

Original Article

DNA repair genotype and lung cancer risk in the beta-carotene and retinol efficacy trial

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Abstract: Many carcinogens in tobacco smoke cause DNA damage, and some of that damage can be mitigated by the actions of DNA repair enzymes. In a case-control study nested within the Beta-Carotene and Retinol Efficacy Trial, a randomized chemoprevention trial in current and former heavy smokers, we examined whether lung cancer risk was associated with variation in 26 base excision repair, mismatch repair, and homologous recombination repair genes. Analyses were limited to Caucasians (744 cases, 1477 controls), and logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for individual SNPs and common haplotypes, with adjustment for matching factors. Lung cancer associations were observed ($p < 0.05$) with SNPs in *MSH5* (rs3131379, rs707938), *MSH2* (rs2303428), *UNG* (rs246079), and *PCNA* (rs25406). *MSH5* rs3131379 is a documented lung cancer susceptibility locus in complete linkage disequilibrium with rs3117582 in *BAT3*, and we observed associations similar in magnitude to those in prior studies (per A allele OR 1.37, 95% CI 1.13-1.65). *UNG* was associated with lung cancer risk at the gene level ($p = 0.02$), and the A allele of rs246079 was associated with an increased risk (per A allele OR 1.15, 95% CI 1.01-1.31). We observed stronger associations with *UNG* rs246079 among individuals who carried the risk genotypes (AG/AA) for *MSH5* rs3131379 ($p_{\text{interaction}} = 0.038$). Our results provide additional evidence to suggest that the *MSH5/BAT3* locus is associated with increased lung cancer risk among smokers, and that associations with other SNPs may vary depending upon *MSH5/BAT3* genotype. Future studies to examine this possibility are warranted.

Keywords: Lung cancer, base excision repair, mismatch repair, homologous recombination repair, DNA repair, genetic polymorphism

Introduction

Lung cancer is the leading cause of cancer death worldwide, with over a million deaths annually [1]. The large majority (80-90%) of lung cancers develop in individuals who are either current or former cigarette smokers [2]. Tobacco smoke exposure can result in various types of damage to DNA, either directly by forming DNA adducts, or through the production of reactive oxygen or nitrogen species. These lesions are repaired by a wide variety of DNA repair mechanisms, including (but not limited to) base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and

double-strand break repair (DSB) which includes homologous recombination (HR) and non-homologous end-joining [3]. Therefore, it is plausible that genetic variation in these important pathways might influence lung cancer risk. Indeed, two of the five validated lung cancer susceptibility loci to date map to regions that include genes related to DNA repair. The 6p21.33 locus in the HLA region contains the genes *BAT3* and *MSH5*, and *MSH5* is a member of the mutS homolog gene family, involved in MMR. The association with the 12p13 locus is specific to squamous cell lung cancer, and this locus contains the *RAD52* homolog gene which is involved in DSB and HR [4]. A recent meta-

analysis of 16 GWAS studies with 14,900 cases and 29,485 controls of European descent confirmed these associations as well as those with 5p15 (*TERT/CLPTM1L*), and 15q25.1 (*CHRNA5/CHRNA3/CHRNA4*), and reported an additional association for squamous cell carcinoma at 9p21 (*CDKN2A/p16^{INK4A}/p14^{ARF}/CDKN2B/p15^{INK4B}/ANRIL*) [5]. An additional locus at 6p21.31, containing *HLADQA1*, was reported in a Japanese GWAS study [6].

Many candidate gene and candidate pathway studies as well as meta-analyses have investigated whether genetic variants in DNA repair pathways are associated with lung cancer risk, with mixed results for genes in MMR [7-15], BER [8, 15-32], and HR [8, 15, 16, 19-22, 27, 29, 32]; NER will not be discussed since we have previously reported our findings from analyses of NER genes and lung cancer risk [33]. Herein we report results from our systematic evaluation of associations between 176 tag and functional SNP variants in genes involved in MMR (*MLH1*, *MSH2*, *MSH4*, *MSH5*, and *MSH6*), BER (*APEX1*, *LIG3*, *MBD4*, *MPG*, *MUTYH*, *NEIL1*, *NEIL2*, *NTHL1*, *OGG1*, *PCNA*, *PNKP*, *POLB*, *POLI*, *PPP1R13L*, *RAD18*, *SMUG1*, *TDG*, *UNG*, and *XRCC1*), and HR (*XRCC2* and *XRCC3*) and risk of lung cancer in a nested case-control study of heavy smokers.

Materials and methods

Study population

Details of this study have been published previously [33]. In brief, this nested case-control study is comprised of participants from the multicenter β -Carotene and Retinol Efficacy Trial (CARET), which was a randomized, double-blinded, placebo-controlled chemoprevention trial to assess safety and efficacy of daily supplementation with β -carotene and retinyl palmitate among individuals at high risk of developing lung cancer [34-36]. The trial included men and women ages 50-69 years who were current or former heavy smokers (i.e., quit within six years prior to enrollment) with a cigarette smoking history of ≥ 20 pack-years ($n=14,254$). The trial also included men ages 45-69 years with a documented history of occupational asbestos exposure who were current or former heavy smokers (i.e., quit within fifteen years prior to enrollment) ($n=4,060$). Participants were asked to complete a questionnaire at baseline and

annually thereafter, to obtain extensive information about smoking history as well as other risk factors. At baseline and every two years following, they were also asked to complete a food frequency questionnaire (FFQ) describing dietary intake in the prior year. After a mean of four years of follow up, the intervention was stopped in 1996 due to higher lung cancer incidence and overall mortality rates in the intervention versus placebo arm. CARET continued follow up for lung cancer and other outcomes until 2005. Tumor histology data were obtained from pathology reports collected as part of the CARET endpoint review process and through the California, Oregon, and Washington state cancer registries, since about 85% of all participants resided in these states at the time of CARET enrollment.

Participants were eligible for the present nested case-control study if they had provided a whole blood specimen for genetic research between February 1994 and January 1997. Cases included the 793 individuals who were diagnosed with primary lung cancer, and two lung cancer-free controls were matched to each case on age (± 4 years), sex, race/ethnicity, enrollment year (two year intervals), baseline smoking status (current or former), history of occupational asbestos exposure, and length of follow-up. Controls were additionally required to have completed at least one FFQ. DNA was extracted from whole blood, and eighteen controls were excluded due to low DNA yield (≤ 10 μg), leaving a total of 793 cases and 1,568 controls available for genotyping. Three cases were excluded after genotyping, because their diagnoses were later learned to be benign or carcinoid lung tumors.

The Institutional Review Board of the Fred Hutchinson Cancer Research Center and the five other participating institutions approved all study protocols, and all participants provided written informed consent.

SNP selection and genotyping

Tag SNPs were selected from HapMap Phase I and II Centre d'Etude du Polymorphisme Humain (CEU; NCBI build 36, dbSNP build 129) for the region spanning $\pm 2,500$ base pairs of each candidate gene using the *ldselect* algorithm [37] to classify SNPs with a minor allele frequency (MAF) of $\geq 5\%$ into bins with a pair-wise

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linkage disequilibrium (LD) threshold of $r^2 \geq 0.8$. Additional putative functional SNPs were also selected (for more details, please see Sakoda et al. [33]). We assayed a total of 185 SNPs using three methods: 137 were genotyped in a custom 384-plex Illumina GoldenGate assay that included SNPs in DNA repair, cell cycle control and drug metabolism; 45 were genotyped using individual Applied Biosystem TaqMan assays; and three were genotyped using Sequenom at the Genome Analysis Core Facility at the University of California, San Francisco. Eleven SNPs failed assays, were monomorphic, or genotype frequencies among the non-Hispanic white controls deviated from those expected under Hardy-Weinberg equilibrium as assessed using Fisher's exact test ($p < 0.001$). After excluding these SNPs, the large majority of SNPs had genotype call success of greater than 99%; 8 SNPs had call success between 95.1 and 98.9%. Genotype concordance for all SNPs was 100% in a set of 82 randomly-placed blind duplicates. Data were excluded for 3 case and 6 control samples that failed the Illumina assays or were identified by Illumina to be gender-mismatched, leaving 787 cases and 1,562 controls available for analysis. A subset of the CARET samples (397 cases and 393 controls) were previously analyzed using the Illumina HumanHap300 BeadChip in an initial GWA study of lung cancer by Hung et al. [38], and these data (394 cases and 391 controls) are also included in the latest metaanalysis [5].

Genotype analysis

Due to small numbers of Hispanic and non-White individuals (43 cases, 85 controls), all analyses were restricted to non-Hispanic whites (744 cases, 1,477 controls). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using logistic regression (Stata® 11, StataCorp, College Station, TX) and were adjusted for the case-control matching variables (age, sex, enrollment year, baseline smoking status, and occupational asbestos exposure), using the most common homozygous genotype as the reference group. Per allele ORs and 95% CIs were calculated by coding SNP genotypes according to the number of minor alleles carried (0, 1, or 2).

We examined whether SNP associations varied by age (<70, ≥ 70 years), sex (male, female),

smoking status at baseline (former, current), the number of pack-years smoked at baseline or time of blood draw (defined as the product of the average number of cigarette packs smoked per day and the total number of years smoked, divided into thirds of the distribution among controls), occupational asbestos exposure (yes, no), trial arm assignment (intervention, placebo), and tumor histology (non-small cell lung cancer, small cell lung cancer). Since *MSH5* rs3131379/*BAT3* rs3117582 and *CHRNA5/CHRNA3/CHRNA4* rs16969968 are validated lung cancer susceptibility loci, we also examined associations stratified by these SNPs. Wald p-values of the cross product of SNP genotype and the categorical exposure of interest were generated to formally test for departure from multiplicative relationships. As these are exploratory analyses, the reported p-values are not adjusted for multiple comparisons.

Haplotype analysis

Pairwise linkage disequilibrium (LD) patterns were visualized for each gene region using Haploview, version 4.2 [39]. Haplotype imputation from tagSNP genotype data was conducted using the haplo.stats package (http://mayo-research.mayo.edu/schaid_lab/software.cfm) in R, version 2.10.1. The expectation-maximization algorithm was used to calculate haplotype frequencies and global tests for each gene were used to evaluate whether there were case-control differences in haplotype frequencies. Additive model ORs and 95% CIs were calculated for each imputed haplotype with a frequency of >1% using the most common haplotype as the reference group, and adjusting for the matching variables.

In order to address issues of multiple testing, we performed gene-set analyses which take into account the number of SNPs tested and the LD between SNPs in each gene (PLINK version 1.04) [40]. Test statistics were averaged for SNPs in each gene and max(T) permutation was performed 10,000 times to calculate empirical p-values taking into account the matching factors.

Results

Baseline characteristics of this nested case-control study have been reported previously [33]. Two thirds of the participants were male,

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and 73% of participants were current smokers. The distribution of matching factors was broadly similar between cases and controls, though cases were slightly older than controls and were more likely to have reported a heavier smoking history. We successfully evaluated a total of 175 SNPs, with SNP coverage (the proportion of common SNPs represented by the genotyped SNPs through LD in the HapMap Phase I and II CEU populations) for all genes at $\geq 95\%$, except for *MLH1* (89%), *MBD4* (93%) and *XRCC2* (94%).

