SHOULD MAMMOGRAPHIC SCREENING BE INTRODUCED IN LOW- AND MIDDLE-INCOME COUNTRIES?

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Breast cancer is the commonest cancer of women. In high-income countries, the impact of adjuvant treatment has caused the balance of benefits to harm of mammographic screening to be questioned. In low- and middle-income countries, women being "breast aware" and having health workers capable of skilled breast examination are the basis for clinical down-staging (early diagnosis). However, there is an obligation to ensure that women so identified have access to competent diagnosis and treatment.

The World Health Organization (WHO) defines early detection of cancer as encouraging people with the first symptoms or signs of cancer to come to a health care professional so their cancer can be diagnosed early (early diagnosis) or testing (screening) people with no signs of a common cancer (asymptomatic people) for an early cancer or precancer.[1] The rationale is that some early cancers or precancers will be more curable and less likely to be fatal than if diagnosed later when the cancer is at an advanced stage.[2] Therefore in some high-income countries there are now established population based "invitation to screening" programmes for cervical, breast and colorectal (bowel) cancer.[3-5] Opportunistic cancer screening has also been practised in many countries for decades, but, with the exception of cervical cancer screening, is generally of unproven effectiveness.[1-4]

Therefore, since the 1980s randomized controlled trials (RCTs), where participants have been invited to screening, have been used to evaluate whether screening for a particular cancer is efficacious before government-funded, population-based "invitation to screening" programmes are started; that is whether screening significantly reduced mortality in the people randomized to screening versus those who were not (controls).[3] However, cervical cancer screening was introduced decades before RCTs were used to evaluate whether cancer screening was efficacious and it has so far proven, in practice, to be the most effective cancer screening test.[4,6] The current state of evidence for early detection programmes for cancer is shown in Table 1.[2] Cancers that have been tested in RCTs, which produced either positive or negative evidence of efficacy, are shown. Cancers for which early detection (early diagnosis and/or screening) in clinical practice has been shown to reduce population mortality are grouped as "Successful in practice". Those cancers for which early detection has not been shown to reduce population mortality are grouped as "Unsuccessful in practice". It is important to note screening for liver and lung cancer have been

Table 1: Implementation of early detection of cancers in populations for some common cancers[2]			
Successful in Practice	**RCT +/- Meta-analysis**	**Unsuccessful in practice**	**RCT +/- Meta-analysis**
Breast	Positive	Prostate	Positive
Colorectal	Positive	Lung	Positive
Cervix	No/Positive*	Liver	Positive
Oral	Positive**	Ovary	Negative

*Only for a once in a lifetime HPV cervical screening test with referral if positive and Visual Inspection with Acetic Acid application (VIA) and immediate cryotherapy if positive.[7,8]
**In smokers [9]

shown to be efficacious in at least one RCT, but these screening tests have thus far not been shown to be effective in practice.

It is most important to note that the Papanicolaou (Pap) smear screening test for cervical cancer has been used very successfully in practice in many countries that have introduced regular repeated Pap smear population-based screening.[6] Most importantly, in contrast to breast cancer screening, which is secondary prevention, the Pap smear screening test detects cancer precursors that can be successfully treated and therefore reduces cervical cancer mortality by first reducing incidence (primary prevention). However, a "once in a lifetime" Pap smear was not efficacious in the only reported RCT in which it has ever been tested. This 4 arm RCT compared "once in a lifetime" Pap smear versus a HPV virus test of cervical cells versus VIA, followed by referral of test positive women for further diagnostic tests and treatment, versus an observation only arm (controls).[8] Only those women screened with the HPV test had a significant reduction in cervical cancer mortality as compared to the controls.

Breast cancer, with 1.7 million new cases, 12% of all global cancers, and 520,000 deaths in 2012, is the commonest potentially fatal cancer of women and its incidence has been increasing worldwide for decades.[10] There is currently at least a four-fold variation in age-standardized incidence rates between countries with the lowest (east and southern Africa) and countries with the highest (Western Europe, North America and Australia/New Zealand) rates. Furthermore, it is potentially one of the most curable of cancers. However, five-year relative survival rates worldwide currently cover a seven-fold range based on analysis of data from cancer registries: from 13% in Gambia to 46% in Uganda to 57–66% in Thailand to 60–80% in Europe to 70% in Cuba and Costa Rica to 88% in Australia and 92% in the United States.[11-14] Breast cancer mortality trends are available for many high-income countries, mostly European, North American and Asian: Korea, Japan, Australia and New Zealand. After being on a plateau for decades breast cancer mortality began falling in a number of those countries about 1990, although in some

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countries, such as Sweden, this fall began as early as 1975.[15] These declines in breast cancer mortality have mainly occurred in countries where either or both of two interventions were introduced:
➤ endocrine and/or chemotherapy administered immediately after the primary surgical treatment (adjuvant therapy);
➤ mammographic screening (secondary prevention).

