Original Article

Efficacy of Risk-Reducing Salpingo-Oophorectomy in Women with BRCA-1 and BRCA-2 Mutations

Olufunmilayo I. Olopade, MD and Grazia Artioli, MD

Center for Clinical Cancer Genetics, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois

Abstract: Recognizing the emerging role of genetics in clinical care, in 1996 the American Society of Clinical Oncology established a Task Force on Cancer Genetics Education to develop educational opportunities and resources for its members. These efforts, and recent advances in the understanding of genetic predisposition to breast and ovarian cancers, have resulted in growing numbers of women participating in genetic testing protocols. The first prospective clinical trial involving women with known BRCA-1 and BRCA-2 mutations was recently published. In a prospective study involving 170 BRCA-1 and BRCA-2 mutation carriers and a mean follow-up of 2 years, the estimated 5-year cancer-free estimates were 96% for the 98 women choosing prophylactic bilateral salpingo-oophorectomy and 69% for the 72 women choosing intensive surveillance (p = 0.006). Three cases of stage I ovarian cancers were diagnosed at the time of prophylactic surgery. These results are consistent with published literature and data from the Prevention and Observation of Surgical Endpoints (PROSE) study group, which reported a 96% reduction in ovarian cancer risk and a 53% reduction in breast cancer risk among BRCA-1 and BRCA-2 mutation carriers who had prophylactic bilateral oophorectomy compared to matched controls. Thus prophylactic bilateral salpingo-oophorectomy can be regarded as an effective risk-reducing procedure that permits early diagnosis of ovarian cancer at the time of surgery and significantly reduces the risk of breast and ovarian cancer in women with germ-line mutations in the BRCA-1 and BRCA-2 genes.

Breast cancer is a leading cause of cancer deaths among women, and is expected to claim the lives of more than 40,000 individuals in the United States in 2002 (1). The majority of breast cancer cases occur sporadically, but 5–10% of cases are caused by inherited mutations in the breast cancer susceptibility genes, BRCA-1 and BRCA-2. Recognizing the emerging role of genetics in clinical care, in 1996 the American Society of Clinical Oncology established a Task Force on Cancer Genetics Education to develop educational opportunities and resources for its members (2). These efforts, and recent advances in the understanding of genetic predisposition to breast and ovarian cancers, have resulted in growing numbers of women who are identified as having a significantly increased risk for cancer.

Mutations in BRCA-1 and BRCA-2 predict probabilities of breast cancer by age 70 years of 45–87% and 26–84%, respectively, making these the strongest known predictors of breast cancer. The lifetime risks of ovarian cancer for BRCA-1 and BRCA-2 mutation carriers are 16–63% and 10–27%, respectively (3–10). Thus BRCA-1 and BRCA-2 mutation carriers are at significantly increased risk for cancers when compared to a 10% lifetime risk for breast cancer and a 1.8% lifetime risk for ovarian cancer for women in the general population (see Figs 1 and 2). The risk of breast cancer in BRCA-1 and BRCA-2 carriers increases significantly after the age of 30 years but appears to taper off after menopause in BRCA-1 carriers, while it appears to continue to increase after menopause in BRCA-2 carriers. The risk of ovarian cancer rises steeply after age 40 years in both BRCA-1 and BRCA-2 carriers, with an average age of diagnosis of 51.2 years. Given these levels of risk of ovarian cancer, several

Figure 1. Cumulative breast cancer risk (3,5,9).
strategies for primary prevention, such as tubal ligation, the use of oral contraceptives, and prophylactic surgery, have been proposed, although until recently there were no data supporting the efficacy of the various interventions (11–17).

Secondary prevention options include screening with transvaginal ultrasound and serial serum CA-125, and there are several potential new serum markers in clinical trials. There has been great uncertainty about the effectiveness of prophylactic oophorectomy, and the prospective trial recently published by Kauff et al. (18) provides important data that will be useful to clinicians and high-risk women as they consider the various risk-reducing options (19,20).

Although it has been well recognized that women who undergo prophylactic oophorectomy resulting in premature menopause dramatically reduce their risk for both breast and ovarian cancers, the degree of risk reduction for women with strong family histories or germ-line BRCA mutation carriers was not known. Indeed, a number of studies reported peritoneal carcinomatosis among women with strong family histories of ovarian cancer who had prophylactic oophorectomy, and data were limited with regard to breast cancer risk reduction (10,21–24).

