Population-based study of the association of variants in mismatch repair genes with prostate cancer risk and outcomes

Wendy J. Langeberg[1,2], Erika M. Kwon[3], Joseph S. Koopmeiners[1,2], Elaine A. Ostrander[3], and Janet L. Stanford[1,2]

[1] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[2] School of Public Health, University of Washington, Seattle, WA

[3] National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

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Requests for reprints: Janet L. Stanford, Program in Epidemiology, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, M4-B874, PO Box 19024, Seattle, WA 98109-1024. Phone: 206-667-2715; Fax: 206-667-4787; E-mail: jstanfor@fhcrc.org

Abstract

Background: Mismatch repair (MMR) gene activity may be associated with prostate cancer (PC) risk and outcomes. This study evaluated whether single nucleotide polymorphisms (SNPs) in key MMR genes are related to PC outcomes.

Methods: Data from two population-based case-control studies of PC among Caucasian and African-American men residing in King County, Washington were combined for this analysis. Cases (n=1,458) were diagnosed with PC in 1993-96 or 2002-05 and identified via the Seattle-Puget Sound SEER cancer registry. Controls (n=1,351) were age-matched to cases and identified via random digit dialing. Logistic regression was used to assess the relationship between haplotype-tagging SNPs and PC risk and disease aggressiveness. Cox proportional hazards regression was used to assess the relationship between SNPs and PC recurrence and PC-specific death.

Results: Nineteen SNPs were evaluated in the key MMR genes: five in *MLH1*, 10 in *MSH2*, and 4 in *PMS2*. Among Caucasian men, one SNP in *MLH1* (rs9852810) was associated with: overall PC risk (OR=1.21, 95% CI=1.02, 1.44; p=0.03), more aggressive PC (OR=1.49, 95% CI=1.15-1.91; p<0.01), and PC recurrence (HR=1.83, 95% CI=1.18, 2.86; p<0.01), but not PC-specific mortality. A non-synonymous coding SNP in *MLH1,* rs1799977 (I219V), was also found to be associated with more aggressive disease. These results did not remain significant after adjusting for multiple comparisons.

Conclusion: This population-based case-control study provides evidence for a possible association with a gene variant in *MLH1* in relation to risk of overall PC, more aggressive disease, and PC recurrence, which warrants replication.

Introduction

This year alone, an estimated 30,000 deaths will occur among US men due to prostate cancer [1]. Established risk factors for PC (age, race/ethnicity, and a family history of PC) and features of more aggressive disease (e.g., higher Gleason score, advanced tumor stage, and high prostate-specific antigen [PSA] levels) are not adequate to predict which cases will become life-threatening; therefore, active investigation is underway to identify biomarkers that will enhance the ability to identify patients at higher risk for adverse PC outcomes [2]. In this analysis, we evaluated the association of variants in key mismatch repair (MMR) genes, *MSH2* (on 2p22-21), *MLH1* (on 3p21), and *PMS2* (on 7p22), in relation to overall PC risk, risk of more aggressive disease, PC recurrence, and PC-specific mortality.

Mutations in MMR genes (*MLH1*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*) can lead to instability of microsatellites (MSI) and failure to repair DNA damage during DNA replication. This damaged DNA can accumulate and eventually lead to the development of neoplasms, such as hereditary nonpolyposis colon cancer (HNPCC), which is characterized by mutations in five microsatellites [3]. A number of studies have reported more MSI in PC tumor tissue compared to normal prostatic tissue [4-9], but some PC tissue studies have found a low frequency of MSI [10-14]. In addition, reduction or loss of MMR protein expression has been found in human PC cell lines, such as LNCaP, PC-3 and DU145 [15-20]. And some studies, but not all, have correlated *hMSH2* immunohistochemical staining intensity with a higher Gleason score and lower disease-free survival [21-23]. Recently, Norris et al. found elevated levels of PMS2 in the prostate tumor tissue of patients who recurred compared with non-recurrent patients [24].

The non-synonymous coding SNP rs1799977 in *MLH1* (also referred to as Ile-219Val or I219V) has been evaluated in two studies of PC risk, with mixed results. Using 275 PC sibships and 556 unrelated controls, Burmester et al. found the rare allele of the SNP rs1799977 was significantly associated with PC [25]. Fredriksson et al., however, found no difference in allele frequency for rs1799977 between 121 patients with hereditary PC (allele frequency=54.5%), unselected patients with PC (54.0%), 202 patients with benign prostatic hyperplasia (54.0%), and 200 controls (55.0%) [26].

