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Variation in detection of ductal carcinoma in situ (DCIS) during screening mammography A survey within the International Cancer Screening Network (ICSN)

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Abstract

Background—There is concern about detection of Ductal Carcinoma in Situ (DCIS) in screening mammography. DCIS accounts for a substantial proportion of screen detected lesions but its effect on breast cancer mortality is debated. The International Cancer Screening Network conducted a comparative analysis to determine variation in DCIS detection.

Patients and Methods—Data were collected during 2004–2008 on number of screening examinations, detected breast cancers, DCIS cases, and Globocan 2008 breast cancer incidence rates derived from national or regional cancer registers. We calculated screen-detection rates for breast cancers and DCIS.

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Conflict of interest statement
No authors have declared a conflict of interest.

Results—Data were obtained from 15 screening settings in 12 countries; 7,176,050 screening examinations; 29,605 breast cancers; and 5,324 DCIS cases. The ratio between highest and lowest breast cancer incidence was 2.88 (95% confidence interval (CI) 2.76–3.00); 2.97 (95% CI 2.51–3.51) for detection of breast cancer; and 3.49 (95% CI 2.70–4.51) for detection of DCIS.

Conclusions—Considerable international variation was found in DCIS detection. This variation could not be fully explained by variation in incidence nor in breast cancer detection rates. It suggests the potential for wide discrepancies in management of DCIS resulting in overtreatment of indolent DCIS or undertreatment of potentially curable disease. Comprehensive cancer registration is needed to monitor DCIS detection. Efforts to understand discrepancies and standardize management may improve care.

Keywords

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

Introduction

In the United States (US), the rate of ductal carcinoma in situ (DCIS) has increased fivefold in the last 25 years.[1] This dramatic increase has been attributed to the diffusion of screening mammography. Among cases detected by screening in the US between the years 2002 and 2006 close to 24% were DCIS.[2] A marked increase in DCIS incidence rates has also been found in Europe.[3–6] Common belief is that DCIS advances to invasive cancer in the absence of treatment, but the time trend in incidence of invasive breast cancer is not consistent with this expectation for all cases of DCIS.[7–9] It is likely that some forms of DCIS would remain indolent throughout the lifespan of a patient, whereas other types have a greater propensity to advance into life-threatening invasive disease. The natural history of screen-detected DCIS therefore remains ambiguous. To a large extent this is related to the variety of histological subtypes grouped under the one label DCIS. Observational data indicate tumor size, nuclear grade, presence/absence of comedo-type necrosis, and age to be independent prognostic factors for DCIS progression.[10] While detection of DCIS is thought to contribute to screening effectiveness,[11] there is considerable debate about the overdiagnosis of DCIS and the negative impact of screening if non-lethal disease is identified and treated.

To determine the variation in DCIS detection in screening mammography, we undertook a survey within the framework of the International Cancer Screening Network (ICSN).[12] We focused on the age group 50 to 69 years for which screening is recommended in all ICSN countries.

Patients and Methods

We sought data from the ICSN countries regarding DCIS cases identified within well-defined screening settings between January 1, 2004 and December 31, 2008. These programs are described in some detail at (http://appliedresearch.cancer.gov/icsn/breast/screening.html). Most of the screening settings were population-based, organised screening programs like the national program in the Netherlands, while the US data from the Breast Cancer Surveillance Consortium (BCSC) derived from opportunistic screening in well-defined populations. Italy included five and Switzerland four regional programs. For simplicity we refer to all the screening settings as programs. One screening mammography examination in a woman was defined as a screening test. We asked each program to complete Excel spreadsheets of aggregate data regarding number of screening tests performed, number of screen-detected invasive breast cancers, DCIS cases, and lobular carcinoma in situ (LCIS) cases. Screen detected cases were defined according to the procedures of the individual programs. In some programs, the final diagnostic conclusion

was directly linked to each screening examination. In the BCSC, a diagnosis within 12 months of an abnormal or positive screening examination was defined as a screen-detected case. We included data for women aged 50–69 years. Data were reported separately for initial screens, the women's first known screen or the first registered in an organised screening program, and subsequent screens. All detected cases were included independently of whether it was a first or a subsequent lesion in a given women or whether there were bilateral lesions. We attempted to collect data for DCIS grade and size, but these variables were unknown for large parts of the data set, 18% for grade and 37% size, and were consequently not used in the analysis.

