PROTOCOL FOR A TRIAL TO STUDY THE EFFECT OF ROUTINE MAMMOGRAPHIC SCREENING STARTING AT AGE 40 ON BREAST CANCER MORTALITY (Updated June 2002)

An NCRI trial sponsored by MRC and CR UK: ISRCTN 24647151

Background

The effectiveness of screening for breast cancer by mammography in women below age 50 remains unproven, and is the subject of much debate. Despite lower mortality from the disease at younger ages, the issue is an important public health question in this country, due both to the demands of the women concerned and the possible implications for the NHS.

Whilst evidence from randomised controlled trials increasingly suggests the existence of some benefit from screening in women below age 50 at trial entry, these trials were not specifically designed to address this question, and the extent to which observed benefit results from screening in these women after they reach age 50 remains unclear. The Canadian NBSS1 trial, which was designed to compare the effect of screening by mammography and physical examination with an initial physical examination only in women aged 40-49 at entry, has suffered from low statistical power, as well as being criticised for the use of a volunteer population and doubts about the quality of mammography. The current evidence for the effectiveness of screening in women under 50 from other trials is reviewed in more detail in Appendix 1.

A number of meta-analyses of the randomised controlled trials have been performed. The most recent overview of the Swedish trials found a relative risk of 0.77 (95% CI 0.59, 1.01) in the population offered screening aged 40-49 at entry, and a recent meta-analysis of all randomised trials found a reduction of 24% in this age group if the Canadian trial was included, and 16% if it was excluded (see Appendix 1).

Reasons suggested for a lesser effect in younger women include lower sensitivity due to a tendency for younger women to have denser breasts, and a faster average growth rate in younger women necessitating more frequent screening.

This trial is restricted to cohorts of women aged 40-41 at their first possible entry into the screening programme because this avoids the problem of women reaching age 50 shortly after their entry to the study, and also because this means that the estimates obtained will be relevant to the situation where a service has been in existence for several years, as opposed to one which is newly introduced. Annual screening is offered in order to maximise the potential benefit, since if screening women aged 40-49 is effective in reducing mortality the magnitude of the effect is likely to be less than in older women. The evidence that this is so arises from studies in Sweden and the Netherlands showing that (i) the prevalence to incidence ratio is smaller (indicating less lead-time), and (ii) the incidence following a negative screen returns to 'normal' more quickly[1,2].

Possible disadvantages of screening

One of the concerns raised about regular mammographic screening from age 40 is the possible harmful effect of radiation in inducing additional breast cancers. It is generally accepted that the screening of women from the age of 50 for breast cancer, yields benefits which substantially exceed the radiation risk in terms of lives and years-of-life saved or lost. However, the screening of younger women is expected to have lower benefit-to-risk ratios. Since the trial began a number of publications have further considered the risk of breast cancer induction in screening women from age 40 to 49.

Beermsterboer et al [3] concluded that extending screening to younger women as in the UK age trial had a marginal benefit-to-risk ratio of 8:1 (i.e. 8 extra cancer deaths prevented for 1 extra cancer death induced by radiation). As expected this is much lower than for screening over 50.

Mattson et al [4] also concluded that screening in the age range 40 to 49 could result in benefit risk ratios in excess of 10. However they also warn that where higher doses are involved or benefits are lower than expected there may be much smaller net benefits.

Such studies are based on somewhat pessimistic assumptions about the risk of cancer induction and the true effect of low dose radiation is not known. Guidelines have been produced for participating centres on the need to routinely monitor dose, and to keep dose as low as possible, particularly in those women with large breasts who may be most at risk. Sample radiation doses for women in the age trial are collated nationally and have recently been reviewed[5].

False positive results: Approximately 3% of women at each screening round will have a false positive mammogram. However, with increasing use of techniques for pre-operative diagnosis, the rate of biopsy resulting in diagnosis of benign disease is now low.

