

Evidence-Based Screening and Management of Abdominal Aortic Aneurysm

Each year, approximately 10 000 Americans die of abdominal aortic aneurysm (AAA), making this condition the 14th leading cause of death in the United States. Because most of these patients die of rupture of previously undetected AAAs, many researchers advocate earlier diagnosis using screening ultrasonography. A recent meta-analysis of 4 large, randomized clinical trials suggested that population-based screening substantially reduces AAA-related mortality in selected patient groups (1–5). In light of these findings, the U.S. Preventive Services Task Force (USPSTF) and a consortium of leading professional organizations recommend 1-time screening with abdominal ultrasonography for all men age 65 to 74 years who have ever smoked (6, 7).

In this issue, late results from the Multicentre Aneurysm Screening Study (MASS) provide more compelling evidence in support of these guidelines (8). Based in the United Kingdom, this trial randomly assigned 67 770 men age 65 to 74 years to receive an invitation for screening or to not receive an invitation. At 4-year follow-up, screening was associated with a substantial reduction in AAA-related mortality (42%) but only borderline cost-effectiveness (\$44 900 per life-year gained) (1). Kim and colleagues' study, based on a mean 7-year follow-up period, shows that mortality benefits continue to accrue over the longer term in screened patients. For the first time, population-based screening was found to reduce all-cause mortality, not just AAA-related mortality—a high bar given the numerous competing mortality risks in this patient population. Because much of the cost of AAA screening is incurred up front (the screening test and treatment for large aneurysms), these longer-term benefits imply much more favorable cost-effectiveness ratios (\$19 500 per life-year based on AAA-related mortality and \$7600 per life-year based on all-cause mortality). In effect, the investment in screening and early treatment for AAA keeps paying dividends in the form of sustained improvement in life expectancy.

Results from the study probably underestimate the true benefits of screening in reducing AAA-related mortality. First, only 80% of patients invited for screening were actually tested, so apparent benefits were diluted by higher AAA-related mortality in patients who declined to be screened. Second, deaths from thoracic aortic aneurysms were included in determinations of AAA-related mortality, further diluting the apparent benefits of screening (at least in terms of relative risk reductions). Finally, deaths from ruptured AAAs usually occur outside the hospital and are frequently attributed to other causes, including ischemic heart disease. Thus, MASS investigators probably underestimated true AAA-related mortality in the unscreened group.

None of the 4 randomized clinical trials, including MASS, compared the benefits of AAA screening in smokers

and nonsmokers, so we don't have direct evidence to support limiting screening to patients who ever smoked. Of note, the USPSTF does not recommend screening men who have never smoked (<100 cigarettes in a lifetime). In supporting its recommendation, the USPSTF noted that prevalence rates in patients who never smoked were only approximately one third as high as those in men who have ever smoked. Furthermore, estimates based on statistical modeling suggested that screening only patients who ever smoked would avert 89% of AAA-related deaths, compared with strategies that target all men age 65 to 74 years. Among the counterarguments to the USPSTF exclusion recommendation is the likely small difference in the prevalence of AAAs between patients who never smoked and patients with histories of very limited cigarette use. Moreover, patients who never smoked have longer life expectancies and probably have lower surgical risks than those who smoke and thus may benefit more by early detection and repair of AAAs. Finally, because of the very favorable cost-effectiveness ratio associated with screening all men age 65 to 74 years (\$7600 per life-year gained), screening patients who never smoked might still be cost-effective, even if the average benefit was only one sixth as large as that in all men.

Screening for AAA is recommended for 65- to 74-year-old men who have ever smoked. What about screening other subpopulations? Although current USPSTF recommendations do not explicitly consider family history, American College of Cardiology/American Heart Association guidelines advise screening men older than age 60 years who have a strong family history (parents or siblings) of AAA. Although none of the randomized clinical trials has assessed screening that is specific to this group, extremely high prevalence rates of AAA in such patients (15% to 28%) seem sufficient to support screening (9, 10). Neither set of guidelines currently recommends routine screening. The evidence in men older than age 75 years and women does not support screening, and neither guideline recommends routine screening. Only 1 of the 4 population-based trials (the Western Australian trial) reported AAA-related mortality by age (4). Screening was associated with a nonsignificant trend toward increased AAA-related mortality in men older than age 75 years. Similarly, only 1 trial (in Chichester, United Kingdom) examined screening in women and found no evidence of reduced AAA-related mortality (5). Additional trials assessing AAA screening in women are not likely to take place, principally because they would require hundreds of thousands of patients to detect clinically plausible benefits. Because of the lack of strong evidence or the prospect of it, we will have to individualize decisions about screening women for AAA. In addition to patients with a strong family history for AAA, women with multiple comorbid conditions associated with increased

AAA prevalence, including hypertension, coronary disease, and chronic obstructive pulmonary disease, may be reasonable candidates for screening.

Another article in this issue focuses on surgical treatment for patients with AAAs (11). Although many clinicians consider AAA growth rates and other risk factors when making decisions regarding the timing of surgical intervention, the emerging consensus is that most patients with small AAAs should receive ultrasonography surveillance until the aneurysm reaches 5.5 cm in diameter. For patients requiring surgery, the merits of endovascular repair over traditional open repair are hotly debated. Although the former reduces costs of intensive care, hospital days, and blood transfusions associated with the procedure itself, Lederle and coworkers (11) confirm that endovascular repair is much more expensive overall. The higher costs of endovascular repair seem to result from the cost of the graft prosthesis, the need for longitudinal graft surveillance, and substantially higher rates of late reintervention. Although reintervention rates have improved considerably over time, 1 recent trial showed that 14% of patients undergoing endovascular repair required second procedures within 4 years (12). Endovascular repair is associated with lower perioperative mortality but does not improve overall survival or quality of life. Lederle and colleagues concluded that endovascular repair of large AAAs is not cost-effective.

Nonetheless, it would be premature to write the epitaph for endovascular repair of AAAs. By 2003, almost half of all elective AAA repairs in the United States were performed by using endovascular techniques (13); that proportion is no doubt substantially higher today. American patients and surgeons share a strong affinity for new technologies that they perceive to reduce the invasiveness, immediate risks, and recovery time associated with surgery, even if the technologies are more expensive and are not associated with better long-term outcomes (for example, percutaneous coronary interventions vs. bypass surgery for multivessel coronary heart disease and laparoscopic surgery vs. open surgery). Moreover, the costs and benefits of endovascular surgery are subject to change. Prices for endovascular graft prostheses, which generally exceed \$10 000, may decrease over time in response to competition among suppliers or pressure from payers or providers. Historically, new surgical techniques and devices have improved over time substantially after their introduction, reducing costs and improving outcomes in the process.

