Impact of extending screening mammography to older women Information to support informed choices

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From 2013 through 2017, the Australian national breast cancer screening programme is gradually inviting women aged 70–74 years to attend screening, following a policy decision to extend invitations to older women. We estimate the benefits and harms of the new package of biennial screening from age 50–74 compared with the previous programme of screening from age 50–69. Using a Markov model, we applied estimates of the relative risk reduction for breast cancer mortality and the risk of overdiagnosis from the Independent UK Panel on Breast Cancer Screening review to Australian breast cancer incidence and mortality data. We estimated screening specific outcomes (recalls for further imaging, biopsies, false positives, and interval cancer rates) from data published by BreastScreen Australia. When compared with stopping at age 69, screening 1,000 women to age 74 is likely to avert one more breast cancer death, with an additional 78 women receiving a false positive result and another 28 women diagnosed with breast cancer, of whom eight will be overdiagnosed and overtreated. The extra 5 years of screening results in approximately 7 more overdiagnosed cancers to avert one more breast cancer death. Thus extending screening mammography in Australia to older women results in a less favourable harm to benefit ratio than stopping at age 69. Supporting informed decision making for this age group should be a public health priority.

Introduction

Screening mammography is offered in many developed countries, and most programmes target women aged 50–69 years.[1] With increasing life expectancy and an ageing population, however, there has been a trend to extend invitations to older women. Screening older women is intuitively attractive as the incidence of breast cancer increases with age. But cancers detected in older women are likely to have more favourable biology and be slow-growing,[2] and breast cancer mortality as a proportion of all-cause mortality decreases with age due to competing causes of death.[3] Although breast screening in women aged 65 years and older may be beneficial when life expectancy is greater than 5–10 years, this must be weighed

against the increasing risk of harm due to overdiagnosis and false positives.[4]

In The Netherlands, France, New Zealand, Israel, Japan, and Korea, screening has been offered to women until age 75 for some time. This practice is relatively new to Australia, the United Kingdom and some regions of Canada, Italy and Sweden.[1,5,6] Guidelines in North America recommend screening for women in the target age group of 50–74 years on the evidence that screening prevents breast cancer deaths, even though there is risk of false positive results and overdiagnosis.[7,8] The World Health Organisation conditionally recommends including women aged 70–75 years in breast screening programmes.[9] In the UK, however, the uncertainty around the additional benefit versus harm of continuing to screen past 70 years has led to the establishment of a trial to formally evaluate the effects.[10]

It is widely accepted that women should be offered balanced and complete, evidence-based information to enable them to make informed choices about screening.[9,11,12] Yet there is a lack of information available on the benefit and harms of continuing to screen past age 70 to help women with this decision. Only 3 randomised controlled trials from Sweden included a small proportion of women over 70 years,[13] and a meta-analysis of these trials found a 20% reduction in breast cancer mortality for women aged 70–74 years, though it was not statistically significant.[14] In Australia, an ecological evaluation of the national breast screening programme, BreastScreen Australia, concluded that the mortality

What's new?

In Australia, invitation to screening mammography recently was extended to women ages 50–74 years, whereas the previous age range was 50–69 years. Consequently, participation by older women has almost doubled. This study shows, however, that extending the upper age limit of screening mammography to 74 is likely to result in a small decrease in breast cancer mortality but a substantial increase in overdiagnosis. Analyses indicate that one additional breast cancer death, 78 false positives, and eight instances of overdiagnosis would occur for every 1,000 women screened biennially. The findings emphasise the importance of patient-clinician discussion and informed decision-making by screening-eligible women.

reduction associated with screening women over 70 years was half that seen in women aged 50–69 years, but did not consider the potential harms.[15] In the Netherlands, the extension of screening mammography to women aged 75 years resulted in a small decrease in the incidence of advanced-stage breast cancer with a disproportionate increase in early-stage disease.[16] Given the observational nature of these data they should, however, be interpreted with caution.

BreastScreen Australia offers free biennial screening to women over age 40 using 2-view digital mammography with double-reading. Since 1991, women aged 50–69 years have been specifically targeted via letters of invitation. Despite limited evidence of the benefits of screening older women, in 2013 the Australian Government announced a phased extension of the target age group to women aged 70–74 over 4 years and subsequently began sending letters of invitation to this age group.[17] We aim to evaluate the benefits and harms of this change in screening policy by comparing it to a programme that stops inviting women at age 69. Our goal is to provide women with information about the outcomes they could expect from the new policy, to help them make an informed choice. This information is intended to be used in decision aids for women considering screening, which are effective in improving women's knowledge about breast cancer screening including the risk of overdiagnosis.[18,19]

