HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2014 August 01.

Published in final edited form as:

Gynecol Oncol. 2013 August ; 130(2): 334–339. doi:10.1016/j.ygyno.2013.04.053.

Endometrial Cancer and a Family History of Cancer

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Abstract

Objective—Lynch Syndrome (LS), an inherited genetic syndrome, predisposes to cancers such as colorectal and endometrial. However, the risk for endometrial cancer (EC) in women not affected by LS, but with a family history of cancer, is currently unknown. We examined the association between a family history of cancer and the risk for EC in non-LS patients.

Methods—This population-based case-control study included 519 EC cases and 1015 age-matched controls and took place in Alberta, Canada between 2002 and 2006. Information about risk factors, including family history of cancer in first and second degree relatives, was ascertained via in-person interviews. Microsatellite instability (MSI) status of tumor tissue was assessed to determine involvement of DNA mismatch repair genes.

Results—A first or second degree family history of uterine cancer was modestly associated with the risk for overall EC [odds ratio (OR), 1.3; 95% confidence interval (CI), 0.9,1.9], and the risks were similar for MSI+ cancer (OR= 1.5, 95%CI=0.7, 3.3) and MSI- cancer (OR= 1.3, 95%CI=0.8, 2.4). Although consistent, these associations were modest and not significant. In contrast, the risk for MSI+ cancer was elevated with a reported family history of colorectal cancer (OR= 1.4, 95%CI=1.0, 2.2), but not for MSI- cancer.

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FINANCIAL SUPPORT This study was funded by grants from the National Cancer Institute of Canada (NCIC) and the Canadian Institutes of Health Research (CIHR), with additional support from the University of New Mexico Cancer Research and Treatment Center (NCI 2P30 CA118100-07). L.S. Cook and C.M. Friedenreich received career awards from the Alberta Heritage Foundation for Medical Research (AHFMR). L.S. Cook also held a Canada Research Chair.

CONFLICTS OF INTEREST: The authors have no conflicts of interest to disclose.

Conclusions—A family history of uterine cancer may be modestly associated with EC risk in non-LS patients regardless of MSI status, suggesting that risk was not related to inherited defects in the MMR gene pathway. These results provide preliminary support for an EC-specific genetic syndrome.

Keywords

endometrial cancer; family history; risk factor; case-control study; microsatellite instability

INTRODUCTION

In Canada, endometrial cancer (EC) is the most common malignancy of the female genital tract, with an estimated 5300 new cases and 900 deaths expected in 2012 [1]. Well established risk factors for EC include obesity, nulliparity, exposure to unopposed estrogen, early age at menarche, late age at menopause, and diabetes [2-5]. For patients with inherited cancer syndromes such as Lynch Syndrome (LS), a family history of cancer is associated with an increased risk for EC [6]. However, the risk for EC in patients with a family history of cancer, and without LS, is currently unknown. Analogous studies of a family history of breast or ovarian cancer in patients without BRCA gene mutations have reported elevated risks for these cancers [7,8].

LS, also known as hereditary non-polyposis colorectal cancer syndrome (HNPCC), is an autosomal dominantly inherited cancer syndrome that predisposes affected individuals to an increased risk for cancer, especially colorectal and endometrial cancers [9]. In population-based samples, approximately 2% to 6% of women with EC are found to have LS [10,11]. LS is caused by loss of expression of one of the DNA mismatch repair (MMR) genes, leading to errors in DNA replication, and the presence of multiple repeating genetic alleles known as microsatellite instability (MSI). An estimated 90% of EC patients with LS are found to have MSI in their tumor tissue [12].

LS is a unique cancer syndrome with a defined genetic pathway and currently one of the only inherited syndromes known to be associated with EC. The inclusion of LS patients with non-LS patients in family history studies may lead to inaccurate risk estimates, driven by the LS-EC relationship. To our knowledge, previous studies assessing the association of a family history of cancer and risk for EC did not exclude LS (or suspected LS) patients from their analyses. We therefore sought to determine whether or not a family history of cancer (either endometrial or colorectal) was associated with an increased risk for EC among non-LS patients enrolled in a population-based case-control study in Alberta, Canada.

