Honing the Health Message on BRCA Mutations

By Charlie Schmidt

Angelina Jolie’s announcement that she had undergone a double mastectomy to ward off potential tumors induced by her BRCA1 mutation served as what Kenneth Offit, MD, called a teachable moment.

“Public figures can have seismic impacts on health communication when they speak about their own experiences,” said Offit, chief of the Clinical Genetics Service at the Memorial Sloan–Kettering Cancer Center (MSKCC) in New York. “Angelina Jolie’s disclosure was no exception.”

After the actress revealed her surgery with a May 17 editorial in the New York Times, Offit and other well-known cancer specialists appeared on news outlets around the country, coalescing around several core themes:

- BRCA mutations statistically significantly elevate risks for both breast cancer (according to Offit, from 40% to 87% for BRCA1 and from 30% to 80% for BRCA2) and for ovarian cancer (up to 50%).
- Only a tiny fraction of breast and ovarian cancers can be attributed to either mutation, except among Ashkenazi Jews, who have a 1 in 40 chance of carrying a mutated BRCA gene (a rate 10 times higher than that of the general population).
- BRCA-positive women have options apart from mastectomy, particularly if they’re younger than 40 years and aiming to have children.
- Women should be tested for the mutations only if they meet criteria that include a strong family history for BRCA-related cancers.

The media coverage fell short, Offit said, by failing to highlight a more urgent priority for BRCA-positive women that the public’s obsession with Jolie’s mastectomy overshadowed: oophorectomy, or removal of the ovaries. Early-stage breast tumors can be easily detected with routine surveillance, but this isn’t an option for ovarian cancers deep in the body, which are often diagnosed late in their development.

“We find roughly four microscopic ovarian cancers for every 100 oophorectomies performed in response to genetic screening,” Offit said. “That’s as close to curative surgery as we can get in the cancer-prevention business.”

Oophorectomy reduces risk for breast cancer presumably because of the resulting decrease in estrogen; however, the estrogen–breast cancer link is complex. For example, replacing estrogen (without progesterone) in women who have had both ovaries and uterus removed preventively is not believed to increase breast cancer risk substantially. Also, Offit’s analysis showed that the major breast cancer–preventive role for oophorectomy is for BRCA2 and not BRCA1 mutation carriers, presumably because many more BRCA2 mutation carriers develop estrogen receptor-positive breast cancers. Jolie, whose breasts were cancer free when removed, didn’t mention oophorectomy in her editorial. She has since announced that she will have the procedure.

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Emerging Options

Susan Domchek, MD, a professor of oncology and founding executive director of the Basser Research Center for Inherited Cancers at the University of Pennsylvania in Philadelphia, said that BRCA-positive women have more options now than a decade ago, largely on account of surveillance improvements with magnetic resonance imaging (MRI) and newer opportunities for chemoprevention. Jolie chose mastectomy, but these other options can be tailored to a woman’s circumstances.

“We don’t want to scare women away,” Domchek said. “In many cases, there’s no rush. Jolie’s editorial cites an upper-bound lifetime risk of 87% from a BRCA1 mutation, but cancer risks for these women also grow with age. A younger BRCA-positive woman in her 20s, for instance, can have risks as low as 5% in any given year.”

But for younger women, child rearing can be a priority that also limits preventive options in the near term. According to Nancy Davidson, MD, director of the University of Pittsburgh Cancer Center, raloxifene in the BRCA-positive setting is indicated only for postmenopausal women, whereas tamoxifen—which is also antiestrogenic—can interfere with a healthy pregnancy. That leaves surveillance as the sole option. Offit pointed out that MRI detects breast tumors in BRCA-positive women with a sensitivity approaching 90%, compared with 50% for mammography. Consensus surveillance strategies for high-risk women aren’t available. But Domchek cited a recent study presented at the American Society of Clinical Oncology’s annual meeting last June, showing that...
No Clear Link Between Passive Smoking and Lung Cancer

By Judy Peres

A large prospective cohort study of more than 76,000 women confirmed a strong association between cigarette smoking and lung cancer but found no link between the disease and secondhand smoke.

