

Hereditary Breast Cancer in Korea

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About 7% of all breast cancer (BC) cases result from a genetic predisposition, and approximately 1,000 patients develop hereditary BC (HBC) every year in Korea. *BRCA1* and *BRCA2* are the primary genes underlying HBC. The average cumulative risks in *BRCA1* mutation carriers at 70 years of age are 65% (95% confidence interval 44-78%) for BC and 39% (18-54%) for ovarian cancer (OC). The corresponding estimates for *BRCA2* are 45% (31-56%) and 11% (2.4-19%), respectively. The penetrance of *BRCA* mutations is not the same between patients and can depend on factors such as race and birth-cohort. The Korean Hereditary Breast Cancer (KOHBRA) study is a large prospective nationwide study that includes 39 participating centers. Between May 2007 and May 2010, the first phase of the KOHBRA study was planned and fulfilled successfully. The primary aim of phase I was to estimate the prevalence of *BRCA1/2* mutations and OC among a high-risk group of patients with HBC and their families. According to data collected during phase I of the study, the prevalence and penetrance of *BRCA* mutations were comparable to corresponding data from Western countries. For the second phase of the KOHBRA study, we are currently investigating a Korean *BRCA* mutation prediction model, prognostic factors in *BRCA*-related BC, environmental/genetic modifiers, and implementing a genetic counseling network. The final goal of the KOHBRA study is to create clinical practice guidelines for HBC in Korea. In this article, I review the genetics of HBC, summarize the characteristics of Korean HBC, and discuss current and future HBC research in Korea.

Key Words: Hereditary breast cancer, *BRCA* mutation, KOHBRA study

Introduction

Breast cancer (BC) is the second most common cancer in Korean women. The age-adjusted annual incidence rate of BC in Korea is 43.8 per 100,000 women, and an estimated 13,400 new BC cases were expected to occur among Korean women in 2009.¹⁾ Incidence rates for female BC have increased annually over the past decade, and the current incidence rate is almost double that in 1999 (24.5/100,000). Although the exact causes of this increase are not known, changes in dietary habits, reproductive factors, as well as increased screening and awareness of BC are all likely to have

contributed to the observed rate.

While the incidence rate of BC is on the rise in Korea, it is still lower than that in Western countries (US: 76.0/100,000 for 2008). However, in contrast to Korea, the incidence rate for female BC has declined in the US since 2000. The dramatic decrease of almost 7% from 2002 to 2003 has been attributed to reductions in the use of menopausal hormone therapy.

BC is a multifactorial disease, and the cause of BC is still not well defined. Both genetic and environmental factors have been linked to BC, and include hormone therapy, ionizing radiation, lifestyle, diet, and aging. Familial clustering of BC is common, and genetic

Received: 25 April 2012, Revised: 17 May 2012, Accepted: 22 May 2012, Published: 30 June 2012

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predisposition accounts for 5% to 10% of all BC cases.²⁾ Most hereditary breast cancer (HBC) cases are autosomal dominant, and disease characteristics include the early onset of disease (<45 years of age), cancer of both breasts, and a high risk for the development of multiple cancers. Familial BC is defined as the occurrence of 2 or more BC cases within first and second degree relatives when there is no evidence of HBC, whereas BC cases are characterized as sporadic when no BC has been reported within 2 generations. Many potential factors have been put forth to explain familial clustering and include exposure to common carcinogen/s between family members living in close proximity; shared common risk factors associated with cultural or social behaviors (e.g., age at first full-term pregnancy); and the overlap of cancer-related dietary factors between family members due to socio-economic status.

The Korean Hereditary Breast Cancer (KOHBRA) study is a large, prospective, nationwide study.³⁾ Thirty-nine centers are registered in the Korean Breast Cancer Study Group and are participating in the KOHBRA study. Between May 2007 and May 2010, the first phase of the KOHBRA study was fulfilled successfully. The primary aims of the KOHBRA study leading up to 2010 were to estimate the prevalence of *BRCA1/2* mutations and ovarian cancer (OC) among a high-risk group of patients with HBC and their families. The second aim of the KOHBRA study was to identify a Korean founder mutation related to familial breast or ovarian cancer, in order to determine non-familial predictors of *BRCA1/2* mutations and to establish a *BRCA1/2* mutation carrier cohort. At the time of the last update of patient enrollment (February 2012), more than 2500 patients were enrolled, and more than 600 mutation carriers had been identified in the KOHBRA study. In this article, I review the genetics of HBC and summarize and discuss these findings in the context of HBC research in Korea.

