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EPIDEMIOLOGY

The impact of selected risk factors among breast cancer molecular subtypes: a case-only study

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Abstract

Purpose Breast cancer (BC) risk factors have been differentially associated with BC subtypes, but quantification is still undefined. Therefore, we compared selected risk factors with BC subtypes, using a case-case approach.

Methods We retrieved 1321 invasive female BCs from the Piedmont Cancer Registry. Through record linkage of clinical records, we obtained data on estrogen (Er) and progesterone (Pr) receptors, Ki67 and HER2+ status, BC family history, breast imaging reporting and data system (BI-RADS) density, reproductive risk factors and education. We defined BC subtypes as follows : luminal A (Er+ and/or Pr+, HER2−, low Ki67), luminal BH- (Er+ and/or Pr+, HER2−, Ki67 high), luminal BH+ (Er+ and/or Pr+, HER2+), HER2+ (Er−, Pr−, HER2+),) and triple negative (Er−, Pr−, HER2−). Using a multinomial regression model, we estimated the odds ratios (ORs) for selected BC risk factors considering luminal A as reference.

Results For triple negative, the OR for BC family history was 1.83 (95% confidence interval (CI) 1.13–2.97). Compared to BI-RADS 1, for triple negative, the OR for BI-RADS 2 was 0.56 (95% CI 0.27–1.14) and for BI-RADS 3–4 was 0.37 (95% CI 0.15–0.88); for luminal BH+, the OR for BI-RADS 2 was 2.36 (95% CI 1.08–5.11). For triple negative, the OR for high education was 1.78 (95% CI 1.03–3.07), and for late menarche, the OR was 1.69 (95% CI 1.02–2.81). For luminal BH+, the OR for parous women was 0.56 (95% CI 0.34–0.92).

Conclusions This study supported BC etiologic heterogeneity across subtypes, particularly for triple negative.

Keyword Breast cancer subtypes · Molecular epidemiology · Tumour heterogeneity · Breast cancer risk factors · Triple negative

Abbreviations

BC	Breast cancer
Er	Estrogen receptor
Pr	Progesterone receptor
BI-RADS	Breast imaging reporting and data system
OR	Odds ratio
CI	Confidence interval
IHC	Immunohistochemistry
Registro Tumori Piemonte – RTP	Piedmont Cancer Registry
ICD-O-3	International Classification of Disease for Oncology 3rd edition
AOU	Azienda Ospedaliera Universitaria
BMI	Body mass index
WHO	World Health Organization
BD	Breast density
FISH	Fluorescence in situ hybridization
pTNM	Pathological Tumour-Node-Metastasis
CDI	Invasive ductal carcinoma
BCAC	Breast Cancer Association Consortium

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Introduction

Breast cancer (BC) is a heterogeneous disease, with multiple intrinsic molecular subtypes [1]. Subtypes are assessed by immunohistochemistry (IHC) and grouped, based on estrogen (Er) and progesterone (Pr) receptors, HER2 and Ki67 status, into luminal (A, BH−, BH+), HER2+ and triple negative [2]. Although BC subtypes vary in biological features, clinical and prognostic implications [3], it is still unclear if subtypes are etiologically distinct [4]. Data from epidemiologic studies suggest a different effect of risk factors on subtypes: some common risk factors may be restricted to certain subtypes, while others may be shared across subtypes [5, 6]. Thus, established BC risk factors may reflect the risk related to the most common subtypes (such as luminal A) [7].

The aim of this study is to compare, using a case-case approach, selected risk factors with each BC subtype, by comparing luminal A with other subtypes, using data from the Piedmont Cancer Registry (Registro Tumori Piemonte—RTP). Clarifying and quantifying which BC risk factors are subtype specific is particularly relevant for less frequent and more clinically aggressive subtypes (i.e. HER2+ and triple negative) [8]. This may have implications to improve subtype-targeted prevention.

Materials and methods

Study population and data collection

Using data from RTP, we identified a series of invasive female BCs ($n = 1332$) (International Classification of Disease for Oncology, 3rd edition, (ICD-O-3) site codes C50.0–50.9 [9]), diagnosed between January 2008 and December 2014 and treated at AOU (Azienda Ospedaliera Universitaria) Città della Salute e della Scienza, in Turin, Italy.

We retrieved information from RTP and clinical records from the hospital discharge form and reports. We carried out a deterministic record linkage based on unique patient-based variables.

For each cancer case included in this study, we collected age at diagnosis, education (we defined primary and middle school as low education, and high school and college as high education), age at menarche, parity (defined as number of births), age at menopause, BC family history in first- or second-degree relatives.

From pre-anaesthesia examination, additional data on tobacco smoking habits, as well as on weight and height, were obtained. Body mass index (BMI) was defined according to World Health Organization (WHO) criteria [10]. In addition, information on anti-diabetes drugs was considered.

