Breast Cancer Research and Treatment (2019) 174:525–535
https://doi.org/10.1007/s10549-018-05095-7

EPIDEMIOLOGY

The mammography screening detection of ductal carcinoma in situ and invasive breast cancer according to women's characteristics: is it the same?

Isabelle Théberge[1,2] · Nathalie Vandal[1] · Marie-Hélène Guertin[1] · Linda Perron[1,2,3]

Received: 16 October 2018 / Accepted: 8 December 2018 / Published online: 18 December 2018

Abstract

Purpose Detection of ductal carcinoma in situ (DCIS) has increased with the mammography dissemination. Given the potential role of DCIS as a precursor of invasive breast cancer (IBC), we aimed to assess whether women's characteristics have a different effect on the DCIS compared to IBC detection rate.

Methods This study included 3,609,569 screening mammograms performed from 2002 to 2015 in our organized breast cancer screening program, which actively invites women 50–69 years of age. The association between women's characteristics and the DCIS detection rate, the IBC detection rate and the odds ratio of DCIS among screen-detected cancers was assessed by logistic regression and generalized estimating equations with independent correlation matrix and sandwich estimator.

Results A total of 4173 DCIS and 15,136 IBC were screen-detected. Increasing women's age, current hormone replacement therapy use and higher body mass index were less associated with the DCIS than with IBC detection rates (p value for the odds of DCIS among screen-detected cancers of, respectively, < 0.0001, 0.0244 and < 0.0001). In contrast, having a previous breast aspiration or biopsy and increasing breast density were more strongly associated with DCIS than with IBC detection rates (p value of, respectively, 0.0050 and < 0.0001).

Conclusion The results suggest that some women's characteristics could be playing a role in the initiation and other in the progression from in situ to invasive breast cancer. These characteristics can also affect the screening sensitivity, and this effect may differ depending on whether screen-detected cases were DCIS or IBC.

Keywords Breast cancer · Mammography · Screening · Detection rate · Ductal carcinoma in situ

Abbreviations

BMI	Body mass index
CDR	Cancer detection rate
CI	Confidence interval
CR	Computed radiography
DCIS	Ductal carcinoma in situ
DR	Direct radiography
GEE	Generalized estimating equations
HRT	Hormone replacement therapy
IBC	Invasive breast cancer
ICD-9	International Classification of Diseases, 9th edition
ICD-10	International Classification of Diseases, 10th edition
OR	Odds ratio
PQDCS	Programme québécois de dépistage du cancer du sein (Quebec Breast Cancer Screening Program)

✉ Isabelle Théberge
isabelle.theberge@inspq.qc.ca

[1] Institut national de santé publique du Québec, 945, Av. Wolfe, Quebec City G1V 5B3, Canada

[2] Département de médecine sociale et préventive, Faculté de Médecine, Université Laval, Quebec City, Canada

[3] Département de santé publique et médecine préventive, CHU de Québec-Université Laval, Hôpital Saint-François d'Assise, Quebec City, Canada

Introduction

Ductal carcinoma in situ (DCIS) is a neoplastic proliferation of epithelial cells confined to the ductal system without tumor invasion through the basement membrane [1]. DCIS is described as a non-obligate precursor of invasive carcinoma [2–4]. The proportion of DCIS among diagnosed

breast cancers went from less than 5% to about 20% after the dissemination of screening mammography [5]. Among the drawbacks of screening mammography is the plausible detection and treatment of some DCIS that would have never progress toward invasiveness [6, 7]. Why and how often DCIS progress to invasive disease remains to be clarified [5].

Given the potential role of DCIS as a precursor, it is expected that DCIS and IBC would share common risk factors [8–11]. Factors more strongly associated with DCIS compared to IBC can represent factors affecting disease initiation or factors associated with DCIS which do not progress to IBC [8, 11]. Factors affecting progression would only be associated with IBC risk [8, 11]. Understanding up to what point DCIS and IBC share the same risk factors could help better distinguish DCIS that will progress toward IBC from those that will not. This will also help to avoid overtreatment by tailoring treatment according to risk of progression [11].

To our knowledge, only one study [12] reported the difference in DCIS detection rates and IBC detection rates according to several characteristics among only screened women. This study, based on 39,542 women aged 30 years or older, concluded that risk factors for DCIS are similar to those for IBC. However, this study included few screen-detected DCIS ($n = 102$) diagnosed in 1995 or earlier and did not take into account potentially important confounding variables such as HRT or breast density.

The aim of our study is to examine, in our population-based screening program, a wide array of women's characteristics in relation to DCIS and IBC detection rates. We also aimed to assess whether some characteristics have a different effect on the DCIS detection rate compared to IBC detection rate. Finally, we want to verify whether these associations are maintained with the change in technology from film to digital mammograms.

Methods

Study population

The Quebec Breast Cancer Screening Program (Programme Québécois de Dépistage du Cancer du Sein, PQDCS) is an organized population-based mammography screening program launched in 1998 that actively invites women 50–69 years of age to receive biennially 2-views screening mammography in accredited facilities. The study is based on screening mammograms performed in the PQDCS from January 1, 2002, to September 30, 2015. Among the 3,888,262 screening mammograms performed during the study period, 278,693 (7.2%) were excluded (Fig. 1). A total of 3,609,569 screening mammograms, performed in 1,105,824 women in 102 facilities and interpreted by 469 radiologists, were used for the analysis.

Characteristics of women

Information on women's characteristics was obtained from a self-administered questionnaire completed at each screening examination and captured in the PQDCS information system. Size and weight of women were self-reported, and the body mass index (BMI) was then calculated (weight in kilogram divided by the height in meters squared). Breast density in 4 categories (< 25%, 25–49%, 50–75%, > 75%) was assessed by the radiologist who read the screening mammogram.

Technology used

Since 2007, digital mammography (computed radiography (CR) and direct radiography (DR)) gradually replaced screen-film mammography. In 2014, 58% of PQDCS mammograms were performed in CR, 41% in DR and 0.7% in film. The information on mammography technology was obtained from the Laboratoire de Santé Publique du Québec, including the date of change in the mammography unit from film to CR or DR systems.

