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Cross-cancer pleiotropic analysis of endometrial cancer: PAGE and E2C2 consortia

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Genome-wide association studies (GWAS) have identified a large number of cancer-associated single nucleotide polymorphisms (SNPs), several of which have been associated with multiple cancer sites suggesting pleiotropic effects and shared biological mechanisms across some cancers. We hypothesized that SNPs associated with other cancers may be additionally associated with endometrial cancer. We examined 213 SNPs previously associated with 14 other cancers for their associations with endometrial cancer in 3758 endometrial cancer cases and 5966 controls of European ancestry from two consortia: Population Architecture Using Genomics and Epidemiology and the Epidemiology of Endometrial Cancer Consortium. Study-specific logistic regression estimates adjusted for age, body mass index and the most significant principal components of genetic ancestry were combined using fixed-effect meta-analysis to evaluate the association between each SNP and endometrial cancer risk. A Bonferroni-corrected *P* value of 2.35×10^{-4} was used to determine statistical significance of the associations. SNP rs7679673, ~6.3 kb upstream of *TET2* and previously reported to be associated with prostate cancer risk, was associated with endometrial cancer risk in the direction opposite to that for prostate cancer [meta-analysis odds ratio = 0.87 (per copy of the *C* allele), 95% confidence interval = 0.81, 0.93; $P = 7.37 \times 10^{-5}$] with no evidence of heterogeneity across studies (*P* heterogeneity = 0.66). This pleiotropic analysis is the first to suggest *TET2* as a susceptibility locus for endometrial cancer.

Abbreviations: E2C2, Epidemiology of Endometrial Cancer Consortium; GWAS, genome-wide association studies; MEC, Multiethnic Cohort; PAGE, Population Architecture Using Genomics and Epidemiology; SNP, single nucleotide polymorphism.

Introduction

Endometrial cancer is the most common gynecologic cancer, with >52 600 new cases expected in the USA in 2014 (1). Although survival is favorable, with a survival rate similar to that of breast cancer, >8500 women are estimated to die of this disease in 2014 (1). Three genome-wide association studies (GWAS) of endometrial cancer (2–4) have been conducted to date with only one identifying a novel genome-wide significant risk variant for endometrial cancer, namely, rs4430796 at the 17q12 (*HNF1B*) locus (3).

GWAS have successfully identified a large number of susceptibility loci for various cancers. Among the many risk loci identified, several have been associated with multiple cancer sites supporting the existence of carcinogenic pleiotropy (5). For example, *HNF1B* at 17q12 has been identified as a susceptibility locus for endometrial, prostate and ovarian cancers (3,6–8). Loci in the 8q24 region (9) and a locus on chromosome 5 (5p15.33) that includes the telomerase reverse transcriptase (*TERT*) gene (10) have been associated with multiple cancer sites. Despite these striking examples, pleiotropic effects have not been systematically explored in endometrial cancer. Evidence of carcinogenic pleiotropy can improve our understanding of disease etiology by identifying shared molecular components underlying disease risk and by validating the pathogenicity of variants at a locus (11).

In this study, we examined variants identified by GWAS for 14 other cancers for their association with endometrial cancer in a large-scale analysis of cases and controls from nine studies in two consortia: the National Human Genome Research Institute (NHGRI) Population Architecture Using Genomics and Epidemiology (PAGE) (12) and the Epidemiology of Endometrial Cancer Consortium (E2C2) (13).

