

**CANCER SCREENING EVALUATION UNIT (CSEU)
FINAL REPORT '2006-2010'**

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INDEX

LAY SUMMARY	Page 3
OVERVIEW OF WORK PROGRAMME 2006-2010	Page 4
Objectives of the Unit	
Research programme	Page 4
<ul style="list-style-type: none">• Breast cancer screening• Cervical screening• Prostate cancer screening• Bowel cancer screening• Screening for other cancer sites• Methodological work• Screening in people at high risk of cancer	
Relevance of work programme to DH policy	Page 10
UPDATE SINCE LAST PROGRESS REPORT (FEBRUARY 2010)	Page 11
<ul style="list-style-type: none">• Breast cancer screening• Cervical screening• Prostate cancer screening• Bowel cancer screening• Screening in people at high risk of cancer	
KEY ACHIEVEMENTS 2006-2010	Page 16
<ul style="list-style-type: none">• Publications• Dissemination activities	
CONCLUSION	Page 23

ANNEX

Moss SM et al Lancet 2006; 368:2053-60.

Blanks RG et al . Br J Cancer 2009 100(11):1832-6.

Weller D et al Br.J .Cancer 2007 ;97(12):1601-5.

3. LAY SUMMARY

The aims of the Cancer Screening Evaluation Unit over the past five years have been to carry out research that will assist those making decisions about what screening programmes should be implemented, and on the best ways of carrying out such screening. Our work has been mainly involved with the four cancers (breast, cervical, bowel and prostate) for which screening programmes exist or are under consideration.

We have carried out large scale studies in order to determine how effective existing screening programmes are in terms of their main objectives, and randomised trials to study possible ways in which these programmes could be extended (e.g. by offering breast screening to women at younger ages) or implemented more effectively (e.g. by using automated technology to read cervical screening samples). We have also evaluated pilot studies (such as those of screening for bowel cancer, and the use of testing cervical samples for human papilloma virus to determine which women need referral for further investigation) that have informed decisions to implement screening or change screening policy.

4. OVERVIEW OF RESEARCH PROGRAMME

Objectives of the Unit

Screening is one of the major areas of health care for cancer in England. The breast and cervical screening programmes cost £200 million per annum, include millions of women, and are often the subject of media attention. Screening for prostate cancer is not at present NHS policy, but is increasing in frequency in the UK and has become an important health issue. A national programme for bowel cancer screening by faecal occult blood (FOB) testing was introduced in 2006.

The aims of the Unit have been to evaluate national cancer screening, both in the general population and in high risk groups, focussing on cancers where screening is already NHS policy (breast, cervix), planned for the NHS (bowel) or being conducted in NHS practice (prostate). Our programme of work for 2006-10 included large-scale cohort studies, randomised controlled trials and statistical modelling as well as evaluation using routine data.

Our programme of work during 2006-10 focused on four of the six cancers discussed in the screening section of the National Cancer Plan, and aimed to address likely developments in screening for these cancers over this period. Approximately half our effort was expended on breast cancer screening.

Studies conducted by the Unit with funding from outside the programme grant are included in this document, because a number of these were funded by DH, and all involved input from senior staff employed on the Unit programme. The sources of funding for these studies are identified.

Research programme

Breast cancer screening

Observational individual based evaluation of the efficacy of the national breast screening programme

- It is important to evaluate the actual effect of the NHS breast screening programme (NHSBSP), conducted in a service rather than a trial setting. It is difficult to estimate the magnitude of the effect of the NHSBSP on breast cancer mortality from population trends, because of the impact of other factors such as changes in treatment.
- In order to evaluate the effectiveness of the programme in meeting its primary objective and to identify factors that affect this, we started in 2003/4 a large-scale individual based cohort study linking screening information on 700,000 women in parts of England and Wales with data on their breast cancer incidence and mortality.

- This study continued to be a major component of our work throughout the period 2006-10. The primary objectives of the study are to estimate the effectiveness of the NHSBSP, as operated in recent years, in reducing the risk of death from breast cancer in women invited and screened by the programme.

Studies of factors in radiological and pathological practice

- NHSBSP policy was changed to include two view mammography at incident as well as prevalent screens in 2003, with all programmes intended to be using two views by the end of 2004. We continued to study the effect of this change on cancer detection and recall rates in the screening years 2004/5 and 2005/6.
- The unit conducted a joint project with the national screening office to design and conduct an observational study in order to evaluate the relative performance of screening programmes using radiographer film reading compared with those using only radiologists. Information on film reading practices since April 2000 was related to screening outcomes such as recall rates, cancer detection rates and positive predictive value.

Interval cancers

- Interval cancer rates are important as they provide information on the sensitivity of screening and appropriate screening intervals. Timely collection and analysis of nation-wide data on interval cancers, including time since last screen and pathology information, is an important priority for evaluation of the NHSBSP. However, the confidence with which results on interval cancers can be interpreted depends on the completeness and accuracy of data collection.
- The Unit brought together complete national data on interval cancers (for 1997/8 onwards) by 2010. Such data are of use for international comparisons of the performance of the NHS breast screening programme.

Evaluation of extension of national screening to women aged 65-70

- National extension of the screening programme to include women aged 65-70 in the invitation system began in 2001/2, with full implementation due to be achieved by the end of 2004. The Unit evaluated the performance and estimate the long-term effectiveness of this extension in order to determine whether results from the earlier demonstration studies were maintained, and to provide further estimates of long-term effectiveness.

Trial of the effect of mammographic screening starting at age 40

- This multi-centre trial began in 1991 with the aim of estimating the effectiveness of annual screening in young women. A total of 160,000 women aged 40-41 in 23 centres have been randomised, two-thirds to a control arm offered no intervention and one-third to an intervention arm offered annual screening. Analyses of surrogate outcome measures have been conducted, and a mortality analysis based on 10 years of follow up was completed in 2006.

- The Unit continued the follow up of this trial during 2006-10, with follow up funded by MRC and CRUK, to include obtaining information on all women's first screening invitation as part of the national programme, and pathology review of breast cancers diagnosed up to this point.

Work on performance measures and quality assurance

- The Unit was funded by the NHS Cancer Screening Programmes to analyse data for routine breast screening returns, develop performance measures, and collaborate with regional Quality Assurance (QA) staff on the application of these measures. This work also helped to improve data quality and provide data for further research by the Unit. The Unit was also funded to carry out the data collection and analysis for the NHS Breast Screening Pathology External Quality Assurance (EQA) Scheme.

2 Cervical screening

Observational individual based evaluation of cervical screening

- Previous work by the Unit identified considerable limitations with the use of aggregated routine data for evaluation of the cervical screening programme, and led us to develop in 2002/3 an observational individual-based cohort study.
- The cohort comprises 2.4 million women in parts of England with a total of over 6 million smear results. The study links screening information on these women with information from cancer registries and pathology laboratories on invasive cervical cancer and its precursors.
- We aimed during this period to use the study to determine the risk of invasive cervical cancer and CIN III in women between the ages of 50 and 64 who have a history of negative smears, and the risk of these in relation to frequency of screening. The study also aimed to provide important information on how the screening programme operates in practice.

Automated cytology

- Together with Professor H. Kitchener, University of Manchester, we were funded by the HTA programme to conduct a three-arm randomised controlled trial comparing automated screening technologies with manual screening, that would include a total of 100,000 liquid based cytology cervical samples. The primary objective was to determine the comparative diagnostic performance of automated and manual reading in terms of relative sensitivity, specificity and positive predictive value. The trial also examined the addition of using human papilloma virus (HPV) testing to triage women for referral, and included an economic analysis.

Quality assurance and development of performance measures

- The Unit is funded by the National Cancer Screening Programmes to undertake work on the development of performance measures for the cervical screening programme. These measures are based on annual return data, and were developed in collaboration with regional Quality Assurance staff.

Liquid based cytology/Human papilloma virus studies

- Following the evaluation by the Unit and others of the pilot studies that were set up to investigate the effect of liquid based cytology (LBC) and triage of women with borderline or mildly dyskaryotic smears according to HPV status, LBC is being implemented nationally. We undertook both evaluation of the wider implementation of HPV triage and further follow up of the previous pilot studies, with funding from the National Cancer Screening Programme.

Prostate cancer screening

- The effectiveness of screening for prostate cancer by prostate specific antigen (PSA) testing has not yet been demonstrated, and there is no organised screening programme in England. However, the use of such screening in an ad hoc manner has been increasing and is likely to continue to increase. We therefore aimed to work on the evaluation of screening both to understand its extent and socio-demographic and ethnic balance, and to improve the information available to relate the extent of screening to trends in incidence and mortality.

Study of referral rates in men with a raised level of prostate specific antigen

- In September 2000 the DH launched a Prostate Cancer Risk Management Programme (PCRMP), which provides information for GPs to assist them in the counselling of men who enquire about testing. The DH funded the Unit to conduct a study of the referral rates in asymptomatic and symptomatic men following a PSA test, in order to assess changes in these rates over time before and after the distribution of leaflets to GPs in September 2002. The study began in October 2004, in collaboration with five pathology laboratories and their associated general practices. The study was completed in September 2006.
- We also investigated the feasibility of a prospective, routine system of recording and reporting in general practice to study trends in PSA screening and variation in screening schedules between GPs.

European Randomised Study of Screening for Prostate Cancer database

- The ongoing European randomised trial of screening for prostate cancer (ERSPC) involves centres in eight countries. It is one of only two randomised trials worldwide examining the effect of routine screening by PSA testing on mortality from prostate cancer, and has recruited over 160,000 men in the core age-group, 55-69 at entry. Pooled analyses with the other trial, (the US

Prostate, Lung, Colorectal and Ovarian cancer screening trial), are also planned.

- The Unit took over the responsibility for the central database and analyses of the study in May 2003. Interim analyses were carried out during the period 2006-2010, with the first formal mortality analysis planned when data to 2008 are available. This work is funded from European grants

Bowel cancer screening

Evaluation of second round of English pilot of faecal occult blood screening

- In collaboration with Professor David Weller, University of Edinburgh, we were funded by DH to carry out the evaluation of the second round of the English pilot of screening by FOB testing taking place in Warwickshire. This evaluation was almost completed by the start of the new programme of work, but a third round of screening took place in 2005 and 2006, and we were funded to evaluate this by NHS Cancer Screening Programmes.

Evaluation of population screening for bowel cancer

- Screening by FOB testing was introduced in phases amongst men and women in their sixties from April 2006. We agreed a protocol with DH to evaluate the screening programme, including both initial evaluation in terms of performance indicators and outcome measures, and evaluation of the impact on mortality and incidence, including studying the availability of baseline data on stage-specific incidence from cancer registries and pathology laboratories.

Nottingham randomised controlled trial of faecal occult blood screening

- This randomised controlled trial, the fieldwork for which was conducted in Nottingham between 1981 and 1995, has studied the effect of biennial screening by faecal occult blood (FOB) testing on mortality from colorectal cancer. It is a collaboration between the Department of Surgery, University Hospital, Nottingham and the Unit.
- The follow up was funded by the MRC. One of the aims of longer follow up was to determine whether detection of pre-cancerous adenomas by FOB testing results in an eventual reduction in the incidence of invasive cancer in the population offered screening. Such a reduction has been observed in one trial in the US, but did not appear until 18 years of follow up.

Screening for other cancer sites

- We maintained a watching brief on screening for other cancers, such as lung and ovary, for which screening trials are in progress either in the UK or elsewhere, and for other cancer sites for which new screening tests may become available.

Methodological work

- The Unit has undertaken statistical modelling of natural history and screening for breast cancer in the over 70s and for bowel cancer. Both Markov-type models and analytical models of natural history are of potential use across a number of cancer sites in studying optimum screening interval and age-range for inclusion in screening programmes, and in studying cost-effectiveness.
- Case-control studies provide an alternative to large-scale randomised controlled trials as a method of evaluating screening, but are liable to bias. The Unit has investigated sources of bias in order to contribute to improved designs for such case-control studies.

Screening in people at high risk of cancer

Modelling of screening in individuals at genetically high risk of cancer

- The question of what screening programmes should be offered to genetically (or other) high risk individuals is becoming of increasing importance as knowledge of cancer predisposition genes is expanding rapidly.
- We have begun to develop models to estimate the health service burden and potential effect of screening in genetic high risk groups. Such models can be applied to a range of cancer sites and will inform policy-makers on likely benefits and resource implications.

