Fat May Fuel Breast Cancer Growth

By Karyn Hede

Maintaining a healthy weight and exercising regularly have become standard advice for lowering the risk of breast cancer. But researchers are finding that these lifestyle changes may also be associated with better survival and lower recurrence in women with breast cancer.

New evidence from several fronts suggests that excess body fat promotes breast cancer growth and that reducing body fat and increasing physical activity improve the odds of survival. Results of the Million Woman Study, a longitudinal cohort study of 1.2 million women in the U.K., concluded that being overweight or obese is associated with a higher risk of postmenopausal breast cancer and lower survival. The report, published in December in the British Medical Journal, also found an association between high body mass index and other cancers, such as endometrial cancer and cancer of the esophagus.

That report, along with several other large prospective studies, should put to rest any doubt that excess weight contributes to the risk of developing breast cancer after menopause, said Heather Eliassen, Sc.D., an epidemiologist at the Harvard School of Public Health in Boston and a lead investigator in the Nurses’ Health Study. The confusion has been over the observed inverse association between weight and premenopausal breast cancer.

Rebecca Cleveland, Ph.D., an epidemiologist at the University of North Carolina at Chapel Hill and colleagues at four collaborating institutions studied long-term outcomes of 1,508 women diagnosed with breast cancer between 1996 and 1997 as part of the Long Island Breast Cancer Study Project. The researchers looked at whether weight gain before diagnosis is associated with breast cancer survival. They reported in the journal Cancer Epidemiology, Biomarkers and Prevention in September that 5 years after diagnosis, 84% of obese women were alive versus 94% of nonobese women. Further analysis showed that for every 7 pounds of weight gained after age 18, the risk of dying from breast cancer increased 7%. When they looked specifically at women who were premenopausal at diagnosis, those who had gained less than 35 pounds were at little increased risk, but those who had gained more than 35 pounds had a twofold-increased risk of dying of breast cancer. Among those who were postmenopausal at diagnosis, weight gain of 30 pounds or more since age 50 was associated with a threefold increase in the risk of dying.

After diagnosis, breast cancer survivors who gained more than 22 pounds had an increased risk of dying of breast cancer, according to a study presented at the Frontiers in Cancer Prevention Research meeting in December. The research, presented by Hazel Nichols, a graduate student at the Johns Hopkins Bloomberg School of Public Health, was a follow-up study of participants in the Collaborative Women’s Longevity Study, a multicenter case-control study of more than 18,000 women diagnosed with breast cancer between 1988 and 2001. The study included 3,993 women who returned questionnaires sent an average of 6 years after diagnosis and were followed up for an additional 6 years afterward. During the study, 121 women died of breast cancer and 421 died of other causes.

“There's been quite a lot of work with relation to breast cancer incidence and weight gain, but the literature for breast cancer mortality or survival in relation to postdiagnosis weight is much smaller,” Nichols said. “What distinguishes this research is that we were able to look at changes in body weight in the years after diagnosis, whereas some of the work that’s out there looks only at your weight when you were diagnosed and then subsequent survival.”

The group Nichols studied was selected from the subset who returned questionnaires and contained more women who reported normal weight than the general population. Nonetheless, when the scientists controlled for age, menopausal status, cigarette smoking, and stage of diagnosis, the association with weight did not change. Patients who lost weight unintentionally, had recurrence before follow-up, or had distant metastases at the time of enrollment were excluded. Half the women enrolled in the study were normal weight at enrollment, one-third were overweight, and 16% were obese. Only 1% were underweight.

“The big take-away message from this analysis was that regardless of starting weight, for every 5-kg [11 pound] increase in body weight, we saw this 14% increase in risk of mortality, not just of breast cancer, but of all causes,” Nichols said.
A study by Nichols’ collaborators, Crystal Holick, Sc.D., Polly Newcomb, Ph.D., and their colleagues at the Fred Hutchinson Cancer Research Center in Seattle looked at the associations between physical activity and survival in the same group. An increment of 5 MET hours per week of moderate activity was associated with a 15% lower risk of breast cancer death. (Three MET hours is equivalent to walking at an average pace of 2–2.9 mph for 1 hour.) They found that women who engaged in more than 2.8 MET hours/week of recreational physical activity had a 33%–49% decreased risk of death from breast cancer compared with women who were less active. The result appeared in the February issue of Cancer Epidemiology, Biomarkers and Prevention.

"Women diagnosed with breast cancer are eager for ways in which they can improve both the quality of their lives and their long-term survival,” Holick said. “Our results suggest that physical activity after a breast cancer diagnosis may reduce the risk of death from this disease.”

The results echo a similar finding by investigators in the Nurses’ Health Study, an observational study based on responses from 2,987 female registered nurses who were diagnosed with breast cancer between 1984 and 1998. In that study, published in the Journal of the American Medical Association in 2005, participants who engaged in the equivalent of walking 3–5 hours per week at an average pace had a 6% absolute reduction in risk of breast cancer death.

Newcomb said that the impetus for the follow-up studies to the Collaborative Women’s Longevity Study came from her interviews with many thousands of breast cancer patients since 1988 who want to know what they can do to increase their chance of survival. “After you’ve been diagnosed, it’s not helpful to know what you could have done before to avoid breast cancer,” Newcomb said. “This is practical information that breast cancer survivors can use.”

Currently, there are few factors known to be associated with breast cancer recurrence and mortality that one might change. But recent investigations looking at biological markers associated with breast cancer—like estrogen, insulin, and leptin—have provided clues to why excess body weight appears to encourage breast cancer growth. The research has centered on biologically active molecules secreted by fat tissue, such as estrogen, insulin, and insulin-like growth factor I, which is known to promote breast cancer growth and generalized inflammatory responses.

“The most likely mechanism is thought to be excess estrogen made in fat tissue in obese postmenopausal women because fat tissue contains aromatase that converts androgens into estrogen,” which fuels cancer growth.

Whereas estrogens, insulin, and insulin-like growth factor I have been extensively studied, the potential role of leptin is just beginning to be recognized. “The most prominent molecule that is secreted by fat tissue is leptin,” said Eva Surmacz, Ph.D., director of the obesity and cancer program at Temple University in Philadelphia. Leptin’s main role is to inform the brain about energy balance, but “we and others have found that it acts as a growth promoter and that it can influence breast cancer growth and can contribute to changes in epithelial mammary cells that lead to transformation.”

Clinical studies of leptin levels in breast cancer patients have been inconsistent, which Surmacz said is not surprising because circulating leptin levels fluctuate with food intake. She is focusing instead on local production of leptin within breast tissue itself. Surmacz and her colleagues showed in a 2007 Oncogene article that leptin is overexpressed in breast cancer tissue and that overexpression is tied to excess insulin, a common metabolic condition in people who are overweight and another hormone linked to breast cancer.

The role of excess leptin in breast cancer remains unclear, but Surmacz and others are investigating a possible link between leptin’s growth-promoting activity and reduced effectiveness of chemotherapy drugs such as antiestrogens and trastuzumab. The group is also looking at small-peptide inhibitors of leptin receptors.

“We want to develop something that can perhaps be delivered to tumors to inhibit tumor growth in terms of molecular action on the leptin receptor,” Surmacz said. But, she added, losing weight, and thereby body fat, is already proven to reduce leptin levels in the body.