Breast density (BD) was assessed from the preoperative mammogram report closest to the time of diagnosis. Density measurement was performed by a single radiologist from diagnostic digital mammograms of the unaffected breast. BD is routinely classified according to the Breast Imaging Reporting and Data System (BI-RADS) 5th edition into four categories: almost entirely fat, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense [11]. In this study, we re-categorized BI-RADS densities into low BD (BI-RADS density 1), medium BD (BI-RADS density 2) and high BD (BI-RADS density 3 and 4).

From pathology reports, information on Er, Pr, HER2 and Ki67 status (assessed by IHC) was extracted and classified on the basis of St. Gallen criteria [2] and ASCO-CAP guidelines [12, 13]. In particular, Er and Pr status are positive for a nuclear staining in at least 1% of tumour cells. HER2 positivity (IHC result 3+) is defined as a complete, intense and in at least 10% of tumour cells membrane staining. HER2 is negative (IHC score 0 and 1+) if the membrane staining is incomplete and faint perceptible or if no staining is observed. In case of an equivocal IHC score of 2+ (weak membrane staining with circumferential distribution in at least 10% of cells), an amplification test (Fluorescence in situ hybridization—FISH), which overruled results of IHC, was considered. The Ki67 index represents the percentage of positively staining cells among the total number of invasive cells in the scored area [14]. A cut-off of 20% was used to dichotomize (low versus high) Ki67 score. Considering Er, Pr, HER2 and Ki67 status together, we defined molecular subtypes as: luminal A (Er+ and/or Pr+, HER2−, low Ki67), luminal BH- (Er+ and/or Pr+, HER2−, Ki67 high), luminal BH+ (Er+ and/or Pr+, HER2+), HER2+ (Er−, Pr−, HER2+), triple negative (Er−, Pr−, HER2−). Moreover, pathology reports included information on tumour features categorized according to AJCC Cancer Staging Manual criteria [15]. In particular, we retrieved information on histotype and pathological Tumour-Node-Metastasis (pTNM) stage.

Statistical analysis

To evaluate the association between the five BC subtypes and selected risk factors, we simultaneously estimated the odds ratios (ORs), and their corresponding 95% confidence intervals (CIs), using a multinomial (baseline category) logistic regression model. We considered luminal A subtype as the reference category of the polytomous response variable. The model included terms for age at diagnosis (modelled as a continuous variable), histotype (invasive ductal carcinoma (CDI)/other), pTNM stage (1/2–3), family

history of BC (Yes/No), parity (Yes/No), age at menarche (< 13/ ≥ 13), age at menopause (< 45/45–54/ ≥ 55), BMI (< 25/ ≥ 25 kg/m^2), diabetes (Yes/No), BD (1/2/3 + 4), education level (Low/High) and tobacco smoking habits (Yes/No). We applied the same adjusted multinomial model stratifying by age at diagnosis (< 50/50–69/ ≥ 70). Likelihood ratio test and the Akaike's Information Criterion statistics were used to assess the goodness of fit of the models. Pearson Chi-Square test was also used to evaluate association between categorical variable.

The analyses were performed using SAS software, 9.4 version.

Results

In the study, we included 1321 invasive BCs, after exclusion of 7 cases with missing data for Er, Pr, HER2 or Ki67 status and 4 cases treated with only systemic therapy (no surgery performed).

Table 1 shows sociodemographic, reproductive and clinical characteristics of patients by molecular subtype of BC. Of the 1321 cases, 729 (55.2%) were luminal A, 317 (24%) luminal BH−, 115 (8.7%) luminal BH+, 56 (4.2%) HER2+ and 104 (7.9%) triple negative. The median age was 61 in luminal A, 65 in luminal BH−, 59 in luminal BH+, 62 in HER2+ and 58 in triple negative. Regarding tumour characteristics, 89.3% of HER2+ and 78.8% of triple-negative subtypes were CDI, compared to only 58.8% of luminal A. PTNM 1 was the most common stage in all subtypes, except for triple negative (48.3%). Median age at menarche was around 13 years in all subtypes, except for triple negative. Parous women were less frequent in luminal BH+. About 30% of women in each luminal subtype had positive BC family history, over 35% in HER2+ and more than 40% in triple negative. Shifting from BI-RADS 1 and BI-RADS 2, percentages quadrupled in luminal BH+ and did not modify in triple negative. All subtypes showed higher percentages for low education, except for triple negative.

Table 2 compares selected risk factors with cancer subtypes and gives the multivariate ORs and the corresponding 95% CIs. We considered luminal A as reference category of the response variable. With comparison to a negative BC family history, the OR for a positive BC family history was 1.83 (95% CI 1.13–2.97) for triple negative (versus luminal A). The OR for BI-RADS 2 (versus BI-RADS 1) was 0.56 (95% CI 0.27–1.14) and the OR for BI-RADS 3–4 was 0.37 (95% CI 0.15–0.88) for triple negative (versus luminal A). With reference to BI-RADS 1, the OR for BI-RADS 2 was 2.36 (95% CI 1.08–5.11) for luminal BH+ (versus luminal A).Compared to a lower education, the OR for a higher education was 1.78 (1.03–3.07) for triple negative (versus luminal A). The OR for late menarche (versus early) was 1.69 (1.02–2.81) for triple negative (versus luminal A).Compared to nulliparous women, the OR for parous women was 0.56 (95% CI 0.34–0.92) for luminal BH+ (versus luminal A). Considering number of births, with reference to nulliparity, for luminal BH+ (versus luminal A) the OR for one birth was 0.59 (95% CI 0.33–1.05) and the OR for at least 2 births was 0.55 (95% CI 0.32–0.93) (data not shown). When we stratified for age at diagnosis, for luminal BH+ (versus luminal A) the OR for parous women w as 0.36 (95% CI 0.12–1.03) in the < 50 stratum, the OR was 0.68 (95% CI 0.34–1.36) in the 50–69 stratum, and 0.99 (95% CI 0.20–5.01) in the ≥ 70 stratum (data not shown).