Ascertainment of breast cancer

A screen-detected breast cancer is a DCIS or invasive carcinoma diagnosed within 6 months following a positive mammogram. A screening mammogram was classified as positive (abnormal) if the patient was referred for assessment; otherwise, it was considered negative (normal). Diagnoses of breast cancer were identified by validated algorithms that linked PQDCS data with other provincial databases [13, 14]. A breast cancer case is defined as DCIS if the pathology report from the PQDCS information system is completed for an 'in situ ductal carcinoma (intraductal noninvasive)' or if the International Classification of Diseases (ICD) recorded in a provincial database (MedEcho) is DCIS (ICD-9: code 233.0,ICD-10: code D05.1, D05.7, D05.9). A breast cancer case is defined as IBC if the pathology report from the PQDCS information system is completed for an 'invasive carcinoma' or if the ICD in MedEcho is IBC (ICD-9: 174, ICD-10: C50). For bilateral breast cancers, only the one with the most aggressive histopathological features was considered. Otherwise, it was chosen randomly.

The DCIS detection rate was the number of screen-detected DCIS over the total number of screening mammograms. The IBC detection rate was the number of invasive screen-detected breast cancers over the total number of screening mammograms. The percentage of DCIS among screen-detected breast cancer was calculated as the number

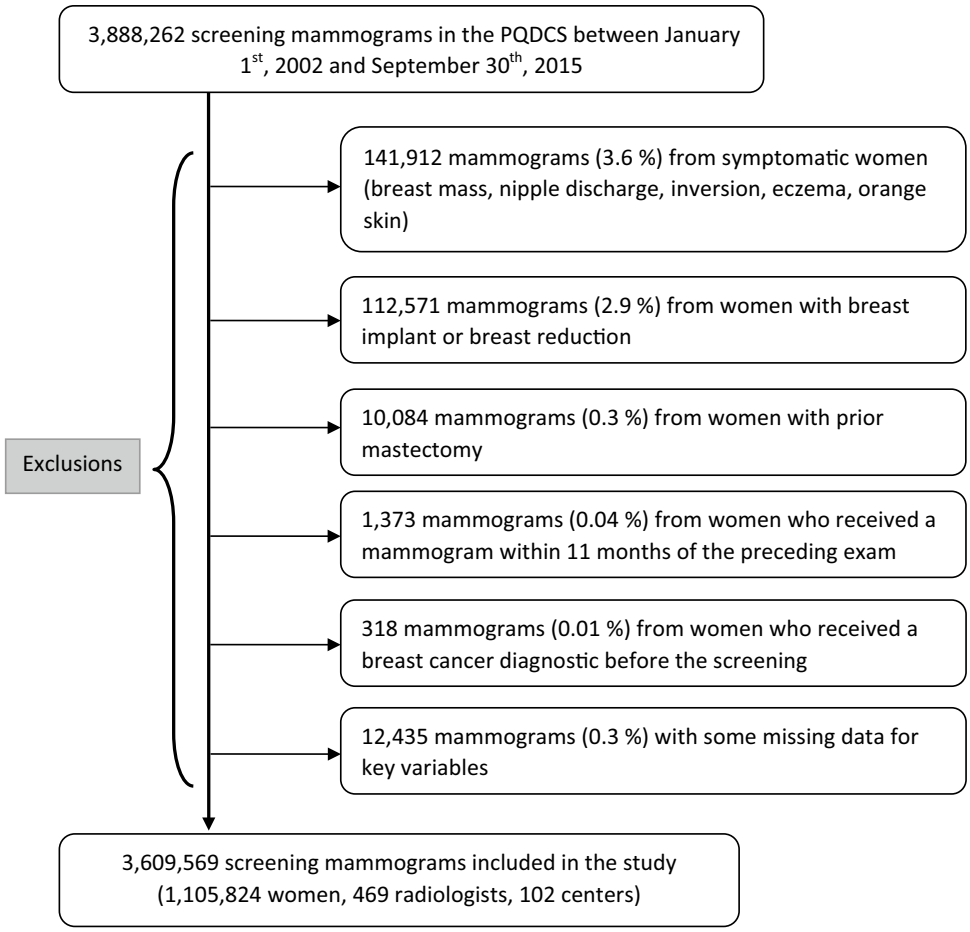

Fig. 1 Study population from the Quebec Breast Cancer Screening Program

of screen-detected DCIS over the total number of screen-detected breast cancer whose type is known.

Statistical analysis

The analyses were conducted in a threefold manner. First we measured the association between women characteristics and the risk of screen-detected DCIS. Second, we assessed the association between women characteristics and the risk of screen-detected IBC. Third, we compared the odds of DCIS detection against the odds of IBC detection according to women characteristics.

All analyses were conducted using the screening mammograms as the unit of analysis. We used logistic regression and generalized estimating equations (GEE) with independent correlation matrix and sandwich estimator to account for correlation between mammograms. We considered radiologist-level and center-level correlations and estimated empirical variance matrix with the three-step method developed by Miglioretti and Heagerty [15]. Adjusted detection rate ratios were estimated using exponential of the model parameters. Wald 95% confidence intervals and p values were derived from the empirical variance estimator. We also estimated DCIS and IBC detection rates according to women's characteristics from the adjusted GEE model using marginal standardization [16]. Thus, adjusted rates represent the average of the model predicted probabilities assuming all units would possess the characteristic of interest, but keeping other covariates as observed.

Models were adjusted for all women's characteristics, year of screening mammogram (2002–2006, 2007–2011, 2012–2015) and technology used (film, CR, DR). A complementary analysis was carried out in order to assess whether restricting our analysis to digital mammograms changed results.

The GENMOD procedure of the SAS software (version 9.4, Copyright © 2016 by SAS Institute Inc., Cary, NC, USA) was used. Statistical significance was tested at 5% for all tests (2-sided).

Results

Characteristics of the women studied

Among the 3,609,569 screening mammograms in the study, 362,817 were positive (recall rate = 10.0%) and 19,384 breast

cancers were screen-detected (4173 DCIS, 15,136 IBC and 75 with unknown type). Among the screen-detected breast cancer, 21.5% were DCIS. The detection rate was 1.2/1000 screens for DCIS and 4.2/1000 screens for IBC.

The distributions of the screening mammograms according to characteristics of the women and mammograms by breast cancer status are presented in Table 1. About half of screening mammograms were made on film (51%), while 35% were made on CR and 13% on DR. About 11% and 24% of screening mammograms were performed in, respectively, women who had a previous breast aspiration or biopsy and women who currently use HRT. The proportion of mammograms performed in women with an elevated BMI (≥ 30 kg/m^2) is higher in women with IBC screen-detected (27%) compared to women with DCIS screen-detected (21%) or all screening mammograms (23%). Finally, the proportion of women with breast density > 50% is higher in women with DCIS screen-detected (49%) compared to women with IBC screen-detected (40%) and all screening mammograms (36%).

