RESEARCH COMMUNICATION

Changes in Incidence of In Situ and Invasive Breast Cancer by Histology Type following Mammography Screening

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Abstract

Objective: To investigate secular trends and correlates of incidence of breast cancer by histology type following the introduction of population-based mammography screening. Methods: Analysis of age-standardised incidence rates for 1,423 in situ and 16,157 invasive carcinomas recorded on the South Australian population-based cancer registry for the 1985-2004 diagnostic period. Multiple logistic regression was undertaken to compare socio-demographic characteristics by histology. Progression from in situ disease was investigated using the Kaplan-Meier method. Results: The incidence of in situ lesions increased approximately seven-fold over the 20-year period, compared with an increase of about 40% for invasive cancers. The increase for in situ lesions was due to increases for ductal carcinomas, with little change for lobular lesions. By comparison, the percentage increase in incidence for invasive cancer was greater for lobular than ductal cancers. Both for in situ and invasive cancers, percentage increases were greatest for the screening target age range of 50-69 years. One in 14 in situ cases was found to progress to invasive cancer within seven years of diagnosis, but insufficient detail was available to determine whether the invasive cancers were a progression of the in situ lesions or whether they originated separately. These invasive cancers were smaller than generally applying for other invasive cancers of the female breast. Conclusions: The larger secular increases in incidence for in situ than invasive cancers would reflect the dominant role of mammography in the detection of ductal carcinoma in situ. The lack of an increase for lobular in situ lesions may have resulted from their poorer radiological visibility. The greater percentage increase for lobular than ductal invasive lesions may have been due to an increase in imaging sensitivity for these lesions, plus real increases in incidence. The smaller sizes of invasive cancers found in women with a prior in situ diagnosis may have resulted from more intensive medical surveillance, although the possibility of biological differences cannot be discounted.

Key Words: Breast cancer - histology type - secular trends - mammography

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Introduction

Population-based screening mammography was introduced in Australia in 1991, following pilot programs of up to two years duration in regional jurisdictions (AHMAC, 1990; SACR, 1996; AIHW & AGDHA, 2003). The principal target age range was 50-69 years, although females over 40 years of age were eligible to be screened.

In South Australia, the proportion of invasive breast cancers detected through the population screening program increased progressively as the program extended, reaching 32% for all ages combined and 51% for the 50-69 year screening target age range by 1999-2001 (Gill et al., 2006). For in situ lesions, the proportion found through the screening program increased to 65% in 1999-2001 for all ages combined, and 77% for 50-69 year olds (SACR, 2000; 2001; 2003), which is similar to observations in New South Wales (Kricker et al., 2004). In addition, a number of invasive and in situ breast carcinomas would have been detected by screening mammography provided through private radiology clinics (Gill et al., 2006; SACR, 1996).

Meanwhile the population-based proportion of invasive tumours detected with diameters smaller than 15mm increased from 13% prior to mammography screening to around 37% in 1997-2002, whereas the proportion with large diameters of 30mm or more decreased from 43% to 19% (Luke et al., 2004). Other observations included an elevation in proportions of screen-detected invasive lesions that were low-grade, oestrogen receptor positive, and without vascular invasion or evidence of spread to regional nodes (SACR, 1996; Clayforth et al., 2005). Meanwhile, population-based age-standardised breast cancer mortality reduced by about 20% during the 1990s (AIHW & AACR, 2004), with mortality increases attributed to combined effects of earlier detection and treatment advances (TCCSA, 2005; Smith et al., 1998).

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Another change has been an increased detection of in situ breast carcinomas, with around 20% of all screen-detected lesions being classified as in situ (AIHW & AGDHA, 2003). While it is recognised that these lesions have potential to progress to invasive cancer, the proportion that do so is not known (Vainio & Bianchini, 2002). This has raised questions about over-treatment and underscored the need to find mechanisms for identifying those lesions that are likely to progress.

USA data indicate that about 16% of female breast carcinomas in that country would now be found as ductal carcinomas in situ, due mostly to mammography (Li et al., 2005; Ries et al., 2005). This follows a seven-fold increase in age-standardised incidence of ductal carcinoma in situ between 1980 and 2001. Meanwhile a smaller two to three-fold increase in incidence was reported for lobular carcinoma in situ (Li et al., 2005).

