Published in final edited form as:
Gynecol Oncol. 2014 May ; 133(2): 283–286. doi:10.1016/j.ygyno.2014.02.030.

Acceptability of Prophylactic Salpingectomy with Delayed Oophorectomy as Risk-Reducing Surgery Among BRCA Mutation Carriers

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Abstract

OBJECTIVE—Given emerging evidence for the fimbria as the site of origin for many serous carcinomas in BRCA mutation carriers, consideration is being given to studying prophylactic salpingectomy with delayed oophorectomy (PSDO) as risk-reducing surgery. We aimed to determine the interest in a study of PSDO among these women.

METHODS—We evaluated the results of an online survey conducted by Facing Our Risk of Cancer Empowered (FORCE), a patient advocacy group, from October 2010 to August 2012. Premenopausal BRCA mutation carriers with no history of ovarian cancer or prior bilateral salpingo-oophorectomy (BSO) were included.

RESULTS—Of the 204 women meeting inclusion criteria, median age was 35 years, 92.5% were white, 25.7% Jewish, and 16.7% had a history of breast cancer. Overall, 34.3% reported interest in a study of salpingectomy, 35.3% were unsure, and 30.4% were not interested in the study. Women noted the possibility of lowering ovarian cancer risk without menopause as a compelling reason to participate (83.8%). Reasons for not participating in a salpingectomy study included surgical complications (46.6%), potential ovarian damage (42.2%), planning BSO soon (32.4%), and surgical costs (32.8%). Acceptable study risks included the need for two surgeries (77.2%), possibility of not lowering ovarian cancer risk (68%), and disruption of ovarian blood supply (66.5%).

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Conflict of Interest
The authors have no conflicts of interest to report.

CONCLUSIONS—One-third of BRCA mutation carriers indicated definite interest in a PSDO study. Potential study risks were acceptable to most women. These findings suggest that patient accrual for a clinical trial of prophylactic salpingectomy with delayed oophorectomy is possible.

Keywords

Prophylactic Salpingectomy; Delayed Oophorectomy; BRCA; Risk-Reducing Surgery

Introduction

Of the 22,000 ovarian cancer cases that will be diagnosed in 2013, approximately 10% can be attributed to an inherited predisposition.[1, 2] The most common hereditary cause of ovarian cancer is a mutation in the *BRCA1* or *BRCA2* genes. Women who have a *BRCA1* mutation have a 39% to 46% risk of developing ovarian cancer by age 70, while women with a *BRCA2* mutation carry a 10% to 27% risk by age 70.[3] In contrast, women in the general population have a 1.4% lifetime risk of developing ovarian cancer.[4]

The National Comprehensive Cancer Network (NCCN) has developed guidelines to aid with the management of these high-risk women. These guidelines state that risk-reducing salpingo-oophorectomy (RRSO) should be recommended to BRCA mutation carriers between the ages of 35 to 40, or when childbearing is complete.[5] RRSO provides a 75% to 96% reduction in ovarian cancer risk, and is the most efficacious method of ovarian cancer prevention for these women.[6–9] RRSO also appears to provide a survival advantage as studies have demonstrated a 60% to 70% decrease in overall mortality among BRCA mutation carriers who have undergone the procedure compared with those who have not.[10, 11]

Though RRSO has profound benefits, there are significant concerns regarding the adverse effects of surgical menopause on these young women. Oophorectomy prior to natural menopause is associated with an increased risk for osteoporosis, cardiovascular disease, cognitive impairment, and overall mortality.[12–14] Furthermore, women who undergo RRSO before menopause experience significant changes in sexual functioning as well as vasomotor symptoms.[15] These side effects can lead BRCA mutation carriers to avoid RRSO.