Statistical power

The trial was designed to have 80% power to detect a 20% reduction in breast cancer mortality over 10 years, at the 5% significance level and using a 1-tailed test. (The use of a 1-tailed test was agreed at the time of the original protocol review to be justified on the basis that the aim of the trial was to determine the level of reduction in the intervention arm, and any result in the opposite direction would be ascribed to chance).The estimated sample size was calculated as 130,000 in the control arm and 65,000 in the intervention arm. This was based on an estimated breast cancer mortality of 3.3 per 1000 over 10 years in the control arm in an initially disease free population. It is recognised that increased use of adjuvant therapy in recent years may result in improved survival and hence lower mortality in the control arm. However it will be possible to include up to 14 years of follow up before screening in the control arm from age 50 begins to affect mortality, and this will give increased power. The 20% reduction which the trial aims to detect is that considered feasible, and important to the NHS, and is that in the whole of the intervention arm (including non-responders and those moving out of trial areas) compared with

the control arm. It thus takes into account a level of non-compliance, and control arm contamination. A reduction of 20% in the intervention arm as a whole with 70% compliance is equivalent to a reduction of 29% in those accepting screening (assuming no selection bias).

Whilst the percentage of women screened will fall over time, due largely to women moving from trial areas, this is true of all screening trials on which the likely reduction has been based.

Estimates of contamination of the control group by private screening suggest this is likely to be low.

It has now been agreed by the Trial Steering Committee that recruitment to the trial should stop with 160,000 women randomised. The DMC considered the effect of this reduced sample size in September 1999, and concluded that the current numbers provided an acceptable sample size for completion of the study, and retained 79% power to detect a (plausible) 24% mortality reduction.

Plan of Investigation

Women are randomised into two arms: an intervention arm (originally intended to be 65,000) who will be invited for annual screening by mammography, and a control arm (originally of 130,000) with no intervention.

Participating screening units are all screening as part of the NHSBSP. Two-view mammography is used for the first screen, with single-view only thereafter unless otherwise indicated. Physical examination is not performed routinely, but units may follow local policy (as for screening in the 50+ age-group) as to physical inspection by radiographers. Women in the intervention arm recalled for further assessment are assessed and, if necessary, treated according to usual practice. Most units include approximately 2,000 women in the intervention arm and 4,000 in the control arm, although some have randomised more than this.

The inclusion of any unit was subject to the approval of the Trial Management Group, and was subject to the following criteria : units should have carried out at least 5,000 mammographic examinations and achieved a prevalence detection rate of at least 4 invasive cancers per 1,000 women seen in the age group 50-64. Compliance in this age-group should be at least 60%. In centres where compliance is particularly low (and in some others), the trial population is being selected from areas with above average compliance.

The follow-up of the study will continue for 10-15 years; the primary analysis will be of breast cancer deaths in the study and control arms restricted to cases diagnosed after entry to the study.

Both study and control arm women will enter the national screening programme from age 50, and in the original protocol it was planned to offer women in the intervention arm seven annual screens, since any effects on mortality in a 10-year period would be likely to come from these screens. It has since become clear that, because of the way in which the national screening programme is organised, some women will not receive their first invitation within the programme until they are

age 52, and under the original protocol would receive their last invitation within the trial at age 46 or 47. Therefore the protocol was altered to continue inviting all women until the calendar year of their 48th birthday. Whilst this additional screening will add little power to the initial mortality analysis, it will have an impact on a 14 year analysis.

Women will therefore receive 8 or 9 invitations. Those not responding are re-invited at the next screening round unless they specifically request not to be invited.

No intervention takes place in the control arm; these women will receive their first invitation for screening in the NHS Breast Screening Programme between ages 50 and 52. Women in the intervention arm will be invited in the NHSBSP at the same time as the general population, and will be screened by two views at their first NHSBSP screen.

Ethical committee approval

The trial was approved by North Thames MREC in 1998. Local ethical committee approval was obtained by each unit. All local general practitioners in the screening offices catchment areas were also informed of the trial. It was made clear that the consent of the intervention arm women was to be obtained through the process of invitation to screening.

Randomisation

Randomisation has been carried out by the Health Authority computer software which has been specifically adapted for the trial. Individual randomisation was performed, but stratified by GP practice so that one-third of the women in any practice are allocated to the intervention arm. Women are identified for inclusion in the trial by a screening centre requesting a 'batch' of women from the HA, as is done in the national screening programme, but selected on specific years of birth. Prior notification lists are sent to general practitioners before randomisation for correction of addresses and removal of ineligible women.

