

National Breast Screening Programmes

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ABSTRACT

Breast cancer screening has been incorporated into many national cancer screening programs. The premise for screening is early detection of the cancer, enabling earlier treatment which results in improved outcomes in mortality. This paper examines the evidence regarding clinical examination, mammography and biopsy and the way these screening tools have been incorporated into national screening programs. National programs have variations with regard to screening interval and target group age. Evidence for mammography as a screening tool effective in reducing overall mortality has been questioned. Current evidence to support screening although suboptimal suggests national screening programs are effective in reducing mortality. Further research is required to confirm the effectiveness of mammographies as a population screening tool, as well as refining protocols for high-risk groups.

INTRODUCTION

Breast cancer is the most common cancer affecting European women today and is the leading cause of cancer mortality. In 2004 alone, breast cancer incidence was 370,000 and accounted for 130,000 deaths.¹ These alarming statistics have led the International Agency for Research on Cancer to recommend a concerted attack on breast cancer if progress is to be made. Since breast cancer's pathogenesis is poorly understood, primary prevention is still a distant goal. Thus, secondary prevention through early detection is the only feasible approach at present.² Breast self-examination, clinical examination and mammography have been incorporated into different screening programmes, but the effectiveness of these methods in reducing breast cancer mortality has been questioned.³ Furthermore, there is varied opinion as to how these screening tools are best implemented. This paper aims to evaluate the efficacy of current screening methods in reducing breast cancer mortality and components necessary for implementing a cost-effective and successful screening program.

Screening Methods

Certain criteria for screening are essential. These include methods that are simple, safe, inexpensive and easy to perform, and results that clearly distinguish those with and those without disease. The ideal screening method will detect a cancerous growth in breast tissue at an early stage, allowing earlier treatment of the tumour to produce an improved outcome. Screening programmes should be implemented with guidelines to assure quality and consistency across regions as large discrepancies in execution of programs currently exist.⁴

The mainstay of all current breast screening programmes is mammography. Other modes of screening include regular breast self-examination, clinical examination and biopsy as part of a triple assessment. Newer methods using magnetic resonance imaging (MRI), ultrasound, and computer-aided detection have been introduced. Their effectiveness in reducing breast cancer mortality is currently under assessment.⁵ The evaluation of breast cancer screening programmes is challenging as randomised controlled trials (RCT), the cornerstone of evidence-based medicine, are difficult to conduct for clinical and ethical reasons. In addition to requiring large sample sizes (tens of thousands of patients), years of follow-up are necessary to monitor outcome. This is further complicated by concurrent advances in breast cancer treatment impacting historical survival curves.

Mammography

Mammography is an x-ray examination of the female breast using low-energy x-rays to visualise fine details of breast tissue, particularly calcification or soft tissue masses, enabling early diagnosis of breast cancer.⁶

For the past 20 years mammography has been the gold standard for early detection of breast cancer. Two mammographic views of each breast (mediolateral oblique and craniocaudal) have been shown to be the most effective means of screening. This has been proven to significantly improve both sensitivity and specificity for mammographic detection of small breast cancers.² Community screening programmes in the United States (US) using mammography have an overall sensitivity of 75 percent and specificity of 93 percent. This is similar to the sensitivities and specificities found in previously conducted RCT.⁵

Eight RCTs in the US, Sweden, Canada and the UK have proven the effectiveness of mammography.⁵ However, two Danish investigators carried out a meta-analysis for the Cochrane Collaboration in 2000, which questioned the validity of six of the eight randomised controlled trials. The paper indicated that there was a significant difference between the screened and controlled groups in these trials which could bias the results. When these trials were excluded from the meta-analysis, screening was not found to decrease overall mortality, relative risk (RR) 0.99 (95 percent confidence interval (CI) 0.94 to 1.05). More surprisingly breast cancer specific mortality also failed to show improvement, with a RR of 1.04 (95 percent CI 0.84 to 1.27).^{3, 7-16} The debate created by these results lead to the creation of an independent review by the International Agency for Research on Cancer (IARC). The IARC working group concluded that the flaws in the trials randomisation did not negate mammography's efficacy.¹⁷ This conclusion was further supported by Freedman *et al.* who suggested that exclusion of the trials was unjustified and due to a misunderstanding of study design and misinterpretation of tabulated results.¹⁸ From this review, the IARC also concluded that those women aged 50 to 69 years who participated in screening programmes showed reduced mortality from breast cancer by 35 percent. The evidence for screening younger women, between 40 and 49 years was less conclusive.¹⁷

