Invasive breast cancer and breast cancer mortality after ductal carcinoma in situ in women attending for breast screening in England, 1988-2014: population based observational cohort study

**Supplementary Material** 

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## A Tabulation of person-years at risk and observed events

The analyses were conducted using the standard epidemiological approach of considering the length of time during which a woman was at risk of experiencing an event of interest (invasive breast cancer, invasive ipsilateral breast cancer, invasive contralateral breast cancer, breast cancer death, or death from any cause). The methods described here are for invasive breast cancer (IBC). The methods for the other endpoints are similar.

For each woman who was eligible for the study, the length of time from 6 months after her DCIS diagnosis until the earliest of IBC diagnosis, death, emigration, or 31st December 2014 was calculated. These lengths of time were added together and formed the person-years at risk. These were assumed fixed in the analyses. The number of women whose contribution to the person-years was terminated by an IBC occurring was also obtained. For each analysis both the person-years and the number of IBCs were then tabulated according to the factors needed for that particular analysis.

## **B** Observed and expected rates and ratios of observed to expected rates (Supplementary Tables S3- S12, Supplementary Figure S5)

Observed rates per 1000 person-years were calculated by tabulating the IBCs and the personyears according to categories of the factor of interest (e.g. Age at DCIS diagnosis or Time since DCIS diagnosis) and then for each category dividing the number of IBCs by the number of personyears and multiplying by 1000. The categories for age at DCIS diagnosis were chosen by subdividing the women into 4 groups of approximately equal size whilst remaining close to the age-boundaries used in the screening program while the categories of time since diagnosis were chosen after tabulating the rates in finer time categories to ensure that no features of the data would be concealed by the categorisation. Confidence intervals for observed rates were calculated by assuming that the numbers of IBCs in each category had a Poisson distribution.

Calculation of the numbers of IBCs expected in the study population were based on IBC incidence rates for women in the entire population of England and Wales in five-year groups of attained age for each individual calendar year from 1988-2014. These were provided by Public Health England. The person-years for the study population were then tabulated by these same categories (i.e. five-year groups of attained age within each individual calendar year) as well as for the factors of interest for each specific analysis (e.g. Age at DCIS diagnosis, Time since DCIS diagnosis, Calendar year of DCIS diagnosis). Within each combination of all the tabulated factors, the number of person-years was then multiplied by the relevant attained-age and calendar year specific IBC incidence rate for England and Wales. This provided the number of IBCs expected for that combination of factors. The expected IBCs were then summed over all the factors that were not of direct interest in that analysis (e.g. in Supplementary Table S5 attained age, calendar year of DCIS diagnosis and either Age at DCIS diagnosis or Time since DCIS diagnosis) to provide the number of IBCs expected subdivided by categories of the factor(s) that were of interest in the analysis. For each of these categories, the ratio of observed to expected IBCs (sometimes referred to as the Standardised Incidence Ratio) was then calculated by dividing the number of IBCs observed by the number expected. The confidence intervals for the ratios of observed to expected IBCs were calculated assuming that the number of IBCs observed had a Poisson distribution while the number expected was fixed.

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# C Cumulative observed risk of IBC, accounting for competing risks from causes of death other than breast cancer (Figure 2, Supplementary Tables S7 & S11)

To derive the cumulative risk that a woman in the study population would develop IBC at 1, 2, 3, ..., 18, 19, 20 years after her diagnosis of DCIS, it is necessary to take into account the fact that she may, during this period, die from a cause other than breast cancer before any IBC has had time to develop, thereby reducing the risk that she will develop IBC compared with that suggested just by consideration of the age-specific IBC. The calculation was carried out as follows.

First we divided the time since diagnosis of DCIS into time intervals. The first time interval was of length six months (to account for the fact that women entered the study six months after their diagnosis of DCIS) and subsequent time intervals had length one year. We denote the annual IBC rate (i.e. the observed number of IBCs divided by the person-years) during the t<sup>th</sup> interval by  $r_{ibc,t}$  and the annual competing cause death (CCD) rate during the t<sup>th</sup> interval by  $r_{ccd,t}$ .

Based on the standard theory of Poisson processes, the probability that a woman who has survived up to the beginning of time interval t without developing IBC will develop IBC during interval t is:

$$p_{ibc,t} = 1 - \exp[-r_{ibc,t}T_t], \qquad (1)$$

where  $T_t$  is the length of time interval t in years, while the probability that a woman who has survived up to the beginning of time interval t will die from a CCD during interval t is:

$$p_{\text{ccd},t} = 1 \text{-} \exp[-r_{\text{ccd},t} T_t],$$

and the probability that a woman who has survived up to the beginning of time interval t without developing IBC will either develop IBC or die from a CCD during interval t is:

$$p_{ibc+ccd,t} = 1 - exp[-(r_{ibc,t} + r_{ccd,t})T_t]$$

and the probability that she will experience neither event during interval t is:

 $1\text{-}p_{ibc+ccd,t}$  .

The probability that a woman will survive up to the end of interval (t-1) without developing IBC can then be calculated recursively by the formula:

$$Q_{ibc+ccd,t-1} = Q_{ibc+ccd,t-2} (1-p_{ibc+ccd,t-1}),$$

(2)

where  $Q_{ibc+ccd,0}$  is set to 1.

It then follows that, by combining (1) and (2) above, the probability that a woman will develop an IBC during interval t, accounting for the competing risk of dying previously from another cause is:

$$Q_{ibc+ccd,t-1} [1-exp(-r_{ibc,t}T_t)].$$
 (3)

For each interval, t, the quantities in (3) can then be summed over previous time intervals to obtain the cumulative probability of developing an IBC by the end of interval t. This value can then be multiplied by 100 to provide the corresponding risk in terms of percent. The confidence intervals for the cumulative observed risk of IBC were calculated assuming that the number of IBCs observed had a Poisson distribution.

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D Cumulative expected risk of IBC, accounting for competing risks from causes of death other than breast cancer (Figure 2, Supplementary Tables S7 & S11)

The calculation of the cumulative expected risk accounting for competing risks from causes of death other than breast cancer was calculated in a similar fashion to that for the observed risk derived above, except that rather than using the observed annual IBC rate (i.e. the observed number of IBCs divided by the person-years) we used the expected rates (i.e. the expected number of IBCs divided by the person-years) where the expected number of IBCs had been calculated as described above in the section 'Calculation of numbers of IBCs expected'.

## E Comparability between results for women diagnosed with DCIS in different calendar years (Figure 2, Supplementary Tables S7 & S11)

Death rates in women in the general population have changed during the period in which the National Health Service Breast Screening Programme (NHSBSP) has been in operation and we wished to find a way of examining whether the cumulative risk of developing breast cancer following a diagnosis of screen-detected DCIS had changed that took account of competing causes of death but was not heavily influenced by changes over calendar period in the age-specific death rates from causes other than breast cancer during the study period. Therefore, rather than using individual calendar-year specific values for the CCD rates, we instead used the 2014 death rates for all causes other than breast cancer for England and Wales to account for competing causes of death throughout. This enabled us to be sure that any changes in the cumulative risks of IBC for women diagnosed with DCIS in different calendar years would be attributable to changes in the rate of development of IBC rather than changes in the death rate over calendar time, whilst still taking account of deaths from competing causes.

# **F** Multiple imputation for missing data on some characteristics (Figures 3-6, Supplementary Figures S1-S9, Supplementary Tables S13-S15)

Information was available for all the women in the study for dates of screening and DCIS diagnosis, age at DCIS diagnosis, region of residence and treatment, together with dates of emigration, IBC, or death, if any of these occurred before the end of follow-up. For 9,537 of the 29,044 (32.8%) of the women diagnosed between April 2000 and March 2014, information was also available on all the remaining characteristics (DCIS size, DCIS grade, oestrogen-receptor (ER) status, final margin distance and laterality). However, for 50.1%, 14.1%, 2.6%, and 0.4% of women respectively information was missing on 1, 2, 3 or 4 of these characteristics (Tables S1 and S2).

For analyses requiring adjustments, in order to be able to include all the women in every analysis in an appropriate way, irrespective of whether data on some characteristics were missing, the method of multiple imputation was used (Rubin DB, 1987; van Buuren S, 2018). In this method, multiple datasets are created in which the missing values are replaced by imputed (i.e. predicted) values that have been sampled from their predictive distributions. Hence, as well as providing estimates, the method is able to take into account the uncertainty arising from the imputed values as well as the uncertainty in the estimates in any ensuing confidence intervals and significance tests.

All the variables for which any values were missing were categorical and there were no complex design features in the data. For each missing value, its predictive distribution was obtained using chained multinomial logistic regressions for the variables for which some values were missing, starting with the variable for which there were fewest missing values. Additional independent variables in the predictions were year of DCIS diagnosis, age at DCIS diagnosis, region, treatment, invasive breast cancer, and death from breast cancer.

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Calculations involving multiple imputation were carried out using the multiple imputation suite of programs in Stata [StataCorp]. The default burn-in period was 10 iterations and, to confirm that this number was sufficient, trace plots for a burn-in period of 100 iterations were produced and examined. To examine the plausibility of the imputed values, the distributions of the imputed and recorded values for each variable were compared and in every case good agreement was found. Results presented in the paper are based on a total of 60 imputed datasets. This number was chosen because the largest percentage missing for any variable was 53.3%, for ER-status.

For the variables where imputation was necessary, the numbers of women given in each category in the tables in this report are the numbers of women averaged over the imputed datasets. For analyses requiring adjustments, each analysis was carried out separately on every imputed dataset, as described in sections G. H. and I. below. The resulting estimates and their variances were then combined via Rubin's rules [Rubin, 1987].

Every analysis involving multiple imputation was also carried out on the original dataset with any missing values assigned to a separate category, rather than imputed. In every case, the results from the two different approaches were virtually identical.

## G Variation in incidence of ipsilateral IBC rate (or the BCD rate) with patient and tumour characteristics and treatment (Figure 3, Supplementary Figures S1-S3 & S6-S9)

The extent to which the incidence of ipsilateral IBC (iIBC) varied with the patient and tumour characteristics and the treatment given (e.g. Figure 3) was studied using Poisson regression. To do this both the numbers of iIBCs and the relevant person-years were tabulated according to all the factors shown in Figure 3, and for each factor the categories shown in that figure were used. The boundaries of these categories were chosen by tabulating each variable individually to have as many categories as needed in order to preserve the features of the data whilst avoiding categories with very little data. The numbers of iIBCs in each cell of the table were assumed to have a Poisson distribution and, to study the variation in one particular characteristic, the number of iIBCs expected in the jth cell of the table were assumed to be given by:

 $\exp(y_1 + \mu + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k)$ where  $y_i$  is the number of person-years in the cell,  $\mu$  is an unknown constant common to all cells,

 $x_1, x_2, ..., x_k$  are indicator variables denoting the different categories of the factor under study,  $\beta_1$ is assumed to be 0 (i.e. setting the first category of the factor as the baseline category), and  $\beta_2$ , ...,  $\beta_k$  are unknown parameters. Models of this form were fitted to the data by the method of maximum likelihood and the results are shown in the left-hand panel of Figure 3, where the values displayed are the estimates of the  $exp(\beta_i)$  (which correspond to rate ratios) with confidence intervals estimated by the standard errors of the  $exp(\beta_i)$ . The models in the right-hand side of Figure 3 were similar, but in this case additional terms representing all the other factors shown in Figure 3 (apart from final margin distance, where information was available only from 2007 onwards) were also included in the model.

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(4)

## H Significance tests for heterogeneity or trend in the rate ratios for different levels of a factor and in interactions between two factors (Figure 3, Supplementary Figures S1-S3, Supplementary Table 12, Supplementary Figures S6-S9)

Significance tests for heterogeneity between the rate ratios for the different levels of a factor were based on models of the form (4) in the previous section. For analyses involving multiple imputation they were carried out using the Wald test and assuming that the between-imputation variance was proportional to the within-imputation variance, while for other analyses they used the likelihood ratio. Where the rate ratio involved the number of IBCs expected from national cancer incidence rates, rather than the number of IBCs in the baseline category,  $y_j$  was replaced by the number of IBCs expected in cell j. Where there was a natural ordering to the factor of interest, then for the significance test the indicator variables in (4) above were replaced by a variable that took values 1, 2, 3, ..., k over the different levels of the factor. Significance tests for interactions between the different factors (see Supplementary Table S14) were carried out in a similar fashion with inclusion of terms for the interaction between two variables in models of the form (4) above.

