



Breast cancer screening for women aged 40 to 49 years— what does the evidence mean for New Zealand?

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Abstract

Aim To review the evidence on the benefits, harms and costs of breast cancer screening for women aged 40 to 49 years in New Zealand.

Methods A review of the two most recently published meta-analyses of breast cancer screening, combined with a web-based literature search and review.

Results The meta-analyses demonstrated that mammography reduces breast cancer mortality among women aged 40 to 74 years. Benefit is greatest, and harms are lowest, for women aged over 50. Cost-effectiveness is also greater for women aged over 50.

Conclusion The risks of developing and dying of breast cancer are continuous variables that increase with age. The United Kingdom Age Trial will provide further important evidence to guide policy on breast screening for women aged 40 to 49. The most recent reports of this trial suggest a smaller reduction in predicted deaths than observed in many other studies that included women below the age of 50, and less than in either of the meta-analyses reported in this article. Any further lowering of the age range of BSA should be informed by the results of this trial as well as other high quality studies that examine both the benefits and harms of breast screening for women aged 40 to 44.

Between December 1998 and June 2004, the New Zealand breast cancer screening programme—BreastScreen Aotearoa (BSA)—offered publicly funded, two-yearly, two-view mammography to all New Zealand women without symptoms of breast disease aged 50–64 years, with the aim of reducing mortality from breast cancer in this population.

In February 2004, the New Zealand Government announced an extension to the eligible age-range of BSA. In addition to women aged 50 to 64 years, from 1 July 2004, women aged 45 to 49 years and 65 to 69 years became eligible for publicly-funded mammography.

As part of the policy work to inform the age extension, the National Screening Unit (NSU) needed to examine the evidence on breast screening for women age 40 to 49 years (little evidence is published by five-year age group). This paper summarises that work—reviewing and commenting on the evidence on the benefits, harms, and costs of breast screening for women aged 40 to 49 years in New Zealand.

Methods

The most recently published meta-analysis of breast cancer screening, by the United States Preventive Services Taskforce (USPSTF) in September 2002, was used as a basis for evaluating the evidence of efficacy of breast cancer screening at different ages.¹ A major review of breast cancer screening carried out by the International Agency for Research on Cancer (IARC) was used as an additional source,²

both for evidence on efficacy and effectiveness of breast cancer screening, and as a high-quality review of all relevant issues not covered by the USPSTF meta-analysis. Articles relevant to this literature review, and referenced in the USPSTF paper and IARC handbook, were retrieved and reviewed, to ensure that the representation in the USPSTF paper and IARC handbook was accurate.

Finally, a web-based literature search and retrieval service (PubCrawler) was used to access all articles published since the USPSTF meta-analysis and IARC handbook (until March 2005). The search terms *screening*, *screen*, *mammogram*, and *mammography* were used for searches in the title field, and titles and abstracts were reviewed for relevance.

Results

The USPSTF meta-analysis was reviewed using a structured critical appraisal approach adapted from Oxman et al,³ and found to be of high quality. Specifically the meta-analysis addressed a focused question; contained an explicit description of the literature search; used appropriate inclusion and exclusion criteria; included all key studies; appraised the validity of included studies; and tested results for homogeneity.

The USPSTF meta-analysis demonstrated that mammography reduces breast cancer mortality among women aged 40–74 years. Evidence of benefit was greatest for women aged 50–74 years (Table 1).¹

Table 1. Summary of results from USPSTF meta-analysis of mammography screening¹

Variable	Age group (years)	
	40–49	50+
Relative risk (CrI*)	0.85 (0.73 to 0.99)	0.78 (0.70 to 0.87)
Relative risk reduction	15%	22%
Number needed to screen (CrI) to prevent one death from breast cancer after 14 years	1792 (764 to 10,540)	838 (494 to 1676)
Reduction in number of deaths from breast cancer after 14 years of mammography screening (per 10,000 women)—the absolute risk reduction	6	12

*Credible Interval; a statistical tool that gives an idea of the range within which the true relative risk (RR) will likely lie. Simply put, a credible interval is a Bayesian version of a confidence interval.

The review of breast cancer screening by age revealed the following key points:

- **Sensitivity by age**—The sensitivity is the proportion of people with the disease who are detected as having it by the test. There is a consistent trend for increasing sensitivity of mammography with increasing age, meaning that a larger proportion of cancers are detected in older women. For example, in a review of the British Columbia (Canada) breast-screening programme, the sensitivity was 76% for women aged 40–49, 85% for those aged 50–59, and 90% for those aged 60–69.⁴
- **False negatives by age**—People with false-negative tests may be falsely reassured that they do not have breast cancer— and as a result, may delay seeking help if symptoms develop later. Clinicians may also be falsely reassured.⁵ Up to

25% of all invasive cancers are not detected by mammography in 40–49 year-olds, compared with 10% of invasive cancers in 50–59 year olds.⁶