MATERIAL AND METHODS

Study Population

The methods used have been previously reported [13]. Briefly, women with first primary endometrial cancer were identified through the population-based Alberta Cancer Registry. Eligible cases were less than 80 years of age, diagnosed between January 2002 and February 2006, and residents of central or southern Alberta (n=900). Physicians provided permission

to contact 808 cases and 549 (68%) were successfully interviewed. Seven cases were excluded because of questionable interviews, resulting in 542 cases. Female controls were identified through random digit dialing, and were frequency age-matched to cases in 5-year age groups [14]. Eligible controls had no previous diagnoses of cancer, no prior hysterectomy, and met the age and residence requirements as per cases. Out of 29,970 random residences contacted, 18,264 (60.9%) residences were screened for potentially eligible women. A total of 1,984 eligible women were identified in this screen and invited to participate. Of these, 1,036 (52.2%) were interviewed. Four controls were excluded because of questionable interviews, resulting in 1,032 controls. This study received ethics approval from the Alberta Cancer Research Ethics Committee and the University of Calgary, and all women provided written informed consent.

Interviews

Calendars recording major life events and photographic displays aided recall during structured, in-person interviews. Extensive interview information was recorded only for exposures that occurred before the diagnosis date among cases (the date of hysterectomy) and the reference date for controls (an assigned date that preceded the control interview date by the average time between hysterectomy and date of interview for the cases). To facilitate recall of cancer history in first and second degree relatives, women were provided with worksheets prior to the interview. These worksheets were completely filled out for 466 (86.0%) cases and 882 (85.5%) controls prior to the interview. During the interview, all women, whether they completed the worksheets or not, verbally provided information about cancer history for each first and second degree family member.

Blood, Tumor Tissue, and Microsatellite Instability (MSI)

We obtained DNA from paraffin-embedded tumor blocks for 513 of our 542 cases. We were unable to obtain tissue for the following reasons: no hysterectomy performed (n=10), refused tissue testing (n=4), no available pathological slides/tissue (n=3), or no observable cancer at slide review (n=12). In addition, we could not determine MSI status if there was no matching blood sample (n=16), leaving 497 potential cases for MSI testing. From these, the assay either failed (n=6) or there was missing information on some aspect of MSI testing (n=11). Thus, MSI status was determined for 480 cases.

Laboratory methods have been previously described in detail [15]. Briefly, genomic DNA was extracted from buffy coat samples and archival paraffin-embedded tumor tissue blocks. Using polymerase chain reactions (PCR), with the blood DNA serving as the control for the corresponding tumor DNA, we evaluated a panel of five microsatellite markers (Bat25, Bat26, D5S346, D2S123 and D17S250) that are widely used for MSI determination [16]. Additional alleles in the tumor DNA relative to the blood DNA was considered a mismatch error. Samples with ambiguous results were repeated, and 10% of the samples were re-run for validation. We observed 100% reproducibility when we scored the microsatellite status of patients as microsatellite-stable (MSS) or MSI.

Statistical Analysis

When assessing a family history of cancer, we excluded all relatives that did not survive the first year of life (n= 453 case relatives and n= 930 control relatives) because, as expected, infant mortality was relatively high, and all the infants died of causes other than cancer. Family cancer history was assessed in the remaining first and second degree relatives. The current EC diagnosis that defined the cases was excluded. Because environmental and genetic risk factors of EC and colorectal cancer are shared, and because of the association of both cancers with MSI, we chose to focus our analyses on the family history of these two site-specific cancers only. Given that 85-90% of all uterine cancers are endometrial in nature, we used any reported uterine cancers as a proxy for endometrial cancer.

To identify suspected LS patients, we assessed family history as meeting the Amsterdam II criteria (a set of criteria routinely used by clinicians and genetic counselors to help identify patients who are at high risk for LS) [17]. To assess if cases were generally over-reporting cancer relative to controls, we also assessed lung cancer as there was no *a priori* reason to expect a reported family history of lung cancer to differ between cases and controls.

Women with unknown family history (adopted: n=9 cases and n=11 controls; no family information: n=4 controls) were excluded, as well as those that met the Amsterdam II criteria (n=14 cases and n=2 controls), so that we could assess the association of family history of cancer with EC risk that was, presumably, not driven by LS. Thus, 519 cases and 1015 controls were in the final analysis.

