Is There a Relation Between Family History of Different Types of Cancers with the Development of Endometrial Cancer and Menopausal State?

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(Ann Coll Med Mosul 2025; 47 (2):194-199).
Received: 12th May 2025; Revised 16th May 2025; Accepted: 1st July 2025.

ABSTRACT

Objectives: To determine whether the family's history of colonic, uterine, breast, or other malignancies raises the risk of developing cancer of the endometrium in women in Nineveh Province, northern Iraq.

Subjects and Methods: A case-control study included 300 female participants: 100 with endometrial cancer and 200 age-matched controls. The researcher identified and selected cases from the medical records of the Oncology and Nuclear Medicine Hospital and its departments, then contacted them directly via phone. For the controls, the data were obtained during direct interviews with participants who were attending the local hospitals in Nineveh Province for non-neoplastic and non-gynecological conditions.

Results: The associations between familial history of colonic, uterine, or breast cancer in the first degree and the occurrence of cancer of the endometrium in the study sample groups revealed a risky association with a statistically significant difference (OR = 29.74, 95% CI = 3.83; 230.87, P< 0.001); (OR = 6.38, 95% CI = 2.71; 15.01, P < 0.001); (OR = 3.92, 95% CI = 1.83; 8.39, P = 0.002), respectively. However, no statistically significant difference exists between the occurrence of endometrial cancer and other forms of cancer. Furthermore, there is no statistically significant association between the family's history of cancer and menopausal status.

Conclusion: According to the study, a first-degree relative's family history of colonic, uterine, or breast cancer is significantly associated with an elevated risk of endometrial cancer. However, other malignancies and menopausal status have non-significant associations.

Keywords: Endometrial cancer; family history; risk factors.

هل هناك علاقة بين التاريخ العائلي لأنواع مختلفة من السرطانات وتطور سرطان بطانة الرحم وحالة انقطاع الطمث؟

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الخلاصة

الأهداف: تحديد ما إذا كانت التاريخ العائلي للإصابة بسرطان القولون، الرحم، الثدي أو غيرها من الأورام الخبيثة يزيد من خطر الإصابة بسرطان بطانة الرحم لدى النساء في محافظة نينوى، شمال العراق.

المشاركات والطرق: شملت دراسة الحالة والشاهد ٣٠٠ انثى مشاركة: ١٠٠ منهن مصابات بسرطان بطانة الرحم و٢٠٠ شاهدات متطابقات في العمر. حددت الباحثة الحالات واختارتها من السجلات الطبية لمستشفى الأورام والطب النووي وأقسامه، ثم اتصلت بهم مباشرة عبر الهاتف. بالنسبة لمجموعة الشواهد، تم الحصول على البيانات خلال المقابلات المباشرة مع المشاركين الذين كانوا يراجعون المستشفيات المحلية في محافظة نينوى لحالات غير ورمية وغير نسائية.

النتائج: كشفت الروابط بين التاريخ العائلي لسرطان القولون، الرحم أو الثدي من الدرجة الأولى وحدوث سرطان بطانة الرحم في المجموعات المدروسة عن ارتباط خطير مع فرق ذو دلالة إحصائية (OR = 29.74، 95% CI = 3.83؛ 230.87 ، P < 0.001) (OR = 6.38، 95% CI = 2.71؛ 15.01 ، P < 0.001) (OR= 3.92، 95% CI = 1.83؛ 8.39 ، P = 0.002) ، على التوالي. ومع ذلك، لا يوجد فرق ذو دلالة إحصائية بين حدوث سرطان بطانة الرحم وأشكال السرطان الأخرى. علاوة على ذلك، لا يوجد ارتباط ذو دلالة إحصائية بين تاريخ العائلة في الإصابة بالسرطان وحالة انقطاع الطمث.

الخاتمة: وفقًا للدراسة، فإن التاريخ العائلي لسرطان القولون أو الرحم أو الثدي لدى أحد الأقارب من الدرجة الأولى مرتبط بشكل كبير إحصائيًا بزيادة خطر الإصابة بسرطان بطانة الرحم. ومع ذلك، فإن الأورام الخبيثة الأخرى وحالة انقطاع الطمث لم تُظهر ارتباطًا ذا دلالة إحصائية.

الكلمات المفتاحية: سرطان بطانة الرحم، التاريخ العائلي، عوامل الخطر.

