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Cancer Risks for *PMS2*-Associated Lynch Syndrome

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ABSTRACT

Purpose

Lynch syndrome due to pathogenic variants in the DNA mismatch repair genes *MLH1*, *MSH2*, and *MSH6* is predominantly associated with colorectal and endometrial cancer, although extracolonic cancers have been described within the Lynch tumor spectrum. However, the age-specific cumulative risk (penetrance) of these cancers is still poorly defined for *PMS2*-associated Lynch syndrome. Using a large data set from a worldwide collaboration, our aim was to determine accurate penetrance measures of cancers for carriers of heterozygous pathogenic *PMS2* variants.

Methods

A modified segregation analysis was conducted that incorporated both genotyped and non-genotyped relatives, with conditioning for ascertainment to estimates corrected for bias. Hazard ratios (HRs) and corresponding 95% CIs were estimated for each cancer site for mutation carriers compared with the general population, followed by estimation of penetrance.

Results

In total, 284 families consisting of 4,878 first- and second-degree family members were included in the analysis. *PMS2* mutation carriers were at increased risk for colorectal cancer (cumulative risk to age 80 years of 13% [95% CI, 7.9% to 22%] for males and 12% [95% CI, 6.7% to 21%] for females) and endometrial cancer (13% [95% CI, 7.0%–24%]), compared with the general population (6.6%, 4.7%, and 2.4%, respectively). There was no clear evidence of an increased risk of ovarian, gastric, hepatobiliary, bladder, renal, brain, breast, prostate, or small bowel cancer.

Conclusion

Heterozygous *PMS2* mutation carriers were at small increased risk for colorectal and endometrial cancer but not for any other Lynch syndrome-associated cancer. This finding justifies that *PMS2*-specific screening protocols could be restricted to colonoscopies. The role of risk-reducing hysterectomy and bilateral salpingo-oophorectomy for *PMS2* mutation carriers needs further discussion.

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INTRODUCTION

Lynch syndrome is most commonly associated with colorectal cancer and endometrial cancer. However, when first described in 1913, the observation of the co-occurrence of gastric cancer and endometrial cancer led to the initial identification of these families, underlining the apparently diverse phenotype.¹ The genetic background of Lynch syndrome is now known,

and it is caused by heterozygous germline mutations in one of the four mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, or *EPCAM* deletions. The broad Lynch syndrome-associated tumor spectrum includes not only colorectal cancer and endometrial cancer but also gastric, ovarian, small bowel, brain, urothelial cell, skin, pancreas, prostate, and biliary tract cancers.^{2,3} The involvement of germline MMR mutations in the development of breast cancer is still a subject of debate.⁴⁻⁷ Although the reported

cumulative risk (penetrance) to age 70 years for these non-colorectal, nonendometrial cancers in MMR gene mutation carriers is generally < 10%, mutation carriers still have a higher risk relative to the general population.³ The Lynch syndrome-associated tumor phenotypes and their penetrance could depend on the type of MMR gene mutated or the specific variant.^{8,9}

For heterozygous *PMS2* mutation carriers, accurate estimation of penetrance, especially for extracolonic cancers, has been hampered both by difficulties in variant analysis related to the existence of multiple pseudogenes and, perhaps more importantly, by problems in identifying *PMS2* mutation carriers because of a markedly lower penetrance.¹⁰⁻¹² Our previous study of penetrance for *PMS2* mutation carriers, using 98 *PMS2* families ascertained through family cancer clinics in several European countries, reported standardized incidence ratios for extracolonic cancers and found an increased *PMS2*-related risk of cancer of the small bowel, ovaries, renal pelvis and—most notably—of the breast.¹¹ Although that study presented the largest data set then available, we were unable to generate reliable estimates of penetrance for these cancers because of their infrequency. In addition, there was an ascertainment bias in this cohort because of the recruitment via family cancer clinics. Another study from Iceland reported significant increases in the risk of colorectal, endometrial, and ovarian cancer for two pathogenic *PMS2* founder variants.¹³ This study and others have reported relatively high prevalence of *PMS2* variants in the population,¹³⁻¹⁵ thus underlining the need for *PMS2*-specific cancer risks. In the current study, we have expanded the previous study database to 284 families, including several that were identified through a population-based ascertainment, with the aim of generating accurate penetrance estimates of colorectal, endometrial, and other cancers for patients with *PMS2*-associated Lynch syndrome.

