COMMENTARY

Screening for Breast Cancer -is There an Alternative to Mammography?

Anthony B Miller

Abstract

Given the continuing increase in mammary cancer incidence and in many cases also mortality across the world, as well as the difficulty with primary prevention, the question of whether screening for early detection is effective is of prime importance. If there is a real benefit in terms of reduced mortality then attention should clearly be focused on the modality which should be recommended in different resource settings. In the developed world where mammography is generally available the results are less than conclusive. It seems possible that there is a segment of breast cancer benefited both by screening and by treatment, and that far from these effects being additive, they affect the same spectrum of cases, so that as treatment improves, the benefit we can expect to see from screening falls. In the Asian Pacific setting, randomized trials on the basis of the cost and benefit should be a high priority. However, the lesson from all programmes of breast screening, is that for success, attention has to be paid to all aspects of the programme, compliance with screening, high quality screening tests, quality in the referral, diagnosis and treatment process, as well as adequate follow-up.

Asian Pacific J Cancer Prev, **6**, 83-86

In the last two decades, many articles in the world literature have spelt out the potential benefits of mammography screening for breast cancer (Day et al., 1986; Miller et al., 1990). All anticipated that if the right management decisions were taken, and women at risk attended for screening, there would be major reductions in breast cancer mortality, at least among women age 50-69.

However, doubt has been expressed as to whether the randomised trials that showed a benefit from breast screening were valid (Gotzsche et al., 2000; Olsen and Gotzsche, 2001). Also, the fact that there has been no increase in the magnitude of effect of screening in the trials which have shown a benefit since the HIP trial of the 1960s, suggests that improvements in mammography have not resulted in improvement in the efficacy of screening. Further, there has been an unprecedented fall in mortality from breast cancer in the United States, as well as in Canada and the United Kingdom. Yet, surprisingly, there has not been a similar dramatic fall in Sweden, nor in the Netherlands or Finland, countries that also introduced organised screening programmes for breast cancer. The explanation appears to be that it is too early to expect a benefit from mammography screening, while in those countries where falls have occured, it is largely attributable to improved adjuvant therapy for breast cancer (Blanks et al., 2000; Jatoi and Miller, 2003).

The efficacy of screening is entirely dependent on the effectiveness of treatment for the lesions discovered. For breast cancer, screening does not abolish death from the disease, though most trials show it reduces the risk of death, at least in women over the age of 50. So treatment seems to be working for some screen-detected cases. However, adjuvant treatment, chemotherapy and tamoxifen, also reduces deaths in women whose disease was not detected by screening. In the past, it was believed that screening would become more effective if treatment for breast cancer improved. However, there are reasons to doubt that optimistic viewpoint. It seems possible that there is a segment of breast cancer benefited both by screening and by treatment, and that far from these effects being additive, they affect the same spectrum of cases, so that as treatment improves, the benefit we can expect to see from screening falls.

In many countries, for a number of reasons, mammography screening has not generally been advocated (Miller, 1989; National cancer control programmes, 2002). Mammography requires expensive technology, highly trained radiologists and radiographers, and has been shown to result in high health care costs, especially in women under the age of 50 (Salzmann et al., 1997). Further, in routine screening there is considerable variability in mammography interpretation (Kerlikowske et al., 1998), while there are reservations as to its efficacy in women under the age of 50 (National Institutes of Health Consensus Development Panel, 1997).

Professor Emeritus, Department of Public Health Sciences, University of Toronto, Canada E-mail: ab.miller@sympatico.ca

In 2002, an IARC Working Group evaluated the data concerning the efficacy of breast screening (IARC Handbooks on Cancer Prevention, 2002). They concluded that all the trials except the Edinburgh trial were sufficiently valid to include in their evaluation. However, they largely concentrated on the trials that considered mammography alone, as these were most relevant to policies in developed countries. Their principal conclusions were:

1. There is sufficient evidence for the efficacy of screening women aged 50–69 years by mammography as the sole screening modality in reducing mortality from breast cancer.

This conclusion was based on the fact that the findings from the latest follow-up for women aged 50-69 in the five trials of mammography alone that included this age group and the Finnish programme were consistent, showing a rate ratio of 0.75 (95% confidence interval, 0.67-0.85). The HIP trial in this age group was consistent with this result, although, as discussed below, it seems unlikely that the mammography used in that trial was largely responsible. The Canadian trial in women age 50-59 had a different design, and this is also discussed further below.

2. There is limited evidence for the efficacy of screening women aged 40-49 years by mammography as the sole screening modality in reducing mortality from breast cancer. This conclusion was based on the fact that the findings for women aged 40-49 (43-49 in one trial and 45-49 in another) in the six trials of mammography alone that included this age group were less consistent, giving an overall rate ratio of 0.81 (95% confidence interval, 0.65-1.01), and it is uncertain how much of this effect could have been due to screening after the age of 50. Further, although the HIP trial in this age group showed similar findings, the Canadian trial among women age 40-49 showed no benefit (Miller et al., 2002), and if both the HIP and Canadian trials were included in the evaluation, the estimated effect was weak and non-significant, a rate ratio of 0.88 (95% confidence interval 0.74-1.04).

