Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Hormonal and Reproductive Risk Factors for Sporadic Microsatellite Stable and Unstable Endometrial Tumors

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Abstract

Hormonal and reproductive factors modulate bioavailable estrogen to influence endometrial cancer risk. Estrogen affects the microsatellite status of tumors, but the relation between these estrogen-related factors and microsatellite instability (MSI) status of endometrial tumors is not known. We evaluated associations between hormonal and reproductive factors and risks of microsatellite stable (MSS) and MSI endometrial cancer among postmenopausal women (MSS cases = 258, MSI cases = 103, and controls = 742) in a population-based case–control study in Alberta, Canada (2002–2006). Polytomous logistic regression was used to estimate ORs and 95% confidence intervals (95% CI). We observed a significant trend in risk reduction for MSI (P_{trend} = 0.005) but not MSS (P_{trend} = 0.23) cancer with oral contraceptive use; with 5-year use or more, the risk reduction was stronger for MSI (OR = 0.42; 95% CI, 0.23–0.77) than for MSS cancer (OR = 0.80; 95% CI, 0.54–1.17; $P_{heterogeneity}$ = 0.05). For more recent use (<30 years), the risk reduction was stronger for MSI (OR = 0.36; 95% CI, 0.19–0.69) than for MSS cancer (OR = 0.77; 95% CI, 0.51–1.15; $P_{heterogeneity}$ = 0.032). No differential risk associations were observed for menopausal hormone use, parity and age at menarche, menopause or first pregnancy. We found limited evidence for statistical heterogeneity of associations of endometrial cancer risk with hormonal and reproductive factors by MSI status, except with oral contraceptive use. This finding suggests a potential role for the MMR system in the reduction of endometrial cancer risk associated with oral contraceptive use, although the exact mechanism is unclear.

This study shows for the first time that oral contraceptive use is associated with a reduced risk for MSI but not for MSS endometrial cancer. *Cancer Epidemiol Biomarkers Prev; 22(7); 1325–31. ©2013 AACR.*

Introduction

Endometrial cancer is the most common gynecologic cancer among women in Western countries. In Canada, an estimated 5,300 new endometrial cancer cases and 900 associated deaths were expected in 2012 (1). The "unopposed estrogen" hypothesis, one of the main hypotheses for endometrial cancer pathogenesis, states that high levels of bioavailable estrogens that are not counterbalanced by progesterone increase the mitogenic activity of endometrial cells (2), resulting in endometrial cancer. Established hormonal and reproductive risk factors for endometrial cancer, such as hormonal contraception (3, 4), menopausal hormone use (5, 6), age at menarche, age at menopause, and parity (6), all modulate the bioavailability of estrogen. Estrogen affects the microsatellite status of colorectal tumors (7), and limited evidence from endometrial cancer studies suggests a similar relationship in endometrial cancer (8). However, the relationship between hormonal and reproductive factors (which are surrogate markers of estrogen) and the microsatellite status of endometrial tumors is not known.

Microsatellite instability (MSI) is a molecular phenotype characterized by alterations in the length of short (1–5 base pairs) tandem repeats of DNA in tumor cells compared with normal cells (i.e., cells with germline DNA) of the same patient (9). MSI is an underlying aspect in hereditary nonpolyposis colorectal cancer (HNPCC), a syndrome that includes colon and endometrial cancer; but MSI also occurs in approximately 30% of endometrial cancers that are not associated with any inherited syndromes, that is, sporadic endometrial cancer (10–12). Findings from colon cancer studies suggest that hormonal and reproductive risk factors for sporadic MSI and microsatellite stable (MSS) colon cancer differ (7). However, this relation has not been studied in endometrial cancer.

Here, we evaluated the associations between hormonal and reproductive factors and the risk of MSS and MSI

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endometrial cancer among postmenopausal cases and controls in a population-based case–control study.