METHODS

Data Collection

European data set. Pedigree data on families with a segregating pathogenic variant were originally collected between 2009 and 2012, as previously described.¹¹ These data were supplemented with *PMS2* families identified between 2012 and 2017. Briefly, data were collected in collaboration with the Netherlands Foundation for the Detection of Hereditary Tumors and with clinical genetic departments in the Netherlands, Norway, Germany, Sweden, Denmark, and Spain. Data collection from patient records included demographic data, family pedigrees, age and location of cancer diagnosis, polypectomy, and hysterectomy if applicable. When available, clinical and pathologic diagnoses were confirmed using patient records. Data collection and subsequent analysis protocols were approved by the local ethical review board (Leiden University Medical Center Ethics Review Board, protocol ID: P01.019).

Ohio State data sets. For the Ohio State data sets, the first set of patients included both population-based patients with colorectal and endometrial cancer from Columbus, Ohio, as described elsewhere,^{10,16-19} and patients with cancer identified at family cancer clinics with absence of *PMS2* only on immunohistochemistry. The second set of patients from Ohio included only population-based patients with colorectal and endometrial cancer from 50 hospitals throughout the state of Ohio, as described previously.²⁰ All patients provided informed consent (Ohio State University Biomedical Sciences Institutional Review Board protocol IDs: 1999C0051, 1999C0245, and 2012C0123).

Colon Cancer Family Registry data set. The study cohort from the Colon Cancer Family Registry has been described in detail elsewhere.²¹⁻²³

Between 1998 and 2012, the Colon Cancer Family Registry recruited families via population-based probands, recently diagnosed with colorectal cancer, in state or regional population cancer registries in the United States (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria), and Canada (Ontario). In addition, clinic-based probands were enrolled from multiple-case families referred to family cancer clinics in the United States (Mayo Clinic, Rochester, Minnesota and Cleveland Clinic, Cleveland, Ohio), Canada (Ontario), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney, and Newcastle), and New Zealand (Auckland). Probands were asked for permission to contact their relatives to seek their enrollment in the Cancer Family Registry (detailed in Newcomb et al²¹). Informed consent was obtained from all study participants, and the study protocol was approved by the institutional research ethics review board at each registry. Information on demographics, personal characteristics, personal and detailed family history of cancer in first- and second-degree relatives, cancer-screening history, history of polyps, polypectomy, and other surgeries was obtained by questionnaires from all probands and participating relatives. Participants were followed approximately every 5 years after baseline to update this information. For the current study, each individual's lifetime cancer history was based on the most recent data (baseline or most recent follow-up). Reported cancer diagnoses and age at diagnosis were confirmed using pathology reports, medical records, cancer registry reports, and death certificates, where possible.

Mutation Analysis and Clinical Variant Classification

Probands included in the cohorts were screened for point mutations as well as large genomic rearrangements in the *PMS2* gene (Data Supplement). Relatives of probands were tested for the specific family mutation. A detailed description of specific variants detected and their classification can be found in the Data Supplement.

Statistical Analysis

For estimation of the hazard ratios (HRs) and age-specific cumulative risks (penetrance), we used a modified segregation analysis.²⁴ This analytical method is not subject to population stratification, can rigorously adjust for ascertainment, and uses data on all study participants, whether genotyped or not, thereby maximizing statistical power. Models were fitted by the method of maximum likelihood with the statistical package MENDEL 3.2.²⁵ Estimates were appropriately adjusted for the ascertainment of families using a combination of retrospective likelihood and ascertainment-corrected joint likelihood. A conditional likelihood was maximized, in which each pedigree's data were conditioned on the proband's *PMS2* mutation status, cancer history, and ages of cancer diagnoses (for population-based families) or on the proband's *PMS2* mutation status and the cancer history and ages of cancer diagnoses of all family members (for clinic-based families).

