Childhood cancers in families with and without Lynch syndrome

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ABSTRACT

Background: Inheritance of a germline mutation in one of the DNA mismatch repair (MMR) genes or the *EPCAM* gene is associated with a well-defined increased risk of colorectal cancer, endometrial cancer, and other adult malignancies (Lynch syndrome). The risk of childhood cancers in Lynch syndrome families, however, is not well studied.

Materials and Methods: Using data from the Colon Cancer Family Registry, we compared the proportion of childhood cancers (diagnosed before 18 years of age) in the first-, second-, and third-degree relatives of 781 Lynch syndrome families in which at least one relative had a pathogenic mutation in one of the MMR genes; *MLH1* (n=275), *MSH2* (n=342), *MSH6* (n=99), or *PMS2* (n=55) or in *EPCAM* (n=10), with that of 5,073 families in which the proband's colorectal cancer showed tumor MMR-proficiency (non-Lynch syndrome).

Results: There was no evidence of a difference in the proportion of relatives with a childhood cancer between Lynch syndrome families (41/17,230; 0.24%) and non-Lynch syndrome families (179/94,302; 0.19%; p = 0.19). Incidence rate of all childhood cancers was estimated to be 147 (95% CI = 107–206) per million population per year in Lynch syndrome families and 115 (95% CI = 99.1–134) per million population per year in non-Lynch syndrome families. There was no evidence for a significant increase in the risk of all childhood cancers, hematologic cancers, brain and central nervous system cancers, Lynch syndrome-associated cancers, or other cancers in Lynch syndrome families compared with non-Lynch syndrome families.

Conclusion: The risk of childhood cancers does not appear to be significantly increased in Lynch syndrome families compared with non-Lynch syndrome families.

Larger studies, however, are required to more accurately define the risk of specific individual childhood cancers in Lynch syndrome families.

INTRODUCTION

The DNA mismatch repair (MMR) system contributes to the maintenance of genome integrity and the *MLH1*, *MSH2*, *MSH6,* and *PMS2* genes play a critical role in this process. The MMR system is involved in the correction of single base-pair incorporation errors and small insertion-deletion loops that occur during DNA replication. The MMR system is also involved in cellular responses to a variety of agents that damage DNA [1]. Lynch syndrome is an autosomal dominant inherited disorder of cancer susceptibility caused by a heterozygous germline mutation in one of the MMR genes [2] or a deletion in the 3' end of the *EPCAM* gene, which leads to epigenetic silencing of the closely linked *MSH2* [3]. Carriers of a heterozygous MMR gene mutation are at increased risk of multiple adult cancers, most notably colorectal and endometrial cancer, but also cancer of the stomach, ovary, ureter, renal pelvis, brain, small bowel, and hepatobiliary tract [4], as well as breast [5] and prostate [6]. The development of these cancers generally occurs in mutation carriers at a younger age than in the general population.

Investigating risk factors for childhood cancers, especially any hereditary factors, is clinically important and warranted for families already predisposed to early-onset cancers such as Lynch syndrome families. Inheritance of homozygous or compound heterozygous MMR gene mutations has been found to predispose carriers to a range of childhood cancers including brain, hematologic and gastrointestinal cancers, and is now called constitutional mismatch repair deficiency (CMMR-D) syndrome [7, 8]. To date, however, no large studies have been performed to examine the association, or lack thereof, between heterozygous MMR or *EPCAM* gene mutations and the risk of childhood

cancers in families with heterozygous MMR or *EPCAM* gene mutations (Lynch syndrome) was estimated using a large dataset from the Colon Cancer Family Registry.

MATERIALS AND METHODS

Study Sample

Data from the Colon Cancer Family Registry were used for this study. Details of the Registry have been published previously [9] and can be found at http://coloncfr.org. Briefly, families were recruited between 1997 and 2012 and were ascertained via incident colorectal cancer cases diagnosed older than age 18 years identified from population cancer registries (population-based probands) in the United States (Arizona, California, Colorado, Hawaii, Minnesota, New Hampshire, North Carolina, and Washington), Australia (Victoria), and Canada (Ontario) or via those attending family-cancer clinics who are older than age 18 years (clinic-based probands) in the United States (Cleveland Clinic, Cleveland, OH and Mayo Clinic, Rochester, MN), Canada (Ontario), Australia (Adelaide, Brisbane, Melbourne, Perth and Sydney), and New Zealand (Auckland). Informed consent was obtained from all study participants and the study protocol was approved at each center.

