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Female Hormonal Factors and the Risk of Endometrial Cancer in Lynch Syndrome

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DISCLOSURE

The authors have no conflict of interest to declare with respect to this manuscript.

Author Contributions

Drs Dashti and Win had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

Importance—Apart from hysterectomy, there is no consensus recommendation for reducing endometrial cancer risk for women with a mismatch repair (MMR) gene mutation (Lynch syndrome).

Objective—To investigate the association between hormonal factors and endometrial cancer risk in Lynch syndrome.

Design, Setting, and Participants—A retrospective cohort study including 1,128 women with a MMR gene mutation identified from the Colon Cancer Family Registry was conducted. Data were analyzed using a weighted cohort approach. Participants were recruited between 1997 and 2012, from centers across the United States, Australia, Canada, and New Zealand.

Exposures—Age at menarche, first and last live birth, and menopause, number of live births, hormonal contraceptive use, and postmenopausal hormone use.

Main Outcome and Measures—Self-reported diagnosis of endometrial cancer.

Results—Endometrial cancer was diagnosed in 133 women (incidence per 100 person-years, 0.29; 95% confidence interval [CI], 0.24 to 0.34). A lower risk of endometrial cancer was associated with later age at menarche (hazard ratio [HR] per year, 0.85 [95%CI, 0.73 to 0.99]; *P*=.04), parity (parous vs nulliparous: HR, 0.21 [95%CI, 0.10 to 0.42]; *P*<.001), and hormonal contraceptive use (≥1 year vs <1 year: HR, 0.39 [95%CI, 0.23 to 0.64]; *P*<.001). There was no statistically significant association between endometrial cancer and age at first and last live birth, age at menopause, and postmenopausal hormone use.

Conclusions and Relevance—For women with a MMR gene mutation, some endogenous and exogenous hormonal factors were associated with a lower risk of endometrial cancer. These directions and strengths of associations were similar to those for the general population. If replicated, these findings suggest that women with a MMR gene mutation may be counseled like the general population in regard to hormonal influences on endometrial cancer risk.

Keywords

mismatch repair; endometrial cancer; reproductive factors; hormonal factors; pregnancy; contraceptives; Lynch syndrome

Introduction

Endometrial cancer is the most common type of gynecologic cancer in developed countries.[1, 2] Two to five percent of all endometrial cancer cases are associated with a hereditary susceptibility to cancer, mainly Lynch syndrome.[3] Lynch syndrome is an

autosomal dominant disorder caused by a germline mutation in one of the DNA mismatch repair (MMR) genes *MLH1* (RefSeq NM_000249), *MSH2* (RefSeq NM_000251), *MSH6* (RefSeq NM_000179), *PMS2* (RefSeq NM_000535), and *EPCAM* (RefSeq NM_000535).[4] Though estimates vary, the incidence of Lynch syndrome may be as high as 1 in 370 in the general population in the USA.[5] Depending on the mutated gene, cumulative risk of developing endometrial cancer by age 70 years for women is thought to be between 15% and 30%.[678] Apart from hysterectomy, there is no consensus recommendation for reducing endometrial cancer risk for women with a MMR gene mutation.[9,10]

Studies in the general population have shown factors that increase the bioavailability of estrogen unopposed by progesterone, including obesity,[11] early age at menarche, late age at menopause, nulliparity, and use of estrogen-only menopausal hormone therapy increase endometrial cancer risk.[12, 13] On the other hand, hormonal contraceptive use, higher number of pregnancies, and later age at first and last live birth have been shown to reduce endometrial cancer risk.[12, 13]

For Lynch syndrome, the association between female hormonal factors and endometrial cancer risk is not clear. Results from a multicenter randomized trial that studied the influence of oral contraceptive and medroxyprogesterone acetate on endometrial proliferation in 51 women with Lynch syndrome suggested that, similar to the general population, short-term exposure to exogenous progesterone reduced endometrial epithelial proliferation in this group of women.[14]

In the present study, we estimated the associations between endometrial cancer risk and hormonal factors for women with a MMR gene mutation, using the Colon Cancer Family Registry.

Materials and Methods

Study Sample

This was a retrospective cohort study that included women with a heterozygous germline pathogenic mutation in a MMR gene, who had been recruited by the Colon Cancer Family Registry. Study design and recruitment strategy have been published in detail and are available at http://coloncfr.org.[15] Probands were those who had either recently received a diagnosis of colorectal cancer that was reported to state or regional population cancer registries in the USA (Washington, Minnesota, California, Arizona, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria), and Canada (Ontario); or they were persons from multiple-case families referred to family-cancer clinics in the USA (Mayo Clinic, Rochester, Minnesota and Cleveland Clinic, Ohio), Canada (Ontario), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney), and New Zealand (Auckland). Individuals were recruited and interviewed between 1997 and 2012 and were asked for permission to contact their relatives and seek their enrollment in the Colon Cancer Family Registry. For population-based families, first-degree relatives of probands were recruited at all centers and, at some centers, recruitment was extended to more distant relatives. For clinic-based families, recruitment was attempted up to second-degree relatives of affected individuals (detail in Newcomb *et al.*).[15] Participants were followed up approximately every

5 years after baseline to update this information. For this study, 2011 was the last date of outcome assessment and censoring. Informed consent was obtained from all study participants and the study protocol was approved at each involved center by their institutional research ethics review boards.

