Cancer screening

Benefits, harms and making an informed choice

BACKGROUND
Screening is a two edged sword, with potential benefits and harms. Despite professional and public enthusiasm for cancer screening there are substantial harms, and increasing evidence that it is not always a good idea to detect cancer early. On the other side, the benefits of cancer screening are quite rare and have been oversold.

OBJECTIVE
This article discusses the potential harms of cancer screening and evidence for the benefits.

DISCUSSION
Well recognised harms include the psychological and physical harms of false positive and false negative tests. More recent research is uncovering what may turn out to be the biggest downside of cancer screening; the potential to uncover clinically irrelevant disease (pseudo-disease) and therefore harm from unnecessary treatment.

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To assess the value of screening, the downsides need to be weighed against the benefits. While there are randomised trials of breast and bowel cancer screening there are not randomised trials to show benefit from screening for lung, prostate, or ovarian cancer. There is a risk that enthusiasm for screening for cervical, breast and bowel cancer will lead to uncritical enthusiasm for all screening, without appreciation of the lack of evidence of benefit and the substantial downsides.

Screening can be described as a close call, or a preference sensitive decision. We should be providing evidence based, balanced information to people who want it to help them make informed choices about cancer screening. Decision support may be effectively provided by patient decision aids about cancer screening.

Since Geoffrey Rose's influential paper 'Sick individuals and sick populations'[1] we have seen increasing emphasis on population strategies to prevent disease. One component, perhaps the flagship, of preventive medicine is screening: detecting and treating disease before it causes symptoms.[2]

Screening is so intuitively appealing that it has enormous professional and public support. For example, a recent survey in the USA found strong public enthusiasm for cancer screening with 87% of adults reporting that routine cancer screening is almost always a good idea, 74% said finding cancer early saves lives most or all of the time, and many people believed that an 80 year old who chose not to be tested was irresponsible.[3]

We are surrounded by messages that reinforce the idea that finding disease early (whether cancer, asthma, diabetes, heart disease or kidney disease) is a good thing and responsible health behaviour. Increasingly celebrities are being used to effectively support and endorse screening.[4] Unfortunately the celebrities' opinions may be based more on hope and belief than on scientific evidence.[5]

However, there are downsides of finding disease early, downsides that may make it wise to choose not to be tested. The remainder of this article will focus on cancer screening, but the principles apply broadly across early disease detection.

The problem with finding cancer early

The most important and least understood downside of cancer screening is the potential for overdetection and overtreatment because of the risk that screening will detect clinically irrelevant disease (or pseudo-disease). As we become more experienced with cancer screening it is becoming clear that cancer is a spectrum of disease.

We've all known people who have died of aggressive, rapidly progressing cancer. But not all cancer is like that, and there is a large reservoir of 'innocuous' cancer out there.

For example, up to 40% of middle aged women have evidence of ductal carcinoma of the breast.[6] This astounding fact comes from carefully conducted autopsy studies of women who have died of other causes. Pathologists sectioned their breasts and examined the slides for ductal cancer in situ (DCIS). In a systematic review of these studies it is clear there is a direct relationship between the number of sections and the probability of finding DCIS. About 15–20% of the cancers found by screening are DCIS (*Table 1*).[7]

Other examples are more familiar – many adults have low grade thyroid cancer and many older men have low grade prostate cancer although few are bothered by these conditions. The general principle applies – to a greater or lesser extent – to all forms of cancer screening: the harder you look the more cancer you find.

Therefore cancer screening will always carry a risk of detecting cancer that might not have bothered a person in their lifetime had they not been screened. The phenomenon of length time bias is well established.[8,9] Length time bias is the tendency of screening to detect slower progressing rather than faster progressing disease. It is an inevitable characteristic of screening because the slower growing cancers are more likely to still be present in an asymptomatic state at the time of the next screen. Faster more aggressive cancers are more likely to cause symptoms between screening rounds and therefore be detected clinically rather than by screening (*Figure 1*). Particularly slow progressing disease might be missed by one screening round and detected in the next. Another problem with data on screening is lead time bias. This is the idea that screening means the disease is diagnosed earlier, so survival time is extended not by moving the date of death later but by increasing the amount of 'disease' time in a person's lifetime. For this reason, 5 year survival rates always look better once screening is introduced, even if there is no real survival benefit from earlier detection. So screening can appear to be effective even if it is absolutely useless.[8,9]

Unfortunately with current technology we cannot accurately distinguish the screen detected cancers that are destined to be clinically relevant from those that are not. As a result we have to offer treatment to everyone, and therefore screening must inevitably lead to overdetection and overtreatment. This is very problematic because, in addition to the psychological burden of a cancer diagnosis, cancer treatments including surgery, radiotherapy and chemotherapy, carry risks of side effects and occasionally mortality. This downside is not generally included in descriptions of screening to the public.

