considerable associations between the age of menarche and menopause with EC risk [2,5,8]. An Italian case-control study (454 cases and 908controls) by Zucchetto et al.,[25] found that the risk of EC increased with increasing years of menstruation. This disparity is hard to explain. The discrepancy may be due

to genetic factors interfering with menarche age or different categories of menarche age. Asian research has employed a different menarche age group, with the lowest and highest groups being 13 or younger and 17 or older, respectively.

In comparison, European and US studies used the lowest and highest age categories of 11 and 14 or 15 years, respectively.[23,26] Additionally, Misclassification may have occurred because we gathered reproductive factor data at baseline, particularly for variables such as menopausal state, which vary over time. Some studies have suggested that confounding factors may modify these relationships,[27] so further research is needed to understand these associations and consider time-varying data harmonization.

This study's uniqueness is one of its advantages since it is the only one in the Nineveh Province to evaluate the connection between reproductive factors and EC risk. Furthermore, to ensure high data accuracy, each participant was contacted and questioned independently to avoid depending solely on the information from the medical files, which may contain errors. In addition, the age matching and selection of patients and controls from similar locations led to similarities between the groups.

The retrospective nature of this study makes it challenging to evaluate the cause and effect. Another constraint is the control group's selection. Hospital controls are a source of conflict in epidemiological research. Even if the authors attempted to exclude patients with diseases associated with an increased risk of EC, the hospital setting may have introduced bias. Furthermore, although the data were gathered through direct interviews, recall bias may still exist. Additionally, the results might apply to people with traits similar to the study group, but they might not be as reliable when applied to women outside Nineveh Province. A future extensive, well-designed, multi-center cohort studies are required to address this issue.

CONCLUSION

Multiparity and younger age at first birth were significantly related to a decreased risk of EC in Nineveh Province. Our results indicate that the age of menarche and menopause did not relate to EC risk. Identifying risk variables that are highly associated with EC will help us identify females who are at the highest risk and could benefit from preventative and screening measures. This study underscores the need for further targeted research to address differences in cancer incidence and outcomes.

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Author Contribution

Zahraa Dheyauldin Abdulwahhab: Conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, proofreading, final approval.

Humam Ghanim Ibrahim: Conception and design, analysis and interpretation of data, critical revision for important intellectual content, final approval.

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