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Gastroenterology. Author manuscript; available in PMC 2010 November 1.

Published in final edited form as:
Gastroenterology. 2009 November ; 137(5): 1621–1627. doi:10.1053/j.gastro.2009.07.039.

Calculation of Risk of Colorectal and Endometrial Cancer Among Patients with Lynch Syndrome

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Abstract

Background & Aims—Lynch Syndrome is the most common hereditary colorectal cancer (CRC) syndrome. Previous estimates of lifetime risk for CRC and endometrial cancer (EC) did not control for ascertainment and were susceptible to bias towards overestimated risk.

Methods—We studied 147 families with mismatch repair (MMR) gene mutations (55 *MLH1*, 81 *MSH2*, and 11 *MSH6*) identified at 2 U.S. cancer genetics clinics. Age-specific cumulative risks (penetrance) and hazard ratio (HR) estimates of CRC and EC risks were calculated and compared to the general population using modified segregation analysis. The likelihood for each pedigree was conditioned on the proband and first-degree relatives affected with CRC to reduce ascertainment bias and overestimation of penetrance.

Results—We analyzed 628 cases of CRC, diagnosed at median ages of 42 and 47 years for men and women, respectively. Cumulative risk of CRC was 66.08% (95% confidence interval [CI 59.47%–76.17%) for men and 42.71% (95% CI 36.57%–52.83%) for women, with overall HRs of 148.4 and 51.1, respectively. CRC risk was highest for males with mutations in *MLH1*. There were 155 cases of EC, diagnosed at median age of 47.5 years. Cumulative risk of EC was 39.39% (95%

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CI 30.78%–46.94%) with overall HR of 39.0% (95% CI 30.4%–50.2%). For women, the cumulative risk of CRC or EC was 73.42% (95% CI 63.76%–80.54%).

Conclusions—Lifetime risks of CRC and EC in MMR gene mutation carriers are high even after adjusting for ascertainment. These estimates are valuable for patients and providers; specialized cancer surveillance is necessary.

Keywords

Lynch Syndrome; penetrance; cumulative risk

Introduction

Lynch Syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is the most common hereditary colorectal cancer syndrome and accounts for 3-5% of CRC cases.[1] Lynch syndrome tumors develop as a consequence of defective DNA mismatch repair associated with germline mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2*. Individuals with LS typically develop young-onset, rapidly progressive neoplasms, which usually demonstrate a phenotype of microsatellite instability. While there have been a variety of tumor types described in LS, adenocarcinomas of the colorectum and endometrium are the most common, and clinical management guidelines recommend aggressive surveillance for these cancers. [2]

Prior to the discovery of MMR gene mutations, the diagnosis of LS was made on the basis of a family's cancer history. The classic Amsterdam Criteria, originally developed for research purposes, required that a LS family contain 3 individuals with CRC in 2 generations with one case diagnosed at age less than 50 years.[3] Once linkage analysis led to the positional cloning of the MMR gene mutations in these Amsterdam Criteria families, it became possible to use molecular analysis to diagnose LS in clinical practice. As many MMR mutation carriers have family histories that do not meet Amsterdam Criteria,[4] the more inclusive revised Bethesda guidelines [5] are now used to identify patients at risk for LS.

A number of studies have sought to quantify cancer risks in Lynch Syndrome. Lifetime risks for developing colorectal and endometrial cancer have previously been estimated at 70-80% and 40-60%, respectively, on the basis of data collected through European familial cancer registries.[6-10] It has been suggested that estimates of cancer risk in LS may be artificially inflated, due to ascertainment bias resulting from overrepresentation of families with unusually striking cancer histories[11] and failure to control for Amsterdam-defining tumors in calculations of cancer risks. Recent studies using different statistical methodologies to control for these potential biases have estimated risks for colorectal and endometrial cancer of 22-47% and 14-30%, respectively [11-13], which are significantly lower risks than previously reported.

We sought to quantify risk estimates for colorectal and endometrial adenocarcinoma in families with pathogenic MMR gene mutations associated with Lynch Syndrome. We used statistical methods that control for ascertainment bias and used information derived from observed genotype data and pedigree structure to probabilistically infer the genotypes of individuals who have not undergone genetic testing.