Of the cases for which MSI status was determined (n=480 cases), cases that were adopted and could not provide family history information (n=8), as well as those that met the Amsterdam II criteria (n=13), were excluded, for a total of 459 cases included in the MSI analysis. Of these 459 cases, 330 (71.9%) had one or less markers with instability (MSS / MSI-), and 129 (28.1%) had two or more markers with instability (MSI-H / MSI+).

Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) describing EC risk associated with the various measures of family history [18]. Family history of cancer was grouped as: 1) any uterine cancer; 2) any colorectal cancer; and, 3) any uterine or colorectal cancer or both (hereafter referred to as UCca). Final ORs were adjusted for age, residential status, body mass index (BMI), parity, hormone contraceptive use, number of first or first and second degree relatives as appropriate, menopausal status as appropriate, and menopausal hormone use as appropriate. We performed all analyses with SAS version 9.1.3.

RESULTS

Cases were more likely than controls to have a body mass index (BMI) ≥30 kg/m^2, and, among postmenopausal women, to have used estrogen only (E-only) therapy (Table 1). Cases were less likely than controls to be married, to have an older age at menarche, to have used hormone contraception, to be parous, and among postmenopausal women, to have used combined continuous estrogen plus progesterone (CCE+P) therapy.

In total, the cases and controls in this study reported 11,673 first and 34,374 second degree relatives (Table 2). The distribution of relatives was very similar between cases and controls, except that cases had a smaller percentage of children among first degree relatives than controls and, perhaps consequently, a smaller percentage of grandchildren among second degree relatives. The smaller percentage of children among cases than controls (Table 2) is consistent with the lower reported parity in cases versus controls (Table 1).

Cases were slightly more likely than controls to report a first degree family history of uterine cancer (5.4% vs. 4.3%, respectively), or to report a family history of UCca (15.8% vs. 14.1%, respectively) (Table 3). However, neither type of family history by itself was significantly associated with an elevated EC risk after adjusting for the number of first degree relatives and other confounders (for uterine cancer: adjusted OR=1.3, 95% CI=0.8, 2.2; and, for UCca: adjusted OR=1.2, 95% CI=0.9, 1.9). When stratified by menopausal status, premenopausal women had higher risks than postmenopausal women with reported first degree family histories of uterine and/or colorectal cancer, but none of the risk estimates were statistically significant. Considering the broader group of both first and second degree relatives, a family history of uterine cancer was associated with a possible modest elevation in endometrial cancer risk (adjusted OR=1.3, 95% CI=0.9,1.9), as was a family history of UCca (adjusted OR=1.1, 95% CI=0.9,1.4), but neither estimate was statistically significant. Overall, a first degree, or a first and second degree, family history of colorectal cancer showed little, if any, association with endometrial cancer risk. As expected, no elevation in risk was noted with a reported first degree, or a first and second degree, family history of lung cancer.

When stratified by MSI status, either a first degree, or a first and second degree, family history of uterine cancer was associated with modest, non-statistically significant elevations in risk regardless of MSI status (Table 4). For example, the risk for MSI+ cancer associated with a first and second degree family history of uterine cancer was OR=1.4, 95% CI=0.8, 2.5, and for MSI- cancer was OR=1.4, 95% CI=0.9, 2.1. In contrast to the overall results, there was also an elevation in risk for MSI+ cancer with a first or second degree family history of colorectal cancer (adjusted OR=1.4, 95% CI 1.0, 2.2), and with a first or second degree family history of UCca (adjusted OR=1.6, 95% CI=1.1, 2.4).

DISCUSSION

The association of a family history of cancer with the risk for EC is not well-established, particularly in non-LS patients and from a population-based perspective. In the present study, we generally found that first or second degree family histories of uterine cancer were associated with modest, non-statistically significant increases in the risk for EC, and that these risks were somewhat stronger among premenopausal women. Investigating further by MSI status indicated that risk was similar for both MSI+ and MSI- cancers by reported family history of uterine cancer. However, the risk for MSI+ cancer was elevated with a reported family history of colorectal cancer, or a reported family cancer history of UCca, but not for MSI- cancer.

