

The benefits and harms of screening for cancer with a focus on breast screening

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KEY WORDS

benefits, breast cancer, informed consent, harms, screening

ABSTRACT

The balance between benefits and harms is delicate for cancer screening programs. By attending screening with mammography some women will avoid dying from breast cancer or receive less aggressive treatment. But many more women will be overdiagnosed, receive needless treatment, have a false-positive result, or live more years as a patient with breast cancer.

Systematic reviews of the randomized trials have shown that for every 2000 women invited for mammography screening throughout 10 years, only 1 will have her life prolonged. In addition, 10 healthy women will be overdiagnosed with breast cancer and will be treated unnecessarily. Furthermore, more than 200 women will experience substantial psychosocial distress for months because of false-positive findings.

Regular breast self-examination does not reduce breast cancer mortality, but doubles the number of biopsies, and it therefore cannot be recommended. The effects of routine clinical breast examination are unknown, but considering the results of the breast self-examination trials, it is likely that it is harmful. The effects of screening for breast cancer with thermography, ultrasound or magnetic resonance imaging are unknown.

It is not clear whether screening with mammography does more good than harm. Women invited to screening should be informed according to the best available evidence, data should be reported in absolute numbers, and benefits and harms should be reported using the same denominator so that they can be readily compared.

Why do we screen for cancers? The theoretical background for screening is that early detection and early treatment should improve the prognosis. This seems so intuitively reasonable that some screening programs have been introduced without reliable evidence about possible benefits and harms, e.g., no randomized trials have been performed on cervical cancer screening.

During the last 5 decades, screening programs for different cancers have been investigated and several have been implemented. Others have been avoided as they failed to reduce mortality (e.g., screening smokers for lung cancer with chest X-ray),¹ or because they led to serious harm by detecting cancers that disappeared again when left untreated (e.g., screening children for neuroblastoma).¹ As stated by the former program director of the United Kingdom National Screening

Committee, Muir Gray, it should be remembered that “all screening programs do harm; some do good as well”.² This balance is particularly delicate for screening programs for cancer because the inevitable harmful effects may be serious and need to be balanced against a potential reduction in cancer mortality.

Prior to the introduction of any screening program, all important benefits and harms must be quantified, including the psychosocial harms. However, it cannot be easily determined if the benefits outweigh the harms, as this is essentially a value judgment that involves personal experiences and preferences. As there are important trade-offs between benefits and harms with cancer screening, a decision to attend is not more “correct” than a decision not to attend, and this must be made clear to potential participants. Therefore,

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health authorities that wish to offer cancer screening should offer it, and not advocate it, and the invited citizens should be given adequate evidence-based information to allow them to make a truly informed decision.

Breast screening The most common cancer among women in industrialized countries is breast cancer. This has led to an intensive search for factors that increase the risk of developing breast cancer. The only amenable risk factor that has been identified is hormone replacement therapy given to postmenopausal women.³ Factors such as age at first pregnancy, alcohol consumption, and birth control pills also raise the risk of getting breast cancer,⁴ but the elevated risk is small and these risk factors cannot be easily modified. High socioeconomic status is considered an independent risk factor⁵ that cannot be explained by the fertility pattern alone.⁶ Primary prevention of breast cancer is therefore focused on limiting the use of hormone replacement therapy in postmenopausal women.

Because no amenable risk factor of major importance has been identified, little can be done to avoid breast cancer, and researchers and clinicians have therefore looked for opportunities to identify breast cancer as early as possible. Screening has been the method of choice and is defined as “secondary prevention”. The term “secondary” implies that it is not the disease that is prevented but some of its complications, in this case primarily death. Screening for breast cancer has focused on breast self-examination and on mammography.

What are the possible benefits of mammography screening? Mortality reduction Screening mammography aims to reduce mortality from breast cancer. If the mortality rate of cancer is high, screening can affect the prognosis of a high proportion of patients. Conversely, if the mortality rate is already low, few people could benefit from screening. In breast cancer, survival rates are good without screening and therefore only a minor proportion can benefit from screening.

