Original Article

The association of single nucleotide polymorphisms (SNPs) with breast density and breast cancer survival: the Malmö Diet and Cancer Study

Acta Radiologica
2020, Vol. 61(10) 1326–1334

DOI: 10.1177/0284185119900436
journals.sagepub.com/home/acr

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Abstract

Background: Genetic factors are important in determining breast density, and heritable factors account for 60% of the variation. Certain single nucleotide polymorphisms (SNPs) are associated with density and risk of breast cancer but the association with prognosis is not clear.

Purpose: To investigate associations between selected SNPs and breast cancer survival in the Malmö Diet and Cancer Study (MDCS).

Material and Methods: A total of 724 unrelated women with breast cancer and registered radiological and pathological data were identified in MDCS 1991–2007, with genotyping available for 672 women. Associations among 15 SNPs, density, and breast cancer-specific survival were analyzed using logistic/Cox regression, adjusted for factors affecting density and survival. Variants significantly associated with either density or survival were validated in a large independent breast cancer cohort (LIBRO-1).

Results: Minor homozygotes of SNPs rs9383589, *CCDC170* and rs6557161, *ESR1* were associated with high breast density (adjusted odds ratio [AOR] 8.97, 95% confidence interval [CI] 1.35–59.57; AOR 2.08, 95% CI 1.19–3.65, respectively) and poorer breast cancer survival (adjusted hazard ratio [HR_{adj}] 6.46, 95% CI 1.95–21.39; HR_{adj} 2.30, 95% CI 1.33–3.96, respectively) compared to major homozygotes. For SNP rs3757318, *ESR1*, minor homozygotes (HR_{adj} 7.46, 95% CI 2.28–24.45) were associated with poorer survival. We confirmed that rs6557161, *ESR1* was significantly associated with both density and survival in the LIBRO-1 study.

Conclusion: These findings support a shared genetic basis for density and breast cancer survival. The SNP significantly associated with both density and survival in both cohorts may be of interest in future research investigating polygenic risk scores for breast cancer risk and screening stratification purposes.

Keywords
Mammography, screening, breast, epidemiology, primary neoplasms, normal variants

Date received: 5 June 2019; accepted: 16 December 2019

Introduction

Breast cancer prognosis has improved over the years due to advances in diagnostics and treatments. Still, 522,000 women die of breast cancer each year, making breast cancer the fifth most common cause of death among women worldwide (1). Understanding factors related to breast cancer survival is paramount in order to identify women at risk for fatal breast cancer at earlier stages of the disease.

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Breast imaging is a central priority for prevention and treatment (2). Breast density is a readily available mammographic biomarker and high density has proven to be associated with increased risk of breast cancer (3). Previous studies on density and survival are inconclusive with some publications not showing an association (4,5), but some, including a study on the cohort described in the present study (6), report an impaired survival with higher density (6,7). Further speaking for a role of density in survival is the notion that women responding with decreased density during tamoxifen treatment have a better prognosis (8). The biological links between density, risk of breast cancer, and survival are complex and not yet fully understood. However, a recent review suggested a possible biological mechanism involving stroma cells and proteins (e.g. fibroblasts, immune cells, and collagen), which may contribute to or facilitate breast cancer development and progression (9).

In addition to the well-known, high-penetrance genes that increase the risk of breast cancer, the aggregate polygenetic effect of low-penetrant variants (i.e. single nucleotide polymorphisms [SNPs]) may contribute at least 14% to the heritability of breast cancer (2). Several SNPs are associated with breast density parameters and risk of breast cancer (10,11). Further, there may be genetic components common to risk of breast cancer and prognosis (12–14). Speaking against, however, a previous large study including several SNPs showed that there was no evidence that any of the SNPs associated with breast cancer susceptibility were associated with breast cancer survival (15). Importantly, none of the previously mentioned studies on risk of breast cancer and survival SNPs has considered density. This may be of importance since genetic variants associated with breast density and breast cancer survival may identify SNPs that could be used to optimize present risk scores. Such improved risk scores (based on image parameters, familial history, and genetic factors) could be used to assess an individual's breast cancer risk, as well as develop individualized breast cancer screening programs (16,17).

