ORIGINAL PAPER

Modelling the impact of detecting and treating carcinoma *in situ* in a breast screening programme

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Objectives: Screening has substantially increased the detection of carcinoma *in situ* of the breast (CIS). Opinions vary as to whether this constitutes over-diagnosis or an opportunity to interrupt breast cancer's natural history. In England, incidence of invasive cancer and CIS increased in women of screening age (50–64 years), leading to a subsequent deficit in invasive incidence in women aged 65–69 years immediately beyond the invited age range. We aimed to model underlying incidence of invasive cancer and CIS expected in the absence of screening, and to quantify the likely relative contributions of their early detection to the observed reduction in invasive cancer in women of post-screening age.

Setting: UK NHS breast screening programme in England.

Methods: Poisson regression modelling was used to establish the underlying incidence of invasive and *in situ* cancers in the absence of screening. We then estimated age- and year-specific excess detection rates attributable to screening. Applying these to population figures we estimated conservatively the relative contributions of early diagnosis of CIS and invasive cancer at 50–64 years of age to the subsequent deficit in invasive cancer in women beyond invitation age (65–69 years), for screening early in the programme and at steady state.

Results: Our model estimated a 1.6% annual increase in incidence, giving an estimated deficit of 4.22 invasive cancers per 10,000 women aged 65–69 years in 1996. Carcinoma *in situ* contributed 13–17% to the deficit, assuming a mean six year lead time and 75–100% progression to invasive cancer. At steady state, with current screening performance and with lead times of 3–4 years (invasive cancer) and 6–9 years (CIS), invasive incidence might be reduced by 5–6 cancers per 10,000 women aged 65–69 years in 2010 (15–20% of underlying incidence), CIS contributing 20–40%.

Discussion: The longer lead time associated with CIS attenuates the impact its early detection has on subsequent invasive incidence. At steady state screening, its detection contributes significantly to the deficit in invasive incidence. Our results suggest that, cancer for cancer, there may be just as much benefit in detecting and treating a case of CIS as there is in treating a case of invasive cancer.

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The introduction of breast cancer screening in the UK and elsewhere[1–3] has seen a significant rise in the number of cases of non-invasive breast cancer (carcinoma *in situ*; CIS). Since 1988, when screening was introduced in the UK, the number of extra cases of CIS detected each year in England amongst invited women (aged 50–64 years) has risen to exceed 1000. The proportion of total breast cancers contributed by CIS in this age group rose from around 3.5% over the period 1979–1987 to 11% by 1998; an extra 2.6 CIS cancers per 10,000 women per year. The majority of women in whom CIS is detected proceed to surgery – either local excision followed by radiotherapy, or full mastectomy possibly followed by Tamoxifen treatment.[1,4] However, the benefits associated with detecting and treating CIS remain largely unquantified.

As soon as CIS is detected, it is removed. There is surprisingly little information regarding the natural history of CIS.[5,6] What little there is comes predominantly from small case series of women whose breast symptoms were misdiagnosed as benign and whose only treatment was biopsy, the CIS diagnosis being made much later on re-review of pathology specimens.[2,6–13] From such series we see between 11% and 60% of cases progressing to invasive cancer within 10–20 years, although numbers of cases are extremely small (maximum 80 cases). It is also clear from autopsy studies, in which 0.2–18% of women who were not known to have had breast cancer were shown at post mortem to have CIS, that there is a proportion of latent disease in the population destined perhaps never to progress to becoming clinically apparent.[2,14–18] However, it is clear that cases included in such studies as these almost certainly represent an extremely biased subset of very slow growing cancers which are unlikely to be representative of the majority of CIS detected by screening.[2,6]

Opinion on how CIS should be approached remains very much divided. Some believe that the means to reducing invasive breast cancer incidence lie in detecting and treating CIS,[19] whilst others believe that only a small proportion of screening-detected CIS is of clinical significance, and therefore its detection and treatment constitute gross over-diagnosis with severe associated financial and emotional costs.[20,21] While it appears that CIS cases detected by screening show similar biological aggressiveness (distribution of grade, presence of necrosis) as do symptomatically presenting CIS,[22] we still remain ignorant of the malignant potential of CIS; therefore the tendency is to treat all cases as potentially progressive, which for some cases may constitute overtreatment.[5]

Given the large numbers of women in whom CIS is diagnosed, and the uncertainties regarding their optimal management, we need some measure of the relative benefits of detecting CIS and invasive cancer through screening. The

aims of this study were therefore to examine changes in age-specific breast cancer incidence with the introduction of screening, through modelling of invasive and CIS incidence expected in the absence of screening; and then to quantify the possible contributions of CIS to the observed reduction in invasive incidence in women of post-screening age.

METHODS

Modelling underlying cancer incidence

In order to reliably assess the impact of detecting and treating CIS on subsequent invasive cancer incidence, one must first estimate accurately the underlying incidence of invasive cancer and CIS expected in the absence of screening. To do this, numbers of cases of invasive cancer (International Classification of Diseases [ICD]9 174; ICD10 C50) and CIS (ICD9 2330; ICD10 D05: these include lobular CIS), and populations of women by single year of age, were obtained for England from the Office of National Statistics.[23] Of the CIS cases, the vast majority are ductal CIS, but a small proportion (<10%) of lobular CIS cases will also be included. For steady state estimations (see below) population projections for females at midyear by age last birthday were obtained from the Government actuary (http://www.gad.gov.uk/Population/index.asp); mid year projections from 2001 were used for 2001, then mid year projections from 2002 were used to estimate populations for 2002 onwards.

