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Interaction Effect Between Breast Density and Reproductive Factors on Breast Cancer Risk in Korean Population

ORIGINAL ARTICLE

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Background: This study was conducted to explore the effect of known risk factors, focusing on risk factors including age at menarche, age at menopause, number of children, family history of breast cancer, and age at first birth according to breast density, in consideration of interaction among East-Asian women.

Methods: Case-control study with 2,123 cases and 2,121 controls with mammographic density was conducted. Using the mammographic film, breast density was measured using Breast Imaging-Reporting and Data System. To identify the association of selected reproductive factors including age at menarche, age at menopause, number of children, family history of breast cancer, and age at first birth according to breast density, stratified analysis was conducted according to breast density groups and interaction effects was assessed. The results were presented with adjusted OR and 95% CIs.

Results: Significant interaction effect between age at first birth and breast density on breast cancer ($P = 0.048$) was observed. Women with age at first birth $\geq$ 28 years old showed increased breast cancer risk in extremely dense breast group ($\geq$ 75%) (OR = 1.627, 95% CI = 1.190-2.226). However, women with fatty breast ($<$ 50%) and heterogeneously dense breast (50%-75%) did not show an increased association. Age at menarche, age at menopause, number of children, and family history of breast cancer did not show significant interaction with breast cancer and similar risk patterns were observed.

Conclusions: Age at first birth showed significant interaction with breast density on breast cancer risk. Further studies considering biologically plausible model between exposure, intermediate outcomes and breast cancer risk with prospective design need to be undertaken in East Asian women.
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Key Words: Breast neoplasms, Breast density, Reproductive history

INTRODUCTION

Breast cancer has been the most commonly diagnosed cancer among women in Korea. In 2016, 21,747 women were newly diagnosed with breast cancer which is around 20 percent of all types of estimated new cancer for Korean women [1]. Not only in Korea but also worldwide, breast cancer was the most common cancer and leading cause of death in women [2]. Previous researches have introduced several risk factors [3] and also explained that due to the changes in lifestyle and reproductive

risk factors, breast cancer incident rate has been rapidly increasing, especially in Asian countries [4].

Mammographic density is a measure of dense breast tissue based on radiological mammogram. Mammographic breast density is well known and one of the most important non-modifiable risk factors of breast cancer, which increases breast cancer risk by about five times for those with percent density $\geq$ 75% compared to women with percent density $<$ 5% [5]. Several studies have revealed that the effect of mammographic density as a non-modifiable factor could be

modified by other known breast cancer risk factors, such as family history, reproductive factors, behavioral factors, or body mass index (BMI) [6-10]. Moreover, studies also showed breast density is also associated with other breast cancer risk factors, especially with reproductive factors [11-13].

Considering that the non-amendable factors are considered as the effect modifier and amendable factors as main effect variable from the preventive point [14], the effects of known breast cancer risk factors need to be accessed by breast density, considering the interaction between known risk factors and breast density on breast cancer risk. However, to the best of the authors' knowledge, that kind of approach has been conducted rarely. Rather, the effect of mammographic density was assessed by other risk factors. Therefore, this study was conducted to explore the effect of known risk factors, focusing on risk factors including age at menarche, age at menopause, number of children, family history of breast cancer, and age at first birth according to breast density, in consideration of interaction among East-Asian women.

MATERIALS AND METHODS

1. Study population

Participants of this study were recruited from those who visited National Cancer Center in South Korea. Cases were females aged 20 or more who confirmed ductal carcinoma in situ or invasive breast cancer histologically between February 2014 and January 2018. Controls consisted of females aged 20 or more free of cancer who visited for regular health check-up from March 2014 to September 2016. After obtaining informed consent, they were asked to participate in the study. Face to face interviews were conducted by trained interviewers. Among 4,690 females recruited, 4,244 females including 2,123 cases and 2,121 controls with mammographic density information from the National Cancer Center were included in the analysis. In the case of breast cancer, those whose mammographic results before breast cancer diagnosis were considered. This study was approved by the National Cancer Center Institutional Review Board (IRB No. NCC 2015-0177). All procedures were performed in accordance with the Declaration of Helsinki 7th.