Early breast cancer is defined by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) as "loco-regional breast cancer that can all be removed surgically".[16] The EBCTCG have, since 1988, been publishing five-yearly systematic reviews of adjuvant endocrine and chemotherapy for breast cancer and advised in 2005 that "allocation to about six months of anthracycline-based poly-chemotherapy reduces the annual breast cancer death rate by about 38% for women aged under 50 at diagnosis and by about 20% for those aged 50–69 years; and that for ER-positive disease only, at any age, allocation to about five years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%. These effects were each seen irrespective of other treatment or tumour characteristics".[16]

At the end of the twentieth century the message was clear: in countries with a significant breast cancer burden that also had a sufficient level of resources, implementing a population-based mammographic screening programme could reduce breast cancer mortality in women aged 50–69 years by about 25%. This is well covered in the WHO International Agency for Research on Cancer (IARC) monograph on breast cancer screening.[3] Most importantly, all the RCT, which are the basis for this recommendation[3] were completed at a time when few women received adjuvant endocrine and/or chemotherapy (adjuvant therapy) that can cure many women with early breast cancer.[17,18]

Therefore, mammographic screening is now very controversial. Kirwan wrote in the *British Medical Journal (BMJ)* in 2013: "In the past 12 months alone the *BMJ*, the *Lancet* and *New England Journal of Medicine* have published 24 articles or communications debating the value of breast cancer screening".[19] In theory, screening asymptomatic women for an earlier and more treatable form of a potentially fatal disease like breast cancer should reduce all-cause and breast cancer specific mortality, although screening always has intrinsic harms (see later). However, this will not occur if screening is ineffective because it is opportunistic/ad-hoc or population-based but poorly organized with low participation. Screening will also fail if the treatment of the disease at early and later stages improves so that earlier

diagnosis by screening has a diminishing impact on mortality.[20] This may now be the case for breast cancer, where adjuvant therapy can substantially reduce mortality from early disease whether it is diagnosed clinically or by mammographic screening.[16,19,20,21,22,23,24]

The analytic techniques that are used to evaluate population-based mammographic screening programmes are also controversial. The advice of WHO-IARC is that observational studies, especially case-control studies, should not be used; they were used extensively in a review of European mammographic screening programmes.[3,25] This WHO advice is important, and echoes earlier cautions published in the *BMJ*: "that confounding and selection bias often distort the findings from observational studies and that there is a danger that meta-analyses of observational studies produce very precise but equally spurious results".[26]

It is increasingly apparent that over-diagnosis of in situ and invasive breast cancers, which would never have troubled women in their lifetimes, is substantial and has been estimated in a meta-analysis as being 52% of women diagnosed by screening[27], although published estimates of over-diagnosis vary widely.[27,28,29,30] Over-diagnosis is a common consequence of screening asymptomatic people and finding biological forms of a disease that will never cause clinical disease. This leads to unnecessary investigations and unnecessary treatment, so the ratio of mortality reduction (benefit) to over-diagnosis (harm) consequent upon mammographic screening for breast cancer in some countries may now be unfavourable. Evaluations of mammographic screening programmes that report on over-diagnosis must make an estimate of the lead time from screening. It has been reported that modelling generally overestimates lead time and hence underestimates over-diagnosis as compared to clinical measures of lead time.[30] Therefore estimates of over-diagnosis that come from modelling studies should be viewed with caution.