Genetic high risk of bowel cancer

- There is increasing interest in the screening management of families at moderately raised risk of bowel cancer.
- We conducted a pilot study of the feasibility of collecting information on family history, and of collecting blood samples, from people being screened for bowel cancer.

Women at high risk of breast cancer

- Data from our trial of breast screening starting at ages 40-41 were used to assist in the evaluation of screening in young women at genetic high risk of breast cancer.
- Women at high risk of breast cancer as a result of receiving chest radiotherapy for Hodgkin's disease are being offered screening nationally. The Unit has collected data to evaluate the process and outcomes of this screening.

Relevance of programme to DH policy

Our programme of work during 2006-10 focused on four of the six cancers discussed in the screening section of the National Cancer Plan, including all for which there are current screening programmes, and aimed to address likely developments in screening for these cancers over this period. Our work has been specifically focussed on policy related issues for these screening programmes, such as age at and frequency of screening, quality assurance and technologies for screening, with the aim of supporting and providing information for policy making.

We have conducted randomised trials of screening that have influenced national screening policy, such as the AGE trial of breast screening in young women. The Unit has also been centrally involved in the European Randomised Trial of Screening for Prostate Cancer, one of only two large trials addressing this important issue for health service policy.

Our programme of work has included evaluating possible or planned changes to the national screening programmes, such as consideration of the age range invited, or the use of alternative technologies. We have evaluated potential changes to existing screening programmes, again with a significant impact on future health policy, for example in changes to the age range of screening, or use of alternative technologies. Our studies of screening performance have been of relevance in improving the quality of screening and providing information to help reduce variation in performance between screening units and laboratories.

5. UPDATE SINCE LAST PROGRESS REPORT (FEBRUARY 2010)

BREAST CANCER SCREENING

Observational cohort study

We have established a large cohort study, the objective of which is to estimate the effectiveness of the NHS breast screening programme (NHSBSP), as operated in recent years, in reducing breast cancer mortality in women invited and screened by the programme. The cohort comprises over 2.6 million women; identification details and exposure data on screening history have been collected from Primary Care Trusts (PCTs). Outcome data on all-cause mortality and breast cancer registrations have been obtained by linking this database with information held by the Office for National Statistics, a process now completed for the entire cohort. In order to validate our screening data, particularly for the early years, specially commissioned software has been run at five screening offices to provide data for comparison. Preliminary analyses of the effect on mortality have now been undertaken, and have estimated the mortality reduction over 10 years in women invited in the early years of the programme. Further analyses, including those of uptake and deprivation, are ongoing. We are also currently completing analyses comparing attenders and non-attenders for screening in a nested case-control study.

Studies of the effects of factors in radiological and pathological practice.

The objective of this work is to study the impact of radiological methods on the performance of the NHSBSP, and to help in the standardisation and interpretation of the national data on pathology variables. We have conducted an observational study of the use of radiographer film reading, in collaboration with the national screening office. Information from 65 screening units on screening practice and the experience of film readers has been analysed together with screening outcomes to examine the performance of programmes using radiographer film reading compared with those using only radiologists. Following a report to the DH Advisory Committee in 2008, data for 2009 were also received and the data re-analysed. A paper has now been submitted for publication.

Interval cancers.

The rate of occurrence of interval cancers provides important information on sensitivity of screening and appropriate screening intervals. It has proved difficult to collect information in the past but data on interval cancers are now being collected on an annual basis by regional QA centres and collated by ourselves. In 2009 we collated further data from women screened in 2002/3 in order to include 6 years of data in a paper which has now been submitted for publication. We have also collected data for a further screening year during 2010.

Evaluation of extension of national screening to women aged 65-70

The NHS breast screening programme was extended from 2004 to invite women to up to age 70, following successful demonstration studies that were evaluated by the CSEU.

We have analysed data on screening to March 2007 for 36 units that had completed a full three year screening round of the 50-70 age group, examining uptake, screening outcomes and prognostic factors; 23 of these units also provided data on a second round. The results showed that uptake and recall to assessment were similar to repeat screening in younger women and cancer detection rates were higher, in line with the results from the demonstration studies. We published a paper describing the results in 2009. We have now submitted for

publication a paper describing screening outcomes in women above age 70; the results show that only a small proportion of all women aged over 70 utilise the self referral policy of the NHSBSP.

Trial of mammographic screening in young women (AGE trial).

In 2006 we published mortality results from this trial of 160,000 women, showing a non-significant 17% reduction in breast cancer mortality at 10 years of follow-up in women invited to annual screening from age 40. This is the only randomised trial designed specifically to study effectiveness of screening from age 40. A paper describing results of longer term follow up is in preparation. In 2010 we completed the collection of data on the first NHSBSP screen in women in both trial arms which will provide important information on the extent of any over-diagnosis as a result of screening at younger ages. Also in 2010 we published papers on the screening patterns in trial women, rates of false positive results, and contamination by screening in the control arm. The latter showed that the extent of screening in the control arm was low and would have had little impact on the trial results.

We have applied to the HTA for funding to continue long-term follow-up of the trial.

Analysis of performance measures.

The Unit collates and validates the routine screening outcome data from England, in collaboration with DH Statistics Division, and also receives processes and validates data from Wales, Scotland and North Ireland. Annual reports have been produced for the DH Advisory Committee on breast cancer screening, the NHS Screening Programme (for the annual review) and the National Coordinating Committee for QA Radiologists.

Breast pathology EQA scheme.

The national breast EQA scheme was set up primarily to investigate the level of consistency that pathologists involved in the screening programme could achieve in reporting breast lesions. We carry out an analysis of this twice a year. The scheme has CPA accreditation, and is now being used for performance appraisal. We are currently working with the organisers to move to a web-based scheme.

CERVICAL SCREENING

Observational cohort study

We have established an individual-based cohort study of women undergoing cervical screening; the objectives include determining the risk of cervical cancer and CIN III in women between the ages of 50 to 64 with a history of negative cytology, and in relation to frequency of screening. The cohort comprises nearly 2 million women, for whom we have linked screening history data from PCTs to data from cancer registries on CIN III and invasive cervical cancer. Papers describing cytological and histological outcomes by episodes, and reporting an analysis of screening outcomes in women aged 50 to 64 according to previous screening history were published in 2009.

Evaluation of automated cytology.

In collaboration with Prof. Kitchener (University of Manchester) we have conducted a randomised controlled trial funded by the HTA comparing automated cervical cytology technologies with manual screening. The target of 75,000 samples randomised was reached in February 2009. The trial concluded that there was a significantly reduced sensitivity of automated reading combined with marginal cost effectiveness compared with manual reading, and that automation assisted reading for routine cervical screening cannot be recommended on the basis of the trial results. The report has now been accepted by the HTA, and a paper published in *Lancet Oncology*.

Quality assurance and performance measures.

We receive annual routine national data for the cervical screening programme, and use these to develop performance measures. Feedback to QA directors using the performance measures developed has identified variation in sensitivity/specificity trade-off between cytopathology laboratories. In 2010 we published a paper describing a method to identify outlier laboratories in the screening programme.

Evaluation of HPV triage

Following our evaluation of pilot studies of liquid based cytology and HPV triage, we have undertaken the evaluation of six sentinel sites using human papilloma virus (HPV) testing to triage women with borderline or mildly dyskaryotic cytology to immediate referral to colposcopy or to routine recall. Outcomes include HPV positive rates and results of colposcopy. We have also obtained further follow-up data for women in the original pilot studies of LBC/HPV in order to update results on risk of disease in HPV negative women and on detection rates of high grade CIN. Papers on the results of the sentinel sites evaluation, and on the outcomes of HPV positive women with negative colposcopy, have now been submitted for publication.

We are also currently undertaking the evaluation of studies to assess the performance of different HPV assays in terms of sensitivity and specificity relative to Hybrid Capture II.

PROSTATE CANCER SCREENING

European Randomised Trial of Screening for Prostate Cancer (ERSPC).

The aim of this multi-centre trial is to examine the effect of routine screening by PSA testing on mortality from prostate cancer. We are responsible for compiling and analysing the central database. Data are obtained from all eight centres twice a year, and analyses produced for the data monitoring and scientific committees. Three interim analyses have so far been conducted for the data monitoring committee; and the results of the third interim analysis were published in 2009, showing a 20% reduction in mortality from prostate cancer in men invited to screening, but at the expense of considerable overdiagnosis. The first formal mortality analysis including data to the end of 2008 is now being undertaken.

Prostate pathology EQA

The aims are to study observer variation in the pathological diagnosis of prostate biopsies, the grading of prostate cancers and measurement of other features of prostate cancer biopsy material, and provide an educational forum for pathologists to improve biopsy reporting. About 40 pathologists participated in an initial slide based circulation in 2003-4, and following evaluation of this circulation we now run online image based circulations with over 100 participants.

BOWEL CANCER SCREENING

Evaluation of the English pilot of FOB screening.

In the light of results from RCTs of screening by faecal occult blood testing, a pilot was established in the UK in 2000 to examine the feasibility of population based screening for colorectal cancer. The aim of the current evaluation is to provide detailed estimates of key outcomes of the third round of the bowel cancer screening pilot in England with a focus on trends in uptake rates and positive rates of the FOBt, and to explore factors affecting participation in bowel screening among both responders and non-responders.

We were funded by NHS Cancer Screening Programmes to evaluate the third round of this pilot. Analysis was completed in 2009 and a final report submitted. A paper describing the results of all three rounds of the pilot has been submitted for publication.

Evaluation of the population bowel cancer screening programme.

The objectives of this project are to study factors that will provide early information on the performance of the programme prior to any evidence on mortality benefit, and to assess methods to evaluate the impact of the programme on mortality from bowel cancer.

We have obtained data, including Dukes stage and tumour grade, on all bowel cancer registrations in England for a nine year period prior to the implementation of the screening programme. These data have been analysed to assess completeness of data on tumour stage, and to study trends in overall and stage-specific incidence, and a paper describing these results was published in 2009. We are currently undertaking analyses of bowel cancer mortality for this period, and also updating the data on cancer incidence to include first data on interval cancers.

We have used data from the Nottingham RCT and the English pilot to develop screening performance measures; however, no routine data are yet available from the screening programme.

Nottingham randomised controlled trial of FOB screening.

Long term follow-up is complete until June 2009, and a paper describing long-term cumulative incidence of colorectal cancer as well as mortality has now been submitted for publication.

SCREENING IN PEOPLE AT HIGH RISK OF CANCER

Women at high risk of breast cancer.

An evaluation study of screening in women under age 50 at high familial risk of breast cancer, using the unscreened arm of our AGE trial as a baseline comparison group, published results in 2010 showing that yearly mammography in women with a medium familial risk of breast cancer is likely to be effective in prevention of deaths from breast cancer. We are also collecting data on women who have received chest radiotherapy for Hodgkin's disease at young ages, who have been referred for screening as a result of the national notification scheme, and currently have data on over 4000 screens in over 1400 women.

A PhD student (funded by ICR, commencing in September 2009) is undertaking a project on modelling the effect of screening for cancer in high risk groups.

6. KEY ACHIEVEMENTS 2006-2010

During this programme of work both of our large cohort studies have come to fruition, with papers published from the cervical cohort study on the risk of abnormalities in women over 50 with a history of negative smears and on the extent of opportunistic smear taking, whilst a paper on the mortality results from the breast cohort study is nearing completion. A key achievement of the Unit was the publication of first mortality results from the trial of breast screening in young women, showing a non-significant 17% reduction in breast cancer mortality; longer term follow up will provide further evidence both on mortality and on possible overdiagnosis.

We have successfully evaluated the pilot studies of bowel cancer screening that have been influential in the implementation of the national screening programme, developed performance measures for the screening programme and published a baseline study of incidence rates. Following our evaluation of the earlier pilot studies of liquid based cytology (LBC) and HPV triage in the cervical screening programme, we have evaluated the use of HPV triage in further 'sentinel sites', and the results of this evaluation have been influential in the recent decision to implement HPV triage throughout the screening programme.

