Journal of Breast Cancer

J Breast Cancer 2017 September; 20(3): 279-285 https://doi.org/10.4048/jbc.2017.20.3.279

Check for updates

ORIGINAL ARTICLE

The Effect of Reproductive Factors on Breast Cancer Presentation in Women Who Are *BRCA* Mutation Carrier

Ju-Yeon Kim*, Hyeong-Gon Moon[1,*], Young-Joon Kang[1], Wonshik Han[1], Woo-Chul Noh[2], Yongsik Jung[3], Byung-In Moon[4], Eunyoung Kang[5], Sung-Shin Park[6], Min Hyuk Lee[7], Bo Young Park[8], Jong Won Lee[9], Dong-Young Noh[1]

Department of Surgery, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju; [1]Department of Surgery, Laboratory of Breast Cancer Biology, Cancer Research Institute, Seoul National University College of Medicine, Seoul; [2]Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological & Medical Science, Seoul; [3]Department of Surgery, Ajou University School of Medicine, Suwon; [4]Department of Surgery, Ewha Womans University Hospital, Seoul; [5]Department of Surgery, Seoul National University Bundang Hospital, Seongnam; [6]Department of Pathology, Daerim St. Mary's Hospital, Seoul; [7]Department of Surgery, Soonchunhyang University Seoul Hospital, Seoul; [8]Cancer Early Detection Branch, National Cancer Control Institute, National Cancer Center, Goyang; [9]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Purpose: Germline mutations in the *BRCA1* and *BRCA2* genes confer increased risks for breast cancers. However, the clinical presentation of breast cancer among women who are carriers of the *BRCA1* or *BRCA2* (*BRCA1/2* carriers) mutations is heterogenous. We aimed to identify the effects of the reproductive histories of women with the *BRCA1/2* mutations on the clinical presentation of breast cancer. **Methods:** We retrospectively analyzed clinical data on women with proven *BRCA1* and *BRCA2* mutations who were recruited to the Korean Hereditary Breast Cancer study, from 2007 to 2014. **Results:** Among the 736 women who were *BRCA1/2* mutation carriers, a total of 483 women had breast cancers. Breast cancer diagnosis occurred at significantly younger ages in women who experienced menarche at ≤14 years of age, compared to those who experienced menarche at >14 years of age (37.38±7.60 and 43.30±10.11, respectively, $p<0.001$). Additionally, the number of full-term pregnancies was significantly associated with the age of diagnosis, especially in women with the *BRCA2* mutation. The prevalence of advanced stages (stage II or III vs. stage I) of disease in parous women was higher than in nulliparous women (68.5% vs. 55.2%, $p=0.043$). This association was more pronounced in women with the *BRCA2* mutation (hazard ratio, 2.67; $p=0.014$). **Conclusion:** Our results suggest that reproductive factors, such as the age of onset of menarche and the presence of parity, are associated with the clinical presentation patterns of breast cancer in *BRCA1/2* mutation carriers.

Key Words: *BRCA1 genes, BRCA2 genes, Breast neoplasms, Reproductive history*

INTRODUCTION

BRCA1 and *BRCA2* are tumor suppressor genes that are involved in multiple cellular processes, including DNA damage repair, cell cycle control, and transcription [1,2]. These processes perform universally essential functions in the homeostasis of all mammalian cells. However, the prevalence of *BRCA1/2* (*BRCA1* or *BRCA2*) mutation-related cancers is not similar across various organs [3]. Carriers of germline mutations of *BRCA1* and *BRCA2* are more likely to develop cancers of the breast and ovary, followed by those of the colon and prostate, with lesser incidence [4]. Breast and ovarian cancers are known to be regulated by sex hormones; thus, it is possible that *BRCA1/2* may be important regulators of growth and differentiation in hormonally responsive epithelial cells.

BRCA1 can regulate the estrogen receptor (ER)-mediated

Correspondence to: **Dong-Young Noh**
Department of Surgery, Laboratory of Breast Cancer Biology, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2634, Fax: +82-2-766-3975
E-mail: dynoh@snu.ac.kr

*These authors contributed equally to this work.

This study was supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (No. 1020350), by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2015R1D1A1A02061904), by the grant from the National R&D Program for Cancer Control, Ministry for Health and Welfare, Republic of Korea (A1520250), and by the grant of the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI13C2148).

