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Medical And Family History And The Risk Of Endometrial Cancer

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MPH Thesis

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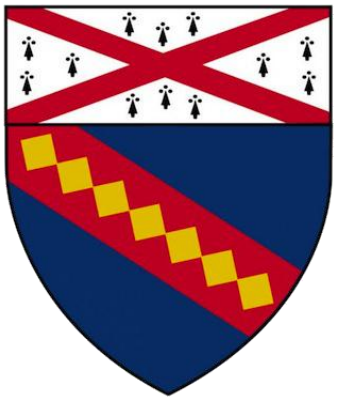
SECOND READER: Prof. Xiaomei Ma



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Abstract

BACKGROUND: Women with a medical history of pelvic inflammatory disease, endometriosis, polycystic ovary syndrome, diabetes, high blood pressure or other selected medical conditions, as well as a family history of cancer, are assumed to be at increased risk of endometrial cancer. This study was designed to test these assumptions, as evidence for them is lacking. METHODS: We carried out a population-based case-control study in Connecticut between 2004 and 2008, including 668 endometrial cancer cases and 674 controls from eligible residents matched with age. Medical histories and family history of cancers were reported and conditional logistic regression was used to estimate odds ratio (OR) and corresponding 95% confidence intervals (95% CI). RESULTS: After adjusting for various covariates, only the association between a history of high blood pressure and endometrial cancer risk remained significant (Adjusted OR = 1.71; 95% CI: 1.25-2.34). A family history of cancer in the uterus was directly associated with endometrial cancer risk (Adjusted OR=2.02; 95% CI: 1.06-3.86). CONCLUSIONS: A history of high blood pressure and a family history of uterus cancer among 1st degree relatives are both associated with an increased risk of endometrial cancer.

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Introduction

Endometrial cancer is the most common type of gynecological cancer in the United States (US). Endometrial cancer develops in the lining of the uterus, also called the endometrium. This project aims to investigate the potential role of medical history and family history of cancer in the etiology of endometrial cancer. We hypothesize that a medical history of pelvic inflammatory disease, endometriosis, polycystic ovary syndrome, diabetes or other selected medical conditions increases the risk of endometrial cancer, and a family history of cancer is associated with a higher endometrial cancer risk.

Background

Endometrial cancer occurs most often in women from the ages of 55 to 70 years old and is responsible for 6% of cancer cases in women. The National Cancer Institute estimates that in 2011, 46,470 American women were diagnosed with endometrial cancer and 8,120 died from the disease.[1] Prolonged exposure to excessive unopposed estrogens results in continued stimulation of the endometrium, which is considered a key mechanism in endometrial carcinogenesis.[2] Therefore, factors involving an increased exposure to estrogen over time may lead to a higher risk of endometrial cancer.

Various studies have shown that hormone replacement therapy (HRT) is associated with the occurrence of endometrial cancer.[3,4] Other conditions that have been suggested include obesity[5], diabetes mellitus[6,7], hypertension[8,9], and

metabolic syndrome[10]. More recently, women with uterine fibroids[11] and/or polysystic ovary syndrome[12] were also found to have a higher risk of developing endometrial cancer, while other gynecological conditions such as endometriosis and pelvic inflammatory disease did not appear to significantly affect the risk of endometrial cancer[11].

Genetic factors likely play a role in the etiology of endometrial cancer. A family history of endometrial cancer was identified as a risk factor for endometrial cancer, although a family history of breast or ovarian cancer had no impact.[13] Young women with mutation in the hereditary non-polyposis colorectal cancer (HNPCC) gene are predicted to have a life-long risk of 50% to develop endometrial cancer.[14]

To better understand the etiology of endometrial cancer, we conducted this research project to systematically evaluate the potential role of medical history and family history of cancer in a population-based case-control study in Connecticut.

