

Title page

Breast cancer risk for Korean women with germline mutations in *BRCA1* and *BRCA2*

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Running title: Risk of breast cancer for *BRCA1/2* mutation carriers

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Abstract

Purpose: The average age-specific cumulative risk (penetrance) of breast cancer has been studied for *BRCA1* and *BRCA2* mutation carriers living in Western countries, but not for those living in East Asian countries where the population breast cancer incidence is lower.

Methods: From 2007-2011, the Korean Hereditary Breast Cancer study identified 151 *BRCA1* and 225 *BRCA2* mutation-carrying families from family cancer clinics. We estimated the hazard ratio (HR) for female carriers relative to the population, and hence the penetrance, using a modified segregation analysis of cancer family histories conditioned on ascertainment.

Results: The breast cancer HR estimates (95% confidence interval [CI]) for *BRCA1* and *BRCA2* mutation carriers were 18 (3-103) and 11 (5-27), respectively. The breast cancer penetrance estimates (95% CI) to age 70 years were 49% (11-98) and 35% (16-65) for *BRCA1* and *BRCA2* mutation carriers, respectively. The breast cancer HR and penetrance estimates were similar for Korean and Western women (all $P > 0.4$). The point estimates of breast cancer penetrance were similar to age 50 years, though less for Korean carriers at older ages.

Conclusions: Breast cancer risk for Korean and Western mutation carriers might reflect underlying population risks which in turn likely reflect differences in environmental and lifestyle factors. This raises the possibility of identifying modifiers of cancer risk for carriers with implications for prevention.

Keywords: average cumulative risk; *BRCA1/2* mutation carrier; breast cancer risk; penetrance

Introduction

BRCA1 and *BRCA2* are tumor suppressor genes which play a role in DNA-damage repair, regulation of gene expression, and cell-cycle control [1]. Germline mutations in *BRCA1* and *BRCA2* are the most common known cause of hereditary breast and ovarian cancer [2], and screening for mutations in these genes is widely offered to women with a strong family history or early-onset breast cancer in countries with genetic counseling centers. Once a mutation carrier is identified, other family members are recommended to be tested for that particular mutation. Accurate estimate of the breast cancer risk for mutation carriers is critical to inform risk reducing options [3].

The initial estimates of average cumulative breast cancer risk (penetrance) to age 70 years for female mutation carriers were 85% for *BRCA1* [4] and 84% for *BRCA2* [5]. Since these estimates were from studies of extreme multiple-case families with at least four family members with breast or ovarian cancer, these penetrance estimates might not be relevant for counseling mutation carriers without such a strong cancer family history [6,7]. Consistent with this, studies of the relatives of population-based or hospital-based cases selected regardless of a family history have found lower estimates of penetrance to age 70 years; less than 60% for breast cancer risk for *BRCA1* mutation carriers, and 30-56% for *BRCA2* mutation carriers [8-10,6,11,12]. In addition, some studies have found evidence that risk varies by specific mutations [13,14], other genetic modifiers [15-17], birth cohort [18,19], and reproductive and lifestyle factors [20,21].

But these studies have been conducted in Western populations, and breast cancer incidences are different in other populations. For women living in East Asia, the breast cancer

incidences are lower and age-specific incidence rates which are higher in younger ages in many countries are also different. Therefore the published estimates might not be applicable for mutation carriers living in East Asian countries where, due to the combined size of their populations, a large proportion of the world's *BRCA1* and *BRCA2* mutation carriers live. The aim of this study was to estimate the breast cancer penetrance for female carriers of germline mutations in *BRCA1* and *BRCA2* using a Korean nationwide study.

Materials and Methods

Study participants

This study comprised families recruited into the Korean Hereditary Breast Cancer (KOHBRA) study during the period 2007-2011 from family cancer clinics. A proband is defined to be a person suspected of having hereditary breast cancer and who attended to the family cancer clinic after referred by breast cancer surgeons based on their personal and family cancer histories. Details of the study design are described in full elsewhere [22]. The KOHBRA study is a prospective, nationwide, multicenter cohort study whose aims include determining the penetrance of breast cancer for *BRCA1* and *BRCA2* mutation carriers identified from mutation testing of eligible families. Mutation screening for *BRCA1* and *BRCA2* was performed for female probands with breast cancer aged 20 years or older, referred to the family cancer clinic, and who had: (1) a family history of breast or ovarian cancer in any relatives; or (2) no family history of breast or ovarian cancer but was either 40 years or younger at diagnosis, had bilateral breast cancer, or was diagnosed with another primary malignancy. Male probands with breast cancer were also screened, irrespective of their cancer family history. If a screened person was found to have a mutation (see below for definition) in *BRCA1* or *BRCA2*, they were asked to contact their female and male relatives age 20 years of older to see if they too could be approached to participate in the KOHBRA study.