For modelling invasive cancer incidence, Poisson regression modelling using Stata (Stata Corporation, Texas, USA)[24] was used to fit incidence data for women aged 40–79 years by year of age for the period 1971–1987.[25,26] The model chosen incorporated age as a categorical variable and calendar year of diagnosis as a continuous variable as the main effects, with an age:year interaction term. Although likelihood ratio testing showed the fit of this model to be significantly poorer than that of the fully saturated model, the use of year of diagnosis as a continuous variable allowed, importantly, prediction of incidence beyond the period of model fitting (1971–1987), to the screening period 1988–1998.

The same method was then used to model total breast cancer incidence (invasive and CIS) over the period 1979–1988, and to predict total incidence in the absence of screening for the period 1989–1998. Data earlier than 1979 were not available for CIS by single year of age. We then estimated the underlying incidence of CIS based on its age-specific contribution to total incidence. We used age-adjusted logistic regression to establish that in the period before screening there was no difference between years of diagnosis in the proportion of total incidence contributed by CIS (odds ratio for year in the regression analysis, having adjusted for age, was 1.00 [95% CI 0.99–1.01]). To model underlying incidence of CIS after the introduction of screening, we then applied the age-specific proportions of total incidence contributed by CIS to the modelled values for total underlying incidence expected for each year after 1987 in the absence of screening.

Using this method, plots of incidence by age, year of diagnosis, or birth cohort showed good correlation with those generated using a Poisson model for CIS of the same kind as for invasive cancer and total cancer. The proportion of total incidence method using logistic regression estimates, however, gave less random fluctuation between ages or years of diagnosis. As with modelled invasive cancer incidence, the correspondence between observed and predicted values was good except where the population was affected by screening.

Estimating the contribution of early detection of invasive cancer and of CIS to subsequent deficit in invasive cancer observed in the programme

We wished to estimate the total number of cancers whose earlier diagnosis by screening at 50–64 years contributed to the subsequent deficit in invasive cancer seen in 1996 in women in the post screening age group (65–69 years). To do this, we first needed to estimate the numbers of cancers detected earlier by screening, for each year of age and year of screening, then secondly to estimate when these cancers would have arisen had screening not occurred (i.e. when they might have contributed to a deficit in incidence). This latter factor is a measure of lead time, the length of time between when a cancer is detected by screening and when it would have presented clinically.[27]

A cohort approach was used. The population of women aged 65–69 years in 1996 was followed back in time, for a period determined by a range of possible mean lead times for screening (from 1.5 to 12 years for invasive cancer, and from 3 to 15 years for CIS), in order to identify increases of invasive cancer or CIS incidence above the expected underlying incidence which might be attributed to screening. The proportion P of the excess cancers that would have arisen clinically had screening not taken place, for any given year i after screening, and for any given mean lead time (in years) x, was estimated based on a continuous exponential distribution of lead time which has been shown to be an appropriate fit,[28] using the formula

$$P = e^{(-1/x)(i-1)} - e^{(-1/x)i}$$

Since, with an exponential distribution for lead time, the screening-associated reduction in clinically presenting cancers each year following a screen will never actually reach zero, it was decided arbitrarily to follow women aged 65–69 years back from 1996 for a period over which at least 95% of cancers detected by screening would have arisen clinically. For any given mean lead time, this period was obtained by adding the proportions whose diagnosis was advanced in each year following a screen (as given by the exponential distribution) until they reached 95%. Thus, for an average two year lead time, follow up time would be six years because this is the time it would take for 95% of cancers destined to arise in the absence of screening to present clinically. The follow up times for other lead times are included in Table 1. For long lead times, follow up was arbitrarily set at a maximum 20 years for invasive cancer, and 30 years for CIS. Whilst such long lead times are perhaps implausible, they have been included for completeness.

Any excess in observed cancers above the modelled underlying rate that was detected during the period of follow up was attributed to the effect of screening and was considered to represent early diagnosis. This gave a conservative estimate for excess because no adjustment was made for the fact that observed incidence would be attenuated by prior screening in earlier years. We made assumptions that there was no screening prior to 1988, no screening outside the invited age range (50–64 years), no over-diagnosis, and no loss from the cohort (e.g. by death). We also assumed that between 25% and 100% of CIS would have progressed to the invasive state within the lead time, and we made estimations for a range of proportions progressing (25%, 50%, 75% and 100%), assuming no dependence of this proportion on actual lead time. For the final calculation of estimated number of cancers diagnosed early and contributing to the subsequent deficit in invasive cancers, the age- and year-specific excess cancers were

Table 1 Deficit in invasive cancers at 65–69 years in 1996 accounted for by early diagnosis of invasive cancers and CIS, with various lead times, during the programme

