Maturitas 158 (2022) 55–60

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Tumour characteristics of screen-detected and interval cancers in the Flemish Breast Cancer Screening Programme: A mammographic breast density study

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ARTICLE INFO

Keywords:
Breast cancer
Screening mammography
Interval cancer
Tumour characteristics
Breast density

ABSTRACT

Objective: The objective is to investigate tumour prognostic factors versus breast density in screen-detected cancers and interval cancers. The results may highlight the need for more personalised screening protocols based on breast density in organized screening programmes.

Study design: A retrospective study was performed of tumour characteristics of screen-detected cancers (n=468) and interval cancers (n=515) of 983 women who participated in the Flemish Breast Cancer Screening Programme in 2009-2010. Breast density was obtained from the screening programme data. Information on nodal invasion and histological grading was taken from the Belgian Cancer Registry. Tumour size and proliferation and receptor expression status were retrieved from pathology reports. The differences in tumour characteristics between screen-detected and interval cancers as well as the variation in these variables with breast density in both groups were studied by logistic regression.

Results: A comparison of tumour characteristics between screen-detected cancers and interval cancers systematically showed features of more aggressive tumours in interval cancers: larger tumour size, nodal invasion, grade 3 tumours, and hormone receptor negative phenotype ($p<0.05$). The analysis of tumour characteristics versus breast density in screen-detected cancers showed higher numbers of aggressive grade 3 tumours in low-density breasts and of the luminal A subtype with good prognosis in high-density breasts ($p<0.05$). This analysis for interval cancers highlights a high proportion of the difficult-to-treat triple-negative subtype in low-density breasts compared with high-density breasts. In conclusion, the study data support arguments against changes in breast cancer screening programmes with prolongation of screening intervals in low-density breasts.

1. Introduction

Registry data show that Belgium has the highest breast cancer incidence rate in Europe [1]. A screening programme was started in Flanders in 2001, which offers all women between the ages of 50 and 69 years, a completely reimbursed two-view mammogram every two years. In menopausal women with a low risk of breast cancer (low density breasts (BI-RADS I)), an increase in screening interval could be an acceptable strategy to, both reduce the burden of screening and its cost to society [2].

Some participants are diagnosed with breast cancer in the two-year interval after a negative screening result but before the next planned screening mammography. These are called interval cancers (IC). As defined in European guidelines, IC include 'true' IC or occult cases, 'missed' cancers or false negatives, and cancers representing only minimal signs [3].

Breast cancer is a heterogeneous disease with a large variety of clinical, pathological and molecular features. Although gene-profiling models to predict outcomes are available, conventional tumour characteristics, such as expression of oestrogen receptor (ER), progesterone

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https://doi.org/10.1016/j.maturitas.2021.12.006
Received 5 April 2021; Received in revised form 29 July 2021; Accepted 12 December 2021
Available online 17 December 2021

receptor (PR) and human epidermal growth factor receptor 2 (HER2) status are routinely investigated in breast cancer biopsies and/or resection pieces for therapeutic decision-making [4]. Based on hormone/HER2 receptors and tumour proliferation markers, breast cancers are categorised in molecular subtypes which have a strong prognostic value [5].

Most breast cancers detected in screening exhibit favourable tumour characteristics, such as small tumour size, negative nodal invasion and oestrogen/progesterone positivity [6,7]. On the other hand, IC tend to be more aggressive than screen-detected cancers (SDC) [8] and are more likely to have less favourable molecular features [9,10]. Some studies even report a higher proportion of triple-negative (TN) cancers among IC [9,11]. These tumours are associated with an aggressive behaviour pattern and less favourable prognosis.

Mammographic breast density (BD) reflects the proportion radiodense, fibroglandular tissue in the mammogram which is scored and categorised in BI-RADS breast density classes [12]. Women with a high breast density are considered to have a four to six times enhanced risk for breast cancer compared to women with completely fatty breasts [13]. High-density breasts are also associated with a decreased sensitivity of cancer detection in screening programmes [14,15]. Consequently, women with dense breasts are more likely to be diagnosed with an interval cancer [15–17] but the role of breast density has not yet been completely elucidated [16]. A masking effect related to hiding tumours by fibroglandular tissue as well as a biological effect related to tumour growth has been proposed [17,18]. Previous research showed a strong increase of IC rate with breast density [19].