- **Positive predictive value by age**—The positive predictive value (PPV) of mammography is the likelihood of having breast cancer if the screening test is abnormal, and is usually expressed as a percentage. Estimates from community settings show a graded, continuous increase in positive predictive value with age (as expected) given the increasing prevalence of breast cancer with age. For example, among 32,000 average-risk women screened in California (USA) from 1985 to 1992, the PPV of first-screening mammography (for further evaluation) was 4% among those aged 40 to 49 years, 9% among those aged 50 to 59 years, and 17% among those aged 60 to 69 years.⁷
- **Cancer detection rate by age**—The breast-cancer detection rate is the number of women who have breast cancer detected within a breast-screening programme, and is usually expressed as a rate per 1000 women screened. The breast-cancer detection rate increases steadily with age, since breast-cancer incidence increases with age, and breast cancer becomes easier to detect on mammograms with age. For example, in the British Columbia screening programme, the cancer detection rate (per 1000 women) was estimated to be 1.8 for women aged 40–49, 3.2 for women aged 50–59, and 5.1 for women aged 60–69.⁴
- **Specificity and false positives by age**—The harm of false-positive mammograms relates to the inconvenience, additional outpatient visits, testing, invasive procedures (and consequently, healthcare costs), administration, and anxiety that would not have occurred in the absence of screening.⁸ Age is related to specificity, and is inversely related to the false-positive rate, at least partly because younger women have denser breasts, and dense breasts are more difficult to read radiologically.² For example, in a review of a breast screening programme in New England (USA), the false positive rate was 7.8% for women aged 40 to 49, 7.4% for women aged 50–59, and 5.3% for woman aged 60–69.⁸ On the basis of the USPSTF meta-analysis, after 10 years of two-yearly screening among 40-year-old women, 400 women would have false-positive results, and 100 women would undergo biopsy or fine needle aspiration (FNA) for each death from breast cancer prevented.¹
- **Overdiagnosis by age**—Overdiagnosis refers to the diagnosis and treatment of cancers that would never have caused symptoms. There is some evidence that more overdiagnoses occurs among women aged 40–49 years than among older women.⁷ In addition, some cancers that might be detected in women in their 40s are so slow growing that they could be detected by mammograms after the age of 50, and be treated at that time without compromising outcomes.⁶
- **Radiation exposure by age**—Radiation exposure is also a potential risk associated with mammography, although breast cancer as a result of the radiation dose associated with mammography has never been conclusively demonstrated. If it exists, the risk would be highest for younger women, as there are more potential years of life in which an induced cancer can develop.⁶ For example, if screening is commenced at age 50, the number of radiation-induced deaths from breast cancer during the remaining lifespan has been estimated at 10–50 per million regularly screened women (10–20 screens, 2–5 mGy per screen). If regular screening is

begun at age 40, the number of radiation-induced deaths from breast cancer would be 100–200 per million regularly screened women.²

- **Cost-effectiveness by age**—Intuitively, screening women under 50 would seem to offer greater benefits, since more life-years should be gained. However, the cost-effectiveness of breast screening in 40 to 49 year old women is lower than that for women over 50, due to the lower breast cancer incidence and the poorer performance of the screening test due to denser breast tissue in the younger age group.² It has been estimated that screening women aged 40–49 years costs approximately five times as much per life-year saved as screening older women (aged over 50).^{9,10}

Discussion

Screening differs from other health interventions in that it is offered to asymptomatic people with the understanding that they can benefit. Those to be screened are free of symptoms, so it is hard to improve their situation, and easy to cause harm.¹¹ This places an ethical obligation on those offering screening to ensure that it can provide this benefit and that (overall) this benefit will outweigh any harms. Indeed, any harm to an asymptomatic person should not be considered lightly.¹¹

False-positive and false-negative tests cause harm to people participating in screening programmes. People with false-positive tests may experience anxiety, unnecessary investigations, and their associated side effects. On the other hand, people with false-negative tests feel reassured that they do not have breast cancer, and as a result may delay seeking help if symptoms develop later. No screening test is perfect, so inevitably there will be some false-positive and some false-negative tests with any screening. New Zealand criteria for assessing screening programmes have been developed that carefully consider these issues.¹² BreastScreen Aotearoa uses a comprehensive range of indicators and targets, to minimise the inevitable negative effects of screening.¹³

A prerequisite for offering any form of screening is evidence for efficacy and effectiveness in improving outcomes.² The USPSTF meta-analysis demonstrated that there is limited evidence for benefit in mortality reduction among 40–49 year old women. The relative risk reduction is estimated at 15% (compared with 22% in women aged over 50), but could be less, depending on the extent to which it is due to screening women after they reached the age of 50.¹

Likewise, despite the potentially greater number of life-years that should be gained from screening women under 50, such screening is less cost-effective than screening women over 50. At the same time, there is evidence of greater harms when screening women under 50, compared to those over 50.

