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International variation in management of screen-detected ductal carcinoma in situ of the breast

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Abstract

Background—Ductal carcinoma in situ (DCIS) incidence has grown with the implementation of screening and its detection varies across International Cancer Screening Network (ICSN) countries. The aim of this survey is to describe the management of screen-detected DCIS in ICSN countries and to evaluate the potential for treatment related morbidity.

Methods—We sought screen-detected DCIS data from the ICSN countries identified during 2004–2008. We adopted standardised data collection forms and analysis and explored DCIS diagnosis and treatment processes ranging from pre-operative diagnosis to type of surgery and radiotherapy.

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¹See Appendix A.

Conflict of interest statement

None declared.

Results—Twelve countries contributed data from a total of 15 screening programmes, all from Europe except the United States of America and Japan. Among women aged 50–69 years, 7,176,050 screening tests and 5324 screen-detected DCIS were reported. From 21% to 93% of DCIS had a pre-operative diagnosis (PO); 67–90% of DCIS received breast conservation surgery (BCS), and in 41–100% of the cases this was followed by radiotherapy; 6.4–59% received sentinel lymph node biopsy (SLNB) only and 0.8–49% axillary dissection (ALND) with 0.6% (range by programmes 0–8.1%) being node positive. Among BCS patients 35% received SLNB only and 4.8% received ALND. Starting in 2006, PO and SLNB use increased while ALND remained stable. SLNB and ALND were associated with larger size and higher grade DCIS lesions.

Conclusions—Variation in DCIS management among screened women is wide and includes lymph node surgery beyond what is currently recommended. This indicates the presence of varying levels of overtreatment and the potential for its reduction.

Keywords

Breast cancer; Ductal carcinoma in situ (DCIS); Screening mammography; Overtreatment; Axillary staging; Cancer registration

1. Introduction

Ductal carcinoma in situ (DCIS) has become a relatively common disease after the introduction of screening mammography, representing up to 20–25% of all incident breast malignancies in industrialised countries [1–4]. The natural history of screen-detected DCIS is not yet completely understood [5] and we are therefore in large part unable to distinguish different conditions that are likely to exist under the same label of DCIS [6,7].

Management guidelines increasingly take this uncertainty into account by trying both to provide adequate care and to avoid unnecessary treatment. For example, axillary lymph node dissection (ALND) is not recommended for women with DCIS [8–10]. The International Cancer Screening Network (ICSN) oversees organised programmes that include quality monitoring of the process of screening and care. The purpose of the report is to assess practice variation in the management of screen-detected DCIS and the potential morbidity associated with detection of DCIS among participants in the ICSN.

2. Patients and methods

A survey was launched within the ICSN. All of the screening settings covered were population-based, organised screening programmes, with the exception of Czech Republic, which at the time did not adopt personal invitations, and of the United States, whose data, provided by the Breast Cancer Surveillance Consortium, derived from opportunistic screening in well defined populations.

Selected characteristics of participating programmes were collated from the ICSN web site (<http://appliedresearch.cancer.gov/icsn>) and reported in Table 1. Attendance rates exceeded 60% in all programmes for which this information was available with the exceptions of Switzerland and Japan.

A previous paper [4] on DCIS detection reports in detail the design of this survey. In brief, we sought data from the 33 ICSN member countries regarding the pure DCIS cases they identified within their screened population between January 1, 2004 and December 31, 2008. We asked sites to complete, based on individual data records from their screening and clinical databases often obtained by linkage with population-based cancer registries, a structured questionnaire that summarised data on DCIS detection, diagnosis and treatment. The questionnaire was piloted in a regional screening programme before distribution. Internal data consistency was checked routinely and outlying data were verified with data providers. All data were stratified by calendar year and age in decades, both referred to the date of the screening test. The following data stratifications were also included in the questionnaire: type of breast surgery by DCIS size; nodal surgery by DCIS size; nodal surgery by nuclear grade; nodal surgery by type of breast surgery; and radiotherapy by type of breast surgery. As size by clinical imaging was often unavailable, all sites were asked to provide pathological size (< 10 mm, 11–20 mm, >20 mm).