We observed associations with lung cancer for SNPs in the MMR genes *MSH5* and *MSH2*, and in the BER genes *PCNA* and *UNG*. We observed a marginal association with a SNP in *MPG*. Specifically, the minor alleles of the *MSH5* SNPs rs3131379 and rs707938 were associated with an increased risk of lung cancer, and there was no association with the only non-synonymous SNP in that gene (rs6905572). Per-allele ORs (95% CI) for rs3131379 (A allele) and rs707938 (G allele) were, respectively 1.37 (1.13-1.65) and 1.15 (1.01-1.31) (**Table 1**). For rs3131379, the ORs and 95% CIs for one or two copies of the A allele (compared to none) were 1.31 (1.06-1.62) and 2.30 (1.12-4.72). The rs3131379 A allele was carried in a single haplotype that also contained the minor allele for rs707938 (although the minor allele for rs707938 was carried in several additional haplotypes), at a frequency of 11% in controls and 14% in cases. Compared to the haplotype containing no variant alleles, this haplotype was associated with an increased risk (OR 1.43, 95% CI 1.15-1.77; global p-value 0.02) (**Table 3**). Risk of lung cancer associated with this SNP/haplotype did not appear to vary by gender, current/former cigarette smoking, pack-years of smoking, asbestos exposure, or randomization arm, nor did it differ between small cell and non-small cell histologies (data are not shown, but are available upon request). *MSH2* rs2303428 was associated with an increased risk of lung cancer (per-G-allele OR 1.24, 95% CI 1.01-1.52), and this association did not vary by any subgroup. The only haplotype that included the rs2303428 G allele was not associated with risk, nor were any other haplotypes in this gene (**Table 3**).

For the BER genes, the A allele of *PCNA* rs25406 was associated with an increased risk

of lung cancer (per-allele OR 1.14, 95% CI 1.01-1.29; **Table 1**), with an association present only among individuals ages 70 years and older (per allele OR 1.38 (1.14-1.66)); among women (1.37 (1.10-1.70)); and among participants who had not been exposed to asbestos (1.22 (1.06-1.40))(data are not shown, but are available upon request). The G allele of *UNG* rs246079 was associated with lung cancer risk (per-allele OR 1.15, 95% CI 1.01-1.31; **Table 1**), and associations did not vary by subgroup. The p-value for gene-level significance for *UNG* was 0.02, and the haplotype that contained the major allele for all of the SNPs was more frequent in controls than cases (41.1% versus 37.9%, respectively). Four out of five of the other haplotypes included the minor allele of rs246079 and all had ORs that were greater than 1. Only the combined rare genotypes were strongly associated with an increased risk (OR 2.35, 95% CI 1.27-4.36; **Table 3**). The G allele of *MPG* rs2562182 was marginally associated with a decreased risk of lung cancer (per-allele OR 0.84, 95% CI 0.70, 1.00; **Table 1**), and this association was present only among individuals receiving placebo (per allele OR 0.68 (0.51-0.90)). While the p-value for gene-level significance for *XRCC2* was 0.03, no SNPs (**Table 1**) or haplotypes in this gene were individually associated with risk. None of the SNPs in *XRCC1* were associated with lung cancer risk overall, but the magnitude of the associations between 4 SNPs (representing 2 SNPs with $r^2 < 0.80$) in *XRCC1* and lung cancer risk appeared to differ between men and women, with interaction p-values less than 0.004 and 0.0001 for rs3213334 (data are not shown, but are available upon request).

In exploratory analyses stratified by the known lung cancer susceptibility loci *CHRNA5* rs16969968 and *MSH5* rs3131379 genotypes, we observed a departure from a multiplicative relationship ($p < 0.05$) for SNPs in *MSH2*, *MSH4*, *MSH5*, *LIG3*, and *XRCC2* by rs16969968 genotype, with generally stronger associations among individuals carrying the rs16969968 GG genotype than the AG/AA (risk) genotypes. When we stratified by *MSH5* rs3131379 genotype, associations with lung cancer were generally stronger among individuals carrying at least one of the rs3131379 A (risk) alleles compared to the GG genotype (**Table 2**), with a departure from a multiplicative relationship for at least

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Table 1. Per-allele ORs for BER, HR, and MMR SNPs and lung cancer risk among non-Hispanic white smokers

Pathway	Gene	SNP	Major allele (A)	Minor allele (a)	MAF ^c (%)	Genotype distribution ^a						All (744 cases, 1,477 controls)		
						Cases			Controls			OR	(95% CI)	p-value
MMR ^b	<i>MLH1</i>	rs1800734	G	A	23.0%	470	212	46	858	520	66	0.91	(0.78,1.06)	0.215
MMR	<i>MLH1</i>	rs1540354	T	A	17.0%	499	226	18	1026	399	50	1.05	(0.89,1.24)	0.553
MMR	<i>MLH1</i>	rs4579	G	A	45.0%	224	361	159	454	719	304	1.03	(0.91,1.17)	0.652
MMR	<i>MSH2</i>	rs10188090	G	A	37.0%	275	366	102	576	706	194	1.06	(0.93,1.21)	0.394
MMR	<i>MSH2</i>	rs2059520	A	G	34.0%	299	355	84	626	675	166	1.05	(0.92,1.20)	0.442
MMR	<i>MSH2</i>	rs2303428	A	G	9.0%	589	142	13	1204	266	6	1.24	(1.01,1.52)	0.043
MMR	<i>MSH2</i>	rs12998837	T	A	13.0%	532	165	12	1068	313	32	1.00	(0.83,1.21)	0.991
MMR	<i>MSH2</i>	rs6544991	A	C	18.0%	506	220	17	1008	413	52	0.97	(0.82,1.14)	0.699
MMR	<i>MSH2</i>	rs13425206	C	A	4.0%	690	53	1	1356	118	2	0.90	(0.65,1.24)	0.509
MMR	<i>MSH2</i>	rs17036577	A	G	9.0%	623	117	4	1227	241	8	0.96	(0.76,1.20)	0.723
MMR	<i>MSH2</i>	rs1863332	A	C	8.0%	614	120	9	1239	226	12	1.09	(0.88,1.36)	0.423
MMR	<i>MSH2</i>	rs1981929	A	G	41.0%	272	348	124	513	712	251	0.95	(0.84,1.08)	0.459
MMR	<i>MSH2</i>	rs4638843	G	C	12.0%	581	151	11	1135	313	27	0.92	(0.76,1.12)	0.41
MMR	<i>MSH2</i>	rs4952887	G	A	8.0%	627	108	9	1255	209	11	1.08	(0.86,1.35)	0.506
MMR	<i>MSH2</i>	rs6741393	G	A	3.0%	697	45	2	1380	92	2	1.00	(0.71,1.42)	0.992
MMR	<i>MSH2</i>	rs6753135	G	A	12.0%	579	152	12	1139	317	19	0.98	(0.81,1.19)	0.828
MMR	<i>MSH2</i>	rs10191478	G	T	43.0%	229	376	139	477	730	270	1.04	(0.92,1.18)	0.54
MMR	<i>MSH2</i>	rs4987188	G	A	2.0%	713	31	0	1428	47	1	1.29	(0.82,2.04)	0.27
MMR	<i>MSH4</i>	rs5745325	G	A	28.0%	384	306	54	773	576	128	0.98	(0.86,1.13)	0.797
MMR	<i>MSH4</i>	rs5745433	A	C	26.0%	424	247	69	823	547	106	1.02	(0.89,1.17)	0.752
MMR	<i>MSH4</i>	rs3819949	A	G	34.0%	339	297	91	633	614	188	0.94	(0.82,1.07)	0.333
MMR	<i>MSH4</i>	rs2047435	G	A	13.0%	552	173	17	1110	343	22	1.06	(0.89,1.28)	0.507
MMR	<i>MSH4</i>	rs1146644	G	A	42.0%	249	363	131	515	683	278	1.00	(0.88,1.13)	0.995
MMR	<i>MSH4</i>	rs1498313	A	G	40.0%	275	327	141	528	717	230	1.05	(0.92,1.19)	0.477
MMR	<i>MSH4</i>	rs5745513	T	A	8.0%	616	122	4	1248	219	8	1.10	(0.88,1.39)	0.39
MMR	<i>MSH4</i>	rs5745549	G	A	3.0%	690	53	1	1388	85	3	1.19	(0.85,1.67)	0.317
MMR	<i>MSH5</i>	rs6905572	G	A	13%	572	162	10	1120	333	24	0.95	(0.79,1.15)	0.621
MMR	<i>MSH5</i>	rs3131379	G	A	11%	548	180	16	1166	292	15	1.37	(1.13,1.65)	0.001

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MMR	<i>MSH5</i>	rs707937	C	G	20%	477	236	29	948	469	56	1.01	(0.86,1.18)	0.884
MMR	<i>MSH5</i>	rs707938	A	G	32%	322	318	104	681	635	161	1.15	(1.01,1.31)	0.038
MMR	<i>MSH5</i>	rs707939	C	A	35%	326	343	73	620	673	176	0.91	(0.80,1.04)	0.184
MMR	<i>MSH5</i>	rs2299851	G	A	10%	604	133	5	1202	256	17	0.99	(0.80,1.22)	0.928
MMR	<i>MSH5</i>	rs3117572	G	A	17%	514	201	29	1014	416	47	1.00	(0.85,1.18)	0.999
MMR	<i>MSH5</i>	rs3131382	G	A	6%	645	80	6	1273	164	4	1.04	(0.80,1.35)	0.76
MMR	<i>MSH5</i>	rs1802127	C	T	2%	716	28	0	1427	49	1	1.10	(0.69,1.76)	0.683
MMR	<i>MSH6</i>	rs1800932	A	G	18%	498	220	25	990	428	53	1.00	(0.85,1.18)	0.984
MMR	<i>MSH6</i>	rs1800937	G	A	11%	599	136	9	1169	297	10	0.95	(0.77,1.17)	0.615
MMR	<i>MSH6</i>	rs1800935	A	G	29%	381	289	66	736	604	125	0.97	(0.84,1.11)	0.641
MMR	<i>MSH6</i>	rs2710163	A	G	39%	278	340	124	551	690	233	1.02	(0.90,1.16)	0.748
MMR	<i>MSH6</i>	rs2348244	A	G	14%	545	185	13	1084	358	33	0.98	(0.82,1.18)	0.856
MMR	<i>MSH6</i>	rs3136245	G	A	19%	488	226	27	960	465	48	1.00	(0.85,1.17)	0.972
MMR	<i>MSH6</i>	rs330792	A	C	11%	565	170	9	1156	307	14	1.13	(0.93,1.37)	0.23
MMR	<i>MSH6</i>	rs1800936	C	T	13%	574	155	15	1110	350	17	0.94	(0.77,1.13)	0.501
MMR	<i>MSH6</i>	rs3136329	A	G	42%	242	359	140	481	731	259	1.03	(0.90,1.16)	0.701
BER ^b	<i>APEX1</i>	rs1760945	C	T	8%	637	100	4	1249	213	10	0.92	(0.73,1.17)	0.509
BER	<i>APEX1</i>	rs1760944	C	A	39%	270	352	119	547	694	231	1.03	(0.91,1.18)	0.607
BER	<i>APEX1</i>	rs3136817	T	C	25%	411	276	57	840	541	96	1.08	(0.93,1.24)	0.313
BER	<i>APEX1</i>	rs1130409	A	C	47%	192	361	190	413	723	338	1.10	(0.98,1.25)	0.116
BER	<i>LIG3</i>	rs3135962	A	C	7%	647	95	2	1264	207	6	0.91	(0.71,1.16)	0.443
BER	<i>LIG3</i>	rs3135989	A	C	6%	644	97	2	1301	174	1	1.17	(0.90,1.51)	0.249
BER	<i>LIG3</i>	rs2074516	G	C	10%	598	135	8	1184	276	17	0.96	(0.78,1.18)	0.696
BER	<i>LIG3</i>	rs4796030	C	A	42%	242	377	123	486	730	261	0.99	(0.87,1.13)	0.904
BER	<i>LIG3</i>	rs1052536	G	A	47%	189	396	156	415	742	320	1.04	(0.91,1.18)	0.584
BER	<i>MBD4</i>	rs3138360	G	A	6%	666	77	1	1292	174	3	0.85	(0.64,1.12)	0.253
BER	<i>MBD4</i>	rs140696	G	A	9%	604	137	3	1210	257	10	1.04	(0.84,1.29)	0.727
BER	<i>MBD4</i>	rs9821282	G	A	16%	537	185	20	1035	408	34	0.94	(0.79,1.11)	0.453
BER	<i>MPG</i>	rs1013358	T	C	14%	577	153	14	1093	354	30	0.86	(0.71,1.04)	0.110
BER	<i>MPG</i>	rs2562182	A	G	16%	559	164	18	1044	400	32	0.84	(0.70,1.00)	0.050
BER	<i>MPG</i>	rs743725	C	T	19%	518	203	23	978	450	49	0.88	(0.75,1.04)	0.140
BER	<i>MUTYH</i>	rs3219489	G	C	25%	417	279	42	825	562	79	1.00	(0.86,1.15)	0.948

