The Cardiovascular Perils of Cancer Survivorship

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Since 1990, breast cancer mortality has decreased yearly in developed nations. In 2012, there were an estimated 3 million survivors of breast cancer in the United States alone. This decrease in mortality can be partly attributed to effective treatment strategies developed through collaborations among breast surgeons and medical and radiation oncologists. Radiation therapy has evolved as a critical component of treatment for women who have undergone breast-conservation surgery and for those with a high risk of recurrence who have undergone mastectomy. Older radiation techniques for breast cancer are associated with subsequent cardiac disease. Less clear is the cardiac risk associated with modern radiation techniques, which presumably reduce the heart’s exposure to radiation. Early studies were limited by their relatively short follow-up periods; the effects of radiation on the heart accumulate over time and typically manifest more than a decade after exposure.

In this issue of the Journal, Darby et al. report the results of a population-based study of the incidence of major ischemic cardiac events in women who received radiation therapy for breast cancer. The authors use stringent criteria for ischemic cardiac disease, with a major coronary event defined as myocardial infarction, coronary revascularization, or death from ischemic cardiac disease. For each patient, the authors estimate the mean doses of radiation to the heart. The study provides several intriguing results. First, exposure of the heart to radiation, regardless of a minimum dose, increases the rate of ischemic heart disease, with each gray of radiation associated with a 7.4% increase in the occurrence of a subsequent major coronary event. Second, the risk of a major coronary event increases within 5 years after exposure to radiation and continues for at least two decades after radiation treatment. Third, this increased risk of a major coronary event applies to radiation technology used after 1990. Finally, the absolute radiation-related risk of a major coronary event is far greater for women with preexisting cardiac risk factors or ischemic cardiac disease.

This last finding is important given advances in preventive cardiovascular medicine. Atherosclerosis — the pathologic condition that leads to ischemic heart disease — has been recognized as a systemic process resulting from the accumulation of multiple risk factors over a patient’s lifetime. Early and aggressive efforts to reduce cardiac risk factors (even before the onset of a coronary event) through lifestyle modification or with medical therapy represent the most important intervention that helps prevent illness and death from ischemic heart disease. The current study points to radiation therapy as a significant risk factor for coronary disease in patients with breast cancer. This finding suggests that cardiac risk factors should be assessed and aggressively managed — starting at the time of radiation treatment (or even before) and continuing throughout survivorship.

Nevertheless, the findings of Darby et al. may represent just the tip of the iceberg. In addition to ischemic cardiac disease, radiation therapy has been associated with other cardiac conditions, including pericardial disease, peripheral vascular disease, cardiomyopathy, valvular dysfunction, and arrhythmias — diseases that were not included in this analysis. Furthermore, breast cancer therapy may include anthracyclines and therapies targeting human epidermal growth factor receptor 2 (HER2) that have additional cardio-
tive effects. In the current study, only 8 patients (of 963 who had a major coronary event) and 9 controls (of 1205) received anthracyclines, and none appear to have received HER2-targeted therapies.

The advent of novel approaches to the treatment of cancer has introduced survivorship as a new theme in oncologic care. In addition, “cardio-oncology” (cardiovascular care of patients with cancer) has emerged as a new discipline in medicine. Cardio-oncology is relevant to cancer survivorship in two ways. First, early cardiovascular toxicities that arise during treatment may interfere with completion of the very therapies needed to enhance survivorship. Moreover, cardiac issues may arise years after the completion of cancer treatment. Cardio-oncology also represents a new frontier in medicine, since novel targeted therapies currently being tested in breast cancer clinical trials may have cardiovascular toxicities. For example, vascular endothelial growth factor (VEGF) signaling-pathway inhibitors (VSP inhibitors) have been associated with hypertension, thrombosis, and cardiomyopathy.

Cardiovascular sequelae of other classes of therapies, including the use of mammalian target of rapamycin (mTOR) inhibitors or PI3 kinase inhibitors, have been incompletely defined, although biologically plausible mechanisms predict adverse cardiometabolic consequences.

Given the widespread use of radiation therapy in the treatment of breast cancer, and the continually expanding arsenal of novel therapies, the current study calls for greater collaboration between oncologists and cardiologists. An important lesson for the oncologist may be that the time to address concerns about cardiovascular “survivorship” is at the time of cancer diagnosis and before treatment rather than after completion of therapy. Similarly, cardiologists need to assess prior exposure to radiation therapy as a significant cardiovascular risk factor in survivors of breast cancer.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1215300
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