

# One Case of *BRCA2* Germline Mutation Ovarian Cancer Mother and Carrier Daughter found by Genetic Counseling

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Among cause of carcinogenesis, heredity is believed to take about 10 percent in ovarian cancer. *BRCA1* or *BRCA2* account for largest portion of Hereditary Breast and Ovary Cancer (HBOC). Frequency of *BRCA1/2* germ line mutations varies according to region and ethnicity from 1.1-39.7 percent. The identification of ovarian cancers with a *BRCA* mutation is will be more and important due to the possibility to offer a genetic counseling and also due to potential beneficial treatment effects with a poly-ADP-ribose polymerase inhibitor in some individuals. We report the case of a 41 year old woman with a stage Ic mucinous ovarian adenocarcinoma and carrier daughter found on family genetic counseling. We indentified other family members with a history of breast cancer of 1st degree and pancreatic cancer of 2nd degree relative. After a screening with immunohistochemistry, the absence of nuclear expression for *BRCA1* and *BRCA2* was revealed. The gene sequencing confirmed heterozygous mutations of *BRCA2* gene. The daughter of the case subject consented for a test. This test was shown the daughter is positive for *BRCA2* mutation. Regular surveillance, chemoprophylaxis with oral contraceptive and prophylactic surgery after childbearing were offered to her.

**Key words:** Ovarian carcinoma, BRCA mutation

## Introduction

Among cause of carcinogenesis, heredity is believed to take about 10 percent in ovarian cancer. *BRCA1* or *BRCA2* account for largest portion of Hereditary Breast and Ovary Cancer (HBOC).<sup>1)</sup> Frequency of *BRCA1/2* germ line mutations varies according to region and ethnicity from 1.1-39.7percent.<sup>2)</sup> Among korean ovarian cancer patients, they have been reported to be 2.7% (1/37)<sup>3)</sup> and 23.8% (15/63)<sup>4)</sup> regardless of family history. It is hard to counsel patient's family and encourage genetic test for them. In addition, there is

not much report about family counseling and penetrance report among ovary cancer patient in korea.

The average lifetime risk of breast or ovarian cancer in women with a *BRCA1* mutation is 65% and 39%. The corresponding estimates for women with a *BRCA2* mutation are 45% and 11%, respectively.<sup>5)</sup> *BRCA1/2*-associated ovarian carcinomas were associated with a longer overall survival time,<sup>6,7)</sup> an increased sensitivity to platinum-based chemotherapy<sup>7,8)</sup> and an increased sensitivity to a therapy with poly-ADP-ribose polymerase (PARP) inhibitors,<sup>9)</sup> compared to their sporadic counterparts.

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Recognition of inherited risks allows a targeted prevention. The genetic *BRCA* mutation testing is usually offered to women with a strong family history of breast and ovarian cancers. To estimate the risk for clinically-significant *BRCA* mutations is the first step of the genetic test process. However to select suitable patients for a genetic testing in the clinic is not common yet.

Until today, ovarian cancer surveillance was not effective. Screening with CA 125 and ultrasound is not believed to reduce mortality.<sup>10)</sup> However the risk of ovarian, fallopian tube and breast cancer can be reduced due to a risk-reducing salpingo-oophorectomy.<sup>11)</sup>

We report a case of a mother with an ovarian carcinoma and a daughter who was a *BRCA2* mutation carrier which was identified by genetic counseling.

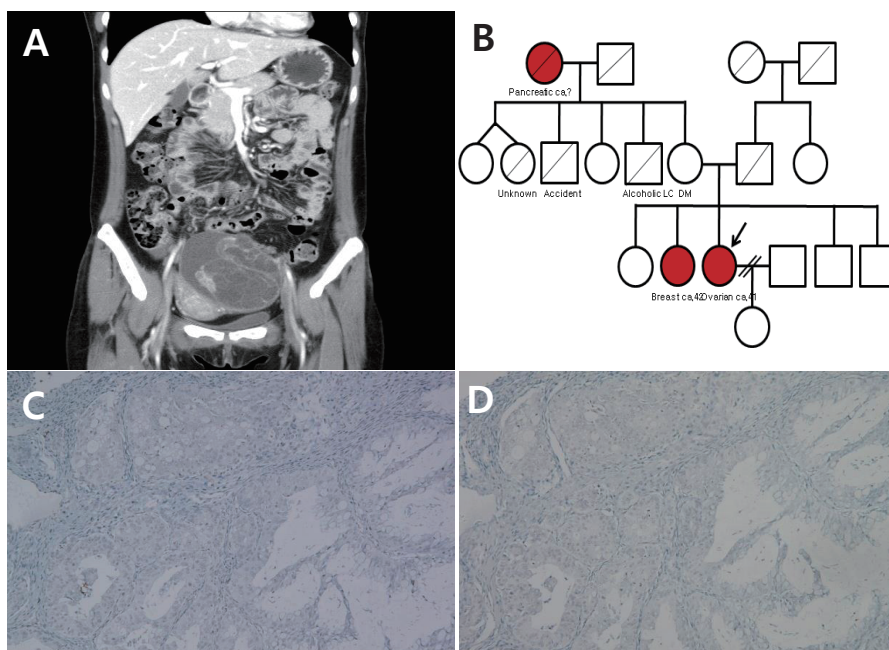
## Case

A 41 year old woman G1P1 with findings concerning for an ovarian mass was referred from a local clinic to the Samsung Changwon Hospital. Due to a computed tomography (CT) scan of the abdomen and pelvis the presence of a 12-cm cystic and solid mass in the left ovary was confirmed. No ascites or significant lymphadenopathy were detected (Fig. 1A). In the preoperative laboratory sample a slight elevation of CA-125 (37.71 U/mL) was shown.

