

Tumor Size and Breast Cancer Detection: What Might Be the Effect of a Less Sensitive Screening Tool Than Mammography?

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■ **Abstract:** In some limited-resource areas, a state-of-the-art mammography program is not affordable. In such circumstances, one might consider a less resource-intensive, but also less sensitive screening tool such as clinical breast examination (CBE). We used data from the Swedish Two-County Trial to estimate the shift in tumor size resulting from invitation to mammographic screening. By postulating a lesser benefit of a less sensitive screening tool (CBE), particularly in terms of detecting very small tumors, we predicted its likely effect on tumor size distribution. In addition, using the observed association between tumor size and nodal status, and between tumor size and fatality, we predicted the likely benefit in terms of reductions in node-positive disease and in breast cancer mortality. An invitation to mammographic screening was associated with a 27% reduction in the number of node-positive tumors and a 31% reduction in the number of breast cancer deaths. We estimate that in the trial population, screening with CBE alone would have led to an 11% reduction in node-positive tumors and an 11% reduction in breast cancer deaths (approximately 42 deaths prevented per 1000 cases). Assuming instead a tumor size distribution typical of a limited-resource setting (70% of tumors are 30 mm at presentation), we estimate that screening with CBE alone would lead to a 13% reduction in node-positive tumors and a 12% reduction in breast cancer deaths (approximately 72 deaths prevented per 1000 cases). Thus, although the relative benefit of CBE is only slightly greater in the limited-resource setting, the absolute reduction in deaths per case is about 70% higher. Our findings suggest that a less sensitive tool might be expected to confer a breast cancer mortality reduction about half of that observed with mammography. ■

Key Words: breast cancer, clinical breast examination, early detection, mammography, mortality, screening, tumor size

Randomized trials show that breast cancer mortality reductions on the order of 20–30% are observed in association with invitation to breast cancer screening with mammography, and that greater reductions may be expected in association with actually being screened (1,2). More recent research on service screening programs suggests that participation in modern, organized service screening may well reduce the risk of dying from breast cancer by 40% or more (3).

Mammography is the only single screening modality with a strong evidence base for its efficacy in reducing

breast cancer mortality, and as such it is the first recommendation for advancing the diagnosis of breast cancer and thus preventing death from the disease. In a developed country with a high level of awareness about the importance of early detection, and thus prompt seeking of health care services when new symptoms develop, stage at clinical presentation is such that one could not reasonably expect a substantial improvement in stage by any less sensitive screening modality than mammography. There is, however, interest in considering the use of less resource-intensive methods for countries that cannot afford a mass mammography program. It should be noted, however, that in countries with very limited resources, where there is not even general access to surgical treatment for cancer, early detection is not worth considering at this time, and the main objective for such countries must be the delivery of basic treatment.

Possible less sensitive and less resource-intensive methods for earlier diagnosis of breast cancer include education in

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breast awareness, training in breast self-examination (BSE), and regular clinical breast examination (CBE) by experienced personnel (4). Breast awareness is a difficult concept to measure, but it is clear that increased awareness has contributed to a downshift in stage at diagnosis in the absence of, or in addition to, that contributed by formal screening (5). Although it seems reasonable that physical examination could be a pathway to earlier diagnosis in limited-resource settings, at the moment, there are no randomized trial results establishing a mortality-reducing benefit of BSE or CBE (6,7), so these approaches cannot be recommended outside of the research/evaluation setting. However, it would be useful to those planning such research studies to have some prior idea of the likely benefit of such less sensitive screening tools.

In this article we examine the effect of mammographic screening, within a randomized controlled trial, on the size distribution of tumors diagnosed and the consequences for risk of node-positive disease and subsequent death from breast cancer. We postulate lesser effects on the size distribution of CBE, a screening test of lower sensitivity, and estimate the likely consequences of these effects for node-positive disease and breast cancer mortality. We provide estimates both for the trial population with its observed tumor size distribution and for the same population after applying a tumor size distribution typical of a limited-resource setting.