Univariate analysis of DCIS and IBC detection according to women's characteristics

The DCIS detection rates and the percentages of DCIS among screen-detected breast cancer according to women's characteristics are presented in Fig. 2. The highest DCIS detection rate was observed in mammograms from women without previous breast aspiration or biopsy, with a DCIS detection rate of 1.8/1000 screens. The lowest DCIS detection rate, 0.6/1000 screens, was observed in mammograms from women with a breast density < 25%. Otherwise, the proportion of DCIS among screen-detected breast cancer was lower in mammograms done on older women. It went from 26% in mammograms done on women aged 50–54 to 19% in mammograms done on women aged 60–64 and 65–69 years. The highest proportions of DCIS among screen-detected breast cancers were observed in mammograms done on pre-menopausal women (27%), women with BMI < 20 kg/m^2 (31%) and women with breast density > 75% (28%).

Multivariate analysis of DCIS and IBC detection according to women's characteristics

Relationship of characteristics of women and mammograms with DCIS and IBC detection rate is presented in Table 2. Compared to mammograms from women without breast clinical examination in the last year, mammograms from women with clinical breast examination in the last year had a similar DCIS detection rate (adjusted cancer detection rate (CDR) ratio = 1.04, 95% CI 0.96–1.12), but had a lower IBC detection rate (adjusted CDR ratio = 0.96, 95% CI 0.93–0.99).

Increasing women's age, current HRT use and higher BMI are associated with higher IBC detection rates than DCIS detection rates (Table 2). For example, women with a BMI ≥ 35 kg/m^2 showed DCIS and IBC detection rates of, respectively, 1.2 times (adjusted CDRratio = 1.21, 95% CI 1.07–1.36) and 1.7 times (adjusted CDR ratio = 1.73, 95% CI 1.63–1.84) higher than that of mammograms from women with a BMI between 20.0 and 24.9 kg/m^2. This translated into an adjusted odds of DCIS on IBC among screen-detected cancers lower for mammograms from women with a BMI ≥ 35 kg/m^2 compared with mammograms from women with a BMI between 20.0 and 24.9 kg/m^2 [adjusted odds ratio (OR) 0.70, 95% CI 0.60–0.81].

In contrast, having a previous breast aspiration or biopsy and increasing breast density were more strongly associated with DCIS detection rates than with IBC detection rates. Mammograms from women with a previous aspiration or biopsy had a 49% higher DCIS detection rate (adjusted CDR = 1.49, 95% CI 1.38–1.61) and a 29% higher IBC detection rate (adjusted CDR = 1.29, 95% CI 1.22–1.35) compared to mammograms from women without this antecedent. This translated into an OR of DCIS among screen-detected of 1.15 (95% CI 1.04–1.27). Also, mammograms from women with breast density > 75% had a 2.8 times higher DCIS detection rate (adjusted CDR = 2.79, 95% CI 2.43–3.20) and a 1.8 times higher IBC detection rate (adjusted CDR = 1.83, 95% CI 1.67–2.01) compared to mammograms from women with breast density < 25%. Then, the odds of DCIS on IBC among screen-detected cancers are higher in mammograms from women with breast density > 75% compared to mammograms from women with breast density < 25% (adjusted OR = 1.53, 95% CI 1.32–1.77).

Similar patterns of association for detection of DCIS and IBC were observed according to screening history, women family history of breast cancer, age of the first birth and menopausal status (Table 2).

We observed no association between technologies used for mammogram and either DCIS or IBC detection rates (Table 2).

Multivariate analysis of DCIS and IBC detection according to women's characteristics for digital mammograms only

Associations between DCIS and IBC detection rates according to women's characteristics for digital mammograms are presented in Table 3. Compared to the whole cohort (main analysis), the same pattern of associations was observed between DCIS or IBC detection rates for age, screening history, breast clinical examination, family history, age

Table 1 Characteristics of women and mammograms for the screen-detected breast cancer (DCIS and invasive) and all screening mammograms

Characteristics	Screen-detected		All screening mammograms
	DCIS	IBC	
	N = 4173 *n* (%)	*N* = 15,136 *n* (%)	*N* = 3,609,569 *n* (%)
Age (years)			
50–54	1206 (28.9)	3363 (22.2)	1,098,736 (30.4)
55–59	1067 (25.6)	3751 (24.8)	1,002,479 (27.8)
60–64	1000 (24.0)	4190 (27.7)	856,316 (23.7)
65–69	900 (21.6)	3832 (25.3)	652,038 (18.1)
Year of the mammogram			
2002–2006	1171 (28.1)	4100 (27.1)	1,030,872 (28.6)
2007–2011	1428 (34.2)	5572 (36.8)	1,388,124 (38.5)
2012–2015	1574 (37.7)	5464 (36.1)	1,190,573 (33.0)
Technology used			
Film	2027 (48.6)	7448 (49.2)	1,856,828 (51.4)
CR	1474 (35.3)	5470 (36.1)	1,279,269 (35.4)
DR	672 (16.1)	2218 (14.7)	473,472 (13.1)
Screening history			
Ini. without prior mam	394 (9.4)	1225 (8.1)	235,429 (6.5)
Ini. with prior mam	693 (16.6)	2103 (13.9)	534,126 (14.8)
Subsequent	3086 (74.0)	11,808 (78.0)	2,840,014 (78.7)
Breast clinical examination			
No	1637 (39.2)	6410 (42.3)	1,475,822 (40.9)
Yes	2536 (60.8)	8726 (57.7)	2,133,747 (59.1)
Previous breast aspiration or biopsy			
No	3453 (82.8)	12,851 (84.9)	3,205,771 (88.8)
Yes	720 (17.2)	2285 (15.1)	403,798 (11.2)
Family history of breast cancer			
No	3201 (76.7)	11,632 (76.8)	2,975,835 (82.4)
Yes	972 (23.3)	3504 (23.2)	633,734 (17.6)
Age at first birth (years)			
Nulliparous	864 (20.7)	3076 (20.3)	643,081 (17.8)
≤ 24	1593 (38.2)	6138 (40.6)	1,578,455 (43.7)
25–29	1164 (27.9)	3992 (26.4)	973,532 (27.0)
≥ 30	552 (13.2)	1930 (12.8)	414,501 (11.5)
Menopausal status			
Pre	696 (16.7)	1855 (12.3)	517,329 (14.3)
Post	3477 (83.3)	13,281 (87.7)	3,092,240 (85.7)
HRT use			
Never	2202 (52.8)	7500 (49.6)	1,923,952 (53.3)
Previously	842 (20.2)	3428 (22.6)	807,297 (22.4)
Currently	1129 (27.0)	4208 (27.8)	878,320 (24.3)
BMI (kg/m^2)			
< 20.0	224 (5.4)	505 (3.3)	182,972 (5.1)
20.0–24.9	1683 (40.3)	5054 (33.4)	1,353,958 (37.5)
25.0–29.9	1403 (33.6)	5479 (36.2)	1,226,485 (34.0)
30.0–34.9	580 (13.9)	2687 (17.8)	552,765 (15.3)
≥ 35.0	283 (6.8)	1411 (9.3)	293,389 (8.1)
Breast density			
< 25%	553 (13.2)	2799 (18.5)	935,245 (25.9)
25–49%	1556 (37.3)	6267 (41.4)	1,379,989 (38.2)
50–75%	1599 (38.3)	4902 (32.4)	1,007,177 (27.9)
> 75%	465 (11.1)	1168 (7.7)	287,158 (8.0)