The aim of this study was to examine the association between breast density, breast cancer risk-associated SNPs, and breast cancer-specific survival among women participating in a large Swedish cohort study: the Malmö Diet and Cancer Study (MDCS) and with replication in a second cohort.

Material and Methods

The Malmö Diet and Cancer Study

The MDCS (LU 51-90) and the present study (Dnr 652/2005, Dnr 23/2007, and Dnr 2009/682) were approved by the regional Ethical Committee in Lund, Sweden. All women gave written informed consent.

The MDCS (18–20) was a population-based, prospective cohort study, which included 17,035 women (1991–1996). Cases of breast cancer were identified prospectively, and the associated pathological and radiological variables at breast cancer diagnosis (e.g. categorical breast density, mammographic tumor appearance, mode of detection) were collected and added to the database, in addition to baseline variables. The present study population (821 women) with exclusions is shown in Fig. 1. Cause of death (breast cancer as an underlying or subordinate cause of death) and vital status (alive or dead from another cause than breast cancer was classified as alive) was registered with last follow-up on 31 December 2016.

The LIBRO-1 study

The LIBRO-1 study was approved by the Regional Ethical Review Board (registration no. 2009/254-31). LIBRO-1 is a breast cancer cohort of patients diagnosed between 2001 and 2008 in the Stockholm/Gotland area who gave informed consent. The study was approved by the local ethics review board at Karolinska Institutet. Breast cancer risk factors, socioeconomic factors, and reproductive events were assessed by questionnaire. In addition, tumor characteristics were retrieved from the Swedish cancer registry and survival after breast cancer was ascertained from the Swedish causes of death registry, as described before with virtually no missing data (21). We only included patients with invasive breast cancer with available genotype information (see below).

Genotyping

DNA was extracted from stored blood samples and genotyping was successful for 780 women before study population exclusions (Fig. 1). Genotyping was performed using the HumanOmniExpressExome-BeadChip (OEE) version 1.0 or 1.1 Ch37 and iScan System (Illumina, San Diego, CA, USA) according to the manufacturer's recommended protocols. The OEE chip included 244,194 primarily exon markers and 706,924 markers for coverage of common genome-wide variation. Analyses were performed at MIT's Broad Institute and Harvard (USA), in addition to the Clinical Research Center (CRC) in Malmö, Sweden. During quality control (QC) for SNPs, 169,775 SNPs were excluded due to a lack of variation in European populations (monomorphic SNPs), a deviation from Hardy–Weinberg equilibrium in controls ($P < 10^{-6}$) or a variant call rate of <95% in all samples. This resulted in approximately 750,000 SNPs

