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BRIEF REPORT

Low-grade screen-detected ductal carcinoma in situ progresses more slowly than high-grade lesions: evidence from an international multi-centre study

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Abstract

Purpose Nuclear grade is an important indicator of the biological behaviour of ductal carcinoma in situ (DCIS). De-escalation of treatment has been suggested for low-grade DCIS. Our aim is to estimate the relative rate of progression of DCIS by nuclear grade by analysing the distribution of nuclear grade by detection at initial or subsequent screening.

Methods We asked International Cancer Screening Network sites to complete, based on their screening and clinical databases, an aggregated data file on DCIS detection, diagnosis and treatment.

Results Eleven screening programs reported 5068 screen-detected pure DCIS in nearly 7 million screening tests in women 50–69 years of age. For all programs combined, low-grade DCIS were 20.1% (range 11.4–31.8%) of graded DCIS, intermediate grade 31.0% and high grade 48.9%. Detection rates decreased more steeply from initial to subsequent screening in low compared to high-grade DCIS: the ratios of subsequent to initial detection rates were 0.39 for low grade, 0.51 for intermediate grade, and 0.75 for high grade ($p < 0.001$).

Conclusions These results suggest that the duration of the preclinical detectable phase is longer for low than for high-grade DCIS. The findings from this large multi-centre, international study emphasize that the management of low-grade DCIS should be carefully scrutinized in order to minimize overtreatment of screen-detected slow-growing or indolent lesions. The high variation by site in the proportion of low grade suggests that further pathology standardization and training would be beneficial.

Keywords Breast cancer screening · Ductal carcinoma in situ · Low-grade DCIS · Overtreatment

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Background

It is recognized that the detection of ductal carcinoma in situ (DCIS) contributes to breast cancer screening efficacy [1] as well as to overdiagnosis [2, 3] and overtreatment [4, 5]. The heterogeneity of this disease is a major focus of investigation [6], and nuclear grade has been identified as an important indicator of biological behaviour [7, 8]. De-escalation of treatment and of nomenclature have been suggested for low-grade DCIS [9, 10].

The detection rate of DCIS is a proportion defined as the number of screen-detected cases divided by the number of screening tests. It depends on the prevalence of DCIS, which reflects the occurrence of newly detectable lesions and the duration of their preclinical phase [11]. In the presence of a short interval between screens (1–2 years), the relative prevalence of slow versus rapidly growing lesions is larger at the initial (I) than at subsequent (S) screens [12]. Therefore, a lower ratio of detection rates at subsequent to initial screening (S/I) is expected in slow than in rapidly growing lesions. The aim of this paper is to contribute to the understanding of the natural history of DCIS by analysing S/I ratios by nuclear grade.

Methods

This study was conducted within the International Cancer Screening Network (ICSN) (https://healthcaredelivery.cancer.gov/icsn), an activity funded by the US National Cancer Institute (NCI) at the National Institutes of Health. Methods have been reported in detail previously [13, 14]. In brief, we sought data from the 33 ICSN member countries regarding pure DCIS screen-detected between 2004 and 2008. We asked sites to complete, based on their screening and clinical databases, an aggregated data file on DCIS detection, diagnosis, and treatment. Nuclear grade [15] was available from most centres, being used directly or as a component of the Van Nuys Prognostic Index [16]. All data were stratified by calendar year, age at screening in decades, and by initial and subsequent screening tests.

The analysis was restricted to the age span 50–69. S/I ratios were computed in the subgroup of 50–59-year-old women, as virtually no initial tests were performed at later ages. They were compared by the Chi square test of the corresponding odds ratio (i.e. the odds of detecting low-grade DCIS among all DCIS in initial tests divided by the odds of detecting low-grade DCIS among all DCIS in subsequent tests, and so on). The number of screening tests in the denominator of the detection rates is the same for all grades so the entire information is in the cases.

All tests of statistical significance were two-sided and $p = 0.05$ was adopted as cut-off. Pearson's r was used for testing the correlation between detection rates. The direct standardization method was used for adjusting the proportions of low-grade DCIS by the frequency of initial and subsequent screening in the different countries.

Results

Twelve countries (10 from Europe plus the United States of America and Japan) contributed data from 15 screening programs. All programs adopted mammography as the screening test with two-year intervals, except for the United States where the screening interval was 1–2 years. Screening mammography was in some cases complemented with clinical breast examination in United States and in Japan. A total of 5324 screen-detected pure DCIS and 29679 invasive breast cancers were reported in women 50–69 years of age [13]. DCIS grade was reported with varying completeness by 11 programs for 5068 cases detected in nearly 7 million screening tests (Table 1). Attendance rates, reported in a previous paper [12], ranged from 48% in Switzerland to 87% in Spain (Navarra).