In light of these provocative but inconclusive findings, this study evaluated the association between variants in the key MMR genes and the risk of PC and PC outcomes.

Methods

Study Population

Data were combined for this analysis from two population-based case-control studies of risk factors for PC among Caucasian and African-American men residing in King County, Washington, described previously [27-28]. Both studies ascertained cases from the Seattle-Puget Sound Surveillance Epidemiology and End Results (SEER) cancer registry. The first study included 753 cases diagnosed between January 1, 1993 and December 31, 1996 who were 40 to 64 years of age at diagnosis. The second

study included 1,001 cases diagnosed between January 1, 2002 and December 31, 2005 who were 35 to 74 years of age at diagnosis. Controls (n=703 for the first study, n=942 for the second study) were men without a self-reported history of PC, who were recruited via random digit dialing (RDD) during the same ascertainment period and from the same underlying general population as the cases; they were frequency matched to cases by five-year age groups. Among eligible subjects ascertained for the first study, 82% of cases and 75% of controls participated in the study interview, and of these participants, 84% of cases and 80% of controls provided a blood sample. Among eligible subjects ascertained for the second study, 75% of cases and 63% of controls participated in the study interview, and of these participants, 83% of cases and 84% of controls provided a blood sample. After combining these two studies, there were 1,457 PC cases and 1,351 controls with DNA available for the analysis.

Background information was collected from participants at the time of interview and included demographic and lifestyle factors, medical history, PC screening history, and family history of PC. This information was assessed prior to date of diagnosis for cases and prior to a pre-assigned reference date for controls. Clinical information such as Gleason score, tumor stage, serum PSA level at diagnosis, and primary treatment was obtained from the cancer registry. Patient files have been linked to the registry on a regular basis to obtain vital status and primary cause of death of cases; death certificates are requested from the state to confirm underlying cause of death. In 2004, a follow-up survey was sent to 631 of the cases from the first study, 82% of whom responded, to assess secondary treatment(s) and evidence for PC recurrence or progression.

The Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center approved study procedures and materials, and written informed consent was obtained from all study participants. Genotyping was approved by the National Human Genome Research Institute's IRB.

TagSNP Selection and Genotyping

DNA samples were genotyped for 20 single nucleotide polymorphisms (SNPs) in the *MLH1*, *MSH2*, and *PMS2* genes. The SNPs were selected using the Genome Variation Server (gvs.gs.washington.edu/gvs) to cover the genes as haplotype-tagging SNPs. The Applied Biosystems (ABI) SNPlex® Genotyping System was used for genotyping and proprietary GeneMapper® software was used for allele assignment (www.appliedbiosystems.com). Discrimination of the specific SNP allele was carried out with the ABI 3730xl DNA Analyzer and is based on the presence of a unique sequence assigned to the original allele-specific oligonucleotide. Quality control included genotyping of 144 blind duplicate samples distributed across all genotyping batches. There was ≥99% agreement between blinded samples for all SNP genotypes. Each batch of DNA aliquots genotyped incorporated similar numbers of case and control samples, and laboratory personnel were blinded to the case-control status of samples. Genotype frequencies in *MLH1*, *MSH2*, and *PMS2* were evaluated among Caucasian and African-American controls separately; all SNPs were consistent with the expected proportions under Hardy-Weinberg, except for rs12112229 among Caucasians, and so this SNP was removed from the analysis.

Statistical Methods

Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the relative risk of PC among cases relative to controls for each SNP genotype. Polytomous logistic regression was used to calculate ORs and 95% CIs to estimate the relative risk of more aggressive and less aggressive PC relative to controls for each SNP genotype. More aggressive PC was defined by a Gleason score of 7(4+3) or 8-10, regional or distant tumor stage, or a diagnostic PSA value $\geq$20 ng/mL. Codominant and dominant genetic models were considered for each SNP. All models were adjusted for age at reference date, and tested for possible confounding by PC screening history and/or family history of PC. In addition, permuted p-values were calculated to adjust for multiple comparisons, as described previously [29].

