

one high-risk feature. A recent joint analysis of the NSABP B-31 and NCCTG N9831 randomized phase III trials that led to these approvals showed that adjuvant trastuzumab added to chemotherapy increased 10-year overall survival from 75.2% to 84% and 10-year DFS from 62.2% to 73.7%, Salazar said. "So the question becomes, if you add the vaccine to trastuzumab to prevent recurrence, does it improve survival even more? And with this vaccine, it's limited to those who are HLA-A2*, so that's a small pool of breast cancer patients." (About 40%–55% of the population has the HLA-A2 allele.)

Mittendorf acknowledged that obstacles to bringing a HER2 vaccine forward exist.

"The HER2 space is crowded," she said. "Trastuzumab is no longer the only player. There is TDM-1 (Kadcyla). There is pertuzumab (Perjeta). These agents are being tested in the neoadjuvant and adjuvant setting. We will need to further investigate and see who really needs what. [HER2-targeted] therapies are expensive regimens" to combine, and they have side effects. The vaccine is nontoxic, is very inexpensive and might stimulate a memory response that would work against HER2 for life."

And that excites researchers.

"The logic to test these vaccines is there and the potential is definitely there," Slamon said. "It's been known for a long time you that you could

get an immune response to what you are immunizing against. But just because you can measure an immune response doesn't mean it will translate into a clinical response or clinical benefit. You only know that by looking at clinical outcomes and that takes time."

Norwell owns the GP2 vaccine. Mittendorf is the principal investigator on vaccine trials that Galena Biopharma (NeuVax), Antigen Express (AE37), and Norwell sponsored. The M. D. Anderson Cancer Center receives financial support for each study patient enrolled. George E. Peoples Jr., M.D., F.A.C.S., a coauthor of the GP2 study, holds inventor rights to GP2.

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Rising Double-Mastectomy Rates Attract Increasing Scrutiny

By Susan Jenks

Researchers say that a recent uptick in double mastectomies may be tied, in part, to a "pink ribbon culture" that both heightens disease awareness and stokes women's fears.

"It's a startling number," said Steven J. Katz, M.D., referring to the rise in these procedures among average-risk women diagnosed with early disease. "I think it caught many surgeons by surprise." Katz is a professor of medicine, health management, and policy at the University of Michigan in Ann Arbor.

The trend occurs primarily in younger, more affluent women—despite a recent study showing that removing both breasts didn't improve survival more than lumpectomy plus radiation, the standard of care (*JAMA* 2014;312:902–14). The researchers analyzed registry data between 1998 and 2011 for nearly 190,000 women in California, all eligible for breast-conserving surgery, who chose this option, double mastectomy, or single mastectomy. They found that women self-select for these more invasive procedures for reasons that appear almost as complex as the disease itself, said Allison W. Kurian, M.D., M.Sc., assistant professor of medicine at Stanford. She cowrote the study with Scarlett Lin Gomez, Ph.D., M.P.H., of the Cancer

Prevention Institute of California in Fremont, and colleagues.

"To my mind, a bilateral mastectomy is such a big surgery; it's always highly personal," Kurian said. "But the motivation is not always about survival. It may be about regaining a sense of control."

One recent estimate (*JAMA Surg*; doi:10.1001/jamasurg.2014.2895) from a retrospective cohort involving more than 1.2 million women with stage I/II breast cancer found that rates of double mastectomy climbed from 1.9% in 1998 to 11.2% in 2011.

The greatest increase occurred in women with node-negative and in situ disease—a result, researchers say, suggesting that some women overestimate their risk for second primary cancers or for cancer recurrence in the unaffected breast. Over time, improved systemic therapies have lowered the latter risk, data show, to between 1% and 2%.

"It's an intuitive reaction—to tell the doctor to 'throw the book at me' when hearing bad health news, even when bigger, or more aggressive, is not necessarily better," said Katz, lead investigator for several federally funded research projects on cancer treatment communication and decision making. "This is your gut speaking to you."

In an editorial (*JAMA* 2013;310:793–4), Katz and Monica Morrow, M.D., chief of breast surgery at Weill Medical College of Cornell University in New York, argued that fear is not the only reason women choose double mastectomies. They also choose them because interest in these surgeries is "fueled by word of mouth and the focus of attention in the media on high-profile patients," such as Angelina Jolie. But Jolie's molecular profile (she carries BRCA mutations) puts her in a small group of women at particularly high risk for breast cancer, and clinical guidelines support prophylactic intervention in this group, they said. Another reason for the increase, the two wrote, may be due to increasingly sensitive imaging technologies that pick up abnormalities missed in the past, casting "greater uncertainty about the extent of local spread of disease."

