Breast Cancer Risk High In Hodgkin's Survivors

BY JANE SALODOF MacNEIL
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LOS ANGELES — Increased risk of breast cancer after successful treatment for Hodgkin's lymphoma "definitely exists," and is very much a matter of time, according to a researcher who reviewed records for 248 women cured of Hodgkin's lymphoma from 1964 through 2001.

Women who were younger than 30 years of age at the time of radiotherapy and those who survive 15 years or more after their treatments face the greatest risk of breast cancer, Dr. Mohamed Alm El-Din of Massachusetts General Hospital, Boston, reported at the annual meeting of the American Society for Therapeutic Radiation and Oncology.

The younger the patient at the time of treatment for Hodgkin's and the longer the time since radiation, the greater the patient's risk for breast cancer.

Radiation dose and technique were not significant predictors when Dr. Alm El-Din and his coinvestigators compared the records of 36 women diagnosed with breast cancer with the rest of the survivors. Neither was a history of splenectomy, mediastinal disease, or chemotherapy with alkylating agents.

Perhaps the most striking finding, Dr. Alm El-Din noted, was that 11 (31%) of the 36 had bilateral breast cancer. Whether these women had other risk factors, such as a BRCA 1 or 2 gene or family history of breast cancer, is not known. Although slightly more than half (56%) of the breast cancers were detected by mammography, 11% were found incidentally during elective mastectomies.

"The younger the patient at the time of treatment for Hodgkin's lymphoma, the higher the risk, and the longer the time since radiation, the higher the risk," Dr. Alm El-Din said in an interview. Patients who were irradiated for the disease at a young age "should be counseled about the higher risk, and we should design long-term surveillance, so we can detect any breast cancer very early and enhance their chances for a cure again."

The presentation expanded upon an earlier Massachusetts General Hospital study of 111 Hodgkin's lymphoma patients, 14 of whom developed breast cancer (Cancer 1997;79:1203-10).

In the larger updated group, the median age at the time of supradiaphragmatic irradiation (SDI) was 26 years and median follow-up 15.2 years. Among the 36 women who developed breast cancer, the median age at first breast cancer diagnosis was 43.8 years, and the median time since radiation for Hodgkin's lymphoma was 18.4 years. Of these patients, 19 had their breast cancer treated at Massachusetts General. They developed 28 cancers: 9 ductal carcinomas in situ and 17 invasive ductal carcinomas. One had a mixed ductal and lobular tumor, and another had unknown histology.

Overall, the researchers reported a standardized morbidity ratio (SMR) of 9.78 for a woman developing a first breast cancer after SDI for Hodgkin's lymphoma. The ratio represents the number of observed breast cancers in a cohort divided by the number of breast cancers expected based on age-specific and calendar-year specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) database.

The highest SMR, 279.23, was for those irradiated before the age of 14 years. For all women treated before the age of 30, the SMR was significantly higher compared with those who were 30 years of age or older when originally treated: 19.05 vs. 4.64.

Looking at the interval between radiation and the diagnosis of a first breast cancer, the researchers found a peak SMR of 18.90 for the period 15-20 years afterward during which 14 women were diagnosed with breast cancer. Dr. Alm El-Din said survivors had an SMR of 14.34 when they were 15 or more years past radiotherapy as opposed to 5.01 when they were within 15 years of treatment.

In his conclusion, he recommended that all female survivors of Hodgkin's lymphoma, but especially those treated before the age of 30, be counseled about their increased risk. He said breast MRI, chemoprevention, and intensive screening should be considered for high-risk Hodgkin's survivors, many of whom are likely to be in primary care. Prophylactic mastectomy might be considered, he added, "in view of the high incidence of bilaterality and cases discovered incidentally."

Physicians at Massachusetts General have already started to contact these patients to put them on long-term screening protocols. "Prophylactic mastectomy could be an option, but it is a very personal decision that should be discussed between doctor and patient." ■

DRUGS, PREGNANCY, AND LACTATION

Increasing Folic Acid Supplementation

BY GIDEON KOREN, M.D.