No associations were detected between tumour subtypes and BMI, age at menopause, tobacco smoking habits, diabetes (Supplementary Table S1). Results of multinomial model adjusted for age, family history, parity, age at menarche, age at menopause, education, density BI-RADS are shown in Supplementary Table S2.

Discussion

This case-only study showed that triple negative, compared to luminal A, was negatively associated with higher BD, while it was positively associated with positive family history of BC, higher education and late age at menarche. Further, this study suggested that luminal BH+, compared to luminal A, was positively associated with higher BD, whereas it was negatively associated with parity.

As regards to family history, one Asian case-case analysis showed an inverse association between family history and triple negative (OR 0.52, 95% CI 0.32–0.82) [16], but several case-only studies did not find any association [17–24]. Notably, most of these studies did not include Ki67 status, thus no distinction between luminal A and luminal BH− was possible. Further, different criteria were used to define positive family history: Edwards et al. [17] and Song et al. [24] included women with BC history in first- or second-degree relatives (as in our study), others restricted to first-degree relatives [21–23]. Only one study included women with a family history of breast and/or ovarian cancer [19], and some studies did not report degree-related information [16, 18, 20].

According to our results, Anderson et al. [25] showed, in a cohort of 1150 BC women, that the risk of triple negative (versus no triple negative) increased for women with a family history of BC in a first- or second-degree relative (OR 2.04, 95% CI 1.40–2.98). Moreover, Jiang et al. [26], analysing 645 BC cases, suggested that women with a BC family history in a first- or second-degree relative (versus without) were more likely to develop hormone receptor-positive tumours (OR 1.43, 95% CI 0.91–2.26). This association was significant when limited to cancers diagnosed before age 50

Table 1 Baseline characteristics and selected risk factors of 1321 breast cancer patients according to molecular subtypes

	Luminal A		Luminal BH−		Luminal BH+		HER2+		Triple negative	
	729	55.2	317	24	115	8.7	56	4.2	104	7.9
	N	%	N	%	N	%	N	%	N	%
Age										
<40	13	1.8	18	5.7	9	7.8	3	5.4	10	9.6
40–50	139	19.1	40	12.6	21	18.3	15	26.8	13	12.5
50–60	187	25.7	63	19.9	30	26.1	9	16.1	30	28.8
60–70	195	26.7	82	25.9	28	24.3	10	17.9	20	19.2
≥70	195	26.7	114	36.0	27	23.5	19	33.9	31	29.8
Median age	61		65		59		62		58	
Histotype										
CDI	429	58.8	236	74.4	84	73.0	50	89.3	82	78.8
Other	300	41.2	81	25.6	31	27.0	6	10.7	22	21.2
pTNM[a]										
1	381	79.7	96	57.5	38	57.6	23	63.9	28	48.3
2–3	97	20.3	71	42.5	28	42.4	13	36.1	30	51.7
Age at menarche[a]										
<13	288	48.3	138	52.3	49	52.1	23	48.9	29	36.7
≥13	308	51.7	126	47.7	45	47.9	24	51.1	50	63.3
Age at menopause[a]										
<45	52	11.1	17	7.9	14	18.4	7	18.4	10	14.9
45–54	352	75.4	168	77.8	50	65.8	28	73.7	53	79.1
≥54	63	13.5	31	14.4	12	15.8	3	7.9	4	6.0
Parity[a]										
0	117	16.7	44	14.2	30	26.8	10	18.5	16	16.7
1	212	30.2	90	29.1	31	27.7	17	31.5	26	27.1
≥2	373	53.1	175	56.6	51	45.5	27	50.0	54	56.3
Family history[a]										
No	433	68.6	170	70.0	66	67.3	27	62.8	48	56.5
Yes	198	31.4	73	30.0	32	32.7	16	37.2	37	43.5
BMI (kg/m^2)[a]										
<25	375	55.1	141	47.0	61	55.0	21	40.4	48	48.5
≥25	305	44.9	159	53.0	50	45.0	31	59.6	51	51.5
Density BI-RADS[a]										
1	101	25.3	44	31.7	10	14.3	8	28.6	22	39.3
2	171	42.9	58	41.7	43	61.4	13	46.4	22	39.3
3–4	127	31.8	37	26.6	17	24.3	7	25.0	12	21.4
Education[a]										
Low	309	57.9	117	57.4	41	51.3	28	73.7	35	47.3
High	225	42.1	87	42.6	39	48.8	10	26.3	39	52.7
Smoking habit[a]										
No	208	29.9	70	23.9	38	34.5	14	25.9	28	27.7
Yes	487	70.1	223	76.1	72	65.5	40	74.1	73	72.3
Diabetes										
No	671	92.0	287	90.5	109	94.8	53	94.6	99	95.2
Yes	58	8.0	30	9.5	6	5.2	3	5.4	5	4.8