For the analysis of DCIS management process we selected a number of measures encompassing issues ranging from diagnosis to surgical and adjuvant treatment, namely: pre-operative diagnosis (PO); time from abnormal screen to surgery; use of breast conserving surgery (BCS) as definitive intervention; use of ALND and sentinel lymph nodes biopsy (SLNB); radiotherapy after BCS. Indicators were identified, following a systematic literature review, from two main sources [9,10], by selecting measures believed to be collectable retrospectively from participating screening programmes. A pre-operative diagnosis was defined as the presence prior to open surgery of a definitive diagnosis of malignancy based on either fine needle aspiration cytology (FNAB) or core biopsy. Waiting time applied to patients with surgery as first treatment only. SLNB rates refer to patients who received this procedure as the only axillary procedure.

For all parameters, project documentation instructed sites to indicate the number of missing values. All analyses reported in this paper were restricted to ages 50–69, as this was the age range covered by most participating programmes, and in order to minimise confounding by age. As not all programmes were able to provide data for the entire time period, time trend analysis was restricted to the years 2004–2007.

All files provided by participating centres were included in a flat file and the resulting database analysed by using the R environment (v. 3.0.0). All measures were expressed as proportions, where the numerator was the number of cases managed as described in the measure definition and the denominator the number of eligible cases, after subtraction of missing values. The χ^2 test was used for studying differences between pairs of parameters or trends.

3. Results

Screening co-ordination centres in 12 countries volunteered to participate and contributed data from a total of 15 screening programmes, all from Europe except United States of America (USA) and Japan. Denmark and Spain provided separate regional data. In the age

group 50–69 years 7,176,050 screening tests and 5324 screen-detected DCIS were reported, ranging from 48 from Luxembourg to 1066 from Italy (Table 1).

Results of process of care measures are illustrated in Table 2. Not all programmes were able to provide information for all items. In total, a pre-operative diagnosis was reported for 73% of the DCIS cases ranging from 21% to 93% across areas, surgical-waiting-time-within-60-days was 47% ranging from 25% to 85%, BCS was performed for 78% of cases ranging from 67% to 90%, radiotherapy (RT) after BCS for 66% of cases ranging from 41% to 100%, ALND for 7.9% ranging from 0.8% to 49%, and SLNB (with no ALND) for 35% ranging from 6.4% to 59%. Any nodal surgery was performed for 43% of all DCIS, ranging from 19% in The Netherlands to 63% in Ireland. Most centres reported to use more frequently SLNB only than ALND, with the exceptions of Japan, Luxembourg and the USA (Table 2).

Results for each indicator stratified by time period are shown in Table 3. Use of pre-operative diagnosis and SLNB increased over time. There was a slight decrease in the proportion of DCIS cases operated within 60 days of diagnosis.

Both ALND and SLNB were more frequent at mastectomy (Table 4) and in high grade and larger tumours (Table 4 and Figs. 1, 2). ALND and SLNB were performed in about 20% and more than 50% of mastectomies, respectively, and in 5% and 35% of BCS. Their usage approximately doubles from low to high nuclear grade and from small (< 10 mm) to large (>20 mm) pathological size. Of cases with any type of nodal surgery (1980/4607 or 43%), only 0.6% were node positive (range by programmes 0–8.1%, Table 2).

4. Discussion

We evaluated six measures of DCIS management across 15 active screening programmes in Europe, Japan and the USA. As reported by us elsewhere [4], age-standardised detection rates of DCIS varied from 0.41 to 1.38/1000 women. In this report we observed that pre-operative evaluation, surgical wait times, use of nodal surgery, and radiation therapy also varied substantially across programmes. The implications are that women with potentially detectable DCIS may experience very different morbidity depending upon where they are screened and seek care because both their likelihood of a diagnosis and how it is treated vary across countries. Despite this wide variation, practices overall seem to be moving towards the consensus recommendations on DCIS treatment except SLNB has increased over time also in low and intermediate grade and small DCIS treated with BCS.