In total 115 Excel files were collected from 12 countries. Detection rates for invasive breast cancer and DCIS, respectively, were calculated as the number of screen-detected cases in the age group 50–69 divided by the number of screening tests performed in this age group. Age-standardized detection rates were calculated using the age distribution of all screening tests across all countries as the standard.

Characteristics of the screening programs such as age group targeted and screening interval were retrieved from the ICSN website.[12] In several of our data collection countries, the collection period co-insided with a gradual shift from analogue to digital mammography, and the programs can therefore not be classified by type of mammography. The ICSN website furthermore includes only limited information on each programs; no information is for instance provided on criteria for mammogram classification, referral strategy or referral rate. National breast cancer incidence rates (invasive cases only) in 2008 for women aged 50–54, 55–59, 60–64 and 65–69 years were retrieved from the Globocan website[13] and age-standardised. It should be noted that only part of the Globocan 2008 data derive from national cancer registers, see Table 1 for specification.

The program performance was evaluated by the ratio between the age-standardized detection rate for invasive cases at subsequent screens and the background breast cancer incidence rate as estimated by Globocan data. In rough terms, in a biennial screening program a ratio of 1.5 corresponds to a program with 75% sensitivity for invasive cases. The international gradient in screening detection rates was illustrated by the ratio between the highest and the lowest age-standardized rates. We investigated the correlation between various performance indicators. As the size of the individual data sets varied considerably, and as we were interested in the variation across programs, we used Spearman's rank coefficients without weights for the size of each observation point. We merged data from the programs for the initial and the subsequent screening tests and calculated invasive and DCIS detection rates for women aged 50–59 and 60–69, respectively.

Results

Twelve countries contributed data, 10 with national data although with different population coverage, and 2 (Denmark and Spain) with regional data (Table 1). In total, observations were available from 15 screening programs. Screening started between 1987 and 2002 and involved an increasing number of screened women in some countries during the data reporting period. In all countries, women aged 50–69 years were targeted by screening, the interval being 2 years except for the US where the interval was 1–2 years, Table 1. Between the 12 countries the age-standardized breast cancer incidence for women aged 50–69 varied from 1.31 per 1000 in Japan to 3.75 per 1000 in Denmark, with a RR of 2.88 (95% CI 2.76–3.00), Figure 1.

In the age group 50–69 years, 7,176,050 screening tests, 29,605 invasive breast cancer cases, 5,324 DCIS cases, and 233 LCIS cases were reported (Table 2). DCIS as a proportion of all

detected cases averaged 16% across all programs, and the rate was 0.82 per 1000 examinations. The lowest proportion was in Finland (9%, 95% confidence interval (CI) 8%–10%) and highest in the US (24%, 95% CI 22%–25%). The proportions were close to or above 20% in Denmark, Copenhagen; Ireland; Japan; and the US, while the proportions were 10% or below in the Czech Republic; Denmark, Fyn; and Finland. Rates were less than 0.8 per 1000 examinations for Czech Republic, Denmark Fyn, Finland, Italy, Japan, The Netherlands, Spain Barcelona, Spain Navarra, Spain Valencia and greater than 0.8 per 1000 examinations for Denmark Copenhagen, Ireland, Luxembourg, Norway, Switzerland, and US.

The age-standardized detection rates for invasive breast cancer cases varied from 6.65 per 1000 in Denmark, Copenhagen to 2.24 per 1000 in Japan, resulting in a RR for Denmark, Copenhagen vs Japan of 2.97 (95% CI 2.51–3.51), Figure 1.

The age-standardized detection rates for DCIS varied from 1.55 per 1000 in Denmark, Copenhagen to 0.45 per 1000 in Finland, resulting in a RR of 3.49 (95% CI 2.70–4.51) (Figure 1). Both the detection rate of invasive cancer and of DCIS decreased gradually from the highest to the lowest rates, but the sequences were not identical. Denmark, Copenhagen; the US and Ireland had high DCIS detection rates as compared with their invasive detections rates, while the Czech Republic; Finland and Denmark, Fyn had relatively low DCIS detection rates, Figure 2. The differences across programs were less dramatic when second highest and second lowest rates were compared, but the pattern prevailed; the ratios being 1.66; 2.13; and 2.47 for breast cancer incidence, detection of invasive breast cancer and detection of DCIS, respectively.

