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Commentary: No multiplicative GXE interactions for breast cancer risk: Have we reached a verdict or is the jury still out?

Mary Beth Terry

Department of Epidemiology, Columbia University Mailman School of Public Health, 722 W 168th St Room 1607, New York, NY 10032, USA. E-mail: mt146@cumc.columbia.edu

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In this issue of the *IJE*, Kapoor *et al.*[1] report findings from the most comprehensive breast cancer (BC) study to date evaluating gene–environment (GXE) interactions, with 205 BC susceptibility genes and 13 established BC risk factors. With both its size and scope, this study provides evidence specific to the evaluation of the potential use of GXE interactions in risk models and for considering potential aetiologic mechanisms. The study used data from the Breast Cancer Association Consortium (BCAC) and assessed genetic variants with two platforms—iCOGS (28 176 cases and 32 209 controls) and OncoArray (44 109 cases and 48 145 controls). The OncoArray platform has ~2.5 times the coverage of single nucleotide polymorphisms (SNPs), with 533 000 SNPs compared with 211 155 SNPs on iCOGS. The investigators performed analyses separately by platform and then combined data using meta-analytic techniques. Specifically, they examined interactions with age at menarche, parity (ever, number and age at first birth), breastfeeding (ever and overall duration), ever use of oral contraceptives, body mass index (BMI), adult height, lifetime alcohol consumption, cigarette smoking (current and overall pack-years based on duration and intensity) and menopausal hormone therapy (MHT, opposed and unopposed). The key finding was an overall lack of multiplicative GXE interactions with established BC risk factors with few exceptions.

Model discrimination for BC risk models is still only moderate,[2] leading some to hope that improvement may be achieved through inclusion of additional non-genetic risk factors (most models focus primarily on reproductive risk factors), wider incorporation of genetic variants through polygenetic risk scores, and the inclusion of GXE interactions. This BCAC paper[1] provides strong evidence that GXE interactions will not improve model performance, at least for the established BC risk factors they included and genetic variants they considered. Nonetheless, the absence of multiplicative interaction means that there will be additive interactions when both G and E are associated with the outcome. Table 1 supports an association between all established risk factors and overall BC and oestrogen receptor positive (ER+) BC in the expected direction and Supplementary Table 2 shows the SNP associations. The presence of additive interactions means that modifying BC risk factors will have a larger impact for women who are at higher absolute risk. For example, we have demonstrated a lack of multiplicative interactions with absolute predicted risk estimated from a pedigree-based model, but impact on absolute risk difference, for a number of BC risk factors including BMI,[3] aspirin use,[4] benign breast disease[5] and physical inactivity.[6]

The absence of multiplicative interactions simplifies the clinical and public health translation, as the relative risk for a given factor not included in the risk model can be multiplied by the absolute predicted risk from the model. This reduces the number of factors that need to be added (and independently validated) to risk models. It also facilitates the communication of absolute risk before and after the addition of the relative risk factor. For example, Phillips and colleagues have developed such an algorithm-based tool that uses absolute predicted risk from pedigree models and overlays different risk reduction strategies (e.g. tamoxifen and risk-reducing surgeries) to improve risk counselling and clinical management decisions through the iPrevent tool which has been independently validated.[7] Such an approach could be extended to other risk factors including use of other chemopreventive options or lifestyle changes (e.g. NSAID use, weight loss, alcohol reduction, physical activity uptake).

In addition to providing an answer related to whether risk models should include GXE interactions, this BCAC

study was also important for aetiologic reasons as it provided independent replication of two previous interactions, and found three new multiplicative interactions, after stringent methods were applied to avoid false discovery. Although these interactions likely are not informative for risk prediction, they provide some additional information to consider for aetiology. Specifically, the authors found GXE interactions related to current opposed MHT and a genetic variant in the *IGFBP5* (rs4442975) gene, and increasing parity and age at first birth with a genetic variant in the heat shock protein family (*HSPA4*). However, although these three findings may have aetiologic relevance, it is unlikely that they will help in making decisions about MHT. Even with the negative multiplicative interaction (odds ratio = 0.85), the increased risk from opposed MHT reported in Table 1 supports that risk from MHT is still >1 in each variant subgroup for ER+ BC [but not ER negative (ER−) BC], albeit lower than in women with the minor allele. A recent meta-analysis supports that the BC risk from MHT may be even higher than previously expected,[8] though the medication is also related to reduced risk of other outcomes including colorectal cancer.[9] Thus, like with many medications, the risks and benefits may differ greatly across individuals.

Despite the size of this BCAC study, it had limited power to detect interactions for genetic variants and established risk factors for the ER− cases compared with controls (Table 1). The study was also limited, as the authors acknowledge, to women of European ancestry. Further, the study cannot be used to answer questions about GXE for a broader set of environmental risk factors as it was limited to the established, and mainly reproductive, BC risk factors. For example, we have found multiplicative interactions between absolute predicted risk and biomarkers of environmental factors like polycyclic aromatic hydrocarbons.[10] It remains to be fully tested, but there may be more GXE interactions for other environmental exposures, as variants in genes related to DNA repair may affect environmental carcinogens more than established reproductive risk factors. Thus, it should be more widely acknowledged that even though there have been major advances in the comprehensiveness of genetic risk assessment, only a small set of established BC risk factors have been included in most clinical risk models.

Kapoor *et al.* should be commended for providing robust evidence on the absence of multiplicative GXE interactions with established BC risk factors and for providing novel data related to three interactions. Thinking through ways to improve how we communicate the absence of multiplicative interactions while at the same time promoting a greater awareness of additive interactions, and absolute risk, remains a challenge.

Conflict of interest: None declared.

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