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ARTICLE

Risks of Colorectal and Other Cancers After Endometrial Cancer for Women With Lynch Syndrome

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Background Lynch syndrome is an autosomal dominantly inherited disorder caused by germline mutations in DNA mismatch repair (MMR) genes. Previous studies have shown that MMR gene mutation carriers are at increased risk of colorectal, endometrial, and several other cancers following an initial diagnosis of colorectal cancer. We estimated cancer risks following an endometrial cancer diagnosis for women carrying MMR gene mutations.

Methods We obtained data from the Colon Cancer Family Registry for a cohort of 127 women who had a diagnosis of endometrial cancer and who carried a mutation in one of four MMR genes (30 carried a mutation in *MLH1*, 72 in *MSH2*, 22 in *MSH6*, and 3 in *PMS2*). We used the Kaplan-Meier method to estimate 10- and 20-year cumulative risks for each cancer. We estimated the age-, country-, and calendar period–specific standardized incidence ratios (SIRs) for each cancer, compared with the general population.

Results Following endometrial cancer, women carrying MMR gene mutations had the following 20-year risks of other cancer cancers: colorectal cancer (48%, 95% confidence interval [CI] = 35% to 62%); cancer of the kidney, renal pelvis, or ureter (11%, 95% CI = 3% to 20%); urinary bladder cancer (9%, 95% CI = 2% to 17%); and breast cancer (11%, 95% CI = 4% to 19%). Compared with the general population, these women were at statistically significantly elevated risks of colorectal cancer (SIR = 39.9, 95% CI = 27.2 to 58.3), cancer of the kidney, renal pelvis, or ureter (SIR = 28.3, 95% CI = 11.9 to 48.6), urinary bladder cancer (SIR = 24.3, 95% CI = 8.56 to 42.9), and breast cancer (SIR = 2.51, 95% CI = 1.17 to 4.14).

Conclusions Women with Lynch syndrome who are diagnosed with endometrial cancer have increased risks of several cancers, including breast cancer.

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Approximately 5% of all women with endometrial cancers have a family history of endometrial cancer and 2% have a family history of colorectal cancer (1). Approximately 2% of all endometrial cancers (2–4) and 6% of endometrial cancers diagnosed before age 70 years are due to Lynch syndrome (5). Lynch syndrome is an autosomal dominantly inherited disorder caused by a germline mutation in one of four DNA mismatch repair (MMR) genes—*MLH1*, *MSH2*, *MSH6*, or *PMS2* (6)—or deletions in the *EPCAM* gene that result in inactivation of *MSH2*, which is located nearby (7). MMR mutation carriers are at substantially increased risks of cancers of the colorectum, endometrium, stomach, ovary, urinary tract, brain, small bowel, hepatobiliary tract, and pancreas (8–10) compared with the general population.

The risk of a subsequent cancer following a diagnosis of endometrial cancer in MMR gene mutation carriers has not been clarified. To our knowledge, only one study has reported cancer risks following a diagnosis of endometrial cancer in women with Lynch syndrome. Aarnio et al. (11) estimated a 40% cumulative risk of colorectal cancer and 75% cumulative risk of any malignant tumor at 26 years after endometrial cancer. However, the study was small (39 women) and used the Amsterdam criteria [ie, a family history of cancers commonly associated with inherited mutations in MMR genes (12)] to diagnose Lynch syndrome rather than the subject's MMR gene mutation status.

Knowledge of the risks of subsequent cancers for women who carry MMR gene mutations and have been diagnosed with endometrial cancer potentially impacts the clinical management of these women, including subsequent cancer surveillance. In this study, we estimated the risks of colorectal and other cancers following endometrial cancer for women who were confirmed carriers of a pathogenic germline mutation in an MMR gene.

Methods

Study Sample

We used data from the Colon Cancer Family Registry to identify women who were known to carry a pathogenic germline mutation

in an MMR gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or a deletion in *EPCAM* and who had been diagnosed with endometrial cancer. Details of recruitment methods, data collection, and MMR gene mutation testing have been described in detail in previous studies (13,14). In brief, from 1997 to 2010, families were recruited either by identification of recently diagnosed colorectal cancer patients ascertained through cancer registries (population-based), or by identification of persons from families with multiple cancers that were referred to family cancer clinics (clinic-based) in Australia, New Zealand, Canada, and the United States. Written informed consent was obtained from all study participants, and the study protocol was approved by the institutional human ethics committee at each center of the Colon Cancer Family Registry.