A critical question is: just how much

Table 1. Outcomes for women who undergo mammographic screening compared with those who do not (Figures are cumulative number out of 1000 women over 10 years)

Event over 10 years	Age 40 years		Age 50 years		Age 60 years	
	Begin screening at age 40, five biennial screens	No screening	Begin screening at age 50, five biennial screens	No screening	Have five more biennial screens	No screening
Are recalled for more tests	250.9		242.0		184.6	
Recall for:						
Extra imaging only (clinical examination plus mammography and/or ultrasound)	191.4		177.9		128.6	
Biopsy (total having at least one biopsy)	59.5		64.1		56.0	
Fine needle aspiration biopsy	31.7		30.5		25.4	
Core biopsy	21.7		27.2		25.3	
Open biopsy	6.1		6.4		5.3	
Invasive breast cancer detected at screening	8.5		17.6		23.3	
Develop interval cancer	9.1		10.4		9.2	
Diagnosis of invasive breast cancer	17.6	13.2	28.1	19.8	32.5	23.9
DCIS*	3.4	0.3	4.9	0.4	5.5	0.5
Breast cancer diagnosis of any type	21.0	13.5	32.9	20.2	38.0	24.4
Die from breast cancer	2.0	2.5	4.0	5.9	5.1	8.1
Die from causes other than breast cancer	10.8	10.8	25.3	25.2	68.5	68.4
Total who die	12.8	13.3	29.3	31.1	73.6	76.5

*Ductal carcinoma in situ, detected by screening in screening group, and presenting clinically with symptoms in unscreened group

overdetection and overtreatment is there in screening? This is likely to vary for different cancers. It has been estimated that annual prostate specific antigen (PSA) testing in men aged 55–70 years leads to about 50% overdetection; in other words half of the cancers detected are clinically irrelevant.[10] In breast cancer screening there is clearly overdetection and overtreatment of DCIS. DCIS is very largely a screening diagnosis; rates of DCIS incidence have increased 5–6 fold since screening began.[11] DCIS is generally treated in the same way as breast cancer using surgery, radiotherapy and endocrine therapy and has a very low 10 year mortality regardless of treatment mode.[12]

While it has been argued that DCIS is a precursor of invasive cancer, treatment of screen detected DCIS has not led to a reduction in the incidence of invasive cancer as might be expected. Indeed, the effect of breast screening programs seems to be a sustained increase in the incidence of invasive breast cancer, leading to suggestions that there is overdetection and overtreatment of invasive breast cancer as well. Current estimates of the extent of overdetection of invasive breast cancer range from 2–30%.[13,14]

	Age 70 years	
	Have five more biennial screens	Finish screening at age 69
	166.6	
	110.2	
	56.4	
	25.4	
	25.8	
	5.2	
	26.4	
	8.8	
	35.1	25.1
	5.7	0.5
	40.8	25.6
	6.2	8.4
	199.5	199.3
	205.7	207.8

Other downsides of cancer screening

There are also the more familiar downsides of cancer screening: false positive and false negative tests.

False positive screening test results cause anxiety and lead to increasingly invasive tests to determine whether disease is really present. This is inevitable as screening tests are only designed to categorise people into low or high risk of disease. Unfortunately they cumulate over time. For example, an Australian woman in her 50s participating in 10 years of biennial screening has a 24% chance of being recalled for more tests and a 6% chance of having a biopsy (*Table 1*). Some screening tests require more invasive follow up tests. For example, people with a positive faecal occult blood test will be offered colonoscopy. We have little experience of colonoscopy safety rates in this context in Australia as yet, but international data suggests that 5 per 1000 people undergoing colonoscopy may suffer bleeding or perforation[17] and 5 per 100 000 may die.[18]

False negative screening test results are the most familiar downside of cancer screening and have been the subject of legal action in the past. Again they are an inevitable part of screening but at least people seem to be becoming more aware that screening will not detect all cases of disease and that such events do not mean the screening program has failed them in some way.

The benefit from finding cancer early

While cancer screening will always do harm, it can lead to benefits as well. For the reasons outlined above (length and lead time bias) the only way we can be sure of the benefits of cancer screening is to undertake randomised trials. We have randomised trials that show mortality benefits for bowel and breast cancer screening. (There is also very strong observational evidence that cervical cancer screening also delivers a mortality benefit.)

