Impact of population screening programs on cancer outcomes

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Abstract
Age-standardised breast cancer mortality fell by around 26% in Australian females in the 15 years following introduction of the BreastScreen Australia program. The relative contributions of breast screening and treatment advances to this reduction are open to debate. Three evaluations of breast screening in Australia point to reductions in breast cancer mortality in screening participants consistent with the collective trial results, estimated to be around 35% by an expert panel of the International Agency for Research on Cancer. The collective results of evaluations in other countries are similar but individual results vary widely, from little or no benefit to reductions of up to 76%. Over-diagnosis is a controversial issue, with some results indicating it to be of negligible magnitude and others indicating that it could represent 30% or more of breast cancers in populations exposed to breast screening. Meanwhile, age-standardised cervical cancer mortality reduced by over 50% in the 15 years following introduction of an organised approach to screening. This followed earlier reductions also likely to reflect cervical screening. The roll-out of bowel screening in 2006 is too recent for reporting on effects on colorectal cancer mortality, although it is expected that effects from the one-off screening offered at 50, 55 and 65 years of age would be less than in trials where annual or biennial screening was undertaken.

BreastScreen effects
Australia has an elevated age-standardised female breast cancer mortality rate at about 18% higher than the estimated world average. In the 15 years following the BreastScreen rollout in 1991, the age-standardised breast cancer mortality rate decreased by about 26% (figure 1). When compared with a linear projection of mortality increases in the 1980s, the observed rate was 38% lower after 15 years. The relative contribution of treatment and early detection gains to these differences and similar

Figure 1: Mean annual mortality rates (95%CLs) from breast cancer per 100,000 Australian females*.

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality Rate (95%CLs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968-70</td>
<td>29.8 [28.9, 30.7]</td>
</tr>
<tr>
<td>1971-73</td>
<td>29.9 [29.0, 30.7]</td>
</tr>
<tr>
<td>1974-76</td>
<td>29.8 [29.0, 30.6]</td>
</tr>
<tr>
<td>1977-79</td>
<td>28.9 [28.1, 29.7]</td>
</tr>
<tr>
<td>1980-82</td>
<td>29.6 [28.8, 30.4]</td>
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<tr>
<td>1983-85</td>
<td>31.0 [30.2, 31.8]</td>
</tr>
<tr>
<td>1986-88</td>
<td>30.7 [30.0, 31.4]</td>
</tr>
<tr>
<td>1989-91</td>
<td>31.2 [30.5, 31.9]</td>
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<tr>
<td>1992-94</td>
<td>30.3 [29.6, 31.0]</td>
</tr>
<tr>
<td>1995-97</td>
<td>28.7 [28.1, 29.3]</td>
</tr>
<tr>
<td>1998-2000</td>
<td>25.5 [24.9, 26.1]</td>
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<tr>
<td>2001-2003</td>
<td>24.8 [24.3, 25.3]</td>
</tr>
<tr>
<td>2005-2017</td>
<td>23.1 [22.6, 23.6]</td>
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</tbody>
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*Age-standardised to Australian population 2001.
changes in some other countries is open to debate. Modelling funded by the National Cancer Institute produced widely different estimates of contributions to US breast cancer mortality reductions, which varied with the model design and assumptions. An important screening contribution would be expected from results of 10 field trials. Although trial results varied, an International Agency for Research on Cancer (IARC) expert panel indicated that the collective data were consistent with a 35% breast cancer mortality reduction in 50-69 year-old screening participants. A recent meta-analysis of these trial data by Australian researchers also showed a mortality reduction in screening participants, estimating this to be 25% when including participants of all ages.

An international review of evaluations of 12 screening services published in 2005 indicated a collective reduction in breast cancer mortality of 32% in screening participants, without evidence of heterogeneity of results across studies. Meanwhile, eight case-control studies indicated a collective reduction of 37%, and a review by other researchers of 13 service evaluations published in 2000-08 indicated a collective reduction of 36%. Since then, service evaluations reported in 2010-11 have indicated reductions ranging from zero to 76%, whereas a recently published follow-up of women 29 years after completion of the Swedish two county trial indicated a sustained breast cancer mortality reduction of 29% in women invited to attend breast screening whose cancers were detected during the trial period.