Data Collection

Information on demographics, personal characteristics, personal and family history of cancer, cancer screening history, and history of polyps, polypectomy, hysterectomy, and other surgeries were obtained via questionnaires from all participants. The questionnaires are available at https://cfrisc.georgetown.edu/isc/dd.questionnaires.do. Blood and tumor tissue samples were collected for genetic testing from all participants.

MMR Gene Mutation Testing

Mutation testing for the *MLH1*, *MSH2*, and *MSH6* genes was performed by Sanger sequencing or denaturing high-performance liquid chromatography, 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) (13,15,16). *PMS2* mutation testing involved a modified protocol from Senter et al. (17), in which exons 1 to 5, 9, and 11 to 15 were amplified in three long-range polymerase chain reactions followed by nested exon-specific polymerase chain reaction and 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).

Statistical Analysis

Time at risk for each woman started at her age at endometrial cancer diagnosis and ended at her age at diagnosis of any subsequent cancer, last known age, or age at death, whichever occurred first. For colorectal cancer risk estimation, we excluded one woman who was diagnosed with colorectal cancer at unknown age and nine women who reported having a polypectomy before or at their age at endometrial cancer diagnosis, leaving 117 women for analysis. We censored seven women who reported having a polypectomy after being diagnosed with endometrial cancer at their age at polypectomy.

The Kaplan–Meier failure function was used to estimate cumulative risks (penetrance) for subsequent primary cancers at 10 and 20 years after endometrial cancer diagnosis.

We estimated the standardized incidence ratio (SIR) for cancer at each of the following sites, as defined by *International Classification of Diseases for Oncology*, third edition (18), site codes: colon and/or rectum (C18, C19, C20, C26.0); "kidney, etc" including kidney except renal pelvis (C64), renal pelvis (C65), and ureter (C66); urinary bladder (C67); breast (C50); small intestine (C17); and pancreas (C25). First, we estimated the risk of each primary cancer following endometrial cancer for women who carried MMR gene mutations compared with the risk of the primary cancer for women from the general population. We calculated the SIRs as the observed numbers of primary cancers following endometrial cancer in women carrying MMR gene mutations divided by the expected numbers of cancers. The expected numbers of cancers were calculated by multiplying the age-, country-, and calendar period–specific incidence for women from the general population with the corresponding follow-up time in the study cohort. Age-, country-, and calendar year–specific cancer incidences for the general population were obtained from *Cancer Incidence in Five Continents* for the following calendar periods: 1983 to 1987 (19), 1988 to 1992 (20), 1993 to 1997 (21), and 1998 to 2002 (22). The SIRs were stratified by the MMR gene that was mutated. We calculated 95% confidence intervals (CIs) for the cumulative risks and the SIRs using the 2.5th and 97.5th percentiles from 10 000 bootstrap samples, with the family as the resampling unit to allow for clustering within families.

Next, we compared the risk of each primary cancer following endometrial cancer for women carrying an MMR gene mutation with the risk of the primary cancer following endometrial cancer for women from the general population. To do this, we divided the SIR described above by the risk of the primary cancer following endometrial cancer for women from the general population, which was obtained from the New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973 to 2000 (23). We calculated 95% confidence intervals for this ratio based on the observed and expected numbers of each cancer using the method described by Breslow and Day (24).

We estimated the frequency of colonoscopy or sigmoidoscopy before a diagnosis of colorectal cancer following endometrial cancer from the self-reported questionnaire data as in a previous study (25). Endoscopic examinations within 1 year before the subject's age at diagnosis of colorectal cancer were excluded because they were considered to be diagnostic rather than screening tests. The frequency of colonoscopy or sigmoidoscopy was assumed to be distributed uniformly in the period between first and last age of endoscopy.