The 2 studies support a more evidence-based approach for detecting and managing AAAs. With regard to screening, current evidence on the benefits of screening men age 65 to 74 years, particularly those who have ever smoked, is sufficiently strong to suggest that this practice should evolve from guideline to quality indicator status. Thus, AAA screening should be considered along with breast cancer screening, medical therapy for hyperlipemia, and other accepted preventive measures that now are being used as quality measures in pay-for-performance and other large-scale quality improvement initiatives. Regarding treatment, current data suggest caution

in the dissemination of endovascular repair, at least until it can be made less expensive and its outcomes are more durable.

John D. Birkmeyer, MD
Gilbert R. Upchurch Jr., MD
University of Michigan
Ann Arbor, MI 48104

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: John D. Birkmeyer, MD, M-SCORE, 211 North 4th Avenue, Ann Arbor, MI 48104; e-mail, jlbirkmey@med.umich.edu.

Ann Intern Med. 2007;146:749-750.

Current author addresses are available at www.annals.org.

References

1. Multicentre Aneurysm Screening Study Group. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet*. 2002;360:1531-9. [PMID: 12443589]
2. Fleming C, Whitlock EP, Beil TL, Lederle FA. Screening for abdominal aortic aneurysm: a best-evidence systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2005;142:203-11. [PMID: 15684209]
3. Lindholm JS, Juul S, Fasting H, Henneberg EW. Hospital costs and benefits of screening for abdominal aortic aneurysms. Results from a randomised population screening trial. *Eur J Vasc Endovasc Surg*. 2002;23:55-60. [PMID: 11748949]
4. Norman PE, Jamrozik K, Lawrence-Brown MM, Le MT, Spencer CA, Tuohy RJ, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *BMJ*. 2004;329:1259. [PMID: 15545293]
5. Scott RA, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. *Br J Surg*. 1995;82:1066-70. [PMID: 7648155]
6. U.S. Preventive Services Task Force. Screening for abdominal aortic aneurysm: recommendation statement. *Ann Intern Med*. 2005;142:198-202. [PMID: 15684208]
7. American Association for Vascular Surgery/Society for Vascular Surgery. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)—summary of recommendations. *J Vasc Interv Radiol*. 2006;17:1383-97; quiz 1398. [PMID: 16990459]
8. Kim LG, Scott RA, Ashton HA, Thompson SG, for the MASS Study Group. A sustained mortality benefit from screening for abdominal aortic aneurysm. *Ann Intern Med*. 2007;146:699-706.
9. Darling RC 3rd, Brewster DC, Darling RC, LaMuraglia GM, Moncure AC, Cambria RP, et al. Are familial abdominal aortic aneurysms different? *J Vasc Surg*. 1989;10:39-43. [PMID: 2787414]
10. Webster MW, Ferrell RE, St Jean PL, Majumder PP, Fogel SR, Sreed DL. Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. *J Vasc Surg*. 1991;13:9-13; discussion 13-4. [PMID: 1987400]
11. Lederle FA, Kane RL, MacDonald R, Wilt TJ. Systematic review: repair of unruptured abdominal aortic aneurysm. *Ann Intern Med*. 2007;146:735-41.
12. EUROSTAR Collaborators. Secondary interventions following endovascular abdominal aortic aneurysm repair using current endografts. A EUROSTAR report. *J Vasc Surg*. 2006;43:896-902. [PMID: 16678679]
13. Cowan JA Jr, Dimick JB, Henke PK, Recrenwald J, Stanley JC, Upchurch GR Jr. Epidemiology of aortic aneurysm repair in the United States from 1993 to 2003. *Ann N Y Acad Sci*. 2006;1085:1-10. [PMID: 17182917]

Annals of Internal Medicine

Current Author Addresses: Drs. Birkmeyer and Upchurch: M-SCORE,
211 North 4th Avenue, Ann Arbor, MI 48104.

Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial

Sue M Moss, Howard Cuckle, Andy Evans, Louise Johns, Michael Waller, Lynda Bobrow, for the Trial Management Group*

Summary

Background The efficacy of screening by mammography has been shown in randomised controlled trials in women aged 50 years and older, but is less clear in younger women. A meta-analysis of all previous trials showed a 15% mortality reduction in invited women aged 40–49 years at study entry, but this finding could be due in part to screening of women after age 50 years. The Age trial was designed to study the effect on mortality of inviting women for annual mammography from age 40 years.

Methods 160 921 women aged 39–41 years were randomly assigned in the ratio 1:2 to an intervention group of annual mammography to age 48 years or to a control group of usual medical care. The trial was undertaken in 23 NHS breast-screening units in England, Wales, and Scotland. The primary analysis was based on the intention-to-treat principle and compared mortality rates in the two groups at 10 years' follow-up. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN24647151.

Findings At a mean follow-up of 10·7 years there was a reduction in breast-cancer mortality in the intervention group, in relative and absolute terms, which did not reach statistical significance (relative risk 0·83 [95% CI 0·66–1·04], $p=0\cdot11$; absolute risk reduction 0·40 per 1000 women invited to screening [95% CI –0·07 to 0·87]). Mortality reduction adjusted for non-compliance in women actually screened was estimated as 24% (RR 0·76, 95% CI 0·51–1·01).

Interpretation Although the reduction in breast-cancer mortality observed in this trial is not significant, it is consistent with results of other trials of mammography alone in this age-group. Future decisions on screening policy should be informed by further follow-up from this trial and should take account of possible costs and harms as well as benefits.

Introduction

Screening women from age 50 years by mammography has been shown in randomised controlled trials to reduce mortality from breast cancer by around 25% in those offered screening.¹ Although efficacy of mammography in women younger than 50 years is less certain, evidence from long-term follow-up of some randomised controlled trials has increasingly suggested a benefit of screening in this age-group. The Malmö Mammographic Screening Trial, which included two cohorts of women aged 45–49 years and 43–49 years at entry, invited for screening by mammography at 18–24 month intervals, showed a significant 36% reduction in breast-cancer mortality in the combined intervention groups at an average follow-up of 15·5 years and 10 years for the two cohorts in this age-group;² however, when the cohorts were analysed separately with a different model the results were non-significant.¹ The Gothenburg trial,³ which invited women aged 39–49 years at entry for mammography at an 18 month interval, showed a significant 44% reduction in the intervention group at 14 years of follow-up. Table 1^{1,3–7} shows the details of previous randomised trials. Various meta-analyses of these trials have been undertaken;^{8–11} one that included trials of screening by mammography alone estimated a 19% reduction in breast-cancer mortality in women aged 40–49 years at entry (relative risk 0·81, 95%

CI 0·65–1·01),¹² similar to the findings of an updated Swedish overview, which did not include the Kopparberg group of the Two County study.¹ A meta-analysis¹¹ of all trials showed a significant 15% reduction in breast-cancer mortality (0·85, 0·73–0·98) in women aged 40–49 years at entry who were invited to screening. Many countries have now introduced population-based screening, and whereas most programmes include women from age 50 years, several include younger women too.