Methodology

a. Study Participants

Connecticut residents newly diagnosed with primary endometrial cancer between October 2004 and September 2008 were recruited to a population-based case-control study. Over the study period, study staff from the Rapid Case Ascertainment (RCA) at the Yale Cancer Center visited 28 Connecticut hospitals on 1-4 week cycles to obtain medical records and diagnosis reports. Out of 1,663 potentially eligible patients diagnosed at ages 35–80 years, physician consent was sought for 1,270 patients and obtained from 1,242 (97.8%). Consent for the remaining 393 patients was not sought because of attainment of planned sample size. Of the doctor- consented patients, 1,216 were attempted to contact for study participation and 26 were not contacted due to completion of the study enrollment. Among the patients for whom contact was attempted, 317 (26.1%) refused to participate, 19 (1.6%) had died, 13 (1.1%) were too ill to participate, 44 (3.6%) were unable to be located, 68 (5.6%) were unable to be reached through available telephone numbers, 62 (5.1%) were found to be ineligible due to ineligible residence (n = 8), mental impairment (n = 7), facility resident (n = 10) or language barrier (n = 27), and 25 (2.1%) of potential participants had ineligible diagnoses based on review of their medical records. A total of 668 patients participated in the study, with a response rate of 59.2% (668 of 1,129) after excluding 87 ineligible patients.

Controls were matched to cases by age group (35–51, 52–59, 60–64, 65–69, 70–74 and 75–79 years) and identified through a pre-letter assisted random-digit

dialing (RDD) method. Each selected landline telephone number was first searched in reverse directories to find an address for the number, in order to mail a study letter prior to telephone contact. Potential control subjects were initially contacted by telephone for determination of study eligibility. Our RDD screen gathered 8,168 residence numbers, of which 1,995 appeared to have female residents whose ages were within the desired range of our study. Of these, 1,447 (72.5%) agreed to be further contacted for possible participation in the study. From the list of potential candidates, we sequentially contacted 1,248 subjects before the end of the study enrollment, and found 111 subjects ineligible for the study due to ineligible residence, mental impairment, language barrier, diagnosis of cancer and ineligible medical conditions, as well as 92 disqualified for the study due to illnesses, death, relocation and no response. Of the remaining subjects, 674 completed in-person interview and 371 refused to participate. The response rate among the controls was 64.5% (674 of 1,045 subjects).

b. Procedures

Upon the participation agreement, in-home appointments were scheduled for in-person interview and collection of biological specimens. Written informed consent was obtained at the appointment prior to the start of interview. A structured questionnaire was used for interview, collecting information on birth weight, place and date of birth, years of education, self-identified race and ethnicity, menstrual and reproductive features during each decade from 20s

through 40s, use of oral contraceptives and hormone replacement therapies, medical history of major chronic illnesses and gynecological disorders, family history of cancer, smoking and drinking habits, current and lifetime physical activities, current and lifetime body weight, including weight at age 20s, 30s, 40s, 50s, 60s and 5 years before the interview. Subject's height and other physical dimensions were also measured at the time of interview.

c. Statistical Analysis

Our specific variables of interest included medical histories of pelvic inflammatory disease, endometriosis, polycystic ovary syndrome (PCOS), ovarian cysts, diabetes, both diabetes and PCOS, wrist fracture/broken after 25 years old, hip fracture /broken after 25 years old, aspirin regular intake, high blood pressure, high cholesterol/triglycerides/blood lipids, insulin resistance/metabolic syndrome, coronary artery disease/heart attack, cirrhosis/hepatitis/other liver problems, kidney problem/dialysis, growth hormone replacement therapy, ulcerative colitis/bowel inflammation, mumps , cone or punch biopsy (conization) of cervix/ cryotherapy /freezing therapy of the cervix, and history of breast, uterus, ovary, colorectal, prostate or lung cancer among 1^{st} degree blood relatives (parents, siblings, and children). Questionnaire data were first cleaned, merged and examined using SAS for distributions, outliers and missing values. Univariate analyses were then performed using the t-tests for continuous variables and χ^2 tests for categorical variables. Descriptive statistics on each variable among the cases and controls were obtained, including means and standard deviations for