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BER	<i>MUTYH</i>	rs3219487	G	A	8%	628	112	3	1240	225	9	0.96	(0.76,1.21)	0.728
BER	<i>MUTYH</i>	rs3219484	G	A	7%	638	106	0	1273	198	6	1.01	(0.79,1.30)	0.930
BER	<i>MUTYH</i>	rs3219474	A	G	8%	631	109	4	1255	212	6	1.04	(0.82,1.32)	0.747
BER	<i>NEIL1</i>	rs7182283	G	T	50%	185	359	192	349	777	339	1.04	(0.91,1.18)	0.578
BER	<i>NEIL1</i>	rs4462560	C	G	26%	428	274	41	813	565	99	0.91	(0.78,1.05)	0.194
BER	<i>NEIL2</i>	rs4841593	C	G	8%	621	120	2	1256	209	11	1.08	(0.86,1.36)	0.510
BER	<i>NEIL2</i>	rs904009	A	C	24%	434	252	57	851	535	88	1.02	(0.88,1.18)	0.804
BER	<i>NEIL2</i>	rs2010628	G	T	23%	445	248	51	881	521	75	1.03	(0.89,1.20)	0.664
BER	<i>NEIL2</i>	rs8191529	G	C	9%	634	105	5	1229	240	8	0.87	(0.69,1.10)	0.238
BER	<i>NEIL2</i>	rs804267	A	G	33%	333	319	92	669	651	155	1.05	(0.92,1.20)	0.456
BER	<i>NEIL2</i>	rs8191534	T	A	23%	441	250	53	865	528	82	1.01	(0.88,1.17)	0.858
BER	<i>NEIL2</i>	rs8191542	G	C	22%	437	260	38	889	503	70	1.06	(0.91,1.24)	0.422
BER	<i>NEIL2</i>	rs8191589	T	A	22%	443	263	37	889	516	72	1.04	(0.89,1.20)	0.645
BER	<i>NEIL2</i>	rs4840581	G	A	45%	232	359	153	442	724	309	0.96	(0.85,1.09)	0.563
BER	<i>NEIL2</i>	rs4840583	C	T	45%	219	367	158	425	771	281	1.03	(0.90,1.17)	0.687
BER	<i>NEIL2</i>	rs804256	T	C	36%	304	338	102	597	695	185	1.01	(0.88,1.15)	0.914
BER	<i>NEIL2</i>	rs8191604	A	C	26%	409	276	57	807	569	99	1.00	(0.87,1.15)	0.987
BER	<i>NEIL2</i>	rs4840585	A	C	8%	627	115	2	1258	208	10	1.05	(0.83,1.32)	0.700
BER	<i>NEIL2</i>	rs1874546	C	G	24%	456	254	31	859	526	83	0.87	(0.75,1.01)	0.074
BER	<i>NEIL2</i>	rs8191649	C	T	22%	466	233	45	889	519	69	0.96	(0.83,1.12)	0.620
BER	<i>NEIL2</i>	rs6982453	A	G	49%	200	389	154	374	755	345	0.92	(0.81,1.04)	0.189
BER	<i>NEIL2</i>	rs1534862	G	A	23%	454	243	46	864	534	78	0.95	(0.82,1.10)	0.464
BER	<i>NEIL2</i>	rs6997097	A	G	7%	654	84	4	1281	186	7	0.92	(0.71,1.19)	0.514
BER	<i>NEIL2</i>	rs1043180	G	A	12%	575	160	8	1127	333	17	0.94	(0.77,1.14)	0.533
BER	<i>NEIL2</i>	rs2645450	T	C	23%	426	273	45	878	531	68	1.10	(0.95,1.28)	0.187
BER	<i>NEIL2</i>	rs904015	G	A	35%	321	327	95	614	678	174	0.99	(0.87,1.13)	0.877
BER	<i>NTHL1</i>	rs12447809	G	T	19%	474	233	37	960	463	54	1.07	(0.92,1.26)	0.361
BER	<i>NTHL1</i>	rs1132368	G	A	4%	689	54	1	1348	128	0	0.86	(0.62,1.20)	0.379
BER	<i>NTHL1</i>	rs2531213	A	G	3%	697	47	0	1378	99	0	0.93	(0.65,1.33)	0.672
BER	<i>NTHL1</i>	rs3211995	G	A	17%	517	205	22	1009	427	41	0.95	(0.81,1.13)	0.579
BER	<i>NTHL1</i>	rs2516740	A	C	23%	452	255	37	880	524	73	0.96	(0.83,1.12)	0.593
BER	<i>NTHL1</i>	rs2516739	G	A	22%	459	248	37	886	517	72	0.95	(0.82,1.10)	0.495

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BER	<i>OGG1</i>	rs159153	A	G	29%	353	307	84	748	584	140	1.11	(0.97,1.27)	0.127
BER	<i>OGG1</i>	rs1052133	C	G	23%	440	265	39	873	519	85	1.00	(0.86,1.16)	0.992
BER	<i>OGG1</i>	rs293795	A	G	18%	498	222	24	990	438	49	0.98	(0.83,1.15)	0.815
BER	<i>OGG1</i>	rs293794	A	G	18%	499	221	24	986	439	49	0.97	(0.83,1.14)	0.736
BER	<i>OGG1</i>	rs293796	G	A	8%	623	110	8	1260	207	8	1.14	(0.91,1.43)	0.253
BER	<i>PCNA</i>	rs3729558	G	C	47%	223	373	148	422	719	335	0.92	(0.81,1.05)	0.205
BER	<i>PCNA</i>	rs17349	G	A	12%	594	140	8	1147	309	19	0.88	(0.72,1.07)	0.199
BER	<i>PCNA</i>	rs25406	G	A	40%	239	370	135	553	675	249	1.14	(1.01,1.29)	0.038
BER	<i>PCNA</i>	rs25405	A	G	12%	591	141	8	1145	306	19	0.89	(0.73,1.09)	0.262
BER	<i>PCNA</i>	rs4239761	A	G	19%	476	233	34	970	439	68	1.04	(0.90,1.22)	0.587
BER	<i>PNKP</i>	rs7257463	T	A	34%	319	327	98	628	685	164	1.04	(0.92,1.19)	0.518
BER	<i>PNKP</i>	rs1290646	G	A	50%	188	383	172	373	734	366	0.96	(0.85,1.09)	0.558
BER	<i>PNKP</i>	rs3739177	C	T	8%	615	124	5	1259	211	7	1.20	(0.96,1.51)	0.112
BER	<i>PNKP</i>	rs2257103	G	A	39%	265	362	115	546	699	224	1.04	(0.92,1.19)	0.519
BER	<i>PNKP</i>	rs2353005	G	A	16%	543	187	14	1057	379	41	0.92	(0.77,1.10)	0.356
BER	<i>POLB</i>	rs3136711	T	C	8%	627	111	6	1247	219	11	1.03	(0.82,1.29)	0.829
BER	<i>POLB</i>	rs2976244	A	T	7%	645	95	2	1288	177	11	0.98	(0.76,1.25)	0.851
BER	<i>POLB</i>	rs3136790	A	C	11%	585	154	5	1170	286	18	1.00	(0.82,1.22)	0.991
BER	<i>POLB</i>	rs3136797	C	G	2%	716	28	0	1430	46	1	1.15	(0.72,1.84)	0.569
BER	<i>POLB</i>	rs2073664	G	A	6%	647	89	2	1288	168	11	0.96	(0.75,1.24)	0.761
BER	<i>POLI</i>	rs3730668	C	A	41%	283	336	116	524	681	254	0.91	(0.80,1.03)	0.135
BER	<i>POLI</i>	rs476630	G	A	29%	367	300	77	750	600	126	1.08	(0.95,1.24)	0.248
BER	<i>POLI</i>	rs686881	A	G	6%	643	100	1	1310	161	6	1.20	(0.92,1.54)	0.173
BER	<i>POLI</i>	rs3730814	C	A	23%	431	272	40	886	499	89	1.04	(0.90,1.20)	0.593
BER	<i>POLI</i>	rs3218786	A	G	3%	701	40	2	1391	82	0	1.06	(0.73,1.53)	0.771
BER	<i>POLI</i>	rs8305	A	G	30%	359	315	70	716	630	131	1.03	(0.90,1.18)	0.673
BER	<i>POLI</i>	rs596986	G	C	6%	643	100	1	1310	161	6	1.20	(0.92,1.54)	0.173
BER	<i>PPP1R13L</i>	rs6966	T	A	16%	539	185	20	1048	377	47	0.95	(0.80,1.12)	0.524
BER	<i>PPP1R13L</i>	rs4803817	A	G	23%	451	255	36	874	510	88	0.94	(0.81,1.09)	0.425
BER	<i>PPP1R13L</i>	rs10412761	A	G	40%	282	357	105	541	681	252	0.92	(0.81,1.05)	0.204
BER	<i>PPP1R13L</i>	rs1005165	G	A	17%	527	194	22	1016	410	45	0.93	(0.78,1.10)	0.367
BER	<i>RAD18</i>	rs4389469	C	T	40%	282	349	113	547	691	239	0.97	(0.85,1.10)	0.619

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BER	<i>RAD18</i>	rs369032	A	G	38%	285	357	102	579	674	224	0.99	(0.87,1.13)	0.915
BER	<i>RAD18</i>	rs2035221	G	A	9%	613	123	6	1227	235	10	1.05	(0.85,1.31)	0.641
BER	<i>RAD18</i>	rs593205	G	C	8%	605	136	3	1251	211	12	1.23	(0.99,1.53)	0.066
BER	<i>RAD18</i>	rs373572	A	G	26%	402	283	56	800	571	105	1.02	(0.88,1.17)	0.805
BER	<i>RAD18</i>	rs13088787	C	A	13%	569	165	10	1127	326	24	0.98	(0.81,1.19)	0.868
BER	<i>RAD18</i>	rs615967	T	C	21%	461	253	30	920	480	77	0.99	(0.85,1.15)	0.850
BER	<i>RAD18</i>	rs604092	A	G	18%	501	220	22	1004	414	56	1.00	(0.85,1.18)	0.962
BER	<i>SMUG1</i>	rs971	G	A	34%	324	323	93	654	647	172	1.03	(0.90,1.17)	0.654
BER	<i>SMUG1</i>	rs3087404	G	A	46%	226	358	157	437	714	325	0.96	(0.85,1.09)	0.573
BER	<i>TDG</i>	rs172814	A	G	16%	548	186	10	1052	384	40	0.87	(0.72,1.03)	0.113
BER	<i>TDG</i>	rs4135054	G	A	11%	573	163	8	1170	291	16	1.11	(0.91,1.35)	0.290
BER	<i>TDG</i>	rs4135061	A	G	27%	404	297	41	788	578	109	0.93	(0.80,1.07)	0.305
BER	<i>TDG</i>	rs4135064	G	A	9%	599	140	4	1221	246	9	1.13	(0.91,1.40)	0.274
BER	<i>TDG</i>	rs4135081	A	G	37%	273	370	101	579	695	200	1.06	(0.93,1.21)	0.388
BER	<i>TDG</i>	rs3751206	G	A	7%	644	96	2	1292	174	9	1.04	(0.81,1.34)	0.735
BER	<i>TDG</i>	rs4135087	G	A	10%	610	130	3	1184	278	13	0.87	(0.70,1.08)	0.197
BER	<i>TDG</i>	rs167715	A	G	11%	576	160	8	1164	294	19	1.05	(0.87,1.28)	0.598
BER	<i>TDG</i>	rs10861152	G	A	39%	291	350	97	538	715	216	0.91	(0.80,1.03)	0.142
BER	<i>TDG</i>	rs1866074	A	G	51%	178	387	178	377	689	409	0.96	(0.85,1.09)	0.517
BER	<i>TDG</i>	rs4135106	A	G	7%	654	86	2	1282	183	9	0.88	(0.68,1.14)	0.326
BER	<i>TDG</i>	rs4135128	G	C	9%	617	123	3	1241	218	17	1.02	(0.82,1.27)	0.849
BER	<i>UNG</i>	rs3890995	A	G	18%	491	233	20	986	461	30	1.06	(0.89,1.25)	0.529
BER	<i>UNG</i>	rs1018783	T	A	16%	492	232	20	1033	403	41	1.13	(0.96,1.33)	0.152
BER	<i>UNG</i>	rs2569987	A	G	17%	501	223	19	1009	421	45	1.01	(0.86,1.19)	0.893
BER	<i>UNG</i>	rs246079	A	G	42%	217	381	145	485	750	241	1.15	(1.01,1.31)	0.034
BER	<i>UNG</i>	rs34259	C	G	20%	446	266	30	938	476	62	1.10	(0.94,1.28)	0.245
BER	<i>XRCC1</i>	rs25487	C	T	37%	288	365	91	604	664	209	1.00	(0.88,1.14)	0.950
BER	<i>XRCC1</i>	rs25486	A	G	37%	288	365	90	599	664	209	1.00	(0.87,1.13)	0.946
BER	<i>XRCC1</i>	rs25489	C	T	4%	685	57	2	1348	128	1	0.94	(0.69,1.29)	0.701
BER	<i>XRCC1</i>	rs1799782	G	A	5%	661	82	1	1320	153	4	1.05	(0.80,1.38)	0.733
BER	<i>XRCC1</i>	rs3213344	G	C	5%	661	80	1	1320	150	5	1.03	(0.78,1.35)	0.844
BER	<i>XRCC1</i>	rs3213334	G	A	24%	434	266	44	866	509	102	0.99	(0.85,1.14)	0.851