Methods

Subjects

Kindreds with a pathogenic mutation in the MMR genes *MLH1*, *MSH2*, or *MSH6* were identified through cancer genetics clinics at the Dana-Farber Cancer Institute (Boston, MA)

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and University of Michigan Comprehensive Cancer Center (Ann Arbor, MI). Subjects presented to these clinics either by self-referral or physician referral on the basis of their family history of cancer. Probands had enrolled in a familial cancer registry through protocols approved by each center's institutional review board. Family pedigrees in which one or more family members were confirmed carriers of a pathogenic MMR gene mutation by clinical genetic testing were included in this analysis. Ages and cancer diagnoses of all first, second, third, and fourth degree relatives were obtained through probands' reports and cancer diagnoses were confirmed with medical record reports or death certificates, when available. Each pedigree was reviewed to determine whether the genetic mutation originated from the proband's maternal or paternal lineage and individuals from the unaffected side of the family were excluded from the analysis.

Statistical Analysis

We used the information on the occurrence of colorectal (CRC) and endometrial cancer (EC) in relatives of MMR mutation-positive index cases to estimate age and gender-specific incidences of CRC and EC (females) in MMR mutation carriers by maximum likelihood, using modified segregation analysis. The method was implemented in MENDEL (v3.3.5). [14,15] Relatives were assumed to be followed from 20 years of age and to be censored at the age at diagnosis of CRC, at the age of death, at the age of last follow-up, or at age 70 years, whichever occurred earlier. In estimating the risk of EC and CRC, female relatives were censored at age at diagnosis of EC or CRC, whichever was diagnosed first. Information on MMR mutation status in relatives was included whenever available. The segregation analysis implemented by MENDEL automatically handles missing genotype information by including allele frequencies as parameters in the likelihood and marginalizes the observed joint likelihood of phenotype and genotype of the pedigree over the unobserved genotype matrix, summing over all possible genotype configurations for the unobserved genotype matrix of the pedigree. For individuals with missing age information the age was imputed based on the subject's relationship with the proband, deceased status (dead or alive at last follow up) and their relationship to the proband by the conditional mean of observed age in a given strata defined by these two variables. As an example, if the proband's unaffected father was missing age and he was reported as still alive, we imputed his age by using the average age among all fathers who were living. This led to a more conservative penetrance estimate than imputation conditional on disease status of the individual. In addition, for cases with missing age of onset, we used current age as the age of diagnosis, if current age was available. We al so carried out a sensitivity analysis without imputing the age information to ensure that the age imputation did not artificially inflate estimates of penetrance and relative risk.

To correct for ascertainment, we maximized the conditional likelihood of observing the phenotypes (CRC and/or EC) and genotypes (mutations in *MLH1*, *MSH2*, *MSH6*) of the entire pedigree given the phenotypic and genotypic information of the index case and phenotypic information of all CRC affected first degree relatives of the index case. This choice of conditioning was based on the belief that subjects were ascertained because they had a family history of CRC. Given the usual ascertainment and referral of probands to cancer genetics clinics based on diagnosis of CRC, this conditioning strategy seems reasonable. However, to assess the role of conditioning on the risk estimates, we conducted a sensitivity analysis by evaluating three more conditioning strategies[16] and maximized the conditional likelihood given (a) the phenotypic and genotypic information of the index case and phenotypic information of all first degree relatives (affected and unaffected by CRC) of the index case; (b) the phenotypic and genotypic information of the index case and phenotypic information of the entire pedigree, and (c) the phenotype and genotype of just the index case, which resulted in a much higher estimate of the risk than the other three ascertainment co rrection schemes.

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The results of the sensitivity analysis are available at http://www.sph.umich.edu/bhramar/public_html/software/supplementary-2.doc.