METHODS

Our data are from the Swedish Two-County Trial of mammographic screening for breast cancer (1). In this study, 77,080 women age 40–74 years were randomized to regular invitation to mammographic screening (active study population [ASP]) and 55,985 were randomized to no invitation (passive study population [PSP]). In the ASP, women age 40–49 years at randomization were invited every 2 years, and women age 50–74 years were invited every 33 months. After 7 years, the first mortality results were published, showing a significant 30% reduction in breast cancer mortality with an invitation to screening (8), the control group was invited for screening, and the trial was closed. During the trial, 2468 breast cancers were diagnosed, of which 2299 were invasive. Of the invasive cases, we had tumor size data on 2294 (99.8%) and nodal status data on 2147 (93.4%). At the time of our most recent publication of trial results, we had more than 20-years maximum follow-up (1). Our analyses in this article are based only on the invasive cases, as very few deaths arise from ductal carcinoma in situ (DCIS) and because an

alternative screening tool such as CBE is unlikely to detect large numbers of in situ cases.

We first tabulated the tumor size distributions in the ASP and PSP. We then tabulated the proportions of node-positive cases and the 20-year fatality rates from breast cancer by tumor size. From these, we derived the shifts in tumor size and the consequent changes in proportions of node-positive cases and fatal cases resulting from the mammographic screening. By applying hypothesized lesser shifts in tumor size from a screening test of lesser sensitivity (CBE), we predicted the likely reductions in node-positive disease and breast cancer deaths from such a test. The methodology is as described in our article on detection of early stage invasive disease and DCIS (9), but it is best explained by demonstration, as in the “Results” section below. Finally, to predict possible reductions in node-positive disease and breast cancer deaths in the limited-resource setting with the use of a less sensitive test, we repeated the calculations assuming that the majority of cancers were of a late stage at presentation.

RESULTS

Table 1 shows the observed distribution of sizes of invasive tumors in the ASP and PSP. Clearly there was a considerable shift toward smaller tumors in the ASP. More than 40% of tumors in the ASP were smaller than 15 mm, whereas less than 30% of PSP tumors were of this size.

If we assume that any shift in tumor size as a result of screening in the ASP is no greater than one size category, we can derive the numbers and percentages shifted to and from each category. For example, on the basis of the rate of tumors of size 50 mm or more in the PSP, the number of cancers one would expect in this category in the ASP is

$$E_{50} = 77,080 \times 76/55,985 = 105.$$

Table 1. Size Distribution of Invasive Tumors by Trial Arm^a

Size (mm)	ASP, no. (%)	PSP, no. (%)
1–9	249 (19)	105 (11)
10–14	319 (24)	179 (18)
15–19	259 (20)	202 (20)
20–29	270 (21)	264 (26)
30–49	128 (10)	167 (17)
50+	76 (6)	76 (8)
Total	1301 (100)	993 (100)

^aThe trial randomized 77,080 women to the ASP (active study population: invitation to mammographic screening) and 55,985 women to the PSP (passive study population: no invitation).

Table 2. Estimated Downshifting of Tumor Size in the ASP^a

Size (mm)	Shifted to lower size category (%)
1–9	—
10–14	69
15–19	87
20–29	62
30–49	57
50+	28

^aPercentages of tumors from each size category in the ASP (active study population: invitation to mammographic screening) estimated to have been shifted to the immediate lower size category, assuming shifts of two categories or more are impossible.

In fact, we observed 76 such tumors in the ASP, so we derive a shift of 29 tumors (29/105 = 28%) from size 50 mm or more to 30–49 mm. The same procedure gives the expected number of tumors in the 30–49 mm category in the ASP as 230. Removing the 29 tumors downshifted from the 50 mm or more group, we have 99 tumors observed in this category in the ASP. Thus we calculated that 230 – 99 = 131 tumors have been shifted from size category 30–49 mm to 20–29 mm (131/230 = 57%). Carrying on with this procedure gives the derived size-shifted percentages in Table 2. These percentages correspond to 798 tumors size-shifted in the ASP, which is 86% of the screen-detected tumors. These shifts resulted in an observed 27% reduction in the number of node-positive tumors and a 31% reduction in the number of breast cancer deaths (Table 3).

Figure 1 shows the observed 21-year survival by tumor size (regardless of trial arm). The corresponding observed proportions of node-positive tumors and 20-year fatality rates are shown in Table 4. Clearly there are very strong gradients of increasing fatality and increasing node positivity with increasing tumor size. By applying these rates to the actual number of invasive tumors by size and trial arm, given in Table 1, one can derive the expected number of node-positive cases in each trial arm (407 in the ASP

Table 3. Node Positivity and Breast Cancer Deaths by Trial Arm

	ASP (n = 77,080)	PSP (n = 55,985)
Node-positive tumors		
No.	366	365
RR (95% CI)	0.73 (0.63–0.85)	1.00 (—) ^a
Breast cancer deaths		
No.	319	334
RR (95% CI)	0.69 (0.59–0.81)	1.00 (—) ^a

^aReference group. ASP, active study population (invitation to mammographic screening); CI, confidence interval; PSP, passive study population (no invitation); RR, relative risk.

