What is the most appropriate breast-cancer screening interval for women aged 45 to 49 years in New Zealand?

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Abstract

**Aim** To review the international evidence on the benefits and harms of different screening intervals for women aged 45 to 49 years, and to inform the development of a national policy.

**Methods** A systematic search and review of the literature, up to March 2005.

**Results** There is no robust trial evidence on which to base a decision on the most appropriate breast-cancer screening interval for women aged 45 to 49 years, and it is unlikely that definitive trial evidence will ever emerge. Evidence from less robust studies is equivocal.

**Conclusion** In the absence of definitive evidence, those charged with determining the screening interval for women aged 45 to 49 years in a breast-cancer screening programme have to weigh up the available evidence, and consider it alongside other relevant factors. A two-yearly screening interval for women aged 45 to 49 was decided upon, and became policy in New Zealand.

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 to 64 years, with the aim of reducing mortality from breast cancer in this population.

In February 2004, the Minister of Health announced an extension to the eligible age-range of BSA. In addition to women aged 50 to 64 years already being screened, from 1 July 2004 women aged 45 to 49 years and 65 to 69 years became eligible for publicly-funded screening mammography. This age extension significantly increases the number of women eligible for publicly-funded mammography in New Zealand and will substantially increase demand for breast-screening services.

Women aged 50 to 69 years are screened two-yearly in BSA. Many international breast-screening experts recommend annual screening for women under 50, and there is a strong perception that this is best practice for this age group. One of the key decisions for the age extension was deciding on the most appropriate screening interval for women aged under 50.

A multidisciplinary Expert Advisory Group was convened to consider the evidence and to make a recommendation to the Minister. An earlier version of this review provided the evidence base.

**Methods**

A systematic search and review of the medical literature was carried out in May 2004, using the search terms *breast* and *interval* and *(screening or cancer)* in MEDLINE. A web-based literature search and
retrieval service (PubCrawler) was also used to access articles, and this was continued up to March 2005. The search terms screening, screen, mammogram, and mammography were used for searches in the title field. All titles were reviewed for relevance, and articles retrieved and reviewed when relevant. Further articles were retrieved from reference lists.

Any review of breast cancer screening will want to examine the highest quality evidence available. The randomised controlled trial (RCT), with mortality as the outcome, is the only type of study designed specifically to eliminate the effects of biases that are common in studies of screening programmes—namely lead time bias, length-biased sampling, overdiagnosis, and selection bias. However, there is a limited amount of trial evidence on the most appropriate screening interval for breast cancer. Consequently, less robust forms of evidence were also examined.

**Results**

**Screening interval trials**—There have only been two randomised controlled trials (RCTs) comparing breast screening intervals:

- Klemi et al reviewed the mammography programme in the city of Turku (Finland), in which women had been randomly assigned to receive one-yearly or three-yearly mammograms, and calculated the proportion of invasive interval cancers. An ‘interval cancer’ is a cancer diagnosed between a normal screen, and the time the next screen is due. A programme with a high percentage of interval cancers is unlikely to make a significant difference to breast cancer mortality. The interval cancer rate depends on a number of factors—including the quality of the mammogram, the quality of the reading process, the density of breast tissue, the growth rate of breast cancers, and the screening interval. The authors calculated that 27% of breast cancers found in screened women aged 40 to 49 were invasive interval cancers found within one year of screening on a one-year screening schedule. Among women on a three-yearly screening schedule, 39% of breast cancers found in screened women aged 40 to 49 were invasive interval cancers found within three years of screening (p=0.22 for difference between screening intervals). Mortality and stage distribution were not reported.

- The UK Co-ordinating Committee on Cancer Research (UKCCCR) randomised trial did not include women under 50 years. In this trial, among UK women aged 50 to 62 years following a first screen, shortening the screening interval from three years to one year (RR=0.95, p=0.4) made no statistically significant difference in the predicted mortality from breast cancer.

