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ORIGINAL ARTICLE

Associations between *BRCA* Mutations in High-Risk Breast Cancer Patients and Familial Cancers Other than Breast or Ovary

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Purpose: We investigated the relationship between *BRCA* mutations and the distribution of familial cancers other than breast or ovary in high-risk breast cancer patients. **Methods:** Patients with breast cancer who had at least one of the following risk factors were enrolled: reported family history of breast or ovarian cancer; 40 years of age or younger age at diagnosis; bilateral breast cancer; or male gender. Genetic testing for *BRCA* mutation and questionnaires about personal and family histories of malignancies were performed. **Results:** Among the 238 eligible patients, 49 (20.6%) patients had *BRCA1/2* mutations, which were more frequent in patients with multiple risk factors ($p<0.0001$). There were 271 members of 156 (65.5%) families who had histories of other primary cancer. The distribution of the families was 119 (63.0%) and 37 (75.5%) in the *BRCA*-negative and positive group, respectively ($p=0.0996$). Multiple familial cancers occurred in 70 families, which were significantly more frequent in *BRCA*-positive families ($p=0.0034$). By ordinal logistic regression, the occurrence of multiple familial cancers was associated with *BRCA* mutations ($p=0.0045$), not with other risk factors. The most common site of disease was the stomach, which is the most common in nationwide. And the proportional incidence of pancreatic cancer (6.8%) was significantly higher than that of nationwide cancer statistics (2.4%, $p=0.0137$). **Conclusion:** *BRCA* mutations in high-risk breast cancer patients were associated with multiple risk factors and multiple family members with other primary cancers. Genetic counseling based on accurate information should be provided to families with *BRCA* mutation carriers.

Key Words: *Breast neoplasms, BRCA1, BRCA2, Familial cancer*

INTRODUCTION

A family history of cancer is a predisposing factor for other primary cancers. For example, familial breast cancer and hereditary nonpolyposis colorectal cancer are associated with increased risk of pancreatic cancer [1-4]. The positive association between a family history of pancreatic cancer and risk of lymphoma and ovarian cancer is another example [5]. Since *BRCA1* and *BRCA2* are involved in pathways that regulate DNA repair, cell-cycle progression, and apoptosis, mutations of the genes predispose to breast, ovarian, and other primary cancers such as pancreatic, stomach, biliary tract, and prostate cancer [6-9]. Familial cancers other than breast or ovary are also associated with mutations of *BRCA1* or *BRCA2* [10-12].

BRCA1 or *BRCA2* mutations contribute to the earlier onset of breast cancer [13-15]. A higher prevalence of mutation is also observed in patients with a family history of breast or ovarian cancer, male breast cancer, and bilateral breast cancer [16-18]. A comparative study of population differences in the prevalence of *BRCA* mutation showed nearly identical frequencies of deleterious mutation across populations, but deleterious mutations were associated with higher risk of secondary malignancies [19].

Taken together, *BRCA* mutations influence the development of second primary cancers other than breast or ovary cancer. This effect was observed in patients with mutations or in family members of probands. The risk factors mentioned above are related to a higher mutation incidence. In Korea, previous

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studies have been confined to show the relationships between *BRCA* mutation and the risk factors. One study showed a higher risk of secondary malignancies among patients with deleterious mutation [19], but the relationship between *BRCA* mutation and other primary cancers in family members has not been investigated. In this study, we conducted *BRCA* genetic testing in breast cancer patients with risk factors for carrying mutations. We then analyzed the relationships between mutations and prevalence of other primary cancers in family members including probands.

METHODS

From April 2008 to May 2011, a total of 272 patients were enrolled at a single institute, the Samsung Medical Center. Patients with breast cancer who carried at least one of the following risk factors were included: reported family history of breast or ovarian cancer at any age; 40 years or younger at diagnosis; bilateral breast cancer; or male gender. The members of the family included first- and second-degree relatives, first cousins, and the probands themselves. After informed consent was acquired, genetic counseling was primarily focused on personal and family history of all cancers. The familial pedigree was organized from the information by a research nurse. If any member had a history of cancer other than breast or ovary, the family was regarded as positive for other primary cancer. After excluding 34 patients who refused to participate in the study or provided insufficient information, the number of eligible patients was 238.