Materials and Methods
Overview

To evaluate the benefits and harms of extending screening to women aged 74 years and compare outcomes to stopping at age 69, we have updated and extended our previously published model.[20] Our aim was to produce up-to-date information for use in decision aids to help older women use their values and preferences to assess the trade-off between benefits and harms. The Independent UK Panel on Breast Cancer Screening published estimates of the mortality benefit and risk of overdiagnosis attributable to screening and advised that such information should be provided to women.[11] We aimed to put their recommendation into practice. To do so, we first adjusted their estimates of the relative risk reduction of breast cancer mortality and percentage risk of overdiagnosis attributable to screening, to reflect the likely effects on women who fully participate in screening.[21] We then applied these estimates to aggregate Australian breast cancer mortality and incidence rates. We used current, age-specific Australian screening service data to

obtain estimates of other screening outcomes (recalls, biopsies, false positive rates, and interval cancer rates). Model outcomes are presented as age-specific estimates of benefits and harms for 1,000 Australian women who choose to enter the national BreastScreen programme at age 50 and continue to participate in screening every 2 years according to the new (from age 50–74 years) and former (from age 50–69 years) policies. This comparison enables 50-year-old women to answer the question, if I choose to participate in screening every 2 years for 25 years what outcomes can I expect and what is the chance of experiencing them? We also calculated the marginal benefits and harms of the extended screening programme which is preferable to average benefits and harms when making health decisions about 2 programmes.[22] This analysis enables 69-year-old women to answer the question: what can I expect if I choose to participate in the additional 5 years of screening?

A Markov process model was used to estimate the outcomes of 2 hypothetical groups of women. In one group women undergo biennial screening and in the other group they do not. The model is based on 100% participation in the screening group and no participation in the unscreened group and thus generates outcomes for women who accept regular screening invitations versus those who do not. First, we modelled outcomes for women who start screening at age 50 and continue until age 69 to reflect the previous policy. Second, we modelled outcomes for women who start screening at age 50 and continue to age 74 years to reflect the new age-extension policy.

Data sources and assumptions

Table 1 summarises data sources and assumptions underlying the model. Data for breast cancer incidence, mortality and screening outcomes were taken from the Australian Institute of Health and Welfare (AIHW) BreastScreen monitoring reports, which in turn come from state-base screening programmes and cancer registries. Australian state cancer registries contain records of all new diagnoses of cancer in residents and have almost 100% coverage. All states and territories maintain a population-based BreastScreen register which records the data collected during a woman's contact with a BreastScreen service. BreastScreen Australia has National Accreditation Standards for Services, including stringent data monitoring and quality control.[17] The AIHW compiles BreastScreen Australia data supplied from state and territory BreastScreen registers in order to monitor screening

Table 1. Data sources and assumptions

Parameters	Data sources	Assumptions
Breast cancer incidence in unscreened women	• Modelled expected breast cancer incidence in unscreened women for 2014	• Would be a valid representation of unscreened breast cancer incidence today
Breast cancer incidence in screened women	• BreastScreen Australia monitoring reports (data for first and subsequent rounds of screening, 2005–2014)	
DCIS incidence in unscreened women	• Luke *et al.* (2006): DCIS accounts for 1.4% of total breast cancer incidence in unscreened women	
DCIS incidence in screened women	• BreastScreen Australia monitoring reports (data for first and subsequent rounds of screening, 2005–2014)	
Breast cancer overdiagnosis	• Marmot *et al* (2013): method C: excess cancers as a proportion of all cancers diagnosed during the screening period in women invited to screening • Jacklyn (2016): Deattenuated risk of overdiagnosis of 29.7% for screened women aged 40–74 years	• Trial results are a valid representation of the overdiagnosis attributable to BreastScreen Australia.
Breast cancer mortality in unscreened women	• 2016 Australian Cancer Incidence and Mortality (ACIM) book for Breast Cancer (age-specific breast cancer mortality data from 2005 to 2014) • Marmot *et al.* (2013) • Jacklyn *et al.* (2016): Breast cancer mortality in unscreened women with deattenuated relative risk reduction of 30.4% for women aged 40–74 • BreastScreen Australia monitoring reports (2005–2014)	• Breast cancer mortality in unscreened population = BrCa mortality (unscreened + screened)/(proportion of population unscreened + RR BrCa mortality × proportion of population screened)
Breast cancer mortality in screened women	• 2016 ACIM book for Breast Cancer (age-specific breast cancer mortality data from 2005 to 2014) • Marmot *et al.* (2013) • Jacklyn *et al.* (2016): Breast cancer mortality in unscreened women with deattenuated relative risk reduction of 30.4% for women aged 40–74 • BreastScreen Australia monitoring reports (2005–2014)	• Breast cancer mortality in screened population = RR BrCa mortality screened population x (BrCa mortality (unscreened + screened)/(proportion of population unscreened + RR x proportion of population screened) • Trial results are a valid representation of the breast cancer mortality reduction attributable to BreastScreen Australia • Onset and duration of benefit on breast cancer mortality: benefit accrues linearly to maximum level over first 5 years after starting screening; benefit declines linearly to nothing over 5 years after stopping screening
Mortality from non-breast cancer causes in screened and unscreened women	• Australian Bureau of Statistics age-specific mortality 2013–2015 (life tables) • 2016 ACIM book for Breast Cancer (age-specific breast cancer mortality data from 2005 to 2014)	• Screened and unscreened women experience the same risk of death from causes other than breast cancer
Participation in screening		• 100% participation among screened women and zero participation among unscreened women
Recall rates	• BreastScreen Australia monitoring reports (data for first and subsequent rounds of screening, 2005–2014)	
Type of recall procedure	• State BreastScreen service providers (data from 2004–2013 available from New South Wales, South Australia, Victoria, and Western Australia)	
Interval cancer rate	• BreastScreen Australia monitoring reports (data for 0–12 and 13–24 months after screening, 2005–2014)	

