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Is the BRCA Germline Mutation a Prognostic Factor in Korean Patients with Early-onset Breast Carcinomas?

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Purpose: The purpose of this study was to determine if there were prognostic differences between BRCA related and BRCA non-related Korean patients with early-onset breast carcinomas.

Materials and Methods: Sixty women who had developed breast cancers before the age of 40, and who were treated at the Soonchunhyang University Hospital, were studied independently of their family histories. The age range was 18 to 40 with a median of 34.5 years. Lymphocyte specimens from peripheral blood were studied for the heterozygous mutations of BRCA1 and BRCA2 using direct sequencing methods. Immunohistochemistry was performed on the paraffin-embedded tissue blocks that were available.

Results: Eleven deleterious mutations (18.3%, 6 in BRCA1 and 5 in BRCA2) and 7 missense mutations of unknown significance (11.7%), were found among the 60 patients. More than half of the mutation were novel, and were not reported in the database. Most of the BRCA-associated patients had no history of breast cancer. No treatment related failures were observed in the BRCA carriers, with the exception of one patient that had experienced a new primary tumor of the contralateral breast. The seven year relapse free survival rate were 50 and 79% in the BRCA carrier and BRCA negative patients, respectively. Although the expression of estrogen and progesterone receptors were less common, and histological features more aggressive, in the BRCA associated tumors, the outcome of the patients with BRCA mutations was not poorer than that of the patients without deleterious mutations.

Conclusion: Despite the BRCA mutation carriers having adverse prognostic features, the recurrence rate was relatively lower than that in the BRCA non-carrying Korean patients with early-onset breast carcinomas. In addition, although the prevalence of the BRCA mutation in Korean patients was higher than that in white patients, the penetrance of the cancer seemed to be relatively low in Korean women carrying BRCA mutations. A large population based study of the BRCA mutation, with a long-term follow-up of the study patients will be required to confirm these results.

Key Words: BRCA mutation, Early-onset breast carcinoma, Prognostic factor, Korean

Introduction

Breast cancer is the most common malignancy in female, occurring in approximately one in eight women in western countries. But the incidence and age patterns of breast cancer varies widely between countries.[1] About 25% of invasive breast cancer cases in Korea occur in patients younger than 40 (National Cancer Registry Center in Korea 2000) in contrast to

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4 ~ 8% of total cases occur in the same age group in western countries.

The breast carcinoma susceptibility genes BRCA1 and BRCA2, has been extensively investigated since its isolation from breast cancer patients with family history in 1994 and 1995.[2,3] Through genetic linkage analysis, BRCA1 was localized to 17q21. The BRCA1 gene contains 22 exons distributed over more than 100kb of genomic DNA and encodes for a protein of 1863 amino acids. BRCA2 has been identified on chromosome13q12 ~ 13 and likelyaccounts for a large proportionofnon - BRCA1 familial breastcancer.Many mutations has been described with themajorityresulting in a truncated protein.[4]

Inherited mutations in the BRCA1 and BRCA2 put women at high risk for developing breast cancer at a relatively early age. Early - onset breast cancer (diagnosed before menopause) is considered an important feature of inherited susceptibility. Women who carry mutations in thesegeneshaveasignificantly increased chanceofdevelopingbreast cancer before theageof50between33%and50%.[5] Young women with breast cancer have more aggressive lesions manifestedbyanelevatedS - phasefraction,abnormal p53expression and higherhormone receptor negativity. Eisingeretal.notedthathistologic grade appeared to segregates as a genetic trait, thus establishing a genotype - phenotype correlation.[6] Others report distinct molecular pathogenesis of early - onset breast cancers in theBRCA1andBRCA2mutationcarriers.[7,8]

Currently molecular studies oftheBRCA1orBRCA2 mutations has been focused within North America or western countries, especially in Caucasianpopulations. Theprevalenceof the BRCA1 and BRCA2 mutation were in the range of 5 ~ 15% in young women with breast cancer and three specific mutations are frequent especially Ashkenazi descendant in Jews.[9,10] Similar data pertaining to Asian populations remain limited except a few about Japanese and Chinese.[11,12] There is only one article about BRCA1 and BRCA2 study of Korean women,butitisfocusedontheidentification of the BRCA mutation in patients with strong familial history of breast and/or ovarian cancer.[13]