Three service evaluations have been undertaken in Australia, which included a NSW, SA and national evaluation. The reductions in breast cancer mortality found in these studies for 50-69 year-old screening participants ranged from 34% to 47%. The potential for inflation of reduction estimates from self-selection of low-risk women for screening is unclear. A number of trials and service evaluations in other countries have adjusted for self-selection. If this adjustment for self-selection is applied to the Australian data, the reductions in breast cancer mortality in screening participants would range from about 25% to 35%. However, interview survey data in Australia have indicated an elevation in risk factors in screening participants, not a reduction as assumed in this adjustment. In particular, higher proportions of women with positive histories of breast cancer among first degree relatives and higher proportions with personal histories of hormone replacement therapy have been reported among screening participants. The appropriate adjustment to make for self-selection in the Australian setting is therefore not clear.

Whatever the reduction in breast cancer mortality from screening participation in Australia, there is considerable collective evidence from the trials, service evaluations in other countries, and the Australian evaluation studies that a reduction would be occurring. The collective estimate of the reduction observed in 50-69 year old screening participants from the Australian data was about 43%, reducing to 32% when adjusting for the scale of self-selection assumed in the trials and service evaluations in other countries. This range (32% to 43%) encompasses the 35% estimated by the IARC expert panel from the trial data.

The potential for mammography screening to reduce breast cancer mortality at a population level depends on screening participation levels. Present participation levels of 50-69 year-olds in Australia of around 55% would equate with an approximate 18% to 24% reduction in mortality at a population level in the screening target age range, whereas the 70% national screening target would equate with a population-based reduction of about 22% to 30%, depending on assumptions made about screening selection bias.

The screening participation rate has been fairly stable in Australia since the late 1990s, despite increasing numbers of women being screened, due to offsetting population increases. Re-screening participation has reduced, however, and screening promotion activity has decreased, largely due to capacity constraints. Opportunities exist to increase screening throughput by digitised imaging, either by using computed radiography or digital mammography, both of which avoid the need for film processing and offer enhancements to imaging for screen reading. In addition, opportunities need to be explored to increase screening throughput through analyses of work practices. Women in special need showing lower than average screening participation rates include Aboriginal and Torres Strait Islander women, groups from non-English speaking backgrounds, women living in very remote areas and sub-groups of women from major metropolitan settings.

Breast cancer incidence rates have been higher in Australia since the introduction of BreastScreen. The extent to which this reflects lead time effects of screening, over-diagnosis, changes in pathology and other diagnostic practices, and real increases in incidence due to changes in underlying risk factors (eg. body weight, reproductive behaviour, use of hormone replacement therapy and alcohol consumption) is not clear. It is evident though that increases in incidence were already underway in the 1980s prior to BreastScreen introduction, but the relative contributions of increased use of private mammography and changes in risk factors during that period are not clear. The increase in breast cancer mortality rates in the 1980s suggests that real increases in underlying incidence would have contributed.

There is concern that screening mammography may cause unacceptable levels of over-diagnosis, defined as detection of cancers that would not have otherwise been diagnosed in a woman’s lifetime. In such instances, diagnoses would have been unnecessary and associated treatment an event with adverse effects without benefit.
There is not a consensus however on levels of over-diagnosis, with estimates from studies around the world varying from levels close to zero to 30% or more of diagnosed cancers, irrespective of whether in situ lesions were counted. These estimates vary so widely that interpretation is difficult.

At a population level, approximately 3% of breast lesions prior to the advent of mammography screening were in situ lesions. Since then, the proportion has increased to about 10%. If the difference was due entirely to mammography screening, as opposed to increased diagnostic sensitivity not associated with screening, then an approximate 7% increase would be attributable to screening. If half of these lesions were destined not to progress clinically to invasive cancers, then about 3-4% would constitute over-diagnosis. Using this same line of reasoning for screening participants where about 14% of screen-detected and interval cancers are in situ lesions, then 11% would be attributed to screening and 5-6% would constitute over-diagnosis. For screen-detected lesions, where about 20% are in situ lesions, then about 17% would be attributed to screening and 8-9% would constitute over-diagnosis.

