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Body Mass Index in Early Adulthood and Endometrial Cancer Risk for Mismatch Repair Gene Mutation Carriers

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Abstract

Objective—To investigate the association of body mass index (BMI) and endometrial cancer risk for carriers of a germline mutation in a DNA mismatch repair gene.

Methods—We estimated the association between BMI at age 18-20 years and endometrial cancer risk for mismatch repair gene mutation carriers and, as a comparison group, non-carriers using 601 female carriers of a germline mutation in a mismatch repair gene (245 *MLH1*, 299 *MSH2*, 38 *MSH6* and 19 *PMS2*) and 533 female non-carriers from the Colon Cancer Family Registry using a weighted Cox proportional hazards regression.

Results—During 51,693 person-years of observation, we observed diagnoses of endometrial cancer for 126 carriers and 8 non-carriers. For carriers, there was no evidence for an association between BMI at age 20 years and endometrial cancer (adjusted hazard ratio, HR 0.73 per 5 kg/m^2;

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95% confidence interval, CI 0.40–1.34; $P = 0.31$). For non-carriers, endometrial cancer risk increased by 74% for each 5 kg/m^2 increment in BMI (adjusted HR 1.74; 95% CI 1.27–2.37; $P < 0.001$). The HR for BMI and endometrial cancer for non-carriers was greater than for carriers ($P = 0.04$).

Conclusions—The effect of body mass on endometrial cancer risk depends on the woman's mismatch repair gene mutation carrier status, suggesting obesity-independent endometrial carcinogenesis for carriers.

Introduction

Lynch syndrome is caused by a germline mutation in one of the DNA mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2* (1). Approximately 1 in 3,000 people carry a germline mutation in a MMR gene (2) and are at substantially increased risk of colorectal, endometrial, ovarian and other cancers (4, 5). Cumulative risk of endometrial cancer to age 70 years is estimated to be: 44% for *MLH1* and *MSH2* mutation carriers (3), 26% for *MSH6* mutation carriers (4) and 15% for *PMS2* mutation carriers (5). Physical characteristics or environmental exposures of the mutation carriers could also modify risk of developing endometrial cancer (6).

While obesity is an established risk factor for endometrial cancer in the general population (7-12), the role of obesity in endometrial cancer risk is not well understood for MMR gene mutation carriers. Body mass index (BMI) is a commonly used statistical measure of body mass adjusted for an individual's height. A BMI ≥30 kg/m^2 is a commonly used definition of obesity (13). To date, there have been three clinical studies investigating risk factors including BMI of endometrial cancer in MMR gene mutation carriers, but all of have been based on small numbers of Lynch syndrome families (14, 15). Several studies (16-18) have observed a positive association between BMI in early adulthood and subsequent endometrial cancer risk for the general population. Determining the association of BMI in early adulthood on subsequent cancer risk would be important for MMR gene mutation carriers who learn of their mutation status as young adults with the consequent opportunity to reduce their risk of disease. In this study, we investigated the association between BMI at age 18-20 years and endometrial cancer risk for MMR gene mutation carriers and as a comparison, estimated the association for non-carriers.

Patients and Methods

Recruitment

Study participants for this analysis were recruited and genetically characterized by the Colon Cancer Family Registry. Study designs and recruitment methods can be found at http://epi.grants.cancer.gov/CFR/ and have been described in detail elsewhere (19). Briefly, probands and their relatives were recruited between 1997 and 2007. Probands were either a recently diagnosed colorectal cancer (CRC) case reported to a population complete cancer registry or an attendee to a family cancer clinic. For population-based ascertainment, probands were incident CRC cases recruited from cancer registries in the USA (Puget Sound, Washington State; the State of Minnesota; Los Angeles, California; Arizona; Colorado; New Hampshire; North Carolina; and Hawaii), Australia (Victoria), and Canada (Ontario). Their first-degree relatives were recruited by all centers, and recruitment extended to more distant relatives by some centers. For clinic-based ascertainment, probands were selected from multiple-case colorectal or Lynch syndrome cancer families who attended family cancer clinics in the USA (Mayo Clinic, Rochester, Minnesota; and Cleveland), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney) and New Zealand (Auckland). Their relatives were recruited according to pre-specified rules of recruiting centers (for

details Newcomb et al. (19)). Written informed consent was obtained from all participants, and the study protocol was approved by local institutional research ethics review boards.