Less aggressive treatment Finding a cancer in an earlier stage might lead to less aggressive treatment in an individual patient, e.g., less extensive surgery. However, as explained below, screening for breast cancer leads to more surgery, and also to more extensive surgery, because of overtreatment.

Feeling of reassurance Healthy people who are screened and are told that they do not have cancer after a normal (negative) screening result might feel reassured.^{7,8} The feeling of reassurance is most likely based on the faulty belief that screening cannot miss a cancer. Given the uncertainty of the results, cancer screening can only increase the probability of being healthy, i.e., reduce the likelihood of breast cancer being

present among those screened. How much this likelihood of being healthy is increased can be calculated as the difference between the pre-screening likelihood of not having breast cancer and the postscreening likelihood of not having breast cancer. Breast cancer has a prevalence of less than 1% in the age groups offered screening.⁹ Therefore, more than 99% of those participating in screening will be healthy, both before and after they attend screening. The very small absolute gain in certainty is in considerable contrast to the perceived reassurance.^{8,10}

What are the potential harms of mammography screening? Overdiagnosis and overtreatment Screening for cancer inevitably leads to identification of cancers that would not have caused death or symptoms in the remaining lifetime of the patient if left alone (overdiagnosis). For example, 47 men were overdiagnosed with prostate cancer for every man who had his life extended in the recent European randomized trial on prostate-specific antigen screening.¹¹ These 47 men were treated for a prostate cancer that would not have been clinically detected in their remaining lifespan.¹¹ The detection of such cancers can only be harmful.

Another kind of overdiagnosis is identification of cancer precursors, so called precancers. In cervical cancer screening, for example, the screening program detects many women with dysplasia. Most of these lesions never progress to cervical cancer but are signs of a passing human papillomavirus infection. Similarly, carcinoma in situ (CIS) is often detected with screening mammography. Less than half of CIS will progress to breast cancer.¹²⁻¹⁴ Spontaneous remission or very slow growth can occur in screen-detected cases of invasive cancer and lead to overdiagnosis of these cancers, although this seems counter-intuitive considering our experience with clinically detected cases.^{1,15,16} Of the screen-detected abnormalities, between 10% and 20% are CIS varying between national programs.^{17,18} Practically all women diagnosed with CIS are treated as if the condition would progress to invasive cancer, which leads to considerable overtreatment.

False-positive and false-negative results Because the specificity of screening tests is not perfect, many healthy people will get false-positive screening results. These people undergo additional tests that can sometimes be physically harmful and in rare cases even lethal (e.g., in cases with a perforated colon after colonoscopy, complications to a laparotomy on suspicion of ovarian cancer, or a perforated lung).¹⁹ False-positive findings also lead to adverse psychosocial effects.^{20,21} Some people report negative psychosocial consequences months or even years after being declared free from cancer after a false-positive finding.^{22,23}

Screening primarily detects the nonaggressive, slow-growing cancers with a good prognosis²⁴⁻²⁷ while the fast growing, aggressive cancers with poorer prognosis will more likely appear

between 2 screening rounds. This phenomenon is called length bias¹ and cancers detected between screening rounds are called interval cancers. Little research has been conducted on people having false-negative results. A qualitative study showed that if women are diagnosed with breast cancer less than a year after the latest screening, she might lose confidence in the healthcare system and be mistrustful.²⁸ Having a false-negative screening result may also cause delay in the diagnosis and treatment of the cancer, because both the patient and the physician might tend to rely on the recent normal screening result and therefore dismiss the idea that the patient's symptoms could arise from cancer.

To live longer as a patient with cancer without living longer Another important harm concerns numerous patients whose prognosis is not changed despite the fact that the cancer was detected by screening. For these patients, the earlier diagnosis will result in more years as a patient with cancer.

