

Trends in contralateral prophylactic mastectomy rate according to clinicopathologic and socioeconomic status

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Purpose: There has been an increasing trend in the use of contralateral prophylactic mastectomy (CPM) among women diagnosed with unilateral breast cancer or mutations in *BRCA1* or *BRCA2* to reduce the occurrence of contralateral breast cancer. This study aimed to examine trends in the CPM rate according to clinicopathologic and socioeconomic status at a single institution in Korea.

Methods: This study included 128 patients with mutations in *BRCA1* or *BRCA2*. Patients were divided into a CPM group (n = 8) and a non-CPM group (n = 120) between May 2013 and March 2016. The main outcome variables, including epidemiology, clinical features, socioeconomic status, and tumor characteristics, were analyzed.

Results: A total of 8 CPMs were performed among 128 patients. All CPM patients were married. The proportion of professional working women was higher in the CPM group (P = 0.049). Most patients who underwent CPM graduated college, compared to less than a third of the non-CPM group (P = 0.013). The CPM group had a higher rate of visits to the Hereditary Breast and Ovarian Cancer (HBOC) clinic (P = 0.021). The risk-reducing salpingo-oophorectomy (RRSO) rate was significantly higher in the CPM group (P < 0.01).

Conclusion: CPM rates were significantly different according to socioeconomic status. The CPM rate tends to increase in highly educated and professional working women. The socioeconomic status of patients is an important factor in the decision to participate in the HBOC clinic and undergo CPM or RRSO.

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Key Words: *BRCA1*, *BRCA2*, Breast neoplasms, Mastectomy

INTRODUCTION

There has been an increasing trend in the use of contralateral prophylactic mastectomy (CPM) among women diagnosed with unilateral breast cancer (BC) or mutations in *BRCA1* or *BRCA2*

to reduce the occurrence of contralateral BC.

Therefore, it is desirable to understand the factors associated with the decision to undergo CPM in order to provide appropriate genetic counseling and risk-reduction strategies for high-risk women. Previous studies indicated that women choosing

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CPM are influenced more by their belief in the considerable risk of a new contralateral primary cancer than by medical evidence [1,2].

In 2013, Angelina Jolie announced that she is a carrier of the *BRCA1* mutation and had undergone bilateral prophylactic mastectomy. This public attention was followed by a 2.5-fold increase in risk-reducing mastectomy rates in women with *BRCA* mutations, and has been described as "the Angelina Jolie effect" [3].

Women diagnosed with mutations in *BRCA1* or *BRCA2* have a high risk of developing BC. The average cumulative risk of BC in *BRCA1* and *BRCA2* mutation carriers was 65% and 45%, respectively [4]. Based on these results, a South Korean study found the cumulative risk of BC in *BRCA1* and *BRCA2* mutation carriers by age 70 years was 72.1% and 66.3%, respectively [5-7].

The advantages of CPM are a 95% reduction of risk for contralateral BC development in patients with *BRCA* mutations and a 90% reduction of risk in women with a strong family history [8,9].

Meanwhile, CPM has several disadvantages, including high cost, postoperative complications, and psychological distress [10]. The National Insurance System in the Republic of Korea did not cover the cost of CPM for patients with *BRCA1* or *BRCA2* mutations until October 2017.

Most prior studies in Western countries suggested a relationship between socioeconomic status and trends in CPM rates [11-15]. However, these studies did not consider the relationship between CPM rates and clinicopathologic and socioeconomic status in Asian countries, including the Republic of Korea. To address limitations in the existing research, this study aimed to examine trends in CPM rates according to clinicopathologic and socioeconomic status at a single institution in the Republic of Korea.

METHODS

Patients

This study included 128 patients in the evaluation of CPM rates according to clinicopathologic and socioeconomic status. All participants in this study were enlisted at Severance Hospital between May 2013 and March 2016 and had been diagnosed with mutations in *BRCA1* or *BRCA2*. Clinicopathologic features are described in Table 1. Written consent was obtained before blood sampling. The selection criteria for *BRCA1* or *BRCA2* screening were based on the Korean Hereditary Breast Cancer Study, which is covered by the National Insurance System (NIS). Surgery was performed in the CPM group ($n = 8$), but not in the non-CPM group ($n = 120$). The non-CPM group received chemoprevention or observation alone. Professional occupations included judicial officers, medical service personnel, or educators. Other workers

performed clerical, blue-collar, or food preparation work, or worked as helpers or in sales.

