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Do the risks of Lynch syndrome-related cancers depend on the parent of origin of the mutation?

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Abstract

Background: Individuals who carry pathogenic mutations in DNA mismatch repair (MMR) genes have high risks of cancer, and small studies have suggested that these risks depend on the sex of the parent from whom the mutation was inherited. We have conducted the first large study of such a parent-of-origin effect (POE).

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Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Melbourne Human Ethics Sub-Committee (ethics identification number 1339757) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all study participants.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Methods: Our study was based on all MMR gene mutation carriers and their relatives in the Colon Cancer Family Registry, comprising 18,226 people. The POE was estimated as a hazard ratio (HR) using a segregation analysis approach that adjusted for ascertainment. HR=1 corresponds to no POE and HR>1 corresponds to higher risks for maternal mutations.

Results: For all MMR genes combined, the estimated POE HRs were 1.02 (95% confidence interval (CI) 0.75-1.39, p=0.9) for male colorectal cancer, 1.12 (95% CI 0.81-1.54, p=0.5) for female colorectal cancer and 0.84 (95% CI 0.52-1.36, p=0.5) for endometrial cancer. Separate results for each MMR gene were similar.

Conclusion: Despite being well-powered, our study did not find any evidence that cancer risks for MMR gene mutation carriers depend on the parent-of-origin of the mutation. Based on current evidence, we do not recommend that POEs be incorporated into the clinical guidelines or advice for such carriers.

Keywords

parent-of-origin effect; Lynch syndrome; mismatch repair genes; colorectal cancer; endometrial cancer

Introduction

Two to three percent of all colorectal cancer cases are attributed to Lynch syndrome [1-3], which is a predisposition to a spectrum of cancers (primarily of the colorectum and endometrium) caused by germline mutations in the DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2* and *EPCAM*) [4].

MMR gene mutations are rare in the general population (approximately 1 carrier in 279 people [5]) and almost all mutation carriers are heterozygous, so almost all carriers have a mutation in their maternal or paternal copy of the gene but not both [4]. MMR gene mutation carriers (except for *PMS2* mutation carriers) have very high risks of colorectal cancer, estimated to be 31-47% by the age of 70 years on average [2], with the risks for individual carriers estimated to vary greatly about these average risks [6]. It is not clear why this risk heterogeneity occurs, though one possible explanation could be a parent-of-origin effect (POE) for Lynch syndrome.

A genetic disease is said to display a POE if the phenotypic expression of the disease allele depends on the sex of the parent who passed on the disease allele [7, 8]. POEs have been observed in several genetic diseases, including SDHD-related paraganglioma [9], low penetrance retinoblastoma [10, 11], food allergy [7], Huntington's disease [12], multiple sclerosis [13, 14] and fragile X syndrome [15].

Four studies have previously investigated a POE for Lynch syndrome. Two of these studies [16, 17] found no evidence for a POE while two [8, 18] found marginal evidence for a POE in Lynch syndrome, though in opposite directions. In addition to these four studies, Lindor et al. [19] studied POEs for familial colorectal cancer and found a trend for higher risks in the daughters of affected fathers, though this study excluded all known or suspected MMR gene

mutation carriers. Also, Segui et al. [20] found weak molecular evidence that suggested shortened telomeres could provide a mechanism for the POE of van Vliet et al. [8].

The four previous studies of POEs in Lynch syndrome are consistent with the existence of a POE for all MMR genes except *PMS2*. The study [17] was well-powered and its results rule out a moderate or large POE for *PMS2* mutation carriers, but the remaining three studies were relatively small. A small sample size could explain the null findings of [16] and a focus on different genes could cause the opposite POEs of [8, 18].

If a POE occurs in Lynch syndrome then this would have important implications for screening, counselling and clinical management of carriers, as well as for the study of mechanisms of cancer development in carriers. The present study therefore aimed to determine if a POE operates in Lynch syndrome based on one of the world's largest and highest quality studies of familial colorectal cancer.

