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Lynch Syndrome and Cervical Cancer

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Abstract

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Conflict of Interest

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

Carriers of germline mutations in DNA mismatch repair (MMR) genes are at increased risk of several cancers including colorectal and gynecologic cancers (Lynch syndrome). There is no substantial evidence that these mutations are associated with an increased risk of cervical cancer. A total of 369 families with at least one carrier of a mutation in a MMR gene (133 *MLH1*, 174 *MSH2*, 35 *MSH6*, and 27 *PMS2*) were ascertained via population cancer registries or via family cancer clinics in Australia, New Zealand, Canada, and USA. Personal and family histories of cancer were obtained from participant interviews. Modified segregation analysis was used to estimate the hazard ratio (incidence rates for carriers relative to those for the general population), and age-specific cumulative risks of cervical cancer for carriers. A total of 65 cases of cervical cancer were reported (including 10 verified by pathology reports). The estimated incidence was 5.6-fold (95% CI: 2.3–13.8; $p=0.001$) higher for carriers than for the general population with a corresponding cumulative risk to 80 years of 4.5% (95% CI: 1.9–10.7%) compared with 0.8% for the general population. The mean age at diagnosis was 43.1 years (95% CI: 40.0–46.2), 3.9 years younger than the reported USA population mean of 47.0 years ($p=0.02$). Women with MMR gene mutations were found to have an increased risk of cervical cancer. Due to limited pathology verification we cannot be certain that a proportion of these cases were not lower uterine segment endometrial cancers involving the endocervix, a recognized cancer of Lynch syndrome.

BACKGROUND

Lynch syndrome, formerly known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is caused by a germline mutation in one of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2*.¹ MMR gene mutation carriers are at increased risk of colorectal (10–60% to age 70 years), endometrial (15–55% to age 70 years), and ovarian (12–24% to age 70 years) cancers.^{2–5} While there is some evidence that cervical cancer might be at increased risk of MMR gene mutation carriers, it is not currently recognized as a cancer associated with Lynch syndrome.

There have been several case reports of endocervical or cervical cancers in women suspected or known to carry mutations in MMR genes.^{5–9} Mongiat-Artus *et al* described a 48-year old woman with a germline nonsense mutation of the *MSH2* gene who had developed a pT1b endocervical adenocarcinoma in addition to primary cancers of the ureter, colon and kidney.⁸ Tumoral microsatellite instability (MSI) (a hallmark of loss of MMR function) and loss of expression of both *MSH2* and *MSH6* proteins was observed in the cervical tumor as well as in the ureteric and colorectal tumors.⁸ MSI and loss of MMR protein expression in this cervical tumor suggest that its tumorigenesis could have been related to the inherent MMR defect along with the colorectal and ureteric tumors (already recognised as part of Lynch syndrome). Using a large resource of MMR gene mutation carrier families, we aimed to determine whether female carriers of a MMR gene mutation are at increased risk of cervical cancer.

MATERIALS AND METHODS

Ascertainment of families

Participants in this study were members of *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutation-carrying families recruited by the Colon Cancer Family Registry.¹⁰ Families were recruited between 1997 and 2012, and ascertained via incident cases of colorectal cancer (population-based probands) from population cancer registries in the USA (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria), and Canada (Ontario), or via patients (clinic-based probands) attending family cancer clinics in the USA (Mayo Clinic, Rochester, Minnesota and Cleveland), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney), New Zealand (Auckland), and Canada (Ontario). Probands were asked for permission to contact their relatives to seek their enrollment in the Colon Cancer Family Registry. Informed consent was obtained from all study participants, and the study protocols were approved at each recruitment center. Standardized instruments and protocols¹⁰ have been used to collect family history information, lifestyle and clinical data, and biological specimens (blood samples and tumor blocks).

Data collection

Information on personal and family history of cancer, including cancer site, age at diagnosis and cancer surgery, was obtained from all participants by interview, self-completed questionnaire or examination of clinical records. Participants were asked to consent to the release of tumor tissue, relevant medical records and provide a blood sample at the time of entry into the registry. Verification of all reported colorectal cancer diagnoses was attempted for all Colon Cancer Family Registry families, with some sites of the Colon Cancer Family Registry attempting to verify all reports of cancer recognized as part of Lynch syndrome using multiple sources, including reports from relatives, pathology reports, medical records, cancer registrations and death certificates. As cervical cancer is not a recognized Lynch associated cancer, no active verification was sought by the Colon Cancer Family Registry. Therefore, for this study, we attempted to obtain pathology reports for all reported cases of cervical cancer.

Mutation Screening and Testing

The Colon Cancer Family Registry tested for germline *MLH1*, *MSH2*, *MSH6* and *PMS2* mutations: all population-based probands who had a colorectal tumor displaying evidence of impaired MMR function by either MSI or by lack of MMR protein expression by immunohistochemistry; and the youngest-onset colorectal cancer case in each clinic-based family, regardless of MSI or MMR protein expression status. Details of germline testing methods have been described elsewhere.¹¹ All participants who donated a blood sample, and who were relatives of probands with a pathogenic mutation,¹¹ underwent testing for the same mutation identified in the proband.