Data Collection

At recruitment, baseline information on demographics, personal characteristics, personal and family history of cancer including childhood cancers, cancer screening history, history of polyps, polypectomy, hysterectomy, and other surgical information

was obtained from all participants. Participant information was updated approximately every five years after baseline. Reported cancer diagnoses and ages at which cancers occurred were confirmed using pathology reports, medical records, cancer-registry reports, and/or death certificates, where possible. We attempted to collect blood samples from all participants and tumor tissue samples from all participants with colorectal cancer.

Gene Mutation Testing

Testing for germline mutations in *MLH1, MSH2, MSH6 and PMS2* was performed for all population-based probands who had a colorectal tumor that showed evidence of impaired MMR function by either tumor microsatellite instability (MSI) or a lack of MMR-protein expression by immunohistochemistry, or both. For clinic-based families, testing was performed on the youngest colorectal cancer case regardless of MSI or MMR-protein expression status. Mutation testing for the *MLH1*, *MSH2,* and *MSH6* genes was performed by Sanger sequencing or denaturing high-performance liquid chromatography (dHPLC), followed by confirmatory DNA sequencing. Large duplication and deletion mutations including those involving *EPCAM*, which lead to *MSH2* methylation, were detected by Multiplex Ligation Dependent Probe Amplification (MLPA) according to the manufacturer's instructions (MRC Holland, Amsterdam, the Netherlands). *PMS2* mutation testing involved a modified protocol [10], in which exons 1–5, 9, and 11–15 were amplified in three long-range polymerase chain reactions (PCRs), followed by nested exon-specific PCR/sequencing, whereas the remaining exons (exons 6, 7, 8, and 10) were amplified and sequenced directly from genomic DNA. Large-scale deletions in *PMS2* were detected using the P008-A1 MLPA kit (MRC Holland, Amsterdam, The

Netherlands). The relatives of probands with a pathogenic mutation, who provided a blood sample, underwent testing for the specific mutation identified in the proband. Pathogenic mutations were defined as variants resulting in a stop codon, frameshift mutation, large duplication or deletion, or missense mutation in the coding region or splice site previously reported in the scientific literature or databases [11].

Definitions

Childhood cancer was defined to be any cancer in an individual less than 18 years of age. We defined Lynch syndrome families as families in which at least one family member was a confirmed carrier of a heterozygous germline mutation in one of the four MMR genes (*MLH1, MSH2, MSH6* or *PMS2)* or *EPCAM.* Non-Lynch syndrome families were defined as families in which the proband's colorectal cancer showed tumor MMR-proficiency (displayed microsatellite stability and/or the presence of MMR protein expression by immunohistochemistry). We included proband's first-, second-, and third-degree relatives in the analysis, but excluded all probands from the analysis.

Statistical Analyses

We estimated: (i) the number of childhood cancers per family as the number of relatives diagnosed with a childhood cancer divided by the number of families; and (ii) the proportion of relatives with a childhood cancer as the number of relatives diagnosed with a childhood cancer divided by the total number of relatives.

