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ORIGINAL REPORT

Advanced Breast Cancer and Breast Cancer Mortality in Randomized Controlled Trials on Mammography Screening

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A B S T R A C T

Purpose
We assessed changes in advanced cancer incidence and cancer mortality in eight randomized trials of breast cancer screening.

Patients and Methods
Depending on published data, advanced cancer was defined as cancer $\geq$ 20 mm in size (four trials), stage II+ (four trials), and $\geq$ one positive lymph node (one trial). For each trial, we obtained the estimated relative risk (RR) and 95% CI between the intervention and control groups, for both breast cancer mortality and diagnosis of advanced breast cancer. Using a meta-regression approach, log(RR-mortality) was regressed on log(RR-advanced cancer), weighting each trial by the reciprocal of the square of the standard error of log(RR) for mortality.

Results
RR for advanced breast cancer ranged from 0.69 (95% CI, 0.61 to 0.78) in the Swedish Two-County Trial to 0.97 (95% CI, 0.97 to 1.25) in the Canadian National Breast Screening Study-1 (NBSS-1) trial. Log(RR)s for advanced cancer were highly predictive of log(RR)s for mortality (R^2 = 0.95; $P <$ .0001), and the linear regression curve had a slope of 1.00 (95% CI, 0.76 to 1.25) after fixing the intercept to zero. The slope changed only slightly after excluding the Two-County Trial and the Canadian NBSS-1 and NBSS-2 trials.

Conclusion
In trials on breast cancer screening, for each unit decrease in incidence of advanced breast cancer, there was an equal decrease in breast cancer mortality. Monitoring of incidence of advanced breast cancer may provide information on the current impact of screening on breast cancer mortality in the general population.

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INTRODUCTION

Most breast cancer deaths are due to advanced cancer, diagnosed when metastases have already disseminated to lymph nodes or distant organs. The assumption underlying breast cancer screening is that screening will detect potentially life-threatening cancers at an early stage, before they metastasize. Logically, screening is expected to reduce the incidence of advanced cancer, followed by a reduction in breast cancer mortality.

Organized breast screening programs based on mammography are the only means of decreasing breast cancer mortality that are supported by randomized trials and subsequent meta-analyses.[1-3] In most randomized trials of mammography screening, data on the change in cancer spread in intervention and control groups were reported. In the Swedish Two-County Trial, a decreased incidence of stage II or higher breast cancer was reported in the

intervention group, preceding by 2 years the start of the decrease in breast cancer mortality.[4] More formal exploration of links between rates of advanced cancer and breast cancer mortality has been done only for the Greater New York Health Insurance Plan (HIP) trial[5] and for the Two-County Trial.[6] Models of disease progression have been used to predict mortality from stage at diagnosis[7] or directly from screening sensitivity.[8] However, there has never been an empirical estimate of how changes in the risk of being diagnosed with advanced breast cancer are associated with changes in death from breast cancer, taking into account all the available data from the randomized trials on mammography screening. That is the purpose of this article.

PATIENTS AND METHODS

We examined the eight trials considered to be of acceptable methodologic quality in the major reviews of 2002-2006

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Table 1. Selection of Data From the Randomized Trials on Mammography Screening

Trial	Data on Cancer Stage at Detection	Relative Risk of Breast Cancer Death
Greater New York Health Insurance Plan (HIP), United States	Chu et al, 1988[5]	Gøtzsche and Nielsen, 2006[3]
Two-County Trial (TCT), Sweden*	Duffy et al, 2004[9]†	Tabár et al, 2000[10]
Malmo Mammography Screening Trial (MMST), Sweden	Andersson et al, 1988[11]	Andersson et al, 1995[12]
Stockholm trial, Sweden	Frisel et al, 1997[13]	Nyström et al, 2002[14]
Goteborg trial, Sweden	Bjurstam et al, 2003[15]	Bjurstam et al, 2003[15]
National Breast Screening Study-1 (NBSS-1), Canada	Miller et al, 2002[16]‡	Miller et al, 2002[16]
National Breast Screening Study-2 (NBSS-2), Canada	Miller et al, 2000[17]‡	Miller et al, 2000[17]
Trial on women 40 years old at entry, United Kingdom	Moss et al, 2005[18]	Moss et al, 2006[19]

*The Two-County Trial was conducted in the counties of Ostergotland and Dalarna (formerly Kopparberg).
†The last published results did not report results by county.
‡Breast cancers diagnosed in the control group were considered together, without distinction between cancers detected or missed by clinical examination.