Data Collection

At recruitment, baseline information on demographics, personal characteristics, personal and family history of cancer, cancer screening and surgery including gynaecologic surgery were obtained from all participants. Participants were followed-up approximately five years after baseline to update demographic information, personal characteristics and personal and family history of cancer, cancer screening and surgery. Baseline and follow-up questionnaires are available at the following URL: https://cfrisc.georgetown.edu/isc/dd.questionnaires.do. Reported cancer diagnoses and age at diagnoses were confirmed, where possible, using pathology reports, medical records, cancer registry reports and/or death certificates. Blood samples and tumor tissue samples were collected for mutation testing. This study was based on all available baseline and follow-up data.

Self-reported weight at age 18-20 years and current height were collected at standardized personal interviews (University of Southern California Consortium), telephone interviews (University of Southern California Consortium, Fred Hutchinson Cancer Research Center, and University of Melbourne), or mailed questionnaires (University of Hawaii, Cancer Care Ontario, and Mayo Clinic).

Mutation Testing

Mutation testing for *MLH1, MSH2, MSH6* and *PMS2* was performed for all probands ascertained from family cancer clinics and for those probands from population-based ascertainment who had a colorectal tumor displaying evidence of impaired MMR function as evidenced by either microsatellite instability or lack of MMR protein expression by immunohistochemistry. Mutation testing was performed by Sanger sequencing or denaturing high pressure liquid chromatography (dHPLC), followed by confirmatory DNA sequencing. Large insertion and deletion mutations were detected by Multiplex Ligation Dependent Probe Amplification (MLPA) according to the manufacturer's instructions (MRC Holland, Amsterdam, The Netherlands) (5, 19, 20). All participants who donated a blood sample, and who were relatives of probands with a pathogenic mutation, underwent predictive testing for the same mutation identified in the proband. All non-carriers were therefore relatives who tested negative for the mutation identified for the proband.

Study Sample

For this study, we have included female probands and their participating female relatives who were confirmed carriers and confirmed non-carriers of a MMR gene mutation. We identified a total of 634 female carriers and 574 female non-carriers. Of these, 33 (5%) carriers and 41 (7%) non-carriers were excluded due to missing data for current height or weight at age 18-20 years. The remaining 601 carriers (109 from population-based sources) and 533 non-carriers (57 from population-based sources) were included in the analyses. Excluded subjects did not differ in baseline characteristics from those who entered into the analyses (data not shown).

We were unable to analyse the role of current BMI in this study as it was not available 1-2 years prior to age at diagnosis or censored age for 392 women which is 35% of the total study sample. These constituted 107 endometrial cancer cases (100 carriers and 7 non-carriers) and 164 cases of other cancer (127 carriers and 37 non-carriers), and 116 women with a prior hysterectomy (70 carriers and 46 non-carriers) and 5 women who did not report current weight at last contact.

Definitions

A deleterious mutation was defined as a variant that was predicted to result in a stop codon, a frameshift mutation, a large insertion or deletion, or a missense mutation previously reported in the scientific literature to be pathogenic. Height and weight were defined as self-reported current height and weight at age 20 years. BMI at age 20 years was calculated as weight in kilograms at age 20 years divided by height in metres squared (kg/m^2).

Statistical Analysis

MMR gene mutation carrier and non-carrier women were treated as a cohort from birth and Cox proportional hazard regressions were used to estimate associations between BMI and risk of endometrial cancer. The time at risk for each subject started at birth and ended at age of diagnosis of endometrial cancer or any other cancer, hysterectomy, death or last contact, whichever occurred first. The rationale for censoring at diagnosis of any cancer was that the resultant treatment and surveillance might alter risk of subsequent cancers including endometrial cancer. Of the total 601 mutation carriers, observation time ended at age of diagnosis for 126 endometrial cancer cases, and was censored at age of diagnosis of other cancer for 204 women, at age of hysterectomy for 81 women, at age of death for 2 women, and at age of last contact for 188 women. Of the total 533 non-carriers, time of observation ended at the age of diagnosis for 8 endometrial cancer cases, and was censored at age of diagnosis of other cancer for 60 women, at age of hysterectomy for 57 women, at age of death for 2 women, and at age of last contact for 406 women.