Most previous trials have not been designed specifically to study the effect of screening in younger women, and where women younger than 50 years at study entry have been included, to what extent any benefit in these women was due to screening after they reached age 50 years is unclear. A trial in Canada, in which women aged 40–49 years were randomly assigned either annual mammography and physical examination or usual care after an initial physical examination, with all women being taught self examination of their breasts, showed no effect of mammography at 13 years of follow-up, although the confidence intervals were wide⁷ and concerns have been expressed about the quality of mammography in this trial and the use of a volunteer population.¹⁴

The Age trial was designed specifically to overcome these issues by studying the effect of annual invitation to mammography starting at age 40 years, compared with

Lancet 2006; 368: 2053–60

See [Comment](#) page 2035

*Members of the Trial Management Group are listed at the end of the report

Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton, UK (S M Moss PhD, L Johns MSc, M Waller MSc); Reproductive Epidemiology, University of Leeds, Leeds, UK (H Cuckle DPhil); Nottingham Breast Institute, City Hospital, Nottingham, UK (A Evans FRCR); and Department of Histopathology, Addenbrookes Hospital, Cambridge, UK (L Bobrow FRCPath)

Correspondence to: Sue Moss, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton, UK sue.moss@icr.ac.uk

| | Screening interval (months) | CBE included | Study recruitment | Length of follow-up (years) | Age range at entry (years) | Relative risk of breast-cancer mortality (95% CI) |
|---------------------------|-----------------------------|--------------|-------------------|-----------------------------|----------------------------|---|
| HIP ^a | 12 | Yes | 1963–66 | 18 | 40–49 | 0.77 (0.53–1.11) |
| Ostergotland ^a | 24 | No | 1978–81 | 17 | 38–49 | 1.05 (0.64–1.71) |
| Kopparberg ^a | 24 | No | 1976–78 | 17 | 40–49 | 0.76 (0.42–1.40) |
| Malmö I ^a | 18–24 | No | 1976–78 | 19 | 45–49 | 0.74 (0.44–1.25) |
| Malmö II ^a | 18–24 | No | 1978–90 | 12.7 | 43–49 | 0.65 (0.39–1.08) |
| Gothenburg ^a | 18 | No | 1982–84 | 13 | 39–49 | 0.56 (0.34–0.91) |
| Stockholm ^a | 28 | No | 1981–83 | 15 | 39–49 | 1.52 (0.80–2.88) |
| Edinburgh ^b | 24 | Yes (annual) | 1978–81 | 14 | 45–49 | 0.83 (0.54–1.27) |
| NBSS ^c | 12 | Yes | 1980–85 | 12 | 40–49 | 0.97 (0.74–1.27) |

CBE=clinical breast examination.

Table 1: Randomised trials of breast screening in women younger than 50 years

an uninvited control group. The women in the control group will receive their first invitation between the ages of 50 years and 52 years, as is policy in the NHS breast-screening programme. In 2005, we published results on the predicted reduction in breast-cancer mortality in the intervention group based on surrogate outcomes measures¹⁵ using the pathological characteristics of cancers in both groups to calculate three prognostic indices: the Nottingham Prognostic Index (NPI)¹⁶ and indices developed from the Swedish Two County Study¹⁷ and the Edinburgh randomised trial of breast cancer screening.¹⁸ These indices were used to calculate the predicted number of women dying from breast cancer within 10 years of date of entry in each group of the trial. We present here the first results for observed breast-cancer mortality.

Methods

Patients and procedures

The design of the study has been described in detail elsewhere.¹⁹ Briefly, 160 921 women aged 39–41 years were

randomly assigned between 1991 and 1997 to either an intervention group or a control group in a ratio of 1:2. The trial was undertaken in 23 NHS breast-screening units in England, Wales, and Scotland. Women were identified from lists of patients of general (family) practitioners (GPs) held on local Health Authority databases, and individual randomisation was carried out stratified by GP practice. A prior notification list was prepared by the Health Authority for each GP who could remove before randomisation women for whom it was inappropriate to invite for screening, such as those under care for breast cancer. From 1992 onwards, randomisation and allocation to trial group were carried out on the Health Authority computer system with specifically written software. Before this, for women in three early centres to join the trial, random numbers generated from the coordinating centre computer were applied to GP lists provided by the Health Authority. The trial-group code was then held on each woman's record at the Health Authority and details were sent in batches to the screening centres where screening invitations were generated for those in the intervention group. In a mammography screening trial, it is not possible to blind the screening centres to intervention status. Stratification by GP practice ensured a similar distribution by geographical area in each group of the trial. The average age of women at randomisation was 40.4 years in both the control and intervention groups.²⁰

Women in the intervention group were offered annual screening by mammography up to and including the calendar year of their 48th birthday; those in the control group received usual medical care. Ethics approval was obtained from London (formerly North Thames) Multicentre Research Ethics Committee. Women in the control group received no information about the trial. It was judged acceptable at the time to have an uninvited control group who were unaware of their inclusion in the trial, since such a group is no different to a geographically distinct population who are followed up to monitor cancer incidence and mortality and who are receiving the usual standard of care for the general population. All women in the intervention group were sent an information leaflet

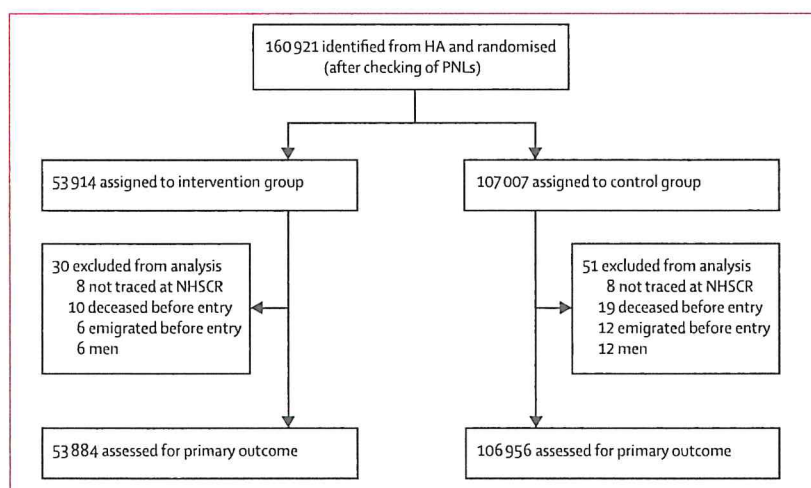


Figure 1: Flow diagram of the progress through the phases of the trial
PNL=prior notification list.

about the trial with their letter of invitation and acceptance of the invitation to attend screening was taken as informed consent to participate.