Induced morbidity In mammography screening, the radiation dose involved in the screening procedure is so small that it induces less than 1 case of breast cancer per million women examined.²⁹ A more important concern is the morbidity induced by overdiagnosis. These healthy women will all have unnecessary surgery, will often receive radiotherapy and sometimes chemotherapy. Both chemotherapy and radiotherapy are known to induce secondary cancers, and radiotherapy also increases the risk of cardiovascular events and death because of damage to the endothelium, as has been shown in comparisons between right- and left-sided treatments.³⁰

Evidence of benefits and harms from the randomized trials **Screening for breast cancer with mammography** The Cochrane review on this issue includes 8 randomized trials involving half a million women.³¹ At 13-year follow-up, the relative risk for breast cancer mortality was 0.81 (95% confidence interval [CI] 0.74–0.87), but some of the trials were flawed. There were only 3 trials with adequate randomization and these trials did not show a significant reduction in breast cancer mortality, relative risk 0.93 (95% CI 0.79–1.02). A more reasonable estimate is therefore a 15% relative risk reduction, rather than a 20% reduction.²⁰ A systematic review was performed by the United States Preventive Services Task Force in response to the Cochrane review. The result of this review was a 16% relative risk reduction, in agreement with the Cochrane review.³¹ However, the absolute risk reduction was only 0.05%. Since about 10% of the women died from other causes than breast cancer in a 10-year period, this means that if women do not attend screening, 90.20% will be alive after 10 years, and if they attend screening, 90.25% will be alive.

Screening mammography leads to considerable overdiagnosis and overtreatment, with

an estimated 30% increase in incidence in the randomized trials,³¹ or an absolute risk of 0.5% of becoming a patient diagnosed unnecessarily with breast cancer. The number of mastectomies and tumorectomies increased by 31% in the randomized trials; for mastectomies only the increase was 20%. It is often argued that because of earlier detection, screening leads to less surgery, but although it may be true for an individual woman, this is not correct at a population level. The net result is that screening mammography leads to 6 more tumorectomies and 4 more mastectomies for every death from breast cancer that is prevented through screening.³¹ The overdiagnosis in publicly organized screening programs is even greater, 52%.³²

The bottom-line in mammography screening is that for every 2000 women invited for screening throughout 10 years, 1 will have her life prolonged. In addition, 10 healthy women will be overdiagnosed with breast cancer and will be treated unnecessarily. Furthermore, it is likely that more than 200 women will experience substantial psychological distress for months because of false-positive findings.^{22,23} It is thus not clear whether screening with mammography does more good than harm.²⁰

Screening for breast cancer with breast self-examination or clinical examination Previously, screening for breast cancer with regular breast self-examination was widely recommended by cancer charities and patient organizations. This screening method can no longer be recommended.³³ Two large randomized population-based trials involving 388,535 women from Russia and Shanghai have been performed and were included in the Cochrane review on this issue.³⁴ There was no statistically significant difference in breast cancer mortality between the screened group and the control group (relative risk 1.05, 95% CI 0.90–1.24; 587 breast cancer deaths in total). Almost twice as many biopsies with benign results were performed in the screened group compared to the control group. Regular breast self-examination therefore appears to be harmful.

One large population-based trial of clinical breast examination by physicians combined with breast self-examination was included in the Cochrane review on breast self-examination.³⁴ The intervention was discontinued because of poor follow-up and no conclusions could be drawn. The benefits and harms of clinical breast examination is therefore unknown, but considering the results of breast self-examination, it is likely that it is harmful. Routine clinical breast examination, for example on patients admitted to hospital for diseases that do not raise a suspicion of breast cancer, should therefore be abandoned.

Screening for breast cancer with thermography, ultrasound or magnetic resonance imaging No randomized trials have been conducted on these

screening methods. The effects are unknown and they cannot be recommended as screening tests for breast cancer. The American Cancer Society has issued guidelines for screening certain high-risk groups with magnetic resonance imaging as an adjunct to mammography screening,³⁵ but the recommendations are based on observational studies and on consensus opinion. Observational studies are notoriously unreliable for estimating the benefits of cancer screening, and a World Health Organization report on breast screening specifically stated that such studies cannot provide evidence for a screening effect, no matter how elaborate the design.²⁹

Informed consent is a requirement that has been neglected Doctors have a duty to inform patients about both benefits and harm of planned interventions. This duty is even more pertinent when healthy people are involved, such as women invited to mammography screening, and when an intervention can lead to serious harms. It is therefore problematic that the information offered to women about mammography screening is unbalanced, both in information leaflets,^{36,37} on websites,³⁸ and in the scientific literature.³⁹ The information exaggerates the benefits, does usually not mention overdiagnosis, and downplays the other harmful effects. As a consequence, women have serious misperceptions about the benefits and harms of screening,⁴⁰ and are therefore prohibited from consenting to screening in an informed way.