Cytological or histological pre-operative diagnosis is recommended in order to limit the need for open surgical biopsies, to allow for surgical planning, and to avoid under or overtreatment. Our overall result of 73% (Table 2), though slightly increasing over time (Table 3), is short of the target of 90% suggested by some guidelines [9,10] and the range among programmes is very wide, with only two Spanish programmes coming close to or above the stated standard. Even though FNAB and core biopsy are both accepted modalities for preoperative diagnosis, the latter allows discriminating invasive from in situ lesions and, in most settings, it is likely to provide a higher proportion of preoperative diagnosis being more sensitive and specific [11]. However, this distinction is not available in our data.

Centres with low level of preoperative diagnosis reported that, at the time under study, cases received exclusively or predominantly FNAB.

Women also face a wide variation in the range of waiting times for the definitive operation. Although it is recognised that two or three months delay from screening to treatment is not likely to affect prognosis (especially in the case of slowly growing lesions such as most DCIS), relatively long waiting times may cause anxiety and affect quality of life [12].

Using BCS for the surgical treatment of DCIS is usually considered good practice, even if it is recognised that patient preference plays a role [13]. The proportion of BCS in our series is high (78% overall) and relatively constant across programmes and time periods, with only one programme reporting slightly short of 70% and with three programmes exceeding 85%. BCS for DCIS not greater than 2 cm in pathological size is even more frequent (88% in 2190 cases of this size). In England, where a report on non-invasive breast cancers diagnosed within and outside the national breast cancer screening programme is periodically issued, the proportion of BCS in screen-detected cases in 2006–2007 is 71% [14], while 70% is the figure reported by a French survey for the period 2003–2004 [15]. Even lower was the proportion of BCS in the East Netherlands during 1999–2003: 55% [16]. In a population-based study in Southern Netherlands, which documented an increasing time trend, it was reported to be 68% in 2010 [17].

BCS is often complemented by radiotherapy [8,18], in order to lower the risk of local in situ or invasive recurrence. In our series radiotherapy is performed in 66% of BCS patients, with the lowest result being 41%. In United Kingdom during 2003–2006 53% of BCS received radiotherapy, with radiotherapy provision significantly related to tumour size and grade [14]. In France in 2003–2004 the corresponding figure was 89% [15]. In the East Netherlands during 1999–2003 [16] and in the Southern part of the country in 2010 [17] radiotherapy was performed respectively in 34% and in 89% of DCIS treated with BCS.

Management of the axilla is a subject of debate in DCIS, but there is consensus regarding the need to avoid ALND, considered unnecessary and a cause of frequent complications [8–10]. This survey documented that ALND takes place in 5% of women with DCIS as final diagnosis treated by BCS and in almost 20% of women treated by mastectomy. The use of SLNB was much more frequent and on the rise over time, with a large variation among programmes, so that in our series almost half of all cases had any type of nodal surgery. We were able to show that the recommendation [8,9,19–21] to limit SLNB to women undergoing mastectomies and/or those with large (where micro-invasion might be more easily overlooked) or high grade DCIS were clearly reflected in actual practice, although not fully followed since we observed one third of BCS patients and many small or low grade DCIS had SLNB only (Table 4 and Figs. 1, 2). Notably, the proportion of all DCIS cases associated with positive lymph nodes in this study was low (0.6%) and thus not likely to be influencing treatment management. These results add support to the limited value of nodal staging in women with screen-detected DCIS [22,23] and to recent guidelines [24] that further restrict the indication for SLNB in DCIS, suggesting that clinicians consider SLNB when mastectomy is planned, in case of clinically evident mass lesions suggestive of invasive cancer, and in very large size DCIS (>5 cm.) only.

Similarly to our observation, the correlation of the use of SLNB with DCIS size and grade has been reported in an analysis of US Seer data 1998–2002 [25], in France during 2003–2004 [15] and in Australia during 1995–2000 [26]. However, in Australia the use of nodal surgery was correlated with the size of the breast lesion but not with its grade.