For the purposes of analysis, we restricted included individuals to the first- and second-degree relatives of the probands. Observation time started at birth and stopped at age at diagnosis of cancer for affected, and last known age or age at death for unaffected, family members. Because age information for each family member was required for the pedigree analysis, missing values were estimated using a defined protocol as follows. If an exact age was unknown but an age range was provided, age was estimated as the midpoint of that range. If age at diagnosis was unknown, it was assumed to be the same as age at death (if the relative was deceased) or the mean age at diagnosis for the specific cancer (if the relative was alive and older than the mean age at diagnosis). For relatives for whom last known age was unknown, ages were censored at the time they were last known to be alive (eg, at the age at a cancer diagnosis). In the absence of any age information, it was assumed that both parents of the proband were born in the same year, that years of birth differed by 25 years in each generation (eg, at birth of proband, parents were age 25 years and

grandparents were age 50 years), and the ages of the siblings were the same. As a sensitivity analysis, we conducted analyses with and without imputing missing age; the results did not differ materially, and therefore results from the nonimputed analysis were not shown in detail.

To calculate HRs, we used a likelihood-based approach in which age-specific incidence for *PMS2* mutation carriers was divided by that for noncarriers. Incidence rates for noncarriers were assumed to be the same as age-, sex-, and country-specific population incidence rates (Australia, Canada, United States, The Netherlands, Germany) for the period 1998 to 2002, as obtained from Cancer Incidence in Five Continents.²⁶ The period of 1998 to 2002 was selected for analysis because it was the closest available data set to the mean calendar year of cancer diagnoses in the sample. For each cancer, the age at cancer diagnosis was modeled as a random variable whose hazard was the relevant population incidence multiplied by a cancer-specific HR. For colorectal cancer, HRs for carriers were assumed to be continuous, piece-wise linear functions of age that are constant before age 40 years; linear in the intervals 40 to 50, 50 to 60, and 60 to 70 years; and constant after age 70 years. For all other cancer sites, HRs were assumed to be independent of age. HRs for colorectal cancer, endometrial cancer, and other cancers were estimated simultaneously to allow proper adjustment for colorectal cancer-based ascertainment schemes when estimating the risks of noncolorectal cancers and to increase power (by helping the model identify likely carriers from the placement of Lynch syndrome-associated cancers within each family). HRs were assumed to be independent of country of recruitment.

Age-specific cumulative risks (penetrance) of each cancer site for *PMS2* mutation carriers were calculated separately for males and females, using the formula:

$$1 - \exp\left(-\int_0^{80} \lambda(t) dt\right),$$

where $\lambda(t)$ is the HR multiplied by the US population incidence.²⁷ Corresponding CIs were calculated using a parametric bootstrap. More specifically, 5,000 draws were taken from the multivariate normal distribution that the maximum likelihood estimates would be expected to follow under asymptotic likelihood theory. For each age, corresponding values of the cumulative risk were calculated, and the 95% CI for the cumulative risks to that age were taken to be the 2.5th and 97.5th percentile of this sample.

RESULTS

The final analysis included 284 families (211 from the European, 19 from the Ohio State, and 54 from the CCFR data set), with 1,904 first- and 2,974 second-degree family members, in whom 513 were confirmed carriers (Table 1). The numbers and mean ages at diagnosis of each cancer site in first- and second-degree relatives are depicted in Table 2.