(Table 1),[1-3] plus a United Kingdom trial on women 40 years of age at random assignment.[19] Those reviews excluded the Malmo Mammography Screening Trial (MMST) II in Sweden, because its design remains unclear and only a few results have been published, and the Edinburgh trial because of a biased randomization process. This report concentrates on invasive breast cancer, and we therefore excluded data related to in situ breast cancer. We also focused on breast cancers diagnosed during the intervention period, defined as the period when mammographic screening was offered to women in the intervention group but not to those in the control group.

Selection of Data From the Randomized Trials on Mammography Screening

Published articles from which data used in this report were extracted are listed in Table 1. Table 2 summarizes features of randomized trials relevant to this study. The relative risk (RR) of being diagnosed with an advanced breast cancer in women in the intervention group versus women in the control group was related to the period during which mammography screening was provided to the intervention group only. The RRs of breast cancer death are the most recent published, with follow-up periods

Table 2. Summary Results of Randomized Trials on Mammography Breast Cancer Screening

Trial	Age at Entry (years)	No. of Patients in Trial for Analysis – Intervention	No. of Patients in Trial for Analysis – Control	Median Duration of Trial (years)*	Attendance Rate, First Round (%)	Definition of Advanced Breast Cancer	No. of Patients With Advanced Breast Cancer – Intervention	No. of Patients With Advanced Breast Cancer – Control	Cumulative Incidence of Advanced Breast Cancer per 1,000† – Intervention	Cumulative Incidence of Advanced Breast Cancer per 1,000† – Control	RR For Advanced Breast Cancer†	95% CI	RR For Breast Cancer Mortality‡	95% CI
Greater New York Health Insurance Plan (HIP), United States	40-64	30,239	30,256	5	67	Stage II+	160	188	5.29	6.21	0.85	0.69 to 1.05	0.83	0.70 to 1.00
Two-County Trial (TCT), Sweden	40-74	77,080	55,985	8	85	Stage II+	524	555	6.80	9.91	0.69	0.61 to 0.78	0.68	0.59 to 0.80
Malmo Mammographic Screening Trial (MMST), Sweden	45-70	21,088	21,195	14	74	Stage II+	190	231	9.01	10.90	0.83	0.68 to 1.00	0.82	0.67 to 1.00
Stockholm trial, Sweden	39-65	40,318	19,943	5	82	Stage II+	172	97	4.27	4.86	0.88	0.68 to 1.12	0.91	0.65 to 1.27
Goteborg trial, Sweden	39-59	21,650	29,961	4.8 (for age 40-49 years); 7.0 (for age 50-59 years)	84	≥ one node involved	85	144	3.93	4.81	0.80	0.61 to 1.05	0.77	0.60 to 1.00
Trial on women 40 years old at entry, United Kingdom	39-41	53,884	106,956	7	68§	Size ≥ 20 mm	171	386	3.17	3.61	0.88	0.73 to 1.05	0.83	0.66 to 1.04
National Breast Screening Study-1 (NBSS-1), Canada	40-49	25,214	25,216	5	86	Size ≥ 20 mm	111	115	4.40	4.56	0.97	0.74 to 1.25	0.97	0.74 to 1.27
National Breast Screening Study-2 (NBSS-2), Canada	50-59	19,711	19,694	5	87	Size ≥ 20 mm	114	136	5.78	6.91	0.84	0.65 to 1.07	1.02	0.78 to 1.33

*Period during which screening was offered to women in intervention group and not to women in control group; follow-up may have lasted for several more years.
†Relative risk and 95% CI calculated by us except for the Goteborg trial, for which we used the relative risk in Bjurstam et al.[15]
‡See Patients and Methods for selection of relative risks. Number of breast cancer deaths after 13 to 18 years of follow-up for all trials.
§Overall, 81% of women attended at least one mammography round.

being longer than the intervention period. We obtained the most current data on size, node status, and stage of invasive breast cancer and on breast cancer mortality from each of these trials.