outcomes at a national level. All data provided by state and territory BreastScreen programmes, once analyzed by AIHW, are supplied back for verification. The high quality of the cancer registry and BreastScreen data provided a solid foundation upon which to apply the pooled estimates from the UK Panel.

Incidence of breast cancer in screened women

We obtained screened breast cancer incidence data from BreastScreen Australia.[23] These data come from greater than 1.5 million women screened biennially, but to minimise any yearly variation and consider the impact of sustained, long-term screening, we pooled data from the most recent 10 years (2005–2014).

Overdiagnosis of breast cancer in screened women

We calculated and expressed the risk of overdiagnosis according to the Independent UK Panel's recommended method for women considering whether to participate in screening (Method C).[11] This includes all screen-detected, interval and clinically detected cancers. Among women aged 50–74 years invited to screening, the probability that a cancer detected during the screening period is overdiagnosed is 19%. We converted this estimate into an outcome that is relevant to women who attend screening (as for benefit) and used an overdiagnosis percentage risk of 29.7%.[21] We then modelled overdiagnosis by applying the adjusted estimate (which allowed for lead time) to the total number of breast cancers diagnosed in screened women during the active screening period. Thus it was not dependent on the estimated incidence of breast cancer in unscreened women, and there was no need to estimate or model lead time, nor make assumptions about its distribution or duration in the model.

Incidence of breast cancer in unscreened women

To provide context to readers and help users of our work compare the benefits and harms of screening to no screening, we included estimates of incidence of breast cancer in unscreened women. We used Poisson regression to estimate age-specific incidence of breast cancer in unscreened women for 2014 using an unscreened population prior to the introduction of government-subsidised mammography and BreastScreen (1974–1983) (Supporting Information Appendix S1). We estimated age-specific incidence of non-invasive cancer in unscreened women by assuming that 1.4% of breast cancer diagnosed clinically is DCIS, based on rates of DCIS reported before screening.[24] For screened women, incidence was accrued during the active screening period.

Mortality of breast cancer in unscreened women

We used data on breast cancer mortality for the most recent 10 years from the AIHW. As these data include women who did and did not undergo screening, we adjusted them using age-specific screening participation rates over the same period to obtain breast cancer mortality for unscreened women. Given that the overall risk in the population is apportioned across both screened and unscreened women, the risk of breast cancer mortality among unscreened women was calculated as:

Breast cancer mortality unscreened = Total breast cancer mortality (unscreened + screened)/(proportion of population unscreened + relative risk breast cancer mortality in screened x proportion of population screened)

Mortality of breast cancer in screened women

Among women aged 50–74 years, invitation to screening reduces the risk of dying from breast cancer by 20%.[11] To convert this estimate into an outcome that is relevant to women who attend screening, we used methods that adjust for adherence to the trial protocol and generated a relative risk reduction of 30.4%.[21] As the benefit of screening on breast cancer mortality is not immediate, we incorporated a time-lag to benefit and assumed that the mortality benefit accumulates linearly over 5 years from the start of screening.[25] Similarly, we assumed that benefit persists after screening stops and declines linearly over 5 years.[26,27] We applied the relative risk reduction to the age-specific mortality from breast cancer for unscreened women (above) to derive mortality for screened women (Supporting Information Appendix S2).

Mortality due to other causes

We used life table data from the Australian Bureau of Statistics for age-specific all-cause mortality.[28] These rates were decomposed into mortality from breast cancer and other causes. As we assume the same baseline risk in screened and unscreened women, rates for causes other than breast cancer for both these groups were fixed at the age-specific rate for unscreened women. We applied these rates to the group at risk in each given year to calculate the number of deaths from causes other than breast cancer in screened women. All rates were converted to annual probabilities.

All-cause mortality

We calculated the total number of deaths in each year by summing the number of deaths due to breast cancer with the number of deaths due to other causes. Both breast cancer and all-cause mortality outcomes were accrued during the active screening period until 5 years after screening stopped to allow for the continued effect of screening on breast cancer mortality.

Other outcomes of screening

For the initial and each subsequent screen we obtained the number of women recalled for extra imaging and biopsy (0–12 and 13–24 months after screening). These outcomes were accrued over the active screening period.

Progression through the model

Each scenario begins with a cohort of 1,000 women aged 50. We then apply age-specific probabilities to reflect the transition of the groups through 1-year cycles.

