Prevalence of Pathogenic BRCA1 Mutation Carriers in 5 US Racial/Ethnic Groups

Q & A with **Esther John, Ph.D.**, Research Scientist at the **Northern California Cancer Center** and lead author of the study.

1. What does your study explore?

We explored whether breast cancer patients of different race and ethnicity are more or less likely to carry a harmful mutation in a breast cancer gene called BRCA1. Genes are inherited from our parents and their function, among other things, is to regulate the growth of cells in our body. If these genes are damaged or what we call mutated, they may not control cell growth. In the case of BRCA1, damaged genes often don't control the growth of cells in the breast or ovary which may lead to the development of breast or ovarian cancer.

We know from other studies that breast cancer patients are more likely to carry a BRCA1 mutation if:

1) they were diagnosed at a young age (before age 35 years),
2) have a strong family history of breast or ovarian cancer (multiple family members with breast or ovarian cancer),
3) are of Ashkenazi Jewish ancestry.

Most of these studies included non-Hispanic white women. Therefore, little information is available on how common harmful mutations are in other populations such as Hispanics, African Americans or Asian Americans.

2. Why did you study mutations in the BRCA1 gene?

Harmful mutations in the BRCA1 gene are relatively rare, but women who have such a mutation are about five times more likely to get breast cancer in their lifetime than women who do not have such mutations. Women with a BRCA1 mutation are also 3 times more likely to get ovarian cancer in their lifetime.

3. How was the study conducted?

We analyzed blood samples from over 1700 breast cancer patients from the San Francisco Bay Area who are enrolled in the Northern California Family Registry for Breast Cancer. This is one of six centers from the US, Canada and Australia collaborating in the Breast Cancer Family Registry, an international consortium established by the National Cancer Institute in 1995.

The Northern California Cancer Center has recruited over 3,000 breast cancer patients and family members into the Breast Cancer Family Registry. The patients were either diagnosed before age 35, had bilateral breast cancer, a prior ovarian cancer, or a family history of breast or ovarian cancer. We also included a random sample of patients who were diagnosed at age 35 to 64 who did not have any family members diagnosed with breast or ovarian cancer.

4. What are the major findings of the study?

We found that harmful mutations in the BRCA1 gene were more common among Hispanic breast cancer patients than among non-Hispanic white patients, and they were least common among Asian American patients.

Percent of patients with a harmful BRCA1 mutation:

- 3.5% or 35 in 1000 Hispanic patients
- 1.3% or 13 in 1000 African American patients
- 0.5% or 5 in 1000 Asian American patients
- 8.3% or 83 in 1000 Ashkenazi Jewish patients
- 2.2% or 22 in 1000 non-Hispanic white patients without Ashkenazi Jewish ancestry

We also found that harmful BRCA1 mutations were most common in patients who were diagnosed at a young age. This was true for all racial/ethnic groups. In patients diagnosed before age 35, the prevalence was particularly high in young African American patients: 16% or 16 in 100 patients had a harmful BRCA1 mutation, compared to 8.9% in Hispanic patients, 7.2% in non-Hispanic white patients without Jewish ancestry, and 2.4% in Asian American patients. There are many different types of mutations in the BRCA1 gene and we found that 5 Hispanic patients carried a particular mutation, the 185delAG mutation, usually found only in Jewish patients. We think that the higher prevalence of harmful BRCA1 mutations in Hispanic patients may reflect the presence of unrecognized Jewish ancestry in this population.

5. What is new about the study findings?

Previous studies have examined BRCA1 mutations in high-risk breast cancer patients seen in clinical settings. We estimated the prevalence of these mutations in a general population sample of breast cancer patients under the age of 65. Thus, our findings apply to all breast cancer patients in the San Francisco Bay area, and not to just a select group of high risk patients.