Mean lead time (years)		Follow up time (years)*	Total cancers arising (%)	Cancers diagnosed early (n)	Deficit per 10,000	Fraction of total deficit (%)†
Invasive cancers						
1.5		5	96.40	187.80	1.62	38.39
2.0		6	95.02	264.16	2.27	53.79
2.5		8	95.92	314.80	2.71	64.22
3.0		9	95.02	337.85	2.91	68.96
3.5		11	95.68	349.10	3.00	71.09
4.0		12	95.02	352.36	3.03	71.80
5.0		15	95.02	345.71	2.98	70.49
6.0		18	95.02	331.09	2.85	67.51
8.0		>20	91.80	296.53	2.55	60.47
10.0		>20	86.50	264.18	2.27	53.86
12.0		>20	81.80	236.79	2.04	48.29
CIS	Proportion progressing (%)					
3	25	9	95.02	21.20	0.18	4.32
	50	9	95.02	42.39	0.36	8.64
	75	9	95.02	63.59	0.55	12.97
	100	9	95.02	84.79	0.73	17.29
6	25	17	95.02	18.35	0.16	3.74
	50	17	95.02	36.69	0.32	7.47
	75	17	95.02	55.04	0.47	11.22
	100	17	95.02	73.39	0.63	14.96
9	25	27	95.02	14.93	0.13	3.04
	50	27	95.02	29.85	0.26	6.09
	75	27	95.02	44.78	0.39	9.13
	100	27	95.02	59.71	0.51	12.18
12	25	>30	91.79	12.41	0.11	2.53
	50	>30	91.79	24.81	0.21	5.06
	75	>30	91.79	37.22	0.32	7.59
	100	>30	91.79	49.63	0.43	10.12
15	25	>30	86.47	10.56	0.09	2.15
	50	>30	86.47	21.12	0.18	4.33
	75	>30	86.47	31.68	0.27	6.46
	100	>30	86.47	42.24	0.36	8.61

*For long lead times, calculations summing cancers were truncated at 20 (invasive) or 30 (CIS) years of follow up hence < 95% of cancers had arisen within this period. †As proportion of total 4.22 per 10,000 deficit in invasive cancers seen in 1,162,029 women aged 65–69 years in 1996.

multiplied by the proportion destined to surface clinically specific to the year post-screening and the given mean lead time. For CIS, it was also necessary to multiply by the proportion progressing to the invasive state. Cancers were summed for the entire follow up period, then divided by the population of women aged 65–69 years in 1996 (1,162,092 women), then multiplied by 10,000 to give the cancer deficit per 10,000 women attributable to earlier detection by screening.

Estimating the contribution of early detection of invasive cancer and of CIS to subsequent deficit in invasive cancer in a future steady state programme

Estimations of numbers of cancers diagnosed early and contributing to a subsequent deficit in invasive cancers were also made for steady state screening, at current programme performance and without effects due to programme set up. Once again, we assumed no screening outside the invited age range (50–64 years), no over-diagnosis, and no loss from the cohort. However, since we were estimating steady state effects, we did not preclude effects of screening prior to 1988, but assumed a constant level of screening performance. We chose to examine the deficit in invasive cancers that would occur in the year 2010; and we considered the level of screening performance achieved in the year 2000, when the programme had been running for 13 years. For expected steady state invasive and CIS cancer rates we used the mean rates achieved over the four screening years 1998–2002.[29–32] Age was used as a proxy for screen type (prevalence or incidence) thus mean first screen rates (5.2 and 1.7 cancers per 10,000 women for invasive and CIS respectively) were used as expected steady state rates for screened women aged 50–52 years, and mean incidence screen rates (4.5 and 1.2 cancers per 10,000 women for invasive and CIS respectively) were used as expected rates for screened women aged 53–64 years.

To estimate the excess cancers detected early by screening and therefore able to contribute to a later reduction in invasive incidence, we subtracted a baseline incidence expected in 2000 in the absence of screening from the steady state rates, to obtain a screening-associated excess rate for each age group. Note that this is a conservative estimate of excess since no allowance is made for interval cancers in the year of screening. Since baseline incidence may not increase indefinitely according to the model fitted over 1971–1987 (or 1979–1988 for CIS), we predicted baseline incidence for the year 2000 in three different ways. Firstly, we used the age group specific annual increases in invasive and CIS incidence as predicted by the age period model for invasive cancer, or the proportion of total incidence model for CIS, to estimate incidence in 2000 for the age groups 50–52 years and 53–64 years. Secondly, we used the actual incidence rates for CIS and invasive cancers in the age groups 50–52 years and 53–64 years observed in 1987, immediately prior to the onset of screening. Thirdly, we used the midpoint of the two preceding baselines. We made the assumption that the excess rate would not vary much between years with steady state screening.

The excess rates calculated using each of the three baselines were then multiplied by the estimated population for each relevant age group in each year to obtain estimates for

the numbers of cancers diagnosed early. Calculations were made for various lead times, multiplying the age group and year specific excess cancers by the proportion destined to surface clinically specific to the year post-screening and the given lead time, and (for CIS) the proportion progressing to the invasive state, as before. Since the screening-associated excess detection rate calculated for women screened in each year was applied to the entire population in each age group, the excess was then adjusted for the proportion of the total population covered by screening (70%)[29–32] and the frequency of screening (three-yearly).

RESULTS

Actual invasive incidence, and incidence predicted by the chosen model, are shown by year of age in Figure 1. Figure 1a illustrates the fit of the model over the period of programme set up (1989–1993) and Figure 1b illustrates fit for the period 1994–1998 after the programme was established. Predicted and actual invasive incidence increased with age, and generally corresponded well for all ages outside those invited to screening (i.e. <50 years, >64 years), indicating a good fit of the model over both periods, as expected. During programme set up, the largest difference between actual and predicted incidence occurred amongst the older invited women (60–64 years), whereas in the later period, a peak in incidence in the younger ages invited to screening (50–52 years) was noteworthy. One exception to the fit of the model in women outside the screening age range occurred once screening was established (Figure 1b), when a deficit in actual incidence compared with predicted was seen in women aged 65–69 years. Plots of incidence by year of diagnosis or birth year also showed a good fit between observed and predicted values, except where the population was affected by screening.

