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.”

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Adjustment for age, fruit and vegetable consumption, sports activity, family history of breast cancer, ethnic group, body mass index, use of calcium supplements, hormone replacement therapy use, number of pregnancies, months of breastfeeding, and age at first pregnancy decreased the effect magnitude somewhat, although the association remained significant (OR, 0.72; 95% CI, 0.57 to 0.90).

The second study (J Clin Oncol. 2010;28:3582-3590) is based on postmenopausal women enrolled in the Women’s Health Initiative (WHI) cohort after the exclusion of subjects who had taken tamoxifen or raloxifene or had been previously diagnosed with breast cancer. Among the remaining women, 2816 had used oral bisphosphonates and 151,952 had not. The researchers compared the risk of breast cancer among the 2 groups. Age-adjusted analyses demonstrated a 31% lower incidence of invasive breast cancer among the bisphosphonate users (hazard ratio [HR], 0.69; 95% CI, 0.54 to 0.88; P = .01).

Several experts not involved with these 2 studies also note that observational studies may yield misleading results.

“Of course these observational studies can only demonstrate associations and not establish causality,” says Rowan T. Chlebowski, MD, PhD, lead author of the WHI study, professor of medicine at the David Geffen School of Medicine at the University of California at Los Angeles (UCLA), and chief of the division of medical oncology and hematology at Harbor-UCLA Medical Center. “Nonetheless, these 3 separate analyses report nearly identical 30% lower incidence of invasive breast cancer comparing bisphosphonate users to nonusers,” says Dr. Chlebowski, referring to these 2 Journal of Clinical Oncology articles plus a third study published in the British Journal of Cancer (2010;102:799-802).

Although cautious, Gad Rennert, MD, PhD, lead author of the Breast Cancer in Northern Israel Study, seems more confident. Dr. Rennert proposes that, “Several facts support the hypothesis that use of bisphosphonates is possibly causally associated with breast cancer risk reduction. These include the fact that the effect is seen only after one year of treatment…” He also notes that bisphosphonates influence the same metabolic pathway as statins, which in some studies have been inversely associated with risk of some cancers, and that his recent analyses (not yet published) suggest “a possible similar negative association between bisphosphonates and the risk of cancers of other sites.” Dr. Rennert is director of the Clalit Health Services National Cancer Control Center and head of the National Israeli Breast and Colorectal Cancer Detection Programs of the Ministry of Health and Israel Cancer Association. He is also chair of the department of community medicine and epidemiology at Carmel Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology in Haifa, Israel.

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“What does estrogen replacement therapy [ERT] do for the risk of coronary artery disease in women?” Clifford Hudis, MD, asks rhetorically. “The answer for 30 years was that it reduced the risk. That was based on association studies that were similar to [the Rennert and Chlebowski studies]. Patients who were given ERT had reduced risk of heart attack. But in the prospective, randomized, placebo-controlled blinded study [conducted as part of the WHI], this was not seen.” Dr. Hudis is chief of the breast cancer medicine service and attending physician at Memorial Sloan-Kettering Cancer Center in New York City, professor of medicine at Weill Cornell Medical College of Cornell University, and an associate editor for the *Journal of Clinical Oncology*. “The point is that these are suggestive results that could be true, but it is not certain that they are.”

**The Estrogen-Bone Connection**

In addition to the usual general concerns over the possibility of “residual confounding” in observational studies, there are more specific challenges to studying bisphosphonates and breast cancer incidence.

“Women who use bisphosphonates may be at lower risk of breast cancer not because of the effect of the drug,” says Eric Jacobs, PhD, strategic director of pharmaco-epidemiology for the ACS, “but because they have low bone mineral density, the usual reason for taking the drug.”

According to Dr. Jacobs, low bone mineral density is often caused by low levels of estrogen, which studies have linked to lower breast cancer risk. He says that, although the current studies were well conducted (and utilized multivariable models that included variables associated with estrogen exposure), data from randomized trials are needed before physicians prescribe bisphosphonates specifically for breast cancer prevention.

However, Dr. Hudis believes that logistical and financial challenges might prevent the initiation of a randomized controlled trial of bisphosphonates for primary breast cancer prevention. Fortunately, bisphosphonates also appear promising for slowing the progression of breast cancer after diagnosis and, according to Dr. Chlebowski and colleagues, “The influence of bisphosphonates in ongoing randomized adjuvant therapy trials in women with early stage breast cancer addressing outcomes, including contralateral breast cancers, will help clarify the clinical significance of the current findings.”

Writing in an editorial appearing in the same issue of the *Journal of Clinical Oncology* as the 2 studies, Michael Gnant, MD, professor of surgery at the Medical University of Vienna in Vienna, Austria, advises that, “At this point, it would be premature to recommend the use of oral bisphosphonates to prevent breast cancer in all postmenopausal women. However, it is not unreasonable to consider the potential anticancer benefits of bisphosphonate therapy, in addition to its bone protecting effects, when evaluating treatment options in women with postmenopausal osteoporosis, especially considering that bisphosphonates are generally well tolerated in this population.”

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