As a proportion of subjects from this study were ascertained from multiple-cancer-case families, and cases were preferentially tested for MMR gene mutations, subject selection for testing MMR gene mutation was not random with respect to the disease status. To obtain a synthetic cohort representative of MMR gene mutation carriers and non-carriers, we adjusted for this non-random ascertainment by applying probability weights to both carriers and non-carriers based on the approach described by Antoniou et al. (21), which has been used for modifier studies of cancer risk for carriers of rare genetic mutations e.g. (22, 23). This method removes bias when the external rates were correctly specified, and reduces bias even when the sampling fractions were not completely accurate (21).

Age-specific incidence rates of endometrial cancer for carriers were calculated by multiplying the country- and age-specific population incidence by the hazard ratio (HR) of endometrial cancer for carriers of specific MMR gene mutations. Due to the rarity of mutations in the population (2), age-specific incidence rates for non-carriers were assumed to equal those for the general population. Average age-specific population incidences in 1998–2002 for each country (Australia, Canada and USA) were obtained from Cancer Incidence in Five Continents (24). Using these age-specific incidence rates of endometrial cancer for carriers and non-carriers, we calculated statistical weights for endometrial cancer-affected carriers, unaffected carriers, affected non-carriers and unaffected non-carriers for each age-stratum.

HRs and 95% CIs were estimated for associations between BMI and endometrial cancer risk. The proportional hazards assumption was tested by examining the relationship between the scaled Schoenfeld residuals and survival time (25). BMI was fitted as a continuous variable as well as a categorical variable ($< 25\ kg/m^2$ and $\geq 25\ kg/m^2$). BMI as a continuous variable was considered to be the main exposure variable. In order to determine whether the association between BMI and the (log) hazard rate was non-linear, we tested a range of non-linear models using fractional polynomials (26). We compared these models to the linear model using the Wald test.

To control for potential confounding factors potentially present at the age that BMI was reported for (i.e. 18-20 years old), we adjusted for (i) hormonal contraceptives use at age 20 (never, ever), (ii) cigarette smoking at age 20 (never, ever), (iii) year of birth (<1940, 1940-1949, 1950-1959, ≥1960), and (iv) age at menarche in years in both mutation carriers and non-carriers, and further adjusted for carriers (v) the MMR gene that was mutated. To compare the associations between BMI and endometrial cancer for mutation carriers with non-carriers, we tested for an interaction between mutation carrier status and BMI. In order to account for correlation of risk between family members, the Huber-White robust variance correction was applied by clustering on family membership (27, 28). All statistical tests were two-sided and, P <0.05 was considered statistical significance for testing a predetermined null hypothesis. All statistical analyses were performed using Stata 10.0 (29).

Results

The study comprised: 601 female carriers of a MMR gene mutation (245 in *MLH1*, 299 in *MSH2*, 38 in *MSH6*, and 19 in *PMS2*) from 286 families contributing 26,027 person-years, of which 126 (21%) were diagnosed with endometrial cancer (incidence 4.84 (95% CI 4.07–5.76) per 1,000 person-years); and 533 female non-carriers from 182 families contributing 25,666 person-years, of which 8 (2%) were diagnosed with endometrial cancer (incidence 0.31 (95% CI 0.16–0.62) per 1,000 person-years). Of all carriers, 847 (75%) were recruited in Australia or New Zealand, 191 (17%) in the USA and 96 (8%) in Canada. Baseline characteristics of the study subjects are summarized in Table 1. The mean age at diagnosis of endometrial cancer was 47.6 (standard deviation (SD) 8.2) years for carriers and 44.5 (SD 9.9) years for non-carriers. The mean BMI at age 20 years was 21.8 (SD 3.7) kg/m^2 for carriers and 21.8 (SD 4.0) kg/m^2 for non-carriers. There was no statistical evidence for the mean BMI, nor the distribution of mutated MMR gene to differ by country or ascertainment source (data not shown).

Table 2 shows no statistically significant evidence for an association between BMI and endometrial cancer risk for carriers of mutations when all carriers of MMR gene mutation are combined (HR 0.73 per 5 kg/m^2; 95% CI 0.40–1.34; P = 0.31) after adjusting for age at menarche, year of birth, hormonal contraceptive use and cigarette smoking at age 20 and specific MMR gene mutated. Table 3 presents associations for BMI and endometrial cancer risk separately for carriers of mutations in each MMR gene.

