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The relative contributions of screen-detected *in situ* and invasive breast carcinomas in reducing mortality from the disease

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Abstract

We aimed to quantify the benefits of detecting ductal carcinoma *in situ* (DCIS) and of downwards stage-shifting within invasive tumours in mammographic screening. Using data from the Swedish Two-County Trial of breast cancer screening, we examined the 20-year death rates from invasive tumours of stage II or worse, invasive tumours of stage I and DCIS. We then used these rates and their respective incidences in invited (active study population, ASP) and control (passive study population, PSP) arms of the trial, to estimate the numbers of deaths avoided by downward stage-shifting the larger stage II or worse tumours to stage I and the stage I cancers to DCIS. We also studied the association between the mortality reduction achieved and the proportion of DCIS cases detected in the randomised trials of breast cancer screening. In the Swedish Two County Trial, 141 breast cancer deaths were avoided in the ASP compared with the PSP at approximately 20 years of follow-up. Of these, 65% (91/141) were avoided as a result of stage-shifting from invasive stage II or worse to invasive stage I, and 5% (7/141) as a result of stage-shifting from invasive stage I to DCIS. If we assumed that 10% of stage II or worse tumours avoided were shifted not to stage I, but to DCIS, the estimated number of deaths prevented by shifting from invasive disease to *in situ* was 17, which is 12% of all deaths prevented. When the results of all the randomised trials of breast cancer screening were reviewed, there was no clear association between the percentage of DCIS cases diagnosed and the observed mortality reduction. We conclude that compared with downward stage-shifting of invasive tumours, detection of DCIS plays a small part in saving lives from breast cancer. Treatment decisions in DCIS, as in invasive carcinoma, should take full account of histopathological, clinical and radiological attributes of the tumour.

Keywords: Mammography; Ductal carcinoma *in situ*; Breast cancer screening; Invasive breast cancer

1. Introduction

The randomised controlled trials of mammographic screening for breast cancer prove that the intervention of offering screening reduces mortality from the disease by 20–30% [1–3]. There is good evidence that in a population that actually attends screening mammography, the reduction can be considerably greater, exceeding 50% [4]. Encouragingly, several organised national mammographic screening programmes have been set up with typical attendance rates of around 70% [5,6]. In other countries that do not offer organised national programmes, there is a considerable amount of private and local screening activity [7], including so-called opportunistic screening. While some concerns have been raised about the human and resource costs of the intervention [8,9], there is a broad consensus in higher-risk areas such as Western Europe and North America, that the benefits of mortality reduction outweigh the costs.

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Yet within this broad consensus there are questions as to the cost-effectiveness of mortality reduction within subsets of breast cancer. One area of uncertainty is in the value of diagnosis of ductal carcinoma *in situ* (DCIS) by screening [10–14]. Some commentators believe that the bulk of such detection is forestalling the incidence of large numbers of invasive tumours and is therefore contributing substantially to saving lives [15]. Others assert that DCIS is a disease wherein a certain percentage of cases will never progress to invasive breast cancer and therefore will not ultimately result in death, so that its detection mainly constitutes over-diagnosis and as such is therefore a net cause of harm rather than benefit [16]. Increased incidence of DCIS has been reported in the USA [11], and relatively high percentages of DCIS cases have been observed elsewhere [12,13]. In addition, considerable variation between the randomised trials of screening with respect to the percentage of DCIS cases has been reported [14].

In this paper, we use data from the Swedish Two-County Study, a randomised controlled trial of invitation to mammographic screening, to quantify that part of the mortality reduction in the invited group which is attributable to the detection of DCIS. We also review the percentages of DCIS diagnosed in all the breast screening trials in relation to the most recently published mortality reductions in those trials.

2. Patients and methods

The Swedish Two-County Study was a randomised controlled trial of invitation to mammographic screening. The trial took place in Kopparberg (W), now called Dalarna, and Östergötland (E) counties in Sweden. The trial randomised 77 080 women aged 40–74 years to invitation to screening (active study population, ASP) and 55 985 women to no invitation (passive study population, PSP). The trial started in 1977 in W-county and 1978 in E-county. Women aged 40–49 years were invited on average every 24 months and women aged 50–74 years every 33 months. On observation of a significant mortality reduction in the ASP (between seven and eight years after randomisation), the PSP was invited to screening and the trial closed thereafter.