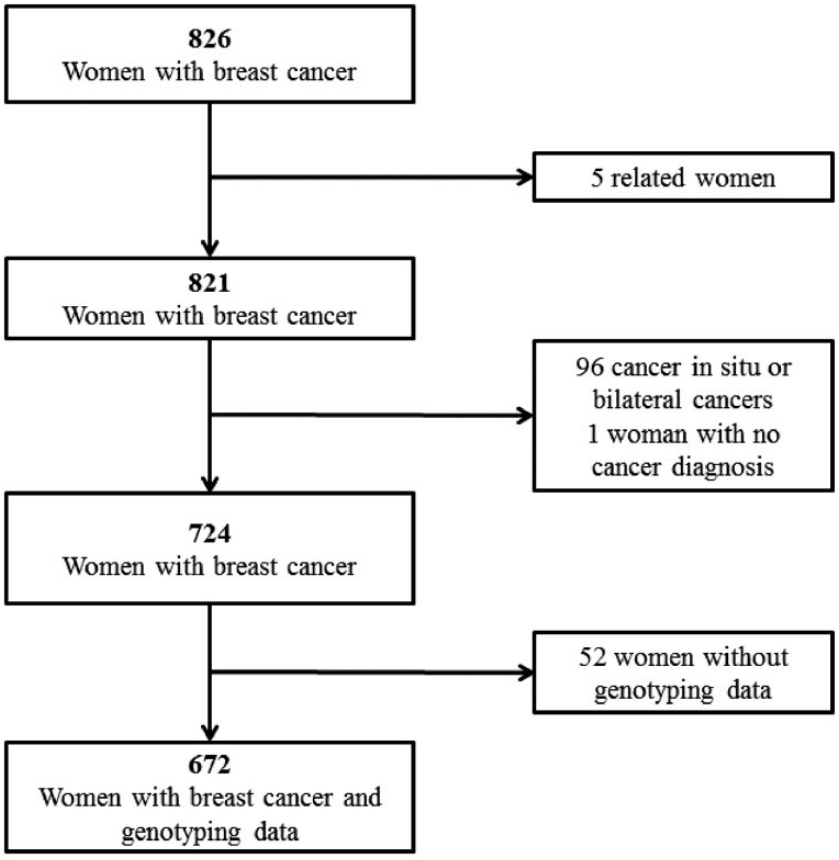

Fig. 1. Study population and exclusions.

remaining after QC. All QC was performed by using PLINK version 1.07 software. We only included individuals with a call rate >95% and inbreeding coefficients of −0.2 to 0.2 to control for excess of heterozygosity. Using identity by descent, shared first- and second-degree relatives were identified. One of the relatives was omitted, excluding five women (Fig. 1). Genotyping of the LIBRO-1 patients was done through the Breast Cancer Association Consortium (BCAC) on a custom Ilumina iSelect genotyping array as part of the Collaborative Oncological Gene-environment Study (iCOGS) (22). Imputation and quality control of variants and patients was performed as previously described (23). Patients without genotype data or which failed quality control were excluded. In total, 4431 breast cancer patients with genotype information were included in this study in order to replicate significant findings in an independent cohort.

SNP selection

We selected 15 SNPs that are associated with breast density and breast cancer risk from two recent meta-analyses based on Genome Wide Association Studies (GWAS) (10,11). Eight SNPs were not included on the OEE chip, and a web-based tool, SNAP Proxy (24), was used to identify SNPs with a linkage disequilibrium (LD) of $r^2 > 0.8$ to the missing SNP. The SNPs, proxy SNPs and genes are listed in Supplemental Table S1. All selected SNPs had a minor allele frequency (MAF) > 5% except for rs7289126 (MAF = 0.03). Genomic data for the 15 candidate SNPs were available for 672 women after QC (Fig. 1).

Breast density

Breast density was graded (fat involuted/moderately dense/dense) in the original radiology report of the breast cancer diagnostic mammogram and retrospectively retrieved for research purposes (6,25–27). The classification can be regarded as a modified Breast Imaging Reporting and Data System (BI-RADS) 4th Ed density categorization. "Fat involuted" corresponded to BI-RADS 1 (almost entirely fat), "moderately dense" to BI-RADS 2 and 3 (scattered fibroglandular densities and heterogeneously dense), and "dense" to BIRADS 4 (extremely dense). The breast density was estimated using both breasts, and all views were assessed by one of five experienced

breast radiologists (with >10 years of experience in breast radiology).

In LIBRO-1, the breast density of each patient was determined by a machine-learning based algorithm called STRATUS (28) and coded as dense (BI-RADS 4) and non-dense/mixed (BI-RADS 1-3), as based on BI-RADS 4th Ed. Breast density was measured at mammogram closest to breast cancer diagnosis.

Statistical analyses

Selected SNPs were analyzed as categorical variables (major homozygote allele (reference)/heterozygote/minor homozygote allele). Logistic regression was used to analyze SNPs in relation to dichotomized breast density (fatty/mixed density versus dense), which yielded odds ratios (OR) and 95% confidence intervals (CI); adjustments were made for age at diagnosis (continuous), hormone replacement therapy (HRT) at baseline (binary), and body mass index (BMI) at baseline (continuous). Associations between selected SNPs and breast cancer survival were analyzed using Cox's proportional hazards analysis, yielding an HR with a 95% CI; adjustments were made for age at diagnosis, tumor size (linear), axillary lymph node involvement (ALNI) (binary), histological grade (categorical on three levels), and estrogen receptor (ER 10% cut-off). In a second step, the survival analysis was adjusted for HRT at baseline and BMI at baseline (known determinants of breast density) in order to study the independent effect of the SNP. No correction for multiple testing was used, to avoid false negatives. The proportional hazards assumption was confirmed using a log-minus-log plot. Three women with unknown vital status at emigration were categorized as alive and included in analyses. For replication, we studied the effect of significant SNPs on density and breast cancer specific survival in 4431 patients with invasive breast cancer from the LIBRO-1 study using corresponding adjustment factors and statistical analyses. SPSS Statistics for Windows was used for the statistical analyses (v.25.0, IBM Corp., Armonk, NY, USA).

