Breast Cancer Online
www.bco.org

Breast Cancer Online (www.bco.org) 2005; **8**(7),
doi:10.1017/S1470903105003494

ISSN 1470-9031

Focus On

Modelling and analysis of DCIS detection and reduction in invasive carcinoma – a review

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Abstract Although much has been written about overdiagnosis in mammographical screening, analytical estimates of the extent of overdiagnosis are rare in the literature. Estimates specific to ductal carcinoma *in situ* (DCIS) and the implications for future invasive disease are even more difficult to find. In this paper, we review studies of incidence of DCIS within breast screening programmes and its association with subsequent incidence of invasive breast cancer. Although sparse, published results suggest that the majority of DCIS cases have the propensity to progress to invasive disease.

Keywords: Breast cancer screening; DCIS; Invasive carcinoma

Introduction

Concerns have been expressed about the possibility of overdiagnosis in breast cancer screening [1]. There is particular interest in the potential for overdiagnosis of ductal carcinoma *in situ* (DCIS) [2]. This interest arises from the following observations:

1. Incidence of DCIS has risen dramatically in proportional terms since the onset of mammographical screening programmes [3].
2. Retrospective studies of DCIS cases which were previously misdiagnosed as benign disease and untreated found that only a minority progressed to invasive disease over a long period of follow-ups [4].
3. Autopsy studies of women with no diagnosis of breast cancer during their lifetime suggest a prevalence of occult DCIS of between 9% and 15% [5].

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Publication date 29/07/05
BCO/349/2005/FO

Here, we review the published evidence on DCIS and its potential to progress to invasive disease if left untreated. Since it is not considered ethical to leave DCIS untreated, the evidence is necessarily indirect, involving deductions from rates of DCIS diagnosed, or inference from outcomes in treated DCIS. We divide the studies reviewed into two groups: clinicopathological studies relating features of tumour and treatment to prognosis and progression in treated DCIS; and inferential estimation of rates of progression from data on numbers of invasive and *in situ* tumours diagnosed in screening programmes.

Clinicopathological studies

A large number of studies have been conducted on the clinical and pathological features of DCIS which relate to future clinical outcomes. For brevity, we shall confine our review to the major implications of the most recent studies. What is very clear in the first instance is that a substantial minority of DCIS cases recur or progress *despite* treatment [6]. In a randomized trial of local excision against local excision plus radiotherapy, 19% of those treated with local excision alone had a local recurrence within a median

follow-up of 5.4 years [6]. Rates were considerably higher in younger patients, larger tumours, highgrade tumours and cases where the surgical margin showed tumour involvement. These prognostic factors in DCIS have been long-established [7], but the high absolute rates of recurrence after treatment strongly suggest that in the absence of treatment, progression would be considerably more common.

This is supported by the findings of Evans *et al*. [8], who observed that the majority of screen-detected DCIS cases were of high grade and necrotic. This suggests that a high proportion of DCIS cases detected at screening are at risk of progression to invasive cancer. Similar observations have been made in other studies of tumour biology, as reviewed by Feig [9].

Clinicopathological studies therefore indicate that the presence of DCIS confers substantial risk of invasive breast cancer. Until the discovery of markers which reliably distinguish progressive and non-progressive lesions, the clinical issue of importance is not whether to treat, but how best to decide individual treatment to prevent subsequent invasive disease [10]. In the meantime, estimation from multistate modelling of data on rates of invasive cancer and DCIS from screening programmes may at least help to quantify the proportion of DCIS tumours which are non-progressive, and so give an estimation of the potential size of the overdiagnosis/overtreatment problem.

Estimation of rates from tumour progression models

The most direct example of this approach is that of Yen *et al*. [2] who used data from screening programmes in Europe, the USA and Australia to estimate the parameters of a *mover–stayer model* as in Fig. 1. In this model, a woman may remain free of breast cancer all her life, may develop non-progressive DCIS which either remains in the breast or spontaneously regresses, or may develop progressive DCIS which in turn may progress to invasive disease.

For any given case of DCIS detected at screening, treated, and with no observed recurrence or progression so far, we cannot know what would have happened if that case had not been treated. This means that we cannot identify individual non-progressive cases. However, we can estimate the proportion of such cases from the rates of DCIS and invasive cancer observed at prevalence (first) and incidence (later) screens.

Table 1 shows the rates per thousand of DCIS at prevalence and incidence screens used by Yen and colleagues for estimation [2]. Table 2 shows the estimates derived from these data. The major implications are that at a prevalence screen, 37% of DCIS cases are estimated to be non-progressive (around 5% of all tumours diagnosed), and at incidence screen 4% of DCIS cases are non-progressive (less than 1% of all tumours).

Less directly, but more simply, Paci *et al*. [11] estimated overdiagnosis rates in the Florence breast screening programme, including and excluding DCIS. They compared incidence of breast cancer in Florence in 1990–1999 after the introduction of screening in 1990, with incidence observed before the introduction, in 1985–1989. Clearly, some excess incidence would be expected in the screening period even if there were no overdiagnosis at all, since some tumours which would otherwise have arisen clinically after 1999 would be diagnosed early by screening during 1990–1999. Paci and colleagues estimated this number using estimates of the average lead time.

Their results are shown in Table 3. An observed significant excess of 11% in invasive tumours only became a non-significant 2% excess after removal of the 'lead time' tumours. When *in situ* cases were included, there remained a significant 5% excess incidence after removal of the tumours anticipated due to lead time. These results suggest that overdiagnosis is largely confined to DCIS and is not of a magnitude which would contraindicate screening.