Another key achievement has been the analysis the trial of automated cytology, the results of which do not support the introduction of such technology in the NHS screening programme,

The analysis of the European Prostate Cancer screening trial has led to the publication of an influential paper showing that whilst screening by PSA testing resulted in a 20% reduction in mortality from prostate cancer, it also resulted in considerable overdiagnosis.

Publications 2006-2010

1. Sweetman J, Watson M, Norman A, Bunstead Z, Hopwood P, Melia J et al. Feasibility of familial PSA screening: psychosocial issues and screening adherence. *Br J Cancer* 2006; Feb 27;94(4): 507-12.
2. Gennari R, Veronesi U, Andreoli C, Betka J, Castelli A, Gatti G, Hugosson J, Llovet JM, Melia J, Nakhosteen JA, Pastorino U, Sideri M, Stephan C, Veronesi P, Zurrida S. Early detection of cancer: ideas for a debate. *Crit Rev Oncol Hematol*. 2007 Feb;61(2):97-103. Epub 2006 Nov 20.
3. Sweetman J, Watson M, Norman A, Bunstead Z, Hopwood P, Melia J, Moss S, Eeles R, Dearnaley D, Moynihan C. Feasibility of Familial PSA Screening: Psychosocial Issues and Screening Adherence. *Br J Cancer* 2006; Feb 27;94(4): 507-12.
4. Melia J, Moseley R, Ball RY, Griffiths DFR, Grigor K, Harnden P, Jarmulowicz M, McWilliam LJ, Montironi R, Waller M, Moss S, Parkinson MC. A UK-based investigation of inter- and intra-observer reproducibility of Gleason grading of prostatic biopsies. *Histopathology* 2006;48: 644-654.
5. Griffiths DFR, Melia J, McWilliam LJ, Ball RY, Grigor K, Harnden P, Jarmulowicz M, Montironi R, Moseley R, Waller M, Moss S, Parkinson MC in collaboration with the participating pathologists A study of Gleason score interpretation in different groups of UK pathologists; techniques for improving reproducibility. *Histopathology* 2006; 48: 655-662.
6. Melia J, Dearnaley D, Moss S, Johns L, Coulson P, Moynihan C et al. The feasibility and results of a population-based approach to evaluating prostate-specific antigen screening for prostate cancer in men with a raised familial risk. *Br J Cancer* 2006; Feb;94(4): 499-506.
7. Ellis I.O, Coleman D, Wells C, Kodikara S, Paish E.M, Moss S, Al-sam S, Anderson N, Bobrow L, Bulley I, Connolly C E, Dallimore N S, Hales S, Hanby A, Humphreys S, Knox F, Lowe J, Macartney J, Nash R, Parham D, Patnick J, Pinder S E, Quinn C M, Robertson A J, Shrimankar J, Walker R A, Winder R. Impact of a national external quality assessment scheme for breast pathology in the UK. *J Clin Pathol* 2006; 59: 138-145.
8. D. M. Parham, D. Coleman, S. Kodikara, S. Moss, I. O. Ellis, S. Al Sam, N. Anderson, L. Bobrow, I. Buley, C. E. Connolly, N. S. Dallimore, S. Hales, A. Hanby, S. Humphreys, F. Knox, J. Lowe, J. Macartney, R. Nash, J. Patnick, S. E. Pinder, C. M. Quinn, A. J. Robertson, J. Shrimankar, R. A. Walker, C. Wells, R. Winder, and N. Patel, "The NHS breast screening programme (pathology) EQA: experience in recent years relating to issues involved in individual performance appraisal," *J Clin Pathol*, 2006, 59: 130-137
9. C. Parker, D. Muston, J. Melia, S. Moss, D. Dearnaley. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br. J Cancer*, 2006, 94:1361-1368
10. Bennett R, Blanks R, Moss S. Does the accuracy of single reading with CAD (computer aided detection) compare to that of double reading: a review of the literature, *Clinical Radiology*, 2006, 61:1023-1028.
11. Bennett R, Blanks R, Moss S, Roche M. The effect of data quality at the time of introduction of population based screening on the estimate of programme impact using surrogate outcome measures, *Journal of Medical Screening*, 2006;13:197-201.

12. R.G. Blanks, S.M. Moss and K. Denton. Improving the NHS cervical screening laboratory performance indicators by making allowance for population age, risk and screening interval. *Cytopathology* 2006, 17: 323-338.
13. S. Moss, H. Cuckle, A. Evans, L. Johns, M. Waller, L. Bobrow for the Trial Management Group*. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomized controlled trial. *Lancet* 2006; 368:2053-60.
14. Griebisch I, Brown J, Boggis C, Dixon A, Dixon M, Easton D, Eeles R, Evans D, Gilbert F.J, Hawnaur J, Kessar P, Lakhani S.R, Moss S.M, Nerurkar A, Padhani A.R, Pointon L.J, Potterton J, Thompson D, Turnbull L.W, Walker L.G, Warren R, Leach M.O. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. *British Journal of Cancer*; 2006 Oct 9;95(7):801-10.
15. Evans AJ, Kutt E, Record C, Waller M, Moss S. Radiological findings of screen-detected cancers in a multi-centre randomized controlled trial of mammographic screening in women from age 40 to 48. *Clin Radiol*. 2006 Sep;61(9): 784-8.
16. Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of NHS pilot studies. *BMJ*. 2006 Jan 14;332(7533):79-85 .
17. Moss S, Gray A, Legood R, Vessey M, Patnick J, Kitchener H; Liquid Based Cytology/Human Papillomavirus Cervical Pilot Studies Group. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ*. 2006 Jan 14;332(7533):83-5.
18. van der Kwast TH, Ciatto S, Martikainen PM, Hoedemaeker R, Laurila M, Pihl CG, Hugosson J, Neetens I, Nelen V, Di Lollo S, Roobol MJ, Maatanen L, Santonja C, Moss S, Schroder FH. Detection rates of high-grade prostate cancer during subsequent screening visit. Results of the European Randomised Screening Study for Prostate Cancer. *Int J. Cancer*. 2006 May 15;118(10):2538-42.
19. Bennett RL, Blanks RG, Moss SM (2006) Workforce issues in breast imaging: radiographers as screen readers. *Breast Cancer Research*, 8 (Supplement 1). p. 31. ISSN 1465-5411
20. Evans AJ, Kutt E, Record C, Waller M, Bobrow L, Moss S. Radiological and pathological findings of interval cancers in a multi-centre randomized, controlled trial of mammographic screening in women from 40-41 years. *Clin Radiol*. 2007 Apr;62(4):348-52.
21. Bennett R.L, Blanks R.G., Patnick J., Moss S.M. Results from the UK NHS breast screening programme 2000-05. *J.Med.Screening*. 2007;14(4):200-4.
22. Weller D., Coleman D., Robertson R., Butler P., Melia J., Campbell C., Parker R., Patnick J., Moss S. The UK colorectal cancer screening pilot: results of the second round of screening in England. *Br.J.Cancer* 2007 Dec 17;97(12):1601-5.
23. Waller M., Moss S., Watson J., Moller H. The effect of mammographic screening and hormone replacement therapy use on breast cancer incidence in England and Wales. *Cancer Epidemiol Biomarkers Prev*. 2007 No;16(11):2257-61.
24. Blanks,R.G.; Moss,S.M.; Coleman,D.A.; Swerdlow,A.J. An examination of the role of opportunistic smear taking in the NHS cervical screening programme using data from the CSEU cervical screening cohort study. *BJOG* Nov. 2007. 114:11: 1408-1413.

25. Moss S, Cuckle H, Evans A, Johns L, Waller M, Bobrow L (2007) Mammographic screening from age 40 years - Reply. *LANCET*, 369 (9563). p. 738. ISSN 0140-6736
26. Bennett RL, Blanks RG. Should a standard be defined for the positive predictive value (PPV) of recall in the UK NHS Breast Screening Programme? *Breast* 2007;16(1) 55-59. Epub 2006 Aug 14.
27. Gray JA, Patnick J, Blanks RG. Maximising benefit and minimizing harm of screening. *BMJ* 2008 Mar 1;336(7642):480-3..
28. Blanks RG. A statistical and epidemiological viewpoint and implications at the research and system level. *Cytopathology*. 2008 Jun;19(3):160-1..
29. Blanks RG. The development of the referral outcome diagram and an analysis of laboratory cancer detection rates in the English NHS cervical screening programme – is there an optimum level of detection of CIN1 and CIN2 lesions? *Cytopathology*. 2008 Aug;19(4):244-53..
30. Harnden P, Coleman D, Moss S, Kodikara S, Patnick J, Melia J. Prostatic pathology reporting in the UK: development of a national external quality assurance scheme. *Histopathology* 2008;52: 147-157.
31. Melia J, Coulson P, Coleman D, Moss S. Urological referral of asymptomatic men in General Practice in England. *British Journal of Cancer* (2008) 98, 1176-1181.
32. Bennett, R. L., Blanks, R. G., Moss, S. M. (2008) Coverage in the National Health Service Breast Screening Programme, 1996-2005: correcting for the first invitation of women between 50 and 52 years. *Journal of Public Health*, 30 (2). pp. 167-170..
33. Sargent, A., Bailey, A., Almonte, M., Turner, A., Thomson, C., Peto, J., Desai, M., Mather, J., Moss, S., Roberts, C., Kitchener, H. C., Grp, Artistic Study (2008) Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. *BJC*, 98 (10). pp. 1704-1709..
34. Sue Moss. Screening for Breast Cancer in India – Is it An Appropriate Strategy? *Journal of the National Cancer Institute (JNCI)* 2008:Vol 100, Issue 18: 1270-1271.
35. Montironi R, Ball RY, Griffiths DFR, Grigor K, Harnden P, Jarmulowicz M, McWilliam LJ, Moseley R, Parkinson MC, Santinelli A, Moss SM, Melia J. Bayesian Belief network for the Gleason patterns in prostatic adenocarcinoma. *Analytical and Quantitative Cytology and Histology*. Feb. 2008: Vol 30: No.1.
36. Macafee, D. A. L., Waller, M., Whynes, D. K., Moss, S., Scholefield, J. H. (2008) Population screening for colorectal cancer: the implications of an ageing population. *BJC*, 99 (12). pp. 1991-2000..
37. Melia J, Moss S. PSA testing in the UK. *Trends in Urology Gynaecology & Sexual Health*. Vol 14;Issue 1;February 2009.
38. Schroder F.H, Hugosson J, Roobol M.J, Tammela T.L.J, Caitto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis L.J, Recker F, Berenguer A, Maattanen L, Bangma C.H, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg B.G, Moss S.M, de Koning H.J, and Auvinen A, for the ERSPC Investigators. Screening and Prostate-Cancer Mortality in a Randomized European Study. *N Engl J Med*. 360;13 2009.

