Variation at 8q24 and 9p24 and Risk of Epithelial Ovarian Cancer

Kristin L. White,[1] Thomas A. Sellers,[2] Brooke L. Fridley,[1] Robert A. Vierkant,[1] Catherine M. Phelan,[2] Ya-Yu Tsai,[2] Kimberly R. Kalli,[1] Andrew Berchuck,[3] Edwin S. Iversen, Jr,[3] Lynn C. Hartmann,[1] Mark Liebow,[1] Sebastian Armasu,[1] Zachary Fredericksen,[1] Melissa C. Larson,[1] David Duggan,[4] Fergus J. Couch,[1] Joellen M. Schildkraut,[3] Julie M. Cunningham[1] and Ellen L. Goode[1]

[1] *Mayo Clinic College of Medicine, Rochester, United States of America*
[2] *H. Lee Moffitt Cancer Research Institute, Tampa, United States of America*
[3] *Duke University, Durham, United States of America*
[4] *The Translational Genomics Research Institute, Phoenix, United States of America*

The chromosome 8q24 region (specifically, 8q24.21.a) is known to harbor variants associated with risk of breast, colorectal, prostate, and bladder cancers. In 2008, variants rs10505477 and rs6983267 in this region were associated with increased risk of invasive ovarian cancer ($p < 0.01$); however, three subsequent ovarian cancer reports of 8q24 variants were null. Here, we used a multi-site case-control study of 940 ovarian cancer cases and 1,041 controls to evaluate associations between these and other single-nucleotide polymorphisms (SNPs) in this 8q24 region, as well as in the 9p24 colorectal cancer associated-region (specifically, 9p24.1.b). A total of 35 SNPs from previous reports and additional tagging SNPs were assessed using an Illumina GoldenGate array and analyzed using logistic regression models, adjusting for population structure and other potential confounders. We observed no association between genotypes and risk of ovarian cancer considering all cases, invasive cases, or invasive serous cases. For example, at 8q24 SNPs rs10505477 and rs6983267, analyses yielded per-allele invasive cancer odds ratios of 0.95 (95% confidence interval (CI) 0.82–1.09, p trend 0.46) and 0.97 (95% CI 0.84–1.12, p trend 0.69), respectively. Analyses using an approach identical to that of the first positive 8q24 report also yielded no association with risk of ovarian cancer. In the 9p24 region, no SNPs were associated with risk of ovarian cancer overall or with invasive or invasive serous disease (all p values > 0.10). These results indicate that the SNPs studied here are not related to risk of this gynecologic malignancy and that the site-specific nature of 8q24.21.a associations may not include ovarian cancer.

Keywords: neoplasms, polymorphisms, molecular epidemiology, genome-wide association study

Ovarian cancer has the highest mortality rate among gynecologic malignancies, indicating a pressing need for better understanding of its etiology as a means to inform prevention approaches. Factors associated with increased risk of ovarian cancer include age, family history, fertility drug use, and postmenopausal hormone therapy (Morch et al., 2009). In *BRCA1* and *BRCA2* mutation carriers, lifetime risk of ovarian cancer is approximately 40% and 20%, respectively (Antoniou et al., 2003), and these mutations are responsible for nearly half of ovarian cancer cases in families with two or more confirmed cases (Ramus et al., 2007). The remaining unexplained familial and sporadic ovarian cancer risk is likely caused by common, low-penetrance alleles which individually cause a modest change in risk, yet may lead to a notable increased risk in combination (Fasching et al., 2009; Pharoah & Ponder, 2002). Thus far, variants in the 9p22.2 chromosomal region (Song et al., 2009b) and in genes involved in cell cycle control (Gayther et al., 2007), steroid hormone metabolism (Pearce et al., 2008), DNA repair (Schildkraut et al., 2009), and one-carbon metabolism (Kelemen et al., 2008) have been associated with ovarian cancer risk.

Genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) in a non-coding 8q24 region (specifically, 8q24.21.a) that are associated with risk of prostate cancer (Gudmundsson et al., 2007; Haiman et al., 2007; Salinas et al., 2008; Suuriniemi et al., 2007; Yeager et al., 2007), breast cancer (Garcia-Closas et al., 2008; Schumacher et al., 2007), colorectal cancer (Ghoussaini et al., 2008; Gruber et al., 2007; Poynter et al., 2007; Tenesa et al., 2008; Tuupanen et al., 2009; Zanke et al., 2007), and bladder cancer (Kiemeney et al., 2008), and variants in the 9p24 region (specifically, 9p24.1.b) have been associated with risk of colorectal cancer (Poynter et al., 2007; Zanke et al., 2007). In 2008, a four-site

Received 24 September, 2009; accepted 24 November, 2009.

Address for correspondence: Ellen L. Goode, Ph.D., M.P.H., Department of Health Sciences Research Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. E-mail: egoode@mayo.edu

study of 1,975 invasive ovarian cancer cases and 3,411 controls revealed the first association between 8q24.21.a loci (rs10505477, rs10808556, and rs6983267; 1.8 kb; $0.65 \leq r^2 \leq 0.93$) and risk of ovarian cancer (odds ratio (OR) 1.14, 95% confidence interval (CI) 1.04–1.23; OR 1.13, 95% CI 1.04–1.22; OR 1.11, 95% CI 1.03–1.20, respectively) (Ghoussaini et al., 2008). However, subsequent examinations of rs6983267 in 618 cases and 1,019 controls, rs13281615 in 2,502 cases and 3,892 controls, and rs1447295 in 274 cases and 682 controls found no association with risk (OR 1.00, 95% CI 0.81–1.23, p trend = 0.10; OR 1.00, 95% CI 0.70–1.30, p trend = 1.00; OR 0.99, 95% CI 0.92–1.06, p trend = 0.69, respectively) (Song et al., 2009a; Wokolorczyk et al., 2008; Wokolorczyk et al., 2009). Due to discrepant ovarian cancer associations in 8q24, associations in both regions with other cancers, and the existence of other genetic factors in common across these cancers (Fasching et al., 2009), we examined risk of ovarian cancer in the 8q24.21.a and 9p24.1.b regions using case-control collections from two study populations.

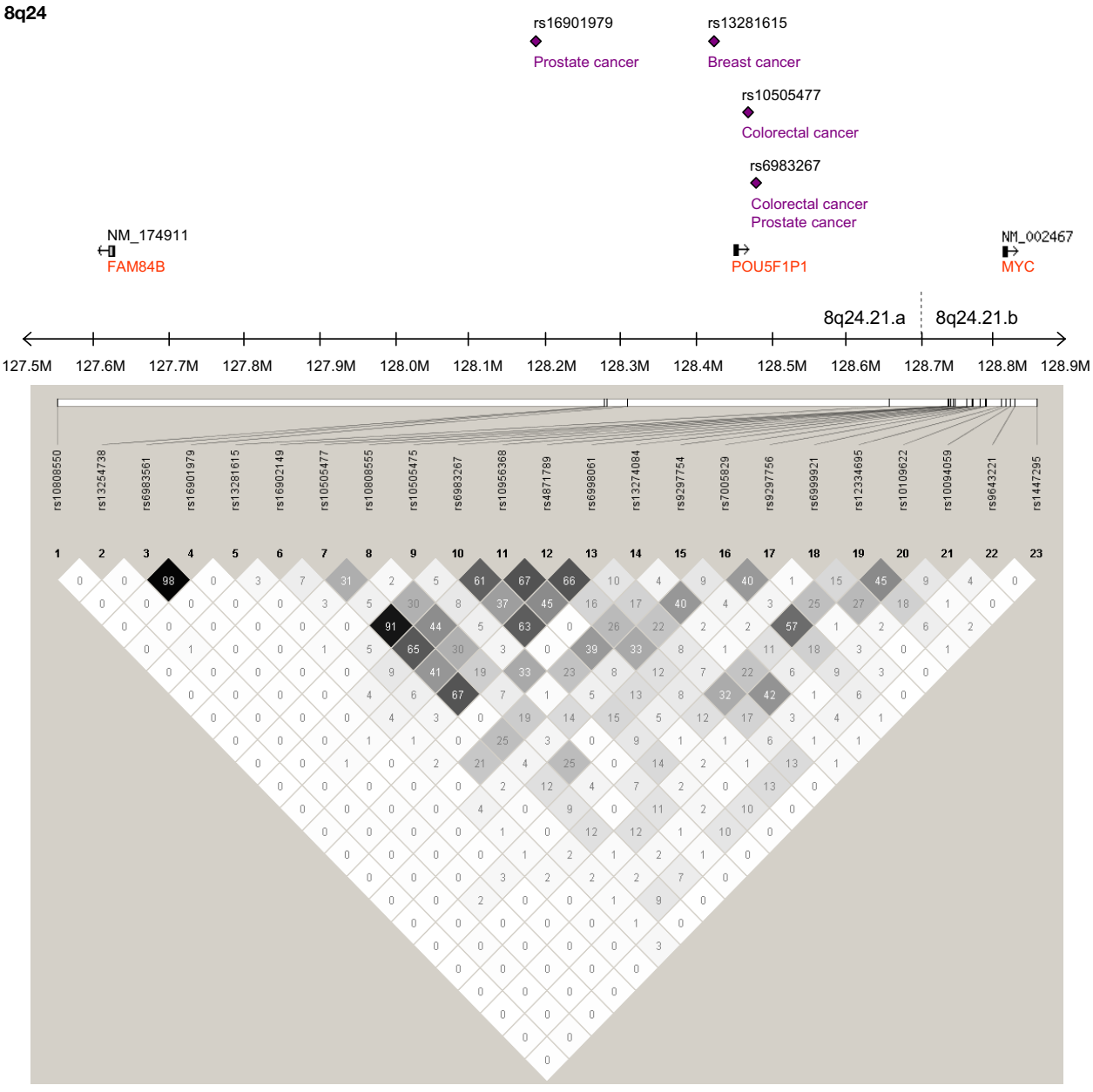

Figure 1

Regional linkage disequilibrium.