During thestudy of BRCAmutation status inKorean women with early - onset breast cancer regardless of familyhistory, we found higher incidenceoftheBRCA1 and BRCA2 mutation (not published data). Despite adverse tumor characteristics, some studies reported thatpatients with the BRCA - associated tumor didnot have poor disease free and overall survival rate and higher local failure than those in patients with sporadic breast cancer.[7] other studies reported the BRCA mutation as a poor prognostic factor.[14] The purpose of this study was todetermine if there wereprognostic differences between BRCA related and BRCA non - related Korean patients with early - onset breast carcinoma.

Materials and Methods

Sixty patients were selected among patients with breast carcinoma that was diagnosed with the age of 40 or younger who were treated at the University Hospital, Seoul, Korea from 1995 to 2000 from hospitals breast cancer registry. None of the patients were selected solely based on a family history of breast cancerorovarian cancer. Four patients treated before 1995 were included among the 60 patients. Themedian and range for the ages ofonset were 34.5and22 ~ 40 years. Twenty - seven patients underwent breast conservativesurgery and radiotherapy and 33 patients underwent modified mastectomy or skin - sparing mastectomy. Allofthepatientsreceivedpostoperative chemotherapy and patients with hormone receptor positive tumor received tamoxipen therapy.

They all were invited to participate this study and informed consent was obtainedfromallsubjects.They were informed of thepossibility thattesting could lead to psychological distress and family disruption, but it could also identify those at risk, thus warranting increased surveillanceorpreventive options that might result in improved health care. All patients were told thatthe results would be kept in locked coded search filesand wouldnotbecomepartoftheirclinical records.

Bloodsampleswere obtained fromphlebotomyin2 tubes from each patient. After collecting blood samples of 15 ~ 20 patients in a day, we sent it instantly to professor Haffty's laboratoryinYaleUniversity Hospital, USA via air borne express mail. We repeated this procedure several times to collect samples of 60

patients with breastcancer. And 31 paraffin embedded tissue blocks were available from the hospitalarchives.

1. Genetic testing

Genomic DNA was isolated from peripheral blood lymphocytes. All analyses of the BRCA1 and BRCA2 were performed by direct gene sequencing at Myriad Genetics Laboratories, Salt Lake City, UT, USA. Aliquotes of patients DNA were each subjected to polymerase chain reaction (PCR) amplification o f entire coding region and intro - exon boundaries (35reactions for BRCA1, 47 reactions for BRCA2). The amplified products wereeachdirectly sequenced in forward and reverse directions using fluorescent dye - labeled sequencing primers. Chromatographic tracingofeach amplicon was analyzed by a proprietary sequence analysis software followed by visual inspection and confirmation.

Genetic variants were detected by comparison with a consensus wild - type sequence constructed foreach gene and were confirmed by repeated analysis, including PCR amplification of the indicated gene regions and sequence determination.

Positive for a deleterious mutation includes all mutations (nonsense, insertions, deletions) that prematurely terminate the protein productofBRCA1at least ten amino acids from C - terminus, or the protein product of BRCA2 at least 110 amino acids from C - terminus. In addition,specificmissense mutations and non - coding intervening sequence(IVS) mutations are recognized as deleterious on the basis of data, functional assays, biochemical evidence and demonstration of abnormal mRNA transcript processing. Genetic variant, suspected deleterious include genetic variants indicates a likelyhood that the mutation is deleterious. Genetic variant of uncertain significance include all missense mutations that occur in analysed intronic regions and mutations that truncate BRCA1 and BRCA2 distaltoaminoacidpositions1853 and 3195, respectively.

2. Immunohistochemistry

Five μm sections cut fromparaffin blocks were dried at60°C for 1 hour. Thesection weredewaxed in xylene and rehydrated through graded alcohols to distilled water. Antigen retrieval used was steam bath at 97°C for 20 minutes for determination of ER, PR, and Her - 2/neu. Dako autostainer was used to for the staining and no blocking steps were required. The sections were incubated in primary antibody atvarious dilutions for 30 minutes at room temperature. Secondary antigen retrieval was performed using detection kits (Envision for ER and PR, Dako Lsab+ and Hercep Test for Her - 2/neu). All sections were counterstained with hematoxylin, dried and coverslipped.