[a]The sum does not add up to the total because of missing values

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer subtypes as compared to luminal A, according to selected risk factors

		Molecular subtypes (reference luminal A)			
		Luminal BH−	Luminal BH +	HER2 +	Triple negative
		OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)
Family history	No	1[b]	1[b]	1[b]	1[b]
	Yes	0.98 (0.70–1.37)	1.00 (0.62–1.60)	1.27 (0.66–2.46)	1.83 (1.13–2.97)
Density BI-RADS	1	1[b]	1[b]	1[b]	1[b]
	2	1.00 (0.61–1.65)	2.36 (1.08–5.11)	1.16 (0.43–3.12)	0.56 (0.27–1.14)
	3–4	0.97 (0.54–1.73)	1.17 (0.47–2.93)	0.85 (0.26–2.79)	0.37 (0.15–0.88)
Education	Low	1[b]	1[b]	1[b]	1[b]
	High	1.18 (0.82–1.70)	1.21 (0.73–2.01)	0.48 (0.22–1.04)	1.78 (1.03–3.07)
Age at menarche	< 13	1[b]	1[b]	1[b]	1[b]
	≥ 13	0.82 (0.60–1.11)	0.91 (0.58–1.43)	1.01 (0.54–1.87)	1.69 (1.02–2.81)
Parity	No	1[b]	1[b]	1[b]	1[b]
	Yes	1.01 (0.68–1.51)	0.56 (0.34–0.92)	0.81 (0.38–1.74)	0.98 (0.54–1.81)

Akaike's Information Criterion 3150.279

[a]Adjusted for age, histotype (CDI/Other), pTNM stage (1/2 + 3), family history (Yes/No), parity (Yes/No), age at menarche (< 13/≥ 13), age at menopause (< 45/45–54/≥ 55), BMI (< 25/≥ 25 kg/m^2), education (Low/High), density BI-RADS (1/2/3–4), smoking (Yes/No) and diabetes (Yes/No)

[b]Reference category for covariates

(OR 2.79, 95% CI 1.34–5.81). Our study provided evidence that triple-negative patients have a familial background of breast cancer, underlying that genetic susceptibility may play a stronger role in triple-negative carcinogenesis as compared to other subtypes.

As regards BD, a meta-analysis of case-only studies [27] showed no differences in risk for estrogen receptor-negative versus estrogen receptor-positive tumours across BD categories, although significant heterogeneity across studies was observed. No BD subtypes association was also reported in two other smaller case-only studies [28, 29]. However, in line with our findings on triple negative-BD inverse association, Arora et al. [30] observed in a cohort of women with BCs (1323) a lower risk of triple negative (versus, according to our subtypes classification, luminal A and luminal BH- considered together due to the lack of information on Ki67 status) in patients with extremely dense breast (OR 0.39, 95% CI 0.20–0.77 for BI-RADS 4 versus others); Kim et al. [31], in a case-only study including 178 BC cases, showed that women with high BD (BI-RADS 3 and 4 versus BI-RADS 1 and 2) were less likely to have triple negative compared to luminal A and BH- (OR 0.23, 95% CI 0.07–0.76). Further, using a quantitative method of BD assessment, Shaikh et al. [32] showed in a small study, including 123 BC cases, that triple negative had a significant lower percent density compared with non-triple negative and Conroy et al. [33] estimated a 26% higher risk of developing hormone receptor-positive cancers per 10% increase in density. Moreover, two other case-only studies suggested an increase in risk for HER2-enriched subtypes in dense breast. In particular, Edwards et al. [17] reported an OR 2.98 (95% CI 1.14–7.83) for extremely dense breast (versus fibroglandular) in HER2+ tumours, compared to luminal A (remarkably, this subtype was assigned by hormone receptor status, tumour grade, and mitotic score); Li et al. [34], in a Chinese study including 2001 BC cases, considering fat and fibroglandular as reference category, showed an increased risk of HER2+ (OR 1.81, 95% CI 1.08–3.06) in extremely dense breast and an increased risk for luminal BH + (OR 1.40, 95% CI 1.01–1.96) in the heterogeneously dense breast, compared to luminal A. Our study described a similar increase in risk for luminal BH + in fibroglandular breast (versus fat) compared to luminal A, but no significant association emerged for HER2+. Our findings suggest that dense breast tissue supports a hormonal microenvironment which could promote hormone receptor-positive tumours development (and maybe HER2− enriched subtypes). Thus, being luminal subtypes of the most widespread cancers, the positive and established association between BD and BC could be driven by these subtypes, while this association may be weaker, or null, for triple-negative tumours.

