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Clinical Practice for Hereditary Breast and Ovarian Cancer (HBOC) in Japan

MASAMI ARAI^{*1)}, REIKO YOSHIDA^{*1)}, HIDETAKA NOMURA^{*2)}, DAI KITAGAWA^{*3)},
ERI NAKASHIMA^{*3)}, NOBUHIRO TAKESHIMA^{*2)}, TAKUJI IWASE^{*3)}, SHINJI OHNO^{*3)}

^{*1)} Clinical Genetic Oncology, Cancer Institute Hospital, Tokyo, Japan, ^{*2)} Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan, ^{*3)} Breast Center, Cancer Institute Hospital, Tokyo, Japan

Hereditary breast and ovarian cancer (HBOC) patients with *BRCA1/2* mutation are estimated to be approximately 1,560,000 in Japan. But general doctors and medical staff do not fully recognize the significance of medical intervention for HBOC in Japan in spite of the large number of potential patients. Thus, investigation into the actual conditions of HBOC has not been established.

So, we have tried to establish a registration system to clarify the clinical and genetic characteristics of HBOC in Japan.

Risk reducing salpingo-oophorectomy (RRSO) has been performed as a clinical examination in our hospital. Average age at the time of RRSO was 49 years. And many of them have a family history of ovarian cancer, with a frequency of 63.3%. Pathological examination revealed a p53 signature in one case out of 30 cases, but no occult cancers were observed at my institute.

Genetic test for *BRCA1/2* could also be used worldwide for companion diagnosis for the PARP2 inhibitor. Appropriate recognition for HBOC by general medical staff and cooperation with other departments will be required.

Key words: hereditary breast and ovarian cancer (HBOC), registration, risk reducing salpingo-oophorectomy (RRSO), risk reducing mastectomy (RRM), Japan

Abbreviation: variant of uncertain significance (VUS)

Clinical significance of genetics for hereditary cancer syndromes

Clinical genetics of hereditary cancer syndrome is to improve the outcome of high risk person of cancer by intervention of appropriate medicine. They were firstly developed for hereditary cancer syndromes which can be usually diagnosed only by clinical findings, and in which genetic tests are not required, such as familial adenomatous polyposis

(FAP). Familial breast and ovarian cancer was defined by clinical criteria before routine use of genetic tests for *BRCA1/2* in clinical practice in Japan¹⁾.

Thirty years ago, the life expectancy of FAP patients were in the early 40s. However, by identifying the *APC* gene and through the clinical use if a genetic test for the *APC* gene, accompanied by the remarkable prognosis in the technology of endoscopy and operation procedures such as the J-pouch, the life expectancy of these patients was increased to approximately that of the general population.

Corresponding author: Masami Arai
Clinical Genetic Oncology, Cancer Institute Hospital
3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
TEL: +81-3-3520-0111 FAX: +81-3-3570-0495 E-mail: marai@jfc.or.jp
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Early medical intervention should be provided to potentially high-risk persons to improve their survival rates overall. Therefore, genetic medicine for hereditary cancer syndromes is a kind of preventive medicine, similar to that of public health or epidemiology.

Outline of clinical practice regarding HBOC in Japan (For example, that of my institute)

Figure-1 shows the data of HBOC clinical practice in our hospital over the last 16 years. A total of 718 clients visited for genetic counseling, concerned with or worried about HBOC. Of those, 420 probands received genetic tests for *BRCA1/2*. Therefore, the rate of intake of genetic test was 58.8%. Furthermore, 115 probands had deleterious mutations. The mutation positive rate is 27.4%. The rate of VUS is 3.1%. VUS is defined to be a variation in a genetic sequence whose association with disease risk is unknown (<https://www.cancer.gov/publications/dictionaries/genetics-dictionary>). Of the 115 mutation positive probands, 80 of their family members received a genetic test, and 30 relatives had the same deleterious mutation as the proband. Thirty-nine people received RRSO (26.9%) and only three people received RRM (2.1%).

Based on the result of our SNP study of *BRCA1/2* for Japanese general population, we estimate that there are over 1.5 million *BRCA1/2* mutation carriers in Japan. In spite of the large number of potential patients, medical insurance

does not cover clinical practice for mutation carriers that includes genetic tests for *BRCA1/2*, and risk reducing surgery, e.g. genetic tests for *BRCA1/2* (PCR-direct sequence and MLPA) costs approximately 2.5 thousand USD. RRSO (including hospitalization and perioperative examinations) costs approximately ten thousand USD.