Genetics in hereditary breast cancer

Recent studies have shown that HBC occurs in an autosomal dominant fashion, and to date, 5 or more high-penetrance genes, 4 intermediate-penetrance genes, and several low-penetrance genes have been identified.^{4,5)} The most common type of HBC is the site-specific breast cancer syndrome, in which familial clustering of breast cancer is observed in the absence of other types of cancer. *BRCA1/2* are the most important genes in this syndrome. Familial clustering of BC and OC are commonly observed in hereditary breast ovarian cancer syndrome, for which *BRCA1/2* have also been identified as primary causative genes. Other rarer but highly

penetrant genes such as *TP53*, *PTEN*, *LKB1*, and *MSH2/MLH1* have also been identified in relation to BC risk; syndromes related to mutations in these genes and *BRCA1/2* are summarized in Table 1. There are also intermediate penetrance genes such as *ATM*, *CHEK2*, *PALB2*, and *BRIP1*, and these genes are associated with a 2- to 3-fold increased lifetime risk of BC.⁶⁾ Lastly, after the introduction of genome-wide association studies (GWAS), many low-penetrance genes (1.25- to 1.65-fold increased lifetime risk of BC) have been identified, and understanding their role in the development of BC is currently an active area of cancer research.

1. *BRCA1/BRCA2* and hereditary breast and ovarian cancer syndromes

1) *BRCA* genes: Structure, function, and mutations

In 1990, the early-onset breast cancer susceptibility gene was found to be located at 17q21 and was later cloned and identified as *BRCA1*.⁷⁾ Shortly after, in 1991, the same genetic marker, D17S74, was also found to be linked to OC risk.⁸⁾ The entire sequence of *BRCA1* was subsequently characterized in 1994.⁴⁾ The second breast cancer susceptibility gene was discovered by linkage analysis of 22 families with multiple early-onset BC and 1 or more male BC patients in a family. Due to a strong association between male BC and a polymorphic marker located at 13q12-13 on chromosome 13, *BRCA2* was identified, and in 1995, its full sequence was also characterized.^{5,9)}

The *BRCA1* gene is composed of 24 exons and encodes a protein of 1,863 amino acids. The large size of this gene makes functional analysis difficult. To date, more than 1,700 kinds of disease-causing *BRCA1* mutations have been reported, all of which are listed on the Breast Cancer Information Core website (BIC; <http://research.nhgri.nih.gov/projects/bic/Member/index.shtml>). Genomic rearrangements occur frequently in the *BRCA1* gene, but these alterations are difficult to detect using standard polymerase chain reaction (PCR)-based techniques. Instead, the multiplex ligation-

Table 1. Hereditary breast cancer syndromes

Syndromes	Genes	% in HBC
Hereditary breast ovarian cancer syndrome	<i>BRCA1/2</i>	25-35%
Site-specific breast cancer syndrome	<i>BRCA1/2</i>	25-35%
	Unknown	25-45%
Li-Fraumeni syndrome	<i>TP53</i>	<1%
Peutz-Jegher syndrome	<i>LKB1</i>	<1%
Cowden syndrome	<i>PTEN</i>	<1%
Muir-Torre syndrome	<i>MSH2, MLH1</i>	<1%

HBC, Hereditary breast cancer

dependent probe amplification (MLPA) method is primarily used to detect these mutations. Between 12% and 36 % of familial BC and OC patients are positive for large genomic rearrangements.¹⁰⁾