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BER	<i>XRCC1</i>	rs2023614	G	C	8%	633	107	1	1249	220	6	0.92	(0.72,1.18)	0.513
BER	<i>XRCC1</i>	rs2854510	A	G	21%	470	245	28	936	461	78	0.96	(0.82,1.12)	0.586
BER	<i>XRCC1</i>	rs2854509	C	A	22%	456	242	42	914	480	80	1.02	(0.88,1.18)	0.793
BER	<i>XRCC1</i>	rs3213266	G	A	8%	630	111	2	1238	232	7	0.92	(0.73,1.16)	0.477
BER	<i>XRCC1</i>	rs3213255	A	G	43.0%	242	375	126	491	712	274	0.98	(0.86,1.11)	0.759
HR ^b	<i>XRCC2</i>	rs3218536	G	A	7%	631	109	2	1262	210	5	1.05	(0.82,1.33)	0.715
HR	<i>XRCC2</i>	rs6964582	G	C	4%	663	77	2	1349	124	2	1.26	(0.95,1.68)	0.114
HR	<i>XRCC2</i>	rs3218438	T	C	9%	598	138	8	1215	247	15	1.10	(0.89,1.35)	0.378
HR	<i>XRCC2</i>	rs3218408	A	C	22%	430	278	35	901	494	78	1.08	(0.93,1.25)	0.316
HR	<i>XRCC2</i>	rs3218373	C	A	9%	617	119	7	1230	235	10	1.03	(0.82,1.28)	0.808
HR	<i>XRCC2</i>	rs2040639	G	A	48%	212	366	166	387	767	322	0.97	(0.85,1.10)	0.625
HR	<i>XRCC3</i>	rs861539	G	A	39%	307	333	104	536	724	217	0.89	(0.78,1.01)	0.067
HR	<i>XRCC3</i>	rs3212102	C	T	3%	711	33	0	1402	75	0	0.88	(0.58,1.33)	0.539
HR	<i>XRCC3</i>	rs3212090	G	A	32%	311	354	78	694	628	151	1.12	(0.98,1.28)	0.087
HR	<i>XRCC3</i>	rs3212079	G	A	7%	644	99	1	1271	191	12	0.93	(0.73,1.19)	0.585
HR	<i>XRCC3</i>	rs861530	C	T	29%	362	328	54	733	625	119	1.01	(0.88,1.17)	0.839
HR	<i>XRCC3</i>	rs1799794	A	G	18%	477	245	22	980	442	48	1.08	(0.92,1.27)	0.340
HR	<i>XRCC3</i>	rs861528	G	A	26%	427	267	45	807	550	107	0.90	(0.78,1.04)	0.157

^aAmong all cases and controls; AA, homozygous major allele; Aa, heterozygous; aa, homozygous minor allele; numbers do not sum to total due to missing. ^bMMR, mismatch repair; BER, base excision repair; HR, homologous recombination. ^cMAF, minor allele frequency.

Table 2. Per-allele ORs for BER, HR, and MMR SNPs and lung cancer risk among non-Hispanic white smokers, stratified by *MSH5* rs3131379 and *CHRNA5* rs16969968 genotypes

Pathway	Gene	SNP	rs16969968 GG (258 ca, 624 co)		rs16969968 AG/AA (483 ca, 852 co)		p ^c	rs3131379 GG (548 ca, 1,166 co)		rs3131379 AG/AA (196 ca, 307 co)		p ^c
			OR	(95% CI)	OR	(95% CI)		OR	(95% CI)	OR	(95% CI)	
MMR ^b	<i>MLH1</i>	rs1800734	0.99	(0.77,1.28)	0.85	(0.70,1.03)	0.410	0.93	(0.78,1.11)	0.84	(0.61,1.15)	0.505
MMR	<i>MLH1</i>	rs1540354	0.99	(0.76,1.30)	1.11	(0.90,1.37)	0.605	0.95	(0.78,1.15)	1.40	(1.01,1.95)	0.039
MMR	<i>MLH1</i>	rs4579	1.01	(0.82,1.25)	1.03	(0.88,1.21)	0.905	1.07	(0.92,1.23)	0.91	(0.70,1.19)	0.344
MMR	<i>MSH2</i>	rs10188090	1.13	(0.91,1.41)	1.00	(0.85,1.18)	0.392	1.01	(0.87,1.17)	1.22	(0.93,1.61)	0.190
MMR	<i>MSH2</i>	rs2059520	1.12	(0.89,1.40)	1.02	(0.86,1.21)	0.561	1.00	(0.85,1.16)	1.25	(0.95,1.65)	0.141
MMR	<i>MSH2</i>	rs2303428	1.42	(1.01,2.01)	1.13	(0.87,1.47)	0.280	1.30	(1.03,1.64)	1.05	(0.67,1.66)	0.457

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MMR	<i>MSH2</i>	rs12998837	1.01	(0.75,1.36)	1.01	(0.79,1.28)	0.992	0.88	(0.71,1.10)	1.47	(1.01,2.13)	0.025
MMR	<i>MSH2</i>	rs6544991	0.99	(0.75,1.30)	0.95	(0.77,1.18)	0.840	0.86	(0.71,1.04)	1.41	(1.00,1.98)	0.012
MMR	<i>MSH2</i>	rs13425206	1.00	(0.59,1.69)	0.84	(0.55,1.28)	0.642	0.89	(0.62,1.29)	0.88	(0.43,1.81)	0.973
MMR	<i>MSH2</i>	rs17036577	0.77	(0.52,1.15)	1.08	(0.81,1.43)	0.179	0.94	(0.72,1.22)	0.98	(0.62,1.56)	0.796
MMR	<i>MSH2</i>	rs1863332	1.08	(0.74,1.57)	1.12	(0.86,1.47)	0.865	1.09	(0.86,1.40)	1.17	(0.73,1.88)	0.816
MMR	<i>MSH2</i>	rs1981929	0.90	(0.73,1.11)	0.98	(0.84,1.15)	0.549	0.97	(0.84,1.12)	0.91	(0.70,1.17)	0.606
MMR	<i>MSH2</i>	rs4638843	0.98	(0.72,1.33)	0.90	(0.70,1.15)	0.595	1.07	(0.86,1.33)	0.57	(0.38,0.86)	0.009
MMR	<i>MSH2</i>	rs4952887	1.53	(1.05,2.22)	0.88	(0.66,1.16)	0.022	1.12	(0.87,1.44)	1.00	(0.62,1.61)	0.663
MMR	<i>MSH2</i>	rs6741393	1.20	(0.66,2.16)	0.85	(0.55,1.32)	0.342	1.12	(0.76,1.65)	0.65	(0.30,1.44)	0.260
MMR	<i>MSH2</i>	rs6753135	0.90	(0.64,1.26)	1.01	(0.79,1.28)	0.616	0.99	(0.80,1.24)	0.90	(0.60,1.35)	0.768
MMR	<i>MSH2</i>	rs10191478	1.16	(0.93,1.44)	0.97	(0.83,1.14)	0.197	1.01	(0.87,1.17)	1.15	(0.89,1.50)	0.354
MMR	<i>MSH2</i>	rs4987188	1.55	(0.73,3.27)	1.09	(0.61,1.97)	0.487	1.71	(1.04,2.83)	0.38	(0.11,1.39)	0.034
MMR	<i>MSH4</i>	rs5745325	1.26	(1.01,1.57)	0.85	(0.71,1.02)	0.009	0.90	(0.77,1.06)	1.26	(0.96,1.66)	0.035
MMR	<i>MSH4</i>	rs5745433	0.97	(0.77,1.23)	1.05	(0.88,1.25)	0.589	0.97	(0.83,1.14)	1.20	(0.91,1.58)	0.250
MMR	<i>MSH4</i>	rs3819949	0.86	(0.69,1.07)	0.97	(0.82,1.15)	0.407	0.97	(0.83,1.13)	0.84	(0.64,1.10)	0.359
MMR	<i>MSH4</i>	rs2047435	0.97	(0.71,1.31)	1.13	(0.90,1.43)	0.464	1.18	(0.96,1.45)	0.74	(0.50,1.09)	0.053
MMR	<i>MSH4</i>	rs1146644	0.85	(0.69,1.05)	1.09	(0.93,1.28)	0.072	1.11	(0.96,1.28)	0.69	(0.53,0.89)	0.002
MMR	<i>MSH4</i>	rs1498313	0.95	(0.78,1.17)	1.11	(0.94,1.30)	0.275	1.05	(0.91,1.22)	1.03	(0.80,1.33)	0.842
MMR	<i>MSH4</i>	rs5745513	1.64	(1.16,2.31)	0.87	(0.64,1.19)	0.008	1.06	(0.81,1.38)	1.23	(0.78,1.94)	0.526
MMR	<i>MSH4</i>	rs5745549	0.83	(0.48,1.44)	1.60	(1.02,2.51)	0.067	1.59	(1.08,2.34)	0.45	(0.21,0.97)	0.005
MMR	<i>MSH5</i>	rs6905572	1.01	(0.74,1.38)	0.93	(0.73,1.19)	0.785	1.01	(0.82,1.25)	0.80	(0.48,1.34)	0.385
MMR	<i>MSH5</i>	rs3131379	1.12	(0.82,1.52)	1.55	(1.22,1.97)	0.101	NA		NA		
MMR	<i>MSH5</i>	rs707937	0.93	(0.72,1.21)	1.07	(0.88,1.31)	0.361	1.02	(0.86,1.22)	1.30	(0.84,2.01)	0.361
MMR	<i>MSH5</i>	rs707938	0.96	(0.77,1.19)	1.28	(1.09,1.51)	0.028	1.03	(0.87,1.21)	1.16	(0.79,1.71)	0.593
MMR	<i>MSH5</i>	rs707939	1.18	(0.95,1.47)	0.78	(0.65,0.92)	0.003	0.96	(0.83,1.12)	0.98	(0.67,1.42)	0.975
MMR	<i>MSH5</i>	rs2299851	0.90	(0.63,1.28)	1.05	(0.80,1.37)	0.418	1.05	(0.83,1.32)	0.85	(0.48,1.49)	0.485
MMR	<i>MSH5</i>	rs3117572	0.90	(0.69,1.19)	1.06	(0.86,1.30)	0.435	1.11	(0.93,1.32)	0.68	(0.40,1.13)	0.094
MMR	<i>MSH5</i>	rs3131382	0.82	(0.53,1.28)	1.19	(0.86,1.65)	0.217	1.15	(0.88,1.52)	0.60	(0.24,1.49)	0.186
MMR	<i>MSH5</i>	rs1802127	0.90	(0.37,2.19)	1.18	(0.68,2.05)	0.596	1.02	(0.61,1.71)	1.99	(0.58,6.82)	0.342
MMR	<i>MSH6</i>	rs1800932	0.93	(0.71,1.22)	1.05	(0.86,1.29)	0.550	1.08	(0.90,1.31)	0.75	(0.54,1.04)	0.068
MMR	<i>MSH6</i>	rs1800937	0.79	(0.55,1.15)	1.03	(0.80,1.33)	0.298	0.81	(0.64,1.04)	1.53	(1.01,2.33)	0.012
MMR	<i>MSH6</i>	rs1800935	0.88	(0.70,1.11)	1.02	(0.86,1.22)	0.370	0.98	(0.83,1.14)	0.91	(0.69,1.21)	0.751