The interpretation of mammograms varies depending on region with 12.5 percent of mammograms in the US considered positive, compared with 7.6 percent in the UK. There are equivalent cancer detection rates in both regions.¹⁹ This suggests that detection sensitivities are the same in both regions, but detection specificity is greater in the UK. Detection by mammogram is not sufficient for diagnosis. A positive mammogram necessitates further evaluation, most commonly by biopsy. Of these biopsies, only 3 to 6 percent are cancerous.²⁰ This high frequency of false positive mammograms has lead to estimates that 50 percent of women will have had a biopsy due to a false positive mammogram, after 10 mammogram screens.²¹

Breast self-examination

Breast self-examination has been promoted widely by organizations such as the American Cancer Society.²² It is non-invasive, free and easy to perform and thus, the appeal of this approach is

evident. The current practice of breast self-examination is poorly adhered to, with as little as one-third of women in the US participating.²³ Also, a recent systematic review for the Cochrane Collaboration, looking at studies from Russia and Shanghai, indicated no benefit in reduction of breast cancer mortality (RR 1.05, 95 percent CI 0.90 to 1.24).²⁴

Clinical Examination

Clinical examination is performed on women during regular examination, as well as upon discovery of a suspicious lump during self-examination, or following an abnormal mammogram. Symptoms such as bloody nipple discharge, breast pain or family history of breast carcinoma qualify as other reasons for examination. Clinical breast examination provides modest benefit in detection of breast cancer. Clinical breast examination alone detects only 21 percent of cancers and along with mammography has been shown to detect an addition four percent of breast cancers. This small benefit in detection has not been shown to decrease mortality.²⁵

Biopsy

Biopsies provide a histological diagnosis of breast cancer. They are used to investigate suspicious abnormalities found in clinical examination, ultrasound or mammogram. The two commonest forms of biopsy are fine needle aspirate (FNA) and core biopsy. The advantage of FNA is that the results can be available immediately once interpreted by a pathologist. Core biopsy has the advantage of differentiating between invasive versus *in situ* disease. However, core biopsy is more time consuming than FNA. Often the biopsy must be carried out under radiological guidance using either ultrasound or x-ray stereotaxis, as up to 70 percent of screening abnormalities are impalpable on examination. Malignancy can be established in up to 95 percent of invasive cancers following biopsy.²

Triple Assessment

Triple assessment is a multi-disciplinary assessment involving radiological screening, clinical examination and biopsy. The assessment team consists of a radiologist, surgeon and pathologist, organised such that all facets of diagnosis are performed on the same day. The results of these three procedures are discussed by the multi-disciplinary team and a management plan decided.

A triple assessment allows the patient to obtain the diagnosis quickly, reducing anxiety. It also prevents patient loss to follow-up between the three assessments.

Implementation of Breast Cancer Screening

Breast cancer screening has been proven to be most effective in women between the ages of 50 and 70 years with a 20 to 35 percent reduction in mortality due to breast cancer.²⁶ This equates to approximately one life saved for every 500 women screened. It is for this reason that most national breast cancer screening programmes target women aged 50 to 69 years. Women aged 40 to 49 years have also been shown to benefit from breast cancer screening, but the advantage is less than that seen in older age groups. This decreased advantage can be explained by denser breast tissue in younger women, decreased sensitivity of the mammograms and by cancers which are less frequent but faster growing.⁵ Therefore, the higher growth rate of these cancers requires more frequent screening.² Current estimates indicate that 500 to 1,800 women aged 40 years need to be screened to prevent one breast cancer death after 14 to 20 years.⁵ There is insufficient evidence in women over the age of 70 years to conclude whether there is screening efficacy within this group.²⁶