We have investigated secular changes in incidence of in situ and invasive breast cancer in Australia during 1985-2004, and compared the socio-demographic characteristics of females with these lesions, using population-based data from the South Australian Cancer Registry. In addition, proportions of patients with in situ lesions, who subsequently developed invasive cancer, were investigated for the 1997-2004 period. The health and research implications of these data are discussed.

Materials and Methods

Data collection

The South Australian Cancer Registry has received statutory notifications of invasive cancers, including breast cancers, since 1977, and of in situ breast carcinomas since 1985 (SACR, 2000). Statutory notifications principally came from hospitals and pathology laboratories, with radiotherapy centres, the Registrar of Deaths, and service providers providing additional notifications under Section 42a of the Public and Environmental Health Act. The Registry is population-based and covers all regions of South Australia. Its procedures have been described in previous publications (SACR, 1996; 2000; 2001; 2003).

This study covered all 1,423 in situ and 16,157 invasive female breast carcinomas (ICDO-3: C50) with a diagnosis between 1985 and 2004 (Fritz et al., 2000). These tumours were classified as ductal or lobular, using corresponding histological codes. In this broad categorisation, medullary, mucinous, tubular and papillary lesions were combined with infiltrating ductal carcinomas, since the former constituted a small proportion of the total and there was evidence that laboratories had not classified them uniformly throughout the study period (SACR, 1996; 2000).

In accordance with Registry protocols, females were only recorded as having in situ disease if there was not an accompanying invasive breast cancer, or an earlier diagnosis of invasive breast cancer. Diagnoses of second or subsequent in situ lesions were not recorded. Initially, data for in situ and invasive breast lesions were stored separately in the Registry. Since 1997, however, the file structure of the Registry was altered, such that it became possible to track times from diagnoses of in situ disease to diagnoses of subsequent invasive cancers.

Data also were collected on socio-demographic descriptors of cancer cases, including age at diagnosis; region of residence, classified as metropolitan (4 metropolitan Sub-divisions of the State capitol of Adelaide) or non-metropolitan (16 Statistical Sub-divisions outside Adelaide); country of birth (expressed as Australia; the United Kingdom/Ireland; other English-speaking countries; Southern Europe – mostly Italy, Malta, Greece, former Yugoslav states, or other; Northern/Eastern Europe; Asia/Middle East; or other); race, classified as Caucasian, Aboriginal, Asian or other; and residential location, classified into four ordinal categories by socio-economic status of postcode, using the SEIFA index (SACR, 2000; ABS, 1998).

Statistical analyses

Registry data were analysed in-house with STATA 8.0 software, using a de-identified file extract, under authorisation of Section 42a of the Public and Environmental Health Act (STATACORP, 2003; SACR, 2000).

To assist visual interpretation of the data, diagnostic periods were categorised into the four-year groups of 1985-88, 1989-92, 1993-96, 1997-2000, and 2001-04. Period-specific incidence rates were directly standardised by five-year age group (with an open-ended category from age 85 years) to the age distribution of the 2001 Australian population, in accordance with national convention, and 95% confidence limits were calculated as described by the Australian Institute of Health and Welfare in its national statistics publications (AIHW & AACR, 2004). Incidence rates were obtained for all ages combined and separately for 0-39, 40-49, 50-59, 60-69, 70-79 and 80+ year olds.

Incidence rates were analysed separately for in situ and invasive cancers, and according to whether lesions were ductal or lobular. Socio-demographic features of in situ and invasive cases were compared, initially as individual variables, using the Mann-Whitney U test for ordinal and continuous variables, and the Pearson chi-square test for binary and nominal variables (substituting Fisher's Exact Test when expected values were less than five) (Armitage, 1987).

In addition, logistic regression was undertaken to determine those characteristics that were predictive of in situ as opposed to invasive disease in a multivariable context (Armitage, 1987). All person and tumour variables were entered, with backwards elimination of those whose elimination did not reduce model fit ($p>0.050$ for change in chi-square goodness-of-fit) (STATACORP, 2003).