Data Collection

At recruitment (baseline), information on demographics, personal characteristics, personal and family history of cancer, and history of cancer screening and any surgery including gynecologic surgery, was obtained using standardized questionnaire via personal interviews, telephone interviews, or mailed questionnaires from all participants. The questionnaires used at each Colon Cancer Family Registry center are available at http://coloncfr.org/questionaires. When possible, reported cancer diagnoses and age at diagnosis were confirmed using pathology review and reports, medical records, cancer registry reports, and/or death certificates. We attempted to obtain blood samples from all participants and tumor tissue samples from all participants affected with colorectal cancer.

MMR gene mutation testing

Testing for germline mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* was performed for all population-based probands who had a colorectal tumor displaying evidence of impaired MMR function as evidenced by tumor microsatellite instability (MSI) and/or by lack of MMR-protein expression in immunohistochemical (IHC) analysis. Testing was undertaken for the youngest-onset colorectal cancer participant from each clinic-based family regardless of MSI or MMR-protein expression status. Mutation testing for the *MLH1*, *MSH2*, and *MSH6* genes was performed by Sanger sequencing or denaturing high performance liquid chromatography (dHPLC), followed by confirmatory DNA sequencing. Large duplication and deletion mutations were detected by Multiplex Ligation Dependent Probe Amplification (MLPA) according to the manufacturer's instructions (MRC Holland, Amsterdam, The Netherlands).[15–17] *PMS2* mutation testing involved a modified protocol from Senter *et al.* [8] where exons 1–5, 9 and 11–15 were amplified in three long-range PCRs, followed by nested exon specific PCR/sequencing, with the remaining exons (6, 7, 8 and 10) being amplified and sequenced direct from genomic DNA. Large-scale deletions in *PMS2* were detected using the P008-A1 MLPA kit (MRC Holland, Amsterdam, The Netherlands). Relatives of probands with a pathogenic MMR germline mutation[18] who provided a blood sample underwent testing for the specific mutation identified in the proband.

Statistical analysis

Cox proportional regression models with age as the time scale were used to estimate any association between female hormonal factors (see Box 1 for definitions) and endometrial cancer risk. Time at risk started at birth and ended at age of endometrial cancer diagnosis, any other cancer diagnosis, hysterectomy, or interview, whichever occurred first. We censored at age of diagnosis of any primary cancer because resultant treatment and surveillance might have altered endometrial cancer risk. In addition, carriers might have changed their behavior following the diagnosis of cancer.

Box 1

Definitions of outcome and exposures

All the definitions were pre-defined prior to analysis of the data.

Primary Outcome: Self-reported diagnosis of endometrial cancer.

Primary Exposures: Self-reported endogenous and exogenous hormonal factors.

Number of live births was defined as the number of pregnancies that resulted in a live birth. Given that the questionnaires did not elicit age at each birth, we defined number of live births based on self-reported number of live births, age at first and last live birth and censored age. Women with age at first live birth younger than censored age were categorized as parous and women with age at first live birth older than censored age were categorized as nulliparous.

Ever use of hormonal contraceptive was defined as use of oral contraceptives or other hormonal contraceptives (implants or injections) for at least one year. Based on the reported age at first use and number of years of hormonal contraception use, and assuming that the use had been continuous, age at last use of hormonal contraception was calculated. When this age was older than censored age, years of hormonal contraception use was calculated based on censored age and age at first use.

Age at menopause was defined as age when menstrual cycles stopped for at least 12 months. Natural menopause was defined as self-reported cessation of menstrual cycles for at least 12 months. Induced menopause was defined as cessation of menstrual cycles for at least 12 months due to gynecologic surgery, radiation or chemotherapy, or other reasons.

Women with unknown menopausal status were assumed to have had natural menopause if they were 60 years or older at the time of censoring. For this group of women, age at menopause was considered at 56, which was the oldest age at natural menopause reported in this cohort. Ever use of postmenopausal hormones (PMH) was use of a pill or patch for at least one year. Estrogen-only use was defined as having used estrogen-only pills or patches for at least 1 year. Estrogen and progesterone combination was defined as having used progesterone along with estrogen for at least one year. Based on the reported age at first use and number of years of PMH use and assuming that the use had been continuous, age at last use of PMH was calculated. When this age was older than censored age, years of PMH use was calculated based on censored age and age at first use.

