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Risk of invasive breast cancer in women diagnosed with ductal carcinoma in situ in Australia between 1995 and 2005

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Abbreviations

ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
AIHW	Australian Institute of Health and Welfare
ASR	age-standardised rate
CI	confidence interval
DCIS	ductal carcinoma in situ
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
NBOCC	National Breast and Ovarian Cancer Centre
NMD	National Mortality Database
NT	Northern Territory
SA	South Australia

Summary

Ductal carcinoma in situ (DCIS) of the breast is a non-invasive lesion diagnosed in approximately 1,600 women each year in Australia. It has been estimated that around 40% to 70% of DCIS lesions may progress to invasive breast cancer if left untreated, but the evidence is uncertain. Although DCIS is almost always treated when diagnosed, there is increasing interest in better understanding the heterogeneity of DCIS characteristics and treatment implications.

A number of studies indicate that women with a history of DCIS diagnosis may be at increased risk of invasive breast cancers at a later time. These may be in the opposite breast or arise independently in the same breast as the DCIS. Risk factors common to DCIS and invasive breast cancer may be involved.

Existing Australian data on the risk of subsequent invasive breast cancers following a DCIS diagnosis are limited and have not been collated and analysed at a national level until now. This national study covered the period from 1995 to 2005. Results indicate that women who had been diagnosed with DCIS had, on average, a 5.3% risk of being diagnosed with invasive breast cancer within five years of the DCIS diagnosis. The same women had a 10.9% chance of being diagnosed with invasive breast cancer within 10 years of the DCIS diagnosis. These women were approximately four times as likely to develop invasive breast cancer as normally experienced by Australian women of similar age.

In Australian women who had been diagnosed with invasive breast cancer, the women with a prior diagnosis of DCIS generally had smaller invasive tumours and the cancer was less likely to have spread to regional lymph nodes. These characteristics are well-established prognostic indicators and are associated with higher survivals.

Women aged less than 40 years at the time of DCIS diagnosis:

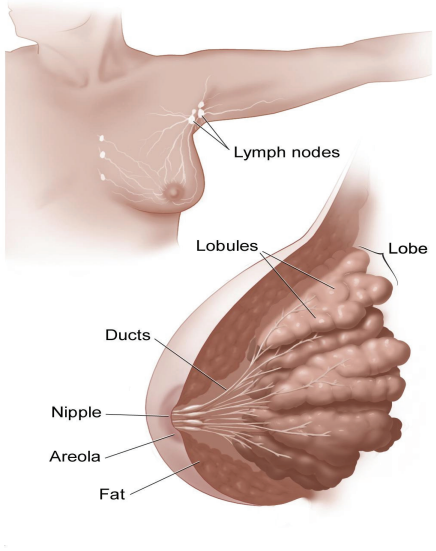
- had an 8.4% chance of being diagnosed with a subsequent invasive breast cancer within five years of the DCIS diagnosis, compared with a 5.3% chance averaged over all ages
- had a 15.5% chance of being diagnosed with invasive breast cancer within 10 years of the DCIS diagnosis, compared with 10.9% averaged over all ages
- were nearly 20 times as likely as other Australian women in this age range to develop a subsequent invasive breast cancer, compared with approximately four times as likely when averaged over all ages.

However, women aged less than 40 years at DCIS diagnosis who subsequently developed invasive breast cancer generally had relatively small invasive cancers, although the likelihood of nodal spread was only slightly lower than that normally seen for all Australian women with invasive breast cancer in this age range.

This report supports evidence that women previously diagnosed with DCIS are at higher risk than other women of similar age of later developing invasive breast cancer. The management practice of placing these women under closer medical surveillance may be responsible for earlier diagnosis of their invasive breast cancers, which generally show smaller sizes and less evidence of nodal spread than seen in other women.

1 Introduction

Ductal carcinoma in situ (DCIS) is a non-invasive tumour arising from, and contained entirely within, a milk duct of the breast. Prior to the introduction of mammography screening, DCIS diagnoses were uncommon. Since the introduction and progressive extension of breast screening in Australia from 1988, the detection of DCIS has increased substantially.



Source: National Cancer Institute, 2009.

Figure 1.1: Anatomy of the female breast

The objectives of this report are:

- to determine the probability of a future diagnosis of invasive breast cancer following initial diagnosis of DCIS, and to compare this probability with the probability of invasive breast cancer generally encountered by Australian women
- to describe and compare two staging features, namely tumour size and nodal status, of invasive breast cancers that follow a DCIS diagnosis with corresponding features of breast cancers generally presenting in Australian women.

DCIS may progress to invasive breast cancer if left untreated, although the probability of this occurring would vary with characteristics of the DCIS, including its size, grade and whether necrosis is present (WHO & IARC 2002). Early studies indicated that progression to invasive cancer might occur in 40% to 70% of untreated DCIS lesions, although progression may be more likely for the types of lesions detected through mammography screening (were they not treated), due to their more unfavourable prognostic features (WHO & IARC 2002). There is increasing research evidence that DCIS is a heterogeneous group of lesions and that management protocols may need to be developed that take account of differences in DCIS characteristics (Patani et al. 2008).

The risk of progression of DCIS to invasive cancer can be eliminated or greatly reduced by treatment, but if common risk factors exist, DCIS may still be a risk indicator for invasive cancer of the other breast or cancers arising independently of the DCIS in the same breast. Some early studies indicated a 4- to 12-fold increase in risk of invasive breast cancer in women with a prior DCIS diagnosis, whereas more recent studies, while confirming an increase in risk, have indicated that it may be of smaller magnitude (Habel et al. 1997; WHO & IARC 2002; Claus et al. 2003; Li et al. 2006; Luke et al. 2006; Innos et al. 2008).

Information on the likely scale and timing of any elevation in risk of invasive breast cancer following a DCIS diagnosis is an important consideration when planning the medical surveillance of women diagnosed with DCIS. In this report, data provided by the eight Australian state and territory cancer registries to the National Cancer Statistics Clearing House at the Australian Institute of Health and Welfare are used to investigate this risk.

Existing Australian data on this topic are limited and have not previously been collated and analysed at a national level.

Although DCIS can occur in men, the Australian data are too sparse for meaningful analysis of DCIS in males. Therefore this report is restricted to DCIS and invasive breast cancer in women.

2 Incidence of DCIS

Although DCIS is not an invasive cancer and is therefore not a primary focus of data collection for cancer registries, it is generally recorded by state and territory cancer registries in Australia. DCIS data are also collected within the national breast cancer screening program, BreastScreen Australia.

This chapter presents background data on trends in DCIS incidence from 1995 to 2005 and on the proportion of DCIS cases detected through BreastScreen Australia from 1996 to 2005.

Incidence of DCIS in Australia

The most recent DCIS data available Australia-wide are for 2005 when there were 1,558 new DCIS cases reported (Table 2.1), giving an age-standardised rate of 14.4 cases per 100,000 females (Table 2.2).

The incidence of DCIS varies considerably by age, being lowest in women under 40 years (2005 incidence rate of 1.1 cases per 100,000 females) and highest in those aged 60 to 69 years (50.8) (Table 2.2). These differences are explained by the following:

- DCIS is most commonly detected on mammogram.
- Women aged 40 years or more are eligible for screening mammography.
- Women aged 50 to 69 years are the 'target population' of BreastScreen Australia, increasing their chances of DCIS detection.