The frequency of mammography for national screening is under debate. Many of the trials proving screening programme efficacy involved annual screening.^{5, 26} However, recent evidence from a Copenhagen study using a screening interval of two years showed a 37 percent reduction in breast cancer mortality in participating women.²⁷ Currently in Ireland, every woman between 50 and 64 years is offered screening every two years.²⁸ In the UK the national screening programme offers mammography every three years for women aged 50 to 64 years and it was recommended that this be extended to 70 years by the year 2004.²⁹

Debate over shortening of breast cancer screening intervals in the UK from three years to two years has centred on the issue of cost-effectiveness. The cost of the current NHS programme is £40 million per year, giving an estimated cost of a life-year gained at £2522. It has been calculated that the marginal cost per life-year gained by reducing the interval from three to two years is £3,545, following a 15.3 percent reduction in mortality.³⁰

Quality assurance for radiological interpretation of mammograms is essential within a national screening programme. It is recommended that the radiologists interpreting the mammograms should have specific training. Also, there are guidelines that recommend a minimum number of mammograms that a radiologist should interpret each year to maintain proficiency. Currently, in the UK this is 5,000 mammograms compared with 480 mammograms in the US.⁵

High Risk Screening Groups

Fifteen to 20 percent of breast cancers occur with a strong family history, attributable to breast cancer susceptibility genes BRCA1 and BRCA2. Women who carry mutations in these genes have up to an 80 percent risk of developing breast cancer. In addition, these cancers tend to develop at a younger age. Assessment of breast cancer risk can be predicted by the Gail method. The Gail method risk factors include age of menarche, age of first live birth, previous breast biopsies, presence of atypical hyperplasia and number of first degree relatives with breast cancer. Patients with predicted high risk through family history often undergo genetic screening for the BRCA1 and BRCA2 genes as this will strongly affect outcome and management plan.

Recommendations for breast cancer screening currently employed within Ireland and the UK, at a frequency of every two to three years, may be insufficient for this high risk group. In fact, yearly mammography starting between the ages of 25 and 35 years may also be an ineffective screening strategy. These BRCA gene-driven cancers are highly proliferative, often being detected as high-grade lesions on annual screening mammography. This high risk group may be better managed with prophylactic chemotherapy.³¹ Furthermore, screening using mammography and clinical examination was found to be less sensitive in carriers of BRCA1 and BRCA2 compared to the general population. MRI screening may be more sensitive but requires further evaluation.³²

Screening Method-Associated Benefits and Drawbacks

There are a number of associated benefits, as well as drawbacks for screening of breast cancer. The most obvious benefit is decreased mortality. Also, for a woman with normal screening results there is the reassurance of a negative outcome. It has been proposed that early diagnosis of breast cancer

results in excess years as a patient and may diminish quality of life. However, this has not been reported in practice.² The screening procedure itself causes anxiety, pain and discomfort. These disadvantages are especially true for mammography and biopsy. Also, the radiation from mammography is carcinogenic. A calculation of benefit to harm ratio indicates that for every life lost due to radiation exposure from mammography, fifty lives are saved due to early detection of breast cancer.³³ This benefit to harm ratio is augmented as the prevalence of cancer increases with age. Other concerns of tumour dissemination following biopsy have arisen, however, the significance clinically is unclear.⁵

CONCLUSION

As breast cancer is the leading cause of cancer related deaths in European women it is essential

that effective screening programmes are established to detect early disease and thus improve outcome. Mammography remains the most effective screening tool available with an overall sensitivity of 75 percent and specificity of 93 percent. The proven efficacy of mammography in decreasing mortality outweighs the side effects of anxiety, pain and radiation exposure, particularly in the age group of 50 to 70 years, who experience a 20 to 35 percent reduction in mortality with screening. Further correctly conducted studies are required to clarify the optimal screening frequency, taking into account both mortality rate and cost-effectiveness. In addition, an evaluation of how best to manage patients with a high-risk of breast cancer is required.