Today, the dilemma in countries with mammographic screening programmes is whether the, at most, modest benefits of mammographic screening are now outweighed by the harms of over-diagnosis.[31] In particular, one of the advertised benefits of mammographic screening has been that it detects small breast cancers which can be treated by partial mastectomy and radiotherapy and so preserves the breast.[20] Unfortunately, it is now apparent that external beam radiotherapy, which is the usual mode of administering radiotherapy to the breast after breast-conserving surgery, can later cause cancer of the lung and/or accelerated atherosclerosis of the left anterior descending artery predisposing to myocardial infarction, since both the lungs

and heart lie just a few centimetres beneath the breasts. Therefore, more women treated with radiotherapy in this way may die from these complications than avoid death from breast cancers detected by screening.[20,32] It is important to emphasize that studies of mammographic screening, which do not measure all-cause mortality as well as breast cancer-specific mortality, will not detect these lung cancer and myocardial infarct deaths and therefore give a spurious picture of the benefits of screening.[32]

The balance of benefits and harms for mammographic screening is critical in low- and middle-income countries, where the incidence of breast cancer is lower than in high-income countries and where breast cancer is more likely to be a premenopausal disease, with most women diagnosed with breast cancer at less than 50 years of age.[1,33] Since mammographic screening is more sensitive in postmenopausal women, who have less dense breasts than premenopausal women, this combination of lower incidence and mainly premenopausal breast cancer means that, compared with high-income countries, many more women will have to be screened in low- and middle-income countries to detect one breast cancer.[1] For example, it has been calculated that in a low- or middle-income country where the incidence of breast cancer is half that of the United States "for women aged 40 to 49 years, more than 3,800 women would need to be invited for screening at the cost of more than 41,000 visits for mammography and more than 4,000 false-positive diagnoses, in order to prevent one death from breast cancer during 11 years of follow up".[1] This should give pause for thought to governments contemplating introducing mammographic screening in low- and middle-income countries.

In the United States, where the incidence of breast cancer is one of the highest worldwide[34], the cost effectiveness of mammography has been estimated to be $US 30,000–100,000 per quality adjusted life year gained.[1] Even though a mammogram may be cheaper to deliver in a low- and middle-income country, because of the sensitivity and incidence issues described above, when compared with a high-income country, the cost-effectivenss of mammography in a low- and middle-income country may be worse.

Finally, there has only been one mammographic screening RCT reported for a non-European-derived population which was carried out in Singapore, where a low participation rate amongst Chinese women resulted in selection bias in favour of women of higher socioeconomic status and education in the screened group and no mortality outcomes were reported.[35]

The debate about the balance of benefits and harms of mammographic screening has important implications for all

countries using or considering the introduction of mammographic screening for breast cancer. Most importantly, it emphasizes the importance of concentrating on programmes which educate women and health care professionals so that breast cancer is diagnosed early and women are competently treated.[1] It is wise to heed what Macpherson wrote in the *BMJ* in 2010 about the United Kingdom National Health Service invitation to mammographic screening programme (NHSBSP): "Since all healthy women aged 50–70 are called for breast screening, benefits (reduced mortality) ought to be unambiguous and considerable and the risks of harm small".[36]

Most importantly for low- and middle-income countries, as well as high-income countries, is the consideration of the costs of mammographic screening, including both the costs of the invitation to screen programme and the costs of the unnecessary further investigations and treatment consequent upon over-diagnosis. If early clinical diagnosis and follow up diagnostic testing and treatment for breast cancer are of a high standard in the country, then the opportunity costs of introducing mammographic screening need very careful consideration.

So is there an alternative to mammographic screening? In high-income countries most breast cancer is not usually diagnosed by screening mammography. For example, in Australia only about a third of breast cancer is diagnosed by mammographic screening.[37] Most breast cancer in Australia has been diagnosed early by women who have been educated to be aware of the appearance and "feel" of their breasts: "breast awareness".[38] Some women perform specific breast self-examination (BSE) regularly, but importantly in Australia there is no financial barrier to women attending health care professionals immediately they find any abnormality. Women are also likely to undergo opportunistic clinical breast examination (CBE) by their doctor on a regular basis. Since 1986, prior to the introduction of the "invitation to screening" programme in Australia for women aged 50–69 years[23], more than 80% of Australian women diagnosed with breast cancer have had breast cancer that is confined to the breast and the adjacent axilla[17,39] and so meets the EBCTCG definition of early breast cancer.[16] Since 1995, 85% of breast cancer in Australian women has been diagnosed early.[40]

Population-based treatment surveys have shown that since 1995 the majority of Australian women diagnosed with early breast cancer have been treated as advised by the EBCTCG and breast cancer-specific mortality has been falling in all age groups since then, well before the national mammographic screening programme could have had an impact on mortality.[23] Many European countries have experienced significant reductions in breast cancer-specific mortality, which have also largely been attributed to adjuvant therapy.[41,42,43] Therefore, before contemplating mammographic screening any country with a significant burden of breast cancer should first ensure that women with breast symptoms are educated to present to health care professionals early and that breast cancer is diagnosed promptly and competently and treated as described above.