Thirteen out of 15 programs provided data by initial and subsequent screens, constituting 676,324 and 4,346,708 screens, respectively. For most countries the detection rate of invasive cancer at subsequent screens was close to or above 1.5 times the background incidence, though with Luxembourg, where the ratio was 2.04, as an outlier, and with relative low ratios of 1.21; 1.25; 1.30; and 1.31, respectively, in The Netherlands; Spain, Barcelona; Ireland; and the US (Table 2). The average age-standardized invasive detection rate was 7.13 per 1000 at initial screens and 4.04 at subsequent screens, giving a ratio of subsequent to initial of 0.57 (data not shown). The average DCIS proportion was 18% in initial and 17% in subsequent screens. The subsequent screens on average constituted 87% of the reported screens, and the age-standardized detection rates for DCIS were consequently in most programs close to those for all screens (Table 2). The average age-standardized DCIS detection rate was 1.30 per 1000 at initial screens and 0.78 at subsequent screens, giving a ratio of subsequent to initial of 0.60 (data not shown).

Although the overall DCIS detection rate increased from 0.68 to 0.83 per 1000 from age 50–59 to age 60–69, the DCIS proportion of all detected lesions decreased from 16.6% to 13.9% (Table 3). Among women aged 50–59, the DCIS detection rate per 1000 dropped from 1.01 to 0.64 from initial to subsequent screens, resulting in a ratio of subsequent to initial of 0.63. For invasive breast cancer the equivalent ratio was 0.75; 0.63 versus 0.75 ($p=0.002$), which may indicate a longer lead time for DCIS than for invasive cancer. Among women aged 60–69, both ratios were 0.57. The age-standardised DCIS detection rate was on average 0.66 per 1000 in the five programs without double reading versus 0.91 per 1000 in the remaining programs with double reading, however, with large variation in both groups. A 2 year screening interval was recommended in all programs except in the USA, and it was therefore not possible to investigate DCIS detection as a function of screening interval.

Discussion

We studied DCIS and invasive breast cancer detection through screening mammography in 15 screening programs in Europe, the US, and Japan. The background incidence rate of breast cancer varied 3-fold across these settings. An approximately 3-fold variation was also found for the screening detection rates of invasive breast cancer. For most screening programs the detection rates of invasive disease at subsequent screens divided by the incidence was close to or above 1.5. The ratio of 2.04 for Luxembourg could point to overdiagnosis, and the ratios of 1.21; 1.25; and 1.30 for The Netherlands; Spain, Barcelona; and Ireland, respectively, could point to a somewhat lower sensitivity. Given the cross-sectional nature of the data and the fact that concurrent rather than background incidence expected in the absence of screening has been used, these ratios should be interpreted with caution. The somewhat lower ratio of 1.31 for the US can be explained by the shorter screening interval, compared to European countries, and therefore lower expected incidence.

When it came to DCIS detection there were large differences across programs with an approximately 3.5-fold variation. The DCIS detection rates were considerably higher than expected based in the detection rates for invasive cancer in Denmark, Copenhagen; Ireland, Luxembourg, Switzerland, and the US, while the Czech Republic; Finland; Spain Valencia, and Denmark, Fyn had low detection rates. No other country exceeded the US 24% detection rate for DCIS in screened cases. The variation across programs in DCIS detection rates may in part be due to technology. In Copenhagen, Denmark the detection rate increased when high resolution ultrasound and stereotactic breast biopsies were introduced in the early 2000s for the diagnostic assessment of women with Breast Imaging Reporting and Data System (BI-RADS) 0 screening mammograms.[14] In some[15] but not all[16] settings, DCIS detection has furthermore been found to increase with the introduction of digital mammography. The variation may also be due to variability in diagnostic criteria among pathologists both within and between countries. In a quality assessment scheme for breast pathology in the United Kingdom (UK), the overall kappa value for diagnosis of in situ/microinvasive cases was 0.76,[17] so variation does occur even within a country. Variation across countries can also be expected based on different criteria and norms for diagnosis since at least three systems of classification are in use throughout the world.[18] Comprehensive and standardized registration of all DCIS cases is an important task for national as well as regional cancer registries.

The point of this paper, however, is that variation in DCIS detection is extensive. Our data indicate that this variation cannot be explained by differences in breast cancer incidence in these populations. The amount of DCIS detection is therefore expected to have implications for the unintended morbidity of screening. Women diagnosed with DCIS have a long-term, disease-free survival of 96–98% when treated with current therapies[19] so the morbidity of treatment is very important. In the US approximately 30% of women with DCIS are treated with mastectomy, 30% with conservative surgery alone, and 40% with conservative surgery and radiotherapy.[1] Now that the present study has demonstrated the world-wide variation in DCIS detection, we need in-depth studies on possible determinants of DCIS detection, and we need information about variation in DCIS treatment around the world.

