



CHEK2, *MGMT*, *SULT1E1* and *SULT1A1* Polymorphisms and Endometrial Cancer Risk

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Several single nucleotide polymorphisms (SNPs) in candidate genes of DNA repair and hormone pathways have been reported to be associated with endometrial cancer risk. We sought to confirm these associations in two endometrial cancer case-control sample sets and used additional data from an existing genome-wide association study to prioritize an additional SNP for further study. Five SNPs from the *CHEK2*, *MGMT*, *SULT1E1* and *SULT1A1* genes, genotyped in a total of 1597 cases and 1507 controls from two case-control studies, the Australian National Endometrial Cancer Study and the Polish Endometrial Cancer Study, were assessed for association with endometrial cancer risk using logistic regression analysis. Imputed data was drawn for *CHEK2* rs8135424 for 666 cases from the Study of Epidemiology and Risk factors in Cancer Heredity study and 5190 controls from the Wellcome Trust Case Control Consortium. We observed no association between SNPs in the *MGMT*, *SULT1E1* and *SULT1A1* genes and endometrial cancer risk. The A allele of the rs8135424 *CHEK2* SNP was associated with decreased risk of endometrial cancer (adjusted per-allele OR 0.83; 95%CI 0.70-0.98; $p = .03$) however this finding was opposite to that previously published. Imputed data for *CHEK2* rs8135424 supported the direction of effect reported in this study (OR 0.85; 95% CI 0.65–1.10). Previously reported endometrial cancer risk associations with SNPs from in genes involved in estrogen metabolism and DNA repair were not replicated in our larger study population. This study highlights the need for replication of candidate gene SNP studies using large sample groups, to confirm risk associations and better prioritize downstream studies to assess the causal relationship between genetic variants and cancer risk. Our findings suggest that the *CHEK2* SNP rs8135424 be prioritized for further study as a genetic factor associated with risk of endometrial cancer.

■ **Keywords:** endometrial cancer, single nucleotide polymorphism, *CHEK2*, *MGMT*, *SULT1E1*, *SULT1A1*

Background

History of a first-degree relative with endometrial cancer has been associated with a two-fold increased risk of endometrial cancer (Hemminki et al., 2005), and low-risk genetic factors are likely to be involved in the development of this disease, as has now been demonstrated for several other cancers (<http://www.genome.gov/gwastudies/>). Single nucleotide polymorphisms (SNPs) in genes involved in estrogen and DNA repair processes have been

the focus of many candidate gene association studies for endometrial cancer, since unopposed exposure to endogenous or exogenous estrogen is a well-established risk

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factor for endometrial cancer development and estrogen metabolites have also been reported to cause DNA lesions. However, results from single studies of SNPs in candidate genes are known for being unreliable and chance remains a likely explanation for many reported statistically significant associations, with results from individual studies unfortunately rarely confirmed by subsequent studies. Very large studies with little margin for error and/or validation of results in other populations is thus an essential pre-requisite before reported associations can be accepted as real. In an attempt to validate associations between 5 SNPs in DNA repair and estrogen sulfation genes (*CHEK2*, Einarsdottir et al., 2007; *MGMT*, Han et al., 2006; *SULT1E1* and *SULT1A1*, Rebbeck et al., 2006) and endometrial cancer risk, previously estimated from studies including at least 421–683 cases (Table 1), we genotyped these SNPs in a pooled sample of more than 1500 cases and 1600 controls from the Australian National Endometrial Cancer Study (ANECS) and the Polish Endometrial Case-Cancer Study (PECS). To clarify the results for the *CHEK2* SNP, rs8135424 imputed genotype dosages were used for 666 endometrial cancer patients

from the Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH) cohort and 5190 control subjects from the Wellcome Trust Case Control Consortium, using data drawn from an existing genome-wide association study of endometrial cancer.

Material and Methods

The ANECS and PECS study populations and selection criteria have been described elsewhere (Gaudet et al., 2008; O'Mara et al., 2011). Genotyping for ANECS samples was performed using the Sequenom® MassARRAY platform (Sequenom, San Diego CA, USA), while the genotyping for PECS samples was performed using the Illumina iSelect Custom BeadChip (Illumina INC., San Diego CA, USA). All SNPs passed quality control filters that included Hardy-Weinberg Equilibrium, minimum duplicate concordance and, minimum sample and assay success rates. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the association between SNPs and endometrial cancer risk using logistic regression models, adjusting for age and

TABLE 1

Summary of Previous Significant Results Published for SNPs Assessed for Endometrial Cancer Risk