Information collected from the participants consisted of established or suspected risk factors of breast cancer including age, BMI, reproductive factors (age at menarche, age at menopause, age at first birth, number of children, and breast feeding), oral contraceptive use, hormone replacement therapy after menopause, first degree relatives ever diagnosed with breast cancer, alcohol drinking, tobacco smoking, and exercise [15] through structured questionnaire. Among them, we focused on the age at menarche, age at menopause, number of children, family history of breast cancer, and age at first birth. Age at menarche was classified as < 15 and ≥ 15 years old. Age at menopause was classified as premenopausal, < 50, and ≥ 50 years old. The number of children was classified as 0, 1, and 2 or more. Age at first birth among parous women was classified as < 28 and ≥ 28 years old. Family history of breast cancer was measured as whether the participants have their first relative diagnosed with breast cancer.

2. Breast density measurement

Using the mammographic film, trained radiologists determined breast density using Breast Imaging-Reporting and Data System (BI-RADS). Breast density measured by BI-RADS is classified by 4 stages; BI-RADS 1 (0%-25%): mostly fatty breast, BI-RADS 2 (25%-50%): fibroglandular breast, BI-RADS 3 (50%-75%): heterogeneously dense breast, and BI-RADS 4 (75%-100%): extremely dense breast. Due to short number of patients with fatty breast, BI-RADS breast density 1 and 2 were merged into one category as fatty breast (< 50%). Thus, final classification of breast density included 1 and 2 (< 50%), 3 (50%-75%), and 4 (75%-100%).

3. Statistical analysis

The characteristics of the breast cancer cases and controls were compared using a *t*-test for continuous variable and the chi-square test for categorical variables. In addition, the basic characteristics of cases and controls were compared according to breast density group separately (< 50%, 50%-75%, ≥ 75%). The association between breast density, selected reproductive factors and breast cancer were analyzed using multiple logistic regression, adjusting for the covariates including age, BMI, smoking status, duration of alcohol drinking, and exercise and presented as adjusted OR (aOR) and 95% CIs. Missing variables were treated as dummies. To identify the association of selected reproductive factors including age at menarche, age at menopause, number of children, family history of breast cancer, and age at first birth according to breast density, stratified analysis was conducted according to breast density groups. Heterogeneity of association between breast density groups was assessed using Cochran's Q test [16]. The interaction effects between selected reproductive factors and breast density on breast cancer were estimated by including interaction term in the multiple logistic regression model. All analyses were conducted using SAS ver. 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 presents baseline characteristics of breast cancer cases and controls. The average age for case was 46.86 years and 48.51 years for controls ($P < 0.0001$). Compared with controls, cases had higher BMI ($P = 0.0001$), were more often nulliparous and older at first giving birth ($P < 0.0001$), were younger at the first menstrual period ($P < 0.0001$), and had family history of breast cancer more ($P = 0.0100$). Cases and controls did not significantly differ in age at menopause and number of children. However, when stratified by breast density ($< 50\%$, 50%-75%, $\geq 75\%$), all considered variables, except BMI showed significantly different distribution ($P < 0.05$).

Associations between breast density, reproductive factors and breast cancer were demonstrated in the Table 2. The increased breast density category was likely associated with breast cancer risk (aOR = 1.226, 95% CI = 0.994-1.592) for those with breast density > 75% compared with those with < 50%. In addition, late age at first birth (≥ 28 years old) and family history of breast cancer were associated with increased breast cancer risk significantly (aOR = 1.198, 95% CI=1.031-1.392; aOR = 1.444, 95% CI = 1.188-1.755). Conversely, late age at menarche (≥ 15 years old) and late age at menopause compared to premenopausal showed significant decreased association with breast cancer.