During the course of the trial, 2468 cancers were diagnosed, 1426 in the ASP and 1042 in the PSP. These were then followed-up for mortality. There is now around 20 years of follow-up (maximum 22) on these cases. On long-term follow-up, the basic result of the trial has remained the same, a significant 30% reduction in deaths from breast cancer in the ASP compared with the PSP [17].

From the follow-up data, we calculated the 20-year fatality rates (breast cancer deaths only) from DCIS, stage I invasive carcinoma, and invasive carcinoma of stage II or worse, using the product-limit method. We also calculated the total number of breast cancer deaths avoided in the ASP as $E_D - O_D$, where O_D is the number of breast cancer deaths in the ASP, and E_D the number expected in the ASP on the basis of the cumulative rate of breast cancer deaths in the PSP. That is,

$$E_D = N_{ASP}(D_{PSP}/N_{PSP})$$

where N_{ASP} and N_{PSP} are the numbers of subjects in the ASP and PSP, and D_{PSP} is the number of breast cancer deaths in the PSP. Similarly, we calculated the number of stage II or worse invasive cancers that were avoided as $E_2 - O_2$, where O_2 is the number of stage II or worse cancers observed in the ASP, and E_2 the number expected from the rate in the PSP, i.e.

$$E_2 = N_{ASP}(T_{PSP}/N_{PSP})$$

where T_{PSP} is the number of stage II or worse invasive cancers in the PSP. The number of deaths avoided by stage-shifting from stage II or worse invasive carcinoma downward to stage I was calculated as the number of tumours stage-shifted multiplied by the fatality rate from tumours of stage II or worse, minus the number of stage-shifted tumours multiplied by the fatality rate from stage I cancers. Thus, the number of deaths avoided is estimated to be

$$(E_2 - O_2)(R_2 - R_1)$$

where R_2 is the fatality rate of stage II or worse tumours and R_1 the fatality rate of stage I cancers. The rationale for this is that the stage-shifted tumours have the fatality rate R_1, but would have had the fatality rate R_2 if invitation to screening had not taken place and they had therefore not been stage-shifted.

The number of invasive tumours avoided by stage-shifting tumours from stage I to DCIS in the ASP was calculated as $E_I - O_I$, where O_I is the observed number of invasive tumours in the ASP and E_I the number expected from the rate of invasive cancers in the PSP. The number of deaths avoided in the ASP by stage shifting from invasive disease to DCIS was calculated as

$$(E_I - O_I)(R_1 - R_{DCIS})$$

where R_{DCIS} is the fatality rate of ductal carcinoma *in situ* cases. This assumes that all stage-shifting to DCIS is from stage I invasive carcinoma. DCIS is traditionally supposed to have no associated fatality, but some DCIS cases are followed by recurrence as invasive carcinoma, and sometimes death thereafter. Where the first diagnosis of breast cancer was DCIS, and death from breast cancer results, the survival analysis classifies this as fatality from DCIS.

Percentages of DCIS in the study groups of the various breast cancer screening trials were obtained from Fletcher and colleagues [14]. The most recent mortality reductions reported (from primary research rather than meta-analyses) in the trials were ascertained by a computerised literature search.

3. Results

Table 1 shows the numbers of subjects in the ASP and PSP in the Two-County Study, with the corresponding numbers of DCIS cases, invasive cases, invasive stage II or worse cases, and deaths from breast cancer. The table also gives the cumulative rates of these, and illustrates the calculation of breast cancer deaths, invasive cases and stage II or worse cases avoided. The number of breast cancer deaths avoided in the ASP was 141. There were 240 invasive tumours of stage II or worse avoided. The deficit of invasive cases as a whole in the ASP was 68, balanced approximately by an excess of 60 DCIS cases. Table 2 shows the same cumulative rates per thousand, with relative risks and 95% confidence intervals (CI).

Table 3 shows the 20-year death rates for invasive carcinoma of stage II or worse, stage I invasive carcinoma and DCIS, with the numbers of cases and deaths prevented by stage-shifting in the ASP. The number of lives saved due to stage-shifting from stage II or worse tumours to stage I was estimated as 91. Thus, 65% (91/141) of the deaths avoided were due to stage shifting in the invasive phase rather than the DCIS phase of the tumour (from stage II or worse to stage I). The number of lives saved due to stage-shifting from stage I invasive carcinoma to DCIS was estimated as 7, so that an estimated 5% (7/141) of lives saved were due to stage-shifting from stage I invasive carcinoma to DCIS.