Previous studies examining the relation between a family history of cancer and risk for EC have reported conflicting results [19-24]. One study found no evidence that a first degree family history of EC, or other cancers, contributed to the risk for postmenopausal EC [21]. Several other studies reported modest elevations in risk with a first degree family history of EC (OR=1.5, 95% CI 1.0, 2.3) [22], or a first degree family history of any uterine cancer (OR 1.8, 95%CI 1.0, 3.2) [19], that was even higher in women 55 years of age or younger at diagnosis [19]. In studies restricted to younger women, significant associations between a family history of EC in first degree relatives and risk for EC have been reported, with risks ranging from 2.1 (95% CI 1.1, 3.8) [24] to 2.8 (95% CI 1.1, 3.3) [23]. However, to our knowledge, no other studies examining family history of cancer and risk for EC have excluded EC patients with known, or suspected, LS. Therefore, many of the reported associations between a family history of cancer and risk for EC, particularly among younger women, may be attributable, in part, to the EC-LS relationship. Approximately 9% of women diagnosed with EC before the age of 50 are LS carriers, compared with 2% to 6% of all EC patients [10,11,25]. Had we included LS patients in our analysis, our risk estimates would have been stronger. For example, when suspected LS patients are included, the adjusted OR for endometrial cancer associated with a first or second degree family history of uterine cancer was 1.5 (95% CI=1.1, 1.2), similar to results reported in other studies [19,22]. In addition, because only first primary EC cases were included in this study, women with LS that had a diagnosis of cancer prior to EC were excluded by design. Had we included all LS patients, our risk estimates would likely have been even higher. Thus, our results are distinct from those of previous studies because of our efforts to exclude suspected LS patients.

Our study had a few limitations that need to be considered when interpreting these results. We did not have molecular data to exclude women with germline LS mutations, hence some women with LS may have been included in our study. The expected frequency of LS in a population based cohort of EC cases is expected to be approximately 2% to 6% [10,11,26,27]. At enrollment, we excluded cases and controls with a previous diagnosis of any cancer (except nonmelanoma skin cancer), thereby eliminating any LS patients with a primary diagnosis of colorectal or other LS-related cancer. EC is the sentinel cancer in approximately 50% of female LS patients and, therefore, because of our initial exclusion criteria, we expect approximately 2% of our sample to be LS patients [28]. To ensure that our associations were not driven by LS, we also excluded women who met the Amsterdam II criteria (n=14 cases and n=2 controls). In a recent study, the Amsterdam II criteria identified 58% of LS patients with EC [29]. Though the Amsterdam II criteria may lack sensitivity in identifying all LS patients, based on the expected 2% of our sample to be LS patients (about 10 women), the exclusion of 16 suspected LS carriers may over-represent LS patients. Indeed, we found that seven case women were MSS, but it was necessary to use the same criteria to identify LS in both the cases and controls. The controls did not have cancer (and therefore no cancerous tissue) and LS could only be identified through the Amsterdam II criteria. Consequently, this misclassification would mean that our risk estimates are conservative.

A second limitation of our study was the self-reported data on family structure and family cancer occurrence. We facilitated reporting with family history worksheets, which over 85%

of women completed before the interview. Furthermore, interviews were conducted in a consistent and structured manner, regardless of worksheet completion, and extensive, on-going quality control of the interviews was undertaken throughout the study. A related limitation is that the health status of some family members was incomplete. Cancer history in these relatives was therefore unknown and not accounted for in our analysis. However, less than 0.5% of first degree and less than 4% of second degree relatives had unknown cancer status, suggesting that the impact of this unknown data was minimal. It is also possible that cases recalled family structure and cancer history better than controls. However, reported family structure was very similar between cases and controls, as demonstrated in Table 2, and cases were no more likely than controls to report a family history of lung cancer. In addition, we did not have information about known risk factors for EC in family members such as obesity. Though we adjusted for BMI in our analyses, it is possible that the increased risk for EC observed in some families may be due, at least in part, to shared environmental and lifestyle risk factors.

In the present study, the modest increased risks for EC in non-LS women associated with a first or second degree family history of uterine cancer, which was present for both MSI+ and MSI- cancer, suggests the existence of inherited genetic risk factors specific to EC. While speculative, other studies have also suggested the clustering of EC alone, known as familial site-specific EC, as a genetic syndrome separate from LS [23,26,30-32].