Variation in DNA repair genes and lung cancer

MMR	<i>MSH6</i>	rs2710163	1.05	(0.85,1.29)	1.03	(0.87,1.20)	0.914	1.09	(0.94,1.26)	0.81	(0.62,1.06)	0.063
MMR	<i>MSH6</i>	rs2348244	1.07	(0.80,1.42)	0.95	(0.75,1.19)	0.562	1.05	(0.85,1.28)	0.82	(0.56,1.21)	0.271
MMR	<i>MSH6</i>	rs3136245	1.12	(0.86,1.44)	0.94	(0.76,1.16)	0.371	1.03	(0.86,1.23)	0.93	(0.66,1.32)	0.569
MMR	<i>MSH6</i>	rs330792	1.19	(0.87,1.63)	1.09	(0.85,1.40)	0.675	1.14	(0.91,1.43)	1.08	(0.72,1.60)	0.801
MMR	<i>MSH6</i>	rs1800936	0.85	(0.62,1.19)	0.99	(0.78,1.25)	0.585	0.84	(0.67,1.05)	1.38	(0.93,2.04)	0.032
MMR	<i>MSH6</i>	rs3136329	1.04	(0.84,1.30)	1.01	(0.86,1.18)	0.799	0.96	(0.83,1.11)	1.24	(0.96,1.61)	0.090
BER ^b	<i>APEX1</i>	rs1760945	0.83	(0.55,1.26)	0.96	(0.72,1.29)	0.521	0.97	(0.74,1.27)	0.81	(0.49,1.33)	0.576
BER	<i>APEX1</i>	rs1760944	0.96	(0.78,1.18)	1.09	(0.92,1.28)	0.307	1.05	(0.91,1.21)	0.99	(0.76,1.30)	0.622
BER	<i>APEX1</i>	rs3136817	1.05	(0.84,1.32)	1.10	(0.92,1.32)	0.729	1.01	(0.86,1.20)	1.21	(0.92,1.61)	0.288
BER	<i>APEX1</i>	rs1130409	1.21	(0.99,1.49)	1.05	(0.90,1.23)	0.327	1.06	(0.92,1.22)	1.23	(0.96,1.58)	0.376
BER	<i>LIG3</i>	rs3135962	0.78	(0.51,1.21)	0.97	(0.71,1.33)	0.348	1.01	(0.76,1.33)	0.63	(0.35,1.14)	0.147
BER	<i>LIG3</i>	rs3135989	1.72	(1.11,2.66)	0.94	(0.68,1.30)	0.029	1.18	(0.88,1.60)	1.09	(0.63,1.87)	0.807
BER	<i>LIG3</i>	rs2074516	0.86	(0.61,1.21)	1.01	(0.78,1.31)	0.586	0.97	(0.77,1.22)	1.01	(0.64,1.58)	0.883
BER	<i>LIG3</i>	rs4796030	0.88	(0.71,1.09)	1.04	(0.88,1.22)	0.202	0.99	(0.86,1.15)	0.95	(0.73,1.24)	0.785
BER	<i>LIG3</i>	rs1052536	1.18	(0.96,1.46)	0.98	(0.84,1.16)	0.190	1.03	(0.89,1.19)	1.07	(0.82,1.38)	0.812
BER	<i>MBD4</i>	rs3138360	0.87	(0.56,1.35)	0.85	(0.59,1.22)	0.907	0.84	(0.61,1.17)	0.83	(0.48,1.44)	0.985
BER	<i>MBD4</i>	rs140696	1.02	(0.72,1.45)	1.09	(0.82,1.44)	0.702	1.02	(0.79,1.31)	1.14	(0.73,1.78)	0.756
BER	<i>MBD4</i>	rs9821282	0.94	(0.71,1.25)	0.95	(0.76,1.19)	0.882	0.93	(0.76,1.14)	0.95	(0.67,1.33)	0.977
BER	<i>MPG</i>	rs1013358	1.04	(0.76,1.42)	0.76	(0.61,0.97)	0.146	0.84	(0.68,1.03)	0.95	(0.63,1.42)	0.537
BER	<i>MPG</i>	rs2562182	0.91	(0.67,1.25)	0.80	(0.64,0.99)	0.525	0.82	(0.67,1.01)	0.92	(0.61,1.39)	0.501
BER	<i>MPG</i>	rs743725	0.95	(0.71,1.26)	0.86	(0.70,1.05)	0.628	0.88	(0.73,1.06)	0.92	(0.63,1.32)	0.758
BER	<i>MUTYH</i>	rs3219489	0.90	(0.70,1.16)	1.04	(0.86,1.25)	0.419	0.90	(0.76,1.07)	1.30	(0.97,1.74)	0.028
BER	<i>MUTYH</i>	rs3219487	1.22	(0.86,1.75)	0.85	(0.62,1.16)	0.153	0.93	(0.71,1.21)	1.06	(0.66,1.69)	0.628
BER	<i>MUTYH</i>	rs3219484	0.80	(0.52,1.23)	1.16	(0.85,1.58)	0.159	1.10	(0.83,1.45)	0.77	(0.44,1.34)	0.277
BER	<i>MUTYH</i>	rs3219474	0.86	(0.58,1.28)	1.20	(0.89,1.62)	0.182	1.09	(0.82,1.44)	0.91	(0.58,1.43)	0.487
BER	<i>NEIL1</i>	rs7182283	1.14	(0.92,1.40)	0.98	(0.83,1.15)	0.267	1.04	(0.90,1.21)	1.01	(0.78,1.30)	0.780
BER	<i>NEIL1</i>	rs4462560	0.88	(0.70,1.12)	0.93	(0.77,1.13)	0.705	0.86	(0.72,1.01)	1.11	(0.82,1.51)	0.137
BER	<i>NEIL2</i>	rs4841593	1.01	(0.70,1.46)	1.16	(0.86,1.56)	0.561	1.14	(0.88,1.48)	0.91	(0.56,1.51)	0.462
BER	<i>NEIL2</i>	rs904009	1.07	(0.84,1.37)	0.98	(0.82,1.17)	0.569	0.97	(0.82,1.14)	1.20	(0.90,1.62)	0.221
BER	<i>NEIL2</i>	rs2010628	1.09	(0.85,1.40)	1.00	(0.83,1.20)	0.572	1.01	(0.86,1.20)	1.09	(0.81,1.47)	0.718
BER	<i>NEIL2</i>	rs8191529	0.81	(0.56,1.18)	0.92	(0.68,1.24)	0.666	0.91	(0.70,1.18)	0.75	(0.44,1.25)	0.512
BER	<i>NEIL2</i>	rs804267	1.09	(0.87,1.36)	1.03	(0.87,1.21)	0.716	1.03	(0.89,1.20)	1.11	(0.84,1.46)	0.675

Variation in DNA repair genes and lung cancer

BER	<i>NEIL2</i>	rs8191534	1.05	(0.82,1.34)	0.99	(0.82,1.18)	0.699	0.97	(0.82,1.15)	1.16	(0.86,1.55)	0.333
BER	<i>NEIL2</i>	rs8191542	1.20	(0.94,1.55)	0.98	(0.80,1.18)	0.198	1.04	(0.88,1.24)	1.13	(0.83,1.54)	0.662
BER	<i>NEIL2</i>	rs8191589	1.15	(0.90,1.48)	0.96	(0.80,1.17)	0.292	1.02	(0.85,1.21)	1.09	(0.80,1.48)	0.724
BER	<i>NEIL2</i>	rs4840581	0.89	(0.73,1.09)	1.02	(0.87,1.20)	0.308	0.99	(0.86,1.15)	0.87	(0.68,1.12)	0.372
BER	<i>NEIL2</i>	rs4840583	1.07	(0.86,1.33)	1.00	(0.85,1.17)	0.593	1.00	(0.86,1.16)	1.12	(0.86,1.46)	0.436
BER	<i>NEIL2</i>	rs804256	0.98	(0.80,1.21)	1.04	(0.88,1.23)	0.781	1.03	(0.89,1.20)	0.94	(0.72,1.22)	0.584
BER	<i>NEIL2</i>	rs8191604	0.98	(0.78,1.25)	1.00	(0.84,1.20)	0.949	0.97	(0.82,1.14)	1.11	(0.84,1.48)	0.395
BER	<i>NEIL2</i>	rs4840585	0.99	(0.68,1.45)	1.11	(0.82,1.49)	0.640	1.12	(0.86,1.46)	0.87	(0.52,1.44)	0.417
BER	<i>NEIL2</i>	rs1874546	0.77	(0.59,0.99)	0.94	(0.78,1.14)	0.207	0.87	(0.73,1.04)	0.85	(0.63,1.14)	0.869
BER	<i>NEIL2</i>	rs8191649	1.03	(0.80,1.33)	0.91	(0.75,1.10)	0.447	0.93	(0.78,1.11)	1.07	(0.79,1.44)	0.448
BER	<i>NEIL2</i>	rs6982453	0.90	(0.72,1.11)	0.92	(0.79,1.09)	0.834	0.92	(0.80,1.07)	0.89	(0.69,1.16)	0.787
BER	<i>NEIL2</i>	rs1534862	1.02	(0.79,1.30)	0.89	(0.74,1.08)	0.432	0.92	(0.78,1.10)	1.02	(0.76,1.37)	0.562
BER	<i>NEIL2</i>	rs6997097	0.85	(0.55,1.30)	0.94	(0.68,1.30)	0.728	0.84	(0.62,1.13)	1.18	(0.71,1.96)	0.237
BER	<i>NEIL2</i>	rs1043180	0.94	(0.69,1.29)	0.96	(0.74,1.23)	0.984	0.94	(0.75,1.17)	1.03	(0.67,1.58)	0.688
BER	<i>NEIL2</i>	rs2645450	1.05	(0.82,1.33)	1.16	(0.96,1.40)	0.550	1.09	(0.92,1.29)	1.14	(0.84,1.55)	0.757
BER	<i>NEIL2</i>	rs904015	1.10	(0.88,1.36)	0.92	(0.78,1.09)	0.225	0.96	(0.82,1.12)	1.08	(0.83,1.40)	0.466
BER	<i>NTHL1</i>	rs12447809	0.95	(0.72,1.24)	1.13	(0.93,1.37)	0.336	1.00	(0.83,1.20)	1.30	(0.95,1.79)	0.145
BER	<i>NTHL1</i>	rs1132368	1.04	(0.62,1.75)	0.73	(0.48,1.12)	0.329	0.65	(0.43,0.96)	1.90	(1.01,3.58)	0.007
BER	<i>NTHL1</i>	rs2531213	0.83	(0.47,1.46)	1.09	(0.68,1.77)	0.466	1.02	(0.68,1.54)	0.66	(0.32,1.39)	0.316
BER	<i>NTHL1</i>	rs3211995	0.89	(0.67,1.20)	0.97	(0.79,1.20)	0.753	0.91	(0.75,1.11)	1.03	(0.73,1.44)	0.501
BER	<i>NTHL1</i>	rs2516740	1.01	(0.78,1.30)	0.92	(0.76,1.11)	0.465	0.88	(0.74,1.05)	1.18	(0.87,1.60)	0.097
BER	<i>NTHL1</i>	rs2516739	0.97	(0.75,1.25)	0.92	(0.76,1.11)	0.650	0.88	(0.73,1.05)	1.17	(0.86,1.58)	0.107
BER	<i>OGG1</i>	rs159153	1.01	(0.80,1.26)	1.18	(1.00,1.40)	0.256	1.07	(0.92,1.25)	1.24	(0.95,1.62)	0.332
BER	<i>OGG1</i>	rs1052133	1.02	(0.80,1.29)	1.01	(0.83,1.22)	0.997	1.01	(0.85,1.19)	0.97	(0.71,1.32)	0.804
BER	<i>OGG1</i>	rs293795	0.79	(0.60,1.05)	1.11	(0.90,1.35)	0.066	0.95	(0.79,1.15)	1.08	(0.76,1.54)	0.424
BER	<i>OGG1</i>	rs293794	0.81	(0.61,1.07)	1.08	(0.88,1.32)	0.114	0.95	(0.79,1.14)	1.06	(0.75,1.50)	0.484
BER	<i>OGG1</i>	rs293796	0.96	(0.65,1.41)	1.26	(0.95,1.67)	0.228	1.15	(0.88,1.49)	1.13	(0.71,1.81)	0.918
BER	<i>PCNA</i>	rs3729558	0.93	(0.76,1.14)	0.91	(0.78,1.07)	0.977	0.94	(0.81,1.08)	0.87	(0.67,1.13)	0.607
BER	<i>PCNA</i>	rs17349	1.07	(0.78,1.47)	0.78	(0.60,1.02)	0.165	0.81	(0.64,1.02)	1.11	(0.74,1.69)	0.204
BER	<i>PCNA</i>	rs25406	1.07	(0.87,1.32)	1.19	(1.02,1.40)	0.522	1.16	(1.01,1.34)	1.08	(0.82,1.40)	0.636
BER	<i>PCNA</i>	rs25405	1.07	(0.77,1.47)	0.81	(0.62,1.05)	0.212	0.83	(0.66,1.05)	1.11	(0.73,1.68)	0.263
BER	<i>PCNA</i>	rs4239761	1.10	(0.86,1.41)	1.03	(0.85,1.26)	0.751	1.02	(0.85,1.22)	1.10	(0.81,1.51)	0.670