From 1995 to 2005, the age-standardised incidence rate of DCIS increased on average by 3.0% per year (Figure 2.1). The size of the average annual increase varied by age, ranging from 1.0% for women under 40 years to 5.7% for women aged 60 to 69 years.

DCIS detected by BreastScreen Australia

The detection of DCIS has been shown in various settings to increase markedly with the introduction of screening mammography. For example, South Australian data demonstrated a 7-fold increase in annual incidence of in situ breast lesions (mostly DCIS) from 1.9 per 100,000 females in 1985–1988 to 13.6 per 100,000 in 2001–2004, with most of the increase occurring between 1985–1988 and 1997–2000 (Luke et al. 2006). This coincided with the introduction of pilot screening mammography from 1988 and the roll-out of the national screening program from 1991.

Similar increases are thought to have accompanied the introduction of screening mammography in other states and territories. In New South Wales, DCIS data showed an increase in incidence between 1995 and 2000 that correlated with the increased number of women participating in the screening program (Kricker et al. 2004).

In the period from 1996 to 2005, the number of DCIS cases detected through BreastScreen Australia, expressed as a proportion of the total number of DCIS cases, peaked at 66.9% in 2000 and was 61.9% in 2005 (Table 2.4). These are sizeable proportions that reflect the population coverage achieved by the screening program and the ability of screening

mammography to detect DCIS lesions that are not found by clinical or self examination (Burstein et al. 2004).

The proportion of DCIS cases detected through BreastScreen Australia varies by age, with the highest proportions applying to women in the screening target age range of 50–69 years (Table 2.4). This reflects the contribution made by screening mammography. For women outside the target age range, the reduction between the 2000 and 2005 proportions (Figure 2.2) may reflect an increasing focus placed by the screening program on the principal screening target age range of 50–69 years compared to other age groups during this period.

Table 2.1: Incidence of DCIS expressed as numbers of female cases, Australia, 1995–2005

Age (years)	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Under 40	51	38	58	51	44	57	39	60	43	51	63
40–49	158	194	233	239	237	230	257	250	243	279	263
50–59	261	244	324	361	412	457	497	479	483	520	522
60–69	188	205	264	303	306	321	402	364	388	419	435
70–79	140	121	138	180	157	208	204	190	231	210	208
80+	26	30	25	45	44	36	48	47	48	53	67
Total	**824**	**832**	**1,042**	**1,179**	**1,200**	**1,309**	**1,447**	**1,390**	**1,436**	**1,532**	**1,558**

Notes

1. DCIS counts were not available for SA or NT for 1995.
2. DCIS counts were not available for SA for 1996.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 2.2: Age-standardised incidence rate of DCIS, females, Australia, 1995–2005

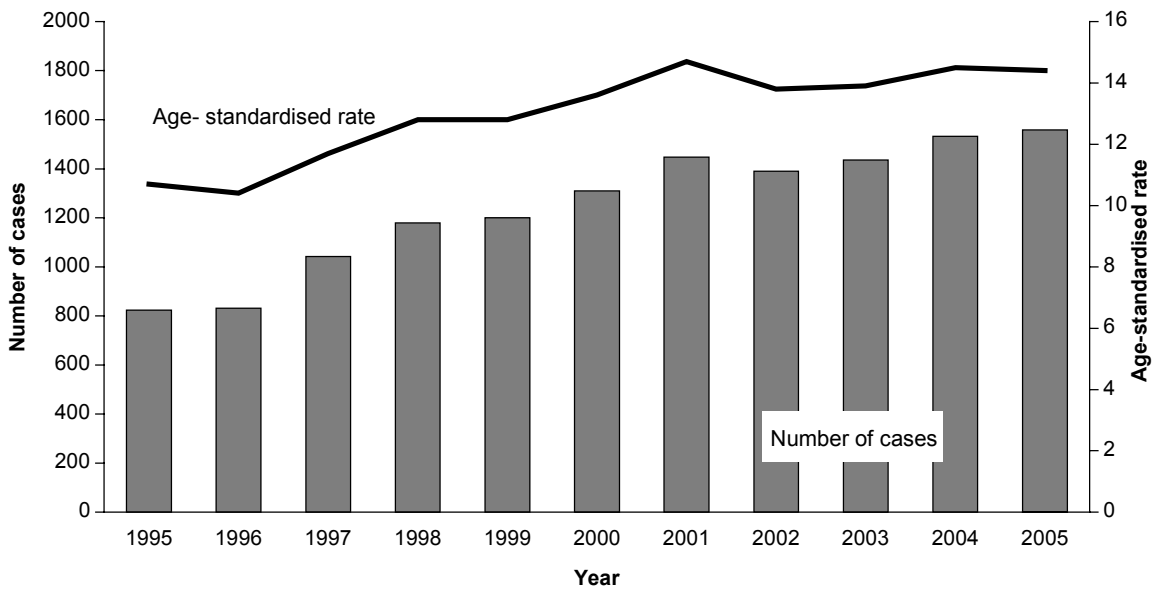
	Age (years)							
Year	Under 40	40–49	50–59	60–69	70–79	80+	ASR[(a)]	95% CI[(b)]
1995	1.0	13.5	32.9	29.2	27.9	9.4	10.7	9.9–11.4
1996	0.8	16.0	29.4	31.6	23.4	10.4	10.4	9.7–11.1
1997	1.1	17.5	33.8	36.9	23.6	7.6	11.7	11.0–12.4
1998	0.9	17.6	35.9	42.0	30.0	13.3	12.8	12.1–13.6
1999	0.8	17.2	39.2	41.9	25.6	12.6	12.8	12.1–13.5
2000	1.1	16.4	41.7	43.3	33.5	9.9	13.6	12.9–14.4
2001	0.7	18.0	43.4	53.2	32.5	12.5	14.7	13.9–15.4
2002	1.1	17.2	40.4	47.0	30.3	11.7	13.8	13.0–14.5
2003	0.8	16.4	39.4	48.8	36.9	11.6	13.9	13.1–14.6
2004	0.9	18.6	41.3	50.9	33.6	12.4	14.5	13.8–15.2
2005	1.1	17.4	40.5	50.8	33.3	15.1	14.4	13.7–15.1

(a) Age-standardised rate. Rates are age-standardised to the Australian population at 30 June 2001 and expressed per 100,000 women. Age-standardisation both within age groups and overall is based on 5-year age groups.

(b) 95% confidence interval for age-standardised rate.

Note: DCIS counts were not available for SA for 1995–1996 or for NT for 1995. The rates for those years have been adjusted to account for this by excluding the respective denominator populations.

Source: AIHW analysis of data supplied by state and territory cancer registries.



Notes

1. Rates are age-standardised to the Australian population at 30 June 2001 and expressed per 100,000 women.
2. DCIS counts were not available for SA for 1995–1996 or for NT for 1995. The rates for those years have been adjusted to account for this by excluding the respective denominator populations.
3. The data for this figure are shown in Tables 2.1 and 2.2.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Figure 2.1: Incidence of DCIS, females, Australia, 1995–2005

Table 2.3: Number of cases of DCIS detected through BreastScreen Australia, females, 1996–2005

Age (years)	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
40–49	60	84	105	94	118	104	103	101	113	89
50–59	169	197	267	275	335	349	356	362	370	386
60–69	153	180	223	233	239	297	260	280	313	339
70–79	73	78	95	98	133	133	129	165	127	102
80+	5	7	8	13	12	17	17	10	17	9
Total for 40+	**460**	**546**	**698**	**713**	**837**	**900**	**865**	**918**	**940**	**925**

Note: Although data for 1996 for SA are available from BreastScreen Australia, they are not included in this table to maintain consistency with Table 2.1.