Interpretation of genomic data

Sanger sequencing was performed by the Seoul Clinical Laboratories (<http://www.scllab.co.kr/>), which is certified by the College of American Pathologists laboratory accreditation program. References used for mutation identification with Sanger sequencing were the Breast Cancer Information Core database (<http://research.nhgri.nih.gov/bic/>) and the Human Genome Mutation Database (<http://www.hgmd.org>). Reporting of Sanger sequencing was performed using guidelines for mutation nomenclature of the Human Genome Variation Society (<http://www.hgvs.org>). Significant mutations were considered "positive" for *BRCA1* or *BRCA2*, and variants of unknown significance and non-significant variants were considered "negative."

Statistical analysis

A comparison of CPM rates was performed using the t-test. Socioeconomic and clinicopathologic status was compared using the chi-square/Fisher exact test and Mann-Whitney U-test in the 2 patient groups. Collected data underwent 2-tailed testing, and a P-value <0.05 was considered statistically significant. Collected data were analyzed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

Ethics

This study was approved by the Institutional Review Board of Severance Hospital (approval number: 2018-1802-001).

RESULTS

Among 8 patients who underwent CPM, 1 had partial mastectomy for a BC diagnosis in 2010, followed by bilateral total mastectomy 4 years later. Another 7 patients who underwent CPM for BC had modified radical mastectomy.

Among 128 patients in the study, the Hereditary Breast and Ovarian Cancer (HBOC) clinic provided treatment counseling for 55, and risk-reducing salpingo-oophorectomy (RRSO) was performed for 21.

Table 1 shows the clinicopathologic features of 128 patients with mutations in *BRCA1* or *BRCA2*. All patients in the CPM group had been diagnosed with BC, compared with 71.7% in the non-CPM group.

The median age at first diagnosis with BC in the non-CPM group was 41.6 years (range, 22.2–81.0 years), and was slightly higher than that in the CPM group, at 38.9 years (range, 30.8–55.5 years). In the non-CPM group, the median age at diagnosis with contralateral BC was 48.9 years (range, 29.7–82.2 years), and the median age at diagnosis with ovarian cancer (OC) was

Table 1. Clinicopathological features of patients with *BRCA1/2* mutations (n = 128)

| Variable | CPM (n = 8) | Non-CPM (n = 120) | P-value |
|--|------------------|-------------------|---------|
| Diagnosis of cancer | | | 0.362 |
| BC | 8 (100) | 86 (71.7) | |
| OC only | 0 (0) | 23 (19.2) | |
| Unaffected carrier | 0 (0) | 11 (9.1) | |
| Age at first diagnosis with BC | 38.9 (30.8–55.5) | 41.6 (22.2–81.0) | 0.542 |
| Age at diagnosis with Contralateral BC | - | 48.9 (29.7–82.2) | |
| Age at diagnosis with OC | - | 49.7 (28.8–78.7) | |
| <i>BRCA</i> mutation | | | 0.729 |
| <i>BRCA1</i> | 4 (50) | 68 (56.7) | |
| <i>BRCA2</i> | 4 (50) | 52 (43.3) | |
| Family history ^{a)} | | | 0.712 |
| Yes | 4 (50.0) | 73 (60.8) | |
| No | 4 (50.0) | 47 (39.2) | |
| Marital status | | | 0.533 |
| Divorced or widowed | 0 (0) | 4 (3.3) | |
| Married | 8 (100) | 95 (79.2) | |
| Single | 0 (0) | 20 (16.7) | |
| Unknown | 0 (0) | 1 (0.8) | |
| Occupations | | | 0.049 |
| Professional | 2 (25.0) | 5 (4.2) | |
| Other workers | 4 (50.0) | 39 (32.5) | |
| Homemaker | 2 (25.0) | 54 (45.0) | |
| Unknown | 0 (0) | 22 (18.3) | |
| Education | | | 0.013 |
| College graduate | 7 (87.5) | 39 (32.5) | |
| High school graduate or lower | 1 (12.5) | 59 (49.2) | |
| Unknown | 0 (0) | 22 (18.3) | |
| Pathology of BC | | | 0.291 |
| IDC | 8 (100) | 75 (62.5) | |
| ILC | 0 (0) | 1 (0.8) | |
| DCIS | 0 (0) | 4 (3.3) | |
| Unknown | 0 (0) | 6 (5.0) | |
| Non-BC | 0 (0) | 34 (28.3) | |
| BC tumor size (T) | | | 0.152 |
| T ≤ 1 | 3 (37.5) | 43 (35.8) | |
| T ≥ 2 | 5 (62.5) | 34 (28.3) | |
| Unknown | 0 (0) | 9 (7.5) | |
| Non-BC | 0 (0) | 34 (28.3) | |
| BC lymph node (N) | | | 0.002 |
| LN negative | 1 (12.5) | 50 (41.7) | |
| LN positive | 7 (87.5) | 27 (22.5) | |
| Unknown | 0 (0) | 9 (7.5) | |
| Non-BC | 0 (0) | 34 (28.3) | |
| BC Stage ^{b)} | | | 0.055 |
| Stage 0–1 | 1 (12.5) | 34 (28.3) | |
| Stage 2–4 | 7 (87.5) | 43 (35.8) | |
| Unknown | 0 (0) | 9 (7.5) | |
| Non-BC | 0 (0) | 34 (28.3) | |