All women are allocated a date of entry to the trial at the time of randomisation. The women's details, together with the trial arm code, are transferred from the HA register to the screening centre. All computer systems for centres currently participating in the trial have been amended to handle trial women.

Prior notifications

Lists of women in both the study and control arms (with no indication as to which group a woman is in) are sent to the GP's. As in the national programme, they will be asked to check addresses, and will also be given the opportunity to exclude women from invitation to screening. However, all women will remain on the population database.

Screening invitation

Women in the intervention arm are sent a letter of invitation, together with an information leaflet; both are in a standard form for the trial, although with some local variation. The letter of invitation states clearly that the woman is being asked to participate in a research trial, and her acceptance of the invitation is taken to be her informed consent to participate, although in one or two centres local ethics committees have also requested completion of written consent.

Rescreening

All eligible women in the intervention arm, including previous non-attenders, are re-invited each year, with the exception of those women who have specifically stated that they do not wish to participate. Women in whom breast cancer has been diagnosed are followed-up according to the existing protocol in each centre.

HA and screening centre computer batch specification software have been modified to enable the re-selection of intervention arm women at annual intervals. Each trial participant has a Trial Research Code which is held on both HA and screening centre computers. When a trial participant changes HA her code is transferred to the new HA with her screening records, enabling her to be recalled for screening at her new location if she moves to another participating centre. If a woman moves to a non-participating centre, she will not be re-invited for screening until she becomes eligible for the national programme at age 50-52. However, she may continue being screened at her previous screening unit on request.

The aim is to rescreen women at a 12 month interval. No woman should be rescreened less than 10 months after her previous screen; if a woman defers by more than 2 months she will not be rescreened until her next annual screen is due, in order to keep appointments in phase as far as possible.

Data Collection

The data recorded on trial women on the screening centre system are identical to those collected for women in the national programme. Detailed pathological information is also required and the co-operation of pathology laboratories, cancer registries and Regional Quality Assurance to supply reasonably complete and up-to-date data has been ensured. At regular intervals selected data are downloaded from each screening centre to the trial co-ordinating centre, where a complete database of trial women is held. These include the women's identification details (including NHS number), trial arm, dates of invitation and screening where relevant, and outcome of screening. Data on breast cancer diagnoses and deaths are obtained from screening centres where known, but more completely from other sources as described below.

Monitoring breast cancer incidence

Mortality from breast cancer will be the main endpoint of the trial. However, information on breast cancer incidence (both control arm cases, interval cases and cases in non-attenders) is of use in assessing the progress of the study before information on mortality becomes available.

Information on screen-detected cancers is included in the data downloaded to the co-ordinating centre from screening centres. Where interval cancers follow a negative screen, or cancers in the non-attenders or control arm become known to the screening programme, they are also notified to the co-ordinating centre.

All women in the trial have been flagged at the ONS Central Register and information on all cancer registrations is supplied back to the co-ordinating centre. However, it is acknowledged that there is a time-lag in obtaining complete cancer registration data, and that the reporting of non-screen detected cases by individual screening centres will vary. To ensure more complete ascertainment, details of all breast cancer cases in the appropriate age-range are identified from pathology laboratories, cancer registries and quality assurance centres, covering the trial centres, and are cross-matched with the trial population database to identify those in trial women.

Pathology Review

A review is being undertaken of the pathology of all breast cancers identified in the trial, studying in particular tumour size, histological grade and nodal status, as well as histological type.
Histopathology slides and forms are requested from the relevant pathology laboratories (includng those outside trial areas where a women has moved away) for all cases of breast cancer identified in the trial, in order that they can be independently reported on by a panel of three pathologists with considerable expertise in the breast screening field. Discussion at regular meetings of the panel enable a consensus to be reached for each case. This review is entirely a research exercise, in order to achieve a consensus on tumour characteristics, to be used in the trial analysis. It may take place several years after original diagnosis and will have no impact on patient management. The pathology review is now planned to continue until each woman has been invited for her first screen as part of the national programme.

Radiology review

The mammograms of women with screen-detected and interval cancers, and of lapsed attenders with subsequent cancer, are being reviewed, with the aim of identifying the radiological features most useful in aiding detection of cancer in women aged 40-49. Three radiologists (comprising Dr. Andy Evans and two others) review each case, and complete a standard proforma. This will also permit future correlation with pathological variables.