Materials and Methods

Study population

Detailed descriptions of the study have been published elsewhere (13) and are described briefly here. The study population consisted of female residents of Alberta aged 40 to 79 years, without a previous diagnosis of cancer (except nonmelanoma skin cancer) or history of hysterectomy and enrolled between September 2002 and February 2006. Incident endometrial cancer cases with a histologically confirmed diagnosis were identified from the Alberta Cancer Registry. Controls were identified using random digit dialing and frequency matched to cases on 5-year age groups. Participation rates were 67.9% and 52.2% for cases and controls, respectively. Informed consent was obtained from all study participants and the study protocol was approved by the Ethics Review Boards of the Alberta Cancer Board and the University of Calgary (Alberta, Canada).

Of the 497 potential cases for MSI testing and 1,032 controls that were eligible for this analysis, we excluded 17 cases with unsatisfactory microsatellite data and 13 cases and 2 controls that belonged to HNPCC families based on the Amsterdam II criteria (14, 15). To limit the analyses to postmenopausal women, a relatively homogeneous population with the highest incidence of endometrial cancer, we also excluded 106 cases and 288 controls that were pre- or perimenopausal. Thus, the final analysis included 361 sporadic postmenopausal cases (258 MSS and 103 MSI) and 742 controls.

Data collection/microsatellite status determination

Exposure and covariate data were obtained through in-person interviews for the time period before diagnosis for cases and an analogous reference time period for controls (13). The laboratory methods have been previously described in detail (16). In brief, genomic DNA was extracted from buffy coat and archival paraffin-embedded tumor tissue sections and microsatellite status was determined with five microsatellite markers (Bat25, Bat26, D5S346, D2S123, and D17S250). A mismatch error was defined as additional alleles in tumor DNA compared with germline DNA. Tumors with two or more mismatch errors were classified as MSI and tumors with one or none were classified as MSS (14). We found 100% reproducibility when we retested 10% of the samples (16).

Statistical analysis

Postmenopausal status was defined as age $\geq$60 years, or self-identified as postmenopausal with the last menstrual period $\geq$12 months before diagnosis/reference date, or 50 to 59 years and using menopausal hormones for $\geq$2 years. Polytomous logistic regression was used to estimate OR and associated 95% confidence intervals (95% CI), and the *P* value for heterogeneity was obtained by computing a z-statistic to compare the coefficients for MSS with MSI cases. Linear trend in risks was examined by modeling categorical hormonal and reproductive characteristics as ordinal variables and calculating the Wald statistic (17).

The following potential confounders identified *a priori* were evaluated in univariate analyses: body mass index (BMI), hypertension, education, and smoking. Factors with a $P < 0.20$ in the univariate analyses (18) were included in the multivariable analysis. Final statistical models were adjusted for the study design variables (reference age and residential type), smoking, BMI, and hypertension.

All statistical analyses were conducted with Stata (version 10, Stata Corporation). A 2-sided *P* value < 0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of the postmenopausal women (258 with MSS, 103 with MSI, and 742 controls) in the study. The mean age at menarche, menopause, or at first pregnancy lasting more than 20 weeks were similar for cases and controls. Cases were more likely than controls to have a higher BMI, never used oral contraceptives or menopausal hormone therapy, to be nulliparous, and to be diagnosed with hypertension. Among cases, oral contraceptive (MSS = 61.0% and MSI = 52.9%) or estrogen-only (E-only; MSS = 5.8% and MSI = 1.9%) use was more common among MSS than MSI cases, whereas estrogen plus progesterone (E+P) only use was more common among MSI (24.3%) than MSS (16.7%) cases (Table 1).