For all eleven screening programs combined, low-grade DCIS were 20.1% of graded DCIS (range 11.4–31.8%), intermediate grade 31.0% (range 11.0–45.6%), and high grade 48.9% (range 22.6–65.3%). The most frequently reported grade was "high" in all programs except Czech Republic, Italy, and Switzerland (where the most frequently reported grade was "intermediate"). After adjustment for initial versus subsequent screening the average proportion of low grade was 21.4% (range 15.5–26.9%) in the nine programs reporting this information (Fig. 1).

Of DCIS detected in women aged 50–59 20.5% were low grade and 49.4% were high grade, while for women 60–69 the corresponding proportions were 19.6% and 48.2% ($p = 0.77$).

The total DCIS detection rate was statistically significantly correlated with the high-grade detection rate (Pearson $r = 0.88$, $p < 0.001$) but not with the low-grade detection rate (Pearson $r = 0.22$, $p = 0.52$).

In nine programs providing the relevant information (from Czech Republic and Italy data on initial versus subsequent screening were not available), among women aged 50–59 years the DCIS detection rate per 1000 tests dropped from 1.0 at the initial to 0.64 at subsequent screens, resulting in a S/I ratio of 0.64 (Table 2). For invasive breast cancer, the equivalent ratio was 0.75 ($p = 0.002$ compared to DCIS) [13]. The S/I ratios indicated a larger decrease of detection rates for low than for high-grade DCIS, being 0.39 for low grade, 0.51 for intermediate grade ($p = 0.09$ compared to low grade), and 0.75 for high grade ($p < 0.001$ compared to low

Table 1 Number of screening tests and of screen detected DCIS and proportion of DCIS by nuclear grade reported by eleven breast cancer screening programs (age 50–69)

Screening programs and data collection years	No. screening tests[a]	No. SD DCIS[a]	No. DCIS by availability of grade		% DCIS by grade (known grade only)		
			Unknown grade (%)	Known grade	Low	Interm.	High
Czech Republic 2007/8	699726	359	54 (15.0%)	**305**	31.8	45.6	22.6
Finland 2004/7	862908	361	136 (37.7%)	**225**	19.6	37.3	43.1
Ireland 2004/8	331854	393	2 (0.0%)	**391**	13.2	33.3	53.4
Italy, five regions 2006/8	1453292	1066	112 (10.5%)	**954**	27.4	40.0	32.6
Netherlands 2007[b]	718202	576	129 (22.4%)	**447**	15.7	31.1	53.2
Norway 2004/8	963424	899	11 (1.2%)	**888**	20.2	14.5	65.3
Spain Barcelona 2004/8	184748	90	8 (0.9%)	**82**	15.9	11.0	73.2
Spain Navarra 2004/8	131948	95	2 (2.1%)	**93**	16.1	31.2	52.7
Spain Valencia 2004/8	739829	422	67 (15.9%)	**355**	20.6	31.0	48.5
Switzerland 2004/8	176318	190	95 (50.0%)	**95**	14.7	43.2	42.1
USA 2004/7	616892	617	75 (12.2%)	**542**	11.4	32.6	56.0
Total	**6899141**	**5068**	**691 (13.6%)**	**4377**	**20.1%**	**31.0%**	**48.9%**

Totals are in bold

SD Screen detected, *DR* Detection rate, *DCIS* Ductal carcinoma in situ

[a]Lynge et al. [13]

[b]Dutch data for 2007–2009 have been published in van Luijt et al. [3]

grade and $p = 0.002$ compared to intermediate grade). Grade was missing in 16.6% of DCIS (Table 2).

Discussion

Our results suggest that the duration of the preclinical detectable phase is longer for low-grade DCIS than for invasive cancers and high-grade DCIS.

A recent analysis on 1970 cases conducted within the German national screening program [17] found a pattern similar to ours, with S/I ratios ranging from 0.51 for low-grade DCIS to 0.81 for intermediate grade ($p = 0.002$ compared to low grade) and to 0.96 for high grade ($p < 0.001$ compared to low grade and $p = 0.04$ compared to intermediate grade).

In our series the total DCIS detection rate was statistically significantly correlated with high-grade detection rate but not with low-grade detection rate, as also found in the German program [18]. However, while they reported [19] that high-grade DCIS are detected more frequently in older women, we did not find any difference by age.

We were not able to discriminate between subsequent screening tests at regular (1 or 2 years) or longer intervals.

The high proportion of missing grade reported by two of the eleven programs may affect the comparisons of the distribution of grades between countries, although it seems reasonable to assume that grades were missing at random, but not our main results that are based on the pool of all cases. Another potential source of selection bias is the variability of attendance rates. Generalizability of our results, finally, is limited by the narrow age range studied (50-59) and by the fact that we have included in the analysis screen-detected cases only.