Cox proportional hazards regression was used to estimate hazard ratios and 95% CIs to assess the relationship between the SNPs found to be significantly associated with aggressive PC and recurrence or death from PC. The analyses of recurrence were restricted to cases diagnosed with local or regional stage disease and who either subsequently died of PC (prior to the follow-up survey) or completed a follow-up survey, which provided recurrence information and consent to obtain medical records. Recurrence was defined as at least one of the following from self-report and/or medical records: a positive bone scan, CT, MRI, or biopsy showing PC after primary treatment; use of secondary therapy (androgen deprivation therapy [ADT], external beam radiation therapy, cryotherapy, or chemotherapy); an elevated PSA ($\geq$0.2 ng/mL) after radical prostatectomy; an elevated PSA after radiation therapy (nadir PSA +2 ng/mL); a rising PSA while on primary ADT; treatment for evidence of progressive disease that was initiated >12 months after diagnosis in patients on active surveillance; or a self-reported physician's diagnosis of disease recurrence/progression. Time from diagnosis until recurrence was calculated as the difference between the date of diagnosis and the earliest date of evidence of recurrence: date of death from PC, date of recurrence or progression abstracted from medical records, date of recurrence from the follow-up survey, or, for those censored, the end of the year during which the follow-up survey was collected (December 31, 2005). For men who died of PC before December 31, 2005, date of recurrence was imputed to be similar to dates of recurrence for comparable subjects. The analyses of PC death included all cases. The censoring date for members last known to be alive was the date of the last vital status update from the cancer registry (December 1, 2008). The proportional hazards models were adjusted for age and tested for possible confounding by PC screening history or a family history of PC, and recalculated including only cases who received radical prostatectomy as primary therapy.

Most analyses were performed in SAS® version 9.1.3 (SAS Institute, Cary, NC). Hardy-Weinberg equilibrium was calculated in STATA/SE® 10.0 for Windows (StataCorp, College Station, TX).

Results

Among the 1,458 cases and 1,351 controls, a higher proportion of cases than controls were African-American (10.2% vs. 6.3%, respectively; Table 1), had a first-degree relative with PC (21.5% vs. 11.3%), and reported having a PSA or DRE screening test in the five years prior to diagnosis or reference date (89.3% and 86.5%).

Nineteen tagSNPs were evaluated: 5 in *MLH1*, 10 in *MSH2*, and 4 in *PMS2*. Among Caucasian men, one SNP in *MLH1* (rs9852810) was associated with overall PC risk (OR=1.21, 95% CI=1.02, 1.44, p=0.03; Table 2 and supplementary data). Rs9852810 and another SNP in *MLH1*, rs1799977, were associated with more aggressive PC among Caucasian men when aggressive cases were compared with controls (rs9852810: OR_{CT+CC}=1.49, 95% CI=1.15, 1.91, p<0.01; rs1799977: OR_{GA+AA}=1.35, 95%CI=1.08, 1.69, p=0.03; Table 2) and when aggressive cases were compared to less aggressive cases (rs9852810: OR_{CT+CC}=1.34, 95% CI=1.03, 1.75, p=0.03; rs1799977: OR_{CT+CC}=1.33, 95% CI=1.05, 1.69, p=0.02; data not shown). After adjustment for multiple comparisons using permutation p-values, rs9852810 did not remain significantly associated with overall PC risk (p_{perm}=0.22); in addition the associations between rs9852810 and rs1799977 with more aggressive disease did not attain statistical significance (when compared to controls, p_{perm}=0.09 for both SNPs). The association with overall PC risk and with disease aggressiveness remained similar after adjustment for a first-degree relative with PC or having a PC screening test in the five years prior to reference date. Similar analyses among African-American men revealed no associations between any SNP genotypes and overall PC risk or disease aggressiveness (Table 2).

Among the 469 Caucasian cases diagnosed with local or regional disease who completed a follow-up survey or died of prostate cancer before December 31, 2005, 143 recurred. Rs9852810, was associated with PC recurrence in Caucasians (110 out of 320 [34.4%] cases with the putative risk genotype and 24 out of 115 [20.9%] cases with the homozygous wild-type genotype recurred; HR_{GA+AA}=1.83, 95%CI=1.18, 2.86, p<0.01; Table 3). Rs1799977 was not associated with PC recurrence and neither SNP was associated with PC-specific mortality (Table 3).