The molecular basis of familial site-specific EC is currently unknown. One study identified 23 families with familial EC, and characterized their tumor tissue to determine the extent of MMR gene involvement [26]. Only 8.7% of cases had germline MMR mutations, suggesting an alternate genetic pathway from LS for familial site-specific EC [26]. Results from our MSI analyses support this alternate genetic pathway hypothesis: risk estimates for MSI+ cancer and MSI- cancer associated with a first or second degree family history of uterine cancer were very similar. These findings suggest that inherited factors in women with familial site-specific EC are not related to alterations in the MMR genes.

We did observe elevated risks for MSI+ EC associated with a first or second degree family history of UCca, as well as for colorectal cancer alone. These results suggest that genetic alterations in the MMR gene pathway, leading to an MSI+ phenotype, are more likely in EC patients with a family history of colorectal cancer. Shared environmental and lifestyle risk factors for colorectal cancer, such as alcohol, smoking and diet, may also contribute to familial clustering of MSI+ cancers, potentially acting through epigenetic mechanisms [33-35]. Hypermethylation of the MLH1 gene promoter is the primary cause of MSI in EC tumors, however the relative contribution of shared environmental factors to methylation status is currently unknown [36,37]. Our results are consistent with other studies that have also reported associations between a family history of colorectal cancer and an increased risk for EC, though the contribution of LS to these other risk estimates is not clear [23,38,39].

In summary, results from the present study suggest that a family history of uterine cancer is associated with an increased risk for EC in women who are not LS patients. Based on results of MSI testing, it appears that the increased risk for EC is not associated with inherited

defects in the MMR gene pathway, thus supporting the hypothesis of familial site-specific EC as a separate genetic entity from LS. Further studies are needed to determine the underlying molecular and genetic basis for this unique syndrome.

ACKNOWLEDGEMENTS

Study coordination was done by Rita Biel, Lisa Strosher, and Aleata Rhyorchuk. Laboratory assays were conducted by Wahida Rahman and Elizabeth Kornaga. Colleen Lachance, Maryann Lester, Lisa Miller, Catherine Munro, and Polly Pratt recruited controls. Participant interviews were conducted by Tamara Bellmont, Kay Christie, Pearl Cooke, Linda Davison, Carolyn Henderson, Tacey Lawrence, Rosalie Merkosky, Jodi Parrotta, Brenda Platzer, Cyndi Rasa, Nicole Slot, Keely Winnitoy and Carol-Anne Zawalykut. Quality control of interviews was performed by Jodi Parrotta. Carla Quesnel assisted with administrative tasks, Holly Wilson identified cases from Calgary Laboratory Service pathology reports and Farit Vakhetov did data management.

Abbreviations

BMI	body mass index
CCE+P	continuous-combined estrogen and progesterone
CI	confidence interval
E-only	estrogen-only
E+P	estrogen plus progesterone
EC	endometrial cancer
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
IUD	intrauterine device
LMP	last menstrual period
LS	Lynch Syndrome
MMR	mismatch repair
MSI	microsatellite instability
ng	nanogram
OR	odds ratio
PCR	polymerase chain reaction
UCca	uterine or colorectal cancer or both

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Table 1

Characteristics of Endometrial Cancer Cases and Controls, 2002-2006, Alberta, Canada

Characteristics	Cases (n = 519)		Controls (n = 1,015)	
	N	%	N	%
Age at diagnosis/reference date, years				
< 40	11	2.1	38	3.7
40–49	66	12.7	127	12.5
50–59	204	39.3	376	37.1
60–69	170	32.8	339	33.4
70+	68	13.1	135	13.3
Residential status				
Urban	349	67.2	652	64.2
Rural	170	32.8	363	35.8
Education				
High school diploma or less	169	32.5	288	28.4
Non-university certificate	237	45.7	483	47.6
University degree	113	21.8	243	23.9
Unknown	0	0	1	0.1
Marital status				
Never married	40	7.7	23	2.3
Ever married	479	92.3	992	97.7
Age at menarche, years of age				
≤ 12	306	59.0	508	50.1
> 12	213	41.0	507	49.9
Oral Contraception				
Never, < 6 months	212	40.5	296	29.2
Ever	305	58.2	709	69.9
6 – 59 months	170	32.4	349	34.4
60+ months	135	25.8	359	35.4
Unknown duration	0	0	1	0.1
Unknown hormone type	7	1.3	10	1.0
Parity				
0	93	17.9	105	10.3
1–2	225	43.4	418	41.2
3+	201	38.7	492	48.5
BMI, kg/m^2				
<18.5	3	0.6	9	0.9
18.5–24.9	90	17.3	320	31.5
25–29.9	137	26.4	375	37.0
30+	289	55.7	310	30.5
Unknown	0	0	1	0.1
Smoking status				