Treatment decisions are made based on the extent and aggressiveness of the disease. Efforts are underway to develop biological markers to distinguish between progressive and non-progressive DCIS lesions,[20–21] but it may still take some time before such markers are available for clinical use. Future biomarkers for DCIS could help to distinguish between low-risk lesions that could be observed versus high-risk lesions requiring treatment. For small invasive cancers, mammographic pattern has been shown to correlate with prognosis[22], and such studies may also be valuable for classification of DCIS. Further

studies into combined mammographic appearance and histopathology might be promising for differentiation between clinically significant and indolent DCIS.

We studied cross-sectional data reported in a standardized format from 15 screening programs. The data collection was standardised. The coordinating centre in Torino, Italy sent the same excel spread sheet to all data providers, and checked for logical inconsistencies and numbers across the tables. Data providers were asked to correct eventual irregularities, and the data were re-checked prior to analysis. The data sets varied considerably in size from the more than 1.4 million screening tests reported from Italy to the 45,000 screening tests reported from Luxembourg. The nationally aggregated data sets, such as the BCSC data from 7 US screening programs,[2] are expected to represent the average across programs. It is not surprising on this basis that the small Danish screening programs fell at the extremes of DCIS detection, whereas the US data came closer to the average.

The low proportion of DCIS cases in Finland is noteworthy as the Finnish screening program has repeatedly been shown to have reduced breast cancer mortality in Finnish women. This was true both in the early phase where an approximately 34% reduction in breast cancer mortality was found,[23] and in a later phase where a 28% reduction was found.[24] A low DCIS detection rate has thus been shown to be no hindrance for a screening program to achieve its aim of reducing breast cancer mortality.

In conclusion, this first international comparison of DCIS detection rates in screening mammography programs reveals considerable variation, indicating an opportunity for standardization. The low DCIS detection rate in Finland in the presence of a mortality reduction suggests there is room to reduce the DCIS detection rates in other programs, and therefore reduce the morbidity associated with screening. The differences in DCIS rates also offers an opportunity for international collaboration on recommendations for DCIS detection and diagnosis in screening mammography to reduce the wide variation in potential morbidity from overtreatment, while optimizing outcomes by avoiding undertreatment of early, high-risk disease.

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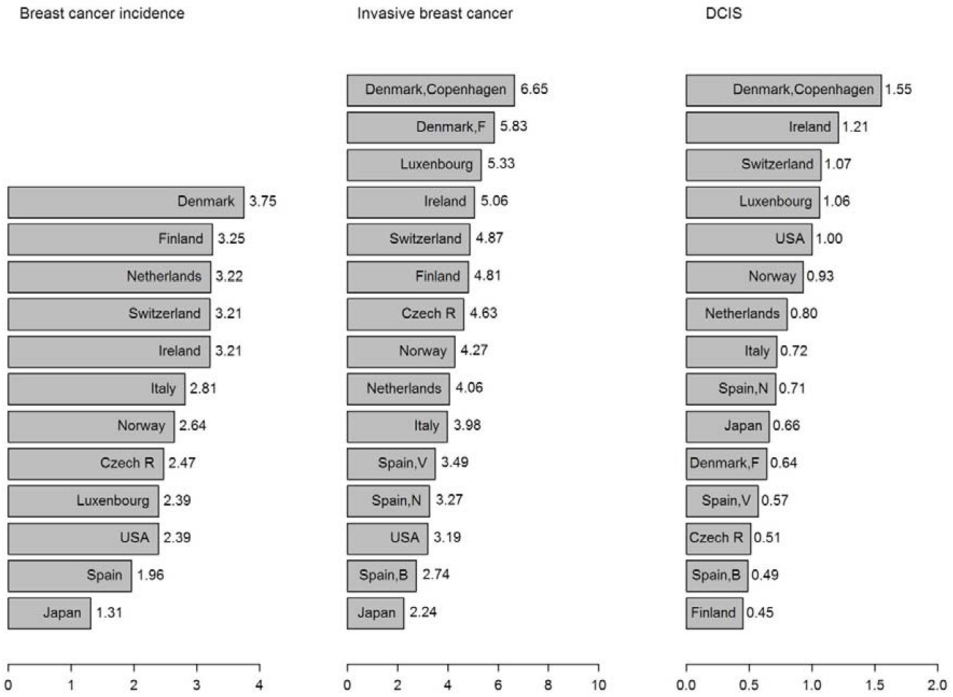

Highest/lowest rate:
2.88 (95% CI 2.76-3.00) 2.97 (95% CI 2.51-3.51) 3.49 (95% CI 2.70-4.51)

Figure 1.
Age-standardized breast cancer incidence rate, detection rate of invasive breast cancer, and detection rate of DCIS per 1000 women aged 50–69 years.