In the Gilda Radner Familial Ovarian Cancer Registry, composed of 931 families with at least two first- or second-degree relatives with ovarian cancer, the degree of risk reduction for women with strong family histories or germ-line BRCA mutation carriers was not known. Indeed, a number of studies reported peritoneal carcinomatosis among women with strong family histories of ovarian cancer who had prophylactic oophorectomy, and data were limited with regard to breast cancer risk reduction (10,21–24).

The single-institution (Memorial Sloan-Kettering Cancer Center) study published by Kauff et al. (18) included 170 BRCA-1 and BRCA-2 mutation carriers who were at least 35 years of age and were offered the opportunity to enroll in a prospective follow-up study after receiving genetic test results. Excluding the three stage I ovarian cancers that were diagnosed at the time of salpingo-oophorectomy, at a mean follow-up of 2 years, three breast cancers and one peritoneal cancer were diagnosed among 98 women who chose risk-reducing salpingo-oophorectomy. In comparison, eight breast cancers, four ovarian cancers, and one peritoneal carcinomatosis were diagnosed among 72 women who chose surveillance. Thus the 5-year cancer-free survival estimates for healthy BRCA-1 and BRCA-2 mutation carriers who had prophylactic bilateral salpingo-oophorectomy was 94% compared to 69% for mutation carriers who chose surveillance after receiving test results. The difference in cancer-free survival estimates was highly statistically significant, with a p-value of 0.006. The complication rate appears to be minimal, as only 4 of the 98 women (4.1%) had any surgical complications. While these data are promising, a number of questions remain unanswered and will likely influence the acceptability of prophylactic oophorectomy by at-risk women and their health care providers.

The most pressing questions relate to the timing of surgery and maturity of the data. To answer both questions, a brief review of a more mature study published by the Prevention and Observation of Surgical Endpoints (PROSE) study group in the New England Journal of Medicine is warranted (28). This multicenter, case-control study includes outcome data on the largest number of BRCA-1 and BRCA-2 mutation carriers published to date, with a mean postoperative follow-up of 8.2 years (range 1–46 years). The incidence of ovarian cancer was determined in 259 women who had undergone bilateral prophylactic oophorectomy at a mean age of 40.9 years and in 292
matched controls who had not undergone the procedure. In addition, the incidence of breast cancer was determined in a subgroup of 99 women with no history of breast cancer or prophylactic mastectomy who had undergone bilateral prophylactic oophorectomy and in 142 matched controls. Observation of cases and controls was from the time of the case’s surgery until the occurrence of the first cancer or until censoring.

Similar to the Memorial Sloan-Kettering Cancer Center study, among the 259 cases, six stage I ovarian cancers (2.3%) were diagnosed at the time of prophylactic surgery and two cases of papillary serous peritoneal cancer were diagnosed at 3.8 and 8.6 years after prophylactic surgery. After a mean follow-up of 8.8 years, 58 ovarian cancers (19.9%) were diagnosed among the 292 controls. Twenty-one (21.2%) breast cancers were diagnosed among the 99 cases, as compared with 60 (42.3%) breast cancers among the 142 controls who were studied for breast cancer questions. Thus, with the exclusion of the six stage I ovarian cancers diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of epithelial ovarian and peritoneal cancers (adjusted hazard ratio 0.04; 95% confidence interval [CI] 0.01–0.16) (see Table 1) (28).

Of interest is that there have been no events in the 124 women who had oophorectomy by age 35 years, which suggests that the timing of oophorectomy may be important. Likewise, for the 241 women who had no history of breast cancer and who had not undergone mastectomy, a 53% breast cancer risk reduction was observed (adjusted hazard ratio 0.47; 95% CI 0.29–0.77). The most benefit in breast cancer risk reduction was observed in women who had prophylactic oophorectomy by age 50 years (see Table 2) (28). Thus the PROSE study provides additional support for the significant cancer risk reduction observed in the Memorial Sloan-Kettering Cancer Center study. The major findings of the two studies are summarized in Table 3 (18,28).