Results

Distributions of covariates in MDCS and LIBRO-1 are summarized by frequencies and percentages by breast cancer vital status (alive or dead from another cause *vs.* breast cancer specific death) (Table 1). All analyzed

Table 1. Distributions of covariates by breast cancer vital status (alive/breast cancer death).

	MDCS		LIBRO-1	
	Alive	Breast cancer death	Alive	Breast cancer death
Age at diagnosis (years)	63.8 (58.8–70.2)	64.5 (59.6–73.3)	59.0 (25.0–79.0)	59.5 (26.0–79.0)
Breast density				
Fatty/mixed	342 (62.6)	62 (49.2)	2706 (64.8)	166 (65.9)
Dense	170 (31.1)	45 (35.7)	1098 (26.3)	48 (19.0)
Missing	34 (6.2)	19 (15.1)	375 (9.0)	38 (15.1)
BMI at baseline (kg/m^2)	24.8 (22.7–27.8)	25.6 (23.4–28.5)	24.7 (16.0–50.4)	24.9 (16.7–44.6)
HRT at baseline				
Yes	155 (28.4)	30 (24)	750 (17.9)	31 (12.3)
No	389 (71.2)	96 (76)	2785 (66.6)	183 (72.6)
Missing	2 (0.4)	0	644 (15.4)	38 (15.1)
Estrogen receptor				
Positive	402 (73.6)	81 (64.3)	2930 (70.1)	162 (64.3)
Negative	53 (9.7)	23 (18.3)	480 (11.5)	40 (15.9)
Missing	91 (16.7)	22 (17.5)	769 (18.4)	50 (19.8)
Axillary lymph node involvement				
Positive	124 (22.7)	77 (61.1)	1215 (29.1)	153 (60.7)
Negative	419 (76.7)	47 (37.3)	2707 (64.8)	76 (30.2)
Missing	3 (0.5)	2 (1.6)	257 (6.2)	23 (9.1)
Tumor size (mm)	14 (10–20)	22 (15–31)	15.0 (2.0–80.0)	22.0 (2.0–80.0)
Missing	6 (1.1)	9 (7.1)	112 (2.7)	15 (6.0)
Histological grade				
I	159 (29.1)	12 (9.5)	542 (13.0)	4 (1.6)
II	255 (46.7)	47 (37.3)	1401 (33.5)	84 (33.3)
III	100 (18.3)	54 (42.9)	711 (17.0)	60 (23.8)
Missing	32 (5.9)	13 (10.3)	1525 (36.5)	104 (41.3)

Values are given as n (%) or median (range).

SNPs in MDCS are described in Supplemental Table S1.

SNPs and breast density

Significant associations among SNPs, breast density, and breast cancer survival are shown in Table 2. For rs9383589, *CCDC170* (adjusted OR [AOR] = 8.97, 95% CI = 1.35–59.57) and rs6557161, *ESR1* (AOR = 2.08, 95% CI = 1.19–3.65), there was a significant association between minor homozygotes and high breast density when compared to major homozygotes. In contrast, for rs7289126, *TMEM184B*, there was a significant association between both heterozygotes (AOR = 0.60, 95% CI = 0.40–0.90) and minor homozygotes (AOR = 0.58, 95% CI = 0.35–0.97) with fatty/mixed breast density when compared to major homozygotes. For 12 of the selected SNPs, no significant association with breast density was observed (Supplemental Table S1).

SNPs and breast cancer survival

Minor homozygotes of SNP rs9383589, *CCDC170* (adjusted hazard ratio [HR_{adj2}] = 6.46, 95% CI = 1.95–21.39) and rs6557161, *ESR1* (HR_{adj2} = 2.30, 95% CI = 1.33–3.96) were associated with impaired breast cancer survival in both steps of adjustment when compared to major homozygotes. For SNP rs3757318, *ESR1*, minor homozygotes (HR_{adj2} = 7.46, 95% CI = 2.28–24.45) were associated with impaired breast cancer survival, but an association with density was not established. For 12 of the selected SNPs, no significant relationship to breast cancer survival was shown.