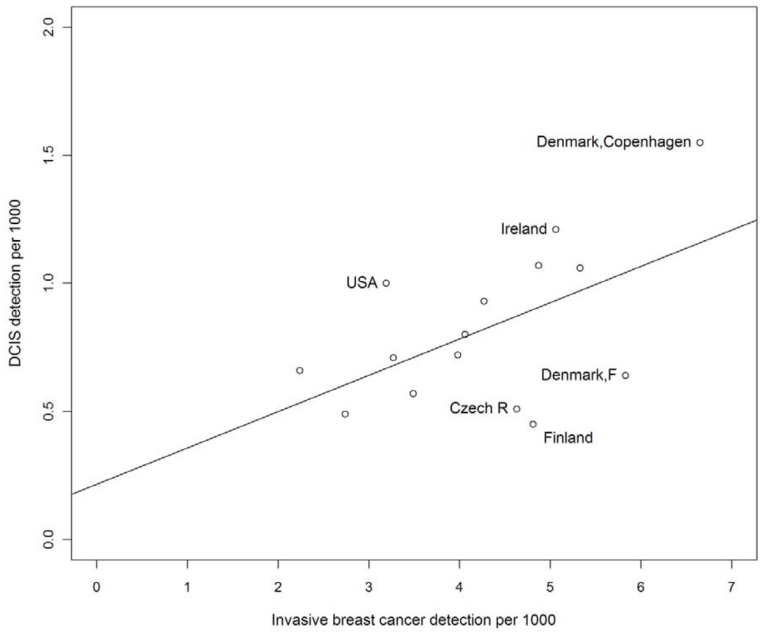

Figure 2.
Detection rate of invasive breast cancer versus detection rate of DCIS both per 1000 women aged 50–69 years.

Table 1

Description of the screening programs included in the analysis

Country/region	Breast cancer rate[1]	Globocan 2008 data[1]	ProGram	Year of start	Type of recruitment	Target age group	Interval	Test offered	Double reading	Data collection years	Number of reported tests
Czech Republic	2.5	CR	Nat	2002	PR	45–69	2	M	No	2007–8	937,718
Denmark Copenhagen	3.8	CR	Reg	1991	PI	50–69	2	M	Yes	2004–7	48,528
Denmark Fyn	3.8	CR	Reg	1993	PI	50–69	2	M	Yes	2004–7	97,498
Finland	3.3	CR	Nat	1987	PI,MA	50–69[4]	2	M	Yes	2004–7	862,908
Ireland	3.2	CR	Reg[2]	2000	PI	50–64	2	M	Yes	2004–8	332,359
Italy[5]	2.8	E-mort	Reg	1990	PI	50–69	2	M	Yes	2006–8	1,521,426
Japan	1.3	E-mort	Nat	2000	PI,MA	50–69	2	M,CBE	Yes	2004–8	160,333
Luxembourg	2.4	E-mort	Nat	1992	PI	50–69	2	M	Yes	2006–8	45,586
Netherlands	3.2	CR	Nat	1989	PI	50–74[6]	2	M	Yes	2007	874,047
Norway	2.6	CR	Nat	1996	PI	50–69	2	M	Yes	2004–8	963,424
Spain Barcelona	2.0	E-mort	Reg	2001	PI	50–69	2	M	No	2004–8	184,748
Spain Navarra	2.0	E-mort	Reg	1989	PI	45–69	2	M	No	2004–8	181,992
Spain Valencia	2.0	E-mort	Reg	1992	PI	45–69	2	M	No	2004–8	983,452
Switzerland[7]	3.2	E-mort	Reg	1999	PI	50–69	2	M	Yes	2004–8	176,318
USA	2.4	E-reg	Reg[3]	1991	PR,MA	40–74+	1–2	M,CBE	No	2004–7	1,029,401

Nat: national; Reg: regional; PR: physician referral; PI: personal invitation; MA: media advertising; M: mammography; CBE: clinical breast examination

Notes:

[1] National average breast cancer incidence rate per 1000 for women aged 50–69 according to Globocan 2008 (13). These data include invasive cases only. Age-standardized according to the age distribution of all reported screening tests. Globocan 2008 data source specified as: CR: National cancer register data; E-mort: Estimated from cancer mortality data; E-reg: Estimated from regional cancer register data.