Since a proportion of women in this study was ascertained from multiple-case cancer-families and cases were tested preferentially for MMR gene mutations, selection of women was not random with respect to disease status. To take this non-random ascertainment of cases into account, we applied probability weights to women based on the approach described by Antoniou *et al*.[19] Age-specific incidences of endometrial cancer for women were calculated by multiplying the country- and age-specific population incidences by the hazard ratio (HR) of endometrial cancer for women with a specific MMR gene mutation.

Average age-specific population incidences in 1998–2002 for each country (Australia, Canada, and USA) were obtained from Cancer Incidence in Five Continents.[20] These age-specific incidences of endometrial cancer for women with MMR gene mutations were used to calculate statistical weights for women with and without endometrial cancer in each age-stratum.

The proportional hazards (PH) assumption was tested using the Schoenfeld and scaled Schoenfeld residuals.[21] Bivariable and multivariable models were fit separately for each hormonal factor. The variables that we considered as potential confounders are listed in Table 1. The variables that did not meet the PH assumption were stratified for in the model. Tests for interactions were assessed by a change in the log-likelihood ratio after the addition of a cross-product term between the exposure and potential effect modifiers identified a priori. The overall model fit was assessed using Cox-Snell residuals as the time variable and plotting them against the Nelson-Aalen cumulative hazard function.[22]

For multivariable models, missing data were handled using both complete case analysis and multiple imputation. Numbers of missing values for all the variables are reported in Table 1a and 1b. Assuming that missing was at random, missing data were imputed using chained equations.[23, 24] Variables included in the imputation model were outcome status, age at the time of endometrial cancer diagnosis or censored age, year of birth, country, mutated gene, ascertainment method (clinic vs. population), and whether the carrier was a proband. Fifty imputed datasets were created.

When age variables (i.e. age at menarche, age at first and last live birth, and age at menopause) were the primary exposures, we analyzed them as categorical variable as well as continuous variable in two different models. We used the median values as the cut-off points to categorize these variables.

We conducted the following additional analyses: i) analyses restricted to women who were diagnosed with endometrial cancer or censored within 5 years before interview to reduce survival bias; ii) analyses restricted to women with verified endometrial cancer diagnosis and unaffected women; iii) analyses for women ascertained through clinic-based and population-based resources, and for the four mutated MMR genes; and iv) analyses in which we did not censor women at age of first diagnosis of any other cancer.

To account for potential correlation of risk between family members, the Huber-White robust variance correction was used by clustering on family membership.[25, 26] All statistical tests were two-sided and P value <.05 was considered statistically significant. All statistical analyses were performed using Stata 13.0.[27]

Results

We identified 1,133 women with a MMR gene mutation from the Colon Cancer Family Registry. Of these, 5 (0.4%) who were younger than age 18 years were excluded. The final sample included 1,128 women from 548 independent families, contributing a total of 45,831 person-years. Of these women, 424 carried a mutation in *MLH1*, 532 in *MSH2*, 117 in *MSH6*, and 55 in *PMS2*.

Time at risk ended at age at: endometrial cancer diagnosis for 133 women; any other cancer diagnosis for 417; hysterectomy for 229; and interview for 349. In this cohort, endometrial cancer incidence rate was 0.29 per 100 person-years (95% confidence interval [CI], 0.24 to 0.34) with a mean age of diagnosis of 45.9 (standard deviation 8.2). We were able to confirm endometrial cancer diagnosis for 101 (76%) women by pathology review or report, cancer registries, or hospital record. Characteristics of women included in this study are summarized in Table 1a and Table 1b.

The results of Cox regression models and adjusted variables in each model are summarized in Table 2 and Table 3. There was a statistically significant association between later age at menarche and a lower risk of endometrial cancer (endometrial cancer incidence rate per 100 person-years for women with age at menarche ≥ 13 vs. <13 years: 0.27 vs. 0.31; rate difference, −0.04 [95%CI, −0.15 to 0.05]; HR per year, 0.85 [95%CI, 0.73 to 0.99]; *P*=.04). There was also an inverse association between endometrial cancer risk and parity (incidence rate per 100 person-years for parous vs. nulliparous women: 0.26 vs. 0.43; rate difference, −0.18 [95%CI, −0.32 to −0.04]; HR, 0.21 [95%CI, 0.10 to 0.42]; *P*<.001). We did not observe statistically significant association between endometrial cancer risk and age at first live birth (*P*=.46), age at last live birth (*P*=.62), or age at menopause (*P*=.96) (Table 2).