Cancer incidence in carriers was assumed to follow a proportional hazards model, with $\lambda(t) = \lambda_0(t)\exp[g(t)]$, where $\lambda_0(t)$ is the background incidence, which was assumed to follow the population incidence from the SEER 13 database (http://seer.cancer.gov). For CRC, the age and gender-specific relative risks in carriers as compared to the gender specific population rates are modeled through the function exp[g(t)]. For males and females we estimated the age specific log(RR) or log hazard ratio parameters for the two age intervals <50 and ≥50. The function g(t) takes the form $\sum_{k=1}^{n} \exp[\beta_{ik}]$, a piecewise constant RR in the k^{th} age band k=1,2 and i^{th} gender where i=Male, Female. When considering EC and either EC or CRC in females the age-specific relative risks in carriers as compared to the population rates were similarly modeled through the function exp[g(t)]. We estimated the age specific log(RR) or log hazard ratio parameters for the two age intervals <50 and ≥50, assuming that $g(t) = \sum_{k=1}^{n} \exp[\beta_k]$, a piecewise constant RR in the kth age band k=1,2. In all analysis, cancer incidences in non-carriers were assumed to follow the population cohort-specific rates as obtained through SEER 13.

To construct confidence intervals (CI) for the log(RR) estimates, we assumed that the maximum likelihood estimates of the parameters were asymptotically normally distributed with covariance matrix given by the inverse of the Fisher information matrix. Cumulative risk (e.g. penetrance) and 95% CI were calculated from the cumulative incidence $\Lambda(t)$ given by $\Lambda(t) = \sum_{k=1}^{n} i_k t_k \exp[\beta_{ik}]$ where i_k is the population incidence, t_k is the length and β_k is the k log (RR) in the k^{th} age interval (and in the case of colorectal cancer this is gender specific). The cumulative risk is given by $F(t) = 1 - \exp[-\Lambda(t)]$ and a 95% confidence interval for $F(t)$ is $1 - \exp\left[-\Lambda(t) \pm 1.96\sqrt{Var(\Lambda(t))}\right]$ where

$$Var(\Lambda(t)) = \sum_{k=1}^{n} i_k^2 t_k^2 \exp[2\beta_k] + 2\sum_{j<k,k=1}^{n} i_k i_j t_k t_j \left[Var(\beta_k)\, Var(\beta_j)\right]^{1/2} \exp(\beta_k + \beta_j)\, corr(\beta_k, \beta_j).$$

[15]

Results

A total of 147 families with deleterious mutations in *MLH1*, *MSH2*, and *MSH6* were identified, including 80 families from Dana-Farber Cancer Institute (DFCI) and 67 from University of Michigan Cancer Center (UMCC). A total of 6,342 individuals were included in the analysis: 147 probands, 1017 first-degree relatives (FDRs), and 5,178 other more distant relatives from the affected side of the family. The breakdown of MMR gene mutations among families were: *MLH1* in 55 (37.4%), *MSH2* in 81 (55.1%), and *MSH6* in 11 (7.5%). Overall, pathogenic gene mutations had been detected in 302/6342 (4.8%) individuals and the numbers of subjects genotyped (200 at UMCCC and 232 at DFCI) were similar between the centers. Additional characteristics of study families are summarized in Table 1.

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Risk of Colorectal Cancer

Six hundred and twenty eight cases of CRC were identified (UMCC=251, DFCI=377). Median age at diagnosis was 42 years for men (range 16-88) and 47 years for women (range 20-85). Among those affected 68.3 % of males and 56.6% of females had been diagnosed with CRC before the age of 50 years.

Age-specific cumulative risks of CRC by decade compared with SEER population rates are shown in Table 2 and Figure 1. For men with MMR mutations the risk of CRC significantly exceeds the risk in the general population by age 30 years and by age 50 is estimated at 33.21% (95% CI 29.33-40.71). Women who carry MMR mutations significantly exceed the population risk of CRC by 40 and by age 50 have a risk of 16.89% (95% CI 13.52-22.4). Risk of CRC continues to increase and by age 70 lifetime risk for CRC in MMR gene mutation carriers is estimated at 66.08% (95% CI 59.47-76.17%) for men and 42.71 (95% CI 36.57-52.83%) for women. The overall hazard ratio (HR) for CRC is significantly higher for men at 148.4 (95% CI 114.6-192.2), compared with 51.1 (95% CI 40.8-64.0) for women (Table 3).