For non-carriers, endometrial cancer risk was estimated to increase by 74% for each increase of 5 kg/m^2 in BMI (HR 1.74; 95% CI 1.27–2.37; P <0.001) after adjusting for age at menarche, year of birth, hormonal contraceptive use and cigarette smoking at age 20. The HR for non-carriers was greater than that for carriers (interaction between mutation carrier status and BMI; P = 0.04).

There was no evidence for a non-linear association between (log) BMI (as a continuous variable) and the hazards for endometrial cancer for either carriers or non-carrier (P = 0.90).

Discussion

The findings of this study suggest that there is a positive association between BMI in early adulthood and risk of endometrial cancer but only for non-carriers of a germline mutation in a MMR gene. We observed no statistical evidence of an association between BMI in early adulthood and endometrial cancer risk for MMR gene mutation carriers. As mutation carriers and non-carriers for this study are from the same families (all non-carriers are relatives of carriers), this study directly compares the association between BMI at early age (18-20 years) and endometrial cancer risk for carriers to that for non-carriers.

Our study and previous studies based on MMR gene mutation carriers (14), and those having endometrial cancers with microsatellite instability (30, 31) suggest that obesity does not appear to be involved, or at least is less involved, in the development of endometrial cancer for MMR gene mutation carriers than it is for non-carriers. A reasonable supposition consistent with these observations is that endometrial carcinogenesis in MMR gene mutation carriers is not via the estrogenic pathway of the most prevalent form of the disease. Type I endometrial cancers (80% of all endometrial cancers) are mostly low grade, endometrioid carcinomas associated with the following estrogen predominant conditions: metabolic syndrome (central obesity, type 2 diabetes, dyslipidemia and hypertension), early menarche, late menopause, infertility, and hyperplasia of the stroma of the ovaries and endometrium (32, 33). Type II endometrial cancers are predominantly serous and clear cell adenocarcinomas arising from polyps or atrophic endometrium of older women and not thought to be related as strongly to estrogenic stimuli as are Type I tumors (32-35). Although the predominant histological subtype in Lynch syndrome-associated endometrial cancers is endometrioid (36-39), they are generally high grade and consistently show lymphangioinvasive growth and tumor-infiltrating lymphocytes (37-39). These features, together with our finding of no evidence that BMI predicts endometrial cancer risk for mutation carriers are consistent with the hypothesis that Lynch syndrome-associated endometrial cancers may arise via alternative carcinogenic pathways that are independent on estrogenic stimulation and insulin resistance and therefore may be more like the group of tumors associated with Type II endometrial cancer.

As MMR gene mutation carriers are rare in the general population (2), our finding of a positive association between BMI in early adulthood and endometrial cancer for non-carriers can be interpreted as an association applicable to the general population. Our finding for non-carriers is consistent with previously published studies (16-18) that observed a positive association between BMI in early adulthood and subsequent endometrial cancer risk for the general population. In terms of the size of effect, the association we found is similar to previous studies e.g. Schouten et al. (16) reported a relative risk per kg/m^2 of 1.07 (95% CI 1.02–1.12).

The strengths of our study include: the use of weighted cohort analysis which could avoid any selection bias caused by the oversampling of subjects from high-risk families (21); the use of a robust variance correction which accounts for dependence between participants from the same family (27, 28); and the use of standardized epidemiologic assessment and uniformly high-quality testing for MMR gene mutations across the Colon Cancer Family Registry (19).

A potential limitation of this study is that participants often had to recall weight many years in the past. However, other studies have shown measures of weight taken at age 20–30 years are well correlated with recalled values at age 50–70 years, with correlation coefficients ranging between 0.73 and 0.95 (40-42). There is a possibility of response bias where endometrial cancer affected women recall their weight at age 20 years differently than unaffected women. Finally, as cases with poorer survival were less likely to be included in this analysis (as unable to provide a blood sample for genetic testing and complete a questionnaire), there is a possibility of survival bias if mortality of cases was related to both BMI and mutation status.