INTRODUCTION

Endometrial cancer (EC) is the sixth most prevalent cancer in women, primarily affecting menopausal women [1]. According to the American Cancer Society, EC accounts for approximately 3% of all cancers in women worldwide. The disease is often asymptomatic in its early stages, making it essential for women to be aware of the symptoms and risk factors associated with EC [2].

Some families are more likely to develop EC, and these families may also have an elevated risk of colon cancer. Hereditary non-polyposis colon cancer (HNPCC) or Lynch syndrome are the names given to this condition. A malfunction in the mismatch repair gene (MMR) [MutS Homolog 2 (MSH2) or MutL Homolog 1 (MLH1)] is frequently the etiology of this illness. However, MutL Homolog 3 (MLH3), MutS Homolog 6 (MSH6), Transforming Growth Factor Beta Receptor 2 (TGBR2), Postmeiotic Segregation Increased 1 (PMS1), and Postmeiotic Segregation Increased 2 (PMS2) are five other genes that might cause HNPCC. Any one of these genes can have an aberrant copy that impairs the body's capacity to repair damaged DNA or regulate cell division and increases the chance of EC as well as colon cancer. Endometrial cancer may occur in as many as 70% of women with this condition. Furthermore, there is an increased risk of developing ovarian cancer. Some families may have an underlying genetic condition that raises their risk of developing EC [3].

Mutations in the tumor suppressor genes phosphatase and tensin homolog cause a rare disorder known as Cowden syndrome, which predisposes to an increased lifetime risk for cancers of the breast, thyroid, kidney, endometrium, colon, and melanoma. Women with Cowden syndrome have a roughly five-fold increased risk of EC compared to the general population.

A study by Johnatty et al. [4] found that women who had at least one first-degree relative or one second-degree relative with EC had an odds ratio (OR) of 3.39 (95% confidence interval (CI) 2.08–5.53). This familial risk is particularly prominent in cases associated with hereditary syndromes such as Lynch syndrome and Cowden syndrome, which account for a notable percentage of EC cases [5,6].

This study examines the association between family history of different types of cancers, the development of EC, and the relation with menopausal status in Nineveh Province. Research on this relationship in Nineveh Province remains limited despite increasing cases.

SUBJECTS AND METHODS

Study Design

This research used a case-control study design to fulfill its aims. To study the potential relationship between exposure to a specific risk factor and the occurrence of EC, a group of women with EC (cases) was compared to those without the disease (controls).

Study Setting

The current study was conducted from September 2024 to April 2025 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.

Inclusion 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 total number of cases recorded during 2022-2024 in Nineveh Province was 165, 25 of whom died.

The controls included adult women visiting the consultation rooms, medical wards, and surgical wards of Nineveh Province's local hospitals 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.

The sample size was 300, with a 1:2 case-control ratio (100 cases and 200 controls). Cases and controls were individually matched based on age (± 5 years) and were selected using convenience sampling.

Exclusion Criteria

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 medical records at the Oncology and Nuclear Medicine Hospital and its departments. Then, they were contacted via phone and took their informed consent.A structured questionnaire was used to conduct phone interviews with those who provided permission to measure the independent variables.

The questionnaire responses are used to collect data on controls during direct interviews with women visiting teaching hospitals in Mosul City for various non-neoplastic and non-gynecological conditions.

The independent variables were age, education, age at menarche and menopause, parity, age at first childbirth, and family history of different cancers. The dependent variable was EC.

Statistical Analysis

Data coding, tabulation, and analysis were performed using Microsoft Excel 2013, MedCalc, and SPSS. Descriptive statistics use Mean ± Standard Deviation (SD) for measurable variables and frequencies and percentages for categorical variables.

All categorical variables were compared using the chi-square test, except colonic cancer, with a frequency of less than five in one cell. Consequently, Fisher's exact test was applied. The odds ratio and 95% confidence interval were applied to determine the association between risk factors and the development of EC. Throughout the data analysis, P-values ≤0.05 were used to evaluate statistical significance.

Ethical Consideration

This study was approved by the Scientific and Ethical Research Committee/Nineveh Health Directorate (Research ID: 2024144) on September 16, 2024. The procedures adhered to the ethical guidelines of the Declaration of Helsinki.

RESULTS

Table 1 shows the distribution of cases and controls based on age, education, reproductive, and menstrual history. Regarding education, there is no significant association among the study sample.