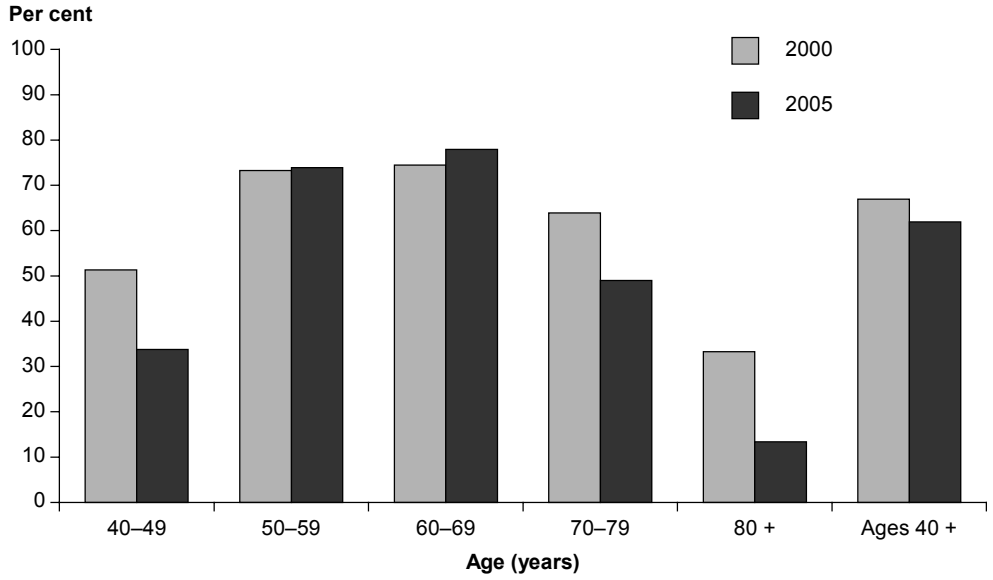
Source: BreastScreen Australia monitoring report.

Table 2.4: Percentage of DCIS cases detected through BreastScreen Australia, females, 1996–2005

Age (years)	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
40–49	30.9	36.1	43.9	39.7	51.3	40.5	41.2	41.6	40.5	33.8
50–59	69.3	60.8	74.0	66.7	73.3	70.2	74.3	74.9	71.2	73.9
60–69	74.6	68.2	73.6	76.1	74.5	73.9	71.4	72.2	74.7	77.9
70–79	60.3	56.5	52.8	62.4	63.9	65.2	67.9	71.4	60.5	49.0
80+	16.7	28.0	17.8	29.5	33.3	35.4	36.2	20.8	32.1	13.4
Total for 40+	**57.9**	**55.5**	**61.9**	**61.7**	**66.9**	**63.9**	**65.0**	**65.9**	**63.5**	**61.9**

Note: Each value in the table is the number of cases of DCIS detected within BreastScreen Australia (Table 2.3) expressed as a percentage of the number of DCIS cases recorded by cancer registries for the same age group (Table 2.1).

Sources: BreastScreen Australia monitoring report and AIHW analysis of data supplied by state and territory cancer registries.



Sources: BreastScreen Australia monitoring report and AIHW analysis of data supplied by state and territory cancer registries.

Figure 2.2: Percentage of DCIS cases detected through BreastScreen Australia, 2000 and 2005

3 Probability of invasive breast cancer following a diagnosis of DCIS

In this chapter, the probability of diagnosis of invasive breast cancer following an earlier diagnosis of DCIS is presented by age at time of DCIS diagnosis and time elapsing since DCIS diagnosis.

Brief description of data and method

The data set used in this analysis comprised unit records for all women diagnosed with DCIS in Australia between 1 January 1995 (1996 for NT and 1997 for SA) and 31 December 2005. There were 13,749 such women. The data set also included information on subsequently diagnosed invasive breast cancers prior to 2006 and deaths occurring from any cause prior to 2006.

The Kaplan-Meier product limit technique was used to calculate the probability of diagnosis with invasive breast cancer by period of time following DCIS diagnosis.

It should be noted that the probability computed was that of a woman being diagnosed with *any* histology type of invasive breast cancer, and in *either* breast, irrespective of the breast in which the DCIS was diagnosed. As no treatment data were available, the analysis did not investigate possible effects of differences in treatment of DCIS on risk of subsequent invasive breast cancer.

Details of how the data set was constructed are given in the appendix.

Results

Following a diagnosis of DCIS, the probability of a woman being diagnosed with an invasive breast cancer was found to be 5.3% within five years and 10.9% within 10 years (Table 3.1, Figure 3.1). These probabilities apply to the whole data set and would not be expected to apply universally to all subgroups of women. For example, the probability of diagnosis with invasive breast cancer following a diagnosis of DCIS was strongly influenced by age at time of the DCIS diagnosis (Table 3.1, Figures 3.2–3.4). The highest probabilities of invasive cancer were seen in women less than 40 years of age at DCIS diagnosis, being 8.4% within 5 years of DCIS diagnosis and 15.5% within 10 years. The lowest probabilities were seen in women aged in their 50s at time of DCIS diagnosis, being 4.4% within 5 years and 8.9% within 10 years.

Table 3.1: Kaplan-Meier estimates of the probability of a female recorded in the DCIS data set being diagnosed subsequently with invasive breast cancer, by age at DCIS diagnosis and number of years since DCIS diagnosis

	Age at DCIS diagnosis (years)													
	Under 40		40–49		50–59		60–69		70–79		80+		All ages	
Years since DCIS diagnosis	Prob. (%)	95% CI	Prob. (%)	95% CI	Prob. (%)	95% CI	Prob. (%)	95% CI	Prob. (%)	95% CI	Prob. (%)	95% CI	Prob. (%)	95% CI
1	1.0	0.1–1.9	0.9	0.5–1.3	0.7	0.4–0.9	0.3	0.1–0.5	0.5	0.2–0.8	1.7	0.4–3.0	0.6	0.5–0.8
2	2.3	0.9–3.6	2.2	1.6–2.8	1.7	1.3–2.1	1.3	0.9–1.7	1.9	1.2–2.5	2.0	0.6–3.4	1.7	1.5–2.0
3	4.2	2.3–6.1	3.5	2.7–4.3	2.7	2.2–3.2	2.8	2.2–3.5	3.6	2.7–4.6	3.4	1.4–5.4	3.1	2.8–3.5
4	8.1	5.4–10.8	4.8	3.8–5.7	3.7	3.0–4.3	3.7	3.0–4.5	5.0	3.8–6.1	5.6	2.9–8.3	4.3	3.9–4.7
5	8.4	5.6–11.2	5.7	4.7–6.8	4.4	3.6–5.1	5.1	4.2–6.0	6.3	4.9–7.6	5.6	2.9–8.3	5.3	4.8–5.8
6	10.9	7.6–14.2	7.4	6.1–8.7	5.1	4.3–5.9	6.6	5.5–7.7	7.7	6.1–9.3	7.8	4.1–11.4	6.6	6.1–7.2
7	12.2	8.6–15.8	8.3	6.9–9.7	5.7	4.8–6.6	8.0	6.7–9.3	9.1	7.3–11.0	8.6	4.6–12.6	7.7	7.0–8.3
8	14.7	10.4–19.0	9.4	7.8–11.0	6.9	5.7–8.0	9.5	8.0–11.1	10.2	8.2–12.2	8.6	4.6–12.6	9.0	8.2–9.7
9	15.5	11.0–20.0	10.0	8.3–11.8	8.1	6.7–9.5	11.0	9.1–12.9	10.5	8.4–12.6	8.6	4.6–12.6	9.9	9.1–10.8
10	15.5	11.0–20.0	10.6	8.7–12.6	8.9	7.2–10.6	12.5	10.2–14.8	11.8	9.0–14.5	8.6	4.6–12.6	10.9	9.8–11.9