Received: January 16, 2017 **Accepted:** June 8, 2017

downstream signaling by inhibiting transcriptional activators, such as activation function 2 (AF-2) [5] and p300 [6]. Further, mutations in the *BRCA1* gene can lead to increased vascular endothelial growth factor secretion and breast epithelial proliferation, via direct interaction between *BRCA1* and the ER protein [7].

As several studies have highlighted the potential interactions between the *BRCA1/2* genes and the ER in developing breast cancers, we hypothesized that the reproductive histories of women who are *BRCA1/2* mutation carriers can influence the clinical presentation of their breast cancer. To address this issue, we investigated the relationship between reproductive factors and the clinical characteristics of breast cancers in Korean women with germline mutations in *BRCA1* and *BRCA2*.

METHODS

This study was conducted on women with either proven *BRCA1/2* mutations, or both, who were recruited to the Korean Hereditary Breast Cancer (KOHBRA) study, from 2007 to 2014. The study design and eligibility criteria have been described in a previously published KOHBRA interim report [8]. All probands received genetic counseling, and the genetic testing for the *BRCA* mutations was performed after obtaining informed consent. For this study, genetic mutations were narrowly defined as protein-truncating and missense mutations. Unclassified variants were not considered as genetic mutations. After extracting the genomic DNA from peripheral blood, genetic testing was carried out using three methods: fluorescence-based conformation sensitive gel electrophoresis, denaturing high performance liquid chromatography, and direct sequencing. *BRCA1/2* mutation testing was conducted by four DNA testing laboratories; all these laboratories are certified annually by the Korean Institute of Genetic Testing Evaluation. Each participating centre was linked to one of four DNA testing laboratories.

In this study, parous women were defined as women with one or more full-term pregnancies. For this analysis, the requirement to obtain separate consents was waived by the Institutional Review Board of Seoul National University Hospital (IRB number: 1511-010-714).

Statistical analysis

We retrospectively analyzed women who carried either the *BRCA1* or the *BRCA2* mutation. *BRCA1* and *BRCA2* mutation carriers were separately analyzed. To assess the association between the reproductive factors of the *BRCA* mutation carriers and breast cancer, we used a cohort study design to compare women with *BRCA* mutations who developed breast cancers with those that did not. Continuous variables were compared using the Student t-test, and categorical variables were compared using the chi-square tests. Hazard ratios (HR) and 95% confidence intervals were calculated using the logistic regression test. All analyses were carried out using SPSS version 19.0 (IBM Corp., Armonk, USA). Values of $p<0.05$ were deemed statistically significant.

RESULTS

The present retrospective analyses were conducted on a cohort of 739 women with either proven *BRCA1* or *BRCA2* mutations, or both, who were registered in the KOHBRA study. Among these, three women for whom reproductive histories were unavailable were excluded from the present analysis. There were 284 women with the *BRCA1* germline mutation, 445 with the *BRCA2* mutation, and seven, who had mutations in both *BRCA1* and *BRCA2*. The characteristics of the entire

Table 1. Characteristics of the study group

Characteristic	Mutation carried		
	BRCA1 (n=284) No. (%)	*BRCA2* (n=445) No. (%)	*BRCA1/2* (n=7) No. (%)
Age at test of mutations (yr)*	42.20±11.62	42.18±12.53	39.67±7.74
Age of menarche (yr)*	14.30±1.61	14.77±1.75	15.29±2.21
≤14	142 (50.0)	175 (39.3)	1 (14.3)
>14	110 (38.7)	202 (45.4)	6 (85.7)
Unknown	32 (11.3)	68 (15.3)	0
Parity			
Nulliparous	83 (29.2)	135 (30.3)	2 (28.6)
Parous	161 (56.7)	258 (58.0)	4 (57.1)
Unknown	40 (14.1)	52 (11.7)	1 (14.3)
No. of full-term pregnancy*	1.33±1.20	1.34±1.25	1.17±0.98
Age at first birth (yr)*	26.82±3.98	26.28±3.27	25.25±4.65
<30	130 (45.7)	222 (49.9)	3 (42.9)
≥30	34 (12.0)	37 (8.3)	1 (14.2)
Unknown	120 (42.3)	186 (41.8)	3 (42.9)
Regularity of menstruation			
Regular	219 (77.1)	313 (70.3)	7 (100)
Irregular	34 (12.0)	65 (14.6)	0
Unknown	31 (10.9)	67 (15.1)	0
Cycle of menstruation (day)			
≤28	141 (49.6)	194 (43.6)	4 (57.1)
>28	103 (36.3)	164 (36.9)	3 (42.9)
Unknown	40 (14.1)	87 (19.5)	0
Patient with breast cancer	195 (68.9)	282 (63.3)	7 (100)
ER and/or PR (+)	65 (33.3)	185 (65.6)	5 (71.4)
ER and PR (–)	106 (54.4)	59 (20.9)	1 (14.3)
Unknown	24 (12.3)	38 (13.5)	1 (14.3)
Patients with any cancers	204 (72.1)	291 (65.5)	7 (100)