We also relaxed the assumption that all stage-shifting to DCIS was from invasive stage I disease only, and re-estimated the number of deaths avoided assuming that 10% of the stage II or worse cancers avoided were stage-shifted to DCIS. This yields an estimate of 17 deaths prevented by shifting from invasive disease to DCIS, 12% of all deaths prevented.

Table 4 shows the percentages of DCIS cases diagnosed in the invited (study) groups of the various screening trials [14] and the most recently reported mortality reductions from those trials [17–24]. There is, if anything, a negative correlation between percentage of DCIS cases and the size of the mortality reduction.

4. Discussion

The results above suggest that detection by screening of those DCIS cases which would otherwise have progressed to invasive carcinoma does indeed save some lives, but considerably fewer than are saved by the early detection of invasive disease. In the Two-County Study, 5% of the deaths avoided were due to stage-shifting from invasive cancer to DCIS, whereas 65% were avoided by stage-shifting from invasive carcinoma of stage II or worse to invasive carcinoma of stage I. The remaining 30% of deaths avoided are likely to be due to further stage-shifting within stage I invasive tumours and within stage II or worse invasive tumours. Our assumption that all of the stage-shifting to DCIS is from the stage I invasive cases is debatable. We therefore also estimated the numbers of deaths prevented by shifting to DCIS assuming that 10% of the stage II or worse tumours avoided were shifted to DCIS. This yielded 17 deaths prevented by detection of DCIS, 12% of the total deaths avoided. It would be of considerable interest to see the corresponding results from other screening trials.

One might argue that had detection rates of DCIS been higher, there would have been a greater mortality reduction. Although this may be true, it is difficult for several reasons to envisage a shift from invasive to *in situ* disease achieving a mortality reduction comparable to that obtained by stage-shifting within the invasive tumours. Ninety-one deaths were avoided by stage-shifting invasive cancers from stage 2 or worse to stage I. To achieve this same magnitude of mortality reduction

Table 1
Breast cancer deaths, stage II or worse cases, invasive cases and *in situ* cases by study group, with cumulative rates and estimated numbers prevented in the ASP

Outcome	PSP			ASP				
	Observed (a)	Population (b)	Rate ($c=a/b$)	Observed (d)	Population (e)	Rate $f=d/e$)	Expected from control ($g=c\times e$)	Outcomes avoided in ASP ($h=g-d$)
Breast cancer deaths	334	55,985	0.00597	319	77,080	0.00414	460	141
Invasive stage II+	555	55,985	0.00991	524	77,080	0.00680	764	240
All invasive	996	55,985	0.01779	1303	77,080	0.01690	1371	68
DCIS	46	55,985	0.00082	123	77,080	0.00160	63	−60[a]

DCIS, ductal carcinoma *in situ*; PSP, passive study population; ASP, active study population.
[a] Excess of 60 cases of DCIS in the ASP.

Table 2
Cumulative rates per 1000 women randomised of DCIS, invasive cancer as a whole, invasive cancer at stage II or worse, and death from breast cancer by study group, with relative risks (RR) (ASP/PSP) and 95% confidence intervals (CI), Swedish Two-County Study. Cases occurred during the period of the trial, approximately 1977–1985, deaths long-term follow-up 1977–1998

Quantity	Rate in PSP	Rate in ASP	RR (95% CI)
Death from breast cancer	5.97	4.14	0.69 (0.59–0.81)
Invasive cancer stage II+	9.91	6.80	0.69 (0.61–0.78)
Invasive cancer	17.79	16.90	0.95 (0.87–1.04)
DCIS	0.82	1.60	1.95 (1.38–2.74)

by stage-shifting stage I cancers to DCIS would require shifting 700 cases (almost 50%) to DCIS. This would mean that around half the tumours in the ASP would have to be DCIS cases. Given the approximate 85% attendance rates, this would require DCIS detection rates of around 4 per thousand at prevalence screen and 2 per thousand at subsequent incidence screens. Even if we assume that 10%, say, of invasive stage II or worse cases could be stage-shifted to DCIS, doing so would still require a total of 491 (34%) of ASP cases to be DCIS; prevalence and incidence screen detection rates of around 3 and 1.5 per thousand, respectively, would be necessary. Achieving detection rates of this magnitude in DCIS cases which are destined to progress to invasive disease would involve a diagnostic approach of such aggressiveness that it would be very likely to lead to considerably greater levels of overdiagnosis (i.e., of non-invasive disease which will not progress) and would certainly give rise to concerns about the balance between benefits and harms.