Discussion

In this population-based case-control study of tagSNPs in key MMR genes (*MLH1*, *MSH2*, and *PMS2)*, we found the SNP rs9852810 in *MLH1* to be associated with a modest increase in overall PC risk, risk of more aggressive PC, and PC recurrence. This intronic SNP is in perfect LD with several other SNPs near the start codon of *MLH1* (such as rs11129748). To our knowledge, the association with this variant and PC has not been evaluated previously. We also found an association between the non-synonymous coding SNP rs1799977 *in MLH1* and more aggressive PC. As noted in the introduction, the association between this SNP and PC has been evaluated previously with mixed results [25-26]. This SNP has also recently been reported to be associated with breast cancer risk (OR = 1.87; 95% CI = 1.11, 3.16) [30], and may be associated with susceptibility to childhood acute lymphoblastic leukemia [31].

One limitation to this study is possible type I error due to multiple testing. For each of the 19 SNPs, we calculated 6 significance tests among Caucasians, so one would expect about 6 results might be due solely to chance. The main result (for rs9852810) did not remain significant based on a permutated p-value; however, it was significant in the PC risk analysis, the analysis of aggressive disease, and the analysis of recurrence, which lends strength to the result. If confirmed, this result lends further support for a potential shared susceptibility for PC and colon cancer, which is consistent with prior findings for a SNP in the 8q24 region that confers risk for both cancer types [32-33].

There are several strengths to this study. The data used for this analysis were from two population-based case-control studies, which means men with all grades and stages of disease, and who received a range of initial treatments, were included. In addition, we have over 10 years of patient follow-up to evaluate recurrence and progression, and clinical and patient information was available for evaluation of potential confounders and effect modifiers.

Conclusion

Evidence from previous studies shows that loss of mismatch repair function may be characteristic of prostate carcinogenesis. This population-based study provides evidence for a possible association with a gene variant in *MLH1* in relation to risk of overall PC, more aggressive disease, and PC recurrence, which warrants replication.

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Table 1. Characteristics of population-based prostate cancer cases and controls

Characteristic	Cases (n=1,458)		Controls (n=1,351)	
	n	(%)	n	(%)
Age at diagnosis/reference date				
35-49	118	(8.1)	126	(9.3)
50-54	215	(14.8)	209	(15.5)
55-59	357	(24.5)	358	(26.5)
60-64	433	(29.7)	348	(25.8)
65-69	177	(12.1)	164	(12.1)
70-74	158	(10.8)	146	(10.8)
Race				
Caucasian	1,309	(89.8)	1,266	(93.7)
African-American	149	(10.2)	85	(6.3)
First-degree relative with prostate cancer				
No	1,145	(78.5)	1,199	(88.8)
Yes	313	(21.5)	152	(11.3)
Screening history[1]				
None	157	(10.8)	182	(13.5)
DRE only	258	(17.7)	519	(38.4)
PSA	1,043	(71.6)	650	(48.1)
PSA value[2]				
< 4.0	189	(13.0)	1,253	(92.8)
4.0-9.9	814	(55.8)	80	(5.9)
10.0-19.9	210	(14.4)	16	(1.2)
≥ 20.0	138	(9.5)	2	(0.2)
Missing	107	(7.4)		
Gleason score				
2-4	72	(4.9)	--	--
5-6	741	(50.8)	--	--
7 (3+4)	408	(28.0)	--	--
7 (4+3)	91	(6.2)	--	--
8-10	140	(9.6)	--	--
Missing	6	(0.4)	--	--
Stage at diagnosis				
Local	1,141	(78.3)	--	--
Regional	280	(19.2)	--	--
Distant	37	(2.5)	--	--
Primary treatment				
RP	831	(57.0)	--	--
RT	412	(28.3)	--	--
ADT	72	(4.9)	--	--
Other treatment	5	(0.3)	--	--
Active surveillance	138	(9.5)	--	--

PSA=prostate-specific antigen; RP=radical prostatectomy; RT=radiation therapy; ADT=androgen deprivation therapy

[1] Screening history within five years prior to diagnosis or reference date.

[2] PSA at diagnosis for cases and measured at interview date for controls.