39. Bennett R.L, Blanks R.G, Moss S.M. Evaluation of extension of breast screening to women aged 65-70 in England using screening performance measures. *BJC* 100;1043-1047:2009.
40. Blanks R.G, Moss S.M, Addou S, Coleman D.A, Swerdlow A.J. Risk of cervical abnormality after age 50 in women with previously negative smears. *BJC* May 2009:Vol 100;Iss 11;1832-1836.
41. Blanks R.G, Moss S.M, Coleman D.A, Addou S, Swerdlow A.J. The use of screening episodes linked to CIN3 and invasive cancer registrations to study outcomes from the NHS Cervical Screening Programme. *Cytopathology* 2009: Jan 21, Vol 20:Issue 3;154-160.
42. A. Auvinen, J. Raitanen, S. Moss, H. J. de Koning, J. Hugosson, T. Tammela, M. Roobol, H. Lilja, M. Hakama. Test Sensitivity in the European Prostate Cancer Screening Trial: Results from Finland, Sweden, and the Netherlands. *Cancer Epidemiol Biomarkers Prev* 2009;18(7). July 2009.
43. Jones AM, Morris E, Thomas J, Forman D, Melia J, Moss SM. Evaluation of bowel cancer registration data in England, 1996-2004. *Br. J Cancer*, 2009 Oct 20;101(8):1269-73.
44. Walker K, Fletcher O, Johnson N, Coupland B, McCormack VA, Folkard E, Gibson L, Hillier SG, Holly JM, Moss S, Dowsett M, Peto J, dos Santos Silva I. Premenopausal mammographic density in relation to cyclic variations in endogenous sex hormone levels, prolactin, and insulin-like growth factors. *Cancer Res.* 2009 Aug 15;69(16):6490-9.
45. Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M, Stenman UH, Ciatto S, Nelson V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis L, Recker F, Berenguer A, Ruutu M, Kujala P, Bangma CH, Aus G, Tammela TL, Villers A, Rebillard X, Moss SM, de Koning HJ, Hugosson J, Auvinen A. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for non-attendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eu Urol.* 2009 Oct;56(4):584-91.
46. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, Gilham C, Baysson H, Roberts C, Dowie R, Desai M, Mather J, Bailey A, Turner A, Moss S, Peto J. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomized controlled trial. *Lancet Oncol.* 2009 Jul;10(7):672-82.
47. Pinto Pereira SM, McCormack VA, Moss SM, dos Santos Silva I. The spatial distribution of radiodense breast tissue: a longitudinal study. *Breast Cancer Res.* 2009;11(3):R33. PMID 19490643.
48. Blanks R.G, Bennett R.L. Quality assurance in breast cancer screening. *Breast Cancer* (13-28) Nov.2009.
49. Weller D, Moss S, Melia J, Coleman D, worth A, Campbell C. Evaluation of the 3rd Round of the English Bowel cancer screening Pilot. Report to the NHS Cancer Screening Programmes. December 2009. NHS website.
50. Blanks RG, Moss SM, Addou S, Coleman DA, Swerdlow AJ. Risk of cervical abnormality after age 50 in women with previously negative smears. *British Journal of Cancer* 2009 Jun 2;100(11):1832-6.
51. Melia J, Coulson P, Moss S, Coleman D. Effects of a prostate awareness pilot on GP consultations and PSA requests. *Family Practice.* Feb 2010;(1):69-76.

52. Aitken Z, Walker K, Stegeman B.H, Wark P.A, Moss S.M, McCormack V.A, dos Santos Silva I. Mammographic density and markers of socioeconomic status: a cross-sectional study. *BMC Cancer* 2010, 10:35.
53. Blanks RG. Using a graph of the abnormal predictive value versus the positive predictive value for the determination of outlier laboratories in the National Health Service cervical screening programme. *Cytopathology* 2010 August 4th.
54. Johns LE, Moss SM; for the Trial Management Group. Randomized controlled trial of mammographic screening from age 40 ('Age' trial): patterns of screening attendance. *Journal of Medical Screening*. 2010;17(1): 37-43.
55. Kingston N, Thomas I, Johns L, Moss S for the Trial Management Group. Assessing the amount of unscheduled screening ('contamination') in the control arm of the UK 'Age' trial. *Cancer Epidemiology Biomarkers and Prevention*. April 2010;19:1132-1136.
56. Moss S. Design issues in cancer screening trials. *Stat Methods Med Res*. 2010 19 (5) 451-461
57. Finne P, Fallah M, Hakama M, Ciatto S, Hugosson J, de Koning H, Moss S, Nelen V, Auvinen A Lead-time in the European Randomised Study of Screening for Prostate Cancer. *Eur J Cancer*. 2010 Nov;46(17):3102-8.
58. Otto SJ, Moss SM, Määttänen L, Roobol M, Zappa M, Nelen V, Kwiatkowski M, Villers A, Hugosson J, Sanchez AB, de Koning HJ. PSA levels and cancer detection rate by centre in the European Randomized Study of Screening for Prostate Cancer. *Eur J Cancer*. 2010 Nov;46(17): 3053-60
59. van Schoor G, Moss SM, Otten JD, Donders R, Paap E, den Heeten GJ, Holland R, Broeders MJ, Verbeek AL. Effective biennial mammographic screening in women aged 40-49. *Eur J Cancer*. 2010 Oct 28. [Epub ahead of print]
60. Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schröder FH, Tammela TL, Aus G, Auvinen AP, Hugosson J. No excess mortality after prostate biopsy: results from the European Randomized Study of Screening for Prostate Cancer. *BJU Int*. 2010 Oct 15
61. FH01 collaborative teams Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study..*Lancet Oncol*. 2010 Dec;11(12):1127-34
62. Johns LE, Moss SM; Age Trial Management Group. False-positive results in the randomized controlled trial of mammographic screening from age 40 ("Age" trial). *Cancer Epidemiol Biomarkers Prev*. 2010 Nov;19(11):2758-64.
63. Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, Mather J, Rana DN, Cubie H, Moore C, Legood R, Gray A, Moss S. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. *Lancet Oncol*. 2011 Jan;12(1):56-64.

Dissemination activities

In addition to peer reviewed papers and presentations at national and international conferences, dissemination activities of the Unit have included numerous reports to the DH Advisory committees on breast cancer, bowel cancer and cervical screening throughout the programme period.

A number of research reports have also been published in full on the NHS Cancer Screening Programmes website.

Other examples of dissemination include the results of our trial of breast screening in young women, which have been communicated to women through the participating screening units and the internet. SM is the lead author on Evaluation and Interpretation of Screening Outcomes in the European Colorectal Cancer Screening Quality Assurance Guidelines, about to be published.

7. CONCLUSION

Our programme of work during 2006-10 focused on four of the six cancers discussed in the screening section of the National Cancer Plan, and aimed to address the operation of the national screening programmes and likely developments in screening for these cancers over this period.

The remit of the Unit has included the evaluation of the effectiveness of existing cancer screening programmes, development of methods to assess their performance and effectiveness, studies of the possible value of screening for cancer sites where benefit is not yet proven, and detailed studies of specific aspects of screening. Our work has focussed on research targeted at practical decisions for national screening in England, and improvement of the implementation of the national screening programmes, and we have successfully completed numerous studies that have both contributed to the scientific literature and helped to inform and policy.

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^{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-analysis¹³ 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

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	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 ⁴	12	Yes	1963-66	18	40-49	0.77 (0.53-1.11)
Ostergotland ¹	24	No	1978-81	17	38-49	1.05 (0.64-1.71)
Kopparberg ²	24	No	1976-78	17	40-49	0.76 (0.42-1.40)
Malmö I ¹	18-24	No	1976-78	19	45-49	0.74 (0.44-1.25)
Malmö II ¹	18-24	No	1978-90	12.7	43-49	0.65 (0.39-1.08)
Gothenburg ³	18	No	1982-84	13	39-49	0.56 (0.34-0.91)
Stockholm ¹	28	No	1981-83	15	39-49	1.52 (0.80-2.88)
Edinburgh ⁶	24	Yes (annual)	1978-81	14	45-49	0.83 (0.54-1.27)
NBSS ⁷	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

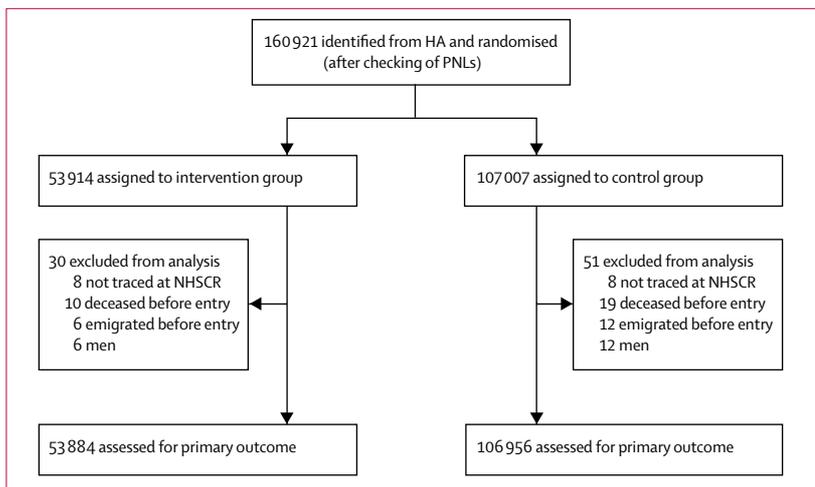


Figure 1: Flow diagram of the progress through the phases of the trial
PNL=prior notification list.

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 women 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

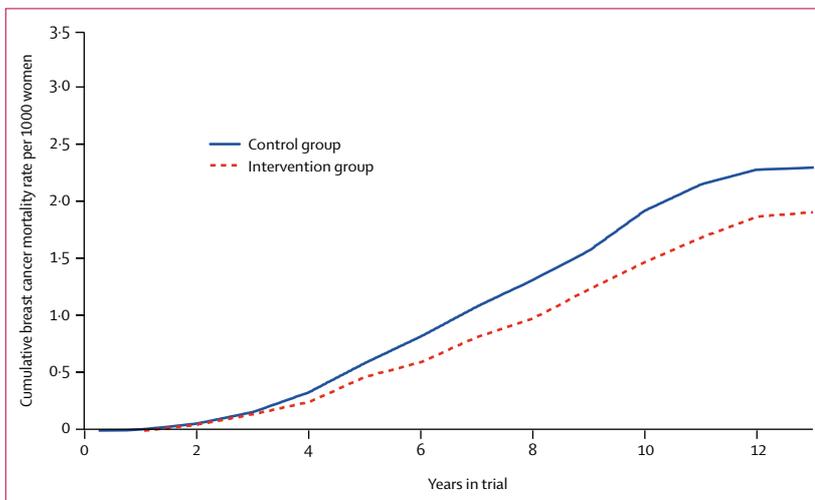


Figure 2: Cumulative breast cancer mortality

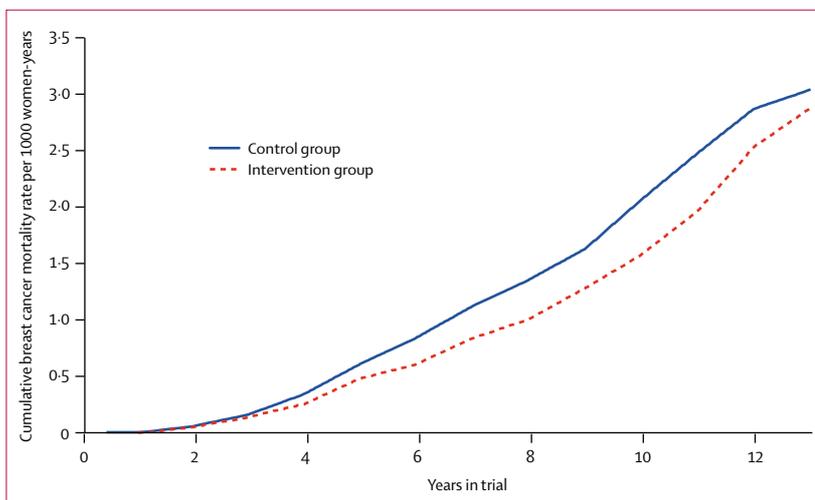


Figure 3: Nelson-Aalen estimate of cumulative breast cancer mortality

	Intervention		Control		Rate ratio (95% CI) intervention vs control group
	Women years n	Rate per 1000 women years	Women years n	Rate per 1000 women years	
0-5 years	267 930	26	532 206	65	0.79 (0.48-1.27)
5-15 years	310 460	79	617 173	186	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 England³³ 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.

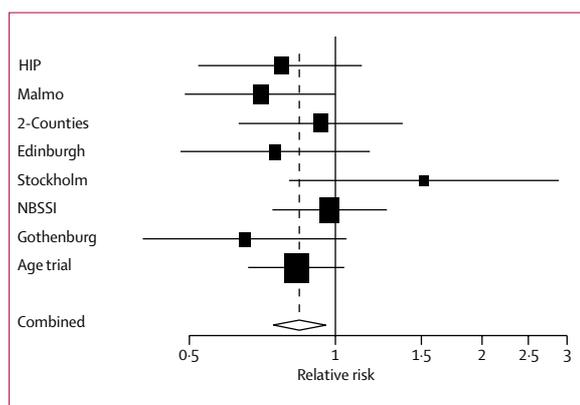


Figure 4: Breast cancer mortality results of the randomised mammography trials in women younger than 50 years

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

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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

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References

- Nystrom L, Andersson I, Bjurstam 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 Malmo Mammographic Screening Program. *J Natl Cancer Inst Monogr* 1997; **22**: 63–67.
- Bjurstam 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 Malmo 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.