In a sensitivity analysis for colorectal cancer risk estimation, we included all women regardless of whether they had had a colorectal polypectomy prior to endometrial cancer diagnosis and calculated the SIR without censoring at the time of polypectomy. All statistical analyses were performed using Stata 11.0 (26).

Results

Of the 198 women identified as MMR gene mutation carriers and having a previous diagnosis of endometrial cancer, we excluded 68 who had been diagnosed with a cancer before being diagnosed with endometrial cancer and three whose age at endometrial cancer diagnosis was not known. Of the 15 women carrying a deletion in *EPCAM*, none had a previous diagnosis of endometrial cancer and were therefore not included in the analyses. A total of 127 women carrying an MMR gene mutation (30 *MLH1*, 72

MSH2, 22 *MSH6*, and 3 *PMS2*) from 105 families (23 *MLH1*, 61 *MSH2*, 18 *MSH6*, and 3 *PMS2*) were identified. Of these women, 58 (46%) were recruited in Australia and New Zealand, 40 (31%) in the United States, and 29 (23%) in Canada. The mean age at endometrial cancer diagnosis was 46.3 years (SD = 8.36 years) and the median age at diagnosis was 46 years (range = 25–68 years). A total of 70 women (55%) developed at least one primary cancer after being diagnosed with endometrial cancer, of whom 19 developed more than one cancer (Table 1). Of the 74 cancers diagnosed following endometrial cancer for which we calculated SIRs, 86% were confirmed by pathology reports, medical records, cancer registry reports, and/or death certificates (Supplementary Table 1, available online).

Among women with an MMR gene mutation, the most common primary cancer following endometrial cancer was colorectal cancer, with a total of 40 cases diagnosed (23 in the proximal colon, six in the distal colon, five in the rectum, and exact location unknown for 6). Approximately 20% of mutation-carrying women were diagnosed with a colorectal cancer during the 10 years and 48% during the 20 years following their endometrial cancer diagnosis (Table 2). Following endometrial cancer, the MMR gene mutation carriers were at approximately 40-fold increased risk of colorectal cancer (SIR = 39.9, 95% CI = 27.2 to 58.3) compared with women from the general population (Table 3). Of the 117 women included in the analysis of subsequent colorectal cancer, 64 reported having had at least one surveillance colonoscopy or sigmoidoscopy after the diagnosis of their endometrial cancer and for these women, the average interval between endoscopies was 2.10 years (95% CI = 1.70 to 2.51 years) (Supplementary Table 2, available online). Details of colorectal cancer diagnosis following endometrial cancer in MMR gene mutation carriers and their surveillance colonoscopy or sigmoidoscopy status is shown in Supplementary Table 3 (available online). In the sensitivity analysis (including all women regardless of whether they had had a colorectal polypectomy prior to endometrial cancer diagnosis and without censoring at the time of polypectomy), the SIR for colorectal cancer was 39.7 (95% CI = 28.2 to 55.8).

The other cancers that occurred after endometrial cancer women carrying MMR gene mutations included 16 cancers in the urinary tract (4 kidney, 1 renal pelvis, 4 ureter, and 7 bladder), 12 in the breast, 3 in the small intestine (2 duodenum and 1 unspecified), and 3 in the pancreas (Table 1). During the 20 years after endometrial cancer, the cumulative risks were 11% (95% CI = 3% to 20%) for cancer of the kidney, renal pelvis or ureter, 9% (95% CI = 2% to 17%) for urinary bladder cancer, and 11% (95% CI = 4% to 19%) for breast cancer (Table 2). Compared with women from the general population, women carrying MMR gene mutations had an increased risk of cancer of the kidney, renal pelvis, or ureter (SIR = 28.3, 95% CI = 11.9 to 48.6), urinary bladder cancer (SIR = 24.3, 95% CI = 8.56 to 42.9), and breast cancer (SIR = 2.51, 95% CI = 1.17 to 4.14) (Table 3).