Next, we estimated incidence rates of childhood cancer diagnoses per 1,000 person-years and corresponding 95% confidence intervals (CIs) for relatives in Lynch syndrome and non-Lynch syndrome families. Cox proportional hazards regression

was used to estimate hazard ratios (HRs) and corresponding 95% CIs to compare the risk of childhood cancers between Lynch syndrome and non-Lynch syndrome families after adjusting for sex, country of recruitment (USA, Canada, and Australia/New Zealand), and source of ascertainment (clinic-based, population-based). We estimated risk of cancers by type: (i) all cancers; (ii) hematologic cancers including leukemias and lymphomas; (iii) brain and central nervous system (CNS) cancers; (iv) Lynch syndrome-associated cancers (which included cancers of the colon, rectum, stomach, small intestine, hepatobiliary tract, pancreas, renal pelvis, ureter, urinary bladder, brain, endometrium, and ovary); and (v) other cancers (all other cancers except hematologic, brain and CNS, and Lynch syndrome-associated cancers). Time at risk for each relative started at birth and ended either at the age of diagnosis of a childhood cancer, the age at death, the last known age, or at 18 years of age, whichever occurred earliest. All reported statistical tests were two-sided. All statistical analyses were conducted using Stata 13.0 [12].

RESULTS

The cohort of Lynch syndrome families included 781 families with a mutation in a MMR gene (275 in *MLH1*, 342 in *MSH2*, 99 in *MSH6*, and 55 in *PMS2*) and 10 families with an *EPCAM* gene mutation. Lynch syndrome families were comprised of 4,725 (28%) first-degree relatives, 7,609 (44%) second-degree relatives and 4,896 (28%) third-degree relatives (Table 1). Of the relatives tested for Lynch syndrome, 1,160 were found to be mutation carriers (420 in *MLH1*, 546 in *MSH2*, 124 in *MSH6*, 57 in *PMS2*, and 13 in *EPCAM*) and 1,106 were non-carriers. Of the 1,160 confirmed carriers, 700 (60%) were first-degree relatives, 262 (23%) were second-degree

relatives, and 198 (17%) were third-degree relatives. The control cohort included 5,073 families of probands with MMR-proficient colorectal cancer (non-Lynch syndrome families) with 31,219 (33%) first-degree relatives, 40,458 (43%) second-degree relatives, and 22,625 (24%) third-degree relatives.

We identified 41 cases of childhood cancer in the 781 Lynch syndrome families (0.05 cases per family). Of these, 35 (85%) were self-reported or reported by relatives. Only 4 cases were genotyped for MMR gene mutation status (2 were *MSH2* mutation carriers and 2 were non-carriers). The number of childhood cancer cases per family did not differ according to the type of MMR gene mutation carried by the family (0.06 for *MLH1*, 0.05 for *MSH2*, 0.04 for *MSH6*, and 0.05 for *PMS2*). There were no cases of childhood cancer documented in families with an *EPCAM* mutation. No evidence was found for a difference in the proportion of relatives affected with a childhood cancer between Lynch syndrome families (41/17,230; 0.24%) and non-Lynch syndrome families (179/94,302; 0.19%) ($p = 0.19$). The mean age at diagnosis of childhood cancers was not different between Lynch syndrome families (9.7 years, 95% CI = 7.8–11.6) and non-Lynch syndrome families (9.1 years, 95% CI = 8.2–9.9) ($p = 0.51$). Male and female relatives appeared to be equally affected by childhood cancers in both Lynch syndrome and non-Lynch syndrome families (Table 1).

The incidence rate of all childhood cancers was estimated to be 147 (95% CI = 107–206) per million population per year in Lynch syndrome families and 115 (95% CI = 99.1–134) per million population per year in non-Lynch syndrome families. There was no evidence for a higher risk of childhood cancers within Lynch syndrome families for all childhood cancers compared with non-Lynch syndrome families (HR = 1.27; 95% CI = 0.88–1.84). Further, no clear evidence was found for a higher risk of

hematologic cancers, brain and CNS cancers, Lynch syndrome-associated cancers, or all other cancers in Lynch syndrome families compared with non-Lynch syndrome families (Table 2).

Details of childhood cancers in Lynch syndrome families from the Colon Cancer Family Registry are summarized in Supplementary Table 1. Hematologic cancers (leukemias and lymphomas) and CNS cancers were the two most commonly diagnosed childhood cancers in Lynch syndrome families (34% and 29%, respectively). These two cancers were also found to be the most commonly diagnosed cancers in non-Lynch syndrome families (31% for hematologic cancers and 11% for CNS cancers, respectively).