“The fact that passive smoking may not be strongly associated with lung cancer points to a need to find other risk factors for the disease [in nonsmokers],” said Ange Wang, the Stanford University medical student who presented the study at the June 2013 meeting of the American Thoracic Society in San Diego.

MRI every 6 months was associated with an absence of interval cancers and with high sensitivity/specificity for detecting tumors smaller than 1 cm. Led by Olufunmilayo I. Olopade, MD, a hematologist-oncologist at the University of Chicago Hospitals, the authors concluded that their results “support this screening strategy as a viable alternative to prophylactic mastectomy.”

According to Domchek, women under surveillance at the Perelman School of Medicine get staggered mammograms and MRI 6 months apart.

When women complete (or forgo) child rearing, chemoprevention alone or in combination with oophorectomy may also offer an alternative to mastectomy. But according to Davidson, the evidence for chemoprevention benefits in BRCA-positive women derives almost entirely from studies showing that agents such as tamoxifen and raloxifene reduce the risk of tumors in the other breast in women who have already had breast cancer. In 2000, for instance, Steven Narod, MD, a fellow of the Royal Society of Canada in Toronto, published findings in The Lancet showing that tamoxifen halves the risk of cancer in the opposite breast in women with BRCA1 and BRCA 2 mutations. And this year, Kelly-Anne Phillips, the National Surgical Adjuvant Breast and Bowel Project’s P1 trial, but since the mutations are so rare, the results so far lack statistical power. Still, Davidson asserted that results from the secondary prevention trials should translate equally to the prevention of primary cancers, even regardless of their estrogen receptor (ER) status. Tamoxifen and raloxifene are both geared toward ER-positive cancer cells, but Davidson pointed out that these cells can become ER negative over time. Moreover, tumors are often heterogeneous with respect to their ER-positive or -negative composition.

“There is some evidence that chemoprevention can prevent ER-negative tumors, or tumors that become ER negative later,” Davidson said. “But the evidence isn’t strong and we need more work to explain why that might be happening.”

Adding oophorectomy to chemoprevention should boost primary cancer prevention even further, because tamoxifen, for instance, does not affect the ovaries, whereas oophorectomy reduces the risk of ovarian cancer by roughly 90% and reduces circulating hormone levels that can promote growth of breast tumors. Narod’s 2000 paper showed that oophorectomy combined with tamoxifen reduced breast cancer risk by 84%, a benefit that, Offit said, approximates that achieved with mastectomy. Later studies have not shown this same degree of combined effect, he said, “but the evidence is clear from these studies that tamoxifen as well as oophorectomy separately confer protection against breast cancer risk in BRCA mutation carriers.”

Survival Benefits

Moreover, oophorectomy can reduce not only cancer risk but also cancer mortality. Experts say it’s logical to assume that by cutting the risk of breast cancer by more than 80%, mastectomy saves the lives of BRCA-positive individuals, even though its survival benefits have never been explicitly documented. However, Domchek showed that oophorectomy is associated with roughly 60% reductions in mortality from both ovarian and breast cancer. The Journal of the American Medical Association published her findings in 2010.

Jolie wrote that she chose mastectomy to minimize her cancer risks as much as possible. That’s also true for Stacy Jacobsen, a 42-year-old mother of two, who responded to BRCA–positive status by having both her breasts and ovaries removed in 2011.

“I’m by nature an anxious person, and I wanted to get my odds down as low as I could get them,” she said. “My doctors were comfortable with surveillance: If I got cancer they could deal with it early on. But I didn’t want to go through that worrying cycle every 6 months.”

According to Larry Norton, MD, deputy physician in chief for Breast Cancer Programs at MSKCC, decisions on surgery may soon be aided by ongoing efforts to identify other genes that exacerbate BRCA risks. Studies at MSKCC this year will focus on 15 modifying single-nucleotide polymorphisms that, preliminary evidence suggests, can boost breast cancer risks among BRCA2-positive women from 50% to 80%.

Meanwhile, Jacobsen is happy with her decision. “I feel fabulous,” she said. “For me, this was the right choice. I feel that my cancer risks are super low.”

© Oxford University Press 2013. DOI:10.1093/jnci/djt364
Advance Access publication December 6, 2013