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Sensitivity analysis

Sensitivity analyses were conducted to explore the uncertainty associated with the relative risk reduction for breast cancer mortality and percentage risk of overdiagnosis. We varied the deattenuated estimates across the 95% CI range which was 18.4–42.3% for the mortality relative risk reduction and 17.8–41.5% for the percentage risk of overdiagnosis. We calculated a best-case scenario using a 42.3% relative risk reduction for the benefit and a 17.8% risk of overdiagnosis for the harms, and a worst case scenario, using 18.4% relative risk reduction and 41.5% overdiagnosis. To explore the uncertainty around the continued effect of mortality reduction after screening stops, we also allowed the benefit to decline linearly over 10 years. To allow for a comparison of outcomes over identical time periods, we cumulated breast cancer incidence over 25 years and mortality over 30 years for both women who stop screening at age 69 and those who continue to age 74.

Results

Table 2 shows outcomes cumulated during the active screening period for women screened biennially from 50–69 years (20 years of screening) and for women screened from 50–74 years (25 years of screening) compared with no screening over the same time periods. These estimates reflect time periods that are most relevant to women who are making informed decisions about screening and also allows for a direct comparison of the difference in outcomes for women screened from 50–74 years to those who choose to stop screening at age 69 years (Table 2).

False positive results

Among 1,000 women aged 50 who are screened biennially until age 69, 444 will receive an abnormal result and be recalled for assessment. Of these, 293 will have more imaging, 150 will undergo biopsy, and 387 will have a false positive result. Screening to age 74 will result in 102 additional recalls, 43 additional biopsies, and 78 additional false positives. Therefore, women who participate in the extended screening programme will increase their chance of experiencing a false positive from 38.7 to 46.5%.

Breast cancer detection and overdiagnosis

Among 1,000 women screened from age 50–69, a total of 75 breast cancers will be diagnosed (57 screen-detected and 18 interval) of which 22 will be overdiagnosed. Continuing to age 74 will result in 24 additional screen-detected cancers, and 103 cancers diagnosed in total. An additional 8 women will be overdiagnosed. Expressed as a percentage, the absolute chance of breast cancer overdiagnosis due to screening is 2.2% in women screened from 50–69 and 3.0% in women screened from 50 to 74.

Breast cancer deaths

Among 1,000 women aged 50-years who are screened for 20 years to age 69 (and mortality outcomes followed up to age 74), around 11 will die from breast cancer compared with 15 unscreened women. If women choose to continue screening for another 5 years until age 74 (and are followed up to age 79), a total of 14 will die from breast cancer compared with 19 among the unscreened women. Whereas biennial screening for 20 years until age 69 results in 4 breast cancer deaths averted for every 1,000 women screened, continuing until age 74 will mean 5 deaths are avoided. Expressed as a percentage, the absolute chance of dying due to breast cancer decreases by 0.4% in women screened from 50–69 (from 1.5% to 1.1%) and 0.5% in women screened 50–74 (from 1.9 to 1.4%) (Fig. 1). Thus screening until age 74 avoids one additional breast cancer death per 1,000 women (0.1%) compared with stopping at age 69.

Harm to benefit ratio

Figure 2 compares outcomes for benefits (reduced risk of dying from breast cancer) and harms (false positives, false positive biopsies, and overdiagnosis). If women screen from age 50–74, we estimate an average of 6.1 overdiagnosed breast cancers for every breast cancer death averted compared with an average of 5.8 overdiagnosed cancers if women screen from age 50–69. Note that the marginal effect for women of participating in the extra 5 years of screening is 7.1 additional overdiagnosed cancers to avert one more breast cancer death.

Sensitivity analysis

When we varied the estimate of the relative risk reduction from 18.4 to 42.3% for 1,000 women screened from age 50–69, as few as 2 or as many as 6 would have a breast cancer death averted, and as few as 3 or as many as 8 per 1,000 women who continue screening to age 74 (Table 3). For overdiagnosis, we varied the estimate from 17.8 to 41.5% and found that for every 1,000 women screened from age 50–69, 13 to 31 would be overdiagnosed; for women who continue to age 74, 18 to 43 would be overdiagnosed. Varying the estimates meant that for every breast cancer death averted, the number of overdiagnosed cases detected and treated was as few as 2.3 or as many as 14.4 for women who screen until age 69 and 2.5–14.8 for those who stop at age 74.

Extending the decline in benefit to 10 years after screening ends instead of 5 years improved the harm to benefit ratio. For women who screen from age 50–69, the ratio changed from 5.8 to 5.1 overdiagnosed cancers for every death averted. For women who screened from age 50–74, the ratio changed from 6.1 to 5.4 overdiagnosed cancers for every death averted.