numerical variables and frequency distributions for categorical or ordinal variables. Bi-variate logistic regression models were employed to assess the association between each variable of interest and case/control status by estimating odds ratios (OR) and their 95% confidence intervals. Multivariate logistic regression analyses were then performed to adjust for various potential confounding variables, including age at interview, race (white or other), education (<12 years, 12 years to 3 years college, college/university, graduate school), smoking status (current, former, never), body mass index (BMI), age at menarche, menopausal status (yes/no), age at menopause, parity, estrogen use (ever/never), HRT (ever/never), oral contraceptive use (ever/never). These covariates were chosen based on existing literature and our subject knowledge about the possible risk factors of endometrial cancer. All tests were two-sided with an alpha value of 0.05. All analyses were conducted with SAS 9.3 (Cary, North Carolina).

Results

Table 1 shows the demographic and reproductive characteristics of the study population. Cases and controls were similar with regard to age at interview, mother's age at their birth, numbers of siblings, sisters and elder siblings, birth weight, height and birth place. Controls were more likely to be white ($p = 0.033$) and better educated ($p < 0.001$) - 34.2% and 25.6% of control subjects received college or higher education, respectively, compared to 28.3% and 18.9% of cases, respectively. Cases had a higher BMI ($p < 0.001$), higher rates of hypertension ($p < 0.001$), diabetes ($p < 0.001$), and a greater percentage of relatives with endometrial cancer ($p = 0.024$). In addition, cases were less likely to be smoker ($p = 0.0187$),menopausal hormones ($p = 0.006$), and they had fewer live births ($p < 0.001$) and have younger age at first pregnancy ($p < 0.001$) compared with controls.

Univariate analyses suggest that patients with PCOS (OR = 4.73; 95% CI: 1.35-16.54), diabetes (OR = 1.95; 95% CI: 1.44-2.64), high blood pressure (OR = 2.06; 95% CI: 1.65-2.56), high cholesterol/triglycerides and blood lipids (OR= 1.37; 95% CI: 1.10-1.71) have significantly higher risk of endometrial cancer (Table 2). However, after adjusting for various covariates, only high blood pressure remained a statistically significant risk factor (Adjusted OR = 1.71; 95% CI: 1.25-2.34) (Table 2). Other medical conditions examined included pelvic inflammatory disease, both diabetes and PCOS, hip fracture/broken hip after 25 years of age, insulin resistance/metabolic syndrome, and growth hormone

replacement therapy. Since few (< 1%) subjects had reported a history of these medical conditions, we decided not to show detailed results for these conditions. No significant associations were found for these conditions, except for pelvic inflammatory disease ($p = 0.001$).

After adjusting for various covariates, multivariate analyses of family history of cancer diagnosis suggests that a diagnosis of cancer in the uterus among 1st degree blood relatives is significantly associated with an increased risk of endometrial cancer (Adjusted OR=2.02; 95% CI: 1.06-3.86) (Table 3). A history of other types of cancers among 1st degree relatives did not appear to influence the risk of endometrial cancer.

Discussion

In this population-based case-control study, a medical history of high blood pressure and a family history of endometrial cancer in the 1st degree relatives were significantly associated with an increased risk of endometrial cancer. Although there was also an indication of elevated risk for women with pelvic inflammatory diseases, the number of subjects reporting such a condition was too few to draw any conclusion. The association between PCOS and endometrial cancer was first suggested in 1949 by Speert, who reported an increased incidence of cystic ovaries in young women with endometrial cancer.[15] Jackson and Dockerty in 1957 further investigated this association by recruiting 43 patients with PCOS. 16 of these women were identified by examining surgical specimens removed from a group of 'several thousand patients' with endometrial cancer. The remaining 27 patients were women with symptoms of the PCOS and a confirmatory ovarian biopsy. Endometrial tissue was available for examination in only 15 of these cases. Thirteen samples showed 'thickening', 2 were atrophic, but there were no reported cases of endometrial cancer. Nevertheless, Jackson and Dockerty concluded that their most important observation concerned the link between the PCOS and endometrial cancer.[16] It has been argued that this study was not reliable due to methodological problems.[17] Many existing studies which claimed to provide evidence of an increased risk of endometrial cancer in women with PCOS did not calculate the relative risk.[18] Although the study by Ramzy and Nisker[19] included a relative risk estimate in their study which compared the patients in their study with a cohort of normal women, the numbers were small and the p value was just reached the level of statistical significance. Another study