Because breast density influences both risk and detection of breast cancer as well as the likelihood of developing certain pathological subtypes [20], studying tumour characteristics in breast density classes of SDC and IC is of great interest. A Swedish study investigated risk factors and tumour characteristics of interval cancers by mammographic density [21]. They concluded that when comparing tumour characteristics in women in the lowest- and highest quartiles of percent mammographic density, IC in women with low mammographic density have a more aggressive phenotype: more lymph node involvement, ER and PR receptor negative, HER2 positive and more triple negative (TN).

The aim of the present study is to compare tumour characteristics and molecular subtypes of IC versus SDC and its implementation.

2. Materials and methods

2.1. Study set-up

This study is a retrospective analysis of characteristics of SDC and IC based on a combination of the dataset from the Centre for Cancer Detection, who organises the Flemish Breast Cancer Screening Programme, and information available at the Belgian Cancer Registry (BCR).

In this screening programme, organized by the state, all eligible women are invited for a screening mammography, except women with bilateral mastectomy or women diagnosed with breast cancer in the past ten years as well as women with a mammographic examination in the past two years. Images are interpreted by two independent radiologists qualified for mammography evaluation. Both perform an independent reading, completely blind from each other. All screening data associated with each participating woman are collected into the centralised database 'Heracles'.

BCR is a national population-based cancer registry collecting tumour characteristics of all new cancer diagnoses. These data are provided by oncological care programmes and laboratories for anatomical pathology as stated in the specific cancer registration law. BCR maps out the nature and extent of cancer in Belgium, supports and evaluates Belgian cancer screening programmes and collaborates in different research projects.

The combination of Heracles with the structured BCR database allows to complete screening data with information on SDC and IC. Linkage on a regular basis of these databases was authorised by the Sector Committee of Social Security and Health within the framework of the Flemish Breast Cancer Screening Programme and allows SDC and IC to be identified and characterised. The study was approved by the Ethical Review Board of the screening programme. Participants are aware that their personal data are protected, collected and processed in the framework of quality assurance of the programme and coded when processed for statistical and scientific purposes, this by signature of an informed consent.

2.2. Breast density

Breast density is scored for each patient by all radiologists involved according to the four-category BI-RADS system developed by the American College of Radiology: BI-RADS I category comprises breasts with less than 25% glandular tissue, BI-RADS II 25-50%, BI-RADS III 51-75% and BI-RADS IV refers to a class with extremely dense breasts with more than 75% glandular tissue [12]. The currently used 5th edition BI-RADS classification was not applied as the present study handles data from 2009 to 2010 when the previous BI-RADS classification version was applied.

Former research showed an intra-class correlation of 0.82 between breast density estimations of second readers and quantitative volumetric density measurements applying dedicated software (Volpara®Solutions^{TM}) [19].

2.3. Population

Women who participated in the screening programme from January 2009 to December 2010 and who were diagnosed with an invasive breast cancer through screening in the period up to 24 months post negative screening were included. The two-year period corresponds to one screening round so every woman is only present once in the study. All three imaging modalities, SF (screen-film, 41%), CR (computed radiography, 21%) and DR (digital radiography, 38%), were still adequately used in the programme.

The study was set up this way that the number of women in four breast density classes was roughly the same to study the effect of breast density on different tumour characteristics. All women in the extreme BI-RADS I and IV categories, representing only 20% of cancer cases, were included. For BI-RADS category II and III, a similar number of cancer cases as for density IV category was selected at random (Table 1). Applying this procedure for SDC and IC resulted in a total population of 983 invasive breast cancer patients. Ductal carcinoma in situ cases were not considered. Out of 515 IC, 184 (36%) patients were diagnosed in the first year (mean= 7,07 months for all density classes) after the last screening and 328 (64%) in the second year (mean= 17,91 months for all density classes). Investigation of this time-interval showed for no differences in time interval after screening between the different breast densities.

Table 1.
The number of patients in the different breast density categories with a screen-detected or an interval cancer included in present study.