We also cumulated incidence and mortality over identical time periods for women who participate in screening from age 50 to 69 and those who continue to age 74 (25 years for incidence and 30 years for mortality). We found that this

Table 2. Cumulative outcomes for women who undergo screening over 20 years (original programme) or 25 years (current programme) and those who do not

	Original programme Target age 50–69 years Begin screening at age 50, 10 biennial screens over 20 years		Current programme Target age 50–74 years Begin screening at age 50, 13 biennial screens over 25 years		Current programme vs. Original programme
Cumulative number of women who:	Screening	No screening	Screening	No screening	Difference in outcomes in screened women
Procedures[1]					
Are recalled for more tests	443.6		545.5		101.9
Undergo:					
Extra imaging (mammography and/or ultrasound) or clinical examination only	293.2		351.9		58.7
Biopsy (total with at least 1 biopsy)	150.4		193.6		43.2
Fine needle aspiration biopsy	29.7		40.2		10.5
Core biopsy	83.8		103.7		19.8
Open biopsy	36.9		49.7		12.9
Receive a false positive result	386.6		464.5		77.9
Breast cancer cases					
Receive a diagnosis of invasive breast cancer at screening	45.1		65.0		19.9
Develop an interval cancer	17.7		21.6		3.9
Receive a diagnosis of DCIS[2]	11.9	0.6	16.0	0.7	4.2
Totals:					
Receive a diagnosis of breast cancer at screening	57.0		81.0		24.0
Receive a diagnosis of invasive breast cancer	62.8	41.0	86.5	52.2	23.8
Receive a breast cancer diagnosis of any kind (invasive, DCIS, or interval)	74.7	41.6	102.6	52.9	27.9
Receive a diagnosis of breast cancer at screening that is overdiagnosed and overtreated	22.1		30.4		8.3
Mortality[3]					
Die from breast cancer	10.9	14.7	13.7	18.6	2.8
Die from causes other than breast cancer	125.6	125.3	213.2	212.4	87.6
Die from all causes	136.5	140.0	226.9	231.1	90.3
Avoid dying from breast cancer	3.8		5.0		1.2
Harm to benefit ratio					
Overdiagnosed cases per breast cancer death averted (average effect over the duration of screening)	5.8		6.1		0.3
Overdiagnosed cases per breast cancer death averted (marginal effect of an extra 5 years of screening)	-		-		7.1

Figures are per 1,000 women. Mortality outcomes are cumulated until age 74 for women aged 50–69 who are screened or unscreened over 20 years, and until age 79 for women aged 50–74 who are screened or unscreened over 25 years.

Due to rounding, some totals may not correspond with the difference of the separate figures.

[1]Diagnostic procedures reflect the number of times the procedure was performed per 1,000 women.

[2]Ductal carcinoma *in situ*, presenting both clinically with symptoms and detected at screening.

[3]Mortality outcomes cumulated to 5 years after screening mammography stops to capture continued benefit in screened women.