The original intention was to offer women in the intervention group seven annual screens because any additional screens would have little effect on 10-year mortality. The protocol was subsequently revised to reduce the potential 6 year interval before a woman received her first invitation in the national programme. All women in the intervention group, including previous non-responders, were re-invited annually unless they requested not to be invited again. In three centres, screening in the trial ceased prematurely (after four, five, and six rounds, respectively) because of insufficient resources to manage the additional workload. These three centres were included in the primary intention-to-treat analysis, although the effect of excluding them was also studied. Screening in the trial was by two-view mammography at first screen, and by single mediolateral oblique view thereafter, with recall for full assessment if an abnormality was suspected. All women in both groups become eligible to join the NHS breast-screening programme and would receive their first invitation between the ages of 50 years and 52 years.

The whole population has been followed up through flagging at the NHS central register (NHSCR) to determine breast-cancer incidence and mortality, mortality from all causes, and emigration.

Statistical analysis

The trial was originally designed to recruit 190 000 women to have 80% power to detect a 20% reduction in breast-cancer mortality after 10 years of follow-up at the 5% significance level. However, financial and workload constraints on NHS breast-screening units hampered recruitment and no new centres entered after 1996. In 1999, the data monitoring committee recommended that, since further accrual would result in only marginal gains in power and would delay achievement of mean follow-up times, recruitment should cease. The revised power, based on the original estimates of breast cancer mortality in the control group of 3.3 per 1000, was 72%.

Information about all deaths was obtained from the NHSCR; cause of death was taken as the underlying cause of death as coded on the death certificate. The analysis included deaths from breast cancer occurring between date of entry to the trial and Dec 31, 2004. Person-years in the intervention and control groups were calculated from date of trial entry to Dec 31, 2004, or to death or loss to

follow-up due to emigration, whichever was earliest. All screening in the trial had been completed by this date. Deaths in cases where the date of diagnosis of breast cancer preceded date of entry to the trial were excluded. Date of diagnosis was obtained from pathology laboratory records or from cancer registrations.

Cumulative mortality rates were calculated by dividing the total number of deaths from breast cancer at each year since randomisation by the total number of women in each group. This calculation provides a crude estimate of cumulative breast-cancer mortality. However, the plots of these rates reflect the decreasing completeness of follow-up with increasing time since randomisation. Nelson-Aalen estimates of the cumulative mortality were calculated as the number of breast-cancer deaths in each year since randomisation divided by the number of woman-years observed during that year and by summing these individual rates.²¹

The primary analysis was based on the intention-to-treat principle and compared the mortality rates in the whole of the intervention group with the control group. Additionally, the method described by Cuzick and co-workers²² was used to estimate breast-cancer mortality and corresponding 95% CIs in those accepting the first screening test relative to the control group, with the assumption that the underlying rate in acceptors is equivalent to that in the control group adjusted for the rate in the non-acceptors. The number needed to screen (NNS)²³ was calculated as the reciprocal of the absolute risk reduction.

This study is registered as an International Standard Randomised Controlled Trial, number 24647151.

Role of the funding source

The funding bodies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 160 921 women were randomised into the trial; more than 99.9% of these have been successfully flagged at NHSCR. The outcomes of screening in the first 10 years of the trial have been described in detail elsewhere.²⁰ Uptake of screening was 68% at the first (prevalent) screen and 69–70% in those re-invited. Overall, 81% of women attended at least one routine screen; the mean number of screens per woman was 4.5, or 5.6 for those attending at

| | Number of women | Women years | All cause deaths | | Breast cancer deaths | | Rate ratio (95% CI) intervention vs control group |
|--------------|-----------------|-------------|------------------|---------------------------|----------------------|---------------------------|---|
| | | | n | Rate per 1000 women years | n | Rate per 1000 women years | |
| Intervention | 53 884 | 578 390 | 960 | 1.66 | 105 | 0.18 | 0.83 (0.66–1.04) |
| Control | 106 956 | 1 149 380 | 1975 | 1.72 | 251 | 0.22 | |

Table 2: Mortality from all causes and from breast cancer in the intervention and control groups

| | Number of women | Women years | All cause deaths | | Breast cancer deaths | | Rate ratio* (95% CI) attenders vs control arm |
|---------------|-----------------|-------------|------------------|---------------------------|----------------------|---------------------------|---|
| | | | n | Rate per 1000 women years | n | Rate per 1000 women years | |
| Attenders | 36 538 | 394 473 | 495 | 1.25 | 68 | 0.17 | 0.76 (0.51–1.01) |
| Non-attenders | 17 346 | 183 917 | 465 | 2.53 | 37 | 0.20 | |

*Adjusted for rates in non-attenders.

Table 3: Mortality in attenders and non-attenders at first screen in intervention group

least one screen. Detection rates of breast cancer (invasive and in situ) were 1.0 per 1000 at the prevalent screen and 1.0–1.6 per 1000 at subsequent screens; they increased with successive screening rounds (and hence with age) in line with underlying incidence and did not increase greatly until the later screening rounds at ages 46 years or older.

Since this earlier publication, a further six women have been excluded from the analysis in the intervention group

(one emigration before randomisation and five mistakenly identified men) and 15 from the control group (seven emigrations and eight mistakenly identified men); 81 have now been excluded in total (figure 1).