To remedy this situation, we have written a leaflet intended for women invited for screening mammography. We selected the information according to 3 principles: it should be based on the best available evidence, data should be reported in absolute numbers, and benefits and harm should be reported using the same denominator so that they could be compared. The leaflet was first written in Danish, and we tested the draft version among general practitioners in Denmark, Iceland, Norway, and Sweden belonging to the Nordic Risk Group Network and among lay people, which led to considerable improvements. We then posted the leaflet to all general practitioners and gynecologists in Denmark and made it available on 2 websites: www.screening.dk and www.cochrane.dk.

Later, we reviewed the new UK National Health Service's leaflet given to women invited for mammography screening and published our findings in the *British Medical Journal* together with an English version of our leaflet.⁴¹ This led to public criticism of the UK leaflet⁴² and extensive media coverage, and a spokesperson for the National Health Service Cancer Screening Program promised that it would be revised. Volunteers in different countries have translated our leaflet into Finnish, French, German, Icelandic, Italian, Norwegian, Spanish, and Swedish, and other translations are ongoing. The translated leaflets will appear on our websites when we have ensured that

the translation process has not changed the meaning in the original Danish leaflet. Together with the *Polish Archives of Internal Medicine*, we now launch our leaflet in Poland and make it available in English on the journal's website, www.pamw.pl, and in Polish on www.mp.pl – the website of Medycyna Praktyczna Publishing Company.

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Korzyści i szkody z badań przesiewowych w kierunku nowotworów złośliwych ze szczególnym uwzględnieniem raka piersi

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SŁOWA KLUCZOWE

badania przesiewowe, korzyści, rak piersi, szkody, świadoma zgoda

STRESZCZENIE

Bilans korzyści i szkód w programach badań przesiewowych w kierunku nowotworów złośliwych jest subtelny. Uczęszczając na mammograficzne badania przesiewowe niektóre kobiety unikną zgonu z powodu raka piersi lub otrzymają mniej agresywne leczenie. Jednak znacznie więcej kobiet otrzyma niepotrzebne rozpoznanie i niekończące się leczenie, będzie miało fałszywie dodatni wynik badania lub przez więcej lat będzie żyć ze stygmatem raka piersi.

Przeglądy systematyczne badań z randomizacją wykazały, że spośród 2000 kobiet wzywanych na mammograficzne badania przesiewowe przez 10 lat jednej uda się przedłużyć życie. Oprócz tego u 10 zdrowych kobiet zostanie niepotrzebnie rozpoznany rak piersi i będą one niepotrzebnie leczone. Ponadto ponad 200 kobiet będzie przez wiele miesięcy doświadczać znaczącego stresu psychicznego z powodu wyników fałszywie dodatnich.

Regularne samobadanie piersi nie zmniejsza umieralności z powodu raka piersi, ale podwaja liczbę biopsji, i dlatego nie może być zalecane. Efekty rutynowego lekarskiego badania piersi są nieznane, ale biorąc pod uwagę wyniki samobadania jest prawdopodobne, że przeważa szkodliwość. Skutki badań przesiewowych w kierunku raka piersi z użyciem termografii, ultrasonografii lub rezonansu magnetycznego są nieznane.

Nie jest jasne, czy badania przesiewowe z użyciem mammografii przynoszą więcej korzyści niż szkód. Kobiety zapraszane na badania przesiewowe powinny być informowane zgodnie z najlepszymi dostępnymi danymi; dane liczbowe należy podawać w wartościach bezwzględnych, a korzyści i szkody przedstawiać z tym samym mianownikiem, tak by można je było porównać.

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