The USPSTF meta-analysis is a thorough and well-conducted overview of the RCTs. The only obvious criticism is that this meta-analysis combined results obtained by using different methods of counting breast cancer deaths. The ‘follow-up’ and ‘evaluation’ methods can produce relative-risk estimates that are significantly different. However it is difficult to see how to avoid this—as different methods were used in the different RCTs that form the basis of the meta-analysis.

The results from the USPSTF meta-analysis are consistent with most previous meta-analyses, and are closely consistent with the next most recent (IARC) meta-analysis of mammography screening.²

In the IARC overview, the combined relative-risk estimates for death from breast cancer were:

- 0.81 (0.65 to 1.01) for women aged 40–49 years, and
- 0.75 (0.67 to 0.85) for women aged 50–69 years.

The IARC authors also state that it is uncertain how much of the effect among 40–49 year olds might be due to screening after the age of 50.²

The value of mammography screening for women aged 40–49 years is a longstanding controversy.¹⁴ In earlier years, the controversy centred on a lack of evidence that relative-risk reductions in mortality were statistically significant. That argument has faded as more evidence has shown improved survival with longer follow-up.¹⁴ However, the evidence for benefit from mammography is clearly stronger for women aged 50 to 69 years than for women aged 40 to 49 years. The relative-risk reductions from screening also appear to be lower for younger than older women, and the benefits take twice as long to appear.⁶

The delay in the separation of the breast cancer survival curves for 40 to 49 year old women has prompted some to question whether the benefits of mammography are due to the detection of cancer after 50 years of age—thus suggesting little incremental benefit from starting screening at 40 years of age, and exposing women to the harms of screening for an extra decade.^{15,16} The USPSTF authors found little evidence to address this issue, and some evidence that part of the benefit from screening women aged 40 to 49 years would be sacrificed if screening began at 50 years. However, definitive estimates of the proportion of benefits due to early screening could not be made.¹

One of the reasons why the relative-risk reduction for women aged under 50 years is lower than for older women may be due to the different natural histories of breast cancer among women younger and older than 50 years. Re-analysis of the Swedish Two-County trial has shed some light on this issue. The mean sojourn time (the duration of the period during which a cancer is symptom free, but potentially detectable by screening) for women aged 40–49 is much shorter than that for women aged 50–74.¹⁷ This may be due to either increased breast density, or faster tumour growth rates, or both.

Buist examined the relative contributions of these factors to the poorer sensitivity of mammography in younger women.¹⁸ Greater breast density explained 68% of the lower sensitivity of mammograms in younger women at 12 months, whereas rapid tumour growth explained 31%, and breast density 38%, of the lower sensitivity in younger women at 24 months.

To some extent, the use of 50 years as a threshold for screening mammography is arbitrary, except that it approximates the age of menopause.¹⁴ The risks of developing and dying of breast cancer are continuous variables that increase with age. The USPSTF recommended screening every one or two years from the age of 40, but also admitted that the evidence was weaker for the 40 to 49 year age-group, that the

balance of benefits and harms was more favourable as women age, and that the absolute benefit (the most important factor for policy and funding decisions) was smaller for younger women than for older women. To illustrate this point, of 24 breast-screening programmes in existence around the World, one country (Japan) recommends beginning breast screening at the age of 30; four countries recommend beginning at the age of 40 (Iceland, Sweden, Portugal, and Greece) three countries begin at the age of 45 (Navarre in Spain, Uruguay, and New Zealand) and 16 countries begin at the age 50.²

As discussed above, test properties, measures of effectiveness, harms, and cost-effectiveness are all less favourable for women in their 40s than for older women. Thus, although mammography at any age poses a trade-off of benefits and harms, the balance between increasing benefits and decreasing harms grows more favourable with age (at least until the age of 70).¹⁹

Sasieni and Cuzick have recommended that the United Kingdom breast screening programme begin at the age of 47, since the UK breast cancer rate for women in their late 40s is closer to that of women aged 50 to 54 than for women in their early 40s—a situation that existed in New Zealand until BSA increased the incidence of breast cancer among the BSA target population of women aged 50 to 64, as breast screening programmes always do.²⁰ Evidence from the Swedish screening programme indicates that screening at age 47 to 49 years is no less sensitive than screening at age 50 to 54 years.²¹

The results of the United Kingdom Age Trial will provide further important evidence to guide policy on breast screening for women aged 40 to 49 years.^{2,16} This multicentre RCT began in 1991, recruited 161,000 women aged 40–41 years, and will include an economic evaluation. The reporting of this trial is still at an early stage, and only preliminary data are available.^{22,23} The most recent report suggests a borderline statistically significant 10 or 11% reduction in predicted deaths at 10 years in women invited for screening—less than that observed in many other studies that included women below the age of 50, and less than in either of the meta-analyses reported in this article. This analysis was based on surrogate outcome measures, and included a number of assumptions. Firm conclusions will need to await further analysis. Any further lowering of the age range of BSA should be informed by the results of this trial and other high quality studies that examine both the benefits and harms of breast screening for women aged 40 to 44 years.

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