Replication analysis

In the LIBRO-1 study, we were able to confirm a significant association of rs6557161, *ESR1* with breast density (OR_{adj} = 1.27, 95% CI = 1.08–1.50 and OR_{adj} = 1.35, 95% CI = 1.02–1.78 for heterozygotes and homozygotes minor, respectively) (Table 3). For the other SNPs, we did not find a significant association with breast density, however, the effect sizes of rs7289126 (heterozygotes and homozygote minors) were in the same orientation as in the MDCS study, although smaller. We found a significant effect of rs6557151, *ESR1* on breast cancer-specific survival (HR_{crude} = 1.36, 95% CI = 1.04–1.77, heterozygotes) and a borderline effect after first set of adjustment (HR_{adj1} = 1.67, 95% CI = 0.99–2.81, homozygote minors). However, in the second set of adjustments (adding BMI and HRT), no association was found. For both, rs9383589, *CCDC170* and rs3757318, *ESR1*, no individuals with the homozygote minor allele died due to breast cancer and, thus, we were not able to compute meaningful HRs.

Discussion

This paper highlights SNPs known to be associated with breast density and risk of breast cancer. This research demonstrates their association with density and impaired breast cancer survival in the MDCS and confirm the association in the same orientation in the LIBRO-1 study for the *ESR1* SNP. To the best of our knowledge, this is the first study to report these associations. Our results support the hypothesis that there might be a shared genetic basis for breast density and breast cancer survival.

For rs6557161, *ESR1* (proxy from rs2046210), there was an association with high breast density and poorer breast cancer survival in both MDCS and LIBRO-1. However, after the second set of adjustment (BMI and HRT) survival analyses (LIBRO-1), the association could no longer be seen, but with effect sizes still in the same direction as in MDCS. The potential reason for this could be a sample size issue, since some cases without data on BMI and HRT will be excluded from analyses in the second set of adjustment. In addition, previous studies on density and breast cancer-specific survival differ on adjustment of BMI and HRT, which questions their contribution in survival analyses (29). The original SNP (rs2046210, *ESR1*) has previously been associated with increased breast cancer risk and prognosis (30,31), and the risk allele (A) has been associated with higher breast density (11). The *ESR1* gene encodes the estrogen receptor, which regulates signal transduction of estrogen and is central in breast carcinogenesis (32). In addition, the *ESR1* gene has been shown to be involved in bone mineral density, which is also affected by estrogen (33).

The A allele of rs3757318, *ESR1* has been shown to correlate with increased risk of breast cancer and breast density (11), and the A allele was associated with poorer rates of breast cancer survival in the MDCS in this study. However, its relationship with breast density could not be significantly established and a statistically significant effect could not be replicated in the LIBRO-1. Of course, the impact on breast cancer survival is complex and facilitated through several mechanisms in addition to breast density. Considering the multifaceted roles of *ESR1* discussed previously, this could possibly involve estrogen-related mechanisms.

Homozygote minors of rs9383589, *CCDC170* (proxy from rs12665607) were associated with high breast density and poorer breast cancer survival in the MDCS. About breast density, this finding is similar to that of a previous study of the original SNP (10). The *CCDC170* gene is part of a breast cancer

Table 2. Selected SNPs in relation to breast density and breast cancer survival in invasive breast cancer – MDCS.