Table 2. Risk of prostate cancer and disease aggressiveness[1] associated with two SNPs in the *MLH1* gene[2]

	Controls (n=1,351)[3]		All cases (n=1,458)[3]						Less aggressive cases (n=967)[3]						More aggressive cases (n=491)[3]					
SNP	n	(%)	n	%	OR[4]	95% CI		p	n	%	OR[4]	95% CI			n	%	OR[4]	95% CI		
rs9852810, chr7:115949965																				
GG	410	(33.1)	364	(28.9)	1.00	Reference			260	(30.9)	1.00	Reference			104	(24.9)	1.00	Reference		
GA	601	(48.5)	651	(51.8)	1.21	1.02	1.45		427	(50.8)	1.12	0.91	1.36		224	(53.7)	1.46	1.12	1.91	
AA	228	(18.4)	243	(19.3)	1.20	0.96	1.51	0.09	154	(18.3)	1.06	0.82	1.37		89	(21.3)	1.54	1.11	2.13	
GA/AA	829	(66.9)	894	(71.1)	1.21	1.02	1.44	0.03	581	(69.1)	1.10	0.91	1.33		313	(75.1)	1.49	1.15	1.91	
rs1799977, chr7:115969290																				
TT	607	(49.1)	578	(46.2)	1.00	Reference			406	(48.5)	1.00	Reference			172	(41.7)	1.00	Reference		
CT	514	(41.6)	555	(44.4)	1.13	0.96	1.33		357	(42.6)	1.04	0.86	1.25		198	(47.9)	1.35	1.07	1.71	
CC	115	(9.3)	118	(9.4)	1.07	0.81	1.42	0.35	75	(9.0)	0.96	0.7	1.32		43	(10.4)	1.33	0.90	1.96	
CT/CC	629	(50.9)	673	(53.8)	1.12	0.96	1.31	0.16	432	(51.6)	1.02	0.86	1.22		241	(58.4)	1.35	1.08	1.69	

SNP=single nucleotide polymorphism; OR=odds ratio; CI=confidence interval

[1] More aggressive PC is defined by a Gleason score of 7(4+3) or 8-10, regional or distant tumor stage, or a diagnostic PSA value ≥20 ng/ml.

[2] Among Caucasian cases and controls only.

[3] Total number of cases and controls vary by SNP due to missing genotype data.

[4] Adjusted for age at reference date.

[5] The first p-value is the test for trend using the co-dominant model; the second p-value is for the dominant model.

Table 3. Risk of prostate cancer recurrence and death associated with two SNPs in the *MLH1* gene[1]

	Risk of recurrence								Risk of death						
SNP	n[2]	no. who recurred[3]	(%)	median time to recurrence/ censorship (years)	HR[4]	95% CI		p	n	no. who died of PC	(%)	HR[4]	95% CI		p
rs9852810, chr7:1159499650															
GG	115	24	(20.9)	9.0	1.00	Reference		0.007	364	13	(3.6)	1.00	Reference		0.42
GA/AA	320	110	(34.4)	8.6	1.83	1.18	2.86		894	43	(4.8)	1.29	0.69	2.4	
rs1799977, chr7:115969290															
TT	195	55	(28.2)	8.9	1.00	Reference			578	25	(4.3)	1.00	Reference		0.74
CT/CC	238	79	(33.2)	8.7	1.22	0.86	1.72	0.260	673	32	(4.8)	1.09	0.65	1.84	

HR=hazard ratio; CI=confidence interval

[1] Among Caucasian cases only.

[2] Cases diagnosed with local or regional disease who completed a follow-up survey or died of prostate cancer before Dec. 31, 2005.

[3] Recurrence is defined as at least one of the following: positive bone scan, CT, MRI, or biopsy showing PC after primary treatment; biochemical failure after RP as primary treatment (PSA $\geq$0.2 ng/mL); biochemical failure after RT as primary treatment (nadir PSA +2 ng/mL); ADT as secondary treatment or a rising PSA on ADT; or RT as secondary treatment.

[4] Risk of recurrence or death, respectively, among PC patients with the at-risk allele relative to PC patients homozygous for the wildtype allele.

Supplemental data. Prostate cancer risk associated with SNPs in the *MLH1*, *MSH2*, and *PMS2* genes, by race