## I Cumulative rates (Figures 4, 5, Supplementary Figure 4)

To obtain cumulative rates, the person-years and IBCs were tabulated simultaneously according to categories of time since DCIS diagnosis and of the factor of interest (e.g. for Figure 4a: Breast-conserving surgery with radiotherapy, Breast conserving surgery without radiotherapy, and Mastectomy). For time since exposure the cut-points used to define the categories were chosen after inspection of the observed rates in Supplementary Table S3. For level k of the factor of interest, the cumulative rate in per-cent up to time T is then

## $100\Sigma(O_{ibc,t}/d_ty_t)$

where  $O_{ibc,t}$  is the number of observed events in time category t,  $y_t$  is the number of person-years in category t,  $d_t$  is the length of category t in years, and summation is over all categories of t up to T. Confidence intervals for cumulative rates were calculated by first assuming that the numbers of IBCs in each category had a Poisson distribution for each individual dataset. In all the figures where cumulative rates are presented (Figure 4, 5, Supplementary Figure S4) checks were made that adjustment for the potential confounding factors made no material difference to the results.

## **References for Supplementary Text S1:**

StataCorp. Stata Statistical Software: Release 15.1 [program] StataCorp, Texas. 2017.

Rubin D. B. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons, New York. 1987.

Royston, P. and Lambert P.C. Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model. Stata Press, College Station, TX. 2011.

## Supplementary Table S1. Missing values in the characteristics of 29,044 women in England diagnosed with DCIS as a result of screening between April 2000 and March 2014.

	BCS + RT	BCS - RT	Mastectomy	Total
DCIS size (mm)				
<=10	1523 (28.4)	6487 (427)	779 (9.2)	8789 (30 3)
11-20	2057 (38.3)	4450 (29.3)	1547(18.2)	8054 (27.7)
21-50	1487(27.7)	2829 (18.6)	3745 (44.1)	8061 (27.8)
51+	72 (1.3)	208 (1.4)	1791 (21.1)	2071 (7.1)
Missing	229 (4.3)	1214 (8.0)	626 (7.4)	2069 (7.1)
DCIS grade				
Low/intermediate	1319 (24.6)	7631 (50.2)	2214 (26.1)	11,164 (38.4)
High	3831 (71.4)	6810 (44.8)	5823 (68.6)	16,464 (56.7)
Missing	218 (4.1)	747 (4.9)	451 (5.3)	1416 (4.9)
Oestrogen receptor st	atus and endocrine the	erapy		
ER+, no endocrine	1367 (25.5)	3640 (24.0)	2032 (23.9)	7039 (24.2)
ER+, endocrine	478 (8.9)	2340 (15.4)	775 (9.1)	3593 (12.4)
ER-	524 (9.8)	1230 (8.1)	1184 (13.9)	2938 (10.1)
Missing	2999 (55.9)	7978 (52.5)	4497 (53.0)	15,474 (53.3)
Laterality of DCIS				
Left	2797 (52.1)	7767 (51.1)	4349 (51.2)	14,913 (51.3)
Right	2562 (47.7)	7314 (48.2)	4108 (48.4)	13,984 (48.1)
Missing	9 (0.2)	107 (0.7)	31 (0.4)	147 (0.5)
Final margin distance	e (mm)			
5+	1763 (32.8)	3148 (20.7)	2297 (27.1)	7208 (24.8)
3-4	542 (10.1)	1132 (7.5)	317 (3.7)	1991 (6.9)
1-2	683 (12.7)	1605 (10.6)	535 (6.3)	2823 (9.7)
Involved	77 (1.4)	203 (1.3)	128 (1.5)	408 (1.4)
Before 2007	1184 (22.1)	5885 (38.7)	3223 (38.0)	10,292 (35.4)
Missing	1119 (20.8)	3215 (21.2)	1988 (23.4)	6322 (21.8)
Total	5368 (100.0)	15,188 (100.0)	8488 (100.0)	29,044 (100.0)

BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded ER+, no endocrine: oestrogen-receptor positive DCIS, endocrine therapy not recorded ER+, endocrine: oestrogen-receptor positive DCIS, endocrine therapy recorded ER-: oestrogen-receptor negative DCIS

Supplementary Table S2. Numbers of women according to number of characteristics missing among the 29,044 women in England diagnosed with DCIS as a result of screening between April 2000 and March 2014.

Number of characteristics missing	Laterality	DCIS grade	DCIS size	Final margin distance	ER status	Number of women
None	-	-	-	-	-	9,537 (32.8%)
1 missing						14,549 (50.1%)
8	-	-	-	-	m	11,274
	-	-	-	m	-	2,782
	-	m	-	-	-	233
	-	-	m	-	-	219
	m	-	-	-	-	41
2 missing						4099 (14 1%)
	-	_	-	m	m	2.676
	-	-	m	-	m	478
	-	m	m	-	-	337
	-	m	-	-	m	236
	-	-	m	m	-	209
	-	m	-	m	-	77
	m	-	-	-	m	74
	m	-	-	m	-	6
	m	-	m	-	-	4
	m	m	-	-	-	2
3 missing						755 (2.6%)
8	-	-	m	m	m	317
	-	m	m	-	m	268
	-	m	m	m	-	121
	-	m	-	m	m	34
	m	-	m	-	m	11
	m	m	-	-	m	3
	m	m	m	-	-	1
4 missing						104 (0.4%)
·	_	m	m	m	m	99
	m	m	m	-	m	4
	m	m	m	m	-	1
Total number of	f women					29,044

Supplementary Table S3. Person-years at risk and numbers of observed and expected deaths from all causes by age at DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year age-groups.

	Person- years at risk	Total number of deaths observed	Observed rate per 1000 person-years (95% confidence interval)	Total number of deaths expected	Ratio of observed to expected* (95% confidence interval)
Ago of DCIS					
diagnosis					
<55	81,859	396	4.84 (4.38 to 5.34)	422.23	0.94 (0.85 to 1.03)
55-59	60,505	482	7.97 (7.29 to 8.71)	533.71	0.90 (0.83 to 0.99)
60-64	59,421	697	11.73 (10.89 to 12.63)	856.38	0.81 (0.76 to 0.88)
65+	43,302	659	15.22 (14.10 to 16.43)	1070.43	0.62 (0.57 to 0.66)
P for heterogeneity:			<0.001		<0.001
P for trend:			<0.001		<0.001
Time since DCIS diagn	osis (years)				
5-	121,250	655	5.40 ( 5.00 to 5.83)	1026.38	0.64 (0.59 to 0.69)
10-	79,072	762	9.64 (8.98 to 10.35)	949.09	0.80 (0.75 to 0.86)
15+	32,512	502	15.44 (14.15 to 16.85)	544.85	0.92 (0.84 to 1.01)
15+	12,253	315	25.71 (23.02 to 28.71)	362.43	0.87 (0.78 to 0.97)
P for heterogeneity:			<0.001		<0.001
P for trend:			<0.001		<0.001
Total	245,087	2234	9.12 ( 8.74 to 9.50)	2882.75	0.77 (0.74 to 0.81)
P for test of observ	ved/expected =	1:			<0.001

Supplementary Table S4. Numbers of observed and expected deaths from all causes by calendar period of DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year age-groups.

Time since DCIS													
diagnosis		1988-1999 2000-2004					2005-2009				2010-2014		
(years)	Obs	Exp	Ratio* (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio (95%CI)	
0.5- 5- 10-	105 211 294 315	156.15 237.29 324.33 362.43	0.67 (0.56 to 0.81) 0.89 (0.78 to 1.02) 0.91 (0.81 to 1.02) 0.87 (0.78 to 0.07)	177 310 208	256.97 391.9 220.52	0.69 (0.59 to 0.80) 0.79 (0.71 to 0.88) 0.94 (0.82 to 1.08)	263 241	426.94 319.91	0.62 (0.55 to 0.70) 0.75 (0.66 to 0.85)	110	186.32	0.59 (0.49 to 0.71)	
Total P for trend wi	925 th year o	1080.2 of diagnos	0.86 (0.80 to 0.91) <i>is: &lt;0.001 (unadju</i>	695 sted), 0.5	869.38 50 (adjuste	0.80 (0.74 to 0.86) d for time since diagno.	504 sis and age	746.85 at diagno	0.67 (0.62 to 0.74)	110	186.32	0.59 (0.49 to 0.71)	

Obs: total number of deaths observed

Exp: total number of deaths expected

CI: confidence interval

Supplementary Table S5. Person-years at risk and numbers of observed and expected invasive breast cancers by age at DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on cancer incidence rates for England in single calendar years and five-year age-groups.

	Person-years at risk	Number of invasive breast cancers observed	Observed rate per 1000 person-years (95% confidence interval)	Number of invasive breast cancers expected	Ratio of observed to expected* (95% confidence interval)
Age of DCIS diagnosis					
Age at DCIS diagnosis	78 517	692	$9.70(9.07 \pm 0.027)$	247 17	$2.76(2.56 \pm 0.208)$
< <u>55</u> 55 50	70,342 57 775	507	8.70(8.07 to 9.57) 8.78(8.04 to 9.57)	247.17	2.70(2.30  to  2.98) 2.48(2.27  to  2.71)
60.64	56.058	504	8.78(8.04109.57) 8.85(8.11 to 9.66)	204.32	2.40(2.27  to  2.71) 2.37 (2.17 to 2.59)
00-04 65⊥	12 125	382	9.07 (8.11 to 9.00)	160.35	2.37(2.17  to  2.39) 2 38 (2 16 to 2 63)
P for haterogeneity:	42,125	562	0.03	100.55	2.50 (2.10 to 2.05)
P for trend:			0.52		0.007
Time since DCIS diagn	osis (vears)				
0.5-	16,264	56	3.44 (2.65 to 4.47)	53.00	1.06 (0.81 to 1.37)
1-	30.086	211	7.01 (6.13 to 8.03)	98.89	2.13 (1.86 to 2.44)
2-	27,041	240	8.88 (7.82 to 10.1)	90.05	2.67 (2.35 to 3.02)
3-	46,172	448	9.70 (8.84 to 10.6)	157.06	2.85 (2.60 to 3.13)
5-	36,842	347	9.42 (8.48 to 10.5)	129.30	2.68 (2.42 to 2.98)
7-	38,368	394	10.3 (9.30 to 11.3)	139.57	2.82 (2.56 to 3.12)
10-	29,781	283	9.50 (8.46 to 10.7)	113.40	2.50 (2.22 to 2.80)
15-	9015	77	8.54 (6.83 to 10.7)	35.61	2.16 (1.73 to 2.70)
20+	1830	20	10.9 (7.05 to 16.9)	7.71	2.59 (1.67 to 4.02)
P for heterogeneity:			<0.001		<0.001
P for trend excluding	1 <sup>st</sup> 3 years:		<0.001		0.53
<b>Total</b> <i>P for test of observed/ex</i>	235,400 pected = 1:	2076	8.82 (8.45 to 9.21)	824.59	2.52 (2.41 to 2.63) <0.001
<b>Total 3+ years</b> P for test of observed/exp	162,009 pected 3+ years=	1569 1:	9.68 (9.22 to 10.2)	582.65	2.69 (2.56 to 2.83) <0.001

Supplementary Table S6. Numbers of observed and expected invasive breast cancers by calendar period of DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on cancer incidence rates for England in single calendar years and five-year age-groups.