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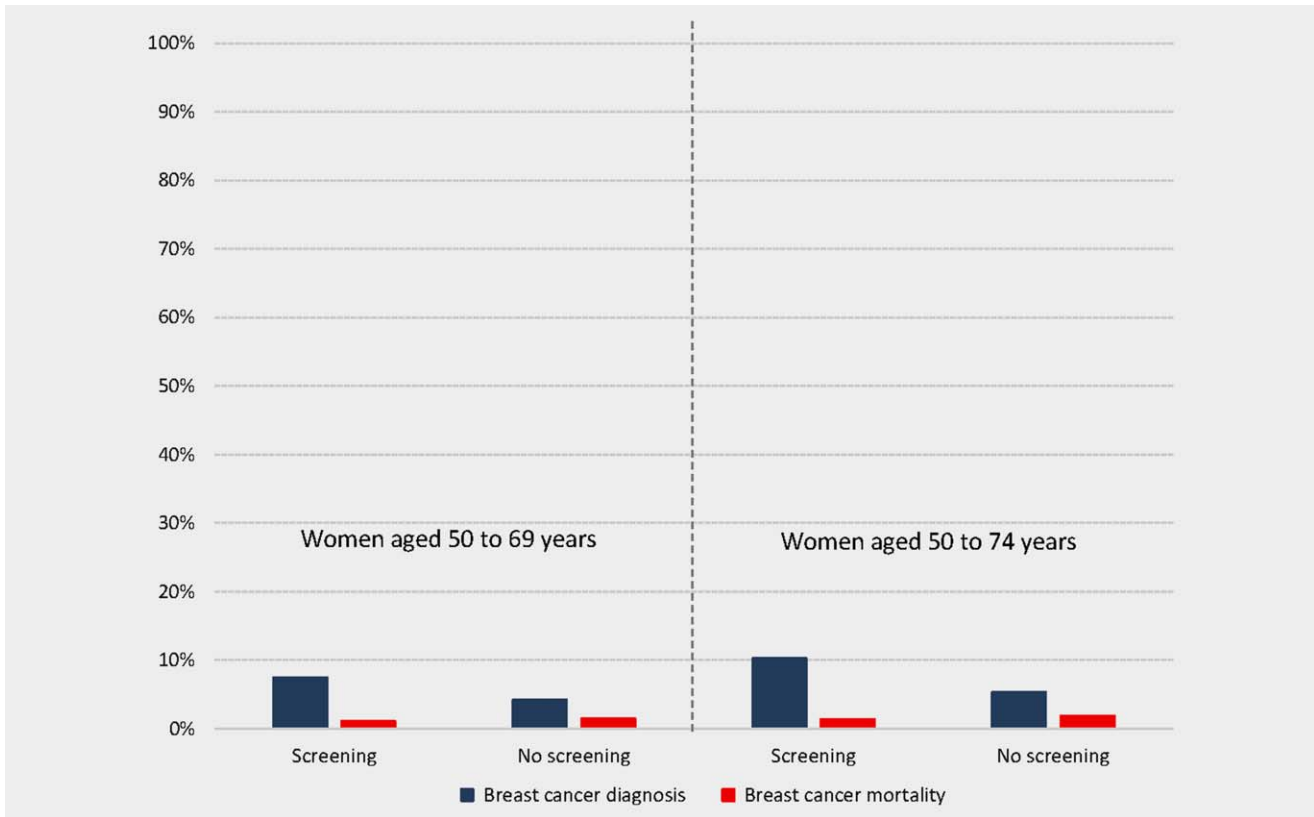
Figure 1. Absolute risk of diagnosis of and death due to breast cancer with and without screening in Australia. Figure 1 shows 20-year absolute risks for incidence (including overdiagnosis) and mortality for women aged 50–69 years, and 25-year risks for women aged 50–74 years. [Color figure can be viewed at wileyonlinelibrary.com]
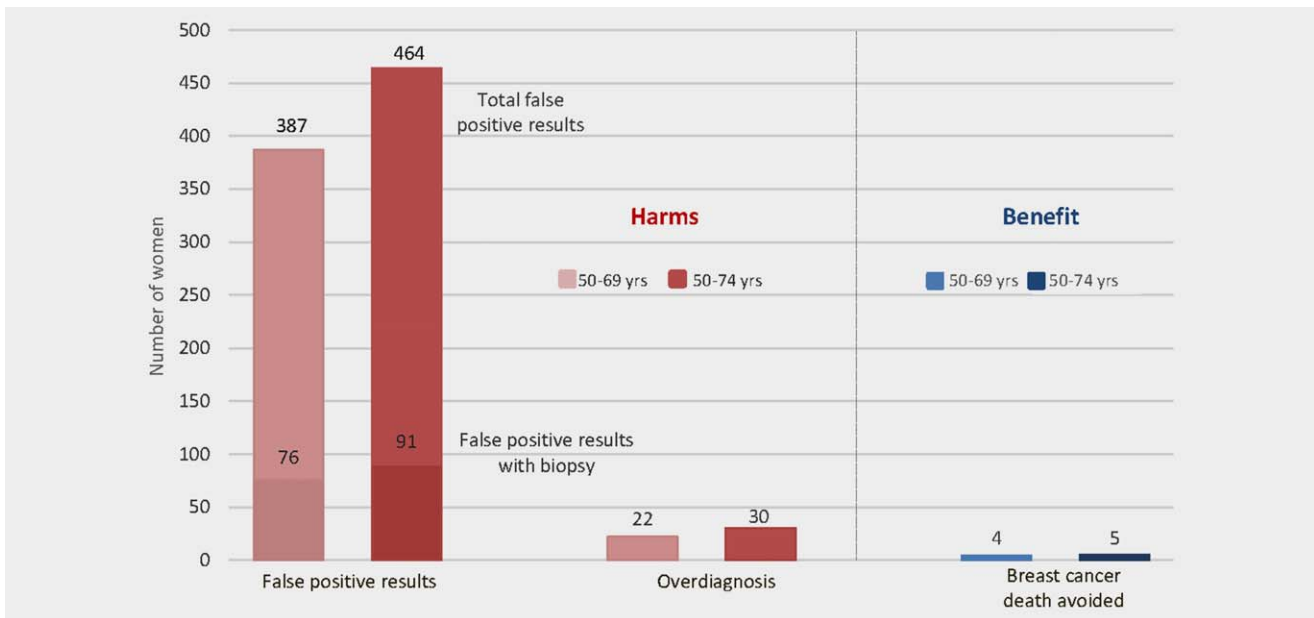
Figure 2. Benefits and harms for 1,000 women who undergo screening every 2 years over 20 years (ages 50–69) or 25 years (ages 50–74). [Color figure can be viewed at wileyonlinelibrary.com]

reduced the difference between the total number of breast cancers diagnosed and mortality outcomes. However, it did not change the difference in screening outcomes such as

procedures, screen-detected cancers, overdiagnosis and mortality benefit, nor the ratio of harm to benefit for screening (Supporting Information Appendix S3).

