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Breast cancer susceptibility polymorphisms and endometrial cancer risk: a Collaborative Endometrial Cancer Study

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Recent large–scale association studies, both of genome-wide and candidate gene design, have revealed several single-nucleotide polymorphisms (SNPs) which are significantly associated with risk of developing breast cancer. As both breast and endometrial cancers are considered to be hormonally driven and share multiple risk factors, we investigated whether breast cancer risk alleles are also associated with endometrial cancer risk. We genotyped nine breast cancer risk SNPs in up to 4188 endometrial cases and 11 928 controls, from between three and seven Caucasian populations. None of the tested SNPs showed significant evidence of association with risk of endometrial cancer.

Abbreviations: ANECS, Australian National Endometrial Cancer Study; AOCS, Australian Ovarian Cancer Study; CI, confidence interval; GWAS, genome-wide association study; LES, Leuven Endometrial Study; NSECG, National Study of Endometrial Cancer Genetics; OR, odds ratio; PECS, Polish Endometrial Cancer Study; SASBAC, Singapore and Sweden Breast/Endometrial Cancer Study; SEARCH, Studies of Epidemiology and Risk factors in Cancer Heredity; SNP, single-nucleotide polymorphism; WISE, Women's Insight and Shared Experiences Study.

Introduction

Endometrial cancer is the fourth most common cancer in women in the UK, representing 5% of all female cancers, with most cases developing postmenopausally. The most common subtype, ∼80% of cases, is Type 1 estrogen-dependent endometrioid adenocarcinoma, which arises from the lining of the uterus and is associated with excessive estrogen exposure, especially that unopposed by progesterone (1). The known risk factors for this disease are hormone related, e.g. early menarche or late menopause, nulliparity, irregular menstrual periods and obesity. Exogenous hormones, such as oral contraceptives and estrogen hormone replacement therapy, can also increase risk of developing endometrial cancer, although the addition of progesterone counteracts this risk (2). Interestingly, breast cancer risk is increased with the use of progesterone. Furthermore, use of the breast cancer drug, Tamoxifen, is associated with an increased risk of endometrial cancer (3). In normal breast cells and most breast tumors, Tamoxifen acts as an estrogen receptor antagonist and has an antiproliferative effect, but in endometrial cells, it acts in the opposite direction—as an estrogen receptor agonist that increases proliferation and risk of endometrial cancer (4). As there are known similarities and differences in the risk factors for breast and endometrial cancer, it is probably that some but not all genetic risk factors will be shared between these two diseases. A recent genome-wide association study (GWAS) of endometrial cancer (5) revealed a single-nucleotide polymorphism (SNP) at 17q12 (*HNF1B*), which was associated with risk of endometrial cancer at a genome-wide level of significance [odds ratio (OR) = 0.84, 95% confidence interval (CI) = 0.79–0.89, $P = 7 \times 10^{-10}$]; however, this SNP does not appear to be associated with breast cancer risk (6).

In this study, we assessed risk of endometrial cancer associated with genetic variants that have previously been identified to be associated with breast cancer risk. SNPs were selected for this study, if they fulfilled one or both of the following criteria: (i) At the time this study was initiated, they were SNPs identified to be significantly associated with breast cancer susceptibility in GWAS or candidate studies carried out by the Breast Cancer Association Consortium (BCAC): rs889312 (*MAP3KI*), rs3817198 (*LSP1*) and rs13281615 (8q24) (7–9); rs13387042 (2q35) (8,10); rs1045485 (*CASP8*) (11); and rs3020314 (*ESR1*) (12). (ii) They showed evidence for significant ($P < 0.05$) association with endometrial cancer in the Studies of Epidemiology and Risk factors in Cancer Heredity (SEARCH) study during an analysis of 81 SNPs that had originally been selected as candidates for breast cancer susceptibility: rs3803662 (*TOX3*), rs1045485 (*CASP8*) and rs3857481 (6q14). We note that rs3857481 was not subsequently confirmed as a breast cancer susceptibility variant (7).

The nine SNPs that fitted these criteria were genotyped in three to six collaborating endometrial studies, comprising 2449–4188 cases and 2711–11928 controls.