Risk of Endometrial Cancer and Cumulative Cancer Risk in Women

One hundred fifty-five cases of endometrial cancer were identified (UMCC=50, DFCI=105). Median age at diagnosis was 47.5 years (range 29-73 years) and 56% of cases were diagnosed before age 50 years. Age-specific cumulative risks of endometrial cancer by decade compared with SEER population rates are shown in Table 2 and Figure 1. The risk of EC in MMR gene mutation carriers is significantly higher than the general population by age 40 and by age 50 is 16.36% (95% CI 11.77-20.72). By age 70 lifetime risk of EC is estimated at 39.39% (95% CI 30.78-46.94). The overall HR for endometrial cancer was 39.0 (95% CI 30.4-50.2) (Table 3).

A relatively small number of female MMR gene mutation carriers in this cohort were diagnosed with both CRC and EC (46 out of 3047 female relatives). Recognizing that women are at risk for both CRC and EC, we calculated the risk of being diagnosed with either colorectal or endometrial cancer. The joint analysis of CRC and EC in females yields a cumulative lifetime risk by age 70 of 73.42% (95% CI 63.76-80.54%) for developing either cancer, with an overall HR of 65.5 (95% CI 52.4-81.9).

Risks of Cancer by MMR Genotype

Of the 628 cases of CRC, 302 (48%) occurred in *MLH1* families, 301 (48%) in *MSH2* families, and 25 (4%) in *MSH6* families. In men, the cumulative risk of CRC by age 70 was 97.3% and 51.8% for *MLH1* and *MSH2* mutation carriers, respectively, and the overall HR was significantly higher for mutations in *MLH1* compared with *MSH2* (HR 342, 95% CI 264-442) vs 78.1, 95% CI 56.9-107.1). In our dataset, the exact magnitude of HR and penetrance estimates for CRC in *MLH1* male carriers were found to be sensitive to the conditioning strategies and choice of number of independent age-specific HR parameters used in the model, the details of which can be found in online supplementary documentation. However, irrespective of the analytical strategy, the HR corresponding to CRC in men with an *MLH1* mutation was always estimated to be greater than 200. In women, lifetime risk of CRC was 52.6% and 39.5% for *MLH1* and *MSH2* carriers respectively; however differences between overall HR did not achieve statistical significance (*MLH1* HR 75.8, 95% CI 56-103 vs *MSH2* HR 46.3, 95% CI 33-65). The small number of CRC cases contributed by *MSH6* families afforded limited power in calculating cumulative risk of CRC for male *MSH6* carriers (HR 5.8, 95% CI 0.9-34.7) and precluded calculation of the corresponding risk estimates for women.

Of the 155 cases of endometrial cancer, 50 (32%) occurred in *MLH1* families, 95 (61%) in *MSH2* families, and 10 (6.5%) in *MSH6* families. The cumulative risk of EC by age 70 was

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32.5% and 44.7% for female *MLH1* and *MSH2* carriers, respectively. HRs for EC for carriers of mutations in *MLH1* (31.4, 95% CI 20-50), *MSH2* (47, 95% CI 35-64) and *MSH6* (18.3, 95% CI 6-55) were not statistically different. Cumulative risk of developing either CRC or EC was similar for women with mutations in *MLH1* and *MSH2* (80.5% vs 73.83%).

Discussion

Our estimates of cancer risk using data from families with Lynch Syndrome ascertained clinically through 2 US cancer centers reveal a cumulative risk of colorectal and endometrial cancer in male and female MMR gene mutation carriers of approximately 70% by age 70. We calculated an overall hazard ratio for CRC of 148.4 for men and 51.1 for women. CRC risk appears to be highest for male carriers of mutations in the *MLH1* gene, with a HR of 342 (95% CI 264-442.1). For women, cumulative risk of endometrial cancer approaches 40% by age 70, and when combined with risk for CRC, results in a lifetime cancer risk of 73%. Our data demonstrate that the cumulative risk for colon and endometrial CA continue to increase with age, with the most dramatic elevation in age-specific hazard ratios seen in individuals age 20 to 49 years.

