One Korean Patient with a Family History of *BRCA1*-associated Ovarian Cancer

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Germline mutations in *BRCA1* and *BRCA2* confer high risks of breast and ovarian cancer. Among *BRCA1*- and *BRCA2*- mutation carriers, the average cumulative risks for ovarian cancer by age 70 years were 39% and 11%, respectively. There are other hereditary cancer syndromes such as Hereditary nonpolyposis colorectal cancer also confer a higher risk for developing ovarian cancer, but over 90% of all hereditary ovarian cancers are thought to be associated with *BRCA1* or *BRCA2* mutations. This report concerns a Korean woman diagnosed with ovarian cancer present with a family history of ovarian and various other cancers, in whom a germline *BRCA1* mutation was identified and the same mutation was found in one of two daughters of her's. Since there could be more hereditary ovarian cancer patients in Korean than clinicians thought, both primary and secondary prevention of ovarian cancer based on family history and genetic information is important to reduce cancer incidence and mortality.

Key Words: Ovarian cancer, *BRCA*, Hereditary breast-ovarian cancer syndrome

Introduction

Ovarian cancer is the 7th most commonly occurring cancer among women worldwide. It consists 4.0% of all incident cancer cases and 4.2% of all cancer deaths[1]. In Korea, ovarian cancer was the 10th most common cancers in women (age-standardized incidence rate 5.1 per 100,000) in the year 2005 and 9th leading cause of death from cancer in women in year 2005 (age-standardized mortality rate 3.1 per 100,000). Five-year survival rate is 62.1% in patients diagnosed during year 2001-2005[2].

There is good evidence that in some women genetic factors are important. Germline mutations in *BRCA1* and *BRCA2* confer high risks of breast and ovarian cancer. The average cumulative risks for ovarian cancer in *BRCA1*- and *BRCA2*- mutation carriers by age 70 years were 39% and 11%, respectively[3]. There are other hereditary cancer syndromes which confer a higher risk for developing ovarian cancer such as hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch II syndrome), but over 90% of all hereditary ovarian cancers are thought to be associated with *BRCA1* or *BRCA2* mutations[4].

This report concerns a Korean woman diagnosed with ovarian cancer with a family history of ovarian and

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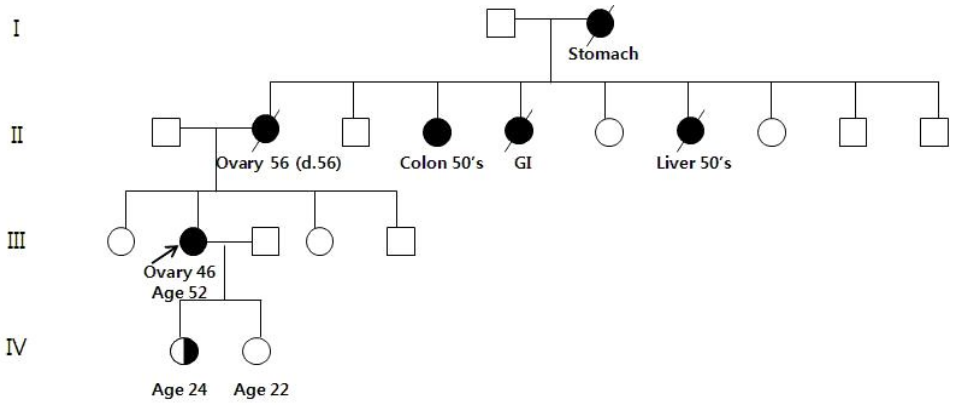

Fig. 1. Pedigree of the family with a *BRCA1* mutation as of Nov, 2009. Circles and squares indicate females and males, respectively. Crossed symbols are used for deceased subjects; age at death is given after the letter "d". Black circles correspond to individuals affected by cancer; half-filled circles are used for yet healthy *BRCA1* mutation carriers; GI - gastrointestinal; Index case is designated by an arrow.