DCIS Ductal carcinoma in situ, *IBC* invasive breast cancer, *Ini*. initial, *mam*. mammogram, *HRT* hormone replacement therapy, *BMI* body mass index

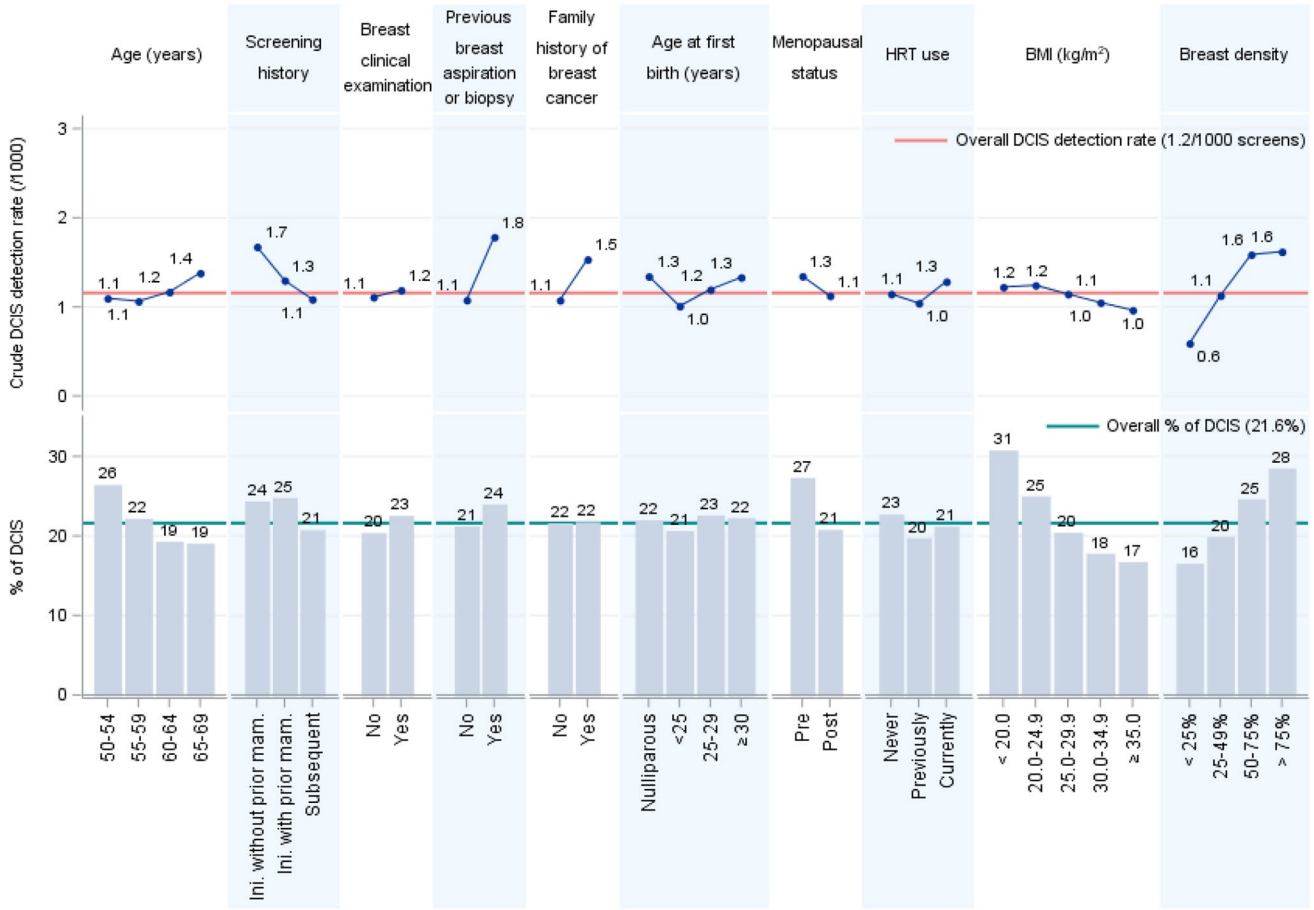

Fig. 2 DCIS detection rate and proportion of DCIS among screen-detected breast cancer according to characteristics of women. *DCIS* ductal carcinoma in situ, *HRT* hormone replacement therapy, *BMI* body mass index, *Ini*. initial, *mam*. mammogram

at first birth, BMI and breast density when only digital mammograms were considered. The odds of DCIS among screen detected cancers were no longer statistically significant according to previous breast aspiration of biopsy (p value = 0.3562) and HRT use (p value = 0.2253) with the digital mammograms only (these p values were, respectively, 0.0050 and 0.0244 in the whole cohort).

Discussion

Among the screening mammograms of the PQDCS between 2002 and 2015, the DCIS detection rate was 1.2/1000 screens, which is comparable with other breast cancer screening programs [17–20]. In our breast cancer screening program, clinical breast examination in the last year was not associated with the DCIS detection rate, but was associated with a decrease in the IBC detection rate. The age of the women at screening, the use of HRT and the BMI were less associated with the DCIS detection rate than with IBC detection rate. On the opposite, previous breast aspiration or biopsy and breast density were more strongly associated with the DCIS detection rate rather than the IBC detection rate.