**Sojourn time**—The choice of screening interval in a breast-screening programme depends directly on the epidemiology and natural history of breast cancer in the age group of interest and, in particular, on the ‘sojourn time’. The sojourn time is the duration of the period during which a cancer is symptom free, but potentially detectable by screening. The shorter the sojourn time of a cancer, the less likely it is that a screening programme will improve mortality from that disease—as the cancer is more likely to have spread before it is detected.

Estimates suggest that the sojourn time among women aged 40 to 49 is between 1½ and 2½ years, compared to between 3 and 6½ years in women aged 50 to 74. It is generally recommended that the screening interval should not exceed the sojourn time. As the sojourn time is shorter among younger women, a shorter screening interval is usually recommended for younger women.
Doubling time—The ‘doubling time’ is the time taken for a tumour to double in volume. In a study from the Netherlands, Peer et al estimated that the doubling time for breast cancer in women aged 40 to 49 years was 80 days (95%CI=44–147 days), compared to 157 days (95%CI=121–204 days) in women aged 50 to 70 years.23

The authors concluded by suggesting that the screening interval should be shorter in younger women, although they also pointed out that more frequent screening will not necessarily lead to a clear mortality reduction in this age group. Tabar et al calculated a doubling time for breast cancer of 178 days among women aged 40 to 49 years, compared to 255 days for women aged 50 to 74 years (p value not given).9

Breast cancer screening trials—In the RCTs of breast cancer screening—designed to examine the efficacy of breast screening rather than the screening interval—women were invited to be screened at a mixture of 12 month, 18 month, 24 month and 33 month intervals—the majority being screened at two-year intervals.1 Trials using a shorter screening interval for women aged 45 to 49 have not produced a greater reduction in breast cancer mortality than those using a longer interval.24,25 Preliminary results from the UK ‘Age’ Trial suggest a 10 or 11% reduction in predicted deaths at 10 years in 40 to 49 year old women invited for annual screening26,27—less than in recent meta-analyses of screening in this age group, which included trials in which women were screened at 24 and 33 month intervals.1,24 An ideal screening interval has not been determined from these trials.28

Tabar et al analysed the Swedish Two-County Trial. Among women over 50 years of age at entry to the trial, relatively few interval cancers were seen in the first two years after a screening test; in the third year, the rate rose to 45% of the comparable rate in the control group.14 By contrast, among women aged 40 to 49 years at entry, the proportion of interval cancers (even in the first post-screening year) was 38% of that in controls, and in the second year, it was 68% (p value<0.001 for difference between age groups), suggesting a shorter screening interval may be more appropriate in younger women.

Modelling—Some authors have used mathematical modelling to assess the effect of different screening intervals. Pelikan and Moskowitz used modelling based on the Health Insurance Plan (HIP) trial to predict that the mortality reduction for annual screening of women aged 40 to 49 should be the same, or somewhat less, than that for two yearly screening of women aged 50 and over.29

Tabar et al used modelling based on tumour size and nodal status to predict deaths from breast cancer among women under 50 years,9 and predicted a 12% (RR=0.88, 95%CI=0.54–1.41) reduction in mortality from breast cancer from two-yearly screening, compared to a 19% (RR=0.81, 95%CI not given) reduction in mortality from annual screening.

Feig used data from the Swedish Two-County Trial, and calculated that if women aged 40 to 49 years were screened every year, their ratio of interval to control incidence cancers at one year would have been similar to the same ratio for older women two to three years after screening, suggesting that annual screening among 40 to 49 year old women would produce a mortality reduction close to that of women aged 50 to 74 years who are screened every two or three years. Mathematic modelling suggested a mortality reduction of 35% versus 23% (assuming a 100% compliance
rate, p value not given) for annual versus biennial screening of women aged 40 to 49.\textsuperscript{30,31}

The results of Markov-chain modelling of breast tumour progression to determine the optimal screening interval using data from the Swedish trials suggested that the screening interval is critical for women aged 40 to 49 years, but less so for older women. Among women aged 40 to 49 years, a three-year screening interval was predicted to result in only a 4% reduction in breast cancer mortality. A two-year screening interval was predicted to result in an 18% reduction in breast cancer mortality, while annual screening should result in a 36% reduction (p value for differences not given).\textsuperscript{8,21} Jansen and Zoetelief produced similar results when modelling data from the Swedish Two County study.\textsuperscript{32}