There are several unresolved issues that were not addressed by these studies that will have to be evaluated in subsequent prospective studies. What is the best type of surgery—laparoscopic bilateral salpingo-oophorectomy as was done in 88% of the women choosing oophorectomy or salpingo-oophorectomy and removal of the uterus? Should women receive hormone replacement therapy after oophorectomy, given the morbidity associated with premature menopause? What is the role of selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene or aromatase inhibitors in further reducing the risk of breast cancer after oophorectomy? Will a combination of different approaches for risk reduction ultimately lead to improved survival for women who harbor deleterious BRCA-1 or BRCA-2 mutations?

To gain insight into how health care providers can help their patients make decisions about various prevention approaches, one will have to rely on decision analysis models that have addressed these issues. In a recent update, Grann et al. (29) concluded that there is survival

| Table 1. Ovarian Cancer Risk Reduction After Bilateral Salpingo-Oophorectomya |
|--------------------------------|
| Group                  | Hazard ratio (95% CI) |
|------------------------|----------------------|
| Overall (n = 551)      | 0.04 (0.01–0.16)     |
| Age at bilateral salpingo-oophorectomy (years) |                     |
| <35 (n = 124)          | No events            |
| 35–50 (n = 348)        | 0.03 (<0.01–0.02)    |
| ≥50 (n = 79)           | 0.11 (0.02–0.76)     |

| Table 2. Breast Cancer Risk Reduction After Bilateral Salpingo-Oophorectomya |
|--------------------------------|
| Group                  | Hazard ratio (95% CI) |
|------------------------|----------------------|
| Overall (n = 241)      | 0.47 (0.29–0.77)     |
| Age at bilateral salpingo-oophorectomy (years) |                     |
| <35 (n = 76)           | 0.39 (0.15–1.04)     |
| 35–50 (n = 146)        | 0.49 (<0.26–0.90)    |
| ≥50 (n = 79)           | 0.52 (0.10–2.70)     |

| Table 3. Bilateral Salpingo-Oophorectomy in BRCA-1 Mutation Carriers |
|--------------------------------|
|                         |
| MSKCC cohort (~2 years)  | PROSE study (>8 years) |
|                         |                      |
| Ovarian cancer (%)      | Ovarian cancer (%)  |
| Peritoneal cancer (%)   | Peritoneal cancer (%)|
| Breast cancer (%)       | Breast cancer (%)   |
| No bilateral salpingo-oophorectomy | 5.5 | 19.9 | 42 |
| Bilateral salpingo-oophorectomy | 3.1a | 1.0 | 4.3 | 2.3a |

| Notes | |
|-------|---|
| aStage I ovarian cancers diagnosed at the time of prophylactic surgery. |
benefit to most prevention strategies, but that the benefit is age dependent. The model assumes the following: tamoxifen reduces breast cancer risk about 50% and it is as efficacious in BRCA-1 and BRCA-2 mutation carriers; tamoxifen retains its efficacy over time; oral contraceptives reduce the risk of ovarian cancer; oophorectomy reduces the risk of breast cancer in carriers and the effects of oophorectomy and tamoxifen are additive and independent of each other. The survival benefit in years after oophorectomy appears equivalent to mastectomy and oophorectomy and better than tamoxifen alone or mastectomy alone. Indeed, the model predicts that BRCA-1 or BRCA-2 mutation carriers who take tamoxifen after oophorectomy or who undergo mastectomy and oophorectomy by age 30 years have an overall survival similar to women in the general population who do not harbor deleterious mutations in BRCA-1 or BRCA-2. Tamoxifen alone or intensive surveillance do not appear to provide a similar survival benefit (30,31). These assumptions do not, however, take into consideration the clinical utility that may accrue from the inclusion of novel screening modalities such as magnetic resonance imaging (MRI), ultrasound, or ductal lavage in the surveillance of high-risk women (32,33).

In conclusion, prophylactic bilateral salpingo-oophorectomy can be regarded as an effective risk-reducing procedure that permits early diagnosis of ovarian cancer at the time of surgery and significantly reduces the risk of breast and ovarian cancer in women with germ-line mutations in the BRCA-1 and BRCA-2 genes. A strong rationale for cancer risk assessment and genetic testing now exists because risks associated with the prophylactic procedure appear minimal.

