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Study: Screen all Ashkenazi women for BRCA mutations rather than wait for family history

Israeli research team makes breakthrough recommendation

• By JUDY SIEGEL

Instead of Ashkenazi women being tested for the two defective BRCA genes only if a close blood relative contracted breast or ovarian cancer, a research team headed by Shaare Zedek Medical Center Prof. Ephrat Levy-Lahad recommends that all women of Ashkenazi origin be screened for the genetic mutations from age 30.

This important finding, which could lead later to screening recommendations in non-Jewish populations, was published on Friday in the prestigious *PNAS* (*Proceedings of the [US] National Academy of Sciences*) journal and aroused interest around the world.

The study, which was first thought of in 2004 by Levy-Lahad – head of the hospital's medical genetics institute – took nearly two years to get approval from the National Helsinki Committee on Human Medical Experimentation. It will probably change screening practices in Israel and in Jewish communities abroad, she predicted. Until now, only a family history or previous signs of breast or ovarian cancer was a condition for looking for any of three inherited "founder mutations" in the cancer-predisposition genes BRCA1 and BRCA2.

BRCA1, carried on a single gene on chromosome #17, was discovered in 1990 by Prof. Mary-Claire King, an esteemed geneticist and cancer researcher at the University of Washington. Between 5 percent and 10% of breast cancer is hereditary, but among Ashkenazi Jews, 10% of breast cancer and 40% of ovarian cancer are caused by these mutations.

King, a close colleague of Levy-Lahad and other Israeli researchers and a frequent visitor to Israel, is arriving in Jerusalem this week to participate in Tuesday's Second Annual Breast Cancer Symposium, which will be held at SZMC and open to the public. Other experts from Israel and abroad will speak about the paper, along with prevention and early detection of breast cancer. The *PNAS* study was financed by New York's Breast Cancer Research Foundation, Israel's National Institute for Health Policy Research and the Israel Cancer Association.

The paper's authors, including researchers at Sheba Medical Center and TEREM Urgent Care Clinics, examined the risk of breast and ovarian cancer in BRCA1 and BRCA2 carriers.

The research was conducted on a random group of Jewish women of Ashkenazi origin who were not selected because of a family history of the disease. The aim was to determine how much risk they had of contracting breast or ovarian cancer and whether it was justified to screen all women of this ethnic background.

To find a randomized group for the testing, they checked 8,000 healthy Ashkenazi men who represented the research families. A total of 175 of the men were found to be carriers of one of the mutations, which rarely raise their risk of prostate or male breast cancer. The researchers then invited women from the men's families (mothers, sisters and daughters) to be screened for the mutations and asked if they had a family history of the malignancy. According to accepted criteria, these women would not have otherwise been checked for being carriers; the defective gene would have been discovered only if and when they had contracted the disease.

The team stated that many Israeli women are unaware of the fact that they are carriers. By that time they develop breast or ovarian cancer, it is too late to take preventive measures, such as mammography, physical examination, removal of the Fallopian tubes, oophorectomy (risk-reducing surgical removal of the ovaries) or risk-reducing mastectomy.

Levy-Lahad told *The Jerusalem Post* on Friday that with the advancement of testing techniques, it is reasonable that later, screening could be performed on women of other ethnic origins, both Jewish and non-Jewish.

Testing young Ashkenazi women for the "Jewish mutations" of BRCA today costs only around $50, but including it in the basket of health services would be a significant expense. Sequencing whole genes costs thousands of dollars each, but this will become much cheaper as time goes on, said Levy-Lahad. In the non-Jewish population, the range of mutations is much wider, thus testing Ashkenazi Jews is a good and cheaper way to begin. "They can be models of testing, just as they were for carrier testing for Tay-Sachs disease or cystic fibrosis, which are also found mostly in Jews," Levy-Lahad noted.

As BRCA is a "dominant" rather than "recessive" mutation, intermarriage with non-Jews, or inter-ethnic marriage of Ashkenazim and Sephardim "doesn't change the risk. If you have it, you can pass on to children, each with a 50% risk. But in a generation or less, when a Jewish woman comes in for screening, she will not be asked about her ethnic background because of this mingling and because geneticists will be testing for all kinds of disease carriers and not only specific mutations," she said.

Risk-reducing mastectomy, performed less in Israel than in the US, is very effective in preventing breast cancer, but it is not for every woman carrier, said the SZMC geneticist. Today, there are better drugs that can turn breast cancer into a chronic disease. If one has the BRCA1 gene, removal of the ovaries and Fallopian tubes between the age of 35 and 40 (if the woman has finished having babies) almost eliminates the risk of ovarian cancer. If it is BRCA2, one can wait to 40 to have an oophorectomy.

Universal screening of young Ashkenazi women raises controversial issues. Perhaps, instead of having comprehensive genetic counseling before a screening test, it might be enough to give counseling only to women found to be carriers or who have a significant family history of the cancer. The remaining women would get written information, fill out a questionnaire and undergo only a saliva or blood test to obtain DNA. Such a study is already being conducted.

Levy-Lahad described a case four years ago of a 30-year-old, healthy woman with no family history of breast or ovarian cancer. Her mother was healthy, and her father had two brothers, with no one having had such cancer. But the woman decided nevertheless to be tested for the mutations and was found to be a carrier. She then was made part of a follow-up program that significantly increases her chances of early detection if the cancer appears. Her father was then tested and found to be a carrier as well. Because he had no sisters and his mother died many years before, it was impossible to know if the family members were carrying BRCA mutations. Thus her decision to be tested probably saved her life, Levy-Lahad stressed.

At the end of Tuesday's symposium, a program called "Prevention GENEration" – run by Levy-Lahad and sponsored by the Israel Cancer Association and New York's Northern Charitable Foundation – will be launched. It is meant to increase the awareness of the importance of undergoing genetic testing in women with breast or ovarian cancer and to help carry it out. A computerized questionnaire put on the Internet and a special pamphlet will be available.

An interview with Profs. Mary-Claire King and Ephrat Levy-Lahad and coverage of the SZMC symposium will appear on two Sunday Health Pages in the coming weeks.