We observed no statistically significant differences in the 10- and 20-year cumulative risk of each cancer when stratified according to the specific MMR gene mutated (data not shown). We observed no statistically significant difference in the SIRs by the specified MMR gene that was mutated except for colorectal cancer risk (Table 4). The risk of colorectal cancer following endometrial cancer for *MLH1* (SIR = 38.7, 95% CI = 19.5 to 70.2) and *MSH2* mutation carriers (SIR = 58.5, 95% CI = 36.0 to 98.4) was substantially higher than that for *MSH6* mutation carriers (SIR = 4.46, 95% CI = 0.00 to 24.2).

The increased cancer-specific risks we observed were similar whether the reference incidences were for any primary cancer or for cancer diagnosed following endometrial cancer. That is, the increased risk we observed for cancer following endometrial cancer for women carrying an MMR gene mutation was substantially greater than the increased risk expected based on a similar analysis of women with endometrial cancer in the general population (Table 3).

Table 1. Baseline characteristics of women participating in the study

Characteristic	No.	%
Center of recruitment		
Cancer Care Ontario	29	23
University of Southern California	10	8
Australia and New Zealand	58	46
Hawaii	3	2
Mayo Clinic	26	20
Seattle	1	1
Source of ascertainment		
Clinic-based	94	74
Population-based	33	26
Mismatch repair gene mutated		
MLH1	30	24
MSH2	72	57
MSH6	22	17
PMS2	3	2
Age at diagnosis of endometrial cancer, y		
Mean (SD)	46.3	(8.36)
Median (range)	46	(25–68)
Cancers following endometrial cancer*		
Colorectum	40	31
Breast	12	9
Urinary bladder	7	6
Kidney and renal pelvis	5	4
Ureter	4	3
Small intestine	3	2
Pancreas	3	2
Skin	9	7
Stomach	1	1
Thyroid	1	1
Gall bladder	1	1
Biliary tract	1	1
Vulva	1	1
Head and neck (ill-defined tumor)	1	1

* Percentages are based on the total number of women (N = 127) participating in the study.

Table 2. Cumulative risks (percentage) and 95% confidence intervals (CIs) of primary cancers at 10 and 20 years after endometrial cancer for mismatch repair gene mutation carriers

	10 years	20 years
Cancer site	Risk, % (95% CI)	Risk, % (95% CI)
Colorectum	20 (13 to 28)	48 (35 to 62)
Kidney, etc*	2 (0 to 5)	11 (3 to 20)
Urinary bladder	1 (0 to 4)	9 (2 to 17)
Breast	5 (1 to 10)	11 (4 to 19)

* "Kidney, etc" included kidney, renal pelvis, and ureter.

Table 3. Standardized incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) of primary cancers following endometrial cancer for mismatch repair gene mutation carriers*

Cancer site	O	E	Median age, y, at diagnosis (range)	Median year of observation for cancer following endometrial cancer (range)	SIR (95% CI)	SIR_2 (95% CI)
Colorectum	40	1.00	55 (34–80)	11 (1–36)	39.9 (27.2 to 58.3)	36.27 (25.8 to 49.6)
Kidney, etc†	9	0.32	64 (45–72)	17 (2–37)	28.3 (11.9 to 48.6)	29.31 (13.2 to 56.9)
Urinary bladder	7	0.29	69 (58–84)	17 (9–42)	24.3 (8.56 to 42.9)	16.95 (6.77 to 35.2)
Breast	12	4.79	63 (37–80)	12 (3–42)	2.51 (1.17 to 4.14)	2.41 (1.24 to 4.22)
Small intestine	3	0.05	53 (51–53)	22 (17–28)	63.0 (0.00 to 150)	38.34 (7.65 to 119)
Pancreas	3	0.35	65 (65–67)	26 (16–30)	8.61 (0.00 to 20.5)	8.92 (1.83 to 26.3)

* O = observed number of cancers; E = expected number of cancers; SIR = standardized incidence ratio of primary cancer following endometrial cancer for mismatch repair gene mutation carriers compared with risk of primary cancer for the general population; SIR_2 = standardized incidence ratio of primary cancers following endometrial cancer for mismatch repair gene mutation carriers compared with that for the general population (see Statistical Analysis for details).

† "Kidney, etc" included kidney, renal pelvis, and ureter.

