Consider Genetic Testing for Hereditary Cancers

BY MARY ELLEN SCHNEIDER
Senior Writer

WASHINGTON — Clinical genetic testing for the *BRCA1* and *BRCA2* genes allows physicians to more precisely identify who is at high risk for certain cancers, Dr. Karen H. Lu said at the annual meeting of the American College of Obstetricians and Gynecologists.

Armed with this knowledge, physicians can recommend risk-reducing strategies including prophylactic surgery, said Dr. Lu, associate professor of gynecologic oncology and co–clinical medical director of the Clinical Cancer Genetics program at the MD Anderson Cancer Center in Houston.

For example, performing a bilateral salpingo-oophorectomy in someone who is a *BRCA* mutation carrier decreases their risk for ovarian cancer by 85%-95%, she said.

"In someone who is at such high risk for developing a disease for which we have no current effective screening, performing this surgery effectively saves their lives," Dr. Lu said.

In terms of breast cancer management, a 35-year-old woman with breast cancer and a strong family history might otherwise be advised to undergo a lumpectomy, radiation, and chemotherapy.

However, if she knew she carried either a *BRCA1* or *BRCA2* mutation, she might choose to undergo a bilateral mastectomy with reconstruction upfront to decrease her risk of developing a second cancer, Dr. Lu said.

Physicians can identify women who may be good candidates for genetic testing by asking a few targeted questions during the annual visit, Dr. Lu said.

The hallmarks of hereditary cancers are generally a younger age of onset, more than one cancer in a single family member, and multiple individuals in a family who have developed cancer, she said.

Consider asking these three questions:

► Do you have multiple members of your family who have had breast, ovarian, colon, or uterine cancer?

► Is there anyone in your family who has had both breast and ovarian cancer?

► Is there anyone in your family who has had these cancers under the age of 50?

Keep in mind that these cancers can be inherited through both maternal and paternal relatives, so ask about cancer on the father's side as well, Dr. Lu said.

The Ashkenazi Jewish population has three founder mutations that put them at about a 10-fold increased risk; instead of a 0.2% risk, there is a 2%-3% frequency.

Also consider ethnicity, she said. The prevalence of *BRCA* genes in the general population is about 1 per 500, or 0.2%.

However, some populations have "founder" mutations in the *BRCA1* and *BRCA2* genes that increase their risk. For example, the Ashkenazi Jewish population has three founder mutations that put them at about a 10-fold increased risk for having a *BRCA1* or *BRCA2* gene mutation. So instead of a 0.2% risk of having the mutation, there is a 2%-3% frequency of the mutation among this population.

Overall, about 5%-10% of all cancers are hereditary. For breast cancer, that translates into about 10,000 to 20,000 cases a year in the United States and about 2,000 cases each year of ovarian cancer.

The frequency of *BRCA1* or *BRCA2* carriers in the United States is about 1 in 500 in the general U.S. population. "Individuals who carry these mutations have staggering risks of cancer," Dr. Lu said.

The *BRCA1* mutation carries a lifetime risk of 50% to 85% for breast cancer and a 40% to 60% risk of developing a second breast cancer. And there is a 20%-50% lifetime risk for ovarian cancer with the *BRCA1* gene. This is significantly higher than the lifetime risk in the general population of about 11% for breast cancer and 1.7% for ovarian cancer.

In addition, the *BRCA2* gene carries a lifetime risk of 50%-85% for breast cancer and a 10%-25% risk for ovarian cancer.

Genetic testing can be useful both for cancer patients who want to find out if they face an increased risk of a second cancer and for women unaffected by cancer but with a strong family history.

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Adding MRI Sensible in *BRCA* Carriers Age 35-54

BY MARY ANN MOON
Contributing Writer

For women who carry the *BRCA1* or *BRCA2* genetic mutations, adding MRI screening to mammography screening for breast cancer can be cost effective even though MRI is so expensive, according to Sylvia K. Plevritis, Ph.D., of Stanford (Calif.) University and her associates.

Breast MRI screening is "at least 10 times more expensive than mammographic screening."

It also produces more false-positive results, which generate further costs for unneeded diagnostic workups.

"Because cost may be the greatest barrier to broader evaluation and dissemination of breast MRI screening, its cost-effectiveness is a critical consideration," the investigators noted.

Currently there are no randomized clinical trials examining the cost-effectiveness of MRI screening for women at high risk of breast cancer.

And even if such a trial were initiated today, "mortality outcomes would not be available for at least 15 years," Dr. Plevritis and her associates noted (J. Am. Med. Assoc. 2006;295:2374-84).

They estimated the cost-effectiveness of adding breast MRI screening to mammographic screening in women carrying *BRCA1* and *BRCA2* mutations using a computer simulation model that incorporated health benefits as well as expenses.

The model projected the long-term effects on clinical and economic outcomes of no breast cancer screening, annual mammography alone for women aged 25-69 years, and annual mammography plus MRI for specific age groups.

The model used a simulated cohort of women carrying the *BRCA* mutations who were aged 25 in 2005.

MRI screening was found to reduce breast cancer mortality by 23% over that obtained by mammography alone in women carrying either the *BRCA1* or *BRCA2* mutations.

For women with the *BRCA1* mutation, "adding MRI increases the sensitivity of annual screening from 35% to 85%, the proportion of axillary lymph-node–negative cancers from 57% to 81%, the mean lead time from approximately 1.5 to 3 years, and the false-positive rate from approximately 5% to 25%." Outcomes for women with the *BRCA2* mutation were similar.

"With MRI, life expectancy increases from 71.2 to 73.3 years for *BRCA1* mutation carriers and from 78.2 to 79.6 years for *BRCA2* mutation carriers," Dr. Plevritis and her associates wrote in their article.

Adding MRI to mammography was found to be cost effective for women aged 35-54 years.

It was not cost effective for the younger women in the simulation model (those aged 25-34 years) because of their lower incidence of the disease, and added MRI was not cost effective for the older women (those aged 55 and older) because of the competing risk of death from other causes. ■

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The ideal person to test in a family is someone who has had ovarian or breast cancer, Dr. Lu said. In the case of a patient unaffected by cancer with a strong family history, advise them to be tested with someone in their family who has had cancer. The person who has had cancer must be tested first.

Pretest counseling is critical, Dr. Lu commented. Patients need to be aware of the range of possible results and the limitations of the test. They may also have questions about genetic discrimination, she said.

The test itself is a simple blood test and does not require fasting. It generally costs about $3,000 to do a full analysis with complete sequencing of both the *BRCA1* and *BRCA2* genes. The cost of predictive tests on a previously identified familial mutation is about $200-$400.

Insurance companies have generally been covering these tests. An analysis of MD Anderson data in 2004 showed that 87% of insurance preauthorization requests for genetic testing were covered. Of those covered, about 90% were covered at 80% or more.

"The bottom line is that insurance companies are paying for this test," Dr. Lu said. "The access to this genetic testing is much wider now than it was in the past." ■