Note: Haploview 4.1 (Barrett et al., 2005) based on self-reported White non-Hispanic controls; $r^2 = 0$ = White and $r^2 = 1$ = Black; numbers represent $r^2 * 100$; associations with risk of other cancers with at least one replication study and a p value $< 1 \times 10^{-15}$ are shown for genotyped SNPs based on Hindorff LA, Junkins HA, Mehta JP, and Manolio TA. A Catalog of Published Genome-Wide Association Studies, available at www.genome.gov/gwastudies, accessed July 29, 2009.

9p24

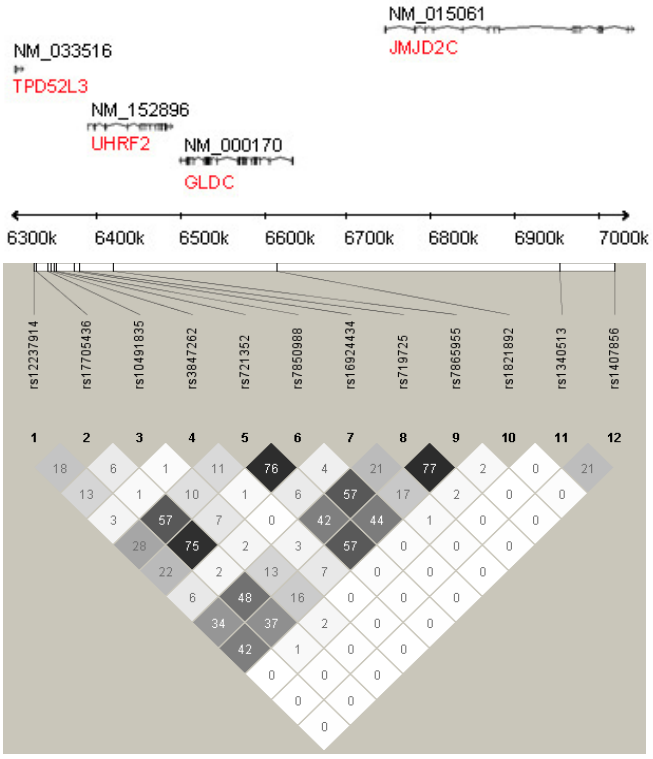

Figure 1 (continued)

Regional linkage disequilibrium.

Note: Haploview 4.1 (Barrett et al., 2005) based on self-reported White non-Hispanic controls; $r^2 = 0$ = White and $r^2 = 1$ = Black; numbers represent r^2 * 100; associations with risk of other cancers with at least one replication study and a p value $< 1 \times 10^{-15}$ are shown for genotyped SNPs based on Hindorff LA, Junkins HA, Mehta JP, and Manolio TA. A Catalog of Published Genome-Wide Association Studies, available at www.genome.gov/gwastudies, accessed July 29, 2009.

Materials and Methods

Study Participants

Participants were recruited at Mayo Clinic in Rochester, MN and at Duke University in Durham, NC and included cases enrolled within one year of histologically confirmed epithelial ovarian cancer and controls without ovarian cancer and without bilateral oophererectomy (Sellers et al., 2005). At Mayo Clinic, cases were women over 20 years of age living in the Upper Midwest. Controls were recruited from among women seen for general medical examinations and frequency-matched to cases on age and area of residence. At Duke University, cases were women between 20 and 75 years of age identified using the North Carolina Central Cancer Registry's rapid case ascertainment system within a 48-county region. Controls were identified from the same region as the cases using list-assisted random digit dialing and frequency-matched to cases on race and age. Information on known and suspected risk factors was collected through in-person interviews at both sites using similar questionnaires. Mayo Clinic participants had an extra vial of blood drawn during their scheduled medical visit, and DNA was extracted using the Gentra AutoPure LS Purgene salting out methodology (Gentra, Minneapolis, MN). Duke University participants had venipuncture performed at the conclusion of their interview, and DNA samples were transferred to Mayo Clinic for whole-genome amplification (WGA) with REPLI-G (Qiagen Inc, Valencia CA) which we have shown yielded highly reproducible results with these samples (Cunningham et al., 2008). Samples were barcoded to ensure accurate and reliable sample processing, and DNA concentrations were adjusted to 50 ng/µl and verified using PicoGreen dsDNA Quantitation kit (Molecular Probes, Inc., Eugene, OR).

SNP Selection and Genotyping

A broad SNP selection approach was applied. In 8q24.21.a, we included seven SNPs due to a prior ovarian cancer report (Ghoussaini et al., 2008), one due to a prior prostate cancer report (Haiman et al., 2007), five SNPs which tagged 1 kb surrounding the regional pseudogene *POU5F1P1*, and twelve SNPs which additionally tagged the region; in 9p24.1.b, we included three SNPs from a colorectal cancer report (Poynter et al., 2007) and nine additional regional tagSNPs (see Table 1 and Figure 1). Genotyping of 897 genomic and 1,279 WGA DNA samples (2,176 including 129 duplicates) on 2,047 unique study participants was performed at Mayo Clinic using the Illumina GoldenGate BeadArray assay and BeadStudio software (Oliphant et al., 2002). Briefly, of 2,047 participants

Table 1

SNP and Genotype Information

rsid	Position	Alleles	Selection Strategy	Nearest gene	Location to gene	Distance to gene	Call Rate	HWE *p* value	MAF	Case Genotype, *N*			Control Genotype, *N*		
										AA	AB	BB	AA	AB	BB
8q24.21.a															
rs10808550	127,691,632	A/G	Ghoussaini et al., 2008	*FAM84B*	5′ upstream	51,984	0.997	0.78	0.16	667	243	26	729	287	23
rs13254738	128,173,525	A/C	Ghoussaini et al., 2008	*POU5F1P1*	5′ upstream	323,769	0.998	0.50	0.33	430	383	126	465	453	120
rs6983561	128,176,062	A/C	Ghoussaini et al., 2008	*POU5F1P1*	5′ upstream	321,232	0.999	0.62	0.07	822	101	16	921	93	26
rs16901979	128,194,098	C/A	Ghoussaini et al., 2008	*POU5F1P1*	5′ upstream	303,196	0.999	0.62	0.07	825	99	15	924	94	22
rs13281615	128,424,800	A/G	Ghoussaini et al., 2008	*POU5F1P1*	5′ upstream	72,494	0.996	0.77	0.40	338	439	158	371	506	162
rs16902149	128,476,287	G/C	regional tagSNP	*POU5F1P1*	5′ upstream	21,007	0.992	0.71	0.07	794	131	6	897	133	4
rs10505477	128,476,625	A/G	regional tagSNP	*POU5F1P1*	5′ upstream	20,669	0.998	0.81	0.48	270	445	222	287	500	254
rs10808555	128,478,693	A/G	regional tagSNP	*POU5F1P1*	5′ upstream	18,601	0.998	0.34	0.33	422	420	97	465	468	105
rs10505475	128,480,639	A/C	regional tagSNP	*POU5F1P1*	5′ upstream	16,655	0.999	0.30	0.06	824	109	7	921	116	2
rs6983267	128,482,487	C/A	Haiman et al., 2007	*POU5F1P1*	5′ upstream	14,807	0.998	0.77	0.47	288	433	217	311	483	245
rs10956368	128,492,832	G/A	regional tagSNP	*POU5F1P1*	5′ upstream	4,462	0.998	0.59	0.41	325	435	177	366	494	181
rs4871789	128,497,243	A/G	*POU5FIP1* tagSNP	*POU5F1P1*	5′ upstream	51	0.999	0.48	0.50	244	452	243	273	494	273
rs6998061	128,497,820	G/A	*POU5FIP1* tagSNP	*POU5F1P1*	rna_exon	0	0.991	0.93	0.40	346	431	154	376	479	177
rs13274084	128,497,933	A/G	*POU5FIP1* tagSNP	*POU5F1P1*	rna_exon	0	0.999	0.29	0.13	716	206	16	796	223	22
rs7002225	128,498,005	C/G	*POU5FIP1* tagSNP	*POU5F1P1*	rna_exon	0						Failed, cluster compression			
rs9297754	128,498,444	C/G	*POU5FIP1* tagSNP	*POU5F1P1*	3′ downstream	71	0.989	0.42	0.22	560	330	41	628	356	45
rs7005829	128,504,126	G/A	regional tagSNP	*POU5F1P1*	3′ downstream	5,753	0.995	0.72	0.28	504	362	71	545	405	85
rs9297756	128,509,349	C/A	regional tagSNP	*POU5F1P1*	3′ downstream	10,976	0.995	0.89	0.14	698	219	19	763	249	24
rs6999921	128,510,110	A/G	regional tagSNP	*POU5F1P1*	3′ downstream	11,737	0.999	0.21	0.09	781	150	8	874	157	10
rs7000448	128,510,352	C/T	Ghoussaini et al., 2008	*POU5F1P1*	3′ downstream	11,979						Failed, cluster compression			
rs12334695	128,523,110	A/G	regional tagSNP	*POU5F1P1*	3′ downstream	24,737	0.998	0.14	0.38	411	397	131	415	465	158
rs10109622	128,527,333	G/A	regional tagSNP	*POU5F1P1*	3′ downstream	28,960	0.997	0.87	0.25	552	308	78	589	371	78
rs10094059	128,530,789	G/C	regional tagSNP	*POU5F1P1*	3′ downstream	32,416	0.999	0.14	0.26	517	359	63	576	381	83
rs9643221	128,534,669	G/A	regional tagSNP	*POU5F1P1*	3′ downstream	36,296	0.998	0.13	0.21	592	291	53	655	326	60
rs1447295	128,554,220	C/A	Ghoussaini et al., 2008	*POU5F1P1*	3′ downstream	55,847	0.997	0.33	0.12	725	203	9	812	206	20

(continued over)

Table 1 (continued)