Table 1. Clinical Characteristics of 60 Patients

Characteristics	Total no. (n=60)	B
AgeatDx(years)		
<35	35	
36 ~ 40	25	
Median age	34.5	
Tumor histology		
Infiltrating ductal	55	
Medullary	3	
Tubular	1	
Mucinous	1	
Tumor size		
T1	31	
T2	26	
T3	2	
Lymph node involvement		
Yes	27	
No	33	
Nucleargrade		
GI (most anaplastic)	17	
GII	32	
GIII	1	
no data	10	
Family history of br or ov (1st and 2nd degree)	8	

*Including BRCA mutation with variant of uncertain significanc

Tumors known to express the 3 markers served as positive control. For HER-2/neu, primary antibody was omitted for negative control and DAKO K5204 was used forreference grade. A cut-point of ? 10% tumor cells stained without considering intensity was used to categorize positive results for ER and PR. For HER-2/neu, only membrane staining was scored positive and cytoplasmic staining was ignored. A numeric score ranging from 0 to 3 that reflects the staining intensityandpatternsin10% ormoreoftumor cell is employed. Numeric score 2+ or 3+ was considered positive by Hercep Test guideline. All immunostained section were examined andscoredby twooftheauthors.Anydiscrepancies were resolvedby subsequentconsultationto breast pathologist, D. Carter. in the Yale University Hospital.

After completion of the study, we reviewed all the medical chart including pathology reports and immunohistochemistry reports. Some of the immunohistochemistry data notavailableinthistissue block study were included in this analysis. Details of familyhistory of cancer were repeatedly obtained during renewed contact andfollow-upfor notifying the test results.

3. Statistical analysis

All thepatient data including clinical immunological and BRCA mutations wereentered into a computerized database employing SPSS (StatisticalPackage for the Social Science). Differences in categorical variables between wildtype (and genetic variant of uncertain significance) and mutations were compared using standard chi-square analysis orFishersexacttest, as appropriate. For analysis of extent of bivariate correlations, Pearson's Correlation Coefficients were used. We used Kaplan-Meiertocalculate relapsefree survival probabilities and the log-rank test was used to compare survival distributions of cases with and without deleterious germline mutations.

Results

Characteristics of patients and tumors of the BRCA-associated and sporadic breast cancers are summarized in Table 1. Weincludedpatients with BRCA missense mutation (variants with uncertain significance) into the BRCA non-carrier cohorts for convenience of analysis.Infiltratingductal carcinoma was the predominant histology in both groups and 3 medullary carcinoma in the study belonged to women without mutations. One patient with bilateral disease and two patients with primary tumors larger than 5.0 cm werealsonotedin women withoutmutation. Four of the 9 BRCA carrier had lymph node metatasis, but none ofthem had 4 or more lymph node metastasis.

Deleterious germline BRCA mutation were detected in 9 patients (15%) with 11 mutations (18.3%, 6 in BRCA1 and 5 in BRCA2). Sequence variants with uncertain significance were detected in seven of 60 participants including 2 patients with coincidental deleterious mutations. Six of 11 deleterious mutations and 4 of 7 missense mutations were novel mutation, native to Korean up to dateandtheywerenotpreviously reported in the Breast Cancer Information Core database. The median onset age for BRCA mutation carriers wassimilartothatofmutationnegative cases.

Table2.DetailsofCaseswith 2 or MoreMutations in BRCA1 and BRCA2 Genes

ID	Age	Mutation	Gene	Site	Citation*	Type	FH†	FH‡
60071	33	E1661X	BRCA1	Exon 17	Novel	Nonsense	No	Stomach
		6174del4	BRCA2	Exon 11	(8)	Frameshaft		Larynx
60351	26	1635del5	BRCA1	Exon 11	(17)	Frameshift	No	Stomach
		3026delCA	BRCA2	Exon 11	Novel	Frameshift		
		M1628T	BRCA1	Exon 16	(39)	Missense		
60261	37	1775delT	BRCA2	Exon 10	Novel	Frameshift	No	Leukemia
		K1533N	BRCA2	Exon 11	Novel	Missense		Leukemia