Chen et al used Markov chain modelling to predict deaths from breast cancer among women under 50 years. Results suggested that two-yearly screening would yield a mortality reduction of 10–20%, while annual screening would yield a mortality reduction of 20–30%.\textsuperscript{33}

Boer et al used modelling to estimate the benefits and harms of different screening intervals for women aged over 50 years. The authors postulated that longer screening intervals would tend to pick up slower growing cancers—cancers that may benefit less from early detection. The authors demonstrated that the ratio of benefits to harms increases with shorter screening intervals, but that cost-effectiveness decreases markedly.\textsuperscript{34}

**Service screening**—The sensitivity of a screening test is commonly reported. The sensitivity is the proportion of people with the disease who are detected as having it by the test. A test with a low sensitivity will miss a lot of cancers. A test with a sensitivity of 100% will detect all cancers present. Brekelmans et al analysed data from the DOM project—a breast screening programme established in Utrecht (the Netherlands) in 1974. Among women aged 40 to 49 years, the age-specific sensitivity at six months was 89% (95%CI=77–101%)—close to the age-specific sensitivity among women aged 50 to 64 after 12 months (88%, 95%CI=81–95%). Similarly, the age-specific sensitivity at one year among women aged 40 to 49 (76%, 95%CI=61–91%), was close to the sensitivity at two years among women aged 50 to 64 (72%, 95%CI=63–81%).\textsuperscript{35}

Feig reviewed an analysis of the Uppsala programme in Sweden, and concluded that women aged 40 to 49 need to be screened every 12 months to attain roughly the same mortality reduction as older women screened every 24–30 months.\textsuperscript{36}

Peer et al examined the interval cancer rate among women aged 40 to 49 years in the Nijmegen breast screening programme in the Netherlands. In the second year after screening, the interval cancer rate for women aged 40 to 49 years approached the expected breast cancer incidence rate in the absence of screening, leading the authors to suggest that a two-year interval for women under 50 appears to be too long. However, this result was heavily influenced by the very poor performance of mammography in the 40 to 44 age-group (interval cancers making up 94% of the expected breast cancer incidence rate in the absence of screening). The performance of screening was better in the 45 to 49 age-group (71%). For comparison, the rate for women aged 50 to 54 years was 55% (p values for differences not given).\textsuperscript{11}
Using data from the University of California San Francisco screening programme, Kerlikowske et al demonstrated that the sensitivity of screening for women aged 40 to 49 at a one-year screening interval is virtually the same (84%) as that of screening women age 50 and older at a two-year interval (86%). Breast density did not influence the sensitivity of mammography in women under 50 years—thus supporting the view that rapid tumour growth, rather than breast density, is the main reason for the reduced sensitivity of mammography in younger women.

Proportional incidence is also commonly measured in screening programmes. The proportional incidence is the number of interval breast cancers, expressed as a proportion of the number of breast cancers expected in the absence of screening. The higher the proportional incidence, the less likely it is that the programme will reduce mortality from breast cancer. A review of the two-yearly BreastScreen Victoria (Australia) programme revealed a proportional incidence among women aged 40 to 49 years of 59% (95%CI=39–85%) in the first year after screening, and 93% (95%CI=59–140%) in the second year.

Hunt et al reported on the outcome of screening annually versus two-yearly in a screening programme for American women aged 40 to 79. Although women in their dataset were not assigned to annual versus two-yearly screening at the outset, Hunt et al were able to extract estimates of the effect of various screening intervals by sorting women into those who returned to screening at either 10–14 month intervals (‘annual’), or those who returned at 22–26-month intervals (‘two-yearly’). The authors combined this data with information from the cancer registry on women found to have interval tumours (defined as tumours not detected at screening that were noted within either one year [annual], or two years [two-yearly] of a negative screen). They found that the size of the tumours was smaller in the annual group (p=0.04), suggesting an enhanced value of annual screening. Differences between annual and two-yearly screening in tumour size did not reach statistical significance when the age group 40-49 years was analysed separately.