6. What are the implications of the study findings?

- We found that Hispanic and young breast cancer patients have a higher prevalence of BRCA1 mutations than non-Hispanic white patients. Yet, minority women are less likely to undergo genetic testing for BRCA1 mutations. This finding could help doctors decide which women to refer to genetic counseling and testing, so that they can be informed about cancer risks to themselves and their relatives.
- Women who carry a BRCA1 mutation may benefit from cancer prevention strategies, such as close monitoring through mammography, magnetic resonance imaging (MRI), clinical breast examination, and breast self-examination; prophylactic surgery such as mastectomy and oophorectomy; or chemoprevention such as tamoxifen use.
- Information on the prevalence of BRCA1 mutations in specific populations will guide resource allocation for genetic testing, genetic counseling, and planning of preventive interventions in all population subgroups.
- Information on the spectrum of BRCA1 mutations found in specific population groups will facilitate mutation screening in a clinical setting. For example, we found that the 185delAG mutation was present in 5 of 21 (24%) Hispanic patients who carried a BRCA1 mutation. Other studies have found this mutation in Hispanic patients also. Doctors may want to test Hispanic patients for this mutation first.

7. I am in a high risk group, what should I do?

Discuss your concerns with your doctors who may refer you to a genetic counselor who can advise whether or not genetic testing for BRCA1 or BRCA2 is recommended.

8. Is the Northern California Cancer Center doing more studies in this area?

Together with researchers from Stanford University School of Medicine and the Dana-Farber Cancer Institute we are examining whether the prevalence of harmful mutations in a second breast cancer gene, BRCA2, also varies between racial/ethnic groups.

Together with researchers from the Breast Cancer Family Registry we have been interested in exploring whether certain lifestyle factors can reduce the high risk of breast cancer development in BRCA1 or BRCA2 mutation carriers. To date we have studied the effects of oral contraceptives, alcohol consumption, and cigarette smoking. Scientific articles on this work can be found in the following journals:

Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Southey MC, Giles GG, McCredie MRE, Hopper HL, and Whittemore AS, for the Breast Cancer Family Registry. Oral contraceptive use and risk of early-onset breast cancer in carriers and non-carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005;14:350-56.

McGuire V, John EM, Felberg A, Haile RW, Boyd NF, Thomas DC, Jenkins MA, Milne RL, Daly MB, Ward J, Terry MB, Andrulis IL, Knight JA, Godwin AK, Giles GG, kConFab Investigators, Southey M, West DW, Hopper KL, Whittemore AS. No increased risk of breast cancer associated with alcohol consumption among carriers of BRCA1 and BRCA2 mutations under age 50 years. Cancer Epidemiol Biomarkers Prev 2006;15:1565-7.

Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne RL, Hopper JL, Jenkins MA, Levine AJ, Daly MM, Buys SS, Senie RT, Andrulis IL, Knight JA, Godwin AK, Southey M, McCredie MRE, Giles GG, Andrews L, Tucker K, Miron A, Apicella C, Tesoriero A, Bane A, Pike MC, kConFab Investigators, Ontario Cancer Genetics Network Investigators, Whittemore AS. BRCA1 and BRCA2 mutation carriers, oral contraceptive use and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863-1870.

Breast Cancer Family Registry; Kathleen Cuningham Consortium for Research into Familial Breast Cancer (Australasia); Ontario Cancer Genetics Network (Canada). (Whittemore AS, John EM, Felberg A, McGuire V, West DW, Miron A, Thomas DC, Haile R., Daly M, Godwin A, Ross E, Beck J, Terry MB, Buys SS, Venne V, Hopper JH, Giles GG, McCredie MRE, Milne RL, Southey MC, Jenkins M, Apicella C, Andrulis I, Boyd NF, Knight J, Ozcelik H). Smoking and risk of breast cancer in carriers of mutations in BRCA1 or BRCA2 aged less than 50 years. Breast Cancer Res Treat 2007 Oct 31; [Epub ahead of print]

We are also collaborating with other research groups to identify other genes that may modify the high risk of breast cancer development in BRCA1 or BRCA2 mutation carriers.