Materials and methods

Study population

Two consortia contributed data to this meta-analysis study: PAGE (6,12) and E2C2 (13,14). Due to a limited number of cases of non-European descent in the contributing studies, the current analysis was restricted to women of European descent and included 3758 primary incident invasive endometrial cancer cases and 5966 controls who were free of endometrial cancer and did not have a history of hysterectomy (Table I). Contributing PAGE studies included: Multiethnic Cohort (MEC) (15); Women's Health Initiative (WHI) (16) and Epidemiologic Architecture for Genes Linked to Environment (EAGLE), which accesses the Vanderbilt University biorepository (BioVU) (17). Participating E2C2 studies included: Connecticut Endometrial Cancer Study (CECS) (18); Fred Hutchinson Cancer Research Center case-control study (FHCRC) (19); Polish Endometrial Cancer Case-Control Study (PECS); MEC; California Teachers' Study (CTS) (20); Nurses' Health Study (NHS) (21) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (22,23). All studies are from the USA, except for the Polish study. While MEC participates in both PAGE and E2C2, only MEC data as part of E2C2 were used. Details of these studies have been published elsewhere (6,14). Study design characteristics for each study (case–control definitions and matching factors) are summarized in the Supplementary Material, available at *Carcinogenesis* Online. Institutional review board approval was obtained for all studies.

SNP selection and genotyping

Single nucleotide polymorphisms (SNPs) previously associated with 14 cancers other than endometrial cancer were identified by PAGE researchers

from the NHGRI GWAS catalog ($P < 5.0 \times 10^{-5}$) as of January 2010 (24,25) and review of more recent cancer GWAS and fine mapping literature. These SNPs were selected irrespective of racial/ethnic composition of the initial published GWAS. Out of >300 SNPs identified, 213 SNPs have been genotyped and passed quality control in at least two studies across PAGE and E2C2 (Supplementary Table 1, available at *Carcinogenesis* Online). In PAGE, these SNPs were genotyped using a custom panel for each study (26). In E2C2, genotype data were abstracted from previously generated stage 1 GWAS data (2).

To control for potential bias due to population stratification, each PAGE study genotyped 128 ancestry informative markers that capture the major continental genetic diversity (European, East Asian, Amerindian, African, South Asian, Mexican and Puerto Rican) (27). Principal components of genetic ancestry were estimated from these markers by EIGENSTRAT (28) and included in regression models as an estimate of genetic ancestry. In E2C2, principal components of genetic ancestry were derived from the GWAS data using EIGENSTRAT (28). We did not exclude individuals based on principal component-based ancestry in the PAGE. In the E2C2 studies, we excluded 146 participants due to non-European principal component-based ancestry (2).

Standard quality assurance and quality control measures were utilized to ensure genotyping quality. In PAGE, samples and SNPs were excluded based on call rates (<90%), concordance of blinded replicates (≤98%) and departure from Hardy–Weinberg equilibrium ($P < 0.001$). Each PAGE laboratory also genotyped 360 HapMap samples to serve as cross-laboratory and cross-platform quality control samples (12). In E2C2, samples were excluded based on call rates (<90%), unexpected duplicates, heterozygosity, departure from Hardy–Weinberg equilibrium ($P < 0.0001$), minor allele frequencies (<1%) and outlying the CEU HapMap2 cluster in principal component analysis (as only participants of European descent were included) (2). The majority of the 213 SNPs of interest were available across most studies (89% of the SNPs were genotyped in at least six studies; Supplementary Table 1, available at *Carcinogenesis* Online).

Statistical analyses

For each study, the association between each SNP and endometrial cancer was estimated using unconditional logistic regression. The modeled allele was the 'risk' allele for each SNP as defined as the allele associated with an increased risk of cancer in prior publications. For SNPs associated with multiple cancer sites, the first reported GWAS was used in assigning the risk allele. SNPs were coded additively with 0, 1, 2 referring to the number of risk alleles. Models were adjusted for age (years), body mass index [kg/m^2 obtained from self-report at time of diagnosis for cases and interview for controls, or for most cohort (nested case–control) studies at baseline assessment] and the most relevant principal components of genetic ancestry to account for population substructure for each study. Log odds regression estimates were combined across studies using inverse-variance weighted, fixed-effect meta-analysis as implemented in METAL (29). Heterogeneity *P* values were estimated based