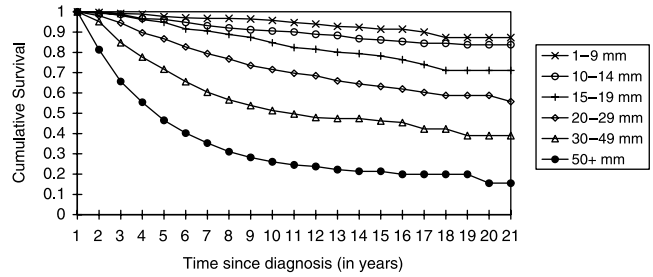


Figure 1. Survival of 2294 invasive breast cancer cases by tumor size.

and 380 in the PSP)—note that greater numbers of cases (and not a higher rate) are expected in the ASP because the size of the ASP was 38% larger than that of the PSP. The expected incidence of node-positive disease in the ASP and PSP is therefore 5.28 and 6.78 per 1000 women, respectively. This represents an expected 22% reduction in the incidence of node-positive disease with an invitation to screening. The actual reduction achieved was 27% (Table 3). Similarly we would expect 419 breast cancer deaths in the ASP and 383 in the PSP and respective fatality rates of 5.43 and 6.83 per 1000 women. The expected reduction in fatality is therefore 21%, considerably less than the actual reduction of 31% (Table 3). Thus this methodology gives a conservative estimate of the mortality-reducing benefit of screening.

The percent of cases shifted to a lower size category, assuming a less sensitive screening tool such as CBE instead of mammography, are given in Table 5. The assumed relative benefit of CBE (when compared with mammography) is somewhat arbitrary, due to a lack of available evidence, but we nevertheless believe the predicted estimates to be reasonable. The hypothesized effect of using this screening tool on the distribution of tumor size (assuming for simplicity, equal-size study arms) is shown in Table 6. The predicted number of cases in the size group of 50 mm, for example, is

$$P_{50} = 76 \times 0.72 = 55.$$

Therefore, for the 30–49 mm category,

Table 4. Node Positivity and Fatality by Tumor Size for the Trial Population Overall

Size (mm)	Node-positive tumors (%)	20-year fatality rate (%)
1–9	5	13
10–14	19	16
15–19	29	29
20–29	42	43
30–49	65	62
50+	82	85

Table 5. Predicted Downshifting of Tumor Size in the ASP with the Use of CBE, a Less Sensitive Tool Than Mammography^a

Size (mm)	Shifted to a lower size category: screening with mammography (%)	Assumed relative benefit of CBE as a screening tool	Shifted to a lower size category: screening with CBE (%)
1–9	—	—	—
10–14	69	0	0
15–19	87	0.4	35
20–29	62	0.6	37
30–49	57	0.8	46
50+	28	1.0	28

^aPercentages of tumors from each size category in the ASP estimated to have been shifted to the immediate lower size category, assuming use of a less sensitive screening tool than mammography and that shifts of two categories or more are impossible. ASP, active study population (invitation to mammographic screening); CBE, clinical breast examination.

$$P_{30-49} = 167 \times 0.54 + (76 - 55) = 90 + 21 = 111$$

(i.e., the number of cases not expected to downshift to the 20–29 mm category plus the number of cases downshifted from the 50 mm category). Again applying the observed node-positive and fatality rates from Table 4 to the hypothesized tumor size distribution (Table 6), we obtain respective estimates of 11% for the predicted reduction in node-positive tumors and 11% for the reduction in breast cancer deaths. This corresponds to a total of 42 deaths avoided in 993 cases. We carried out similar calculations using the joint effects of tumor size and nodal status, and found the predicted reductions in the number of node-positive cases and breast cancer deaths to be the same.

Unlike the situation described above, which derives from a northern European population, in many limited-resource countries, stage at presentation is typically more advanced (10). Thus in order to obtain more pragmatic estimates of the effects on nodal status and breast cancer deaths, we reweighted our PSP numbers to ensure that

Table 6. Hypothesized Distribution of Tumor Size When Screening with CBE, Equalized Over the Study Arms

Size (mm)	ASP, predicted no. (%)	PSP, observed no. (%)
1–9	105 (11)	105 (11)
10–14	250 (25)	179 (18)
15–19	229 (23)	202 (20)
20–29	243 (24)	264 (26)
30–49	111 (11)	167 (17)
50+	55 (6)	76 (8)

ASP, active study population (invitation to mammographic screening); CBE, clinical breast examination; PSP, passive study population (no invitation).