Does the finding that detection of DCIS makes a relatively small contribution to the reduction in mortality conferred by mammographic screening mean that the detection and treatment of DCIS is not worthwhile? The answer must be no. There may be a further reduction in invasive cases after the screening phase of the trial which is not observed here, but is due to DCIS detection during the screening phase. Furthermore, in our study, the excess of DCIS cases in the ASP was balanced by a deficit of invasive cases, suggesting no serious overdiagnosis of DCIS. In our companion paper [25], the rate of overdiagnosed cases is estimated to be very small from our study and from various service screening programmes worldwide. When a case of DCIS is excised it cannot be known for certain what would have happened had the excision not taken place. The fact that a number of such cases recur as DCIS or invasive disease despite excision and further treatment strongly suggests that treatment is worthwhile and that a much larger number would progress to invasion in the absence of early detection and treatment. Furthermore, the findings of Evans and colleagues [26], that the majority of screen-detected DCIS are of high grade and necrotic strongly suggests that such cases are at a high risk of progression to invasive disease.

There is a convention that very high rates of DCIS have resulted from the widespread adoption of mammographic screening [11]. This is true in relative terms, since before the era of mammography, DCIS was almost unheard of, and therefore the modest absolute incidence of DCIS of 15–20 per 100 000 in the mid-1990s is nevertheless 2–300% higher than in the early 1980s [27]. Absolute detection rates of DCIS tend to be around 1 per thousand at the prevalence screen and 0.5 per thousand at subsequent screens [1,12,13,17,28–32].

Many DCIS cases are detected on the mammogram by finding calcifications of varying patterns. This is a relatively easy sign to observe, whereas the perception of subtle, non-specific asymmetric densities as the earliest signs of small invasive tumours are considerably more difficult. Programmes that have the radiographic quality and radiological sensitivity to detect small invasive tumours should be emphasised and supported; these programmes inevitably will detect DCIS.

In recent years, there has been a growing emphasis in the literature on the harms associated with mammographic screening. Included in this list of harms has been the detection of DCIS, based on evidence suggesting that perhaps only 25–35% of detected DCIS are likely to progress to invasive disease. However, much of this evidence comes from the observation of the behaviour of DCIS tumours which were mistaken for benign conditions, and these tend to be very different from the DCIS cases detected at screening, notably in that the former are of a lower grade. Clearly, overdiagnosis and overtreatment should be avoided, but it is worth quantifying these before coming to a conclusion. This is the aim of our companion paper [25]. In addition, treatment

Table 3
20-year fatality rates (product-limit estimate) by invasive status and stage, numbers shifted by stage and deaths prevented as a result

Shifted from	20-year fatality rate (%)	Shifted to	20-year fatality rate (%)	Number avoided in ASP	Deaths prevented in ASP
Invasive stage I	17	DCIS	6	68	7
Invasive stage II+	55	Invasive stage I	17	240	91

Table 4
Mortality reductions in the randomised trials of breast cancer screening and percentages of DCIS cases in the study arm of each trial

Study [Ref.]	Age range (years)	DCIS (%)	Mortality reduction (%)
HIP [18]	40–64	13	24
Malmö [19]	45–69	16	19
Two-County [17]	40–74	8	32
Edinburgh [20]	45–64	10	21
Stockholm [21]	40–64	11	26
NBSS-1 [22]	40–49	19	3
NBSS-2 [23]	50–59	17	−2
Gothenburg [24]	39–49	14	45

HIP = Health Insurance Plan of Greater New York; NBSS = Canadian National Breast Screening Study.

must be tailored to the histopathological characteristics of the tumour [33].

In conclusion, our results indicate that:

1. Most of the reduction in mortality from mammographic screening occurs as a result of the early diagnosis of invasive carcinoma.
2. The detection of DCIS within a screening programme is worthwhile, but it contributes in only a minor way to the mortality reduction gained by screening.
3. Quality control and training in mammographic screening programmes should be aimed at the detection of small invasive tumours; a programme that is efficient in the detection of such tumours will also be effective in the detection of DCIS.

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