There have been two RCTs testing BSE in Russia and China, and BSE did not reduce breast cancer mortality in the intervention groups, who were taught and practiced BSE, as compared to the control groups who were only observed.[44,45] Furthermore, results from several studies that suggested that BSE screening greatly increases the number of benign lumps detected, led the United States preventive services task force to issue clear recommendations against teaching BSE, stating that "For the teaching of BSE, there is moderate certainty that the harms outweigh the benefits".[46] However, it must be noted that in both the China and Russian trials, there was limited room for BSE screening to achieve a mortality reduction since breast cancer awareness in the populations was already high and the clinical stage at diagnosis was relatively good.[1] In the trial in Shanghai, China, 45% of the control women were Stage I and only 1.5% of the BSE intervention and 2.5% of the control women were Stage IV. These trial results demonstrated that the specific process of BSE does not carry benefit in those settings. The question remains open for countries where a higher proportion of cancers are diagnosed at late/advanced stages.

Evidence about the efficacy of population-based screening for breast cancer with CBE is controversial. A Canadian RCT of breast cancer screening evaluated the combination of mammography and CBE versus CBE alone.[47] This RCT showed that there was no benefit in adding mammography to CBE. Since the reduction in mortality in this Canadian trial was the same in both arms and equivalent to that achieved in some mammography-only RCT[47], a reasonable conclusion would be that CBE was equivalent to mammography as a screening test in this Canadian setting. A RCT of CBE versus observation is currently being conducted in Mumbai (India) on 150,000 women aged 35–64 years. This study has now entered its tenth year and more than 3 rounds of screening have taken place. Early results show that the stage distribution is significantly better in the screened group than in the control groups. The principal objective of the trial, i.e. demonstration of a reduction in mortality, will become evident only after a further 5 to 8 years.[48]

A clinical down-staging programme conducted in Malaysia covering a population of 1.1 million women, based on the

principles of early diagnosis and referral and competent treatment described above, managed to reduce breast cancer late presentation from 60% to 35% in less than 5 years[49], so most women were then being diagnosed with early potentially curable breast cancers. So the experience of many high-income countries in Europe and Australia of falling breast cancer-specific mortality is being replicated in a middle-income Asian country and emphasizes the importance of educating women to be "breast aware" so that they detect changes in their breasts early. They must be educated to visit a health care professional as soon as any breast abnormality is found and there must be a system of referral for diagnosis and competent surgical and adjuvant therapy treatment.

The recommended adjuvant therapy by the EBCTCG of anthracycline chemotherapy and tamoxifen endocrine therapy is now very cheap and almost equal in effectiveness to much more expensive chemotherapy with taxanes and endocrine therapy with aromatase inhibitors.[50,51]

Conclusions

Unfortunately and tragically, population-based mammographic screening in higher income countries has not lived up to the promise of the RCT which began half a century ago and concluded with the AGE RCT for women aged less than 50 years in the mid-1990s.[24] It is now likely that in a number of high-income countries population-based mammographic screening is causing considerably more harm than good.

For low- and middle-income countries, education programmes that make women breast aware, together with the removal of financial or cultural barriers to access to a health care system which can competently manage women who present with breast abnormalities is the optimal approach.[52] However, it is critical that a system of affordable and competent primary health care, which can offer CBE and refers women with abnormalities for further diagnosis and treatment are in place before women are educated to try and detect breast cancer early. Raising women's awareness about breast cancer would only make them anxious and reduce their quality of life, unless there is a health care system that can competently follow up on any breast abnormalities that are discovered and diagnose and treat them competently; adjuvant therapy is a critical component.

Although the benefits of early diagnosis (down-staging) programmes have had little study, and their effect on breast cancer has not yet been comprehensively assessed, WHO recommends this approach as the minimal breast cancer early detection intervention in low resources settings.[53] WHO guidelines state that "A cancer screening programme is a far more costly and complex undertaking than a down-staging programme. Therefore, where resources are limited, and where the majority of cases are diagnosed in late stages, down-staging of the most frequent cancers, linked to appropriate treatment, is likely to be the best option to reduce premature deaths and suffering due to cancer."

There is a caveat to following this advice without a careful analysis of resources for breast cancer control. "A major potential hazard of a population early diagnosis programme is overloading primary and secondary health care facilities with women with breast complaints, given that up to 95% of breast symptoms reported by women may not be cancer. In this regard, the content and the quality of the breast awareness messages delivered to the public are critical".[1]

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