The risk of triple negative appeared also influenced by a high education. Few studies have addressed the association between the level of education and BC risk (an Italian case–control reported that an elevated level of education accounted for 20.3% of BC cases [35], and fewer have focused on the relation among subtypes. A population-based study of 476 Atlanta (USA) women with BC showed, in a case-case analysis, no association between education (college degree versus other) and triple negative [36]. Education

is a general indicator of lifestyle habits such as diet, physical exercise and hormone preparation use, which might explain this increase in risk.

Despite the vast amount of literature addressing the relationship between reproductive factors and subtypes-related risk, no clear patterns have already been defined [37]. In a large case-only analysis from the Breast Cancer Association Consortium (BCAC) Studies [23], which considered together luminal A and luminal BH- as reference, no significant differences emerged for the age at menarche (≤ 12 versus ≥ 15) in triple negative (OR 1.08, 95% CI 0.92–1.28) as well as no significant differences emerged for parity (nulliparity versus parity) in luminal BH + (OR 1.00, 95% CI 0.85–1.18) and in HER2+ (OR 0.98, 95% CI 0.81–1.20). Moreover, a more recent case-only study using BCAC data [38] did not observe, comparing to luminal A (grade was used to categorize this subtype instead of Ki67 positivity), associations between parity (yes versus no) and both luminal BH + (OR 1.04, 95% CI 0.88–1.24) and HER2+ (OR 1.04, 95% CI 0.83–1.29). Further, smaller case-only studies, compared to luminal A and BH-, did not find any significant differences in the association between triple negative and age at menarche (< 13 versus ≥ 13) [16, 20], as well as between luminal BH + and number of births (nulliparity, versus 1–2, versus 3 or more) [16, 18, 20]. In contrast with our findings, two case-only studies showed that women with early age at menarche were more likely to be found in triple negative. In particular, a Chinese study [22] including 8067 BCs reported an increase in risk (OR 1.33, 95% CI 1.02–1.74) for age at menarche ≤ 13 (versus ≥ 16) compared to luminal A and a population-based study of 476 BCs [36] reported an increase in risk (OR 1.55, 95% CI 1.08–2.23) for age at menarche < 12 (versus ≥ 12) compared to luminal A and BH-. Similarly to our findings, a case-only study [39], conducted on 1041 women with invasive BCs, suggested, comparing to luminal A and BH-, that triple negative was more likely in women with shorter menstruation duration (OR 1.27, 95%CI 0.88–1.82 for age at menarche ≥ 13), and tumours expressing HER2+ (both luminal BH + and HER2+) were less likely in parous women (OR 0.87, 95% CI 0.61–1.24 comparing at least 3 births with 2 births). Our results indicate that hormonal risk factors have a greater impact on luminal type BC than on triple negative. This is confirmed by our findings about BD, which could suggest that hormonal factors have a minor role on triple-negative development. Indeed, the decrease in risk of luminal BH + (and likely HER2+) in parous women suggests that hormonal factors linked to pregnancy could induce a somewhat protective effect against HER2-positive BCs [38].

Limitations of this study included BD assessment that was relied on BI-RADS classification, a visual and subjective method; held by a single reader, no assessment of intra o inter observer variability was performed. Moreover, prior studies addressing this topic are heterogeneous, due to differences in study populations, BD and receptor status assessment, subtype classification criteria as well as adjustment for covariates. These disparities limited comparison with other studies and could partly explain lack of concordance across studies. Further, our data sources did not include details on alcohol intake and age at first birth; thus, adjustment for these factors was not possible.

Strengths included its case-only design, which reduces selection and information bias. Information bias was also minimized since data were collected by doctors and hormone receptor status was assessed in the same hospital laboratory. Further, considering that women plausibly did not differentially recall according to their BC subtype, recall bias unlikely impact our findings. Moreover, other strengths include the spectrum of BC-related factors considered (reproductive, sociodemographic, anthropometric and lifestyle risk factors, radiologic index (BD), tumour characteristics) and the accurate criteria adopted to define molecular subtypes. Notably, tumour classification included Ki67 status.

Conclusion

This study provided further quantification of BC heterogeneity. This could redefine the role of some risk factors among subtypes, reflecting, in an etiological perspective, potential mechanisms of carcinogenesis.

Author contributions Margherita Pizzato: study concepts and design, data acquisition, data analysis and interpretation, manuscript writing, editing and review. Greta Carioli: data analysis and interpretation, manuscript preparation, editing and review. Stefano Rosso: study design, data acquisition, manuscript writing and review. Roberto Zanetti: study design, manuscript writing and review. Carlo La Vecchia: study concepts and design, results interpretation, manuscript writing and review.

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Data availability The data that support the findings of this study are available from Piedmont Cancer Registry (Registro Tumori Piemonte – RTP), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of RTP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflict of interest.

Ethical approval The investigation did not involve any human contact, but only record linkage analysis of administrative healthcare databases.