Monitoring breast cancer mortality

The main notification of date and cause of death in trial women will come from ONS Central Register where the whole trial population have been flagged. Additional sources of data include, deduction lists from participating HAs (which include dates but not cause of death), and information from trial centres.

Mortality Analysis

The trial is aiming to demonstrate whether deaths from breast cancer can be prevented in women below 50 by a policy of screening and if so, how many. The most valid measure of outcome is therefore a comparison of the rates of death from breast cancer in the different populations under study. For each death in which breast cancer is certified as a cause or contributory cause, the date of diagnosis will be determined, and those diagnosed prior to the woman's date of entry to the trial will be excluded. The mortality analysis will refer to a cohort of women in whom breast cancer had not been diagnosed at the start of the trial. It is proposed to carry out the first mortality analysis when there has been an average of seven years follow-up. This is likely to be reached at the end of 2001, meaning that the analysis could be carried out in the second half of 2002, allowing six months for data collection and validation. Analysis of the time since trial entry of any mortality effect will provide information on the possible benefit of starting screening at different ages.

Additional Aspects of the Trial

Pilot Study

The first two years of the trial were considered a pilot stage with two units entered in the first year and another six in the second. The aims of this two year pilot stage were:

i) to assess the level of compliance which can be achieved in this age group.

ii) to assess the extent to which the control population is 'contaminated' with screening taking place in this population.

iii) to monitor the rates of referral and of benign biopsy as a result of screening.

iv) to ensure the feasibility of the study as proposed, and to enable any alteration to practical details to be made at an early stage.

A decision to proceed with the main study was made and phased entry of new centres commenced.

Estimating control arm 'contamination'

A potential problem in the trial is the 'contamination' of the control arm by private screening. If for example 10% of the control arm were screened and the mortality reduction in this 10% were

the same as in the intervention arm, a 'true' 20% reduction in overall mortality between the two groups would be diluted to an observed 18%. If the percentage of controls screened reached 50% then the observed reduction would be only 11%. In the trial's pilot study, an assessment of the extent of contamination in women of the trial age group was made by postal survey. Questionnaires were sent to 200 women in each of three trial centres prior to their entry to the trial, targeting women who would not be randomised. The results showed that less than 6% of responders had ever had a routine mammogram and only 2% of these had one in the previous year. Similar surveys are being conducted in the trial's control population during the course of the trial.

Economic Analysis

An economic evaluation associated with the trial was funded by the MRC and carried out between December 1993 and May 1996 by a team of researchers at Brunel and Newcastle Universities (K. Johnston, K. Gerard and J. Brown). Estimates of the health service costs associated with each screening phase (invitation, screening and assessment) were estimated and their generalisability in the context of the NHS Breast Screening Programme as a whole was addressed [6 7]. These costs can be combined with trial data to give an average incremental cost per additional cancer detected and per woman screened and per life year gained. Costs incurred by the women attending for screening or for further assessment have also been estimated [8]. The project also obtained valuations for the health states associated breast cancer screening and treatment which can be used to estimated the incremental cost per quality adjusted life year gained [9, 10]. The project investigated whether the values differed according to the age of the women.

Women with a family history of breast cancer

There is increasing awareness of the risk associated with a family history of breast cancer, resulting in a number of women with such a history requesting screening at young ages, and details of women with a strong family history may be passed to one of the groups investigating this area.

Trial Management Group

The Trial Management Group currently comprises of some members of the group who drew up the original protocol (Dr. S. Moss, Professor H Cuckle, Dr. T. Anderson), the trial co-ordinator, together with representatives of NCRI, the trial's two pilot centres and three further centres. The group also includes a representative radiographer.

The Trial Steering Committee comprises;

Professor Freda Alexander (statistician, chair), Dr. Clive Wells (consultant histopathologist), Dr. Hilary Dobson (consultant radiologist). (The TSC was formed in 2000, and it was agreed with the MRC that a lay member was not required at this stage).