BRCA2 is composed of 26 exons, and the coding region of this gene includes approximately 11.2 Kb. This is almost twice the size of the *BRCA1* gene and is one of the largest genes identified. Like the *BRCA1* gene, due to its large size, the functional study of *BRCA2* is difficult to perform. However, in contrast to *BRCA1*, large genomic rearrangements are not commonly observed in *BRCA2* due to the absence of repeated sequences within the gene region. More than 1,800 disease-causing mutations have been identified and are reported in the BIC database. Interestingly, many characteristics are common between the mutations identified in both genes: mutations are found across each gene and do not occur in mutation "hot spots"; the majority of disease-causing mutations result in protein truncation; and none of the mutations identified in either gene are observed frequently in sporadic BC patients.¹¹⁾

The proteins encoded by the 2 major breast cancer susceptibility genes, *BRCA1* and *BRCA2*, are both involved in DNA repair and serve as protectors of the genome.¹²⁾ However, the 2 proteins work at different stages in the DNA damage response (DDR) and in DNA repair. *BRCA1* is a pleiotropic DDR protein that functions in both checkpoint activation and DNA repair, whereas *BRCA2* is a mediator of the core mechanism of homologous recombination. The links between the 2 proteins are not well understood but must exist given the marked similarity in human cancer susceptibility associated with germline mutations in these genes. Both proteins work in concert to protect the genome from double-strand DNA damage during DNA replication.

2) Founder mutation

The roles of *BRCA* mutations in the occurrence of BC in general

populations were clarified through the study of a small number of founder mutations. A founder mutation is a mutation that appears in the DNA of 1 or more individuals who are founders of a distinct population. Founder mutations result from changes that occur in the DNA sequence and get passed down to subsequent generations. For example, 3 founder mutations that are frequently seen in Ashkenazi Jewish populations are *BRCA1* 185delG and 5382insC and *BRCA2* 6174delT.¹³⁾ The frequency of these 3 founder mutations in Ashkenazi women are about 2.5% but 12% in the general population of Ashkenazi BC patients and 30% in Ashkenazi early-onset BC patients. Although other *BRCA* mutations are also seen in the Ashkenazi Jewish population, these 3 founder mutations account for 90% of all mutations found in this population.¹⁴⁻¹⁶⁾ The most common *BRCA2* founder mutation, *BRCA2* 999del5, was identified in the Icelandic population; in Icelanders, this mutation occurs at a frequency of 0.5% in women, but its frequency is at 8% in the general population of BC cases and 24% in early-onset BC patients.¹⁷⁾ In addition to these populations, common founder mutations have also been reported in other countries, including Finland, Hungary, Russia, France, the Netherlands, and Norway.

Mutations reported in the KOHBRA study are listed in Table 2 in the order of frequency. Unlike in Western countries, *BRCA2* mutations are seen more frequently in the Korean population, *BRCA2* 7708C>T (c.7480C>T) being the most frequent. This mutation has been reported many times, and was identified as a founder mutation by Seong et al. on the basis of haplotype analysis.¹⁸⁾

3) Prevalence of *BRCA* mutations

Most of the prevalence studies have been conducted in families with a high incidence of BC and/or OC. Linkage analysis of HBC families participating in the Breast Cancer Linkage Consortium

Table 2. The candidates for the Korean founder mutation³⁾

	Systematic nomenclature	BIC nomenclature	Effect on amino acid	N*	%
<i>BRCA2</i>	c.7480C>T	7708C>T	p.Arg2494X	18	12.2
<i>BRCA1</i>	c.390C>A	509C>A	p.Tyr130X	11	7.4
<i>BRCA1</i>	c.5496_5506del11insA	5615_5625del11insA	p.Val1833SerfsX7	11	7.4
<i>BRCA2</i>	c.1399A>T	1627A>T	p.Lys467X	8	5.4
<i>BRCA2</i>	c.3744_3747delTGAG	3972_3975delTGAG	p.Ser1248ArgfsX10	7	4.7
<i>BRCA2</i>	c.6724_6725delGA	6952_6953delGA	p.Asp2242PhefsX2	5	3.4
<i>BRCA1</i>	c.3627_3628insA	3746_3747insA	p.Glu1210ArgfsX9	4	2.7
<i>BRCA1</i>	c.5445G>A	5564G>A	p.Trp1815X	4	2.7
<i>BRCA2</i>	c.5576_5579delTTAA	5804_5807delTTAA	p.Ile1859LysfsX3	4	2.7
<i>BRCA1</i>	c.992_994delAGCinsT	1041_1043delAGCinsT	p.Ser308X	3	2

*Number of times mutation observed (total=148).
BIC, Breast Cancer Information Core.