After the workup, the surgery was laparoscopic performed. Mucinous borderline tumor of the left ovary with a frozen section diagnosis was reported during operation. But a re-operation for cancer staging was recommended because final pathology showed mucinous adenocarcinoma. The patient underwent a total laparoscopic hysterectomy, right salpingo-oophorectomy, pelvic lymph nodes dissection, para-aortic lymph nodes dissection and an infracolic omentectomy. The pathologic analysis by a gynecologic pathologist revealed no additional evidence of malignancy. The patient's final surgical staging was Ic. After the surgery, combination chemotherapy with six cycles of paclitaxol and carboplatin of 3-week intervals was given to the patient.

We found she had family members with a history of breast and pancreatic cancer (Fig. 1B). She consented to an IHC screening for the expression of *BRCA1* and *BRCA2*. The IHC for *BRCA1* and *BRCA2* was negative (Fig. 1C, 1D). After obtaining an informed consent for the collection of blood samples, a genomic strand of DNA was extracted from peripheral blood and analyzed for mutations of the *BRCA1* and *BRCA2* genes. Following results were revealed: Nonsense mutation (Arg2494X) at the 7480<sup>th</sup> base of Exon 15 in *BRCA2* (Fig. 2).

Based on this genetic evaluation, we advised the patient to investigate her family members. Only her 23 year old daughter accepted for a test. This test was positive for the same *BRCA2* mutation.



**Fig. 1.** A) Abdomen and Pelvis CT, B) Pedigree, C) BRCA1 immunohistochemistry (X200), D) BRCA2 immunohistochemistry (X200).

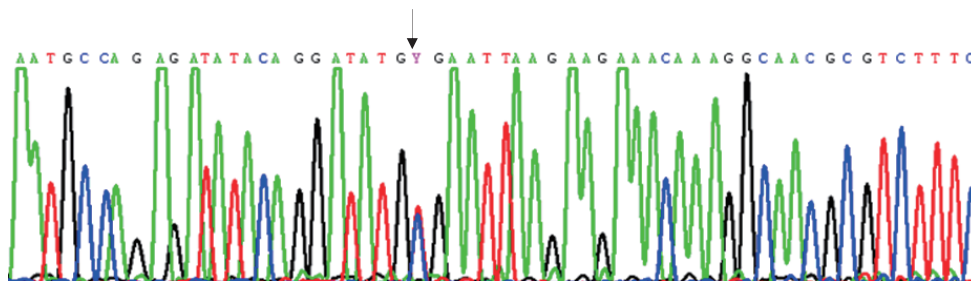


Fig. 2. *BRCA2* gene sequencing result [Exon15, 7480 C>T (Arg2494X)].

## Discussion

Prevention and early detection are key factors for an ovarian carcinoma risk reduction.

It is important to find the germ line mutations because they have a high risk of cancer penetrance. Otherwise we should be very careful to recommend an expensive genetic sequencing based on objective evidence. This is the first case of an ovarian carcinoma mother and a *BRCA2* germ line mutation carrier daughter found by genetic counseling in Korea.

Genetic counseling for the patient and the daughter are different. A prophylactic surgery or close observation for breast cancer were offered to patient. A prophylactic mastectomy reduces the risk of developing breast cancer by more than 95% and consequently reduces the breast cancer-specific mortality by 90%.<sup>12)</sup> A daughter was provided information with close surveillance, chemoprevention with oral contraceptive and risk reducing surgery after childbearing.

*BRCA1* mutations are found in 1.4% to 13.3% of sporadic ovarian cancers, and mutations of *BRCA2* are identified in 0.9% to 8.0% of sporadic ovarian cancers. New advances in genomic technologies will likely accelerate the discovery of additional cancer susceptibility genes and increase the feasibility of comprehensive, simultaneous evaluation of multiple genes at low costs. Theoretically, most inherited risks for ovarian carcinoma could be identified before the onset of cancer if the recognition of genetic risks will improve. Also the proportion of ovarian carcinomas associated with inherited risk factors could be effectively prevented. The genetic of hereditary ovarian cancer is rapidly evolving, but *BRCA1/2* mutations remain the most common cause of the hereditary ovarian cancer.

Therefore, active family counseling can be a help in the diagnosis of *BRCA* mutations and can also suggest the need for genetic sequencing in patients without a known family history of cancer.

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