The Data Monitoring Committee comprises;

Dr. David Spiegelhalter (senior statistician and chair), Mr. Stephen Duffy (senior statistician), Dr. Ian Ellis (consultant histopathologist), Dr. M. Chaudary (consultant surgeon) and Dr. A. Tucker (consultant radiologist).

References

1. Peeters PH, Verbeek AL, Hendriks JH, van Bon MJ. Screening for breast cancer in Nijmegen. Report of 6 screening rounds, 1976-1986. *Int J Cancer* 1989;**43**:226-30.

2. Tabar L, Fagerberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer* 1987;**55**:547-51.

3. Beemsterboer PMM, de Koning HJ, Warmerdam PG, et al. Prediction of the effects and costs of breast cancer screening in Germany. *Int J Cancer* 1994;**58**:623-8.

4. Mattsson A, Leitz W, Rutqvist L-E.
Radiation risk and mammographic screening of women from 40 to 49 years of age: effect on breast cancer rates and years of life. *Br J Cancer* 2000;**82**:220-6.

5. Young KC. Radiation doses in the United Kingdom trial of breast screening in women aged 40 to 48. *Br J Radiol* 2001;

6. Johnston K, Gerard K, Morton A, Brown J. NHS costs for the Breast Screening Frequency and Age Trials. *HERG Discussion Paper November* 1996;**No. 16**:

7. Johnston K, Gerard K, Brown J. Analyzing center selection bias in a breast screening trial. *Int J Technol Assess Health Care* 1998;**14**:494-504.

8. Brown J, Johnston K, Gerard K, Morton A. Attending breast screening and assessment: women's costs and opinions. *Radiography* 1998;**4**:121-4.

9. Johnston K, Brown J, Gerard K, O'Hanlon M, Morton A. Valuing temporary and chronic health states associated with breast screening. *Social Sci Med* 1998;**47**:213-22.

10. Gerard K, Johnston K, Brown J. Feasibility study to investigate the use of a pre-scored multi-attribute health classification measure in valuing condition-specific health-related quality of life. *Health Econ* 1999;**8**:685-99.

APPENDIX I

EVIDENCE OF EFFICACY IN THE UNDER 50S

The benefit of mammographic screening was established principally from mortality data on women screened at age 50 or older. Whilst comparable data in young women are available from eleven published studies (see Table 1), none of them included sufficient numbers of deaths to reliably estimate the mortality effect. The randomised trials carry most weight because they avoid potentially strong selection bias, but even they present difficulties of interpretation.

Health Insurance Plan (HIP) Study Carried out in New York in the 1960's, women aged 40-64 in the screening arm were offered a series of four screens by clinical examination and mammography at annual intervals. A reduction in breast cancer mortality of 35% was found by comparison with the control arm for the first seven years of the trial with a beneficial effect persisting for up to 18 years[1]. Approximately 15,000 women in each arm were aged 40-9 at entry, and although there was a 25% reduction in breast cancer mortality in the screening arm, this did not achieve statistical significance. A recent re-analysis restricted to breast cancer cases did show statistical significance[2], but this is potentially biased. The HIP results in young women are difficult to interpret. Firstly, the lack of statistical significance does not count against a true effect. With the relatively small number s included there is a 50% chance that a true reduction as great as 30% would be missed (using a 1-sided test with a 5% significance level). Secondly, some of the reduced mortality in women aged 45-9 at entry is attributable to the cancer being detected by screening when the women were over 50. However, there was also a 36% mortality reduction in the 40-4 age group which cannot be accounted for in this way.

Swedish '2-Counties' Study This was carried out at a time when there had been technical improvements in the quality of mammography. Screening by single-view mammography only was offered to women aged 40-74 with a routine recall period of 2½-3 years at for women aged 50-74 and 2 year for younger women. Overall there was a reduction in breast cancer mortality of 30% over an average 11 year follow-up period [3]. After 13 years of follow-up there was a non-significant 13% mortality reduction in this age-

group [4]. The screening and control arms included approximately 20,000 and 15,000 women aged 40-49 respectively. Statistical power in this study was even lower than for the HIP Study: follow-up was shorter and the breast cancer mortality in the control arm was considerably lower.