found an association between PCOS and endometrial cancer, but the relation was limited only to premenopausal women.[17] Overall, the evidence for an increased risk of endometrial cancer in women with PCOS was inconsistent and inconclusive. The finding of our study may provide additional evidence to support a possible association between endometrial cancer and PCOS, but the risk attributable to PCOS is likely to be small since fewer women with the condition were involved in endometrial cancer.

Diabetes mellitus has been frequently linked to endometrial cancer. Parazinni has reported an increased risk of endometrial cancer in diabetic women at age ≥40 years (OR=3.1; 95% CI: 2.3–4.2), after controlling for age, calendar year at interview, education, body mass index (BMI) (as categorized variable, <25, 25–30, >30), parity, oral contraceptive and hormonal replacement therapy use, age at menopause, hypertension and smoking.[20] A population-based prospective cohort study concluded that diabetes was associated with a 2-fold increased risk, and combination of diabetes with obesity and low physical activity was associated with a further increased risk for endometrial cancer. [21] Another case-control study showed a history of diabetes was significantly related to the risk for endometrial cancer after adjusting for weight and other reproductive factors, (RR= 2.0; 95% CI: 1.1- 3.6).[22] However, our results indicated that the association between diabetes and the risk of endometrial cancer became statistically insignificant after multivariate adjustment, which may be attributable to the relatively small number of women who had diabetes in this study. The discrepancy in results compared with previous studies could also arise from the

difference in methodology, covariates being adjusted for, study population, as well as sample size.

High blood pressure has been reported as a characteristic of endometrial cancer patients, but the data are less convincing than other risk factors such as overweight, nulliparity and late manopause. [23] Wynder et al. found a higher proportion of cases than controls with high blood pressure, [24] but there was a similar excess of patients with low pressures and the mean pressure did not differ between cases and controls. Kaplan and Cole stated the relative risk associated with a history of high blood pressure, after controlling for age and weight, was 1.5,[25] but this did not differ significantly from unity. A history of high blood pressure was identified as a significant risk factor for endometrial cancer in our study, which confirmed the association between the two. The putative biologic mechanisms that underlie this association are unclear at present. It has been speculated that long-term exposure to high blood pressure may lead to inhibition of apoptosis.[14]

Our finding regarding family history of uterus cancer is consistent with other studies. There is some evidence for familial aggregation of endometrial cancer. [26,27] In a case-control study conducted in northern Italy between 1983 and 1993, a family history of endometrial cancer was found to increase the risk of the disease.[12] However, the proportion of cases attributable to this factor was small in that study- less than 1% of endometrial cancer patients in that population had a family history. In a large multicentre case-control study conducted by Lucenteforte and Talamini in

Italy between 1992 and 2006, ORs were 2.1 (95% CI: 0.7-6.4) for those reporting a family history of endometrial cancer and 1.8 (95% CI: 1.0-3.2) for a family history of any uterine cancer, indicating a family history of endometrial or any uterine in first-degree relatives is associated with an increased risk of endometrial cancer. [28]

There are several limitations in our study. First, it is possible that the interviewer-administered questionnaires were subject to differential misclassification due to recall bias. Second, medical history data were self-reported, so misreporting (especially underreporting) was a possibility. Response rates were modest - 54.9% of cases and 64.5% of controls approached were finally enrolled in the study. Selection bias may have occurred if the cases and controls who participated were not representative of the underlying population bases.

Strengths of our study include the population-based study design, the rapid case ascertainment, and the use of detailed and thorough medical history questionnaires, measuring 27 different types of medical conditions prior to the diagnosis of endometrial cancer. Since our study is population-based and included only incident cases who are confirmed by medical records, survival bias was not a concern, and the potential for reverse causality was also minimized, if it had not been eliminated completely.