Genotype	Cases (n=1,458)[1]		Controls (n=1,351)[1]		OR[2]	95% CI		p[3]
	n	(%)	n	(%)				
Caucasians								
MLH1								
rs9852810, chr7:115949965								
GG	364	(28.9)	410	(33.1)	1.00	Reference		
GA	651	(51.8)	601	(48.5)	1.21	1.02	1.45	
AA	243	(19.3)	228	(18.4)	1.20	0.96	1.51	0.09
GA or AA	894	(71.1)	829	(66.9)	1.21	1.02	1.44	0.03
rs749072, chr7:115962947								
TT	686	(55.7)	679	(56.1)	1.00	Reference		
TC	468	(38.0)	439	(36.3)	1.06	0.89	1.25	
CC	77	(6.3)	93	(7.7)	0.81	0.59	1.12	0.28
TC or CC	545	(44.3)	532	(43.9)	1.01	0.86	1.19	0.86
rs1540354, chr7:115965061								
AA	843	(67.2)	824	(66.9)	1.00	Reference		
GA	370	(29.5)	357	(29.0)	1.02	0.85	1.21	
GG	42	(3.4)	51	(4.1)	0.81	0.53	1.24	0.59
GA or GG	412	(32.8)	408	(33.1)	0.99	0.84	1.17	0.32
rs1799977, chr7:115969290								
TT	578	(46.2)	607	(49.1)	1.00	Reference		
CT	555	(44.4)	514	(41.6)	1.13	0.96	1.33	
CC	118	(9.4)	115	(9.3)	1.07	0.81	1.42	0.35
CT or CC	673	(53.8)	629	(50.9)	1.12	0.96	1.31	0.16
rs9311149, chr7:115973477[4]								
GG	342	(27.1)	307	(24.9)	1.00	Reference		
GA	638	(50.5)	607	(49.2)	0.94	0.78	1.14	
AA	284	(22.5)	320	(25.9)	0.80	0.64	1.00	0.13
GA or AA	922	(72.9)	927	(75.1)	0.89	0.75	1.07	0.20
MSH2								
rs4583514, chr7:115977833								
CC	482	(38.2)	470	(38.1)	1.00	Reference		
CT	594	(47.1)	591	(47.9)	0.98	0.82	1.16	
TT	185	(14.7)	173	(14.0)	1.05	0.82	1.34	0.86
CT or TT	779	(61.8)	764	(61.9)	0.99	0.85	1.17	0.97
rs3732183, chr7:115986931								
CC	666	(53.0)	654	(53.3)	1.00	Reference		
CA	497	(39.6)	491	(40.0)	0.99	0.84	1.17	
AA	93	(7.4)	82	(6.7)	1.12	0.82	1.53	0.77
CA or AA	590	(47.0)	573	(46.7)	1.01	0.86	1.18	0.86
rs10495944, chr7:115987328								
TT	959	(75.8)	931	(75.1)	1.00	Reference		
CT	289	(22.8)	294	(23.7)	0.96	0.79	1.15	
CC	18	(1.4)	15	(1.2)	1.18	0.59	2.35	0.80
CT or CC	307	(24.3)	309	(24.9)	0.97	0.81	1.16	0.74
rs4608577, chr7:115987616								
GG	864	(68.1)	844	(68.1)	1.00	Reference		
GA	369	(29.1)	366	(29.5)	0.99	0.83	1.17	
AA	35	(2.8)	29	(2.3)	1.18	0.71	1.95	0.80
GA or AA	404	(31.9)	395	(31.9)	1.00	0.85	1.18	0.98
rs17036577, chr7:115987823								