Values are presented as number (%) or median (range).

CPM, contralateral prophylactic mastectomy; BC, breast cancer; OC, ovarian cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; LN, lymph node.

^{a)}BC or OC, within second degree. ^{b)}AJCC (American Joint Committee on Cancer) 7th edition.

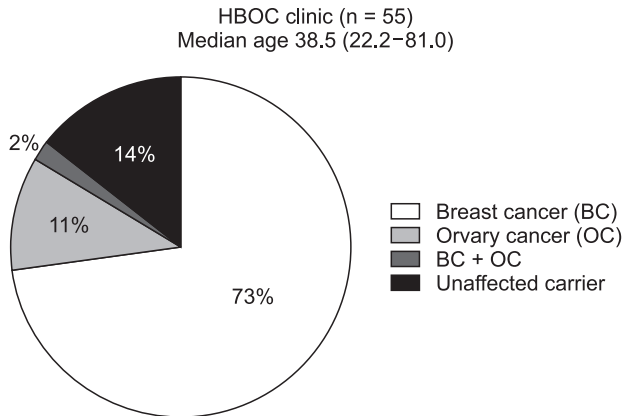


Fig. 1. Clinical information on patients visiting the Hereditary Breast and Ovarian Cancer (HBOC) clinic with mutations in *BRCA1/2* (n = 55).

49.7 years (range, 28.8–78.7 years).

Half of the CPM group had a mutation in *BRCA1*, compared with 56.7% of the non-CPM group. A second-degree family history of BC was present in 73 patients in the non-CPM group (60.8%), compared with 4 patients in the CPM group (50%). All CPM group patients were married, compared with 95 in the non-CPM group (100% vs. 79% $P = 0.533$).

Half of the CPM group patients were nonprofessional (other) workers and a fourth were professional workers; however, 54 of the non-CPM patients were homemakers (45%), 39 were nonprofessional (other) workers (32.5%), and only 5 were professional workers (4.2%). The proportion of professional working women was significantly higher in the CPM group (25.0% vs. 4.2%, $P = 0.049$).

All patients in the CPM group were college graduates, except for 1 who was a high school graduate. The educational level was significantly higher than in the non-CPM group, with only 32.5% graduating college ($P = 0.013$).

The HBOC clinic provided treatment counseling for 55 patients (43%). Fig. 1 shows clinical data for patients visiting the HBOC clinic. The median age was 38.5 years (range, 22.2–81.0 years). Among the 55 patients, 41 (75.0%) had been diagnosed with BC and 8 were unaffected carriers of mutations in *BRCA1/2*. Fig. 2 compares the HBOC clinic attendance rates for the CPM and non-CPM groups. The CPM group had a higher rate of HBOC clinic attendance (87.5% vs. 40.0%, $P = 0.021$).

RRSO was performed in 21 patients (16.4%). Fig. 3 compares RRSO rates between the CPM and non-CPM group. Among 8 patients in the CPM group, 6 (75%) underwent RRSO. RRSO was performed in 15 of 120 patients in the non-CPM group (12.5%). The RRSO rate was significantly higher in the CPM group (75.0% vs. 12.5%, $P < 0.01$).

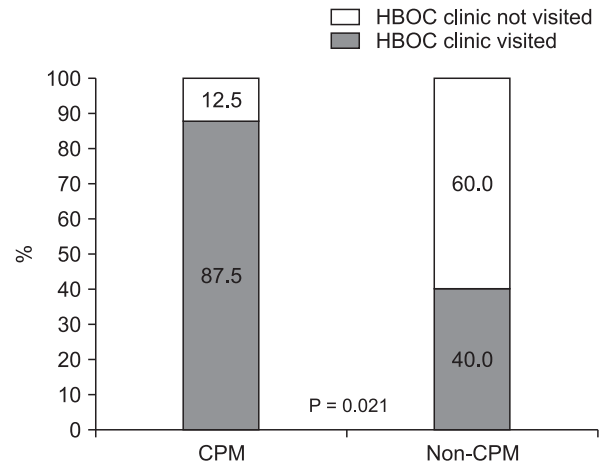


Fig. 2. Rates of attendance at the Hereditary Breast and Ovarian (HBOC) clinic in contralateral prophylactic mastectomy (CPM) group and non-CPM group patients with mutations in *BRCA1/2* (n = 128).

