Growing uncertainty about breast cancer screening

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When they were introduced over 20 years ago, national breast screening programs were a milestone in public health. They were based on evidence from randomised trials that screening saved lives. But there are now serious doubts about what these programs can and have achieved.

The first major challenge came with the Cochrane Collaboration's review of the benefits and harms of breast cancer screening in 2001.

At that time, publication was delayed while the Cochrane reviewers and authors sorted out their differences. Meanwhile, *The Lancet* published the review, triggering a heated debate about the value of breast cancer screening that has continued ever since.

The latest update of the review, however, went quietly by.

In 2001, reviewers Peter Gotzsche and Ole Olsen pronounced mammography screening "unjustified" on the evidence from randomised trials. But an editorial in the same edition of The Lancet challenged their assertion.

It noted that: "Evaluation of the outcome of cancer screening at a national level is very much a long-term proposition."

In the latest update, the summary from all the available randomised trials of mammography screening hasn't changed much. That's because, in the intervening decade, the result of only one more trial has been published.

This hasn't changed the bottom line: taken together, the eight randomised trials found screening reduced breast cancer deaths by about 20%. But the three best-quality trials did not show a significant reduction, even after following up for 13 years.

What is new in this review is a discussion of the evidence about breast screening that's accumulated from other sources since screening became common practice.

Does breast screening save lives?

First, it's clear that breast cancer treatment has advanced significantly in the last few decades. A 2012 meta-analysis found that polychemotherapy can reduce breast cancer deaths by about one third, and earlier work demonstrated the benefits of hormone therapy.

A 2012 study assessing the impact of screening in Australia found that advances in treatment (rather than screening) were primarily responsible for the decline in breast cancer deaths seen over the last 20 years.

So it's plausible that screening isn't as necessary now as it was back in the 1960s to 1980s, when most of the randomised trials of screening began.

What's more, there's a very mixed picture emerging from non-randomised (observational) studies of screening, including screening program evaluations. BreastScreen Australia (established in 1991) reports that the national screening program has reduced breast cancer deaths by between 22% and 30%. It notes that the biggest effects are in areas where participation in screening is greatest.

This is at odds with the Australian study described above. There, researchers found the benefit happened too early (before breast

screening was fully implemented) to be attributed to screening, and was greatest among women between the ages of 40 and 49, who have the lowest participation in screening. It was lowest among women aged 60 to 69 years, who have the highest participation in screening.

The Cochrane review outlines a similarly confused picture from international observational studies. Some claim screening has delivered expected declines in breast cancer deaths across Europe, the United Kingdom and the United States.

A US analysis, for instance, estimated that between 28% and 65% of the decline in breast cancer mortality is due to screening with the rest coming from better treatment.

But other studies show that declines in breast cancer death rates have been just as great or greater among women too young for screening, or in areas where screening has been limited or not provided at all. Increased breast cancer awareness - or hyperawareness - may also play a part.

If screening works, it must do so by picking up breast cancers earlier so that there should be a drop in the rates of advanced breast cancer, as well as a drop in deaths. But there has been only an 8% decline in the rate of advanced (late stage, or metastatic) cancer in the United States over the last 30 years. This suggests that screening is having, at best, a small effect.

This something is better than nothing, right? Not quite, because breast screening can also cause harm.

How much harm does breast screening cause?

The randomised trials did not adequately measure the harms of breast

screening. For the most part, they didn't measure them at all. But evidence of harm has been steadily accumulating.

The main harm is through over-diagnosis: harmless breast cancers found by screening are treated when without screening they wouldn't have been found at all.

In contrast to the small decline in advanced cancer rates, early-stage breast cancer rates have doubled over the last 30 years, strongly suggesting over-diagnosis. An estimated 1.3 million US women are thought to have been over-diagnosed due to screening.

The impact on these women's lives, on the lives of their families and the social and economic effects of over-diagnosis is worth serious consideration.

While the frequency of over-diagnosis is still contested (estimates range from one-and-a-half to ten over-diagnosed cases for every breast cancer death prevented), its existence has been documented in countries including Canada, France, Australia, Norway and Sweden.

Advocates of screening point out that even if some women are over-diagnosed, the side effects of early breast cancer treatment (surgery, radiotherapy, hormone therapy and chemotherapy) are worth it. Better to be safe than sorry.

But evidence of unexpected side effects is also growing. We know now that radiotherapy increases women's risk of having and dying from heart attacks five to 20 years after treatment. It also increases the risk of lung cancer.

Late effects of radiotherapy are important as most women with breast cancer have radiotherapy, and live for many years after it. It's especially

important in light of over-diagnosis of screened women in their 50s and 60s.

This uncertain picture of breast screening from 20 years of observational (non-randomised) studies isn't surprising. Observational studies provide only "silver medal" evidence about the benefit and harms of screening because they are very susceptible to bias.

In particular, they suffer selection bias - comparing groups of screened and unscreened women who are different in key ways, such as their risk of breast cancer, use of hormone replacement therapy, and lifestyle factors including diet, obesity, reproductive lives and alcohol consumption.

This can lead to misleading conclusions about how many lives are saved by screening and how many cases of over-diagnosis are caused.

Observational studies are also liable to length bias (the tendency of screening to find slow-growing cancers that have excellent prognosis, contributing to over-diagnosis) and lead-time bias (screening finds cancers earlier but may just advance the time of diagnosis rather than prevent death, giving people more "disease time" but no extra years of life).

These are prone to make screening look more effective than it really is.

This is why both the UK Independent Breast Screening Review Panel and the Cochrane Review continue to rely on the older randomised trials that date back to the 1960s. They may be old, but these randomised trials at least provide evidence with a much lower risk of bias.

What do we do now?

It's 50 years since the first breast screening randomised trial began, and ten years since the first Cochrane review spoke strongly of screening's harms.

Evaluation of national breast screening programs has clearly been a long-term proposition but one that has failed to resolve our most important questions: does screening work today? And how much over-diagnosis does it cause?

It's time to acknowledge the true depth of our uncertainty about both the benefits and the harms of breast cancer screening as it is practiced today.

To resolve these questions, we need to do new randomised trials of modern breast cancer screening. New trials are needed because the practice (the quality of mammographic imaging has improved) and context (breast cancer treatments are so different now) of screening has changed so much that we can't reliably apply the results of the old trials any more.

And we need to do randomised trials because more than ever we need "gold medal" evidence - 20 years of observational studies has proved that observational studies are just not good enough to answer our fundamental questions about modern screening.

The forthcoming expansion of screening to women aged between 70 and 74 is a rare opportunity for Australia to do just this. We may manage to find data that will be valued by the rest of the world.