		Density			Breast cancer survival*			
SNP (gene)	Genotypes	Fatty, mixed/dense	Crude OR (95% CI)	AOR[†] (95% CI)	Alive/dead	Crude HR	HR_{adj1}[‡]	HR_{adj2}[§]
rs3757318 (*ESR1*)	GG (ref)	359/183	1.00	1.00	484/108	1.00	1.00	1.00
	GA	43/29	1.32 (0.80–2.19)	1.34 (0.78–2.29)	60/15	1.11 (0.65–1.91)	1.39 (0.75–2.56)	1.40 (0.76–2.59)
	AA	2/3	2.94 (0.49–17.77)	4.87 (0.76–31.27)	2/3	4.49 (1.43–14.17)	7.13 (2.19–23.17)	7.46 (2.28–24.45)
rs9383589 (*CCDC170*)	AA (ref)	357/179	1.00	1.00	477/108	1.00	1.00	1.00
Proxy from	AG	44/30	1.36 (0.83–2.24)	1.34 (0.79–2.27)	63/15	1.09 (0.64–1.88)	1.17 (0.62–2.20)	1.17 (0.62–2.20)
rs12665607	GG	2/4	3.99 (0.72–21.99)	8.97 (1.35–59.57)	3/3	3.32 (1.05–10.46)	6.37 (1.95–20.82)	6.46 (1.95–21.39)
Missing		1/2			3/0			
rs6557161 (*ESR1*)	AA (ref)	185/89	1.00	1.00	249/53	1.00	1.00	1.00
Proxy from	AG	183/90	1.02 (0.72–1.46)	1.09 (0.74–1.59)	241/51	1.03 (0.70–1.51)	0.96 (0.62–1.48)	0.97 (0.62–1.50)
rs2046210	GG	36/36	2.08 (1.23–3.52)	2.08 (1.19–3.65)	56/22	1.81 (1.10–2.98)	2.30 (1.34–3.97)	2.30 (1.33–3.96)
rs7289126 (*TMEM184B*)	CC (ref)	124/82	1.00	1.00	171/50	1.00	1.00	1.00
	CA	203/93	0.69 (0.48–1.01)	0.60 (0.40–0.90)	265/55	0.74 (0.50–1.08)	0.72 (0.47–1.10)	0.72 (0.47–1.10)
	AA	77/40	0.79 (0.49–1.26)	0.58 (0.35–0.97)	110/21	0.67 (0.40–1.11)	0.60 (0.33–1.08)	0.61 (0.34–1.11)

*Alive or dead from another cause than breast cancer was classified as alive.

[†]Adjusted for age at diagnosis, HRT at baseline, and BMI at baseline.

[‡]Adjusted for age at diagnosis, ALNI, histological grade, tumor size, ER.

[§]Adjusted for the above and BMI and HRT at baseline.

ALNI, axillary lymph node involvement; AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; HRT, hormone replacement therapy; MDCS, Malmö Diet and Cancer Study; SNP, single nucleotide polymorphism.

Table 3. Selected SNPs in relation to breast density and breast cancer survival in invasive breast cancer – LIBRO1.

		Density			Breast cancer survival*			
SNP	Genotypes	Fatty, mixed/dense	Crude OR (95% CI)	AOR[†] (95% CI)	Alive/dead	Crude HR	HR_{adj1}[‡]	HR_{adj2}[§]
rs3757318	GG (ref)	2517/1005	1.00	1.00	3661/220	1.00	1.00	1.00
	GA	342/135	0.99 (0.80–1.20)	1.07 (0.84–1.36)	497/32	1.06 (0.73–1.53)	1.11 (0.67–1.85)	1.16 (0.66–2.04)
	AA	13/6	1.16 (0.41–2.93)	1.54 (0.51–4.24)	21/0	NA	NA	NA
rs9383589	AA (ref)	2510/985	1.00	1.00	3639/217	1.00	1.00	1.00
	AG	344/155	1.15 (0.93–1.40)	1.24 (0.98–1.56)	511/35	1.14 (0.79–1.62)	1.29 (0.81–2.06)	1.12 (0.65–1.93)
	GG	18/6	0.85 (0.31–2.03)	1.08 (0.37–2.82)	29/0	NA	NA	NA
rs6557161	AA (ref)	1368/482	1.00	1.00	1943/98	1.00	1.00	1.00
	AG	1246/546	1.24 (1.08–1.44)	1.27 (1.08–1.50)	1845/127	1.36 (1.04–1.77)	1.04 (0.72–1.49)	0.86 (0.57–1.28)
	GG	258/118	1.30 (1.02–1.65)	1.35 (1.02–1.78)	391/27	1.39 (0.91–2.13)	1.67 (0.99–2.81)	1.32 (0.73–2.39)
rs7289126	CC (ref)	891/366	1.00	1.00	1310/71	1.00	1.00	1.00
	CA	1412/560	0.97 (0.83–1.13)	0.91 (0.76–1.09)	2041/142	1.27 (0.95–1.68)	1.33 (0.90–1.96)	1.46 (0.95–2.23)
	AA	569/220	0.94 (0.77–1.15)	0.85 (0.68–1.06)	828/39	0.88 (0.59–1.30)	0.87 (0.50–1.52)	0.71 (0.36–1.38)

*Alive or dead from another cause than breast cancer was classified as alive.