Colorectal Cancer

PMS2 mutation carriers were at increased risk of developing colorectal cancer, with an HR depending on age and sex of the mutation carrier: 6.51 (95% CI, 2.03 to 20.9) for males younger than 40 years; 1.70 (95% CI, 0.89 to 3.24) for males older than 70 years; 6.48 (95% CI, 2.24 to 18.8) for females younger than 40 years; and 2.23 (95% CI, 1.21 to 4.12) for females older than 70 years. Estimated cumulative risks of colorectal cancer to age 80 years for *PMS2* mutation carriers were approximately 13%

Table 1. Study Data Set Description

Individuals	No. of Family Members		
	Total	Male	Female
Probands (= No. of families)	284	149	136
FDR	1,904	953	951
SDR	2,974	1,487	1,487
Confirmed <i>PMS2</i> mutation carriers	513	209	304
FDR	339	128	211
SDR	174	81	93
Confirmed <i>PMS2</i> noncarriers	404	167	237
FDR	230	100	130
SDR	174	67	107

Abbreviations: FDR, first-degree relative; SDR, second-degree relative.

(95% CI, 7.9% to 22%) for male carriers and 12% (95% CI, 6.7% to 21%) for female carriers (general population 6.6% and 4.7%, respectively; Fig 1A).

Gynecologic Cancers

PMS2 mutation carriers were also at small increased risk of endometrial cancer, with an HR of 5.73 (95% CI, 2.98 to 11.0) and estimated cumulative risk to age 80 years of approximately 13% (95% CI, 7.0% to 24%), compared with females from the general population (2.4%; Fig 1B). There was no clear evidence of increase in the risk of ovarian cancer (HR, 1.52; 95% CI, 0.45 to 5.05; Fig 2).

Other Cancers

There was no clear increase in risk of gastric, hepatobiliary, bladder, renal, brain, breast, or prostate cancer for *PMS2* mutation carriers (HR for each cancer shown in Fig 2). There were too few occurrences of small bowel cancer (n = 5) to generate an HR.

DISCUSSION

On the basis of the results from this large, international study of heterozygous *PMS2* mutation carriers, the *PMS2*-associated Lynch

Table 2. No. and Mean Age at Diagnosis of Each Cancer Site in the FDRs and SDRs of Probands

Cancer	FDR (n = 1,904)		SDR (n = 2,974)	
	No.	Mean (SD) Age At Diagnosis (years)	No.	Mean (SD) Age at Diagnosis (years)
Colorectal	116	59.6 (14.7)	112	62.7 (3.0)
Endometrial	33	55.7 (9.04)	21	54.8 (13.7)
Ovarian	9	52.2 (14.8)	5	41.6 (22.8)
Brain	18	42.3 (26.9)	10	56.3 (26.0)
Hepatobiliary	5	56.2 (13.6)	3	60.7 (9.87)
Gastric	14	57.8 (8.72)	11	57.3 (11.0)
Bladder	7	71.7 (14.5)	5	70.0 (14.3)
Breast	47	58.1 (12.0)	50	59.2 (13.5)
Prostate	19	70.7 (12.2)	24	69.8 (14.1)
Renal	7	65.0 (13.7)	5	61.2 (10.8)
Small bowel	4	45.0 (9.6)	1	38

Abbreviations: FDR, first-degree relative; SD, standard deviation; SDR, second-degree relative.