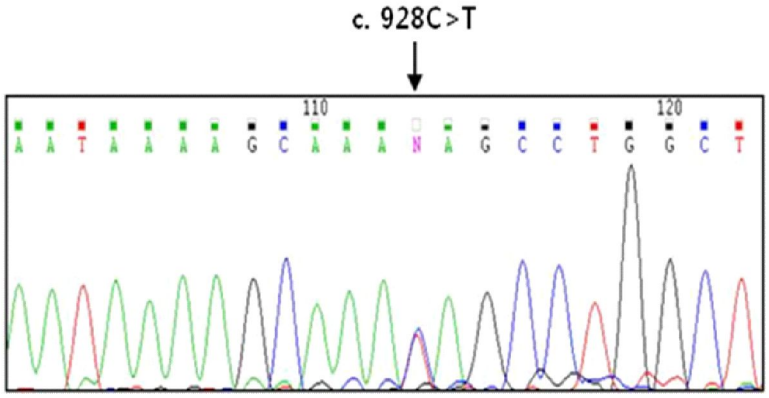

Fig. 2. Heterozygous nonsense mutation in the exon 11 of the *BRCA1* gene

various other cancers, in whom a germline *BRCA1* mutation was identified and the same mutation was found in one of two daughters of hers.

Case report

The proband, who is indicated by an arrow in the pedigree (Fig. 1), is a multiparous, 52-year-old, Korean woman who has been diagnosed in 2007 and treated for a serous papillary adenocarcinoma in the left ovary. During genetic counseling in our center, the pedigree of the patient was constructed including four generations, and revealed a strong family history of cancer. Her mother died of ovarian cancer at the age of 56, and other family members had several other types of tumors including colon, stomach, liver, and one gastrointestinal cancer of unknown primary site. The family history of this patient leads us to consider that the ovarian adenocarcinoma diagnosed could be *BRCA1* and/or *BRCA2*-associated or hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch II syndrome). After written informed consent was obtained, genomic DNA was obtained from a peripheral blood sample and direct sequencing of the complete *BRCA1*, *BRCA2*, *MLH1*, and *MSH2* genes was done by standard methods on an automated sequencer ABI PRISM3130XL Genetic Analyzer (Applied Biosystems, Inc., Foster City, CA). A c.928C>T nonsense mutation in exon 11 was detected in *BRCA1* (Fig. 2), but no mutation was found in other genes. The mutation was confirmed by independent exon sequencing. The analysis of exon 11 of the gene *BRCA1* was offered to two daughters of

the patient's. The genetic analysis showed exactly the same c.928C>T nonsense mutation in one of her daughters aged 24.

Discussion

At least two defined inheritable genetic aberrations are well-known to confer a higher risk of ovarian cancer. Mutations in the genes *BRCA1* and *BRCA2* account for approximately 65-85% of all hereditary ovarian cancers and mutations in the mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*) in the Lynch syndrome account for another 10-15%[5]. It is reported that the penetrance of *BRCA1* mutations exceeds that of *BRCA2* mutations in predisposing to ovarian carcinoma. Antoniou et al. estimated from 22 studies an average of 39% and 11% cumulative lifetime risk for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers, respectively[3].

The prevalence of *BRCA1* and/or *BRCA2* mutations in Korean ovarian cancer patients has not been properly evaluated. However, one report based on 337 patients suggested that the proportion of Korean ovarian cancer patients with a strong family history is significant (16%), and the prevalence of *BRCA1* and *BRCA2* mutations in such patients is high (33%), which is not very different from the results of previous reports from various populations (about 25%)[6].

The mutation c.928C>T on exon 11 of *BRCA1* found in the case and her daughter was reported in one Korean breast cancer patient without a family history, but not in the Breast Information Core (BIC) database (available at http://research.nhgri.nih.gov/projects/bic/Member/index.shtml)[7]. One Korean study reported 13 BRCA mutations from 40 Korean women with ovarian cancer and demonstrated that exon 11 of *BRCA1* is frequently mutated in Korean ovarian cancer patients[6]. However, our mutation was not found in their study. Since we performed direct sequencing twice for the proband, independently, and exon 11 sequencing for two daughters, we are very sure that this mutation is true positive. Therefore, to our knowledge, this is the first report of the mutation c.928C>T on exon 11 of *BRCA1* in a Korean ovarian cancer patient.