Since the adoption of RRSO for BRCA mutation carriers in the 1990’s, thousands of women have undergone the procedure. Study of their pathology specimens has resulted in the discovery of a small number of occult malignancies. The majority of these tumors have been located in the fallopian tube.[16–23] These findings have led to the hypothesis that the fallopian tube is the true site of origin of many BRCA-associated high-grade serous pelvic malignancies. This theory, along with the risks associated with early menopause, has brought increasing interest to the role of salpingectomy with delayed oophorectomy (PSDO) as a potential alternative to RRSO for BRCA mutation carriers.[24, 25]

PSDO is an investigational surgical strategy where women decrease their risk of ovarian cancer, but delay the side effects associated with menopause. Women who undergo PSDO would have both of their fallopian tubes removed upon completion of childbearing, but

oophorectomy would be performed as a separate surgical procedure at a later date. Though some researchers have expressed enthusiasm for PSDO, it is unknown how BRCA mutation carriers perceive the procedure. The objective of this study was to determine the acceptability of and interest in a clinical trial of PSDO among BRCA mutation carriers.

Materials and Methods

Between October 2010 and August 2012 an online survey was conducted by Facing Our Risk of Cancer Empowered (FORCE). FORCE is a patient advocacy group for women with hereditary breast and ovarian cancer. The survey was developed by FORCE and administered on their website. The survey assessed participants' beliefs about PSDO as a form of ovarian cancer prevention. (Supplementary Material) Demographic information and medical history were also collected, but participants were not asked to provide personal identifiers. This study was approved by the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center. As no protected health information was collected, a waiver of informed consent was granted by the IRB.

The online survey was available to all visitors to the FORCE website during the study period and was promoted through FORCE's social media pages, website, and electronic newsletter. However, to limit this study to women who would be eligible for a PSDO trial, only premenopausal BRCA mutation carriers were included in the analysis. Women who reported prior bilateral salpingo-oophorectomy or a history of ovarian, fallopian tube, or primary peritoneal carcinoma were also excluded.

Demographics and medical history of participants were summarized using descriptive statistics, including medians, means, standard deviations, ranges, and frequencies. Chi-square tests were used to compare differences between groups. IBM SPSS Statistics for Windows, Version 19.0, was used for statistical analysis (IBM Corp., Armonk, NY). A two-sided p value of less than 0.05 was considered statistically significant.

Results

Of the 488 women who completed surveys, 204 met inclusion criteria and were included in further analysis. Table 1 details the characteristics of these women. When queried about their desire to participate in a study of PSDO, approximately one-third of respondents (34.3%) reported definite interest. An additional 35.3% of women were unsure if they would participate in this type of study, although many requested more information about PSDO in their survey comments. When asked about reasons to participate in a PSDO study, 83.8% of women agreed that it was the possibility of lowering ovarian cancer risk without menopause. The majority of participants (84.2%) also agreed that helping to further ovarian cancer research for high-risk women was an important reason to participate. Overall, potential PSDO study risks were acceptable to the majority of survey participants (Table 2).

Sixty-one women (30.3%) stated they were not interested in participating in a PSDO study. When all respondents were queried regarding reasons to not participate in a PSDO study, 46.6% cited surgical complications, 32.8% reported surgical costs, and 14.7% noted

anesthesia concerns. Additionally, 32.4% of women did not want to participate because they already planned to undergo RRSO.

Comparisons of risk acceptability were made between women who were interested in a PSDO study and those who were not interested (Table 3). As expected, women that were interested in a PSDO trial were more likely to find the study risks to be acceptable as compared with women that were not interested in a PSDO study.

Post-hoc subgroup analyses were performed on the surveys of nulliparous and parous women. There was no difference between the groups in the number of women interested in participating in a PSDO study (parous 37.9% vs nulliparous 29.8%, p=0.42). Parous women were more likely than nulliparous women to find the possibility of undergoing two surgical procedures (28.9% vs 15.1%, p=0.04) and the potential to not lower their ovarian cancer risk (39.2% vs 22.1%, p=0.02) unacceptable. However, nulliparous women were more likely to report concerns about potential disruption of ovarian blood supply as a reason to not participate in a PSDO trial (52.9% vs 34.2%, p=0.01).

