Attitudes toward preventive oophorectomy among *BRCA1* mutation carriers in Poland

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Summary

Currently genetic testing for *BRCA1* and *BRCA2* susceptibility genes is performed throughout Europe and North America. In Poland three founder mutations in *BRCA1* account for 14% of all invasive ovarian cancers and oophorectomy is frequently recommended to mutation carriers as a preventive measure. The purpose of the present study was to evaluate patient acceptance of the recommendation for prophylactic oophorectomy in a hereditary cancer clinic. Seventy-two women over the age of 40 and who carried a *BRCA1* mutation were advised to undergo prophylactic oophorectomy. After a mean follow-up period of 19 months, 43 of the women (60%) had undergone the procedure. Of the 29 women who had not had an oophorectomy, five indicated that they did not intend to do so, 19 indicated that they intended to have the operation in the near future and five were undecided. In conclusion, preventive oophorectomy is acceptable to most Polish women at high risk of hereditary ovarian cancer and should be among the range of services offered in cancer genetics clinics.

Key words: BRCA1 mutation; Prophylactic oophorectomy.

Introduction

Genetic testing for breast and ovarian cancer susceptibility is becoming widespread in many countries. In Poland, genetic testing for *BRCA1* mutations is facilitated by a very high frequency of a small number of founder mutations present in the breast cancer population [1]. Clinical cancer genetics services are coordinated through a small number of hereditary cancer centers situated throughout the country. Because of the increasing popularity of genetic testing for breast/ovarian cancer in Poland there is a demand for clinical guidelines for the prevention and management of cancer in women who are identified as carriers of a deleterious *BRCA1* mutation. Preventive oophorectomy has been recommended as a means of reducing the risk of both breast and ovarian cancer in *BRCA1* carriers [2, 3]. Recent studies from North America found reductions in the risks of both ovarian and breast cancer following oophorectomy among women with *BRCA1* or *BRCA2* mutations [4, 5]. Prophylactic oophorectomy is now recommended to most Polish women with a *BRCA1* mutation, but the extent to which the procedure is acceptable has not yet been assessed. The purpose of the present study was to estimate the extent of patient compliance with the recommendation for a prophylactic oophorectomy and to identify factors associated with patient compliance.

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Material and Methods

The study population consisted of 72 women who underwent genetic testing at the Hereditary Cancer Center of the Pomeranian Academy of Medicine between January 1998 and March 2002 and who were subsequently identified as carriers of a *BRCA1* mutation. Each of these women had undergone genetic testing as part of her clinical evaluation due to familial aggregation of breast or ovarian cancers, occurrence at *BRCA1* of a constitutional mutation among relatives or because of a personal history of early-onset breast cancer (< 50 years). All women provided informed written consent for genetic testing. Patients received the result of the genetic test within six months of providing a blood sample and then were counseled regarding preventive options. In this clinic, women with *BRCA1* mutations who are 40 years of age or older are routinely advised to undergo a preventive oophorectomy. Women with a previous diagnosis of ovarian cancer or who had a previous oophorectomy for another reason were excluded. Patients were contacted by telephone from seven months to 40 months following disclosure of the genetic results. All patients were interviewed by the same physician (JM). The patient was asked whether or not she had undergone a prophylactic oophorectomy and if not, why and whether she intended to do so. Patients were asked whether they had been diagnosed with a new malignancy. The slides of the ovarian specimens of the 43 women who underwent oophorectomy were reviewed by the reference pathologist (JL) to assess any potential occult malignancy.

Results

We were able to make contact with all 72 eligible study subjects. Forty-three of 72 indicated that they had already undergone an oophorectomy (60%). Of the remaining 29

patients, 19 indicated that they had not yet had an oophorectomy but were intending to do so, five indicated that they had not had an oophorectomy and had no intention of doing so, and five remained undecided. Reasons for refusal were lack of acceptance of the elevated risk estimate (two patients), concern about sexuality (one patient) and reliance on screening (one patient). One 72-year-old woman believed that she was too old to benefit from the operation. The frequency of oophorectomy was 23 of 37 (62%) among those with a past history of breast cancer and 20 of 35 (57%) among those who had not had breast cancer; it was 26 of 45 (58%) among those under age 50 and 17 of 27 (63%) among those age 50 or above. No cancers of the ovaries or fallopian tubes were identified in the surgical specimens of the 43 patients, but dysplasia of the fallopian tube was noted in seven women (16%). One peritoneal cancer was diagnosed in the follow-up period in a 50-year-old woman one year after oophorectomy - this corresponds to an incidence of primary peritoneal cancer in our cohort of approximately one per 63 persons year, or 1.6% per year. Similarly, there was one ovarian cancer reported among the 29 women who had not had an oophorectomy, corresponding to a rate of 2.3% per year. We also observed a single case of breast cancer in a 45-year-old woman 19 months following oophorectomy.