Materials and methods

Study populations

Seven studies from Australia, USA and Europe contributed pre-existing data from SNP genotyping at each site to these analyses—hence not all SNPs have been analyzed in all studies. Controls recorded as having had a hysterectomy were excluded from all analyses. The majority of endometrial cancer cases were of endometrioid histology (85.5%). Additional details about each study are provided below.

Australian National Endometrial Cancer Study and Australian Ovarian Cancer Study controls. The Australian National Endometrial Cancer Study (ANECS) is an Australian population-based case–control family study of cancer of the uterine corpus (13). Women aged 18–79 years, registered on

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the Electoral Roll and newly diagnosed with primary cancer of the endometrium between July 2005 and December 2007 were identified through major hospitals nationally and also from state-based cancer registries. Female controls with no personal history of endometrial cancer or hysterectomy were recruited using two sources. A population-based control group comprising women randomly selected using the Australian Electoral Roll (voting is compulsory in Australia) and matched to the age and geographic distribution of the cases. A second control group of female blood donors were recruited with the aid of the Australian Red Cross Blood Service in Queensland. All participants completed a detailed questionnaire providing clinical and epidemiological information including body mass index and ethnicity. In addition, we also accessed available genotype data from controls only (with no prior history of hysterectomy) from the Australian Ovarian Cancer Study (AOCS). This is a national population-based case–control study of ovarian cancer with recruitment strategies almost identical to ANECS, the details of which have been previously published (14).

The Leuven Endometrial Study. The Leuven Endometrial Study (LES) is a hospital based case–control study (15). Eligible cases, identified by active surveillance of electronic patient files at the Leuven University Hospital, were white women aged 27–80 years diagnosed with endometrial cancer. Clinical and information of endometrial cancer patients was recorded during interview at the time of diagnosis and from pathology reports. All medical records were reviewed by trained abstractors and pathology reports compatible with primary, invasive, epithelial endometrial adenocarcinoma of all stages (I–IV) and all grades were consulted. A control group of healthy female blood donors was recruited with the aid of the Red Cross Blood Service in the University Hospital. Participants completed a detailed questionnaire providing epidemiological information, including age, weight, height and self-reported Belgian (Flemish) ethnicity for three generations.

National Study of Endometrial Cancer Genetics. NSECG, National Study of Endometrial Cancer Genetics. Cases were identified from collaborating clinicians throughout the UK from 2008 to present, taking care not to recruit from centers involved in SEARCH. Inclusion criteria were adenocarcinomas of the uterus presenting at $\leq$70 years of age. Almost all cases were incident and sampled within 6 months of diagnosis. Peripheral blood was collected from each participant and DNA extracted using standard methods. Tumor histology was confirmed from routine hospital reports and further details of histopathology and other tumor pathology characteristic was abstracted from these clinical pathology reports. Controls (45% males and 55% females) were drawn from the ColoRectal tumour Gene Identification study (16) and were unaffected by cancer. All cases and controls were of white UK ethnic origin.

The Polish Endometrial Cancer Study. The Polish Endometrial Cancer Study (PECS) is a population-based case–control study carried out in two cities in Poland (Warsaw and Łódz) during 2001–2003 (17). The cases were women aged 20–74 years old, newly diagnosed with pathologically confirmed endometrial cancer and identified through participating hospitals and local cancer registries. Controls without a history of breast or endometrial cancer and with an intact uterus at time of enrollment were randomly selected from a database of all residents and frequency matched to cases (1:2 case:control ratio) by study site (Warsaw and Łódz) and age in 5 years categories. In-person interviews, including information on demographic characteristics and known or suspected endometrial cancer risk factors, were obtained from 551 cases (79% of the 695 eligible cases) and 1925 controls (68% of the 2843 eligible controls). Trained interviewers collected venous blood from 88% of participating cases and 94% of participating controls. To approximate a 1:1 case–control ratio for genotyping, cases and randomly selected 5 years age categories and study site frequency-matched controls who had donated blood were selected. The study protocol was reviewed and approved by local Polish and US National Cancer Institute institutional review boards. All participants provided written informed consent.