(all of which had at least 4 cases of breast cancer either in women under the age of 60 years, with or without OC, or in men) indicated that 87% of such families could be genetically linked to mutations in either *BRCA1* or *BRCA2*.¹⁹⁾ For unselected families that had a low incidence of BC or OC, the prevalence of *BRCA* mutations was 55% for BC and OC families and 75% for families with cases in which both BC and OC were observed in a single patient.^{20,21)} Taken together, the prevalence of *BRCA* mutations in early-onset BC (diagnosis <45 year of age) is 10–18% (6–13% for *BRCA1* and 4–5% for *BRCA2*),^{20,22–24)} whereas the prevalence of *BRCA* mutations in the general population of BC patients is estimated to be less than 3%.^{25,26)}

The *BRCA1* W1815X mutation was first reported in Korea by Oh et al. in 1995.²⁷⁾ Studies on early-onset BC patients in Korea revealed that 15% of patients were mutation carriers.²⁸⁾ However, only 3% of sporadic BC patients have been identified with *BRCA* mutations.²⁹⁾ According to an interim analysis of data collected by the KOHBRA study, 24.8% of BC patients with a family history of BC or OC, 11.3% of early-onset (age, <35 years) BC, 22.1% of bilateral BC, 8.3% of male BC, and 33.4% of patients with both BC and OC were carriers of *BRCA* mutations.³⁰⁾

Genomic rearrangement occasionally affects the *BRCA1/2* genes in Caucasian breast cancer patients. Seong et al. investigated the contribution of *BRCA1/2* genomic rearrangements in high-risk breast cancer patients in the Korean population.¹⁸⁾ They screened for *BRCA1/2* genomic rearrangements using MLPA in 122 high-risk breast cancer patients who tested negative for *BRCA1/2* mutations. A novel deletion of exons 13–15 in *BRCA1* was identified in 1 patient (frequency=0.8%). They concluded that subsequent screening for *BRCA1/2* genomic rearrangements should be considered in high-risk Korean breast cancer patients who test negative for *BRCA1/2* mutations. However, *BRCA1/2* genomic rearrangements are likely to make only a small contribution to breast cancer in high-risk Korean population.³¹⁾

4) Penetrance of *BRCA* mutations

Germline mutations in *BRCA1* and *BRCA2* confer high risks of BC and OC, and according to modified segregation analysis, the average cumulative risks for *BRCA1* mutation carriers by the age of 70 years was estimated to be 65% (95% confidence interval 44–78%) for breast cancer and 39% (18–54%) for OC; and the corresponding estimates for *BRCA2* were 45% (31–56%) and 11% (2.4–19%).³²⁾

In Korea, to estimate the cumulative risk of BC and OC for each age group among female family members of patients with *BRCA1* and *BRCA2* mutations, Kaplan–Meier analyses were performed

for 61 *BRCA1* mutation carriers in 42 families and 47 *BRCA2* mutation carriers in 31 families. By the age of 70 years, female breast cancer risk for the *BRCA1* and *BRCA2* mutation carriers was estimated to be 72.1% (59.5–84.8%) and 66.3% (41.2–91.5%), respectively, and OC risk, 24.6% (0–50.3%) and 11.1% (0–31.6%), respectively. The contralateral breast cancer risk at 5 years after primary breast cancer was estimated to be 16.2% (9.3–23.1%) for *BRCA1* mutation carriers and 17.3% (9.7–24.0%) for *BRCA2* mutation carriers. According to these findings, the penetrance of *BRCA* mutations in Korea is largely consistent with previous studies in Western populations. However, the small number of cases, the high proportions of probands in the study subjects, access to only short term follow-up data, and large confidence intervals limit the conclusions that can be made from this study.³³⁾