As ovarian cancer risk differs among BRCA1 and BRCA2 mutation carriers, analysis was also performed on the survey responses of these two groups. There were no statistically significant differences between these groups in any of the survey responses, including the acceptability of disruption of ovarian blood supply (68.9% vs 62.5%, p = 0.4), acceptability of requiring two procedures (78% vs 74.2%, p = 0.58), and acceptability of the potential for surgery to not lower ovarian cancer risk (72.1% vs 60.9%, p = 0.13).

Discussion

Currently, RRSO is the only surgical method available for BRCA mutation carriers to decrease their risk of ovarian cancer. However, despite the significant benefits of RRSO, the side effects of early menopause are substantial. Screening for ovarian cancer with CA-125 and transvaginal ultrasound is recommended for women who do not want RRSO.[5] However, the ability of screening to detect early stage disease is unproven. These concerns, along with the emerging evidence for the fallopian tube as the origin of many high-grade pelvic serous carcinomas, has led to increasing interest in the role of PSDO in BRCA mutation carriers.

To date, the body of literature regarding PSDO is limited, and there are no published clinical trials of this surgical strategy. However, preliminary studies regarding PSDO are promising. A recent cost-effectiveness analysis modeled a comparison between PSDO with RRSO among BRCA mutation carriers. They found that while RRSO gave the greatest risk-reduction for breast and ovarian cancer, PSDO was a cost-effective strategy when quality-adjusted life expectancy was taken into consideration.[26] Leblanc and colleagues published their experience on “radical fimbriectomy” in 14 BRCA mutation carriers. With an aim to demonstrate safety of the technique, the patients underwent bilateral salpingectomy and removal of a portion of each ovary. This was followed by oophorectomy at the end of the procedure. Though the authors found the surgery to be safe, they caution that the risks of an “incomplete risk-reducing surgery” are unknown and further studies are warranted.[27] Of

interest, this group is currently recruiting patients for a clinical trial of radical fimbriectomy, with completion of the study anticipated in 2019. (NCT01608074)

Though PSDO has garnered attention in the research community, the present study is the only one to assess the perspective of women to whom this surgical strategy applies. Encouragingly, results from our survey found that over one-third of BRCA mutation carriers eligible for risk-reducing surgery had definite interest in a trial of prophylactic salpingectomy. Though 35.3% of survey respondents were unsure about their study participation, their survey comments indicated that many of them wanted additional information about PSDO.

When queried about the risks associated with PSDO, the majority of our study population found them to be acceptable. Parous women were more likely than nulliparous women to believe the need for two procedures and the possibility of not lowering their cancer risk to be unacceptable. Reasons for this are unclear, but may be related to differences between groups in medical and surgical history or preparedness to undergo risk-reducing surgery. These findings should be further explored in future studies.

The most worrisome PSDO risk is that some pelvic tumors likely originate in the ovary instead of the fallopian tube. In fact, there is some evidence that up to 21% of occult cancers may involve the ovary alone.[23] In the present study, 58.3% of all respondents and 78.3% of women who stated interest in a PSDO trial found the risk of undergoing salpingectomy without lowering their chance of ovarian cancer to be acceptable. However, it is imperative that future PSDO trials emphasize this risk to participants.

While premature ovarian failure is another potential risk of salpingectomy, more than half of the women in our population found this risk to be acceptable. Interestingly, studies of women at normal-risk for ovarian cancer have found no difference in ovarian function, as measured by FSH and AMH, between women who underwent salpingectomy and those who did not.[28, 29] This has not yet been investigated in high-risk women.

Another concern regarding PSDO is its lack of effect on breast cancer risk. RRSO can decrease the risk of breast cancer in BRCA mutation carriers by approximately 50%.[30] While prophylactic mastectomy would be an option for women that undergo PSDO, it is not realistic to expect that all women who have PSDO will also have a bilateral mastectomy. Though we did not ask our study participants their thoughts about this risk, future PSDO trials will need to address it with study participants.

A limitation of our study is that the women were mostly white and highly educated. As such, these findings may not be generalizable to a minority or lesser-educated population of BRCA mutation carriers. Additionally, we have a relatively small number of study participants, which restricts the conclusions that can be made. Finally, we provided very limited education on PSDO as part of this survey. As such, our participants may not have had an accurate understanding of PSDO prior to completing the survey. Patient education about potential risks and benefits will be an integral part of any future PSDO trial.