Table 3. Upper and lower bound estimates for the cumulative number of breast cancer deaths averted and overdiagnosed cancers for 1,000 women who begin biennial screening mammography at age 50

	Best case			Worst case		
	Target age 50–69 years 10 biennial screens	Target age 50–74 years 13 biennial screens	Difference	Target age 50–69 years 10 biennial screens	Target age 50–74 years 13 biennial screens	Difference
Cumulative number of women who:						
are overdiagnosed	13.3	18.3	5.0	31.0	42.6	11.6
Avoid dying from breast cancer[1]	5.7	7.4	1.7	2.2	2.9	0.7
Harm to benefit ratio:						
Overdiagnosed cases per breast cancer death averted (average effect over the duration of screening)	2.3	2.5	0.1	14.4	14.8	0.5
Overdiagnosed cases per breast cancer death averted (marginal effect of an extra 5 years of screening)	—	—	3.0	—	—	16.2

Best case: 42.3% reduced risk of dying from breast cancer, 17.8% risk of overdiagnosis (upper bound RRR, lower bound % risk of overdiagnosis).
Worst case: 18.4% reduced risk of dying from breast cancer, 41.5% risk of overdiagnosis (lower bound RRR, upper bound % risk of overdiagnosis).
Due to rounding, some totals may not correspond with the difference of the separate figures.
[1]Mortality outcome cumulated to 5 years after screening mammography stops.

Discussion

In this study of outcomes of screening mammography, we model the impact of extending the national programme to Australian women aged 74 years. We focus on 3 key outcomes: breast cancer mortality reduction, false positives, and overdiagnosis. When compared with screening 1,000 women from age 50–69 years, extending screening mammography to age 74 is likely to avert one more breast cancer death but lead to an additional 78 women experiencing a false positive and 8 more women being overdiagnosed and overtreated. Our analysis shows that the benefit to harm ratio for the new, extended screening packages is less favourable compared with the previous policy.

Strengths and limitations of this study

We have developed the first model of the Australian BreastScreen programme that provides outcomes for the entire 25-year package of screening mammography for women at an individual level. Our results should help Australian women aged 50 make an informed choice about whether or not to have breast cancer screening. Our findings are also relevant internationally, where almost all programmes offer biennial screening to women within the age range of 50–74 years (excluding the US, UK, Uruguay, and China).[1] Our analysis enables us to present the marginal benefits and harms of the new policy compared with the previous policy, which can help older women answer the question: what would be the consequences of participating in screening mammography for 5 more years from age 70 to 74?

Criticism of a modelling approach is frequently concerned with difficulty in assessing biases, particularly when models are based on many assumptions and lack transparency.[29,30] We do not make complex assumptions about the natural progression of breast cancer or mean sojourn time in our model. Instead, we use estimates from an independent meta-analysis of randomised trials, adjust for the effect of attending screening, and apply these to contemporary Australian data and time periods relevant to screening delivery. The data that underpin our model are robust, and the assumptions are plausible and transparent (Table 1).

We convert directly observed population data on breast cancer incidence (including screen-detected and interval cancers), mortality and other screening outcomes in Australia into absolute risks for women who screen from age 50–69 and compare these to women who screen from age 50–74, thus providing accurate and easy to use information on the benefits and harms for individual women who attend screening. Nonetheless, there are limitations to these data. The data used in our analysis were collected during the roll-out of digital mammography across BreastScreen Australia services. Replacement of plain-film units with digital may slightly change outcomes of future analyses.

Our risk of reduced breast cancer mortality and overdiagnosis are based on estimates derived by the Independent UK Panel.[11] Although randomised trials offer the most reliable evidence on screening outcomes, important uncertainties remain as outlined by the Independent UK Panel in their report. For example, there is heterogeneity between studies, as well as biases that could distort the estimates of both mortality benefit and overdiagnosis risk.[11,31] Therefore we present best and worst case scenarios based on the 95% confidence limits of the estimates provided by the Independent UK Panel, adjusted for adherence.[21] Although we acknowledge the limitations of this approach, which deals with only the statistical uncertainty, it may help communicate to women the uncertainty around these estimates.

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Some may be concerned about the applicability of the mortality benefit and overdiagnosis risk estimated by the Independent UK Panel to the Australian context. A recent analysis by Birnbaum (2016)[32] found that screening mammography is likely to have the same relative mortality benefit despite advances in treatment for breast cancer, suggesting the relative risk of mortality benefit estimated by the Independent UK Panel, (which assumes independent effects of screening and treatment advances), remains applicable. Although the UK Panel estimates do not exclude women younger than 50, both the estimate of mortality benefit and overdiagnosis used in our model fall within ranges of local figures. In Australia (where no screening mammography trials have been conducted), observational estimates of breast cancer mortality reduction for women screened from age 50–69 range from 21 to 49%.[15,33–36] For overdiagnosis, figures for women aged 50–74 range from 15 to 42%.[37–39] These local estimates, however, are subject to potential biases inherent in observational studies of screening.

In Figures 1 and 2 we attempt to summarise visually the main outcomes of screening over 20 and 25 years. We use absolute event rates to convey this information according to best risk communication practice.[40] We note, however, that overdiagnosis accrues early during screening mammography programmes whereas the mortality benefit accrues in the future. Incidence increases with the first screen as a reservoir of undiagnosed breast cancer is detected (converted to diagnosed cancer). Mortality reduction occurs in the future, at the time when a woman would have been expected to die from breast cancer had she not been screened. Therefore overdiagnosis and the resulting overtreatment are experienced immediately, while breast cancer deaths are avoided sometime in the future. This temporal relationship cannot be appreciated with single number summaries of the benefit and harm, which is a limitation of all existing approaches to quantifying trade-offs.

