Breast Cancer Online, **10**(12), Page 1 of 3, ***e23***
doi:10.1017/S1470903107006554

ISSN 1470-9031

Breast Cancer Online
www.bco.org

Journals Club

Review of: Genetic variation at the CYP19A1 locus predicts circulating estrogen levels but not breast cancer risk in postmenopausal women

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Citation of original article:
C. A. Haiman, L. Dossus, V. W. Setiawan, D. O. Stram, A. M. Dunning, G. Thomas, M. J. Thun, D. Albanes, D. Altshuler, E. Ardanaz, H. Boeing, J. Buring, N. Burtt, E. E. Calle, S. Chanock, F. Clavel-Chapelon, G. A. Colditz, D. G. Cox, H. S. Feigelson, S. E. Hankinson, R. B. Hayes, B. E. Henderson, J. N. Hirschhorn, R. Hoover, D. J. Hunter, R. Kaaks, L. N. Kolonel, L. Le Marchand, P. Lenner, E. Lund, S. Panico, P. H. Peeters, M. C. Pike, E. Riboli, A. Tjonneland, R. Travis, D. Trichopoulos, S. Wacholder, R. G. Ziegler. ***Cancer Research*** 2007; **67**(5): 1893–1897.

Abstract of the original article:
The CYP19A1 gene encodes the enzyme aromatase, which is responsible for the final step in the biosynthesis of estrogens. In this study, we used a systematic two-step approach that included gene resequencing and a haplotype-based analysis to comprehensively survey common genetic variation across the CYP19A1 locus in relation to circulating postmenopausal steroid hormone levels and breast cancer risk. This study was conducted among 5,356 invasive breast cancer cases and 7,129 controls comprised primarily of White women of European descent drawn from five large prospective cohorts within the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. A high-density single-nucleotide polymorphism (SNP) map of 103 common SNPs (⩾5% frequency) was used to identify the linkage disequilibrium and haplotype patterns across the CYP19A1 locus, and 19 haplotype-tagging SNPs were selected to provide high predictability of the common haplotype patterns. We found haplotype-tagging SNPs and common haplotypes spanning the coding and proximal 5′ region of CYP19A1 to be significantly associated with a 10% to 20% increase in endogenous estrogen levels in postmenopausal women [effect per copy of the two-SNP haplotype rs749292-rs727479 (A-A) versus noncarriers; $P = 4.4 \times 10(-15)$]. No significant associations were observed, however, with these SNPs or common haplotypes and breast cancer risk. Thus, although genetic variation in CYP19A1 produces measurable differences in estrogen levels among postmenopausal women, the magnitude of the change was insufficient to contribute detectably to breast cancer.

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Received: 21/11/07
Accepted: 22/11/07
BCO/655/2007/JC

Review

An exciting chapter in breast cancer research has been the identification of specific genes that potentially confer a high risk of developing breast cancer. Breast and ovarian cancer are components of several cancer syndromes in women with one or two copies of deleterious mutations in specific genes (autosomal dominant cancer syndromes). The two genes with the strongest association with breast cancer risk are BRCA1 and BRCA2. The discovery of these breast-cancer-susceptibility genes included the identification of families with multiple cases of breast cancer, screening family members for loci associated with the familial segregation of breast cancer (linkage analysis) and subsequent identification of the gene responsible for the association through positional cloning. Mutations in BRCA1 and BRCA2 are rare with around 1 in 1000 women carrying a mutation and they account for less than 5% of breast cancers in the general population.

In addition to these so-called high-risk genes, in recent years research has focused on common genetic variants that contribute to the development of breast cancer, although by influencing risk to a much lesser degree. Research into these so-called low-risk genes is intensive now for three reasons:

- they promise to provide additional insights into the underlying biology of breast cancer;
- they may modify the influence of other risk factors through gene-environment interaction, thereby explaining why many of the known risk factors appear to be such weak causes of breast cancer;
- because the variants of these genes are likely to be relatively common in the population, they may account for a more substantial proportion of breast cancers than the high-risk susceptibility genes.