Table 3 demonstrates the association between selected risk factors and breast cancer, stratified by breast density groups and

Table 1. Characteristics of case and controls by selected reproductive risk factors

Risk factor	Total		P-value	BI-RADS 1 and 2 (< 50%)		BI-RADS 3 (50%-75%)		BI-RADS 4 (≥ 75%)		P-value
	Case	Control		Case	Control	Case	Control	Case	Control	
Age (yr)	46.86 ± 9.35	48.51 ± 9.93	< 0.0001							< 0.0001
< 30	39 (1.8)	85 (4.0)	< 0.0001	3 (1.4)	0 (0)	8 (0.8)	2 (0.2)	25 (4.0)	14 (3.3)	
30-39	436 (20.5)	213 (10.0)		27 (12.5)	3 (1.1)	175 (18.3)	33 (3.8)	175 (27.7)	55 (12.8)	
40-49	864 (40.7)	864 (40.7)		49 (22.7)	43 (15.9)	377 (39.4)	353 (41.0)	312 (49.4)	251 (58.4)	
50-59	572 (26.9)	640 (30.2)		74 (34.3)	97 (35.9)	308 (32.2)	348 (40.4)	106 (16.8)	91 (21.2)	
60-69	182 (8.6)	260 (12.3)		53 (24.5)	107 (39.6)	79 (8.3)	111 (12.9)	13 (2.1)	13 (3.0)	
≥ 70	28 (1.3)	36 (1.7)		10 (4.6)	20 (7.4)	9 (0.9)	10 (1.2)	0 (0)	1 (0.2)	
Age at menarche (yr)			< 0.0001							0.0016
< 15	1,520 (71.6)	1,212 (57.1)		118 (54.6)	99 (36.7)	658 (68.8)	442 (51.3)	502 (79.6)	276 (64.2)	
≥ 15	574 (27.0)	706 (33.3)		93 (43.1)	136 (50.4)	281 (29.4)	322 (37.4)	123 (19.5)	120 (27.9)	
Unknown	29 (1.4)	184 (8.7)		5 (2.3)	35 (13.0)	17 (1.8)	97 (11.3)	6 (1.0)	34 (7.9)	
Age at menopause (yr)			0.0518							< 0.0001
Premenopausal	1,320 (62.2)	1,130 (53.9)		59 (27.3)	42 (15.6)	548 (57.3)	376 (43.9)	511 (81.0)	305 (71.8)	
< 50	390 (18.4)	475 (22.6)		65 (30.1)	93 (34.4)	199 (20.8)	233 (27.2)	69 (10.9)	65 (15.3)	
≥ 50	411 (19.4)	493 (23.5)		92 (42.6)	135 (50.0)	209 (21.9)	248 (28.9)	51 (8.1)	55 (12.9)	
Number of children			0.8015							< 0.0001
0	358 (16.9)	285 (13.4)		10 (4.6)	10 (3.7)	146 (15.3)	61 (7.08)	143 (22.66)	72 (16.7)	
1	420 (19.8)	352 (16.6)		30 (13.9)	32 (11.9)	175 (18.3)	130 (15.10)	162 (25.67)	76 (17.7)	
≥ 2	1,317 (62.0)	1,286 (60.6)		172 (79.6)	200 (74.1)	618 (64.6)	573 (66.55)	320 (50.71)	237 (55.1)	
Unknown	28 (1.3)	198 (9.3)		4 (1.9)	28 (10.4)	17 (1.8)	97 (11.27)	6 (0.95)	45 (10.5)	
Age at first birth (yr)			< 0.0001							< 0.0001
< 28	822 (38.7)	871 (41.1)		133 (61.6)	144 (53.3)	394 (41.2)	387 (44.9)	164 (26.0)	153 (35.6)	
≥ 28	910 (42.9)	734 (34.6)		69 (31.9)	79 (29.3)	398 (41.6)	298 (34.6)	315 (49.9)	155 (36.0)	
Nulliparous	358 (16.9)	285 (13.4)		10 (4.6)	10 (3.7)	146 (15.3)	61 (7.1)	143 (22.7)	72 (16.7)	
Unknown	33 (1.6)	231 (10.9)		4 (1.9)	37 (13.7)	18 (1.9)	115 (13.4)	9 (1.4)	50 (11.6)	
Breast cancer in first-degree relatives			0.0100							0.0173
0	1,597 (75.2)	1,633 (77.0)		163 (75.5)	212 (78.5)	719 (75.2)	667 (77.8)	473 (75.0)	345 (81.2)	
≥ 1	317 (14.9)	228 (10.7)		37 (17.1)	24 (8.9)	143 (15.0)	80 (9.3)	85 (13.5)	29 (6.8)	
Unknown	209 (9.8)	240 (11.3)		16 (7.4)	34 (12.6)	94 (9.8)	110 (12.8)	73 (11.6)	51 (12.0)	
Body mass index (kg/m²)			0.0001							0.4964
< 25	1,572 (74.0)	1,581 (74.5)		114 (52.8)	159 (58.9)	664 (69.5)	620 (72.3)	560 (88.7)	369 (86.8)	
≥ 25	484 (23.5)	355 (16.7)		91 (42.1)	81 (30.0)	259 (27.1)	153 (1.9)	57 (9.0)	28 (6.6)	
Unknown	65 (2.5)	162 (7.6)		11 (5.1)	30 (11.1)	33 (3.5)	84 (1.1)	14 (2.2)	28 (6.6)	