Risk of cervical abnormality after age 50 in women with previously negative smears

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There is discussion over the benefit of continuing cervical screening in women over the age of 50 with a history of negative cytology. We aimed to determine the risk of abnormal cytology in such women. Screening history data from 1985 to 2003 were obtained for a cohort of 2 million women from the NHS cervical screening programme from four Health Authorities in England. The 57 651 women in the cohort who reached age 40 between 1 January 1985 and 31 December 1990 and had at least one routine or opportunistic smear between ages 50 and 54 were included in the analysis. Exposure groups (negative cytology history, negative but including inadequate smears, and positive history) were defined on the basis of screening histories from ages 40 to 49. Sixty-four percent (134/206) (95% CI: 57–71%) of the moderate dyskaryosis or worse lesions at ages over 50 were detected from women in the negative smear history group. After allowance for time since last negative smear, the relative risk for the first primary smear over the age of 50 having moderate dyskaryosis or worse decreased from 0.60 (95% CI: 0.41–0.84) for two negative smear episodes to 0.25 (95% CI: 0.10–0.56) for four negative smear episodes, compared with the positive history group. If screening were discontinued for all women over 50 with a negative history, the majority of cytological abnormalities now being detected at these ages that lead directly to referral to colposcopy would be missed.

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There has been much discussion since the early 1990's about the benefit of continuing cervical screening in women over the age 50 years with a history of repeated negative cytology. It has been suggested that such women are at very low risk of having pre-invasive lesions and therefore of developing invasive cancer, and that ceasing screening in this group could alleviate anxiety and enable better allocation of resources (Van Wijngaarden and Duncan, 1993; Cruickshank *et al*, 1997).

Cervical screening aims to prevent the occurrence of invasive cancer by detecting pre-invasive lesions (CIN 1, 2 and 3). The prevalence of pre-invasive cervical lesions decreases with age and women screened over the age of 50 have a considerably lower risk of having abnormal cytology results. The risk of mild or worse dyskaryosis varies from around 10% for women in their early twenties to only around 1% for women over 50 years (Cervical screening programme, England 2007–08 statistical bulletin). The rate of progression of most lesions destined to become invasive cancer is generally considered to be slow, and one might therefore anticipate that a negative smear history before the age of 50 would considerably reduce the risk of positive cytology or histology in women aged 50–64 years (the upper age of invitation to screening in the UK), who have been regularly screened. In the 1990's it was suggested, based on evidence from the Tayside area of Scotland, that women over the age of 50 years with an adequate history of negative results on smear testing every 3 years may be safely discharged from further screening

(Van Wijngaarden and Duncan, 1993). There have been few studies to test this, however (Cruickshank *et al*, 1997; Flannelly *et al*, 2004; Armaroli *et al*, 2008), and the only large study directly considering the question had relatively short screening histories (Flannelly *et al*, 2004).

We have therefore undertaken a large cohort study to investigate the risk of a positive primary smear result at the first routine recall episode after the age of 50 years in women with a negative smear history at ages 40–49 years compared with women with other histories, and how the number of negative smears relates to this risk.

METHODS

We assembled a population-based cohort of 2 million women from four health authorities (two areas invited 3 yearly and two other areas 5 yearly) in England with cervical screening histories covering the period 1 January 1985 to around March 2004 (the exact date dependent on the area of residence), using information obtained from the national computerised call-recall system. Women within this cohort with dates of birth between 1 January 1945 and 31 December 1950 and still resident and eligible in the same areas for invitation to screening at March 2004 have been included in the current analysis. These women reached age of 40 years between 1 January 1985 and 31 December 1990 (around the start of the national computerised call-recall system circa 1988) and we have details on the computerised system of 10 years of screening history between ages of 40 and 49 years and a minimum of 3 years follow-up after reaching age of 50 years.

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For analysis, we divided the screening histories into 'episodes' starting with a routine or opportunistic ('primary') smear and ending with a ('closing') smear that returned the woman back to routine recall or cessation of screening (e.g., because of a hysterectomy). For most episodes the primary smear was negative with an action of return to routine recall, and therefore the primary smear was also the closing smear. We included in our analysis women in the cohort with a primary smear between the ages of 50 and 54 years; these are therefore routine or opportunistic smears and not repeat or follow-up tests. The cohort and our use of episodes is described in detail in an earlier paper (Blanks *et al*, 2007).

We allocated women to three groups for analysis on the basis of their screening history between ages of 40 and 49 years. 'Negative' history was defined as at least two episodes, all of which were single smear episodes with a negative result and an action of return to routine recall. 'Inadequate' history was defined as one or more episodes that included an inadequate smear result, but no abnormal cytology results. 'Positive' history was defined as one or more episodes that included a smear with results of borderline abnormal cytology or worse. Women with smear histories consisting of only one negative episode were not included in the study.

The main outcome measure was the prevalence of cytological disease in the primary smear from the first episode starting after the age of 50 years, with the additional criterion that the episode must have occurred before age of 55 years. We analysed the prevalence ratio (also alluded to in the text as relative risk) of cytological disease in this first primary smear over 50 years in the 'negative' compared with the 'positive' group and the effect of increasing numbers of negative episodes before age of 50 years. A logistic regression analysis was used to determine any confounding effect of duration between the last smear under age 50 years and the first smear after age of 50 years, because the length of this interval affects the risk of abnormality after age of 50 years, and could be related to whether the earlier smear was positive, inadequate or negative and the frequency of past screening. The exposure of two, three or four negative smear episodes before age of 50 years was entered into the model as a categorical variable. There were four final models with outcomes of, respectively, borderline disease or worse; mild dyskaryosis or worse; moderate dyskaryosis or worse and severe dyskaryosis or worse. The outcomes of the models were odds ratios, but these can be treated as relative risks as the vast majority of women (with adequate smear results) will have negative results and therefore positive cytological disease outcomes can be considered rare.

In addition, the probability of referral to colposcopy during the first episode after age of 50 years was calculated for 'negative', 'positive' and 'inadequate' groups and the prevalence ratio of referral to colposcopy for the 'negative' and 'inadequate' groups relative to the 'positive' group was calculated. All statistical analyses were conducted using STATA version 8 (StataCorp, College Station, TX, USA).

To examine the effects of 3- and 5-yearly screening policy, we examined the probability of women with negative smear histories of either two or three episodes between the ages of 40 and 49 years having a primary smear result of mild dyskaryosis or worse at their first episode after age of 50 years.

RESULTS

There were 71 283 women in the three exposure groups defined by their screening history between ages of 40 and 49 years, of whom 57 671 (81%) also had a primary smear between the ages of 50 and 54 years and were therefore included in the analysis. Of these, 42 124 were in the 'negative' group, 7056 in the 'inadequate' group and 8471 in the 'positive' group. The group of women included in the study reached age of 50 years between 1 January 1995 and 31 December 2000 and the study outcome primary smears occurred between 9 January 1995 and 17 March 2004. The mean age for the outcome primary smear was 51.4 years (s.d. 1.2 years).

Table 1 shows details of the primary smear results for the first screening episode over the age of 50 years for the three study groups. The 'negative' group had a higher proportion of negative smear results (91.7%) from the first smear over 50 years compared with the 'inadequate' (88.1%) and 'positive' (89.4%) groups. The 'inadequate' group, however, had a notably higher proportion of inadequate smear results, suggesting that an earlier inadequate smear history is predictive of future inadequate smears. Table 1 also shows the proportion of adequate smears with moderate dyskaryosis or worse for all three groups, with 95% confidence limits. Of 209 moderate dyskaryosis or worse smear results, 134 (64% (95% CI: 57–71%)), were from the negative history group.

Table 2 shows an analysis according to whether women had two, three or four negative smear episodes between ages of 40 and 49 years. For moderate dyskaryosis or worse, the risk compared with the 'positive' group for two negative episodes was 0.60 (95% CI: 0.41–0.84), for three negative episodes 0.47 (95% CI: 0.32–0.71) and for four negative episodes 0.25 (95% CI: 0.10–0.56). It is

Table 1 Result of the first primary smear test after age of 50 years by outcome of screening at ages of 40–49 years

Reported outcome of first primary smear after age of 50 years	Screening history between ages 40 and 49 years					
	Negative ^a		Inadequate ^b		Positive ^c	
	Number	%	Number	%	Number	%
Negative	38 633	91.71	6218	88.12	7569	89.35
Inadequate	2283	5.42	607	8.60	503	5.94
Borderline	895	2.12	172	2.44	287	3.39
Mild dyskaryosis	179	0.42	36	0.51	60	0.71
Moderate dyskaryosis	69	0.16	11	0.16	22	0.26
Severe dyskaryosis	43	0.10	6	0.09	20	0.24
Severe dyskaryosis-query invasive	3	0.01	0	0.00	1	0.01
Glandular neoplasia	19	0.05	6	0.09	9	0.11
Total	42 124		7056		8471	
Median no. of primary smears between ages of 40 and 49 years	3		3		3	
Moderate dyskaryosis or worse (% of adequate smears and 95% CI)	134 (0.34% 95% CI: 0.28–0.40)		23 (0.36% 95% CI: 0.22–0.53)		52 (0.65% 95% CI: 0.48–0.85)	

^aNegative: at least two episodes, all of which were single smear episodes with a negative result and an action of return to routine recall. ^bInadequate: one or more episodes that included an inadequate smear result, but no abnormal cytology results. ^cPositive: one or more episodes that included a smear with results of borderline cytology or worse.

Table 2 Prevalence ratio (relative risk) of various levels of abnormal primary smear at the first smear over age of 50 years in relation to smear histories between ages of 40 and 49 years

Screening history between 40 and 49 years	Adequate primary smears	Borderline or worse No. PR (95% CI)	Mild or worse No. PR (95% CI)	Moderate or worse No. PR (95% CI)	Severe or worse No. PR (95% CI)
Negative	39 841	1 208 0.61 (0.54–0.68)***	313 0.56 (0.45–0.79)***	134 0.52 (0.37–0.72)***	65 0.43 (0.28–0.69)***
Two negative episodes	17 250	621 0.72 (0.63–0.82)***	163 0.67 (0.53–0.86)***	67 0.60 (0.41–0.84)**	34 0.52 (0.31–0.89)*
Three negative episodes	17 746	455 0.51 (0.45–0.59)***	118 0.47 (0.36–0.62)***	55 0.47 (0.32–0.71)***	26 0.39 (0.22–0.68)***
Four negative episodes ^a	4 211	103 0.49 (0.39–0.61)***	22 0.37 (0.22–0.59)***	7 0.25 (0.10–0.56)***	2 0.13 (0.01–0.50)***
Inadequate	6 449	231 0.72 (0.61–0.84)***	59 0.65 (0.47–0.90)**	23 0.55 (0.32–0.91)*	12 0.49 (0.23–0.99)*
Positive	7 968	399 1.00	112 1.00	52 1.00	30 1.00

PR = Prevalence ratio, 95% CI = 95% confidence interval. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. ^aIn addition there were 634 women with 5+ negative smear episodes not included in sub-group analysis because of small numbers and because the women are less likely to be representative of normal screening histories as a history of five or more episodes over a 10-year period is not consistent with routine 3 (or 5) yearly screening.

Table 3 Odds ratios (relative risks) for various levels of abnormality for the first smear after the age of 50 years by number of negative smear episodes between the ages of 40 and 49 years, after allowance for time since last smear

Exposure group	Borderline or worse OR (95% CI)	Mild dyskaryosis or worse OR (95% CI)	Moderate dyskaryosis or worse OR (95% CI)	Severe dyskaryosis or worse OR (95% CI)
Positive	1.00	1.00	1.00	1.00
Two negative episodes	0.67 (0.59–0.77)***	0.62 (0.48–0.80)***	0.58 (0.39–0.84)**	0.49 (0.30–0.83)**
Three negative episodes	0.54 (0.47–0.62)***	0.50 (0.38–0.65)***	0.49 (0.33–0.73)***	0.39 (0.23–0.68)***
Four negative episodes	0.52 (0.42–0.66)***	0.40 (0.25–0.64)***	0.27 (0.12–0.61)***	0.13 (0.03–0.56)**

** $P < 0.01$, *** $P < 0.001$.

relatively uncommon for a woman to have had four routine episodes between 40 and 49 (usually occurring when a woman has been screened every 3 years and her first smear included in the study was at exactly the age of 40 years) and this group is therefore small and the confidence limits wide.

