

Is it worth screening women over 70 for breast cancer — or indeed any women?

Screening by high-quality programs successfully detects cancers at an earlier stage

IN 2002, the 10th anniversary of Australia's national program of mammographic screening for breast cancer, it is perhaps timely to reflect and review. The need for reassessment is highlighted by the recent furore in the breast-screening world¹⁻⁴ precipitated by a Cochrane review by Olsen and Gøtzsche.¹ In this issue of the Journal, the article by Barratt et al⁵ (page 45) also encourages us to review breast-screening policies — in this case for women 70 years and over who are no longer in the target group for free mammographic screening (50–69 years).

Barratt et al⁵ estimated the benefit of screening women 70–79 years to be about one-third to three-quarters that achieved in women aged 50–69 years. As women age, the benefit of screening — reduced risk of death from breast cancer — is increasingly offset by the other causes of death. Furthermore, while the benefit is delayed, the hazards of screening — tests for false-positive films, discomfort and anxiety — are immediate. Thus, with increasing age, the data show a further decline in benefit, which is exaggerated when adjustment is made for quality-of-life factors.⁵

Barrett et al also provide a rough estimate of the cost-effectiveness of screening older women. The wide range of cost estimates (per quality-adjusted life-year saved) underlines their imprecise nature, but suggests that mammographic screening of women aged 70–79 years is as cost-effective as screening the other outlier group — women 40–49 years. However, Barratt et al remind us that the estimation of benefits, harms and costs would be improved with data from randomised trials in the appropriate age group — which unfortunately are still lacking.

In 1999, 63.7% of women in the target age group for mammographic screening in Victoria (50–69 years) were screened.⁶ In view of Barratt and colleagues' estimates of benefits and costs per quality-adjusted life-year saved, it could be argued that money for screening older — or younger — women could be better spent on recruiting more women in the target group to achieve the desired 70% participation.

Trials of mammographic screening commenced in the 1960s and seven have been completed and reported. On the basis of these trials, which showed a reduction in mortality from breast cancer in screened women, mammographic screening recommendations have been drawn up (eg, in the United States), and in several countries political decisions were made to institute national programs (eg, in the United Kingdom, Australia and New Zealand).

In 2000, Gøtzsche and Olsen, publishing a "Cochrane review" of the seven trials in the *Lancet*,⁷ reported that they found no reliable evidence that screening for breast cancer reduced mortality. However, this report did not fulfil the Cochrane Group protocol for such a review. Since then Gøtzsche and Olsen have worked with the Cochrane Breast Cancer Editorial Group, and in October 2001 part of their review was accepted and included in the Cochrane Library.¹ Almost simultaneously, the *Lancet* published Gøtzsche and

Impact of breast screening on stage at which cancer is detected¹¹

Tumour size/node involvement	Screen detected	All cancers
< 15 mm	60.3%	42.7%
Node positive	22.5%	30.0%
1–3 nodes positive	18.7%	23.4%
> 3 nodes positive	8.4%	14.2%

Olsen's review in full on its website, and a research letter in its printed journal² with an editorial commentary³ criticising the Cochrane Breast Cancer Editorial Group for interference. The whole episode has drawn a flurry of criticism and counter-criticism.⁴

After all this, what should women believe, especially as the systematic review of Barratt et al⁵ suggests that screening for women over 70 years may be of some benefit (and as cost-effective as it is for those under 50 years), on the basis that screening is beneficial in women aged 50–69 years?

Although clinical-trial methodology has improved in four decades, population-health intervention studies remain notoriously difficult to perform because of problems associated with large cohort numbers, the randomisation process and guaranteeing reliable stratification. It is not surprising that the seven, now old, trials can be criticised. However, not all would suggest ditching them and their conclusions on these grounds. The Cochrane Breast Cancer Editorial Group has not accepted the other conclusion of Olsen and Gøtzsche — that screening leads to more aggressive treatments⁸ — and has not included that section of their review in the Cochrane Library.

Others⁴ reject Olsen and Gøtzsche's conclusions because they are based on all-cause mortality, which may be inappropriate in population studies.