Methods

Colon Cancer Family Registry

Our study was based on all MMR gene mutation-carrying families from the Colon Cancer Family Registry (CCFR), except those carrying *EPCAM* mutations (who were excluded due to low numbers). The CCFR has been described elsewhere [21, 22] so a summary is given here.

The CCFR is an international consortium of six studies of residents in Australia, New Zealand, Canada and USA. A major strength of the CCFR is that protocols for data collection and the testing of biospecimens have been standardized across the six studies. Data was collected at baseline and then at follow-up waves every 4-5 years after that. The CCFR recruited probands and their families in phases from 1998 until 2012, where the proband refers to the first member of the family through whom the family was recruited into the study [4, 23]. These families were recruited via both population- and clinic-based approaches. The population-based probands were individuals with a recently diagnosed colorectal cancer who were identified from state or regional population cancer registries. The clinic-based probands were patients recruited from family cancer clinics. Probands gave blood and detailed cancer family histories. When informed consent was given by the proband, other family members were also recruited. Tests for germline mutations in *MLH1, MSH2, MSH6, PMS2* and *EPCAM* were performed for all population-based probands and for those clinic-based probands who had colorectal cancer with an MMR deficient tumour. When a pathogenic MMR gene mutation was identified in a proband, all recruited family members were also tested for that mutation.

Table 1 shows that there were 262 population- and 487 clinic-based MMR gene mutation-carrying families, containing a total of 5,791 and 12,435 non-probands, respectively. The non-probands in the population- and clinic-based families (respectively) included: 515 and 1,439 colorectal cancer cases; 116 and 317 endometrial cancer cases; 230 and 674 known MMR gene mutation carriers; and 292 and 868 known MMR gene mutation non-carriers.

Statistical methods

Our study used two statistical methods to test for a POE in Lynch syndrome, namely logistic regression and segregation analysis (described separately below).

Logistic regression approach—Logistic regression was performed on a case-control study nested within the CCFR cohort. These analyses were based on the non-probands in population-based families. Probands and clinic-based families were excluded because they were oversampled for cases, so their inclusion would introduce ascertainment bias into the penetrance estimates. However, these biases are likely to affect maternally- and paternally-derived mutations equally, in which case they would not affect our estimation of the POE, so we also conducted supplementary analyses without these exclusions.

Before performing the logistic regression analyses, pedigree analysis techniques (described below) were used to calculate a weighting variable and an exposure variable for every family member. The weighting variable was defined to be the carrier probability, i.e. the probability that the person carries the family's MMR gene mutation. The exposure variable (which we also call the POE variable) was defined to be the conditional probability that the person inherited his or her mutation from his or her mother, given that the person is a mutation carrier. The exposure and weighting variables were calculated from the family structure and known genotypes, but not cancer or other data.

All logistic regression analyses were weighted by the carrier probability and performed using Stata version 14 [24]. For the main analyses, the outcome variable was colorectal cancer (for each sex separately) or endometrial cancer (for females only), and the main exposure variable was the POE variable described above. These analyses were adjusted for age, age-squared and country, where age was either the age at diagnosis (for cases) or the last known age (for controls).

Note that carriers were not categorised into groups according to the likely parental origin of their mutations. Instead, the exposure variable (a probability) was defined for all family members and was treated as a continuous variable in the logistic regression analyses. The exposure variable therefore accurately reflects our level of uncertainty about which of a person's parents is more likely to be a carrier. For example, when the parental origin is not clear from the pedigree, the exposure variable will be close to the neutral value of 0.5 (which corresponds to an equal chance of inheriting the mutation from the mother or the father).

People with a carrier probability of 0 (such as known non-carriers) were arbitrarily given the neutral value of 0.5 for their exposure variable, though these people are effectively excluded from the logistic regression analyses due to the weighting. An example of the exposure and weighting variables for a hypothetical family is given in Figure 1.