Time since DCIS				Year of diagnosis of DCIS									
diagnosis		1988-1999			200	00-2004	2005-2009				2010-2014		
(years)	Obs	Exp	Ratio* (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio (95%CI)	
0.5-	12	5.55	2.16 (1.23 to 3.80)	14	11.67	1.20 (0.71 to 2.03)	15	18.06	0.83 (0.50 to 1.38)	15	17.71	0.85 (0.51 to 1.40)	
1-	35	11.34	3.09 (2.22 to 4.30)	46	23.46	1.96 (1.47 to 2.62)	73	35.90	2.03 (1.62 to 2.56)	57	28.18	2.02 (1.56 to 2.62)	
2-	32	11.67	2.74 (1.94 to 3.88)	62	23.50	2.64 (2.06 to 3.38)	90	35.64	2.52 (2.05 to 3.10)	56	19.24	2.91 (2.24 to 3.78)	
3-	76	24.65	3.08 (2.46 to 3.86)	128	46.89	2.73 (2.30 to 3.25)	191	70.88	2.69 (2.34 to 3.11)	53	14.65	3.62 (2.76 to 4.74)	
5-	71	25.80	2.75 (2.18 to 3.47)	109	46.11	2.36 (1.96 to 2.85)	167	57.38	2.91 (2.50 to 3.39)				
7-	121	38.96	3.11 (2.60 to 3.71)	192	68.71	2.79 (2.43 to 3.22)	81	31.9	2.54 (2.04 to 3.16)				
10-	167	63.33	2.64 (2.27 to 3.07)	116	50.06	2.32 (1.93 to 2.78)							
15-	77	35.61	2.16 (1.73 to 2.70)										
20+	20	7.71	2.59 (1.67 to 4.02)										
Total	611	224.62	2.72 (2.51 to 2.94)	667	270.41	2.47 (2.29 to 2.66)	617	249.77	2.47 (2.28 to 2.67)	181	79.78	2.27 (1.96 to 2.62)	
P for trend wi	th year o	of diagnosis:	0.03 (unadjusted), 0.	.26 (adju	sted for time	e since diagnosis and age	at diagnos	is)					

Obs: number of cancers observed

Exp: number of cancers expected

CI: confidence interval

Supplementary Table S7. Numbers of person-years at risk, numbers of observed and expected invasive breast cancers, and cumulative risks by date of DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on cancer incidence rates for England in single calendar years and five-year age-groups

$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Date of diagnosis of DCIS	Time since DCIS diagnosis (years)	Number of person- years	Number of invasive breast cancers observed	Cumulative observed risk*	95% confidence interval for cumulative observed risk*	Number of invasive breast cancers expected*	Cumulative expected risk*
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1988-1999	0.5-	2081	12	03	0.1 to 0.5	5.6	0.1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1700-1777	1	4125	35	0.5	$0.1 \pm 0.5$	11.3	0.1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		1-	4123	33	1.1	1.5  to  2.2	11.5	0.4
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		2-	4070	32	1.9	1.5 10 2.5	11./	0.7
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		5-	4024	33	2.7	2.2 10 5.2	12.1	1.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		4-	3962	43	5.7	3.1 to 4.3	12.5	1.5
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		5-	3899	35	4.6	3.9 to 5.2	12.8	1.6
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		6-	3827	36	5.4	4.7 to 6.1	13.0	1.9
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		/-	3/58	37	0.3	5.6 to 7.1	13.0	2.3
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		8-	3687	45	/.4	6.6 to 8.2	13.0	2.6
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		9-	3611	39	8.3	7.5 to 9.2	13.0	2.9
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		10-	3534	43	9.4	8.5 to 10.3	12.9	3.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		11-	3456	28	10.0	9.1 to 11.0	12.7	3.6
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		12-	3382	32	10.8	9.9 to 11.8	12.6	3.9
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		13-	3317	16	11.2	10.2 to 12.1	12.6	4.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		14-	3241	48	12.3	11.3 to 13.3	12.6	4.6
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		15-	2839	22	12.9	11.9 to 13.9	11.2	4.9
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		16-	2221	17	13.5	12.4 to 14.5	8.8	5.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		1/-	1/18	10	13.9	12.8 to 15.0	0.8 5 1	5.5
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		18-	1280	18	14.9	13.7 to 16.0	5.1	5.8
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		19+	2786	30	15.67	14.3 to 16.8	11.5	6.17
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2000-2004	0.5-	3516	14	0.2	0.1 to 0.3	11.7	0.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		1-	6987	46	0.9	0.6 to 1.1	23.5	0.5
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		2-	6905	62	1.7	1.4 to 2.0	23.5	0.8
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		3-	6800	67	2.7	2.3 to 3.1	23.5	1.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		4-	6702	61	3.5	3.1 to 4.0	23.4	1.5
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		5-	6600	61	4.4	3.9 to 4.9	23.2	1.8
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		6-	6504	48	5.1	4.6 to 5.6	22.9	2.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		7-	6414	51	5.8	5.3 to 6.3	22.8	2.5
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		8-	6299	91	7.1	6.5 to 7.7	22.8	2.8
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		9-	6163	50	7.8	7.2 to 8.4	23.1	3.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		10-	5265	40	8.4	7.8 to 9.1	20.2	3.5
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		11-	3723	47	9.5	8.8 to 10.2	14.5	3.9
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		12-	2325	17	10.1	9.3 to 10.8	9.2	4.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		13-	1208	10	10.7	9.9 to 11.6	4.9	4.5
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		14+	331	2	11.2+	10.1 to 12.2	1.4	4.9†
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2005-2009	0.5-	5358	15	0.1	0.1 to 0.2	18.1	0.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		1-	10635	73	0.8	0.7 to 1.0	35.9	0.5
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		2-	10507	90	1.7	1.4 to 1.9	35.6	0.8
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		3-	10358	101	2.6	2.3 to 2.9	35.4	1.2
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		4-	10211	90	3.4	3.1 to 3.8	35.5	1.5
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		5-	9075	121	4.7	4.3 to 5.1	32.2	1.8
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		6-	6937	46	5.3	4.8 to 5.7	25.2	2.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		7-	4769	42	6.1	5.6 to 6.5	17.8	2.5
9+         906         6         7.7 <sup>+</sup> 6.9 to 8.4         3.6         3.2 <sup>+</sup> 2010-2014         0.5-         5310         15         0.1         0.1 to 0.2         17.7         0.2           1-         8339         57         0.8         0.6 to 1.0         28.2         0.5           2-         5553         56         1.8         1.5 to 2.1         19.2         0.8           3-         3127         34         2.8         2.4 to 3.3         11.1         1.2           4+         989         19         4.6 <sup>+</sup> 3.7 to 5.6         3.6         1.5 <sup>+</sup>		8-	2762	33	7.1	6.5 to 7.7	10.6	2.9
2010-2014       0.5-       5310       15       0.1       0.1 to 0.2       17.7       0.2         1-       8339       57       0.8       0.6 to 1.0       28.2       0.5         2-       5553       56       1.8       1.5 to 2.1       19.2       0.8         3-       3127       34       2.8       2.4 to 3.3       11.1       1.2         4+       989       19       4.6 <sup>+</sup> 3.7 to 5.6       3.6       1.5 <sup>+</sup>		9+	906	6	7.7+	6.9 to 8.4	3.6	3.2†
1-8339570.80.6 to 1.028.20.52-5553561.81.5 to 2.119.20.83-3127342.82.4 to 3.311.11.24+989194.6†3.7 to 5.63.61.5†	2010-2014	0.5-	5310	15	0.1	0.1 to 0.2	17.7	0.2
2-5553561.81.5 to 2.119.20.83-3127342.82.4 to 3.311.11.24+989194.6†3.7 to 5.63.61.5†		1-	8339	57	0.8	0.6 to 1.0	28.2	0.5
3-     3127     34     2.8     2.4 to 3.3     11.1     1.2       4+     989     19     4.6 <sup>+</sup> 3.7 to 5.6     3.6     1.5 <sup>+</sup>		2-	5553	56	1.8	1.5 to 2.1	19.2	0.8
4+ 989 19 4.6 <sup>+</sup> 3.7 to 5.6 3.6 1.5 <sup>+</sup>		3-	3127	34	2.8	2.4 to 3.3	11.1	1.2
		4+	989	19	4.6†	3.7 to 5.6	3.6	1.5+

Cumulative risks take into account competing risks from other causes of death. See supplementary text 1 for further details

\*Risks given for the end of each period, i.e. risks in line '9-' refer to 10 years after diagnosis, etc †Risks at 20, 15, 10, and 5 years after diagnosis of DCIS respectively.

Supplementary Table S8. Person-years at risk and numbers of observed and expected invasive breast cancers by surgery, whether both breasts were affected and time since diagnosis in 30,559 women with DCIS detected as a result of screening between April 2000 and March 2014. Expected values are based on cancer incidence rates for England in single calendar years and five-year age-groups.

	Person- years at risk	Number of invasive breast cancers observed	Observed rate per 1000 person-years (95% confidence interval)	Number of invasive breast cancers expected	Ratio of observed to expected* (95% confidence interval)
Less than 5 years since diagnosis of DCIS	50 518	282	$6.42(5.92 \pm 0.7.11)$	201.21	1.00(1.72  to  2.10)
Unilateral with no (unimour autoon)	39,310	203	0.43 (0.02 to 7.11)	201.31	1.90(1.72  to  2.10)
Dilateral with no/unknown surgery	2875	57	12.87 (9.52 to 17.8) 15.82 (2.06 to 62.2)	9.73	$5.60(2.75 \pm 0.5.24)$
P for heterogeneity:	120	2	<0.001 <0.001	0.45	4.03 (1.10 to 18.3) <0.001
Total less than 3 years since diagnosis of DCIS	62,520	422	6.75 (6.14 to 7.43)	211.49	2.00 (1.81 to 2.20)
At least 3 years since diagnosis of DCIS					
Unilateral with surgery	98,639	933	9.46 (8.87 to 10.1)	354.54	2.63 (2.47 to 2.81)
Unilateral with no/unknown surgery	6121	75	12.25 (9.77 to 15.4)	22.16	3.38 (2.70 to 4.24)
Bilateral	212	3	14.12 (4.55 to 43.8)	0.76	3.96 (1.28 to 12.30)
P for heterogeneity:			0.09		0.11
Total at least 3 years since diagnosis of DCIS	104,972	1011	9.63 (9.06 to 10.24)	377.46	2.68 (2.52 to 2.85)
All years since diagnosis of DCIS					
Unilateral with surgery	158,157	1316	8.32 (7.88 to 8.78)	555.85	2.37 (2.24 to 2.50)
Unilateral with no/unknown surgery	8996	112	12.45 (10.4 to 15.0)	31.91	3.51 (2.92 to 4.22)
Bilateral	339	5	14.75 ( 6.14 to 35.5)	1.19	4.21 (1.75 to 10.1)
P for heterogeneity:			<0.001		<0.001
Total	167,492	1433	8.56 ( 8.12 to 9.01)	588.95	2.43 (2.31 to 2.56)

Supplementary Table S9. Person-years at risk and numbers of observed and expected breast cancer deaths by age at DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year age-groups.

	Person-years at risk	Number of breast cancer deaths observed	Observed rate per 1000 person-years (95% confidence interval)	Number of breast cancer deaths expected	Ratio of observed to expected* (95% confidence interval)
Age at DCIS diagnosis					
<55	81 859	92	1 12 (0 92 to 1 38)	44 37	2 07 (1 69 to 2 54)
55-59	60,505	78	1.12(0.92  to  1.50) 1.29(1.03  to  1.61)	42.13	1.85 (1.48  to  2.31)
60-64	59.421	82	1.38 (1.11  to  1.71)	50.21	1.63 (1.32  to  2.03)
65+	43.302	58	1.34 (1.04  to  1.73)	45.38	1.28 (0.99  to  1.65)
P for heterogeneity:			0.54		0.03
P for trend:			0.20		0.003
Time since DCIS diagn	iosis (years)				
0.5-	121,250	70	0.58 (0.46 to 0.73)	80.58	0.87 (0.69 to 1.10)
5-	79,072	118	1.49 (1.25 to 1.79)	59.69	1.98 (1.65 to 2.37)
10-	32,512	84	2.58 (2.09 to 3.20)	28.09	2.99 (2.41 to 3.70)
15+	12,253	38	3.10 (2.26 to 4.26)	13.74	2.77 (2.01 to 3.80)
P for heterogeneity:			<0.001		< 0.001
P for trend excluding	1 <sup>st</sup> 5 years:		<0.001		0.01
Total	245,087	310	1.26 (1.13 to 1.41)	182.1	1.70 (1.52 to 1.90)
P for test of observ	ved/expected = 1:				<0.001
Total 5+ years	123,837	240	1.94 (1.71 to 2.20)	101.52	2.36 (2.08 to 2.68)
<i>P</i> for test of observed/ex	pected $3 + years = 1$	:			<0.001

\*i. e. estimated ratio of observed rate to expected rate. See supplementary text 1 for further details

Supplementary Table S10 Numbers of observed and expected breast cancer deaths by calendar period of DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year agegroups.