According to the findings of this large multi-centre, international study low-grade DCIS progresses more slowly than high-grade lesions. This adds evidence to the fact that the management of low-grade DCIS should be carefully scrutinized in order to minimize overtreatment of screen-detected slow-growing or indolent lesions [9, 20, 21]. The high variation in the distribution of nuclear grade by site suggests

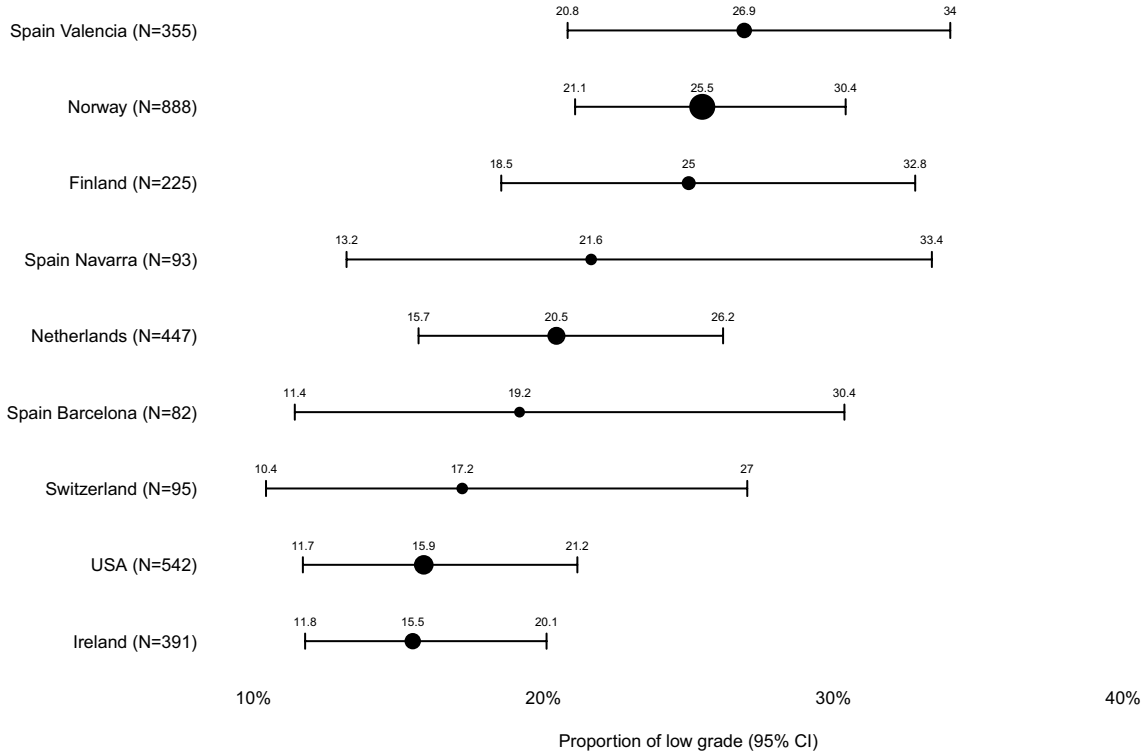

Fig. 1 Adjusted proportions (by initial vs. subsequent screening) of low-grade DCIS by screening program, with 95% confidence intervals

Table 2 DCIS detection rates per 1000 screening tests by nuclear grade and by initial and subsequent screening (age 50–59)

Screening tests	All	Initial	Subsequent	S/I DR ratio
No. tests	2970706	539599	2431107	
No. DCIS	2095	540	1555	
DR all DCIS (×1000)	0.71	**1.00**	**0.64**	**0.64**
No. DCIS with unknown grade (% of all cases)	348 (16.6%)	66 (12.2%)	282 (18.1%)	
No. low-grade DCIS	299	108	191	
DR low-grade DCIS (×1000)	0.10	**0.20**	**0.08**	**0.39**
No. intermediate-grade DCIS	472	143	329	
DR intermediate-grade DCIS (×1000)	0.16	**0.27**	**0.14**	**0.51**
No. high-grade DCIS	976	223	753	
DR high-grade DCIS (×1000)	0.33	**0.41**	**0.31**	**0.75**

Main figures are in bold

Czech Republic and Italy were excluded because they did not provide data stratified by initial versus subsequent screening. DCIS with missing grade have been excluded in the calculation of detection rates by grade

DR Detection rate, *DCIS* Ductal carcinoma in situ, *S/I* Subsequent to initial screening

that further pathology standardization and training would be beneficial at international as well as national [22] levels.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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