The difference in the exposure variable between carriers with maternally-derived mutations (exposure = 1) and those with paternally-derived mutations (exposure = 0) is one unit, so the OR corresponding to the exposure variable in these analyses can be interpreted as the odds of cancer for carriers with maternally-derived mutations divided by the odds for those with paternally-derived mutations. We call this the POE OR because it is a direct measure of the

POE. A POE OR=1 corresponds to no POE, i.e. the cancer risks for carriers who inherited their mutations from their mothers is the same as for carriers who inherited their mutations from their fathers. A POE OR<1 means that the risk of cancer is higher when the mutation is inherited from the father and a POE OR>1 means the risk of cancer is higher when the mutation is inherited from the mother.

The weighting and exposure variable were calculated using Mendel [25] version 3.2, with Mendel run in product mode so that it tracked phased genotypes and hence could distinguish between maternally- and paternally-derived mutations. Standard techniques for calculating carrier probabilities [26] were used to calculate the phased carrier probabilities for each person, i.e. the probabilities for the four events that the person carries no mutation, a maternally-derived mutation, a paternally-derived mutation and a homozygous mutation. The weighting and exposure variables were then calculated as combinations of these probabilities: the weighting variable was calculated as one minus the probability that the person carries no mutation; and the exposure variable was calculated as the probability that the person carries a maternally-derived mutation divided by the carrier probability.

Weighted logistic regression analyses (weighted by carrier probability) were also used in a sensitivity analysis to test the association between the above exposure variable and some dichotomised potential confounders. This analysis was based on the subset of the above participants who had non-missing values for the potential confounders. The potential confounders considered here were: cigarette smoking [27]; alcohol intake [28]; physical exercise [28, 29]; red/processed meat intake [28, 30, 31]; low fruit intake [28, 32] and aspirin intake [33].

Segregation analysis approach—We used a segregation analysis approach [8], based on data on all CCFR clinic- and population-based carrier families, to estimate a hazard ratio (HR) that measures the size of the POE. This analytical method is asymptotically unbiased and efficient, it can be rigorously adjusted for many ascertainment schemes, and it can be applied to large and complicated pedigrees.

Models were fitted by the method of maximum likelihood using Mendel [25] version 3.2 in product mode, which keeps track of phased genotypes, so maternally- and paternally-derived mutations could be distinguished. All models were adjusted for the mixed clinic- and population-based ascertainment of families using a combination of retrospective likelihood and ascertainment-corrected joint likelihood [34-36]. More explicitly, models were fitted by maximising a conditional likelihood, in which each family's data was conditioned on the proband's genotype, cancer status, and age of onset (for population-based families) or on the proband's genotype and the colorectal and endometrial cancer affected statuses and ages of onset of all family members (for clinic-based families). Families were assumed to be independent of each other, so the overall log-likelihood was calculated as the sum of the (conditional) log-likelihoods of all families.

The ages at cancer diagnosis of different family members and for different cancer sites within the same individual were assumed to be conditionally independent, given genotype. For each anatomical site, the age at diagnosis was modelled as a random variable whose

hazard function is the relevant country-, site-, sex- and age-specific population incidence [37] multiplied by a genotype-, site-, sex- and age-specific HR. HRs were modelled as continuous functions of age that are locally constant before age 40 and after age 60, and linear in between. HRs for carriers with maternally-derived mutations were modelled as the POE HR (an age-independent parameter, to be estimated) times the HR for carriers with paternally-derived mutations. Homozygote carriers were absent from our data, but they arise as very rare cases in our likelihood calculations, where they were given HRs equal those of paternal carriers. HRs for non-carriers were determined by the requirement that the average cancer incidence at each age (averaged over genotype) was equal to the relevant population incidence.

We assumed Hardy-Weinberg equilibrium for each MMR gene and an allele frequency of 0.001 for all MMR gene mutations combined. The asymptotic likelihood ratio test was used to compare the goodness of fit of nested models.

Results

There was no evidence of a POE for any combination of gene, sex or cancer site, with all $p \geq 0.1$ (see Table 2 and Figure 2). This does not rule out a small POE, since even large studies lack the statistical power to rule out very small effects, but the confidence intervals (CIs) of Table 2 give bounds on the size of any possible POE. There was also no evidence of a POE in supplementary analyses that were based on all data, i.e. without the data exclusions of Table 2 (see Supplementary Table 1).

