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Endometrial cancer and a family history of cancer

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HIGHLIGHTS

- We evaluated family cancer history and EC risk in non-LS patients.
- Risk for EC was similar by MSI status suggesting limited involvement of MMR genes.
- Our results support an EC-specific genetic syndrome in non-LS patients.

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ABSTRACT

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

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

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

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

Introduction

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

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

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

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

Material and methods

Study population

The methods used have been previously reported [13]. Briefly, women with first primary EC were identified through the population-based Alberta Cancer Registry. Eligible cases were less than 80 years of age, diagnosed between January 2002 and February 2006, and residents of central or southern Alberta (n = 900). Physicians provided permission to contact 808 cases and 549 (68%) were successfully interviewed. Seven cases were excluded because of questionable interviews, resulting in 542 cases. Female controls were identified through random digit dialing, and were frequency age-matched to cases in 5-year age groups [14]. Eligible controls had no previous diagnoses of cancer, no prior hysterectomy, and met the age and residence requirements as per cases. Out of 29,970 random residences contacted, 18,264 (60.9%) residences were screened for potentially eligible women. A total of 1984 eligible women were identified in this screen and invited to participate. Of these, 1036 (52.2%) were interviewed. Four controls were excluded because of questionable interviews, resulting in 1032 controls. This study received ethics approval from the Alberta Cancer Research Ethics Committee and the University of Calgary, and all women provided written informed consent.

Interviews

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

Blood, tumor tissue, and MSI

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

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

Statistical analysis

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

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

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

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

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