The results for the association between exogenous hormones and endometrial cancer risk are presented in Table 2. Overall, women who used oral contraceptive for 5 or more years or quit using it within the past 30 years had a reduced risk for endometrial cancer, but the risks for MSS and MSI cancers differed. We observed a significant trend in risk reduction for MSI ($P_{trend} = 0.005$), but not MSS ($P_{trend} = 0.23$) cancer, with increasing duration of oral contraceptive use. Women who had used oral contraceptive for 5 or more years had a statistically significant reduced risk of MSI (OR = 0.42; 95% CI, 0.23–0.77), but not for MSS (OR = 0.80; 95% CI, 0.54–1.17) cancer ($P_{heterogeneity} = 0.05$). Similarly, a reduction in risk associated with cessation of use within the past 30 years was stronger for MSI (OR = 0.36; 95% CI, 0.19–0.68) than for MSS (OR = 0.77; 95% CI, 0.51–1.15) cancer ($P_{heterogeneity} = 0.032$).

Though no differential association with risks for MSS and MSI cancer was observed for menopausal hormone use, women who had used E-only in the past had an increased risk for MSS cancer (OR = 1.87; 95% CI, 0.91–3.84), but a decreased risk for MSI cancer (OR = 0.67; 95% CI, 0.15–3.00). However, the results were based on a few number of cases (MSS = 15 and MSI = 2), and the associations were not statistically significant. Women who had used E+P only had a reduced risk for overall (OR = 0.60; 95%CI, 0.43–0.84) and for MSS cancer (OR = 0.53; 95%CI, 0.36–0.78), but for MSI cancer, there was no

Table 1. Characteristics of postmenopausal endometrial cancer cases and controls, Alberta, Canada, 2002–2006

Variable	Controls ($N = 742$) Mean (SD)[c]	All cases ($N = 361$) Mean (SD)[c]	MSS[a] cases ($N = 258$) Mean (SD)[c]	MSI[b] cases ($N = 103$) Mean (SD)[c]
Age at reference, y	62.6 (7.2)	62.1 (7.4)	62 (7.5)	62.4 (7.3)
Age at menarche, y	12.6 (1.5)	12.4 (1.5)	12.3 (1.5)	12.4 (1.5)
Age at menopause, y	50 (4.1)	50.1 (4.9)	50.2 (4.9)	50.1 (5.0)
Age at first pregnancy[d], y	23.7 (4.7)	23.3 (4.2)	23.4 (4.3)	23.0 (4.2)
BMI, kg/m^2	28.2 (5.6)	31.8 (7.4)	31.5 (7.4)	32.8 (7.4)
	N (%)	*N* (%)	*N* (%)	*N* (%)
Education				
High school diploma or less	228 (30.8)	117 (32.4)	73 (28.3)	44 (42.7)
Non-university certificate	363 (49)	163 (45.2)	122 (47.3)	41 (39.8)
University degree	150 (20.2)	81 (22.4)	63 (24.4)	18 (17.5)
Residence (type)				
Urban	463 (62.4)	240 (66.5)	170 (65.9)	70 (68)
Rural	279 (37.6)	121 (33.5)	88 (34.1)	33 (32.04)
Oral contraceptive use				
Never (<6 months)	254 (34.5)	147 (41.3)	99 (39.0)	48 (47.1)
Ever	483 (65.5)	209 (58.7)	155 (61.0)	54 (52.9)
Menopausal hormone therapy use				
Never (<6 months)	365 (49.5)	209 (58.1)	149 (58.0)	60 (58.3)
E-only	23 (3.1)	17 (4.7)	15 (5.8)	2 (1.9)
E+P only	227 (30.8)	68 (18.9)	43 (16.7)	25 (24.3)
Other[e]	122 (16.6)	66 (18.3)	50 (19.5)	16 (15.5)
Parity				
Never	61 (8.2)	50 (13.9)	36 (14.0)	14 (13.6)
Ever	681 (91.8)	311 (86.1)	222 (86.0)	89 (86.4)
Smoking				
Never (<100 cigarettes in lifetime)	364 (49.1)	175 (48.5)	132 (51.2)	43 (41.8)
Ever	378 (50.9)	186 (51.5)	126 (48.5)	60 (58.3)
Hypertension				
No	509 (68.7)	190 (52.6)	133 (51.6)	57 (55.3)
Yes	233 (31.4)	171 (47.4)	125 (48.5)	46 (44.7)