SNP and Genotype Information

rsid	Position	Alleles	Selection Strategy	Nearest gene	Location to gene	Distance to gene	Call Rate	HWE *p* value	MAF	Case Genotype, *N*			Control Genotype, *N*		
										AA	AB	BB	AA	AB	BB
9p24.1.b															
rs12237914	6,296,896	A/G	regional tagSNP	*TPD52L3*	5′ upstream	21,479	0.983	0.20	0.38	335	431	159	409	453	161
rs17705436	6,300,908	G/C	regional tagSNP	*TPD52L3*	5′ upstream	17,467	0.998	0.35	0.22	600	282	56	647	337	56
rs10491835	6,315,345	G/A	regional tagSNP	*TPD52L3*	5′ upstream	3,030	0.998	0.17	0.17	649	262	27	726	277	36
rs3847262	6,318,947	G/A	regional tagSNP	*TPD52L3*	F118L	0	0.999	0.35	0.06	820	114	6	913	122	4
rs721352	6,322,901	C/A	regional tagSNP	*TPD52L3*	3′ downstream	2,231	0.998	0.02	0.34	440	364	133	479	413	148
rs7850988	6,325,760	T/A	regional tagSNP	*TPD52L3*	3′ downstream	5,090	0.998	0.10	0.26	539	327	73	579	379	80
s16924434	6,348,334	A/G	regional tagSNP	*TPD52L3*	3′ downstream	27,664	0.999	0.26	0.11	756	174	10	823	198	18
rs719725	6,355,683	A/C	regional tagSNP	*TPD52L3*	3′ downstream	35,013	0.997	0.32	0.37	395	421	120	417	466	156
rs7865955	6,398,247	C/G	regional tagSNP	*UHRF2*	5′ upstream	4,904	0.998	<0.01	0.45	306	442	190	342	459	238
rs1821892	6,606,648	G/C	CRC Affymetrix 10k 2.0	*GLDC*	intron	0	0.998	0.88	0.15	674	234	30	750	259	30
rs1340513	6,967,633	A/G	CRC Affymetrix 10k 2.0	*JMJD2C*	intron	0	0.997	0.97	0.25	541	345	51	595	378	66
rs1407856	7,036,901	G/C	CRC Affymetrix 10k 2.0	*JMJD2C*	Q767E	0	0.998	0.43	0.17	646	265	26	720	286	35

Note: Position from genome build 36.3; Refseq release 29 (May 4, 2008); Gene information: *FAM84B*, – strand, geneID 157638, protein-coding, NM_174911.3, mRNA; *POU5F1P1*, + strand, geneID 5462, pseudo-gene, NR_002304.1, misc_RNA; *TPD52L3*, + strand, geneID 89882, protein-coding, NM_001001875.2, mRNA; *UHRF2*, + strand, geneID 115426, protein-coding, NM_152896.1, mRNA; *GLDC*, – strand, geneID 2731, protein-coding, NM_000170.2, mRNA; *JMJD2C*, + strand, geneID 23081, protein-coding, NM_015061.2, mRNA; Call rate among all participants; MAF calculated using all controls; HWE *p* value calculated using White non-Hispanic controls only; AA, common homozygotes; AB, heterozygotes; BB, rare homozygotes.

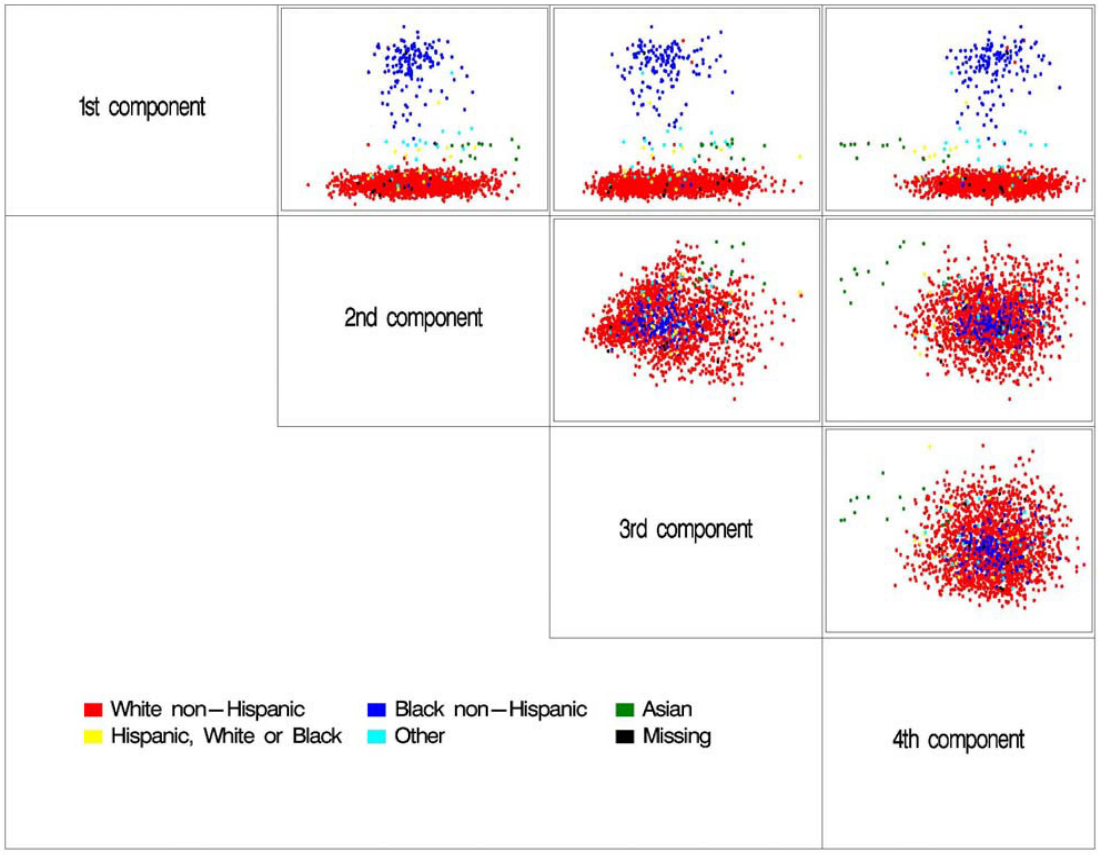

Figure 2

Matrix of scatterplots for four population structure principal components by self-reported race.

Note: Population structure principal components analysis based on 1,981 participants and 2,517 SNPs including imputed genotypes; for each scatterplot, vertical axis corresponds to the component listed in diagonal element to the left of the plot, and horizontal axis corresponds to the component listed in diagonal underneath the plot; results suggest that the first component differentiated white non-Hispanic and black non-Hispanic from other samples, while the fourth component helped to further differentiate Asian from other samples; these four population structure principal components were used as covariates in association analyses.

genotyped, we excluded 44 due to call rate < 90% and 22 due to study ineligibility; thus 1,981 participants were analyzed here. We assessed departures from Hardy-Weinberg equilibrium (HWE) among white non-Hispanic controls using a Pearson goodness-of-fit test or, for SNPs with a minor allele frequency (MAF) < 5%, a Fisher exact test (Weir, 1996). Of 1,152 total attempted SNPs, we excluded 15 due to call rate < 90%, nine due to poor clustering, one due to unresolved replicate errors, 64 due to MAF < 0.01, and eleven due to HWE p value < 0.0001. In the 8q24.21.a and 9p24.1.b regions, 37 SNPs were attempted, and two failed (*POU5F1P1* tagSNP rs7002225 and prostate cancer-associated SNP rs7000448 (Ghoussaini et al., 2008). Estimates of pair-wise linkage disequilibrium (LD) among genotyped SNPs were obtained for self-reported white non-Hispanic control participants using Haploview v. 4.1 (Barrett et al., 2005).

Statistical Methods

Data were summarized using frequencies and percents for categorical variables and means and standard deviations for continuous variables; we compared distributions of demographic variables across case status using chi-square tests and t-tests, as appropriate. Individual SNP associations with ovarian cancer risk were assessed using logistic regression models, in which ORs and 95% CIs were estimated. Separate analyses were carried out using all ovarian cancer cases (N = 940), all invasive cases (N = 749), and all serous invasive cases (N = 452). Primary tests of association assumed an ordinal (log-additive) effect using simple tests for trend. Association analyses included adjustment for the following covariates: study site, age, body mass index (BMI), hormone therapy, oral contraceptive use, number of live births, age at first live birth, geographic region, and principal components which accounted for the possibility of population stratification using an approach similar to that described previously (Price et al., 2006). Briefly, population structure principal components were created using 2,517 SNPs from this and prior genotyping panels (Kelemen et al., 2008); scatter-plot matrices by self-reported race indicated that the first four principal components reasonably approximated racial differences across individuals and were thus included as covariates in all models (see Figure 2). No adjust-

ments were made for multiple testing; all statistical tests were two-sided and, unless otherwise indicated, analyses were carried out using SAS software (SAS Institute, Inc., Cary, NC).

Results

Demographic, lifestyle, reproductive, and tumor characteristics of 940 epithelial ovarian cancer cases and 1,041 controls are described in Table 2. In general, the expected distributions of risk factors were observed: a larger proportion of cases than controls had a first or second degree relative with ovarian cancer, had not used oral contraceptives, had used postmenopausal hormone therapy, and were nulliparous. Overall, 80% of tumors were invasive and 20% were borderline; the distribution of histologic subtypes was 61% serous, 14% endometrioid, 10% mucinous, 6% clear cell, and 9% other histologies. LD (defined as $r^2 \geq 0.65$) was observed between six pairs of 8q24.21.a SNPs and four pairs of 9p24.1.b SNPs in these study populations.