In England in 2006–2007 the use of SLNB in screen-detected non-invasive breast cancers having breast conserving surgery was 4.0% [14], a figure lower than in any of the programmes included in our survey. In France in 2003–2004 SLNB was performed in 21% of patients and the proportion of ALND was 10% [15]. In the East Netherlands during 1999–2003 any axillary staging procedure was performed in 25% of DCIS [16] while in Southern Netherlands use of SLNB was reported being 65% in 2010 [17]. In Italy the use of SLNB in screen-detected DCIS increased from 20% to slightly over 50% from 2001 to 2007 and then remained virtually stable through 2010 [27].

Limitations of this study are those specific to aggregate data surveys: limited detail in available data, possible use of different definitions of study parameters in the different sites, need to restrict overall data analyses to data stratifications being planned in advance. Not all programmes could contribute all required data and the number of missing values for some of the parameters was high. However, we minimised these limitations by providing strictly structured data collection forms, with several prespecified stratification tables, detailed documentation on definitions used, and internal consistency checks. It must be also acknowledged that this paper provides a picture of DCIS management during 2004–2008, and practice is likely to have evolved since then, both in detection, with the gradual introduction of digital mammography [4], and in treatment. ICSN will consider updating these results seeking data from an even larger number of programmes.

This survey covered screen-detected DCIS cases only. Few countries have yet similar information available from the in situ carcinoma diagnosed at all ages outside organised screening programmes, which have been quantified as 51% of all cases in Southern Netherlands [17], 43% in Finland [28], and 38% in United Kingdom [14]. Projects conducted in co-operation between clinical Centres and population Cancer Registries [17] could cover this gap.

This study is, to our knowledge, the first large (more than 5000 cases) international survey of DCIS management practices. We found wide variation in clinical management for all of the parameters studied. While awaiting progress from research enabling to differentiate indolent lesions amenable of follow up only from those at high risk of subsequent invasive cancer [29–31], efforts should be made to optimise diagnostic assessment and management of screen-detected cases to mitigate overdiagnosis and overtreatment [32]. Specifically, we found that axillary surgery, although used more often in high grade and large size lesions, showed an increasing time trend and was performed, with large variation between centres, beyond what is recommended by guidelines. This indicates the presence of varying levels of overtreatment and the potential for the reduction of treatment-related morbidity. In fact, although less frequently harmful than ALND, SLNB is not exempt from complications. According to the update of the SLNB American Society of Clinical Oncology Clinical Practice Guidelines [24], which includes a literature review of adverse events, important

morbidity of node surgery includes lymphoedema, infections, seroma and neurologic complications. These were found to be more frequent in patients receiving ALND as opposed to SLNB only, but they are still not negligible even in the latter. For example, in the ALMANAC trial [33] at 12 months after operation lymphoedema occurred in 5% of patients having received SLNB only versus 13% of patients having received ALND, and sensory loss 11% and 31% respectively.

Specialised multidisciplinary care for breast cancer has proved to improve process of care [34] and decrease mortality [35]. Screening programmes should link to specialised clinical Units and Cancer Registries and jointly set up or expand multidisciplinary teams in charge of quality assurance of diagnosis and treatment of screen-detected lesions, including DCIS, so to assure that current guidelines are applied and opportunities for research in the heterogeneity of these lesions are taken.