Note: The 'Prob. (%)' column gives the estimated probability, expressed as a percentage, of diagnosis with invasive breast cancer, by age at DCIS diagnosis and number of years elapsing since DCIS diagnosis. The '95% CI' column gives a 95% confidence interval for the estimated probability.

Source: AIHW analysis of data supplied by state and territory cancer registries.

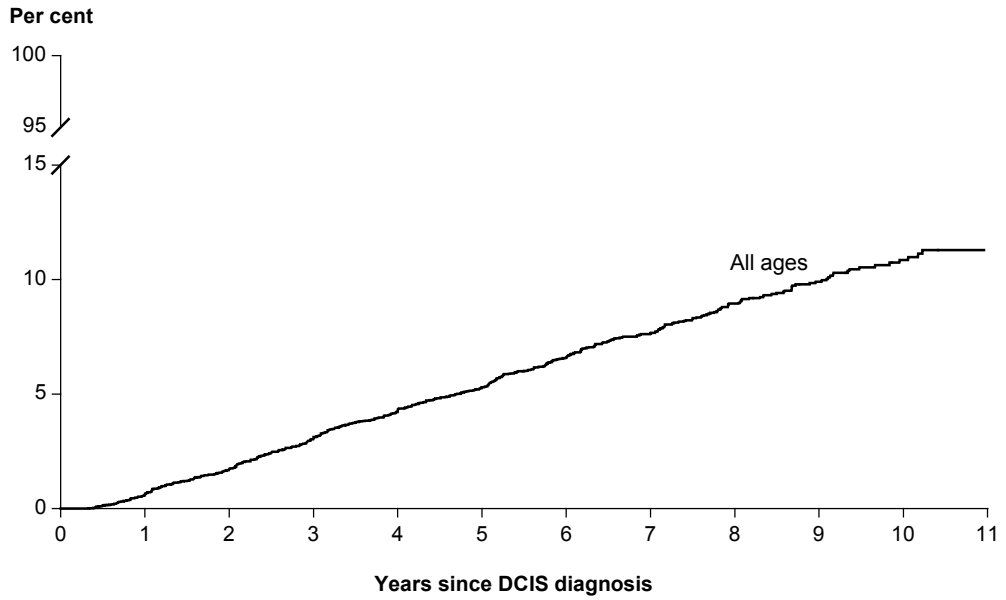


Figure 3.1: Kaplan-Meier estimates of the probability of a woman recorded in the DCIS data set being diagnosed subsequently with invasive breast cancer, by number of years since diagnosis of DCIS

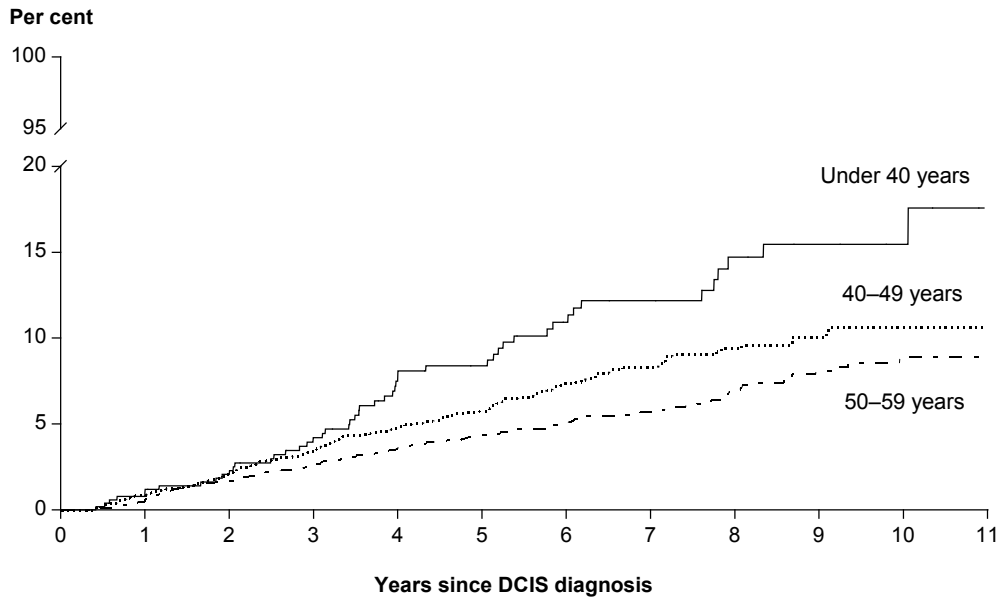


Figure 3.2: Kaplan-Meier estimates of the probability of a woman recorded in the DCIS data set being diagnosed subsequently with invasive breast cancer, by number of years since diagnosis of DCIS, for women aged less than 60 years at DCIS diagnosis

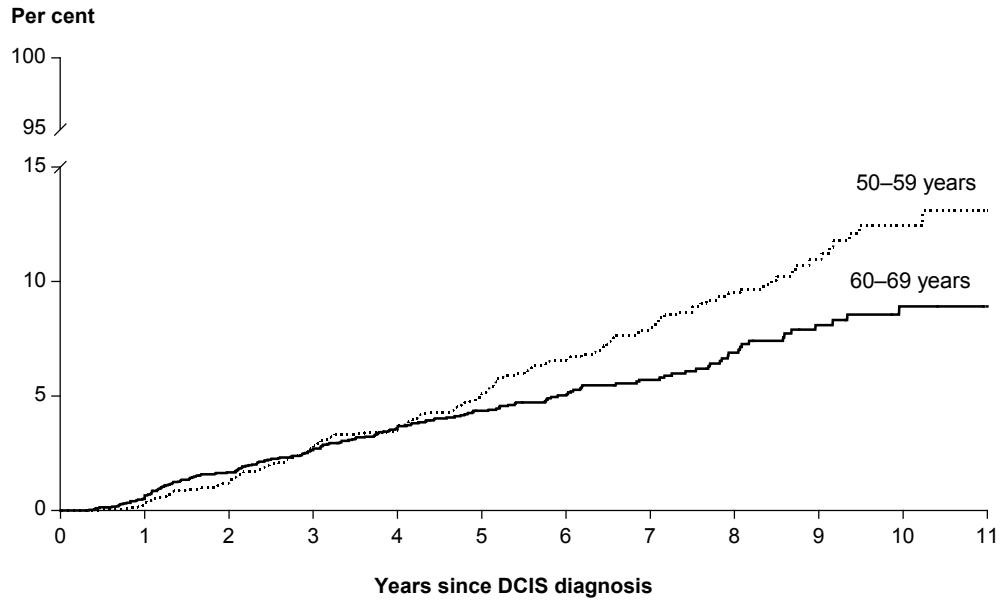


Figure 3.3: Kaplan-Meier estimates of the probability of a woman recorded in the DCIS data set being diagnosed subsequently with invasive breast cancer, by number of years since diagnosis of DCIS, for women aged 50 to 69 years at DCIS diagnosis