The actual penetrance of *BRCA* mutations varies according to modifiers. Tamoxifen might be one of the most potent modifiers of *BRCA* penetrance. For example, 5-years of tamoxifen therapy lowers the chance of BC development by 50%. Risk-reducing salpingo-oophorectomy also reduces BC risk by 50% and OC risk by 95%.³⁴⁾ Several studies have investigated the roles of genetic modifiers of *BRCA* genes. The Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA) is a multinational consortium focused on characterizing genetic modifiers of *BRCA* genes. To date, candidate gene studies and GWAS have revealed several genetic modifiers of *BRCA1/2* genes, such as *RAD51*, *FGFR2*, *CASP8*, *TOX3/TNRC9*, *MAP3K1*, *LSP1*, *2q35*, and *C19orf62/ANKLE1*.³⁵⁾

2. Clinical characteristics and management of HBC

1) Clinical characteristics of HBC

The clinical and pathologic features of *BRCA*-related BC are summarized in Table 3. The characteristic features of *BRCA1*-related BC include a high histologic grade, a high proliferation index, and increased occurrence of atypical medullary cancer. Mean age at diagnosis of *BRCA1*-related BC is 10 years earlier than that for *BRCA2*-related and sporadic BC. The primary characteristic of *BRCA1*-related BC is ER negativity; 70% of *BRCA1*-related BC cases are negative for estrogen receptor (ER) and progesterone receptor (PR). Also, Her2 overexpression is rare, and thus, triple negative BC is common for *BRCA1* carriers. *BRCA1*-related BC showed a basal-like phenotype in mRNA expression profile, with higher expression of *p53*, *cyclin E*, and *MYC*, and lower expression of *KIP1*.³⁶⁾ Angiogenesis is also more common for *BRCA1* carriers. Ductal carcinoma in situ is rare in *BRCA1* carriers. In contrast, ductal carcinoma is common in *BRCA2*-related BC, as is ER expression

(70%). The mean age at diagnosis of *BRCA2*-related BC is the same as that for sporadic BC.

There are conflicting data for the prognosis of *BRCA*-related BC.³⁷⁾ Some of the discrepancies may be explained by methodological differences or biases. Triple negative type BC is common in *BRCA1*-related BC, and it has been suggested that *BRCA1*-related BC cases tend to have worse prognoses; to date, no studies have shown a survival advantage for *BRCA1* mutation carriers. The prognosis for *BRCA2*-related BC cases is more similar to that of sporadic cases.³⁸⁾

2) Management of unaffected *BRCA* mutation carriers

The primary goals for the management of unaffected *BRCA* mutation carriers are prevention and early detection of cancer development. To this end, 3 strategies have been implemented: surveillance, chemoprevention, and risk-reducing surgery. According to National Comprehensive Cancer Network (NCCN) Guidelines 2011, training in breast self-examination with regular monthly practice should begin at 18 years of age, and semiannual clinical breast examinations should begin by age 25 for women who are carriers of *BRCA1/2* mutations. In addition, these women should begin having annual mammograms and breast MRI screening at age 25 or on an individualized timetable based on the earliest age of cancer onset in family members. For the purpose of early detection of OC, women not opting for OC risk-reducing surgery should consider concurrent transvaginal ultrasonography and CA125 determination every 6 months, starting at age 35, or 5-10 years before the earliest age of first diagnosis of OC in the family.

Carriers of *BRCA* mutations should also consider chemoprevention options for BC and OC, including discussing risks and benefits. Half of BC cases can be prevented by 5 years of tamoxifen use in *BRCA2* mutation carriers. However, tamoxifen use has not been associated with a reduction in BC risk in those with *BRCA1* muta-

tions,³⁹⁾ although it is important to note that this analysis was conducted on a very small number of individuals with *BRCA1/2* mutations. Oral contraceptive use significantly reduced the risk of OC by approximately 50% for both *BRCA1* and *BRCA2* mutation carriers.⁴⁰⁾ However, studies on the effects of oral contraceptive use on BC risk among *BRCA* mutation carriers have reported conflicting data.^{41,42)}

