No Gene-Environment Interactions Found in Million Women Study of Breast Cancer

Twelve low-penetration genetic polymorphisms appear to have relatively little effect on breast cancer risk, and do not seem to interact significantly with 10 known environmental risk factors, according to a study published recently in The Lancet (2010;375:2143-2151).

“Nature” Versus “Nurture”
Epidemiologists typically classify risk factors for cancer and other diseases as either genetic or environmental (defined broadly to include behavioral, reproductive, and anthropometric factors, as well air or water pollution and others). The prevalence of clinically significant BRCA1 and BRCA2 genetic mutations in the general population is less than 1%. High-penetrance genetic mutations in one of these genes can result in a lifetime breast cancer risk as high as 74%, corresponding to relative risks in the range of 4 to 6. In contrast, the majority of other breast cancer susceptibility polymorphisms have much higher prevalence (for some, greater than half of the general population) and much lower penetrance (increasing risk by less than 50% and in some cases by only a small percentage).

According to second author Gillian Reeves, PhD, a reader in epidemiology in the cancer epidemiology unit at Oxford University in Oxford, United Kingdom, “It is fair to say that known genetic risk factors still account for a very small proportion of total breast cancer risk and only a relatively small proportion of familial breast cancer risk. By contrast, a substantial proportion of breast cancer risk can be attributed to certain environmental risk factors [such as reproductive patterns].”

“Nature” and “Nurture”
Gene-environment interactions refer to the influence of genotype (such as cancer sensitivity polymorphisms) on an individual’s sensitivity to environmental risk factors such as diet, use of hormone therapy, and exposure to ionizing radiation, or vice versa: the effects of environmental factors as modifiers of genetic susceptibility. Recognizing that these interactions could have clinical relevance may aid in advising individuals with these genetic factors that it is especially important for them to avoid certain environmental exposures or to undertake certain behaviors to reduce risk.

The Million Women Study is an epidemiologic investigation into breast cancer and other women’s health issues being conducted in the United Kingdom. The current Lancet study included a subset of the Million Women Study cohort: 7610 women who had developed breast cancer and 10,196 cancer-free women who served as controls. The researchers examined interactions among 12 low-penetrance breast cancer susceptibility polymorphisms (FGFR2-rs2981582, TNRC9-rs3803662, 2q35-rs13387042, MAP3K1-rs889312, 8q24-rs13281615, 2prs4666451, 5p12-rs981782, CASP8-rs1045485, LSP1-rs3817198, 5q-rs30099, TGFB1-rs1982073, and ATM-rs1800054) and 10 environmental characteristics (age at first birth, age at menarche, age at menopause, alcohol consumption, body mass index, history of breastfeeding, height, menopausal status, parity, and use of hormone replacement therapy) that had been determined by previous research to influence breast cancer incidence.

“When the effects of the 7 polymorphisms most strongly related to overall breast cancer risk were combined using a polygenic risk score, the cumulative risk of breast cancer to age 70 among women in the top fifth for such a score was twice that among women in the bottom fifth (8.8% vs 4.4%). However, the difference in absolute risk between

The researchers examined the relationships among 12 genetic and 10 reproductive, behavioral, and anthropometric characteristics that had been determined by previous research to be risk factors for breast cancer.

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women in extreme fifths of polygenic risk score was much greater for estrogen receptor-positive (7.4% vs 3.4%) than for estrogen receptor-negative disease (1.4% vs 1.0%),” explains Dr. Reeves.

Regarding the question of gene-environment interactions, lead author Ruth Travis, MD, PhD, adds that “Results from this study suggest that common genetic and environmental factors (reproductive and lifestyle factors) act independently on breast cancer risk, so regardless of common inherited genetic variation, a woman can still reduce her risk by modifying her lifestyle, for example by maintaining a healthy body weight and limiting alcohol intake.”

The absence of interactions means that priorities for risk-reducing strategies are similar for most women (for example, being based on known risks associated with lifestyle and reproductive factors) regardless of the common genetic risk factors for the disease, she says. Dr. Travis is an epidemiologist, research fellow, and senior scientist in the cancer epidemiology unit at Oxford University.

What Is Next?

What can researchers do with the information derived from this study? According to Susan Gapstur, PhD, MPH, vice president of the epidemiology research program at the American Cancer Society (ACS), researchers must retrench and join forces to find the answers to the questions that are raised by this article. “The more we [epidemiologists] can work together with our colleagues in basic science and clinical practice to do truly translational research, the better off we’re going to be.”

Some of these areas may be informed by the ACS’s recently launched Cancer Prevention Study 3 (CPS-3). Similar to the Million Women Study, the new ACS cohort study includes plans for the analysis of DNA from blood samples, thereby potentially offering further insight into the interplay between environmental and genetic risk factors.

“There are a number of large cohorts being assembled throughout the world and the ACS CPS-3 is going to be able to play a critical role in large international collaborations,” Dr. Gapstur says. “That’s really important in cancer in large part because…differences across countries are not just genetic but they’re also environmental. International collaborations will allow us to look at a much broader range of exposures which may help us to assemble the puzzle of that broad range of exposures and genetic alterations.”

Oral Bisphosphonate Use Associated With a Decreased Risk of Breast Cancer

A pair of observational studies published recently in the Journal of Clinical Oncology link the use of oral bisphosphonates to a significantly decreased risk of invasive breast cancer in postmenopausal women. Experts, however, urge caution in interpreting the results.

Breast Cancer in Northern Israel Study

Data from the Breast Cancer in Northern Israel Study were used in a population-based, case-control study that compared pharmacy data regarding the postmenopausal use of bisphosphonates in 1832 breast cancer patients and 2027 controls (J Clin Oncol. 2010;28:3577-3581). According to the article, “The use of bisphosphonates for longer than one year before diagnosis, but not for shorter than one year, was associated with a significantly reduced relative risk of breast cancer (odds ratio [OR], 0.61; 95% confidence interval CI, 0.50 to 0.76). Breast cancer risk did not change if bisphosphonates were used for additional years.”