	Screen-Detected Cancers (SDC)	Interval Cancers (IC)
BI-RADS I	107	33
BI-RADS II	120	162
BI-RADS III	120	163
BI-RADS IV	121	157
TOTAL	**468**	**515**

Footnotes: BI-RADS I entirely fatty, BI-RADS II scattered areas of fibroglandular density, BI-RADS III heterogeneously dense, BI-RADS IV extremely dense
Not all BI-RADS II and III patients were included in the study so the distribution over de BI-RADS classes is not the real patient distribution

2.4. Tumour characteristics

In the combined database, mammography date, imaging modality and breast density originated from Heracles. Information on patient age, nodal invasion, histological grading and incidence date were deduced directly from the BCR database as these variables are stored systematically in this database. Information of tumour size, expression of ER, PR, HER2 as well as Ki67 positivity, was retrieved from pathology reports of a tumour biopsy and/or resection specimen added per patient to the standardised BCR database. When findings from biopsy and resection did not match, (in 0.9%, 3.4% and 2.6% of patients for respectively ER-, PR- and HER2-receptor status), they were not included in the analysis. According to St. Gallen International Expert Consensus recommendation 2011 [22], five molecular subtypes of invasive breast cancer can be differentiated by expression of their tumour markers: Luminal A-Like (LumA), Luminal B-/HER2-positive-like (LumB/HER2+), Luminal B-/HER2-negative-like (LumB/HER2-), HER2-type (HER2), Triple Negative (TN). As information on Ki67 positivity was only available for 41.8% of patients, histological grade (available in 99.6% of patients) was used to differentiate between LumA and LumB/HER2- molecular subtypes following Brouckaert et al [23].

2.5. Statistical analysis

Statistical calculations were performed using SPSS Statistics25 (IBMcorp, USA). For analysing the risk of having a large tumour, nodal invasion, ER-/PR-negative cells, HER2 positivity, grade 3 tumours and TN tumours, briefly all binary endpoints between SDC and IC, a binomial logistic regression was used. This analysis was adjusted for breast density (BI-RADS I-IV), screening modality (SF vs CR vs DR) and patient age.

For each group separately (SDC vs IC) a multinomial logistic regression was applied with tumour characteristics (tumour size, nodal invasion, ER negativity,…) as outcome variable and breast density as a categorical predictor, adjusted for patient age and image modality (SF vs CR vs DR).

In order to test significance, a p value of .05 was adopted. For differences in tumour size, a Mann-Whitney U test was applied.

3. Results

3.1. Comparison of tumour characteristics between SDC and IC

Data show that the odds ratio of having a tumour larger than 20 mm is three times larger comparing IC to SDC. The average tumour size in SDC is 16 mm (SD ±10 mm) which is also significantly smaller than the average tumour size of IC which is 23 mm (SD ±15 mm). It is also significantly more likely to have nodal invasion, a grade 3 tumour or ER-/PR-negative phenotype, which are all characteristics of more aggressive tumours, in IC than in SDC. The probability of having a Luminal A cancer is half as likely in IC than in SDC. On the other hand, the odds ratio of having a TN tumour in IC compared to SDC is 2.5 (Table 2).

Luminal A cancers occur significantly more in SDC in comparison with IC based on the 95% odds ratio range. On the contrary, TN cancers are significantly more represented in IC. The same effect is visible for LumB/HER2- which are also more represented in IC with odds ratio 1.72 (95% CI 1.18-2.51). For LumB/HER2+ and HER2+ groups, differences between SDC and IC are not significant.

3.2. Effect of density on tumour characteristics in SDC and IC

The effect of density on different tumour characteristics was analysed for SDC and IC separately (Table 3). A multinomial logistic regression model with density I as reference, adjusting for age and imaging modality, was applied.