Actual CIS incidence, and incidence predicted by the CIS proportion of total incidence model, are shown by year of age in Figure 2 for the period of programme set up (1989–1993; Figure 2a) and the period following programme establishment (1994–1998; Figure 2b). Although there was considerable variation in actual CIS incidence, presumably due to the small number of cases, predicted and actual incidence corresponded reasonably well outside the screening ages in both periods, although in the later period, for women aged over 64 years, the model appeared to slightly underestimate the CIS rate. During programme set up, when the prevalence screen dominated, there was a large excess in observed cancers compared with predicted cancers across the entire invited age range. In the later period, when the majority of screens were incidence screens, the excess was maximal in younger women aged 50–52 years. Unlike the invasive incidence, CIS did not exhibit the trend of increasing with age: outside the screening ages, predicted incidence was maximal around 40 years of age thereafter decreasing slightly. This is consistent with the observation that the proportion of total incidence contributed by CIS actually decreases with age, as illustrated in Figure 3 which shows changes in CIS as a proportion of total incidence over time by five year age band. Amongst women aged 50–64 years, the proportion of total incidence contributed by CIS increased markedly with the onset of screening in 1988. In age groups outside those invited for screening, there was no change over time in the age-specific contribution of CIS to total incidence, indicating that the post-screening rise in CIS amongst invited age groups represents a genuine increase rather than an artefact due to improved registration.

Given that both the invasive and CIS models gave robust predictions of incidence by age, year of diagnosis and birth year, we used them to estimate age-specific underlying incidence in the absence of screening. The results for invasive cancer are shown for the age group 60–64 years in Figure 4a, and for women aged 65–69 years in Figure 4b. When screening was introduced in 1988 actual incidence increased markedly, as expected, for women aged 60–64 years (as for all screening ages), whereas predicted incidence increased smoothly with time, continuing the pre-screening trend. The difference between actual and predicted incidence reached its greatest value over the study period in 1991, when there was an excess of 9.49 invasive cancers per 10,000 women compared with the predicted number of cancers (32.11 actual *versus* 22.62 predicted cancers per

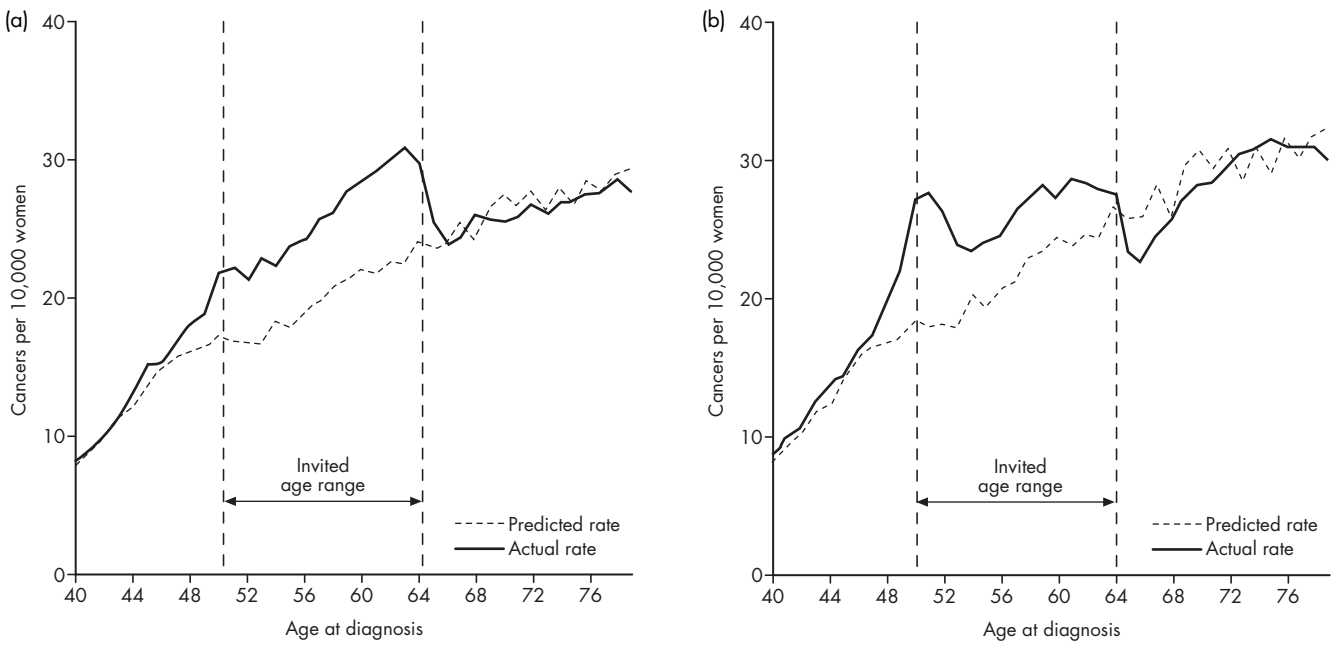

Figure 1 Actual and predicted invasive incidence by age at diagnosis, in periods 1989–1993 (Figure 1a) and 1994–1998 (Figure 1b).

