Multiple childbirth linked to increased risk of rare, aggressive 'triple-negative' breast cancer

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Full-term pregnancy has long been associated with a reduced risk of breast cancer, but a new study finds that the more times a woman gives birth, the higher her risk of "triple-negative" breast cancer, a relatively uncommon but particularly aggressive subtype of the disease. Conversely, women who never give birth have a 40 percent lower risk of such breast cancer, which has a poorer prognosis than other types of breast cancer and doesn't respond to hormone-blocking therapies such as tamoxifen.

These findings, from a study led by Amanda Phipps, Ph.D., a postdoctoral research associate in the Public Health Sciences Division of Fred Hutchinson Cancer Research Center, are published online ahead of the March 16 issue of the Journal of the National Cancer Institute.

"Unlike most breast cancers, triple-negative tumors don't depend on hormonal exposures to grow and spread, so our assumption going into the study was that reproductive factors would not be associated with a woman's risk of this cancer subtype," Phipps said. "We were surprised by these findings because researchers have known for quite some time that women who have children, especially those who have them at an early age and have multiple full-term pregnancies, have a lower risk of breast cancer overall."

While never giving birth appears to be protective against triple-negative

breast cancer, the researchers found that women who remain childless have about a 40 percent higher risk of estrogen-receptor-positive breast cancer – the most common form of the disease, which can be treated with estrogen-blocking drugs – as compared to those who have one or more offspring. This higher risk of estrogen-receptor-positive breast cancer among women who have not had children is well established, and it is thought to be related to the fact that such women do not undergo pregnancy-related changes in the breast that confer a lifelong protective effect.

"The mechanisms by which full-term pregnancy contributes to an increased risk of triple-negative breast cancer and a decreased risk of other forms of the disease are not clear," Phipps said. "We do know that the hormones of pregnancy induce certain changes in the cellular structure of the breast. Overall, those changes seem to make the breast less susceptible to cancer. It is possible, however, that the increased risk of triple-negative breast cancer we found in women who had given birth may be due to some abnormal response of their breast tissue to the hormones of pregnancy. Another possibility is that pregnancy somehow makes the breast more susceptible to certain carcinogens even while reducing breast cancer risk overall," she said.

For the study, which was based on data from the Women's Health Initiative, Phipps and colleagues analyzed the detailed reproductive histories of some 150,000 postmenopausal women, more than 300 of whom went on to develop triple-negative breast cancer. "This particular study is significant because it is one of the largest studies ever conducted on the impact of reproductive history on triple-negative breast cancer," Phipps said.

Triple-negative breast cancer, which refers to any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu, accounts for only 10 percent to 20 percent of all

breast cancers, and only in the past decade have researchers become aware that this cancer subtype exists. "This research reinforces the notion that breast cancer is not just one disease," Phipps said.

"The mechanisms that lead to triple-negative breast cancer are likely different from those that lead to other forms of the disease. We still have a lot to learn about what causes this more aggressive form of breast cancer, but we hope that research like this will help us develop better tools to identify those women at greatest risk."

It is known that this cancer subtype is more predominant in African American women and it tends to be diagnosed at an earlier age. Researchers also know there is a strong link between genetic mutations in the so-called "breast cancer gene," BRCA1, and triple-negative breast cancer.

"More research is needed to better understand the causes of the most aggressive and lethal forms of breast cancer. While this study adds to our knowledge base, it should not change women's approaches to breast cancer screening," Phipps said.

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