Not all the trials reported on the presence or absence of distant metastases at the time of diagnosis. Four trials reported the size of the tumor,[16-18,20,21] four reported the number of positive lymph nodes,[15,18,20-23] and four reported the stage of breast cancers diagnosed during the intervention period.[4,5,9,11,13] We gave preference to breast cancer size as a proxy for disease extension, because size is strongly correlated with lymph node status and stage,[17,24] and its characterization has remained more constant over time and across institutions. A cancer of 20 mm or more does not automatically mean that it is advanced, but the probability of advanced cancer increases with increasing size. We chose 20 mm as the threshold for distinguishing between early and advanced cancers, because this threshold also distinguishes tumor classes T1 and T2 in both the TNM and American Joint Committee on Cancer (AJCC) evaluation of breast cancer stage at diagnosis.[25,26] If size was not available, we used stage at diagnosis, which is based on cancer size, node status, and existence of metastasis in distant organs. Additionally, in published reports, missing values for stage and node status were more common than missing values for tumor size. For the Two-County Trial, we used data on breast cancer stage at diagnosis published in 2003[9] because they were more recent than data on breast cancer size at diagnosis that were published in 1992.[20] For the Canadian National Breast Screening Study-1 (NBSS-1) and NBSS-2 trials,[16,17] we took into account advanced breast cancers detected by mammography and/or clinical breast examination. For the RR of breast cancer death, we used the most recently published RR of dying from breast cancer, because this typically provided the longest follow-up of the women included in trials.

Statistical Analysis

We calculated incidence rates of advanced breast cancer found in intervention and control groups. RRs for advanced breast cancer with respect to mammographic screening were provided only by the Goteborg trial[15]; thus, in the remaining trials we estimated RRs and 95% CIs for advanced breast cancer using Poisson regression.

We assessed the relationship between the risk of advanced cancer and cancer mortality using a meta-regression approach. The log(RR) for cancer mortality in each study was regressed on the log(RR) of advanced breast cancer. Each study was weighted by the reciprocal of the squared standard error in log(RR) for mortality. The regression line was forced through the origin, equivalent to assuming the risk ratio for mortality will be 1.0 if the risk ratio for the incidence of advanced breast cancer is also equal to 1.0. To guard against basing conclusions on a few anomalous results, we refitted the regression after omitting various combinations of studies as a sensitivity analysis.

RESULTS

Table 2 summarizes features of randomized trials relevant to this study. At study-level, the risk of dying from breast cancer during the entire study follow-up was strongly associated with decreasing risk of being diagnosed with an advanced breast cancer during the intervention period (Fig 1). The slope of the regression line is 1.00 (95% CI, 0.76 to 1.24), indicating that decreased risk of advanced breast cancer and of breast cancer mortality were approximately proportional. Moreover log(RR) for advanced breast cancer explained 95% of the between-study variation in log(RR) for breast cancer mortality, as measured by the R^2 statistic.

In seven trials, the ratio of the RR of death and the RR of advanced breast cancer ranged from 0.94 to 1.04. The only major deviation from this trend was the NBSS-2 trial (ratio, 1.22), which reported a substantial decrease in the risk of advanced cancer that did not translate to a parallel reduction in breast cancer mortality.
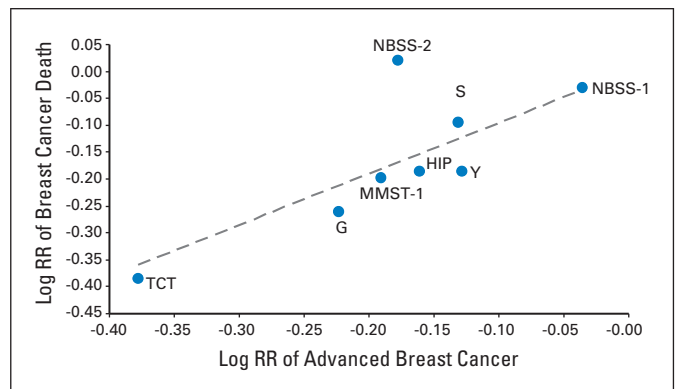