In conclusion, our data suggest that BMI in early adulthood might not influence the risk of endometrial cancer risk for carriers of MMR gene mutations. Given the strong association between BMI and endometrial cancer for non-carriers (and the general population), the lack of association for mutation carriers is suggestive of pathways of endometrial carcinogenesis that are independent of obesity.

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References

1. Vasen HFA, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology. 1999; 116(6):1453–6. [PubMed: 10348829]
2. Dunlop MG, Farrington SM, Nicholl I, Aaltonen L, Petersen G, Porteous M, et al. Population carrier frequency of hMSH2 and hMLH1 mutations. Br J Cancer. 2000; 83(12):1643–5. [PubMed: 11104559]
3. Chen S, Wang W, Lee S, Nafa K, Lee J, Romans K, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA. 2006 Sep 27; 296(12):1479–87. [PubMed: 17003396]
4. Baglietto L, Lindor NM, Dowty JG, White DM, Wagner A, Gomez Garcia EB, et al. Risks of Lynch Syndrome Cancers for MSH6 Mutation Carriers. J Natl Cancer Inst. 2010 February; 102(3):193–201. [PubMed: 20028993]
5. Senter L, Clendenning M, Sotamaa K, Hampel H, Green J, Potter JD, et al. The Clinical Phenotype of Lynch Syndrome Due to Germ-Line PMS2 Mutations. Gastroenterology. 2008; 135(2):419–28.e1. [PubMed: 18602922]
6. Jenkins M, Southey M, Giles G, Hopper J. Rationale for, and approach to, studying modifiers of risk in persons with a genetic predisposition to colorectal cancer. Curr Oncol Rep. 2007; 9(3):202–7. [PubMed: 17430691]
7. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2007; 18(4):399–413. [PubMed: 17297555]
8. McCullough ML, Patel AV, Patel R, Rodriguez C, Feigelson HS, Bandera EV, et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev. 2008; 17(1):73. [PubMed: 18187388]
9. Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer. 2008; 98(9):1582. [PubMed: 18362938]
10. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: The Multiethnic Cohort. Int J Cancer. 2009
11. Shoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. Am J Epidemiol. 1998; 148(3):234. [PubMed: 9690359]
12. Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Weight change and risk of endometrial cancer. Int J Epidemiol. 2006 February 1; 35(1):151–8. [PubMed: 16278243]
13. World Health Organization. Report of a WHO consultation on obesity Obesity: preventing and managing the global epidemic. Geneva, Switzerland: WHO; 1998.
14. Lu KH, Schorge JO, Rodabaugh KJ, Daniels MS, Sun CC, Soliman PT, et al. Prospective Determination of Prevalence of Lynch Syndrome in Young Women With Endometrial Cancer. J Clin Oncol. 2007 November 20; 25(33):5158–64. [PubMed: 17925543]
15. Schmeler KM, Soliman PT, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Endometrial cancer in young, normal-weight women. Gynecol Oncol. 2005 Nov; 99(2):388–92. [PubMed: 16051336]

16. Schouten L, Goldbohm R, Van Den Brandt P. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. J Natl Cancer Inst. 2004; 96(21):1635. [PubMed: 15523093]

17. Blitzer P, Blitzer E, Rimm A. Association between teen-age obesity and cancer in 56,111 women: all cancers and endometrial carcinoma. Prev Med. 1976; 5(1):20–31. [PubMed: 1264967]

18. Terry P, Baron J, Weiderpass E, Yuen J, Lichtenstein P, Nyrén O. Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. Int J Cancer. 1999; 82(1):38–42. [PubMed: 10360818]

19. Newcomb PA, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, et al. Colon Cancer Family Registry: An International Resource for Studies of the Genetic Epidemiology of Colon Cancer. Cancer Epidemiol Biomarkers Prev. 2007 November 1; 16(11):2331–43. [PubMed: 17982118]

20. Southey MC, Jenkins MA, Mead L, Whitty J, Trivett M, Tesoriero AA, et al. Use of Molecular Tumor Characteristics to Prioritize Mismatch Repair Gene Testing in Early-Onset Colorectal Cancer. J Clin Oncol. 2005 September 20; 23(27):6524–32. [PubMed: 16116158]

21. Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol. 2005; 29(1):1–11. [PubMed: 15880399]