Citation*: Citation number in Breast Cancer Information Core database, FH†: Family history of breast orovarian cancer in the1stand2ndrelatives,FH‡: Family history of other cancer

Three patients had more than 2 sequence variants including 2 patients with deleterious double heterozygotes mutations (Table 2). Patient with ID# 60071 had twodeleterious mutations, one of them is the germline BRCA1 nonsense mutation E1661X, resulting in premature truncation of the BRCA1 protein atamino acidposition1661(Fig. 1). All of the 3 patients had no historyofbreast orovariancancer in their first or second relatives. In fact, there was a significant absence of a family historyofbreastorovariancancer in many of the patients with mutation. Onlytwoofnine deleterious mutation carrier had family history of BRCA-related cancer, and this result is not different from the incidence offamily history ofBRCA-related cancer in the BRCAnegativepatients andpatients with missense mutation of uncertain significance (6/51).

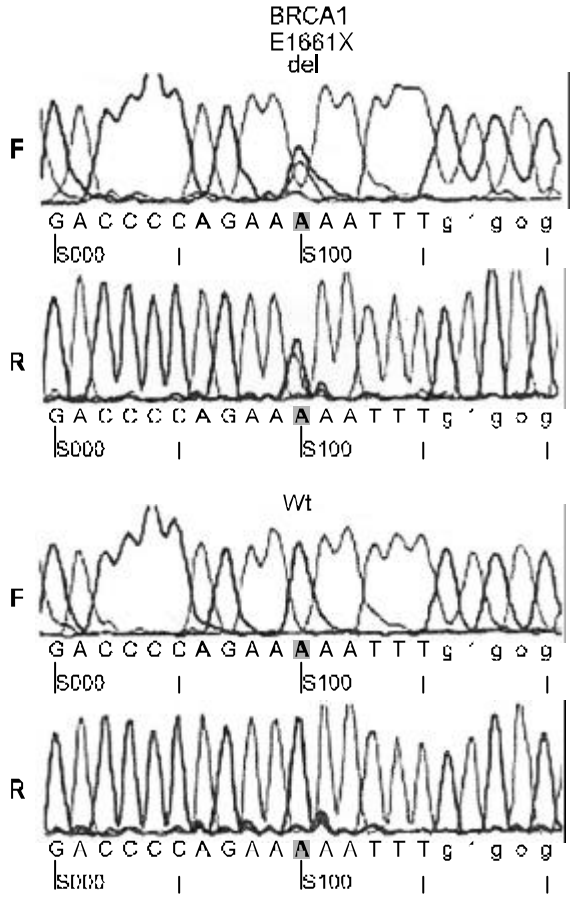

Fig.1. BRCA1E1661Xfigure.Mutationsequencechange in central area (G→T) from the wt (wild type) to del (deleteriousmutation) resulted in stop codon by F (forward) and R (reverse) directions.

For immunohistochemistry, BRCA-associated tumorswere shown to have less estrogen, progesterone receptor. Peason's correlation coefficient between the BRCA positivity and estrogen receptor negativity was -0.333 and the negative correlation was statistically significant at the 0.05 level (p=0.038). Although statistically not significant, nuclear grade I (most anaplastic) was more frequentlyobserved in the BRCA associated tumors (4/9) than in the tumors of BRCA non-carrier (13/41). None of the BRCA mutation carriers, studied by Hercep Test(n=5)hadHER-2/neu positivity while BRCA negative (including missense mutation o f uncertain significance) were shown to have 38% positivity (p=0.092).