No associations between SNP genotypes and ovarian cancer risk were seen in the current study (see Table 3). In the 8q24.21.a region, SNPs previously associated with increased risk (rs10505477 and rs6983267) revealed invasive cancer per-allele ORs of 0.95 (95% CI 0.82–1.09, p trend = 0.46) and 0.97 (95% CI 0.84–1.12, p trend = 0.69), respectively. Thus, these results contradict prior findings from the first report (OR 1.14, 95% CI 1.04–1.23, p trend < 0.01; OR 1.11, 95% CI 1.03–1.20, p trend < 0.01, respectively; Ghoussaini et al., 2008), but are consistent with other null results for rs6983267 (OR 1.00, 95% CI 0.81–1.23, p trend = 0.10) (Wokolorczyk et al., 2008). Our null invasive cancer results for

Table 2

Characteristics of Study Participants

	Mayo Clinic			Duke University		
	Cases (*N* = 401)	Controls (*N* = 469)	*p* value	Cases (*N* = 539)	Controls (*N* = 572)	*p* value
Age						
Mean (*SD*) yrs	59.9 (13.27)	60 (12.98)	0.88	54 (11.47)	54.5 (12.14)	0.48
Race						
White	386 (98%)	460 (98.9%)	0.61	453 (84.2%)	484 (84.6%)	0.71
African–American	3 (0.8%)	2 (0.4%)		70 (13.0%)	77 (13.5%)	
Asian	2 (0.5%)	2 (0.4%)		6 (1.1%)	3 (0.5%)	
Other	3 (0.8%)	1 (0.2%)		9 (1.7%)	8 (1.4%)	
Missing	7	4		1	0	
Body mass index						
< 23 kg/m^2	84 (21.8%)	109 (24.9%)	**0.03**	134 (25.5%)	142 (25.6%)	0.24
23–26 kg/m^2	87 (22.5%)	122 (27.9%)		117 (22.3%)	125 (22.5%)	
26–29 kg/m^2	99 (25.6%)	112 (25.6%)		105 (20.0%)	135 (24.3%)	
≥ 29 kg/m^2	116 (30.1%)	95 (21.7%)		169 (32.2%)	153 (27.6%)	
Missing	15	31		14	17	
Age at menarche						
< 12 years	54 (18.1%)	68 (15.8%)	0.58	133 (24.8%)	118 (20.6%)	0.36
12 years	78 (26.1%)	100 (23.2%)		153 (28.5%)	164 (28.7%)	
13 years	81 (27.1%)	127 (29.5%)		136 (25.3%)	163 (28.5%)	
≥ 14 years	86 (28.8%)	136 (31.6%)		115 (21.4%)	127 (22.2%)	
Missing	102	38		2	0	
Oral contraceptive use						
Never	178 (47.5%)	166 (38.4%)	**<0.001**	185 (35%)	180 (31.7%)	0.26
1–48 months	100 (26.7%)	92 (21.3%)		158 (29.9%)	161 (28.4%)	
≥ 48 months	97 (25.9%)	174 (40.3%)		186 (35.2%)	226 (39.9%)	
Missing	26	37		10	5	
Hormone therapy						
Never	241 (63.3%)	249 (58.9%)	0.44	193 (37.5%)	339 (62.8%)	**<0 .001**
1–60 months	65 (17.1%)	79 (18.7%)		206 (40.1%)	106 (19.6%)	
≥ 60 months	75 (19.7%)	95 (22.5%)		115 (22.4%)	95 (17.6%)	
Missing	20	46		25	32	
Parity, *n*/Age at first birth, yrs						
Nulliparous	71 (18.3%)	66 (15.0%)	0.09	115 (21.4%)	75 (13.1%)	**<0.001**
1–2 / ≤ 20 yrs	29 (7.5%)	25 (5.7%)		75 (13.9%)	72 (12.6%)	
1–2 / > 20 yrs	105 (27.1%)	132 (30.0%)		191 (35.5%)	233 (40.7%)	
≥ 3 / ≤ 20 yrs	73 (18.8%)	64 (14.5%)		82 (15.2%)	91 (15.9%)	
≥ 3 / > 20 yrs	110 (28.4%)	153 (34.8%)		75 (13.9%)	101 (17.7%)	
Missing	13	29		1	0	

(continued over)

Table 2 (continued)

Characteristics of Study Participants

	Mayo Clinic			Duke University		
	Cases (*N* = 401)	Controls (*N* = 469)	*p* value	Cases (*N* = 539)	Controls (*N* = 572)	*p* value
Ovarian cancer family history						
Yes	51 (13.1%)	33 (7.4%)	**0.01**	48 (8.9%)	31 (5.4%)	**0.02**
No	338 (86.9%)	411 (92.6%)		491 (91.1%)	541 (94.6%)	
Missing	12	25		0	0	
Ovarian or breast cancer family history						
Yes	168 (43.2%)	189 (42.6%)	0.86	202 (37.5%)	195 (34.1%)	0.24
No	221 (56.8%)	255 (57.4%)		337 (62.5%)	377 (65.9%)	
Missing	12	25		0	0	
Smoking, pack years						
None	236 (64.8%)	285 (68.3%)	0.28	300 (57.6%)	293 (53.4%)	0.37
≤ 20	72 (19.8%)	84 (20.1%)		132 (25.3%)	150 (27.3%)	
> 20	56 (15.4%)	48 (11.5%)		89 (17.1%)	106 (19.3%)	
Missing	37	52		18	23	
	Mayo Clinic Cases (*N* = 401)			Duke University Cases (*N* = 539)		
Histology						
Serous	242 (60.5%)			331 (61.8%)		
Mucinous	28 (7.0%)			64 (11.9%)		
Endometrioid	65 (16.3%)			65 (12.1%		
Clear Cell	23 (5.8%)			33 (6.2%)		
Other	42 (10.5%)			43 (8.0%)		
Missing	1			3		
Stage						
I	102 (25.9%)			189 (35.6%)		
II	29 (7.4%)			41 (7.7%)		
III	205 (52.0%)			281 (52.9%)		
IV	58 (14.7%)			20 (3.8%)		
Missing	7			8		
Grade						
0	62 (15.7%)			127 (25.3%)		
1	13 (3.3%)			52 (10.4%)		
2	42 (10.7%)			121 (24.2%)		
3	156 (39.6%)			193 (38.5%)		
4	121 (30.7%)			8 (1.6%)		
Missing	7			38		
Behavior						
Invasive	339 (84.5%)			410 (76.2%)		
Borderline	62 (15.5%)			128 (23.8%)		
Missing	0			1		

Note: Data are counts (percentage) unless otherwise indicated; *p* values are from *t* test for continuous variables and Chi square test for categorical variables; family history indicates first or second degree relative.

8q24.21.a SNPs rs13281615 (OR 0.92, 95% CI 0.74–1.15, *p* trend = 0.48), and rs1447295 (OR 0.97, 95% CI 0.85–1.12, *p* trend = 0.72) are also consistent with results from prior studies (Ghoussaini et al., 2008; Song et al., 2009a; Wokolorczyk et al., 2009). Analyses also failed to reveal associations between any of the 23 selected 8q24 SNPs and risk of serous invasive disease. To examine potential heterogeneity due to sample characteristics or statistical methods, we repeated analyses restricted to self-reported white non-Hispanic women and used minimal covariate adjustments. No suggestion of association with increased risk was observed for previously-reported SNPs (see Table 4) or for any other 8q24 SNPs (data not shown). In the 9p24 region, no SNPs were associated with risk of ovarian cancer overall or with invasive or invasive serous disease (*p* values > 0.10).

Discussion

Association studies have highlighted the undisputed importance of variation in the 8q24.21.a chromosomal region in etiology of breast cancer, prostate cancer, and colorectal cancer (Garcia-Closas et al., 2008; Ghoussaini et al., 2008; Gruber et al., 2007; Gudmundsson et al., 2007; Haiman et al., 2007; Poynter et al., 2007; Salinas et al., 2008; Schumacher et al., 2007; Suuriniemi et al., 2007; Tenesa et al., 2008; Tuupanen et al., 2009; Yeager et al., 2007; Zanke et al., 2007). Growing evidence, at least in colorectal cancer, suggests that rs6983267 lies

Table 3

8q24 and 9p24 Polymorphisms and Covariate-Adjusted Risk of Epithelial Ovarian Cancer