The NCCN Guidelines also support discussion of the option of risk-reducing mastectomy (RRM) for women on a case-by-case basis. Counseling regarding the degree of protection offered by such surgery and the degree of cancer risk should be provided. The panel recommends bilateral risk-reduction salpingo-oophorectomy (RRSO) for women with a known *BRCA* mutation, ideally between the ages 35 and 40 years, upon completion of child bearing, or at an individualized age based on the earliest age of OC diagnosed in the family. Ninety percent of BC can be prevented by RRM, and 97% of OC can be prevented by RRSO.⁴³⁾ RRSO is also reported to reduce the risk of BC in carriers of *BRCA* mutations by approximately 50%.⁴⁴⁾ According to a prospective, multicenter cohort study, RRSO is associated with a lower risk of OC, first diagnosis of BC, all-cause mortality, BC-specific mortality, and OC-specific mortality.⁴⁵⁾ RRS is not commonly performed in Korea;⁴⁶⁾ the first reports of contralateral RRM and bilateral RRM were in 2008 and 2010, respectively.^{47,48)}

3. Rare gene mutations and syndromes

1) *TP53* and Li-Fraumeni syndrome

Germline mutations in the *TP53* gene cause Li-Fraumeni syndrome (LFS), which is inherited in an autosomal dominant fashion. LFS was first reported in 1969 by Li and Fraumeni and is often referred to as SBLA syndrome, named after the first letter

Table 3. Genetic modifiers of cancer risk for *BRCA1* and *BRCA2* mutation carriers

Genes/Loci	SNP	<i>BRCA1</i>		<i>BRCA2</i>	
		RR	95% CI	RR	95% CI
<i>RAD51</i>	rs1801320	1.59	0.96-2.63	3.18	1.39-7.27
<i>CAPS</i>	D302H	0.85	0.76-0.97	1.06	0.88-1.27
<i>FGFR2</i>	rs2981522	1.02	0.95-1.09	1.32	1.20-1.45
<i>TOX3/TNRC9</i>	rs3803662	1.11	1.03-1.19	1.15	1.03-1.27
<i>MAP3K1</i>	rs889312	0.99	0.93-1.06	1.12	1.02-1.24
<i>LSP1</i>	rs3817198	1.05	0.99-1.11	1.16	1.07-1.25
<i>2q35</i>	rs13387042	1.14	1.04-1.25	1.18	1.04-1.33
<i>8q24</i>	rs13281615	1.00	0.94-1.05	1.06	0.98-1.14
<i>C19orf62/ANKLE1</i>	rs8170	1.26	1.17-1.35	0.90	0.77-1.05
<i>C19orf62/ANKLE1</i>	rs2363956	0.84	0.80-0.89	1.12	0.99-1.27

Table adapted from reference 34. CI, confidential interval; RR, relative risk

of the cancers that occur frequently in LFS: soft tissue sarcoma, osteosarcoma, brain tumor, BC, leukemia, lymphoma, and adrenocortical carcinoma.⁴⁹ Fifty percent of LFS cases are due to mutations in the *TP53* gene, and unlike *BRCA* gene mutations, missense mutations are most common. Lifetime cancer risk for *TP53* mutation carriers is 73% in men and 100% in women. The cumulative risk of BC in women over the age of 40 with *TP53* mutations is greater than 60%.⁵⁰ The first report of LFS in Korea was in 1995 by Bang et al., and the first report of an LFS case with a *TP53* missense mutation was in 2008.⁵¹

2) *PTEN* and Cowden syndrome

Lloyd and Dennis were the first to report a case of Cowden syndrome in 1963; they also identified a mutation in the *PTEN* gene as the causative factor.⁵² This syndrome is characterized by breast, endometrial, thyroid, kidney, and colorectal cancers; dermatologic features, such as oral and skin papillomas, trichilemmomas; gastrointestinal features, such as mixed polyposis, including hamartomas; and neurologic features, such as autism and Lhermitte-Duclos disease. Lifetime risk of BC in patients with Cowden syndrome is 25–50%. There have been 3 reports of Cowden syndrome with BC in Korea.^{53–55} However, *PTEN* mutations were not involved in any of these 3 cases.^{56,57}