Five year relapse free survival rate was 92% for T1 and 67% for T2 and this difference was statistically significant (p=0.0412) (Fig. 2). Statisticallysignificant relapse free survival difference was not observed according to axillary lymph node status (data not shown), but the survival difference was strongly observedbysubdividing axillarymetastasis into one to three positive group and 4 or more positive group (Fig. 3). Among the patients not associated with BRCA mutations (n=51), three experienced local recurrence and four had distant metastasis as the first event. In contrast,nooneoutofthenineBRCAmutationcarrier had loco-regional failure or distant metastasis. Only one patients with BRCA mutation carrier experienced new primary cancer in the contralateral breast 6 and

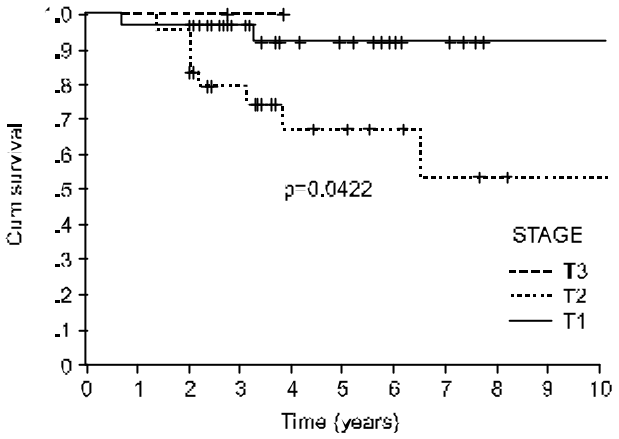

Fig. 2. Event free survival rates according to T-stage.

half years after treatment. She had estrogen receptor negative tumor and received 6 cycles of CMF chemotherapy without tamoxipen therapy. The 7 year event free survival rate was 79% for BRCAnon - carrier and 50% for BRCA carrier, and the difference was statistically not significant (Fig. 4).

Statistically significant survival differences were not observed according to estrogen and progesterone receptor, nuclear grade, HER - 2/neu status.

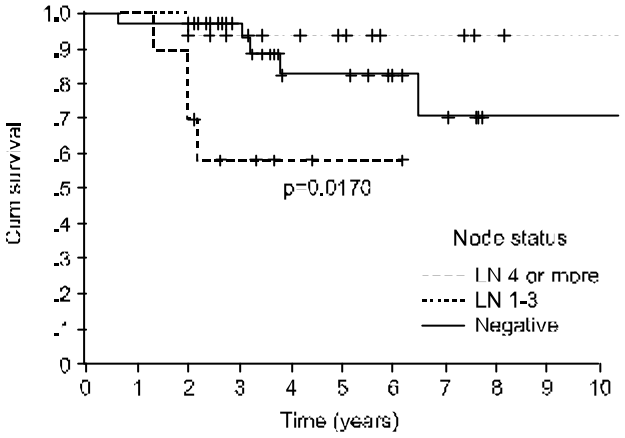

Fig. 3. Event free survival rates according to status and numbers of axillary lymph node.

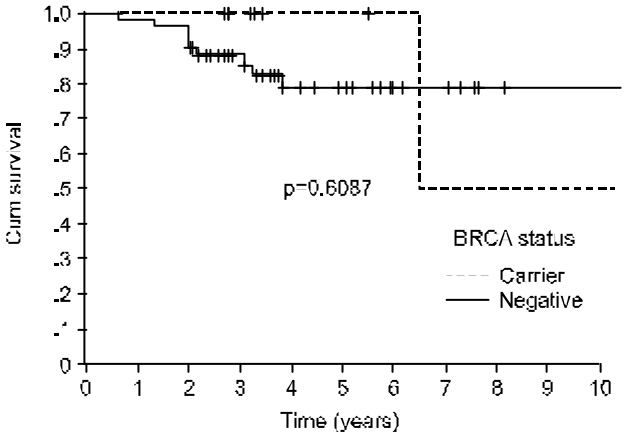

Fig. 4. Event free survival rate according to BRCA status (BRCA negative includes missense mutation of uncertain significance).

Discussion

Recently, Kang et al. reportedexistence of the BRCA1 and BRCA2 germlinemutation in Korean patients with multiple family history of breast cancer or ovarian cancer.[13] In this study of Korean women with early onset breast cancer, the prevalence of 11 mutations (18.3%) and 9 cases (15%) out of 60 patients was highest among outbred populations in the published series andnorecurrent founder mutation was observed.