Ever use of hormonal contraceptives was associated with a lower endometrial cancer risk compared with never use (incidence rate per 100 person-years for ≥1 year vs. <1 year use: 0.22 vs. 0.45; rate difference, −0.23 [95%CI, −0.36 to −0.11]; HR, 0.39 [95%CI, 0.23 to 0.64]; *P*<.001). There was no statistically significant association between PMH use and endometrial cancer risk (*P*=.57), even after stratifying the type of PMH (estrogen-only or estrogen and progestin combination) (Table 3). Due to small number of women (1%) who reported use of anti-estrogen drugs (including Tamoxifen and Raloxifene), we were unable to investigate associations between these drugs and endometrial cancer risk in this study.

There was no statistically significant evidence that cigarette smoking status, BMI at age 20, country, specific MMR gene, and ascertainment method modified any of observed associations (eTable 1).

In an analysis restricted to women who were diagnosed with endometrial cancer or censored within 5 years before interview, we found the results similar to the main analysis (eTable 2). In sensitivity analyses restricted to women with verified endometrial cancer diagnosis and unaffected women, results were similar to the main analysis. Although the statistical power was poor, the patterns of associations remained the same in analyses stratified by ascertainment (clinic- and population-based) and by mutated gene (*MLH1*, *MLH2*, *MSH6*, and *PMS2*) (eTables 3 – 6). We also observed similar results in analyses that did not censor women at their age of first diagnosis of any other cancer (eTable 7). When we additionally adjusted for recent BMI in the multiple imputation analyses, the results were similar to the main analyses (eTable 8).

There was no evidence that main exposure variables violated the PH assumption in any of the final models. The directions and strengths of associations were similar in both un-

weighted and weighted cohort analyses although the standard errors of the estimates were increased in weighted analyses.

Discussion

In this study, an inverse association was observed between the risk of endometrial cancer for women with a MMR gene mutation and late age of menarche, increased parity, and use of hormonal contraceptives. The directions of the observed associations are similar to those that have been reported for the general population suggesting a possible protective effect of these factors.[12, 13, 28–32] Unlike observations for women from the general population,[12, 13, 33, 34] there was no statistically significant association between age at menopause and endometrial cancer risk in Lynch syndrome. About 80% of women in our cohort were pre-menopausal and age at menopause was unknown for about 22% of post-menopausal women. Similarly, we did not observe statistically significant association between endometrial cancer risk and age at first and last live birth in Lynch syndrome, which is in line with some[13, 35] but not all studies[35, 36] conducted in the general population.[37] The lack of an observed association between endometrial cancer risk and PMH use in this study could be attributed to lack of statistical power (only 2.8% reported use of estrogen-only and 4.3% reported use of combined estrogen and progesterone for at least one year). Additional unmeasured confounding or information bias could also account for this finding.

Given that Lynch syndrome-associated cancers typically exhibit high level of MSI and/or loss of MMR protein expression by IHC, these tests have been widely used as screening methods for likely MMR germline mutation carriers. However, neither of these tests is diagnostic and germline testing is required to confirm mutation carrier status.[38] For example, MSI is seen in approximately 30% of sporadic endometrial cancers.[39] Amankwah *et al.*[40] investigated the association between hormonal factors and the risk of microsatellite stable (MSS; n=103) and MSI (n=258) endometrial cancer. Similar to our results, Amankwah *et al.* reported a reduced risk of MSI endometrial cancer for parous women compared with nulliparous women (odds ratio [OR], 0.53 [95%CI, 0.28 to 1.02]), and for women who used oral contraceptives for at least 5 years compared with those who used less than 6 months (OR, 0.43 [95%CI, 0.23 to 0.77]). There was an increasing risk reduction of endometrial cancer associated with a longer duration of oral contraceptives use, and a stronger inverse association for women with a MSI tumor compared with women with a MSS tumor.

An inverse association between endometrial proliferation and hormonal contraceptives in Lynch syndrome was also reported in a multicenter randomized trial.[14] In that study, 51 women with a known MMR gene mutation or a personal history of Lynch syndrome-associated cancer who met Amsterdam criteria were randomly assigned to receive either oral contraceptive pills or medroxyprogesterone acetate for 3 months and assessed for endometrial proliferation before and after treatment. A significant decrease in endometrial epithelial proliferation was observed post treatment in both groups compared with before treatment, suggesting that hormonal contraceptives may be useful chemopreventive agents in these high-risk women. Our results provide further evidence supporting the hypothesis

that long-term exposure to hormonal contraceptives may significantly reduce the risk of endometrial cancer in Lynch syndrome.

To our best knowledge, this is the largest study to date investigating the association between endometrial cancer risk and hormonal factors in Lynch syndrome. To overcome bias in retrospective studies where subjects are selected on the basis of disease, we used a weighted cohort approach,[19] which has been successfully used in studies of modifiers of cancer risk associated with rare genetic mutations.[10, 41, 42] Data for this study came from the Colon Cancer Family Registry, which used standardized and uniform materials for collection of epidemiology, family, and cancer data as well as genetic testing.