Acknowledgments

Supported by the U.S. Army Medical Research and Materiel Command DAMD 99-1-9123 (to O.I.O.), the National Women’s Cancer Research Alliance, and the Falk Medical Research Trust (to O.I.O.). Dr. Olopade is a Doris Duke Distinguished Clinical Scientist.

REFERENCES

1. American Cancer Society. Breast Cancer Facts and Figures 2001–2002. American Cancer Society, Atlanta.
2. Resource document for curriculum development in cancer genetics education. ASCO Task Force on Cancer Genetics Education. J Clin Oncol 1997;15:2157–69.
3. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998;62:676–89.
4. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994;343:692–95.
5. Struwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8.
6. Thorlacius S, Struwing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 1998;352:1337–39.
7. Satagopan JM, Offit K, Foulkes W, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2001;10:467–73.
8. Antoniou AC, Gayther SA, Stratton JF, et al. Risk models for familial ovarian and breast cancer. Genet Epidemiol 2000;18(suppl):173–79.
9. Easton DF, Ford D, Bishop DT, et al. Breast and ovarian cancer incidence in BRCA1 mutation carriers. Am J Hum Genet 1995;56:256–71.
10. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999;91:1475–79.
11. Risch HA, Mclaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001;68:700–710.
12. Naarod SA, Rish HA, Malehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998;339:424–28.
13. Modan B, Harte P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives and the risk of ovarian cancer among carriers and non carriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:233–40.
14. Naarod SA, Risch HA. Ovarian cancer, oral contraceptives and BRCA mutations [letter]. N Engl J Med 2001;345:1706–07.
15. Eisen A, Rebbeck TR, Wood WC, et al. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Oncol 2000;18:1980–95.
16. Naarod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet 2001;357:1467–70.
17. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002;359:572–77.
18. Kauff ND, Satagopan JM, Scheuer L, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–15.
19. NIH Consensus Conference: ovarian cancer screening, treatment and follow up. JAMA 1995;273:491–97.
20. Buke W, Daly M, Garber J, et al. Recommendations for follow up care of individuals with an inherited predisposition to cancer. JAMA 1997;277:997–1003.
21. Tobakman JK, Tucker M, Kase R, et al. Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer prone families. Lancet 1982;2:795–97.
22. Schorge JO, Muto MG, Welch WR, et al. Molecular evidence for multifocal papillary serous carcinoma of the peritoneum in patients with germ-line BRCA1 mutations. J Natl Cancer Inst 1998;90:841–45.
23. Chen KT, Schooley JL, Flam MS. Peritoneal carcinomatosis after prophylactic oophorectomy in familial ovarian cancer syndrome. Obstet Gynecol 1985;66:S93–S94.
24. Weber AM, Hewett WJ, Gajewski WH, et al. Serous carcinoma of the peritoneum after oophorectomy. Obstet Gynecol 1992;80:558–60.
25. Kemp GM, Hsuu JG, Andrews MC. Papillary peritoneal carcinomatosis after prophylactic oophorectomy. Gynecol Oncol 1992;47:395–97.
26. Piver MS, Jishi MF, Tsukada Y, et al. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. Cancer 1993;71:2751–55.
27. Strewing JP, Watson P, Easton DF, et al. Prophylactic oophorectomy...
in inherited breast/ovarian cancer families. J Natl Cancer Inst Monogr 1995;17:33–35.

28. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA 1 or BRCA2 mutations. N Engl J Med 2002;346:1616–22.

29. Grann VR, Jacobson JS, Thomason D, et al. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA 1/2 mutations: an updated decision analysis. J Clin Oncol 2002;15:2520–29.

30. Fisher B, Costantino JP, Wickerham L, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90:1371–88.

31. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1). Breast cancer prevention trial. JAMA 2001;286:2251–56.

32. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography and ultrasound for surveillance of women at risk for hereditary breast cancer. J Clin Oncol 2001;19:3524–31.

33. O'Shaughnessy JA, Ljung BM, Dooley WC, et al. Ductal lavage and clinical management of women at high risk for breast carcinoma. Cancer 2002;94:292–98.