The mean follow-up to Dec 31, 2004, was 10.7 years; follow-up ranged from 7 years to 14 years. Table 2 shows mortality in the two groups of the trial from all causes and from breast cancer. The risk of all-cause mortality in the intervention group relative to that in the control group was 0.97 (95% CI 0.89–1.04). The reduction in breast-cancer mortality in the intervention group, relative to the control group, of 17% did not reach statistical significance (RR 0.83, 95% CI 0.66–1.04). The absolute observed reduction in breast cancer mortality was 0.037 per 1000 women-years or 0.40 per 1000 women randomly assigned to the intervention group (95% CI –0.07 to 0.87).

Table 3 shows mortality in women in the intervention group according to whether they attended in response to their first invitation to screening. All-cause mortality in first screen non-attenders was significantly higher than in attenders (2.53 vs 1.25 per 1000 women-years; RR 2.01, 95% CI 1.78–2.29; $p < 0.0001$) and in women in the control group (2.53 vs 1.72 per 1000 women-years; RR 1.47, 1.33–1.63, $p < 0.0001$; tables 2 and 3). Breast cancer mortality in the non-attenders did not differ from that in the control group (0.20 vs 0.22 per 1000 women-years; 0.92, 0.63–1.30). After adjustment for non-attendance at the first screen there was a 24% reduction in breast cancer mortality in women accepting their first invitation (table 3). The absolute reduction was 0.59 per 1000 (95% CI –0.11 to 1.28) women attending (who were at slightly increased risk) or 0.56 per 1000 women attending, adjusted for selection bias.

There was no evidence of heterogeneity between screening units, either when analysed individually ($\chi^2 = 11.17$, $p = 0.97$) or when grouped into those where the number of screens per woman (including all trial screens) was above or below the mean of 4.87 ($\chi^2 = 0.08$, $p = 0.78$). Exclusion of the three centres where screening in the trial ceased prematurely²⁰ gave a similar estimated mortality reduction. Figure 2 shows the crude cumulative breast cancer mortality in the two trial groups by time since entry to the trial. Figure 3 shows the Nelson-Aalen estimate of cumulative breast cancer mortality. The curves begin to diverge after 3 years of follow-up but appear to converge again after around 10 years; however, the

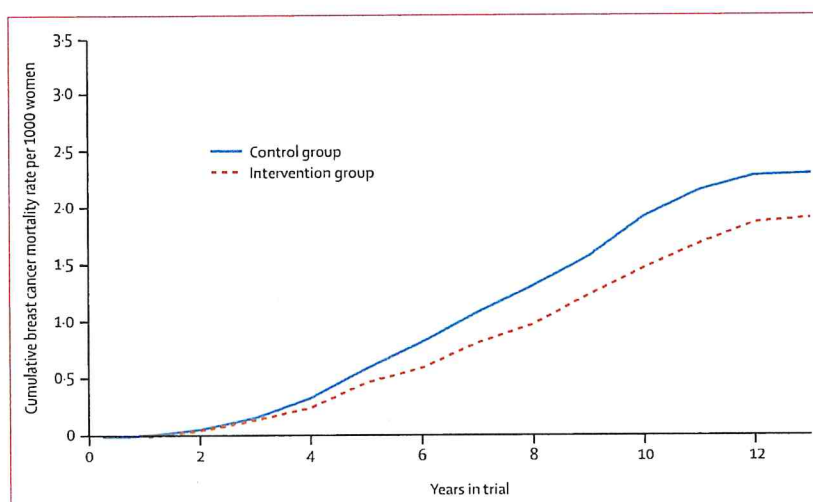


Figure 2: Cumulative breast cancer mortality

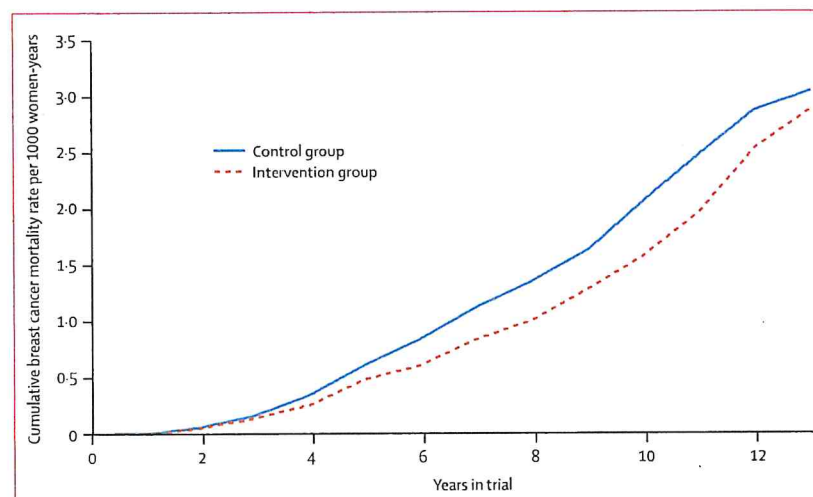


Figure 3: Nelson-Aalen estimate of cumulative breast cancer mortality

| | Women years | Intervention | | Women years | Control | | Rate ratio (95% CI) intervention vs control group |
|------------|-------------|--------------|------------------------------|-------------|---------|------------------------------|--|
| | | n | Rate per 1000 women years | | n | Rate per 1000 women years | |
| 0-5 years | 267 930 | 26 | 0.10 | 532 206 | 65 | 0.12 | 0.79 (0.48-1.27) |
| 5-15 years | 310 460 | 79 | 0.25 | 617 173 | 186 | 0.30 | 0.84 (0.64-1.10) |

Table 4: Breast cancer mortality in intervention and control groups by time period

women-years of follow-up beyond 10 years is small at present.

Table 4 shows the breast cancer mortality in the first 5 years from date of entry and at 5-15 years of follow-up. There was no significant difference between the effect of invitation to screening on breast-cancer mortality in the two periods. Although some of those women with more than 10 years of follow-up (in both groups of the trial) will have been invited for their first screen as part of the NHS breast-screening programme by Dec 31, 2004, such screening would not yet be expected to have an influence on breast cancer mortality. Screening in the intervention group continued for 8-9 years, and after excluding deaths in individuals diagnosed with breast cancer in both groups after 10 years of follow-up, the mortality reduction is 19% (RR 0.81, 95% CI 0.64-1.02).

The analysis based on surrogate outcome measures using the pathological characteristics of cancers in both groups to calculate prognostic indices, indicated a 10-11% reduction in breast cancer mortality at 10 years from date of entry.¹⁵ We have therefore repeated both the surrogate analysis and that of observed mortality restricted to those women with dates of entry before Jan 1, 1995, who have the potential for 10 years of follow-up. The relative risk of observed mortality from breast cancer was 0.79 (95% CI 0.60-1.06) compared with a predicted reduction based on surrogate outcome measures of 10-14%, depending on the prognostic index used. The surrogate analysis was based only on those cases diagnosed up to Dec 31, 1999, and part of the difference between the surrogate and observed results is due to breast cancer deaths in cases diagnosed since Dec 31, 1999. If these are excluded the relative risk of observed mortality from breast cancer was 0.81 (95% CI 0.58-1.11).