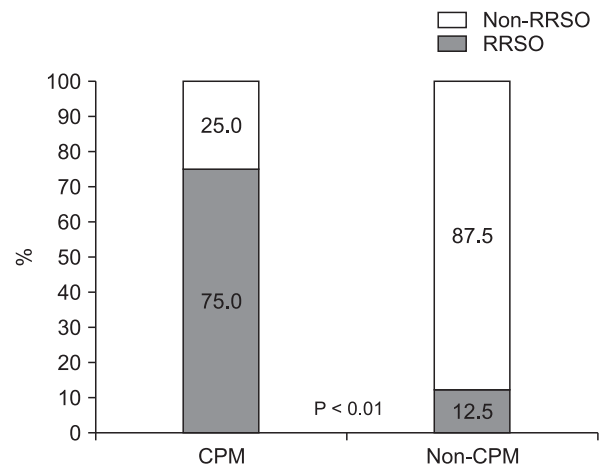


Fig. 3. Risk-reducing salpingo-oophorectomy (RRSO) rates in contralateral prophylactic mastectomy (CPM) and non-CPM group patients with mutations in *BRCA1/2* (n = 128).

DISCUSSION

This study showed that CPM rates were significantly different according to socioeconomic status. The CPM rate tended to increase in highly educated and professional working women. Socioeconomic status is an important factor in the decision to attend the HBOC clinic or undergo CPM and RRSO. The results are similar to those in previous studies in the United States showing that the CPM rate was associated with socioeconomic status, rather than tumor or biological characteristics [16,17].

In the current study, CPM rates were higher in professional workers than in other workers and homemakers ($P = 0.049$). The educational level in the CPM group was higher than in the non-CPM group ($P = 0.013$). As educational levels of professional workers are generally higher than those of

nonprofessional workers, the findings confirmed that this was a significant factor in the decision to undergo CPM.

In addition, the study showed that the attendance rate in the HBOC clinic and the RRSO rate in the CPM group were significantly higher than in the non-CPM group ($P = 0.021$, $P < 0.01$). This result also reflected the higher educational level in the CPM group. This may imply that women with a higher educational level have access to better health care information and are more likely to understand this information.

Socioeconomic status was determined using 3 criteria: income, education, and occupation. Higher levels of education are associated with better economic and psychological outcomes. The occupational status reflects the educational attainment required to obtain a better job and income level [18,19]. Thus, the current study verified that socioeconomic status is an important factor in the decision to attend the HBOC clinic or undergo CPM and RRSO.

The trends in CPM rates according to clinicopathologic and socioeconomic status should be considered in clinical practice, because providing adequate information and appropriate education according to socioeconomic status is important for women with *BRCA1/2* mutations who are considering risk-reduction procedures. It is necessary to provide more detailed information and to construct a care system for breast reconstruction.

The efficacy of CPM has been controversial since its inception. Many studies showed that CPM significantly reduces the risk for contralateral BC among *BRCA1/2* mutation carriers, but without improvement of overall survival in a follow-up period [20-22]. And, although mastectomy is generally safe and associated with high satisfaction rate, women still experience long-term effects as cosmetic, psychological, and social domains [22,23]. Further studies for a survival benefit and long-term side effects from CPM are necessary to provide the information to women with *BRCA1/2* mutations so that they can make the

right choice for risk-reducing strategies.

Our study has limitations. This was a retrospective study with a small sample size in single institution. Enrolled patients were heterogeneous including unaffected carrier. The collected data regarding socioeconomic factors did not represent income levels and careers, which may have contributed to the lack of significant results. However, this is the first study on trends in CPM in the Republic of Korea.

Fortunately, the NIS began to cover the cost of CPM for patients with *BRCA1* or *BRCA2* mutations in October 2017 [24]. Further study to evaluate the impact of support by the NIS for CPM is necessary.

In conclusion, the rate of CPM tends to increase in highly educated and professional working women. Socioeconomic status is an important factor in the decision to attend the HBOC clinic or undergo CPM and RRSO. Clinicians should take socioeconomic differences into account to provide individualized risk-reducing strategies for women with *BRCA1/2* mutations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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