Mutation screening and definition

Screening for mutations in *BRCA1* and *BRCA2* was performed by four laboratories

certified annually by the Korean Institute of Genetic Testing Evaluation. Each laboratory used various techniques, including fluorescence-based conformation sensitive gel electrophoresis, denaturing high-performance liquid chromatography or direct sequencing. This study was approved by the Institutional Review Board (IRB #B-0707-047-005) of each participating center and all participants provided their written informed consent. A variant was considered a mutation if it was a protein-truncating mutation, or a missense mutation which has a confirmed association with disease [22].

Data collection

All participants were asked to complete a structured questionnaire and offered genetic counselling, during which a pedigree covering at least three generations was constructed. For each participant, information on year of birth, year of death, types of cancer, age at cancer diagnosis, genetic mutation status (carrier, non-carrier, not tested), and year of genetic counselling and mutation testing of both participants and family members was collected. If a participant could not give information on year of birth or year of death of a family member, we asked current age for living family members and age at death for deceased relatives. For living family members, participants had missing ages if they did not give information on either year of birth or current age. The missing information was imputed from the known birth year and/or current age of the siblings or spouse using average age differences between siblings or spouses in the general Korean population, or estimated from average age differences between generations within the general Korean population. Missing information on age at death for deceased individuals was imputed from individual age at cancer diagnosis if they had a cancer, and otherwise treated as missing. Missing information

was imputed for 14% of living family members with missing information on age and 29% of deceased family members with missing information on age at death, respectively. We excluded those with missing ages as the ages were considered to be unreliable.

Statistical Analysis

Breast cancer penetrance for female mutation carriers was based on mutation-carrying families and was estimated using modified segregation analyses implemented in the pedigree analysis software MENDEL v3.3.5 [23]. The details of the model have been described previously [18,23-25].

Estimation and statistical inference were carried out using the method of maximum likelihood. To adjust for the fact that families with multiple affected individuals were ascertained, we conditioned the likelihood on the genotype of the proband and the phenotypes (cancer statuses and related ages) of all family members. Female family members were assumed to be at risk for developing breast or ovarian cancer from birth until the earliest of: breast cancer diagnosis; ovarian cancer diagnosis; death; last known age; or age 80 years.

A major gene model with mutation frequency of 0.001 for both genes was assumed (though risk estimates are not sensitive to this assumption, data not shown). Given the rarity of carriers, the incidences for non-carriers were assumed to be equal to the Korean population incidences obtained from the Korean Central Cancer Registry for the year 2010 [26]. The hazard ratio (HR) at age t years, defined as the age-specific incidence $\lambda(t)$ for carriers divided by the age-specific incidence $\lambda_0(t)$ for non-carriers, was estimated as both a constant function of age and as a log-linear function of age.

The modified segregation analysis therefore incorporated a parametric survival

analysis, where $\lambda(t) = \text{HR } \lambda_0(t)$. The cumulative risk to age t years ($\text{CR}(t)$) was estimated from the HR estimates as one minus the exponential of minus the cumulative risk to age t years (where the cumulative risk is the integral of $\lambda(s)$ from 0 to t). The 10-year risk at age t years was estimated as $(\text{CR}(t+10) - \text{CR}(t))/(1 - \text{CR}(t))$. Confidence intervals for cumulative and 10-year risks were estimated using a parametric bootstrap in which the HR estimates were sampled from their distributions under asymptotic likelihood theory.

To test if our HR estimates depended on calendar year of birth, we multiplied the above HRs by a log-linear function of age and tested if this function differed from 1.

Results

Table 1 shows there were 151 *BRCA1* and 225 *BRCA2* mutation-carrying families. Data were available for in total 12,820 family members (5,012 were family members from *BRCA1* mutation carriers' pedigree information and 7,808 were family members from *BRCA2* mutation carriers' pedigree information), among whom there were 227 confirmed carrier family members and 205 confirmed non-carrier family members through mutation test. The mean age at diagnosis for breast cancer cases was 41.9 (standard deviation [SD] = 10.8) years for the *BRCA1* mutation-carrying families, earlier than for the *BRCA2* mutation-carrying families (44.8 [SD=11.4], $P=0.001$). For proven *BRCA1* mutation carrier breast cancer cases, the mean age at diagnosis was earlier than for proven *BRCA2* mutation carriers (37.8 vs. 42.1 years, $P<0.001$). The maximum age at diagnosis of breast cancer was 75 years for *BRCA1* mutation carriers and 80 years for *BRCA2* mutation carriers and for ovarian cancer the corresponding ages were 75 years and 79 years. There were no differences in mean age at diagnosis for ovarian cancer cases between *BRCA1* and *BRCA2* mutation-carrying families ($P=0.4$) or between proven *BRCA1* and *BRCA2* carriers ($P=0.7$).

