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Family history of cancer predicts endometrial cancer risk independently of Lynch Syndrome: Implications for genetic counselling

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HIGHLIGHTS

- Endometrial cancer risk is predicted by cancer in first and second degree relatives.
- The strongest predictor was a first degree relative with endometrial cancer <50 y.
- Risk was significantly greater with increasing Lynch cancers reported in relatives.
- Risk associated with cancer in relatives did not differ by proband tumor MMR status.

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ABSTRACT

Objective. To determine endometrial cancer (EC) risk according to family cancer history, including assessment by degree of relatedness, type of and age at cancer diagnosis of relatives.

Methods. Self-reported family cancer history was available for 1353 EC patients and 628 controls. Logistic regression was used to quantify the association between EC and cancer diagnosis in ≥1 first or second degree relative, and to assess whether level of risk differed by degree of relationship and/or relative's age at diagnosis. Risk was also evaluated for family history of up to three cancers from known familial syndromes (Lynch, Cowden, hereditary breast and ovarian cancer) overall, by histological subtype and, for a subset of 678 patients, by EC tumor mismatch repair (MMR) gene expression.

Results. Report of EC in ≥1 first- or second-degree relative was associated with significantly increased risk of EC ($P = 3.8 \times 10^{-7}$), independent of lifestyle risk factors. There was a trend in increasing EC risk with closer relatedness and younger age at EC diagnosis in relatives ($P_{Trend} = 4.43 \times 10^{-6}$), and with increasing numbers of Lynch cancers in relatives ($P_{Trend} \leq 0.0001$). EC risk associated with family history did not differ by proband tumor MMR status, or histological subtype. Reported EC in first- or second-degree relatives remained associated with EC risk after conservative correction for potential misreported family history (OR 2.0; 95% CI, 1.24–3.37, $P = 0.004$).

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Conclusion. The strongest predictor of EC risk was closer relatedness and younger EC diagnosis age in ≥1 relative. Associations remained significant irrespective of proband MMR status, and after excluding MMR pathogenic variant carriers, indicating that Lynch syndrome genes do not fully explain familial EC risk.

1. Introduction

Endometrial cancer (EC) is the fifth most common cancer in women in developed countries, accounting for 4.8% of new cancers and 2.1% of cancer deaths. The highest incidence rates in 2012 were estimated to be 19.1 and 15.6 per 100,000 in North America and Western Europe respectively [1,2], attributed to the greater overall prevalence of obesity and metabolic syndromes in these regions [3].

Established non-genetic risk factors for EC include age and exposure to exogenous estrogens, or endogenous estrogens associated with nulliparity, early age at menarche, late-onset menopause and obesity [4]. A role for genetic factors in EC susceptibility is supported by the fact that a family history of EC is associated with a ~2–3-fold increased risk of EC [5]. Genome-wide association studies and large-scale candidate gene studies have identified common modest-risk genetic variants, currently estimated to account for ~5% of the familial relative risk of EC [6–12]. High-risk pathogenic variants in the DNA mismatch repair (MMR) genes associated with Lynch syndrome confer a high lifetime risk of EC in carriers (reported risks 18–71%), but account for only ~5% of population-based EC (reviewed in [14,15]). Germline loss-of-function variants in the *PTEN* tumor suppressor gene cause Cowden syndrome, and are associated with a lifetime risk of EC of up to 28% in this context [16], but there is insufficient evidence regarding their contribution to EC risk in the population setting [17]. Variants within the exonuclease domains of the DNA replication and polymerase proof-reading genes *POLD1* and *POLE* have also been implicated in susceptibility to EC, although the level of risk is yet to be quantified in the familial [18] or population setting. While there is convincing evidence that both carriers and non-carriers of *BRCA1/2* pathogenic variants have an increased risk of EC following tamoxifen treatment [19], there remains debate about the role of *BRCA1/2* in EC risk outside such settings [14].