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BER	<i>PNKP</i>	rs7257463	1.02	(0.82,1.27)	1.05	(0.89,1.24)	0.821	1.08	(0.93,1.26)	0.96	(0.73,1.26)	0.472
BER	<i>PNKP</i>	rs1290646	0.97	(0.78,1.21)	0.96	(0.82,1.12)	0.859	0.92	(0.80,1.07)	1.09	(0.84,1.41)	0.297
BER	<i>PNKP</i>	rs3739177	1.40	(0.97,2.02)	1.09	(0.81,1.45)	0.309	1.24	(0.96,1.59)	1.11	(0.66,1.87)	0.775
BER	<i>PNKP</i>	rs2257103	1.00	(0.81,1.24)	1.07	(0.91,1.26)	0.553	1.06	(0.92,1.23)	0.99	(0.76,1.30)	0.688
BER	<i>PNKP</i>	rs2353005	0.76	(0.57,1.02)	1.04	(0.83,1.30)	0.106	0.98	(0.81,1.20)	0.76	(0.53,1.10)	0.221
BER	<i>POLB</i>	rs3136711	0.99	(0.67,1.45)	1.05	(0.79,1.39)	0.853	1.02	(0.79,1.33)	1.02	(0.64,1.63)	0.952
BER	<i>POLB</i>	rs2976244	1.14	(0.76,1.71)	0.88	(0.64,1.21)	0.324	0.95	(0.71,1.26)	1.05	(0.64,1.73)	0.706
BER	<i>POLB</i>	rs3136790	1.11	(0.79,1.54)	0.94	(0.73,1.22)	0.468	0.96	(0.76,1.22)	1.12	(0.74,1.67)	0.562
BER	<i>POLB</i>	rs3136797	1.79	(0.93,3.44)	0.73	(0.35,1.49)	0.076	0.88	(0.48,1.63)	1.67	(0.76,3.67)	0.211
BER	<i>POLB</i>	rs2073664	1.14	(0.75,1.72)	0.88	(0.64,1.22)	0.330	0.94	(0.70,1.27)	1.00	(0.60,1.66)	0.834
BER	<i>POLI</i>	rs3730668	0.89	(0.72,1.10)	0.89	(0.76,1.05)	0.892	0.94	(0.81,1.08)	0.83	(0.64,1.08)	0.423
BER	<i>POLI</i>	rs476630	1.02	(0.82,1.27)	1.15	(0.97,1.37)	0.362	1.14	(0.98,1.34)	0.94	(0.70,1.25)	0.210
BER	<i>POLI</i>	rs686881	1.14	(0.74,1.77)	1.20	(0.87,1.65)	0.888	1.17	(0.87,1.56)	1.37	(0.78,2.42)	0.581
BER	<i>POLI</i>	rs3730814	0.99	(0.78,1.25)	1.11	(0.92,1.34)	0.389	1.12	(0.95,1.32)	0.83	(0.61,1.15)	0.093
BER	<i>POLI</i>	rs3218786	1.62	(0.85,3.08)	0.84	(0.53,1.33)	0.087	1.07	(0.71,1.63)	1.16	(0.48,2.81)	0.924
BER	<i>POLI</i>	rs8305	1.12	(0.89,1.41)	1.00	(0.84,1.18)	0.471	0.94	(0.81,1.11)	1.26	(0.96,1.66)	0.059
BER	<i>POLI</i>	rs596986	1.14	(0.74,1.77)	1.20	(0.87,1.65)	0.888	1.17	(0.87,1.56)	1.37	(0.78,2.42)	0.581
BER	<i>PPP1R13L</i>	rs6966	0.99	(0.74,1.33)	0.91	(0.74,1.13)	0.735	0.95	(0.78,1.16)	0.94	(0.67,1.33)	0.933
BER	<i>PPP1R13L</i>	rs4803817	0.96	(0.75,1.22)	0.94	(0.78,1.14)	0.996	0.99	(0.83,1.17)	0.80	(0.58,1.09)	0.252
BER	<i>PPP1R13L</i>	rs10412761	0.92	(0.75,1.14)	0.91	(0.78,1.07)	0.936	0.94	(0.81,1.09)	0.87	(0.67,1.12)	0.657
BER	<i>PPP1R13L</i>	rs1005165	0.91	(0.69,1.20)	0.91	(0.73,1.12)	0.840	0.90	(0.74,1.10)	1.01	(0.71,1.44)	0.563
BER	<i>RAD18</i>	rs4389469	0.93	(0.75,1.15)	0.99	(0.84,1.16)	0.623	1.00	(0.87,1.16)	0.87	(0.67,1.13)	0.307
BER	<i>RAD18</i>	rs369032	0.93	(0.75,1.15)	1.04	(0.88,1.22)	0.414	1.00	(0.87,1.16)	0.96	(0.73,1.25)	0.724
BER	<i>RAD18</i>	rs2035221	1.02	(0.70,1.49)	1.05	(0.80,1.38)	0.922	1.23	(0.95,1.58)	0.67	(0.42,1.08)	0.029
BER	<i>RAD18</i>	rs593205	1.37	(0.96,1.97)	1.15	(0.87,1.53)	0.453	1.28	(1.00,1.66)	1.06	(0.67,1.66)	0.439
BER	<i>RAD18</i>	rs373572	1.01	(0.80,1.28)	1.01	(0.84,1.21)	0.970	1.04	(0.88,1.22)	0.95	(0.71,1.26)	0.533
BER	<i>RAD18</i>	rs13088787	0.94	(0.69,1.29)	1.01	(0.80,1.29)	0.666	1.09	(0.88,1.35)	0.72	(0.48,1.09)	0.072
BER	<i>RAD18</i>	rs615967	0.95	(0.74,1.21)	1.02	(0.84,1.25)	0.584	0.94	(0.78,1.12)	1.13	(0.83,1.53)	0.356
BER	<i>RAD18</i>	rs604092	0.99	(0.76,1.29)	1.01	(0.82,1.24)	0.927	0.95	(0.79,1.15)	1.14	(0.83,1.57)	0.383
BER	<i>SMUG1</i>	rs971	0.92	(0.73,1.14)	1.10	(0.94,1.30)	0.181	0.95	(0.82,1.11)	1.28	(0.98,1.67)	0.064
BER	<i>SMUG1</i>	rs3087404	0.92	(0.75,1.13)	0.99	(0.85,1.16)	0.601	0.92	(0.80,1.06)	1.10	(0.85,1.43)	0.200
BER	<i>TDG</i>	rs172814	1.05	(0.79,1.41)	0.77	(0.61,0.97)	0.107	0.88	(0.72,1.08)	0.81	(0.56,1.18)	0.711