				All cases		Invasive cases		Invasive serous cases	
				Ordinal model OR (95% CI)		Ordinal model OR (95% CI)		Ordinal model OR (95% CI)	
Region	rsid	kb to next	MAF	per-allele	*p* value	per-allele	*p* value	per-allele	*p* value
8q24.21.a	rs10808550	481.9	0.16	0.97 (0.81–1.16)	0.73	0.96 (0.79–1.16)	0.68	0.92 (0.74–1.16)	0.50
	rs13254738	2.5	0.33	1.01 (0.88–1.17)	0.84	0.98 (0.85–1.14)	0.83	0.96 (0.80–1.15)	0.65
	rs6983561	18.0	0.07	0.93 (0.70–1.23)	0.61	1.00 (0.74–1.36)	0.98	0.86 (0.60–1.25)	0.43
	rs16901979	230.7	0.07	0.95 (0.72–1.26)	0.73	1.04 (0.76–1.41)	0.82	0.87 (0.59–1.26)	0.45
	rs13281615	51.5	0.40	1.01 (0.88–1.15)	0.90	0.97 (0.85–1.12)	0.72	0.94 (0.80–1.11)	0.48
	rs16902149	0.3	0.07	1.22 (0.94–1.57)	0.13	1.28 (0.98–1.68)	0.07	1.14 (0.82–1.59)	0.42
	rs10505477	2.1	0.48	0.99 (0.87–1.13)	0.87	0.95 (0.82–1.09)	0.46	0.90 (0.76–1.06)	0.22
	rs10808555	1.9	0.33	0.99 (0.86–1.14)	0.93	0.99 (0.86–1.15)	0.92	1.11 (0.93–1.32)	0.25
	rs10505475	1.8	0.06	1.11 (0.85–1.45)	0.46	1.11 (0.83–1.48)	0.47	1.15 (0.82–1.60)	0.43
	rs6983267	10.3	0.47	1.01 (0.88–1.15)	0.90	0.97 (0.84–1.12)	0.69	0.92 (0.78–1.09)	0.35
	rs10956368	4.4	0.41	1.02 (0.89–1.16)	0.80	1.07 (0.93–1.24)	0.33	1.12 (0.95–1.33)	0.17
	rs4871789	0.6	0.50	1.00 (0.88–1.14)	0.99	0.95 (0.83–1.09)	0.46	0.94 (0.80–1.11)	0.47
	rs6998061	0.1	0.40	0.98 (0.85–1.12)	0.74	0.93 (0.81–1.08)	0.34	0.92 (0.78–1.09)	0.35
	rs13274084	0.5	0.13	1.01 (0.83–1.22)	0.92	1.02 (0.84–1.26)	0.82	0.94 (0.74–1.21)	0.64
	rs9297754	5.7	0.22	0.99 (0.84–1.16)	0.92	1.03 (0.87–1.22)	0.71	1.05 (0.86–1.28)	0.66
	rs7005829	5.2	0.28	0.99 (0.86–1.14)	0.90	1.01 (0.87–1.18)	0.88	1.01 (0.85–1.21)	0.87
	rs9297756	0.8	0.14	0.98 (0.81–1.18)	0.82	1.00 (0.82–1.21)	0.98	1.08 (0.86–1.36)	0.49
	rs6999921	130.0	0.09	1.00 (0.79–1.25)	0.98	1.01 (0.79–1.28)	0.96	0.92 (0.68–1.24)	0.59
	rs12334695	4.2	0.38	0.92 (0.81–1.05)	0.20	0.95 (0.82–1.09)	0.45	0.94 (0.80–1.11)	0.50
	rs10109622	3.5	0.25	0.97 (0.83–1.13)	0.68	0.98 (0.83–1.14)	0.76	0.98 (0.80–1.19)	0.82
	rs10094059	3.9	0.26	0.97 (0.84–1.12)	0.69	0.94 (0.81–1.10)	0.45	0.95 (0.79–1.14)	0.57
	rs9643221	19.6	0.21	0.97 (0.82–1.14)	0.68	0.92 (0.77–1.09)	0.34	0.94 (0.77–1.15)	0.54
	rs1447295	n.a.	0.12	0.96 (0.78–1.18)	0.72	0.92 (0.74–1.15)	0.48	0.92 (0.71–1.20)	0.53
9p24.1.b	rs12237914	4.0	0.38	1.09 (0.96–1.25)	0.19	1.08 (0.94–1.24)	0.30	1.11 (0.94–1.31)	0.23
	rs17705436	14.4	0.22	0.98 (0.84–1.15)	0.85	0.99 (0.84–1.17)	0.88	1.09 (0.90–1.32)	0.40
	rs10491835	3.6	0.17	1.03 (0.87–1.22)	0.75	1.02 (0.85–1.22)	0.85	0.95 (0.76–1.18)	0.63
	rs3847262	4.0	0.06	1.13 (0.87–1.48)	0.36	1.21 (0.91–1.60)	0.18	0.93 (0.65–1.32)	0.67
	rs721352	2.9	0.34	1.00 (0.88–1.15)	0.94	1.01 (0.87–1.17)	0.89	1.01 (0.85–1.20)	0.91
	rs7850988	22.6	0.26	0.98 (0.85–1.14)	0.81	0.99 (0.85–1.15)	0.86	1.06 (0.89–1.27)	0.50
	rs16924434	7.3	0.11	0.89 (0.72–1.10)	0.27	0.91 (0.73–1.13)	0.40	1.02 (0.80–1.32)	0.85
	rs719725	42.6	0.37	0.92 (0.81–1.05)	0.24	0.93 (0.81–1.07)	0.33	1.04 (0.88–1.22)	0.66
	rs7865955	208.4	0.45	0.97 (0.85–1.10)	0.62	0.98 (0.86–1.13)	0.81	1.02 (0.87–1.20)	0.80
	rs1821892	361.0	0.15	1.04 (0.87–1.25)	0.65	1.01 (0.83–1.22)	0.93	0.95 (0.76–1.19)	0.67
	rs1340513	69.3	0.25	0.97 (0.83–1.12)	0.66	0.97 (0.83–1.14)	0.73	0.96 (0.80–1.16)	0.69
	rs1407856	n.a.	0.17	0.96 (0.81–1.15)	0.68	1.01 (0.84–1.21)	0.93	1.10 (0.90–1.36)	0.36

Note: Kb to previous represents distance in kilo-base pairs between SNPs; MAF, minor allele frequency among controls; adjusted for study site, population structure, age area of residence, body mass index, hormone therapy use, oral contraceptive use, parity, and age at first birth.

in a transcriptional enhancer and that the risk G allele increases binding of the transcription factor TCF4 (also called TCF7L2) (Pomerantz et al., 2009; Tuupanen et al., 2009). TCF4 interacts with β-catenin to activate transcription of Wnt target genes, thus a connection between inherited associations and cancer-related functional consequences including possible interaction with the *MYC* promoter (335 kb downstream) is emerging (Pomerantz et al., 2009; Tuupanen et al., 2009). Somatic amplifications at 8q are trademarks of prostate tumors (Cher et al., 1996; van Duin et al., 2005; Visakorpi et al., 1995), indicating that 8q24 risk variants may lead to amplification of a larger chromosomal region, which contains the protooncogene *MYC* (Haiman et al., 2007; Harismendy & Frazer, 2009; Sole et al., 2008; Witte, 2007). The 9p24.1.b chromosomal region has also been shown to contain colorectal cancer associated SNPs (Poynter et al., 2007; Zanke et al., 2007), although mechanisms are unknown.

In ovarian cancer, seven 8q24.21.a SNPs (rs13254738, rs6983561, rs16901979, rs13281615, rs10505477, rs6983267, and rs1447295) have been evaluated in more than one report, including the current analysis (Ghoussaini et al., 2008; Song et al., 2009a; Wokolorczyk et al., 2008; Wokolorczyk et al.,

Table 4

8q24.21.a SNPs and Risk of Invasive Ovarian Cancer in Self-Reported White Non-Hispanic Women Across Multiple Studies

		Ghoussaini et al., 2008		Wokolorczyk et al., 2008		Wokolorczyk et al., 2009		Song et al., 2009a		Current Sample	
	N Cases	1,975		618		274		2,502		671	
	N Controls	3,411		1,019		682		3,892		939	
	Studies	MAL, SEA, STA, UKO		POL1		POL1		AOS, MAL, SEA, STA, UKO, USC		MAY, NCO	
	Adjustments	Study site		None		None		Study site		Study site	
rsid	kb to next	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs13254738	2.5	1.02 (0.94–1.11)	0.64	—	—	—	—	—	—	0.98 (0.84–1.14)	0.77
rs6983561	18.0	0.90 (0.72–1.13)	0.36	—	—	—	—	—	—	1.13 (0.77–1.66)	0.53
rs16901979	230.7	0.89 (0.71–1.11)	0.30	—	—	—	—	—	—	1.15 (0.78–1.69)	0.48
rs13281615	51.8	0.99 (0.91–1.07)	0.75	—	—	—	—	0.99 (0.92–1.06)	0.69	1.00 (0.87–1.15)	1.00
rs10505477	5.9	**1.14 (1.04–1.23)**	**< 0.01**	—	—	—	—	—	—	0.94 (0.82–1.08)	0.40
rs6983267	71.7	**1.11 (1.03–1.20)**	**< 0.01**	1.00 (0.81–1.23)	0.10	—	—	—	—	0.95 (0.83–1.09)	0.46
rs1447295	n.a.	1.07 (0.93–1.22)	0.35	—	—	1.00 (0.70–1.30)	1.00	—	—	1.00 (0.79– 1.27)	0.98

Note: Citations provided in References (Ghoussaini et al., 2008; Song et al., 2009a; Wokolorczyk et al., 2008; Wokolorczyk et al., 2009); study names based on Ovarian Cancer Association Consortium study acronyms: MAL, Malignant Ovarian Cancer Study (Copenhagen, Denmark); SEA, SEARCH Cambridge UK (UK); STA, Genetic Epidemiology of Ovarian Cancer Study (California, USA); UKO, United Kingdom Ovarian Cancer Population Study (UK); POL1, Polish Ovarian Cancer Study (Poland); AOS, Australian Ovarian Cancer Study (Australia); USC, Los Angeles County Case-Control Studies of Ovarian Cancer (Los Angeles, USA); MAY, Mayo Clinic Ovarian Cancer Study (Upper Midwest, USA); NCO, North Carolina Ovarian Cancer Study (North Carolina, USA); kb to next represents distance in kilo-base pairs between SNPs; per-allele ORs are shown; pair-wise $r^2 > 0.90$ indicated by dotted lines (based on self-reported white non-Hispanic controls in current analysis; rs6983561-rs16901979 r^2=0.98, rs6983267-rs10505477 r^2= 0.91); all other pair-wise $r^2 < 0.67$; only SNPs analyzed in more than one report are shown.

2009). The first association study of 1,975 invasive ovarian cancer cases and 3,411 controls found evidence of the 8q24 ovarian cancer susceptibility SNPs rs10505477, rs10808556, and rs6983267 (Ghoussaini et al., 2008), but another examination of 618 invasive cases and 1,019 controls found no association with rs6983267 (OR 1.00, 95% CI 0.75–1.30, p trend = 0.10) (Wokolorczyk et al., 2008) and other reports at 8q24 SNPs were null (Ghoussaini et al., 2008; Song et al., 2009a; Wokolorczyk et al., 2008; Wokolorczyk et al., 2009). Additionally, no endometrial cancer 8q24 susceptibility loci were revealed in a recent study (Setiawan et al., 2007), suggesting that not all cancers will have an 8q24 association. The 9p24 region has not yet been targeted in gynecologic cancer studies; our data suggest that additional study of this region in ovarian cancer is not warranted.