ER=estrogen receptor; PR=progesterone receptor.
*Mean±SD.

https://doi.org/10.4048/jbc.2017.20.3.279

study cohort and the distribution of reproductive factors among them are presented in Table 1.

The effect of reproductive factors on the development of breast cancers in women with the *BRCA* mutations

Among the 736 women, a total of 483 had developed breast cancers at the time of their interview. Characteristics of the women with or without breast cancers are listed in Table 2. There were no differences in the risks of breast cancer in these women, based on their regularity and cycles of menstruation. Compared with parous women, nulliparous women were significantly associated with women who did not develop breast cancers, and this association was also observed in the subgroup with *BRCA1/2* mutations. However, except in the nulliparous women, the number of full-term pregnancies was lesser in women with breast cancers than in those who did not develop breast cancer, in the group with the *BRCA1* mutation (1.87±0.77 vs. 2.44±1.26, $p=0.002$). The age of first childbirth was not associated with the risks of developing breast cancer.

In this study, the mean age of diagnosis of breast cancer in all patients was 39.0 years; in women with the *BRCA1* mutation, 38.01±8.31 years, and in women with the *BRCA2* mutation, 42.36±10.04 years. The age at menarche and the parity were significantly associated with the age of diagnosis. Women who experienced menarche at 14 years of age or earlier were

Table 2. Reproductive factors and breast cancer risk among mutation carriers

Characteristic	All patients			*BRCA1* mutation patients			*BRCA2* mutation patients		
	Women with breast cancer (n=483) No. (%)	Unaffected women (n=253) No. (%)	*p*-value	Women with breast cancer (n=155) No. (%)	Unaffected women (n=89) No. (%)	*p*-value	Women with breast cancer (n=255) No. (%)	Unaffected women (n=164) No. (%)	*p*-value
Age at test of mutations (yr)*	42.61±11.01	41.42±14.05	0.243	42.50±10.00	41.84±14.51	0.707	42.81±11.61	41.18±13.83	0.214
Age of menarche (yr)*	14.58±1.78	14.71±1.73	0.454	14.36±1.82	14.73±1.76	0.221	14.81±1.78	14.70±1.72	0.620
≤14	230 (48.9)	89 (53.0)	0.419	80 (52.39)	36 (60.0)	0.360	111 (44.9)	53 (49.1)	0.489
>14	240 (51.1)	79 (47.0)		73 (47.7)	24 (40.0)		136 (55.1)	55 (50.9)	
Parity			<0.001			<0.001			<0.001
Nulliparous	77 (19.1)	143 (59.3)		25 (19.8)	35 (41.2)		39 (18.2)	93 (59.6)	
Parous	327 (80.9)	98 (40.7)		101 (80.2)	50 (58.8)		175 (81.8)	63 (40.4)	
No. of full-term pregnancy†	2.00±0.92	2.14±1.00	0.215	1.87±0.77	2.44±1.26	0.002	2.06±0.92	1.97±0.79	0.494
Age at first birth (yr)*	26.60±3.53	25.98±3.53	0.131	27.26±3.53	26.03±3.53	0.118	26.24±3.53	25.95±3.53	0.547
<30	275 (82.8)	82 (84.5)	0.759	79 (76.7)	28 (82.4)	0.634	155 (87.6)	54 (85.7)	0.668
≥30	57 (17.2)	15 (15.5)		24 (23.3)	6 (17.6)		22 (12.4)	9 (14.3)	
Regularity of menstruation			0.173			0.646			0.044
Regular	404 (85.6)	136 (81.0)		134 (87.0)	54 (90.0)		209 (84.3)	82 (75.9)	
Irregular	68 (14.4)	32 (19.0)		20 (13.0)	6 (10.0)		39 (15.7)	26 (24.1)	
Cycle of menstruation (day)			0.643			0.552			0.552
≤28	253 (56.2)	86 (53.8)		128 (54.9)	52 (51.0)		128 (54.9)	52 (51.0)	
>28	197 (43.8)	74 (46.3)		105 (45.1)	50 (49.0)		105 (45.1)	50 (49.0)	