The IARC Working Group (IARC Handbooks on Cancer Prevention, 2002) also concluded that there is inadequate evidence for the efficacy of screening women by clinical breast examination in reducing mortality from breast cancer, and that there is inadequate evidence for the efficacy of screening women by breast self-examination in reducing mortality from breast cancer.

These conclusions were based on the lack of clinical trial data confirming efficacy for either of these procedures. However, there is some, largely indirect evidence, that breast physical examination without mammography is effective in reducing mortality from breast cancer. The HIP study was the first to show some evidence of an effect of breast screening using the combination of mammography and breast physical examination (Shapiro et al., 1971). Benefit in women over the age of 50 began to be seen within 3 years, suggesting an effect from the early detection of fairly advanced breast cancers. In women age 40-49 no benefit was seen for some time, but by 18 years, there seemed to be little difference in effectiveness at different ages at entry (Shapiro et al., 1988). Given the state of mammography in the 1960s, and the high quality of the physical examinations offered, it seems likely that a major part of the benefit in the HIP trial derived from the breast physical examination rather than mammography (Miller, 1986).

Of all the breast screening trials that have reported results, only one, the Canadian trial among women age 50-59 on entry (CNBSS 2) was designed to assess the net benefit of annual mammography screening over and above a regular annual health professional breast physical examination and the teaching and re-enforcement of breast self-examination. No effect of the addition of mammography in reducing breast cancer mortality was seen (Miller et al., 2000), even though the mammography screening achieved its anticipated performance parameters (Fletcher et al., 1993; Narod, 2001), and 47% of the invasive breast cancers detected on screening were detected by mammography alone. This suggests that the small (impalpable) cancers detected by mammography represent good prognosis cancers, and that they do not reach an incurable phase in the absence of mammography detection, providing they are detected early by breast physical examination. Some may even represent pseudo-disease, or over-diagnosis, i.e. cancers that would never have progressed in the absence of mammography detection. So mammography alone screening works not by detecting impalpable cancers, but by detecting relatively advanced cancers at an earlier, but still curable stage in their natural history. Similar benefit can probably be derived from breast physical examination, without the overdiagnosis associated with mammography.

There is, of course an alternative hypothesis that could explain the lack of benefit seen in the Canadian trial. That is that the treatment for breast cancer has now improved to the extent that screening can no longer achieve any benefit. A model analysis, using the parameters of the Swedish Two County Trial and the Netherlands screening programme suggests this is not so, In the model, the benefit from the physical examination and breast self-examination arm (without mammography) was estimated to be a 20% reduction in breast cancer mortality (Rijnsburger et al., 2004).

A case-control study was performed in two Japanese prefectures where breast screening was performed by clinical breast examinations by physicians (Kanemura et al., 1999). There was a suggestion of reduced risk of death for women who had received breast examination at least once in the five years before diagnosis, becoming statistically significant if those women who were symptomatic at diagnosis were classified as not screen detected.

Recognition of the possibility that if a properly designed trial was performed, evidence could accrue on efficacy of breast physical examination, led the IARC working group (IARC Handbooks on Cancer Prevention, 2002) to make two recommendations for research:

- a randomised trial of clinical breast examination versus no screening should be conducted in a country or countries

where resources are unlikely to permit implementation of mammography screening in the foreseeable future, and

- a randomised trial of clinical breast examination versus mammography should be conducted, in a country or countries where resources may permit some mammography screening but are insufficient to cover the whole at risk population.

It is clear that before a low cost alternative to mammography can be promulgated, a definitive trial to assess the effectiveness of thorough breast physical examinations in reducing mortality from breast cancer is needed. In countries that have already established organized programmes of mammography screening, such as Australia and New Zealand, it is unlikely that they would wish to consider changing to breast physical examination screening without good randomised trial evidence. This is the current situation in Canada. However, in countries who have not initiated such programmes, especially those that can not afford mammography screening, a trial comparing breast physical examination with no screening would be highly desirable. However, in a country that can afford mammography screening, a trial comparing screening with breast physical examination with mammography screening would be far more relevant, as if equally effective, health costs would be reduced if breast physical examination were adopted, and it is likely that women would prefer it to mammography. Given the simplicity and relatively low cost of breast physical examination, if it is effective, it should be widely used (Barton et al., 1999). However, if it is ineffective, definitive knowledge to this effect would save health care costs, while helping to resolve some of the uncertainties regarding the stage of disease that must be detected so that earlier detection combined with effective treatment can have a benefit.