Broeders et al examined the Nijmegen breast screening programme in The Netherlands, and calculated a non-significant, 44% reduction in breast cancer mortality among women aged 45 to 49 years who were screened two-yearly. The authors suggested that, even in a programme with a two-year screening interval, there may be a benefit of starting screening around age 45.

Buist et al examined outcomes among women aged 40 and over, who developed invasive breast cancer, enrolled in a health maintenance organisation in Washington State. Within 12 months of a negative screen, interval cancers had occurred in 28% of women aged 40 to 49, and 14% of women aged 50 plus (OR=2.36, 95%CI=1.14–4.77). Within 24 months of a negative screen, interval cancers had occurred in 52% of women aged 40 to 49, and 25% of women aged 50 plus (OR=3.58, 95%CI=2.15–5.97). Greater breast density explained 68% of the decreased mammographic performance in younger women at 12 months. At 24 months, greater breast density explained 38%, and rapid tumour growth explained 31% of the decreased mammographic performance in younger women. The authors concluded that mammography screening of younger women at 12 versus 24 month intervals may remove the adverse effect of faster growing tumours on mammographic sensitivity, but will not remove the adverse effect of breast density on mammographic sensitivity.
Taylor et al analysed the New South Wales (Australia) screening programme, and calculated a proportional incidence in the 40 to 49 year age group of 56% (95%CI =50–62%) for the first year, and 86% (95%CI =82–90%) for the second year.\textsuperscript{43}

White et al investigated whether American women diagnosed with breast cancer after having screening mammograms separated by a two-year interval were more likely to be diagnosed with late-stage disease (positive lymph nodes or metastases) than women diagnosed with breast cancer after having screening mammograms separated by a one-year interval.\textsuperscript{44} Women aged 40 to 49 with a two-year interval were more likely to have late-stage disease than those with a one-year interval (28% vs 21%, OR=1.35, 95%CI=1.01–1.81). No differences were observed in older women, and there was no indication that women with dense breasts would benefit more from a one-year rather than a two-year screening interval.

Wai et al compared the long-term impact of one- and two-year screening intervals among 50 to 74-year-old Canadian women, using prognostic modelling. The shorter screening interval was associated with a higher proportion of screen-detected cancers, compared to interval cancers—but this translated to only a 1.2% increase in the estimated 10-year breast cancer-specific survival among women screened every year, compared to those screened every second year.\textsuperscript{45}

Meta-analyses—Kerlikowske et al performed a meta-analysis of the association between screening interval and mortality across the eight randomised controlled trials. Mortality reductions for screening every 18–33 months were similar to reductions for annual screening for women aged 40 to 49.\textsuperscript{25}

The United States Preventive Services Taskforce (USPSTF) concluded (in their meta-analysis) that annual screening may be more important among women aged 40 to 49 years—but they found no direct proof for this hypothesis in the controlled trials that had been completed at the time the meta-analysis was undertaken.\textsuperscript{24} However, the authors noted that some experts recommended annual mammography for women aged 40 to 49 years—based on the lower sensitivity of the test, and on evidence that tumours grow more rapidly among this younger age-group.\textsuperscript{46}

Taylor et al carried out a meta-analysis of proportional incidence rates for women aged 40–49 years\textsuperscript{43} (both for randomised trials of screening, and for service screening), and they included some of the studies already documented in this report.\textsuperscript{12,14,35,37,38,47,48} The meta-analysed proportional incidence rate for women aged 40 to 49 for randomised trials was 42% (95%CI=21–62%) for the first year, and 63% (95%CI=55–71%) for the second year—and for service screening it was 44% (95%CI=31–58%) for the first year, and 72% (95%CI=51–92%) for the second year.