Kerlikowske et al. [12] found, in their cross-sectional study of screened women, that the magnitude of the associations were similar between their studied risk factors and DCIS or IBC screen-detected, except for increasing age and the presence of a palpable mass. These factors were more strongly associated with IBC rather than DCIS screen-detected. In our analysis, we also observed the same results for age, but we also found other characteristics for which the strength of the associations varies with DCIS or IBC detection rate.

Other studies have examined the association between risk factors and DCIS or IBC diagnoses [9, 10, 21–29]. Results of these studies are divergent. Some studies concluded that, in general, risk factors for DCIS are similar to those for IBC [10, 12, 21, 24–27, 29, 30]. However, some studies have observed differences in associations for DCIS and IBC, particularly for HRT use, BMI and breast density [10, 12, 21–24, 26–28, 31, 32]. For example, Ko et al. [21] and

Table 2 Multivariate association of women characteristics with DCIS and IBC detection rate, and with the odds ratio of DCIS among screen-detected breast cancers

Characteristics	DCIS ($N=4173$)			IBC ($N=15{,}136$)			DCIS versus IBC[a]	
	Adjusted[b] CDR (‰)	Adjusted[b] CDR ratio[c] (95% CI)	*p* value	Adjusted[b] CDR (‰)	Adjusted[b] CDR ratio[c] (95% CI)	*p* value	Adjusted[b] OR (95% CI)	*p* value
Age (years)								
50–54	0.86	1.00	< 0.0001	2.59	1.00	< 0.0001	1.00	< 0.0001
55–59	1.15	1.33 (1.21–1.45)		3.95	1.53 (1.45–1.61)		0.88 (0.80–0.98)	
60–64	1.35	1.56 (1.43–1.70)		5.37	2.08 (1.97–2.20)		0.77 (0.69–0.86)	
65–69	1.66	1.92 (1.73–2.14)		6.62	2.57 (2.42–2.73)		0.77 (0.68–0.87)	
Screening history								
Ini. without prior mam	2.13	1.00	< 0.0001	7.98	1.00	< 0.0001	1.00	0.8252
Ini. with prior mam	1.43	0.67 (0.59–0.76)		5.13	0.64 (0.59–0.69)		1.02 (0.90–1.15)	
Subsequent	1.05	0.49 (0.44–0.56)		3.88	0.48 (0.45–0.52)		0.98 (0.86–1.12)	
Breast clinical examination								
No	1.13	1.00	0.2997	4.30	1.00	0.0108	1.00	0.0430
Yes	1.17	1.04 (0.96–1.12)		4.12	0.96 (0.93–0.99)		1.09 (1.00-1.18)	
Previous breast aspiration or biopsy								
No	1.09	1.00	< 0.0001	4.05	1.00	< 0.0001	1.00	0.0050
Yes	1.62	1.49 (1.38–1.61)		5.20	1.29 (1.22–1.35)		1.15 (1.04–1.27)	
Family history of breast cancer								
No	1.08	1.00	< 0.0001	3.93	1.00	< 0.0001	1.00	0.6232
Yes	1.51	1.40 (1.32–1.48)		5.40	1.38 (1.33–1.43)		1.01 (0.96–1.07)	
Age at first birth (years)								
Nulliparous	1.28	1.00	< 0.0001	4.82	1.00	< 0.0001	1.00	0.3266
≤ 24	1.04	0.81 (0.74–0.88)		3.78	0.78 (0.75–0.82)		1.03 (0.95–1.12)	
25–29	1.19	0.93 (0.87–0.99)		4.20	0.87 (0.83–0.91)		1.06 (0.98–1.15)	
≥ 30	1.31	1.02 (0.92–1.13)		4.86	1.01 (0.96–1.06)		0.99 (0.90–1.10)	
Menopausal status								
Pre	1.35	1.00	< 0.0001	4.39	1.00	0.1230	1.00	0.0866
Post	1.12	0.83 (0.78–0.89)		4.17	0.95 (0.89–1.01)		0.91 (0.82–1.01)	
HRT use								
Never	1.14	1.00	< 0.0001	4.01	1.00	< 0.0001	1.00	0.0244
Previously	1.03	0.90 (0.83–0.98)		3.82	0.95 (0.91-1.00)		0.95 (0.86–1.05)	
Currently	1.30	1.14 (1.06–1.22)		5.00	1.25 (1.19–1.31)		0.89 (0.82–0.97)	
BMI (kg/m^2)								
< 20.0	0.97	0.88 (0.76–1.01)	< 0.0001	2.41	0.69 (0.63–0.76)	< 0.0001	1.26 (1.04–1.52)	< 0.0001
20.0–24.9	1.11	1.00		3.49	1.00		1.00	
25.0–29.9	1.18	1.06 (1.00-1.13)		4.49	1.29 (1.24–1.34)		0.83 (0.77–0.89)	
30.0–34.9	1.26	1.13 (1.03–1.24)		5.41	1.56 (1.47–1.64)		0.72 (0.66–0.79)	
≥ 35.0	1.34	1.21 (1.07–1.36)		6.01	1.73 (1.63–1.84)		0.70 (0.60–0.81)	
Breast density								
< 25%	0.59	1.00	< 0.0001	2.68	1.00	< 0.0001	1.00	< 0.0001
25–49%	1.13	1.92 (1.70–2.17)		4.50	1.68 (1.60–1.77)		1.15 (1.02–1.31)	
50–75%	1.59	2.70 (2.42–3.01)		5.26	1.97 (1.85–2.10)		1.39 (1.24–1.56)	
> 75%	1.64	2.79 (2.43–3.20)		4.89	1.83 (1.67–2.01)		1.53 (1.32–1.77)	
Technology used								
Film	1.14	1.00	0.2794	4.21	1.00	0.2928	1.00	0.4853
CR	1.11	0.97 (0.85–1.11)		4.11	0.97 (0.91–1.05)		1.00 (0.88–1.12)	
DR	1.31	1.14 (0.89–1.47)		4.35	1.03 (0.94–1.14)		1.10 (0.89–1.36)	

DCIS ductal carcinoma in situ, *IBC* invasive breast cancer, *CDR* cancer detection rate, *CI* confidence interval, *OR* odds ratio, *Ini*. initial, *mam*. mammogram, *HRT* hormone replacement therapy, *BMI* body mass index, *CR* computed radiography, *DR* direct radiography

[a]Odds of DCIS relative to IBC for a given characteristics

[b]Models adjust for all the characteristics included in the table and year of screening mammogram (2002–2006, 2007–2011, 2012–2015)

[c]Logistic regression was used. However, in this situation, the odds ratio can be interpreted as approximations of the breast cancer detection rate ratios

Reeves et al. [10] have found similar associations between the use of HRT and DCIS or invasive ductal cancer, whereas Trentham-Dietz et al. [26] observed that HRT use was more strongly associated with IBC compared to in situ.