Table I. Study population characteristics by study

Study name	Study design	Location	Study period	Number of cases/controls	Mean age[a] (years)		Mean BMI (kg/m^2)	
					Cases	Controls	Cases	Controls
Connecticut Endometrial Cancer Study (CECS)	Case–control	Connecticut, USA	2004–2009	477/567	60.6	61.9	32.5	26.6
California Teachers Study (CTS)	Cohort	California, USA	1995–2004	295/285	65.3	66.7	27.0	25.2
Epidemiologic Architecture for Genes Linked to Environment (Eagle-BioVU)	Case–control	Tennesse, USA	2007 –	20/156	88.1	89.0	25.8	25.5
Fred Hutchinson Cancer Center (FHCRC)	Case–control	Washington, USA	1994–2005	697/693	59.7	59.2	30.2	25.6
Multiethnic Cohort (MEC)	Cohort	Hawaii/California, USA	1993–2008	100/199	65.4	64.5	28.8	25.5
Nurses' Health Study (NHS)	Cohort	11 states, USA	1976–2008	396/348	62.4	63.0	28.6	26.3
Polish Endometrial Cancer Case-Control Study (PECS)	Case–control	Poland	2001–2003	459/558	60.9	55.6	28.6	26.4
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)	Cohort	USA	1993–2008	446/123	67.9	62.7	29.3	26.9
Women's Health Initiative (WHI)	Cohort	USA	1991–2009	868/3037	63.9	65.2	28.9	27.3

BMI, body mass index.
[a]Age at diagnosis for cases and at reference date for controls.

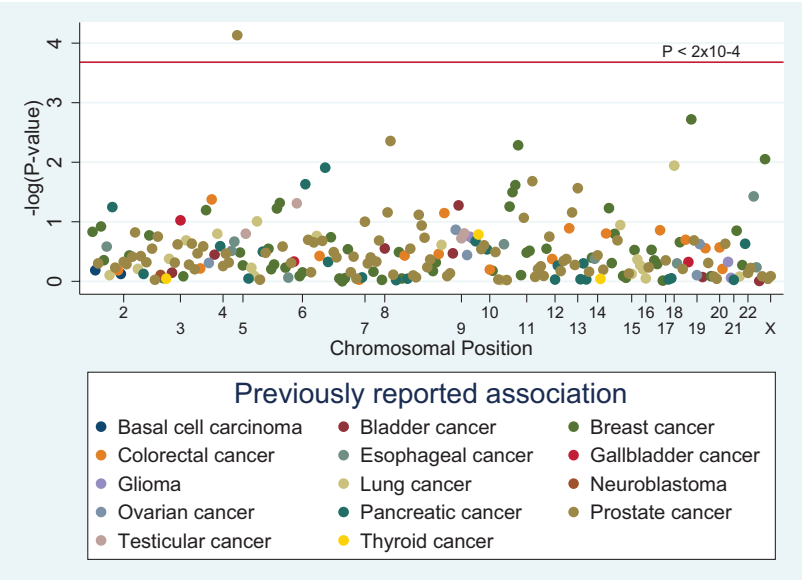

Fig. 1. Manhattan plot of the meta-analysis association between risk variants of 14 other cancers and endometrial cancer. The solid line is the Bonferroni-corrected significance threshold ($0.05/213 = 2.35 \times 10^{-4}$). Each association result is color coded according to the cancer for which the SNP was originally reported and positioned on the *x*-axis according to its genomic position.