Table 2.
Comparison of tumour characteristics of screening detected cancers (SDC) and interval cancers (IC).

tumour characteristics	SDC n = 468	IC n = 515	Odds RATIO (95% CI)
TUMOUR SIZE (>20MM)	(102/447) 22.8% ± 2.0%	(220/469) 46.9% ± 2.3%	3.05 (2.24-4.16)*
NODAL INVASION	(114/442) 25.8% ± 2.1%	(184/472) 39.0% ± 2.2%	1.76 (1.30-2.40)*
OESTROGEN RECEPTOR-NEGATIVE	(50/414) 12.1% ± 1.6%	(78/468) 16.7% ± 1.7%	1.72 (1.12-2.65)*
PROGESTERONE RECEPTOR-NEGATIVE	(80/401) 20.0% ± 2.0%	(115/455) 25.3% ± 2.0%	1.50 (1.05-2.16)*
HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)-POSITIVE	(48/390) 12.3% ± 1.7%	(68/453) 15.0% ± 1.7%	1.36 (0.87-2.12)
GRADE 3	(123/443) 27.8% ± 2.1%	(210/477) 44.0% ± 2.3%	2.51 (1.85-3.41)*
LUMINAL A	(240/373) 64.3% ± 2.5%	(213/419) 50.8% ± 2.4%	0.48 (0.35-0.65)*
TRIPLE NEGATIVE (TN)	(22/373) 5.9% ± 1.2%	(49/419) 11.7% ± 1.6%	2.58 (1.44-4.61)*

Data are presented as fractions of SDC and IC populations showing the tumour characteristic with missing values not included. The percentages are given with standard error of proportions as uncertainties. The odds-ratios for IC with SDC as reference for the different tumour characteristics are also given with a 95% confidence interval. Tumour characteristics with a statistical significant difference between SDC and IC at 95% confidence level are indicated with an * symbol. Odds-ratios were calculated with a binary logistic regression model adjusted for age, breast density and imaging modality.

Breast cancers with large tumour size (>20 mm) and nodal invasion were more frequently found in higher-density breasts compared to low density I reference group, and this for SDC as well as IC. However, resulting odds ratios were not significant. On the contrary, ER- and PR-negative phenotypes were represented less in higher-density categories for both SDC and IC. However, this difference was also not significant. Aggressive grade 3 tumours were also more observed in the lowest breast density I group reaching statistical significance with the highest breast density IV group in SDC. For HER2+ breast cancers, no significant differences were found between high- and low-density breasts. Tumour characteristics versus breast density of incidence screening obtained by exclusion of the first round participants in the dataset showed the same tendencies.

In SDC, the presence of LumA subtype increases with breast density class, with an odds-ratio of 2 when comparing BIRADS IV with I resulting in a statistically significance. For LumB/HER2- subtype, this significant trend is reversed. For IC, trends in LumA and LumB/HER2- breast density data are less clear, but LumB/HER2- subtype suggests an increase with breast density class. For LumB/HER2+ and HER2+ subtypes, no systematic variation with breast density is observed for SDC or IC.

A study of molecular subtypes as a function of breast density in SDC and IC showed a higher proportion of TN tumours for low-breast-density class I compared to higher-density classes. For IC the odds ratio of a TN subtype was 0.27 (0.08-0.91) in BI-RADS IV compared to I resulting in statistical significance at the 95% confidence level.

Adjustments for imaging modality was made in these logistic regression models. However, no significant difference with respect to image modality was observed.

Table 3.
Tumour characteristics as a function of breast density (BI-RADS) in screening detected cancers (SDC) and interval cancers (IC).

