COMMENTARY

Late-onset recurrence in breast cancer: Implications for women's health clinicians in survivorship care

Data show that late-onset recurrence is more likely among patients with an initial tumor size >2 cm, lymph node–positive disease, and hormone receptor–positive tumors

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Improved treatments for breast cancer (BC) and effective screening programs have resulted in a BC mortality rate reduction of 41% since 1989.[1] Because BC is the leading cause of cancer in women, these mortality improvements have resulted in more than 3 million BC survivors in the United States.[2,3] With longer-term survival, there is increasing interest in late-onset recurrences.[4,5] A recent study has provided an improved understanding of the risk of late-onset recurrence in women with 10 years of disease-free survival, an important finding for women's health providers because oncologists do not typically follow survivors after 10 years of disease-free survival.[4]

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Recent study looks at incidence of late-onset recurrence

Pederson and colleagues evaluated all patients diagnosed with BC in Denmark from 1987 through 2004.[4] Those patients without evidence of recurrence at 10 years were then followed utilizing population-based linked registries to identify patients who subsequently developed a local, regional, or distant late-onset recurrence. The authors evaluated the frequency of late recurrence and identified associations with demographic and tumor characteristics.

What they found

A total of 36,920 patients were diagnosed with BC in Denmark between 1987-2004, of whom 20,315 (55%) were identified as disease free for at least 10 years. Late-onset recurrence occurred in 2,595 (12.8%) with the strongest associations of recurrence seen in patients who had a tumor size >2 cm and lymph node-positive (involving 4 or more nodes) disease (24.6%), compared with 12.7% in patients with tumors <2 cm and node-negative disease. Several other factors were associated with a higher risk of late-onset recurrence and are included in the **TABLE**. Half of the recurrences occurred between 10 and 15 years after the primary diagnosis.

Prior research

These findings are consistent with another recent study showing that BC patients have a 1% to 2%/year risk of recurrence after 10 disease-free years.[5] Strengths of this study include:

- population-based, including all women with BC
- long-term follow-up for up to 32 years
- universal health care in Denmark, resulting, which results in robust and linked databases and very few missing data points.

There were two notable weaknesses to consider:

- Treatment regimens changed considerably during the time frame of the study (1997-2018), particularly the duration of tamoxifen use in patients with HR-positive disease. In this study nearly all patients received 5 years or less of tamoxifen. Since the mid-2010s, 10 years of hormonal adjuvant therapy has become routine in HR-positive BC, which reduces recurrences, including late-onset recurrence.[6] The effect of 10 years of tamoxifen would very likely have resulted in less late-onset recurrence in the HR-positive population in this study.
- There is a lack of racial diversity in the Danish population, and the study findings may not translate to Black patients who have a higher frequency of triple-negative BC with a different risk of late-onset recurrence.[7]

TABLE Demographic and tumor characteristics associated with the likelihood of late-onset recurrence

Higher rates of late-onset recurrence	Lower rates of late-onset recurrence
• Tumor size >2 cm	• Patients who received chemotherapy
• Lymph node–positive disease	• High-grade tumors
• Hormone receptor (HR)-positive	• Triple-negative disease
• Women <40 years at primary diagnosis	

Practice takeaways

Cancer surveillance. There are 3+ million BC survivors in the United States, and a 55%+ likelihood that they will be disease free for 10 years. This is clearly an important population to the women's health care provider. This study, and previous research, suggests that among 10-year-disease-free survivors, 1% to 2% will recur annually, with higher rates amongst HR-positive, lymph-node positive women under age 40, and in the first 5 years following the 10-year post–initial diagnosis mark, so ongoing surveillance is imperative. Annual clinical breast examinations along with annual (not biennial) mammography should be performed.[8] Digital breast tomosynthesis has improved specificity and sensitivity for BC detection and is the preferred modality when it is available.

Management of menopausal symptoms. These findings also have implications for menopausal hormone therapy for patients with symptoms. Because HR-positive patients have an increased risk of late-onset recurrence, nonhormonal therapies should be considered as first-line therapy for patients with menopausal symptoms. If hormone therapy is being considered, providers and patients should use shared decision making to balance the potential benefits (reduction in symptoms, possible cardiovascular benefits, and reduction in bone loss) with the risks (increased risk of recurrence and venous thromboembolism), even if patients are remote from the original diagnosis (ie, 10-year disease-free survival).

Topical estrogen therapies would be preferred for patients with significant urogenital atrophic symptoms who fail nonhormonal therapies due to substantially less systemic absorption and the lack of need to add a progestin.[9,10] If oral therapy is being considered, I carefully counsel these women about the likely increased risk of recurrence and, if possible, include their breast oncologist in the discussion. ●

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