The number needed to screen (NNS) to prevent one death over 10 years was 2512 (95% CI 1149 to -13 544) for 7-9 years. In practice, women in the intervention group received an average of seven invitations, so that this figure is equivalent to approximately 17 600 invitations. A negative number needed to screen at the upper end of the confidence interval indicates the non-significance of the rate ratio. This estimate is more favourable when the analysis is restricted to women with the potential for 10 years of follow-up and breast cancer deaths within 10 years (NNS 2315, 95% CI 1059 to -12495).

Discussion

This trial did not find a significant reduction in breast cancer mortality in women offered annual screening between the ages of 40 years and 48 years. The trial was designed specifically to look at the effect on breast-cancer mortality of inviting women to screening from age 40 years compared with invitation from age 50 years as in the current NHS breast-screening programme. This approach was used to avoid the problem present in previous trials in which some women reached age 50 years shortly after entry, and to provide results relevant to decisions on public-health policy.

The power of the trial to show a reduction was diminished both by the smaller than planned sample size and by the lower than anticipated mortality from breast cancer in the control group (2.35 per 1000 vs 3.3 per 1000), resulting in a revised power of 60% to detect a 20% mortality reduction, and the CI does not exclude a reduction of 34% or an increase of 4%. The lower than expected mortality in the control group is probably due to improvements in treatment and survival since the initial calculations were made. Around 13% of all deaths in the control group were due to breast cancer and the 3% reduction in all-cause mortality in the intervention group (RR 0.97 95% CI 0.89-1.04) was consistent with a 17% reduction in deaths from breast cancer.

The estimated mortality reduction in women accepting their first invitation was 24%, with those not accepting being at a slightly lower risk than the control arm. A higher mortality from all causes in non-acceptors of screening than in either acceptors or controls has been observed in other screening trials.²⁴

The reduction in mortality from breast cancer in the intervention group becomes apparent relatively soon after the start of the trial, consistent with a shorter lead time in this age group than in women aged 50 years and over. Although the effect seems to be reduced slightly with longer follow-up, there is relatively little follow-up beyond 10 years at present. The later screens in the trial took place at 7-8 years from date of entry, and the effect of these screens is unlikely to have emerged yet. Furthermore, the percentage of women who are screened out of the total number randomised to the intervention group (as opposed to the uptake of invitation) falls in later years due to women moving out of the areas included in the trial and therefore no longer being invited for screening. By the fourth screening round the

percentage of all women randomised to the intervention group who were screened had fallen to 58%. In a national screening programme all women would continue to be invited, irrespective of movement around the country, and the effect of intervention would therefore be expected to be greater than reported here.

The observed mortality reduction remains larger than that previously predicted based on surrogate outcome measures, even when the tumour population and follow-up are restricted to make the two analyses as comparable as possible. Morrison²⁵ has suggested that use of surrogate endpoints could lead to an under estimate of the effect of screening. Improvements in treatment since the time when the prognostic indices were validated might also have increased the potential benefit of earlier diagnosis by screening.

In a number of cancer screening trials, review of case notes is undertaken to improve ascertainment of cause of death. Use of underlying cause of death from the death certificate could potentially cause bias in either direction. Treatment of early cancers by lumpectomy and radiotherapy might increase the likelihood that deaths among screen-detected breast cancers will be misclassified as death from other causes,²⁶ thus biasing the results in favour of screening. Conversely, because breast cancer is more likely to be diagnosed in the intervention group of a screening trial, deaths in this group are more likely to be attributed to breast cancer, resulting in a bias against screening.²⁷ However, a previous UK trial of screening for breast cancer, in which verification of cause of death was undertaken, concluded that certified underlying cause of death was an adequate endpoint.²⁸ That trial found an almost equal number of errors in either direction when verified cause of death was compared with that from the death certificate, with an overall bias of less than 1%. Similar findings have been reported from Sweden.²⁹

We have not attempted to adjust for contamination of the control group by private screening, but the evidence we have suggests that the extent of such screening is small.²⁰ Any such contamination would reduce the observed benefit of screening in the intervention group.

There are a number of possible harmful effects of screening which need to be weighed against any beneficial effects. One potential disadvantage of mammographic screening is the risk of radiation induced breast cancer. In 2001, Law and Faulkner³⁰ calculated the ratio of detected cancers to those induced, assuming annual two-view mammography before age 50 years. Allowing for the true benefit-to-risk ratio to be lower than the ratio of detected to induced cancers and for some uncertainty in the cancer induction risk factors, they estimated that this ratio would exceed 1, and hence the benefit of screening would probably outweigh the risk for women down to age 40 years for all but 2% of women receiving the higher dose.

In the present trial the use of single-view mammography after the first screen reduced the dose received. The average received dose in the trial based on samples from

participating centres was about 7% higher than those for older women in the NHS breast screening programme,³¹ probably due to increased breast density; assuming that 5% of screens other than the first are by two views, the number of cancers induced per 1000 women screened between 40 years and 49 years is reduced by a factor of around 0.75, whereas our detection rates are some 30% higher than assumed by Law and Faulkner, thus increasing the benefit-to-risk ratio by a factor of 1.7. The percentage of women for whom the risk might outweigh benefit as estimated by this method will therefore be very small.

Whereas a study has estimated the potential harmful effect of mammographic screening due to radiation exposure to be higher in this age-group than previously estimated,³² our estimated benefit is higher than that at which their calculations suggested that harm outweighed benefit, which was a mortality reduction of below 10% in women screened annually with two-view mammography.

Other disadvantages include false positive results, which can cause increased anxiety as well as further investigations and could possibly lead to an unnecessary biopsy. In the present trial, the recall rates for assessment varied from 5% at prevalent screen to 3% at later screens. Whereas these figures are lower than those in women aged 50 years and older (and those at subsequent screens would be reduced if two views had been used), the lower cancer detection rate means that the positive predictive value will be substantially reduced. Overall, 5% of first screens and 3% of subsequent screens in the trial resulted in false positive outcomes. 17030 women in the intervention group accepted all invitations to routine trial screens and have attended at least seven screens. Of these regular attenders, 23% (3913) had at least one false positive result, compared with an estimated 12% of women older than 50 years screened regularly as part of the national programme.³³ Of these 3913, 92% (3616) were not required to undergo cytology or surgical biopsy procedures, 4% (171) required cytology only, 2% (90) required surgical biopsy only, and 1% (36) underwent both cytology and surgical biopsy.