REFERENCES

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005;16:481-8.
2. Blamey RW, Wilson AR, Patnick J. ABC of breast diseases: screening for breast cancer. *BMJ* 2000;321:689-93.
3. Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000;355:129-34.
4. Elmore JG, Miglioretti DL, Carney PA. Does practice make perfect when interpreting mammography? Part II. *J Natl Cancer Inst* 2003;95:250-2.
5. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005;293:1245-56.
6. Concise Colour Medical Dictionary. In: Martin E, ed: Oxford University Press, 1998.
7. Hayes C, Fitzpatrick P, Daly L, Buttner J. Screening mammography re-evaluated. *Lancet* 2000;355:749; author reply 752.
8. Law M, Hackshaw A, Wald N. Screening mammography re-evaluated. *Lancet* 2000;355:749-50; author reply 752.
9. Leung GM, Lam TH, Hedley AJ. Screening mammography re-evaluated. *Lancet* 2000;355:750-1; author reply 752.
10. Miller AB, Baines CJ, To T, Wall C. Screening mammography re-evaluated. *Lancet* 2000;355:747; author reply 752.
11. Moss S, Blanks R, Quinn MJ. Screening mammography re-evaluated. *Lancet* 2000;355:748; author reply 752.
12. Nystrom L. Screening mammography re-evaluated. *Lancet* 2000; 355:748-9; author reply 752.
13. Rozenberg S, Liebens F, Ham H. Screening mammography re-evaluated. *Lancet* 2000;355:751-2; author reply 752.
14. Baum M. Screening mammography re-evaluated. *Lancet* 2000;355:751; author reply 752.
15. Cates C, Senn S. Screening mammography re-evaluated. *Lancet* 2000;355:750; author reply 752.
16. Duffy SW, Tabar L. Screening mammography re-evaluated. *Lancet* 2000;355:747-8; author reply 752.
17. Vainio H BF. Breast Cancer Screening. IARC Handbooks of Cancer Prevention. Vol. 7. Lyon: IARC Press, 2002:248.
18. Freedman DA, Petitti DB, Robins JM. On the efficacy of screening for breast cancer. *Int J Epidemiol* 2004;33:43-55.
19. Smith-Bindman R, Chu PW, Miglioretti DL, et al. Comparison of screening mammography in the United States and the United Kingdom. *JAMA* 2003;290:2129-37.
20. Brown ML, Houn F, Sickles EA, Kessler LG. Screening mammography in community practice: positive predictive value of abnormal findings and yield of follow-up diagnostic procedures. *Am J Roentgenol* 1995;165:1373-7.
21. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med* 1998;338:1089-96.
22. Smith RA SD, Sawyer KA, et al. American Cancer Society guidelines for breast cancer screening: update 2003. *Cancer J Clin* 2003;53:141-69.
23. O'Malley MS, Fletcher SW. US Preventive Services Task Force. Screening for breast cancer with breast self-examination. A critical review. *JAMA* 1987;257:2196-203.
24. Kösters JP GP. Regular self-examination or clinical examination for early detection of breast cancer. *The Cochrane Database of Systematic Reviews* 2003:Art.

No.:CD003373.

25. Oestreicher N, Lehman CD, Seger DJ, Buist DS, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. *Am J Roentgenol* 2005;184:428-32.

26. Fletcher SW, Elmore JG. Clinical practice. Mammographic screening for breast cancer. *N Engl J Med* 2003;348:1672-80.

27. Olsen AH, Njor SH, Vejborg I, et al. Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study. *BMJ* 2005;330:220.

28. BreastCheck, the National Breast Screening Programme (Accessed March 22, 2005, at <http://www.breastcheck.ie/>).

29. NHS Breast Screening Programme (Accessed March 22, 2005, at

<http://www.cancerscreening.nhs.uk/breastscreen/>).

30. Boer R, de Koning H, Threlfall A, et al. Cost effectiveness of shortening screening interval or extending age range of NHS breast screening programme: computer simulation study. *BMJ* 1998;317:376-9.

31. Pichert G, Bolliger B, Buser K, Pagani O. Evidence-based management options for women at increased breast/ovarian cancer risk. *Ann Oncol* 2003;14:9-19.

32. Calderon-Margalit R, Paltiel O. Prevention of breast cancer in women who carry BRCA1 or BRCA2 mutations: a critical review of the literature. *Int J Cancer* 2004;112:357-64.

33. Feig SA, Hendrick RE. Radiation risk from screening mammography of women aged 40-49 years. *J Natl Cancer Inst Monogr* 1997:119-24.