The cases and controls had no mean age differences, indicating successful age-individual matching. The average age at menarche and menopause was identical in cases and controls with non-significant association. Cases reported later ages at first birth and had more instances of nulliparity with significant association.

A first-degree family history of colonic, uterine, and breast cancer was related to a higher risk of EC, with statistically significant differences within the study sample (OR = 29.74, 95% CI = 3.83; 230.87, P < 0.001); (OR = 6.38, 95% CI = 2.71; 15.01, P < 0.001); (OR = 3.92, 95% 95% CI = 1.83; 8.39, P = 0.002), respectively. Nevertheless, there is no statistically significant variance between other cancers and the occurrence of EC, as shown in Table 2.

We investigated further the link between family histories of colonic, uterine, and breast cancers, as well as other cancers, and menopausal status among cases, as shown in Table 3.

Among the 100 patients in our study, 35 were premenopausal, and 65 were postmenopausal. No statistically significant association was found between the family history of cancer and menopausal status.

Table 1: Distribution of 100 endometrial cancer cases and 200 controls according to selected variables.

Variables		Cases		Controls		P-value [b]
		No.	%	No.	%	
Age	<40	2	2.00	7	3.50	0.677
	40-50	19	19.00	36	18.00	
	51-60	33	33.00	69	34.50	
	>60	46	46.00	88	44.00	
Mean ± SD		59.00 ± 11.00		58.86 ± 10.68		
Education	Illiterate	33	33.00	106	53.00	0.069 c
	Primary schools	38	38.00	67	33.50	0.421 c
	Secondary schools	25	25.00	24	12.00	1.000 c
	University+a	4	4.00	3	1.50	
Menarche	<12	9	9.00	15	7.50	0.740
	≥16	4	4.00	12	6.00	
	12-15	87	87.00	173	86.50	
Mean ± SD		12.89 ±1.39		12.84±1.29		
Menopause	≥55	12	18.46	21	13.29	0.325
	<55	53	81.54	137	86.71	
Mean ± SD		49.63±5.03		49.42±4.65		
Age at 1st child	≥30	10	12.10	13	7.07	0.001
	<30	72	87.80	171	92.93	
Mean ± SD		23.13±5.60		20.53±5.16		
Parity	Nulliparous	12	12.77	10	5.15	<0.001
	Parous	82	87.23	184	94.85	
Mean ± SD		5.16 ±2.45		6.51±2.66		

a) Reference group. b) Independent T-test of two means was used. c) Fisher exact test was used.

Table 2: The relationship between family history of colonic, uterine, breast and other cancers with occurrence of endometrial cancer in the study sample.

Family history of Cancer		Cases "EC"		Controls "No EC"		OR	95% CI	P-value d
		No.	%	No.	%			
Uterine Ca	Yes	21	21.00	8	4.00	6.38	2.71 ; 15.01	<0.001
	No	79	79.00	192	96.00			
Colonic Ca	Yes	13	13.00	1	0.50	29.74	3.83 ; 230.87	<0.001 c
	No	87	87.00	199	99.50			
Breast Ca	Yes	20	20.00	12	6.00	3.92	1.83 ; 8.39	0.002
	No	80	80.00	188	94.00			
Other Ca	Yes	18	18.00	31	15.50	1.20	0.63 ; 2.26	0.581
	No	82	82.00	169	84.50			
Total		100	100.00	200	100.00			

c) Fisher exact test was used. d) Chi-square test was used.

Table 3: The relationship between family history of cancers and menopausal status.

Family history of Cancer		Pre-menopausal women		Post-menopausal women		OR	95% CI	P-value d
		No.	%	No.	%			
Uterine Ca	Yes	9	25.71	12	18.46	1.53	0.57 ; 4.09	0.396
	No	26	74.29	53	81.54			
Colonic Ca	Yes	5	14.29	8	12.31	1.19	0.36 ; 3.95	0.779
	No	30	85.71	57	87.69			
Breast Ca	Yes	9	25.71	11	16.92	1.70	0.63 ; 4.61	0.295
	No	26	74.29	54	83.08			
Other Ca	Yes	7	20.00	11	16.92	1.23	0.43 ; 3.51	0.702
	No	28	80.00	54	83.08			
Total		35	100.00	65	100.00			

d) Chi-square test was used.

