Published in final edited form as:

Am J Obstet Gynecol. 2011 January ; 204(1): 19.e1–19.e6. doi:10.1016/j.ajog.2010.05.038.

Does Bilateral Salpingectomy with Ovarian Retention Warrant Consideration as a Temporary Bridge to Risk-Reducing Bilateral Oophorectomy in *BRCA1/2* Mutation Carriers?

Mark H. GREENE, M.D.,

Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20852

Phuong L. MAI, M.D., M.S., and

Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20852

Peter E. SCHWARTZ, M.D.

Division of Gynecologic Oncology, Yale University School of Medicine, New Haven, CT 06520

Abstract

Risk-reducing salpingo-oophorectomy (RRSO) is the most definitive surgical intervention for ovarian cancer risk reduction among *BRCA1/2* mutation carriers. For women who have completed child-bearing but who are not ready for RRSO, bilateral salpingectomy with ovarian retention (BSOR) might serve as a temporary measure while definitive risk-reducing surgery is being contemplated. Here we summarize recent insights into the pathogenesis of hereditary ovarian cancer which might provide a basis for considering the proposed BSOR management strategy and outline the evidence for and against this potential risk-reducing intervention. Based on the evidence presented, we suggest that there may be sufficient merit in this proposed intervention to consider evaluating it formally, perhaps through an intergroup-based clinical trial. In the meanwhile, we believe that BSOR should be considered an investigational risk management option of unproven clinical utility, particularly since delay in bilateral oophorectomy could theoretically reduce the protective effect against breast cancer that has been documented in women undergoing RRSO.

Keywords

bilateral oophorectomy; bilateral salpingectomy; *BRCA1/2* mutation carriers; ovarian cancer risk; risk-reducing surgery

Introduction

The mapping and cloning of *BRCA1* and *BRCA2*, the two major breast/ovarian cancer susceptibility genes, and the subsequent widespread application of clinical germline mutation testing of these genes as the basis for cancer risk assessment and management in

Corresponding Author: Mark H. Greene, MD Clinical Genetics Branch, National Cancer Institute 6120 Executive Boulevard, Room EPS 7032 Rockville, MD 20852 Voice: 301-594-7641 Fax: 301-496-1854 greenem@mail.nih.gov .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

familial breast/ovarian cancer kindred, have presented providers and patients with many challenging clinical decisions. The steady accumulation of evidence upon which these choices are considered comprises one of the major scientific accomplishments in clinical cancer genetics during the past decade.¹

Nonetheless, there remain some clinical scenarios for which we do not yet have sufficient data for evidence-based decision-making. The complexities involved in considering when a premenopausal *BRCA1/2* mutation carrier should undergo risk-reducing salpingo-oophorectomy (RRSO) are among the most daunting. Although it is increasingly clear that RRSO in this setting is associated with the largest currently-available reductions in the risks of ovarian, fallopian tube, and breast carcinoma,² numerous questions regarding the timing of the procedure, post-RRSO non-oncologic morbidity, and the safety of menopausal hormonal therapy (MHT) remain unresolved.

Concerns and uncertainties for at-risk women and health care providers regarding the frequency and severity of symptoms related to premature menopause are among the greatest deterrents to more widespread acceptance of RRSO as the routine risk management strategy for *BRCA1/2* mutation carriers who have completed child-bearing. Although previous studies suggested that short-term use of MHT post-RRSO among *BRCA1/2* mutation carriers does not mitigate the impact of RRSO on breast cancer risk,^{3, 4} and use of short-term (*e.g.*, <5 years) MHT is increasing among pre-menopausal women who undergo RRSO, the existing evidence needs to be confirmed and many providers and patients remain wary of the potential adverse effects of post-surgical MHT.

The suggestion regarding a potentially new management option for mutation carriers who are not yet prepared to undergo premature menopause and its consequences emerged during a discussion at the 24th Annual Ella T. Grasso Ovarian Cancer Symposium, held at Yale University, in November 2008. We consider whether bilateral salpingectomy with ovarian retention (BSOR) represents a potentially useful risk-reducing strategy as a temporary, short-term intermediate step towards eventual bilateral oophorectomy in this group of women. The following discussion outlines the rationale for, and reviews the potential risks and benefits of, such a strategy, to open this novel idea for debate. We emphasize that this commentary is not intended to encourage or support *ad hoc* application of this unproven strategy.