3) *LKB1* and Peutz-Jegher syndrome

Peutz-Jeghers syndrome, also known as hereditary intestinal polyposis syndrome, is an autosomal dominant genetic disease characterized by the development of benign hamartomatous polyps in the gastrointestinal tract and hyperpigmented macules on the lips and oral mucosa. These patients have elevated risks of breast, uterine cervix, ovarian, testicular, and pancreatic cancer. The risk of BC is up to 20-fold higher than the risk of the general population, and the *STK11/LKB1* gene is known as the primary

cause of the syndrome.⁵⁸ To date, two cases of Peutz-Jeghers syndrome with BC have been reported.⁵⁹

4) *MSH2*, *MLH1*, and Muir-Torre syndrome

Muir-Torre syndrome (MTS) is an inherited cancer syndrome that is thought to be a subtype of hereditary nonpolyposis colorectal cancer. Individuals with MTS are prone to develop cancers of the colon, breasts, and genitourinary tract, as well as skin lesions, such as keratoacanthomas and sebaceous tumors. Causative mutations have been identified in *MLH1* and *MSH2*, which are involved in DNA mismatch repair. BC develops in 25% of MTS patients.⁶⁰ The first report of the MTS syndrome with BC was reported in 2010.⁶¹

5) Other genes

The *CHEK2* gene is located on chromosome 22 and encodes a protein kinase involved in the cell cycle that is activated in response to DNA damage. Patients with the *CHEK2* 110delC mutation have twice the elevated risk of BC in the European population. The *CHEK2* mutation has been detected in 13.5% of *BRCA*-negative BC patients with at least 1 family member with BC. This mutation also results in a 10-fold increase of BC risk in men.⁴³ However, the *CHEK2* mutation appears to be rare in the Korean population.⁶²

The *PALB2* gene encodes a protein that functions in genome maintenance (double strand break repair). The *PALB2* protein binds to and colocalizes with *BRCA2* in nuclear foci and likely permits the stable intranuclear localization and accumulation of *BRCA2*. The *PALB2* gene is also known as the Fanconi anemia gene, *FANCN*; a biallelic mutation of this gene results in N type Fanconi anemia. The monoallelic *PALB2* gene mutation results in elevated risk of BC (2- to 3-fold) and pancreatic cancer.⁶³ The prevalence of this gene mutation is about 0.6–3% in familial BC patients,^{64,65} although it is rare in the Korean population.⁶⁶

BRIP1 is a helicase and works with the *BRCA1* protein to repair

Table 4. Clinical features of hereditary breast cancer

	<i>BRCA1</i> carriers	<i>BRCA2</i> carriers
Age of onset of breast cancer	80% at <50 years of age	Same as sporadic cases
Pathologic features	Invasive ductal cancer (75%) Atypical medullary cancer (~10%)	Invasive ductal cancer (75%) Atypical medullary cancer (<5%) Invasive lobular cancer (~10%)
Histologic grade	Poorly differentiated (75%)	Moderately differentiated (45%) or poorly differentiated (45%)
Estrogen receptor	Negative (75%)	Positive (75%)
Her2	Negative (95%)	Negative (95%)
p53	Positive (50%)	Positive (40%)
Cyclin D1	Negative (90%)	Positive (60%)
Ductal carcinoma in situ	Rare	Common

of DNA. This gene is also called *FANCF* because biallelic *BRIP1* mutations result in J type Fanconi anemia. Monoallelic mutations in *BRIP1* elevate BC risk 2-fold.⁶⁷⁾