We provided counseling to the proband and her daughters regarding the genetic testing results and suggested the cancer surveillance guidelines for each of them. In the case of mutation carriers, surveillance programs should be considered using physical examinations, imaging studies and serum tumor marker determination until they ultimately undergo prophylactic oophorectomy with and without salpingectomy and hysterectomy[8]. Even after prophylactic surgery, patients need to be followed closely because of their small but continued risk for peritoneal carcinomatosis and other associated cancers such as breast cancer. Patients need to be counseled and educated to be alert to early symptoms and signs that may be related to associated cancers. However, since current surveillance programs are not satisfactory, much work needs to be done to optimize the protocols. For the proband, we recommended a regular breast self-exam, a semiannual clinical breast exam and annual mammography along with her gynecological surveillance using CA-125 and imaging studies. For the mutation carrier, we recommended the same breast and ovarian cancer screening schemes till she gets the risk-reducing salpingo-oophorectomy, ideally between 35 and 40 years, or upon completion of child bearing following the National Cancer Comprehensive Network Clinical Practice Guidelines[9].

Since there could be more hereditary ovarian cancer patients in Korean than clinicians have thought, more efforts should be made to identify high-risk individuals based on family history and genetic information and to provide appropriate primary and secondary prevention services which is important to reduce cancer incidence and mortality.

국문초록

*BRCA1*과 *BRCA2* 유전자 돌연변이는 상염색체 우성양상

으로 유전되면서 유방암과 난소암 발생위험을 높이는 것으로 알려져 있다. *BRCA1* 유전자 돌연변이를 가진 사람은 70세까지 난소암이 발생할 평균 누적위험도가 39% 가량 되고, *BRCA2*의 경우는 11% 가량된다. 이 외에도 린치 신드롬이라고도 불리는 유전성 비용종성 대장암의 경우에도 난소암의 위험도가 높아지는 것으로 알려져 있으나, 유전성 난소암의 90% 정도는 *BRCA* 유전자 돌연변이에 기인하는 것으로 생각된다. 본 증례는 난소암 및 다른 암의 가족력을 보이면서 난소암으로 진단된 한국 여성의 사례로 본인과 두 딸 중 한명에서 *BRCA1* 유전자 돌연변이가 발견된 경우로, 가족력과 유전자 검사에 근거한 유전성 난소암 고위험군의 식별과 관리의 중요성을 시사한다.

References

1) Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.
2) Han SH, Lee KR, Lee DG, Kim BY, Lee KE, Chung WS. Mutation analysis of BRCA1 and BRCA2 from 793 korean patients with sporadic breast cancer. Clin Genet 2006;70:496-501.
3) Jung K, Won Y, Park S, Kong H, Sung J, Shin H, et al. Cancer statistics in korea: Incidence, mortality and survival in 2005. J Korean Med Sci 2009;24:995-1003.
4) Kim I, Yoon SS, Lee KH, Keam B, Kim TM, Kim JS, et al. Comparative outcomes of reduced intensity and myeloablative allogeneic hematopoietic stem cell transplantation in patients under 50 with hematologic malignancies. Clin Transplant 2006;20:496-503.
5) Lim MC, Kang S, Seo SS, Kong SY, Lee BY, Lee SK, et al. BRCA1 and BRCA2 germline mutations in korean ovarian cancer patients. J Cancer Res Clin Oncol 2009;135:1593-9.
6) Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M, et al. Hereditary ovarian carcinoma: Heterogeneity, molecular genetics, pathology, and management. Mol Oncol 2009;3:97-137.
7) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
8) Russo A, Calo V, Bruno L, Rizzo S, Bazan V, Di Fede G. Hereditary ovarian cancer. Crit Rev Oncol Hematol 2009;69:28-44.
9) The NCCN Clinical Practice Guidelines in Oncology™ Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version.1.2009)