Values are presented as Mean ± SD or number (%). BI-RADS, Breast Imaging-Reporting and Data System.

Table 2. ORs and 95% CIs of breast cancer for breast density and selected risk factors

Risk factor	OR (95% CI)	
	Age adjusted	Multivariate adjusted[a]
Breast density		
BI-RADS 1 and 2 (< 50%)	1	1
BI-RADS 3 (50%-75%)	1.057 (0.855-1.307)	1.110 (0.886-1.391)
BI-RADS 4 (≥ 75%)	1.102 (0.866-1.402)	1.226 (0.994-1.592)
Age at menarche (yr)		
< 15	1	1
≥ 15	0.647 (0.564-0.742)	0.681 (0.588-0.789)
Age at menopause (yr)		
Premenopausal	1	1
< 50	0.695 (0.592-0.816)	0.812 (0.679-0.971)
≥ 50	0.703 (0.598-0.825)	0.752 (0.626-0.904)
Number of children		
0	1.222 (1.024-1.458)	1.167 (0.962-1.417)
1	1.178 (1.002-1.386)	1.128 (0.949-1.341)
2 or more	1	1
Age at first birth (yr)		
< 28	1	1
≥ 28	1.326 (1.156-1.521)	1.198 (1.031-1.392)
Family history of breast cancer		
No history	1	1
1st degree	1.438 (1.196-1.730)	1.444 (1.188-1.755)

BI-RADS, Breast Imaging-Reporting and Data System. [a]Adjusted for body mass index, smoke, drink duration, exercise, age, age at menarche, age at menopause, number of child, number of first-degree relatives with breast cancer.

interaction effect between selected reproductive factors and breast density on breast cancer. We identified statistically significant interaction effect between age at first birth and breast density on breast cancer ($P = 0.048$). Women with older age at first birth (≥ 28 years old) showed increased breast cancer risk in extremely dense breast group (≥ 75%) with OR of 1.627 (95% CI = 1.190-2.226). However, women with fatty breast (< 50%) and heterogeneously dense breast (50%-75%) did not show such an increased association. Age at menarche, age at menopause, number of children, and family history of breast cancer did not show significant interaction with breast cancer ($P > 0.05$) and similar risk patterns were observed as shown in the Table 2.

DISCUSSION

In this study with 2,123 breast cancer cases and 2,121 controls, most of the reproductive risk factors including age at menarche, age at menopause, number of children, and family history of breast cancer did not show interaction with breast density on

breast cancer risk. However, age at first birth showed significant interaction with breast density on breast cancer risk – later age at first birth increased breast cancer risk in women with dense breast (≥ 75%) but not increased risk in women with breast density < 75% (< 50% and 50%-75%).