This month, the Society of Obstetricians and Gynecologists of Canada is releasing new guidelines on folic acid supplementation in pregnant women, recommending prenatal vitamins that include 5 mg of folate in certain patients. Unless providers can ensure excellent daily compliance with the typical prenatal vitamin containing 0.8-1.1 mg of folate, the society is recommending this higher folate dose during pregnancy.

The basis of the new recommendation is evidence indicating that compliance with prenatal vitamins is not ideal, and as a result, prevention of neural tube defects with folate supplementation is suboptimal, as shown by several studies.

The current recommendation in the United States and Canada is that women of reproductive age consume at least 400 mcg of folic acid/day through a prenatal multivitamin, foods fortified with folic acid, or both to reduce their risk of having a baby with a neural tube defect (NTD) such as spina bifida, anencephaly, and other malformations. The amount of folic acid currently recommended for women who have already had a child with an NTD is 4 mg/day.

The recommendation for folic acid supplementation prenatally and during pregnancy was formed in the early 1990s. Subsequent fortification of enriched cereal grain products in 1998 in North America has had a marked impact on the rate of babies born with NTDs over the last decade.

Over the last several years, however, there have been questions raised about whether the folic acid dose included in prenatal vitamins is adequate to prevent NTDs.

For example, in a report published in 2001, using data from studies correlating the folic acid supplementation and the associated serum folate concentrations, and a large cohort study of the NTD risk based on serum folate, the authors determined that 5 mg of folic acid per day would prevent almost 90% of women from having a baby with an NTD. Nicholas Wald and his colleagues concluded that the currently recommended dose would protect only part of the population from NTDs, and recommended that women planning to become pregnant should take a 5-mg dose of folic acid per day (Lancet 2001;358:2069-73).

Corroborating this calculation were findings from a study of a large group of reproductive-aged Ontario women aged 15-45 years in 2005 and 2006, whose folic acid intake was unknown. We measured erythrocyte folate levels and determined that 40% of these women did not achieve the 900-nmol level needed to protect against NTDs, despite the fortification of flour and the recommendation that all women of reproductive age consume 400 mcg of folic acid daily. These findings, published in an abstract last year, strengthened our belief that the 5-mg recommendation is probably correct.

One of the two main arguments against an increase in folic acid is that an excess of folic acid in the diet can mask pernicious anemia, caused by vitamin B_{12} deficiency in older people. However, since flour was fortified, there has been no evidence of an increasing problem with pernicious anemia.

The second major concern is the potential effect of folate in increasing the risk of some cancers, which includes evidence that folic acid supplementation may increase the growth or number of colorectal polyps. However, the bulk of currently available data indicate that an adequate folic acid level decreases the risk of about 10 cancers, including colon cancer. Clearly, if a risk of cancer exists, it would be associated with long-term exposure to folic acid and would be a potential concern for people who consume a large amount of folic acid in flour-based products, not pregnant women who take an increased amount for a limited period of time.

In a recently completed clinical study of pregnant women at the Motherisk Program, we found that despite the women being under supervision, the compliance rate with prenatal multivitamins was surprisingly low—an average of 53%-58%, ranging from 0% to 100%. The likelihood that a substantial proportion of women prescribed a prenatal vitamin containing 1 mg of folic acid per tablet will miss a few days every week strengthens the recommendation that the inclusion of a higher dose of folic acid in prenatal vitamins would be beneficial for women who may not be entirely compliant with their daily vitamin intake, and that many more women, with less than ideal compliance, would have protective folate levels if the supplement contained 5 mg/day.

In October, the Centers for Disease Control and Prevention reported on a California Department of Public Health survey of women in the state who were aged 18-44 years, which found that the overall prevalence of women taking folic acid-containing supplements was stable from 2002 (40%) to 2006 (41%). But the rate decreased among Hispanic women, who are at a greater risk of having a baby with an NTD, from about 33% in 2002 to about 30% in 2006, a significant difference (MMWR 2007; 56:1106-9).

One prenatal vitamin tablet typically contains 1 mg of folic acid. A Canadian manufacturer recently introduced a prenatal vitamin containing 5 mg of folic acid, which was approved by the Canadian authorities in response to our conviction that such a product is necessary, and other companies may follow.

Now is the time, we believe, to move forward with this new guideline, and we hope that the American College of Obstetricians and Gynecologists will follow. ■

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