Our risk estimates for CRC and EC in this large cohort of U.S. families with Lynch Syndrome further clarify the cancer experience of mutation carriers. These estimates are similar to those from European familial cancer registries,[6,8,10] [9] and other more recent studies in smaller clinically ascertained cohorts[17]. Interestingly, our risk estimates are considerably higher than those presented by other recently-published studies which sought to control for ascertainment bias, as well as a recent analysis of a fairly large series of families from England without appropriate correction for ascertainment. [18] Using “ascertainment-corrected maximum likelihood estimation”, Quehenberger *et. al*. analyzed cancer histories of 84 families with mutations in *MLH1* or *MSH2* from the Dutch HNPCC registry and found a cumulative risk of CRC by age 70 of 26% for men and 22% for women, which led them to conclude that risk of CRC in LS is considerably lower than suggested by the original reports.[11] In examining cancer histories of 17 families with MMR mutations, Jenkins *et al*. calculated cumulative risks for CRC of 45% for men and 38% for women. [12] In addition to concluding that risks of CRC were lower than expected, they reported that while CRC risk increases to age 50, the incidence decreases to general population levels at older ages.[12] The recently published English series of 121 families[18] included far fewer relatives (n=1420) than our series and did not use segregation analysis to estimate penetrance, making it difficult to directly compare our results. However, the penetrance estimates derived from our series of 147 families are higher than the English series as well.

Our study, which used similar statistical methodology to control for ascertainment bias, yielded strikingly different risk estimates than those of Quehenberger and Jenkins. Our data demonstrate that the risk of CRC for MMR gene mutation carriers is already twice the population risk for males by age 30 and 4.5 times the population risk for females by age 40, and that the risks continue to increase with age. Our finding of the even more dramatic elevation in CRC risk in males with *MLH1* mutations corroborates the genotype-phenotype variability that has been observed in other cohorts of MMR mutation carriers.[19,20] We found that risk for endometrial cancer is similarly increased for all female MMR mutation carriers. These results provide evidence in support of current cancer screening recommendations for LS which include CRC screening every 1-2 years in all MMR gene mutation carriers beginning at age 20-25 and annual uterine cancer screening for women beginning at age 30-35 [2] with the options of continued surveillance over the patients lifetime or prophylactic surgery. In addition, our results provide new and important data that can be easily incorporated into computational software routinely used to estimate the lifetime risk of cancer among gene carriers, such as MMRpro.[21]

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Our study has several strengths. Our cohort of 147 families with MMR gene mutations is the largest U.S. study of lifetime cancer risks associated with Lynch Syndrome. Our use of segregation analysis affords ma ny advantages to estimating cancer risk, as it calculates the probability of being a mutation carrier for all relatives whose mutation status is unknown. By conditioning the analysis on the available phenot ypic information from the pedigree, we were able to minimize ascertainment bias by excluding diagnoses of CRC in probands and first-degree relatives. Using this methodology in our large cohort of families identified through two clinical cancer genetics programs allowed us to calculate what we believe is a conservative estimate of cumulative and gene-specific cancer risk among MMR gene mutation carriers. Finally, our findings in this U.S. cohort confirm the substantially elevated risk estimates for CRC and EC presented in the original descriptions of Lynch Syndrome and demonstrate that, despite some variation by MMR genotype, these lifetime cancer risk estimates are generalizable between MMR mutation carriers seen in European cancer registries and in clinical cancer genetics programs in North America.