References

1. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295(21):2492–2502. https://doi.org/10.1001/jama.295.21.2492
2. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, Senn HJ, Panel M (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24(9):2206–2223. https://doi.org/10.1093/annonc/mdt303
3. van Maaren MC, Strobbe LJA, Smidt ML, Moossdorff M, Poortmans PMP, Siesling S (2018) Ten-year conditional recurrence risks and overall and relative survival for breast cancer patients in the Netherlands: taking account of event-free years. Eur J Cancer 102:82–94. https://doi.org/10.1016/j.ejca.2018.07.124
4. Holm J, Eriksson L, Ploner A, Eriksson M, Rantalainen M, Li J, Hall P, Czene K (2017) Assessment of breast cancer risk factors reveals subtype heterogeneity. Cancer Res 77(13):3708–3717. https://doi.org/10.1158/0008-5472.CAN-16-2574
5. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, Boffetta P, Weiss M (2015) Breastfeeding and breast cancer risk by receptor status–a systematic review and meta-analysis. Ann Oncol 26(12):2398–2407. https://doi.org/10.1093/annonc/mdv379
6. Barnard ME, Boeke CE, Tamini RM (1856) Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochim Biophys Acta 1:73–85. https://doi.org/10.1016/j.bbcan.2015.06.002
7. Puig-Vives M, Sanchez MJ, Sanchez-Cantalejo J, Torrella-Ramos A, Martos C, Ardanaz E, Chirlaque MD, Perucha J, Diaz JM, Mateos A, Machon M, Marcos-Gragera R (2013) Distribution and prognosis of molecular breast cancer subtypes defined by immunohistochemical biomarkers in a Spanish population-based study. Gynecol Oncol 130(3):609–614. https://doi.org/10.1016/j.ygyno.2013.05.039
8. Brouckaert O, Laenen A, Vanderhaegen J, Wildiers H, Leunen K, Amant F, Berteloot P, Smeets A, Paridaens R, Christiaens MR, Floris G, Moerman P, Van Limbergen E, Peeters S, Weltens C, Vergote I, Neven P (2012) Applying the 2011 St Gallen panel of prognostic markers on a large single hospital cohort of consecutively treated primary operable breast cancers. Ann Oncol 23(10):2578–2584. https://doi.org/10.1093/annonc/mds062
9. WHO International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Available at: https://www.hoint/classifications/icd/adaptations/oncology/en/ (Last accessed August 2019)
10. Body mass index - BMI Available at: https://www.eurowhoint/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi (Last accessed August 2019)
11. Spak DA, Plaxco JS, Santiago L, Dryden MJ, Dogan BE (2017) BI-RADS((R)) fifth edition: A summary of changes. Diagn Interv Imaging 98(3):179–190. https://doi.org/10.1016/j.diii.2017.01.001
12. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M (2018) Human epidermal growth factor receptor 2 testing in breast cancer: american society of clinical oncology/college of american pathologists clinical practice guideline focused update. Arch Pathol Lab Med 142(11):1364–1382. https://doi.org/10.5858/arpa.2018-0902-SA
13. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S (2010) American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 6(4):195–197. https://doi.org/10.1200/JOP.777003
14. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T, McShane L, Paik S, Penault-Llorca F, Prudkin L, Regan M, Salter J, Sotiriou C, Smith IE, Viale G, Zujewski JA, Hayes DF, International Ki-67 in Breast Cancer Working G (2011) Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 103(22):1656–1664. https://doi.org/10.1093/jnci/djr393
15. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Hortobagyi GN (2017) Breast Cancer Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 67(4):290–303. https://doi.org/10.3322/caac.21393
16. Devi CR, Tang TS, Corbex M (2012) Incidence and risk factors for breast cancer subtypes in three distinct South-East Asian ethnic groups: Chinese, Malay and natives of Sarawak. Malaysia Int J Cancer 131(12):2869–2877. https://doi.org/10.1002/ijc.27527
17. Edwards BL, Atkins KA, Stukenborg GJ, Novicoff WM, Larson KN, Cohn WF, Harvey JA, Schroen AT (2017) The Association of Mammographic Density and Molecular Breast Cancer Subtype. Cancer Epidemiol Biomarkers Prev 26(10):1487–1492. https://doi.org/10.1158/1055-9965.EPI-16-0881
18. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, Lee MM, Ambrosone CB, Caan BJ (2009) Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res 11(3):R31. https://doi.org/10.1186/bcr2261
19. Redondo CM, Gago-Dominguez M, Ponte SM, Castelo ME, Jiang X, Garcia AA, Fernandez MP, Tome MA, Fraga M, Gude F, Martinez ME, Garzon VM, Carracedo A, Castelao JE (2012) Breast feeding, parity and breast cancer subtypes in a Spanish cohort. PLoS ONE 7(7):e40543. https://doi.org/10.1371/journal.pone.0040543
20. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, Livasy C, Carey L, Earp HS, Perou CM (2008) Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 109(1):123–139. https://doi.org/10.1007/s10549-007-9632-6
21. Abubakar M, Sung H, Bcr D, Guida J, Tang TS, Pfeiffer RM, Yang XR (2018) Breast cancer risk factors, survival and recurrence, and tumor molecular subtype: analysis of 3012 women from an indigenous Asian population. Breast Cancer Res 20(1):114. https://doi.org/10.1186/s13058-018-1033-8
22. Zhang L, Huang Y, Feng Z, Wang X, Li H, Song F, Liu L, Li J, Zheng H, Wang P, Song F, Chen K (2019) Comparison of breast cancer risk factors among molecular subtypes: a case-only study. Cancer Med 8(4):1882–1892. https://doi.org/10.1002/cam4.2012
23. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, Gaudet M, Schmidt MK, Broeks A, Cox A, Fasching PA, Hein R, Spurdle AB, Blows F, Driver K, Flesch-Janys D, Heinz J, Sinn P, Vrieling A, Heikkinen T, Aittomaki K, Heikkila P, Blomqvist C, Lissowska J, Peplonska B, Chanock S, Figueroa J, Brinton L, Hall P, Czene K, Humphreys K, Darabi H, Liu J, Veer LJ, van Leeuwen FE, Andrulis IL, Glendon G, Knight JA, Mulligan AM, O'Malley FP, Weerasooriya N, John EM, Beckmann MW, Hartmann A, Weihbrecht SB, Wachter DL, Jud SM, Loehberg CR, Baglietto L, English DR, Giles GG, McLean CA, Severi G, Lambrechts D, Vandorpe T, Weltens C, Paridaens R, Smeets A, Neven P, Wildiers H, Wang X, Olson JE, Cafourek V, Fredericksen Z, Kosel M, Vachon C, Cramp HE, Connley D, Cross SS, Balasubramanian SP, Reed MW, Dork T, Bremer M, Meyer A, Karstens JH, Ay A, Park-Simon TW, Hillemanns P, Arias Perez JI, Menendez Rodriguez P, Zamora P, Benitez J, Ko