[a]MSS, microsatellite stable.
[b]MSI, microsatellite instability.
[c]SD, standard deviation.
[d]Pregnancy lasting more than 20 weeks.
[e]Includes all other combinations and types of menopausal hormone therapy.

significant risk reduction (OR = 0.80; 95% CI, 0.47–1.34). However, when we evaluated continuous combined estrogen (CCE)+P, the most common form of E+P use in our study population, 5 years use or more was associated with a reduced risk for both MSS (OR = 0.37; 95% CI, 0.20–0.69) and MSI (OR = 0.30; 95% CI, 0.10–0.87) cancer.

No statistically significant evidence of heterogeneity was observed between MSS and MSI subtypes for other aspects of reproductive history (Table 3). Interestingly, early age (<11 years) at menarche (overall: OR = 1.79; 95% CI, 1.06–3.03; MSS: OR = 2.03; 95% CI, 1.15–3.57; MSI: OR = 1.28; 95% CI, 0.58–2.92; $P_{\text{heterogeneity}} = 0.28$) or late age (≥55 years) at menopause (overall: OR = 1.55; 95% CI, 1.03–2.33; MSS: OR = 1.68; 95% CI, 1.06–2.65; MSI: OR = 1.26; 95% CI, 0.65–2.44; $P_{\text{heterogeneity}} = 0.43$) was associated with an increased risk of overall endometrial cancer that was statistically significant for MSS but not MSI cancer. Parity was associated with a reduced risk for overall and both subtypes of endometrial cancer, whereas age at first pregnancy was not associated with either of the subtypes or overall endometrial cancer in these postmenopausal women.

Discussion

In this study, we evaluated the associations between hormonal and reproductive factors and endometrial

Table 2. Association between hormonal factors and overall, MSS and MSI endometrial cancer, Alberta, Canada, 2002–2006

	Controls	All cases		MSS[a]		MSI[b]		
Characteristic	***N***	***N***	**OR (95%CI)[c]**	***N***	**OR (95%CI)[c]**	***N***	**OR (95%CI)[c]**	**Phet[d]**
Oral contraceptive use								
Never (<6 months)	254	147	Reference	99	Reference	48	Reference	
Ever (≥6 months)	483	209	0.99 (0.86–1.15)	155	1.02 (0.88–1.19)	54	0.86 (0.61–1.20)	0.31
Duration (y)								
0.5–4.9	261	120	0.72 (0.52–1.00)	84	0.74 (0.52–1.07)	36	0.68 (0.41–1.14)	0.77
≥5	221	88	0.68 (0.48–0.96)	70	0.80 (0.54–1.17)	18	0.42 (0.23–0.77)	0.05
P_{trend}			0.024		0.23		0.005	
Time since last use (y)								
0–30	223	94	0.63 (0.44–0.92)	75	0.77 (0.51–1.15)	19	0.36 (0.19–0.69)	0.032
≥30	259	114	0.76 (0.55–1.04)	79	0.79 (0.55–1.13)	35	0.69 (0.42–1.14)	0.64
P_{trend}			0.002		0.27		0.41	
Menopausal hormone therapy use								
Never (< 6 months)	365	209	Reference	149	Reference	60	Reference	
Ever use								
E[e] only	23	17	1.55 (0.78–3.10)	15	1.87 (0.91–3.84)	2	0.67 (0.15–3.00)	0.19
E+P[f] only	227	68	0.60 (0.43–0.84)	43	0.53 (0.36–0.78)	25	0.80 (0.47–1.34)	0.17
CCE+P[g] Only duration (y)								
0.5–4.9	62	17	0.44 (0.24–0.80)	10	0.36 (0.17–0.74)	7	0.66 (0.28–1.55)	0.24
≥5	103	17	0.35 (0.20–0.62)	13	0.37 (0.20–0.69)	4	0.30 (0.10–0.87)	0.73
P_{trend}			<0.001		<0.001		0.019	
Other combinations of hormones[h]	122	66	1.09 (0.76–1.57)	50	1.14 (0.77–1.69)	16	0.97 (0.53–1.78)	0.63