Discussion

Oophorectomy is now becoming common as a preventive measure for the management of high hereditary cancer risk in Poland. In Szczecin approximately 60% of women with a *BRCA1* mutation elected to have an oophorectomy after receiving their results and an additional 26% indicated their willingness to do so in the near future. This high frequency reflects a relatively small number of treating physicians in this academic center with a strong interest in hereditary cancer. We believe that prophylactic oophorectomy is acceptable to Polish women as a measure for reducing the risk of breast and ovarian cancer. It is expected that increasing awareness of the beneficial effects of oophorectomy will expand the use of genetic testing and of oophorectomy throughout the country. Reported uptake rates of prophylactic oophorectomy in women with a *BRCA1* or *BRCA2* mutation are lower in other countries [6-9], with the exception of the Netherlands [10]. High-risk women attending cancer genetics clinics in France, England, and Canada were surveyed in a single study about the acceptance of prophylactic oophorectomy [11]. French women were the most reluctant and English women were the most in favour of prophylactic oophorectomy. In Austria, women who were given positive *BRCA1/2* mutation results were questioned about their intention to undergo prophylactic oophorectomy [7]. Fifty percent of carriers showed a positive attitude towards prophylactic oophorectomy. However, these two studies surveyed intentions rather than actual practices of prophylactic oophorectomy.

Actual uptake rates of prophylactic oophorectomy in *BRCA1/2* mutation carriers have been examined in several countries. In Canada, 46% of *BRCA1/2* mutation carriers with no previous diagnosis of ovarian cancer underwent a prophylactic oophorectomy following result disclosure [6]. In the Netherlands, 64% of unaffected eligible mutation carriers 35 years and older had a prophylactic oophorectomy [10]. In the United States, only 13% of female carriers reported having a prophylactic oophorectomy within one year following genetic testing [9]. To some extent the high rates in Poland, Canada and the Netherlands reflect the directive approach to counselling taken in these countries, as compared to the United States, but the time frames of the studies must also be taken into account and it is likely that prophylactic oophorectomy is gaining in popularity in the United States as well.

Age has been shown to be a significant predictor in the uptake of prophylactic oophorectomy. Prophylactic oophorectomy has been described as more acceptable for older women and in general, uptake of the surgery has been greater in older women. In one study of high-risk women, 59% of women found prophylactic oophorectomy acceptable from the age of 50 but only 19% of the women found prophylactic oophorectomy acceptable from the age of 35 [11]. In the Netherlands study, women aged 40 to 54 years were more likely to opt for this intervention than were younger women [10]. In Poland similar uptake rates were seen for women before and after age 50, to some degree this practise reflects emerging evidence that premenopausal oophorectomy can be used to prevent breast cancer.

Hereditary breast cancer may be a greater problem in Poland than it is in North America due to the presence of three common founder mutations [1]. We have recently identified a founder *BRCA1* mutation in 49 of 364 (13.6%) unselected cases of ovarian cancer [12] and in ten of 119 (8.4%) cases of early-onset breast cancer (unpublished data). These prevalence figures are second only to those for the Ashkenazi Jewish population [13, 14], and are similar to those from other countries with strong founder effects, such as Iceland [15], Pakistan [16] and the Philippines [17].

There is no consensus yet on the optimum age of surgery, but most physicians believe that it should occur at some time between ages 35 and 45. Oophorectomy in young women will limit fertility and may be associated with a prolonged and more severe menopause but will provide protection against breast cancer. Deferring oophorectomy to age 45 has the advantage of reducing the impact of surgical menopause; however a significant proportion of hereditary breast and ovarian cancers will occur before age 45. In the Szczecin registry, the mean age of diagnosis of hereditary breast cancer is 42.2 years and 61.3% of the breast cancer cases were diagnosed before the age of 45. The possibility remains that a primary peritoneal cancer will develop after oophorectomy in a *BRCA1* carrier. We identified a single case of peritoneal cancer in a woman 12 months following oophorectomy and a single case of ovarian cancer in

women with intact ovaries. Although the study is very small, the observed cancer rates in the two groups were comparable and are comparable to published rates of invasive ovarian cancer in *BRCA1* carriers with intact ovaries [4, 5].

Future prospective studies will document the uptake of preventive oophorectomy throughout Poland and will generate more precise estimates of the residual risk of breast and peritoneal cancer following oophorectomy. It is important that we compare all the risks and benefits of surgical oophorectomy in young women including the effects of cardiovascular disease, sexuality and psychosocial functioning.

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