*Mean±SD; †Except to nulliparous.

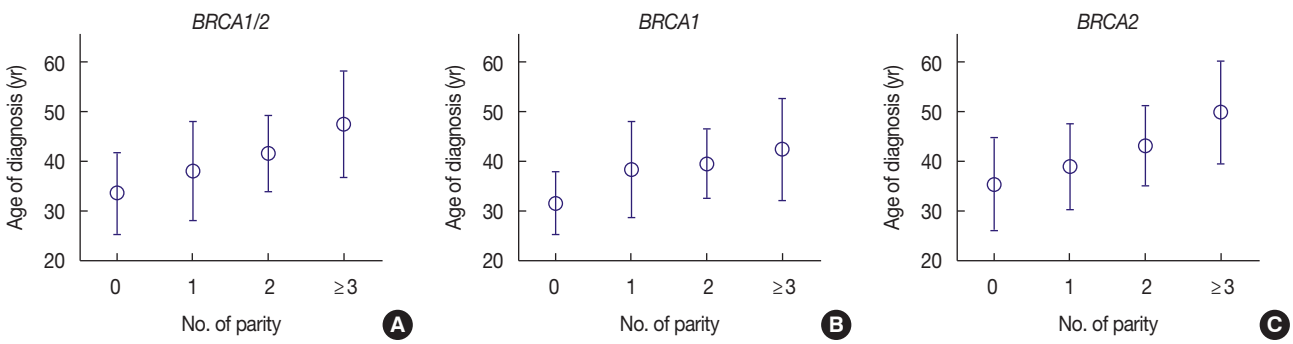

Figure 1. Bar plot with 95% confidence interval of diagnosed age of breast cancer according to number of full-term pregnancy. Diagnosed age of breast cancer was increased according to the number of full-term pregnancy. (A) All patients, $p<0.001$; (B) *BRCA1* mutation group, $p=0.234$; and (C) *BRCA2* mutation group, $p<0.001$.

Table 3. Diagnosed age of breast cancer according to reproductive factors

Characteristic	All patients				*BRCA1* mutation patients				*BRCA2* mutation patients			
	No.	Mean±SD	95% CI	*p*-value	No.	Mean±SD	95% CI	*p*-value	No.	Mean±SD	95% CI	*p*-value
Age of menarche (yr)			4.29 to 7.54	<0.001			-6.71 to -2.01	<0.001			-8.85 to -4.50	<0.001
≤14	230	37.38±7.60			106	36.12±7.07			123	38.57±7.84		
>14	240	43.30±10.11			87	40.48±9.04			147	45.24±10.30		
Parity			5.83 to 10.12	<0.001			-10.73 to -5.32	<0.001			-11.18 to -4.76	<0.001
Nulliparous	77	33.85±8.42			33	31.52±6.51			42	35.48±9.46		
Parous	332	41.83±9.13			131	39.54±8.32			197	43.44±9.29		
Age at first birth (yr)			-0.38 to 4.81	0.094			-2.78 to 4.21	0.685			-1.24 to 6.20	0.190
<30	275	42.20±9.33			103	39.61±8.34			169	43.88±9.52		
≥30	57	39.98±7.76			28	38.89±8.08			28	41.39±7.29		
Regularity of menstruation			-2.19 to 2.69	0.837			-4.04 to 2.64	0.681			-2.18 to 4.47	0.500
Regular	404	40.47±9.42			166	37.98±8.00			231	42.44±9.92		
Irregular	68	40.22±9.70			28	38.68±9.85			40	41.30±9.58		
Cycle of menstruation (day)			-2.14 to 1.33	0.650			-2.44 to 2.41	0.990			-3.04 to 1.72	0.587
≤28	253	40.20±8.69			107	38.15±8.06			142	41.84±8.85		
>28	197	40.60±10.02			79	38.16±8.58			115	42.50±10.54		

CI=confidence interval.