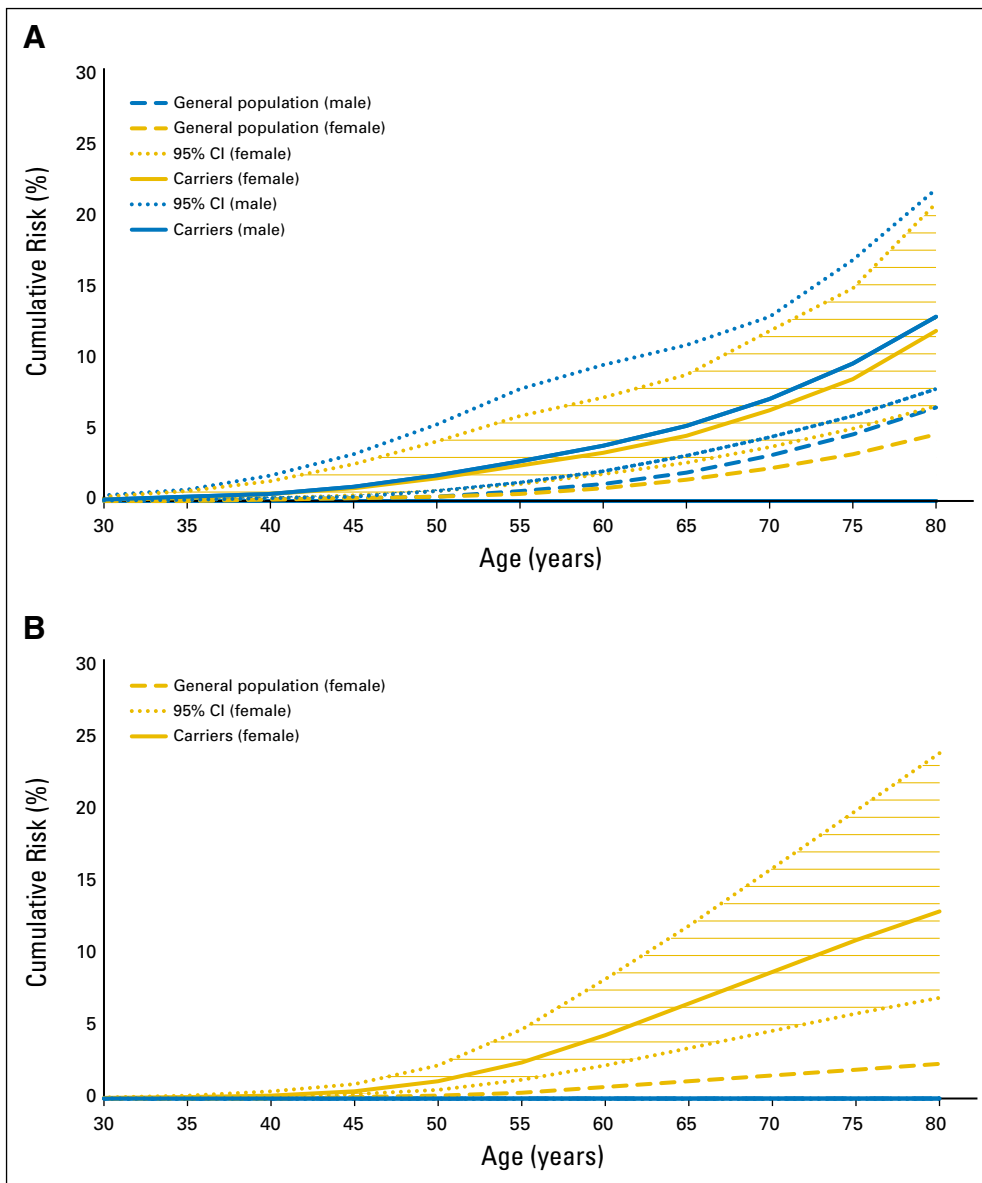


Fig 1. Cumulative risks (solid lines) and corresponding 95% CIs (dotted lines) of (A) colorectal cancer, and (B) endometrial cancer for heterozygous *PMS2* mutation carriers, and for the US general population (dashed lines). Blue and gold represent males and females, respectively.

syndrome spectrum seems to be restricted to colorectal and endometrial cancer only, underlining the distinct phenotype for *PMS2* mutation carriers. We have also shown that *PMS2* mutation carriers have much lower cancer risks compared with other MMR gene mutation carriers.