YD, Fischer HP, Hamann U, Pesch B, Bruning T, Justenhoven C, Brauch H, Eccles DM, Tapper WJ, Gerty SM, Sawyer EJ, Tomlinson IP, Jones A, Kerin M, Miller N, McInerney N, Anton-Culver H, Ziogas A, Shen CY, Hsiung CN, Wu PE, Yang SL, Yu JC, Chen ST, Hsu GC, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Lindblom A, Margolin S, Jakubowska A, Lubinski J, Huzarski T, Byrski T, Gorski B, Gronwald J, Hooning MJ, Hollestelle A, van den Ouweland AM, Jager A, Kriege M, Tilanus-Linthorst MM, Collee M, Wang-Gohrke S, Pylkas K, Jukkola-Vuorinen A, Mononen K, Grip M, Hirvikoski P, Winqvist R, Mannermaa A, Kosma VM, Kauppinen J, Kataja V, Auvinen P, Soini Y, Sironen R, Bojesen SE, Orsted DD, Kaur-Knudsen D, Flyger H, Nordestgaard BG, Holland H, Chenevix-Trench G, Manoukian S, Barile M, Radice P, Hankinson SE, Hunter DJ, Tamimi R, Sangrajrang S, Brennan P, McKay J, Odefrey F, Gaborieau V, Devilee P, Huijts PE, Tollenaar RA, Seynaeve C, Dite GS, Apicella C, Hopper JL, Hammet F, Tsimiklis H, Smith LD, Southey MC, Humphreys MK, Easton D, Pharoah P, Sherman ME, Garcia-Closas M (2011) Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 103(3):250–263. https://doi.org/10.1093/jnci/djq526