Progression times of women from diagnosis of in situ disease to diagnosis of invasive cancer were investigated, using the Kaplan-Meier product-limit estimate (Armitage, 1987). This analysis was applied to all in situ cases diagnosed from 1997 when the Registry file had been modified to enable progression times to be tracked. In situ cases not

experiencing an invasive cancer during 1997-2004 were censored at death or on December 31st, 2004, whichever came first.

Results

Incidence trends

In situ lesions: Annual incidence rates for all ages combined increased 7.1 fold (from 1.9 to 13.6 per 100,000) between 1985-88 and 2001-04, with little change between 1997-2000 and 2001-04 (Table 1). Increases were suggested for all ages, but were highest at 19.0-fold for 60-69 year olds and 8.8-fold for 50-59 year olds.

Because most in situ lesions were ductal (94.0%), they showed similar trends to those for all lesions in aggregate (Table 1). By comparison, lobular lesions, which accounted for only 5.3% of the total, did not show a consistent change during the study period. The annual incidence per 100,000 (95% confidence limits) for all ages combined was 0.4 (0.1, 0.6) in 1985-88, 0.9 (0.5, 1.3) in 1989-92, 0.6 (0.3, 0.9) in 1993-96, 0.4 (0.2, 0.6) in 1997-2000, and 0.4 (0.2, 0.6) in 2001-2004. Similarly, secular changes were not apparent within age-specific groups.

Only 0.8% of lesions were of unknown histology type, such that numbers were too small for analyses of trends.

Invasive cancers: Annual incidence rates for all ages combined increased by 42.7% (from 82.6 to 117.9 per 100,000) between 1985-88 and 1997-2000 (Table 2). A slightly lower incidence applied in 2001-04 than 1997-2000.

Incidence increases were found in the 40-79 year age range, but not in younger or older women (Table 2). The increase between 1985-88 and 1997-2000 was 39.2% for 40-49 year olds, 90.5% for 50-59 year olds, 49.2% for 60-69 year olds, and 17.9% for 70-79 year olds.

Ductal carcinomas comprised 85.9% of invasive lesions and showed similar secular trends to all invasive lesions in aggregate (Table 2). However, lobular carcinomas, which comprised only 8.2% of invasive lesions, showed a more pronounced increase in annual incidence per 100,000 of 91.1% for all ages combined from 5.6 (4.7, 6.5) in 1985-88 to 10.7 (9.6, 11.9) in 1997-2000. Similar incidence rates applied in 1997-2000 and 2001-04. While increases were suggested for all age groups over 40 years of age, they were most pronounced for 50-59 years olds, where there was a 104.7% increase in annual incidence per 100,000 from 14.9 (10.3, 19.5) in 1985-88 to 30.5 (24.6, 36.4) in 1997-2000, and in 60-69 year olds, where the corresponding increase was 140.7% from 15.0 (10.3, 19.8) to 36.1 (28.7, 43.5).

Meanwhile, 5.9% of all invasive cancers were of unknown histological type. Similar incidence rates applied for these lesions in each diagnostic period, except 2001-2004, when the annual rate was only about half that for preceding periods (i.e., 3.3 compared with 6.4 per 100,000).

Socio-demographic comparison

In situ compared with invasive cancers

Ages at diagnosis differed between in situ and invasive lesions ($p<0.001$), with means of 58.0 years and 60.7 years respectively. There were also differences in distribution by diagnostic period ($p<0.001$), with a higher proportion of lesions presenting at an in situ stage in more recent periods. No differences were found by socio-economic status ($p=0.524$), country of birth ($p=0.477$), race ($p=0.897$), Statistical Sub-division of residence ($p=0.380$), or whether resident in a metropolitan or country region ($p=0.306$).