Even so, we recognize that our study has certain limitations. This study of families with Lynch Syndrome was not population-based. It is possible that families with MMR gene mutations that present to genetics clinics may be phenotypically different from those that do not seek genetic evaluation. However, the frequency of MMR gene mutations in the general population is so low and genetic evaluation is still so uncommon that even large, well-conducted population-based study designs have been limited by very small sample sizes of carriers.[4] Unconfirmed cancer diagnoses were another limitation. Unfortunately a centralized reporting system for cancers does not exist in the U.S.; consequently, the cancer histories included in each family's pedigree were obtained mostly through proband reports and only a minority of cancer diagnoses had corresponding medical record confirmation. Although a number of studies have demonstrated that patient reports of family cancer history are largely accurate [22,23], reports of gynecologic cancers may be less accurate [24] and it is likely that some cancers may have been misclassified. Nevertheless, in a study of this size with such a large number of colorectal and endometrial cancers, non-differential misclassification would be expected to attenuate our findings, and would be unlikely to substantially alter our conclusions. Missing information was a limitation; however, we imputed subject ages in a conservative manner and checked these in sensitivity analyses which demonstrated no significant inflation of risk estimates. Our cohort contained only 11 families with mutations in *MSH6*, which provided limited power for comparison of risk estimates for this subgroup. Our methods required that we exclude CRC diagnoses in the probands and first-degree relatives, which may have led us to underestimate cancer risk in carriers of MMR gene mutations.

In summary, in this large study of U.S. families we have quantified the elevated risks of colorectal and endometrial cancer associated with Lynch Syndrome with improved precision relative to the published literature. We have clarified that these risks are substantial, clinically meaningful, and higher than recent reports that used similar statistical methods. MMR gene mutation carriers have a lifetime risk of developing either colorectal or endometrial cancer of 70% by age 70, which provides justification for current recommendations for early and continued intensive surveillance for these cancers. While our findings suggest some phenotypic differences among *MLH1, MSH2*, and *MSH6* mutation carriers, further study is needed to determine whether gene-specific cancer risks may warrant tailoring cancer screening recommendations by genoytpe, such as more intensive colorectal surveillance for male *MLH1* mutation carriers. [20]

Acknowledgments

The authors wish to thank Antonis Antoniou for his technical advice in implementing the modified segregation analysis and penetrance models.

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Grant Support: This work was supported in part by the National Cancer Institute RO1 CA81488 (Dr. Gruber), K07 CA 120448-01-A2 (Dr. Stoffel), K24 CA 113433 (Dr. Syngal), the University of Michigan's Cancer Center Support Grant (5 P30 CA46592), R03 CA130045 (Dr. Mukherjee)

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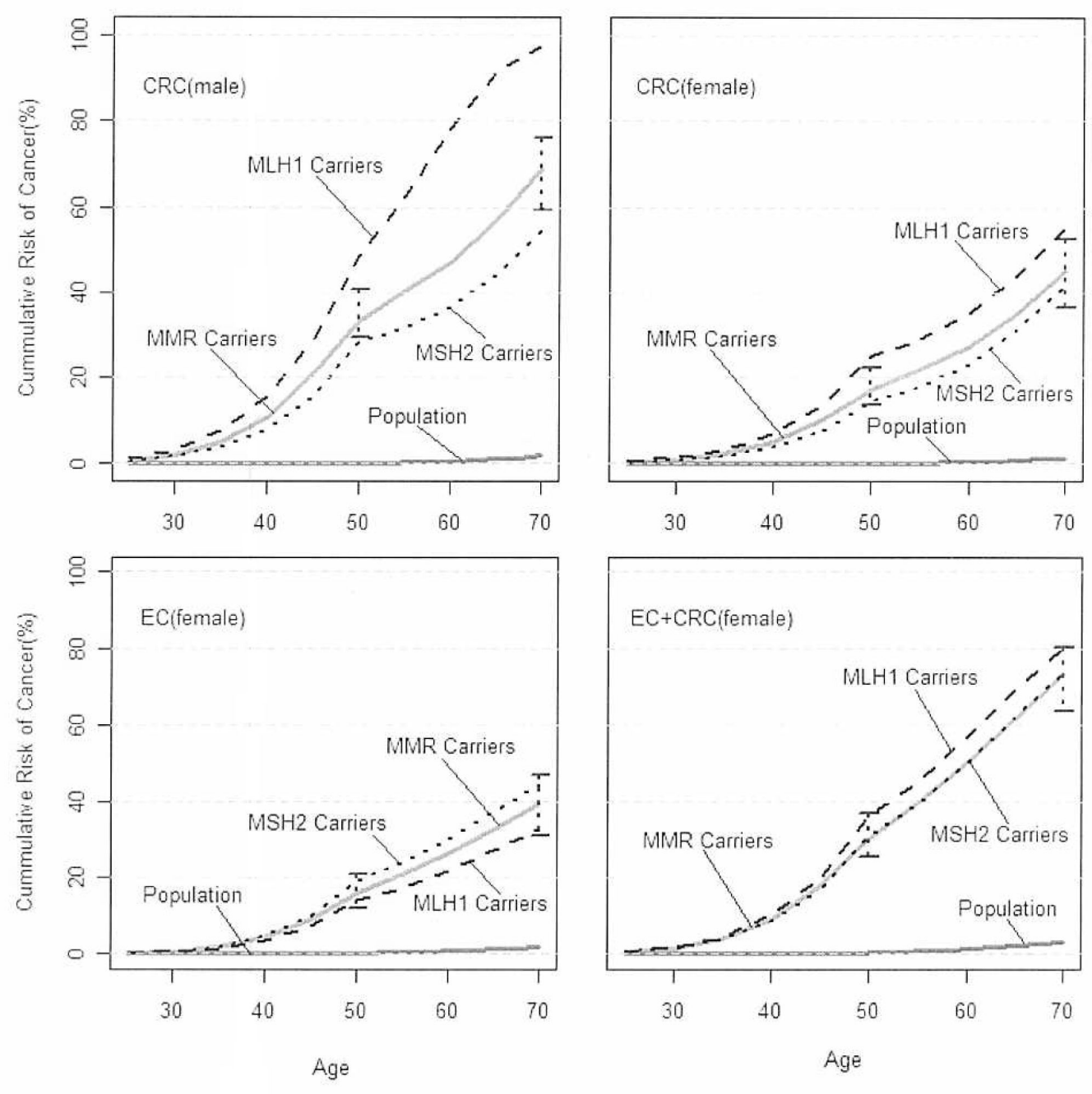