To date the association between EC risk and number or age of affected relatives, degree of relatedness, or reported family cancer history outside the clinical definition of Lynch Syndrome has not been assessed. Here we report a comprehensive analysis of the risk of EC associated with a family history of EC and other cancers, using the well-characterised, population-based Australian National Endometrial Cancer Study (ANECS). We also considered if family history-associated risk of EC differs according to proband endometrial tumor MMR proficiency status, to assess evidence for novel familial cancer syndromes.

2. Patients and methods

2.1. Study population

All ANECS participants provided informed written consent, and approval was obtained from the QIMR Berghofer Medical Research Institute Human Research Ethics Committee, participating hospitals and cancer registries.

Women newly diagnosed with EC, and a comparable group of cancer-free women identified through the national electoral roll (enrolment to vote is compulsory in Australia) were invited to participate in ANECS, a population-based case-control study [20]. Additional details on eligibility criteria, questionnaires and data collection, including tissue and blood samples for molecular testing, have been reported previously [21]. Data were available for 1420 patients and 744 controls. Women were excluded from our analysis if they provided very little or no information about their family cancer history (48 patients, 62 controls), or if they were adopted and therefore their family cancer history was unknown (19 patients). The final analysis dataset with family cancer information comprised 1353 patients and 682 controls. This included 38 women (37 patients and 1 control) who met the Amsterdam II criteria [22] for Lynch Syndrome; of these 7 patients had undergone further testing and were proven to carry a pathogenic MMR gene variant (Supplementary Methods and Table S1).

In addition, patients who reported a family history of cancer were asked permission for the study to contact their relatives; relatives of a subset of 119 patients consented to provide risk factor data and complete the same family cancer history questionnaire as patients. A total of 258 relatives (179 first, 32 second, and 47 third and fourth degree) completed the family history questionnaire.

2.2. Assessment of family history of cancer

Family history of cancer for each patient or control proband was not formally verified by medical records, but was based on each proband's report of cancer and age at diagnosis (if known) in first degree relatives (FDR; parent, sibling, child of proband) and second degree relatives (SDR; maternal or paternal grandmother/grandfather/aunt/uncle, grandson, granddaughter, niece, nephew), as documented by questionnaire. Hereafter, cancer in a relative refers to FDR or SDR unless otherwise specified. Any cancer occurring twice in the same relative was counted as two cancers if they were diagnosed at least one year apart. Cancers reported in questionnaires as 'fallopian tube' were combined with ovarian cancer, 'rectum' with colorectal cancer, and 'GI' were analysed as gastrointestinal cancer. Lymphomas were variously reported as Hodgkin/Non-Hodgkin Disease/lymphoma, lymphosarcoma, or cancer of the lymph node. Reports of Hodgkin lymphoma in relatives ($n = 18$) were insufficient to analyse separately. We therefore analysed Non-Hodgkin lymphoma (NHL) if specifically reported as NHL, and pooled NHL with all reports of lymphoma as a secondary analysis since approximately 85% of all lymphomas are NHL [1]. Questionnaires on cancer history provided by the subset of relatives of patients invited to participate in the ANECS study were used to evaluate the concordance between patient reports of family cancer history and relative self-reports of cancer, overall, and by degree of relationship. This information was used to estimate the percentage of over-reported (e.g. benign conditions reported as malignant at a specific site) and misreported (different site) cancers by patients for the specific cancers relevant to this study.

2.3. Statistical analysis

In order to obtain population-based risk estimates for EC risk according to family cancer history, patients with known germline pathogenic MMR gene variants ($n = 21$) were included in analyses using the full dataset, but excluded from analyses using the subset of patients with known MMR status to assess evidence for genetic risk outside Lynch Syndrome. The association between EC and proband-reported family history of cancer was estimated using age-adjusted logistic regression models (age at EC diagnosis for patients and age at interview for controls) to obtain the odds ratios (ORs) and 95% confidence intervals (CIs) for risk of EC associated with any cancer reported in at least one FDR or SDR. Analyses assessing EC risk associated with report of non-EC cancers in relatives were additionally adjusted for report of EC in relatives to remove any potential inflation of risk estimates due to EC

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