There has been much debate over the extent of overdiagnosis of breast cancer as a result of screening.³⁴ A report by the Advisory Committee on Breast Screening in England³⁵ has estimated that one in eight women would not have had their breast cancer diagnosed if they had not gone for screening. The extent of overdiagnosis in the current trial cannot be estimated at this stage because screening in the intervention group has only recently ended and there will still be an excess of breast cancers in this group due to lead time. The cumulative incidence of breast cancer (invasive and in situ) to Dec 31, 2001, was 1.53 and 1.29 per 1000 women years in the intervention and control groups, respectively. Once all women in both groups have been invited for their first screen as part of the national programme, any overdiagnosis due to screening in the trial should be apparent.

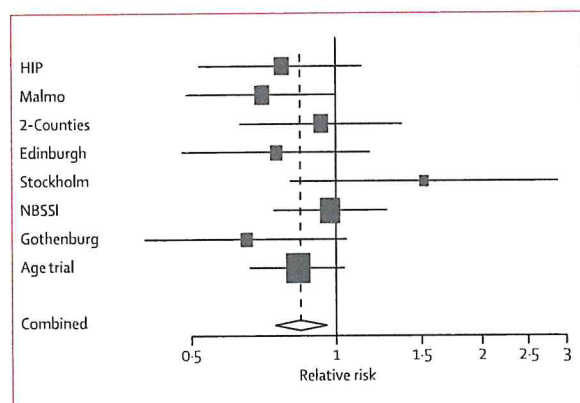


Figure 4: Breast cancer mortality results of the randomised mammography trials in women younger than 50 years

The absolute benefit of screening in this age-group in terms of deaths prevented will be lower than that in older women, but the life-years saved per death prevented will tend to be greater. If we assume an average of 35 life-years saved per death prevented and a cost of £37.50 per woman invited, the results of the trial to date suggest a cost per life year saved of £18 838 (95% CI £8620–∞), based on seven invitations per woman. The upper limit of the confidence interval was set to infinity because the absolute observed reduction in breast cancer mortality was not significant at the 5% level. This figure is higher than for other screening interventions, but remains lower than the threshold included in guidance from the National Institute for Health and Clinical Excellence.³⁵ Additionally, as discussed above, we do not believe that the full effect of screening in the trial has yet emerged, whereas the full costs are included so that this figure may be reduced in the future. The NNS is dependent on follow-up time and will decrease if the size of mortality reduction increases with increased time after the end of fieldwork.

The decision to use only single view mammography after the initial screen was taken partly because of concerns about the effects of radiation in this age-group. We have observed that sensitivity at subsequent screens seems lower than that at initial screens.²⁰ The NHS breast-screening programme now routinely uses two-view mammography at all screens and this approach has resulted both in improved detection rates and reduced recall rates.³⁶ Use of two-view mammography in younger women might result in similar benefit, although it would also increase radiation dose. Double reading of films is not policy in the NHS breast-screening programme, but most trial centres used double reading. Use of double reading could be of particular value in women with dense breasts and hence in younger women in whom dense breasts are more common.³⁷

Although the reduction in breast cancer mortality observed in this trial is not significant, it is consistent

with results of other trials of mammography alone. Table 1 summarises the previous randomised trials and the results for women younger than 50 years. Figure 4 summarises these results and those of a meta-analysis including the current trial. Including all trials, there is an overall 16% reduction in breast cancer mortality (RR 0.84, 95% CI 0.74–0.95). However, all trials except the Age trial have included women up to age 49 years at entry, so that at least some of the benefit is likely to have arisen from screening beyond age 50 years. The overview of the Swedish trials showed a 15% reduction in women aged 40–44 years at entry, the closest age-group to that in our trial, at a median of 14.7 years' follow-up. These are the only published data available we are aware of for this age-group. Combination of this result with that from our study in a meta-analysis also gives an estimated 16% reduction (RR 0.84, 95% CI 0.69–1.01). The greatest reductions in the Swedish trials were observed in Gothenburg, which had an 18 month screening interval, and in Malmo where the interval was 18–24 months. These results together with those of our study therefore lend support to the possibility that mammographic screening with an interval of 12–18 months from age 40 years could reduce breast cancer mortality by 15–17%. The use of two views and re-invitation of all women would probably have increased the efficacy observed in this trial.

Further follow-up of this trial will provide more information about the full effect of screening in this age-group. We will analyse mortality at an average of 14 years of follow-up; longer follow-up will be possible but will require censoring of breast cancer diagnoses to exclude the effect of the national screening programme from age 50 years. There is a need for research to identify more accurately, perhaps by modelling, the benefit of commencing screening at different ages below 50 years. Costs, both financial and in terms of false positive examinations, will be higher than with screening after the age of 50 years in view of the fact that the absolute risk reduction will be less in younger women.

The UK national screening programme has only recently completed the extension of invitations to age 70 years. Future decisions on screening policy should consider all possible variables, including screening frequency as well as both ends of the age range. Meanwhile it is important that individual women are provided with full information about both the possible harms and costs of screening.

Contributors

SMM and HC developed the protocol and are principal investigators for the trial and HC chairs the Trial Management Group. AE was responsible for radiological review and is a member of the Trial Management Group. LB is a member of the pathology review panel and represents the panel on the Trial Management Group. MW did the statistical analysis. LJ was responsible for data management and for assistance with the analysis. All authors have participated in planning the analysis and interpretation of the results and have seen and approved the final version.

For more on cost of breast cancer screening see <http://www.cancerscreening.nhs.uk/breastscreen/index.html#cost>

Trial Management Group

H Cuckle (Chair), T J Anderson, M Cohen, A Evans, J Hayes, E Kutt, S M Moss, B Muir, C Record, B A Thomas, I Thomas (Trial Coordinator).