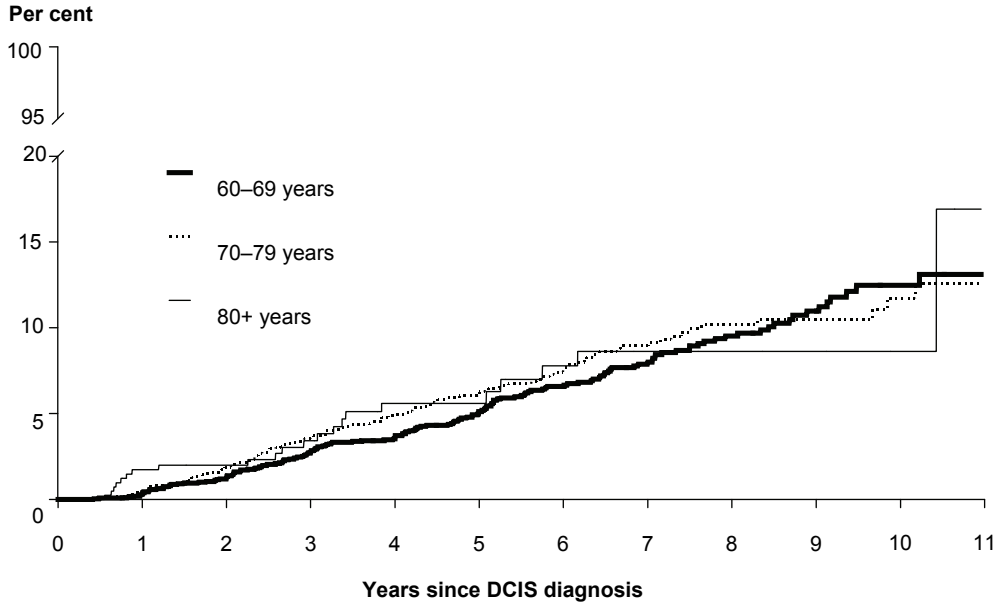


Figure 3.4: Kaplan-Meier estimates of the probability of a woman recorded in the DCIS data set being diagnosed subsequently with invasive breast cancer, by number of years since diagnosis of DCIS, for women aged 60 years or over at DCIS diagnosis

4 Relative risk of invasive breast cancer for women diagnosed with DCIS

In the previous chapter, the probability of diagnosis with invasive breast cancer by time elapsed since diagnosis with DCIS was described. In this chapter, complementary information is provided by comparing this probability with the probability of invasive breast cancer generally encountered by Australian women. The purpose is to assess whether diagnosis of DCIS is an indicator of increased risk of a subsequent diagnosis of invasive breast cancer, and, if so, the magnitude of the increased risk.

Brief description of method

The incidence rate of invasive breast cancer for all Australian women by age and calendar year was used to compute the number of invasive breast cancers that would be *expected* in the DCIS cohort, if these cohort women had the same risk of invasive breast cancer as all Australian women. The actual number of invasive breast cancers observed in the DCIS cohort was compared with this 'expected' number. The observed number divided by the expected number was used as an estimate of the 'relative risk' of invasive breast cancer for the women in the DCIS cohort. For example, if the number observed was twice the number expected, the relative risk would be 2.

Results

Women who had been diagnosed with DCIS were at greater risk of being diagnosed with invasive breast cancer than were Australian women overall (of similar age). The relative risk of invasive breast cancer for women in the DCIS cohort was 3.9 (Table 4.1). That is, women diagnosed with DCIS were, on average, 3.9 times as likely to develop invasive breast cancer as generally seen for Australian women of similar age. This figure is a little lower than the relative risk of 4.5 estimated in a Swedish study (Wärnberg et al. 2000), although the results were subject to influence from differences in methodology and possible differences in the age structures of the cohorts of women studied.

The relative risk varied by age at DCIS diagnosis and was greater for younger women (Table 4.1). For women aged less than 40 years of age at DCIS diagnosis, the relative risk was 19.8 and for women age 40 to 49 years, the relative risk was 5.6. For women aged 50 years and over the relative risk ranged between 3.0 and 4.2.

In order to determine if the relative risk had changed over the period under study, the relative risk by year of DCIS diagnosis was calculated (Table 4.2). Although the risk was variable from year to year, the data suggest a decreasing risk over the period of study.

A further question was whether the relative risk varied by the period of follow-up. Table 4.3 indicates that the relative risk in the period up to five years from DCIS diagnosis was 3.6. This was lower than the relative risk of 5.3 seen in the subsequent period from 5 up to 11 years. This suggests that women previously diagnosed with DCIS and not diagnosed with invasive breast cancer within 5 years have an even greater relative risk of being diagnosed in the next 5 years.

Table 4.1: Relative risk of developing invasive breast cancer by end of 2005 for women diagnosed with DCIS in 1995–2005, by age group, Australia

Age at DCIS diagnosis (years)	Number of women in DCIS cohort	Number of women in DCIS cohort expected to develop invasive breast cancer (E)	Number of women in DCIS cohort who did develop invasive breast cancer (O)	Relative risk (O/E)	95% confidence interval for relative risk
Under 40	555	2.5	50	19.8	14.2–25.4
40–49	2,583	26.9	151	5.6	4.7–6.5
50–59	4,560	62.6	186	3.0	2.5–3.4
60–69	3,595	53.4	182	3.4	2.9–3.9
70–79	1,987	28.3	115	4.1	3.3–4.8
80+	469	5.3	22	4.2	2.4–5.9
Total	**13,749**	**179.0**	**706**	**3.9**	**3.6–4.2**

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 4.2: Relative risk of developing invasive breast cancer by end of 2005 for women diagnosed with DCIS in 1995–2005, by year of DCIS diagnosis, Australia

Year of DCIS diagnosis	Number of women in DCIS cohort	Number of women in DCIS cohort expected to develop invasive breast cancer (E)	Number of women in DCIS cohort who did develop invasive breast cancer (O)	Relative risk (O/E)	95% confidence interval for relative risk
1995	824	22.6	94	4.2	3.3–5.0
1996	832	20.8	80	3.8	3.0–4.7
1997	1,042	23.4	109	4.7	3.8–5.5
1998	1,179	23.6	112	4.7	3.9–5.6
1999	1,200	21.0	81	3.8	3.0–4.7
2000	1,309	19.5	80	4.1	3.2–5.0
2001	1,447	17.7	52	2.9	2.1–3.8
2002	1,390	12.8	49	3.8	2.7–4.9
2003	1,436	9.6	27	2.8	1.7–3.9
2004–2005	3,090	8.0	22	2.8	1.6–3.9
Total	**13,749**	**179.0**	**706**	**3.9**	**3.6–4.2**

Note: Due to the observation period ending in 2005, DCIS diagnoses in 2005 have been combined with those in 2004 for analysis purposes.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 4.3: Relative risk of developing invasive breast cancer by end of 2005 for women diagnosed with DCIS in 1995–2005, by period of follow-up, Australia

Period of follow-up (years since DCIS diagnosis)	Number of women in DCIS cohort who could be observed for part or all of this period	Number of women in DCIS cohort expected to develop invasive breast cancer during this period (E)	Number of women in DCIS cohort who did develop invasive breast cancer during this period (O)	Relative risk (O/E)	95% confidence interval for relative risk
Less than 5	13,749	141.9	510	3.6	3.3–3.9
5 to less than 11	6,126	37.1	196	5.3	4.5–6.0
Less than 11	**13,749**	**179.0**	**706**	**3.9**	**3.6–4.2**

Source: AIHW analysis of data supplied by state and territory cancer registries.