One way to identify common variants associated with a small increase or decrease in risk of disease is through genome-wide association studies (GWAS). This approach was used recently in a collaborative study to identify eight common genetic variants associated with a small decrease or increase in breast cancer risk [1,2]. In that study, researchers initially performed a GWAS of a panel of more than 200 000 SNPs genotyped in 408 breast cancer cases and 400 controls from the UK. In the second stage, ~5% of the original SNPs selected on the basis of the statistical significance of the difference in genotype frequency between cases and controls were tested using a further ~4000 breast cancer cases and ~4000 controls from the SEARCH study.

The third stage tested the 30 most significant (lowest *P*-values) SNPs in 22 additional case–control studies participating in the Breast Cancer Association Consortium. The eight common variants identified are located in CASP8, TGFB1, FGFR2, TNRC9, MAP3K1, LSP1 and H19 genes, and in the 8q region. Among this group of variants, the one in CASP8 is the rarest with only 2% of women carrying two copies while the variant in TNRC9 is the most common with 21% of women carrying two copies. Relative risks for breast cancer for women carrying two copies of the variant allele compared with women carrying two copies of the common allele ranged from 0.73 (95% CI = 0.60–0.90) for CASP8 to 1.63 (95% CI = 1.53–1.72) for FGFR2. The main limitation of these findings is that the causative alleles are still unknown because the genetic variants identified might just be correlated (i.e. in linkage disequilibrium – LD) with the causative alleles.

An alternative approach to identify common genetic variants associated with risk of disease is being followed by the National Cancer Institute (NCI) Breast and Prostate Cancer Cohort Consortium. Candidate genes, mostly in the hormonal pathway to breast and prostate cancer, were selected on the basis of their function, sequenced, and tag single nucleotide polymorphisms (SNPs) were selected to capture most of the genetic variation across the genes [3]. An interesting example of this approach can be found in a recent publication from the Consortium that reports the results on CYP19A1 – the gene that encodes for the aromatase enzyme – and breast cancer risk [4]. The CYP19A1 gene was chosen because of its importance within the steroid hormone pathway. In postmenopausal women, oestrogens are mainly produced in adipose tissue from androgens through the action of the aromatase enzyme. We also know that a doubling of the concentration of oestrogen levels in the circulation is associated with an increased risk of breast cancer in postmenopausal women [5]. For example, postmenopausal women with oestradiol or oestrone levels two-fold higher than levels in a comparison group of women have a 30% increase in risk of developing breast cancer.

The NCI Cohort Consortium resequenced CYP19A1 to identify all the SNPs with a minor allele frequency of at least 5% in 95 women of different ethnic origin from the Multi Ethnic Cohort (MEC). Subsequently, 349 women in the MEC study were genotyped for 103 common SNPs and two rare missense variants. CYP19A1 contains four LD blocks and within these blocks 19 tag SNPs were identified that predicted 15 common haplotypes.

To test for association between these SNPs and breast cancer risk or circulating hormone levels, 5356 breast cancer cases and 7129 controls from the five large cohorts in the NCI consortium were

https://doi.org/10.1017/S1470903107006554 Published online by Cambridge University Press

genotyped for the 19 tag SNPs. SNPs in LD blocks 3 and 4 were significantly associated with higher levels of oestrogens with carriers of two copies of the minor allele having between 10% and 20% higher levels of oestrone or oestradiol than carriers of two copies of the major allele (*P*-values from the codominant models between 1×10^{-3} and 6×10^{-11}). No SNP was associated with breast cancer risk with odds ratios ranging from 0.95 to 1.05 (all *P*-values >0.3). This study provides robust statistical evidence that common genetic variants in the CYP19A1 gene are associated with variation in oestrogen levels in the circulation but not with breast cancer risk.

The increase in circulating oestrogen levels associated with common variants in CYP19 may not be enough to produce a detectable effect on breast cancer risk though such effect might be detected when genetic variation in multiple genes within the hormonal pathway is studied further. Although this 'candidate gene' approach is a promising complement to GWAS it shares with GWAS the same important limitation – that is, that the variants identified might just be in LD with functional variants responsible for the association between this locus and oestrogen levels. These causative variants are still unknown and considerable further work will be necessary to identify them.

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