Our study had several limitations. There might be errors in the measurement of exposure variables and other adjusted variables, as the measurements came from self-reported questionnaires. For individuals who were diagnosed with endometrial cancer or censored at an age younger than their age at interview, years of hormonal contraception and PMH use were calculated based on self-reported age at first use and number of years of hormone use, assuming that use had been continuous. This method may have overestimated the years of hormone use in some carriers. However, this potential misclassification would more probably bias the results towards the null and would not account for the observed inverse association between endometrial cancer risk and years of hormonal contraceptive. Recall of all exposure may have been affected by disease status in our cohort because women were diagnosed with endometrial cancer before interview. To determine whether survival bias influenced the observed associations, we conducted a sensitivity analysis restricted to women who were diagnosed with endometrial cancer or censored within 5 years before interview; we observed findings similar to the main analysis. Another potential limitation of our study is the lack of a valid measure of recent BMI for 52% of all women. BMI is a strong and consistent risk factor for endometrial cancer and has been reported to be a confounder for the association between endometrial cancer risk and hormonal factors for the general population.[11, 43] However, there is some evidence that recent BMI is not associated with endometrial cancer in Lynch syndrome.[44–47] In our complete case analysis, BMI at age 20 was available and did not confound or modify the association between endometrial cancer risk and any of hormonal factors. Further, imputed recent BMI did not confound any of those associations.

Conclusions

For women with a MMR gene mutation, some endogenous and exogenous hormonal factors were associated with a lower risk of endometrial cancer. These directions and strengths of associations were similar to those for the general population. If replicated, these findings suggest that women with a MMR gene mutation may be counseled like the general population in regard to hormonal influences on endometrial cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1a

Characteristics of women with a germline mutation in a DNA mismatch repair gene

	No endometrial cancer N = 995 (88.2%)	Endometrial cancer N = 133 (11.8%)	Total N = 1,128
Study Centers, n (%)			
Australia or New Zealand	557 (56.0)	52 (39.1)	609 (54.0)
USA	290 (29.2)	50 (37.6)	340 (30.1)
Canada	148 (14.9)	31 (23.3)	179 (15.9)
Race			
Caucasian	923 (92.8)	128 (96.1)	1,051 (93.2)
Other	51 (5.1)	4 (3.0)	55 (4.9)
Missing	21 (2.1)	1 (0.8)	22 (1.9)
Ascertainment method			
Clinic	742 (74.6)	102 (76.7)	844 (74.8)
Population	253 (25.4)	31 (23.3)	284 (25.2)
Age (year),[1]			
mean (SD)	39.9 (11.4)	45.9 (8.2)	40.6 (11.3)
median [range]	40 [18 – 86]	46 [25 – 68]	40 [18 – 86]
Year of Birth, n (%)			
1914–1943	215 (21.6)	47 (35.3)	262 (23.2)
1944–1954	237 (23.8)	53 (39.9)	290 (25.7)
1955–1965	278 (27.9)	26 (19.6)	304 (27.0)
1966–1990	265 (26.6)	7 (5.3)	272 (24.1)
Education level, n (%)			
Primary or less	19 (1.9)	2 (1.5)	21 (1.9)
Some high school	201 (20.2)	31 (23.3)	232 (20.6)
Completed high school/ some tertiary study	355 (35.7)	45 (33.8)	400 (35.5)
Vocational/technical school	171 (17.2)	15 (11.3)	186 (16.5)
University degree	232 (23.3)	39 (29.3)	271 (24.0)
Missing	17 (1.7)	1 (0.8)	18 (1.6)
Mismatch repair gene mutated, n (%)			
MLH1	392 (39.4)	32 (24.1)	425 (37.6)
MSH2	457 (45.9)	75 (56.4)	532 (47.2)
MSH6	94 (9.5)	23 (17.3)	117 (10.4)
PMS2	52 (5.2)	3 (2.3)	55 (4.9)
Family history of colorectal and/or endometrial cancer			
No family history	178 (17.9)	21 (15.8)	199 (17.6)
First-degree relative	137 (13.8)	28 (21.1)	165 (14.6)
Second-degree relative	79 (7.9)	7 (21.1)	86 (7.6)