Singapore and Sweden Breast/Endometrial Cancer Study. Details of the population selection process for the Singapore and Sweden Breast/Endometrial Cancer Study (SASBAC) have been published previously (18). Briefly, this population-based case–control study was conducted among Swedish women aged 50–74 years, who were residing in Sweden between 1 January 1994 and 31 December 1995. Endometrial cancer cases were identified through the nationwide cancer registries in Sweden. Controls, frequency matched for age, were randomly selected from the Swedish Registry of Total Population. The study was restricted to postmenopausal women with an intact uterus and no previous diagnosis of endometrial cancer. All participants provided detailed questionnaire information. For endometrial cancer, histological specimens were reviewed and reclassified by the study pathologist. Genomic analyses were conducted by the Singapore node of the study.

The Studies of Epidemiology and Risk factors in Cancer Heredity. The SEARCH is an ongoing UK population-based study with cases ascertained through the Eastern cancer Registration and Information Centre (http://www.ecric.org.uk). All women diagnosed with endometrial cancer between the ages of 18–69 years (average age diagnosis 58 years) from 31 July 2001 to 1 September 2007 were eligible for inclusion. Approximately 54% of eligible patients have enrolled in the study. Women taking part in the study were asked to provide a 20 ml blood sample for DNA analysis and to complete a comprehensive epidemiological questionnaire. Controls were matched to cases in geographical profile and age and were drawn from two sources: (i) SEARCH participants (http://www.srl.cam.ac.uk/search/Homepage.htm), who were female with no prior history of cancer at the time of recruitment. Approximately 35% of eligible SEARCH controls enrolled in the study and (ii) European Prospective Investigation of Cancer-Norfolk, a population-based study of diet and cancer (19). There were 1127 endometrial cases and 6824 controls available for genotyping analysis at the time of this study.

The Women's Insight and Shared Experiences Study. The Women's Insight and Shared Experiences Study (WISE) is a population-based case–control study conducted from among residents from a contiguous nine county region around Philadelphia and has been described previously (20). Eligible cases, identified by active surveillance at 61 hospitals, were African-American or Caucasian women aged 50–79 years, who were newly diagnosed with endometrial cancer between 1 July 1999 and 30 June 2002. Pathological reports and medical records were reviewed by trained abstractors and case status was validated by a pathology report that was compatible with primary, invasive, epithelial endometrial adenocarcinoma of all stages (I–IV) and all grades. Frequency-matched control subjects were selected by random digit dialing and restricted to women with no history of endometrial cancer or hysterectomy. Telephone interviews to complete detailed questionnaires were conducted for all participants.

Genotyping

For three studies (ANECS/AOCS, LES, SASBAC), genotyping was performed using matrix-assisted laser desorption/ionization time of flight mass spectrometry for the determination of allele-specific primer extension products using Sequenom's MassARRAY system and iPLEX technology (Sequenom San Diego, CA). Oligonucleotides were designed using MassARRAY Assay Design software (version 3.1; Sequenom) and results analyzed using TYPER software (version 3.4; Sequenom).

SEARCH genotyping was carried out by nuclease assay (Taqman; Applied Biosystems, Foster City, CA). Taqman genotyping reagents were design by Applied Biosystems (http://www.appliedbiosystems.com/) as Assays-by-Design. Genotyping was performed using the ABI Prism 7900HT Sequence Detection Systems according the manufacturer's instructions.

PECS genotyping was completed at the Core Genotyping Facility of the National Cancer Institute's Division of Cancer Epidemiology and Genetics using the Illumina iSelect Custom BeadChip for all the SNPs presented except for two SNPs: rs3857481 and rs4777792 were genotyped using Taqman as described above.

NSECG cases were genotyped using Sequenom iplex methodology, as described above. NSECG control genotype data were extracted from existing Illumina 550K genome-wide scan data (16) or genotyped using the Kaspar method if the SNP was not present on the Illumina 550K platform.

WISE samples were genotyped using the SNaPShot method (Applied Biosystems) and analyzed on an ABI 3130 capillary sequencer according to manufacturer's instructions.

All studies complied with quality control standards by including $\geq$2 negative (no DNA) polymerase chain reaction controls per 384-well assay plate and at least 2% of samples in duplicate. A genotyping call rate >95% and at least 98% concordance between duplicated samples for each SNP assay was required. Additionally, the genotype distributions in the control samples of each study were required to conform to Hardy–Weinberg equilibrium (HWE) at $P > 0.005$. Three subsets were excluded from the meta-analyses on this basis: SASBAC: SNPs rs13281615, $P = 1 \times 10^{-13}$ and rs1045485, $P = 0.0002$; LES: SNP rs3020314, $P = 0.002$.