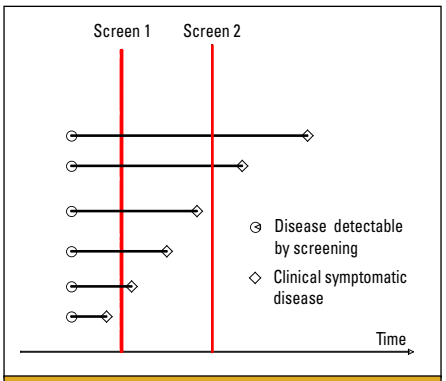

Figure 1. A potential source of bias in observational studies of screening is called length time bias. The concept comes from the fact that even within 'one' type of disease, for example prostate cancer, disease does not progress at the same pace in all people. Whether this is a function of heterogeneity of the disease or a complex interaction between individual disease and environment, we don't currently know. But some diseases progress slowly, and tend to have a better prognosis – some progress rapidly through the preclinical phase, and also through the clinical phase, with generally poorer prognosis

Randomised trials of breast cancer screening show that screening mammography reduces the risk of death from breast cancer by about 40% in women aged over 50 years who attend screening regularly.[15,16] For example, among 1000 Australian women aged 60 years who decline screening, about eight will die of breast cancer over the next 10 years (*Table 1*). Among 1000 women aged 60 years who are regularly screened, about five will die over the next 10 years. You can choose to describe the benefit in relative or absolute terms. In relative terms the death rate from breast cancer is reduced by 37% (3/8). In absolute terms it is reduced by 0.3% (from 8/1000 to 5/1000).

This does not mean that screening mammography does not work or that it is a poor screening intervention. It merely reflects the fact that in screening generally, the outcome you are seeking and seeking to change is relatively rare in the population.

Weighing it all up

Screening is complex and involves trading off benefits and harms. People who are at high risk of the outcome (in this case death from cancer) for example because of a strong family cancer history, are more likely to benefit and the trade off of benefit versus harm will be more favourable for them.

This approach has been adopted by the US Preventive Services Taskforce which rates cancer screening on a 5 point scale ranging from A–D, and I.[18] A ratings are given for cancer screening for which there is good evidence that benefits outweigh harms; bowel cancer screening with FOBT and cervical cancer screening both have A ratings. Breast cancer screening has a B rating indicating fair evidence that benefits outweigh harms. Testicular and ovarian cancer both have D ratings indicating current evidence is that harms are likely to outweigh benefits. Prostate cancer screening has an I rating indicating insufficient evidence pending the results of randomised trials currently in progress.

Helping patients make decisions

It can be argued that screening is a preference sensitive decision. As is indicated in *Table 1*, even if there is a benefit, whether people perceive that benefit outweighs the inconvenience, anxiety and physical risks is a value judgment. People can and do come to different conclusions, all of which can be valid and rational. Therefore at a minimum we should give patients balanced and accurate information about both sides of the story. At the Screening and Test Evaluation Program (STEP) we have developed decision aids[19] about cancer screening; several are being trialled including mammography screening for women aged 40 years (www.mammmogram.med.usyd.edu.au).

Conclusion

While screening may deliver benefits it always does harm. We have probably overstated the benefits and understated the harms. There are sound reasons for exercising caution before rushing ahead with more screening programs or extending current ones. Detection and treatment of clinically irrelevant disease is likely to be the most important downside of cancer screening. Medical practitioners and the public need to be adequately informed about both the benefits and the harms of cancer screening.

Conflict of interest: none declared.

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Poetry

The Idiot

Bewitched, Prince Leo Nikolayevich
Myshkin, last and poorest of a line
of noblemen stares across the room
at her tattooed shoulder, gripped by
the itch to approach her. Nastasya
Filippovna gulps her wine and glances
back at him across the room.
Gripped by a fit by the throat in its
garrotte, he falls to the floor and
froths, the idiot!

By the time that he comes to, she's
gone and he is lying in his own shit.
After the seizure, his state of mind
is one of insight and shame. (He'll
get over it.)
He knows he wants to tell her she has
better tatts than Tank girl, so he writes
her a letter.

Andrew Leggett

Dostoyevsky's epileptic has moved to the 21st century, but is caught nevertheless in his moment of most acute shame. The turning point of his relationship with Nastasya, the fit, is located at the traditional place in this subtle Shakespearean sonnet – whose rhyme is barely noticed until the tragi-comic final couplet.

Tim Metcalf