There were two groups of races who had higher prevalence of the BRCA-associated cancer than that of this study. Results carried out in isolated populations such as Ashkenazi Jews[10] or Icelanders[16,17] showed that the prevalence of the BRCA- associated breast tumors in youngpatients is about 30% for Ashkenazi Jewsand about25%fortheIcelanders.Inthose inbred populations, individual, highly recurrent founder mutations accountforthemajority of all mutations.Over 2% of Ashkenazi Jews carry mutations in the BRCA1 (185delAG, 5382insC) and 6174delT in the BRCA2 and about 0.5% ofIcelanders have 999del5 in the BRCA2 gene. Among Ashkenazi Jews, BRCA1 mutations appear to make a greater contribution to early-onset breast cancer than do BRCA2 mutations. Conversely in Iceland, BRCA2 accounts for a major portion and BRCA1 makes a verysmall contribution. Therefore, the results derived from such populations are not comparable to outbred populations.

In the other series, most of them have outbred populations, the prevalence rate of the BRCA1 and BRCA2 mutations lie between 6 and 12%.[18~26] Mutations in the 2 genes make approximately equal contributions to early-onset breastcancer in this study. This is consistent with other results in outbred populations. Approximately equal numbers of the families had numbers in the BRCA1 andBRCA2 genes by the Breast Cancer Linkage Consortium of families with breast cancer only.[27] One study had a large proportion of the BRCA1 mutation, because they includemissensemutations in the analysis, and all of the missense mutations were BRCA1 genes.[23] The BRCA2 gene mutations contributed more than the BRCA1 mutation to breast in the Philippines.[25] The Philippines consists of manyislands, and they also had many common founder mutations in the BRCA2 gene.

One of the most important findings ofthis study is thatmostofthepatientswithBRCA do nothave family historyofbreast or ovarian cancer. We observedonly 2casesout of9patientshave family history, onefrom her mother and the other from her paternal aunt. The observation that seven of nine carriers donothavea relative withbreastorovariancancerisneverthelessin accordance with previous studies. Family history is observed more than 80% of cases in theAshkenaziand Icelander,[10,16] 40~90% in theotherpopulations.[19~23,25] Only onestudy with ethnic Chinese had similar family history pattern to this study.[26] It could mean that mutationsobserved inKorean or Chinese confer a lower penetrance than previously estimated in western countries especially in Ashkenazi population. Early studies of families with multiple cases of breast and ovarian cancer suggested that BRCA1mutation carriers mayhavealifetimebreastriskofupto84%andovarian risk of up to 44%.[27] However, studies of less selected families have suggested thattheriskmaybesomewhat lowerthan those initialestimates,[5] and the penetrance of the BRCA2mutation is lowerthanthat of the BRCA1 mutation, especially in Jewish population.[28,29] Therefore, mutations in Korean population may have lower susceptibility or lower risk sitemutations to breast cancer than those in western European ancestry throughgenetic and environmental modifying effects.

The identification of a histologic pattern characterizing BRCA associated breast cancerhasnot been conclusive, but many have noted an excess of medullary histology was observed (19% vs 0%) in a series of the BRCA1-associated breast cancers compared tosporadic cases in a study from France,[30] in a carriers from theBreast Cancer linkage Consortium, and among women with early-onset breast cancer in apopulation-based study,[31] suggesting thatmedullary histology itself may be an indication for the BRCA1 testing. In this studyofKoreanwomenwith early-onset breast carcinoma, all the three patients with medullary histology belonged to the BRCA non-carrier.

The phenotypic expression of the BRCA1 and 2 breast cancer indicates distinctive prognostic features. The Breast Cancer Linkage Consortium examined histopathologicfeatures ofbreastcancerinwomenwith the BRCA1mutations and, when compared to controls,

showed an excess of high grade tumors, high mitotic rates as well as higher rates of aneuploidy and high proliferative fraction in the BRCA1 carriers. Another case control study among women of Jewish descent found that the BRCA1-associated tumors were significantly more likely to be high grade and estrogen receptor negative.[10]

For immunohistochemistry study, results from this study are not different from others. BRCA mutation carriers are typically estrogen receptor negative, progstrone receptornegative and HER-2/neu negative in all age groups from tumors with family history,[10,14] but similar results were observed in the early-onset breastcancerregardless of family historyandmutation sites.[26,31] These data suggest that neither hormone receptor nor Her-2/neu stimulation seem tobeimportant in the pathogenesis ofcancersarising in women with the BRCA mutation carrier.