BRCA mutation analysis was performed at the Department of Laboratory Medicine and Genetics, Samsung Medical Center. Genomic DNA was extracted and purified from peripheral blood leukocytes. The whole exons and their flanking intrinsic sequences of the *BRCA1/2* genes were amplified by polymerase chain reaction. The amplified products were directly sequenced and the sequences were compared with reference sequences using Sequencher software (Gene Codes Co., Ann Arbor, USA). The genetic mutations analyzed were confined to deleterious mutations such as frameshift or nonsense mutation in accordance with the breast cancer information core (BIC) database (http://research.nhgri.nih.gov/bic). And variants of unknown significance were excluded. Genetic testing of high risk breast cancer patients was approved by the Institutional Review Board of Samsung Medical Center (2010-09-006-001).

Fisher's exact or chi-square tests were used to analyze the relationships between the distributions of risk factors and *BRCA* mutation. These tests were also used to assess the relationships between the family history of other primary cancers and *BRCA* mutations. To identify factors associated with family history of other primary cancer, an ordinal logistic regression analysis was applied including *BRCA* mutations and risk factors for the inclusion criteria. SAS software (SAS 9.1.3; SAS Institute Inc., Cary, USA) was used for statistical analysis. Probability values less than 0.05 were considered statistically significant.

RESULTS

The median age of the 238 eligible patients was 41 years (range, 21-68 years). *BRCA* mutations were detected in 49 (20.6%) of the patients, while variants of unknown significance were detected in 13 (5.5%) patients. *BRCA1* and *BRCA2* mutations were detected in 23 (9.7%) and 25 (10.5%) patients, respectively. One patient, the subject of a recent case report, had mutations in both *BRCA1* and *BRCA2* [20]. The distributions of risk factors according to *BRCA* mutation status are presented in Table 1. The *BRCA*-positive group had a higher frequency of family history and bilateral breast cancer. There were 27 (55.1%) patients who had two or more risk factors in the *BRCA*-positive group, while 43 (22.8%) patients had multiple risk factors in the *BRCA*-negative group ($p < 0.0001$).

There were 271 members of 156 (65.5%) families who had histories of cancer other than breast or ovary. The familial pedigree of a representative patient who had two risk factors, family history of breast cancer and younger age at diagnosis, is shown in Figure 1. There were two family members who had histories of other cancers, thyroid and uterus. The members with breast or other cancer had *BRCA1* mutations revealed by genetic testing. The mother of the sibling also had the mutation.

Table 1. Distributions of age and risk factors according to *BRCA* mutation status

	BRCA (–) (n=189) No. (%)	*BRCA* (+) (n=49) No. (%)	*p*-value*
Age (yr)†	41 (21-67)	39 (24-68)	0.3401
Risk factors			
Family history of breast or ovarian cancer‡	121 (64.0)	43 (87.8)	0.0014
Younger at diagnosis (≤40)	91 (48.2)	27 (55.1)	0.3856
Bilateral breast cancer	16 (8.5)	10 (20.4)	0.0169
Male gender	5 (2.7)	0	0.5864
No. of risk factors			<0.0001
Single	146 (77.2)	22 (44.9)	
Multiple	43 (22.8)	27 (55.1)	

The relationships between the distributions of risk factors and *BRCA* mutation were examined by chi-square test except for male gender, which by Fisher's exact test.
*The t-test was applied for comparing the distribution of age; †Median age (range); ‡First- and second-degree relatives, first cousins.

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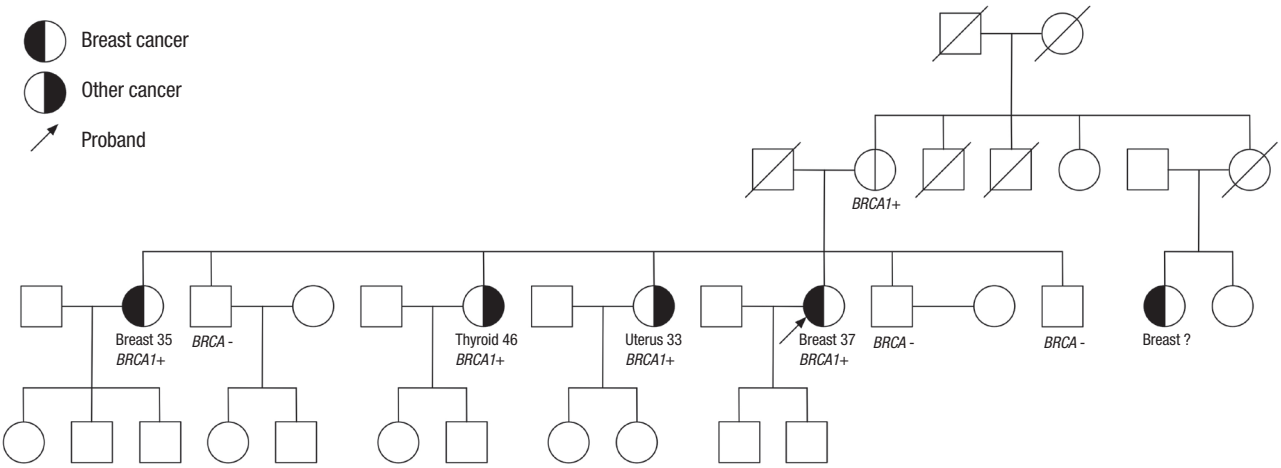