Characteristics	Cases (n = 519)		Controls (n = 1,015)	
	N	%	N	%
Never	261	50.3	520	51.2
Former	196	37.8	367	36.2
Current	62	11.9	128	12.6
Age at Menopause				
≥ 50	254	63.7	436	59.6
< 50	145	36.3	296	40.4
Menopausal hormone therapy[a]				
Never use, < 6 months	235	58.9	362	49.5
Estrogen only	18	4.5	23	3.1
E+P continuous combined only	42	10.5	162	22.1
6 – 59 months	22	5.5	61	8.3
60+ months	20	5.0	101	13.8
Other combinations	103	25.8	180	24.6
Unknown hormone therapy type	1	0.3	5	0.7

BMI, body mass index; E+P, estrogen plus progesterone; IUD, intra-uterine device

[a]Restricted to post-menopausal women (n=399 cases, n=732 controls).

Table 2

Type and Number of First and Second Degree Family Members of Cases (n=519) and Controls (n=1015)

Relatives with respect to proband	Cases Total Relatives (n= 15163)		Controls Total Relatives (n= 30884)		Total Relatives (n= 46047)	
	N	%	N	%	N	%
All First Degree	3768	100[d]	7905	100[d]	11673	100[d]
Brother	826	21.9	1730	21.9	2556	21.9
Sister[a]	807	21.4	1575	19.9	2382	20.4
Sibling Sex Unknown	0	0.0	0	0.0	0	0.0
Son	574	15.2	1338	16.9	1912	16.4
Daughter	529	14.0	1250	15.8	1779	15.2
Child Sex Unknown	0	0.0	0	0.0	0	0.0
Fathers[b]	512	13.6	1002	12.7	1514	13.0
Mothers[c]	520	13.8	1010	12.8	1530	13.1
All Second Degree	11395	100[e]	22979	100[e]	34374	100[e]
Maternal Grandfather	438	3.8	870	3.8	1308	3.8
Maternal Grandmother	460	4.0	911	4.0	1371	4.0
Paternal Grandfather	380	3.3	792	3.5	1172	3.4
Paternal Grandmother	397	3.5	814	3.5	1211	3.5
Male Grandchildren	638	5.6	1438	6.3	2076	6.0
Female Grandchildren	657	5.8	1419	6.2	2076	6.0
Grandchildren Sex Unknown	0	0.0	0	0.0	0	0.0
Maternal Uncle	1134	10.0	2219	9.7	3353	9.8
Maternal Aunt	1036	9.1	2136	9.3	3172	3172
Maternal Aunt/Uncle Sex Unknown	72	0.6	55	0.2	127	0.4
Paternal Uncle	1006	8.8	2104	9.2	3110	9.1
Paternal Aunt	1052	9.2	1947	8.5	2999	8.7
Paternal Aunt/Uncle Sex Unknown	41	0.4	77	0.3	118	0.3
Maternal Half-brother	40	0.4	72	0.3	112	0.3
Maternal Half-sister	44	0.4	63	0.3	107	0.3
Maternal Half-siblings Sex Unknown	0	0.0	1	0.0	1	0.0
Paternal Half-brother	24	0.2	42	0.2	66	0.2
Paternal Half-sister	28	0.3	48	0.2	76	0.2
Paternal Half-siblings Sex Unknown	0	0.0	4	0.0	4	0.0
Nephew	2004	17.6	4059	17.7	6063	17.6
Niece	1876	16.5	3866	16.8	5742	16.7
Niece/Nephew Sex Unknown	68	0.6	42	0.2	110	0.3

[a] Case (n=2) or control (n=2) identical twin siblings excluded.

[b] Identical twins of father for cases (n=2) and control (n=2) included.