Fig 1. Randomized trials on mammography breast cancer screening for intervention versus control group. Change in log-transformed relative risk (RR) of death from breast cancer according to log-transformed change in RR of advanced breast cancer at diagnosis, after weighting on the variance of each risk estimate. The slope of the regression line is 1.00 (95% CI, 0.76 to 1.25). NBSS-2, National Breast Screening Study-2 (Canada); S, Stockholm trial (Sweden); NBSS-1, National Breast Screening Study-1 (Canada); HIP, Greater New York Health Insurance Plan (United States); Y, trial on women 40 years old at entry (United Kingdom); MMST, Malmo Mammographic Screening Trial (Sweden); G, Goteborg trial (Sweden); TCT, Two-County Trial (Sweden).

We conducted a sensitivity analysis by progressively excluding trials that yielded the most extreme results on mortality, from no change (NBSS-1 and NBSS-2) to greatest change (Two-County Trial) (Table 3). In all cases, the 95% CI included 1.0, although the estimated slope increased as the trials were excluded. The R^2 statistic remained above 0.98 after exclusion of the three trials.

DISCUSSION

In all randomized trials of breast cancer screening in which a decrease in breast cancer mortality was observed, there was a decrease in the risk of being diagnosed with an advanced breast cancer. This decrease in the risk of advanced cancer was often noticeable years before the follow-up ended, and it was approximately proportional to the decrease in breast cancer mortality observed during the follow-up. It follows that changes in the incidence of advanced disease can act as a leading indicator of the effectiveness of a screening program. Moreover, since diagnosis is, in principle, independent of treatment, analysis of trends in the incidence of advanced disease may help disentangle the effects of screening from improvements in treatment. In the context of randomized trials, however, advanced disease rate does not replace disease-specific mortality as the main end point.

Limitations

Ideally one would want to have a single definition of advanced breast cancer, applicable across all the trials included in the analysis. In reality, trials reported different markers of advanced disease. Where more than one marker was given, we gave preference to tumor size because size has long been known to predict the probability that axillary lymph nodes are invaded by metastasis.[17,24] Second, the basic notion underlying mammographic screening is the detection of breast tumors when they are still small (ie, the downsizing of breast cancer by screening). Third, evaluation of cancer size has remained stable over time, whereas evaluation of lymph node status has varied with changes

Table 3. Sensitivity Analysis of the Associations Between the Relative Risk of Advanced Breast Cancer and the Relative Risk of Breast Cancer Death in Randomized Trials on Mammography Screening

Trial	Trial Included in Regression Model (linear regression model number)			
	1	2	3	4
Greater New York Health Insurance Plan (HIP), United States	Yes	Yes	Yes	Yes
Two-County Trial (TCT), Sweden	Yes	Yes	Yes	No
Malmo Mammographic Screening Trial (MMST), Sweden	Yes	Yes	Yes	Yes
Stockholm trial, Sweden	Yes	Yes	Yes	Yes
Goteborg trial, Sweden	Yes	Yes	Yes	Yes
Trial on women 40 years old at entry, United Kingdom	Yes	Yes	Yes	Yes
National Breast Screening Study-1 (NBSS-1), Canada	Yes	Yes	No	No
National Breast Screening Study-2 (NBSS-2), Canada	Yes	No	No	No
Slope	1.00	1.06	1.06	1.14
95% CI	0.76 to 1.25	0.96 to 1.16	0.94 to 1.18	0.92 to 1.35
R^2	0.95	0.99	0.99	0.98

in surgical practice such as the number of axillary lymph nodes removed and changes in histologic handling of removed lymph nodes.[27,28] TNM stage is likely to have remained more constant over time than lymph node status because cancer size is necessary for its evaluation. A review paper displayed the RR of breast cancer deaths according to the risk of node-positive cancer in randomized trials (not including the United Kingdom trial on women 40 years of age at random assignment and not providing CIs).[29] Because data on CIs were missing, we could not estimate the strength of association between mortality and lymph node status, but we suspect that this association was not as strong as with cancer size or TNM stage.