	No endometrial cancer N = 995 (88.2%)	Endometrial cancer N = 133 (11.8%)	Total N = 1,128
First- and second- degree relative	601 (60.4)	77 (57.9)	678 (60.1)
Body mass index at age 20,[2] n (%)			
Normal	672 (67.5)	97 (72.9)	769 (68.2)
Overweight	95 (9.6)	15 (11.3)	110 (9.8)
Obese	36 (3.6)	4 (3.0)	40 (3.6)
Underweight	136 (13.7)	10 (7.5)	146 (12.9)
Missing	56 (5.6)	7 (5.3)	63 (5.6)
Body mass index 2 years before diagnosed/ censored age,[2*] n (%)			
Normal	294 (29.6)	10 (7.5)	304 (27.0)
Overweight	129 (13.0)	2 (1.5)	131 (11.6)
Obese	78 (7.8)	9 (6.8)	87 (7.7)
Underweight	22 (2.2)	2 (1.5)	24 (2.1)
Missing	472 (47.4)	110 (82.7)	582 (51.6)
Diabetes, n (%)			
No	965 (967.0)	128 (96.2)	1,093 (96.9)
Yes	15 (1.5)	1 (0.8)	16 (1.4)
Missing	15 (1.5)	4 (3.0)	19 (1.7)
Aspirin and/or ibuprofen intake,[3] n (%)			
<1 month	799 (80.3)	97 (72.9)	896 (79.4)
≥1 month	127 (12.8)	16 (12.0)	143 (12.7)
Missing	69 (6.9)	20 (15.0)	89 (7.9)
Multivitamin intake,[3] n (%)			
<1 month	661 (66.4)	96 (72.2)	757 (67.1)
≥1 month	258 (25.9)	20 (15.0)	278 (24.7)
Missing	76 (7.6)	17 (12.8)	93 (8.2)
Calcium intake,[3] n (%)			
<1 month	821 (82.5)	101 (75.9)	922 (81.7)
≥1 month	120 (12.1)	15 (11.3)	135 (12.0)
Missing	54 (5.4)	17 (12.8)	71 (6.3)
Folic acid intake,[3] n (%)			
<1 month	816 (82.0)	117 (88.0)	933 (82.7)
≥1 month	135 (13.6)	6 (4.5)	141 (12.5)
Missing	44 (4.4)	10 (7.5)	54 (4.8)
Cigarette smoking,[4] n (%)			
Never smoker	539 (54.2)	84 (63.2)	623 (55.2)
Former smoker	183 (18.4)	19 (14.3)	202 (17.9)

	No endometrial cancer N = 995 (88.2%)	Endometrial cancer N = 133 (11.8%)	Total N = 1,128
Current smoker	267 (26.8)	29 (21.8)	296 (26.2)
Missing	6 (0.6)	1 (0.8)	7 (0.6)
Average number of alcoholic beverages consumed per day, [5] n (%)			
Never	328 (33.0)	54 (40.6)	382 (33.9)
<1	336 (33.8)	41 (30.8)	377 (33.4)
≥1	183 (18.4)	18 (13.5)	201 (17.8)
Missing	148 (14.9)	20 (15.0)	168 (14.9)
Regular physical activity,[6] n (%)			
<3 months	122 (12.3)	19 (14.3)	141 (12.5)
≥3 months	873 (87.7)	114 (85.7)	987 (87.5)

[1] Age of diagnosis of endometrial cancer for affected women; age of diagnosis of another cancer or hysterectomy or interview for endometrial cancer-unaffected women (whichever came first)

[2] underweight <18.5 kg/m^2, normal (18.5 – 25.0) kg/m^2, overweight (25.0 – 29.9 kg/m^2), obese (≥30 kg/m^2)

[3] at least twice a week

[4] former smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and had quit more than 2 years before age at endometrial cancer or censored age; current smokers defined as carriers who had smoked at least 1 cigarette per day for at least 3 months and continued within 2 years of age at endometrial cancer or censored age.

[5] 4-oz. glasses of wine, or 12-oz. cans or bottles of beer or hard cider, or 1-oz. servings of sake or liquor (spirits)

[6] regular physical activity defined as any physical activity for at least 30 minutes per week for at least 3 months

[*] carriers who were diagnosed with endometrial cancer or censored more than 2 years before interview had missing for this variable

Table 1b

Hormonal and reproductive characteristics of women with a germline mutation in a DNA mismatch repair gene