6) Low-penetrance genes

Common low-penetrance alleles are important to public health because a large proportion of the population carries such alleles, and together with multiple environmental factors, such mutations make an important contribution to disease susceptibility. Recently, an association study revealed many candidate genes, which can be categorized in the following way; genes related to steroid hormone metabolism (*COMT*, *CYP17*, *CYP19*, *CYP2D6*, *ER*, *PR*, *EDH17β2*, etc.); genes related to carcinogen metabolism (*CYP1A1*, *CYP2E1*, *CYP1B1*, *GSTM1*, *GSTT1*, *GSTP1*, *NAT1*, *NAT2*, *NQO1*, etc.); DNA repair genes (*XRCC1*, *XRCC3*, *ERCC1*, *ATM*, *MGMT*, *XPD*, *XPF*, *OGG1*, etc.); epigenetic genes related to tumor growth (*TNF-α*, *TNF-β*, *IGF*, *IL-1β*, *IL-6*, *IL-10*, etc.); and other gene groups (*cyclin D1*, *MnSOD*, *MTHFR*, *VDR*, etc.). In addition, a recent meta-analysis of 279 genes further defined associations between many of these genes with BC. They found that 10 variants in 6 genes (*ATM*, *CASP8*, *CHEK2*, *CTLA4*, *NBN*) exhibited strong association to BC, 4 variants in 4 genes (*ATM*, *CYP19A1*, *TERT*, *XRCC3*) had a moderate level of association, and 37 variants had a weak association with BC risk.⁶⁸⁾

7) Genetic counseling in Korea

Genetic counseling is an essential part of genetic testing and should be performed by the specialist. Before the initiation of the KOHBRA Study in 2007, we performed a nationwide survey that included questionnaire data from 43 doctors from 42 institutions. According to the survey, 81.4% of the respondents answered that they collected information about family history of BC and OC, and 58.2% recommended genetic testing to patients with proper indication. However, only half of the respondents answered that they offered genetic counseling alongside genetic testing. When genetic counseling was conducted, it was carried out by the breast surgeons themselves (81%) or by nurses (19%).⁶⁹⁾

We conducted a follow-up survey 2 years after the initiation of the KOHBRA study. According to the 2009 follow-up survey, most physicians (60.0%) tended to draw a pedigree, which was higher than that reported in the initial 2007 survey (48.0%). The rate of genetic test recommendations for patients at risk for HBC was higher in the 2009 survey (84.0%) compared to the 2007 survey (64.0%). Fifteen of 25 participants (60.0%) provided genetic counseling before their patients underwent a genetic test, which was higher than that (40.0%) in the 2007 survey. We believe that the

KOHBRA study has played an important role in the appropriate selection of candidates for genetic testing.⁷⁰⁾

In 2011, to enhance the quality of genetic counseling and to increase the rate of genetic counseling, the Korean Breast Cancer Society set up genetic counseling as part of a HBOC training program and certified 13 genetic counselors for HBC in 2012; this program currently operates annually, and there are no plans for its discontinuation.

8) Future research

The KOHBRA Study is planned as a 10-year project to develop clinical practice guidelines (CPG) for HBC in Korea. In the first phase of the KOHBRA study, we investigated the prevalence of *BRCA* mutations in the Korean population. Currently, we are in the second phase, the aims of which are as follows: (1) to develop a Korean *BRCA* mutation prediction model; (2) to discover the characteristics and prognostic factors contributing to *BRCA*-related BC; (3) to study the environmental/genetic modifiers of *BRCA* gene mutations; and (4) to build and implement an HBC genetic counseling network in Korea. The Korean Breast Cancer Society has been publishing the CPG for BC every other year and is currently under revising process for the fifth edition in 2013. CPG for HBC will be incorporated into the fifth edition of BC management CPG. More detailed information about the KOHBRA study is available on the KOHBRA homepage (www.kohbra.kr).

The KOHBRA Study is actively participating in an international collaborative study of BC. We are collaborating with the International *BRCA* Carrier Cohort Study (IBCCS) and CIMBA. The IBCCS is focusing on epidemiological risk factors, and CIMBA is focusing on the involvement of genetic modifiers of *BRCA* mutations in BC risk. In addition to this collaboration, KOHBRA recently started the Asian *BRCA* Consortium (*ABRCA*) which involves collaborations among 7 countries: Korea, Japan, China, Indonesia, Hong Kong, Malaysia, and Singapore. The primary aims of *ABRCA* are as follows. First, to share the knowledge of HBOC between Asian countries; second, to improve the quality of care for HBOC patients in Asia; and third, to undertake collaborative research on HBOC in Asia. *ABRCA* will also hold annual meetings to promote each of these initiatives.

Acknowledgment

This study was partly supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (#1020350).

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