Imputation

Rs3857481 was the only SNP that had not been genotyped in the ANECS study. We were able to obtain imputed genotype dosages for this SNP for 599 ANECS cases with endometriod histology genotyped as part of a GWAS of endometrial cancer using an Illumina Infinium 610k array (5) 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 (21). Non-genotyped SNPs were imputed using the HapMap Phase 3 data as a reference panel (22). Imputed genotype dosages were compared between cases and controls, adjusting for the first three 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 (23), ProbABEL (24) and MACH (25).

Statistical methods

For each SNP, deviation of genotype frequencies in controls from Hardy–Weinberg equilibrium was assessed by a χ^2 test with one degree of freedom. Genotype risks were estimated as ORs with 95% CIs, and significance levels were calculated using logistic regression. Meta-analysis was carried out and Forest plots generated using the Metan command within Stata™(http://www.stata.com).

Results and discussion

A total of nine breast cancer-associated SNPs were genotyped in up to six different endometrial cancer case/control studies of European ancestry from Sweden, UK, Belgium, Poland, Australia and the USA. Genotype counts and ORs (95% CIs) for individual studies and overall minor allele frequencies and risk estimates are shown in Supplementary Table 1, available at *Carcinogenesis* Online. Per allele ORs (95% CIs) for each SNP are shown as Forest plots in Figure 1 with the original reported breast cancer per allele risk estimates also shown for