Such inconsistencies in findings may be explained, at least in part, by variation in the population studied and the women characteristics considered. Some studies are based on a selected sample of women and the women's screening history or whether or not the breast cancer was likely to have been screen-detected are not take into account [10, 23, 29]. When interpreting the findings of etiological breast cancer studies, the mix of screen-detected and women/clinician-detected cases in the study population will influence the results [10, 33]. Furthermore, each study does not consider the same confounding factors, such as breast density [8–10, 12, 25–27, 29]. Breast density is an important variable since it was recognized as a risk factor for breast cancer [34, 35], a factor that also influences the screening sensitivity of mammography [35–37] and is correlated with the BMI [35] and the use of HRT [35, 37, 38]. Only three studies [21–23] have considered together breast density, HRT use and BMI in their analysis.

In our data, we observed that being older, HRT use and higher BMI were more strongly associated with IBC detection rate than DCIS detection rate. These results are consistent with the hypothesis that these characteristics may have an effect on cancer progression from the in situ phase to the infiltrating phase [8, 9, 11]. Some authors have already discussed this possibility, especially concerning HRT use [39–41]. Gapstur et al. [28] show that there was no association between ever HRT use and the incidence of DCIS, while exposure to HRT was associated with an increased risk of IBC with a favorable histology. The study by Marshall et al. [31] also observed that the discontinuation of HRT reduced the incidence of IBC, but not the incidence of DCIS.

Like others studies [22, 26, 27], our data also suggest that having a previous breast aspiration or biopsy and higher breast density were more strongly associated with DCIS detection rate than IBC detection rate. These characteristics may play a greater role in cancer initiation rather than progression of cancer and could play a role on screening sensitivity, or both. For example, the decrease in screening sensitivity according to breast density may be less important for DCIS compared to IBC. A large proportion of DCIS is screen-detected due to the presence of microcalcifications [42, 43], and they could remain more visible on mammograms even in the presence of higher breast density [22]. Moreover, the biological properties of the breast tissue components associated with breast density may increase the probability of the transition of normal epithelium to malignant cells [44]. Hence, breast density can create an environment that promotes the initiation of breast cancer. Thus, the DCIS pool would be higher in women with previous breast aspiration or biopsy and in women with higher breast density. Given these larger reservoir of DCIS, the risk of overdiagnosis in these women can be higher. Further studies will be needed to determine the individually effect of these characteristics on the initiation of the disease and the screening mammography sensitivity.

This study had some limitations. DCIS or IBC is determined according to provincial databases and not by a revision of the pathology reports; thus, some cases may have been misclassified. Moreover, we studied all invasive breast cancer and we cannot restrict our analysis on invasive ductal carcinoma. However, the invasive ductal carcinoma is the commonest type of invasive breast cancer [28, 45]. We could not adjust for some behavioral women's characteristics such as alcohol consumption or smoking habit. Also, we do not have detailed information about such as specific regimens of HRT used as well as duration of the exposition to HRT. Moreover, this study included film and digital screening mammograms. We have checked the robustness of our results in a complementary analysis restricted to digital mammograms. Although the analysis had lower statistical power (they were based on about half of the DCIS and IBC), we found the same associations. These results reassure us that the findings of this study are still valid even in the era of digital mammography.

Our study also had several strengths. We used a large population-based cohort of women participating in an organized screening program, avoiding potential selection bias due to differential participation. Compared to previous studies, we have, to our knowledge, the largest number of screen-detected DCIS. We also have a wide array of women characteristics, including HRT use, BMI and breast density, reducing concerns about residual confounding.

In conclusion, our study shows that women's age, HRT use and BMI appear to be more strongly associated with IBC than DCIS. These results suggest that these characteristics seem to play a role in the progression of breast cancer from in situ to invasive stage. On the other hand, having a previous breast aspiration or biopsy and breast density seems to be more strongly associated with DCIS rather than IBC detection by mammography. These findings suggest that these characteristics could be playing a role in the initiation of the breast cancer. However, we must not forget that cases studied are all screen-detected cancers by mammography. All these characteristics can also have an effect on the screening sensitivity. This effect on sensitivity may be different depending on whether the screen-detected cases were DCIS or IBS. Although these findings do not provide direct evidence regarding the mechanisms underlying the development of DCIS and IBC, they deepen our understanding of the characteristics that affect DCIS and IBC detection.

Table 3 Multivariate association of women characteristics with DCIS and IBC detection rate and with the odds ratio of DCIS among screen-detected breast cancers, for digital screening mammograms only