The risks of cytological abnormality at the first primary smear over age of 50 years in relation to number of negative smears at ages of 40–49 years, relative to the 'positive' group and adjusting for the effects of time since last smear, are shown in Table 3. The relative risks of moderate dyskaryosis or worse for two, three and four negative episodes were 0.58 (95% CI: 0.39–0.84), 0.49 (95% CI: 0.33–0.73) and 0.27 (95% CI: 0.12–0.61), respectively. The results are similar to the unadjusted values and confirm that after allowing for time since last smear there is a continuing reduction in risk associated with increasing numbers of negative smear episodes and suggestive evidence that the reduction may be greatest for higher levels of disease (i.e., those most likely to progress to invasive cancer).

Cancer registry information obtained by the CSEU has included information on cases of CIN 3 in the study subjects, but the data were not sufficiently complete or timely to be analysed statistically as an outcome measure in this study. However, even in these incomplete data there were 19 CIN 3 registrations and six invasive cancer registrations from women in the 'negative' group (including two invasive cancer registrations occurring in women with four negative smear episodes between ages of 40 and 49 years), showing clearly that a negative smear history between ages of 40 and 49 years does not preclude the occurrence of invasive cancer after age of 50 years. We have checked the screening histories of the six women with invasive cancers detected from the first smear after the age of 50 years after negative smear histories. The smear test results and the actions taken as a consequence of the smears are consistent with the detection of such an abnormality, and hence we are confident that the recorded abnormalities are not data entry errors.

The percentage of women referred to colposcopy (Table 4) for the 'negative' group was 1.18% compared with 2.35% for the 'positive group', a relative risk of 0.48 (95% CI: 0.41–0.57).

Table 4 Probability of being referred for colposcopy, and prevalence ratio (relative risk) of referral for colposcopy, during the first episode after age of 50 years, by screening history

Screening history between ages of 40 and 49 years	Screening episodes No.	Colposcopy referral No. (%)	Prevalence ratio of referral (95% CI)
Negative	42 124	477 (1.18)	0.48 (0.41–0.57)***
Inadequate	7 056	121 (1.71)	0.73 (0.58–0.92)**
Positive	8 471	199 (2.35)	1.00

** $P < 0.01$, *** $P < 0.001$.

The negative smear history group can be divided into women in 3- or 5-yearly screening policy areas with two or three negative episodes between ages 40 and 49 years. The percentage adequate smears with mild or worse cytology was 0.67% (95% CI: 0.48–0.91) for two negative episodes and 0.61% (95% CI: 0.48–0.76) for three negative episodes. For women in 5 yearly screening areas these figures were 1.09% (95% CI: 0.91–1.30) and 0.80% (95% CI: 0.58–1.08), respectively. As might be expected, the probability of mild or worse cytology is higher in 5-yearly than 3-yearly screening policy areas.

DISCUSSION

Our results show that women over the age of 50 years with a history of a minimum of two negative screening episodes between the ages of 40 and 49 years, have a lower risk of cytological disease found at screening than women with a 'positive' history. The relative risk for borderline or worse disease at ages over 50 years varied from 0.67 for women with two negative episodes to 0.52 for women with four negative episodes compared with women with a positive disease history. For severe dyskaryosis or worse the relative risk decreased from 0.49 for two negative episodes to 0.13 for four negative episodes. There is therefore evidence that the risk of higher levels of cytological disease is reduced more with

increasing numbers of earlier negative smear episodes than is the case for lower levels of cytological disease. Of the 209 moderate dyskaryosis or worse smear results 134 (64% (95% CI: 57–71%)) were from the negative history group and about 75–80% of these women would be expected to have histological outcomes of CIN 2 or worse, based on the reported positive predictive value of moderate dyskaryosis or worse for histology of CIN 2 or worse by the local laboratories (Cervical Screening Programme bulletin, 2000–01). The negative history group were therefore clearly not a group for whom withdrawal of screening would not be material in public health policy terms.

Some of the women in the cohort will have received 5-yearly screening invitations and some 3-yearly invitations, although in practice because of the use of 'opportunistic' smear tests many women in 5-year policy areas will have had screening at a shorter interval than this (Flannelly *et al*, 2004). Women receiving 5 yearly invitations were more likely to have had only two invitations. The 3-year policy areas may be considered more important to current UK screening policy as they reflect the current screening policy more closely. The results suggest a marginally reduced risk of mild dyskaryosis or worse with number of negative episodes if 3-year policy areas only are considered, but the conclusion remains that if screening were discontinued in women with negative smear histories an appreciable number of abnormalities would be missed.

The four Health Authority areas included in the study were chosen because they had demographically similar populations to each other and therefore might have similar disease risk, but had different screening policies. Note that the screening history of women in our cohort (if any) before 1985 is unknown and this is why our study is limited to using only the screening history of women between ages of 40 and 49 years to determine 'exposure' groups. The computerised national call-recall system started in 1988 and there is some possibility that records of a very few smears from 1985 to 1987 may be missing from the files we used for these years, but too few to have affected the results materially.

In general the risk of pre-invasive disease in women aged over 50 years is much lower than in younger women and therefore women over the age of 50 years with a negative smear history (and particularly with at least four negative smear episodes) are the lowest identifiable risk group in our cohort. Nevertheless, our results, suggest that if screening were discontinued for women over 50 years with past negative smears, appreciable morbidity would be missed. Selectively stopping screening at age 50 years for just those with four serial negative smears would result in far less missed morbidity, but with lower cost savings because the number of subjects with four serial negatives was only one-eighth of the number with two or three serial negatives. It is possible that taking account of negative smears over a longer age-span than 40–49 years, or considering cessation of screening at age of 55 years, would identify a group with clearer cost benefit from cessation of screening, but the NHS screening programme data do not, yet, run for a long enough period to assess this. When longer follow-up becomes available, with the passage of time, we will investigate risk of disease in women with a negative history for the 15-year period between the ages of 35–49 years, and outcomes for ages older than 55 years.

The cohort is formed from residents of Health Authority areas in the South of England, which are likely to have a lower risk of cervical cancer than the English average (Swerdlow and dos Santos Silva, 1993). This is borne out by the percentage of adequate smears having mild or worse dyskaryosis being 1.4% for women aged of 50–54 years in England (Cervical screening programme, England 2007–08 statistical bulletin), but only 0.9% in our cohort sample. This suggests that the number of abnormalities being missed would be even greater in the national screening programme as a whole than in our cohort.

There have been a number of earlier investigations into the risk of cervical disease in women aged over 50 years with negative smear histories. Van Wijngaarden and Duncan (1993) reported

that of 26 women with micro-invasive and invasive cancer registered in the Tayside area of Scotland at ages over 50 years, none had had two or more serial negative 3-yearly smears. They also reported that newly occurring cases of CIN were not seen in women over 50 years who had been screened every 3 years. They, therefore, suggested that women should cease screening at age 50 years if they had had three previous negative smears. Cruickshank *et al* (1997) reported that among ~9000 women regularly screened every 3 years before the age of 50 years, one case of CIN 3 and one case of invasive cancer were detected between 50 and 60, giving a low disease rate, but with very wide confidence limits. Flannelly *et al* (2004), by contrast, reported that 1.8% of 36512 women with a negative smear history still showed subsequent dyskaryosis over the age of 50. The period of screening considered was relatively short, however; both the negative smears and the smear over age of 50 years had to have occurred within an 8-year period.

Other studies have investigated smear outcomes after negative smears, but not specifically the question put forward by Van Wijngaarden (Van Wijngaarden and Duncan, 1993), that is, risks of abnormality detected at smears after the age of 50 years in women with a negative history before that age. Armaroli *et al* (2008) reported that the cumulative risk of CIN 2 or worse was at least eightfold higher in women aged less than 50 years after one earlier negative test than in women over 50 years with four serial negative tests at any age. Armaroli *et al* (2008) also found, as we did, that risks of abnormality decreased with increasing numbers of negative smears – a finding also noted in a Canadian study (Coldman *et al*, 2005).

Consideration of whether screening should cease beyond the age of 50 years for those with a past negative history needs to take account of both the potential benefits and harms of screening. The potential harm associated with screening includes unnecessary treatment from over-diagnosis and increased anxiety as well as the cost of screening. It has been suggested that HPV testing could be beneficial in identifying the small proportion of women still at risk after the age of 50 years (Cruickshank *et al*, 2002). Sherlaw-Johnson *et al* (1999) used mathematical modelling to study the effects of withdrawing women at the age of 50 years from screening, who had a recent history of negative results, or where the last smear was negative and they tested negative for high-risk HPV. They concluded that early withdrawal of women from the programme could give resource savings of up to 25% for cytology and 18% for colposcopy at the cost of an increased risk for cervical cancer of up to two cases per 100 000 women per year.

In conclusion, from our data the risk of pre-invasive cervical disease at the age of 50 years in women with a history of multiple negative smears between ages 40 and 49 years was moderately reduced. At present, the NHS cervical screening programme using the national call-recall system (which started in 1988) can only determine a negative history over a limited period of time, and the same was therefore true for our study. Our data give evidence that the risk of abnormality, and particularly the risk of more severe pre-invasive lesions, may decline with increasing numbers of earlier negative smear episodes. Longer follow-up of the cohort will enable the outcome of women with more extensive negative histories to be studied, to determine if there are potentially very low risk groups for whom further screening may not be the best use of resources.

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REFERENCES

- Armaroli P, Gallo F, Bellomi A, Ciatto S, Consonni D, Davi D, Giorgi-Rossi P, Iossa A, Mancini E, Naldoni C, Polla E, Ronco G, Serafini M, Vergini V, Zanier L, Zapa M, Segnan N (2008) Do women ≥ 50 years of age need as much screening as women < 50 years after they have had negative screening results. *Br J Cancer* **99**: 239–244
- Blanks RG, Moss SM, Coleman DA, Swerdlow AJ (2007) An examination of the role of opportunistic smear taking in the NHS cervical screening programme using data from the CSEU cervical screening cohort study. *Br J Obstet Gynaecol* **114**: 1408–1413
- Cervical screening programme, England 2000–01 statistical bulletin (2000–01) *Government Statistical Service*. Department of Health: London. September 2001
- Cervical screening programme, England 2007–08 statistical bulletin (2007–08). The Information Centre for Health and Social Care: Leeds
- Coldman A, Phillips N, Kan L, Maticic J, Benedet L, Towers L (2005) Risk of invasive cervical cancer after pap smears: the protective effect of multiple negatives. *J Med Screening* **12**: 7–11
- Cruikshank ME, Angus V, Kelly M, McPhee S, Kitchener HC (1997) The case for stopping cervical screening at age 50. *Br J Obstet Gynaecol* **104**: 586–589
- Cruikshank ME, Chambers G, Murray G, McKenzie L, Donaldson C, Andrew J, Campbell MK, Kitchener HC (2002) Age restricted cervical screening: HPV testing at age 50 identifies a high risk group for cervical disease. *Int J Gynaecol Cancer* **12**: 735–740
- Flannelly G, Monaghan J, Cruickshank M, Duncan I, Johnson J, Jordan J, Campbell M, Patnick J (2004) Cervical screening in women over age of 50: results of a population-based multicentre study. *Br J Obstet Gynaecol* **11**: 362–368
- Sherlaw-Johnson C, Gallivan S, Jenkins D (1999) Withdrawing low risk women from cervical screening programmes: mathematical modelling study. *Br Med J* **318**: 356–361
- Swerdlow A, dos Santos Silva I (1993) *Atlas of Cancer Incidence in England and Wales 1968–85*. Oxford University Press: Oxford
- Van Wijngaarden WJ, Duncan ID (1993) Rationale for stopping cervical screening in women over 50. *Br Med J* **306**: 967–971

The UK colorectal cancer screening pilot: results of the second round of screening in England

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An evaluation of the second round of faecal occult blood (FOB) screening in the English site of the UK Colorectal Cancer Screening Pilot (comprising the Bowel Cancer Screening Pilot based in Rugby, general practices in four Primary Care Trusts, and their associated hospitals) was carried out. A total of 127 746 men and women aged 50–69 and registered in participating general practices were invited to participate. In all, 15.9% were new invitees not included in the previous round. A total of 52.1% of invitees returned a screening kit. Uptake varied with gender, age, and level of deprivation; was lower than in the first round (51.9 vs 58.5% $P < 0.0001$), but was high (81.1%) in those who had participated in the first round with a negative result. Test positivity was 1.77%, significantly higher than in the first round, and the detection rate of neoplasia similar (5.67 per 1000), resulting in a lower positive predictive value. The sensitivity of FOBt in the first round was estimated as 57.7–64.4%. There was a significant impact on workload, particularly on endoscopy services. The cancer detection rate (0.94 per 1000) was lower than in the first round. Effort will be required to minimise inequalities in uptake, and to ensure adequate capacity of endoscopy services.