Previous studies regarding the interaction effect between known risk factors and breast density on breast cancer risk showed various results. A previous study showed that parity and breast density had the interaction effect on breast density – increment effect in parous women but not in nulliparous women. However, other reproductive and lifestyle risk factors including age at first birth did not modify the effect of breast density [6]. The modifying effect of breast density for the parity was replicated in another study [10]. In this study, we observed only borderline significance in the interaction effect between parity and breast density on breast cancer risk. To compare our result with that of previous studies, we re-analyzed data applying same approaches with most previous studies – breast density as effect variable and other reproductive factors as effect modifiers (Appendix Table 1). In our study, we identified increased breast cancer risk in those with breast density 50%-75% among nulliparous women and among parous women, the increment pattern of breast cancer was not prominent according to higher breast density. In addition, unlike a previous study [6], we found an interaction with breast density only in age at first birth. In this study, the wide age range of study participants from < 30 years old to ≥ 70 years old, rapid changes in reproductive factors in East Asia, especially in Korea [17] and age effect on breast density [18] could affect the interaction effect between breast density and age at first birth on breast cancer. Otherwise, the relationship between breast density and reproductive factors could contribute to the result [11,12].

Other studies showed that women with family history of breast cancer had a higher risk of breast cancer as breast density increased than women without family history in both whites and Asians [7,9]. This is consistent with our results (Appendix Table 1) – increment of breast cancer risk as breast density increased in those with family history of breast cancer, but not in those without family history. Heritability of mammographic density within family members has been well demonstrated [19,20] and some studies suggested that mammographic density could explain the effect of family history on breast cancer risk partially [21].

Other studies also showed that the effect of mammographic density was not modified by BMI or [8] the effect of breast density was more prominent in hormone replacement therapy users

Table 3. ORs and 95% CIs[a] of breast cancer for selected risk factors by breast density groups and their interaction effects

Variable	BI-RADS 1 and 2 (< 50%)			BI-RADS 3 (50%-75%)			BI-RADS 4 (≥ 75%)			P-interaction
	No. of case/control	OR (95% CI)	P-value	No. of case/control	OR (95% CI)	P-value	No. of case/control	OR (95% CI)	P-value	
Age at menarche (yr)										
< 15	118/99	1.176 (0.765-1.809)	0.46	658/442	1.375 (1.103-1.715)	0.0047	502/276	1.528 (1.113-2.096)	0.0086	0.6806
≥ 15	93/136	1		281/322	1		123/120	1		
Age at menopause (yr)										
Premenopausal	59/42	1		548/380	1		511/310	1		0.9109
< 50	65/93	1.621 (0.822-3.195)	0.1633	199/233	0.949 (0.710-1.267)	0.7211	69/65	0.858 (0.563-1.308)	0.4767	
≥ 50	92/135	1.746 (0.852-3.577)	0.128	209/248	1.092 (0.794-1.501)	0.5899	51/55	0.865 (0.513-1.458)	0.5855	
Number of children										
0	10/10	0.547 (0.195-1.532)	0.251	146/60	1.823 (1.287-2.582)	0.0007	143/72	1.085 (0.747-1.576)	0.6676	
1	30/32	0.771 (0.424-1.403)	0.3947	175/127	1.141 (0.868-1.499)	0.3439	162/74	1.442 (1.027-2.023)	0.0344	0.0921
2 or more	172/200	1		618/573	1		320/234	1		
Age at first birth (yr)										
< 28	133/144	1		394/387	1		164/153	1		0.0048
≥ 28	69/79	0.781 (0.493-1.236)	0.2904	398/298	1.087 (0.865-1.365)	0.4734	315/155	1.627 (1.190-2.226)	0.0023	
Family history of breast cancer										
No	163/212	1		719/671	1		473/349	1		0.7925
1st degree	37/24	2.140 (1.158-3.954)	0.0152	143/80	1.653 (1.215-2.249)	0.0014	85/30	1.690 (1.064-2.685)	0.0261	

BI-RADS: Breast Imaging-Reporting and Data System. [a]Adjusted for body mass index, smoke, drink duration, exercise, age, age at menarche, age at menopause, number of child, number of first-degree relatives with breast cancer.

[6,22]. However, another study showed opposite results that the effect of mammography was not different by menopausal status or in hormone replacement therapy use [23]. This study only focused on the reproductive factors and breast density on breast cancer risk and not considered lifestyle related factors such as BMI, oral contraceptive use, and hormone replacement therapy. Thus, other risk factors need to be further considered.