Endometrial cancer is currently the fourth most common cancer among women. It is estimated that there will be 47,130 new cases and 8,010 deaths from endometrial

cancer in the United States in 2012.[29] As the incidence/prevalence of high blood pressure continues to rise in the US and around the world, [30] endometrial cancer incidence will likely increase. Future studies need to consider how to decrease the risk of developing endometrial cancer in women with known risk-prone medical conditions or a family history of endometrial cancer.

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Table 1. Characteristics of the Study Population

	Cases		Controls		
	Number	**Mean(SD)**	**Number**	**Mean(SD)**	**p value**
Age at interview	668	60.6 (9.5)	665	61.5(10.8)	0.123
Mother's age at birth	618	28.6 (6.6)	638	28.3 (6.1)	0.444
Number of siblings	667	3.9 (2.3)	663	3.7 (2.1)	0.730
Number of sisters	665	2.4 (1.4)	661	2.3 (1.3)	0.324
Number of elder siblings	665	1.4 (1.8)	660	1.3 (1.6)	0.817
Birth weight (lb)	392	7.1 (1.4)	409	7.0 (1.5)	0.701
Height (cm)	668	162.7 (6.5)	665	162.5 (6.5)	0.553
Weight (kg)	665	86.5 (23.7)	663	71.5 (16.4)	<0.001
BMI	665	32.7 (8.5)	663	27.1 (6.1)	<0.001
Number of live births	667	1.8 (1.4)	662	2.1(1.3)	<0.001
Age at first pregnancy	667	23.5(4.7)	662	24.7 (5.0)	<0.001
Birth Place					0.254
US	602 (90.3)		612 (92.0)		
Non-US	65 (9.7)		53(8.0)		
Ethinic group					0.033
White	607(90.9)		628 (94.6)		
Other	61(9.1)		36 (5.4)		
Education					<0.001
<12 yrs	237 (35.5)		175 (26.4)		
12 yrs. to 3 yrs. college	116 (17.4)		92 (13.9)		
College/university	189 (28.3)		227 (34.2)		
Graduate school	126 (18.9)		170 (25.6)		
Smoking Status					0.0187
Never smoker	364 (54.6)		311 (47.0)		
Former smoker	251 (37.6)		285 (43.1)		
Current smoker	52 (7.8)		66 (10.0)		
Menopausal status					0.031
Premenopausal	91 (13.7)		119 (18.0)		
Postmenopausal	575 (86.3)		586 (88.5)		
Oral contraceptive use(ever)	374 (56.3)		440 (66.7)		<0.001
Menopausal hormone use(ever)	198 (30.2)		239 (37.5)		0.0056
Menarche age					0.047
<12 year	186 (28.1)		153 (23.3)		
>=12 year	476 (71.9)		503 (76.7)		
Family history (1st degree relative with endometrial cancer)	46 (6.9)		27 (4.1)		0.024
Diagnosis of hypertension (ever)	378 (56.7)		257 (38.8)		<0.001
Diagnosis of diabetes (ever)	1.36 (20.4)		77 (11.6)		<0.001