This analysis evaluated the largest number of 8q24.21.a SNPs (N = 23) in ovarian cancer to date. Although associations were non-significant, it is also noteworthy that rs10505477 and rs6983267 risk estimates were close to 1.0, consistent with a prior report of rs6983267 (Wokolorczyk et al., 2008), but contradicting the larger first report (Ghoussaini et al., 2008). Our smaller sample size is a concern; however, current risk estimates were also inconsistent with increased risk. Differing analytical approaches and study populations could also contribute to the opposing 8q24.21.a results; yet, our analyses of invasive cancer in white non-Hispanic women with study site as the only covariate also yielded no suggestion of association with risk of ovarian cancer. These results indicate that differing covariate adjustments, including our adjustment for population structure, do not account for the contradictory results. Based on data from the Ovarian Cancer Association Consortium (Song et al., 2006), cases recruited at the largest site in the first report may have longer survival times than other studies. Thus, SNPs in 8q24.21.a may confer risk of invasive ovarian cancer only among women with longer survival times; however, this situation is unlikely. Additionally, it is likely that case populations have varied histological distributions (Goode et al., 2009). Although risk estimates from other study populations have not been reported by histological subtype, our results for women with serous disease were also null and nonsuggestive. Finally, a true association may exist only between ovarian cancer risk and rs10808556, which we did not assess. However, because $r^2 \geq 0.65$ with this SNP and both rs10505477 and rs6983267 (Ghoussaini et al., 2008), a modest signal would likely have been detected in our analysis.

In conclusion, SNPs in 9p24.1.b are not worthy of follow-up in ovarian cancer, and SNPs in 8q24.21.a are increasingly unlikely to represent ovarian cancer susceptibility alleles. Thus, much remains to be learned about the cancer site-specific role that variants in these regions play in carcinogenic processes, and the search for additional ovarian cancer loci must continue.

Acknowledgments

This work was supported by the National Cancer Institute [R01 CA122443, R01 CA88868, and R01 CA76016], the Ovarian Cancer Research Fund, and the Mayo Foundation. We thank Mr. Matt Kosel for statistical analysis, Dr. Paul P.D. Pharoah for advice on SNP selection, Ms. Ashley Pitzer and Ms. Karin Goodman for subject recruitment, and Ms. Katelyn Goodman for assistance with preparation of Tables and Figures.

References

Antoniou, A., Pharoah, P. D., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., Loman, N., Olsson, H., Johannsson, O., Borg, A., Pasini, B., Radice, P., Manoukian, S., Eccles, D. M., Tang, N., Olah, E., Anton-Culver, H., Warner, E., Lubinski, J., Gronwald, J., Gorski, B., Tulinius, H., Thorlacius, S., Eerola, H., Nevanlinna, H., Syrjakoski, K., Kallioniemi, O. P., Thompson, D., Evans, C., Peto, J., Lalloo, F., Evans, D. G., & Easton, D. F. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: A combined analysis of 22 studies. *American Journal of Human Genetics, 72*, 1117–1130.

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics, 21*, 263–265.

Cher, M. L., Bova, G. S., Moore, D. H., Small, E. J., Carroll, P. R., Pin, S. S., Epstein, J. I., Isaacs, W. B., & Jensen, R. H. (1996). Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization and allelotyping. *Cancer Research, 56*, 3091–3102.

Cunningham, J. M., Sellers, T. A., Schildkraut, J. M., Fredericksen, Z. S., Vierkant, R. A., Kelemen, L. E., Gadre, M., Phelan, C. M., Huang, Y., Meyer, J. G., Pankratz, V. S., & Goode, E. L. (2008). Performance of amplified DNA in an Illumina GoldenGate BeadArray assay. *Cancer Epidemiology Biomarkers & Prevention, 17*, 1781–1789.

Fasching, P. A., Gayther, S., Pearce, L., Schildkraut, J. M., Goode, E., Thiel, F., Chenevix-Trench, G., Chang-Claude, J., Wang-Gohrke, S., Ramus, S., Pharoah, P., & Berchuck, A. (2009). Role of genetic polymorphisms and ovarian cancer susceptibility. *Molecular Oncology, 3*, 171–181.

Garcia-Closas, M., Hall, P., Nevanlinna, H., Pooley, K., Morrison, J., Richesson, D. A., Bojesen, S. E., Nordestgaard, B. G., Axelsson, C. K., Arias, J. I., Milne, R. L., Ribas, G., Gonzalez-Neira, A., Benitez, J., Zamora, P., Brauch, H., Justenhoven, C., Hamann, U., Ko, Y. D., Bruening, T., Haas, S., Dork, T., Schurmann, P., Hillemanns, P., Bogdanova, N., Bremer, M., Karstens, J. H., Fagerholm, R., Aaltonen, K., Aittomaki, K., von Smitten, K., Blomqvist, C., Mannermaa, A., Uusitupa, M., Eskelinen, M., Tengstrom, M., Kosma, V. M., Kataja, V., Chenevix-Trench, G., Spurdle, A. B., Beesley, J., Chen, X., Australian Ovarian Cancer Management, G., Kathleen Cuningham Foundation Consortium For Research Into Familial Breast, C., Devilee, P., van Asperen, C. J., Jacobi,

C. E., Tollenaar, R. A., Huijts, P. E., Klijn, J. G., Chang-Claude, J., Kropp, S., Slanger, T., Flesch-Janys, D., Mutschelknauss, E., Salazar, R., Wang-Gohrke, S., Couch, F., Goode, E. L., Olson, J. E., Vachon, C., Fredericksen, Z. S., Giles, G. G., Baglietto, L., Severi, G., Hopper, J. L., English, D. R., Southey, M. C., Haiman, C. A., Henderson, B. E., Kolonel, L. N., Le Marchand, L., Stram, D. O., Hunter, D. J., Hankinson, S. E., Cox, D. G., Tamimi, R., Kraft, P., Sherman, M. E., Chanock, S. J., Lissowska, J., Brinton, L. A., Peplonska, B., Klijn, J. G., Hooning, M. J., Meijers-Heijboer, H., Collee, J. M., van den Ouweland, A., Uitterlinden, A. G., Liu, J., Lin, L. Y., Yuqing, L., Humphreys, K., Czene, K., Cox, A., Balasubramanian, S. P., Cross, S. S., Reed, M. W., Blows, F., Driver, K., Dunning, A., Tyrer, J., Ponder, B. A., Sangrajrang, S., Brennan, P., McKay, J., Odefrey, F., Gabrieau, V., Sigurdson, A., Doody, M., Struewing, J. P., Alexander, B., Easton, D. F., & Pharoah, P. D. (2008). Heterogeneity of breast cancer associations with five susceptibility Loci by clinical and pathological characteristics. *PLoS Genetics, 4*, e1000054.

Gayther, S. A., Song, H., Ramus, S. J., Kjaer, S. K., Whittemore, A. S., Quaye, L., Tyrer, J., Shadforth, D., Hogdall, E., Hogdall, C., Blaeker, J., DiCioccio, R., McGuire, V., Webb, P. M., Beesley, J., Green, A. C., Whiteman, D. C., Goodman, M. T., Lurie, G., Carney, M. E., Modugno, F., Ness, R. B., Edwards, R. P., Moysich, K. B., Goode, E. L., Couch, F. J., Cunningham, J. M., Sellers, T. A., Wu, A. H., Pike, M. C., Iversen, E. S., Marks, J. R., Garcia-Closas, M., Brinton, L., Lissowska, J., Peplonska, B., Easton, D. F., Jacobs, I., Ponder, B. A., Schildkraut, J., Pearce, C. L., Chenevix-Trench, G., Berchuck, A., & Pharoah, P. D. (2007). Tagging single nucleotide polymorphisms in cell cycle control genes and susceptibility to invasive epithelial ovarian cancer. *Cancer Research, 67*, 3027–3035.

Ghoussaini, M., Song, H., Koessler, T., Al Olama, A. A., Kote-Jarai, Z., Driver, K. E., Pooley, K. A., Ramus, S. J., Kjaer, S. K., Hogdall, E., DiCioccio, R. A., Whittemore, A. S., Gayther, S. A., Giles, G. G., Guy, M., Edwards, S. M., Morrison, J., Donovan, J. L., Hamdy, F. C., Dearnaley, D. P., Ardern-Jones, A. T., Hall, A. L., O'Brien, L. T., Gehr-Swain, B. N., Wilkinson, R. A., Brown, P. M., Hopper, J. L., Neal, D. E., Pharoah, P. D., Ponder, B. A., Eeles, R. A., Easton, D. F., & Dunning, A. M. (2008). Multiple loci with different cancer specificities within the 8q24 gene desert. *Journal of the National Cancer Institute, 100*, 962–966.

Goode, E. L., Fridley, B. L., Vierkant, R. A., Cunningham, J. M., Phelan, C. M., Anderson, S., Rider, D. N., White, K. L., Pankratz, V. S., Song, H., Hogdall, E., Kjaer, S. K., Whittemore, A. S., DiCioccio, R., Ramus, S. J., Gayther, S. A., Schildkraut, J. M., Pharaoh, P. P., & Sellers, T. A. (2009). Candidate gene analysis using imputed genotypes: cell cycle single-nucleotide polymorphisms and ovarian cancer risk. *Cancer Epidemiology Biomarkers & Prevention, 18*, 935–944.

Gruber, S. B., Moreno, V., Rozek, L. S., Rennerts, H. S., Lejbkowicz, F., Bonner, J. D., Greenson, J. K., Giordano, T. J., Fearson, E. R., & Rennert, G. (2007). Genetic variation in 8q24 associated with risk of colorectal cancer. *Cancer Biology and Therapy, 6*, 1143–1147.