Table 1. Annual Age-standardised (Australian Population, 2001) Incidence per 100,000 of In Situ Female Breast Cancers by Calendar Year and Age at Diagnosis; South Australia 1985-2004

Years	1985-88	1989-92	1993-96	1997-2000	2001-04	Total (all years)
<40 (n=60)	0.38 (0.08,0.68)	0.85 (0.40,1.29)	0.76 (0.35,1.17)	0.76 (0.35,1.18)	0.87 (0.41,1.33)	0.73 (0.55,0.91)
40-49 (n=259)	3.49 (1.43,5.56)	13.4 (9.63,17.1)	12.6 (9.21,16.0)	18.6 (14.5,22.6)	14.0 (10.6,17.5)	13.0 (11.4,14.5)
50-59 (n=503)	5.13 (2.34,7.91)	26.3 (20.1,32.6)	32.7 (26.1,39.3)	43.4 (36.4,50.4)	45.3 (38.6,51.9)	32.4 (29.6,35.3)
60-69 (n=353)	2.33 (0.47,4.19)	17.9 (12.9,23.0)	29.8 (23.1,36.5)	42.4 (34.3,50.5)	44.3 (36.3,52.4)	27.2 (24.4,30.1)
70-79 (n=192)	4.09 (1.06,7.12)	8.83 (4.63,13.0)	21.1 (14.9,27.3)	24.2 (17.8,30.6)	30.2 (23.0,37.3)	18.5 (15.9,21.1)
80+ (n=56)	4.78 (0.10,9.47)	6.14 (1.23,11.1)	14.5 (7.62,21.4)	5.28 (1.37,9.19)	14.4 (8.37,20.4)	9.61 (7.09,12.1)
Total (n=1,423)	1.91 (1.38,2.44)	7.67 (6.63,8.71)	10.2 (9.05,11.4)	13.2 (11.9, 14.5)	13.6 (12.3, 14.8)	9.64 (9.14,10.2)

Table 2. Annual Age-standardised (Australian Population, 2001) Incidence per 100,000 of Invasive Female Breast Cancers by Calendar Year and Age at Diagnosis; South Australia 1985-2004

Years	1985-88	1989-92	1993-96	1997-2000	2001-04	Total (all years)
<40 (n=1,043)	11.7 (10.0,13.4)	12.7 (11.0,14.4)	11.7 (10.0,13.3)	13.4 (11.6,15.1)	13.6 (11.8,15.4)	12.6 (11.8,13.4)
40-49 (n=2,825)	114 (102,126)	142 (130,154)	146 (135,158)	159 (147, 171)	137 (126,148)	141 (136,146)
50-59 (n=3,910)	157 (142,172)	214 (196, 231)	268 (249,287)	298 (280, 317)	285 (269,302)	251 (243,259)
60-69 (n=3,764)	216 (198,234)	252 (233,271)	297 (276,318)	322 (300,344)	358 (335,381)	289 (280,298)
70-79 (n=2,842)	238 (216,261)	265 (242,288)	305 (281,328)	281 (259,303)	275 (253,296)	274 (264,284)
80+ (n=1,773)	313 (275, 351)	310 (275,345)	305 (273,337)	320 (289,350)	274 (248,300)	302 (288,316)
Total (n=16,157)	82.6 (79.2,86.1)	98.3 (94.7,102)	111 (107,114)	118 (114,122)	114 (111,118)	106 (104,107)

Table 3. Relative Odds of In Situ as Opposed to Invasive Stage at Diagnosis; Female Breast Cancers, South Australia, 1985 to 2004, by Multiple Logistic Regression

Characteristic	Relative odds (95% CI)
Age at diagnosis (yrs):	
Under 40 (reference) (n=1,103)	1.00
40-49 (n=3,084)	1.50 (1.13, 2.00)
50-59 (n=4,413)	2.02 (1.54, 2.64)
60-69 (n=4,117)	1.55 (1.18, 2.04)
70-79 (n=3,034)	1.12 (0.85, 1.50)
80+ (n=1,829)	0.52 (0.36, 0.75)
Diagnostic period:	
1985-88 (reference) (n=2,251)	1.00
1989-92 (n=2,999)	3.33 (2.41, 4.60)
1993-96 (n=3,654)	4.04 (2.96, 5.53)
1997-2000 (n=4,238)	4.79 (3.52, 6.51)
2001-04 (n=4,438)	5.14 (3.79, 6.98)

Multiple logistic regression analysis confirmed that only age and diagnostic period were predictive of in situ as opposed to invasive disease, and that retention of other socio-demographic variables in the model had little effect on regression coefficients. Tables 3 shows that the relative odds of in situ rather than invasive disease increased progressively from 1985-88 to 2001-04, after adjusting for age. The odds of in situ disease were elevated for 40-69 year olds, and highest for 50-59 year olds. Carcinomas detected in females over 80 years and over were least likely to be *in situ*.