Characteristics	DCIS ($N=2145$)			IBC ($N=7678$)			DCIS versus IBC[a]	
	Adjusted[b] CDR (‰)	Adjusted[b] CDR ratio[c] (95% CI)	*p* value	Adjusted[b] CDR (‰)	Adjusted[b] CDR ratio[c] (95% CI)	*p* value	Adjusted[b] OR (95% CI)	*p* value
Age (years)								
50–54	0.88	1.00	< 0.0001	2.64	1.00	< 0.0001	1.00	0.0196
55–59	1.16	1.31 (1.13–1.52)		3.96	1.50 (1.39–1.63)		0.89 (0.76–1.05)	
60–64	1.49	1.68 (1.46–1.95)		5.55	2.11 (1.94–2.28)		0.82 (0.69–0.98)	
65–69	1.78	2.02 (1.73–2.36)		6.98	2.66 (2.45–2.88)		0.78 (0.66–0.92)	
Screening history								
Ini. without prior mam	2.30	1.00	< 0.0001	8.60	1.00	< 0.0001	1.00	0.9838
Ini. with prior mam	1.56	0.68 (0.54–0.85)		5.62	0.65 (0.58–0.73)		1.02 (0.83–1.25)	
Subsequent	1.13	0.49 (0.40–0.60)		4.10	0.47 (0.43–0.52)		1.00 (0.81–1.25)	
Breast clinical examination								
No	1.13	1.00	0.0050	4.53	1.00	0.0163	1.00	0.0002
Yes	1.29	1.14 (1.04–1.25)		4.28	0.94 (0.90–0.99)		1.22 (1.10–1.35)	
Previous breast aspiration or biopsy								
No	1.17	1.00	< 0.0001	4.23	1.00	< 0.0001	1.00	0.3562
Yes	1.64	1.41 (1.25–1.58)		5.50	1.30 (1.23–1.38)		1.07 (0.93–1.22)	
Family history of breast cancer								
No	1.15	1.00	< 0.0001	4.09	1.00	< 0.0001	1.00	0.1849
Yes	1.53	1.33 (1.23–1.43)		5.67	1.39 (1.32–1.47)		0.95 (0.88–1.02)	
Age at first birth (years)								
Nulliparous	1.35	1.00	0.0008	5.06	1.00	< 0.0001	1.00	0.4081
≤ 24	1.11	0.82 (0.74–0.91)		3.98	0.79 (0.74–0.84)		1.05 (0.93–1.18)	
25–29	1.26	0.93 (0.85–1.02)		4.36	0.86 (0.81–0.91)		1.09 (0.98–1.21)	
≥ 30	1.31	0.97 (0.84–1.12)		4.83	0.95 (0.88–1.03)		1.00 (0.86–1.15)	
Menopausal status								
Pre	1.47	1.00	< 0.0001	4.56	1.00	0.3318	1.00	0.0554
Post	1.18	0.81 (0.72–0.90)		4.36	0.96 (0.88–1.05)		0.87 (0.75-1.00)	
HRT use								
Never	1.20	1.00	0.0022	4.21	1.00	< 0.0001	1.00	0.2253
Previously	1.12	0.93 (0.84–1.04)		4.08	0.97 (0.91–1.04)		0.96 (0.85–1.10)	
Currently	1.40	1.16 (1.05–1.29)		5.32	1.27 (1.20–1.34)		0.89 (0.79–1.02)	
BMI (kg/m^2)								
< 20.0	1.03	0.89 (0.73–1.09)	0.0011	2.68	0.75 (0.66–0.84)	< 0.0001	1.19 (0.93–1.52)	< 0.0001
20.0–24.9	1.15	1.00		3.59	1.00		1.00	
25.0–29.9	1.25	1.09 (1.00-1.18)		4.64	1.29 (1.24–1.36)		0.84 (0.77–0.91)	
30.0–34.9	1.35	1.17 (1.05–1.31)		5.77	1.61 (1.49–1.75)		0.72 (0.64–0.82)	
≥ 35.0	1.50	1.30 (1.08–1.57)		6.49	1.81 (1.66–1.99)		0.72 (0.58–0.89)	
Breast density								
< 25%	0.61	1.00	< 0.0001	2.73	1.00	< 0.0001	1.00	0.0002
25–49%	1.14	1.86 (1.57–2.21)		4.62	1.70 (1.58–1.82)		1.12 (0.94–1.33)	
50–75%	1.72	2.80 (2.38–3.30)		5.57	2.05 (1.88–2.22)		1.41 (1.19–1.66)	
> 75%	1.79	2.91 (2.33–3.64)		5.36	1.97 (1.78–2.18)		1.50 (1.21–1.85)	
Technology used								
CR	1.17	1.00	0.1251	4.31	1.00	0.1255	1.00	0.2270
DR	1.38	1.18 (0.95–1.46)		4.58	1.06 (0.98–1.15)		1.11 (0.94–1.31)	

DCIS ductal carcinoma in situ, *IBC* invasive breast cancer, *CDR* cancer detection rate, *CI* confidence interval, *OR* odds ratio, *Ini*. initial, *mam*. mammogram, *HRT* hormone replacement therapy, *BMI* body mass index, *CR* computed radiography, *DR* direct radiography

[a]Odds of DCIS relative to IBC for a given characteristics

[b]Models adjust for all the characteristics included in the table and year of screening mammogram (2002–2006, 2007–2011, 2012–2015)

[c]Logistic regression was used. However, in this situation, the odds ratio can be interpreted as approximations of the breast cancer detection rate ratios

Funding This study was financially supported by the Direction générale de cancérologie of the Quebec Ministry of Health and Social Services.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All women included in this analysis signed a consent form agreeing to participate in the PQDCS, which includes transmission of their data to central database for analysis.