Time since DCIS		Year of diagnosis of DCIS												
diagnosis	1988-1999			2000-2004			2005-2009			2010-2014				
(years)	Obs	Exp	Ratio* (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio (95%CI)	Obs	Exp	Ratio		
0.5-	9	14.51	0.62 (0.32 to 1.19)	22	21.55	1.02 (0.67 to 1.55)	32	31.13	1.03 (0.73 to 1.45)	7	13.38	0.52 (0.25 to 1.10)		
5-	41	16.47	2.49 (1.83 to 3.38)	50	24.96	2.00 (1.52 to 2.64)	27	18.26	1.48 (1.01 to 2.16)					
10-	58	16.91	3.43 (2.65 to 4.44)	26	11.18	2.32 (1.58 to 3.41)								
15+	38	13.74	2.77 (2.01 to 3.80)											
Total	146	61.63	2.37 (2.01 to 2.79)	98	57.7	1.70 (1.39 to 2.07)	59	49.4	1.19 (0.93 to 1.54)	7	13.38	0.52 (0.25 to 1.10)		
<i>P</i> for trend with year of diagnosis: <a href="https://www.enablight.com"></a> (unadjusted), 0.09 (adjusted for time since diagnosis and age at diagnosis)														

Obs: number of breast cancer deaths observed

Exp: number of breast cancer deaths expected

CI: confidence interval

Supplementary Table S11. Numbers of person-years at risk, numbers of observed and expected breast cancer deaths, and cumulative risks by date of DCIS diagnosis and time since DCIS diagnosis in 35,024 women with DCIS detected as a result of screening between January 1988 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year age-groups.

Date of diagnosis of DCIS	Time since DCIS diagnosis (years)	Number of person- years	Number of breast cancer deaths observed	Cumulative observed risk*	95% confidence interval for cumulative observed risk*	Number of breast cancer deaths expected*	Cumulative expected risk*
1988-1999	0.5-	2084	1	0	0.00 to 0.04	1.6	0.0
	1-	4156	1	0	0.00 to 0.09	3.2	0.1
	2-	4137	2	0.1	0.03 to 0.19	3.2	0.2
	3-	4113	4	0.2	0.1 to 0.3	3.2	0.3
	4-	4084	1	0.2	0.1 to 0.4	3.2	0.3
	5-	4053	7	0.4	0.2 to 0.6	3.3	0.4
	6-	4011	8	0.6	0.3 to 0.8	3.3	0.5
	7-	3964	10	0.8	0.5 to 1.1	3.3	0.6
	8-	3919	7	1.0	0.7 to 1.3	3.3	0.7
	9-	3879	9	1.2	0.9 to 1.5	3.3	0.7
	10-	3824	13	1.5	1.1 to 1.9	3.4	0.8
	11-	3766	12	1.8	1.4 to 2.2	3.4	0.9
	12-	3709	15	2.2	1.7 to 2.6	3.4	1.0
	13-	3654	3	2.2	1.8 to 2.7	3.4	1.1
	14-	3593	15	2.6	2.1 to 3.1	3.4	1.2
	15-	3174	4	2.7	2.2 to 3.2	3.1	1.2
	16-	2492	8	3.0	2.4 to 3.5	2.6	1.3
	17-	1934	6	3.2	2.7 to 3.8	2.1	1.4
	18-	1458	5	3.5	2.9 to 4.1	1.7	1.5
	19+	3196	15	3.8+	3.2 to 4.5	4.3	1.6†
2000-2004	0.5-	3519	1	0	0.00 to 0.04	2.3	0.0
	1-	7022	2	0	0.00 to 0.09	4.7	0.1
	2-	6991	5	0.1	0.03 to 0.19	4.8	0.2
	3-	6951	6	0.2	0.1 to 0.3	4.8	0.2
	4-	6902	8	0.3	0.2 to 0.4	4.9	0.3
	5-	6851	12	0.5	0.3 to 0.6	4.9	0.4
	6-	6791	10	0.6	0.4 to 0.8	5.0	0.4
	7-	6738	7	0.7	0.5 to 0.9	5.0	0.5
	8-	6681	10	0.9	0.6 to 1.1	5.0	0.6
	9-	6605	11	1.0	0.8 to 1.2	5.1	0.7
	10-	5675	13	1.2	1.0 to 1.5	4.4	0.7
	11-	4036	10	1.4	1.2 to 1.7	3.2	0.8
	12-	2546	1	1.5	1.2 to 1.8	2.1	0.9
	13-	1338	2	1.6	1.3 to 2.0	1.1	0.9
	14+	372	0	1.6†	1.3 to 2.0	0.3	1.0+
2005-2009	0.5-	5360	2	0	0.00 to 0.04	3.4	0.0
	1-	10682	10	0.1	0.05 to 0.18	6.8	0.1
	2-	10631	7	0.2	0.1 to 0.3	6.9	0.2
	3-	10576	8	0.3	0.2 to 0.3	6.9	0.2
	4-	10511	5	0.3	0.2 to 0.4	7.0	0.3
	5-	9428	10	0.4	0.3 to 0.5	6.5	0.4
	6-	7248	5	0.5	0.3 to 0.6	5.2	0.4
	7-	5014	7	0.6	0.4 to 0.8	3.7	0.5
	8-	2925	4	0.7	0.5 to 0.9	2.2	0.6
	9+	966	1	0.8†	0.5 to 1.1	0.7	0.6†
2010-2014	0.5-	5313	0	0	0.00 to 0.00	2.9	0.0
	1-	8382	4	0	0.00 to 0.09	4.7	0.1
	2-	5623	3	0.1	0.02 to 0.18	3.3	0.1
	3-	3189	0	0.1	0.02 to 0.18	1.9	0.2
	4+	1023	0	0.1+	0.02 to 0.18	0.6	0.3+

Cumulative risks take into account competing risks from other causes of death. See supplementary text 1 for further details

\*Risks given for the end of each period, i.e. risks in line '9-' refer to 10 years after diagnosis, etc

+Risks at 20, 15, 10, and 5 years after diagnosis of DCIS respectively

Supplementary Table S12. Person-years at risk and numbers of observed and expected breast cancer deaths by surgery, whether both breasts were affected and time since diagnosis in 30,559 women with DCIS detected as a result of screening between April 2000 and March 2014. Expected values are based on mortality rates for England and Wales in single calendar years and five-year age-groups.

	Person- years at risk	Number of breast cancer deaths observed	Observed rate pre 1000 person-years (95% confidence interval)	Number of breast cancer deaths expected	Ratio of observed to expected* (95% confidence interval)
Less than 5 years since diagnosis of DCIS					
Unilateral with surgery	96 650	52	0.54 (0.41  to  0.71)	62.05	0.84 (0.64  to  1.10)
Unilateral with no/unknown surgery	4748	9	1.90(0.99  to  3.64)	3.15	2.86(1.49  to  5.49)
Bilateral	207	Ó		0.13	-
P for heterogeneity:	207	0	0.009	0.15	0.01
1 joi neterogeneuy.			0.009		0.01
Total less than 5 years since diagnosis of DCIS	101,605	61	0.60 (0.47 to 0.77)	35.33	0.93 (0.73 to 1.20)
At least 5 years since diagnosis of DCIS					
Unilateral with surgery	66 169	84	1 27 (1 03 to 1 57)	48 97	1 72 (1 38 to 2 12)
Unilateral with no/unknown surgery	4666	14	3.00(1.78  to  5.07)	3.6	3.89(2.31  to  6.57)
Bilateral	141	1	7.07(1.00  to  50.2)	0.1	9.96(1.40  to  70.7)
P for heterogeneity:	111	1	0.01	0.1	0.02
Total at least 5 years since diagnosis of DCIS	70977	99	1.39 (1.15 to 1.70)	52.67	1.88 (1.54 to 2.29)
All years since diagnosis of DCIS					
Unilateral with surgery	162,820	136	0.84 (0.71 to 0.99)	111.03	1.22 (1.04 to 1.45)
Unilateral with no/unknown surgery	9414	23	2.44 (1.62 to 3.68)	6.75	3.41 (2.27 to 5.13)
Bilateral	349	1	2.87 (0.40 to 20.4)	0.23	4.30 (0.61 to 30.5)
P for heterogeneity:			<0.001		<0.001
Total	172,583	160	0.93 (0.79 to 1.08)	118	1.36 (1.16 to 1.58)

Supplementary Table S13. Characteristics and vital status on 31 December 2014 of 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery. Women recorded with oestrogen-receptor positive DCIS and receiving endocrine therapy are excluded.

			Treatment		
	BCS + RT	BCS - RT	Mastectomy	P for heterogeneity	Total
Year of DCIS diagno	sis				
2000-04	531 (10.8)	2734 (55.6)	1651 (33.6)	< 0.001	4916 (100.0)
2005-09	1132 (13.2)	4631 (54.0)	2805 (32.7)		8568 (100.0)
2010-14	3136 (27.8)	5076 (44.9)	3083 (27.3)		11,295 (100.0)
Age at DCIS diagnos	is (years)				
<55	1422 (18.5)	3755 (48.9)	2496 (32.5)	< 0.001	7673 (100.0)
55-59	1010 (19.9)	2488 (48.9)	1590 (31.2)		5088 (100.0)
60-64 65+	1054 (19.3) 1312 (20.0)	2802 (51.4) 3396 (51.7)	1592 (29.2) 1860 (28.3)		5448 (100.0) 6568 (100.0)
Region	× ,				
Eastern	1266 (37.0)	1227 (35.9)	926 (27.1)	< 0.001	3419 (100.0)
North West	361 (13.6)	1406 (52.9)	893 (33.6)		2660 (100.0)
Northern/Yorkshire	1510 (39.3)	1026 (26.7)	1310 (34.1)		3846 (100.0)
Oxford	157 (10.4)	937 (62.2)	413 (27.4)		1507 (100.0)
South West	198 (4.9)	2699 (66.6)	1156 (28.5)		4053 (100.0)
Thames	531 (11.2)	2792 (59.0)	1406 (29.7)		4729 (100.0)
Trent	395 (19.4)	942 (46.2)	702 (34.4)		2039 (100.0)
West Midlands	382 (15.1)	1411 (55.9)	731 (29.0)		2524 (100.0)
DCIS size (mm)					
<=10	1416 (17.5)	5950 (73.4)	738 (9.1)	< 0.001	8104 (100.0)
11-20	1939 (26.7)	3837 (52.7)	1498 (20.6)		7274 (100.0)
21-50	1383 (18.6)	2470 (33.1)	3599 (48.3)		7452 (100.0)
51+	65 (3.3)	185 (9.5)	1704 (87.2)		1954 (100.0)
DCIS grade	1202 (12.2)		2002 (20.2)	.0.001	0.950 (100.0)
Low/intermediate	1202(12.2)	6647 (67.5) 5705 (28.8)	2003(20.3)	<0.001	9852 (100.0)
High	5599 (24.1)	5795 (38.8)	5554 (57.1)		14,928 (100.0)
Oestrogen-receptor s	3579 (19 3)	9948 (53 7)	5000 (27.0)	<0.001	18 527 (100 0)
Negative	1221 (19.5)	2491 (39.9)	2535 (40.6)	<0.001	6247 (100.0)
Laterality of DCIS					
Left	2510 (19.7)	6414 (50.2)	3842 (30.1)	0.36	12,766 (100.0)
Right	2290 (19.1)	6028 (50.2)	3695 (30.8)		12,013 (100.0)
Final margin distanc	e (mm)				
5+	2184 (22.6)	4080 (42.2)	3408 (35.2)		9672 (100.0)
3-4	684 (26.0)	1484 (56.3)	466 (17.7)		2634 (100.0)
1-2	855 (23.0)	2094 (56.2)	775 (20.8)		3724 (100.0)
Involved	99 (17.7)	280 (50.2)	179 (32.1)		558 (100.0)
Before 2007	977 (11.9)	4505 (55.0)	2705 (33.0)		8187 (100.0)
Duration of follow-uj	p (years)				
0-4	3176 (27.2)	5285 (45.3)	3205 (27.5)		11,666 (100.0)
5-9	1129 (13.2)	4619 (54.0)	2803 (32.8)		8551 (100.0)
10-14	494 (10.8)	2538 (55.6)	1530 (33.5)		4562 (100.0)
Laterality of IBC					
Ipsilateral	66 (11.7)	398 (70.6)	100 (17.7)		564 (100.0)
Contralateral	75 (15.2)	238 (48.3)	180 (36.5)		493 (100.0)
Unknown	7 (11.1)	26 (41.3)	30 (47.6)		63 (100.0)
Vital status on 31 De	c 2014				
Alive	4673 (19.6)	11,897 (50.0)	7216 (30.3)		23,786 (100.0)
Emigrated	6 (10.5)	32 (56.1)	19 (33.3)		57 (100.0)
Dead	120 (12.8)	512 (54.8)	303 (32.4)		935 (100.0)
Cause of death					
Breast cancer	15	49	43		107
Other causes	105	457	249		811
Unknown cause	-	7	10		17
Total	4700 (10 A)	12 441 (50 2)	7530 (20 4)		24 770 (100 0)
Total	4/77(19.4)	12,441 (30.2)	1559 (50.4)		24,779 (100.0)