Table 4. Standardized incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) of primary cancers following endometrial cancer for mismatch repair gene mutation carriers stratified by the mismatch repair gene that was mutated*

	MLH1			*MSH2*			*MSH6*			*PSM2*		
Cancer site	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Colorectum	12	0.31	38.7 (19.5 to 70.2)	26	0.44	58.5 (36.0 to 98.4)	1	0.22	4.46 (0.00 to 24.2)	1	0.02	44.0 (0.00 to 824)
Kidney, etc†	1	0.07	13.4 (0.00 to 49.1)	6	0.19	31.4 (9.72 to 57.6)	2	0.04	44.82 (0.00 to 156)	0	0.01	—
Urinary bladder	2	0.06	33.8 (0.00 to 92.5)	5	0.18	27.1 (6.40 to 51.6)	0	0.04	—	0	0.01	—
Breast	2	1.16	1.72 (0.00 to 4.21)	7	2.92	2.39 (0.82 to 4.47)	3	0.62	4.84 (0.00 to 11.7)	0	0.08	—
Small intestine	0	0.01	—	2	0.02	68.3 (0.00 to 196)	1	0.01	161 (0.00 to 644)	0	0.00	—
Pancreas	1	0.08	12.9 (0.00 to 49.8)	2	0.21	9.32 (0.00 to 26.1)	0	0.05	—	0	0.01	—

* O = observed number of cancers; E = expected number of cancers; — = not estimable due to low numbers of cancers.

† "Kidney, etc" included kidney, renal pelvis, and ureter.

Discussion

Previous research on cancer risks for people with Lynch syndrome has almost exclusively focused on the risks of first cancers with minimal investigation of the risk of cancers following an initial cancer diagnosis. Endometrial cancer is one of the most commonly diagnosed cancers in women with Lynch syndrome, and clarification on the risks of subsequent cancers potentially facilitates the development of appropriate cancer surveillance strategies for endometrial cancer survivors. In this study, we have estimated these risks for women with Lynch syndrome who have been diagnosed with endometrial cancer and observed an increased risk for a wide range of cancers, including breast cancer.

In general, the cancers that occurred subsequent to endometrial cancer in this study were not unexpected given the previously described risks of first cancers for women who carry MMR gene mutations (8–10). The notable exception was the increased risk of breast cancer. One explanation for the modest increased risk of breast cancer we observed is that mammographic screening may be more prevalent in women carrying MMR gene mutations (who may be more concerned about cancer risk) compared with the general population, thus resulting in breast cancer diagnoses being brought forward due to early detection. Another possible explanation is that the study cohort of women who have already had endometrial cancer are more susceptible to other cancers than MMR mutation carriers who have not had a previous cancer and therefore may be a more sensitive cohort in which to detect any real increase in breast cancer risk. A previous study from the Colon Cancer Family Registry observed that approximately half of the breast cancers in women with Lynch syndrome exhibited absence of mismatch repair protein expression consistent with the gene that was mutated (27), suggesting that germline mutations in MMR genes may contribute to breast cancer development in some women. A Finnish study (28) showed that the proportion of MMR-deficient breast cancers (defined as the absence of MMR protein expression and/or presence of microsatellite instability) was statistically significantly higher in mutation carriers than in noncarriers (65% vs 0%; $P < .001$). A prospective study from the Colon Cancer Family Registry (7 women from that study overlapped with this study, but none of them developed a breast cancer) also found an increased risk of breast cancer for women carrying MMR gene mutations (8). In this study, the 20-year risk for breast cancer was 11% (95% CI = 4% to 19%), which may not rise to the level suggested by the American Cancer Society for MRI screening for breast cancer, although that is based on lifetime risks and we can only report on 10- and 20-year cumulative risks. The threshold risk of breast cancer required for recommended breast MRI screening suggested by the American Cancer Society is approximately 20% to 25% or greater lifetime risk (29).