Spurdle AB, Antoniou AC, Duffy D, Kelemen L, Holland H, Peock S, Cook MR, Smith PL, Greene MH, Simard J, Plourde M, Southey M, Godwin A, Beck J, Miron A, Daly M, Santella R, Hopper J, John EM, Andrulis I, Durocher F, Struewing JP, Easton DF, Chenevix-Trench G, Australian Breast Cancer Family Study, Australian Jewish Breast Cancer Study, Breast Cancer Family Registry, Interdisciplinary Health Research International Team on Breast Cancer Susceptibility, The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer, and Epidemiological Study of Familial Breast Cancer Study Collaborators. The AIB1 polyglutamine repeat does not modify breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev 2006;15:76-9.

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recent articles on the BRCA1 gene by Dr. Esther John

1. John EM, Miron A, Gong G, Phipps AI, Felberg I, Li FP, West DW, Whittemore AS. Prevalence of Pathogenic BRCA1 Mutation Carriers in Five US Racial/Ethnic Groups. JAMA 2007;298(24):2869-76.

2. Apicella C, Dowty JG, Dite GS, Jenkins MA, Senie R, Daly MB, Andrulis IL, John EM, Buys SS, Li FP, Glendon G, Chung W, Ozcelik H, Miron A, Kotar K, Southey MC, Foulkes W, Hopper JL. Validation study of the LAMBDA model for predicting the BRCA1 or BRCA2 mutation carrier status of North American Ashkenazi Jewish women. Clin Genet 2007; 72:87-97.

3. Breast Cancer Family Registry; Kathleen Cuningham Consortium for Research into Familial Breast Cancer (Australasia); Ontario Cancer Genetics Network (Canada). (Whittemore AS, John EM, Felberg A, McGuire V, West DW, Miron A, Thomas DC, Haile R., Daly M, Godwin A, Ross E, Beck J, Terry MB, Buys SS, Venne V, Hopper JH, Giles GG, McCredie MRE, Milne RL, Southey MC, Jenkins M, Apicella C, Andrulis I, Boyd NF, Knight J, Ozcelik H). Smoking and risk of breast cancer in carriers of mutations in BRCA1 and BRCA2 aged less than 50 years. Breast Cancer Res Treatment 2007, Oct 31; [Epub ahead of print].

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5. Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne RL, Hopper JL, Jenkins MA, Levine AJ, Daly MM, Buys SS, Senie RT, Andrulis IL, Knight JA, Godwin AK, Southey M, McCredie MRE, Giles GG, Andrews L, Tucker K, Miron A, Apicella C, Tesoriero A, Bane A, Pike MC, kConFab Investigators, Ontario Cancer Genetics Network Investigators, Whittemore AS. BRCA1 and BRCA2 mutation carriers, oral contraceptive use and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863-1870.

6. McGuire V, John EM, Felberg A, Haile RW, Boyd NF, Thomas DC, Jenkins MA, Milne RL, Daly MB, Ward J, Terry MB, Andrulis IL, Knight JA, Godwin AK, Giles GG, kConFab Investigators, Southey M, West DW, Hopper KL, Whittemore AS. No increased risk of breast cancer associated with alcohol consumption among carriers of BRCA1 and BRCA2 mutations under age 50 years. Cancer Epidemiol Biomarkers Prev 2006;15:1565-7.

7. Lee JS, John EM, McGuire V, Felberg A, Ostrow KL, DiCioccio RA, Li FP, Miron A, West DW, Whittemore AS. Breast and ovarian cancer in relatives of cancer patients with and without BRCA mutations. Cancer Epidemiol Biomarkers Prev 2006;15:359-63.

8. Spurdle AB, Antoniou AC, Duffy D, Kelemen L, Holland H, Peock S, Cook MR, Smith PL, Greene MH, Simard J, Plourde M, Southey M, Godwin A, Beck J, Miron A, Daly M, Santella R, Hopper J, John EM, Andrulis I, Durocher F, Struewing JP, Easton DF, Chenevix-Trench G, Australian Breast Cancer Family Study, Australian Jewish Breast Cancer Study, Breast Cancer Family Registry, Interdisciplinary Health Research International Team on Breast Cancer Susceptibility, The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer, and Epidemiological Study of Familial Breast Cancer Study Collaborators. The AIB1 polyglutamine repeat does not modify breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev 2006;15:76-9.

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