CC	1,067	(84.2)	1,017	(81.9)	1.00	Reference		
CT	191	(15.1)	215	(17.3)	0.85	0.68	1.05	
TT	10	(0.8)	10	(0.8)	0.99	0.41	2.40	0.31
CT or TT	201	(15.9)	225	(18.1)	0.85	0.69	1.05	0.13
rs1863332, chr7:115924762[4]								
GG	1,033	(84.0)	1,020	(83.6)	1.00	Reference		
GA	189	(15.4)	190	(15.6)	0.98	0.79	1.23	
AA	8	(0.7)	10	(0.8)	0.80	0.31	2.03	0.88
GA or AA	197	(16.0)	200	(16.4)	0.97	0.79	1.21	0.80
rs1981929, chr7:115924913								
AA	472	(37.2)	464	(37.3)	1.00	Reference		
GA	585	(46.1)	589	(47.4)	0.97	0.82	1.16	
GG	212	(16.7)	190	(15.3)	1.09	0.86	1.38	0.63
GA or GG	797	(62.8)	779	(62.7)	1.00	0.85	1.18	0.99
rs4638843, chr7:115925128								
TT	985	(77.6)	956	(77.0)	1.00	Reference		
GT	266	(21.0)	267	(21.5)	0.95	0.79	1.16	
GG	18	(1.4)	19	(1.5)	0.91	0.48	1.75	0.88
GT or GG	284	(22.4)	286	(23.0)	0.95	0.79	1.15	0.63
rs4952887, chr7:115933310								
CC	1,052	(83.0)	1,040	(83.9)	1.00	Reference		
CG	203	(16.0)	189	(15.2)	1.07	0.86	1.33	
GG	13	(1.0)	11	(0.9)	1.20	0.53	2.68	0.79
CG or GG	216	(17.0)	200	(16.1)	1.08	0.87	1.33	0.53
rs10191478, chr7:115935144								
CC	393	(31.2)	390	(31.5)	1.00	Reference		
GC	635	(50.4)	620	(50.0)	1.02	0.85	1.22	
GG	232	(18.4)	230	(18.6)	1.01	0.80	1.27	0.98
GC or GG	867	(68.8)	850	(68.6)	1.02	0.86	1.20	0.85
PMS2								
rs2286680, chr7:115935606								
TT	959	(76.1)	923	(74.4)	1.00	Reference		
GT	280	(22.2)	291	(23.5)	0.93	0.77	1.12	
GG	21	(1.7)	27	(2.2)	0.75	0.42	1.33	0.47
GT or GG	301	(23.9)	318	(25.6)	0.91	0.76	1.10	0.32
rs6463524, chr7:115938105								
TT	813	(64.0)	791	(63.7)	1.00	Reference		
CT	411	(32.4)	409	(33.0)	0.98	0.83	1.67	
CC	46	(3.6)	41	(3.3)	1.08	0.70	1.67	0.91
CT or CC	457	(36.0)	450	(36.3)	0.99	0.84	1.16	0.91
rs2345060, chr7:115938188								
CC	703	(55.6)	693	(55.8)	1.00	Reference		
CA	489	(38.7)	474	(38.2)	1.02	0.86	1.20	
AA	73	(5.8)	74	(6.0)	0.97	0.69	1.37	0.96
CA or AA	562	(44.4)	548	(44.2)	1.01	0.86	1.18	0.90
African Americans								
MLH1								
rs9852810, chr7:115949965								
GG	96	(66.2)	44	(55.7)	1.00	Reference		
GA	42	(29.0)	32	(40.5)	0.57	0.31	1.07	
AA	7	(4.8)	3	(3.8)	0.98	0.22	4.41	0.21
GA or AA	49	(33.8)	35	(44.3)	0.61	0.33	1.11	0.10
rs749072, chr7:115962947								
TT	89	(62.7)	49	(62.0)	1.00	Reference		
TC	47	(33.1)	23	(29.1)	1.18	0.62	2.25	