22. Brohet RM, Goldgar DE, Easton DF, Antoniou AC, Andrieu N, Chang-Claude J, et al. Oral Contraceptives and Breast Cancer Risk in the International BRCA1/2 Carrier Cohort Study: A Report From EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol. 2007 September 1; 25(25):3831–6. [PubMed: 17635951]

23. Andrieu N, Goldgar DE, Easton DF, Rookus M, Brohet R, Antoniou AC, et al. Pregnancies, Breast-Feeding, and Breast Cancer Risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). J Natl Cancer Inst. 2006 April 19; 98(8):535–44. [PubMed: 16622123]

24. Curado, MP.; Edwards, B.; Shin, HR.; Storm, H.; Ferlay, J.; Heanue, M., et al., editors. Cancer Incidence in Five Continents. Vol. IX. Lyon, France: IARC; 2007.

25. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994; 81(3):515–26.

26. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol. 1999 October 1; 28(5):964–74. [PubMed: 10597998]

27. Rogers WH. Regression standard errors in clustered samples. Stata Technical Bulletin. 1993; 3(13):19–23.

28. Williams RL. A Note on Robust Variance Estimation for Cluster-Correlated Data. Biometrics. 2000; 56(2):645–6. [PubMed: 10877330]

29. StataCorp. Stata Statistical Software: Release 10. College Station TX: StataCorp LP; 2007.

30. Cohn DE, Pavelka J, Frankel W, Morrison C, Hampel H, Copeland L, et al. Correlation between patient weight and defects in DNA mismatch repair: is this the link between an increased risk of previous cancer in thinner women with endometrial cancer? Int J Gynecol Cancer. 2008; 18(1): 136–40. [PubMed: 17466051]

31. McCourt CK, Mutch DG, Gibb RK, Rader JS, Goodfellow PJ, Trinkaus K, et al. Body mass index: Relationship to clinical, pathologic and features of microsatellite instability in endometrial cancer. Gynecol Oncol. 2007; 104(3):535–9. [PubMed: 17109938]

32. Bokhman J. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983; 15(1):10–7. [PubMed: 6822361]

33. Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. Endocr Relat Cancer. 2000; 7(4):227. [PubMed: 11174845]

34. Kaaks R, Lukanova A, Kurzer M. Obesity, Endogenous Hormones, and Endometrial Cancer Risk. Cancer Epidemiol Biomarkers Prev. 2002; 11(12):1531. [PubMed: 12496040]

35. Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol. 2004; 35(6):649–62. [PubMed: 15188130]

36. Nieminen TT, Gylling A, Abdel-Rahman WM, Nuorva K, Aarnio M, Renkonen-Sinisalo L, et al. Molecular Analysis of Endometrial Tumorigenesis: Importance of Complex Hyperplasia Regardless of Atypia. Clin Cancer Res. 2009 September 15; 15(18):5772–83. [PubMed: 19723644]

37. Walsh MD, Cummings MC, Buchanan DD, Dambacher WM, Arnold S, McKeone D, et al. Molecular, Pathologic, and Clinical Features of Early-Onset Endometrial Cancer: Identifying Presumptive Lynch Syndrome Patients. Clin Cancer Res. 2008 March 15; 14(6):1692–700. [PubMed: 18310315]

38. Broaddus R, Lynch H, Chen L, Daniels M, Conrad P, Munsell M, et al. Pathologic features of endometrial carcinoma associated with HNPCC. Cancer. 2006; 106(1):87–94. [PubMed: 16323174]

39. van den Bos M, van den Hoven M, Jongejan E, van der Leij F, Michels M, Schakenraad S, et al. More differences between HNPCC-related and sporadic carcinomas from the endometrium as compared to the colon. Am J Surg Pathol. 2004; 28(6):706. [PubMed: 15166662]

40. Stevens J, Keil JE, Waid LR, Gazes PC. Accuracy of current, 4-year, and 28-year self-reported body weight in an elderly population. American journal of epidemiology. 1990; 132(6):1156. [PubMed: 2260547]

41. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by US adults. Epidemiology. 1995; 6(1):61–6. [PubMed: 7888448]

42. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity. 1995; 19(8):570. [PubMed: 7489028]

Table 1
Baseline characteristics of study subjects by mismatch repair mutation status