Statistical Analysis

Hazard ratios (age-specific cancer incidence rates for carriers divided by the corresponding population rates) and corresponding 95% confidence intervals (CIs) were estimated from carrier families using modified segregation analysis. Models were fitted by maximum likelihood and all estimates were adjusted for ascertainment by conditioning the likelihood of each family on the proband's phenotype and genotype (for population-based families) or on all of the family's phenotypes and the proband's genotype (for clinic-based families). Families were assumed to be independent so estimates were obtained by maximizing the sum of the conditional likelihoods over all families.

The hazard ratio for cervical cancer was estimated simultaneously with hazard ratios for colorectal, endometrial and other Lynch syndrome-associated cancers. This was necessary to correct for ascertainment and is likely to increase power (as these other cancers give probabilistic information about the carrier status of un-genotyped relatives). Hazard ratios were allowed to depend on age. Country-specific population cancer incidence rates were used as the incidences for non-carriers and were obtained from the Cancer in Five Continents 1998–2002,¹² with this compilation chosen because its time-period is the closest to the median year of diagnosis of all cancers in the MMR gene mutation families. Individuals were censored at any cancer diagnosis (since the resultant treatment and surveillance might alter the risk of subsequent endometrial and cervical cancers) and at hysterectomy (since this is likely to remove the cervix).

Age-specific cumulative risk estimates were calculated from the estimated hazard ratios and population incidence rates as one minus the exponential of minus the cumulative incidences. Corresponding 95% CIs were calculated using a parametric bootstrap with 5000 replications, and were based on the joint distribution of the hazard ratio estimates known from asymptotic likelihood theory. We assumed Hardy-Weinberg equilibrium for each MMR gene and an allele frequency of 0.0001 for all MMR gene mutations combined.

All p-values were two-sided and were based on the likelihood ratio test (for the modified segregation analyses) or *t*-tests (for age comparisons). Modified segregation analyses were conducted using the statistical package MENDEL version 3.2,¹³ and all other calculations were performed using R version 2.11.1 (R development core team, 2010).

RESULTS

A total of 369 MMR gene mutation families were included in this analysis (distribution of the MMR gene mutation of the proband: 133 in *MLH1*, 174 in *MSH2*, 35 in *MSH6* and 27 in *PMS2*). Data were available on 14,931 individuals within these families (7,119 females and 7,812 males). Mutation testing identified 1,073 carriers (including the probands) and 960 non-carriers.

A total of 65 cases of cervical cancer were self-reported or reported by a relative among the female relatives of the MMR gene mutation carrying probands (distribution of the MMR gene mutation of the proband: 23 *MLH1*, 35 *MSH2*, 3 *MSH6* and 4 *PMS2*). Of these 65 reports of cervical cancer cases (included 2 in-situ cases) in the relatives: 16 (25%) cases

were verified by either pathology report (n = 10), clinical record (n = 2) and/or cancer registry record (n = 4); with the remainder (n = 49; 75%) not clinically verified. None of the 65 reported cases were verified as not being a cervical cancer. Of the 10 cervical cancer cases verified by pathology reports, 7 were reported as being either adenocarcinoma or mixed histology with a predominance of adenocarcinoma, and 3 as squamous cell carcinomas.

Of the 65 females with reported cervical cancer, 11 were confirmed MMR mutation carriers, 13 were confirmed non-carriers, and the remaining 41 were untested but were genetically related to known carriers. The mean age at diagnosis was 43.1 years (95% CI: 40.0–46.2) (range 18–70), 3.9 years younger than the reported USA population mean of 47.0 years¹⁴ (p = 0.02). The incidence of cervical cancer was estimated to be 5.6-fold (95% CI: 2.3–13.8; p = 0.001) higher for MMR gene mutation carriers than for the general population. There was no evidence that the cervical cancer hazard ratios varied by MMR gene (p = 0.3 for heterogeneity). The corresponding estimated cumulative risks are given in Table 1 and, illustrated in Figure 1. The cumulative risk to age 80 years was 4.5% (95% CI: 1.9–10.7%) for MMR gene mutation carriers compared with 0.8% for the general population.¹²

DISCUSSION

In this study, we estimated that female MMR gene mutation carriers have incidence rates of reported cervical cancer which are approximately six-times higher than those for the general population and that the reported cervical cancers of carriers are diagnosed an average of approximately four years earlier. Our findings are suggestive that cancer of the cervix may be an additional extracolonic cancer associated with germline MMR gene mutations. The very limited number of retrievable pathology reports importantly ruled out the ability for verification as to whether a proportion of these cases were in fact endometrial tumors arising from the lower uterine segment and involving the endocervix, a recognized phenomenon of MMR-deficient uterine tumors,^{15–17} either because of germline MMR gene mutations or *MLH1* methylation. Based on our observation that all 10 pathology reports we could obtain, verified the reports as true cervical cancer, and assuming that the cases for which we could obtain these pathology reports were representative of all 65 reported cases, we estimate that the 95% CI for the true proportion of the 65 reported cases would be 74% to 100%.