BCS+RT: breast-conserving surgery, radiotherapy recorded

BCS-RT: breast-conserving surgery, radiotherapy not recorded



BCS+RT: breast-conserving surgery, radiotherapy recorded

BCS-RT: breast-conserving surgery, radiotherapy not recorded

CI: confidence interval P: results of tests for heterogeneity or trend

\* Tests for trend excluding years 0.5-2.9: crude P=0.40; adjusted P=0.87

† Tests for trend across clear margin categories: crude P=0.004; adjusted P=0.02

Supplementary Figure S1. Incidence of ipsilateral invasive breast cancer according to various factors in 24,779 women diagnosed with unilateral DCIS as a result of screening between April 2000 and March 2014 and who received surgery showing final margin distances of 1 and 2 mm separately. Women recorded with oestrogen-receptor positive DCIS and receiving endocrine therapy are excluded. For each factor rates are shown relative to first category and adjustment is for all other factors except final margin distance. Final margin distance was not included in the adjustment as information on this variable was available only from 2007 onwards.

#### Breast-conserving surgery with radiotherapy

#### Cases/ Ratio of rates Ratio of rates 95% CI 95% CI Women (crude) (adjusted) $(p_{trend} = 0.19)$ (p<sub>trend</sub> = 0.93) (a) Year of DCIS diagnosis 26/531 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 2000-04 2005-09 27/1132 0.77 (0.45 to 1.34) 0.92 (0.51 to 1.67) 1.33 (0.52 to 3.41) 13/3136 0.62 (0.32 to 1.21) 2010-14 . at DCIS diagnosis (years) $(p_{trend} = 0.20)$ $(p_{trend} = 0.17)$ (b) Age 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 14/1422 <55 2.40 (1.23 to 4.69) 2.44 (1.24 to 4.78) 55-59 25/1010 1.53 (0.74 to 3.18) 1.56 (0.75 to 3.26) 60-64 16/1054 1.04 (0.47 to 2.31) 1.08 (0.48 to 2.39) 65+ 12/1312 (c) Region (pheterogeneity = 0.63) (p<sub>heterogeneity</sub> = 0.27) 28/1266 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Eastern North West 1.85 (0.56 to 6.08) 3.74 (0.94 to 14.98) 3/361 0.93 (0.55 to 1.57) 0.90 (0.53 to 1.53) Northern/York, 29/1510 Oxford 0/157 0/198 South West Thames 1/531 0.21 (0.03 to 1.54)-0.22 (0.03 to 1.64) Trent 4/395 1.56 (0.55 to 4.44) 2.56 (0.83 to 7.92) 0.42 (0.06 to 3.06) 0.70 (0.09 to 5.68) West Midlands 1/382 (d) Time since DCIS diagnosis (years) $(p_{\text{heterogeneity}} = 0.002)$ (pheterogeneity = 0.001) 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 0.5-2.9 12/49458 3.0-4.9 23/29158 4.03 (2.00 to 8.12) 13/21687 3.27 (1.49 to 7.17) 4.78 (1.88 to 12.15) 5.0-6.9 - 3 92 (1 79 to 8 57 - 5 63 (2 18 to 14 50) 7.0-9.9 13/19663 3.75 (1.23 to 11.42) 5.38 (1.48 to 19.49) 10 +5/8216 (e) DCIS size (mm) $(p_{trend} = 0.55)$ $(p_{trend} = 0.45)$ 1.00 (1.00 to 1.00) <=10 19/1416 1.00 (1.00 to 1.00) 1.10 (0.59 to 2.07) 1.07 (0.57 to 2.02) 11-20 27/1939 21-50 20/1383 1.38 (0.71 to 2.69) 1.44 (0.73 to 2.85) 51+ 0/65 $(p_{trend} = 0.73)$ (f) DCIS grade $(p_{trend} = 0.62)$ 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 18/1202 Low/inter 47/3599 0.91 (0.51 to 1.60) 0.86 (0.49 to 1.53) Hiah $(p_{trend} = 0.42)$ (g) Laterality of DCIS (p<sub>trend</sub> = 0.49) 38/2510 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Left Right 28/2290 0.82 (0.50 to 1.34) 0.84 (0.51 to 1.38) (p<sub>heterogeneity</sub> = 0.47)<sup>†</sup> (p<sub>heterogeneity</sub> = 0.51)<sup>†</sup> (h) Final margin distance (mm) 9/2184 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 5+ 1 62 (0.41 to 6.48) 1 58 (0.39 to 6.38) 3-4 5/684 1-2 9/855 2.40 (0.77 to 7.51) 2.33 (0.73 to 7.42) Involved 1/99 Before 2007 43/977 2.59 (1.13 to 5.96) 2.62 (0.91 to 7.56) . . . 1 1 - 95% CI 0 0.5 1 1.5 2 2.5 3 0 0.5 1 1.5 2 2.5 3

Breast-conserving surgery no radiotherapy

#### Cases/ Ratio of rates Ratio of rates 95% CI 95% CI Women (crude) (adjusted) (a) Year of DCIS diagnosis $(p_{trend} = 0.88)$ (p<sub>trend</sub> = 0.33) 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 2000-04 170/2734 2005-09 179/4631 1.01 (0.82 to 1.25) -1.10 (0.87 to 1.39) 0.91 (0.66 to 1.25) 1.27 (0.88 to 1.83) 2010-14 49/5076 (b) Age at DCIS diagnosis (years) $(p_{trend} = 0.95)$ $(p_{trans} = 0.92)$ 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) <55 125/3755 89/2488 0.98 (0.74 to 1.28) 0.98 (0.74 to 1.28) 55-59 0.80 (0.60 to 1.07) 0.80 (0.60 to 1.06) 60-64 77/2802 106/3396 1.15 (0.89 to 1.49) 1.17 (0.90 to 1.53) 65+ $(p_{heterogeneity} = 0.47)$ (p<sub>heterogeneity</sub> = 0.46) (c) Region Eastern 44/1227 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) North West 32/1406 0.67 (0.42 to 1.05)0.69 (0.44 to 1.10) 0.77 (0.48 to 1.25) 0.79 (0.49 to 1.28) Northern/York 27/1026 1.08 (0.69 to 1.67) 1.14 (0.73 to 1.79) Oxford 37/937 South West 93/2699 0.96 (0.67 to 1.39) 1.01 (0.70 to 1.45) Thames 85/2792 0.85 (0.59 to 1.23) 0.89 (0.61 to 1.29) 0.75 (0.46 to 1.22) 0.79 (0.48 to 1.28) Trent 27/942 West Midlands 52/1411 0.90 (0.60 to 1.35) 0.94 (0.63 to 1.42) (d) Time since DCIS (p<sub>heterogeneity</sub> < 0.001) (pheterogeneity < 0.001) diagnosis (years) 0.5-2.9 104/49458 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 112/29158 1.76 (1.35 to 2.30) 1.83 (1.39 to 2.42) 3.0-4.9 5.0-6.9 74/21687 1.54 (1.14 to 2.08) 1.65 (1.19 to 2.27) 7.0-9.9 73/19663 -1.68 (1.24 to 2.26) 1.84 (1.32 to 2.55) 10 +34/8216 1.84 (1.24 to 2.72) 2.11 (1.37 to 3.25) (e) DCIS size (mm) $(p_{trend} = 0.15)$ $(p_{trend} = 0.18)$ <=10 203/5950 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 0.99 (0.78 to 1.24) 1.00 (0.79 to 1.26) 11-20 129/3837 --0.79 (0.59 to 1.07) 0.80 (0.59 to 1.09) 21-50 61/2470 -51+ 4/185 0.67 (0.22 to 2.05) 0.65 (0.21 to 2.01) $(p_{trend} = 0.68)$ $(p_{trend} = 0.89)$ (f) DCIS grade Low/inter 206/6647 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 0.96 (0.78 to 1.17) 0.98 (0.79 to 1.22) High 191/5795 (g) Laterality of DCIS $(p_{trend} = 0.08)$ $(p_{trend} = 0.07)$ 187/6414 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Left Right 210/6028 1.19 (0.98 to 1.46) 1.20 (0.98 to 1.46) (h) Final margin distance (mm) (p<sub>heterogeneity</sub> < 0.001)<sup>†</sup> (pheterogeneity < 0.001)<sup>†</sup> 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 56/4080 5+ 3-4 28/1484 1.26 (0.70 to 2.30) 1.27 (0.70 to 2.31 1-2 47/2094 1.61 (1.00 to 2.61) 1.68 (1.03 to 2.74) Involved 4.04 (2.01 to 8.08) 4.32 (2.13 to 8.78) 16/280 1.34 (0.95 to 1.89) 1.17 (0.78 to 1.77) Before 2007 250/4505 - 95% CI 0 0.5 1 1.5 2 2.5 3 0 0.5 1 1.5 2 2.5 3

Cases/ Ratio of rates Ratio of rates 95% CI 95% CI Women (crude) (adjusted)  $(p_{trend} = 0.31)$ (p<sub>trend</sub> = 0.30) (a) Year of DCIS diagnosis 2000-04 37/1651 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 2005-09 54/2805 1.39 (0.91 to 2.13) 1.33 (0.85 to 2.08) 0.74 (0.36 to 1.54) 0.89 (0.40 to 1.97) 2010-14 9/3083 (b) Age at DCIS diagnosis (years)  $(p_{trend} = 0.02)$  $(p_{trend} = 0.01)$ 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) <55 43/2496 0 71 (0 42 to 1 18) 55-59 23/1590 0 74 (0 44 to 1 23) 0.53 (0.30 to 0.96) 0.52 (0.29 to 0.93) 60-64 16/1592 -65+ 18/1860 0.63 (0.36 to 1.09) 0.58 (0.33 to 1.01)  $(p_{heterogeneity} = 0.05)$  $(p_{heterogeneity} = 0.05)$ (c) Region 10/926 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Eastern North West 9/893 1.09 (0.44 to 2.74) 1.11 (0.44 to 2.77) 1.40 (0.64 to 3.07) Northern/York 19/1310 1.39 (0.63 to 3.04) + 2.04 (0.79 to 5.24) -> 2.06 (0.80 to 5.32) 8/413 Oxford South West 27/1156 2.31 (1.09 to 4.87) → 2.32 (1.10 to 4.91) Thames 14/1406 1.02 (0.45 to 2.35) 1.00 (0.44 to 2.30) Trent 3/702 0.49 (0.13 to 1.81) 0.49 (0.13 to 1.80) West Midlands 10/731 1.27 (0.52 to 3.11) 1.31 (0.53 to 3.20) (d) Time since DCIS diagnosis (years)  $(p_{\text{heterogeneity}} = 0.05)$ (pheterogeneity = 0.12) 1.00 (1.00 to 1.00) 0.5-2.9 28/49458 1.00 (1.00 to 1.00) 3.0-4.9 29/29158 1.70 (1.01 to 2.85) 1.61 (0.95 to 2.74) 50-69 25/21687 1.91 (1.11 to 3.28) 1.76 (0.99 to 3.11) 7.0-9.9 16/19663 1.37 (0.74 to 2.52) 1.31 (0.69 to 2.52) 0.34 (0.06 to 1.90) 0.35 (0.06 to 2.02) 10 +2/8216 (e) DCIS size (mm)  $(p_{trend} = 0.61)$ (p<sub>trend</sub> = 0.53) 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) <=10 16/738 0.88 (0.45 to 1.70) 0.91 (0.47 to 1.78) 11-20 26/1498 39/3599 0.64 (0.35 to 1.18) 0.64 (0.35 to 1.19) 21-50 19/1704 0.80 (0.40 to 1.63) 0.78 (0.38 to 1.61) 51+ (f) DCIS grade  $(p_{trend} = 0.53)$ (p<sub>trend</sub> = 0.38) 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Low/inter 25/2003 High 75/5534 1.17 (0.72 to 1.88) 1.24 (0.77 to 2.01) (g) Laterality of DCIS  $(p_{trend} = 0.04)$  $(p_{trend} = 0.03)$ Left 40/3842 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) Right 59/3695 1.53 (1.02 to 2.28) 1.54 (1.03 to 2.31)  $(p_{heterogeneity} = 0.54)^{\dagger}$  $(p_{heterogeneity} = 0.66)^{\dagger}$ (h) Final margin distance (mm) 1.00 (1.00 to 1.00) 1.00 (1.00 to 1.00) 5+ 3-4 21/3408 1.53 (0.47 to 5.04) 1.45 (0.44 to 4.78) 5/466 1-2 9/775 1.81 (0.68 to 4.80) 1.65 (0.62 to 4.39) Involved 3/179 2.28 (0.41 to 12.65) - 2.12 (0.38 to 11.91) 1.26 (0.73 to 2.15) 1.18 (0.61 to 2.27) Before 2007 62/2705 - 95% C 0 0.5 1 1.5 2 2.5 3 0 0.5 1 1.5 2 2.5 3