Figure 1.

Cumulative risk of CRC and EC by gender in MMR gene mutation carriers compared to SEER population.

(males (top left), females (top right), endometrial cancer in females (bottom left) and either colorectal or endometrial cancer in females (bottom right) in MMR Carriers and the population. 95% Confidence intervals at reported at age 50 and at age 70)

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Table 1

Characteristics of study population by Study Center

	UMCCC	DFCI	Total
Number of probands/ pedigrees	67	80	147
Number of FDR	459	558	1017
Total number of individuals	2660	3682	6342
Number of females	1265	1782	3047
(Male: Female)	1:1	1:1	1:1
Number of males	1395	1900	3295
Number of subjects genotyped	200	232	432
Number of mutation positive subjects	144	158	302
Mutated Gene			
Number (%) of Pedigrees			
MLH1 mutation type	18 (26.9%)	37 (46.3%)	55 (37.4%)
Indels	7	9	16
Large deletions	4	10	14
Missense	2	2	4
Nonsense	1	6	7
Splice site	4	10	14
MSH2 mutation type	42 (62.7%)	39(48.8%)	81 (55.1%)
Indels	16	11	27
Large deletions	11	16	27
Missense	4	3	7
Nonsense	5	6	11
Splice site	4	2	6
Duplication	1	1	2
Unknown	1	0	1
MSH6 mutation type	7 (10.4%)	4 (5.0%)	11 (7.5%)
Indels	6	4	10
Nonsense	1	0	1

UMCC=University of Michigan Cancer Center, DFCI=Dana-Farber Cancer Institute

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Table 2

Age-specific cumulative risk of CRC and EC for Male and Female MMR gene mutation carriers compared with SEER population rates to age 70 (SEER 13)