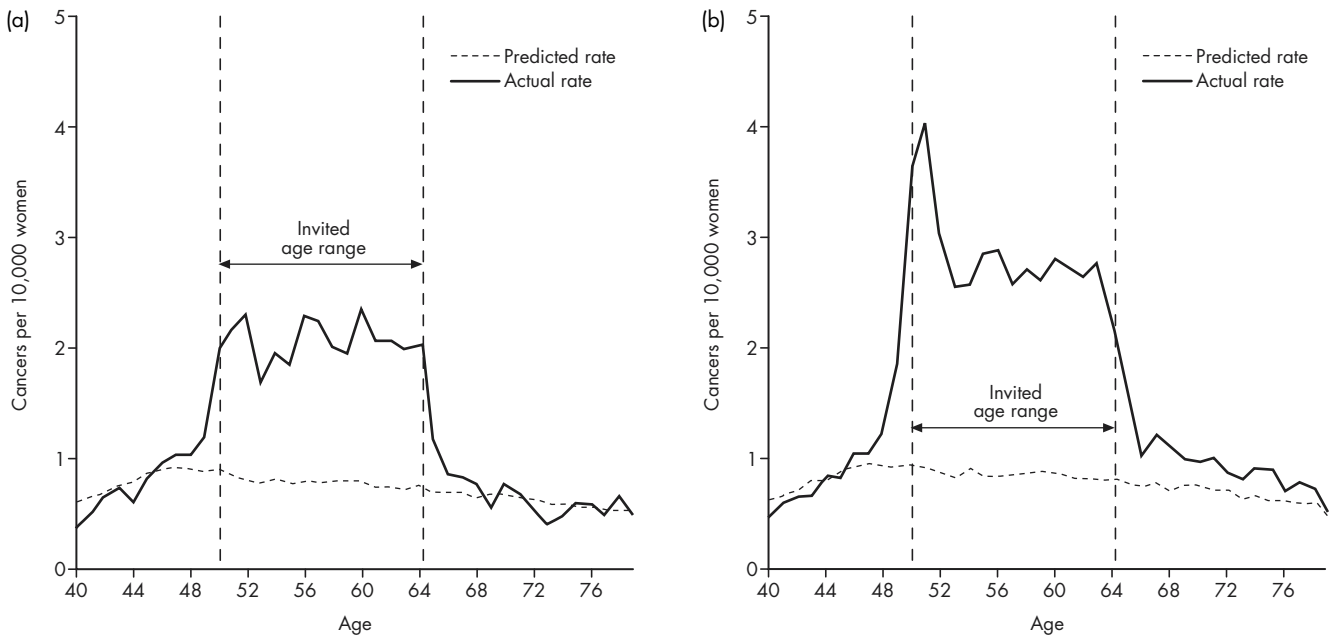

Figure 2 Actual and predicted CIS incidence by age at diagnosis, in periods 1989–1993 (Figure 2a) and 1994–1998 (Figure 2b).

10,000 women, Figure 4a). For CIS, the difference between actual and predicted incidence for women aged 60–64 years peaked in 1992 with an excess of 1.91 CIS per 10,000 women compared with predicted, thereafter falling but rising again to 2.34 CIS per 10,000 in 1998. For women aged 65–69 years, actual invasive incidence followed predicted incidence until around 1991, when actual incidence started to fall. It had reached a minimum by 1996, giving a large deficit of 4.22 cancers per 10,000 women (22.68 actual *versus* 26.91 predicted cancers per 10,000 women, Figure 4b).

We then estimated the relative contributions of the early detection of invasive cancers, and of CIS, to the observed subsequent reduction in invasive incidence. We initially focused on the deficit of 4.22 invasive cancers per 10,000 women aged 65–69 years observed in 1996 and resulting from screening early on in the programme. The contributions toward this deficit made by the early detection of both invasive cancer and CIS are shown in Table 1. The numbers of cancers diagnosed early, the corresponding deficit this would bring about in women aged 65–69 years,

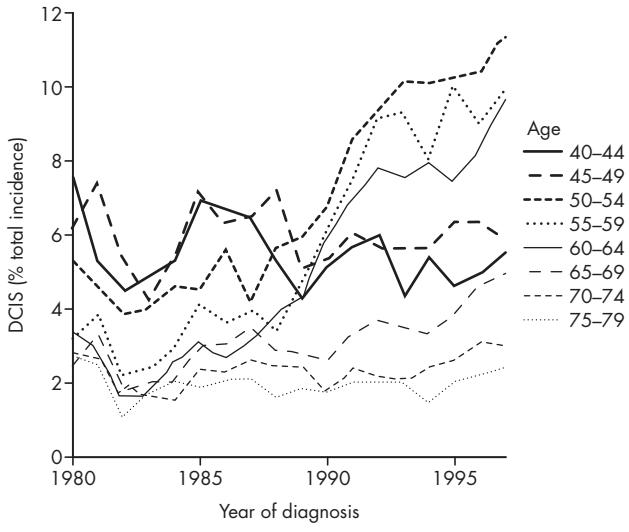

Figure 3 CIS as a proportion of total incidence in different age groups, by year of diagnosis.

and the percentage proportion this represents of the total observed deficit are given assuming various mean lead times and proportions of CIS progressing to invasive cancer. Also given are the percentage proportions of total cancers expected in the absence of screening that would arise during the given period of follow up. The maximum deficit accountable through the early detection of invasive cancer early in the programme was around 3.03 cancers per 10,000 women: it assumes a mean lead time of four years and represents 72% of the total deficit. The maximum deficit accountable through the early detection of CIS was a further 0.73 cancers per 10,000 women, 17% of total deficit, assuming a three year mean lead time and 100% progression to the invasive state. This deficit falls with longer lead times and lower proportions progressing.

