EDITORIALS

POSITIVE Results for Breast Cancer Survivors Who Desire Pregnancy

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Advances in cancer screening and treatment have led to a large and growing population of cancer survivors. In the United States, the number of cancer survivors is expected to increase from approximately 15 million in 2016 to 26 million by 2040.[1] Cancer survivors are at risk for many long-term and late effects related to their previous cancer treatments, including the loss of fertility owing to treatment with chemotherapy, radiation therapy, or both. The potential loss of fertility can be a major source of distress for young patients with cancer, and professional guidelines recommend that the possibility of infertility be addressed before cancer treatment begins and that fertility preservation approaches be offered for patients who are interested.[2]

Among young patients with breast cancer, the desire to have children is common, and approximately one third to one half of patients express the wish to do so.[3,4] However, for breast cancer survivors, concerns about childbearing extend beyond issues of fertility. Questions have arisen as to whether elevations in estrogen and progesterone levels during pregnancy could increase the risk of recurrence of breast cancer, particularly among women who had hormone receptor–positive cancers. Previous retrospective studies have been reassuring in that they have not shown worse cancer outcomes among women with a history of breast cancer who subsequently have children,[5] although it remains possible that these results could be related to a "healthy mother" effect, whereby the healthiest women have the highest chances of pregnancy. Further complicating the decisions regarding pregnancy after breast cancer is the current recommendation of adjuvant endocrine therapy for 5 to 10 years for patients with hormone receptor–positive breast cancer. Endocrine therapy is a key component of the management of breast cancer; it is associated with a lower risk of recurrence and an improvement in survival.[6,7] However, pregnancy is contraindicated during endocrine therapy, and a delay in pregnancy for 5 to 10 years will reduce the chances of a subsequent live birth owing to age-related declines in fertility. Whether a break in endocrine therapy would be detrimental has been unclear. A lower incidence of adherence to endocrine therapy has been associated with worse breast cancer outcomes,[8] but the results of a large trial in which intermittent endocrine therapy (with 3-month breaks) was evaluated in postmenopausal women who had completed 4 to 6 years of endocrine therapy suggested no adverse effect on outcomes after temporary breaks in treatment.[9]

The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial, reported by Partridge et al. in this issue of the *Journal*,[10] was designed to address the safety of a temporary break in endocrine therapy in young women with hormone receptor–positive breast cancer who wish to become pregnant. This single-group trial enrolled 518 women who were 42 years of age or younger; had stage I,

II, or III disease; had completed 18 to 30 months of endocrine therapy; and wanted to become pregnant. A 3-month washout period after stopping endocrine therapy was followed by an interruption of endocrine therapy of up to 2 years to allow for pregnancy, childbirth, and breast-feeding (if desired). The primary end point was the number of breast cancer events (defined as ipsilateral or locoregional invasive disease, distant recurrence, or contralateral invasive breast cancer) during follow-up. In addition, the incidence of breast cancer events was compared with that in an external control cohort of premenopausal women enrolled in two trials of adjuvant endocrine therapy who would have met the eligibility criteria for the POSITIVE trial.[7]

After a median of 3.4 years of follow-up, the incidence of breast cancer events was below the prespecified safety threshold, a finding that supports the short-term safety of this approach. In addition, the 3-year incidence of breast cancer events was similar among the patients in the trial (referred to as the treatment-interruption group) and among those in the external control cohort (8.9% and 9.2%, respectively). In total, 74.0% of the patients reported becoming pregnant, and 63.8% had at least one live birth; 43.3% had used assisted reproductive technology. In the treatment-interruption group, the incidence of breast cancer events among patients who became pregnant was similar to that among patients who did not become pregnant. In addition, the percentage of patients who resumed endocrine therapy was encouraging; only 15.4% of the women who had been expected to resume endocrine therapy had not done so by 4 years after treatment interruption.

Because having children remains a high priority for many young breast cancer survivors, some women will choose to pursue a pregnancy after a breast cancer diagnosis. The results of the POSITIVE trial provide the strongest evidence to date on the short-term safety of this choice. However, the enrolled patients were a selected cohort of women who were highly motivated to become pregnant. In addition, recurrences of breast cancer are reported to occur at a steady rate for up to 20 years after diagnosis among patients with hormone receptor–positive disease[11]; the protocol-specified 10-year follow-up data will be essential to establish longer-term safety. Meanwhile, the POSITIVE trial provides prospective data showing that the temporary interruption of endocrine therapy to attempt pregnancy after hormone receptor–positive early breast cancer does not appear to increase the risk of recurrence or of contralateral breast cancer in the subsequent 3 years. Physicians should now incorporate these positive data into their shared decision-making process with patients.

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

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