

# Modelling the early detection of breast cancer

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A mathematical model was developed to predict the outcome of early detection clinical trials or programs targeted at evaluating mortality benefit from earlier diagnosis of breast cancer. The model was applied to eight randomized breast cancer trials, which were carried out to evaluate the benefits of mammography, physical examination or their combination. The model assumes that breast cancer is a progressive disease and any mortality benefit from earlier diagnosis is generated from a favorable shift in the stage at diagnosis relative to usual care. The model predicted the reduction in mortality for seven of the eight trials within the reported confidence intervals. Input data required by the models are: stage shift distribution, examination schedules, population age distribution, follow up time, and survival conditional on stage at diagnosis. Survival distributions were obtained from the 1973–82 SEER database whereas the remaining data was obtained for each of the trials. Information on sensitivity and stage was ordinarily available during the early phase of the trials. The theoretical model has the promise of being able to predict the long-term outcome of early detection trials or programs during the initial examination phase. The theoretical model is general and may be applied to other chronic diseases, which satisfy the basic assumptions.

**Key words:** breast cancer, clinical trials, mammography, mathematical models

## Introduction

This paper introduces a probability model for predicting the potential mortality benefit when breast cancer is diagnosed earlier relative to usual care. Under usual care, a woman may have signs or symptoms of breast cancer that result in her seeking medical attention and breast cancer diagnosis. Earlier detection is associated with a woman having no signs or symptoms who is diagnosed with breast cancer by virtue of receiving a special examination.

There have been eight randomised clinical trials evaluating the benefit of mammography, physical examinations or their combination in diagnosing asymptomatic breast cancer. These are often referred to as the HIP trial [1], the Malmö study [2], the Swedish Two-County studies [3, 4], the Stockholm study [5, 6], the Gothenburg study [7], the Edinburgh study [8, 9] and the two Canadian studies (NBSS-1 and -2 [10, 11]).

Some of these trials have been severely criticised by Gøtzsche and Olsen [12, 13]. They raised serious doubts about the evidence showing mortality benefit for early detection. The criticism dealt with the quality of the trials. Recently, Nyström et al. [14] updated the analysis for nearly all of the trials carried out in Sweden and responded to the Gøtzsche and Olsen criticisms. The updated analysis showed a mortality benefit for early detection of breast cancer.

These screening trials are difficult to implement compared with therapeutic trials. They require a large number of subjects, as the

eligibility requirement is that subjects are disease-free. Long-term follow-up, in the neighbourhood of 10–15 years, is necessary to have sufficient numbers of breast cancer deaths to adequately compare mortality. Compliance is a major issue in these trials. Women are randomised to receive (or not receive) invitations to have special examinations. A significant proportion may not respond to the initial invitation. Even those starting an early detection examination schedule may not attend all scheduled examinations. Furthermore, subjects randomised to the usual care (control) group may independently seek mammogram examinations.

It is doubtful whether there will be future clinical trials initiated to further evaluate mammography. Such trials may not be feasible due to ethical, compliance and resource issues. In addition, because minimum follow-up is likely to be a decade, during that time advances in detection modality may make the intervention being compared obsolete.

Here we present a probability model that predicts breast cancer mortality as a function of both the characteristics of the case finding process and the detection modalities. In many fields of science and technology, models are used for prediction when experiments cannot be carried out. One of the objectives of the modelling is to predict outcomes when input variables are changed. We believe that many unanswered questions about breast cancer early detection may be answered with our model.

## Model description

There are many open issues with respect to the early diagnosis of breast cancer, which have not or could not be answered by the eight randomised early detection trials. Two of these major issues

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**Table 1.** Stage shift: summary for eight trials

Trial	Stage	Control (%)	Study (%)	Screen detected (%)	Interval detected (%)
HIP	N+	52	41	30	50
NBSS-1	N+	42	42	35	49
NBSS-2	N+	(MP)	41	35	50
		(PE)	43	42	41
Two-county	II–IV	46	30	19	45
Malmö-1	II–IV	59	39	23	56
Stockholm	II–IV	63	42	–	–
Edinburgh	II–IV	87	64	50	72

MP, mammogram and physical examination; N+, node-positive; PE, physical examination.

are: (i) evaluating the relationship between magnitude of potential benefit and age of diagnosis; and (ii) evaluating various possible screening schedules in order to balance potential benefit and costs.

All models make assumptions. Our two major assumptions are: (i) breast cancer is a progressive disease; and (ii) potential benefit from early detection arises because of a stage shift. The progressive disease assumption implies that the disease stage never becomes more favourable with delay in diagnosis. The stage-shift assumption means that screen-detected cases have a distribution of disease stages that have more favourable prognosis compared with usual care. Furthermore, the shift in the stage distribution is greater than could be expected from length-biased sampling. An ancillary assumption is that ultimate survival depends on stage of diagnosis, treatment and age, but is independent of mode of detection.

The input variables for the model are: age-specific incidence, survival conditional on stage, age of diagnosis and treatment, stage distribution at diagnosis, mode of detection and screening variables (pattern of screening, sensitivity and stage shift). Many of these variables may depend on chronological time. The variables associated with patterns of screening can be obtained from the early detection clinical trials. The other variables (incidence, survival and usual care stage distribution) can be obtained from population databases such as SEER.

One important implication of the model is that a reduction in mortality will only occur if there is a stage shift in exam-detected cases. The model can compare changes in mortality rates, for example screening versus no screening, different screening schedules, effect of changes in sensitivity and effect of advances in treatment.

