

## Wilms Tumor and Breast Cancer

Malignant tumors are a well-documented late complication of therapy for Wilms tumor.<sup>1</sup> Lange et al reported that female survivors of Wilms tumor who were treated with radiotherapy to the thorax at a dose of 12 to 14 gray (Gy) had an elevated risk of developing early breast cancer, with nearly 15% having invasive disease by age 40 years.<sup>2</sup>

Radiotherapy to the thorax is a risk factor for male breast cancer as well. Chest radiography does not increase the risk, but chest radiotherapy does. Moreover, in survivors of the atom bomb, this risk was found to be increased by a factor of 8.<sup>3</sup> Therefore, we wondered whether men, as well as women, had an increased risk of breast cancer after a diagnosis of Wilms tumor and receipt of radiotherapy.

Bassal et al calculated standardized incidence ratios from Surveillance, Epidemiology, and End Results (SEER) data and found that the risk of subsequent breast cancer in survivors of childhood cancer was 24.7.<sup>4</sup> Using SEER data, we found that the risk of breast cancer was indeed elevated in women after a diagnosis of Wilms tumor and receipt of radiotherapy, but the risk of breast cancer in men was not.

In the SEER data, 416 women had received beam radiotherapy. At  $\geq 20$  years of follow-up, 4 women had developed breast cancer, for an observed/expected (O/E) ratio of 7.4, which was significantly elevated ( $P < .05$ ). Among 475 women who had not received beam radiotherapy, there were 2 cases of breast cancer, for an O/E ratio of 1.9, which was not significantly elevated. The elevation in the O/E ratio is not as great as reported by Lange et al,<sup>2</sup> no doubt because SEER does not specify whether radiotherapy was given to the chest or abdomen.

It is interesting to note that of the 372 men who had received beam radiotherapy, none had developed breast cancer, nor had any of the nonirradiated men shown signs of breast cancer.

Low-dose radiation (3-23 Gy) is often given to men with prostate cancer who are receiving antiandrogen therapy to prevent gynecomastia, although the long-term effects are unknown.<sup>3</sup> Our finding of no breast cancer in men after irradiation for Wilms tumor suggests that a dose of at least 14 Gy for the prevention of gynecomastia should be free of long-term effects.

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### CONFLICT OF INTEREST DISCLOSURES

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## Reply to Wilms Tumor and Breast Cancer

We appreciate this opportunity to respond to the question raised by Drs. Lehrer and Rosenzweig and by others regarding Wilms tumor and male breast cancer.

Males account for <1% of breast cancers diagnosed in the United States, and the disease is especially rare in younger men.<sup>1</sup> Using data from the 9th (1973-1991), 13th (1992-1999), and 18th (2000-2010) Surveillance, Epidemiology, and End Results registries, we calculated incidence rates of invasive plus in situ breast cancer for men and women aged <40 years of 0.0433 and 13.99 per 100,000 person-years, respectively. This yielded a male:female (M:F) ratio of 0.0031.

Assuming that the standardized incidence ratio for male survivors of Wilms tumor was the same as we found for females (ie, 9.2), we made a rough calculation of the number of male breast cancer cases we might have expected had we included men in our study.<sup>2</sup> This calculation also assumed that the number of person-years of observation among males equaled that among females. The latter assumption was conservative because fewer males than females were enrolled on the National Wilms Tumor Studies, whereas death rates for teenage and young adult males are generally slightly higher. We multiplied the number of female cases observed (ie, 29 invasive cases plus

6 in situ cases, for a total of 35 cases) by the M:F ratio to arrive at an expected number of male breast cancer cases of 0.1. Using Poisson statistics, the corresponding probability of observing  $\geq 1$  cases of male breast cancer was also only 0.1. In fact, no cases were observed.

Thus, the answer to the question of whether men as well as women had an increased risk of breast cancer after Wilms tumor and radiotherapy in our study is no.<sup>2</sup> Had we restricted the calculation above to patients receiving chest radiotherapy, assuming that the 30-fold increase we observed for females also held for males, we would have expected only 0.0031 multiplied by 22, for a total of 0.07 cases. More accurately, however, the study was simply uninformative with regard to male breast cancer. We believe it is likely that chest irradiation for Wilms tumor increases the risk of subsequent breast cancer in men, just as it does in women. However, a much larger population of survivors of Wilms tumor, and/or follow-up through the advanced ages at which male breast cancer is more frequent, would be needed to prove the point.

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We thank Drs. Lehrer and Rosenzweig for their insightful comments and opportunity to expand on our discussion regarding breast cancer in survivors of Wilms tumor.<sup>1</sup> We acknowledge that the development of breast cancer in men was not specifically addressed in our comments.

To our knowledge, breast cancer in male survivors of Wilms tumor or other pediatric cancers has not been reported. Reports from the Childhood Cancer Survivor Study on breast cancer as a second malignant neoplasm have focused exclusively on female survivors, making it difficult to ascertain whether male survivors were affected.<sup>2,3</sup> According to the Surveillance, Epidemiology, and End Results program, breast cancer in the general population occurs in 1.44 per 100,000 men, compared with 129.56 per 100,000 women.<sup>4</sup> If radiotherapy increases the relative risk of secondary breast cancer by a multiple of the risk in the general population, one would expect that the incidence of secondary breast cancer in male cancer survivors would be substantially lower than in female cancer survivors, but not nonexistent. The pediatric cancer survivorship cohorts may not be sufficiently large to detect breast cancer in male survivors. Another consideration is that the peak age of male breast cancer is 71 years.<sup>4</sup> The late onset may contribute to the lack of cases in childhood cancer survivors because the current cohorts may not have aged sufficiently. It appears prudent that clinicians who care for cancer survivors be aware of a potential risk of breast cancer in men who received chest radiotherapy. Because male breast cancer typically presents as a palpable lump,<sup>5</sup> it should usually be readily detectable on physical examination without the use of surveillance imaging.

Although the risk of male breast cancer after radiotherapy is very low, we caution against concluding that radiotherapy is safe for boys and young men. We hope that continued longitudinal studies will address the development of breast cancer in men and women so that we can continue to provide our patients and their providers with the most up-to-date surveillance guidelines.

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