Table II. Meta-analysis association results between the top 14 SNPs ($P < 0.05$) and endometrial cancer

SNP	Region	Position (bp)	Locus	Risk Allele[a]	Other Allele	Number of studies[b]	OR per allele[c] (95% CI)	*P* value	*P* heterogeneity	Initial GWAS (reference)
rs10936599	3q26.2	169 492 101	*MYNN*	C	T	7	1.10 (1.00, 1.20)	0.042	0.52	Colorectal cancer (34)
rs7679673	4q24	106 061 534	*TET2*	C	A	8	0.87 (0.81, 0.93)	7.37×10^{-5}	0.66	Prostate cancer (30)
rs889312	5q11.2	56 031 884	*MAP3K1*	C	A	9	0.93 (0.87, 1.00)	0.048	0.02	Breast cancer (35)
rs4624820	5q31.3	141 681 788	*SPRY4*	G	A	8	1.06 (1.00, 1.14)	0.049	0.12	Testicular cancer (36)
rs763780	6p12.2	52 101 739	*IL17F*	G	A	6	0.76 (0.62, 0.94)	0.012	0.73	Pancreatic cancer (37)
rs9502893	6p25.3	1 340 189	*FOXQ1*	G	A	7	1.10 (1.01, 1.19)	0.023	0.32	Pancreatic cancer (38)
rs2981582	10q26.13	123 352 317	*FGFR2*	A	G	8	0.90 (0.84, 0.97)	0.005	0.07	Breast cancer (35)
rs1219648	10q26.13	123 346 190	*FGFR2*	G	A	8	0.92 (0.87, 0.99)	0.024	0.02	Breast cancer (39)
rs2981579	10q26.13	123 337 335	*FGFR2*	T	C	8	0.93 (0.87, 0.99)	0.032	0.02	Breast cancer (40)
rs7127900	11p15.5	2 233 574	*IGF2, IGF2AS, INS, TH*	A	G	8	0.91 (0.84, 0.98)	0.021	0.60	Prostate cancer (30)
rs9600079	13q22.1	73 728 139	None	T	G	7	0.91 (0.84, 0.99)	0.027	0.08	Prostate cancer (41)
rs1978503	18q21.2	53 664 282	None	A	G	9	0.88 (0.81, 0.95)	0.002	0.55	Breast cancer (42)
rs16951095	18p11.31	7 042 911	*LAMA1*	C	T	6	0.78 (0.94, 0.66)	0.011	0.08	Lung cancer (43)
rs738722	22q12.1	29 130 012	*CHEK2*	T	C	7	1.10 (1.01, 1.20)	0.037	0.71	Esophageal cancer (44)

CI, confidence interval; OR, odds ratio.
[a]Allele associated with increased risk as indicated in the first published GWAS paper.
[b]Number of studies with association result.
[c]Adjusted for age, body mass index, top principal components for each study and calculated using fixed effects model.

on Cochran's Q statistics. A Bonferroni-corrected $P = 2.35 \times 10^{-4}$ (nominal alpha/number of SNPs tested = 0.05/213) was used to determine the statistical significance of the association for each SNP with endometrial cancer.

Results

The study population characteristics are shown in Table I. The number of endometrial cases ranged from 20 in the BioVU to 868 in the WHI. The average age varied across studies, but the majority of women were older than 55 years. On average, cases had higher body mass index than controls.

A total of 213 risk variants for 14 cancers other than endometrial cancer were tested in 3758 cases and 5966 controls from a total of nine studies in the two consortia (Figure 1; Supplementary Table 1, available at *Carcinogenesis* Online). Fourteen variants were nominally associated with endometrial cancer at $P < 0.05$ (Table II). These 14 variants were previously associated with breast cancer (5 SNPs), prostate cancer (3 SNPs), pancreatic cancer (2 SNPs), testicular cancer (1 SNP), colorectal cancer (1 SNP), lung cancer (1 SNP) and esophageal cancer (1 SNP). Three of the breast cancer-associated variants in *FGFR2* are in linkage disequilibrium ($r^2 \geq 0.92$ in HapMap CEU) and thus may not represent independent results.