DISCUSSION

In this study, we found no evidence of a difference in the risks of childhood cancers between Lynch syndrome families and non-Lynch syndrome families. Further, there did not appear to be a difference in the types of childhood cancers observed in Lynch syndrome families compared with non-Lynch syndrome families.

Hematologic cancers and CNS cancers are the two most commonly diagnosed childhood cancers in Lynch syndrome families, similar to the pattern observed in the general population [13, 14]. The proportion of hematologic cancers (leukemias and lymphomas) among all childhood cancers is estimated to be 40% in the United States [15], 41% in Ireland [16], 42.9% in China [17], and 43.5% in Australia [14]. The estimated proportion of childhood CNS cancers is 27.6% in the United States [15], 21.5% in Ireland [16], 20.2% in China [17], and 22.7% in Australia [14].

There have been several case reports on the occurrence of cancers in children and adolescents with Lynch syndrome [18-21]. The youngest case of colorectal cancer reported occurred in a 13 year old female carrying a *MLH1* mutation [18-21]. Huang et al. reported the sigmoid colon cancer in a 14 year old female carrying a complex mutation of *MLH1* at codon 226 [21]. Further, the diagnosis of colorectal cancer was also reported in a 15 year old male, who had a family history of colorectal cancer in his father and grandmother, and found to carry a *MSH2* axonal deletion [20]. More recently, a case of extracolonic cancer (anaplastic oligodendroglioma) in a 15 year old male with a *MSH2* mutation was also reported [18]. These case reports, in addition to our study, emphasize the importance of investigations for the presence of Lynch syndrome-associated cancers, as well as other cancers, especially in children from Lynch syndrome families or with a family history of multiple cancers.

The current study is the largest to date, with 781 families available to assess the risk of childhood cancers in Lynch syndrome families. There has been only one other study that investigated the prevalence of childhood cancers in families carrying a MMR gene mutation [22]. At a regional oncogenetic clinic in Sweden, the prevalence of childhood cancers was found to be significantly higher in families with a MMR gene mutation compared with population-based control families (19.4% [6/31] vs. 0.8% [7/854]; odds ratio 29.0, 95% CI = 9.1 – 92.6; $p<0.001$). This study was based on a small number of cases recruited from an oncology clinic, possibly resulting in a selection bias and, therefore, risk estimates were biased upwards.

In the current study, we compared childhood cancers between Lynch syndrome families and non-Lynch syndrome families after adjusting for the source of ascertainment (clinic- vs. population-based) to minimize the selection bias. However,

the retrospective nature of our study and the relatively small number of childhood cancers observed in Lynch syndrome families (n=41), do not allow us to totally exclude MMR or *EPCAM* gene mutations as a risk factor for childhood cancers. Given that relatives of the probands were only tested for the specific variant of MMR gene identified in the proband, we do not know whether or not they carried other variants of MMR genes. So it is possible that some of the childhood cancers may have occurred in carriers of compound heterozygotes. However, this is highly unlikely because of the rarity of pathogenic MMR gene mutations in the general population (one in 370 to one in 3,100 individuals [23, 24]). Further, there was no consanguinity within Lynch syndrome families in our dataset.

Incidence rates for all childhood cancers in Lynch syndrome families and non-Lynch syndrome families in the current study appear to be lower than the age-adjusted incidence rates for children aged 0-14 years in the general population (178 per million for boys and 160 per million for girls) [25]. This may be a result of the Colon Cancer Family Registry recruitment strategies in which we did not recruit individuals younger than 18 years of age and only enquired about family history of cancers from adult participants. Some survivors of very early-onset childhood cancers might not know their diagnosis and, further, some survivors simply choose to deny that they had a cancer in childhood, so some of these histories may be under-reported. Finally, as the likelihood of dying from childhood cancer was much higher in the period up until the 1970s than it is now, there may be childhood deaths in some families that have been forgotten, which is much more likely to occur in second- and third-degree relatives. As a consequence, we may not have been able to reliably estimate incidence of childhood cancers compared with the population incidences.