Lobular compared with ductal in situ lesions

Age and period of diagnosis both varied between lobular and ductal in situ lesions ($p<0.001$). No differences were found, however, by socio-economic status ($p=0.187$), country of birth ($p=0.831$), race ($p=0.901$), Statistical Sub-division of residence ($p=0.895$), or according to residence in a metropolitan or country region ($p=0.256$).

Multiple logistic regression analysis confirmed that only age and diagnostic period were predictive of lobular rather than ductal histology type, and that retaining other socio-demographic variables had little effect on regression coefficients. The relative odds of lobular rather than ductal in situ lesions reduced progressively with age (Table 4). A progressive secular reduction also applied, although with similar relative odds presenting for 1997-2000 and 2001-04.

Lobular compared with ductal invasive lesions

Lobular and ductal invasive lesions varied by age ($p=0.008$) and period of diagnosis ($p<0.001$), but not by socio-economic status ($p=0.195$), country of birth ($p=0.144$), Statistical Sub-division of residence ($p=-0.854$), or according to residence in a metropolitan or country region ($p=0.273$). Caucasians were more likely than other races to have lobular rather than ductal lesions ($p=0.010$).

Multiple logistic regression analysis also indicated that age and period were predictive of a lobular as opposed to a ductal cancer, and that retaining other socio-demographic variables had little effect on regression coefficients. The relative odds of a lobular as opposed to a ductal cancer increased with age to 60-69 years, with the indication of a decline in older age groups (Table 4). A secular increase in relative odds of lobular lesions emerged in 1993-96 and continued to 1997-2004.

Progression from in situ to invasive cancer

A total of 874 in situ cases diagnosed in 1997-2004 were tracked. The proportion (±standard error) without a subsequent diagnosis of invasive cancer reduced with period from in situ diagnosis to 99.3% (±0.3) at one year, 97.6% (±0.6) at three years, 94.7% (±1.0) at five years, and 92.8% (±1.4) at seven years. In other words, after seven years from diagnosis, about one in 14 in situ cases had progressed to a subsequent diagnosis of invasive cancer.

The resulting invasive cancers (n=35) did not differ from others diagnosed in 1997-2004 by histology type (ductal or lobular) ($p=0.901$), grade ($p=0.487$), or number of involved nodes ($p=0.180$). However, they were smaller ($p=0.019$), with 60.0% being less than 15mm in diameter compared with a corresponding 37.5% for other invasive cancers.

Table 4. Relative Odds of Lobular as Opposed to Ductal Carcinomas among In Situ and Invasive Cancers; Female Breast Cancers, South Australia, 1985 to 2004, by Multiple Logistic Regression

	In situ			Invasive		
Characteristic	n	Relative odds (95% CI)		n	Relative odds (95% CI)	
Age at diagnosis (yrs.):						
<40 (reference)	60	1.00		1,017	1.00	
40-49	257	0.82	(0.34, 1.99)	2,750	2.50	(1.03, 6.06)
50-59	499	0.55	(0.23, 1.31)	3,799	2.98	(1.84, 4.83)
60-69	351	0.26	(0.10, 0.72)	3,640	3.18	(2.25, 4.48)
70+	245	0.14	(0.04, 0.50)	3,998	2.59	(1.77, 3.78)
Diagnostic period:						
1985-88 (reference)	45	1.00		2,011	1.00	
1989-92	202	0.50	(0.21, 1.20)	2,618	1.01	(0.78, 1.32)
1993-96	298	0.27	(0.11, 0.67)	3,143	1.20	(0.96, 1.49)
1997-2000	410	0.14	(0.05, 0.36)	3,596	1.34	(1.09, 1.64)
2001-04	457	0.13	(0.05, 0.34)	3,836	1.36	(1.11, 1.66)

* Excludes carcinomas of unknown histology (5.5%).