24. Song N, Choi JY, Sung H, Chung S, Song M, Park SK, Han W, Lee JW, Kim MK, Yoo KY, Ahn SH, Noh DY, Kang D (2014) Heterogeneity of epidemiological factors by breast tumor subtypes in Korean women: a case-case study. Int J Cancer 135(3):669–681. https://doi.org/10.1002/ijc.28685
25. Anderson K, Thompson PA, Wertheim BC, Martin L, Komenaka IK, Bondy M, Daneri-Navarro A, Meza-Montenegro MM, Gutierrez-Millan LE, Brewster A, Madlensky L, Tobias M, Natarajan L, Martinez ME (2014) Family history of breast and ovarian cancer and triple negative subtype in hispanic/latina women. Springerplus 3:727. https://doi.org/10.1186/2193-1801-3-727
26. Jiang X, Castelao JE, Chavez-Uribe E, Fernandez Rodriguez B, Celeiro Munoz C, Redondo CM, Pena Fernandez M, Novo Dominguez A, Pereira CD, Martinez ME, Garcia-Caballero T, Fraga Rodriguez M, Antunez J, Carracedo A, Forteza-Vila J, Gago-Dominguez M (2012) Family history and breast cancer hormone receptor status in a Spanish cohort. PLoS ONE 7(1):e29459. https://doi.org/10.1371/journal.pone.0029459
27. Antoni S, Sasco AJ, dos Santos SI, McCormack V (2013) Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis Breast Cancer Res Treat 137(2):337–347. https://doi.org/10.1007/s10549-012-2362-4
28. Ma H, Luo J, Press MF, Wang Y, Bernstein L, Ursin G (2009) Is there a difference in the association between percent mammographic density and subtypes of breast cancer? Luminal A and triple-negative breast cancer. Cancer Epidemiol Biomarkers Prev 18(2):479–485. https://doi.org/10.1158/1055-9965.EPI-08-0805
29. Eriksson L, Hall P, Czene K, Dos Santos SI, McCormack V, Bergh J, Bjohle J, Ploner A (2012) Mammographic density and molecular subtypes of breast cancer. Br J Cancer 107(1):18–23. https://doi.org/10.1038/bjc.2012.234
30. Arora N, King TA, Jacks LM, Stempel MM, Patil S, Morris E, Morrow M (2010) Impact of breast density on the presenting features of malignancy. Ann Surg Oncol 17(Suppl 3):211–218. https://doi.org/10.1245/s10434-010-1237-3
31. Kim MY, Choi N, Yang JH, Yoo YB, Park KS (2015) Background parenchymal enhancement on breast MRI and mammographic breast density: correlation with tumour characteristics. Clin Radiol 70(7):706–710. https://doi.org/10.1016/j.crad.2015.02.017
32. Shaikh AJ, Mullooly M, Sayed S, Ndumia R, Abayo I, Orwa J, Wasike R, Moloo Z, Gierach GL (2018) Mammographic Breast Density and Breast Cancer Molecular Subtypes: The Kenyan-African Aspect. Biomed Res Int 2018:6026315. https://doi.org/10.1155/2018/6026315
33. Conroy SM, Pagano I, Kolonel LN, Maskarinec G (2011) Mammographic density and hormone receptor expression in breast cancer: the Multiethnic Cohort Study. Cancer Epidemiol 35(5):448–452. https://doi.org/10.1016/j.canep.2010.11.011
34. Li E, Guida JL, Tian Y, Sung H, Koka H, Li M, Chan A, Zhang H, Tang E, Guo C, Deng J, Hu N, Lu N, Gierach GL, Li J, Yang XR (2019) Associations between mammographic density and tumor characteristics in Chinese women with breast cancer. Breast Cancer Res Treat 177(2):527–536. https://doi.org/10.1007/s10549-019-05325-6
35. Tavani A, Braga C, La Vecchia C, Negri E, Russo A, Franceschi S (1997) Attributable risks for breast cancer in Italy: education, family history and reproductive and hormonal factors. Int J Cancer 70(2):159–163. https://doi.org/10.1002/(sici)1097-0215(19970117)70:2<159:aid-ijc4>3.0.co;2-w
36. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, Eley JW (2009) The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control 20(7):1071–1082. https://doi.org/10.1007/s10552-009-9331-1
37. Anderson KN, Schwab RB, Martinez ME (2014) Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat 144(1):1–10. https://doi.org/10.1007/s10549-014-2852-7
38. Brouckaert O, Rudolph A, Laenen A, Keeman R, Bolla MK, Wang Q, Soubry A, Wildiers H, Andrulis IL, Arndt V, Beckmann MW, Benitez J, Blomqvist C, Bojesen SE, Brauch H, Brennan P, Brenner H, Chenevix-Trench G, Choi JY, Cornelissen S, Couch FJ, Cox A, Cross SS, Czene K, Eriksson M, Fasching PA, Figueroa J, Flyger H, Giles GG, Gonzalez-Neira A, Guenel P, Hall P, Hollestelle A, Hopper JL, Ito H, Jones M, Kang D, Knight JA, Kosma VM, Li J, Lindblom A, Lilyquist J, Lophatananon A, Mannermaa A, Manoukian S, Margolin S, Matsuo K, Muir K, Nevanlinna H, Peterlongo P, Pylkas K, Saajrang S, Seynaeve C, Shen CY, Shu XO, Southey MC, Swerdlow A, Teo SH, Tollenaar R, Truong T, Tseng CC, van den Broek AJ, van Deurzen CHM, Winqvist R, Wu AH, Yip CH, Yu JC, Zheng W, Milne RL, Pharoah PDP, Easton DF, Schmidt MK, Garcia-Closas M, Chang-Claude J, Lambrechts D, Neven P (2017) Reproductive profiles and risk of breast cancer subtypes: a multi-center case-only study. Breast Cancer Res 19(1):119. https://doi.org/10.1186/s13058-017-0909-3
39. Martinez ME, Wertheim BC, Natarajan L, Schwab R, Bondy M, Daneri-Navarro A, Meza-Montenegro MM, Gutierrez-Millan LE, Brewster A, Komenaka IK, Thompson PA (2013) Reproductive factors, heterogeneity, and breast tumor subtypes in women of mexican descent. Cancer Epidemiol Biomarkers Prev 22(10):1853–1861. https://doi.org/10.1158/1055-9965.EPI-13-0560