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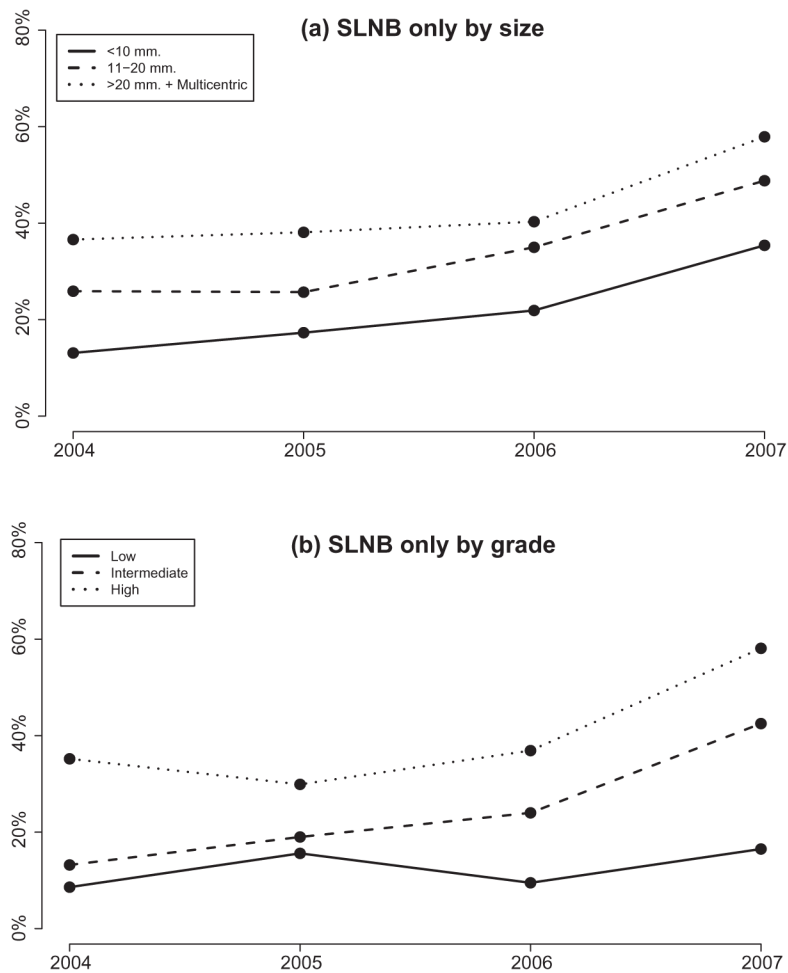


Fig. 1. Ductal carcinoma in situ: performance of sentinel lymph node biopsy (SLNB) only by pathological size and time period (a), and by nuclear grade and time period (b). Any type of breast surgery included. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 or lacking the stratification by size and grade were excluded from this analysis. Data are included for Finland, Ireland, Norway, Spain, Switzerland and United States of America (USA).

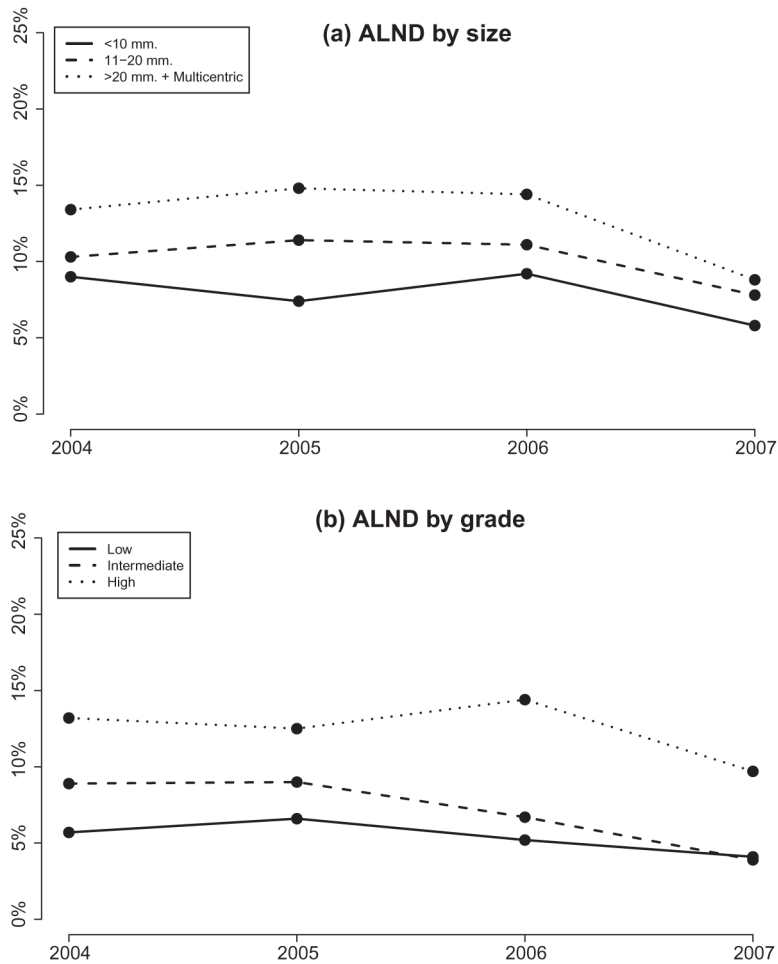


Fig. 2. Ductal carcinoma in situ: axillary lymph node dissection (ALND) by pathological size and time period (a), and by nuclear grade and time period (b). Any type of breast surgery included. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 or lacking the stratification by size and grade were excluded from this analysis. Data are included for Finland, Ireland, Norway, Spain, Switzerland and United States of America (USA).