A review of the literature revealed three reports including cervical cancers from registries of known or potential Lynch syndrome families; two supportive,^{18, 19} and one contrary to our findings.²⁰ A study from the Hereditary Colorectal Cancer Registry of the AC Camargo Hospital in Brazil, observed that cervical cancer was the most frequently reported extracolonic tumor among known MMR gene mutation carriers.¹⁸ The authors, however, reported concern that without verification, most of the reported cancers were likely to be misreported endometrial cancers. Casey *et al*¹⁹ recently reviewed all gynaecological cancer records from the Creighton University Hereditary Cancer Registry for patients with known germline *BRCA1/2* and MMR gene mutations. They reported cervical cancers in three known MMR gene carriers: one squamous cell carcinoma (in a *MLH1* mutation carrier) and two adenocarcinomas (one in a *MLH1* and one in a *MSH2* mutation carrier). Contrary to our findings, Bermejo and colleagues reported that Swedish women in families that fulfilled the

Amsterdam or Bethesda criteria for Lynch syndrome (N=5158; note: these were not tested for mutations in MMR genes) had a lower risk of cervical cancer compared with those in the population (relative risk = 0.76, 95% CI: 0.59–0.98, p=0.03).²⁰ The authors postulated that this could have been because women in these families were undertaking regular screening for endometrial cancer, and the low cervical cancer risk estimate was due to serendipitous early detection and management of *in situ* lesions. Another explanation is that hysterectomies conducted as management of endometrial cancer or benign or precancerous conditions reduced risk due to removal of cervix.

The strengths of this study include: the large sample size and the use of statistical methods which utilize data on all subjects (whether genotyped or not), both of which increase the precision of risk estimates; the use of statistical methods which properly correct for ascertainment and so avoid ascertainment bias; the use of standardized questionnaires across recruitment sites, increasing the study's validity and reliability; and the high-quality and sensitive testing for MMR gene mutations across all recruiting centers of Colon Cancer Family Registry. Though we included all female relatives in the analysis, even those not surveyed as participants, one limitation is that for women not surveyed, we do not know whether or not they had a hysterectomy, or the age at which this occurred. We had no hysterectomy data for 62% of women in this analysis. It is likely that a proportion of these women might have had a hysterectomy and therefore, in these women, the observation time in our analysis would have included time after a hysterectomy, thereby underestimating the actual risk. Therefore, our estimate of the increased risk of cervical cancer might be an underestimate of the true increased risk. A major limitation of this study was that most diagnoses of cervical cancers (75%) were self-reported or reported by relatives.

This novel finding highlights one of the current issues associated with understanding the breadth of cancer risk that may be associated with Lynch syndrome. While colorectal and endometrial cancers are the most frequent sites associated with Lynch syndrome, it is also recognized that other sites of cancer origin are reported more frequently in MMR gene mutation carriers than population rates.^{5, 21, 22} Ideally, future prospective collections of epidemiological data, tumor specimens, specimens from risk-reducing surgery from known MMR gene mutation carriers, regardless of the organ should be considered to assess for the likelihood of MMR deficiency. While it is conceivable that cervical cancer development in MMR gene mutation carriers is related to currently known tumorigenic pathways associated with the carcinogenic effects of human papilloma virus exposure, it is also important to establish with certainty the organs at increased risk of carcinogenesis in the setting of MMR deficiency not only for identifying individuals at risk of Lynch syndrome, but also for risk management (individual and familial) and potential future therapeutic options. We suggest that further studies are required to explore this finding.

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Novelty & Impact Statements

Women with a DNA mismatch repair gene mutation (Lynch syndrome) were found to have an increased risk of cervical cancer that is six-times higher than the general population. The reported cervical cancers of carriers were diagnosed an average of approximately four years earlier than the general population. Cervical cancer might be part of Lynch syndrome spectrum cancers.

Figure 1.

Age-specific cumulative risk of cervical cancer for MMR gene mutation carriers (solid bold line) with corresponding 95% confidence intervals (shaded region) and for non-carriers (dashed bold line) from USA.

Estimated cumulative risks (%) of cervical cancer to various ages by country and mismatch repair gene mutation carrier status (non-carriers assumed to have the population incidence).

Table 1

Age (years)	Carriers		Non-carriers			
	USA	Canada	Australia	USA	Canada	Australia
30	0.31 (0.13–0.76)	0.32 (0.13–0.79)	0.2 (0.08–0.48)	0.06	0.06	0.04
40	1.1 (0.44–2.6)	1.0 (0.42–2.5)	0.66 (0.27–1.6)	0.19	0.18	0.12
50	2.0 (0.82–4.8)	1.8 (0.75–4.4)	1.2 (0.51–3.0)	0.36	0.33	0.22
60	2.9 (1.2–6.8)	2.5 (1.0–6.1)	1.8 (0.74–4.4)	0.51	0.46	0.32
70	3.7 (1.5–8.9)	3.3 (1.4–7.9)	2.5 (1.0–6.1)	0.68	0.59	0.46
80	4.5 (1.9–10.7)	4.0 (1.7–9.5)	3.3 (1.4–7.9)	0.82	0.72	0.60