The cancer risks for women carrying MMR gene mutations who have had endometrial cancer might differ from those for women who have not had any cancer, given that there could be an unmeasured polygenic influence that resulted in penetrance for

the first cancer (30). Compared to a prospective study of cancer risks for MMR gene mutation carriers who had not had any cancer (8), our estimates for cancer risks following endometrial cancer were not substantially different (Supplementary Table 4, available online); that is, our study does not provide evidence that a prior diagnosis of endometrial cancer increases risks of subsequent primary cancers.

We also compared the cancer risks following endometrial cancer with previously reported cancer risks following colorectal cancer for MMR gene mutation carriers (14) (Supplementary Table 5, available online). Given the large overlap of confidence intervals of cancer risk estimates from the two studies, we conclude there is no evidence for a substantial difference in risk regardless of the site of the initial cancer. Our analyses do not allow us to make surveillance recommendations for mutation carriers with endometrial cancer that differ from those for mutation carriers with colorectal cancer or those without previous diagnosis of any cancer. Further studies with sufficient statistical power are needed to fully distinguish cancer risks for MMR gene mutation carriers with different types of cancer and without any cancer.

Given previous evidence of heterogeneity of cancer risk by the specific MMR gene mutated (31), we attempted to identify differences in cancer risk where possible. However, we derived most of our conclusions from analyses of all MMR gene mutation carriers combined because even with this large series, there was insufficient statistical power to fully distinguish cancer risks for carriers of each specific gene mutation. We observed that the risk of colorectal cancer following endometrial cancer for *MSH6* mutation carriers was lower than that for *MLH1* and *MSH2* mutation carriers. This finding is consistent with the previous studies reporting lower cancer risks for *MSH6* mutation carriers than for *MLH1* and *MSH2* mutation carriers with no previous cancer diagnosis (31–33).

We also note in our cohort that we identified no endometrial cancer diagnoses in 15 women carrying a deletion in *EPCAM*, a finding consistent with the low risk of endometrial cancer for *EPCAM* deletion carriers observed by Kempers et al. (7). They observed that women with *EPCAM* deletions had a 12% (95% CI = 0% to 27%) cumulative risk of endometrial cancer to age 70 years, which was lower than for carriers of a combined *EPCAM–MSH2* deletion (55%, 95% CI = 20% to 90%, $P < .001$).

This study is, to our knowledge, the largest to investigate the risks for a wide range of cancers following endometrial cancer in women with Lynch syndrome. All participating sites of the Colon Cancer Family Registry used standardized epidemiologic assessment and uniformly high-quality testing for MMR gene mutations. Attempts were made to verify primary cancers using pathology reports, medical records, corroboration by relatives, cancer registry reports, and/or death certificates, where available (13).

This study has some notable limitations. Even with this large series, there was insufficient statistical power to fully distinguish cancer risks for specific MMR gene mutation carriers. We had no information on treatment history for initial diagnosis of endometrial cancer, which may have affected risk of subsequent cancers. It is possible that our results are not applicable to women with a poor prognosis as they were less likely to be included in this analysis (ie, less likely to be able to provide a blood sample for genetic testing and complete a questionnaire). Because of the lack of comparative incidence data, we were unable to estimate site-specific SIRs separately for cancers of the kidney, renal pelvis, and ureter; instead, we reported risks for all urinary tract cancers combined. Finally, because we had limited data on the type of colorectal polyps removed, we censored subjects at polypectomy instead of estimating postpolypectomy risk for colorectal cancer. However, our sensitivity analysis including observation time after polypectomy resulted in essentially the same estimate of colorectal cancer risk.

We do not know whether the women in this study were informed of their MMR gene mutation status, and if so, when in relation to their cancer diagnoses. Mutation testing was done in the context of the research study, and although return of mutation results is offered as part of the protocol, some participants still do not know their mutation status (34). Knowledge of MMR gene mutation status by the women or their clinicians might have altered their frequency of surveillance for colorectal polyps and cancer.

In conclusion, women carrying MMR gene mutations with a previous diagnosis of endometrial cancer have increased risks of a range of cancers, including breast cancer. This study provides the most accurate representation of their ongoing cancer risks, providing a basis for effective long-term surveillance and risk reduction strategies. Further larger studies are recommended for refining risk estimates separately for specific MMR gene mutations to optimally inform practice and policy for clinical risk management.

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Notes

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