The previous two studies of *PMS2* mutation carriers have estimated cumulative risks to age 70 years of 11% to 20% for colorectal cancer and 12% to 15% for endometrial cancer.^{10,11} Our current analysis has confirmed that *PMS2* carriers are at small increased risk of colorectal and endometrial cancer. These penetrance estimates are considerably lower than those for other MMR gene mutation carriers, which have been estimated at 35% to 55% for colorectal cancer and 10% to 45% for endometrial cancer.³ A recent report from the Prospective Lynch Syndrome Database described cancer risk and survival for all patients with Lynch syndrome.⁷ This report included 124 *PMS2* mutation carriers, with 524 observation years. The findings support our study data, in that endometrial cancer was the sole cancer type observed. Notably, colorectal cancer did not occur in

any of the *PMS2* mutation carriers undergoing regular colonoscopic screening. This, together with our penetrance estimates, could justify consideration of less-frequent colonoscopy screening for *PMS2* mutation carriers. This, together with our low penetrance estimates (Fig 1) could justify modification of the colonoscopy surveillance protocol, for example starting at age 35 to 40 years, every 2 to 3 years, similar to what has been proposed in the National Comprehensive Cancer Network guidelines.²⁸

The Prospective Lynch Syndrome Database showed that endometrial cancer survival for all MMR pathogenic variant carriers was excellent, with a 10-year survival of 93% (95% CI, 85% to 97%). The reported survival for ovarian cancer in patients with Lynch syndrome was lower, at 74% (95% CI, 44% to 90%), but still better than that for sporadic ovarian cancer cases. Current surveillance guidelines advise that risk-reducing hysterectomy and bilateral salpingo-oophorectomy should be considered in women with Lynch syndrome, because transvaginal ultrasound with or without biopsy is ineffective in reducing risk of endometrial cancer

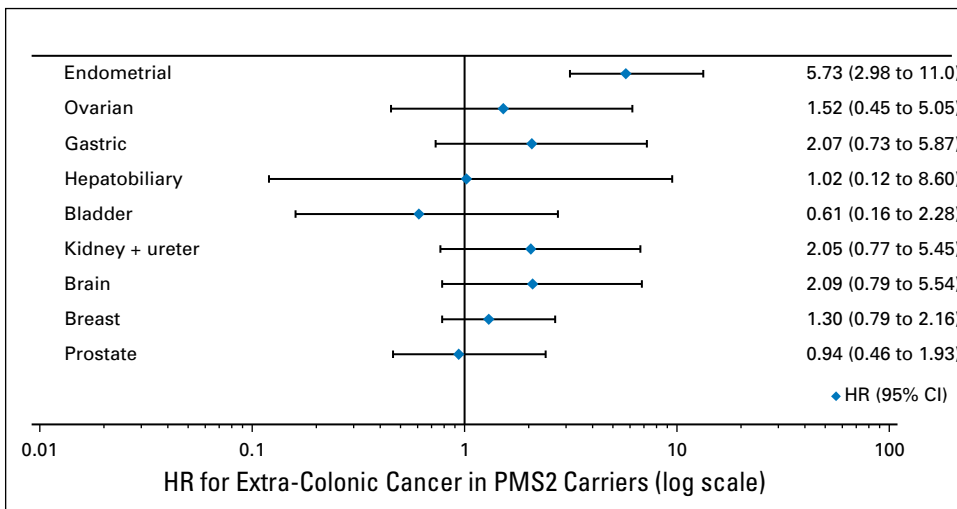


Fig 2. Hazard ratios (HRs) and corresponding 95% CIs of extracolonic cancers for *PMS2* mutation carriers.

and ovarian cancer and might not have a strong influence on survival.²⁹ The good survival rates for endometrial cancer, combined with the data presented in the current study showing no evidence of a clinically relevant increase in ovarian cancer risk for *PMS2* mutation carriers, raise questions about the justification of risk-reducing hysterectomy and bilateral salpingo-oophorectomy, which may be too rigorous in carriers of heterozygous pathogenic *PMS2* mutations.

