Time to Remove the Subspecialty Blinders: Breast Cancer Does Not Exist in Isolation

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As oncologists, we focus on treating cancer and preventing cancer-related deaths. However, how aggressively are our patients treated for non-cancer-related medical problems? This question should be of great importance to oncologists, particularly those who treat breast cancer patients. The survival rates for breast cancer have improved over the past several decades, likely because of an increase in screening and improvements in therapy (1,2). As deaths from breast cancer fall and the population ages, breast cancer patients are increasingly likely to die of other illnesses. Thus, appropriate treatment of medical conditions other than breast cancer is critical for our patients’ overall health. Understanding the risk of death from breast cancer in the context of the competing risk of death from other causes is also essential when estimating the risk and benefits of therapy for breast cancer patients. For instance, if a patient has a limited life expectancy because she has cardiovascular disease, systemic adjuvant therapies for breast cancer are unlikely to impact survival. In a patient who is 70 years old and has a 2-cm estrogen receptor–positive tumor and four positive lymph nodes, adjuvant hormonal therapy is associated with a 32% relative reduction in risk of death from breast cancer (3). If she is in perfect health, the relative risk reduction would translate to a 10% absolute survival benefit at 10 years. However, if she has a major comorbid illness, the absolute survival benefit would be reduced to less than 1%

In this issue of the Journal, Chapman et al. (4) have examined the competing risks of death in a cohort of patients treated in MA.17, a randomized trial that evaluated extended adjuvant therapy with letrozole vs placebo. Overall, the majority of deaths in this postmenopausal patient population were from causes other than breast cancer; only 40% of the deaths were attributable to breast cancer. The results were more striking for older women: non–breast cancer deaths accounted for 72% of the deaths among women who were aged 70 years or older vs 48% of the deaths among women who were younger than 70 years. As would be expected, women with a baseline diagnosis of cardiovascular disease were statistically significantly more likely to die from causes other than breast cancer. These findings highlight our success in treating women with breast cancer because the minority of deaths were from breast cancer. These results also provide an opportunity to reflect on comorbidities in breast cancer patients, some of which may be attributed to cancer therapy.

One potential concern about the study by Chapman et al. (4) is that the population of patients in MA.17 was not representative of all breast cancer patients. The MA.17 trial enrolled patients with estrogen receptor–positive or unknown tumors who had remained free of disease after approximately 5 years of adjuvant endocrine therapy with tamoxifen. Thus, the patients selected had hormonally sensitive tumors and a good prognosis. However, the data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial are very similar to the MA.17 data despite treating patients in the adjuvant rather than “extended adjuvant” setting (5). Sixty percent of all of the reported deaths in the ATAC trial were from causes other than breast cancer. The high risk of death from other causes likely explains why overall survival benefits have been difficult to demonstrate in the adjuvant aromatase inhibitor studies.

Although competing risks of death are particularly relevant in the population of postmenopausal patients with hormone-sensitive breast cancer, it is an important consideration for all patients with breast cancer. Schairer et al. (6) estimated the probability of death from breast cancer and from other causes in 430,510 women from the Surveillance, Epidemiology, and End Results database. The authors reported that the probability of death from breast cancer exceeded the probability of death from other causes only for women younger than 50 years with localized-stage disease or for women younger than 60 years with regional-stage disease. Competing risk of death also partially explains disparities in overall survival between African American and white patients with breast cancer because African American patients have been reported to have higher rates of comorbid illnesses and thus to have worse survival from other causes (7).

The study by Chapman et al. (4) did not provide information on the specific causes of death for women who did not die from breast cancer. However, cardiovascular disease remains the leading cause of death in the United States and likely was a contributing factor in the death of many patients. Cardiovascular disease is of particular concern to breast cancer patients because of its prevalence and the reality that many therapies for breast cancer can cause cardiac dysfunction. In this study, Chapman et al. (4) reported an interaction between cardiovascular disease and treatment, in which patients with baseline cardiac disease who were treated with letrozole had a higher risk of death from non–breast cancer causes. These data raise the question of whether patients with baseline cardiovascular disease may be more likely to experience cardiovascular toxicity from letrozole treatment. However, the absolute number of deaths was quite small and, as the authors note, baseline reporting was not verified. The findings are in line with data from other adjuvant aromatase inhibitor trials, which have shown that a small increase in risk of cardiovascular disease was associated with treatment (8). Other breast cancer adjuvant treatments such as radiotherapy and anthracycline chemotherapy also can increase risk of late cardiovascular disease, so attention to cardiovascular health is a critical aspect of the care of breast cancer survivors (9–11).

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Unfortunately, our understanding of the prevalence and risk factors of cardiovascular disease in breast cancer survivors is still in its infancy. We have no prospective long-term data with which to assess predictors of cardiovascular disease in patients who have received potentially cardiotoxic therapies. Similarly, the role of cardiovascular screening or early interventions for breast cancer survivors has not been established, but such studies are clearly needed. We do know that breast cancer survivors should have regular assessment of cardiovascular risk, as should all women, but the extent to which cancer survivors are receiving this care is uncertain. The false perception of a poor prognosis with a cancer diagnosis may impede routine cardiovascular screening and preventive measures. Finally, we need better tools to assess risk of death from causes other than breast cancer to assist in treatment planning. Risk assessment tools such as Adjuvant! Online have greatly enhanced our ability to counsel patients on risk of recurrence and the benefits of treatment (12). However, our measures of estimating risk of death from competing causes are less refined. Development of such tools would greatly assist patients and oncologists determine the risks and benefits of adjuvant therapies.

References