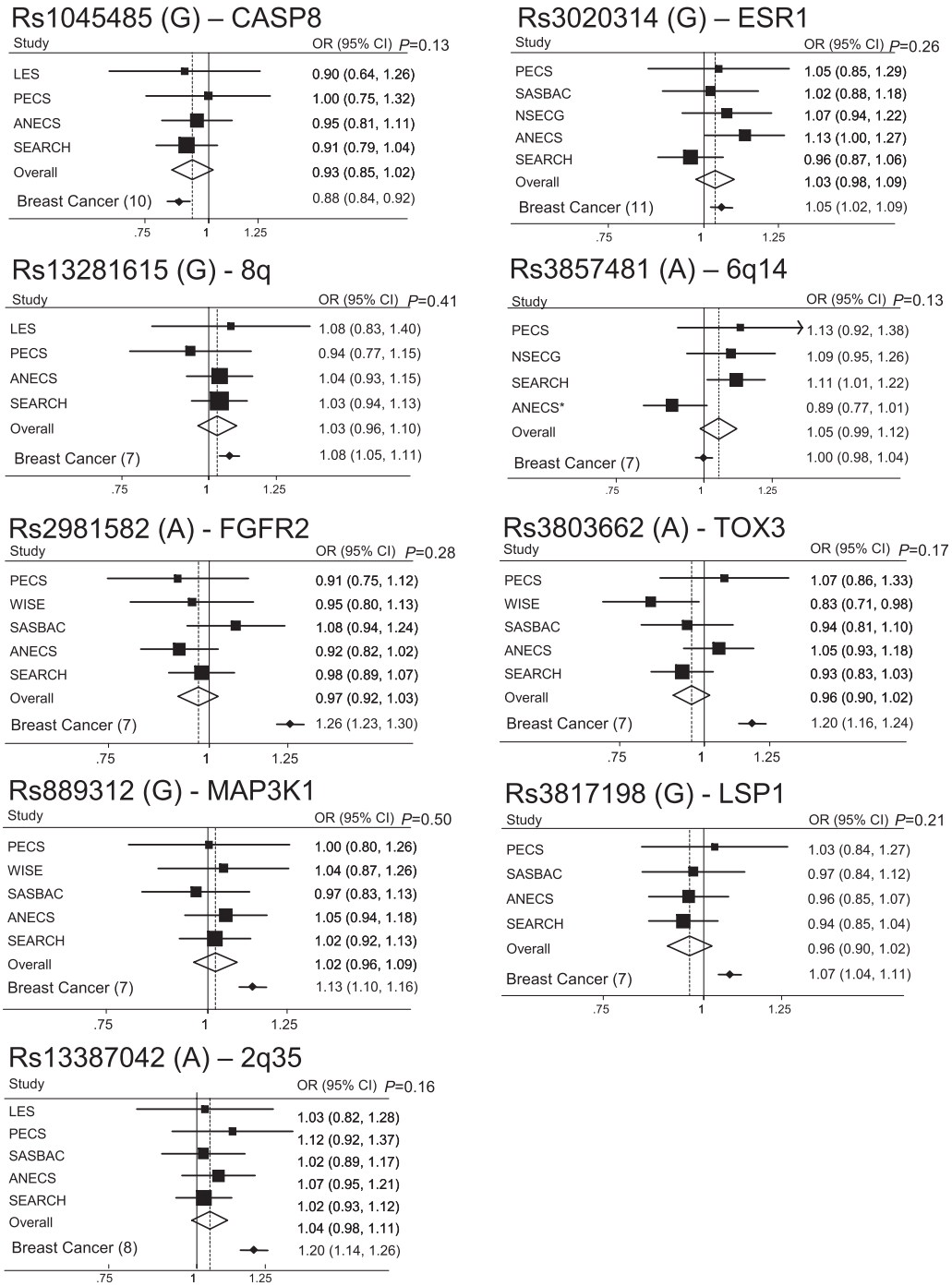

Fig. 1. Forest plots showing per allele OR and 95% CIs for each SNP (risk allele) by study. The size of the black box is proportional to the study size. The diamond represents the OR and 95% CIs for the meta-analysis of each SNP. Per allele ORs and 95% CIs for breast cancer (reference in brackets) are shown for comparison at the bottom of each Forest plot. *Results for ANECS rs3857481 were imputed using a subset of the ANECS cases ($n = 599$) (5) matched to an alternative control group (1958 Birth Cohort controls $n = 2694$ and National Blood Donor controls $n = 2496$) (21).

comparison. There were no significant heterogeneities between studies for any SNP ($P > 0.05$) apart from rs3857481 ($P = 0.041$).

The SNPs in *CASP8* (rs1045485), *ESR1* (rs3020314) and in the GWAS-identified 8q24 region (rs13281615) were not significant, but their point estimates lie within the 95% CIs for the corresponding breast cancer risk estimates (Figure 1). Further collaboration may clarify the effects of these SNPs on endometrial cancer risk.

The other six GWAS-identified breast cancer SNPs: rs3857481 (6q14), rs2981582 (*FGFR2*), rs3803662 (*TOX3*), rs889312 (*MAP3-KI*), rs3817198 (*LSP1*) and rs13387042 (2q35) had no apparent association with risk of endometrial cancer in these studies (Supplementary Table 1 is available at *Carcinogenesis* Online, Figure 1). The CIs for the overall endometrial cancer risk do not overlap with the point estimates for breast cancer risk, indicating that these SNP alleles cannot have similar effects on breast and endometrial cancer risk. We have >90% power to detect associations of the same magnitude as those observed for breast cancer for *FGFR2*, *TOX3*, 2q35 and *MAP3K1*, but the equivalent power is considerably lower for SNPs with more modest effects on breast cancer risk, e.g. 45% for *LSP1* and 28% for *ESR1*.

A smaller study of 692 endometrial cancer cases and 1723 controls by McGrath *et al.* (26) also assessed endometrial cancer risk associated with the six GWAS-identified breast cancer SNPs examined in this study. These authors similarly report no statistically significant associations with endometrial cancer risk that are of similar magnitude and/or direction to that reported for breast cancer, although two of the risk estimates for endometrial cancer (rs2981582, rs13281615) might be interpreted to be consistent with the direction of effect we observed for endometrial cancer in this study.

Given their known associations with breast cancer risk, the SNPs examined here might be considered to have a higher prior probability of association with endometrial cancer than randomly chosen SNPs. The point estimates of the effect sizes of three of these alleles in endometrial cancer were comparable with those in breast cancer but did not reach statistical significance, whereas for breast cancer, they are highly significant due to the large numbers (currently ∼80 000) contributing to the Breast Cancer Association Consortium (BCAC). This emphasizes the need for further collaboration between studies in order to provide the sufficiently large sample sizes needed for confirmation of common low-penetrant associations at appropriate levels of significance.

Supplementary material

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

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