In conclusion, it is evident that mammography screening reduces breast cancer mortality in screening participants. While the extent of reduction is difficult to determine accurately, the collective evidence points to a reduction of similar scale to the 35% reduction estimated from the trial data. It is also likely that mammography screening is leading to some degree of over-diagnosis, but the scale is difficult to determine, given the wide variation in study results. Research is needed to better define levels of over-diagnosis and ideally to develop better means of determining at diagnosis the potential for screen-detected and other breast cancers to progress.

**Cervical screening effects**

Australia has a low age-standardised cervical cancer mortality rate, approximately 80% lower than the estimated world average, with this difference largely attributed to the protective effects of screening.

In 1991 the Organised Approach to Preventing Cancer of the Cervix was established in Australia to: promote routine screening with Pap smears every two years of women from age 18 years (or from two years after first sexual intercourse, whichever is later) to 69 years; establish more reliable and accessible services for taking, interpreting and reporting Pap tests; improve management of screen-detected abnormalities; and monitor and evaluate these initiatives. Cervical cytology registers were established in each state and territory to support these processes.

Since introducing the organised approach, the cervical cancer mortality rate has decreased by over 50% (figure 2), with corresponding incidence decreases of a slightly smaller magnitude. Decreases already were occurring prior to introducing the organised approach (eg. a decrease in mortality of about 25% between the early 1980s and early 1990s was evident), which are most likely attributable to earlier screening activity.

The reduction in cervical cancer rates occurred for most histological types. Between 1991-93 and 2006, the reduction in age-standardised incidence was about 55% for squamous cell cancers, 37% for glandular lesions and 67% for micro-invasive disease.

International research has indicated the effectiveness of cervical screening in reducing incidence rates for invasive cervical cancers, with protective effects reported of at least 80%, and larger effects evident in women over 40 years of age than in younger women. Australian data indicate

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**Figure 2: Mean annual mortality rates (95% CLs) from cervix cancer per 100,000 Australian females**.*

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean Annual Mortality Rate (95% CLs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-84</td>
<td>5.1 [4.9, 5.4]</td>
</tr>
<tr>
<td>1985-89</td>
<td>4.7 [4.5, 4.9]</td>
</tr>
<tr>
<td>1990-94</td>
<td>3.9 [3.7, 4.1]</td>
</tr>
<tr>
<td>1995-99</td>
<td>3.0 [2.9, 3.2]</td>
</tr>
<tr>
<td>2000-04</td>
<td>2.3 [2.1, 2.4]</td>
</tr>
<tr>
<td>2005-07</td>
<td>1.9 [1.8, 2.0]</td>
</tr>
</tbody>
</table>

*Age-standardised to Australian population 2001.
a similar effect. A NSW study indicated, for example, that a single screen in a four-year period was associated with a reduction in cervical cancer incidence of around 81%, whereas two or more screens in a four-year period were associated with a higher reduction.36 On this basis, it is estimated that the approximate 60% participation of 20-69 year-old Australian women in screening during a two year period (excluding women who have had a hysterectomy) would reduce the risk of invasive cervical cancer at a population level by about 50% or more.33,36

The Australian Government is planning a renewal of cervical screening policy, based on a review of evidence of age and screening interval on effectiveness, and determination of the role of screening alongside vaccination against Human Papilloma Virus (HPV).37 Policies for management of screen-detected low-grade and high-grade abnormalities have already been reviewed, with changes to management that include for example triaging women for screening based on a HPV DNA test for cure after treatment of high-grade abnormalities.38 A Safety Monitoring Committee is monitoring cervical cancer incidence in relation to these policy changes.