References

1. Wiechmann L, Kuerer HM (2008) The molecular journey from ductal carcinoma in situ to invasive breast cancer. Cancer 112(10):2130–2142
2. Cowell CF, Weigelt B, Sakr RA, Ng CKY, Hicks J, King TA et al (2013) Progression from ductal carcinoma in situ to invasive breast cancer: revisited. Mol Oncol 7(5):859–869
3. Allred DC (2010) Ductal carcinoma in situ: terminology, classification, and natural history. J Natl Cancer Inst Monogr 41:134–138
4. Casasent AK, Edgerton M, Navin NE (2017) Genome evolution in ductal carcinoma in situ: invasion of the clones. J Pathol 241(2):208–218
5. Leonard GD, Swain SM (2004) Ductal carcinoma in situ, complexities and challenges. J Natl Cancer Inst 96(12):906–920
6. Groen EJ, Elshof LE, Visser LL, Rutgers EJT, Winter-Warnars HAO, Lips EH et al (2017) Finding the balance between over- and under-treatment of ductal carcinoma in situ (DCIS). Breast 31:274–283
7. deGelder R, Heijnsdijk EAM, vanRavesteyn NT, Fracheboud J, Draisma G, deKoning HJ (2011) Interpreting overdiagnosis estimates in population-based mammography screening. Epidemiol Rev 33:111–121
8. Ma H, Henderson KD, Sullivan-Halley J, Duan L, Marshall SF, Ursin G et al (2010) Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among postmenopausal women in the California Teachers Study cohort. Breast Cancer Res 12(3):R35
9. Mullooly M, Khodr ZG, Dallal CM, Nyante SJ, Sherman ME, Falk R et al (2017) Epidemiologic risk factors for in situ and invasive breast cancers among postmenopausal women in the National Institutes of Health-AARP Diet and Health Study. Am J Epidemiol 186(12):1329–1340
10. Reeves GK, Pirie K, Green J, Bull D, Beral V, Million Women Study Collaborators (2012) Comparison of the effects of genetic and environmental risk factors on in situ and invasive ductal breast cancer. Int J Cancer 131(4):930–937
11. Millikan R, Dressler L, Geradts J, Graham M (1995) The need for epidemiologic studies of in-situ carcinoma of the breast. Breast Cancer Res Treat 35(1):65–77
12. Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V (1997) Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. J Natl Cancer Inst 89(1):76–82
13. Théberge I, Major D, Langlois A, Brisson J (2003) [Validation de stratégies pour obtenir le taux de détection du cancer, la valeur prédictive positive, la proportion des cancers in situ, la proportion des cancers infiltrants de petite taille et la proportion des cancers infiltrants sans envahissement ganglionnaire dans le cadre des données fournies par le Programme québécois de dépistage du cancer du sein (PQDCS)] [In French]. Institut national de santé publique du Québec. https://www.inspq.qc.ca/publications/201. Accessed 9 Oct 2018
14. Pelletier E, Major D, Brisson J (2005) [Développement d'algorithmes permettant d'identifier les interventions et les délais liés à l'investigation diagnostique suite à une mammographie de dépistage anormale - Programme québécois de dépistage du cancer du sein (PQDCS)] [In French]. Institut national de santé publique du Québec. https://www.inspq.qc.ca/publications/417. Accessed 9 Oct 2018
15. Miglioretti DL, Heagerty PJ (2004) Marginal modeling of multilevel binary data with time-varying covariates. Biostatistics 5(3):381–398
16. Muller CJ, MacLehose RF (2014) Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. Int J Epidemiol 43(3):962–970
17. Canadian Partnership Against Cancer (2017) Breast cancer screening in Canada: monitoring and evaluation of quality indicators—results report, January 2011 to December 2012. Toronto, Canadian Partnership Against Cancer
18. Australian Insitute of Health and Welfare (2017) BreastScreen Australia monitoring report 2014–2015. Cancer series no. 106. Cat. No. CAN 105. AIHW, Canberra
19. Weigel S, Khil L, Hense H-W, Decker T, Wellmann J, Heidrich J et al (2018) Detection rates of ductal carcinoma in situ with biennial digital mammography screening: radiologic findings support pathologic model of tumor progression. Radiology 286(2):424–432
20. Luiten JD, Voogd AD, Luiten EJT, Duijm EM (2017) Trends in incidence and tumour grade in screen-detected ductal carcinoma in situ and invasive breast cancer. Breast Cancer Res Treat 166(1):307–314
21. Ko H, Shin J, Lee JE, Nam SJ, Nguyen TL, Hopper JL et al (2017) Comparison of the association of mammographic density and clinical factors with ductal carcinoma in situ versus invasive ductal breast cancer in Korean women. BMC Cancer 17(1):821
22. Yaghjyan L, Colditz GA, Collins LC, Schnitt SJ, Rosner B, Vachon C et al (2011) Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. J Natl Cancer Inst 103(15):1179–1189
23. Reinier KS, Vacek PM, Geller BM (2007) Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and post-menopausal women. Breast Cancer Res Treat 103(3):343–348
24. Gill JK, Maskarinec G, Pagano I, Kolonel LN (2006) The association of mammographic density with ductal carcinoma in situ of the breast: the Multiethnic Cohort. Breast Cancer Res 8(3):R30
25. Wohlfahrt J, Rank F, Kroman N, Melbye M (2004) A comparison of reproductive risk factors for CIS lesions and invasive breast cancer. Int J Cancer 108(5):750–753
26. Trentham-Dietz A, Newcomb PA, Storer BE, Remington PL (2000) Risk factors for carcinoma in situ of the breast. Cancer Epidemiol Biomark Prev 9(7):697–703
27. Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM, Ross RK (1996) Risk factors for in situ breast cancer. Cancer Epidemiol Biomark Prev 5(12):961–965
28. Gapstur SM, Morrow M, Sellers TA (1999) Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. JAMA 281(22):2091–2097

29. Granström C, Sundquist J, Hemminki K (2008) Population attributable risks for breast cancer in Swedish women by morphological type. Breast Cancer Res Treat 111(3):559–568
30. Claus EB, Stowe M, Carter D (2001) Breast carcinoma in situ: risk factors and screening patterns. J Natl Cancer Inst 93(23):1811–1817
31. Marshall SF, Clarke CA, Deapen D, Henderson K, Largent J, Neuhausen SL et al (2010) Recent breast cancer incidence trends according to hormone therapy use: the California Teachers Study cohort. Breast Cancer Res 12(1):R4
32. Virnig BA, Wang S-Y, Shamilyan T, Kane RL, Tuttle TM (2010) Ductal carcinoma in situ: risk factors and impact of screening. J Natl Cancer Inst Monogr 2010(41):113–116
33. Sprague BL, Gangnon RE, Hampton JM, Egan KM, Titus LJ, Kerlikowske K et al (2015) Variation in breast cancer risk factor associations by method of detection: results from a series of case-control studies. Am J Epidemiol 181(12):956–969
34. Nazari SS, Mukherjee P (2018) An overview of mammographic density and its association with breast cancer. Breast Cancer Tokyo Jpn25(3):259–267
35. Vinnicombe SJ (2018) Breast density: why all the fuss?Clin Radiol 73(4):334–357
36. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM et al (2003) Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 138(3):168–175
37. Kavanagh AM, Cawson J, Byrnes GB, Giles GG, Marr G, Tong B et al (2005) Hormone replacement therapy, percent mammographic density, and sensitivity of mammography. Cancer Epidemiol Biomark Prev 14(5):1060–1064
38. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G (2003) Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 95(1):30–37
39. Farhat GN, Walker R, Buist DSM, Onega T, Kerlikowske K (2010) Changes in invasive breast cancer and ductal carcinoma in situ rates in relation to the decline in hormone therapy use. J Clin Oncol 28(35):5140–5146
40. Kerlikowske K, Miglioretti DL, Buist DSM, Walker R, Carney PA, for the National Cancer Institute (2007) Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst 99(17):1335–1339
41. Santen RJ, Yue W, Heitjan DF (2012) Modeling of the growth kinetics of occult breast tumors: role in interpretation of studies of prevention and menopausal hormone therapy. Cancer Epidemiol Biomark Prev 21(7):1038–1048
42. Hofvind S, Iversen BF, Eriksen L, Styr BM, Kjellevold K, Kurz KD (2011) Mammographic morphology and distribution of calcifications in ductal carcinoma in situ diagnosed in organized screening. Acta Radiol 52(5):481–487
43. O'Grady S, Morgan MP (2018) Microcalcifications in breast cancer: from pathophysiology to diagnosis and prognosis. Biochim Biophys Acta 1869(2):310–320
44. Boyd N, Berman H, Zhu J, Martin LJ, Yaffe MJ, Chavez S et al (2018) The origins of breast cancer associated with mammographic density: a testable biological hypothesis. Breast Cancer Res 20(1):17
45. Weigelt B, Geyer FC, Reis-Filho JS (2010) Histological types of breast cancer: how special are they? Mol Oncol 4(3):192–208