	No endometrial cancer N = 995 (88.2%)	Endometrial cancer N = 133 (11.8%)	Total N = 1,128
Number of live births, n (%)			
No	238 (23.9)	40 (30.1)	278 (24.7)
1	113 (11.4)	13 (9.8)	126 (11.2)
2	289 (29.1)	29 (21.8)	318 (28.2)
≥3	325 (32.7)	46 (34.6)	371 (32.9)
Missing	30 (3.0)	5 (3.8)	35 (3.1)
Age at first live birth			
No live births	238 (23.9)	40 (30.1)	278 (24.7)
<25 years	431 (43.3)	54(40.6)	485 (43.0)
≥25 years	296 (29.8)	34 (25.6)	330 (29.3)
Missing	30 (3.0)	5 (3.8)	35 (3.1)
Age at last live birth			
No live births	238 (23.9)	40 (30.1)	278 (24.7)
<30 years	382 (38.4)	34.6 (34.6)	428 (37.9)
≥30 years	336 (33.8)	41 (30.8)	377 (33.4)
Missing	39 (3.9)	6 (4.5)	45 (4.0)
Age at menarche, n (%)			
<13 years	397 (39.9)	57 (42.9)	454 (40.3)
≥13 years	569 (57.2)	70 (52.6)	639 (56.7)
Missing	29 (2.9)	6 (4.5)	35 (3.1)
Menopause status, n (%)			
Pre-menopause	803 (80.7)	90 (67.7)	893 (79.2)
Natural menopause	113 (11.4)	19 (14.3)	132 (11.7)
Induced menopause	58 (5.8)	12 (9.0)	70 (6.2)
Missing	21 (2.1)	12 (9.0)	33 (2.9)
Age at menopause, n (%)			
Pre-menopause	803 (80.7)	90 (67.7)	893 (79.2)
<50	109 (11.0)	16 (12.0)	125 (11.1)
≥50	59 (5.9)	15 (11.3)	74 (6.6)
Missing	24 (2.4)	12 (9.0)	36 (3.2)
Hormonal contraception use, n (%)			
<1 year	240 (24.1)	57 (42.9)	297 (26.3)
≥1 year	733 (73.7)	70 (52.6)	803 (71.2)
Missing	22 (2.2)	6 (4.5)	28 (2.5)

	No endometrial cancer N = 995 (88.2%)	Endometrial cancer N = 133 (11.8%)	Total N = 1,128
Years of hormonal contraception use, n (%)			
<1 year	240 (24.1)	57 (42.9)	297 (26.3)
1–4 years	235 (23.6)	32 (24.1)	267 (23.7)
≥5 years	460 (46.2)	35 (26.3)	495 (43.9)
Missing	60 (6.0)	9 (6.8)	69 (6.1)
Postmenopausal hormone use, n (%)			
<1 year	888 (89.3)	112 (84.2)	1000 (88.7)
≥1 year, estrogen only	29 (2.9)	3 (2.3)	32 (2.8)
≥1 year, estrogen and progestin	37 (3.7)	9 (6.8)	46 (4.1)
Missing	41 (4.1)	9 (6.8)	50 (4.4)
Years of postmenopausal hormone use, n (%)			
<1 year	888 (89.3)	112 (84.2)	1000 (88.7)
1–4 years	32 (3.2)	8 (6.0)	40 (3.6)
≥5 years	30 (3.0)	4 (3.0)	34 (3.0)
Missing	45 (4.5)	9 (6.8)	54 (4.8)
Anti-estrogen use, n (%)			
Never	906 (91.1)	115 (86.5)	1,021 (90.5)
Ever	10 (1.0)	1 (0.8)	11 (1.0)
Missing	79 (7.9)	17 (12.8)	96 (8.5)
History of gynecologic surgery			
Never	396 (39.8)	118 (88.7)	514 (45.6)
Hysterectomy (With or without unilateral or bilateral oophorectomy)	229 (23.0)	0	229 (20.3)
Unilateral or bilateral oophorectomy	7 (0.7)	1 (0.75)	8 (0.7)
Other gynecological surgery	30 (3.02)	1 (0.75)	31 (2.8)
History of more than one gynecological surgery	7 (0.7)	5 (3.8)	12 (1.1)
Unknown	326 (32.8)	8 (6.0)	334 (29.6)

Table 2

Hazard ratios for associations between the risk of endometrial cancer and endogenous hormonal factors for women with a germline mutation in a DNA mismatch repair gene

				Bivariable model		Multivariable[1]			
						Complete case analysis		Multiple imputation	
	No. of women with endometrial cancer (%)	Total number of women	Person-Years*	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at menarche									
<13 years	57 (12.6)	454	18110	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥13 years	70 (11.0)	639	26245	0.67 (0.42 – 1.05)	.08	0.69 (0.43 – 1.11)	.13	0.70 (0.44 – 1.11)	.13
Age at menarche (Per year)	127 (11.6)	1093	44355	0.86 (0.74 – 0.99)	.04	0.85 (0.73 – 0.99)	.04	0.85 (0.73 – 0.99)	.04
Live births[2]									
Nulliparous	40 (14.4)	278	9308	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
Parous	91 (11.0)	827	35670	0.27 (0.16 – 0.46)	<.001	0.20 (0.09 – 0.46)	<.001	0.21 (0.10 – 0.42)	<.001
1	13 (10.3)	126	4877	0.45 (0.21 – 0.98)	.05	0.32 (0.12 – 0.86)	.02	0.37 (0.15 – 0.95)	.04
2	29 (9.1)	318	13293	0.26 (0.14 – 0.49)	<.001	0.18 (0.07 – 0.41)	<.001	0.22 (0.10 – 0.49)	<.001
≥3	46 (12.4)	371	17096	0.23 (0.13 – 0.41)	<.001	0.15 (0.06 – 0.37)	<.001	0.19 (0.09 – 0.41)	<.001
Age at first live birth[3]									
<25 years	54 (11.1)	485	20947	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥25 years	34 (10.3)	330	14319	0.89 (0.53 – 1.49)	.67	0.81 (0.46 – 1.45)	.48	0.72 (0.42 – 1.24)	.24
Age at first live birth[3] (Per year)	88 (10.8)	815	35266	1.00 (0.96 – 1.06)	.85	0.99 (0.94 – 1.04)	.71	0.98 (0.93 – 1.03)	.46
Age at last live birth[3]									
<30 years	46 (10.7)	428	17740	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥30 years	41 (10.9)	377	17190	0.70 (0.43 – 1.11)	.13	0.81 (0.46 – 1.42)	.47	0.71 (0.41 – 1.20)	.20
Age at last live birth[3] (Per year)	87 (10.8)	805	34930	0.97 (0.93 – 1.01)	.18	1.00 (0.95 – 1.05)	.98	0.99 (0.94 – 1.04)	.62