There was also no evidence (all $p \geq 0.07$) for a POE in the segregation analyses, which were based on all data (see Table 3 and Figure 3). As above, this does not rule out a small POE, but the 95% CIs in Table 3 bound the size of any POE. For example, for all MMR genes combined, the POE HR is likely to be less than 1.54 for both male and female colorectal cancer, meaning that the colorectal cancer incidences for carriers of maternally-derived mutations are unlikely to be more than 54% larger than those of paternally-derived mutations. Similar reasoning, though based on the lower limits of the 95% CIs in Table 3, shows that colorectal cancer incidences for carriers of paternally-derived mutations are unlikely to be more than 33% (i.e. a factor of 1.33 = 1/0.75) larger than those of maternally-derived mutations.

A sensitivity analysis was also conducted (see Table 4), based on the subset of controls who had filled out an epidemiological questionnaire and had non-missing confounder data (comprising between 290 and 824 subjects, depending on the confounder variable). This sensitivity analysis showed no evidence for an association between the exposure variable from the logistic regression analysis (i.e. the conditional probability of a person inheriting the MMR gene mutation from his or her mother, given that the person is a mutation carrier) and any of the potential confounders listed in Table 4.

Discussion

Despite being well-powered, our study did not observe any evidence of a POE for Lynch syndrome. We measured the POE in two ways, as an OR estimated from a logistic regression

analysis of the population-based non-probands, and as an HR estimated using a segregation analysis approach based on all population- and clinic-based families. Both approaches gave results that were consistent with there being no POE for any combination of gene, sex or cancer site. While this does not rule out a POE entirely, since even a large study like ours can fail to detect a small effect, the confidence intervals of our estimates do rule out a large POE. For example, for all MMR gene mutation carriers combined, the colorectal cancer incidences for carriers with maternally-derived mutations and those with paternally-derived mutations are likely to differ by less than a factor of 1.5 in either direction.

Our findings are contrary to the results of Green et al. [18]and van Vliet et al. [8], who both found marginal evidence for a POE of moderate size, though in opposite directions. The discrepancy between our results and those of these two studies is likely to be due to their relatively small sample sizes. Green et al. [18]studied 12 large families and reported a 2.5 times increased risk of colorectal cancer for carriers whose mutations were inherited from their fathers compared to their mothers. They did not report a CI for this estimate, but the reported p-value was 0.05, so it is possible that this marginally-significant result is simply due to chance. The study by van Vliet et al. [8] (which has many authors in common with the current paper) was based on 17 large families and reported a roughly 3-fold increased risk of colorectal cancer for male carriers with maternally-derived mutations compared to male carriers with paternally-derived mutations (HR=3.2; 95% CI 1.1-9.8; p=0.03). However, due to the marginal p-value of 0.03, it is again possible that this result is simply due to chance. In addition to their small sample size, Green et al. [18]and van Vliet et al. [8] detected POEs in opposite directions and both of their POEs were sex-specific. An elaborate hypothesis would be required to explain these results, which Occam's razor would warn against. By comparison, the only hypothesis needed to explain our results is that there is no POE for either male or female carriers. In any case, our results show that if a POE does exist then it cannot be large, so our results rule out POEs of the size given by the point-estimates of Green et al. [18]and van Vliet et al. [8].

Our findings are consistent with those of Farrell et al. [16]and Suerink et al. [17](2016), who also did not find evidence for a POE. Our study included relatively few *PMS2* mutation carriers, so our results are inconclusive for *PMS2*, but the study of Suerink et al. [17] was well-powered for *PMS2* and their results rule out a moderate or large POE for this gene. In addition to these studies, Lindor et al. [19] also investigated a POE in familial colorectal cancer, though this study is not directly relevant here because it excluded all known or suspected Lynch syndrome cases.