It is, however, unlikely that the mean lead time for CIS is shorter than that for invasive disease. It is therefore reasonable to consider for CIS only lead times in excess of the four years which was the best fit for invasive cancers. This gives a maximum deficit accounted for through the early detection of CIS cases of 15%, with a six year mean lead time and 100% progression. With 75% progression, the proportion accounted for would be 11%, giving a total deficit accounted for of 83%.

We then considered steady state screening conditions and estimated the maximum reduction in invasive incidence in women beyond screening age that might be achieved in the future by the level of programme performance achieved in recent years. The results are given in Table 2, which shows estimated numbers of invasive cancers and CIS diagnosed early, and the corresponding deficit this would bring about in women aged 65–69 years in the year 2010, assuming a range of lead times and proportions of CIS progressing to invasive cancer, for each of three different values for baseline incidence expected in the absence of screening (see Methods).

Steady state screening increased the deficit in invasive cancers attributable to early detection of invasive cancer and CIS, especially at longer lead times. At steady state, and depending on which baseline was used in calculations, the greatest benefit in terms of early detection of invasive cancer was obtained with an eight year mean lead time, yielding an

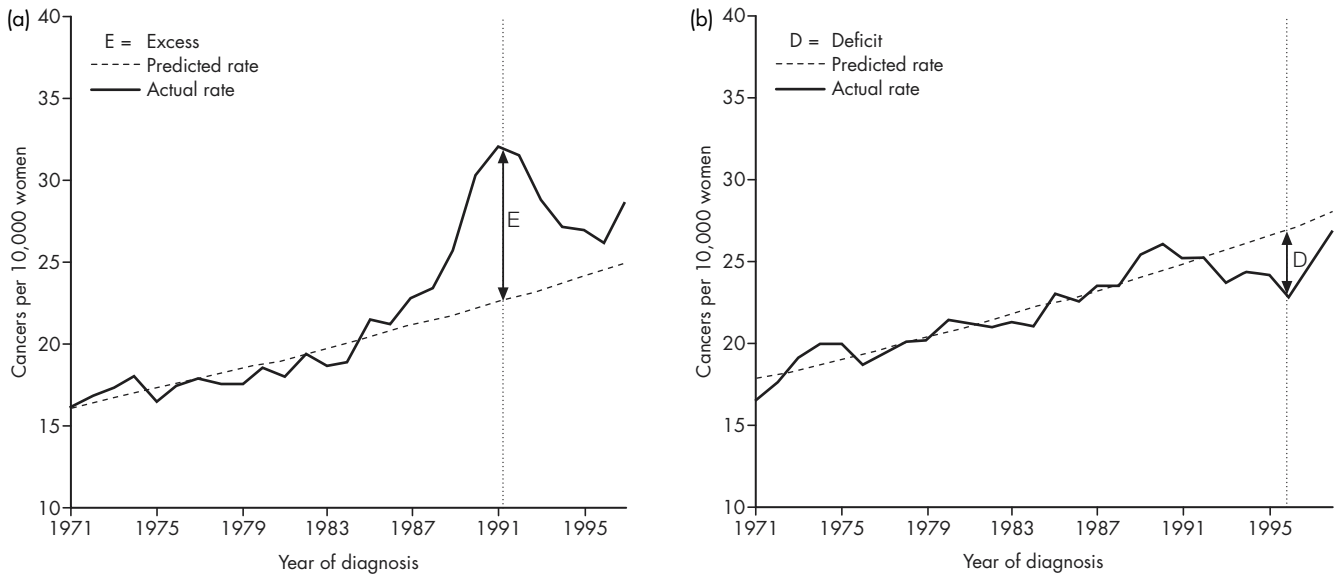

Figure 4 Actual and predicted invasive incidence by year of diagnosis, in age group 60–64 years (Figure 4a) and 65–69 years (Figure 4b).

associated reduction in subsequent invasive incidence of around 3.8–4.4 cancers per 10,000 women. With the more probable three year mean lead time, equivalent to the UK programme's current inter-screening interval, the subsequent reduction in invasive incidence was around 2.8–3.4 cancers per 10,000. The greatest benefit achieved through the early detection of CIS was obtained with a mean six year lead time, and resulted in the subsequent reduction in invasive incidence of around a further 1.9 cancers per 10,000 women, assuming 100% progression to invasive cancer, this falling to around 1.4 if only 75% progress. Thus the early detection of invasive cancer and CIS might reduce subsequent invasive incidence in the age group 65–69 years by as much as 5.7–6.3 cancers per 10,000 women. More conservatively, from the more realistic three year (invasive) and six year (CIS) mean lead time estimates, with 75%

Table 2 Deficit in invasive cancers at age 65–69 years in 2010 accounted for by early diagnosis of invasive cancers and CIS, with various lead times, at steady state screening