Despite these distinctive histologic and immunohistochemical features, the identification of the BRCA-associated tumor as a prognostic factor has been elusive. In accordance with poor prognostic features noted histologically with for the BRCA1-related breast cancer, 2 European studies reported survival rates that were similar to or worse than sporadic cases, with a significantly increased risk of contralateral breast cancer.[7,32,33] One report failed tofindahigher rate of local, regional, or distant metastasis among young women treated with breast conserving surgery and radiation therapy whose family history suggestive of hereditary breast compared to a group without a significant family history.[34] Gaffneyetal.alsoreported that despite their younger age at presentation, BRCA mutation carriers presented at a similar stage, display a nornal acute reaction to radiotherapy and similar prognosis when compared with sporadic breastcancer patients in the Utah CancerRegistry.[35] Another study found that survival of 43 BRCA1 carriers with advanced ovarian cancer was significantly better than that of matched sporadic cases, mediansurivalwas 77months in the BRCA1 carriers versus 29 months in non-carriers.[36] In contrast, a populationbased study from Sweden noted an initial survival advantage in BRCA-associated cases, but this advantage did not persist over time.[32] Studies of prognosis of the BRCA2-associated breast cancer have not shown evidence for substantial differences in comparison with sporadicbreast cancer.[37] In this study, all of thecases with the BRCA non-carriersand 4 ormoreaxillarylymph node metastasis may cause poor outcome in the BRCA negative groups of patients.

Further large studies with appropriate control populations and long-term follow-up will be required to determine whether the BRCA mutation status is prognostic factor or not.

In conclusion, Korean patients with early-onset breast cancer have characteristics of high prevalence of the BRCA mutations, low family history. Despite of poor prognostic features, patients with the BRCA mutationdid not have poor outcome. A large population based screening of the BRCA mutation with a long-term follow-up of the study patients awill be required to establish the frequency, penetrance and prognostic significance of the BRCA mutation.

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국문초록

한국의 젊은 여성유방암 환자에서 BRCA 배선유전자 돌연변이는 예후인자인가?

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목 적: 한국인 젊은여성유방암환자에서유방암유전자 (BRCA)가예후인자가 될 수 있는지 알아보기위하여 본 연구를 시행하였다.

대상및방법: 대학병원에서 치료를받은환자중에서유방암이나난소암의가족력과관계없이 40세이하의환자를 선택하였다. 환자의 나이는 18 ~ 40세이었고 중앙값은 34.5세이었다. 환자의 말초혈액에서 림프구를 모아 DNA를추출하였으며 BRCA1과 BRCA2의 모든 염기 중에서 기능과 관계있는부위의 DNA를 직접염기서열 결정 방식으로 검사하였다. 조직표본 검사가 가능한 환자는 면역화학조직검사를 시행하였다.

결 과: 60명의 환자 중에서 유방암 발생과 직접 관계가 있는 돌연변이가 11개(18.3%) 있었고(BRCA1 6명, BRCA2 5명), 의미를알기가 곤란한 돌연변이가 7개 있었으며 반 수 이상의 돌연변이는 이제까지 보고되지 않은 것이었다. 그리고대부분의돌연변이 환자는유방암이나난소암의 가족력이관찰되지 않았다. 유방암유전자 돌연변이 환자는 한 명도 치료의실패가 없었으며 한 명에서 반대측유방암이 발생하였다. 7년 무병 생존율은 돌연변이 환자에서 50%, 돌연변이와 관계가 없는 환자에서 79%이었고 차이는 없었다. BRCA 관련 종양에서 에스트로젠, 프로제스테론수용체음성의 비율이높았으며조직학적 분화도가낮았으나예후는 비교대상에비해나쁘지 않았다.

결 론: 한국의 젊은여성유방암환자는예후가인자가있어도재발률이낮았으며유전자돌연변이이환율이높았으나 암의 발현율은 상대적으로 낮은 것으로 추정되었다. 이 결과를 확인하기 위해 더 많은 환자 집단과 오랜 추적기간의 연구가 필요하다.

핵심용어: BRCA 돌연변이, 젊은 여성 유방암, 예후인자, 한국인