Sensitivity analyses show that our results are not likely to be affected by confounding by any of the main risk factors for colorectal cancer (see Table 4). It seems plausible that colorectal cancer risk factors like alcohol intake could be associated with carrier status, since carriers are more likely to have family histories of cancer and this could affect their lifestyle choices. However, it seems less likely that these lifestyle choices would differ depending on the side of the family (mother or father's side) affected by cancer. Therefore we would not expect colorectal cancer risk factors to be associated with the main exposure variable, so we would not expect any confounding by lifestyle factors in our analyses (at least in the absence of fairly convoluted hypotheses, such as *in utero* effects of the mother's smoking having a

substantial effect on the offspring's chance of smoking) and the sensitivity analyses of Table 4 are consistent with these expectations.

Our study has many strengths. Unlike previous reports, our study had a large sample size, so it was well-powered to detect moderate-sized POEs. The outcome measurement was of a high quality, since cancer diagnosis was confirmed by reviewing: pathology slides, reports or medical records; cancer registry reports; treatments used for the specific cancer; and death certificates. Mutation detection procedures were also of a high standard [21, 22]. Our study correctly adjusted for the ascertainment of the study subjects by using a likelihood-based approach for the segregation analyses and by basing the logistic regression analyses on population-based non-probands only. We estimated the POE using two different statistical methods and we obtained similar results with both. We used advanced statistical methods that are asymptotically unbiased and efficient to estimate the POE HR [8]. We conducted a sensitivity analysis to test for potential confounding. Lastly, the results of the logistic regression analysis are unlikely to be affected by information bias, since the verification procedures for the outcome variables and the objective measurement of the exposure variable have minimized information bias.

Our study has some limitations. Potential confounders were only measured for a subset of the participants, though sensitivity analyses showed that this is unlikely to affect our findings, since the logistic regression exposure variable was not associated with any of the potential confounders. Also, as in many analyses, our methods assumed that phenotypes of family members were conditionally independent, given the MMR gene genotype, and that the MMR gene was the only cause for familial aggregation of cancer. However, while these assumptions could bias the overall risk estimates for MMR gene mutations [35], they affect maternally- and paternally-derived mutations equally, so they are unlikely to bias our POE estimates.

We have shown that a POE for Lynch syndrome is likely to be small or non-existent, so we recommend that MMR gene mutation carriers be managed the same regardless of the parental origin of their mutations, as far as cancer surveillance and other prevention measures are concerned. This is important for communities where there are challenges in accessing counselling, testing and surveillance services, such as indigenous Australians [38].

In summary, our study used an efficient study design and a large sample size to investigate a POE for Lynch syndrome. Despite being well-powered, our study did not find any evidence for a POE regarding the impact of MMR gene mutations on colorectal or endometrial cancer risk. Our results also show that if a POE does exist then it cannot be large, and we argue that the POEs detected by previous studies are likely to be spurious. Therefore, we recommend that screening and management guidelines for MMR gene mutation carriers should not be changed to reflect the parental origin of their mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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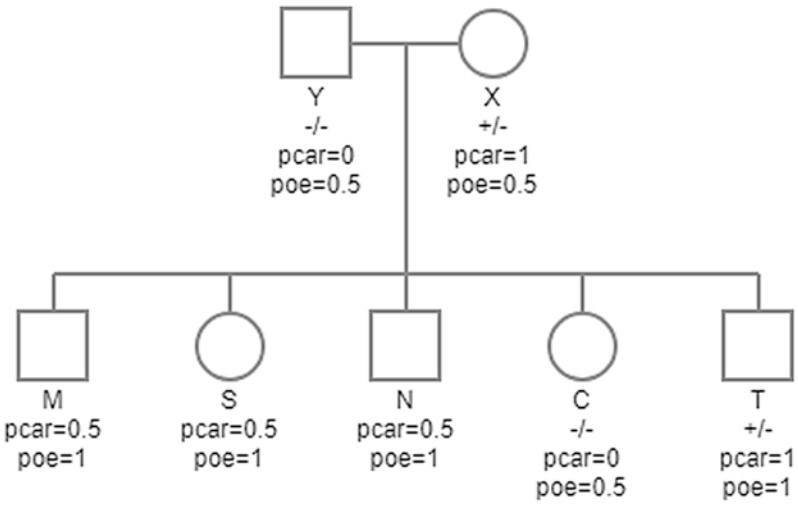

Figure 1.