Finally, an interesting approach was employed by McCann *et al*. [12], who extrapolated pre-screening trends in the UK to the screening epoch, the 1990s. Comparing actual incidence in the screening epoch

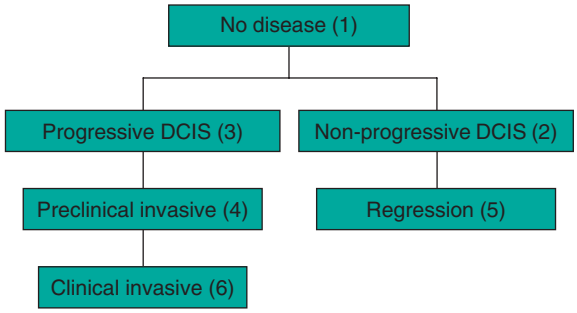

Figure 1.
Representation of a mover–stayer model for DCIS. A woman may remain disease-free, may develop non progressive DCIS or may develop progressive DCIS. If she develops progressive DCIS, this may progress to asymptomatic and subsequently symptomatic invasive breast cancer, although this progression may be arrested if the disease is detected by screening and treated while still DCIS. If she develops non-progressive DCIS, the disease cannot progress to invasive cancer and may regress. If it is detected by screening before it regresses, this consitutes overdiagnosis. The rates of development of non-progressive and progressive DCIS, and rates of further progression of the latter were estimated from the data sources in Table 1.

doi:10.1017/S1470903105003494

with that predicted from the pre-screening trends, they found an excess of all tumours in the screening age group, 50–64, peaking in the early 1990s and a deficit in incidence of invasive tumours at ages 65–69, peaking in the late 1990s. Application of a range of plausible lead times to the early excess of invasive cancers alone, in the cohorts invited to screening, could not fully account for when the DCIS cases in the early excess period were also included.

Table 1. Detection rates of DCIS and invasive breast cancer at prevalence and incidence screens in the data used to estimate the parameters of the mover–stayer model of Yen and colleagues [2].

Data source	Tumour type	Prevalence screen rate/1000	Incidence screen rate/1000
Swedish Two-County, ages 40–49	DCIS Invasive	0.4 1.7	0.4 2.4
Swedish Two-County, ages 50–59	DCIS Invasive	0.7 4.0	0.6 2.6
Swedish Two-County, ages 60–69	DCIS Invasive	0.8 8.1	0.5 4.9
UK programmes	DCIS Invasive	1.1 4.9	0.8 4.0
The Netherlands programmes	DCIS Invasive	0.8 5.1	0.5 2.8
South Australia	DCIS Invasive	1.2 5.8	0.6 2.8
New York programmes	DCIS Invasive	0.8 4.4	0.4 1.5

Table 2. Estimated detection rates of non-progressive (i.e. overdiagnosed) and progressive DCIS, and invasive disease, by screening round (prevalence/incidence), pooled estimates from all five programmes in Yen *et al*. [2].

	Detection rate/1000 of				
Screen	$DCIS_0$	$DCIS_1$	Invasive cancer (I)	$DCIS_0$/ $DCIS_1$	$DCIS_0$/ ($DCIS_1$ + I)
Prevalence	0.3	0.5	5.2	37%	5%
Incidence	0.02	0.5	2.8	4%	0.6%

$DCIS_0$, non-progressive DCIS; $DCIS_1$, progressive DCIS.

These results suggest firstly that the excess in incidence observed in screened cohorts is followed by a later deficit in invasive tumours in the same cohorts, and secondly that earlier diagnosis of DCIS explains some of the later deficit in invasive disease incidence. This is consistent with results in the Swedish Two-County Study, in which an excess of DCIS cases was observed in the group invited to screening, which was almost exactly balanced by a subsequent deficit of invasive cases in the same population [13].

Discussion

The modelling approaches described above provide some reassurance that detection of DCIS by screening is valuable and is forestalling the diagnosis of subsequent invasive disease. They suggest that there is some uncertainty about the exact size of the problem of overdiagnosis of DCIS. It would be helpful to see the results of Yen *et al*. [2] confirmed or refuted by estimation within large screening programmes from individual rather than aggregate data.

There is other published research on overdiagnosis, but not specifically addressing the DCIS question [14,15]. Also, these papers tend to concentrate only on observed rates of disease, without formal correction for lead-time effects.

Evidence from the randomized trials is not conclusive, but does not suggest a substantial problem of overdiagnosis of DCIS. Interpretation is complicated by the varying designs of the trials [16].

How do we reconcile the fact that studies of screening programmes suggest modest overdiagnosis only, with the results of the autopsy studies and the follow-up of cases of untreated DCIS? For the first problem, it should be noted that since the autopsy studies found 9–15% occult DCIS but any screening for the disease finds around 0.1% [3,5] it is likely that screen-detectable DCIS in living women is either a different clinical entity from, or a small and specialized subset of, autopsy-detectable DCIS in dead women. For the second, the untreated DCIS cases were untreated because they were misdiagnosed as benign [4], not a representative group of DCIS as a whole. Evans and colleagues [8] have shown that screen-detectable DCIS has considerably

Table 3. Excess of breast cancer cases in the Florence programme, with and without adjustment for cases anticipated due to lead time.

Tumours	Observed cases	Expected from pre-screening	Excess (%)	Anticipated cases	Observed–anticipated cases	Excess (%)
Invasive only	2626	2357	11	215	2411	2
All tumours	2780	2394	16	258	2522	5

greater aggressive potential in terms of grade and necrosis.

In conclusion, the modelling and clinical research on DCIS progression suggests that detection of DCIS in mammographical screening is conferring benefits in terms of invasive disease avoided. While there is a need for further research, the studies suggest that overdiagnosis of DCIS is a minor phenomenon.

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