The estimated breast cancer HRs were 18 (95% confidence interval [CI] 3-103) and 11 (95% CI 5-27) for *BRCA1* and *BRCA2* mutation carriers, respectively, when the HRs were assumed to be constant with age. There was weak evidence that the *BRCA1* breast cancer HR depends on age ($P=0.15$); the estimated HR decreased by 8% (95% CI 0 - 17) per year either side of a baseline of 29 (95% CI 6-134) at age 40 years. There was no evidence that the *BRCA2* breast cancer HR depends on age ($P=0.4$). Consequently, all cumulative risk and 10-year risks below are based on the HRs being constant with age.

Table 2 shows that the estimated breast cancer penetrances to age 70 years were 49% (95% CI 11-98) and 35% (95% CI 16-65) for *BRCA1* and *BRCA2* mutation carriers, respectively. The estimates to age 50 years were 27% (95% CI 5-84) for *BRCA1* mutation carriers and 18% (95% CI 8-39) for *BRCA2* mutation carriers.

Table 3 shows that the estimated 10-year risks of breast cancer for unaffected *BRCA1* and *BRCA2* carriers peaked at ages 40 and 50 years then decreased for older ages.

There was no evidence that the HRs depend on year of birth (all $P > 0.5$) or on mutation position (all $P > 0.2$, data not shown).

Discussion

To the best of our knowledge, this penetrance study is of the largest number of *BRCA1* and *BRCA2* mutation carrying families living in Asia yet reported. We have derived the average cumulative cancer risks from the HRs estimated by modified segregation analysis and the age-specific breast cancer incidence in the general population in Korea. We have also provided 10-year risks of breast cancer for *BRCA1* and *BRCA2* mutation carriers who have not developed cancer before a given age and this might be helpful in genetic counselling clinics to suggest surveillance strategies or prophylactic options. Previous studies have found that the risk assessment models developed in Western countries have poor performance for both prediction of breast cancer risk [27] and prediction of *BRCA1* and *BRCA2* mutation carrier status [28], suggesting a need for race and country-specific models.

In Korea, the breast cancer incidence in general population increases with age to peak in the mid 40s, and is not dissimilar to the incidence in Western populations up to that age. But from the mid 40s onwards the incidence in Korea declines, in sharp contrast to Western populations where the incidence continues to increase for at least several decades [26,27]. Therefore, if the breast cancer risk for carriers was independent of the country in which the carrier has lived, and equal to that established for Western women, we should have found that the HRs for Korean women increase with age, especially after the mid 40s. We found no evidence for this.

The resulting point estimates of average cumulative breast cancer risks for Korean *BRCA1* and *BRCA2* mutation carriers were less than the corresponding estimates for Western

women found by Antoniou et al [18], in which the average cumulative risk of breast cancer to age 70 years was 65% (95% CI=44-78) for *BRCA1* mutation carriers and 45% (95% CI=31-56) for *BRCA2* mutation carriers. A recent meta-analysis of six family studies of population-based cases and four studies of families selected for family history found similar estimates: 57% (95% CI=47-66) for *BRCA1* and 49% (95% CI=40-57) for *BRCA2* mutation carriers [29]. However, given the wide CIs of the Korean estimates due to limited number of cases, comparison of our estimates with those of Western countries might be difficult statistically. In addition, we found few breast cancers in carrier families, let alone known carriers, diagnosed after the age of 50 years (six carrier breast cancer cases diagnosed after the age 50 years in 54 family members who were more than 50 years old and carriers for *BRCA1/2* mutation).

Our study has several weaknesses. First, we had to rely on the probands' reported family history given during the genetic counselling and could not validate the cancer history of family members. Previous studies have shown that proband's reporting is highly reliable, at least for breast cancers in first-degree relatives, in Western countries [30,31]. Second, missing information on the ages of living family members or ages at diagnosis of deceased relatives with cancer was imputed in a conservative way. Although the misclassification of age could be random and unlikely to cause biased estimates, it would reduce the precision of estimates. Third, while we have taken the first steps to obtain valid unbiased estimates of risk that will be applicable to clinical mutation testing in families living in Korean, and perhaps more broadly, in other Asian families, our estimates are not precise due to limited number of carriers and mutation-tested family members.