Malmo, Stockholm and the Swedish overview Two other Swedish trials initially reported even less promising results among young women. In Malmo, taking the overall population aged 45-69 there was little mortality reduction for those in the study arm and when women aged 45-54 were considered mortality was in fact higher than in the control arm (approximately 8,000 in each arm) [5]. However, a more recent analysis has shown a significant 36% mortality reduction in women aged 40-49 at entry, [6], and a study in Gothenburg has shown a similar effect [7]. In Stockholm a mortality reduction was reported for the overall population aged 40-64 but, this was not the case for younger women aged 40-9 (approximately 14,000 and 7,000 in the screening and control arms respectively) [8]. Recently, a combined analysis of the Swedish studies has shown a 23% reduction in women aged 40-49 (RR 0.77, 95% CI 0.59, 1.01). [9]

Edinburgh Study Women aged 45-64 were randomized according to their GP and there appears to have been a chance allocation to the screening arm of those who were at increased risk of breast cancer [10]. Overall, a 17% mortality reduction was found after 7 years follow-up but there was little reduction in those aged 45-9 (approximately 6,000 in each arm). With a longer follow-up the mortality reduction in younger women is now 23%[11] but, as with the HIP Study, some of this may be due to screening after age 50.

Canadian Study With approximately 25,000 women aged 40-9 in each arm this is the only trial specifically designed to have sufficient power to detect a mortality benefit at young ages[12]. Beginning in 1988, all participants had a clinical examination at entry; those in the screening arm also had a mammogram at entry with both clinical examination and mammography annually thereafter for 5 years. After 11 years of follow-up there was a non significant excess breast cancer mortality in the screening arm RR(1.14, 95% CI 0.83, 1.56)[13] . It has been suggested this is due to chance occurrence of a high number of advanced tumours in this arm at entry. Also the trial has been criticised for poor quality mammography particularly in its early years.

Non-randomised studies The UK Trial of Early Detection of Breast Cancer(TEDBC)[14] compared the mortality from breast cancer in two screening centres with that in four

centres in which no screening had taken place. One of the screening centres is Edinburgh and forms the screening arm of the randomised trial. Screening by mammography and physical examination was biannual with a physical examination only in the intervening years. After 16 years follow-up the mortality reduction overall (age 45-64) was 27%, with similar results in the young women. The US Breast Cancer Detection Demonstration Project (BCDDP) was not population based. Rather open access to mammography and physical examination was provided for 5 annual screens in 29 centres. The effect on mortality has been derived by comparing the observed number of deaths in attenders with that expected from the SEER program, a research orientated registry of cases followed up for mortality[14]. Overall (age 35-74) the observed mortality was 20% less than expected. Although the effect was smaller in younger women, it almost reached statistical significance because of the size of the study (over 200 deaths in young women). The two other studies in Nijmegen[15] (age over 35) and Florence[16] (age 40-70) compared mortality in attenders with that in those who did not attend. Overall, mortality was reduced by about one-half in both centres but part of this large difference was caused by the 'healthy screenee' effect whereby those accepting the offer of screening have reduced mortality *a priori*. The same effect may also be distorting the results in the younger women.

A recent overview of the randomised trials has shown a statistically significant reduction of 18% (RR 0.82, 95% CI 0.71, 0.95) including the Canadian study [17]. Another overview has suggested a lower relative risk in this age group in trials with longer follow-up [18]. Since prognosis is more favourable than in older women very long follow-up may be needed before a mortality benefit emerges, as it did in the HIP study after 18 years. However, some studies (eg 2-Counties) have begun to offer screening to those reaching 50 thereby shortening the average length of unbiased follow-up.

Table 1 Mammographic screening in young women: effect on mortality in 11 studies

Study	Age Group	Screening Interval (yrs)	Relative risk*	(95% CI)
Randomised Trial				
HIP[1]	40-9	1	0.75	(0.52 - 1.10)
2-Counties[3]	40-9	2	0.87	(0.54 - 1.41)
Malmo[6]	40-49	1½-2	0.64	(0.45 - 0.89)
Stockholm[8]	40-9	2	1.08	(0.54 - 2.17)
Gothenberg			0.56	(0.32 - 0.98)
Swedish overview[7**]	40-9	1½-2	0.77	(0.59 - 1.01)
Edinburgh[11]	45-9	2	0.75	(0.48 - 1.18)
Canada[13]	40-9	1	1.14	(0.83 - 1.56)
Geographical Control				
UKTEDBC[19**]	45-9	2	0.70	(0.57 - 0.86
Case Control				
BCDDP[20]	35-49	1	0.89	(0.75 - 1.03)
Nijmegan[15]	34-49	2	1.25	(0.36 - 4.30)
Florence[16]	40-9	2-3	0.83	(0.37 - 1.85)

* Estimated change in breast cancer mortality given screening offered: for the case-control studies it is given screening accepted.