Figure 1. The familial pedigree of a representative patient with two risk factors. Two family members had histories of cancer other than breast or ovary.

Table 2. Distributions of families according to numbers of members having other primary cancers

No. of members having other primary cancers	*BRCA* (–) No. (%)	*BRCA* (+) No. (%)	*p*-value
0	70 (85.4)	12 (14.6)	
1	73 (84.9)	13 (15.1)	0.0034*
2 or more	46 (65.7)	24 (34.3)	

*Examined by chi-square test.

Table 3. Ordinal logistic regression analysis for the distributions of other primary cancers

Response=No. of members having other primary cancers (0 vs. single vs. multiple)	*p*-value	Odds ratio (95% CI)
Variables		
Family history of breast or ovarian cancer	0.7863	1.096 (0.566-2.120)
Younger at diagnosis (≤40)	0.7486	0.908 (0.504-1.635)
Bilateral breast cancer	0.9589	1.021 (0.466-2.238)
Male gender	0.3882	2.190 (0.369-12.998)
BRCA mutation	0.0045	2.493 (1.328-4.681)

CI=confidence interval.

Among the 156 patients with family history of other primary cancer, 37 (23.7%) patients had *BRCA* mutation. It was detected in 12 (14.6%) of the 82 patients without family history (p=0.0996). Multiple cases in a single family occurred in 70 families. Among them, 24 (34.3%) were families of the *BRCA*-positive patients, which was significantly more frequent than expected by chi-square test (p=0.0996) (Table 2). By ordinal logistic regression, the occurrence of multiple other primary cancers was associated with *BRCA* mutations, not with other risk factors (Table 3).

The most common site of other primary cancer was the stomach, which corresponds with research findings that stomach cancer is the most common cancer in Korea [21]. In the *BRCA*-positive group, the proportional incidence of uterine cancer was 12.3%, which was relatively higher than that of the *BRCA*-negative group (5.6%, p=0.0590) (Table 4).

Table 4. Distributions of frequently occurring familial cancers of patients according to *BRCA* mutation

Site of other primary cancer	*BRCA* (–)* (n=198) No. (%)	*BRCA* (+)† (n=73) No. (%)	Relative ratio (95% CI)	*p*-value‡
Stomach	49 (24.7)	15 (20.5)	0.947 (0.822-1.091)	0.4710
Lung	27 (13.6)	10 (13.7)	1.001 (0.899-1.114)	0.9895
Uterus§	11 (5.6)	9 (12.3)	1.077 (0.982-1.182)	0.0590
Thyroid	15 (7.6)	8 (11.0)	1.038 (0.949-1.136)	0.3697
Liver	24 (12.1)	6 (8.2)	0.958 (0.879-1.044)	0.3711
Colorectal	20 (10.1)	6 (8.2)	0.980 (0.902-1.064)	0.6414
Pancreas	10 (5.1)	5 (6.8)	1.019 (0.950-1,093)	0.5663

CI=confidence interval.
*Remaining 42 cases include head & neck, hematologic, brain, skin, biliary, esophageal, and prostatic cancer; †Remaining 14 cases include esophageal, head & neck, prostatic, brain, hematologic, and biliary cancer; ‡Tested by the Cochran-Mantel-Haenszel test; §Includes body and cervix.