Hypothetical pedigree showing the values of the exposure variable (poe) and the weighting variable (pcar) for the logistic regression analysis, where +/− indicates a known mutation carrier, −/− indicates a known non-carrier and blank indicates an ungenotyped individual.

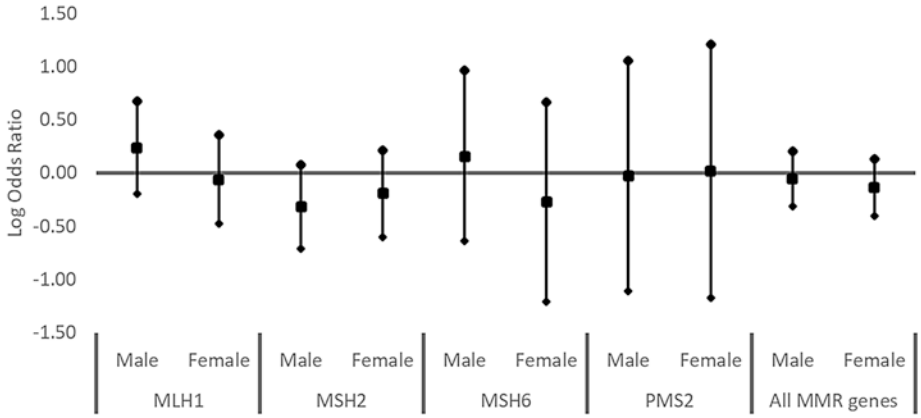

Figure 2.

Adjusted log-odds ratios (squares) and associated 95% confidence intervals (vertical lines) for the association between colorectal cancer and the parent-of-origin effect variable (i.e. the conditional probability of inheriting the mutation from the mother, given that the person is a mutation carrier), adjusted for age, age-squared and country.

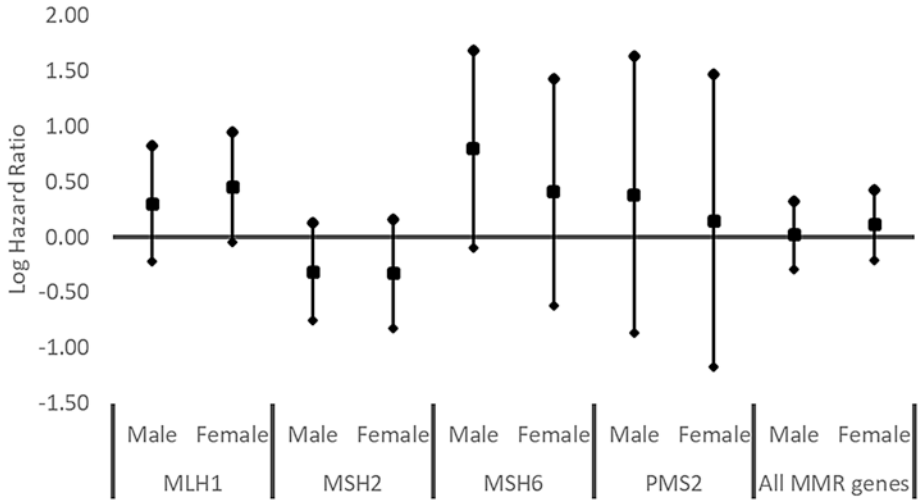

Figure 3.

The logarithm of the estimated parent-of-origin effect hazard ratio for colorectal cancer (squares) with 95% confidence intervals (vertical lines) by sex and the mutated mismatch repair gene.

Table 1.

The number of families and the number of non-probands with various characteristics, by the type of family and the family's mutated MMR gene

Type of family	Family's mutated gene	Number of families	Number of non-probands	Colorectal cancer cases (male)	Colorectal cancer cases (female)	Endometrial cancer cases	Known MMR gene mutation carriers	Known MMR gene mutation non-carriers
Population-based	*MLH1*	93	2093	112	93	39	79	102
	MSH2	98	2182	129	100	53	93	124
	MSH6	40	903	35	24	19	35	35
	PMS2	31	613	11	11	5	23	31
	All MMR genes	262	5791	287	228	116	230	292
Clinic-based	*MLH1*	180	4589	330	289	114	250	334
	MSH2	222	5681	381	291	162	315	398
	MSH6	61	1530	67	48	37	80	91
	PMS2	24	635	17	16	4	29	45
	All MMR genes	487	12435	795	644	317	674	868

MMR = mismatch repair.