Discussion

The seven-fold increase in age-standardised incidence of in situ lesions between 1985-88 and 1997-2004 was similar in scale to increases reported for the USA (Li et al., 2005). It far exceeded the increase of about 40% for invasive cancers, probably due to the more dominant role of screening mammography in the diagnosis of in situ than invasive lesions (Vainio & Bianchini, 2002). The greater increases in incidence of in situ lesions in the screening-target age range of 50-69 years were consistent with a mammography effect.

The result of these incidence trends was that the percentage of lesions that were in situ increased from approximately 2% in 1985-88 to 10% by 2000-04. Multivariable analysis showed that the odds of an in situ as opposed to invasive presentation was highest in the 50-69 year olds and (less so) 40-49 year olds, and increased progressively throughout the study period.

There was little change in incidence of in situ conditions between 1997-2000 and 2001-04, probably due to the plateauing of population screening coverage, which was reported to have occurred around 1996 (BreastScreen SA, 1999), and is likely to have led to a contemporaneous stabilisation of in situ detection.

As seen with USA data (Li et al., 2005), lobular in situ lesions did not show secular increases in incidence commensurate with those reported for ductal in situ lesions. Indeed, lobular lesions showed little overall change in the present study. The result was a marked reduction in odds of lobular as opposed to ductal in situ lesion across the study period, with the odds being lower in older patients.

Conversely the secular increase in incidence of invasive cancer was more pronounced for lobular than ductal lesions. This occurred, despite evidence that lobular lesions are more difficult to detect by mammography (Framarino Dei Malatesta et al., 1995; Ma et al., 1992; Narod et al., 2001). Pronounced increases in incidence have also been observed among lobular carcinomas in North America and Switzerland (Li et al., 2000; Verkooijen et al., 2003). While mammography screening may have been a major contributor to the increase in lobular cancers seen in our study, with a contribution from secular increases in screening sensitivity (Chiu et al., 2006), it is possible that other factors, such as an increase in exposure to hormone replacement therapy, may have played a part (Chen et al., 2002). An increase in use of hormone replacement therapy was shown to have occurred in South Australia during 1991-2000 (MacLennan et al., 2002).

The effect of secular differences in incidence trend was that the odds of a lobular as opposed to ductal presentation increased for invasive cancers across the study period. The older the patient, the greater was the odds of a lobular presentation prior to 70 years of age, which was contrary to the pattern seen among in situ cases.

No differences were observed between in situ and invasive lesions by histology type, socio-economic status of patient, country of birth, race or place of residence. This would be expected, if in situ and invasive carcinomas were related entities, as has been reported (Gump et al., 1998; Silverstein et al., 1996; Burrell et al., 1996).

Approximately one in 14 in situ cases was subsequently diagnosed with an invasive breast cancer within seven years of diagnosis. This may not reflect treatment failure, since invasive lesions may have originated at separate locations and not represented progression of the in situ lesions. In situ lesions have been reported to be risk indicators for subsequent invasive disease in other breast locations (Vainio & Bianchini, 2002).

It would be desirable, in order to develop predictive models for disease progression, to retrieve details on locations of in situ and invasive lesions, and on characteristics of in situ lesions (including their diameters, grades, number of foci, architecture, and whether calcification or necrosis was observed) and on their treatment and surgical margins (Kricker et al., 2004). This information could be obtained from reviews of case notes, mammograms and pathology reports. In addition, molecular characteristics could be retrieved from preserved tissue for this purpose.

Predictive models should be developed for lobular as well as ductal carcinomas in situ. Our data indicate that the odds of lobular compared with ductal in situ lesions are higher for younger females. There is evidence that both lobular and ductal in situ lesions are associated with an increased risk of subsequent invasive cancer (Chuba et. al, 2005; Page et al., 1991). Irrespective of whether these cancers were to arise from the original in situ lesion, or separately, more intensive clinical surveillance may be warranted using clinical breast examination, mammography and/or ultrasound imaging.

Invasive cancers found in women with histories of an in situ diagnosis had relatively small diameters. While biological differences may have contributed to this finding, it seems likely that more intensive medical surveillance would have played a part, reflecting the general clinical understanding that in situ disease is a risk factor for invasive cancer.

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