[a]MSS, microsatellite stable.
[b]MSI, microsatellite instability.
[c]ORs and 95% CI adjusted for age at reference (continuous), residential type (rural or urban), smoking (ever or never), BMI (continuous), and hypertension (ever or never).
[d]*P* value for test of heterogeneity between ORs for MSS and MSI.
[e]Estrogen.
[f]E+P, estrogen plus progesterone.
[g]CCE+P, continuous combined estrogen plus progesterone.
[h]Includes all other types of menopausal hormone therapy.

cancer risk by microsatellite status among postmenopausal women. Consistent with previous studies, we observed a reduced risk of overall endometrial cancer with oral contraceptive use (6) and parity (19); and an increased risk of overall endometrial cancer with early age at menarche (20) and a late age at menopause (19). We also observed a reduced risk of overall endometrial cancer with E+P only use that is consistent with some (21, 22) but not all (23, 24) previous studies. The inconsistency between studies has been attributed to duration of use, with a longer (≥10 years) duration of use potentially increasing risk and a shorter (<10 years) duration of use reducing risk (23). However, we did not have sufficient variation to evaluate durations of use 10 years or more and future studies on this topic are warranted. In addition, we observed for the first time that the reduced risk of endometrial cancer associated with oral contraceptive use seems to be stronger for MSI than MSS cancer.

The epidemiologic evidence for a reduced risk of endometrial cancer with oral contraceptive use is substantial (4), but the exact mechanisms involved are not known. Several hypotheses have been suggested including suppression of plasma pituitary gonadotrophins, inhibition of ovulation, or exposure to high progesterone concentrations (25). Because the effect of oral contraceptive use is observed years after cessation of use, it may cause a long-lasting effect, possibly on gene expression patterns. Given that we found a stronger risk reduction with longer duration of use and more recent use for MSI than MSS cancers, these findings may suggest a potential role of the mismatch repair system (MMR) in this process.

MMR maintains genomic integrity through the correction of DNA biosynthetic errors ensuring the fidelity of genetic recombination, and participates in the earliest steps of checkpoint and apoptotic responses to several

Table 3. Association between reproductive factors and overall, MSS and MSI endometrial cancer, Alberta, Canada, 2002–2006

	Controls	All cases		MSS[a]		MSI[b]		
Characteristic	*N*	*N*	OR (95%CI)[c]	*N*	OR (95%CI)[c]	*N*	OR (95%CI)[c]	Phet[d]
Age at menarche (y)								
≥13	381	158	Reference	108	Reference	50	Reference	
11–12	324	166	1.09 (0.82–1.43)	122	1.18 (0.87–1.61)	44	0.87 (0.57–1.36)	0.22
<11	37	37	1.79 (1.06–3.03)	28	2.03 (1.15–3.57)	50	1.28 (0.58–2.92)	0.28
P_{trend}			0.08		0.027		0.97	
Age at menopause (y)								
<50	297	127	Reference	87	Reference	40	Reference	
50–54	348	176	1.23 (0.92–1.64)	128	1.30 (0.94–1.80)	48	1.06 (0.67–1.68)	0.43
≥55	97	58	1.55 (1.03–2.33)	43	1.68 (1.06–2.65)	15	1.26 (0.65–2.44)	0.43
P_{trend}	259	114	0.031		0.02		0.53	
Parity								
Nulliparous	61	50	Reference	36	Reference	14	Reference	
Parous	681	311	0.53 (0.35–0.81)	222	0.53 (0.33–0.84)	89	0.53 (0.28–1.02)	0.98
1	56	37	0.75 (0.41–1.35)	27	0.76 (0.40–1.45)	10	0.71 (0.28–1.78)	0.88
2	234	103	0.51 (0.32–0.81)	72	0.50 (0.30–0.83)	31	0.55 (0.27–1.12)	0.79
3–4	295	144	0.56 (0.36–0.89)	105	0.58 (0.35–0.95)	39	0.53 (0.26–1.08)	0.82
5+	96	27	0.28 (0.15–0.52)	18	0.27 (0.13–0.53)	9	0.32 (0.12–0.84)	0.72
P_{trend}			<0.001		<0.005		0.023	
Age at first pregnancy (y)[e]								
<20	120	58	Reference	37	Reference	21	Reference	
20–24	315	142	1.08 (0.73–1.59)	102	1.21 (0.77–1.89)	40	0.85 (0.47–1.53)	0.29
25–29	170	83	1.12 (0.73–1.74)	62	1.31 (0.80–2.15)	21	0.78 (0.39–1.54)	0.17
≥30	137	78	1.26 (0.80–1.96)	57	1.42 (0.86–2.36)	21	0.96 (0.48–1.89)	0.30
P_{trend}			0.3		0.17		0.87	