[†]Adjusted for age at diagnosis, HRT at baseline, and BMI at baseline.

[‡]Adjusted for age at diagnosis, ALNI, histological grade, tumor size, ER.

[§]Adjusted for the above and BMI and HRT at baseline.

ALNI, axillary lymph node involvement; AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; HRT, hormone replacement therapy; MDCS, Malmö Diet and Cancer Study; SNP, single nucleotide polymorphism.

susceptibility locus. Together with *ESRI*, it is involved in breast cancer carcinogenesis and progression (31). In addition, rs9383589, *CCDC170* in normal tissues adjacent to a breast tumor is associated with lower BMIs (31). This is interesting because BMI and breast density are inversely correlated (9).

In a recent paper on breast cancer risk loci and survival, Barrdahl et al. (14) reported the influence of two of 35 SNPs on overall survival in patients with breast cancer. Specifically, they found that the C-allele of rs3817198, *LSP1* correlated with improved overall survival, and the T-allele of rs3803662, *TNRC9* correlated with poorer overall survival. These two SNPs and corresponding alleles were previously shown to be related to increased breast density in another study (34). Rs3817198, *LSP1* was included in the present study, but we could not recapitulate any association with density or survival.

There is an increasing interest in developing stratified breast screening programs instead of the "one-size-fits-all" approaches presently in use. Polygenic risk scores (i.e. the combination of high-risk SNPs) in combination with information on family history and breast density could be used to achieve such a stratification (16,17). However, it is not clear which factors to include in such a score. If certain genetic factors (e.g. certain SNPs) influence the association of density, risk and survival, these SNPs would be of interest.

There was no formal assessment of inter-observer variability for density grading in the MDCS. However, same radiologists as in the present study double-read 5928 mammograms with substantial density agreement ($\kappa = 0.77$) (35). MDCS and LIBRO-1 used different density measurements, however, with density categories carefully approximated to be comparable. In the adjusted model in LIBRO-1, the effect sizes for density were in the same orientation as in MDCS, speaking in favor of the comparison. With 15 tested SNPs, one might suspect associations to be chance findings as a type I error. However, the fact that when associations were found, the associations were in general not borderline significant (in terms of CI) and the associations for two of the SNPs were present for both density and survival analyses, this strengthens our findings together with the replication analysis.

Importantly, we were able to confirm our findings on the *ESR1* rs6557161 in a large collection of cases of breast cancer from the LIBRO-1 study. Although only rs6557161, *ESR1* was statistically significantly associated with breast density and survival, one other SNP (rs7289126) had effect sizes in the same orientation as observed in the MDCS. Due to the smaller sample size of the MDCS, the observed effect sizes might be more subject to the winner's curse effect and thus be larger than the effect sizes observed in LIBRO-1. Nevertheless, the results of this study strongly implicate the role of known breast density variants in breast cancer survival.

In conclusion, our findings support a shared genetic basis for breast density and breast cancer survival, presumably representing shared etiologies. The SNP, rs6557161, *ESR1*, significantly associated with both breast density and survival in both cohorts may be of interest in future research investigating polygenic risk scores for risk of breast cancer and screening stratification purposes.

Acknowledgements

The authors thank Susann Ullén and Peter Almgren for statistical support and Anna Hwasser for database management.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received the following financial support for the research, authorship, and/or publication of this article: This work is supported by government funding for clinical research within the National Health Services, Sweden. FG was a Leopoldina Postdoctoral Fellow (Grant No. LPDS 2018-06) funded by the Academy of Sciences Leopoldina.

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Supplemental material

Supplemental material for this article is available online.

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