tumour characteristics		SDC n = 468	ODDS RATIO (95% CI)	IC n = 515	ODDS RATIO (95% CI)
TUMOUR SIZE (>20MM)	**BI-RADS I**	(20/103) 19.4% ± 3.9%		(13/30) 43.3% ± 9.0%	
	BI-RADS II	(27/112) 24.1% ± 4.0%	1.35 (0.68-2.70)	(66/145) 45.5% ± 4.1%	1.12 (0.48-2.60)
	BI-RADS III	(26/118) 22.0% ± 3.8%	1.29 (0.64-2.58)	(63/147) 42.9% ± 4.1%	1.10 (0.47-2.55)
	BI-RADS IV	(29/114) 25.4% ± 4.1%	1.65 (0.81-3.38)	(78/147) 53.1% ± 4.1%	1.70 (0.73-3.96)
NODAL INVASION	**BI-RADS I**	(22/103) 21.4% ± 4.0%		(8/28) 28.6% ± 8.5%	
	BI-RADS II	(28/111) 25.2% ± 4.1%	0.98 (0.50-1.92)	(58/147) 39.5% ± 4.0%	2.17 (0.81-5.80)
	BI-RADS III	(29/115) 25.2% ± 4.0%	1.06 (0.55-2.04)	(61/148) 41.2% ± 4.0%	2.32 (0.87-6.20)
	BI-RADS IV	(35/113) 31.0% ± 4.3%	1.46 (0.75-2.84)	(57/149) 38.3% ± 4.0%	2.03 (0.76-5.44)
OESTROGEN RECEPTOR-NEGATIVE	**BI-RADS I**	(16/97) 16.5% ± 3.8%		(8/31) 25.8% ± 7.9%	
	BI-RADS II	(13/103) 12.6% ± 3.3%	0.62 (0.25-1.54)	(22/146) 15.1% ± 3.0%	0.63 (0.22-1.79)
	BI-RADS III	(12/105) 11.4% ± 3.1%	0.60 (0.24-1.48)	(28/142) 19.7% ± 3.3%	0.80 (0.29-2.24)
	BI-RADS IV	(9/109) 8.3% ± 2.6%	0.38 (0.14-1.02)	(20/149) 13.4% ± 2.8%	0.46 (0.16-1.34)
PROGESTERONE RECEPTOR-NEGATIVE	**BI-RADS I**	(25/98) 25.5% ± 4.4%		(9/30) 30.0% ±8.4%	
	BI-RADS II	(17/98) 17.3% ± 3.8%	0.61 (0.29-1.32)	(34/145) 23.4% ± 3.5%	0.94 (0.36-2.49)
	BI-RADS III	(18/99) 18.2% ± 3.9%	0.74 (0.35-1.56)	(41/136) 30.1% ± 3.9%	1.37 (0.52-3.60)
	BI-RADS IV	(20/106) 18.9% ± 3.8%	0.70 (0.33-1.48)	(31/144) 21.5% ± 3.4%	0.78 (0.29-2.07)
HER2- POSITIVE	**BI-RADS I**	(10/95) 10.5% ± 3.1%		(6/30) 20.0% ± 7.3%	
	BI-RADS II	(11/94) 11.7% ± 3.3%	0.96 (0.34-2.73)	(16/141) 11.3% ± 2.7%	0.50 (0.16-1.56)
	BI-RADS III	(13/98) 13.3% ± 3.4%	1.23 (0.46-3.30)	(28/138) 20.3% ± 3.4%	0.88 (0.30-2.62)
	BI-RADS IV	(14/103) 13.6% ± 3.4%	1.22 (0.45-3.32)	(18/144) 12.5% ± 2.8%	0.52 (0.17-1.61)
GRADE 3	**BI-RADS I**	(37/99) 37.4% ± 4.9%		(17/30) 56.7% ± 9.0%	
	BI-RADS II	(30/115) 26.1% ± 4.1%	0.56 (0.30-1.06)	(64/154) 41.6% ± 4.0%	0.48 (0.20-1.11)
	BI-RADS III	(34/116) 29.3% ± 4.2%	0.70 (0.38-1.30)	(66/146) 45.2% ± 4.1%	0.56 (0.24-1.31)
	BI-RADS IV	(22/113) 19.5% ± 3.7%	0.41 (0.20-0.80)*	(63/147) 42.9% ± 4.1%	0.52 (0.22-1.21)
LUMINAL A	**BI-RADS I**	(50/89) 56.2% ± 5.3%		(11/27) 40.7% ± 9.5%	
	BI-RADS II	(61/91) 67.0% ± 4.9%	1.68 (0.87-3.26)	(77/136) 56.6% ± 4.2%	1.65 (0.68-3.99)
	BI-RADS III	(58/96) 60.4% ± 5.0%	1.23 (0.65-2.32)	(51/123) 41.5% ± 4.4%	0.95 (0.39-2.33)
	BI-RADS IV	(71/97) 73.2% ± 4.5%	2.34 (1.17-4.71)*	(74/133) 55.6% ± 4.3%	1.58 (0.66-3.82)
TRIPLE NEGATIVE	**BI-RADS I**	(8/89) 9.0% ± 3.0%		(7/27) 25.9% ± 8.4%	
	BI-RADS II	(6/91) 6.6% ± 2.6%	0.59 (0.18-1.94)	(14/136) 10.3% ± 2.6%	0.418 (0.13-1.34)
	BI-RADS III	(4/96) 4.2% ± 2.0%	0.45 (0.12-1.62)	(16/123) 13.0% ± 3.0%	0.38 (0.12-1.21)
	BI-RADS IV	(4/97) 4.1% ± 2.0%	0.42 (0.11-1.59)	(12/133) 9.0% ± 2.5%	0.27 (0.08-0.91)*