SNP	Gene	Reference	Genotype	No. of cases (%)	No. of controls (%)	Adj OR (95%CI)
rs1801030 SULT1A1*3, 667A>G, Met233Val	<i>SULT1A1</i>	(Rebbeck, 2006)	AA	392 (93.1)	863 (84.4)	1 (ref)
			GG/AG	29 (6.9)	160 (15.6)	0.51 (0.29-0.92) ^a
rs3736599 -64G>A	<i>SULT1E1</i>	(Rebbeck, 2006)	GG	393 (79.2)	1061 (81.2)	1 (ref)
			AA/AG	103 (20.8)	245 (18.8)	1.45 (1.06-1.99) ^a
rs2308321 520A>G, Ile143Val	<i>MGMT</i>	(Han, 2006)	AA	340 (76.4)	838 (77.0)	1 (ref)
			AG	99 (22.3)	234 (21.5)	
			GG	6 (1.4)	17 (1.6)	
			AG/GG	105 (23.6)	251 (23.0)	1.05 (0.8-1.39) ^b
			AA & never smoked AG/GG & > 30 pack-years smoking			1 (ref) 0.41 (0.19-0.86) ^{b, c}
rs12917 343C>T, Leu84Phe	<i>MGMT</i>	(Han, 2006)	CC	344 (79.3)	822 (75.8)	1 (ref)
			CT	82 (18.9)	242 (22.3)	
			TT	8 (1.8)	21 (1.9)	
			CT/TT	90 (20.7)	263 (24.2)	0.72 (0.53-0.96) ^c
rs8135424 Intron 14, G>A	<i>CHEK2</i>	(Einarsdottir, 2007)	GG	490 (71.7)	1156 (75.9)1 (ref)	
			GA	170 (24.9)	343 (22.5)	1.18 (0.95-1.46) ^d
			AA	23 (3.4)	25 (1.6)	2.11 (1.18-3.77) ^d
			per allele			1.26 (1.06-1.51) ^d

Note: ^a Adjusted for: Education (< high school [HS], HS graduate, HS but < college graduate, or > college graduate); BMI from 40 yrs through 49 yrs (continuous); number of full-term pregnancies (never pregnant or 1–2 or ≥ 3); years of menses, imputed if missing (continuous); type of menopause (known natural, assumed natural at reference age of 50 yrs if menopausal status is unknown, or induced); interaction of never, former, or current smoker by years of smoking; oral contraceptive use (never, < 3 yrs, or ≥ 3 yrs)

^b Adjusted for: age at menarche (< 12, 12, 13, > 13 yrs), age at menopause (< 48, ≥ 48 to < 50, ≥ 50 to < 53 or ≥ 53 yrs), BMI at age 18 yrs (continuous), weight gain since age 18 (< 5, ≥ 5 to < 20, ≥ 20 kg), postmenopausal hormone use at diagnosis (current, not current), parity/age at first birth (nulliparous, with children/age at first birth > 24 yrs, with children/age at first birth > 24 yrs), pack-years of smoking (never, > 0 to < 30, ≥ 30), first-degree family history of endometrial cancer (yes/no), first-degree history of colorectal cancer (yes/no)

^c *p* trend = .01, *p* for interaction with smoking = .04

^d Adjusted for: age (5-year groups)

study. Additional analyses included adjustment for body-mass index (BMI) (World Health Organization categories: < 25, 25 to < 30, 30 to < 35 and ≥ 35 kg/m²) and stratification by histological subtype (endometrioid vs other) and ethnicity (Caucasian vs other). To assess possible interaction with smoking for rs2308321, the significance of multiplicative interaction was assessed by the change in the likelihood ratio estimate after inclusion of smoking*genotype to a simpler model without this term. All statistical analyses were performed using the Statistical Packages of Social Sciences for Window, version 17 (SPSS Inc., Chicago, IL).

Imputed genotype dosages for rs8135424 were obtained for 666 SEARCH cases with endometrioid histology genotyped as part of a genome-wide association study of endometrial cancer using an Illumina Infinium 610K array (Spurdle et al., 2011), and for 5190 UK control subjects who had been genotyped using an Illumina Infinium 1.2M array as part of the Wellcome Trust Case Control Consortium (WTCCC, 2007). Non-genotyped SNPs were imputed using 1000 Genomes data as a reference panel (August 2010 Release <http://www.1000genomes.org>). Imputed genotype dosages were compared between cases and controls, adjusting for the first 3 principal components of the genomic kinship matrix to take into account any differences in population structure between cases and controls. This part of the analysis was performed using

GenABEL (Aulchenko et al., 2007), ProbABEL (Aulchenko et al., 2010) and MACH (Li et al., 2009).

Results

Results are shown in Table 2. The *SULT1A1* SNP (rs1801030) was found to be exceedingly rare in the ANECS study group, and monomorphic in PECS, and was thus excluded from further analysis. Contrary to the previous studies, we found no evidence of association between the individual SNPs from the *SULT1E1* (rs3736599) and *MGMT* (rs2308321 and rs12917) genes and endometrial cancer risk. The results were unchanged when we adjusted for BMI, or excluded non-endometrioid cancers from the analysis (data not shown). Since the previous report suggested a trend for decreased risk of endometrial cancer with increased exposure to smoking for rs2308321-G carriers (p trend = .01), but not for rs2308321-G non-carriers (p trend = .7; p interaction = .04) (Han et al., 2006), we also assessed the interaction of rs2308321 with smoking. There was no evidence for similar interaction of rs2308321 with smoking in our dataset (p = .3).

