Breast cancer patients with BRCA mutations 4 times more likely to get cancer in opposite breast

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Women with breast cancer before age 55 who carry an inherited mutation in the breast cancer susceptibility genes BRCA1 or BRCA2 are four times more likely to develop cancer in the breast opposite, or contralateral, to their initial tumor as compared to breast cancer patients without these genetic defects. These findings, by Fred Hutchinson Cancer Research Center breast cancer epidemiologist Kathleen Malone, Ph.D., and colleagues, were published online April 5 in the *Journal of Clinical Oncology*.

Compared to non-carriers, breast cancer patients with a BRCA1 mutation had a 4.5-fold increased risk and those with a BRCA2 mutation had a 3.4-fold increased risk of a subsequent contralateral breast cancer, the researchers found. Carriers of either mutation who were diagnosed with breast cancer before age 55 faced an 18 percent cumulative probability of developing cancer in the opposite breast within 10 years as compared to a 5 percent cumulative probability among women who were mutation-free.

In addition, the study revealed that among those who harbored a BRCA1 mutation, the younger they were at the time of initial diagnosis the higher was their risk of developing contralateral breast cancer. For example, mutation carriers diagnosed initially in their early to mid 30s had a 31 percent cumulative probability of developing contralateral breast cancer within 10 years as compared to a 7 percent probability

among non-carriers.

"For young women with breast cancer, our results reinforce the message that early-onset disease is much more likely to be associated with a BRCA mutation," said Malone, first author of the paper and a member of the Public Health Sciences Division at the Hutchinson Center.

While only about 5 percent of breast cancer patients across all age groups carry a BRCA mutation, the younger a woman is at the time of her first breast cancer diagnosis, the more likely she is to have such a mutation. "In the youngest patients in our study - those with a first cancer diagnosed before age 35 - we found that 16 percent of those with one breast tumor and 54 percent of those who had developed two primary breast cancers carried a mutation," Malone said. Mutation frequencies were elevated also in women diagnosed with a first cancer between ages 34 and 44; among those initially diagnosed with one breast tumor the mutation frequency was 6.3; those diagnosed with two primary breast cancers had a mutation rate of 22 percent.

"These elevated mutation frequencies and risks for contralateral breast cancer associated with these mutations underscore the need for women diagnosed with a first breast cancer at a young age - regardless of family history - to consider genetic testing and to discuss it with their health care providers," Malone said. "If they are found to carry a mutation in either of the BRCA genes, they should consider strategies for treatment, prevention and heightened surveillance in relation to their increased risk of a subsequent breast cancer diagnosis."

This international, multicenter study, which was coordinated by Memorial Sloan Kettering Cancer Center, analyzed data from 705 women with contralateral breast cancer and a comparison group of 1,398 women with unilateral breast cancer. All of the women had been first diagnosed before age 55.

Participants were gleaned from population-based cancer registries in western Washington, Los Angeles, San Diego, Iowa and Denmark. All study participants were tested for the presence of BRCA1 or BRCA2 mutations. None of the participants had evidence of cancer spread beyond the lymph nodes upon diagnosis.

This is the first population-based study of these two important breast cancer susceptibility genes and their relation to contralateral breast cancer risk," Malone said. It is also the largest study to date of the association between BRCA mutations and contralateral breast cancer. "This study provides the clearest picture yet of the prevalence and risk of contralateral breast cancer among women in the general population who carry mutations in BRCA1 and BRCA2.

Previous research on these genes in relation to the risk of contralateral breast cancer has focused largely on rare, high-risk families and has been constrained by small numbers of cases.

"While contralateral breast cancer risks in our study are quite substantial, it is worth noting that they are also 10 percent to 15 percent lower overall than in past studies in high-risk settings," Malone said. One reason for this, she said, is because this study is among the few to assess risk among substantial numbers of women without a positive family history of breast cancer.

"Getting these risk estimates right is important because of their role in clinical decision-making," Malone said. "Our study is the first to include the full spectrum of family history profiles, from minimal to extreme risk, and thus is likely to more accurately reflect the true risk of contralateral breast cancer among BRCA carriers in the general population," she said.

More than 180,000 U.S. women are diagnosed with breast cancer

annually. "With growing numbers of breast cancer survivors nationwide, the magnitude of the burden associated with the potential risk of second primary contralateral breast cancer is quite large," Malone said.

BRCA1 and BRCA2 belong to a class of genes known as tumor suppressors. These genes help ensure genetic integrity of the cell and help prevent uncontrolled cell growth that can lead to cancer. Mutation of these genes has been linked to the development of hereditary breast and ovarian cancer.

A woman's lifetime risk of developing breast and/or ovarian cancer is greatly increased if she inherits a mutation in either of these genes. Such a woman has an increased risk of developing breast and/or ovarian cancer at an early age (before menopause) and often has a number of close family members who have been diagnosed with these diseases.

More information: "A Population-Based Study of the Risk of Second Primary Contralateral Breast Cancer Associated with Carrying a mutation in BRCA1 or BRCA2," Journal of Clinical Oncology.

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