In summary, we did not find a significant increase in the prevalence of childhood cancers in Lynch syndrome families when compared with colorectal cancer families without Lynch syndrome. Consequently, these data do not support any changes to the current practice of cancer screening in Lynch syndrome families, which currently recommends annual colonoscopy screening starting from age 25 years or 10 years earlier than the age of the youngest diagnosis of colorectal cancer in the family [26, 27]. Larger studies, however, are required to more accurately define the risk of specific childhood cancers in Lynch syndrome families.

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Table 1. Summary of childhood cancers in Lynch syndrome families and non-Lynch syndrome families from the Colon Cancer Family Registry

	No. of families	No. of relatives (female)	Total number of relatives with at least one cancer diagnosis (female)	Number of relatives with cancer diagnosed before age 18 (female)
Lynch syndrome	781	17230 (8522)	4605 (2385)	41 (16)
Degree of relatedness				
First-degree	–	4725 (2386)	1620 (861)	10 (4)
Second-degree	–	7609 (3699)	2041 (1009)	13 (4)
Third-degree	–	4896 (2437)	944 (515)	18 (8)
Ascertainment				
Population-based	276	5546 (2768)	1248 (642)	13 (3)
Clinic-based	505	11684 (5754)	3357 (1743)	28 (13)
Type of MMR gene				
MLH1	275	6120 (3053)	1638 (817)	16 (7)
MSH2	342	7795 (3879)	2264 (1202)	18 (7)
MSH6	99	1977 (954)	459 (241)	4 (2)
PMS2	55	1190 (571)	204 (108)	3 (0)
EPCAM	10	148 (65)	40 (17)	0 (0)
Non-Lynch syndrome	5073	94302 (46843)	15355 (7849)	179 (90)
Degree of relatedness				
First-degree	–	31219 (15520)	6350 (3209)	60 (33)
Second-degree	–	40458 (20049)	6607 (3383)	61 (32)
Third-degree	–	22625 (11274)	2398 (1257)	58 (25)
Ascertainment				
Population-based	4554	74846 (37269)	12837 (6576)	151 (79)
Clinic-based	519	19456 (9574)	2518 (1273)	28 (11)

Table 2. Risk of childhood cancers in Lynch syndrome families and non-Lynch syndrome families from the Colon Cancer Family Registry

	No. of cancer	Mean age at diagnosis (SD)	Incidence rate per million population per year (95% CI)	HR^ (95% CI)
All cancers				
Non-Lynch syndrome	179	9.1 (5.6)	115 (99.1–134)	Reference
Lynch syndrome	41	9.7 (6.1)	147 (107–206)	1.27 (0.88–1.84)
Hematologic cancers				
Non-Lynch syndrome	55	9.1 (5.1)	35.3 (27.1–46.9)	Reference
Lynch syndrome	14	7.2 (5.4)	50.1 (30.3–89.1)	1.63 (0.87–3.05)
Brain and CNS cancers				
Non-Lynch syndrome	19	7.7 (5.6)	12.2 (7.89–19.9)	Reference
Lynch syndrome	12	8.0 (6.5)	42.9 (23.8–85.8)	2.55 (0.84–7.67)
Lynch syndrome-associated cancers*				
Non-Lynch syndrome	40	9.4 (5.7)	25.7 (18.9–35.8)	Reference
Lynch syndrome	14	9.2 (6.7)	50.1 (29.2–93.4)	1.48 (0.68–3.22)
Other cancers**				
Non-Lynch syndrome	84	8.9 (5.9)	53.9 (43.6–67.3)	Reference
Lynch syndrome	13	12 (5.0)	46.5 (27.6–84.9)	0.91 (0.51–1.62)

*Included cancers of the colon, rectum, stomach, small intestine, hepatobiliary tract, pancreas, renal pelvis, ureter, urinary bladder, brain, endometrium, and ovary.

**Included other cancers except hematologic, brain, and Lynch syndrome-associated cancers

^adjusted for sex, country of recruitment, and source of ascertainment

HR, hazard ratio; CI, confidence interval, SD, standard deviation

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