Table 7. Hypothesized Distribution of Tumor Size When Screening with CBE in a Limited-Resource Country Where the Disease Typically Presents at a Late Stage

Size (mm)	ASP, predicted no. (%)	PSP, observed no. (%)
1–9	42 (4)	42 (4)
10–14	99 (10)	71 (7)
15–19	91 (9)	81 (8)
20–29	286 (29)	105 (11)
30–49	340 (34)	477 (48)
50+	135 (14)	217 (22)

ASP, active study population (invitation to mammographic screening); CBE, clinical breast examination; PSP, passive study population (no invitation).

70% of the tumors were in the 30 mm or more categories, thereafter distributing cases among the categories in the same ratios as before. The numbers in each study arm and size category, after this reallocation, are given in Table 7. Applying the node positivity and fatality rates from Table 4 as before, we predict that screening for breast cancer with CBE alone in a limited-resource country would lead to a 13% reduction in node-positive cases and a 12% reduction in breast cancer deaths. This corresponds to the prevention of 72 deaths in 993 cases. Thus, although the relative benefit is only slightly greater in an environment where late stage at presentation prevails, the absolute reduction in deaths per case is about 70% higher.

DISCUSSION

The use of a less sensitive screening tool than mammography would be expected to result in a lesser impact on tumor size, lymph node status, and breast cancer mortality than that observed with mammography. Our results, based on plausible assumptions about the relative effect of a less sensitive screening tool in terms of size shifting, suggest that the benefit might approach half of the benefit of invitation to mammography observed in the trials, with an 11–13% reduction in node-positive disease and in breast cancer deaths. Thomas et al. (6) found an 8% reduction in node-positive cases and an 11% reduction in tumors of stage T2 or worse in a trial of BSE in Shanghai. Our predicted percentage size shifts correspond to an absolute number of size-shifted tumors that is about half of the number estimated from mammography. This is consistent with Alexander's estimates of sensitivity of around 40% for CBE and around 60–80% for mammography (11).

Our predictions are arguably conservative, as the mortality reduction predicted from the observed shift in tumor size distribution with invitation to mammography

underestimated the observed mortality reduction by a factor of one-third. However, the Two-County Trial resulted in a relatively high mortality-reducing benefit compared with the other breast screening trials and had a very high participation rate, 85% on average (12). In a limited-resource country, one would not expect such a high participation rate. However, the effects of the offer of such an intervention would almost certainly include an increase in awareness that would in turn ameliorate stage at presentation, so that the overall benefit might be greater than estimated.

It is therefore unlikely that the benefit of a less sensitive screening method such as CBE would confer a breast cancer mortality reduction substantially greater than the 11–13% predicted here. One would clearly prefer to achieve the substantial benefit of mammographic screening, and indeed mammography is becoming more widespread worldwide, including areas of Africa and eastern Europe that would be considered limited-resource areas (13,14). However, it is not an option for some limited-resource areas, and the lesser benefit might still be worth pursuing, especially if one assumes that some additional improvements could derive from a steady growth in awareness and prompt seeking of health care when a woman first notices a change in her breast. The following caveats should be borne in mind, however:

- Early detection is of no use if treatment facilities are not available. Any early detection or awareness program should be accompanied by efforts to ensure timely delivery of responsive, appropriate treatment of the cases diagnosed.
- In some countries, attitudes are as much a barrier to early detection as limited resources. For example, in a trial of breast cancer screening by CBE in the Philippines, intervention was discontinued due to noncompliance of women recalled for further assessment of suspicious lumps (7). Thus the introduction of screening may also need to be accompanied by behavioral interventions.
- Breast cancer incidence in limited-resource areas is often considerably lower than that in the developed countries of Europe, North America, and Australia. This has implications for cost-effectiveness, even of screening methods requiring minimal resources. However, increas-

ing incidence in some of these settings, and lower average age at onset due to cohort effects, with considerably more potential years of life lost, are also considerations.

Acknowledgments

This article was presented in part at the second biennial Global Summit Consensus Conference on International Breast Health Care, Bethesda, MD, January 12–15, 2005.

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