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BER	<i>TDG</i>	rs4135054	1.03	(0.74,1.44)	1.17	(0.92,1.50)	0.578	1.13	(0.90,1.42)	1.05	(0.70,1.57)	0.817
BER	<i>TDG</i>	rs4135061	0.98	(0.77,1.25)	0.90	(0.75,1.07)	0.518	0.90	(0.76,1.06)	1.04	(0.77,1.41)	0.409
BER	<i>TDG</i>	rs4135064	0.95	(0.66,1.37)	1.25	(0.95,1.64)	0.264	1.14	(0.89,1.47)	1.08	(0.70,1.66)	0.848
BER	<i>TDG</i>	rs4135081	1.10	(0.89,1.37)	1.03	(0.87,1.21)	0.620	1.04	(0.89,1.21)	1.12	(0.85,1.47)	0.651
BER	<i>TDG</i>	rs3751206	1.06	(0.68,1.66)	1.03	(0.76,1.39)	0.891	1.10	(0.83,1.46)	0.91	(0.52,1.57)	0.483
BER	<i>TDG</i>	rs4135087	0.83	(0.59,1.19)	0.92	(0.70,1.22)	0.598	0.85	(0.66,1.10)	0.86	(0.57,1.29)	0.968
BER	<i>TDG</i>	rs167715	0.91	(0.64,1.27)	1.13	(0.89,1.44)	0.348	0.97	(0.77,1.21)	1.43	(0.95,2.16)	0.096
BER	<i>TDG</i>	rs10861152	0.95	(0.77,1.18)	0.89	(0.75,1.05)	0.637	0.88	(0.75,1.02)	0.99	(0.76,1.30)	0.408
BER	<i>TDG</i>	rs1866074	1.09	(0.89,1.33)	0.88	(0.75,1.03)	0.115	0.96	(0.84,1.11)	0.95	(0.73,1.24)	0.940
BER	<i>TDG</i>	rs4135106	0.88	(0.57,1.37)	0.87	(0.63,1.19)	0.912	0.87	(0.65,1.17)	0.94	(0.54,1.61)	0.789
BER	<i>TDG</i>	rs4135128	0.96	(0.65,1.42)	1.03	(0.79,1.36)	0.796	1.09	(0.85,1.39)	0.86	(0.52,1.42)	0.360
BER	<i>UNG</i>	rs3890995	0.95	(0.72,1.27)	1.12	(0.91,1.39)	0.375	1.03	(0.85,1.25)	1.16	(0.82,1.65)	0.601
BER	<i>UNG</i>	rs1018783	1.05	(0.80,1.39)	1.16	(0.95,1.43)	0.576	1.03	(0.85,1.25)	1.45	(1.04,2.03)	0.085
BER	<i>UNG</i>	rs2569987	1.01	(0.77,1.34)	1.00	(0.81,1.23)	0.848	1.08	(0.89,1.30)	0.82	(0.58,1.16)	0.175
BER	<i>UNG</i>	rs246079	1.06	(0.85,1.31)	1.21	(1.03,1.43)	0.326	1.07	(0.92,1.24)	1.48	(1.13,1.94)	0.038
BER	<i>UNG</i>	rs34259	1.13	(0.87,1.45)	1.07	(0.88,1.29)	0.723	1.02	(0.86,1.22)	1.34	(0.98,1.83)	0.128
BER	<i>XRCC1</i>	rs25487	0.91	(0.73,1.13)	1.05	(0.90,1.24)	0.309	0.98	(0.84,1.14)	1.09	(0.83,1.42)	0.566
BER	<i>XRCC1</i>	rs25486	0.90	(0.73,1.13)	1.04	(0.88,1.23)	0.343	0.97	(0.84,1.13)	1.08	(0.83,1.41)	0.548
BER	<i>XRCC1</i>	rs25489	1.06	(0.64,1.74)	0.87	(0.58,1.31)	0.604	0.87	(0.61,1.24)	1.28	(0.64,2.58)	0.323
BER	<i>XRCC1</i>	rs1799782	1.07	(0.68,1.68)	1.05	(0.74,1.49)	0.997	1.05	(0.77,1.42)	1.17	(0.60,2.27)	0.784
BER	<i>XRCC1</i>	rs3213344	1.09	(0.69,1.71)	1.00	(0.70,1.42)	0.799	1.02	(0.75,1.39)	1.17	(0.60,2.27)	0.732
BER	<i>XRCC1</i>	rs3213334	1.09	(0.86,1.38)	0.95	(0.79,1.14)	0.400	0.98	(0.83,1.16)	0.99	(0.74,1.32)	0.990
BER	<i>XRCC1</i>	rs2023614	0.87	(0.59,1.30)	0.96	(0.70,1.31)	0.705	0.86	(0.65,1.14)	1.18	(0.71,1.97)	0.269
BER	<i>XRCC1</i>	rs2854510	1.01	(0.78,1.31)	0.93	(0.76,1.12)	0.574	1.01	(0.84,1.20)	0.82	(0.60,1.12)	0.299
BER	<i>XRCC1</i>	rs2854509	1.17	(0.92,1.50)	0.96	(0.79,1.15)	0.203	1.02	(0.86,1.21)	1.01	(0.75,1.35)	0.952
BER	<i>XRCC1</i>	rs3213266	0.88	(0.60,1.30)	0.94	(0.70,1.27)	0.792	0.85	(0.65,1.12)	1.20	(0.73,1.96)	0.226
BER	<i>XRCC1</i>	rs3213255	1.12	(0.91,1.39)	0.91	(0.78,1.07)	0.124	1.01	(0.87,1.17)	0.88	(0.68,1.14)	0.387
HR ^b	<i>XRCC2</i>	rs3218536	0.90	(0.60,1.36)	1.18	(0.87,1.60)	0.227	1.08	(0.82,1.42)	0.95	(0.57,1.58)	0.644
HR	<i>XRCC2</i>	rs6964582	1.43	(0.90,2.30)	1.18	(0.81,1.70)	0.502	1.18	(0.84,1.66)	1.57	(0.89,2.78)	0.400
HR	<i>XRCC2</i>	rs3218438	1.43	(1.03,1.98)	0.94	(0.72,1.23)	0.047	0.97	(0.76,1.24)	1.62	(1.04,2.52)	0.032
HR	<i>XRCC2</i>	rs3218408	1.00	(0.78,1.30)	1.11	(0.93,1.34)	0.495	1.18	(0.99,1.40)	0.83	(0.61,1.13)	0.049
HR	<i>XRCC2</i>	rs3218373	1.08	(0.76,1.54)	1.02	(0.77,1.35)	0.785	1.08	(0.84,1.39)	0.89	(0.57,1.42)	0.466

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HR	XRCC2	rs2040639	0.93	(0.75,1.15)	0.97	(0.82,1.13)	0.854	0.93	(0.80,1.08)	1.09	(0.84,1.41)	0.340
HR	XRCC3	rs861539	0.90	(0.72,1.11)	0.88	(0.75,1.04)	0.936	0.89	(0.77,1.04)	0.87	(0.67,1.14)	0.852
HR	XRCC3	rs3212102	0.93	(0.47,1.86)	0.85	(0.50,1.46)	0.872	0.73	(0.44,1.23)	1.20	(0.56,2.54)	0.278
HR	XRCC3	rs3212090	1.08	(0.86,1.34)	1.17	(0.98,1.39)	0.646	1.20	(1.03,1.40)	0.95	(0.72,1.26)	0.133
HR	XRCC3	rs3212079	1.18	(0.81,1.74)	0.80	(0.58,1.10)	0.107	0.91	(0.68,1.22)	0.94	(0.59,1.49)	0.881
HR	XRCC3	rs861530	1.05	(0.83,1.33)	0.98	(0.82,1.18)	0.717	0.93	(0.79,1.10)	1.25	(0.93,1.67)	0.070
HR	XRCC3	rs1799794	0.99	(0.75,1.29)	1.13	(0.92,1.39)	0.372	1.02	(0.84,1.22)	1.27	(0.91,1.77)	0.226
HR	XRCC3	rs861528	0.88	(0.69,1.12)	0.90	(0.75,1.08)	0.900	0.91	(0.77,1.07)	0.88	(0.66,1.17)	0.878

^aAmong all cases and controls; AA, homozygous major allele; Aa, heterozygous; aa, homozygous minor allele; numbers do not sum to total due to missing. ^bMMR, mismatch repair; BER, base excision repair; HR, homologous recombination. ^cp-value for interaction.

Table 3. MSH2, MSH5, PCNA, and UNG haplotypes and lung cancer risk

MSH2															Frequency		OR	95% CI	
SNP ^a															Case	Control			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15					
1	1	1	1	1	1	1	1	2	1	1	1	1	1	1	23.0%	23.4%	1.00	Reference	
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14.4%	14.3%	1.04	0.84	1.28
2	2	1	2	2	1	1	1	1	1	1	1	1	2	1	13.0%	12.9%	1.03	0.82	1.28
1	1	1	1	1	1	1	1	2	2	1	1	1	1	1	11.3%	12.2%	0.95	0.76	1.19
2	2	2	1	1	1	1	1	1	1	1	1	1	2	1	8.4%	7.3%	1.16	0.89	1.52
2	2	1	1	1	1	2	1	1	1	1	1	2	2	1	6.0%	6.4%	0.96	0.72	1.28
1	1	1	1	1	1	1	2	1	1	2	1	1	2	1	4.2%	3.9%	1.10	0.79	1.53
2	2	1	1	2	1	1	1	1	1	1	1	1	2	1	3.3%	3.8%	0.86	0.59	1.25
1	1	1	1	1	2	1	1	2	1	1	1	1	1	1	3.2%	3.2%	1.03	0.71	1.51
2	1	1	1	1	1	1	1	1	1	2	2	2	2	1	3.1%	3.2%	1.00	0.69	1.46
*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	10.1%	9.4%	1.11	0.86	1.43

^aSNP order: 1) rs10188090, 2) rs2059520, 3) rs2303428, 4) rs12998837, 5) rs6544991, 6) rs13425206, 7) rs17036577, 8) rs1863332, 9) rs1981929, 10) rs4638843, 11) rs4952887, 12) rs6741393, 13) rs6753135, 14) rs10191478, 15) rs4987188. *global p-value = 0.91.*

MSH5										Frequency		OR	95% CI	
SNP ^a										Case	Control			
1	2	3	4	5	6	7	8	9						
1	1	1	1	2	1	1	1	1		29.5%	31.9%	1.00	reference	
1	1	1	1	1	1	2	1	1		10.7%	11.0%	1.07	0.861	

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1	1	1	1	1	1	1	1	1	10.0%	9.7%	1.12	0.89
2	1	2	2	1	2	1	1	1	9.1%	9.1%	1.09	0.86
1	1	1	1	1	1	2	2	1	6.4%	6.2%	1.12	0.85
1	1	2	1	1	1	1	1	1	4.3%	5.9%	0.83	0.60
1	1	1	2	1	1	1	1	1	4.5%	5.0%	0.96	0.69
2	1	1	2	1	1	1	1	1	2.6%	3.1%	0.94	0.63
1	1	2	1	2	1	1	1	1	3.5%	2.9%	1.33	0.90
1	1	1	2	1	1	1	1	2	1.9%	1.7%	1.23	0.76
1	1	2	2	1	1	1	1	1	2.4%	1.6%	1.63	1.01
*	*	*	*	*	*	*	*	*	1.0%	1.1%	0.86	0.36

^aSNP order: 1) rs3729558, 2) rs3131379, 3) rs707937, 4) rs707938, 5) rs707939, 6) rs2299851, 7) rs3117572, 8) rs3131382, 9) rs1802127. *global p-value* = 0.02.

PCNA

1	SNP ^a				Frequency		OR	95% CI	
	2	3	4	5	Case	Control			
1	1	2	1	1	39.7%	37.5%	1.00	reference	
1	1	1	1	1	1.5%	1.5%	0.89	0.53	1.51
1	1	2	1	2	3.2%	2.1%	1.32	0.82	2.15
1	2	1	2	1	10.5%	11.6%	0.84	0.68	1.05
2	1	1	1	1	27.8%	29.9%	0.88	0.76	1.04
2	1	1	1	2	17.1%	17.0%	0.93	0.77	1.11
					0.2%	0.3%	1.49	0.17	13.36

^aSNP order: 1) rs3729558, 2) rs17349, 3) rs25406, 4) rs25405, 5) rs4239761. *global p-value* = 0.30.

UNG

1	SNP ^a				Frequency		OR	95% CI	
	2	3	4	5	Control				
1	1	1	1	1	41.1%		1.00	reference	
1	1	1	2	1	3.2%		1.25	0.88	1.78
1	1	1	2	2	4.6%		1.11	0.82	1.51
1	1	2	1	1	17.1%		1.07	0.89	1.28
1	2	1	2	2	15.5%		1.15	0.95	1.39
2	1	1	2	1	17.5%		1.14	0.94	1.37
					0.9%		2.35	1.27	4.36

^aSNP order: 1) rs3890995, 2) rs1018783, 3) rs2569987, 4) rs246079, 5) rs34259. *global p-value* = 0.02.

one SNP in each of the MMR genes studied (*MLH1*, *MSH2*, *MSH4*, and *MSH6*), as well as in the BER genes *MUTYH*, *NTHL1*, *RAD18*, and *UNG* and the HR gene *XRCC2*. Among SNPs for which we observed an overall association with lung cancer risk, associations varied by rs3131379 genotype only for *UNG* rs246079. The per G allele ORs and 95% CIs among AA/AG carriers and among GG carriers were 1.48 (1.13, 1.94) and 1.07 (0.92, 1.24), respectively ($p_{\text{interaction}} = 0.038$; **Table 2**).

