Does fertility preservation in patients with breast cancer impact relapse rates and disease-specific mortality?

Evidence continues to **support fertility preservation**, **with or without hormonal ovarian stimulation,** in breast cancer patients, and it **is apparently safe at least for up to 5 years of follow-up.**

Marklund A, Lekberg T, Hedayati E, et al. Relapse rates and disease-specific mortality following procedures for fertility preservation at time of breast cancer diagnosis. JAMA Oncol. 2022;8:1438-1446. doi:10.1001/jamaoncol.2022.3677.

EXPERT COMMENTARY
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Breast cancer is the most diagnosed cancer among US women after skin cancer.[1] As of the end of 2020, 7.8 million women were alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. Given the wide reach of breast cancer and the increase in its distant stage by more than 4% per year in women of reproductive age (20–39 years), clinicians are urged to address fertility preservation due to reproductive compromise of gonadotoxic therapies and gonadectomy.[2] To predict the risk of infertility following chemotherapy, a Cyclophosphamide Equivalent Dose (CED) calculator can be used. A CED of 4,000 mg/m^2 has been associated with a significant risk of infertility.[3]

In 2012, the American Society for Reproductive Medicine removed the experimental label of oocyte cryopreservation then recently endorsed ovarian cryopreservation, thereby providing acceptable procedures for fertility preservation.[4] Gonadotropin-releasing hormone agonist use during chemotherapy, which is used to protect the ovary in premenopausal women against the effects of chemotherapy, has been shown to have inconsistent findings and should not replace the established modalities of oocyte/embryo/ovarian tissue cryopreservation.[2,5]

Details of the study

While studies have been reassuring that ovarian stimulation for fertility preservation in women with breast cancer does not worsen the prognosis, findings are limited by short-term follow-up.[6]

The recent study by Marklund and colleagues presented an analysis of breast cancer relapse and mortality following fertility preservation with and without hormonal stimulation. In their prospective cohort study of 425 Swedish women who underwent fertility preservation, the authors categorized patients into 2 groups: oocyte and embryo cryopreservation by ovarian hormonal stimulation and ovarian tissue cryopreservation without hormonal stimulation. The control group included 850 women with breast cancer who did not undergo fertility

FAST TRACK

Given the wide reach of breast cancer and the increase in its distant stage by more than 4% per year in reproductive-age women, clinicians are urged to address fertility preservation due to reproductive compromise of gonadotoxic therapies and gonadectomy

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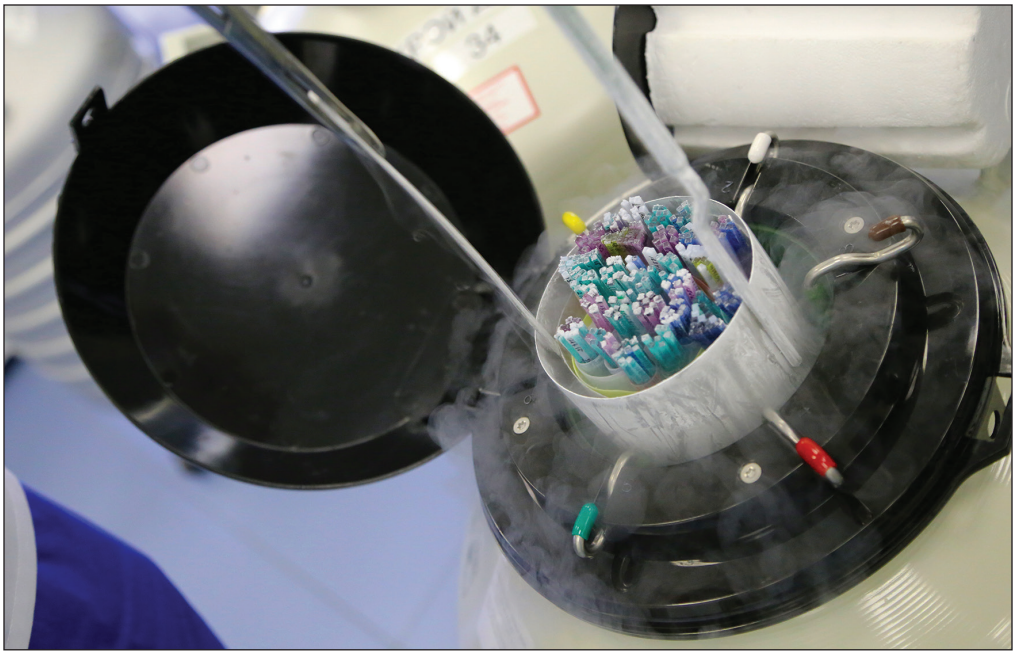

preservation. The cohort and the control groups were matched on age, calendar period of diagnosis, and region. Three Swedish registers for breast cancer were used to obtain the study cohort, and for each participant, 2 breast cancer patients who were unexposed to fertility preservation were used for comparison. The primary outcome was mortality while the secondary outcome was any event of death due to breast cancer or relapse.

Results. A total of 1,275 women were studied at the time of breast cancer diagnosis. After stratification, which included age, parity at diagnosis, tumor size, number of lymph node metastases, and estrogen receptor status, disease-specific mortality was similar in all categories of women, that is, hormonal fertility preservation, nonhormonal fertility preservation, and controls. In the subcohort of 723 women, the adjusted rate of relapse and disease-specific mortality remained the same among all groups.

Study strengths and limitations

This study prompts several areas of criticism. The follow-up of breast cancer patients was only 5 years, adding to the limitations of short-term monitoring seen in prior studies. The authors also considered a delay in pregnancy attempts following breast cancer treatment of hormonally sensitive cancers of 5 to 10 years. However, the long-term safety of pregnancy following breast cancer has shown a statistically significantly superior disease-free survival (DFS) in patients who became pregnant less than 2 years from diagnosis and no difference in those who became pregnant 2 or more years from diagnosis.[7]

Only 58 women in the nonhormonal fertility preservation group (ovarian tissue cryopreservation) were studied, which may limit

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Marklund and colleagues' findings revealed no increase of breast cancer relapse and mortality following fertility preservation with or without hormonal stimulation. They also propose a "healthy user effect" whereby a woman who feels healthy may choose to undergo fertility preservation, thereby biasing the outcome by having a better survival.[8]

Future studies with longer follow-up are needed to address the hormonal impact of fertility preservation, if any, on breast cancer DFS and mortality, as well as to evaluate subsequent pregnancy outcomes, stratified for medication treatment type via the CED calculator. To date, evidence continues to support fertility preservation options that use hormonal ovarian stimulation in breast cancer patients as apparently safe for, at least, up to 5 years of follow-up.

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an adequate evaluation although it is not expected to negatively impact breast cancer prognosis. Another area of potential bias was the use of only a subcohort to assess relapse-free survival as opposed to the entire cohort that was used to assess mortality.

Strengths of this study include obligatory reporting to the registry and equal access to anticancer treatment and fertility preservation in Sweden. Ovarian stimulating drugs were examined, as letrozole is often used in breast cancer patients to maintain lower estradiol levels due to aromatase inhibition. Nevertheless, this study did not demonstrate a difference in mortality with or without letrozole use. ●

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