Industry Influence?

As a breast cancer activist, Karuna Jaggar, M.A., executive director of Breast Cancer Action in San Francisco, takes a harsh view of how industry has influenced women's surgery choices for breast cancer.

"When you look at whose choosing these [bilateral] surgeries, they're

typically younger women with better insurance,” she said. “These are the women who are the targets for breast cancer awareness campaigns. There’s a lot of fearmongering out there.”

Women fail to grasp their low statistical odds of developing breast cancer at a young age, she said, but too much public health information is filtered through corporate marketers. These marketers fail to disclose both the harm and benefit of various treatments, including double mastectomies, which are major surgeries with potential complications.

“For many women, even though doctors tell them double mastectomy will not improve their survival, they don’t want to go through it again,” she said. “One woman told me, ‘I just want to get off the cancer train.’ What’s so hard for women to accept is once you’re on that train, you can’t get off.”

Jaggar said her nonprofit’s mission is not to judge women’s choices or discourage them from choosing the right option.

“Part of what we do is help drive a patient-centered research agenda,” she said, “and to make sure women have access to the information they need.”

Peace of Mind

Morrow said that surgeons have long known from previous studies that double mastectomy brings little in the way of a survival benefit.

“This is not new,” she wrote in an e-mail. “But our society has decided it’s a woman’s right to choose to have a major surgical procedure for peace of mind, even if it is not medically indicated in any traditional way,” she said.

That’s not likely to change, she suggested, until insurance coverage changes, perhaps limiting payments to patients with clear clinical indications

for these procedures. Insurers now cover all three surgical options for breast cancer, regardless of recurrence risk. So even if a surgeon explains to a patient that double mastectomy is unnecessary, Morrow said, if the patient insists on having the procedure, most surgeons will comply. Otherwise, they risk losing that patient to another surgeon who is willing to perform it, as well as future practice

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volume, she said—clear disincentives to change.

Katz, however, said it was surgeons who pushed back against the concept of “bigger is better” in the 1980s, when clinical trials determined that lumpectomy was as good as removing one breast. And he thinks they’ll do so again.

“As surgeons become more uncomfortable in removing the unaffected breast, it will become a quality-of-life issue,” Katz said. “And there’s no empirical evidence that a bilateral mastectomy improves the quality of life.”

Further Research

Meanwhile, few question the need for further research into how patients decide on their cancer care, both in general and for breast cancer.

Worta McCaskill-Stevens, M.D., M.S., chief of the community oncology and

prevention trials research group at the National Cancer Institute, described the Stanford work as an interesting population-based study, which may open up discussions about possible overuse of double mastectomy.

But she warned that a lack of data on the many complex subtypes of breast cancer limits the study’s findings, even though the study enrolled many women. The registry analysis failed to capture HER2 status, for example, or the extent of cancer treatment—key factors in any discussion about risk recurrence, she said.

Regional bias also may come into play, she added, because the so-called Hollywood effect is stronger in California than other areas of the country. Still, McCaskill-Stevens said the study showed an important lack of survival benefit to double mastectomy and raised issues associated with mortality in underserved populations. The study found that women in under-

served areas in California more often underwent single mastectomies for their disease, which carried a higher 10-year mortality rate.

“This [finding] contradicts scientific evidence, going back to the



Allison W. Kurian, M.D., M.Sc.

1980s,” she said. “If mortality is higher in underserved populations, then there may be access issues we need to address,” such as radiation adherence, or whether women in these socioeconomic groups fail to understand the importance of undergoing radiation after surgery for a better outcome

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PDQ (Physician Data Query) is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

Shastri SS, Mittra I, Mishra GA, et al.: Effect of VIA screening by primary health

workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst* 106 (3): dju009, 2014. PMID 24563518

The PDQ Cervical Cancer Screening summary was updated to include the results of a second cluster-randomized trial of VIA screening in low socioeconomic areas of urban Mumbai, India. Similar to the first cluster-randomized trial, the second trial demonstrated its efficacy in reducing cervical cancer mortality. In this trial, primary community health workers (as opposed to

medical personnel) were trained to provide biennial VIA screening to 75,360 women aged 35 to 64 years. Women with positive screening results were referred to a central hospital for free diagnostic confirmation (including Pap smear, colposcopy, and biopsy, if indicated) and treatment—where warranted—according to hospital protocol. A control group (n = 76,178) received general cancer education. After 12 years, the relative risk of dying from cervical cancer was reduced by 31% in the screening arm (rate ratio, 0.69; 95% CI, 0.54–0.88),