[a]MSS, microsatellite stable.

[b]MSI, microsatellite instability.

[c]ORs and 95% CIs adjusted for age at reference (continuous), residential type (rural or urban), smoking (ever or never), BMI (continuous), and hypertension (ever or never).

[d]*P* value for test of heterogeneity between ORs for MSS and MSI.

[e]Pregnancy lasting for more than 20 weeks.

classes of DNA damage (26). Subsequently, defects in MMR results in an increase in spontaneous mutations and a predisposition to tumor development. Though defects in this pathway are the cause of typical and atypical HNPCC, it may also play a role in the development of 15% to 25% of sporadic tumors that occur in a number of tissues (27). The MMR system in humans is composed of *MLH1*, *MSH2*, *MLH3*, *PMS1*, and *PMS2* (26). We speculate that one explanation for the long-term reduction in risk with oral contraceptive use may be attributable to oral contraceptive use triggering a long-lasting activation of the MMR system in the endometrium by epigenetic modification of the MMR-related genes. There is strong evidence that *MLH1*, a gene frequently hypermethylated and inactivated in endometrial cancer, results in MSI tumors (28). This gene may also be hypomethylated leading to activation and a reduction in MSI tumors. The use of oral contraceptive may lead to a long-lasting activation of the MMR genes through hypomethylation resulting in efficient mismatch repair many years later. Further studies comparing the methylation status of MMR-related genes in oral contraceptive users and nonusers may provide more insight on this potential mechanism.

This study has several strengths. Cases were incident cancer cases with histologically confirmed endometrial cancer and were identified from a population-based cancer registry. We also adjusted for important confounders in statistical models, and validated the microsatellite status of a 10% random sample of the cases. The study's limitations include the low response rate among cases and controls. However, the distribution of risk factors among subjects included in the present analysis is similar to our province-wide case–control study, which is representative of Alberta women with respect to the main endometrial cancer risk factors (13). We also combined MSI-low cases (one mismatch error) with MSS cases (no mismatch errors) because of the small

number of MSI-low cases. A sensitivity analysis excluding MSI-low cases did not alter the findings of the study. In addition, germline testing was not conducted so there could be a small proportion of participants with inherited mutations. Data on hormone and reproductive exposures were based on self report and thus the possibility of recall bias cannot be excluded. However, good agreement has been reported between self-reported reproductive and hormonal history and medical records (29).

In summary, we found limited evidence for statistical heterogeneity of the associations of endometrial cancer risk with hormonal and reproductive factors by MSI status, except with oral contraceptive use. This finding suggests that there is a potential mechanistic role for the MMR system in the association between oral contraceptive use and endometrial cancer risk, although the exact mechanism is unclear. We speculate that some long-lasting epigenetic alteration to the MMR system may also be a mechanism through which oral contraceptives may reduce the risk of endometrial cancer. If the finding of the present study is confirmed, future studies may be warranted to examine the biologic effect of oral contraceptives on the MMR system.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Friedenreich, A.M. Magliocco, L.S. Cook
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