Our results did show an association between the *CHEK2* SNP rs8135424 and decreased endometrial cancer risk (per A allele adjusted OR 0.83; 95% CI 0.70-0.99; p = .03). Again the results were not markedly altered by exclusion of non-endometrioid cases from the analysis (OR 0.82; 95% CI 0.69-0.98, p = .03), or with additional adjustment for BMI (OR 0.85; 95% CI 0.70-1.01). There

TABLE 2

Estimated Odds Ratios (OR) and 95% Confidence Intervals (CI) in the Australian and Polish Sample Sets

SNP	Gene	Genotype	Pooled Adj OR (95%CI) ^a	P-value	ANECS		PECS	
					No. of cases (%)	No. of controls (%)	No. of cases (%)	No. of controls (%)
rs1801030	<i>SULT1A1</i>	AA	Not polymorphic		1165 (100)	1094 (100)	392 (100)	404 (100)
RS3736599	<i>SULT1E1</i>	CC	1 (ref)		1110 (81.6)	1050 (82.8)	397 (82.6)	407 (84.1)
		CT	1.10 (0.89-1.35)	0.39	193 (17.4)	171 (16.3)	66 (16.6)	60 (14.7)
		TT	0.83 (0.39-1.75)	0.62	11 (1.0)	10 (1.0)	3 (0.8)	5 (1.2)
		per allele	1.05 (0.87-1.27)	0.60				
rs2308321	<i>MGMT</i>	AA	1 (ref)		924 (79.0)	861 (78.9)	305 (77.0)	317 (78.5)
		AG	1.00 (0.83-1.20)	0.99	231 (19.7)	220 (20.2)	83 (21.0)	80 (19.8)
		GG	1.28 (0.67-2.43)	0.45	15 (1.3)	10 (0.9)	8 (2.0)	7 (1.7)
		per allele	1.03 (0.87-1.21)	0.74				
RS12917	<i>MGMT</i>	CC	1 (ref)		889 (75.8)	810 (73.7)	278 (70.0)	296 (72.9)
		CT	0.94 (0.80-1.12)	0.49	261 (22.3)	270 (24.6)	108 (27.2)	103 (25.4)
		TT	1.22 (0.72-2.10)	0.45	23 (2.0)	19 (1.7)	11 (2.8)	7 (1.7)
		per allele	0.99 (0.85-1.14)	0.84				
rs8135424	<i>CHEK2</i>	GG	1 (ref)		1015 (84.6)	887 (81.4)	277 (72.5)	260 (68.8)
		AG	0.83 (0.69-1.01)	0.06	179 (14.9)	194 (17.8)	99 (25.9)	111 (29.4)
		AA	0.66 (0.31-1.41)	0.28	6 (0.5)	9 (0.8)	6 (1.6)	7 (1.8)
		per allele	0.83 (0.70-0.99)	0.03				

Note: ^a Adjusted for age (continuous) and study (ANECS, PECS)

Abbreviations: ANECS — Australian National Endometrial Cancer Study; PECS — Polish Endometrial Cancer Study

was also no difference in ORs when our analysis was restricted to only Caucasian samples (1288 cases and 1337 controls; data not shown). However, this finding is in the *opposite* direction to that previously observed in a Swedish population (cases $n = 705$, controls $n = 1565$; per *A* allele adjusted OR 1.26; 95% CI 1.06–1.51, $p = .01$) (Einarsdottir et al., 2007). The direction of risk associated with rs8135424 was the same in both sample sets included in this study, despite a somewhat lower minor allele frequency in the Australian (0.19) controls compared to Polish controls (0.33). In an attempt to clarify the findings for rs8135424, we analyzed imputed data from an independent UK dataset. While the results were not significant, the direction of the association was similar to that observed in the Australian/Polish dataset (per *A* allele OR 0.85; 95% CI 0.65–1.10).

Discussion

We were not able to replicate previously reported endometrial cancer risk associations with SNPs from genes involved in estrogen metabolism and DNA repair in our larger study population. The rs8135424 SNP has not been investigated in other cancers and it is also not genotyped, or in strong linkage disequilibrium with SNPs that are genotyped by the Illumina Human 1M Duo BeadChip commonly used for genome-wide association studies. Although the imputed data accessed was less than optimal (Imputation $R^2 = .53$), the conflicting results reported by the original Swedish study compared to the combined larger datasets from Australian, Polish and UK studies suggest that further research using independent sample sets will be important to clarify the association of rs8135424 with endometrial cancer risk.

The SNPs assessed in our study were chosen because of their reported associations with endometrial cancer risk. Our findings do not support those previously reported, although our large sample size from two independent studies provided sufficient power ($> 80\%$) to detect the ORs reported in the previous studies. Our results also highlight the inconsistency of results from single candidate gene SNP association studies with relatively small numbers of cases and emphasize the value of replication in large sample groups and multi-center studies (Gaudet et al., 2010; Lurie et al., 2011; O'Mara et al., 2011; Setiawan et al., 2009; Spurdle et al., 2011).

Competing Interests

The authors have no competing interests to declare.

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