DISCUSSION

There is conflicting research on the relationship between family histories of cancer and the risk of developing EC. In this hospital-based case-control study, first-degree relatives with a history of breast, uterine, or colon cancer were significantly more likely to develop EC. These findings are in line with Win et al.'s [7] systematic review and meta-analysis, which found that women with a first-degree relative's history of colorectal or EC are more likely to develop endometrial malignancy than those without a family history. In the same way, Bharati et al. [8] found that women without a mutation in the MMR gene are more likely to develop EC if there is a family history of either EC (HR = 3.66, 95% CI: 2.63–5.08) or early-onset colorectal cancer (HR = 1.48, 95% CI: 1.15–1.91). Furthermore, a Swedish study reported that women with a family history of breast cancer had 1.8 standardized incidence ratios (SIRs) for subsequent EC [9].

On the other hand, Clarke et al. [10] found no significant connection between EC and family history in a prospective cohort analysis of 1205 women with a mean age of 55. Furthermore, Olson et al.[11] conducted a prospective cohort analysis of 24,848 postmenopausal women. They observed no connection between an elevated risk of EC and a family history of cancer, particularly endometrial, breast, and colon cancer. Moreover, Yousif et al. [12] conducted a retrospective analysis on 1737 patients with stage I EC, finding that 709 had a first-degree family history of cancer and 1028 had no family history of cancer. Although the differences were not statistically significant, patients with a positive family history were more likely to be older, have stage IB (≥50% invasion of the myometrium) illness, and undergo adjuvant radiation. Breast, colon, and endometrial cancers are the most prevalent among first-degree relatives.

Menopausal status and a family history of cancer were not significantly associated in the present research. Green et al.[13] found that premenopausal women had a higher incidence of familial colon cancer history than postmenopausal women (16% vs. 7%, P = 0.001); however, there was no significant association with other cancers.

The heterogeneity in study results on the link between family cancer history and EC risk is due to changes in study design, population characteristics, and data collection methods. Genetic diversity, statistical techniques, and environmental effects are all contributing factors.

The article also notes that the potential for recall bias is one of the main disadvantages. Those with EC may remember and display their family history of cancer more frequently than those without the condition.

There may be distortion in the results if cases overestimate their family history of cancer in comparison to controls. Furthermore, the study struggled to distinguish between cervical cancer and corpus uteri tumors, two separate types of uterine cancer. These tumors were gathered for research since many women couldn't tell what kind of cancer their first-degree relatives had, so the evidence about the risk of EC may become less specific as a result.

The study's retrospective nature makes it difficult to determine cause and effect. Another restriction is the control group's selection. Hospital controls are a topic of debate in epidemiological investigations. Even if the authors tried to eliminate those with conditions linked to the risk of EC, the hospital setting may still introduce biases. Several factors, including the genetic components associated with familial cancer, may have contributed to the hospitalization of the controls. Additionally, the findings might apply to individuals who share characteristics with the study group, but they might not be as trustworthy when applied to women from other regions of Nineveh Province. These areas require more research.

This study's uniqueness is one of its advantages since it is the only one in the Nineveh Province to evaluate the connection between familial history and EC risk. Furthermore, to ensure high data accuracy, each participant was contacted and questioned independently to avoid depending solely on information from medical files, which may contain errors. In addition, the patients and controls were chosen from the same community (Mosul City hospitals), adding to the two groups' similarities.

CONCLUSION

According to the study, a first-degree relative's familial history of colonic, uterine, and breast cancers was significantly associated with an increased risk of EC. Specifically, the odds were higher for women with a family history of breast cancer (OR = 3.92), uterine cancer (OR = 6.38), and colonic cancer (OR = 29.74) than for those without. The results also show that a family history of other cancers and menopausal status are associated with a statistically insignificant increased risk of EC.

The odds ratio for a family history of other cancers was 1.2, highlighting the importance of considering various cancer types in familial assessments. Such research fills knowledge gaps, opening the path for improved EC prevention, diagnosis, and therapy in people who have a familial history of cancer.

Acknowledgments

The authors are very grateful to all doctors and medical staff at the Nineveh Health Directorate for their kind help.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Research Highlights

- First-degree relative's family history of colon, uterine, or breast cancer significantly increases endometrial cancer risk.
- Other malignancies and menopausal status have insignificant increased risk.

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