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Colorectal cancer is a significant public health burden in the UK, and remains the most common internal malignancy (Wild *et al*, 2006). Randomised controlled trials have demonstrated that colorectal cancer mortality can be reduced by screening using the faecal occult blood test (FOBt) (Towler *et al*, 1998). In the light of this, a Pilot was established in the UK in 2000 to examine the feasibility of population-based screening for colorectal cancer. An evaluation of the first round of this Pilot has been reported previously (UK Colorectal Cancer Screening Pilot Evaluation Team, 2003; UK Colorectal Cancer Screening Pilot Group, 2004), and a national programme of screening began in England in 2006 and is being rolled out over several years (NHS Cancer Screening Programmes website). This paper reports on an evaluation of the second round of the Pilot in England (Weller *et al*, 2006); it provides detailed estimates of key outcome measures, including uptake of FOBt and colonoscopy, test positivity and detection rates of neoplasia, and a further analysis of the workforce and health service impact of bowel cancer screening.

MATERIALS AND METHODS

Screening pilot

The first round of the Pilot was conducted at two sites: the West Midlands in England and Tayside, Grampian, and Fife in Scotland.

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This evaluation of the second round includes data from the English site only. Men and women, aged 50–69 years inclusive, registered at general practices in Coventry Teaching Primary Care Trust (PCT), North Warwickshire PCT, Rugby PCT, and South Warwickshire PCT were eligible; however, due to competing service priorities, South Warwickshire PCT withdrew from the Pilot shortly after the commencement of the second round (only people in two practices in the PCT were invited). The policy was to invite people who would become 50 years of age during the year, and so in both rounds, there are a number of people aged 49 years of age. People aged 70 years or older who were registered with general practices in the Pilot area were able to request a kit by contacting the screening unit – strategies for this age group being made aware of the Pilot included information materials in doctors' surgeries, and receiving information from a spouse or other household member.

The English Colorectal Cancer Screening Pilot was administered from the Bowel Cancer Screening Unit (the screening unit) at the Hospital of St Cross in Rugby, which sent out invitations with Hema Screen test kits, comprising a card with six spots. Kits were returned to the laboratory; after testing (Phase 1 of screening) they could be negative, weak-positive (one–four spots), strong-positive (five–six spots) or inadequate. If the result was negative, the person was informed and no further action taken. If the result was weak-positive or inadequate, the person was sent another kit (Phase 2). Test-negative individuals from Phase 2 were sent a further kit (Phase 3). All those who had either a strong positive result at Phase 1 or returned any positive test at either of the two later phases were deemed to have a positive FOBt outcome and referred.

People who were referred were offered an appointment at the screening unit with a screening nurse who provided information and answered their questions. Bookings for screening nurse appointments and any investigations required (the standard follow-up for a FOBt-positive result was colonoscopy at the nearest endoscopy unit) were also arranged at the screening unit.

Screening for the second round began on 10 February 2003 and the last invitations were sent out on 9 November 2004. It was intended that the second round would take place at an interval of 2 years after the first round; however, there was a delay of 5 months before the start of the second round, due to programming and management constraints – consequently the median time between invitations was 28 months.

Analyses of data

Routine individual-based data were extracted from the Pilot site database in June 2005. Additional information on the Index of Multiple Deprivation (IMD) and on ethnicity were linked to individuals using postcodes (Census Dissemination Unit website; Indices of Deprivation, 2004 website). Data on bowel cancers in people included in the first and/or second rounds were obtained from West Midlands Cancer Intelligence Unit, to identify cancers occurring in the interval between screening rounds. Data from the first and second rounds were linked by matching on NHS number and month/year of birth, to categorise people in the second round according to their screening experience in the first round.

To enable a valid comparison to be made between the two rounds, analyses were conducted on restricted populations from both rounds, including only people in those GP practices who were included in both rounds. We also excluded people aged over 70, except for analyses looking at self-referrals, and people participating in a trial of an immunological test in the second round ($n = 5122$). Logistic regression was used to investigate associations between the demographic and ethnic variables and measures of uptake and positivity. Multivariate analyses including all demographic factors have been used to produce odds ratios of estimated effects adjusted for all other factors.

The test sensitivity of FOBt screening in the first round was estimated using the proportional incidence method (Day, 1985). Interval cancers included were those diagnosed within 2 years of a negative FOBt outcome, and before the date of any subsequent invitation; underlying incidence was estimated using both incidence rates for England in 2001 and those for West Midlands for 1998–2000. Cancers of the anus and anal canal were excluded from both the interval cancers and incidence rates. More details of the methods are given elsewhere (UK Colorectal Cancer Screening Pilot Evaluation Team, 2003).

Impact evaluation

Activity data were used to examine any changes in Pilot-generated workload between the two rounds of screening; workload data on pathology, colonoscopy, radiology and surgical activity data were obtained from the first and second round Pilot databases. These were related to the total (unrestricted) population invited, but excluding South Warwickshire. In addition, screening activity was compared with total activity data obtained from each hospital. These data were supplemented by semi-structured interviews, held between December 2004 and December 2005, with key staff (endoscopy unit managers, colonoscopists and surgeons, colorectal cancer nurse specialists, pathologists, pathology laboratory managers, hospital managers, and screening unit staff). A general thematic analysis was undertaken using an iterative approach with analysis beginning after the first interviews to allow emerging themes to be explored in subsequent interviews.

RESULTS

There were 127 746 invitees in the restricted second round population; 15.9% of people were new invitees, of whom 81.0% were aged 49–51 years. The proportion of people below age 55 years was slightly lower in the second round than in the first (30.5 vs 33.0%). The distributions of IMD were similar in both rounds, but there were a slightly higher proportion of people in ethnic minorities in the second round.

Uptake

FOB test uptake Of the 127 746 people invited, 52.1% (66 541) (95% CI: 51.8–52.4) returned a screening kit. Excluding from the denominator those tests returned by the post office ($n = 2185$) and people whose screening episode was closed for one of several reasons (recent colonoscopy, moved from area, under treatment for bowel problems, deceased) ($n = 3504$), the response rate was 54.5% (66 541/122 057).

Uptake (Table 1), defined as the proportion of those invited who returned an adequate kit in response to the invitation, was 51.9% (66 264/127 746) (95% CI: 51.6–52.1). This was lower than first round uptake (58.5% $P < 0.0001$); this was true across all categories of the demographic variables (gender, age and deprivation). If the categories described above are excluded from the denominators, the uptake was 54.3% (66 264/122 057) and 60.6% (76 152/125 648) in the second and first rounds respectively.

Rates of return of inadequate kits were low; only 277 (0.4%) of those responding to the invitation failed to return an adequate kit in Phase 1 of screening. Some participants didn't complete the screening process; of 3105 people with 'weak-positive' test results in Phase 1, 217 (7.0%) failed to complete the screening process (at either Phase 2 or 3 of screening).

Uptake was high (81.1%) in those who had participated in the first round with a negative result, whereas for those who did not respond in the first round it was only 13.1%. In those aged 49–51 years, who were invited for the first time in the second round, uptake was 44.5%, compared with 51.9% in the same age group in the first round.

Uptake was also low in new invitees at older ages, 41.5% (522/1257) in those aged 60 years and over compared with 62.1% in this age group in the first round. Although the numbers are fairly small, this is the group most comparable to those to be invited in the planned roll-out of the screening programme.

Uptake was significantly lower in men than in women (47.7 vs 56.1% $P < 0.0001$), and increased with age, from 45.7% in those aged under 55 years to 58.5% in those aged 65–69 years. People aged over 70 years were not invited routinely in the second round, but were able to request a kit from the screening centre. However, only 348 people did so, of whom 323 returned an adequate kit. Of the 323, only 113 were aged between 70 and 71 and so would have been invited in the first round.

Uptake fell with increasing level of deprivation, from 61.2 to 37.2% in IMD quintiles 1–5 respectively (test for trend $P < 0.0001$), and was lower in areas with a high proportion of people from the Indian subcontinent (40.4%) than in areas with a low proportion (54.0% $P < 0.0001$). These associations remained significant in the multivariate analysis (Table 1).

Colonoscopy uptake A total of 1171 people had an overall positive FOBt outcome, of whom 1074 (91.7%), attended for a nurse appointment and 1001 were recorded as having been referred for colonoscopy, of whom 970 attended. Uptake of colonoscopy using number of positive FOBt outcomes as the denominator was 82.8% (95% CI: 80.6–85.0) in the second round compared with 80.5% (95% CI: 78.3–82.8) in the first round, but the difference was not significant ($P = 0.16$). However, some people may have attended for private colonoscopy, on which we did not have information.

Positivity

The positive rate, defined as the rate of a positive FOBt outcome in those returning an adequate kit, was 1.77%; this was significantly higher than that of 1.59% in the first round (*P* 0.01). As observed in the first round, the positive rate was higher in men than in women, and increased with age. The positive rate increased significantly with increasing level of deprivation, and was highest in areas with a high proportion of people of Indian subcontinent origin. These effects were reduced but remained significant in the multivariate analysis.

Table 1 Uptake of screening by demographic factors

	Uptake			Adjusted OR (95% CI)
	Number invited	n	%	
Total	127 746	66 264	51.9	
<i>Gender</i>				
Male	64 373	30 711	47.7	1
Female	63 373	35 553	56.1	1.42 (1.36–1.48)
<i>Gender – age (years)</i>				
Male: <55	20 016	8 275	41.3	1
Male: 55–59	18 710	8 772	46.9	1.23 (1.18–1.28)
Male: 60–64	14 566	7 434	51.0	1.47 (1.41–1.54)
Male: 65–69	11 081	6 230	56.2	1.82 (1.74–1.91)
Female: <55	18 967	9 528	50.2	1
Female: 55–59	18 209	10 239	56.2	1.26 (1.20–1.31)
Female: 60–64	14 520	8 705	60.0	1.49 (1.43–1.56)
Female: 65–69	11 677	7 081	60.6	1.55 (1.48–1.63)
<i>Deprivation category (IMD)</i>				
1 least	19 159	11 718	61.2	1
2	29 266	16 923	57.8	0.86 (0.83–0.90)
3	31 883	17 210	54.0	0.74 (0.72–0.77)
4	26 114	12 436	47.6	0.60 (0.57–0.62)
5 most	20 595	7 655	37.2	0.41 (0.39–0.43)
Not known	729	322	44.2	
<i>% Indian subcontinent</i>				
Quintiles 1–4 (low)	105 883	57 148	54.0	1
Quintile 5 (high)	19 899	8 039	40.4	0.89 (0.86–0.93)
Not known	1 964	1 077	54.8	

CI = confidence interval; IMD = Index of Multiple Deprivation; OR = odds ratio.

Table 2 Screening outcomes in first and second rounds of screening

	Adequate return n	Positive FOBt		Cancer		Neoplasia		PPV of positive test (%) (95% CI)	
		n	% (95% CI)	n	Rate per 1000 (95% CI)	n	Rate per 1000 (95% CI)	Cancer	Neoplasia
<i>Second round</i>									
<i>Gender</i>									
Male	30 711	665	2.17 (2.01, 2.33)	43	1.40 (1.01, 1.89)	249	8.11 (7.14, 9.18)	6.47 (4.72, 8.61)	37.4 (33.8, 41.2)
Female	35 553	506	1.42 (1.30, 1.55)	19	0.53 (0.32, 0.83)	127	3.57 (2.98, 4.25)	3.75 (2.28, 5.80)	25.1 (21.4, 29.1)
<i>Age at entry (years)</i>									
<60	36 814	538	1.46 (1.34, 1.59)	16	0.43 (0.25, 0.71)	136	3.69 (3.10, 4.37)	2.97 (1.71, 4.78)	25.3 (21.7, 29.2)
60+	29 450	633	2.15 (1.99, 2.32)	46	1.56 (1.14, 2.08)	240	8.15 (7.15, 9.24)	7.27 (5.37, 9.57)	37.9 (34.1, 41.8)
Total	66 264	1 171	1.77 (1.67, 1.87)	62	0.94 (0.70, 1.17)	376	5.67 (5.12, 6.28)	5.29 (4.08, 6.74)	32.1 (29.4, 34.9)
First round	76 152	1 211	1.59 (1.50, 1.68)	103	1.35 (1.12, 1.64)	470	6.17 (5.62, 6.74)	8.51 (7.15, 10.40)	38.8 (36.0, 41.5)

CI = confidence interval.