In our previous study of patients with *PMS2*-associated Lynch syndrome, we found increased standardized incidence ratios (SIRs) for cancer of the small bowel, ovary, renal pelvis, and breast.¹¹ However, that study was limited by inclusion of confirmed mutation carriers identified through family cancer clinics and a limited number of cancer events. The first factor in particular could have been a potential source of ascertainment bias, because a strong family history of cancer and/or early-onset disease increases the likelihood of inclusion and *PMS2* testing. In that report, we did not adjust for this potential ascertainment bias when estimating SIRs for extracolonic cancers. Traditionally, a strong family history of colorectal and endometrial cancers prompted suspicion of Lynch syndrome, and consequently patients were tested for tumor MMR deficiency followed by MMR gene mutation testing. Currently, family histories of other cancers are increasingly being ascertained by clinical genetic centers for additional evaluation as possible Lynch syndrome. Therefore, it is important to take into account and adjust for ascertainment bias when estimating risks of cancers other than colorectal or endometrial cancer. Furthermore, pathogenic *PMS2* variants are relatively frequently observed using extensive gene panel testing for women with hereditary breast and ovarian cancer.³⁰⁻³³ Nevertheless, we could not confirm an increased SIR for breast cancer in the current study (HR, 1.30; 95% CI, 0.79 to 2.16), and the discrepancy with earlier reports can probably be attributed to a high prevalence of *PMS2* (and *MSH6*) mutations in the general population. Conversely, the relative infrequency of *PMS2* variants among patients with Lynch syndrome can be explained by the milder phenotype, which makes ascertainment by family cancer clinics less likely.

The current study is the largest to date, to our knowledge, in estimation of cancer risks for heterozygous *PMS2* mutation

carriers. Previous studies have shown that analyses of retrospective data from clinic-based families (ie, ascertained because of family history of cancer) without (statistical) adjustment can lead to overestimation of cancer risks for mutation carriers.^{24,34,35} In the current study, we used a high-level statistical approach to properly adjust for such ascertainment bias. The modified segregation method used data on all family members, regardless of whether they were genotyped, thereby maximizing statistical power while avoiding survival bias.

A potential limitation of the current study was the use of unverified cancer diagnoses that were self- or proband-reported, thus potentially affecting the accuracy of estimates. However, previous studies showed a high probability of agreement between proband-reported cancer status in first-degree relatives and the validated report (for example, 95.4% [95% CI, 92.6 to 98.3] for breast cancer, 83.3% [95% CI, 72.8 to 93.8] for ovarian cancer, and 79.3% [95% CI, 70.0 to 88.6] for prostate cancer).³⁶ Another possible limitation is that our analysis did not take into account a potential role for genetic or environmental modifiers of risk. The existence of such modifiers is plausible, because a high degree of variability in penetrance and phenotype has been observed,²⁴ and modifiers of cancer risk such as lifestyle, genetic modifiers, and phenotype-genotype correlations have been identified previously.³⁷⁻⁴⁰ Our study estimated cancer risks of all variants combined; however, it is plausible that not all *PMS2* variants confer the same risk. A previous study in a selection of the currently analyzed cohort investigated genotype-phenotype correlations and found no difference in risk between the group of variants with retained versus loss of RNA expression.⁴⁰ However, this study did report that those carrying a variant with loss of RNA expression were diagnosed with colorectal cancer on average 9 years younger than those with retained expression. The influence of these modifiers is still not well understood, especially for *PMS2* mutation carriers, although efforts are currently ongoing to better define such factors and their potential role in modifying disease risk. Our study results highlight that studies of penetrance modifiers should take the specific MMR gene mutated into account.

In the current study, we analyzed the first data set, to our knowledge, large enough to generate the unbiased estimates for the

risk of each extracolonic cancer for *PMS2* mutation carriers. Our results show that *PMS2* carriers are only at small increased risk of colorectal and endometrial cancer. This underlines the importance of gene-specific genetic counseling of patients with Lynch syndrome and the development of appropriate clinical guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Cancer Risks for *PMS2*-Associated Lynch Syndrome

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