Questions about wisdom of early mammograms raise stakes for genetic profiling

In Tig Nataro's HBO 2015 comedy special, breast cancer shares the stage with the comedienne. Toward the end of the performance, Nataro disrobes showing the audience the scars left by the double mastectomy she underwent in 2012 after learning she had cancer in both breasts. Natoro's cancer was discovered when her first ever mammogram yielded abnormal results–and she credits this devastating news with igniting her career.

But most women don't have that experience. Many more healthy women get abnormal results from a mammogram than women who actually have cancer. This high rate of false positives has led some oncologists to recommend that universal mammography isn't the best screening tool, especially in younger women.

A recently as a few years ago, women were told to commence breast cancer screening by as early as 35. But American Cancer Society guidelines say women should start getting mammograms at 45, and that routine manual breast checks by doctors are not necessary at any age for generally healthy women. Average-risk women over the age of 55 are also being told they should reduce the frequency of mammograms to once every two years

"The chance that you're going to find a cancer and save a life is actually very small," Dr. Otis Brawley, the society's chief medical officer, has said.

The ACS recommendations mean that the three most prominent groups who set such standards recommend different ages for commencing regular mammograms:

- American College of Obstetricians and Gynecologists: 40
- American Cancer Society: 45
- U.S. Preventive Services Task Force: 50

The trend of raising recommending the age for undergoing mammograms has resulted from a number of studies showing exceedingly high false positive rate, which results in many women undergoing painful and time-consuming tests only to find out they never had cancer in the first place.

Women under 45 have denser breasts and tumors are harder to spot on an image. "If she starts screening at age 40, she increases the risk that she'll need a breast cancer biopsy that turns out with the doctor saying 'You don't have cancer, so sorry we put you through all this,'" said Brawley. "False positives are a huge deal. These women are so frightened and inconvenienced they swear off mammography for the rest of their lives."

Early detection was long thought to be the key to successful treatment. But in a must-read story in Mother Jones, Christine Aschwanden found that not to be entirely true. Early detection or not, she wrote, it's a cancer's individual biology which will make it slow-growing or fatal. Aschwanden categorizes found kinds of cancers: dodos, which are harmless and get re-absorbed by the body; turtles, which grow too slowly to

do damage; rabbits, which metastasize but not rapidly; and birds which are so virulent they've almost always metastasized before they can be detected.

Finding and treating the rabbit cancers makes a difference, but can come at a high price Aschwanden writes:

> Mammography isn't the infallible tool we wanted it to be. Some things that look like cancer on a mammogram (or the biopsy that comes afterward) don't act like cancer in the body—they don't invade and proliferate in other organs. Some of the abnormalities breast screenings find will never hurt you, but we don't yet have the tools to distinguish the harmless ones from the deadly ones.

According to a 2014 story in the Journal of the American Medical Association, if 10,000 women have an annual mammogram for 10 years, 6,130 of them will get a false positive—an abnormal result requiring more testing. Only 302 women will be correctly diagnosed with breast cancer. Even more worrisome, of those 302 women, only 10 will have their lives saved. The other 292 would have survived anyway because their cancers were slow-growing or died because their cancer was too aggressive to treat.

The false positive problem comes with a hefty price tag and a large emotional one, too. Many women are subjected to multiple surgeries to biopsy the cancer and some even undergo cancer treatment. To break down risk and identify women who should be screened, family history and genetic status are imperative. The National Cancer Institute's risk calculator puts genetics front and center in the discussion. If a woman has mutations in either BRCA genes, she is usually offer more aggressive monitoring like mammograms every six months and special MRIs that are better at detecting cancers.

Mutations in the large BRCA genes can carry a significantly elevated risk of developing breast and ovarian cancer. Some women with these mutations, most famously the actress Angelina Jolie, opt to remove their breasts before cancers can develop. But even within the well-known cancer risk genes, there is some mystery. While there are some very common and well-documented BRCA mutations, hundreds are still unknown, Ed Yong reports at The Atlantic:

> A test might return with a "variant of unknown significance" or a VUS—mutations that, simply put, we know squat about. They could ramp up the odds of cancer, by some unknown degree. Or they could do nothing. For BRCA1, there are at least 350 VUS in total. And around 2 percent of women who go for the most widely used BRCA1 test, offered by Myriad Genetics, will see at least one of these unknown mutations. Their presence on a set of test results is a big lingering question mark, an admission of ignorance, a disquieting clinical shrug.

Genetics may also play a role in determining how women with breast cancer are treated. A New England Journal of Medicine study used genetic analysis to separate women into two groups: one that would get traditional chemo plus hormone-blocking treatment and another that skipped chemo. Groups were picked by the number of mutations in their tumors: those with more variants had a higher risk of cancer spread. The women in the low score group, who had fewer mutations, received hormone therapy only. Ninety-

eight percent of those women were alive five years later. Because of genetic testing, they avoided chemotherapy, its brutal side-effects and costs.

“There is no roadmap for cancer treatment, because everyone’s cancer is different, even if the tissue of origin is the same. However, as the personalized medicine revolution rolls on, studies like this will provide tremendous help to patients and their physicians,” the Genetic Literacy Project’s Nicholas Staropoli has written.

In the quest to save women’s lives, we may have gone too far for women of normal risk levels. Our screening techniques may be over-vigilant and cause harm by finding too many abnormalities and our standard treatments might be overly aggressive. Genetics is helping us refine who needs what and can spare others pain and suffering.

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