The Rationale

This question arose as an unexpected nexus of a discussion that centered on two important clinical observations. First, bilateral tubal ligation has been suggested to be associated with a reduction in the risk of both sporadic⁵ and hereditary⁶ ovarian cancer, particularly among *BRCA1* mutation carriers. However, this risk reduction has not been consistently observed. Although Narod and colleagues showed that bilateral tubal ligation was associated with a 61% reduction in ovarian cancer risk among *BRCA1* mutation carriers,⁷ this observation was not replicated in a larger study.⁸ There has been considerable speculation regarding the physiologic basis for this association, including putative compromise of ovarian blood supply and mechanical interruption of the transport of environmental carcinogens from the lower female reproductive tract to the ovaries. The former is not anatomically compelling, since the ovarian blood supply is typically not altered by tubal ligation.⁹⁻¹¹ The second – most notably in the form of the “talc hypothesis” of ovarian carcinogenesis – remains controversial despite being observed in multiple studies.^{12, 13} Regardless of the mechanism, the association between interruption of the fallopian tubes and ovarian cancer risk reduction is potentially substantial. However, tubal ligation is seldom raised as a treatment option among young mutation carriers.

Second, the increasingly wide-spread application of RRSO as a management strategy in high-risk women, coupled with more careful histopathologic scrutiny of the fallopian tubes obtained at the time of surgery,¹⁴ has shown that a significant proportion of the clinically-occult malignancies detected in these pathology specimens originated in the fallopian tube rather than the ovary.¹⁵ We now know that the fallopian tube is a target for *BRCA1/2*-related malignancies,¹⁶⁻²² an insight that has resulted in the routine incorporation of bilateral salpingectomy into the surgical management of women with *BRCA1/2* mutations.

Furthermore, these findings have led several groups of investigators to more carefully evaluate the role of the fallopian tube in ovarian carcinogenesis.²³⁻²⁸ A potential paradigm-altering hypothesis has emerged from their work, *i.e.*, that a significant proportion of what has historically been classified as ovarian cancer is actually cancer of fallopian tube origin.^{15, 29} Thus the term “pelvic serous carcinoma” (PSC) may be a more precise overarching concept which subsumes the site-specific entities of ovarian, fallopian tube, and primary peritoneal malignancies. This new terminology acknowledges the difficulty related to determining the precise site of initial malignant transformation among these morphologically and clinically similar neoplasms. The full spectrum of proliferative and neoplastic lesions seen in most other epithelial malignancies in adults (but conspicuously absent in the ovaries themselves) has now been observed in the fallopian tube mucosa of *BRCA1/2* mutation carriers. This then raises the question of whether there might be significant risk-reduction associated with a strategy of bilateral salpingectomy, followed later by definitive risk-reducing bilateral oophorectomy, in pre-menopausal women who have completed their planned family but who are not yet ready to undergo bilateral oophorectomy.

Potential Advantages to Bilateral Salpingectomy with Ovarian Retention (BSOR)

The potential advantages for a BSOR strategy are based on three assumptions: a) a clinically meaningful proportion of all *BRCA*-related PSC arises in the fallopian tube; b) these fallopian tube cancers (FTC) can be prevented by bilateral salpingectomy; and c) any risks associated with delaying menopause among genetically-predisposed women are offset by benefits related to removal of the tubes at a younger age than might otherwise be the case.

Within this framework, potential advantages to BSOR as a short-term, intermediate bridge to risk-reducing bilateral oophorectomy (RRBO) include:

1. A proportion of the PSC risk that would otherwise be experienced by a *BRCA1/2* mutation carrier who declines/defers RRSO might be eliminated for the period prior to undergoing definitive ovarian cancer risk-reducing surgery by removing the fallopian tubes. Although we do not know exactly what this proportion is, a review of 11 RRSO series targeting *BRCA1/2* mutation carriers found that 64 of 94 (68%) occult cancers originated in the fallopian tubes (range: 43%-100%).^{14, 17-21, 30-34} These observational data suggest that the risk-reducing impact of bilateral salpingectomy could be substantial.
2. Premature menopause would be temporarily deferred, and the need to consider short-term MHT and its uncertain risks avoided, thus reducing the time during which the patient could experience acute and chronic estrogen deficiency symptoms and, perhaps, reducing the non-oncologic morbidity associated with premature menopause.
3. BSOR could be done laparoscopically in the majority of women. This procedure would also provide an earlier opportunity (compared with awaiting subsequent/