Table 1

International cancer screening network survey on the management of ductal carcinoma in situ (DCIS). Description of the screening programmes included in the analysis, number of reported tests and number of screen-detected DCIS.

Country/region	Year programme started	Target age group	Attendance rate (2010)	Data collection years	No. of reported tests (age 50–69)	No. of screen-detected DCIS (age 50–69)
Czech Republic	2002	45–69	Not available	2007–2008	699,726	359
Denmark Copenhagen	1991	50–69	73%	2004–2007	47,249	73
Denmark Fyn	1993	50–69		2004–2007	97,176	63
Finland	1987	50–69 ^d	85%	2004–2007	862,908	361
Ireland	2000	50–64	Not available	2004–2008	331,854	393
Italy ^b	1990	50–69	61%	2006–2008	1,453,292	1,066
Japan ^c	2000	50–69	19%	2004–2008	106,898	72
Luxembourg	1992	50–69	64%	2006–2008	45,586	48
Netherlands	1990	50–74 ^d	81%	2007	718,202	576
Norway	1996	50–69	76%	2004–2008	963,424	899
Spain Barcelona	2001	50–69	Not available	2004–2008	184,748	90
Spain Navarra	1989	45–69	87%	2004–2008	131,948	95
Spain Valencia	1992	45–69	Not available	2004–2008	739,829	422
Switzerland ^e	1999	50–69	48%	2004–2008	176,318	190
United States of America (USA) ^f	1991	40–74	67%	2004–2007	616,892	617
Total	–	–	–	2004–2008	7,176,050	5,324

^a Targeted women aged 50–59 until 2006.

^b Data from five regional programmes: Piemonte, Valle d'Aosta, Emilia Romagna, Toscana, and Lazio.

^c Data from the Miyagi Prefecture, source The Miyagi Cancer Society.

^d Targeted women aged 50–69 until 1999.

^e Data from four Swiss regional programmes: Vaud, Valais and Fribourg (2004–2008), and Jura-Neuchâtel (2005–2008).

^f Data from the Breast Screening Surveillance Consortium.

Table 2

Ductal carcinoma in situ (DCIS): process of care indicators and lymph node status by country/region, age 50–69. Results are expressed as proportion of cases with known information (PO = pre-operative diagnosis; BCS = breast conserving surgery; RT = radiotherapy; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy, NA = not available).

Area	No. DCIS	% PO	% missing	% surgery 60 days	% missing	% BCS	% missing	% RT in BCS	% missing	% ALND	% SLNB only	% any nodal surgery	% missing	No. DCIS with ALND or SLNB	% N+	% N status missing
Czech Republic	359	81	0	53	17	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Denmark Copenhagen	73	NA	100	25	8.2	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Denmark Fyn	63	NA	100	60	4.8	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Finland	361	60	0.3	NA	100	67	11	NA	100	11	31	42	0	151	2.3	12
Ireland	393	76	0	85	0.3	78	0	NA	100	3.3	59	63	0.3	245	0	0.8
Italy	1066	73	3.8	29	13	86	1.4	83	74	4.4	53	57	8.2	562	0.2	8.2
Japan	72	21	0	54	0	71	0	41	0	49	7.0	56	0	40	0	43
Luxembourg	48	77	0	50	4.2	75	2.1	NA	100	30	6.4	36	2.1	17	0	11
Netherlands	576	74	14	NA	100	70	43	NA	100	0.8	19	19	14	95	0	47
Norway	899	NA	100	55	3.2	72	0	73	25	7.3	43	51	0	454	0	0
Spain Barcelona	90	89	12	NA	100	78	0	78	17	7.5	51	59	11	47	8.1	35
Spain Navarra	95	93	0	30	1.1	90	1.1	100	0	1.1	38	39	0	37	0	0
Spain Valencia	422	63	22	50	4.0	84	5.9	53	60	14	24	38	7.3	147	1.4	17
Switzerland	190	76	0	65	3.2	86	0	54	0	2.6	23	25	0	48	4.2	0
United States of America (USA)	617	68	38	71	78	79	4.7	59	3.9	14	9.1	23	1.8	137	0	0
All Areas ^a	5324	73	11	47^b	5.7	78	7.4	66^c	13	7.9	35	43	4.6	1980	0.6	27