One SNP (rs7679673) in the 4q24 region (~6 kb upstream of *TET2*) previously reported to be associated with prostate cancer risk (30) demonstrated a statistically significant association with endometrial cancer risk in the direction opposite to that for prostate cancer [overall meta-analysis odds ratio = 0.87 (per copy of the *C* allele), 95% confidence interval = 0.81, 0.93; $P = 7.37 \times 10^{-5}$]. This SNP surpassed our conservative Bonferroni-corrected criterion of significance ($P < 2.35 \times 10^{-4}$) and showed a consistency in the results across studies (*P* heterogeneity = 0.66) (Figure 2). A nearby breast cancer risk variant, rs9790517 (31), located ~23 kb from rs7679673 ($r^2 = 0.42$ in CEU samples), was not statistically significantly associated with endometrial cancer risk (per copy of the *T* allele: odds ratio = 1.05; 95% confidence interval: 0.95, 1.17).

Discussion

We conducted a large meta-analysis among women of European ancestry to investigate pleiotropic effects of GWAS-identified risk variants for other cancers on endometrial cancer risk. To our knowledge, this is the first systematic analysis for pleiotropic associations in endometrial cancer. We found that a SNP at chromosome 4q24, rs7679673, previously associated with prostate cancer risk demonstrated a robust association with endometrial cancer risk, using a conservative criterion for statistical significance. This SNP resides ~6.3 kb from the transcription start site of *TET2*.

The *TET2* gene encodes a methylcytosine dioxygenase involved in myelopoiesis. This gene has been characterized as a tumor suppressor gene involved in pathogenesis of acute myeloid leukemia, myelodysplastic syndrome and myeloproliferative neoplasms (32). The *TET2* region has previously been identified as a risk locus for both prostate and breast cancer (30,31). The risk SNPs in the *TET2* region, rs7679673 and rs9790517 ($r^2 = 0.42$), were genotyped in our study, but only rs7679673 was statistically significantly associated with endometrial cancer risk. The *C* allele of rs7679673 was associated with a 13% decreased risk of endometrial cancer, which is in the opposite direction as seen for prostate cancer (30). Currently, there is no direct information about the function of rs7679673. The *T* allele of an intronic SNP rs9790517 has been associated with a 5% increased risk of breast cancer (31). We noted the same direction and magnitude of effect with the *T* allele of rs9790517 although the results were not statistically significant. Despite the opposite direction of association in endometrial and prostate cancer, our results suggest a shared pathway between these two cancers and possibly breast cancer. The different directions of association between cancer sites may be due to linkage disequilibrium with two different functional SNPs that have different effects in the different tissues, or context-specific differences