delayed RRSO) to evaluate the tubes histologically, assess the ovaries and peritoneal space by direct inspection, collect peritoneal cytology specimens, and obtain biopsies if indicated. It is likely that this surgical procedure would result in the detection and definitive treatment of clinically occult PSC in a small but important subset of high-risk women. Malignancies so detected would certainly be at an earlier stage than would be the case if they were diagnosed by screening or based on symptoms. Although incidental diagnosis has not been proven to lead to improvement in overall survival, early-stage ovarian and fallopian tube cancers have a more favorable prognosis.

4. This strategy postpones the difficult and irrevocable decision to undergo premature infertility, since the option of assisted reproductive technologies would still be available. It is conceivable that simply knowing one could potentially still get pregnant brings meaningful emotional benefit.
5. Despite evidence of the clinical benefit for RRSO, a significant fraction of high-risk women are not prepared to undergo this procedure upon completion of reproductive planning. For example, 36% of the 785 women who knew they were *BRCA* mutation-positive at the time they enrolled in GOG-199 (the National Ovarian Cancer Prevention and Early Detection Study) elected an investigational ovarian cancer screening option rather than RRSO.³⁵ Other studies have suggested that the proportion of RRSO uptake ranges from 50% to 70%.³⁶⁻³⁹ Declining RRSO might add to the stress of worrying about the risk of PSC, a set of malignancies for which there is no clinically useful screening strategy. BSOR would, therefore, represent an active, potentially empowering management strategy that might be acceptable to a meaningful number of these women. Choosing BSOR could simultaneously reduce both their risk of PSC and their psychological distress related to delaying RRSO.
6. If the risk-reducing effect of tubal ligation is mediated through prevention of some cancers which truly arise in the ovary, BSOR could produce a larger risk reduction than that anticipated by salpingectomy-related elimination of FTC risk. Theoretically, this is a possibility, given that similar relative magnitude of tubal ligation effect is seen in the sporadic setting, a context in which FTC is exceedingly rare. However, an alternative explanation for this phenomenon may be that the advanced stage at which most sporadic ovarian cancers are diagnosed prevents our recognizing those that actually originated in the fallopian tube.

Potential Problems with Bilateral Salpingectomy with Ovarian Retention (BSOR)

The following constitutes a summary of the potential problems or difficulties involved in considering a BSOR strategy:

1. We do not have an accurate estimate of the proportion of *BRCA1/2* mutation-related PSC risk that is attributable to FTC rather than ovarian or primary peritoneal carcinoma. The smaller this fraction is, the less the benefit that would accrue to BSOR.
2. We do not yet understand how the risk-reducing effect of tubal ligation is mediated. It is uncertain whether this benefit is related solely to a reduction in the risk of FTC, or whether tubal interruption influences the risk of ovarian and/or primary peritoneal carcinoma as well.
3. Despite the intention to perform RRBO at the earliest possible time after BSOR, some women may delay oophorectomy by a substantial amount of time. The longer

the period during which the ovaries are present, the greater the cumulative risk of ovarian cancer. Maximum benefit from BSOR in reducing PSC and breast cancer risk would require bilateral oophorectomy prior to menopause, and that benefit is likely to be inversely related to the interval between salpingectomy and oophorectomy. The BSOR management strategy would therefore create a spectrum of PSC risk reduction, depending on the clinical scenario:

- a. RRSO at completion of family planning: maximum risk reduction (the current “gold standard”);
- b. BSOR at completion of family planning, followed by RRBO at some relatively short interval (? a few years) thereafter: “substantial” risk reduction;
- c. BSOR at completion of family planning, followed by RRBO after a longer delay: “moderate” risk reduction;
- d. BSOR at completion of family planning, with RRBO delayed until after menopause: “lesser” risk reduction, and
- e. BSOR at completion of family planning, without ever having RRBO: “least” risk reduction and one of the major potential adverse consequences of the BSOR approach.