Discussion

As expected, we observed an association between the *MSH5* rs3131379/*BAT3* rs3117582 known susceptibility locus and lung cancer risk. These genes lie in the highly complex human leukocyte antigen (HLA) region on 6p21.33. The HLA locus on 6p21.31 has also been reported to be associated with lung cancer risk among Japanese individuals [6]. Interestingly, one of the major findings from The Cancer Genome Atlas comprehensive genomic analysis of squamous cell cancers is the description of somatic loss-of-function mutations in the HLA-A class I major histocompatibility gene, which is also located in the 6p21.3 region [41]. Our other observations include an increased risk of lung cancer associated with a SNP in *UNG*, particularly among individuals who were already at increased risk because they carried at least one of the *MSH5* rs3131379 A alleles; and an increased risk of lung cancer associated with certain SNPs in *MSH2* and *PCNA*. Like *SMUG1*, *TDG*, and *MBD4*, *UNG* is a BER uracil-DNA glycosylase which repairs the mis-incorporation of the RNA constituent uracil. *UNG* binds to PCNA at replication foci, and is the major enzyme that removes uracil from U:A pairs. It may also be involved in short patch BER of uracil and pre-replication repair of U:G pairs [42]. *MSH2* is typically involved in post-replicative MMR, forming heterodimers with *MSH6* to repair base mismatches and small insertion deletion loops, and with *MSH3* to repair larger insertion deletion loops [43]. *MSH2* also binds to PCNA [42, 44]. Lynch Syndrome, which is associated with a dramatically increased risk of colon, endometrial and ovarian cancers as well as several other cancer types, is characterized by mutations in *MLH1*, *MSH2*, and *MSH6*. Mutations in *MSH2* confer particularly high risks, though this does not appear to be true for lung cancer [45]. PCNA

performs a central role not only in DNA repair, but also in DNA replication and recombination. It forms a trimer that encircles DNA at replication forks, where it recruits other proteins [46].

While *UNG* and *MSH2* perform distinct functions with respect to DNA repair, they have a similar and overlapping role in adaptive immunity [42]. The main function of the adaptive immune system, to recognize and remember specific pathogens, is performed through the differentiation of immunoglobulin (Ig) genes. In humans, this is achieved through two processes, somatic hypermutation (SHM) which yields antibody diversification, and class switch recombination (CSR), which produces the five Ig isotypes IgM, IgD, IgE, IgE, and IgA [42]. Both somatic hypermutation and class switch recombination are initiated by activation-induced cytidine deaminase (AID) which allows the introduction of uracil, forming key intermediate U:G pairings in Ig DNA. Recognition of the U:G pairs in specific regions of Ig by both *UNG* and *MSH2* coupled with *MSH6* allows for accumulation of mutations and diversification. Both *UNG* and *MSH2* bind to PCNA, and additional DNA repair genes including *APE1*, *POLN*, *POLB*, and others are involved in the later steps, particularly for class switch recombination [47]. Mouse models deficient in either *UNG* or *MSH2* result in mice able to produce antibodies at a level 2 to 3-fold lower than in wild type mice [48], and models deficient in *UNG* result in mice that develop B-cell lymphomas late in life [42]. However, deficiency in both *UNG* and *MSH2* results in mice incapable of antibody gene diversification [48]. In humans, mutations in *UNG* alone result in the autosomal recessive hyper-IgM syndrome, a class switch recombination disorder characterized by IgG, IgA, and IgE deficiencies [49].

In the lung, innate and adaptive immunity launch inflammatory responses to a variety of insults such as particulate matter in cigarette smoke and other pollutants, microbial infections, and cell damage/injury. Chronic inflammation, and the interaction between innate and adaptive immune response, play central roles in cancer development [50]. Chronic pulmonary inflammation has been hypothesized to be an underlying mechanism for the increased risk of lung cancer associated with tobacco smoking, chronic obstructive pulmonary disease [51], silicosis, asbestosis [52], and lung

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infections (i.e., tuberculosis, pneumonia [53]), and the increased incidence of lung cancer among individuals with human immunodeficiency virus [54].

Very few prior studies have interrogated variants in *UNG*, *MSH2*, and *PCNA* and lung cancer risk, and only in the context of candidate gene studies of DNA repair. Two comprehensive studies described in more detail below [8, 15] that examined DNA repair pathway genotype data from samples assayed using the Illumina HumanHap300 BeadChip, did not observe differences in the genotype distribution between cases and controls for SNPs in *MSH2*, *UNG* or *PCNA*, but they did not directly measure the SNPs associated with risk in our study. A relatively small study of French Caucasian smokers (151 lung cancer cases and 172 hospital controls) [11] did not observe associations with *MSH2* rs2303428 (G allele frequency 0.10 in cases, 0.12 in controls) or *PCNA* rs25406 (A allele frequency 0.40 in cases, 0.47 in controls ($p=0.09$)); data from this study is also included in the meta-analysis by Kazma et al. [15] described below. Two other studies examined associations with *MSH2* rs2303428. A Korean study with 432 lung cancer patients matched to 432 healthy controls on age and gender observed that carriage of at least one C allele was associated with an increased risk of adenocarcinoma, compared to the TT genotype (adjusted OR, 1.52; 95% CI, 1.02-2.27; $P = 0.04$) [13], and while the confidence limit does not exclude 1, an elevated OR (1.29 (0.83–1.99)) was observed in a Taiwanese study of 156 NSCLC patients and 235 controls matched for age, gender and smoking [14]. A candidate SNP study of Caucasian smokers that included 343 NSCLC cases and 413 population-based controls matched on age, gender and smoking did not observe an association with *PCNA* rs25406 (MAF 0.38 in cases, 0.38 in controls; AG, and AA, versus GG, OR 0.73 (0.52–1.0) and 1.15 (0.74–1.79) [22]. These studies do not provide rigorous support for or against associations with the SNPs of interest, since a much larger sample size is needed in order to obtain stable risk estimates of the magnitude expected.

The largest and most comprehensive interrogations of DNA repair pathways and lung cancer risk were performed by Kazma et al. [15] and Yu et al. [8] Kazma et al. [15] included 1,655

SNPs in 211 DNA repair genes in 6,911 individuals pooled from four studies. Yu et al. [8] interrogated 1806 SNPs in 125 DNA repair genes in 1154 lung cancer cases and 1137 controls matched by smoking status. With the exception of *MSH5* rs3131379, the SNPs that were associated with risk in our study are not present on the HumanHap300 BeadChip, but SNPs in LD with them (in HapMap-CEU) were not associated with risk in either study (*UNG*, rs2430682, in LD with rs246079 ($r^2=0.89$); *MSH2*, rs2042649, in LD with rs2303428 ($r^2=1.0$)). While they examined associations with SNPs in *PCNA*, none of the SNPs were in LD >0.52 with the SNP (rs25406) that we observed to be associated with risk in our study.

The variants (after *MSH5* rs3131379) that were most strongly associated with lung cancer risk in Kazma et al. were in the genes *UBE2N*, *SMC1L2*, and *POLB*, with suggestive associations for variants in *RAD52* and *POLN* [15]. Yu et al. observed associations with SNPs in *XRCC4*, but they were not replicated in a meta-analysis of these SNPs in four GWAS studies totaling ~12,000 cases and ~48,000 controls [8]. Other studies of DNA repair genes have reported associations with additional candidate SNPs. A hospital-based study of smokers including 722 cases and 929 controls interrogated 29 SNPs in the BER genes *MPG*, *OGG1*, *PARP1*, and *XRCC1*, one SNP in *PARP1* and two SNPs in *XRCC1* (rs1799782 and rs3213255) were associated with lung cancer risk [31]. Meta-analyses of selected SNPs have observed associations with *OGG1* Ser326Cys rs1052133 [20, 55, 56] and *XRCC3* T241M rs861539 [20]. Of the genes reported to be associated with lung cancer risk in prior studies, we only examined variants in *POLB*, *XRCC1*, *OGG1* and *XRCC3*, and they were not related to risk in our study.

An important difference between our study and the meta-analysis by Kazma et al. is the prevalence of smoking, because Kazma et al. specifically limited their analysis to studies that included both smokers and non-smokers in order to evaluate interactions between SNPs and smoking. In our study, among the controls, none were never smokers, 27.6% were former, and 72.4% were current smokers, whereas in Kazma et al., 38.8% of the controls were never smokers, 25.6% were former, and 34.5% were

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current smokers. The distribution was identical in the cases and controls for our study because they were matched on smoking exposure, but the distribution in cases from Kazma et al. --9.7% never, 20.5% former, and 68.9% current--differed considerably from the distribution in their controls. It is possible that there are underlying differences in the distribution of genotypes in the controls due to differences in smoking exposure. A well-documented example of this is genetic variation in the nicotinic acetylcholine receptor gene cluster on chromosome 15q25.1. For rs1051730 (which is in complete LD with rs16969968 ($r^2=1.0$, HapMap-CEU)), the frequency of the T allele increases with increasing numbers of cigarettes smoked, with a large difference in frequency between individuals smoking 1-10 cigarettes per day (T allele frequency 0.305) and 31 or more cigarettes per day (T allele frequency 0.391) [57]. Matching controls to cases based on cigarette smoking (as we did) is arguably an advantage when attempting to identify genetic factors that might differentiate between the ~20 % of smokers who develop lung cancer from the ~80 % who do not.

In conclusion, we observed associations with SNPs in *UNG*, *MSH2*, and *PCNA*, all of which are involved both in DNA repair pathways and also in adaptive immunity, and the associations with the *UNG* variants were stronger among individuals carrying the documented *MSH5/BAT3* lung cancer susceptibility allele, which was also associated with risk in our study. We were unable to confirm associations reported in prior studies with *POLB*, *XRCC1*, *OGG1* and *XRCC3* SNPs, and we did not evaluate variation in *UBE2N*, *SMC1L2*, *RAD52*, or *POLN*. Our study was not large enough to be able to reliably identify the presence of true weak associations, and is limited by having genotype data on only two of the five documented lung cancer susceptibility loci described to date in Caucasian populations [5]. However, our study differs from most other prior studies because it is prospective in nature and includes only heavy smokers, with cases and controls matched on smoking history. Because lung cancer is so rapidly fatal, case control study response proportions can be very low, and our study is likely to have a more representative case group, specific to smoking-associated lung cancer, than case-control studies. Furthermore, no prior studies

have reported pathway-based SNP results stratified by known lung cancer susceptibility loci. The patterns of associations observed should be viewed as hypothesis-generating, requiring follow up in other studies of smoking-related lung cancer.

Abbreviations

APEX1, apurinic/aprimidinic-endonuclease-1; CARET, β -Carotene and Retinol Efficacy Trial; CI, confidence interval; *LIG3*, ligase III; *MBD4*, methyl binding domain 4; *MLH1*, MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli); *MPG*, N-methylpurine-DNA glycosylase; *MSH2*, mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli); *MSH4*, mutS homolog 4, colon cancer, nonpolyposis type 1 (E. coli); *MSH5*, mutS homolog 5, colon cancer, nonpolyposis type 1 (E. coli); *MSH6*, mutS homolog 6, colon cancer, nonpolyposis type 1 (E. coli); *MUTYH*, mutY homolog (E. coli); *NEIL1*, nei endonuclease VIII-like 1 (E. coli); *NEIL2*, nei endonuclease VIII-like 2 (E. coli); *NTHL1*, nth endonuclease III-like 1 (E. coli); *OGG1*, 8-oxo-guanine glycosylase-1; OR, odds ratio; *PCNA*, proliferating cell nuclear antigen; *PNKP*, polynucleotide kinase 3'-phosphatase; *POLB*, polymerase (DNA directed), beta; *POLI*, polymerase (DNA directed) iota; *PPP1R13L*, protein phosphatase 1, regulatory subunit 13 like; *RAD18*, RAD18 homolog (S. cerevisiae); SD, standard deviation; *SMUG1*, single strand selective monofunctional uracil-DNA glycosylase; SNP, single nucleotide polymorphism; *TDG*, thymine/uracil mismatch DNA glycosylase; *UNG*, uracil-DNA glycosylase; *XRCC1*, X-ray repair complementing defective repair in Chinese-hamster cells 1; *XRCC2*, X-ray repair complementing defective repair in Chinese-hamster cells 2; *XRCC3*, X-ray repair complementing defective repair in Chinese-hamster cells 3.

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