Table 2.

Parent-of-origin effect (POE) odds ratios (ORs) for each combination of gene, sex and cancer site. Here, OR=1 corresponds to no POE and OR>1 corresponds to higher risks for maternal mutations than paternal ones.

Family mutated gene	Colorectal Cancer						Endometrial Cancer		
	Male			Female			Female		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
MLH1	0.80	0.28, 2.25	0.7	2.45	0.82, 7.28	0.10	2.98	0.60, 14.84	0.2
MSH2	1.03	0.41, 2.55	0.9	1.33	0.46, 3.89	0.60	0.61	0.16, 2.32	0.5
MSH6	3.00	0.53, 17.00	0.2	0.41	0.012, 14.10	0.60	2.21	0.091, 53.30	0.6
PMS2	0.24	0.017, 3.35	0.3	0.89	0.035, 22.80	0.90	0.14	0.0027, 7.75	0.3
All MMR genes	0.98	0.54, 1.77	0.9	1.62	0.82, 3.23	0.20	1.20	0.51, 2.80	0.7

OR = odds ratio; CI = confidence interval; MMR = mismatch repair.

Table 3:

Parent-of-origin effect (POE) hazard ratios (HRs) for each combination of gene, sex and cancer site. Here, HR=1 corresponds to no POE and HR>1 corresponds to higher risks for maternal mutations than paternal ones.

Family mutated gene	Colorectal cancer				Endometrial cancer	
	Male		Female		Female	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
MLH1	1.35 (0.80-2.28)	0.3	1.57 (0.96-2.58)	0.07	1.27 (0.54-3.03)	0.6
MSH2	0.73 (0.47-1.14)	0.2	0.72 (0.44-1.17)	0.2	0.89 (0.45-1.75)	0.7
MSH6	2.22 (0.91-5.42)	0.08	1.51 (0.54-4.18)	0.4	0.45 (0.17-1.23)	0.1
PMS2	1.46 (0.42-5.12)	0.6	1.16 (0.31-4.36)	0.8	NE	0.3
All MMR genes	1.02 (0.75-1.39)	0.9	1.12 (0.81-1.54)	0.5	0.84 (0.52-1.36)	0.5

HR = hazard ratio; CI = confidence interval; NE = not estimable due to too few people; MMR = mismatch repair.

Table 4.

Association of the main exposure variable from the logistic regression analyses with potential confounding variables, based on the subset of the population-based, non-proband controls who had non-missing confounder data.

Potential confounder	Number of subjects	OR (95% CI)	p-value
Screening (ever vs. never)	455	1.80 (0.91, 3.57)	0.09
Education (high vs. low)	692	0.68 (0.34, 1.36)	0.3
Income (high vs. low)	824	0.98 (0.48, 2.00)	1.0
Alcohol drinking (heavy vs. light)	313	0.89 (0.36, 2.18)	0.8
Smoking (ever vs. never)	514	1.45 (0.66, 3.18)	0.4
Obesity (obese vs. not)	458	0.59 (0.23, 1.50)	0.3
Exercise (any vs. none)	290	0.76 (0.33, 1.76)	0.5
Meat (high vs. low intake)	393	2.20 (0.79, 6.17)	0.1
Fruit (high vs. low intake)	404	1.14 (0.56, 2.30)	0.7
Aspirin (high vs. low intake)	448	1.59 (0.71, 3.56)	0.3
Calcium (high vs. low intake)	454	1.31 (0.56, 3.09)	0.5
Folate (high vs. low intake)	451	1.33 (0.45, 3.98)	0.6
HRT (ever vs. never)	346	1.23 (0.42, 3.56)	0.7

OR = odds ratio; CI = confidence interval; vs. = versus; HRT=hormone replacement therapy.