Although breast density is one of the most important risk factors of breast cancer [15], the effect of breast density itself in this study was not significant and the point estimate was much lower than previous meta-analysis which showed about four fold increment of breast cancer risk [5]. This meta-analysis applied breast density < 5% as reference group but in this study those with density < 50% was a reference due to a limited number of participants with fatty breast. Thus, higher cut-off for the reference group could result non-significant result. When breast density was not considered as modifiable factors, the comprehensive effect of selected reproductive factors on breast cancer was comparable with previous studies [15].

The limitations of this study are as follows; First, the existence of selection bias should be considered. The study population was selected from single institute and would not represent target population. However, the comparability between cases and controls would be better because they were recruited from same

hospital. Second, information bias such as recall-bias could affect measurement of variables throught questionnaires. Third, although studies measured breast density as contunuous variables, this study applied BI-RADS classification as categorical variable because BI-RADS classification was widely available in Korea because National Cancer Screening Program in Korea uses BI-RADS system to report the results. Fourth, despite of important effect of age on breast density, we did not match age between cases and controls as a whole and in each age group to include more number of participants. To minimize the age effect on results, we adjusted for age in all analysis but it might not be enough to control it. In addition, the non-significant interaction effects between reproductive factors and and breast density on breast cancer risk could be attributed to the low power of this study.

Despite of these limitations, this is a first study to report the interaction between reproductive factors and breast density on breast cancer risk in Korean female population. In addition, the approach of this study that utilizes breast density as an effect modifier would be a novel approach compared with previous studies which applied breast density as an only exposure variable. Considering that the breast density could be an intermediate factor between reproductive factors and breast cancer [11,12], and the interaction among heretability, known

breast cancer risk especially reproductive risk factors and breast density is under investigation, further studies considering biologically plausable model between exposure, intermediate outcomes and breast cancer risk with prospective design need to be investigated in East Asian women.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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Appendix Table 1. Association of breast density and cancer-related risk factors on breast cancer[a]

	BI-RADS 1 and 2 (< 50%)		BI-RADS 3 (5%-75%)			BI-RADS 4 (≥ 75%)		
	No. of cases/controls	OR (95% CI)	No. of cases/controls	OR (95% CI)	P-value	No. of cases/controls	OR (95% CI)	P-value
Age at menarche (yr)								
< 15	118/99	1	658/442	1.034 (0.763-1.401)	0.8291	502/276	1.059 (0.764-1.468)	0.7308
≥ 15	93/136	1	281/322	1.088 (0.788-1.501)	0.0058	123/120	1.110 (0.744-1.658)	0.0093
Age at menopause (yr)								
Premenopausal	59/42	1	548/380	1.071 (0.688-1.666)	0.7618	511/310	1.100 (0.705-1.716)	0.6746
< 50	65/93	1	199/233	1.079 (0.709-1.643)	0.7225	69/65	1.159 (0.759-1.771)	0.4937
≥ 50	92/135	1	209/248	0.950 (0.640-1.408)	0.7968	51/55	0.831 (0.499-1.383)	0.4755
Number of children								
0	10/10	1	146/60	2.413 (0.924-6.299)	0.072	143/72	1.488 (0.567-3.905)	0.4189
1	30/32	1	175/127	1.042 (0.583-1.864)	0.8889	162/74	1.317 (0.711-2.438)	0.3808
2 or more	172/200	1	618/573	1.024 (0.802-1.308)	0.8464	320/234	1.122 (0.841-1.496)	0.4342
Age at first birth (yr)								
< 28	133/144	1	394/387	0.949 (0.712-1.265)	0.7217	164/153	0.907 (0.637-1.292)	0.5897
≥ 28	69/79	1	398/298	1.199 (0.826-1.742)	0.3395	315/155	1.546 (1.035-2.310)	0.0333
Family history of breast cancer								
No	163/212	1	719/671	1.051 (0.825-1.338)	0.6884	473/349	1.052 (0.801-1.380)	0.7164
1st degree	37/24	1	143/80	1.156 (0.632-2.112)	0.6379	85/30	1.890 (0.921-3.880)	0.0827

BI-RADS, Breast Imaging-Reporting and Data System. [a]Adjusted for body mass index, smoke, drink duration, exercise, age, age at menarche, age at menopause, number of child, number of first-degree relatives with breast cancer.