[2] Program became national in 2007

[3] National database covering screening in selected areas

[4] Targeted women aged 50–59 until 2006

[5] Data from five regional programs: Piemonte, Valle d'Aosta, Emilia Romagna, Toscana, and Lazio.

[6] The age group 70–74 years has been included only since 1999.

[7]Data from all five operating Swiss regional programs: Geneva, Vaud, Valais and Fribourg (2004–8), and Jura-Neuchâtel (2005–8)

Table 2

Number of reported tests, number of screen detected breast cancer cases, and detection rate per 1000 reported tests. Women aged 50–69.

Country/region	Number of reported tests	Invasive breast cancer	DCIS	LCIS	Total detected cases	Invasive per 1000	Invasive per 1000st[1]	DCIS per 1000	DCIS per 1000st[1]	DCIS as percent of total	DCIS per 1000st[1] Subsequent[2]	Invasive per 1000st[1] Subsequent[2]/ breast cancer rate
Czech Republic	699,726	3,276	359	31	3,666	4.68	4.63	0.51	0.51	10%	-	-
Denmark Copenhagen	47,249	317	73	0	390	6.71	6.65	1.55	1.55	19%	1.38	1.71
Denmark Fyn	97,176	577	63	0	640	5.94	5.83	0.65	0.64	10%	0.62	1.55
Finland	862,908	3,810	361	17	4,188	4.42	4.81	0.42	0.45	9%	0.44	1.46
Ireland	331,854	1,626	393	1	2,020	4.90	5.06	1.18	1.21	19%	1.01	1.30
Italy	1,453,292	6,051	1,066	97	7,214	4.16	3.98	0.73	0.72	15%	-	-
Japan	106,898	241	72	1	314	2.25	2.24	0.67	0.66	23%	0.62	1.43
Luxembourg	45,586	241	48	4	293	5.29	5.33	1.05	1.06	16%	1.06	2.04
Netherlands	718,202	2,939	576	1	3,516	4.09	4.06	0.80	0.80	16%	0.76	1.21
Norway	963,424	4,147	899	34	5,080	4.30	4.27	0.93	0.93	18%	0.86	1.60
Spain Barcelona	184,748	508	90	2	600	2.75	2.74	0.49	0.49	15%	0.41	1.25
Spain Navarra	131,948	435	95	4	534	3.30	3.27	0.72	0.71	18%	0.68	1.61
Spain Valencia	739,829	2,607	422	15	3,044	3.52	3.49	0.57	0.57	14%	0.55	1.71
Switzerland	176,318	871	190	7	1,068	4.94	4.87	1.08	1.07	18%	0.83	1.36
USA	616,892	1,959	617	19	2,595	3.18	3.19	1.00	1.00	24%	0.98	1.31
Total	7,176,050	29,605	5,324	233	35,162	4.30[3]	4.29[3]	0.82[3]	0.82[3]	16%[3]	0.78[4]	1.50[4]

DCIS: Ductal carcinoma in situ, including carcinoma in situ unspecified; LCIS: Lobular carcinoma in situ

Notes:

[1] Age standardised, using the age distribution of all screening tests as standard

[2] Subsequent screens only

[3] Average for the 15 programs

[4] Average for the 13 programs

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Table 3

Crude detection rates of invasive breast cancer and DCIS by initial vs. subsequent screening test.

Age	Screening test	Invasive	DCIS	DCIS % of detected lesions	Invasive Per 1000	DCIS Per 1000
50–59	All	14679	2914	16.6%	3.43	0.68
	Initial (I)[1]	2543	584	18.7%	4.39	1.01
	Subseq (S)[1]	8426	1643	16.3%	3.29	0.64
	Ratio S/I				S/I 0.75	S/I 0.63
60–69	All	14926	2410	13.9%	5.13	0.83
	Initial (I)[1]	805	146	15.4%	8.27	1.50
	Subseq (S)[1]	8504	1526	15.2%	4.75	0.85
	Ratio S/I				S/I 0.57	S/I 0.57

Notes:

[1]Data not available from the Czech Republic and Italy