Therefore, even general doctors and medical staff do not fully recognize the significance of medical intervention for HBOC in Japan. Investigation into the actual conditions of HBOC has not yet been established.

So we have tried to establish a registration system to clarify the clinical and genetic characteristics of HBOC in Japan as a part of our work at The Japanese HBOC consortium (JHC). JHC was established in 2012 in order to raise awareness of HBOC in Japan and to provide an effective healthcare system for HBOC patients and their families (<http://hboc.jp/index.html>). Previous report by Japanese eight institutes showed nearly the same prevalence in Japan as in the US or Europe²⁾. We accumulated the data of about 850 probands and their pedigree in the trial registration. Comprehensive nationwide registration began in March 2016. The first results of analysis will be disclosed next year.

RRSO in our institute

As of now, 39 mutation carriers have undergone RRSO (at the time of the end of August, 2016). Table-1 shows the interim result until the 30th entry³⁾.

Figure-1 Rate of genetic test intake and mutation positive rate (Cancer Institute Hospital) (genetic tests for *BRCA1/2*, Jan. 2000–June 2016)

Table-1 RRSO cases in our hospital (n=30)

	<i>BRCA1</i> mutation (n=21)	<i>BRCA2</i> mutation (n=9)	Total (n=30)
Average age at RRSO	49.1 (40–66)	48.8 (45–57)	49 (40–66)
Premenopausal state	9 (42.9%)	2 (22.2%)	11 (36.7%)
Past history of breast cancer	16 (76.2%)	9 (100%)	25 (83.3%)
Parity	13 (61.9%)	7 (77.8%)	19 (66.7%)
Family history of ovarian cancer	14 (66.7%)	5 (55.6%)	19 (63.3%)

- The uterus was simultaneously resected in all but one case.
 - Postoperative complication: incomplete dehiscence of vaginal stump (1 case)
 - Pathological findings: no occult cancers were seen in any case, but a p53 signature was observed in one case.
 - Severe postmenopausal symptoms after RRSO: none
- (Nomura H, *et al*: Obstetrical and Gynecological Practice, 2016; 65: 685–690³⁾)

The average age at the time of RRSO was 49 years, the time at which most females are usually just about to experience menopause. Although many mutation carriers received chemotherapy, the proportion of women with premenopause status at RRSO was 36.7%. And many of them have a family history of ovarian cancer, with a frequency of 63.3%.

Whether a hysterectomy is performed or not is optional during RRSO, however, all but one patient simultaneously received a hysterectomy. Pathological examination revealed a p53 signature in one case, but no occult cancers were observed at my institute. Additionally, no severe postmenopausal symptoms have been observed as harmful events in RRSO cases.

Furthermore, RRSO showed psychosocial effect for reducing worry about ovarian cancer and impact of mutation positiveness by our clinical research⁴⁾.

RRSO is generally recommended for *BRCA1/2* mutation carriers based on the evidence of improvement of overall survival by Japanese breast society clinical practice guidelines as well as NCCN guidelines⁵⁾.

Conclusion

Early medical intervention should be provided to potentially high-risk persons for cancers to improve their survival rates overall. Therefore, genetic medicine for hereditary cancer syndromes is a kind of preventive medicine.

But general doctors and medical staff do not fully recognize the significance of medical intervention for HBOC in Japan, however, there were the large

number of Japanese potential patients.

Recently, a nationwide registration system for HBOC has been established in Japan. Clinical and genetic characteristics of Japanese HBOC will be revealed before long.

RRSO is generally recommended for *BRCA1/2* mutation carriers based on the evidence of improvement of overall survival by Japanese breast society clinical practice guidelines and 30% of mutation carriers were undergone RRSO in our hospital now. RRSO could be effective for reducing worry about ovarian cancer and impact of mutation positiveness.

Genetic test for *BRCA1/2* could also be used worldwide for companion diagnosis for the PARP2 inhibitor. Appropriate recognition for HBOC by general medical staff and cooperation with other departments will be required, both nationwide and globally.

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