Mean lead time (years)		Deficit Cancers (n) and rate per 10,000					
Invasive cancers		Baseline 1*		Baseline 2†		Baseline 3‡	
		n	Rate	n	Rate	n	Rate
1.5		252.25	1.99	276.6	2.18	301.06	2.37
2.0		289.10	2.28	317.00	2.49	345.04	2.72
2.5		333.31	2.62	365.47	2.88	397.79	3.13
3.0		358.77	2.82	393.39	3.10	427.95	3.37
3.5		389.80	3.07	427.42	3.36	465.22	3.66
4.0		407.43	3.21	446.75	3.52	486.26	3.83
5.0		449.04	3.53	491.44	3.87	534.06	4.20
6.0		475.29	3.74	518.98	4.08	562.88	4.43
8.0		477.80	3.76	520.76	4.10	563.93	4.44
10.0		462.60	3.64	503.56	3.96	544.72	4.29
12.0		440.95	3.47	479.55	3.77	518.35	4.08
CIS	Proportion progressing (%)						
3	25	46.46	0.37	46.79	0.37	47.17	0.37
	50	92.91	0.73	93.58	0.74	94.33	0.74
	75	139.35	1.10	140.37	1.10	141.50	1.11
	100	185.81	1.46	187.16	1.47	188.67	1.48
6	25	61.22	0.48	61.65	0.49	62.13	0.49
	50	122.44	0.96	123.30	0.97	124.25	0.98
	75	183.66	1.45	184.94	1.46	186.38	1.47
	100	244.88	1.93	246.59	1.94	248.51	1.96
9	25	60.54	0.48	60.95	048	61.41	0.48
	50	121.07	0.95	121.90	0.95	122.82	0.97
	75	181.61	1.43	182.85	1.44	184.23	1.45
	100	242.15	1.91	243.80	1.92	245.64	1.93
12	25	56.51	0.45	56.89	0.45	57.32	0.45
	50	113.02	0.89	113.79	0.90	114.63	0.90
	75	169.54	1.33	170.68	1.34	171.95	1.35
	100	226.05	1.78	227.57	1.79	229.27	1.80
15	25	51.93	0.41	52.28	0.41	52.66	0.41
	50	103.86	0.82	104.56	0.82	105.33	0.83
	75	155.79	1.23	156.84	1.23	157.99	1.24
	100	207.72	1.63	209.12	1.65	210.65	1.66

* As predicted by the age period model (for invasive cancer) or the proportion of total incidence model for CIS) for age group specific incidence in 2000.
† Midpoint of the baselines 1 and 3. ‡ Actual observed age group specific incidence in 1987 before start of screening.

progression of CIS, the total reduction would be in the range 4.2–4.8 cancers per 10,000 women.

DISCUSSION

As expected[33] we found that the introduction of screening in England in 1988 led to large increases in incidence of both invasive cancer and CIS amongst women in the invited age range. Through modelling the expected incidence rates in the absence of screening we estimated that, during the period of programme set up, the maximum number of extra invasive cases detected by screening was 9.49 per 10,000 women aged 60–64 years, occurring in 1991. This maximum presumably represented the effect of the unique first prevalence screening of the invited population in which more cancers are detected than at any other screen. Excess detection of CIS in this age group occurred one year later, in 1992; although by 1998, once the programme was more established, this excess had risen to 2.34 CIS per 10,000 women. We also observed, as have others previously, that the contribution of CIS to total incidence was highest in younger women,[34,35] and we found that this proportion increased markedly with the introduction of screening amongst women in the invited age range. Once screening was established, invasive incidence actually decreased in women beyond screening age (as reported previously),[36] this deficit reaching its highest value over the study period in 1996, at 4.22 invasive cancers per 10,000 women aged 65–69 years below that expected in the absence of screening.

Our model predicts a year–on-year incidence rate increase of about 1.6%, which agrees well with that found by Prior *et al.* for England and Wales using a similar model.[37] Our estimates for baseline incidence in the absence of screening in England for the year 1996 – the most recent year they modelled – are also in close agreement with theirs for England and Wales (18.09, 21.01 and 24.21 cancers per 10,000 women *versus* 18.95, 21.88 and 24.66 cancer per 10,000 women for ages 50–54 years, 55–59 years and 60–64 years, respectively). Whilst it is not unreasonable to assume that this trend would continue throughout the 1990s, predictions beyond this become increasingly uncertain. For this reason we used a range of baseline incidences expected in the absence of screening when we modelled possible reductions in invasive incidence brought about by steady state screening in women of post screening age for the year 2010.

Incidence data held by the Office for National Statistics are collected by Cancer Registries. It is therefore conceivable that trends in cancer incidence might arise through variations in methods of data collection. Not all registries have access to pathology reports, thus there may be variation in completeness of cancer ascertainment. However, a review of Cancer Registry information in which information was re-extracted from the available records showed that records were largely complete, accurate and reliable.[38] Furthermore, comparing CIS incidence data for East Anglia, where registration involves reference to pathology reports, with national data show no significant shortfall of CIS cases amongst the national data over the period of study (J McCann, unpublished observation).

Our estimated incidence in the absence of screening was based on extrapolation of incidence trends observed in 1971–1987. This probably gives an underestimate of incidence in the 1990s, since an additional increase in incidence after 1987 would be expected to result from the greater use of hormone replacement therapy (HRT). The Million Women Study Collaborative Group[39] found that current use of HRT conferred an increased risk of breast cancer of 66%, and estimated that around 26% of women were current users in 1996–2001. Since use of HRT prior to 1988 was very rare, one might expect breast cancer incidence in the late 1990s to be 17% higher ([0.74 x 1] + [0.26 x 1.66] = 1.17), and incidence in the early 1990s to be higher by some intermediate figure between zero and 17%. This would imply that the true excess is smaller than our estimate and the true subsequent deficit larger. This would tend to reduce the proportion of the deficit accountable for, but would also mean that there was a smaller excess to explain. The implications for future steady state screening are likely to be smaller, since one would anticipate reduced use of HRT in the future as a result of studies such as the Million Women Study.