DISCUSSION

In this study, we described the patterns of familial cancers other than breast or ovary of patients with high risk breast cancer. Among the 238 eligible patients, 156 (65.5%) patients had a total of 271 familial cancers. *BRCA* mutation was detected in 49 (20.6%) patients, which was more prevalent in patients who had family history of other primary cancers (37 patients, 23.7%, p=0.0996). Seventy patients had multiple familial cancers. *BRCA* mutation was also detected prevalently in patients with multiple familial cancers (24 patients, 34.3%, p=0.0034). Ordinal logistic regression analysis supported the finding that *BRCA* mutation was significantly associated with

multiple familial cancers ($p = 0.0045$).

The most prevalent other primary cancer was stomach cancer, which is the most common cancer in Korea [21]. According to the cancer statistics of Korea, 15.7% of all cancer was stomach cancer. In this study, stomach cancer accounted for 24.7% and 20.5% of *BRCA*-negative and positive group, respectively. But the difference of the proportional incidence was not statistically significant. Unlike the Korean characteristics, stomach cancer is the fourth most common malignancy in worldwide after lung, breast, and colorectal cancer [22,23]. In contrast, non-melanoma skin cancer which is relatively prevalent in Western families with *BRCA* mutation was rare in this study [11,24].

Pancreatic cancer showed the most distinctive difference from nationwide statistics. The proportional incidence was 6.8% and 2.4% in this study and nationwide, respectively ($p = 0.0137$). The risk of pancreatic cancer has been known to be higher among carriers of *BRCA* mutations [7,8]. And pancreatic cancer has been shown to the third most common cancer associated with *BRCA* mutation [25]. *BRCA* mutations as a predisposing factor for the development of pancreatic cancer may have contributed to the results of this study [10,12]. In addition to *BRCA* mutations, several environmental, biological, and genetic factors might contribute to the distribution of familial cancers. It may be affected in part by the distributions of cancer nationwide, and also expected to be influenced by cancer susceptibility from the *BRCA* mutation.

In the Korean population, there are several distinctive features in regard to breast cancer. The first is younger age at onset of breast cancer than in other populations [26,27]. However, the incidence of *BRCA* mutations does not differ from that of other racial groups [19]. Although there had been no known founder mutation, the *BRCA2* c.7480C > T mutation (7708C > T according to the BIC nomenclature) has been suggested as candidate for the founder mutation in Korea [18,28,29]. Several studies have dealt with *BRCA* mutations in Korean breast cancer patients, but they have been confined to prevalence of *BRCA* mutations or relationships with risk factors. In high-risk patients, the frequency of *BRCA* mutations varied from 8.3 to 25% according to the risk factors, which was comparable to that of this study (20.6%) [18,29]. Although the relationship between *BRCA* mutations and secondary malignancies was previously investigated [19], the relationship between the mutations and familial malignancies has not been studied yet in Korea. Because *BRCA1*/2 mutation testing in Korean population is still not common, recruitment of more family members of carriers needs to provide more information about second primary malignancies associated with in family members of *BRCA* mutation carriers. The Korean Hereditary Breast Cancer (KOHBRA) study, a nationwide, multicenter study is expected to provide the answer [29]. In the absence of such information, the results of our study suggest such an association from one of the biggest general hospitals in Korea that has nationwide coverage of patients.

Future directions require a focus on providing optimal genetic counseling and testing for family members. According to the National Comprehensive Cancer Network's (NCCN) guideline for genetic/familial high-risk assessment: breast and ovarian, genetic counseling is highly recommended when an individual has one or more of the following factors: early age onset breast cancer, triple negative breast cancer, two incidences of breast cancer in a single individual, male breast cancer, and personal/familial history of pancreatic cancer with familial/personal history of breast and/or ovarian cancer [30]. When the hereditary breast and/or ovarian cancer syndrome testing criteria are met, genetic testing for *BRCA1*/2 and screening for breast and ovarian cancer should be considered. In addition, a full body skin examination for melanoma and investigational protocols for pancreatic cancer might be considered for other cancer screening. Possible inherited cancer risk to relatives, options for risk assessment, and management should be advised.

In conclusion, *BRCA* mutations were associated with having multiple risk factors in patients with high risk breast cancer. In the *BRCA*-positive group, primary cancers of family members were found in pancreas and uterus at higher than nationwide reported incidences. Occurrence of multiple familial cancers was associated with *BRCA* mutation, and not with other risk factors. Tailored genetic counseling based on precise information should be provided to families with *BRCA* mutation carriers.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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