Do we have other surrogate measures to guide us? Cancer registry data from Victoria⁹ suggest a "slight downward trend since 1994" in breast cancer mortality, but it cannot be assumed that any of this trend is due to screening. However, from 1982 to 1996, there was no change in breast cancer mortality in Australia.¹⁰ The impact of breast screening may be seen more readily in the stages at which breast cancer is detected. In 1997, when the national program was six years old and well established, 30% of new breast cancers were detected through screening. Data suggest that screen-detected invasive cancers were smaller, less likely to involve nodes, and, if node positive, more likely to involve fewer nodes (Box).¹¹

Tumour size, nodal involvement and number of nodes involved — the basis of the tumour–node–metastases (TNM) staging system — are all known to be of prognostic significance. Hence, it is likely that the cohort of women with screen-

detected invasive cancer will have a better prognosis and live longer, provided lead-time bias does not negate the prognostic effect of lower staging by detecting cancer earlier while not influencing the natural history of the disease.

The prognostic significance of non-invasive cancer (ductal carcinoma in situ), its treatment and the appropriateness of various local and systemic treatments for any breast cancer can be debated and argued. However, the histopathological prognostic (TNM) data would suggest that mammographic screening by high-quality programs successfully detects cancers at an earlier stage, giving a better prognosis and probably improved survival. Women should be made aware of these facts, along with any doubts raised by reviewers of somewhat out-of-date trials.

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Competing interests: Alan Rodger has been a member of the Cochrane Breast Cancer Editorial Group since June 2001. He is Chair of BreastScreen Victoria.

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Hard lessons from a randomised controlled trial

A study design that was simple, relevant and that avoided particular sensitivities in the study population might have helped, as might considerably more guidance from the national funding body

THE COMBINATION OF HAZARDOUS consumption of alcohol, Aboriginal people, primary care and a randomised controlled trial (RCT) of interventions sets a daunting challenge as a research project. In this issue of the Journal, Sibthorpe et al (*page 273*) describe, with disarming candour, how they took on this challenge and failed.¹ After two false starts, and having recruited only one participant per fortnight (when they had originally aimed to enrol two per working day), the research team felt they had no option but to abandon the project and return the funds to the National Health and Medical Research Council (NHMRC).

There is little that is new for clinical practice here, but there are important lessons about the design, execution and funding of research studies. The project was motivated by concerns about the limited external validity of existing evidence about the impact of simple interventions on hazardous drinking in an Indigenous primary care setting. The attempt to conduct a new RCT in such a setting was laudable, but the NHMRC process of reviewing grant applications apparently did not detect that failure was predictable. The inability of the team to conduct the study as conceived should not compound any negative perceptions about Aboriginal Medical Services and Aboriginal patients. Rather, the NHMRC might have served them better by advising the researchers about simplifying recruitment, need for consent and statistical power, as well as taking a more critical view of the underlying rationale for the project. It is not clear whether the original application to the NHMRC was supported by a feasibility study, but, given the challenge

faced by the investigators, funding should not have been granted without one.

As the project was initially designed, the complexity of the screening and recruitment processes flew in the face of well established principles.² Simple requirements for enrolment make participation in RCTs easy for both patients and providers of healthcare services. By contrast, the combination of a detailed interview about a taboo subject, extensive paperwork and the need for blood all act as disincentives to participation by members of a community whose standard of education and reading ability are often poor, that sees paperwork as the hallmark of an officialdom that too often has been oppressive, and that attaches special significance to body fluids. All of these should have been identified by the NHMRC's assessors as likely to be prejudicial to success.

A requirement to seek informed consent to participation runs contrary to the stated aim of the study to assess "effectiveness" (as opposed to "efficacy"³) of brief advice about drinking in a primary care setting. Alerting potential participants to the existence of a trial of this kind is likely to have a Hawthorne effect, thereby eroding statistical power. It is not clear from the account whether gaining consent was originally proposed by the investigators or imposed by an ethics committee — both would be conscious of the special nature of the target population — but it is another neat example of ethics getting in the way of good science.⁴ Trials of effectiveness do need ethical oversight, but clear thinking about ethical requirements is required when the control group is to receive "usual care".