### Application of the model to early detection trials

Our model is a stochastic model of the natural history of the disease. A series of equations were derived to predict the mortality reductions from screening trials. We applied the model to the eight early detection trials to determine whether the outcomes could be predicted. This serves as a test of the adequacy of the model.

We assumed that breast cancer progresses from no disease (or disease that cannot be detected) to preclinical disease to clinical disease. The sojourn time in the preclinical state was assumed to follow an exponential distribution with an age-dependent mean. The sensitivity of the examinations (mammograms, clinical examinations or a combination) was also assumed to be age dependent. Numerical values for the mean sojourn time in the preclinical state and the sensitivity of the examinations were obtained from the early detection trials. For example, the Swedish Two-County studies reported that the mean sojourn times in the preclinical stage ranged from 1.25 years in 40- to 49-year-old women to 3.9 years in 60- to 69-year-old women. The sensitivity of mammograms also varied from 60% in younger women to 86% in older women. Our model requires age-specific incidence probabilities and transition probabilities from no disease to preclinical stage that would be unaffected by screening. The SEER database for 1973–1982 was used to estimate these probabilities. This time period was selected because early detection programmes would minimally affect these parameters.

In addition, we assumed that the process by which early detection changes prognosis is by a stage shift. Table 1 summarises the stage shifts reported in the early detection trials. The stage shift is expressed as a proportion of cases with positive nodes or with stage II–IV disease.

Table 1 indicates that screen-detected cases had disease stages with better prognosis than the control group. Furthermore, interval-detected cases had a similar stage distribution to those in the control group. This stage-shift information was utilised in constructing survival distributions of screen versus control groups. Breast cancer survival data were used from the SEER database for 1973–1982. We found that survival depended on age and partitioned the data into the age groups 40–49 years and 50–74 years. For each age group, the survival distributions conditional on stage were estimated. A weighted composite of survival distributions conditional on stage was constructed for each trial. The weights corresponded to the reported proportion of cases diagnosed in each stage. Screening schedules from each trial were also incorporated into the model. Integrating all of these quantities resulted in predictions of the long-term mortality reductions for each trial. These are summarised in Table 2.

**Table 2.** Summary of reported and predicted mortality reductions (MR)

Trial	Malmö-1	Stockholm	Gothenburg	Östergötland	Edinburgh	HIP	NBSS-1	NBSS-2
Age (years)	45–70	40–64	40–59	40–74	45–64	40–64	40–49	50–59
Modality	MM	MM	MM	MM	MM + PE, PE	MM, PE	(screen) MM + PE (control) single PE	MM + PE PE
FU time (years)	19	15	13.5	17	14	10	7	7
Reported MR (%)	19	10	22	11	17	30	–36	3
95% CI	(0, 34%)	(–28, 37%)	(–7, 43%)	(–9, 28%)	(–18, 42%)	–	(–121, 16%)	(–52, 38%)
Predicted MR (%)	17	21	20	22	11	3.3	1.4	1

CI, confidence interval; FU, follow-up; MM, mammography; PE, physical examination.

The Swedish trials (Malmö-1, Stockholm, Gothenburg, Östergötland) all used mammography as the sole screening modality. At some point during the follow-up period (13.5–19 years) the control groups were offered mammography. This change was incorporated in our model. The predicted mortality reductions (MR) for the Swedish studies had a range of 17–22%. The model predictions are all within the reported 95% confidence intervals.

The Edinburgh and HIP studies used both mammograms and physical examinations as screening modalities. The model predicted a mortality reduction of 11% after 14 years of follow-up time for the Edinburgh study. The prediction is within the reported 95% confidence limits. The HIP trial reported a 30% mortality reduction for cases diagnosed within 5 years of study entry and 10 years of follow-up time. (No confidence limits were supplied with this estimate.) However, the model predicted a 3.3% mortality reduction. The Canadian studies (NBSS-1, NBSS-2) included physical examinations in the control groups. The studies were designed to assess the additional benefit of mammography. Our model predicted little additional benefit of mammography.

## Discussion

We have presented a stochastic model for predicting the outcomes of clinical trials investigating the benefit of early detection of breast cancer. Application of the model to the eight randomised breast cancer trials has verified that the mortality predictions are reasonably accurate, falling within the reported confidence limits. One conclusion of the model is that mortality benefit requires the existence of a stage shift. Also, benefit is a continuum of age. Benefit is age related, with younger women having less benefit. The controversy surrounding an age cut-off of 50 years is an artifact.

The model predictions may be further improved. In the absence of detailed compliance information, we assumed a 100% compliance rate for both intervention and control groups. The model did not take into account competing risks, which may be important in predictions for older women. US SEER data were used for survival. Comparable Swedish data may be more appropriate to predict outcomes for the Swedish trials. The characterisation of

disease stage can be made more detailed using estrogen receptor status, number of positive nodes, tumour size, etc.

The model can be used to guide public health programmes. It may be applied to evaluate the potential benefit of different screening strategies as a function of age and risk status. Inputting improved sensitivities and longer lead times can assess advances in early detection modalities. Advances may be due to technological innovations or finding breast cancer markers. These issues are all-important but are unlikely to be settled by future clinical trials. Finally, we remark that our model is a general model for evaluating early detection programmes and can be applied to other chronic diseases.

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### Note added in proof

The authors regret that an update to reference 11 was overlooked. Also an update to reference 10 was published after the submission of this paper, e.g. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years to follow-up. A randomized screening trial of mammography in women age 40–49 years. *Ann Intern Med* 2002; 137 305–312 and Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13 year results of a randomized trial in women aged 50–59 years. *J Natl Cancer Inst* 2000; 92: 1490–1499. The updates give additional follow-up results. There are no changes in the general conclusions from the earlier publications.