Pending new trial data, what are the lessons for countries in the Asia-Pacific Region of the world? The first is that early diagnosis, however achieved, must be accompanied by adequate therapy. There is no point in seeking to promote the early detection of breast cancer unless the cases detected can be treated. Second, the background to the achievements in North America was many years of public and professional education, which pointed to the curability of breast cancer if found and treated early. It is likely that in some countries in Asia breast cancer is usually diagnosed at a regionally advanced stage, quite different from the situation in North America. Third, the evidence suggests that routine mammography screening may not be required, if good physical examinations are made available. These can be given by specially trained health workers, preferably operating in circumstances where there is ready access to a breast diagnosis unit, where mammography and ultrasound for diagnosis are available if needed, and preferably also fine needle aspiration biopsy. However, few countries will wish to adopt such a policy without new efficacy information.

Obtaining the evidence, as the IARC (2002) working group emphasized, requires carefully designed research studies, preferably new carefully designed randomised trials, trials that could be carried out in several countries if there was a will. One such study commenced several years ago in Mumbai, India and a second more recently in Cairo, Egypt. A similar trial was initiated by the IARC in conjunction with local investigators in the Phillipines. Unfortunately this trial was stopped after the first screening round, as only a small proportion of the women found to have abnormalities on breast physical examination attended a local centre for diagnosis and management (IARC Biennial Report, 2002/2003). It is not clear whether misunderstandings on the part of the participants of the purposes of the trial or the examination findings were responsible for this, or barriers such as distance to the diagnosis centre or even financial barriers were responsible. Neither the Mumbai nor Cairo trials had such experiences. However, the lesson from the Phillipines, and all programmes of breast screening, is that for success, attention has to be paid to all aspects of the programme, compliance with screening, high quality screening tests, quality in the referral, diagnosis and treatment process, as well as adequate follow-up.

References

Barton MB, Harris R, Fletcher SW (1999). Does this patient have breast cancer? The screening clinical examination: Should it be done? How? *J Am Med Assoc*, **282**, 1270-80.

Blanks RG, Moss SM, McGahan CE, Quinn MJ, Babb PJ (2000). Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-8: comparison of observed with predicted mortality. *BMJ*, **32**1, 665-9.

Day NE, Baines CJ, Chamberlain J et al (1986). UICC project on screening for cancer: Report of the workshop on screening for breast cancer. *Int J Cancer*, **38**, 303-8.

Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S (1993). Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst*, **85**, 1644-56.

Gotzsche PC, Olsen O (2000). Is screening for breast cancer with mammography justifiable? *Lancet*, **355**, 129-34.

IARC Biennial Report (2002/2003). Lyon, International Agency for Research on Cancer, p100.

IARC Handbooks on Cancer Prevention; Volume 7: Breast screening. Lyon, International Agency for Research on Cancer, IARC Press, 2002.

Jatoi I, Miller AB (2003). Why is breast cancer mortality declining? *Lancet Oncology*, **4**, 251-4.

Kanemura S, Tsuji I, Ohuchi N et al (1999). A case control study on the effectiveness of breast cancer screening by clinical breast examination in Japan. *Jpn J Cancer Res*, **90**, 607-13.

Kerlikowske K, Grady D, Barclay J et al (1998). Variability and accuracy in mammographic interpretation using the American College of Radiology breast imaging reporting and data system. *J Natl Cancer Inst*, **90**, 1801-9.

Miller AB (1986). Screening for cancer: issues and future directions. *J Chronic Dis*, **39**, 1067-77.

Miller AB (1989). Mammography: A critical evaluation of its role in breast cancer screening, especially in developing countries. *J Public Health Pol*, **10**, 486-98.

Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC (1990). Report on a workshop of the UICC Project on evaluation of screening for cancer. *Int J Cancer*, **46**, 761-9.

Miller AB, To T, Baines CJ, Wall C (2000). Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women age 50-59 years. *J Natl Cancer Inst*, **92**, 1490-9.

Miller AB, To T, Baines CJ, Wall C (2002). The Canadian National Breast Screening Study-1: Breast cancer mortality after 11 to 16 years of follow-up. *Ann Int Med*, **137**, 305-12.

Narod SA (2001). Re: Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *J Natl Cancer Inst*, **93**, 396.

National cancer control programmes (2002). Policies and managerial guidelines. Geneva, World Health Organization, 2nd Edition.

National Institutes of Health Consensus Development Panel (1997). Consensus statement. *Monographs J Natl Cancer Inst*, **22**, vii-xii.

Olsen O, Gotzsche PC (2001). Screening for breast cancer with mammography (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update software.

Rijnsburger AI, van Oortmarssen GJ, Boer R, et al (2004). Mammography benefit in the Canadian National Breast Screening Study-2: a model evaluation. *Int J Cancer*, **110**, 756-62.

Salzmann P, Kerlikowske K, Phillips K (1997). Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. *Ann Int Med*, **127**, 955-65.

Shapiro S, Strax P, Venet L (1971). Periodic breast cancer screening in reducing mortality from breast cancer. *J Am Med Assoc*, **215**, 1777-85.

Shapiro S, Strax P, Venet L, Venet W (1988). Periodic screening for breast cancer. The Health Insurance Plan Project and its Sequelae, 1963-1986. Baltimore: The Johns Hopkins University Press.