Estimation of penetrance from the cancer histories of carrier families sampled

because they have a cancer family history is non-trivial. One needs to condition the likelihood on why the carrier family came into the study [32], and for ‘clinic-based families’ conditioning only on the proband being affected will result in upwardly biased estimates [33,34]. The likelihood approach we have taken here has been used extensively [18,24,6,25], but is conservative in that it conditions on the entire family cancer history. It enables information on all family members to be used irrespective of their known mutation status, and clearly the more information on which relatives carry mutations the more information on risk. In practice it is often difficult, as we found, to obtain DNA samples from affected relatives in older generations.

In conclusion, the breast cancer risks for Korean and Western carriers might reflect the underlying population risks which in turn likely reflect environmental and lifestyle factors. This raises the possibility of identifying modifiers of risk through prospective studies of Asian and Western carriers. Finding the environmental and lifestyle factors that influence risk for mutation carriers is difficult using retrospective studies, but now that mutation testing has been carried out for two decades some prospective cohorts in Western populations are beginning to have power to address these issues, especially if the data are carefully pooled. It will be important to also establish similar cohorts of Asian women, and KOHBRA is working towards this aim.

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Table 1. Characteristics of the *BRCA1* and *BRCA2* mutation-carrying families

	<i>BRCA1</i>		<i>BRCA2</i>	
	N	(%)	N	(%)
Probands	151	(40.2)	225	(59.8)
Breast cancers in probands	151	(100)	225	(100)
Ovarian cancers in probands	3	(2.0)	4	(1.8)
Family members	5,012	(39.1)	7,808	(60.9)
Male	2540	(50.6)	3929	(50.3)
Female	2472	(49.4)	3879	(49.7)
Breast cancers in family members	137	(2.8)	195	(2.5)

Ovarian cancers in family members	39	(0.8)	10	(0.1)
Number of family members tested for mutations	151		281	
Carriers	67	(44.4)	160	(56.9)
Non-carriers	84	(55.6)	121	(43.1)
Number of family members not tested for mutations	4,861		7,527	
1 st relatives of the probands (%)	1,528	(29.6)	2,635	(32.8)
2 nd relatives of the probands (%)	2,060	(39.9)	2,659	(33.1)
	<u>Median</u>	<u>(IQR)</u>	<u>Median</u>	<u>(IQR)</u>
Family members per family	34	(26-42)	34	(27-43)
Female family members per family	17	(13-21)	18	(13-22)
Male family members per family	17	(12-20)	17	(13-22)
	<u>Mean</u>	<u>(SE)</u>	<u>Mean</u>	<u>(SE)</u>
Age at breast cancer diagnosis	41.9	(0.7)	44.8	(0.6)
Age at breast cancer diagnosis for proven carriers	37.8	(0.7)	42.1	(0.6)
Age at ovarian cancer diagnosis	55.0	(1.7)	58.3	(3.3)
Age at ovarian cancer diagnosis for proven carriers	48.4	(5.1)	51.2	(4.8)

IQR: interquartile range; SE: standard error

¹ Statistical significance of the difference between *BRCA1* and *BRCA2* carrier families

Table 2. Estimated age-specific cumulative risks (penetrances) of breast cancer and corresponding 95% confidence intervals (CIs) for female *BRCA1* and *BRCA2* mutation carriers living in Korea.

Age	<i>BRCA1</i>		<i>BRCA2</i>	
	Penetrance (%)	95% CI	Penetrance (%)	95% CI
30	1	(0-8)	1	(0-2)
40	10	(2-45)	6	(3-15)
50	27	(5-84)	18	(8-39)
60	41	(9-95)	28	(13-56)
70	49	(11-98)	35	(16-65)

Table 3. Estimated 10-year breast cancer risks and corresponding 95% confidence intervals (CIs) for *BRCA1* and *BRCA2* mutation carriers living in Korea.

Age	<i>BRCA1</i>		<i>BRCA2</i>	
	Risk (%)	95% CI	Risk (%)	95% CI
20	1.7	(0.2-7.6)	0.8	(0.3-2.0)
30	8.6	(1.5-41.4)	5.5	(2.3-12.8)
40	19.5	(3.6-72.4)	12.8	(5.4-28.1)
50	18.4	(3.4-70.1)	12.0	(5.0-26.6)
60	14.1	(2.6-59.7)	9.2	(3.8-20.8)
70	8.7	(1.6-42.0)	5.6	(2.3-13.0)



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