Table 2. Medical History and the Risk of Endometrial Cancer

	Case	Control	p value	OR (95% CI)	Adj* OR (95% CI)
	N (%)	N (%)			
Endometriosis			0.4469	1.19 (0.76-1.87)	1.29 (0.61-2.73)
No	620 (93.37)	621 (94.38)			
Yes	44 (6.63)	37 (5.62)			
PCOS			0.0074	4.73 (1.35-16.54)	5.28 (0.49-57.27)
No	652 (97.9)	661 (99.55)			
Yes	14 (2.1)	3 (0.45)			
Ovary Cyst			0.8256	0.97 (0.74-1.28)	0.87 (0.58-1.30)
No	538 (81.15)	530 (80.67)			
Yes	125 (18.85)	127 (19.33)			
Diabetes			<0.0001	1.95 (1.44-2.64)	1.41 (0.93-2.42)
No	532 (79.64)	588 (88.42)			
Yes	136 (20.36)	77 (11.58)			
Wrist Fracture/Broken after 25			0.6316	0.90 (0.58-1.40)	1.40 (0.80-2.47)
No	625 (93.98)	617 (93.34)			
Yes	40 (6.02)	44 (6.66)			
Aspirin regular intake			0.1205	0.84 (0.67-1.05)	0.76 (0.57-1.03)
No	423 (63.51)	393 (59.37)			
Yes	243 (36.49)	269 (40.63)			
High Blood Pressure			<0.0001	2.06 (1.65-2.56)	1.71 (1.25-2.34)
No	290 (43.41)	407 (61.2)			
Yes	378 (56.59)	258 (38.8)			
High Cholestrol/triglycerides/blood lipids			0.0044	1.37 (1.10-1.71)	1.13 (0.84-1.52)
No	350 (52.79)	399 (60.55)			
Yes	313 (47.21)	260 (39.45)			
Coronary Artery Disease/ Heart Attack			0.1476	1.47 (0.87-2.47)	1.66 (0.87-3.15)
No	627 (94.57)	639 (96.23)			
Yes	36 (5.43)	25 (3.77)			
Cirrhosis/Hepatitis/Other liver problem			0.1668	0.68 (0.40-1.18)	0.66 (0.29-1.49)
No	643 (96.55)	630 (95.02)			
Yes	23 (3.45)	33 (4.98)			
Kidney Problem/ Dialysis needed			0.9102	1.03 (0.63-1.68)	0.78 (0.39-1.56)
No	633 (94.9)	632 (95.04)			
Yes	34 (5.1)	33 (4.96)			
Ulcerative Colitis/Bowel inflammation			0.7182	0.89 (0.46-1.72)	0.86 (0.38-1.93)
No	649 (97.45)	642 (97.13)			
Yes	17 (2.55)	19 (2.87)			
Mumps			0.2356	0.86 (0.67-1.10)	0.76 (0.53-1.07)
No	193 (32.94)	176 (29.73)			
Yes	393 (67.06)	416 (70.27)			
Cone/punch Biopsy of cervix/ Cyrotherapy/Freezing therapy of Cervix			0.1703	1.22 (0.92-1.63)	1.05 (0.70-1.58)
No	523 (80.83)	541 (83.75)			
Yes	124 (19.17)	105 (16.25)			

*Adjusted for age, race, smoking, menarche age, menopause age, menopause status, parity, BMI, estrogen usage, oral contraceptives usage, and hormone replacement therapy.

Table 3. Family History of Cancer and Risk of Endometrial Cancer

	Case	Control	P Value	OR (95% IC)	Adj.*OR (95%CI)
	N (%)	N (%)			
Breast			0.396	1.13 (0.85-1.51)	0.90 (0.61-1.32)
No	552 (82.63)	561 (84.36)			
Yes	116 (17.37)	104 (15.64)			
Uterus			0.0234	1.75 (1.07-2.85)	2.02 (1.06-3.86)
No	622 (93.11)	638 (95.94)			
Yes	46 (6.89)	27 (4.06)			
Ovary			0.5944	1.21 (0.59-2.48)	1.01 (0.40-2.60)
No	651 (97.46)	651 (97.89)			
Yes	17 (2.54)	14 (2.11)			
Colorectal			0.3018	0.83 (0.58-1.19)	0.77 (0.48-1.22)
No	607 (90.87)	593 (89.17)			
Yes	61 (9.13)	72 (10.83)			
Prostate			0.1673	1.32 (0.89-1.96)	1.65 (0.96-2.82)
No	607 (90.87)	618 (92.93)			
Yes	61 (9.13)	47 (7.07)			
Lung			0.7792	0.95 (0.69-1.32)	0.85 (0.55-1.30)
No	587 (87.87)	581 (87.37)			
Yes	81 (12.13)	84 (12.63)			

*Adjusted for age, race, smoking, menarche age, menopause age, menopause status, parity, BMI, estrogen usage, oral contraceptives usage, and hormone replacement therapy.

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