Age trial centres

Avon Breast Screening, Aylesbury Breast Screening Service, Breast Test Wales, Cumbria Breast Screening Service, Epping Breast Screening Service, Greater Manchester Breast Screening Service, Hanley Breast Screening, Humberside Breast Screening Service, Newcastle Breast Screening Service, North of London Breast Screening Service, Nottingham Breast Screening, Pennine Breast Screening Programme, Peterborough Breast Imaging, Sheffield Breast Screening, South Derbyshire Breast Screening Service, South East London Breast Screening Service, South East Scotland Breast Screening Programme, Surrey Breast Screening Service, Warrington Breast Screening Service, Welcome Centre Breast Unit, West Sussex Breast Screening Service, Wiltshire Breast Screening Service, Wirral Breast Centre.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The trial is supported by grants from the Medical Research Council and Cancer Research UK and has received funding from the Department of Health and the US National Cancer Research Institute. We thank the multidisciplinary team of doctors, screening office managers, radiographers, nurses, clerical, secretarial, and computing staff working at participating trial centres, administrative staff at relevant Health Authorities, and staff at pathology laboratories, cancer registries, and regional quality assurance centres for the collection of the large volumes of clerical and clinical information required for this trial. We thank staff at the trial coordinating centre for their contributions: Derek Coleman and Nicola Kingston for data processing and analysis; Nicola Bixby and Yvonne Berg for case identification and gathering of pathology material.

References

- Nystrom L, Andersson I, Bjurstram N, Frisell J, Nordenskjold B. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002; 359: 909–19.
- Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmö Mammographic Screening Program. *J Natl Cancer Inst Monogr* 1997; 22: 63–67.
- Bjurstram N, Bjorneld L, Warwick J, et al. The Gothenburg Breast Screening Trial. *Am Can Soc* 2003; 97: 2387–96.
- Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer. Baltimore: Johns Hopkins University Press, 1988.
- Tabar L, Vitak B, Chen HH, et al. The Swedish two-county trial twenty years later: updated mortality results and new insights from long-term follow-up. *Radiol Clin North Am* 2000; 38: 625–51.
- Alexander FE, Anderson TJ, Brown HK, et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* 1999; 353: 1903–08.
- Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study 1: breast cancer mortality after 11 to 16 years of follow-up. *Ann Intern Med* 2002; 137: E305–15.
- Hendrick RE, Smith RA, Rutledge JH, Smart CR. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. *Monogr Natl Cancer Inst* 1997; 22: 87–92.
- Smart CR, Hendrick RE, Rutledge JH, Smith RA. Benefit of mammography screening in women ages 40 to 49 years: current evidence from randomized controlled trials. *Cancer* 1995; 75: 1619–26.
- Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography: a meta-analysis. *JAMA* 1995; 273: 149–54.
- Wald NJ, Chamberlain J, Hackshaw A. European Society of Mastology Consensus Conference on Breast Cancer Screening, Paris, Feb 4–5, 1993. Report of the Evaluation Committee. *Clin Oncol* 1994; 4: 261–68.
- International Agency for Research on Cancer. Breast cancer screening. Oxford, UK: Oxford University Press, 2002.
- Smith RA, Duffy SW, Gabe R, Tabar L, Yen AM, Chen TH. The randomized trials of breast cancer screening: what have we learned? *Radiol Clin North Am* 2004; 42: 793–806.
- Kopans DB, Feig SA. The Canadian National Breast Screening Study: a critical review. *Am J Radiol* 1993; 161: 755–60.
- Moss S, Waller M, Anderson TJ, Cuckle H. Randomised controlled trial of mammographic screening in women from age 40: predicted mortality based on surrogate outcome measures. *Br J Cancer* 2005; 92: 955–60.
- Blamey RW. The design and clinical use of the Nottingham prognostic index in breast cancer. *Breast* 1996; 5: 156–57.
- Tabar L, Fagerberg G, Chen HH, et al. Efficacy of breast cancer screening by age: new results from the Swedish two-county trial. *Cancer* 1995; 75: 2507–17.
- Anderson TJ, Alexander FE, Lamb J, Smith A, Forrest APM. Pathology characteristics that optimize outcome prediction of a breast screening trial. *Br J Cancer* 2000; 83: 487–92.
- Moss S. A trial to study the effect on breast cancer mortality of annual mammographic screening in women starting at age 40. *J Med Screen* 1999; 6: 144–48.
- Moss S, Thomas I, Evans A, Thomas B, Johns L. Randomised controlled trial of mammographic screening in women from age 40: results of screening in the first 10 years. *Br J Cancer* 2005; 92: 949–54.
- Breslow NE, Day NE. Statistical methods in cancer research, vol 1: the analysis of case-control studies. *IARC Sci Publ* 1980; 32: 5–338.
- Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med* 1997; 16: 1017–29.
- Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ* 1998; 317: 307–12.
- Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002; 50: 840–44.
- Morrison AS. Intermediate determinants of mortality in the evaluation of screening. *Int J Epidemiol* 1991; 20: 642–50.
- Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; 358: 1340–42.
- Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002; 94: 167–73.
- Chamberlain J, Coleman D, Ellman R, Moss S. Verification of the cause of death in the trial of early detection of breast cancer. *Br J Cancer* 1991; 64: 1151–56.
- Nystrom L, Larsson L-G, Rutqvist L-E, et al. Determination of cause of death among breast cancer cases in the Swedish randomized mammography screening trials: a comparison between official statistics and validation by an endpoint committee. *Acta Oncol* 1995; 34: 145–52.
- Law J, Faulkner K. Cancers detected and induced, and associated risk and benefit, in a breast screening programme. *Br J Radiol* 2001; 74: 1121–27.
- Young KC. Radiation doses in the UK trial of breast screening in women aged 40–48 years. *Br J Radiol* 2001; 74: 1121–27.
- Berrington de Gonzalez A, Reeves G. Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. *Br J Cancer* 2005; 93: 590–96.
- Advisory Committee on Breast Cancer Screening. Screening for breast cancer in England: past and future. NHSBSP Publication no.61. Sheffield, UK: NHS Cancer Screening Programmes, 2006.
- Zackrisson S, Andersson I, Janzon L, Manjer L, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ* 2006; 332: 689–92.
- National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance, 2005. <http://www.nice.org.uk/page.aspx?o=283494> (accessed Oct 16, 2006).
- Blanks RG, Bennett RL, Patnick J, Cush S, Davison C, Moss SM. The effect of changing from one to two views at incident (subsequent) screens in the NHS breast screening programme in England: impact on cancer detection and recall rates. *Clin Radiol* 2005; 60: 674–80.
- Cornford EJ, Evans AJ, James JJ, Burrell HC, Pinder SE, Wilson AR. The pathological and radiological features of screen-detected breast cancers diagnosed following arbitration of discordant double reading opinions. *Clin Radiol* 2005; 60: 1182–87.