Detection rates and positive predictive value

The detection rate of cancer was 0.94 per 1000; this was significantly lower than in the first round (1.35 per 1000, *P* 0.02). The detection rate was higher in men (1.40) than women (0.53) and increased with increasing age. The detection rate of neoplasia (both cancers and adenomas) was 5.67 per 1000, which was slightly lower than the first round (6.17 per 1000).

The positive predictive value of a positive FOBt outcome for cancer was 5.3%, and for all neoplasia was 32.1%. The positive predictive value for both cancer and neoplasia was significantly lower than that for the first round (8.5 and 38.8, respectively), but the difference is restricted to women.

A summary of the screening outcomes for the first and second round is shown in Table 2.

Interval cancers and sensitivity

There were 98 interval cancers occurring within 2 years of a negative screen in the first round. The sensitivity of FOBt in the first round was estimated as 57.7% (95% CI: 48.4–65.6) or 64.4% (95% CI: 56.6–71.1) according to whether England or West Midlands rates were used to calculate expected incidence in the absence of screening (Table 3).

This estimate of sensitivity is similar to that of 62.7% observed in the Nottingham trial (Moss *et al*, 1999). However, in the Pilot sensitivity was higher in men than in women and this difference is in the opposite direction to that observed in the Nottingham trial.

Table 3 Test sensitivity, interval cancers, and person-years of observation within the 2-year period following the first round, by gender and age at entry

	Person-years	Interval cancers	Observed Rate per 1000	England		West Midlands	
				Expected cancers	% detected by screen	Expected cancers	% detected by screen
				Gender			
Male	100 626	49	0.49	140.5	65.1	169.0	71.0
Female	116 925	49	0.42	91.0	46.2	106.1	53.4
Age at entry (years)							
<60	126 346	36	0.28	75.2	52.1	91.9	60.8
60+	91 205	62	0.68	156.2	60.3	183.2	66.2
Total	217 551	98	0.45	231.5	57.7	275.1	64.4

Table 4 Summary of Pilot workload figures for ages 50–69 years for first and second rounds

	Population ^a n	Initial screening colonoscopies		Biopsy or polyp specimens		Resections specimens		Operations		DCBEs	
		n	Rate per 100 000	n	Rate per 100 000	n	Rate per 100 000	n	Rate per 100 000	n	Rate per 100 000
First round	124 586	1006	807	1150	923	93	75	96	77	61	49
Second round	124 477	1026	824	1271	1021	59	47	59	47	38	31

DCBE = double-contrast barium enema; PCT = Primary Care Trust. ^aThe 'denominator' populations for these data are similar to the underlying populations used in Tables 1–3, except that they include people who were randomised to a trial of an alternative immunological test, and exclude invitees from two practices in South Warwickshire PCT and people aged 49 at invitation.

Impact of screening on hospital services

Our assessment of impact of screening on diagnostic and treatment services was based on procedures directly attributable to Pilot activity and comparisons with overall activity. Workload data generated in the first and second rounds of the screening Pilot (excluding surveillance colonoscopies), for people aged 50–69 years and 60–69 years, are shown in Table 4. There was no decline in colonoscopy activity in the second round. Further, screening-associated activity in the two main hospitals associated with the Pilot increased overall workload by approximately 14 and 28% respectively which was similar to the first round (Weller *et al*, 2006). In the second round there were fewer surgical operations and fewer bowel resection specimens to be examined in pathology departments; there was also less demand for radiology services (principally double-contrast barium enema).

Qualitative data from semi-structured interviews revealed a number of consistent themes. Firstly, the impact was felt most acutely among staff in endoscopy units; managing and performing screening-generated surveillance colonoscopies in a timely manner while meeting the demand for diagnostic work (both Pilot and non-Pilot) was challenging.

Secondly, for pathology services, the additional work created by the screening Pilot had most impact in the already overstretched and understaffed laboratories, although pathology staff were able to accommodate the extra workload. Finally, personnel involved in the provision of surgical services were aware of screening patients increasing their workload and the costs involved in terms of increased waiting times for non-urgent patients and the provision of extra operating and staging services. Further details of health service impact appear in the full report of the Pilot second round evaluation (Weller *et al*, 2006).

DISCUSSION

This analysis of the second round of the English Pilot has provided the opportunity of examining how screening could potentially operate beyond the prevalence round as the programme becomes established in the UK. The dynamics of ongoing/periodic screening are different to those of a one-off prevalence type screen.

A key finding was the lower uptake of screening in the second round. The reasons for this are unclear; recruitment strategies were similar in both rounds, although there was greater publicity when the Pilot was launched, and this may have raised awareness. It is a form of screening, which is potentially distasteful, and requires considerable effort on the part of invitees – this may affect on-going participation. Consideration will need to be given in the roll-out process to devising ways of maintaining interest and motivation in a population, which is asked to participate in this form of screening every 2 years. It is also worth noting that other forms of FOBt such as immunochemical tests are available and may be easier to use (Young *et al*, 2002): the potential of such tests to produce higher levels of uptake warrants further exploration. The findings also reinforce the need to devise strategies to address

low uptake in the subgroups which we identified. It would appear that low levels of uptake persist beyond the first round of screening in more or less the same pattern, and this will be an important consideration in reducing health inequalities in colorectal cancer incidence and outcomes (Smith *et al*, 2006).

The low number of people over age 70 who requested a kit is not unexpected, but consideration will need to be given to information needs for this age group as the Bowel Cancer Screening Programme rolls out; in the elderly it is especially important to weight the potential for harm from screening against the likelihood of benefit, given shorter life expectancy and greater comorbidity (Ko and Sonnenberg, 2005).

We have compared the positive rates in the Pilot with those of the first two rounds of the Nottingham trial, restricting both populations by age and uptake at first round to be comparable (Weller *et al*, 2006). The positive rate in the first round of the Pilot was slightly higher than that in the Nottingham trial (1.61 *vs* 1.38%). In Nottingham, the rate fell to 0.84% in the second round; the higher than expected overall positive FOBt outcome rate in the second round of the Pilot (1.8%) is therefore a cause for some concern. Clearly, the FOBt positive rate is the main driver for the rates of colonoscopy, and this is one of the key workforce/capacity issues in FOBt screening.

There was a drop-off in cancers detected in the second round, which is not unexpected in an 'incidence' *versus* 'prevalence' round of screening. The detection rate for all neoplasia (both cancers and adenomas) remained stable. Increasing positive rates coupled with falling cancer detection rates inevitably means that the predictive value for cancer of a positive test result is lower than in the first round. Positive predictive value is one of the most important markers in screening programmes; high rates of false positives lead to large numbers of unnecessary investigations being undertaken. Ultimately, this has an effect on cost effectiveness of screening (Pignone, 2005), and it will be important to monitor closely trends in positive rates over time as the programme rolls out; we have demonstrated that rates can vary considerably.

It will be particularly important to ensure adequate capacity in endoscopy units as the screening programme rolls out over the next several years (Tappenden *et al*, 2007). The colonoscopy rate per total invited population was similar in both the first and second round as although the positivity rate increased in round 2, the uptake of screening was lower. Importantly, the anticipated fall in demand for initial screening colonoscopies in the second round did not materialise, and our qualitative data further emphasise the impact of screening in endoscopic units. Colonoscopy services are frequently struggling to meet demand for symptomatic referrals. The Bowel Cancer Screening Programme has decided to bring management of screening surveillance colonoscopies into the screening programme; while this will not reduce the number of colonoscopies required, it will reduce the administrative work in the endoscopy units and enable the impact of the surveillance workload to be more clearly determined. There is on-going uncertainty over optimal colonoscopy intervals for adenoma/polyp surveillance (Mathew *et al*, 2006) and there is a need for more

evidence to achieve national consensus on this issue if screening-generated surveillance is to be well planned, and incorporated into existing services.

England, Scotland and Wales are among the first countries in the world to introduce national programmes for colorectal screening. Our results suggest that on-going effort will be required to minimise inequalities in uptake by targeting deprived and certain ethnic groups, and to ensure adequate capacity – particularly in the provision of endoscopy services. It will be important to monitor performance measures such as uptake and positivity in this ‘roll-out’ phase, as these will give the first indication of the likely success of the programmes.

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Ethical approval

Details of ethics approval: Ethical approval was not sought for the Pilot, a decision made by the National Screening Committee, and endorsed by the Department of Health, on the grounds that faecal occult blood screening for colorectal cancer is a technology of proved efficacy, and Evaluation of the 2nd Round of screening in England constituted a feasibility study of maintaining a screening programme in the NHS.

Conflict of interest

All authors declare that they have no competing interests.

REFERENCES

- Census Dissemination Unit Website Homepage. <http://census.ac.uk/cdu> accessed 11 June 2007
- Day NE (1985) Estimating the sensitivity of a screening test. *J Epidemiol Community Health* **39**: 364–366
- Indices of Deprivation 2004. Office of the Deputy Prime Minister <http://www.communities.gov.uk/index.asp?id=1128440>, accessed 11 June 2007
- Ko CW, Sonnenberg A (2005) Comparing risks and benefits of colorectal cancer screening in elderly patients. *Gastroenterology* **129**: 1163–1170
- Mathew J, Saklani AK, Borghol M (2006) Surveillance colonoscopy in patients with colorectal cancer: how often should we be doing it? *Surgeon* **4**: 3–5
- Moss SM, Hardcastle JD, Coleman DA, Robinson MH, Rodrigues VC (1999) Interval cancers in a randomized controlled trial of screening for colorectal cancer using a faecal occult blood test. *Int J Epidemiol* **28**: 386–390
- NHS Cancer Screening Programmes. *The National Bowel Cancer Screening Programme*, <http://www.cancerscreening.nhs.uk/bowel/screening.html>, accessed 11 June 2007
- Pignone M (2005) Is population screening for colorectal cancer cost-effective? *Nat Clin Pract Gastroenterol Hepatol* **2**: 288–289
- Smith JJ, Tilney HS, Heriot AG, Darzi AW, Forbes H, Thompson MR, Stamatakis JD, Tekkis PP, Association of Coloproctology of Great Britain and Ireland (2006) Social deprivation and outcomes in colorectal cancer. *Br J Surg* **93**: 1123–1131
- Tappenden P, Chilcott J, Eggington S, Sakai H, Karnon J, Patnick J (2007) Option appraisal of population-based colorectal cancer screening programmes in England. *Gut* **56**: 677–684; e-pub ahead of print 1 December 2006
- Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C (1998) A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. *Br Med J* **317**: 559–565
- UK Colorectal Cancer Screening Pilot Evaluation Team (2003) Evaluation of the UK colorectal cancer screening pilot. Final Report. <http://www.cancerscreening.nhs.uk/bowel/pilot-evaluation.html>, accessed 11 June 2007
- UK Colorectal Cancer Screening Pilot Group (2004) Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. *Br Med J* **329**: 133–138
- Weller D, Moss S, Butler P, Butler P, Campbell C, Coleman D, Melia J, Robertson R (2006) English pilot of bowel cancer screening: an evaluation of the second round. *Department of Health*, <http://www.cancerscreening.nhs.uk/bowel/pilot-evaluation-2.html>, accessed 11 June 2007
- Wild SH, Fischbacher CM, Brock A, Griffiths C, Bhopal R (2006) Mortality from all cancers and lung, colorectal, breast and prostate cancer by country of birth in England and Wales, 2001–2003. *Br J Cancer* **94**: 1079–1085. Erratum appears in *Br J Cancer* 2006; **95**: 424
- Young GP, St John JB, Winawer SJ, Rozen P (2002) Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies; a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy). *Am J Gastroenterol* **97**: 2499–2507