Data are presented as fractions of the populations with corresponding BI-RADS breast density with missing values not included. The percentages are given with standard error of proportions as uncertainties. Odds ratio within each breast density class with breast density class I as reference is also given with a 95% confidence interval. Tumour characteristics with a statistical significant difference between the considered BI-RADS class and the reference class I at the 95% confidence level are indicated with an * symbol. The first and second columns with data refer to screening detected cancers . The data for interval cancers are presented in the third and fourth columns of the table. For the calculation of the odds-ratios a multinomial logistic model is used, adjusted for age and imaging modality.

4. Discussion

In screening, IC are a representative for the sensitivity of the programme. In the Flemish Breast Cancer Screening Programme, 67% of breast cancers are SDC and 33% are IC [19]. Furthermore, interval cancer rate increases gradually with breast density from 1.11 ‰ for BI-RADS I to 5.36‰ for BI-RADS IV. The link between interval cancer

rate and breast density may be related to masking effect and/or differences in tumour characteristics [18]. To elucidate this, tumour characteristics and biomarker profile of SDC and IC were studied as functions of breast density.

Our data show that IC have worse tumour prognostic features than SDC. IC have a less favourable biomarker profile with a lower frequency of hormone receptor positive cancers and a higher frequency of TN cancers. The frequency of HER2-positive tumours is also higher in IC. These findings are consistent with other breast cancer screening programmes [8,13,14,24]. IC have a significantly lower percentage of LumA tumours and a significantly higher percentage of TN tumours [11, 25]. As LumA tumours have the best five-year survival (e.g. 92% [5]) and TN the worst (e.g. 69% [5]), we may expect that biomarker differences will also result in worse tumour survival in IC. This is confirmed in studies of Eriksson et al [26] and Domingo et al [25] who reported a significantly higher five-year cancer-specific survival of SDC versus IC. Based on differences in biomarker profiles and these survival data, IC contain a subgroup of breast cancers with rapid growth and high aggressiveness [22]. This conclusion holds also to symptom-detected cancers outside screening programmes [27].

Analysis of tumour characteristics versus breast density shows a larger tumour size for BI-RADS IV breasts compared to BI-RADS I breasts for both SDC and IC but the difference is not statistically significant. This larger tumour size can be attributed to a masking effect as it is well documented that high breast density is associated with a larger contribution of occult IC [28] so the increase of the masking effect will involve a delay in diagnosis. Eriksson et al [26] observed a similar trend in tumour size with breast density as in present work but the breast density was divided in non-dense (<25%) and dense (≥25%) classes. The trend of lymph node involvement increasing with breast density can be explained in the same way by delay of diagnosis. On the other hand, grade, hormone receptor status and other histo-pathological tumour characteristics indicate a worse prognosis in low-density breasts for both IC and SDC. A similar conclusion of a more aggressive phenotype in IC for low-density breasts based on receptor status and grade was drawn by Holm et al [21].

Analysis of molecular subtype distributions versus breast density revealed a higher percentage of TN phenotype in BI-RADS I breasts as well in SDC as IC. However, this effect is only significant in IC. In IC, TN tumours amount to over 25% in low-density breasts which differs significantly from 9% in high-density breasts. A similar dependence of TN phenotype on breast density can be found in Spanish screening data [25]. They report TN percentages of 11.7% and 5.7% for <25%- and >75%-density classes in SDC and 28.7% and 14.3% in true IC. Also, data of Holm et al support the prevalence of TN phenotype in non-dense breasts in IC [21]. For patients with TN tumours are often associated with a high grade, with a high proliferation rate. An effective and specific anti-hormonal therapy is lacking. TN tumours have a poorer survival [5].

