Perspective: We need to know better to do better

When people at risk of breast cancer ask, "what's right for me?", we need the evidence to provide answers, says Laura Esserman.

I recently carried out a preventive double mastectomy on a 43-year-old woman whose mother had died of breast cancer in her forties. The woman, herself a physician, had learnt that she carried a gene mutation conferring an 85% chance that she would develop an aggressive breast cancer in 10–15 years.

By contrast, a 47-year-old patient had found out that her breast-cancer risk was low enough that she could delay further screening until she was 50 — a relief, given that screening had already resulted in two biopsies that were benign for all but anxiety.

Both women made decisions about their care on the basis of knowledge about their individual breast-cancer risk. They received the information through their participation in the WISDOM (Women Informed to Screen Depending On Measures of Risk) study, a US nationwide clinical trial designed to address the long-standing question of how screening can best be used to reduce women's chances of dying of breast cancer[1]. Should all women have annual mammograms from the age of 40, or is it more effective to tailor screening frequency and method to an individual's risk?

One of my clinician colleagues, aged 48, whose mother had died of breast cancer, told me that she did not know when she should start being screened, how often to go, or what test to have. Perhaps that's because there are at least eight conflicting guidelines from trusted organizations in the United States alone, most of which differ from guidelines for screening in other countries.

The data that inform screening recommendations come from 20–30 years ago, before we knew much about the risk factors for breast cancer, or that it is not a single homogeneous disease. We now know that not everyone gets the same kind of breast cancer, nor the same treatment. Yet the current US model of annual screening does not take this into account. The conversation around screening has become bitter, with opposing, intransigent positions that have paralysed progress. It is data, gathered in a systematic, scientific way, that will set us free from this debate.

When someone asks me what they should do about screening, it is gratifying to be able to refer them to sign up for participation in the WISDOM study (see wisdomstudy.org). The people enrolled can choose whether to be randomized to either the personalized or annual group, or to join the observational portion of the trial and choose their arm. They will receive screening recommendations and contribute to a data set that will inform screening and risk-reduction efforts.

BARBARA RIES/UCSF

"The conversation around screening has become bitter, with opposing, intransigent positions that have paralysed progress."

Laura Esserman is a surgeon and breast-cancer oncologist at the University of California, San Francisco. She is principal investigator for the WISDOM study.
e-mail: laura.esserman@ucsf.edu

The personalized approach to screening that WISDOM is testing uses everything that we know influences risk — a person's genes, breast density, exposures and family history. Based on a person's risk score, they will receive recommendations for when to start screening, when to stop, how frequently they should be screened and how it should be carried out, as well as any steps they can take to reduce their risk[2]. Women at the lowest risk might be asked to come back every two years, or not until they are 50; those at highest risk will be advised to have mammograms every 6 months, along with a magnetic resonance imaging scan. Those in the top 2.5% of risk receive counselling about risk-reduction options. Advances in risk assessment are incorporated as the study progresses, allowing it to evolve as the science advances.

Many in the radiology community have argued that we should not tolerate missing any cancers. However, not every cancer detected is a life saved. Screening can reveal very low-risk cancers that might never become clinically significant. This causes unnecessary fear and anxiety and can lead to treatment that might never have been needed.

Screening should be able to distinguish consequential cancers from very low-risk or indolent conditions at the time of diagnosis[3]. The WISDOM researchers are doing this by obtaining a molecular profile for every tumour. Over time, we will learn who is at risk for which kinds of cancer, and what risk groups have the most false-positive results that lead to biopsies.

There are many challenges involved in evaluating a personalized strategy for screening. The US National Cancer Institute is supporting efforts to increase diversity in the trial. Any study trying to address cancer screening must make sure that the population it assesses reflects the entire population of the countries where it hopes to influence policy decisions. Importantly, personalized screening allows researchers to investigate variation across ethnic groups to help better tailor care.

The WISDOM study is not the only large-scale trial testing new models of screening; a European initiative called MyPeBS (My Personal Breast Screening) is also studying risk-based breast-cancer screening. Together, these studies will tell us if the personalized approach is safe, and whether it reduces harm, is preferred by people, and facilitates the uptake of preventive interventions relative to standard approaches (in the United States, annual mammography for women age 40 and over). Importantly, these trials will help to build infrastructure to allow personalized risk assessment as part of the screening process at a time when the concept of personalized or precision medicine is pervasive, but implementation is scarce.

Understanding who is at risk for different types of breast cancer will lead to better ways to reduce risk and keep people healthy. The time is now to generate new data to inform breast screening and prevention practices to improve outcomes and save lives.

1. Esserman, L. J. *et al. NPJ Breast Cancer* **3**, 34 (2017).
2. Shieh, Y. *et al. J. Natl Cancer Inst.* **109**, djw290 (2017).
3. Esserman, L. J. *et al. JAMA Oncol.* **3**, 1503–1510 (2017).

© 2020 Springer Nature Limited. All rights reserved.