5 Tumour size and nodal status

Breast cancers have many characteristics that influence treatment requirements and prognosis. Two such characteristics available for this study were tumour size and whether there was evidence of cancer spread to regional lymph nodes. In this chapter, these characteristics are described for invasive breast cancers occurring in women in the DCIS cohort and compared with corresponding characteristics in all Australian women diagnosed with invasive breast cancer (that is, irrespective of whether there was a previous DCIS diagnosis).

Following treatment for DCIS, women are generally advised to be placed under closer medical surveillance than women without a DCIS or invasive breast cancer history. Under such surveillance, it might be predicted that invasive cancers would be detected at an earlier stage than might otherwise occur, with smaller sizes and with potentially less evidence of nodal spread. Therefore it is expected that the sizes of the tumours that developed in the women in the DCIS cohort would tend to be smaller than those in the general population and that fewer of the cancers would have spread to nearby lymph nodes.

Brief description of data and method

When an invasive breast cancer is removed, the surgeon usually removes at least one regional lymph node to check for cancer. If cancer is found, the tumour is said to have *positive nodal status* or to be *node-positive*. Otherwise the tumour is regarded as *node-negative*. The nodal status may be recorded as unknown if no nodes are examined or if the pathologist's analysis is inconclusive. The excised tumour is also studied in a pathology laboratory to determine its diameter and other prognostic characteristics.

In this study, the tumour size and nodal status of invasive breast cancers in the DCIS cohort were compared with corresponding characteristics of all invasive breast cancers diagnosed in Australian women in 1997. The 1997 data had been collected as part of a previous study of breast cancers in Australian women (AIHW & NBCC 2001; AIHW & NBCC 2007). For the purposes of the present study, tumours that were of unknown size were excluded from comparisons of size and those of unknown nodal status were excluded from comparisons of nodal status.

The distributions of tumour sizes in the cohort of all Australian women diagnosed with invasive breast cancer in 1997 are shown by age in Table 5.1. Applying these distributions to the DCIS cohort yielded the numbers of cancers of each size that would be expected in the DCIS cohort if the same size distributions were to apply as in the 1997 cohort (Table 5.2). The actual distributions of sizes observed in the DCIS cohort are shown in Table 5.3. The statistically significant differences between the observed and expected numbers are shown in Table 5.4. The statistical test used to detect differences is explained in the appendix.

Tables 5.5 to 5.8 show the analogous data for nodal status.

Results

As predicted, tumour sizes tended to be smaller for the invasive breast cancers in the DCIS cohort than in the 1997 cohort of all invasive breast cancer cases (Table 5.4). There were more tumours in the smallest size category (10 mm or less) and fewer in the larger size categories than would have been expected from the 1997 cohort. This trend was the same in all the age groups though not as pronounced in women under 40 years of age.

Also as predicted, there were considerably fewer node-positive cancers in the women in the DCIS cohort compared to the 1997 cohort. A separate analysis for each age group (Table 5.8) showed that this finding was statistically significant for two of the age groups, namely women aged 40 to 49 years and women aged 70 years and over. Only a small difference was seen for women under 40 years of age.

The analysis in this chapter confirmed the prediction that invasive breast cancers in the DCIS cohort tended to be found at an earlier stage, when a better prognosis would be expected. Both diameter and nodal status are well-established predictors of survival. In the 1997 cohort of all Australian women diagnosed with invasive breast cancer, better 5-year relative survivals were found for women with smaller tumours and for those whose tumours were node-negative (AIHW & NBCC 2007).

Table 5.1: Observed distribution of tumour sizes for new cases of invasive breast cancer in Australian women for whom tumour size was known, 1997

	Age at diagnosis (years)										
	Under 40		40–49		50–59		60–69		70+		
Size of tumour	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Total number
0–10 mm	123	19.8	344	19.6	587	25.5	511	26.0	413	18.0	1,978
11–15 mm	132	21.3	405	23.1	585	25.4	510	25.9	516	22.4	2,148
16–19 mm	86	13.9	199	11.3	270	11.7	218	11.1	289	12.6	1,062
20–29 mm	145	23.4	454	25.9	469	20.4	433	22.0	591	25.7	2,092
30+ mm	134	21.6	353	20.1	391	17.0	294	15.0	490	21.3	1,662
Total	**620**	**100**	**1,755**	**100**	**2,302**	**100**	**1,966**	**100**	**2,299**	**100**	**8,942**

Notes

1. Tumour sizes are rounded to the nearest millimetre.
2. The DCIS status of women in this cohort was unknown.
3. Excluded from the table and percentages are 1,075 women with unknown tumour size. There were 59 aged under 40 years, 153 aged 40–49, 172 aged 50–59, 163 aged 60–69 and 528 aged 70 years or over.

Source: AIHW & NBCC 2007.

Table 5.2: Expected distribution of tumour sizes for those women in the DCIS cohort who developed invasive breast cancer and had known tumour size, based on the 1997 distribution

	Age at diagnosis (years)										
	Under 40		40–49		50–59		60–69		70+		
Size of tumour	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Total number
0–10 mm	6.0	19.8	19.8	19.6	31.9	25.5	32.2	26.0	14.4	18.0	104.2
11–15 mm	6.4	21.3	23.3	23.1	31.8	25.4	32.2	25.9	18.0	22.4	111.6
16–19 mm	4.2	13.9	11.5	11.3	14.7	11.7	13.7	11.1	10.1	12.6	54.1
20–29 mm	7.0	23.4	26.1	25.9	25.5	20.4	27.3	22.0	20.6	25.7	106.5
30+ mm	6.5	21.6	20.3	20.1	21.2	17.0	18.5	15.0	17.1	21.3	83.6
Total	**30**	**100**	**101**	**100**	**125**	**100**	**124**	**100**	**80**	**100**	**460**

Notes

1. Tumour sizes are rounded to the nearest millimetre.
2. Excluded from the table and percentages are 246 women with unknown tumour size. There were 20 aged under 40 years, 50 aged 40–49, 61 aged 50–59, 58 aged 60–69 and 57 aged 70 years or over.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 5.3: Observed distribution of tumour sizes for those women in the DCIS cohort who developed invasive breast cancer and for whom tumour size was known