** Includes data from the 2-Countries, Mälmo and Stockholm trials together with a trial in Gothenberg.

*** Includes the screening arm of the Edinburgh trial.

References

1. Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer. *The Health Insurance Plan Project and its sequelae, 1963-1986*, Baltimore & London: Johns Hopkins University Press, 1988.

2. Chu KC, Smart CR, Tarone RE. Analysis of breast cancer mortality and stage distribution by age for the Health Insurance Plan clinical trial. *J.Natl.Cancer Inst.* 1988;**14**:1125-32.

3. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish Two-County Program of Mammographic Screening for Breast Cancer. *Radiol.Clin.North Am.* 1992;**30**:187-210.

4. Tabar L. Breast screening in Britain. *J.Med.Screening* 1995;**2**:179-.

5. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F *et al* . Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988;**297**:943-8.

6. Andersson, I. and Janzon, L. Reduced Breast Cancer Mortality in Women Under Age 50: Updated Results From the Malmo Mammographic Screening Program. Journal of the National Cancer Institute Monographs 22, 63-67. 1997.
Ref Type: Journal (Full)

7. Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O *et al*. The Gothenburg Breast Screening Trial. First results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization. *Cancer* 1997;**80**:2091-9.

8. Frisell, J, Lidbrink, E., Hellstrom, L., and Rutqvist, L-E. Follow up after 11 years - update of mortality results in the Stockholm mammographic screening trial. Breast Cancer Research and Treatment 45, 263-270. 1997.

9. Larsson L-G, Andersson I, Bjurstam N, Fagerberg G, Frisell J, Tabar L *et al*. Updated overview of the Swedish randomized trials on breast cancer screening with mammography: age group 40-49 at randomization. *Monogr.Natl.Cancer Inst.* 1997;**22**:57-61.

10. Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest P *et al*. Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990;**335**:241-6.

11. Alexander FE, Anderson TJ, Brown HK, Forrest APM, Hepburn W, Kirkpatrick AE *et al*. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* 1999;**353**:1903-8.

12. Miller AB, Howe GR, Wall C. The National Study of Breast Cancer Screening. Protocol for a Canadian randomized controlled trial of screening for breast cancer in women. *Clin.Invest.Med.* 1981;**4**:227-58.

13. Miller, A. B., To, T., Baines, C. J., and Wall, C. The Canadian National Breast Screening Study: Update on Breast Cancer Mortality. Journal of the National Cancer Institute Monographs 22, 37-41. 1997.

14. UK Trial of Early Detection of Breast Cancer Group. Breast cancer mortality after 10 years in the UK trial of early detection of breast cancer. *The Breast* 1993;**2**:13-20.

15. Verbeek ALM, Hendricks JHCL, Holland R, Mravunac M, Sturmans F, Day NE. Reduction in breast cancer mortality through mass screening with modern mammography (First results of the Nijmegan Project 1975-81). *Lancet* 1984;**i**:1222-4.

16. Palli D, Rosselli Del Turco M, Buiatti E, Bloggs A. A case-control study for the efficacy of a non-randomized breast cancer screening program in Florence (Italy). *Int.J.Cancer* 1986;**38**:501-4.

17. 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.

18. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. *JAMA* 1995;**273**:149-54.

19. UK Trial of Early Detection of Breast Cancer Group. 16 year mortality from breast cancer in the UK Trial of Early Detection of Breast Cancer. *Lancet* 1999;**353**:1909-14.

20. Morrison AS, Brisson J, Khalid N. Breast Cancer incidence and mortality in the Breast Cancer Detection Demonstration Project. *JNatl Cancer Inst.* 1988;**80**:1540-7.