Gudmundsson, J., Sulem, P., Manolescu, A., Amundadottir, L. T., Gudbjartsson, D., Helgason, A., Rafnar, T., Bergthorsson, J. T., Agnarsson, B. A., Baker, A., Sigurdsson, A., Benediktsdottir, K. R., Jakobsdottir, M., Xu, J., Blondal, T., Kostic, J., Sun, J., Ghosh, S., Stacey, S. N., Mouy, M., Saemundsdottir, J., Backman, V. M., Kristjansson, K., Tres, A., Partin, A. W., Albers-Akkers, M. T., Godino-Ivan Marcos, J., Walsh, P. C., Swinkels, D. W., Navarrete, S., Isaacs, S. D., Aben, K. K., Graif, T., Cashy, J., Ruiz-Echarri, M., Wiley, K. E., Suarez, B. K., Witjes, J. A., Frigge, M., Ober, C., Jonsson, E., Einarsson, G. V., Mayordomo, J. I., Kiemeney, L. A., Isaacs, W. B., Catalona, W. J., Barkardottir, R. B., Gulcher, J. R., Thorsteinsdottir, U., Kong, A., & Stefansson, K. (2007). Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nature Genetics, 39*, 631–637.

Haiman, C. A., Patterson, N., Freedman, M. L., Myers, S. R., Pike, M. C., Waliszewska, A., Neubauer, J., Tandon, A., Schirmer, C., McDonald, G. J., Greenway, S. C., Stram, D. O., Le Marchand, L., Kolonel, L. N., Frasco, M., Wong, D., Pooler, L. C., Ardlie, K., Oakley-Girvan, I., Whittemore, A. S., Cooney, K. A., John, E. M., Ingles, S. A., Altshuler, D., Henderson, B. E., & Reich, D. (2007). Multiple regions within 8q24 independently affect risk for prostate cancer. *Nature Genetics, 39*, 638–644.

Harismendy, O., & Frazer, K. A. (2009). Elucidating the role of 8q24 in colorectal cancer. *Nature Genetics, 41*, 868–869.

Kelemen, L. E., Sellers, T. A., Schildkraut, J. M., Cunningham, J. M., Vierkant, R. A., Pankratz, V. S., Fredericksen, Z. S., Gadre, M. K., Rider, D. N., Liebow, M., & Goode, E. L. (2008). Genetic variation in the one-carbon transfer pathway and ovarian cancer risk. *Cancer Research, 68*, 2498–2506.

Kiemeney, L. A., Thorlacius, S., Sulem, P., Geller, F., Aben, K. K., Stacey, S. N., Gudmundsson, J., Jakobsdottir, M., Bergthorsson, J. T., Sigurdsson, A., Blondal, T., Witjes, J. A., Vermeulen, S. H., Hulsbergen-van de Kaa, C. A., Swinkels, D. W., Ploeg, M., Cornel, E. B., Vergunst, H., Thorgeirsson, T. E., Gudbjartsson, D., Gudjonsson, S. A., Thorleifsson, G., Kristinsson, K. T., Mouy, M., Snorradottir, S., Placidi, D., Campagna, M., Arici, C., Koppova, K., Gurzau, E., Rudnai, P., Kellen, E., Polidoro, S., Guarrera, S., Sacerdote, C., Sanchez, M., Saez, B., Valdivia, G., Ryk, C., de Verdier, P., Lindblom, A., Golka, K., Bishop, D. T., Knowles, M. A., Nikulasson, S., Petursdottir, V., Jonsson, E., Geirsson, G., Kristjansson, B., Mayordomo, J. I., Steineck, G., Porru, S., Buntinx, F., Zeegers, M. P., Fletcher, T., Kumar, R., Matullo, G., Vineis, P., Kiltie, A. E., Gulcher, J. R., Thorsteinsdottir, U., Kong, A., Rafnar, T., & Stefansson, K. (2008). Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nature Genetics, 40*, 1307–1312.

Morch, L. S., Lokkegaard, E., Andreasen, A. H., Kruger-Kjaer, S., & Lidegaard, O. (2009). Hormone Therapy and Ovarian Cancer. *JAMA, 302*, 298–305.

Oliphant, A., Barker, D. L., Stuelpnagel, J. R., & Chee, M. S. (2002). BeadArray technology: enabling an accurate, cost-effective approach to high-throughput genotyping. *Biotechniques, Suppl*, 56–58, 60–51.

Pearce, C. L., Wu, A. H., Gayther, S. A., Bale, A. E., Beck, P. A., Beesley, J., Chanock, S., Cramer, D. W., Dicioccio, R., Edwards, R., Fredericksen, Z. S., Garcia-Closas, M., Goode, E. L., Green, A. C., Hartmann, L. C., Hogdall, E., Kjaer, S. K., Lissowska, J., McGuire, V., Modugno, F., Moysich, K., Ness, R. B., Ramus, S. J., Risch, H. A., Sellers, T. A., Song, H., Stram, D. O., Terry, K. L., Webb, P. M., Whiteman, D. C., Whittemore, A. S., Zheng, W., Pharoah, P. D., Chenevix-Trench, G., Pike, M. C., Schildkraut, J., Berchuck, A., & on behalf of the Ovarian Cancer Association Consortium (OCAC). (2008). Progesterone receptor variation and risk of ovarian cancer is limited to the invasive endometrioid subtype: results from the ovarian cancer association consortium pooled analysis. *British Journal of Cancer, 98*, 282–288.

Pharoah, P. D., & Ponder, B. A. (2002). The genetics of ovarian cancer. *Best Practice and Research: Clinical Obstetrics and Gynaecology, 16*, 449–468.

Pomerantz, M. M., Ahmadiyeh, N., Jia, L., Herman, P., Verzi, M. P., Doddapaneni, H., Beckwith, C. A., Chan, J. A., Hills, A., Davis, M., Yao, K., Kehoe, S. M., Lenz, H. J., Haiman, C. A., Yan, C., Henderson, B. E., Frenkel, B., Barretina, J., Bass, A., Tabernero, J., Baselga, J., Regan, M. M., Manak, J. R., Shivdasani, R., Coetzee, G. A., & Freedman, M. L. (2009). The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. *Nature Genetics, 41*, 882–884.

Poynter, J. N., Figueiredo, J. C., Conti, D. V., Kennedy, K., Gallinger, S., Siegmund, K. D., Casey, G., Thibodeau, S. N., Jenkins, M. A., Hopper, J. L., Byrnes, G. B., Baron, J. A., Goode, E. L., Tiirikainen, M., Lindor, N., Grove, J., Newcomb, P., Jass, J., Young, J., Potter, J. D., Haile, R. W., Duggan, D. J., & Le Marchand, L. (2007). Variants on 9p24 and 8q24 are associated with risk of colorectal cancer: results from the Colon Cancer Family Registry. *Cancer Research, 67*, 11128–11132.

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics, 38*, 904–909.

Ramus, S. J., Harrington, P. A., Pye, C., DiCioccio, R. A., Cox, M. J., Garlinghouse-Jones, K., Oakley-Girvan, I., Jacobs, I. J., Hardy, R. M., Whittemore, A. S., Ponder, B. A., Piver, M. S., Pharoah, P. D., & Gayther, S. A. (2007). Contribution of BRCA1 and BRCA2 mutations to inherited ovarian cancer. *Human Mutation, 28*, 1207–1215.

Salinas, C. A., Kwon, E., Carlson, C. S., Koopmeiners, J. S., Feng, Z., Karyadi, D. M., Ostrander, E. A., & Stanford, J. L. (2008). Multiple independent genetic variants in the 8q24 region are associated with prostate cancer risk. *Cancer Epidemiology Biomarkers & Prevention, 17*, 1203–1213.

Schildkraut, J. M., Goode, E. L., Clyde, M. A., Iversen, E. S., Moorman, P. G., Berchuck, A., Marks, J. R., Lissowska, J., Brinton, L., Peplonska, B., Cunningham, J. M., Vierkant, R. A., Rider, D. N., Chenevix-Trench, G., Webb, P. M., Beesley, J., Chen, X., Phelan, C., Sutphen, R., Sellers, T. A., Pearce, L., Wu, A. H., Van Den Berg, D., Conti, D., Elund, C. K., Anderson, R., Goodman, M. T., Lurie, G., Carney, M. E., Thompson, P. J., Gayther, S. A., Ramus, S. J., Jacobs, I., Kruger Kjaer, S., Hogdall, E., Blaakaer, J., Hogdall, C., Easton, D. F., Song, H., Pharoah, P. D., Whittemore, A. S., McGuire, V., Quaye, L., Anton-Culver, H., Ziogas, A., Terry, K. L., Cramer, D. W., Hankinson, S. E., Tworoger, S. S., Calingaert, B., Chanock, S., Sherman, M., & Garcia-Closas, M. (2009). Single nucleotide polymorphisms in the TP53 region and susceptibility to invasive epithelial ovarian cancer. *Cancer Research, 69*, 2349–2357.

Schumacher, F. R., Feigelson, H. S., Cox, D. G., Haiman, C. A., Albanes, D., Buring, J., Calle, E. E., Chanock, S. J., Colditz, G. A., Diver, W. R., Dunning, A. M., Freedman, M. L., Gaziano, J. M., Giovannucci, E., Hankinson, S. E., Hayes, R. B., Henderson, B. E., Hoover, R. N., Kaaks, R., Key, T., Kolonel, L. N., Kraft, P., Le Marchand, L., Ma, J., Pike, M. C., Riboli, E., Stampfer, M. J., Stram, D. O., Thomas, G., Thun, M. J., Travis, R., Virtamo, J., Andriole, G., Gelmann, E., Willett, W. C., & Hunter, D. J. (2007). A Common 8q24 Variant in Prostate and Breast Cancer from a Large Nested Case-Control Study. *Cancer Research, 67*, 2951–2956.

Sellers, T. A., Schildkraut, J. M., Pankratz, V. S., Vierkant, R. A., Fredericksen, Z. S., Olson, J. E., Cunningham, J. M., Taylor, W., Liebow, M., McPherson, C. P., Hartmann, L. C., Pal, T., & Adjei, A. A. (2005). Estrogen bioactivation, genetic polymorphisms, and ovarian cancer. *Cancer Epidemiology Biomarkers & Prevention, 14*, 2536–2543.