**Bowel screening effects**

Bowel cancer is second to lung cancer as the leading cause of cancer death in Australia.2 The age-standardised mortality rate for this cancer is 54% higher than the estimated world average.1 Four randomised field trials indicate that participation in biennial screening can lower the mortality rates from this cancer by around 25%, although larger reductions would have been expected in the approximate two thirds of participants who completed all screening rounds.39-44 Larger reductions would be expected from annual as opposed to biennial screening.40

A pilot screening program employing faecal occult blood testing (FOBT) with follow-up endoscopy (colonoscopy and/or flexible sigmoidoscopy) was implemented in three Australian states from 2002 to 2004.45 This was followed by the introduction of national screening from 2006. People were mailed FOBT screening kits when turning 55 and 65 years of age. In 2008, the program was extended by providing kits to people turning 50 years of age.45 In 2008, 40% of people mailed FOBT kits participated in the screening, with this figure varying from 34% for 50 year-olds to 40% for 55 year-olds and 49% for 65 year-olds.46 It is anticipated that the staggered introduction of bowel screening would provide time for colonoscopy and other health services to adjust to increases in demand.

Since field trials have tested annual or biennial screening, the likely effectiveness of the existing national screening program is difficult to estimate, although a benefit would be expected. Of a small number of 60 cancers detected through the national program for which degree of spread at diagnosis was known, 58% were found to be at the earliest localised stage.46 This compares with about 32% of staged cancers found to be localised in NSW in 2004-08 (note: only NSW collects population-based degree of spread data for bowel cancer in Australia).47

Although age-standardised incidence rates have been relatively stable in Australia since the early 1990s, reductions in mortality from this cancer of around 35% have been observed, with slightly larger percentage reductions apparent in females than males.2 Meanwhile, there was little change in incidence rates since the early 1990s.2 The reductions in mortality are thought to reflect treatment gains and potentially contributions from earlier detection.

**Other screening tests**

Australia’s prostate cancer mortality rate is about twice the world average, after age adjustment.1 Prostate-specific antigen (PSA) testing is widespread in Australia, but population-based screening is not advocated due to uncertainties whether benefits would outweigh adverse effects.48 A randomised population-based trial in Europe indicated that inviting men to four-yearly PSA testing was associated with a 20% reduction in prostate cancer mortality,49 although the data also pointed to high levels of over-diagnosis, indicating that 49 additional prostate cancers would need to be treated to prevent one death from this cancer. Further research using a comparison group chosen for infrequent exposure to PSA testing pointed to a larger reduction of 37%.50 Meanwhile, a North American study found no reduction in prostate mortality from PSA testing, although it was evident that informal testing was commonplace among controls, reducing opportunities to find an effect.51 Prostate screening has been linked to high levels of over-diagnosis and consequently of treatment side-effects, including incontinence and impotence, which need to be weighed against the benefits.48 Men are being advised to discuss the merits of prostate cancer testing with their doctors, in order to make an informed choice, and protocols for testing have been suggested.52

Skin checks for cancer are also commonplace in Australia, but not advocated for population-based screening.52 Australia has a very high skin cancer rate, with melanoma incidence about 13 times the world average and the mortality rate more than five times the world average.1 The more common non-melanoma forms of skin cancer are rarely life-threatening and there is insufficient evidence that screening would reduce morbidity or mortality. Instead, medical surveillance is recommended for patients at high risk of skin cancer and familiarity with one’s own skin and early reporting of unusual changes is recommended.

**Conclusion**

There is clear evidence from research studies around the world and service evaluations in Australia that mammography and cervical screening would be contributing to observed decreases in cancer mortality. Further research is needed into means of optimising cost-effectiveness in service delivery, as relating to target age ranges, screening technology, screening frequency and potential for over-diagnosis. Research studies indicate that bowel screening would be reducing mortality from colorectal cancer, but
it is too early for confirmatory data of mortality effects to be available from local service evaluation in Australia. Meanwhile, more research is needed to determine the role of prostate screening in population health practice and how to limit negative effects. Education about screening benefits and adverse effects is important, irrespective of screening type, such that decisions about screening participation can be well informed.

References