\* Tests for trend excluding years 0.5-2.9: crude P=0.90; adjusted P=0.97
 † Tests for trend across clear margin categories: crude P=0.13; adjusted P=0.13

\* Tests for trend excluding years 0.5-2.9: crude P=0.98; adjusted P=0.61
 † Tests for trend across clear margin categories: crude P=0.05; adjusted P=0.05

\* Tests for trend excluding years 0.5-2.9: crude P=0.06; adjusted P=0.19

† Tests for trend across clear margin categories: crude P=0.20; adjusted P=0.31

Supplementary Figure S2. Incidence of ipsilateral invasive breast cancer according to various factors in 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery. Women with oestrogen-receptor positive DCIS and recorded as receiving endocrine therapy are excluded. For each factor rates are shown relative to first category and adjustment is for all other factors except final margin distance. Final margin distance was not included in the adjustment as information on this variable was available only from 2007 onwards.

#### Mastectomy

### **Breast-conserving surgery with radiotherapy**

#### Breast-conserving surgery no radiotherapy

Ratio of rates

Cases/ Ratio of rates

#### Mastectomy

95% CI

 $(p_{trend} = 0.31)$ 

(p<sub>trend</sub> = 0.02)

1.00 (1.00 to 1.00)

1.39 (0.91 to 2.13)

0.74 (0.36 to 1.54)

1.00 (1.00 to 1.00)

0 74 (0 44 to 1 23)

0.53 (0.30 to 0.96)

0.63 (0.36 to 1.09)

(pheterogeneity = 0.05)

1.00 (1.00 to 1.00)

1.09 (0.44 to 2.74)

1 39 (0 63 to 3 04)

2.04 (0.79 to 5.24)

1.02 (0.45 to 2.35)

0.49 (0.13 to 1.81)

1.27 (0.52 to 3.11)

1.00 (1.00 to 1.00)

1.70 (1.01 to 2.85)

1.91 (1.11 to 3.28)

1.37 (0.74 to 2.52)

0.34 (0.06 to 1.90)

1.00 (1.00 to 1.00)

0.88 (0.45 to 1.70)

0.64 (0.35 to 1.18)

0.80 (0.40 to 1.63)

1.00 (1.00 to 1.00)

1.17 (0.72 to 1.88)

1.00 (1.00 to 1.00)

1.53 (1.02 to 2.28)

 $(p_{heterogeneity} = 0.72)^{\dagger}$ 

1.00 (1.00 to 1.00)

1.53 (0.47 to 5.04)

2.03 (0.50 to 8.32)

1.58 (0.47 to 5.32)

1.26 (0.73 to 2.15)

2.28 (0.41 to 12.65)

(p<sub>trend</sub> = 0.53)

 $(p_{trend} = 0.04)$ 

 $(p_{trend} = 0.61)$ 

-

0 0.5 1 1.5 2 2.5 3

(p<sub>heterogeneity</sub> = 0.05)

2.31 (1.09 to 4.87)

Ratio of rates

(adjusted)

--

--

95% CI

 $(p_{trend} = 0.30)$ 

 $(p_{trend} = 0.01)$ 

1.00 (1.00 to 1.00)

1.33 (0.85 to 2.08)

0.89 (0.40 to 1.97)

1.00 (1.00 to 1.00)

0 71 (0 42 to 1 18)

0.52 (0.29 to 0.93)

0.58 (0.33 to 1.01)

 $(p_{heterogeneity} = 0.05)$ 

1.00 (1.00 to 1.00)

1.11 (0.44 to 2.77)

1 40 (0 64 to 3 07)

2.06 (0.80 to 5.32)

1.00 (0.44 to 2.30)

0.49 (0.13 to 1.80)

1.31 (0.53 to 3.20)

(p<sub>heterogeneity</sub> = 0.12)

1.00 (1.00 to 1.00)

1.61 (0.95 to 2.74)

1.76 (0.99 to 3.11)

1.31 (0.69 to 2.52)

0.35 (0.06 to 2.02)

1.00 (1.00 to 1.00)

0.91 (0.47 to 1.78)

0.64 (0.35 to 1.19)

0.78 (0.38 to 1.61)

1.00 (1.00 to 1.00)

1.24 (0.77 to 2.01)

1.00 (1.00 to 1.00)

1.54 (1.03 to 2.31)

(p<sub>heterogeneity</sub> = 0.81)<sup>†</sup>

1.00 (1.00 to 1.00)

1.45 (0.44 to 4.78)

1.86 (0.46 to 7.59

1.44 (0.42 to 4.88)

1.18 (0.61 to 2.27)

2.12 (0.38 to 11.91)

 $(p_{trend} = 0.53)$ 

 $(p_{trend} = 0.38)$ 

 $(p_{trend} = 0.03)$ 

2.32 (1.10 to 4.91)

Cases/ Ratio of rates

at DCIS diagnosis (years)

-

-

-8

since DCIS diagnosis (years)

(crude)

Women

(a) Year of DCIS diagnosis

37/1651

54/2805

43/2496

23/1590

16/1592

18/1860

10/926

9/893

8/413

3/702

10/731

28/49458

29/29158

25/21687

16/19663

2/8216 (e) DCIS size (mm)

16/738

26/1498

39/3599

19/1704

25/2003

75/5534

40/3842

59/3695

(h) Final margin distance (mm)

5/466 4/323

5/452

3/179

62/2705 

21/3408

(g) Laterality of DCIS

19/1310

27/1156 14/1406

9/3083

2000-04

2005-09

2010-14

(b) Age

(c) Region

Northern/York.

West Midlands

South West

(d) Time

0.5-2.9

3.0-4.9

5.0-6.9

7.0-9.9

10 +

<=10

11-20

21-50

Low/inter.

(f) DCIS grade

51+

Hiah

l eft

5+ 3-4

Involved

Before 2007

- 95% CI

Right

Eastern North West

Oxford

Thames Trent

<55

55-59

60-64

65+

	Cases/ F Women	Ratio of rates (crude)	95% CI	Ratio of rates (adjusted)	95% CI		
(a) Year of	f DCIS diag	gnosis	(p <sub>trend</sub> = 0.19)		(p <sub>trend</sub> = 0.93)		
2000-04	26/531		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)		
2005-09	27/1132	- <b>a</b>	0.77 (0.45 to 1.34)	_ <b>_</b>	0.92 (0.51 to 1.67)		
2010-14	13/3136	╼┼	0.62 (0.32 to 1.21)	_ <b>_</b>	→ 1.33 (0.52 to 3.41)		
(b) Age at	DCIS diag	nosis (years)	(p <sub>trend</sub> = 0.20)		(p <sub>trend</sub> = 0.17)		
<55	14/1422	<b>.</b>	1.00 (1.00 to 1.00)	<b>.</b>	1.00 (1.00 to 1.00)		
55-59	25/1010		<ul> <li>2.40 (1.23 to 4.69)</li> </ul>		→ 2.44 (1.24 to 4.78)		
60-64	16/1054		<ul> <li>1.53 (0.74 to 3.18)</li> </ul>		→ 1.56 (0.75 to 3.26)		
65+	12/1312	-	1.04 (0.47 to 2.31)	-	1.08 (0.48 to 2.39)		
(c) Regior	n		(p <sub>heterogeneity</sub> = 0.63)		(p <sub>heterogeneity</sub> = 0.27)		
Eastern	28/1266	<b>.</b>	1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)		
North West	3/361		<ul> <li>1.85 (0.56 to 6.08)</li> </ul>	_	→ 3.74 (0.94 to 14.98)		
Northern/York	k. 29/1510		0.93 (0.55 to 1.57)		0.90 (0.53 to 1.53)		
Oxford	0/157						
South West	0/198		0.21 (0.03 to 1.54)		0.22 (0.03 to 1.64)		
Trent	4/395		<ul> <li>1.56 (0.55 to 4.44)</li> </ul>	·	→ 2.56 (0.83 to 7.92)		
West Midland	is 1/382 -	•	<ul> <li>0.42 (0.06 to 3.06)</li> </ul>		→ 0.70 (0.09 to 5.68)		
(d) Time s	ince DCIS	diagnosis (yea	re) (n	002)	(p = 0.001) <sup>*</sup>		
0520	12/2072	alugnosis (jeu	1 00 (1 00 to 1 00)		1 00 (1 00 to 1 00)		
3.0-4.9	23/3770	T	<ul> <li>4.03 (2.00 to 8.12)</li> </ul>	T _	+ 5.33 (2.44 to 11.66)		
5.0-6.9	13/2674		<ul> <li>3.27 (1.49 to 7.17)</li> </ul>		+ 4.78 (1.88 to 12.15)		
7.0-9.9	13/2307		<ul> <li>3.92 (1.79 to 8.57)</li> </ul>				
10+	5/813		<ul> <li>3.75 (1.23 to 11.42)</li> </ul>		→ 5.38 (1.48 to 19.49)		
(e) DCIS s	ize (mm)		(p <sub>trend</sub> = 0.55)		(p <sub>trend</sub> = 0.45)		
<=10	19/1416	<b>.</b>	1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)		
11-20	27/1939		1.10 (0.59 to 2.07)		1.07 (0.57 to 2.02)		
21-50	20/1383		1.38 (0.71 to 2.69)		<ul> <li>1.44 (0.73 to 2.85)</li> </ul>		
51+	0/65						
(f) DCIS g	rade		(p <sub>trend</sub> = 0.73)		(p <sub>trend</sub> = 0.62)		
Low/inter.	18/1202	<b>.</b>	1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)		
High	47/3599		0.91 (0.51 to 1.60)		0.86 (0.49 to 1.53)		
(a) Latera	lity of DCIS	s	(p <sub>trend</sub> = 0.42)		$(p_{trend} = 0.49)$		
left	38/2510		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)		
Right	28/2290	- <b>-</b>	0.82 (0.50 to 1.34)		0.84 (0.51 to 1.38)		
(h.) <b>-</b> (h					(,,		
(n) Final n	nargin dist	ance (mm)	(Pheterogeneity = 0.65)'	1	(Pheterogeneity = 0.70)'		
2+4 3-4	9/2184 5/68/		<ul> <li>1.00 (1.00 to 1.00)</li> <li>1.62 (0.41 to 6.48)</li> </ul>				
2	4/444		<ul> <li>2.15 (0.50 to 9.22)</li> </ul>		→ 2.08 (0.48 to 9.11)		
1	5/411		<ul> <li>2.56 (0.66 to 9.89)</li> </ul>		÷ 2.49 (0.64 to 9.76)		
Involved	1/99				_		
Before 2007	43/977		<ul> <li>2.59 (1.13 to 5.96)</li> </ul>		<ul> <li>2.63 (0.91 to 7.60)</li> </ul>		
- 95% CI	L						
- 90 % CI	•	05 1 15 2 25	3 (	05 1 15 2 25	3		
	U	0.5 1 1.5 2 2.5	3 (	0.5 1 1.5 2 2.5	3		