	Age at diagnosis (years)										
	Under 40		40–49		50–59		60–69		70+		
Size of tumour	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Total number
0–10 mm	12	40.0	47	46.5	52	41.6	51	41.1	32	40.0	194
11–15 mm	4	13.3	23	22.8	34	27.2	31	25.0	15	18.8	107
16–19 mm	3	10.0	8	7.9	11	8.8	8	6.5	5	6.3	35
20–29 mm	6	20.0	10	9.9	18	14.4	18	14.5	14	17.5	66
30+ mm	5	16.7	13	12.9	10	8.0	16	12.9	14	17.5	58
Total	**30**	**100**	**101**	**100**	**125**	**100**	**124**	**100**	**80**	**100**	**460**

Notes

1. Tumour sizes are rounded to the nearest millimetre.
2. Excluded from the table and percentages are 246 women with unknown tumour size. There were 20 aged under 40 years, 50 aged 40–49, 61 aged 50–59, 58 aged 60–69 and 57 aged 70 years or over.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 5.4: Statistically significant differences in observed versus expected number of invasive breast cancers, by age and tumour size, for the women in the DCIS cohort who developed invasive breast cancer

	Age at diagnosis (years)				
Size of tumour	**Under 40**	**40–49**	**50–59**	**60–69**	**70+**
0–10 mm	Higher	Higher	Higher	Higher	Higher
11–15 mm					
16–19 mm					Lower
20–29 mm		Lower	Lower	Lower	Lower
30+ mm		Lower	Lower		

Notes

1. Tumour sizes are rounded to the nearest millimetre.
2. 'Higher' (respectively 'Lower') means that the number of observed invasive cancers was statistically significantly higher (respectively lower) than the number expected, using a 5% level of significance. A blank entry means that there was no statistically significant difference between observed and expected numbers. The method used to test for a difference is explained in the appendix.

Table 5.5: Observed distribution of nodal status for all new cases of invasive breast cancer in Australian women for whom nodal status was known, 1997

	Age at diagnosis (years)										
	Under 40		**40–49**		**50–59**		**60–69**		**70+**		
Nodal status	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Total number**
Positive	275	48.2	736	45.9	799	38.2	591	35.0	600	36.3	3,001
Negative	295	51.8	869	54.1	1,295	61.8	1,099	65.0	1,054	63.7	4,612
Total	**570**	**100**	**1,605**	**100**	**2,094**	**100**	**1,690**	**100**	**1,654**	**100**	**7,613**

Notes

1. The DCIS status of women in this cohort was unknown. Some of them would have had a prior diagnosis of DCIS.
2. Excluded from the table and percentages are 2,404 women with unknown nodal status. There were 109 aged under 40 years, 303 aged 40–49, 380 aged 50–59, 439 aged 60–69 and 1,173 aged 70 years and over.

Source: AIHW & NBCC 2007.

Table 5.6: Expected distribution of nodal status for those women in the DCIS cohort who developed invasive breast cancer and had known nodal status, based on the 1997 distribution

	Age at diagnosis (years)										
	Under 40		**40–49**		**50–59**		**60–69**		**70+**		
Nodal status	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Number**	**Per cent**	**Total number**
Positive	8.2	48.2	30.3	45.9	34.3	38.2	31.5	35.0	15.6	36.3	119.9
Negative	8.8	51.8	35.7	54.1	55.7	61.8	58.5	65.0	27.4	63.7	186.1
Total	**17**	**100**	**66**	**100**	**90**	**100**	**90**	**100**	**43**	**100**	**306**

Note: Excluded from the table and percentages are 400 women with unknown nodal status. There were 33 aged under 40 years, 85 aged 40–49, 96 aged 50–59, 92 aged 60–69 and 94 aged 70 years and over.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 5.7: Observed distribution of nodal status for those women in the DCIS cohort who developed invasive breast cancer and for whom nodal status was known

	Age at diagnosis (years)										
	Under 40		40–49		50–59		60–69		70+		
Nodal status	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Total number
Positive	7	41.2	21	31.8	27	30.0	27	30.0	10	23.3	92
Negative	10	58.8	45	68.2	63	70.0	63	70.0	33	76.7	214
Total	**17**	**100**	**66**	**100**	**90**	**100**	**90**	**100**	**43**	**100**	**306**

Note: Excluded from the table and percentages are 400 women with unknown nodal status. There were 33 aged under 40 years, 85 aged 40–49, 96 aged 50–59, 92 aged 60–69 and 94 aged 70 years and over.

Source: AIHW analysis of data supplied by state and territory cancer registries.

Table 5.8: Statistically significant differences in observed versus expected number of invasive breast cancers, by age and nodal status, for the women in the DCIS cohort who developed invasive breast cancer

	Age at diagnosis (years)				
Size of tumour	Under 40	40–49	50–59	60–69	70+
Positive		Lower			Lower
Negative		Higher			Higher

Note: 'Higher' (respectively 'Lower') means that the number of observed invasive cancers was statistically significantly higher (respectively lower) than the number expected, using a 5% level of significance. A blank entry means that there was no statistically significant difference between observed and expected numbers. The method used to test for a difference is explained in the appendix.

Appendix: Technical notes

Data sources (excluding the DCIS data set)

Australian Cancer Database (ACD), AIHW

The ACD contains unit record data, including persons' names, for every cancer diagnosed in Australia since 1 January 1982, excluding non-melanoma skin cancer. The state and territory cancer registries collect these data in their respective jurisdictions (and under their respective legislation) and supply the AIHW with an agreed subset of their data. This data set is standardised and deduplicated by the AIHW to become the ACD.

National Mortality Database (NMD), AIHW

The NMD contains de-identified unit record data for every death registered in Australia since 1 January 1968. The state and territory Registries of Births, Deaths and Marriages collect these data and supply them to the Australian Bureau of Statistics (ABS). The ABS uses the information on the death certificates to code the causes of death in ICD-10. By agreement with the registries the ABS then supplies these data, excluding persons' names, to the AIHW for compilation into the NMD.

National Death Index (NDI), AIHW

The NDI contains unit record data, including persons' names, for every death registered in Australia since 1 January 1980. The state and territory Registries of Births, Deaths and Marriages collect these data and supply the AIHW with an agreed data set, excluding cause of death data, which forms the NDI. The NDI is linked to the NMD, using the death certificate number as the linkage key, in order to transfer the causes of death from the NMD to the NDI.

The four-month rule

Before describing how the DCIS data set was constructed it is necessary to explain the 'four-month rule'. All of the Australian cancer registries use a business rule called the four-month rule, which in its simplest form states that if a woman is diagnosed with a DCIS and then, within four months, is diagnosed with an invasive breast cancer, the record of the DCIS shall be discarded. This rule is based on the consensus view that in such a situation the invasive breast cancer was almost certainly present at the time of the DCIS diagnosis but was not detected. The full version of the rule specifies how to deal with a DCIS in one breast and an invasive breast cancer in the other breast (and bilateral DCIS and/or bilateral invasive breast cancer), and how to deal with the various different histological types of invasive breast cancer that can arise. Unfortunately for this nationally-based project, different jurisdictions applied slightly different variations of this rule over the period of interest. Also, in some

circumstances in the Queensland cancer registry, the four-month time limit was extended to six months.

The DCIS data set

To be eligible for inclusion in the DCIS data set used in this project, a woman must not have had a diagnosis of invasive breast cancer prior to her diagnosis of DCIS.