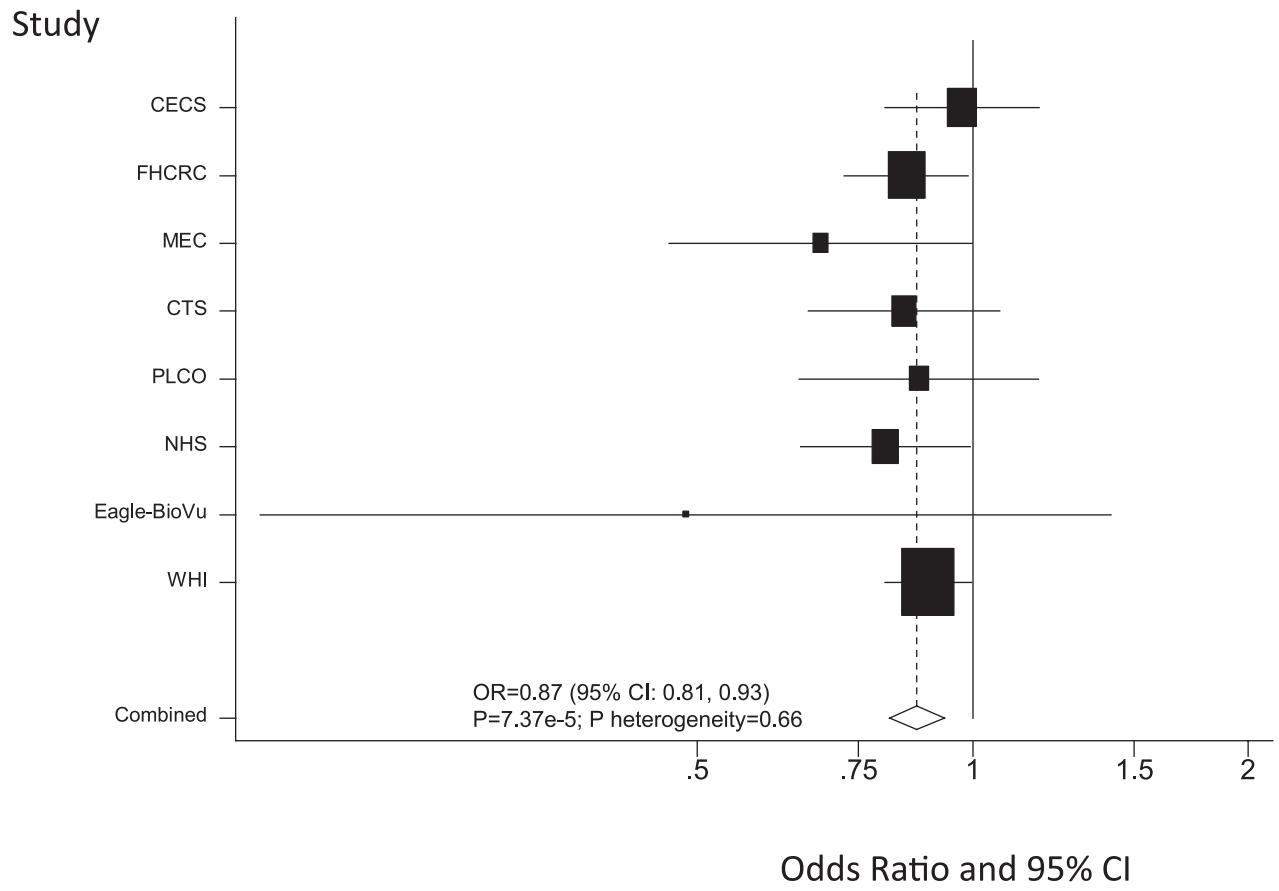

Fig. 2. Forest plot of the association between rs7679673 near the *TET2* gene region 4q24 and endometrial cancer risk. Study-specific and meta-analysis associations are plotted, modeling the *C* risk allele for prostate cancer.

in regulation of nearby genes, just as transcription factors can serve as both oncogenes and tumor suppressors (33). The underlying biological mechanism for which *TET2* may influence carcinogenesis remains to be elucidated.

The major strength of our study is the large number of subjects from well-designed endometrial cancer studies. The limitation of this study is that our analysis was based on individual SNPs from each/most loci and thus we did not have broader coverage of the area. As more recent GWAS have identified many new cancer risk loci, these SNPs remain to be examined for their pleiotropic effects with endometrial cancer. The statistical power to detect an association for the 213 SNPs varied; nonetheless, 89% of the SNPs were genotyped in more than two-third of the studies. We identified 14 variants were nominally associated with endometrial cancer at $P < 0.05$ which was more than the ~11 associations expected by chance (213 SNPs × 0.05 = 10.7). The small numbers of non-European ancestry women in the available studies precluded the possibility of exploring generalizability across race/ethnicity. Finally, because the large majority of cases in this study were type 1 tumors (i.e. endometrioid adenocarcinomas), our results apply mainly to these tumors.

In summary, our cross-cancer pleiotropy analysis suggested a possible role of *TET2* in endometrial cancer susceptibility. Further replication of our results and research into the biological mechanisms by which inherited differences in pleiotropic cancer risk loci influence endometrial cancer will expand our understanding of the key contributors to endometrial cancer development.

Supplementary material

Supplementary Table 1 can be found at http://carcin.oxfordjournals.org/

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Conflict of Interest Statement: None declared.

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