	Carriers		Noncarriers	
	Endometrial cancer	No endometrial cancer	Endometrial cancer	No endometrial cancer
	N (%)	N (%)	N (%)	N (%)
Total number	126	475	8	525
Age (year),* mean (SD)	47.6 (8.2)	42.2 (12.1)	44.5 (9.9)	48.2 (15.4)
MMR gene mutated				
MLH1	42 (33)	203 (43)		
MSH2	68 (54)	231 (49)		
MSH6	14 (11)	24 (5)		
PMS2	2 (2)	17 (3)		
Study Centers				
Australia or New Zealand	75 (60)	330 (69)	4 (50)	438 (83)
USA	21 (17)	47 (10)	3 (38)	60 (12)
Canada	30 (23)	98 (21)	1 (12)	27 (5)
Contraceptive Use†				
Never	63 (53)	151 (33)	3 (43)	170 (33)
Ever	55 (47)	309 (67)	4 (57)	344 (67)
Unknown	8	15	1	11
Year of Birth				
<1940	44 (35)	87 (18)	2 (25)	110 (21)
1940-1949	44 (35)	85 (18)	3 (38)	102 (20)
1950-1959	33 (26)	117 (25)	2 (25)	133 (25)
≥1960	5 (4)	186 (39)	1 (12)	180 (34)
Cigarette Smoking‡				
Never	88 (72)	256 (55)	4 (57)	315 (60)
Ever	35 (28)	210 (45)	3 (53)	206 (40)
Unknown	3	9	1	4
Age at menarche (year), mean (SD)	12.6 (1.4)	12.9 (1.6)	13.3 (0.9)	13.0 (1.6)
Body size, mean (SD)				
Current height (cm)	163.1 (7.3)	163.6 (7.2)	164.4 (4.3)	163.8 (7.2)
Weight at age 20 (kg)	56.5 (10.9)	58.8 (11.1)	59.1 (5.9)	58.5 (11.9)
BMI at age 20 (kg/m^2)§	21.2 (3.4)	21.9 (3.8)	21.9 (2.6)	21.8 (4.0)

*Age at first diagnosis of endometrial cancer for affected participants; age at hysterectomy or diagnosis of another cancer or last interview or death (whichever came first) for unaffected participants.

†Oral contraceptive pills or other hormonal contraceptives (implants or injections) use at age 20 years for at least one year.

‡Cigarette smoking status at age 20 years. Cigarette smoking was defined as ever smoking one cigarette per day for at least three months.

§Calculated from self-reported current height and weight at age 20 years

Table 2

Hazard ratios (HR) for association between body mass index (BMI) at age 20 years and endometrial cancer risk for mismatch repair gene mutation carriers and noncarriers.

				Univariable Analysis*		Multivariable Analysis†	
BMI per 5 kg/m^2	**Total number**	**Total person-years**	**Number (%) of endometrial cancer cases**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Carriers	601	26,027	126 (21)	0.67 (0.38–1.20)	0.18	0.73 (0.40–1.34)	0.31
Non-carriers	533	25,666	8 (2)	1.58 (1.00–2.48)	0.05	1.74 (1.27–2.37)	<0.001

*With robust variance correction for familial correlation in risk.

†Adjusted for age at menarche, year of birth, use of hormonal contraceptives, and cigarette smoking at age 20 in both carriers and noncarriers; further adjusted for specific mismatch repair gene mutated for carriers.

Table 3

Hazard ratios for association between body mass index (BMI, per 5 kg/m^2) at age 20 years and endometrial cancer risk by mutated mismatch repair gene.

Mutated mismatch repair gene	Total number	Total person-years	Number (%) of endometrial cancer cases	Median (range) age of endometrial cancer diagnosis (years)	HR (95% CI)*	*P*
MLH1	245	10,634	42 (17)	49 (35–63)	0.83 (0.41–1.69)	0.61
MSH2	299	12,640	68 (23)	47 (25–74)	0.74 (0.31–1.76)	0.49
MSH6	38	1,819	14 (37)	52 (34–62)	0.68 (0.07–7.16)	0.81
PMS2	19	934	2 (11)	45 (30–60)	0.22 (0.01–13.1)	0.47

*Adjusted for age at menarche, year of birth, use of hormonal contraceptives, and cigarette smoking at age 20 with robust variance correction for familial correlation in risk.