To the extent that ovarian cancer occurs during the interval between salpingectomy and oophorectomy – and it is virtually certain that this will happen for some women – one might regard the BSOR strategy a failure, but the same or greater risk would have pertained for women who deferred, or never underwent, RRSO.

We do not know how the availability of BSOR would affect a woman’s decision regarding the timing of definitive risk-reducing surgery. If the decision to delay RRSO were solely to avoid premature menopause, we would expect that most women electing BSOR would complete their surgery by age ~50, with their PSC risk having been mitigated (but not abrogated) by bilateral salpingectomy. The major concern relative to BSOR is that, for a variety of unforeseeable reasons, some women may never undergo definitive risk-reducing surgery.

A further subtlety: currently a subset of women chooses RRSO reluctantly, after completion of child-bearing, as it represents the best available strategy. The availability of an alternative risk-reduction option might lead some who now accept RRSO to select BSOR instead, thereby delaying definitive surgery until a much later time, relative to their current choice.

4. The ability to make decisions related to the BSOR strategy is compromised by uncertainty regarding the details of *BRCA1*- and *BRCA2*-related ovarian cancer risk between the ages of 30 and 50. The overall age-at-ovarian-cancer-diagnosis clearly differs between *BRCA1* (mean: 51.2 years) and *BRCA2* (mean: 57.5 years) mutation carriers.⁴⁰ It is tempting to speculate that RRSO could be performed safely at a later age among *BRCA2* than *BRCA1* mutation carriers, but what a safe later age might be is not known. The more accurate our information regarding gene- and age-specific ovarian cancer penetrance, the better our ability to make more subtle recommendations related to the timing of RRSO. For example, data from a recent meta-analysis of *BRCA1*- and *BRCA2*-related ovarian cancer penetrance indicate that the risk to age 50 for a 40-year-old *BRCA1* mutation carrier is 6.7%, while the analogous risk for a *BRCA2* mutation carrier is 1.9%,⁴¹ a statistically significant 3.5-fold difference in risk. If this lower risk of ovarian cancer among *BRCA2* carriers during the decade when most surgical risk-reduction

decisions are being made were definitively substantiated, delaying risk-reducing oophorectomy in this sub-group of high-risk women might warrant serious consideration. However, this possibility in delaying oophorectomy must be weighed against potential loss of breast cancer risk reduction.

5. There is a real risk that delay in performing bilateral oophorectomy could blunt the reduction in breast cancer risk, one of the major benefits related to RRSO.² In this recent meta-analysis, the summary estimate hazard ratio for breast cancer associated with RRSO among *BRCA1/2* mutation carriers was 0.49.² This risk reduction appears to be greatest when performed prior to menopause;⁴² thus, shifting oophorectomy closer in time to natural menopause may reduce a benefit that has been viewed as having substantial value among women contemplating RRSO. Furthermore, the effect on breast cancer risk reduction seems to decrease with increased age at the time of surgery. In a study evaluating the effect of RRSO on breast cancer risk among *BRCA1/2* mutation carriers, the odds ratio for developing breast cancer was 0.41 if RRSO was performed at or before the age of 40, 0.47 if RRSO was performed between the ages of 41 and 50, and 0.70 if RRSO was performed after age 50.⁴³ It is not known to what magnitude delaying oophorectomy in a pre-menopausal *BRCA1/2* mutation carrier by, for example, 1 to 3 years, blunts the protective effect on breast cancer risk. However, for women who have elected to have bilateral mastectomy as the definitive breast cancer risk reduction intervention, this potential loss in breast cancer risk reduction is not relevant. Thus, this is an important factor to take into account when considering BSOR.
6. A potentially significant risk related to BSOR is that attributable to the additional procedure. The minimally-invasive laparoscopic surgery is widely used to perform RRSO with acceptable morbidity. However, the proposed strategy requires a second surgery for the risk-reducing oophorectomy. There is potential for greater surgical morbidity the second time around, even if it is also done laparoscopically. It is also possible that the prospect of needing two operations would make this choice unacceptable for some women. There are no published data which provide insight into whether high-risk women would find the BSOR strategy acceptable.
7. An ill-defined syndrome that includes menstrual irregularities, dysmenorrhea, premenstrual syndrome and premature menopause has been suggested to occur after tubal ligation.¹⁰ If this were to occur in association with bilateral salpingectomy, then the time during which ovarian function is retained after BSOR may be less than anticipated. Moreover, these symptoms might be unacceptable to some women. However, definitive evidence supporting this phenomenon is lacking. The U.S. Collaborative Review on Sterilization, in which 9,514 women who underwent tubal sterilization were compared with 573 women whose partners underwent vasectomy, showed that women who underwent tubal sterilization were no more likely to have menstrual abnormalities than those who did not.⁴⁴