Strengths

We collected data from all trials that were judged by expert reviews to be of sufficient methodologic quality.[1-3] The relationship we found between the RR of advanced cancers and breast cancer mortality is not merely significant: the advanced cancer risk ratio explains 95% or more of between-study variation in mortality risk ratio. RR of advanced disease can therefore stand as an excellent proxy for the RR of disease-specific mortality.

Consequences

Typically, the advantage of a proxy for mortality is that the end point can be reached sooner or with more power, but this is not an issue here: it is unlikely that further randomized studies of mammographic screening will be conducted in the short term. However, the fact that classification as advanced or nonadvanced disease precedes treatment allows us to examine some of the methodologic concerns regarding some of the trials, in particular, regarding differential treatment or determination of cause of death.

The randomization status of women included in breast cancer screening trials was known. Therefore, treatment intensity could have been different according to group, for instance, more chemotherapy or hormone therapy in screened than in nonscreened women. This is most plausible where randomization was by cluster, as in the Two-County Trial. While the Two-County Trial reported treatment modalities according to whether women were in the intervention group or in the control group,[30] the trial was conducted from 1977 until 1985, at a time when adjuvant hormone therapy and chemotherapies

were uncommon. Similarly, cluster randomization raises the possibility of differential misclassification of the cause of death. However, the fact that the Two-County Trial shows similar risk ratios for both disease-specific mortality and diagnosis of advanced disease argues against the presence of such biases.

Why a 16% decrease in the risk of advanced breast cancer in the NBSS-2 trial was not followed by a proportional decrease in mortality remains a mystery. The NBSS trials sought to identify the additional benefit of mammography over physical examination. One possibility is that the additional benefit of mammography over clinical examination is in fact minimal. However, both screening techniques are expected to operate through stage-shift, so under this hypothesis there should be no apparent difference in risk of advanced disease. It is tempting to consider the advanced disease RR a fluke, given the wide CI. However if sampling variation favored the intervention group for the incidence of advanced cancer, it is difficult to conceive that the same women suffered a compensating change of fortune between diagnosis and their death. A prediction of the result, based on relative sensitivity of mammography and physical examination, suggested a mortality reduction of only 1%, close to the observed result and thus suggesting that the advanced disease RR was anomalous.[8] A model approach using the MISCAN microsimulation program found that, compared with no screening at all, mammography would have reduced breast cancer mortality by about 13.6% to 34.1% in the absence of breast clinical screening.[31] This study further suggested that the absence of breast cancer mortality reduction in the NBSS-2 trial could be at least partly due to adjuvant treatment and hormone therapy having become common, in contrast to their rarity at the time of HIP and the Swedish trials. Another possible explanation is an error in reporting histology results, with women with advanced cancer being recorded as having early cancer, but we did not find any data to support this hypothesis.

If established mammographic screening is providing the reduction in mortality predicted by the majority of the screening trials and if participation is high, then that benefit should be observed in a reduction in the rate of diagnosis of advanced breast cancers. Because one of the benefits from screening is that detection will occur earlier, the reduction in mortality should be apparent particularly within age groups that are screened, or in slightly older age groups. Monitoring

the incidence of advanced breast cancer in these age groups should therefore be used to monitor the benefit provided by mammographic screening programs. However, caution should still be exercised, because the NBSS-2 trial shows that reduction in advanced disease does not necessarily imply improved mortality.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Philippe Autier
Administrative support: Philippe Autier, Clarisse Héry
Provision of study materials or patients: Philippe Autier, Clarisse Héry
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Manuscript writing: Philippe Autier, Graham Byrnes
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