Table 4. Reproductive factors in relation to stage II and III versus to stage I of breast cancer

Characteristic	All patients					*BRCA1* mutation patients					*BRCA2* mutation patients				
	No.	Adv. stage No. (%)	HR	95% CI	*p*-value	No.	Adv. stage No. (%)	HR	95% CI	*p*-value	No.	Adv. stage No. (%)	HR	95% CI	*p*-value
Age of menarche (yr)				1.00–2.33	0.053				0.63–2.36	0.564				1.01–3.14	0.044
≤14	195	122 (62.6)	1			91	58 (63.7)	1			103	63 (61.2)	1		
>14	195	140 (71.8)	1.52			69	47 (68.1)	1.22			122	90 (73.8)	1.79		
Parity				1.04–3.09	0.037				0.51–2.69	0.702				1.14–5.15	0.021
Nulliparous	67	37 (55.2)	1			31	19 (61.3)	1			34	17 (50.0)	1		
Parous	266	183 (68.8)	1.79			103	67 (65.0)	1.18			161	114 (70.8)	2.43		
Age at first birth (yr)				0.51–2.03	0.847				0.35–2.50	0.901				0.45–3.31	0.690
<30	223	154 (69.1)	1			83	54 (65.1)	1			138	98 (71.0)	1		
≥30	46	32 (69.6)	1.02			22	14 (63.6)	0.94			24	18 (75.0)	1.22		
Regularity of menstruation				0.55–1.81	0.988				0.36–2.36	0.867				0.49–2.30	0.889
Regular	334	223 (66.8)	1			139	91 (65.5)	1			190	128 (67.4)	1		
Irregular	57	38 (66.7)	0.99			22	14 (63.6)	0.92			35	24 (68.6)	1.06		
Cycle of menstruation (day)				0.74–1.77	0.535				0.56–2.11	0.815				0.67–2.12	0.548
≤28	207	135 (65.2)	1			87	56 (64.4)	1			116	76 (65.5)	1		
>28	167	114 (68.3)	1.15			68	45 (66.2)	1.08			98	68 (69.4)	1.19		

Adv. stage=advanced stage; HR=hazard ratio; CI=confidence interval.

diagnosed with breast cancer at younger ages than women who experienced menarche at over 14 years of age (37.38 ± 7.60 and 43.30 ± 10.11 years, respectively, $p < 0.001$). Additionally, the number of full-term pregnancies was significantly associated with the age of diagnosis, especially in women with the *BRCA2* mutation ($p < 0.001$) (Figure 1). However, the regularity and cycles of menstruation were not significant (Table 3).

Differences in breast cancer stage according to the reproductive factors

Among 483 patients with breast cancers, 27 had *in situ* cancers, 391 had stage I–III disease, and 65 had unknown status. We examined the association between the reproductive factors and breast cancer stage. Our analysis showed that the number of parous events was significantly associated with the risk of advanced disease (stage II or III vs. stage I). In all patients, the prevalence of the advanced stage was higher in parous women than in nulliparous women (68.5% vs. 55.2%, $p = 0.043$). The association was more pronounced in women with the *BRCA2* mutation (HR, 2.67; $p = 0.014$) (Table 4). With increase in the numbers of full-term pregnancies, the probability of developing advanced breast cancers was higher in parous women than in nulliparous women, in the group with the *BRCA2* mutation (Supplementary Table 1, available online).

DISCUSSION

As the *BRCA* proteins are known to play protective roles against the carcinogenic effects of estradiol [5-7], we hypothesized that the factors influencing the duration of the reproductive period may affect the characteristics of breast cancer presentation in carriers of the *BRCA1* and *BRCA2* mutations. In accordance with our hypothesis, we observed that younger age at menarche and nulliparity were strongly associated with early onset of breast cancer. However, our analysis also revealed an unexpected finding that breast cancers in *BRCA2* mutation carriers who had early onset of menarche or who were nulliparous were more likely to have early-stage tumors. Bayraktar et al. [9] have reported that late menarche in *BRCA1* mutation carriers was associated with advanced stages of breast cancer; in a population-based study, Alsaker et al. [10] reported worse outcomes for breast cancer in women with higher numbers of parous events. In our study, we observed that as the numbers of full-term pregnancies increased, the probability of advanced breast cancers in parous women was higher than the probability in nulliparous women, in the group with the *BRCA2* mutation.