Overseas programmes—In Sweden, mammography is recommended every 18 months for women aged 40 to 49 years;\textsuperscript{39,49,50} Australia, Iceland, and the Netherlands (Nijmegen) recommend two-yearly mammography for women aged 40 to 49 years;\textsuperscript{39,51,50} Canada offers one-yearly or two-yearly screening (depending on the province); and in the United States, no single group establishes national policy as different institutions recommend either one-yearly or two-yearly screening for women aged 40 to 49.\textsuperscript{50}

Other countries (including Portugal, Spain [Navarre], and Greece) recommend two-yearly mammography for women aged 40 to 49 years.\textsuperscript{1,52} However, screening interval
recommendations do not automatically result in that screening interval in practice—as
capacity is not always present, and women do not always attend as recommended.

**Capacity-limited studies**—Fett et al created a computer model to examine the
mortality benefits of adjusting the balance between population coverage of screening
and screening interval among 50 to 64 year old women. That is, does screening twice
the population half as often produce the same reduction in mortality? Analysis
suggested that (for a given number of screens) the higher the coverage and the longer
the screening interval, the greater the reduction in breast cancer mortality. For
example, screening 30% of the population annually would produce a 20% reduction
in breast cancer mortality, whereas screening 60% of the population every two years
would produce a 29% reduction. The authors concluded that the results supported
policies that seek to deploy resources available for mammographic screening most
evenly across the target population.6

**Prospects for future research**—An RCT to evaluate the relative effect of different
screening intervals (with breast cancer death as the end-point) would require groups
large enough to yield 350 breast cancer deaths in the absence of screening, and a very
long follow-up.4,14 Such a trial would need to be three times the size of the Swedish
trials of 135,000 women, and would need to run for considerably longer.14 It is
unlikely that such a trial will ever be carried out.

**Discussion**

Like other countries, New Zealand is experiencing difficulties meeting demand for
breast screening services, due largely to a shortage of both breast-screening medical
radiation technologists (MRTs) to take mammograms and breast radiologists to read
mammograms and carry out assessments.

Screening women (aged under 50 years) every year would place great demands on
limited resources, to the extent that some women would inevitably need to wait to be
screened. However, if women aged 45 to 49 years were screened every two years in
New Zealand, instead of every one year, more women could be screened sooner. It is
clearly important, however, to make sure that when using a two-yearly screening
interval for women (aged under 50), the benefit of screening this age group is not
diminished.

No robust trial evidence exists on which to base a decision on the screening interval
for women aged 45 to 49 years, and it is unlikely that definitive trial evidence will
ever emerge. Evidence from less robust studies supports a screening interval of one
year or 18 months—although in the randomised controlled trials, shorter screening
intervals did not produce greater benefits among women aged 45 to 49 years.

However, it is important to note that the eight breast screening trials varied on more
than just screening interval. Trials had one or two mammography readers, one or two
mammography views, variable quality of mammography equipment, widely varying
recall rates, and radiologists with differing mammography expertise. All of these
factors independently influence screening performance over and above the screening
interval, thus complicating the interpretation of the RCT data and the subsequent
modelling of the effect of screening interval. Lisby carried out an evidence-based
review, and concluded that there was ‘not enough evidence to recommend optimal
intervals for screening with mammography in women in their forties’.28
Overseas screening programmes either recommend intervals of 12, 18, or 24 months in women aged 45 to 49 years. There is some evidence that, in a situation of limited capacity, screening 1000 women every two years produces a greater mortality benefit than screening 500 women every year. In the absence of definitive evidence, those charged with determining the screening interval for women aged 45 to 49 years in a breast-screening programme have to weigh up the available evidence and consider it alongside other relevant factors.

The Expert Advisory Group, convened to recommend implementation policies for BSA Age Extension, considered the evidence summarised above and the likely ability of the programme to increase capacity to meet the demand. They decided, after much discussion, to recommend a two-yearly screening interval for women aged 45 to 49 at this time—taking into account the available evidence and the ability of the health sector to cope with the increased workload. The Group also recommended that emerging evidence on the screening interval be regularly monitored. The Minister of Health accepted these recommendations.

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