CC	6	(4.2)	7	(8.9)	0.47	0.14	1.59	0.37
TC or CC	53	(37.3)	30	(38.0)	1.01	0.56	1.85	0.97
rs1540354, chr7:115965061								
AA	129	(89.6)	71	(89.9)	1.00	Reference		
GA	15	(10.4)	8	(10.1)	0.81	0.31	2.16	
GG	--	--	--	--	--	--	--	0.68
GA or GG	15	(10.4)	8	(10.1)	0.81	0.31	2.16	0.68
rs1799977, chr7:115969290								
TT	123	(86.0)	67	(83.8)	1.00	Reference		
CT	17	(11.9)	13	(16.3)	0.61	0.26	1.40	
CC	3	(2.1)	--	--	--	--	--	0.50
CT or CC	20	(14.0)	13	(16.3)	0.72	0.32	1.62	0.43
rs9311149, chr7:115973477								
GG	50	(34.5)	28	(35.9)	1.00	Reference		
GA	72	(49.7)	35	(44.9)	1.18	0.61	2.26	
AA	23	(15.9)	15	(19.2)	0.83	0.35	1.94	0.68
GA or AA	95	(65.5)	50	(64.1)	1.07	0.58	1.98	0.83
MSH2								
rs4583514, chr7:115977833								
CC	11	(7.6)	2	(2.6)	1.00	Reference		
CT	60	(41.7)	39	(50.0)	0.37	0.07	1.84	
TT	73	(50.7)	37	(47.4)	0.45	0.09	2.25	0.43
CT or TT	133	(92.4)	76	(97.4)	0.41	0.08	1.99	0.27
rs3732183, chr7:115986931								
CC	23	(16.1)	5	(6.3)	1.00	Reference		
CA	71	(49.7)	48	(60.8)	0.38	0.13	1.13	
AA	49	(34.3)	26	(32.9)	0.50	0.16	1.53	0.20
CA or AA	120	(83.9)	74	(93.7)	0.42	0.15	1.51	0.11
rs10495944, chr7:115987328[4]								
TT	137	(94.5)	75	(93.75)	1.00	Reference		
CT	7	(4.8)	5	(6.3)	0.71	0.20	2.54	
CC	1	(0.7)	--	--	--	--	--	0.87
CT or CC	8	(5.5)	5	(6.3)	0.80	0.23	2.76	0.73
rs4608577, chr7:115987616								
GG	83	(62.9)	42	(57.5)	1.00	Reference		
GA	42	(31.8)	26	(35.6)	0.91	0.48	1.76	
AA	7	(5.3)	5	(6.9)	1.05	0.29	3.80	0.96
GA or AA	49	(37.1)	31	(42.5)	0.93	0.50	1.73	0.83
rs17036577, chr7:115987823								
CC	114	(78.6)	66	(82.5)	1.00	Reference		
CT	27	(18.6)	14	(17.5)	1.03	0.48	2.19	
TT	4	(2.8)	--	--	--	--	--	0.99
CT or TT	31	(21.4)	14	(17.5)	1.22	0.58	2.55	0.60
rs1863332, chr7:115924762								
GG	100	(69.0)	52	(65.8)	1.00	Reference		
GA	39	(26.9)	25	(31.7)	0.71	0.37	1.36	
AA	6	(4.1)	2	(2.5)	1.68	0.30	9.24	0.45
GA or AA	45	(31.0)	27	(34.2)	0.78	0.42	1.45	0.43
rs1981929, chr7:115924913								
AA	113	(77.9)	67	(83.8)	1.00	Reference		
GA	31	(21.4)	12	(15.0)	1.69	0.77	3.72	
GG	1	(0.7)	1	(1.3)	0.26	0.01	5.31	0.28
GA or GG	32	(22.1)	13	(16.3)	1.54	0.72	3.30	0.27
rs4638843, chr7:115925128								
TT	132	(91.0)	77	(96.3)	1.00	Reference		

GT	13	(9.0)	3	(3.8)	3.21	0.84	12.3	
GG	--	--	--	--	--	--	--	0.09
GT or GG	13	(9.0)	3	(3.8)	3.21	0.84	12.3	0.09
rs4952887, chr7:115933310								
CC	114	(78.6)	61	(77.2)	1.00	Reference		
CG	31	(21.4)	18	(22.8)	0.71	0.34	1.46	
GG	--	--	--	--	--	--	--	0.35
CG or GG	31	(21.4)	18	(22.8)	0.71	0.34	1.46	0.35
rs10191478, chr7:115935144								
CC	3	(2.1)	2	(2.5)	1.00	Reference		
GC	53	(36.8)	20	(25.3)	3.68	0.46	29.37	
GG	88	(61.1)	57	(72.2)	1.95	0.26	14.81	0.12
GC or GG	141	(97.9)	77	(97.5)	2.34	0.31	17.47	0.41
PMS2								
rs2286680, chr7:115935606								
TT	96	(66.2)	47	(58.8)	1.00	Reference		
GT	44	(30.3)	28	(35.0)	0.71	0.38	1.33	
GG	5	(3.5)	5	(6.3)	0.49	0.12	1.90	0.39
GT or GG	49	(33.8)	33	(41.3)	0.68	0.37	1.23	0.20
rs6463524, chr7:115938105								
TT	108	(74.5)	54	(67.5)	1.00	Reference		
CT	35	(24.1)	23	(28.8)	0.73	0.38	1.41	
CC	2	(1.4)	3	(3.8)	0.37	0.05	2.66	0.43
CT or CC	37	(25.5)	26	(32.5)	0.69	0.37	1.31	0.26
rs2345060, chr7:115938188								
CC	98	(67.6)	48	(60.0)	1.00	Reference		
CA	40	(27.6)	26	(32.5)	0.70	0.37	1.34	
AA	7	(4.8)	6	(7.5)	0.64	0.19	2.12	0.48
CA or AA	47	(32.4)	32	(40.0)	0.69	0.38	1.27	0.23

SNP=single nucleotide polymorphism; OR=odds ratio; CI=confidence interval

[1] Total number of cases and controls vary by SNP due to missing genotype data.

[2] Adjusted for age at reference date.

[3] The first p-value is the test for trend using the codominant model; the second p-value is for the dominant model.