False positive results are quantifiable with considerable certainty given they are sourced from directly observed Australian BreastScreen data. The chance of being recalled after screening is small for each round, but this risk accumulates over time. Although the chance of a false positive decreases with increasing age,[41] compared with 1,000 women who screen from age 50 to 69 we estimate an additional 78 women will receive a false positive result if they continue screening until age 74. Our results agree with international findings that false positive mammograms are common.[42,43] They can lead to economic costs,[44] unnecessary biopsies, physical pain and scarring. Further, they can negatively impact quality of life[45] and the psychosocial effects may persist for some women.[46]

As screening mammography is well established in Australia, the incidence of breast cancer in the absence of screening cannot be observed without selection bias. Thus we used modelled estimates of unscreened incidence that account for temporal trends. We also assessed our model by comparing the 20-year incidence of breast cancer weighted for participation in screening generated by the model with the 20-year incidence of breast cancer from published national estimates and found they were similar.

Comparison with other studies

In Australia, we estimate 5.8 overdiagnosed cases for every breast cancer death averted for women screened biennially from ages 50 to 69. Our ratio is similar to estimates for Canada, Norway and Switzerland.[47] The UK can expect 3 overdiagnosed cases for every breast cancer death averted for women screened triennially from ages 50 to 70.[11] Both ratios are derived from studies that use pooled estimates from the screening mammography trials and apply these to local screening programmes. However, we adjust these estimates of mortality benefit and overdiagnosis for attendance.[21] There are also differences between the screening programmes. Australia offers more frequent screens and has a lower participation rate of 54.5%[48] compared with 75.4% in the UK.[49] Australia has a higher recall rate but a lower biopsy rate.[49] Digital mammography roll-out occurred later in the UK compared with Australia. Although breast cancer incidence is similar, the breast cancer mortality rate for women aged 50–69 in the UK is comparatively higher,[50] which means the absolute reduction in deaths due to early detection will be higher. We assume that the mortality reduction declines linearly over 5 years after screening stops, in line with trial estimates of when the study-control annual breast cancer mortality rate becomes similar.[26,51] The UK Panel assumed this benefit declines over 10 years which would inflate the estimate of benefit.

Mandelblatt (2009)[52] found an increase in the risk of overdiagnosis with increasing age that accelerated in women older than 69 years. A systematic review of modelling studies concluded that for every 1,000 women who continue biennial screening from age 70–79 there would be 13 overdiagnosed women and 2 breast cancer deaths averted, a marginal harm to benefit ratio of 6.5: 1.[4] An incremental analysis of stopping screening at different ages showed that screening to age 74 *vs.* 72 led to more false positives but similar overdiagnosis to breast cancer deaths averted; screening past age 75 increased harms and decreased benefits.[53] Gunsoy (2014)[54] estimated that the incremental effects of the UK age extension of triennial screening from 50–70 to 47–73 from a population perspective is likely to lead to more incremental cases overdiagnosed than breast cancer deaths averted. Although the frequency of mortality benefit and overdiagnosis remains uncertain, the overall trend appears consistent: international findings generally show that extending screening mammography to older women worsens rather than improves the benefit to harm ratio.

Future research

We focused our analysis on the main outcomes of screening mammography: diagnostic procedures, breast cancer cases (including overdiagnosis) and mortality benefit. We do not include possible benefits such as less invasive therapy due to

detecting cancer at an earlier stage and avoiding metastatic disease because international studies generally show that screening mammography increases the incidence of early-stage breast cancer without significantly decreasing late-stage breast cancer.[55–59] Likewise, we do not estimate the harms of overtreatment due to surgery or adjuvant therapy. Given cancers that will not harm cannot be distinguished from those that will, and over 99% of women with screen-detected breast cancer are treated,[11] these potential harms could be substantial. Quantifying these harms should be the subject of future research. Randomised trials of reduced intervention for low-risk DCIS such as active monitoring and non-surgical treatment (The COMET Trial) are currently in progress and may provide effective means of improving quality of life by minimising overtreatment due to screening.[60,61] Further, research should study the benefits and harms in older women with equal emphasis, preferably using randomised controlled trials, as is currently being done in the UK.[10] Such data will greatly aid the provision of complete, clear and neutral information to older women about when to cease screening.

Conclusions

This information can be used to help women make an informed decision about whether or not to start screening and—if they choose to screen—about when to stop. Some women will be happy to choose to continue screening until age 74, even though they may experience more anxiety, inconvenience, and physical adverse effects; other women will not. Clinicians can also use our study to support balanced discussions with women about the trade-offs of benefits and harms, or it could be included in decision tools provided to women in the target age groups. As extending screening mammography in Australia to older women results in a less favourable harm to benefit ratio than stopping at age 69, supporting informed decision making for this age group should be a public health priority.

<div style="text-align: right">**Cancer Epidemiology**</div>

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