The findings of the present study suggest that there is interest in a PSDO trial among BRCA mutation carriers. However, in order to determine if PSDO has actual benefits for BRCA mutation carriers, formal clinical trials are needed. In addition to the ongoing European study, our group is currently accruing BRCA mutation carriers to a trial of PSDO, with plans to complete patient enrollment within the next two years. (NCT01907789)

In conclusion, results from this study indicate that BRCA mutation carriers would be willing to participate in a clinical trial of PSDO. Furthermore, many of the study-associated risks were acceptable to this population. It is important to remember that RRSO remains the standard of care for these women. PSDO is investigational and should be reserved for the clinical trial setting. However, our findings suggest that adequate patient accrual for a PSDO study is possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA Cancer J Clin. 2013
2. Lancaster, JM. Clinical Relevance of Hereditary Ovarian Cancer. In: Lu, KH., editor. Hereditary Gynecologic Cancer: Risk, Prevention, and Management. New York: Informa Healthcare; 2008. p. 1-13.
3. Lancaster JM, Powell CB, Kauff ND, Cass I, Chen LM, Lu KH, et al. SGO Committee Statement: Society of Gynecologic Oncologists Education Committee Statement on Risk Assessment for Inherited Gynecologic Cancer Predispositions. Gynecologic Oncology. 2007; 107:159–162. [PubMed: 17950381]
4. Howlader, N.; Noone, AM.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W., et al. SEER Cancer Statistics Review, 1975–2009. Bethesda, MD: National Cancer Institute; 2013. p. based on November 2011 SEER data submission
5. National Comprehensive Cancer Network. NCNN Clinical Practice Guidelines in Oncology V12013. Fort Washington (PA): NCCN; 2013. Genetic/familial high-risk assessment: breast and ovarian.
6. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. New England Journal of Medicine. 2002; 346:1601–1615.
7. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. New England Journal of Medicine. 2002; 346:1616–1622. [PubMed: 12023993]
8. Kauff ND, Domcheck SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. Journal of Clinical Oncology. 2008; 26:1331–1337. [PubMed: 18268356]
9. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. JAMA. 2006; 296:185–192. [PubMed: 16835424]
10. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncology. 2006; 7:223–229. [PubMed: 16510331]
11. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010; 304:967–975. [PubMed: 20810374]

12. Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int. 2008; 14:111–116. [PubMed: 18714076]
13. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007; 69:1074–1083. [PubMed: 17761551]
14. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006; 7:821–828. [PubMed: 17012044]
15. Finch A, Metcalfe KA, Chiang JK, Elit L, McLaughlin J, Springate C, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecol Oncol. 2011; 121:163–168. [PubMed: 21216453]
16. Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. Journal of Clinical Oncology. 2007; 25:3985–3990. [PubMed: 17761984]
17. Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley P. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecologic Oncology. 2002; 87:52–56. [PubMed: 12468342]
18. Medeiros F, Muto MG, Y L, Elvin JA, Callahan MJ, Feltmate C, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. American Journal of Surgical Pathology. 2006; 30:230–236. [PubMed: 16434898]
19. Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecologic Oncology. 2006; 100:58–64. [PubMed: 16137750]
20. Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. Journal of Clinical Oncology. 2005; 23:127–132. [PubMed: 15625367]
21. Lu KH, Garber JE, Cramer DW, Welch WR, Niloff J, Schrag D, et al. Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. Journal of Clinical Oncology. 2000; 18:2728–2732. [PubMed: 10894872]
22. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. American Journal of Surgical Pathology. 2001; 25:1283–1289. [PubMed: 11688463]
23. Yates MS, Meyer LA, Deavers MT, Daniels MS, Keeler ER, Mok SC, et al. Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: building a model for early BRCA-associated tumorigenesis. Cancer Prevention and Research. 2011; 4:463–470.
24. Chene G, Rahimi K, Mes-Masson AM, Provencher D. Surgical Implications of the Potential New Tubal Pathway for Ovarian Carcinogenesis. J Minim Invasive Gynecol. 2013
25. Anderson CK, Wallace S, Guiahi M, Sheeder J, Behbakht K, Spillman MA. Risk-reducing salpingectomy as preventative strategy for pelvic serous cancer. Int J Gynecol Cancer. 2013; 23:417–421. [PubMed: 23385282]
26. Kwon JS, Tinker A, Pansegrau G, McAlpine J, Housty M, McCullum M, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol. 2013; 121:14–24. [PubMed: 23232752]
27. Leblanc E, Narducci F, Farre I, Peyrat JP, Taieb S, Adenis C, et al. Radical fimbriectomy: A reasonable temporary risk-reducing surgery for selected women with a germ-line mutation of BRCA1 or 2 genes? Rationale and preliminary development. Gynecologic Oncology. 2011; 121:472–476. [PubMed: 21411127]
28. Findley AD, Siedhoff MT, Hobbs KA, Steege JF, Carey ET, McCall CA, et al. Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a pilot randomized controlled trial. Fertil Steril. 2013; 100:1704–1708. [PubMed: 23993887]
29. Morelli M, Venturella R, Mocciaro R, Di Cello A, Rania E, Lico D, et al. Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: primum non nocere. Gynecol Oncol. 2013; 129:448–451. [PubMed: 23558052]

30. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 2005; 23:7491–7496. [PubMed: 16234515]

Research Highlights

- BRCA mutation carriers are willing to participate in a PSDO trial.
- The majority of participants found potential PSDO study risks to be acceptable.
- These results suggest that adequate accrual for a clinical trial of PSDO is possible.

Table 1

Demographic Characteristics of Participants (N=204)

Age	**Years**
Median (Range)	35 (21–53)
Mean	35.4
Race	**% (n)**
White	90.7 (185)
Hispanic	3.4 (7)
Other	3.9 (8)
Unknown	2 (4)
Ashkenazi Jewish	**% (n)**
	25.7 (52)
Education	**% (n)**
Some High School	0.5 (1)
High School Graduate	2.5 (5)
Some College	13.7 (28)
Bachelor's or Advanced Degree	82.4 (168)
Unknown	1 (2)
BRCA Status	**% (n)**
BRCA 1 Mutation	62.3 (127)
BRCA 2 Mutation	37.7 (77)
Parity	**% (n)**
Parous	57.4 (117)
Nulliparous	41.2 (84)
Unknown	1.5 (3)
Cancer History	**% (n)**
No History	83.3 (170)
Breast Cancer History	16.7 (34)

Table 2

Acceptability of Risks of PSDO

Risks	Found Risk Acceptable % (n=204)
Risk of losing ovarian function due to disruption of ovarian blood supply.	54.4 (111)
Undergoing salpingectomy followed by oophorectomy in 3–5 years.	64.7 (132)
Risk of undergoing a surgery which may prove to not lower the risk of ovarian cancer.	58.3 (119)
Traveling to the study site twice yearly for study-related evaluations.	80.9 (165)
Having blood drawn twice yearly for evaluations from a lab near your home.	94.6 (193)

Table 3

Comparison of PSDO Risk Acceptability Between Women Interested and Disinterested in a PSDO Trial

Risks	Interested PSDO Trial % (n=69)	Disinterested PSDO Trial % (n=61)	p
Risk of losing ovarian function due to disruption of ovarian blood supply is acceptable.	79.7 (55)	26.2 (16)	<0.001
Undergoing salpingectomy followed by oophorectomy in 3–5 years is acceptable.	88.4 (61)	24.4 (21)	<0.001
Risk of undergoing a surgery which may prove to not lower the risk of ovarian cancer is acceptable.	78.3 (54)	37.7 (23)	<0.001
Traveling to the study site twice yearly for study-related evaluations is acceptable.	88.4 (61)	75.4 (46)	0.023
Having blood drawn twice yearly for evaluations from a lab near your home is acceptable.	100 (69)	88.5 (54)	0.09