^aExcluding countries for which information is not available.

^bExcluding USA, in addition to countries for which information is not available, due to the high proportion of missing values.

^cExcluding Italy and Valencia, in addition to countries for which information is not available, due to the high proportion of missing values.

Ductal carcinoma in situ (DCIS): process of care indicators by time period, age 50–69. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 were excluded. Results are expressed as proportion of cases with known information.

Table 3

	2004–2005			2006–2007			Total			<i>p</i> -value ^e
	No. of DCIS	% missing	Result%	No. of DCIS	% missing	Result%	No. of DCIS	% missing	Result%	
Pre-operative diagnosis ^a	977	20	64	914	13	74	1891	17	69	<0.001
Surgery within 60 days from abnormal screening test ^b	790	1.0	62	888	3.4	56	1678	2.3	59	0.01
Breast conservation surgery ^c	1316	4.6	76	1283	1.8	77	2599	3.2	77	0.74
Radiotherapy after breast conservation surgery ^d	678	9.0	66	597	1.6	65	1275	1.2	66	0.94
Axillary dissection ^c	1316	1.7	11	1283	1.2	11	2599	1.5	11	0.86
Sentinel Lymph Node Biopsy only ^c	1316	1.7	26	1283	1.2	35	2599	1.5	31	<0.001

^aIncluding Finland, Ireland, Japan, Spain, Switzerland and United States of America (USA).

^bIncluding Denmark, Ireland, Japan, Norway, Spain (excl. Barcelona), and Switzerland.

^cIncluding Finland, Ireland, Japan, Norway, Spain, Switzerland and USA.

^dIncluding Japan, Norway, Spain (excl. Valencia), Switzerland and USA.

^e χ^2 test between 2004–2005 and 2006–2007.

Table 4

Ductal carcinoma in situ (DCIS): surgery on the axilla by type of breast surgery and by grade and pathological size, age 50–69. Results are expressed as proportion of cases with known information. BCS = breast conserving surgery; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy).

Type of surgery ^a	No. of DCIS	% ALND	p-Value ^d	% SLNB only	p-Value ^d	% missing
BCS	2939	4.8	<0.001	35	<0.001	3.1
Mastectomy	892 ^c	19		51		2.2
Total	3831	8.1		39		2.9

DCIS nuclear grade ^b	No. of DCIS	%ALND	p-Value ^e	%SLNB only	p-Value ^e	% missing
Low	793	4.7	<0.001	22	<0.001	3.2
Intermediate	1241	6.2		33		3.2
High	2059	11		45		1.8
Unknown	587	10		23		9.2
Total	4680	8.4		35		3.3

DCIS pathological size ^b	No. of DCIS	%ALND	p-Value ^e	%SLNB only	p-Value ^e	% missing
10 mm	1442	6.6	<0.001	26	<0.001	2.7
11–20 mm	923	9.3		36		2.6
>20 mm or multicentric	1252	10		49		2.5
Unknown	1063	7.7		32		5.8
Total	4680	8.4		35		3.3

^aIncluding Finland, Ireland, Italy, Japan, Luxembourg, Norway, Spain (excl. Valencia), Switzerland and United States of America (USA).

^bIncluding Finland, Ireland, Italy, Norway, Spain, Switzerland and USA.

^c52 cases with type of surgery unknown included.

^d χ^2 test.

^e χ^2 test for trend.