Our method of attributing deficit in invasive cancers in women of post-screening age to earlier detection of invasive cancers and CIS involved making assumptions about the mean lead time for detection of invasive cancers and CIS by screening; about the proportion of CIS progressing to the invasive state; and about over-diagnosis. The distribution of lead times is a function of the distribution of sojourn times (the latter being the time between the time at which a cancer is theoretically detectable by screening and when it is detectable clinically).[28] Estimates for mean sojourn time for invasive cancers have been as low as 1.5 years for women aged 40–64 years in the HIP programme,[40] but most show it to be around 2.5–4 years for women aged 50–69 years in more recent screening programmes such as the Swedish Two-County Trial and Florence District Programme.[40–45] There are fewer studies modelling progression of CIS but these have suggested times of progression varying from around four years specifically for high grade CIS,[46] with most agreeing that the majority of CIS will progress within 5–10 years.[2,22,47]

The observations that early detection of invasive disease does not entirely account for the subsequent observed deficit in the programme, and that early detection of CIS increases the proportion of the deficit accounted for, adds to the evidence that a substantial proportion of cases would progress to invasive disease if left untreated. This is further supported by the fact that 10% or more of CIS cases progress despite treatment.[48] The question remains as to the exact proportion of progressive CIS. In the above, we have considered 75% as a likely figure. This is consistent with the high grade of screen-detected CIS and the accompanying necrosis,[22] and with the estimates of progression rates from screening and interval cancer data.[43,49]

The argument that most CIS cases would not progress if left untreated is based on two observations. Proportions in excess of 10% for women in whom occult CIS was discovered at autopsy, coupled with low rates for invasive disease amongst women with CIS originally untreated due to misclassification as benign disease but in whom CIS was diagnosed retrospectively upon re-examination of biopsy tissue, suggested that possibly fewer than one third of CIS might progress to invasive cancer. However, if 10% or more have the disease at autopsy, but only 0.1% are diagnosed at the prevalence screen, it is clear that screen-detectable CIS in living women is either a different clinical entity or a very small subgroup of the autopsy-detectable CIS in dead women. Furthermore, CIS which is mistakenly diagnosed as benign disease in also unlikely to be representative of CIS as a whole.

Although much effort has been put recently into identifying the optimum management for CIS detected by screening,[49–51] the challenge still remains to identify those cases of CIS at most risk of progression so that informed decisions

about treatment can be made, in particular with respect to post-operative radiotherapy.[47]

Overall, for the period of screening 1988–1996, our method of attributing deficit in invasive cancers in women of post-screening age to earlier detection of invasive cancers and CIS allowed us to account, at the most generous interpretation, for around 89% of the observed 4.22 cancers per 10,000 women deficit, assuming mean lead times of four years and three years for invasive cancer and CIS, respectively, and all CIS progressing to invasive cancer. Increasing the mean lead time for CIS to a more reasonable six years reduced the proportion of the total deficit accountable for to 84%. This was during the relatively early days of programme, and performance has increased markedly since then. If we model the effect of steady state screening, at current screening performance and with mean lead times for invasive cancer and CIS of 3–4 years and 6–9 years, respectively, we might bring about a reduction in invasive incidence of around 5–6 cancers per 10,000 women in the age group 65–69 years. One might assume all of the observed deficit would be accountable by earlier screening. However, in order to substantiate the role of screening, the magnitude of the deficit must be explicable within a screening framework. Our model gives a conservative estimate of the proportion of the reduction attributable to screening.

The vast majority of the *in situ* carcinomas in these data were ductal CIS but the data also included some cases of lobular CIS, possibly up to 10% (Leigh Roberts, personal communication). This small minority will have a lower risk of progression to invasive cancer than ductal CIS, but this risk will not be zero. The inclusion of these cases means that the mean lead time of CIS is rather longer than would prevail in a pure ductal CIS population.

What are the relative contributions of the early detection of invasive cancer, and of CIS, to the subsequent deficit in invasive cancer? Of course, if progression were 100% and lead time for CIS was equal to that for invasive cancer, then it would be just as advantageous to detect and treat CIS by screening as it is to detect and treat invasive cancer. During programme set up, CIS contributed around 13–17% of the total reduction, assuming a six year lead time and progression of 75–100% of cases. Then some of the benefit due to CIS with its longer lead time was lost, because women were not screened before 1988 and therefore the effect of early detection of CIS is artificially foreshortened: by 1996, full follow up had not yet been achieved. However, the balance changes when it comes to steady state screening. Here, with its longer lead time, CIS contributes more. Assuming 100% progression, CIS contributes 25–40% to the subsequent reduction in invasive incidence, depending on baseline used in calculations, this falling to 19–33% if only 75% progress. This is a more substantial contribution than that estimated previously for mortality reduction in the Swedish Two-County Trial. Using a method based on stage-specific fatality rates and stage down-shifting, Duffy *et al.* estimated that a maximum of 12% of prevented deaths were attributable to the early detection of CIS.[52]

During steady state screening, we estimated the contribution of CIS to total incidence to be 21% for women aged 50–52 years, and 25% for those aged 53–64 years. Our results suggest that early detection of CIS by mammographic screening will prevent between 0.5 and 1.9 invasive cancers per 10,000 per year in the future. This would imply that, cancer for cancer, there is likely to be just as much benefit in terms of subsequent invasive cancer reduction to detecting and treating CIS as there is to detecting and treating invasive cancer.

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