Setiawan, V. W., Ursin, G., Horn-Ross, P. L., Van Den Berg, D., Le Marchand, L., Henderson, B. E., Bernstein, L., & Haiman, C. A. (2007). Germ line variation at 8q24 and endometrial cancer risk. *Cancer Epidemiology Biomarkers & Prevention, 16*, 2166–2168.

Sole, X., Hernandez, P., de Heredia, M. L., Armengol, L., Rodriguez-Santiago, B., Gomez, L., Maxwell, C. A., Aguilo, F., Condom, E., Abril, J., Perez-Jurado, L., Estivill, X., Nunes, V., Capella, G., Gruber, S. B., Moreno, V., & Pujana, M. A. (2008). Genetic and genomic analysis modeling of germline c-MYC overexpression and cancer susceptibility. *BMC Genomics, 9*, 12.

Song, H., Ramus, S. J., Kjaer, S. K., DiCioccio, R. A., Chenevix-Trench, G., Pearce, C. L., Hogdall, E., Whittemore, A. S., McGuire, V., Hogdall, C., Blaakaer, J., Wu, A. H., Van Den Berg, D. J., Stram, D. O., Menon, U., Gentry-Maharaj, A., Jacobs, I. J., Webb, P. M., Beesley, J., Chen, X., Rossing, M. A., Doherty, J. A., Chang-Claude, J., Wang-Gohrke, S., Goodman, M. T., Lurie, G., Thompson, P. J., Carney, M. E., Ness, R. B., Moysich, K., Goode, E. L., Vierkant, R. A., Cunningham, J. M., Anderson, S., Schildkraut, J. M., Berchuck, A., Iversen, E. S., Moorman, P. G., Garcia-Closas, M., Chanock, S., Lissowska, J., Brinton, L., Anton-Culver, H., Ziogas, A., Brewster, W. R., Ponder, B. A., Easton, D. F., Gayther, S. A., & Pharoah, P. D. (2009). Association between invasive ovarian cancer susceptibility and 11 best candidate SNPs from breast cancer genome-wide association study. *Human Molecular Genetics, 18*, 2297–2304.

Song, H., Ramus, S. J., Quaye, L., Dicioccio, R. A., Tyrer, J., Lomas, E., Shadforth, D., Hogdall, E., Hogdall, C., McGuire, V., Whittemore, A. S., Easton, D. F., Ponder, B. A., Kjaer, S. K., Pharoah, P. D., & Gayther, S. A. (2006). Common variants in mismatch repair genes and risk of invasive ovarian cancer. *Carcinogenesis, 27*, 2235–2242.

Song, H., Ramus, S. J., Tyrer, J., Bolton, K. L., Gentry-Maharaj, A., Wozniak, E., Anton-Culver, H., Chang-Claude, J., Cramer, D. W., Dicioccio, R., Dork, T., Goode, E. L., Goodman, M. T., Schildkraut, J. M., Sellers, T., Baglietto, L., Beckmann, M. W., Beesley, J., Blaakaer, J., Carney, M. E., Chanock, S., Chen, Z., Cunningham, J. M., Dicks, E., Doherty, J. A., Durst, M., Ekici, A. B., Fenstermacher, D., Fridley, B. L., Giles, G., Gore, M. E., De Vivo, I., Hillemanns, P., Hogdall, C., Hogdall, E., Iversen, E. S., Jacobs, I. J., Jakubowska, A., Li, D., Lissowska, J., Lubinski, J., Lurie, G., McGuire, V., McLaughlin, J., Medrek, K., Moorman, P. G., Moysich, K., Narod, S., Phelan, C., Pye, C., Risch, H., Runnebaum, I. B., Severi, G., Southey, M., Stram, D. O., Thiel, F. C., Terry, K. L., Tsai, Y. Y., Tworoger, S. S., Van Den Berg, D. J., Vierkant, R. A., Wang-Gohrke, S., Webb, P. M., Wilkens, L. R., Wu, A. H., Yang, H., Brewster, W., Ziogas, A., Houlston, R., Tomlinson, I., Whittemore, A. S., Rossing, M. A., Ponder, B. A., Pearce, C. L., Ness, R. B., Menon, U., Kjaer, S. K., Gronwald, J., Garcia-Closas, M., Fasching, P. A., Easton, D. F., Chenevix-Trench, G., Berchuck, A., Pharoah, P. D., & Gayther, S. A. (2009). A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nature Genetics*.

Suuriniemi, M., Agalliu, I., Schaid, D. J., Johanneson, B., McDonnell, S. K., Iwasaki, L., Stanford, J. L., & Ostrander, E. A. (2007). Confirmation of a positive association between prostate cancer risk and a locus at chromosome 8q24. *Cancer Epidemiology Biomarkers & Prevention, 16*, 809–814.

Tenesa, A., Farrington, S. M., Prendergast, J. G., Porteous, M. E., Walker, M., Haq, N., Barnetson, R. A., Theodoratou, E., Cetnarskyj, R., Cartwright, N., Semple, C., Clark, A. J., Reid, F. J., Smith, L. A., Kavoussanakis, K., Koessler, T., Pharoah, P. D., Buch, S., Schafmayer, C., Tepel, J., Schreiber, S., Volzke, H., Schmidt, C. O., Hampe, J., Chang-Claude, J., Hoffmeister, M., Brenner, H., Wilkening, S., Canzian, F., Capella, G., Moreno, V., Deary, I. J., Starr, J. M., Tomlinson, I. P., Kemp, Z., Howarth, K., Carvajal-Carmona, L., Webb, E., Broderick, P., Vijayakrishnan, J., Houlston, R. S., Rennert, G., Ballinger, D., Rozek, L., Gruber, S. B., Matsuda, K., Kidokoro, T., Nakamura, Y., Zanke, B. W., Greenwood, C. M., Rangrej, J., Kustra, R., Montpetit, A., Hudson, T. J., Gallinger, S., Campbell, H., & Dunlop, M. G. (2008). Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. *Nature Genetics, 40*, 631–637.

Tuupanen, S., Turunen, M., Lehtonen, R., Hallikas, O., Vanharanta, S., Kivioja, T., Bjorklund, M., Wei, G., Yan, J., Niittymaki, I., Mecklin, J. P., Jarvinen, H., Ristimaki, A., Di-Bernardo, M., East, P., Carvajal-Carmona, L., Houlston, R. S., Tomlinson, I., Palin, K., Ukkonen, E., Karhu, A., Taipale, J., & Aaltonen, L. A. (2009). The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling. *Nature Genetics, 41*, 885–890.

van Duin, M., van Marion, R., Vissers, K., Watson, J. E., van Weerden, W. M., Schroder, F. H., Hop, W. C., van der Kwast, T. H., Collins, C., & van Dekken, H. (2005). High-resolution array comparative genomic hybridization of chromosome arm 8q: evaluation of genetic progression markers for prostate cancer. *Genes, Chromosomes and Cancer, 44*, 438–449.

Visakorpi, T., Kallioniemi, A. H., Syvanen, A. C., Hyytinen, E. R., Karhu, R., Tammela, T., Isola, J. J., & Kallioniemi, O. P. (1995). Genetic changes in primary and recurrent prostate cancer by comparative genomic hybridization. *Cancer Research, 55*, 342–347.

Weir, B. S. (1996). *Genetic data analysis II: methods for discrete population genetic data*. Sunderland MA: Sinauer Associates, Inc.

Witte, J. S. (2007). Multiple prostate cancer risk variants on 8q24. *Nature Genetics, 39*, 579–580.

Wokolorczyk, D., Gliniewicz, B., Sikorski, A., Zlowocka, E., Masojc, B., Debniak, T., Matyjasik, J., Mierzejewski, M., Medrek, K., Oszutowska, D., Suchy, J., Gronwald, J., Teodorczyk, U., Huzarski, T., Byrski, T., Jakubowska, A., Gorski, B., van de Wetering, T., Walczak, S., Narod, S. A., Lubinski, J., & Cybulski, C. (2008). A range of cancers is associated with the rs6983267 marker on chromosome 8. *Cancer Research, 68*, 9982–9986.

Wokolorczyk, D., Lubinski, J., Narod, S. A., & Cybulski, C. (2009). Genetic heterogeneity of 8q24 region in susceptibility to cancer. *Journal of the National Cancer Institute, 101*, 278–279.

Yeager, M., Orr, N., Hayes, R. B., Jacobs, K. B., Kraft, P., Wacholder, S., Minichiello, M. J., Fearnhead, P., Yu, K., Chatterjee, N., Wang, Z., Welch, R., Staats, B. J., Calle, E. E., Feigelson, H. S., Thun, M. J., Rodriguez, C., Albanes, D., Virtamo, J., Weinstein, S., Schumacher, F. R., Giovannucci, E., Willett, W. C., Cancel-Tassin, G., Cussenot, O., Valeri, A., Andriole, G. L., Gelmann, E. P., Tucker, M., Gerhard, D. S., Fraumeni, J. F., Jr., Hoover, R., Hunter, D. J., Chanock, S. J., & Thomas, G. (2007). Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nature Genetics, 39*, 645–649.

Zanke, B. W., Greenwood, C. M., Rangrej, J., Kustra, R., Tenesa, A., Farrington, S. M., Prendergast, J., Olschwang, S., Chiang, T., Crowdy, E., Ferretti, V., Laflamme, P., Sundararajan, S., Roumy, S., Olivier, J. F., Robidoux, F., Sladek, R., Montpetit, A., Campbell, P., Bezieau, S., O'Shea A, M., Zogopoulos, G., Cotterchio, M., Newcomb, P., McLaughlin, J., Younghusband, B., Green, R., Green, J., Porteous, M. E., Campbell, H., Blanche, H., Sahbatou, M., Tubacher, E., Bonaiti-Pellie, C., Buecher, B., Riboli, E., Kury, S., Chanock, S. J., Potter, J., Thomas, G., Gallinger, S., Hudson, T. J., & Dunlop, M. G. (2007). Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nature Genetics, 39*, 989–994.