The data set was constructed in the following manner.

1. Each of the state and territory cancer registries was asked to supply a data set of all its eligible DCIS cases (females only) from 1995 to 2005. South Australia and the Northern Territory were only able to supply data from 1997 and 1996 onwards, respectively. Each of the registries applied their own variant of the four-month rule to these data. For simplicity and national consistency, the AIHW applied an overriding four-month rule. The rule took no account of laterality of the DCIS and the invasive breast cancer and no account of the histological type of the invasive breast cancer—instead, the rule simply removed any DCIS record in which an invasive breast cancer was diagnosed in less than or equal to 121 days of a DCIS. This resulted in a data set of 13,792 records of DCIS.
2. The data set just constructed was deduplicated (that is, linked with itself) and 21 duplicate pairs (that is, women with DCIS records in two jurisdictions) were detected. Within each pair, the record with the earliest diagnosis date was retained and the other was removed, leaving 13,771 records. Of these, there were 689 known cases of invasive breast cancer and 557 known deaths ('known' meaning that the information was recorded on the original data sets supplied by the cancer registries).
3. The data set was then linked to the NDI. This resulted in the identification of 590 women in the DCIS data set who were dead but had not been recorded as dead in the original data sets from the registries. The DCIS data set was updated with the fact and date of death for each of these women, bringing the total number of deaths in the DCIS data set to 1,147.
4. In order to detect instances of a woman being diagnosed with DCIS in one jurisdiction and invasive breast cancer in a different jurisdiction, the DCIS data set was linked to the ACD. This resulted in a further 39 cases of invasive breast cancer being discovered. However, for 22 of these women, the invasive breast cancer had been diagnosed either before or within four months of the DCIS diagnosis. Consequently, these 22 women were removed from the data set and the remaining 17 cases of invasive breast cancer were recorded. Of the 22 women deleted, three were dead. Thus, the resulting data set consisted of 13,749 records that included 706 cases of invasive breast cancer and 1,144 deaths.
5. Finally, the relevant cancer registries were asked to supply the tumour size and nodal status for the 17 additional cases of invasive breast cancer that were uncovered in the preceding step.

Caveats

Consider a woman whose DCIS diagnosis occurred between September and December of 2005 who was diagnosed with invasive breast cancer in 2006 within four months of her DCIS diagnosis. Application of the four-month rule would result in her being removed from the

DCIS data set. Since the follow-up period for this study did not extend into 2006 there was no way of identifying such women and it was decided to keep all of them in the DCIS data set. The small number that would have been removed if 2006 data were available would not have appreciably altered the study's findings.

As already mentioned, in some circumstances the Queensland cancer registry applied a 'six-month rule' instead of the four-month rule. Therefore, there were some women who ideally should have been in the DCIS data set used for this study but were not. Based on the project team's analysis of the national data set and discussion with the Queensland cancer registry, it is felt that there would have been very few cases excluded in this way and that their inclusion would not have altered the study's findings.

Some extra information regarding the Kaplan-Meier estimates of probability of invasive breast cancer

The Kaplan-Meier product limit technique was used to calculate the probabilities of invasive breast cancer (Chapter 3). Follow-up commenced at DCIS diagnosis. The event of interest was diagnosis of invasive breast cancer. Censoring occurred at death or 31 December 2005 (i.e. the end of the study period), whichever occurred first. The shortest period elapsing to diagnosis of invasive breast cancer was 123 days. (Given the four-month rule, the shortest possible such period was 122 days.) By comparison, the longest elapsed time was 3,806 days (over 10 years). Of the 13,749 women in the DCIS cohort, 12,038 (87.6%) were censored at the end of the study period and 1,005 (7.3%) at death (Table A.1).

Table A.1: Number of women in various categories in the DCIS cohort

	Invasive status		
Death status	Diagnosed with invasive breast cancer during study period	Not diagnosed with invasive breast cancer during study period	Total
Died during study period	139	1,005	1,144
Did not die during study period	567	12,038	12,605
Total	**706**	**13,043**	**13,749**

The type of censoring varied with age. For women aged less than 40 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and 80 years or over, end-of-study censoring rates were 88.5%, 92.8%, 93.2%, 88.0%, 75.9% and 49.3% respectively, whereas death censoring rates were 2.5%, 1.4%, 2.8%, 7.0% 18.3% and 46.1% respectively.

Details of the test used to detect a difference between observed and expected tumour size and nodal status (Chapter 5)

To keep matters concrete, the following discussion will focus on the number of tumours of size 0–10 millimetres in women aged 50 to 59 years (see Tables 5.1–5.4). The number, X, of tumours of this size in this age group was treated as a binomial random variable. The

'number of trials' is n = 125, which was derived from the fact that there were a total of 125 cases of invasive breast cancer with known tumour size in this age group. The 'probability of success' is unknown but taken to be p = 587/2,302 = 0.255 from the observed Australia-wide distribution in 1997 as shown in Table 5.1. Therefore the expected value of X is $\mu = np = 125 \times 0.255 = 31.9$, as shown in Table 5.3, and the standard deviation of X is $\sigma = \sqrt{np(1-p)} = \sqrt{(31.9 \times 0.745)} = \sqrt{23.7} = 4.87$ (not shown in the tables).

Using conventional practice it was assumed that X is approximately normally distributed because $n \geq 30$ and p is not extremely close to either 0 or 1. Therefore the statistic $Z = (X-\mu)/\sigma$ is approximately a standard normal random variable.

The tests employed were one-sided tests because it was conjectured beforehand that there would be more smaller tumours than expected and fewer large ones. This was quantified by conjecturing more smaller tumours for the two smallest size categories (0–10 mm and 11–15 mm) and fewer large ones for the other three size categories. A 5% level of significance was used. Therefore the alternative hypothesis was accepted for the two smallest size categories when $z \geq 1.645$ and for the three largest size categories when $z \leq -1.645$.

Continuing with the example, the observed value of X was x = 52 (Table 5.3). Therefore the observed value of Z was $z = (52-31.9)/4.87 = 4.13$, which is statistically significantly higher than would be expected.

The same method was used to detect a difference in the number of tumours of a given nodal status in a given age group. The alternative hypothesis was that there would be more node-negative cancers (equivalently, fewer node-positive ones).

Glossary

Age-standardised rate: a method of removing the influence of age when comparing populations with different age structures. This is usually necessary because the rates of many diseases vary strongly (usually increasing) with age. The age structures of the different populations are converted to the same 'standard' structure, which allows comparison of disease rates.

Cancer (malignant neoplasm): a large range of diseases in which some of the body's cells become defective, and begin to multiply out of control. These cells can invade and damage the area around them, and can also spread to other parts of the body to cause further damage.

Confidence interval: a range determined by variability in data, within which there is a specified (usually 95%) chance that the true value of a calculated parameter lies.

Ductal carcinoma in situ (DCIS): a lesion in the breast in which cancerous cells have not infiltrated beyond the duct walls to surrounding tissue.

Malignant: abnormal changes consistent with cancer.

References

Acronyms used in references

AIHW	Australian Institute of Health and Welfare
BSA	BreastScreen Australia
IARC	International Agency for Research on Cancer
NBCC	National Breast Cancer Centre
WHO	World Health Organization

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