				Bivariable model		Multivariable[1]			
						Complete case analysis		Multiple imputation	
	No. of women with endometrial cancer (%)	Total number of women	Person-Years*	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at menopause[4]									
<50 years	5 (8.2)	61	3357	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥50 years	14 (20.0)	70	4375	2.47 (1.06 – 10.8)	.11	1.88 (0.59 – 6.02)	.33	1.64 (0.53 – 5.05)	.39
Age at menopause[4] (Per year)	19 (14.5)	131	7732	1.03 (0.97 – 1.09)	.31	1.02 (0.94 – 1.10)	.65	1.00 (0.94 – 1.06)	.96

[1] All multivariable models were adjusted for country (categorical), education (categorical), and ascertainment (binary).

[2] Additionally adjusted for years of hormonal contraceptive use (categorical) and age at menopause (categorical) in both multivariable models.

[3] Limited to parous women and additionally adjusted for number of live births (categorical) and age at menopause (categorical) in both multivariable models

[4] Limited to women with natural menopause and additionally adjusted for age at menarche (categorical), number of live births (categorical), and years of hormonal contraceptive use (categorical) in both multivariable models.

HR, hazard ratio; CI, confidence interval

Table 3

Hazard ratios for associations between the risk of endometrial cancer and exogenous hormonal factors for women with a germline mutation in a DNA mismatch repair gene

				Bivariable model		Multivariable model[1]			
						Complete case analysis		Multiple imputation	
	No. of women with endometrial cancer (%)	Total number of women	Person-Years	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Postmenopausal hormone use[2]									
<1 year	112 (11.2)	999	39274	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥1 year	12 (15.8)	76	4124	0.47 (0.24 – 0.90)	.02	0.76 (0.35 – 1.68)	.50	0.81 (0.40 – 1.67)	.57
Estrogen only	3 (10.0)	30	1582	0.31 (0.08 – 1.11)	.07	0.34 (0.06 – 1.99)	.23	0.46 (0.11 – 1.82)	.27
Estrogen and progestin	9 (19.6)	46	2542	0.56 (0.26 – 1.19)	.13	1.12 (0.48 – 2.59)	.80	1.10 (0.51 – 2.38)	.80
Hormonal Contraceptive[3]									
<1 year	57 (19.2)	297	12575	1.00 [Referent]		1.00 [Referent]		1.00 [Referent]	
≥1 year	70 (8.7)	803	32142	0.48 (0.30 – 0.79)	.004	0.35 (0.20 – 0.63)	<.001	0.39 (0.23 – 0.64)	<.001
1–4 years*	32 (12.0)	267	10377	0.73 (0.42 – 1.28)	.27	0.57 (0.30 – 1.06)	.07	0.61 (0.33 – 1.10)	.10
≥5 years*	35 (7.1)	495	19931	0.41 (0.23 – 0.74)	.003	0.31 (0.16 – 0.59)	<.001	0.37 (0.20 – 0.67)	.001
Hormonal Contraceptive[3] (Per year)	124 (11.7)	1059	42883	0.94 (0.89 – 0.98)	.007	0.92 (0.88 – 0.97)	.002	0.93 (0.89 – 0.97)	.002

[1] All multivariable models were adjusted for country (categorical), education (categorical), and ascertainment (binary).

[2] Additionally adjusted for years of hormonal contraceptive use (categorical), and age at menopause (categorical) in both multivariable models.

[3] Additionally adjusted for age at menarche (categorical), age at menopause (categorical), and number of live births (categorical) in both multivariable models.

HR, hazard ratio; CI, confidence interval

* The number of women with endometrial cancer and the total number of women reported for each of the 2 time periods do not sum to the overall number for use ≥ 1 year because 41 women (3 with endometrial cancer) had responded “yes” to the question “Have you ever used birth control pills or other hormonal contraceptives for at least one year?” but had not reported the duration of hormonal contraceptive intake.