The control of cell proliferation is stimulated by increased levels of estrogen during puberty, and especially before the first birth, but may be dysregulated in breast cells that harbor *BRCA1/2* mutations [2,11]. However, the different effects of reproductive factors on breast cancer characteristics in the carriers of the *BRCA1* and *BRCA2* mutations suggest that responses to hormones may differ between them. A good example of these differences is the fact that only 10% to 24% of *BRCA1*-associated breast cancers are ER-positive, whereas 65% to 79% of *BRCA2*-associated breast cancers are ER-positive [12,13]. In our study, the age of breast cancer diagnosis was higher in patients with the *BRCA2* mutation patients than in those with the *BRCA1* mutation, and the effect of reproductive factors on surgical stage was pronounced only in women with the *BRCA2* mutation.

Regarding the onset of breast cancer in patients, we found that higher number of parous events and late age of menarche had a protective effect, but this protection may be limited in the number of years. In a recent study, longer time intervals between age at first pregnancy and at breast cancer diagnosis reduced the breast cancer mortalities in premenopausal women [14]. A similar study also found that high parity may have a protective effect against small and low-grade tumors [15,16]; consequently, women with high parity may have relatively advanced and more aggressive disease. Additionally, this protective effect of parity may be limited only to ER-positive tumors [17]; however, it has been suggested that high parity may also increase the risks for triple-negative breast cancer [18].

Pregnancy and childbirth have been shown to be protective factors in terms of the lifetime risk of breast cancer in the general population. However, in *BRCA* mutation carriers, the results from previous studies of the effect of parity on breast cancer have varied. Milne et al. [19] reported that parity was associated with protection from breast cancers in *BRCA1* and *BRCA2* mutation carriers, and each live-birth was associated with an estimated 13% risk reduction. On the other hand, a study based on 55 international collaborating centers [20] observed that increasing parity was associated with increased risk of breast cancer (15% per live-birth) in women who were *BRCA2* carriers. In a recent meta-analysis, the risks of breast cancer in parous women who were *BRCA1/2* mutation carriers were not statistically different from the risks in corresponding nulliparous women. Additionally, the risks of breast cancer associated with increasing parity were not significantly reduced [21].

Our study has several limitations. First, our results are based on retrospective data obtained from women who opted for genetic testing for the *BRCA1* and *BRCA2* mutations. Thus, other factors, such as psychological status or memorial ability, might have influenced the results of the study. Additionally,

well-known lifestyle factors, including obesity and alcohol consumption, could have introduced a bias in the results. Second, data on reproductive factors were not available for all women who were *BRCA* mutation carriers. Third, the relationship between the regularity of menstruation and breast cancer in *BRCA* mutation carriers was not properly examined. Although most women in this study believed that they had regular cycles of menstruation, the meaning of "regular" may differ among individuals.

This study showed the differential risks of breast cancer associated with reproductive factors in women who were *BRCA1/2* mutation carriers. Early menarche and nulliparity were associated with earlier onset of breast cancers in women who were *BRCA1/2* mutation carriers. However, parity was associated with more advanced stage at presentation, especially in women who were *BRCA2* mutation carriers. Our observations need further testing with longitudinal follow-up data, in a larger cohort of women who are *BRCA1/2* mutation carriers.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