Strengths of the present study are the completeness of information, resulting from a combination of screening data with clinical-pathological information and statistical analysis of tumour characteristics with breast density. This study also has limitations. First, no radiological review of IC was made with subdivision in true, minimal signs and missed tumours. A second limitation is that Ki67-positivity information was only available in 42% of cancer cases. Therefore, histological grade was used for molecular subtype assessment. Third, some important variables associated with breast density, such as body mass index, age at menarche and childbirth are not collected in screening programmes and could not be included in the statistical analysis. Fourth there is a possibility that the low grade tumours were picked up during the previous screening, in the low density breast group even though they were small at that time. Small low grade cancers may still have been undetected in the previous screening mammography in high density breasts. This may account for the higher number of lumA cancers in the latter group. This could also account for the relative higher number of aggressive TN in the BI-RADS I group. The main conclusion should be that relative number of TN cancers is not lower in low density breasts. There is no difference in tumour characteristics whether they are detected in low or high density breasts. This observation pleads against prolongation of screening intervals (i.e. three year screening interval) in low-density breasts. As present study deals only with patients participating in organized screening information regarding opportunistic screening cannot be deduced from the collected data. A last limitation is that the use of HRT was not recorded in our data base. Less than 10 percent of women in Flanders use of HRT. In Flanders HRT is mainly prescribed to alleviate vasomotor symptoms. In this respect the use of HRT may have been equally distributed between different density categories.

The observed differences in tumour characteristics between density BI-RADS categories were substantial and clinically relevant, but did not yield statistical significance because of limited statistical power. We recommend future studies to include a larger sample size to examine differences in tumour characteristics between density BI-RADS categories. This may require easy access to and merging of different clinical databases including a density measurement software.

Our study supports changes in breast cancer screening to more individualised protocols. Improved rate of lesion detection in dense breasts [29] to the same level as for low-breast-density categories could reduce IC and improve prognosis. This involves stratification of women into different breast screening strategies as part of a more personalised breast screening programme as in the MyPeBS project funded by the Horizon 2020 programme of the European Commission [30]. In the clinical trial protocol of this project, breast ultrasound and automated breast ultrasound are additional screening techniques for women in the high-density breast group.

5. Conclusions

Present research confirms a significant difference of tumour characteristics in SDC and IC. Although IC express more characteristics that have properties of aggressive tumours, IC in high-density breasts are less likely to be of the TN tumour subtype compared to low-density breasts. This supports changes in screening protocols to improve sensitivity of the screening programme in order to increase survival of breast cancer patients in the high-density breast group. It also pleads against prolongation of screening intervals in low-density breasts, since the tumours are equally aggressive in this BI-RADS I group.

Contributors

Lore Timmermans collected screening data and linked it with histology, and contributed to the writing and revision of the paper.

Isabel De Brabander collected screening data and linked it with histology.

Nancy Van Damme was responsible for mammographic screening.

Luc Bleyen was responsible for mammographic screening.

Patrick Martens was responsible for mammographic screening.

Koen Van Herck was responsible for mammographic screening.

Hubert Thierens designed and supervised the study, and contributed to the writing and revision of the paper.

Klaus Bacher designed and supervised the study, and contributed to the writing and revision of the paper.

Herman Depypere designed and supervised the study, and contributed to the writing and revision of the paper.

All authors read and approved the final version of the article.

Funding

No external funding was received for this study.

Ethical approval

The combination of Heracles with the structured BCR database allows complete screening data with information on SDC and IC. Linkage on a regular basis of these databases was authorised by the Sector Committee of Social Security and Health within the framework of the Flemish Breast Cancer Screening Programme and allows SDC and IC to be identified and characterised. Participants are aware that their personal data are protected, collected and processed in the framework of quality assurance of the programme and coded when processed for statistical and scientific purposes, this by written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We wish to thank all members of the research working group and the general working group of the Breast Cancer Screening of the Flemish Government for their contribution. Special thanks go to the colleagues of the physical-technical quality assurance of LUCMFR, VUB and Controlatom. Finally, we wish to thank the Centre for Cancer Detection and BCR.

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