	Colorectal Cancer (Males)				Colorectal Cancer (Females)			
Age	Cumulative Risk Population %	Cumulative Risk MMR Carriers %	Cumulative Risk *MLH1* Carriers %	Cumulative Risk *MSH2* Carriers %	Cumulative Risk Population %	Cumulative Risk MMR Carriers %	Cumulative Risk *MLH1* Carriers %	Cumulative Risk *MSH2* Carriers %
20	0	0	0	0	0	0	0	0
30	0.01	1.85	2.83	1.43	0.01	0.91	1.30	0.71
40	0.04	9.59	14.35	7.47	0.04	4.49	6.39	3.51
50	0.17	33.21	46.20	26.71	0.16	16.89	23.35	13.42
60	0.63	44.27	75.64*	34.47	0.52	25.16	33.04	21.72
70	1.88	66.08	97.23*	51.77	1.44	42.71	52.56	39.46
	Endometrial Cancer (Females)				**Colorectal or Endometrial Cancer (Females)**			
Age	Cumulative Risk Population %	Cumulative Risk MMR Carriers %	Cumulative Risk *MLH1* Carriers %	Cumulative Risk *MSH2* Carriers %	Cumulative Risk Population %	Cumulative Risk MMR Carriers %	Cumulative Risk *MLH1* Carriers %	Cumulative Risk *MSH2* Carriers %
20	0	0	0	0	0	0	0	0
30	0.01	0.58	0.49	0.69	0.02	1.46	1.72	1.44
40	0.05	4.06	3.41	4.78	0.09	8.55	10.01	8.48
50	0.24	16.36	13.91	19.03	0.39	31.27	35.76	31.08
60	0.79	26.11	21.61	30.06	1.30	50.05	56.93	50.22
70	1.67	39.39	32.50	44.66	3.08	73.42	80.46	73.83

*Indicate maximum likelihood estimates which are less stable due to sparsity of data in certain gene-specific configurations.

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Table 3

Age specific and overall hazard ratio for Colorectal and Endometrial Cancers for MMR gene mutation carriers.

	Colorectal Cancer (Males)			**Colorectal Cancer (Females)**		
Age	**Hazard Ratio MMR Carriers (95% CI)**	**Hazard Ratio *MLH1* Carriers (95% CI)**	**Hazard Ratio *MSH2* Carriers (95% CI)**	**Hazard Ratio MMR Carriers (95% CI)**	**Hazard Ratio *MLH1* Carriers (95% CI)**	**Hazard Ratio *MSH2* Carriers (95% CI)**
20-49	262.7 (214.7-321.5)	403.4* (312.9-525.6)	202.3 (151.0-270.9)	128.0 (97.6-168.0)	184.1 (128.2-264.4)	99.7 (65.7,151.3)
50-69	42.3 (30.7-58.4)	185.3 (113.0-303.9)	26.1 (16.6-41.3)	31.2 (22.4-43.4)	40.2 (25.5-63.3)	30.0 (18.5-48.4)
Overall HR	**148.4 (114.6-192.2)**	**342.0* (264.5-442.1)**	**78.1 (56.9-107.1)**	**51.1 (40.8-64.0)**	**75.8 (56.0-102.6)**	**46.4 (33.0-65.3)**
	Endometrial Cancer (Females)			**Colorectal and Endometrial Cancer (Females)**		
Age	**Hazard Ratio MMR Carriers (95% CI)**	**Hazard Ratio *MLH1* Carriers (95% CI)**	**Hazard Ratio *MSH2* Carriers (95% CI)**	**Hazard Ratio MMR Carriers (95% CI)**	**Hazard Ratio *MLH1* Carriers (95% CI)**	**Hazard Ratio *MSH2* Carriers (95% CI)**
20-49	76.0 (56.3-102.5)	63.7 (36.6-110.8)	89.8 (62.6-128.8)	96.1 (77.2-119.8)	113.5 (80.9-159.0)	95.4 (71.3-127.7)
50-69	22.4 (15.5-32.2)	16.9 (8.3-34.3)	26.4 (16.8-41.5)	34.7 (25.7-46.9)	43.5 (27.3-69.4)	35.4 (23.5-53.4)
Overall HR	**39.0 (30.4-50.2)**	31.4 (19.7-50.2)	47.0 (34.6-64.0)	**65.5 (52.4-81.9)**	78.8 (57.1-108.7)	67.6 (49.9-91.5)

* Indicate maximum likelihood estimates which are less stable due to sparsity of data in certain gene-specific configurations.