[c] Identical twins of mother for cases (n=2) control (n=1) included.

[d]% of all first degree

[e]% of all second degree

Table 3

Family History of Cancer and Endometrial Cancer Risk by Menopausal Status, 2002-2006, Alberta, Canada.

	All Study Participants (n=1534)			Menopausal Status[b]	
	Cases (n=519)	Controls (n=1015)	OR (95% CI)[a]	Pre-menopausal (n=53 cases; n=122 controls) OR (95% CI)[a]	Post-menopausal (n=399 cases; n=732 controls) OR (95% CI)[c]
First degree family history of cancer					
Uterine	28	44	1.3 (0.8, 2.2)	3.1 (0.5, 17.2)	1.2 (0.7, 2.2)
Colorectal	56	105	1.0 (0.7, 1.5)	2.0 (0.2, 22.0)	1.1 (0.7, 1.7)
UCca	82	143	1.2 (0.9, 1.6)	2.8 (0.7, 11.6)	1.2 (0.8, 1.7)
Lung	50	105	0.9 (0.6, 1.3)	1.0 (0.3, 3.6)	0.9 (0.6, 1.4)
First and second degree family history of cancer					
Uterine	61	95	1.3 (0.9, 1.9)	1.4 (0.4, 5.0)	1.2 (0.8, 1.8)
Colorectal	129	251	1.0 (0.8, 1.3)	1.1 (0.4, 3.1)	1.2 (0.9, 1.5)
UCca	174	318	1.1 (0.9, 1.4)	1.4(0.6, 3.4)	1.2 (0.9, 1.6)
Lung	126	252	1.0 (0.7, 1.2)	1.2 (0.5, 3.0)	1.0(0.8, 1.4)

OR, odds ratio; CI, confidence interval; UCca, uterine or colorectal cancer or both.

[a] Adjusted for age (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79), residence (urban, rural), BMI (<24.9, 25-29.9, >30, unknown), parity (0, 1-2, >3), oral contraception use (never, 6-59, ≥60 months, unknown), number of first degree relatives or number of first and second degree relatives (continuous).

[b] Perimenopausal women (n=227), and women with unknown menstrual status (n=1), were excluded from menopausal status analysis.

[c] Additionally adjusted for hormone therapy (nonusers, CCE+P, other combinations, unknown).

Table 4

Family History of Cancer and Endometrial Cancer Risk by Microsatellite Instability (MSI), 2002-2006, Alberta, Canada.

	Controls (n=1015)	Cases				
		MSI +[a](n=129)		MSI - [a](n=330)		P
		N	OR[b] (95% CI)	N	OR[b] (95% CI)	value[c]
First degree family history of cancer						
Uterine	44	8	1.5 (0.7, 3.3)	18	1.3 (0.8, 2.4)	0.84
Colorectal	105	20	1.4 (0.8,2.5)	31	0.9 (0.6, 1.4)	0.14
UCca	143	27	1.5 (0.9, 2.5)	48	1.1 (0.7, 1.5)	0.19
Lung	105	13	0.9(0.5, 1.7)	32	0.9 (0.6, 1.4)	0.99
First and second degree family history of cancer						
Uterine	95	16	1.4(0.8, 2.5)	39	1.4(0.9, 2.1)	0.94
Colorectal	251	41	1.4(1.0, 2.2)	78	1.0 (0.7, 1.3)	0.09
UCca	318	54	1.6(1.1, 2.4)	104	1.0(0.8, 1.4)	0.05
Lung	252	33	1.0 (0.7, 1.6)	80	0.9 (0.7, 1.3)	0.81

OR, odds ratio; CI, confidence interval; UCca, uterine or colorectal cancer or both.

[a] MSI + includes cases with two or more markers with instability; MSI- includes cases with either one or zero markers with instability

[b] Adjusted for age (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79), residence, BMI (<24.9, 25-29.9, ≥30, unknown), parity (0, 1-2, ≥3), oral contraception use (never, 6-59, ≥60 months, unknown), number of first degree relatives or number of first and second degree relatives (continuous) and menopausal status/hormone therapy (premenopausal, peri/postmenopausal without HT, peri/postmenopausal with CCE+P, peri/postmenopausal with other combinations, unknown

[c] Comparing the OR for MSI+ with MSI- cancer