\* Tests for trend excluding years 0.5-2.9: crude P=0.90; adjusted P=0.97 <sup>+</sup> Tests for trend across clear margin categories: crude P=0.12; adjusted P=0.12

	Cases/ F Women	Ratio of rates (crude)	95% CI	Ratio of rates (adjusted)	95% CI
(a) Year o	f DCIS diag	gnosis	(p <sub>trend</sub> = 0.88)		(p <sub>trend</sub> = 0.33)
2000-04	170/2734		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)
2005-09	179/4631	<b>—</b>	1.01 (0.82 to 1.25)		1.10 (0.87 to 1.39)
2010-14	49/5076	- <b>-</b>	0.91 (0.66 to 1.25)	∓∎—	1.27 (0.88 to 1.83)
(b) Age at	DCIS diag	nosis (years)	(p <sub>trend</sub> = 0.92)		(p <sub>trend</sub> = 0.95)
<55	125/3755		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)
55-59	89/2488	- <b></b>	0.98 (0.74 to 1.28)	- <b></b>	0.98 (0.74 to 1.28)
60-64	77/2802	-	0.80 (0.60 to 1.07)	- <b>-</b>	0.80 (0.60 to 1.06)
65+	106/3396		1.15 (0.89 to 1.49)		1.17 (0.90 to 1.53)
(c) Regio	n		(p <sub>heterogeneity</sub> = 0.47)		(p <sub>heterogeneity</sub> = 0.46)
Eastern	44/1227	<b>•</b>	1.00 (1.00 to 1.00)	<b>•</b>	1.00 (1.00 to 1.00)
North West	32/1406		0.67 (0.42 to 1.05)		0.69 (0.44 to 1.10)
Northern/Yor	k. 27/1026		0.77 (0.48 to 1.25)		0.79 (0.49 to 1.28)
Oxford	37/937		1.08 (0.69 to 1.67)		1.14 (0.73 to 1.79)
South West	93/2699		0.96 (0.67 to 1.39)	-	1.01 (0.70 to 1.45)
Thames	85/2792	-	0.85 (0.59 to 1.23)	-	0.89 (0.61 to 1.29)
Trent	27/942		0.75 (0.46 to 1.22)		0.79 (0.48 to 1.28)
west midiano	DS 52/1411		0.90 (0.60 to 1.35)	_	0.94 (0.63 to 1.42)
(d) Time s	since DCIS	diagnosis (yea	ars) (p <sub>heterogeneity</sub> < 0	.001)	(p <sub>heterogeneity</sub> < 0.001)
0.5-2.9	103/25650	<b>P</b> _	1.00 (1.00 to 1.00)	<b>P</b>	1.00 (1.00 to 1.00)
3.0-4.9	112/15743		1.76 (1.35 to 2.30)		1.83 (1.39 to 2.42)
5.0-6.9	73/11/70		1.54 (1.14 to 2.06)		1.03 (1.19 t0 2.27)
10+	34/4549		1.84 (1.24 to 2.72)		-> 2.11 (1.37 to 3.25)
(e) DCIS s	size (mm)		(p <sub>trend</sub> = 0.15)		(p <sub>trend</sub> = 0.18)
<=10	203/5950		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)
11.20	120/2927	I	0.99 (0.78 to 1.24)	王	1.00 (0.79 to 1.26)
21-50	61/2470		0.79 (0.59 to 1.07)	- <b>I</b>	0.80 (0.59 to 1.09)
51+	4/185		0.67 (0.22 to 2.05)		0.65 (0.21 to 2.01)
(f) DCIS g	rade		(p <sub>trend</sub> = 0.68)		(p <sub>trend</sub> = 0.89)
Low/inter.	206/6647		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)
High	191/5795	Ē	0.96 (0.78 to 1.17)	Ē.	0.98 (0.79 to 1.22)
(a) Latora		<u> </u>	(p <sub>mad</sub> = 0.08)	Т	(p <sub>max</sub> = 0.07)
(g) Latera		° ⊥	(Ptrend = 0.00)		(Pirend = 0.01)
Lett	187/6414		1.00 (1.00 to 1.00)		1.00 (1.00 to 1.00)
Right	210/6028		1.19 (0.98 to 1.46)	-	1.20 (0.98 to 1.46)
(h) Final r	nargin dist	ance (mm)	$(p_{heterogeneity} = 0.002)^{\dagger}$		$(p_{heterogeneity} < 0.001)^{\dagger}$
5+	56/4080	<b>\$</b>	1.00 (1.00 to 1.00)	4	1.00 (1.00 to 1.00)
3-4	28/1484	-+	1.26 (0.70 to 2.30)	-+	1.27 (0.70 to 2.31)
2	27/1092		→ 1.95 (1.12 to 3.40)		-> 2.03 (1.16 to 3.56)
1 Invioluted	20/1002		1.29 (0.66 to 2.49)		1.34 (0.69 to 2.61)
nivolved	16/280		- +.04 (2.01 to 8.08)		
Before 2007	250/4505		1.34 (0.95 to 1.89)		1.17 (0.77 to 1.76)
- 95% CI	L				
	0	05 1 15 2 25	3 (	1 05 1 15 2 2	5 3



<sup>\*</sup> Tests for trend excluding years 0.5-2.9: crude P=0.06; adjusted P=0.19 † Tests for trend across clear margin categories: crude P=0.24; adjusted P=0.37

0 0.5 1 1.5 2 2.5 3

Supplementary Figure S3. Incidence of ipsilateral invasive breast cancer according to various factors in 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery showing final margin distances of 1 and 2 mm separately. Women with oestrogen-receptor positive DCIS and recorded as receiving endocrine therapy are excluded. For each factor rates are shown relative to first category and adjustment is for all other factors except final margin distance. Final margin distance was not included in the adjustment as information on this variable was available only from 2007 onwards.

### Supplementary Table S14. Tests for interactions between pairs of factors for analysis shown in Figure 3.

Factors	P-value
	0.02
Treatment x age at diagnosis	0.02
Treatment x year of diagnosis	0.36
Treatment x time since diagnosis	0.16
Treatment x DCIS grade	0.72
Treatment x tumour size	0.46
Treatment x laterality	0.15
DCIS grade x age at diagnosis	0.18
DCIS grade x year of diagnosis	0.19
DCIS grade x time since diagnosis	0.01
DCIS grade x tumour size	0.90
DCIS grade x laterality	0.46
Tumour size x age at diagnosis	0.47
Tumour size x year of diagnosis	0.82
Tumour size x time since diagnosis	0.26
Tumour size x laterality	0.26
Age at diagnosis x year of diagnosis	0.39
Age at diagnosis x time since diagnosis	0.58
Age at diagnosis x laterality	0.20
Year of diagnosis x time since diagnosis	0.77
Year of diagnosis x laterality	0.07
Time since diagnosis x laterality	0.70
*Final margin distance x treatment	0.98
Final margin distance x DCIS grade	0.43
Final margin distance x age at diagnosis	0.85
Final margin distance x year of diagnosis	0.59
Final margin distance x time since diagnosis	0.54
Final margin distance x tumour size	0.80
Final margin distance x laterality	0.50

\* Women diagnosed before 2007 were excluded for testing interaction between final marginal distance and other factors.

Factors are treated as categorical variables with categories as shown in Figure 3, apart from tumour size and final margin distance which are treated as continuous variables in this table. Adjustments are as in Figure 3 except for analyses including interactions with final margin distance, in which final margin distance is included as a main effect as well as an interaction.



BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded No. of IBC: Number of ipsilateral invasive breast cancers during interval No. at Risk: Number of individuals at risk of invasive breast cancer at start of interval

Supplementary Figure S4. Cumulative incidence rate of ipsilateral invasive breast cancer in 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 by treatment and DCIS grade. Women with no surgery and women with oestrogen-receptor positive DCIS and recorded as receiving endocrine therapy were excluded.



BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded

Supplementary Figure S5. Annual incidence rate of ipsilateral invasive breast cancer in 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery by treatment and age at diagnosis of DCIS. Women with oestrogen-receptor positive DCIS and recorded as receiving endocrine therapy are excluded.



BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded

CI: confidence interval

P: results of tests for heterogeneity or trend

\* Tests for trend excluding years 0.5-2.9: crude P=0.36; adjusted P=0.36

† Tests for trend across clear margin categories: crude P=0.66; adjusted P=0.53

Supplementary Figure S6. Incidence rate of contralateral invasive breast cancer according to various factors in 24,779 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery. Women with oestrogen-receptor positive DCIS and recorded as receiving endocrine therapy are excluded. For each factor, rates are shown relative to the first category and adjustment is for all other factors except final margin distance. Final margin distance was not included in the adjustment as information on this variable was available only from 2007 onwards.

	Ipsilatera Contralate	al/ eral	Ratio of rates al (crude)					o of rates    95% Cl <sup>R</sup> crude)							Ratio of rates (adjusted)					
(a) Year of D	CIS diagno	sis							(p <sub>trend</sub>	= 0.40)							(p <sub>tren</sub>	<sub>d</sub> = 0.16)		
2000-04	233/216								1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
2005-09	260/205			Ŧ	-				1.18 (0.91 t	o 1.53)		T				1.2	29 (0.95	to 1.75)		
2010-14	71/72				_				0.92 (0.63 t	o 1.34)	_	•				1.(	0.64 (0.64	to 1.60)		
(b) Age at D	CIS diagnos	sis (	vear	s)					(p <sub>trend</sub>	= 0.78)							(p <sub>tren</sub>	<sub>d</sub> = 0.37)		
<55	182/155		<b>,</b>	-/					1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
55-59	137/110								1.06 (0.76 t	o 1.48)	-	- Te				1.0	)4 (0.73	to 1.49)		
60-64	109/127			нT					0.73 (0.52 t	o 1.02)		⊢T i				0.6	67 (0.47	to 0.95)		
65+	136/102			-+=	<u> </u>				1.13 (0.81 t	o 1.59)	-		_			1.0	00 (0.69	to 1.44)		
(c) Region									(p <sub>heterogeneity</sub>	= 0.32)						(p <sub>he</sub>	eterogeneit	<sub>y</sub> = 0.58)		
Eastern	82/73								1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
North West	44/47			∎					0.85 (0.51 t	o 1.43)		-				0.8	34 (0.48	to 1.48)		
Northern/Yorkshin	re 75/82				-				0.82 (0.52 t	o 1.29)	_					1.0	00 (0.63	to 1.59)		
Oxford	45/39				_	-			1.04 (0.61 t	o 1.77)			_			0.9	90 (0.50	to 1.60)		
South West	120/76			t	-		•		1.41 (0.92 t	0 2.17)		1				1.3	33 (0.82	to 2.15)		
Trant	100/84		-						1.08 (0.70 t	0 1.67)		-				0.8	96 (0.59 34 (0.50	to 1.54)		
West Midlands	34/29 63/63		_			_			0.90 (0.56 t	o 1.90) o 1.44)	_		_	•		0.8	34 (0.30 31 (0.48	to 1.35)		
(d) Timo sinc		anc	eie (		re)			(	'n	0.52)*						(n.		- 0.57)*		
		giic	515 (	уçа	13)			(	Pheterogeneity -	- 0.32) - 1.00)						(Phe	terogeneity	= 0.07		
0.5-2.9	144/150								1.00 (1.00 t	0 1.00)		Τ.				1.0	DU (1.00	to 1.00)		
5.0-4.9	104/133					_			1.26 (0.93 t	o 1.81)				_		1.4	25 (0.88	to 1.86)		
7 0-9 9	102/85					_			1.26 (0.87 t	o 1.82)		_	-			1.3	34 (0.88	to 2.05)		
10+	41/31			+					1.38 (0.81 t	o 2.34)		-	-			1.5	50 (0.82	to 2.76)		
(e) DCIS size	e (mm)								(p <sub>trend</sub> <	0.001)							(p <sub>tren</sub>	d = 0.21)		
<=10	238/156								1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
11-20	182/165		_	J					0.73 (0.53 t	0.0.99)	_	T				0.8	34 (0.60	to 1 17)		
21-50	120/129								0.61 (0.44 t	0 0 86)	_		_			0.0	37 (0.59	to 1 27)		
51+	23/45	-	•						0.34 (0.19 t	o 0.61)		-	-			0.6	67 (0.35	to 1.28)		
(f) DCIS grad	le								(p <sub>trend</sub>	= 0.44)							(p <sub>tren</sub>	a = 0.17)		
Low/intermediate	249/207								1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
High	313/287		-	<b>-</b>					0.91 (0.71 t	o 1.16)		Ŧ	-			1.2	22 (0.92	to 1.61)		
(a) Laterality	of DCIS								(Dtrand	= 0.83)							(ptress	a = 0.56)		
Left	265/229								1.00 (1.00 t	o 1.00)						1.0	00 (1.00	to 1.00)		
Right	297/264			Ē	-				0.97 (0.76 t	, o 1.24)	-	Ē.				0.9	93 (0.72	to 1.20)		
(h) Final mar	ain dictors	·~ /-	nm)					(*	n	0.12) <sup>†</sup>						(p)		- 0 3e)‡		
(n) Final mar	gin distance	e (i	nin)	$\bot$				()	heterogeneity =	0.12)		1				(Phete	erogeneity	= 0.30)		
5+	86/100			T		_		_	1.00 (1.00 t	0 1.00)		T				- 1.0	JU (1.00 75 (0.95	to 1.00)		
3-4 1-2	50/21 65/44							_	2.03 (1.00 t	o 2 91)			_			- 1.1	50 (0.85 50 (0.83	to 2 71)		
Involved	20/13		_					->	1.67 (0.68 t	o 4.08)						-> 1.4	47 (0.58	to 3.74)		
Before 2007	355/313								1.32 (0.92 t	o 1.88)						1.2	23 (0.76	to 1.99)		
(i) Trootmont								(r	)	0.001)						(n:		< 0 001\		
				Ţ				()	I OO /1 OO +	0.001)		1				Phete م	erogeneity	< 0.001)		
BUS + KI	66/75			T					1.00 (1.00 t	0 1.00)		T				1.0		10 1.00)		
BCS - KI	398/238							-	1.91 (1.32 t	0 2.76)						→ 1.9	33 (1.23	to 3.02)		
Mastectomy	100/180								0.64 (0.42 t	o 0.96)		$\uparrow$				0.6	66 (0.41	to 1.06)		
- <b>E-</b> 95% CI										L										
		0	0.5	1	1.5	2	2.5	3		0	0.5	1	1.5	2	2.5	3				
	More	con	tra. —		— Mo	ore ip	osi.		I	More coi	ntra. –	•	— Mo	ore ip	si.					

BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded

CI: confidence interval

P: results of tests for heterogeneity or trend
\* Tests for trend excluding years 0.5-2.9: crude P=0.16; adjusted P=0.12
† Tests for trend across clear margin categories: crude P=0.05; adjusted P=0.15

Supplementary Figure S7. Comparison of the rates of ipsilateral and contralateral invasive breast cancer according to various factors in 24,779 women with unilateral screen-detected DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery. Women recorded with oestrogen-receptor positive DCIS and receiving endocrine therapy are excluded. For each factor rates are shown relative to first category and adjustment is for all other factors except final margin distance. Final margin distance was not included in the adjustment as information on this variable was available only from 2007 onwards.

Supplementary Table S15. Characteristics of 29,044 women diagnosed with unilateral DCIS detected as a result of screening between April 2000 and March 2014 and who received surgery, according to oestrogen-receptor status and whether or not they were recorded as having received endocrine therapy.

_	Oestrogen-recep No endocrine therapy	tor negative Endocrine therapy	Oestrogen- receptor negative	P for heterogeneity	Total
Year of DCIS diagnos	sis				
2000-04	3240 (51.7)	1355 (21.6)	1676 (26.7)	< 0.001	6271 (100.0)
2005-09	6229 (59.8)	1856 (17.8)	2339 (22.4)		10,424 (100.0)
2010-14	9073 (73.5)	1054 (8.5)	2222 (18.0)		12,349 (100.0)
Age at DCIS diagnosi	is (years)				
<55	6296 (69.8)	1344 (14.9)	1377 (15.3)	< 0.001	9017 (100.0
55-59	3621 (59.9)	961 (15.9)	1467 (24.3)		6049 (100.0
60-64	3818 (59.5)	970 (15.1)	1630 (25.4)		6418 (100.0
65+	4798 (63.5)	992 (13.1)	1770 (23.4)		7560 (100.0
Dagion					
Fastern	2505 (70.0)	241 (6.6)	824 (22 5)	<0.001	3660 (100.0
Lastern North West	2393(70.9) 1061(52.2)	241(0.0) 1018(27.7)	624 (22.3)	<0.001	2678 (100.0
North west	1901(33.3)	1010(27.7)	1049(19.0)		4267 (100.0
Northern/Yorkshire	2798 (64.1)	521 (11.9)	1048 (24.0)		4367 (100.0
Oxford	1092 (65.7)	156 (9.4)	415 (25.0)		1663 (100.0
South West	3104 (66.0)	652 (13.9)	949 (20.2)		4705 (100.0
Thames	3563 (62.7)	950 (16.7)	1166 (20.5)		5679 (100.0
Trent	1519 (61.3)	440 (17.7)	520 (21.0)		2479 (100.0
West Midlands	1917 (68.1)	289 (10.3)	607 (21.6)		2813 (100.0
DCIS size (mm)					
<=10	6739 (70.7)	1425 (15.0)	1365 (14.3)	< 0.001	9529 (100.0
11-20	5335 (61.6)	1383 (16.0)	1939 (22.4)		8657 (100.0
21-50	5141 (59 5)	1189 (13.8)	2311 (26.7)		8641 (100.0
51+	1333 (60.2)	262 (11.8)	621 (28.0)		2216 (100.0
DCIE and a					
Low/intermediate	8025 (76.1)	1992 (16.0)	(0, 7, 7, 0)	<0.001	11 724 (100 0
High	9609 (55 5)	1882(10.0) 2384(13.8)	5319 (30.7)	<0.001	17 312 (100.0
Ingn	9009 (55.5)	2504 (15.0)	5517 (50.7)		17,512 (100.0
Laterality of DCIS	0527 ((2, ()	2222 (14.8)	2220 (21.5)	0.75	14,099 (100,0
Right	9557 (65.0) 8993 (64.0)	2222 (14.8) 2043 (14.5)	3229 (21.5)	0.75	14,988 (100.0)
					,
Final margin distance	e (mm) 7/81 (69 3)	1126 (10.4)	2191 (20.3)	<0.001	10798 (100.0
3T 2 4	2000 (60 7)	262(12.1)	544(18.2)	<0.001	2007 (100.0
1.0	2090(09.7)	509 (12.1)	700(18.2)		4220 (100.0
1-2 T 1 1	2952 (67.9)	598 (15.8)	790 (18.3)		4320 (100.0
Involved	437 (68.6)	/9 (12.4)	121 (19.0)		637 (100.0
Before 2007	5602 (54.4)	2105 (20.5)	2585 (25.1)		10,292 (100.0
Surgery and radiothe	rapy				
BCS + RT	3579 (66.7)	569 (10.6)	1220 (22.7)		5368 (100.0
BCS - RT	9948 (65.5)	2747 (18.1)	2493 (16.4)		15,188 (100.0
Mastectomy	5000 (58.9)	951 (11.2)	2537 (29.9)		8488 (100.0
Duration of follow-ur	(vears)				
0-4	9327 (72.8)	1142 (8 9)	2339 (18.3)		12808 (100 (
5_9	6191(594)	1877(18.0)	2360 (22.6)		10428 (100.0
11-14	3020 (52.0)	1246 (21.5)	1542 (26.5)		5808 (100.0
	~ /	· /	× /		
Laterality of IBC	200 (21 0	00 (10 5)	1		e 1 e 1000 -
Ipsilateral	398 (61.6)	82 (12.7)	166 (25.7)		646 (100.0
Contralateral	337 (57.4)	94 (16.0)	156 (26.6)		587 (100.0
Unknown	41 (49.4)	20 (24.1)	22 (26.5)		83 (100.0
Vital status on 31 Dec	2014				
Alive	17,856 (64.2)	4009 (14.4)	5930 (21.3)		27,795 (100.0
Emigrated	41 (55.4)	17 (23.0)	16 (21.6)		74 (100.0
Dead	629 (53.5)	240 (20.4)	306 (26.0)		1175 (100.0
Cause of death					
Breast cancer	65 (17 8)	29 (21 3)	42 (30 0)		136 (100 (
Other causes	557 (54 1)	27 (21.3)	42 (30.9) 250 (25 A)		1021 (100.0
Unknown geweg	332(34.1)	210(20.0)	237 (23.4) 5 (27.9)		1021 (100.0
Unknown cause	12 (00.7)	1 (3.0)	5 (27.8)		18 (100.0
Total	18.542 (63.8)	4265 (14.7)	6237 (21.5)		29.044(100.0

BCS+RT: breast-conserving surgery, radiotherapy recorded BCS-RT: breast-conserving surgery, radiotherapy not recorded



ER+, no endocrine: oestrogen-receptor positive DCIS, endocrine therapy not recorded

ER+, endocrine: oestrogen-receptor positive DCIS, endocrine therapy recorded ER-: oestrogen-receptor negative DCIS

ER-: oestrogen-receptor negat CI: confidence interval

P: results of tests for heterogeneity

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Supplementary Figure S8. Incidence of ipsilateral and contralateral invasive breast cancer in 29,044 women with unilateral screendetected DCIS according to oestrogen-receptor status and endocrine therapy. Rates are shown relative to first category in each section. Adjustment is for year of diagnosis, age at diagnosis, time since diagnosis, tumour size, DCIS grade, laterality and category of surgery/ radiotherapy.



### Breast-conserving surgery with radiotherapy

### Breast-conserving surgery no radiotherapy



### **Mastectomy**

	Cases/ Women		Ratio (c	of rate rude)	S	95% CI			Ratio (ad	o of rate justed)	s	95% CI		
(a) Ipsilateral						(p <sub>heteroge</sub>	<sub>eneity</sub> = 0.7	7)				(p <sub>heteros</sub>	geneity = 0.88)	
ER+, no endocrine	65/5000					1.00 (1	1.00 to 1.0	0)				1.00 (	1.00 to 1.00)	
ER+, endocrine ER-	13/951 35/2537		_	▫ੂ	_	0.80 (0 0.91 (0	).43 to 1.4 ).56 to 1.4	6) 9)		•		0.84 ( 0.99 (	0.45 to 1.56) 0.59 to 1.68)	
(b) Contralatera	ıl					(p <sub>heteroge</sub>	<sub>eneity</sub> = 0.8	3)				(p <sub>hetero</sub>	geneity = 0.83)	
ER+, no endocrine	110/5000					1.00 (1	1.00 to 1.0	0)				1.00 (	1.00 to 1.00)	
ER+, endocrine	26/951				_	0.90 (0	).57 to 1.4	0)				0.91 (	0.57 to 1.43)	
ER-	70/2537		-			1.06 (0	0.71 to 1.5	7)		-		1.07 (	0.70 to 1.64)	
(c) All						(p <sub>heteroge</sub>	eneity = 0.7	7)				(p <sub>heteros</sub>	geneity = 0.77)	
ER+, no endocrine	192/5000					1.00 (1	1.00 to 1.0	0)				1.00 (	1.00 to 1.00)	
ER+, endocrine	44/951		_			0.88 (0	).62 to 1.2	3)	_			0.88 (	0.63 to 1.25)	
ER-	117/2537				-	1.01 (0	0.75 to 1.3	7)			_	1.03 (	0.75 to 1.42)	
- 95% CI			1					L						
		0	0.5	1	1.5	2		0	0.5	1	1.5	2		

ER+, no endocrine: oestrogen-receptor positive DCIS, endocrine therapy not recorded

ER+, endocrine: oestrogen-receptor positive DCIS, endocrine therapy recorded

ER-: oestrogen-receptor negative DCIS

CI: confidence interval

P: results of tests for heterogeneity

Supplementary Figure S9. Incidence of ipsilateral and contralateral invasive breast cancer in 29,044 women with unilateral screendetected DCIS who underwent surgery according to oestrogen-receptor status, endocrine therapy, and whether they received mastectomy, breast conserving surgery with radiotherapy, or breast conserving surgery without radiotherapy. Rates are shown relative to first category in each section. Adjustment is for year of diagnosis, age at diagnosis, time since diagnosis, tumour size, and DCIS grade and laterality.