KOHBRA study: Beom Seok Kwak, Byeong-Woo Park, Byung Ho Son, Cha Kyong Yom, Chan Heun Park, Chan Seok Yoon, Chang Hyun Lee, Dae Sung Yoon, Doo Ho Choi, Eundeok Chang, Eun-Kyu Kim, Hae Kyung Lee, Hai-Lin Park, Hyde Lee, Hyun-Ah Kim, Il-Kyun Lee, Jeong Eon Lee, Jihyoun Lee, Jong-Han Yu, Joon Jeong, Jung Han Yoon, Jung-Hyun Yang, Keumhee Kwak, Ki-Tae Hwang, Ku Sang Kim, Lee Su Kim, Min Hee Hur, Min Ho Park, Myung Chul Chang, Nam Sun Paik, Sang Ah Han, Sang Seol Jung, Sang Uk Woo, Se Jeong Oh, Sehwan Han, Sei Joong Kim, Sei-Hyun Ahn, Seok-Jin Nam, Seung Sang Ko, Sung Hoo Jung, Sung Soo Kang, Sung Yong Kim, Sung-Won Kim, Tae Hyun Kim, Tae Wan Won, Tae Woo Kang, Yong Lai Park, Sue K. Park, Yoon Joo Jung, Su Yun Choi, Young Bum Yoo, and Soo-Jung Lee.

REFERENCES

1. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002;108:171-82.
2. Razandi M, Pedram A, Rosen EM, Levin ER. BRCA1 inhibits membrane estrogen and growth factor receptor signaling to cell proliferation in breast cancer. Mol Cell Biol 2004;24:5900-13.
3. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
4. Ponder BA. Cancer genetics. Nature 2001;411:336-41.
5. Fan S, Wang J, Yuan R, Ma Y, Meng Q, Erdos MR, et al. BRCA1 inhibition of estrogen receptor signaling in transfected cells. Science 1999;284:1354-6.
6. Fan S, Ma YX, Wang C, Yuan RQ, Meng Q, Wang JA, et al. p300 Modulates the BRCA1 inhibition of estrogen receptor activity. Cancer Res 2002;62:141-51.
7. Kawai H, Li H, Chun P, Avraham S, Avraham HK. Direct interaction between BRCA1 and the estrogen receptor regulates vascular endothelial growth factor (VEGF) transcription and secretion in breast cancer cells. Oncogene 2002;21:7730-9.
8. Han SA, Park SK, Ahn SH, Lee MH, Noh DY, Kim LS, et al. The Korean Hereditary Breast Cancer (KOHBRA) study: protocols and interim report. Clin Oncol (R Coll Radiol) 2011;23:434-41.
9. Bayraktar S, Amendola L, Gutierrez-Barrera AM, Hashmi SS, Amos C, Gambello M, et al. Clinicopathologic characteristics of breast cancer in BRCA-carriers and non-carriers in women 35 years of age or less. Breast 2014;23:770-4.
10. Alsaker MD, Opdahl S, Romundstad PR, Vatten LJ. Association of time since last birth, age at first birth and parity with breast cancer survival among parous women: a register-based study from Norway. Int J Cancer 2013;132:174-81.
11. Cabanes A, Wang M, Olivo S, DeAssis S, Gustafsson JA, Khan G, et al. Prepubertal estradiol and genistein exposures up-regulate BRCA1 mRNA and reduce mammary tumorigenesis. Carcinogenesis 2004;25:741-8.
12. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 2004;10:2029-34.
13. Lakhani SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, McGuffog L, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002;20:2310-8.
14. Lee J, Oh M; Korean Breast Cancer Society. Effects of interval between age at first pregnancy and age at diagnosis on breast cancer survival according to menopausal status: a register-based study in Korea. BMC Womens Health 2014;14:113.
15. Albrektsen G, Heuch I, Thoresen SØ. Histological type and grade of breast cancer tumors by parity, age at birth, and time since birth: a register-based study in Norway. BMC Cancer 2010;10:226.
16. Wohlfahrt J, Andersen PK, Mouridsen HT, Adami HO, Melbye M. Reproductive history and stage of breast cancer. Am J Epidemiol 1999;150:1325-30.
17. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res 2006;8:R43.
18. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, et al. Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. J Natl Cancer Inst 2011;103:470-7.
19. Milne RL, Osorio A, Ramón y Cajal T, Baiget M, Lasa A, Diaz-Rubio E, et al. Parity and the risk of breast and ovarian cancer in BRCA1 and

 https://doi.org/10.4048/jbc.2017.20.3.279

BRCA2 mutation carriers. Breast Cancer Res Treat 2010;119:221-32.
20. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, et al. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer 2005;117:988-91.
21. Pan H, He Z, Ling L, Ding Q, Chen L, Zha X, et al. Reproductive factors and breast cancer risk among BRCA1 or BRCA2 mutation carriers: results from ten studies. Cancer Epidemiol 2014;38:1-8.