Although the rationale supporting the potential utility of BSOR as an interim, short-term measure while awaiting definitive ovarian cancer risk-reducing surgery seems reasonable, we have no objective data at present to prove that it is safe and effective, when all the risks and benefits are taken into account.

Where Do We Go from Here?

Weighing the complex set of pros and cons related to BSOR above, it seems that there may be sufficient merit in this proposal to consider evaluating it in a formal fashion. In summary, it appears that:

- there is genuine risk of PSC among pre-menopausal *BRCA1/2* mutation carriers who postpone RRSO after completion of their planned family;
- current data suggest that laparoscopic evaluation of the ovaries, fallopian tubes and peritoneal space at the time of bilateral salpingectomy will both detect some clinically-occult PSC (permitting early treatment) and prevent the development of some FTC;
- the risks associated with this strategy are arguably less than the potential benefits, although this point requires further data;
- this discussion has identified a number of areas in which additional data are clearly needed; and
- a systematic evaluation of this proposal may be warranted, if there is sufficient support from the clinical community and interest from the patients.

If a consensus emerges that BSOR is an interim, short-term management option worthy of serious consideration by women desirous of deferring bilateral oophorectomy, it would be desirable to undertake a formal clinical research protocol. One could register eligible mutation carriers at the time they complete their planned family, and offer standard RRSO to everyone. Those declining RRSO would be offered BSOR. Some women would choose one of the surgical options, although some would likely defer surgical intervention to a later time. The surgical procedure would be stipulated per protocol, and the following outcomes would be obtained:

- proportions electing up-front RRSO vs. BSOR;
- prevalence, characteristics of clinically-occult PSC at the time of BSOR;
- cumulative probability, characteristics of ovarian cancer;
- cumulative probability of breast cancer; and
- psycho-social, behavioral correlates and consequences of this strategy.

A simplified, streamlined study design would make it feasible for an Inter-Group study, thus permitting relatively rapid accrual of the large number of participants required to achieve adequate statistical power. We await the response of care-providers and consumers with interest.

We cannot emphasize enough that the complexities related to a reliable risk/benefit assessment of the BSOR strategy we have described clearly show that there is opportunity for this approach to be seriously flawed. We propose that, pending additional data, BSOR should be considered an investigational procedure of unproven utility, which would be most safely evaluated on the basis of carefully-designed clinical trials. A pilot study of BSOR is currently under consideration by the Gynecologic Oncology Group.

References

1. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - Second edition. J Natl Cancer Inst Monogr. 2008; 2008:3–93.
2. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers. J Natl Cancer Inst. 2009; 101:80–7. [PubMed: 19141781]
3. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers: the PROSE study group. J Clin Oncol. 2005; 23:7804–7810. [PubMed: 16219936]

4. Eisen A, Lubinski J, Gronwald J, et al. Hormone therapy and the risk of breast cancer in *BRCA1* mutation carriers. *J Natl Cancer Inst.* 2008; 100:1361–1367. [PubMed: 18812548]
5. Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. *Am J Epidemiol.* 2007; 166:894–901. [PubMed: 17656616]
6. Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers: Results from the International *BRCA1/2* Carrier Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:601–610. [PubMed: 19190154]
7. Narod 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; 357:1467–1470. [PubMed: 11377596]
8. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations: a case-control study. *Lancet Oncol.* 2007; 8:26–34. [PubMed: 17196508]
9. Kelekci S, Yilmaz B, Yasar L, Savan K, Sonmez S, Kart C. Ovarian reserve and ovarian stromal blood supply after tubal ligation by the Pomeroy technique: comparison with controls. *Gynecol Endocrinol.* 2005; 20:279–83. [PubMed: 16019374]
10. Kutlar I, Ozkur A, Balat O, Ugur MG, Genco Y, Aksoy F. Effects of three different sterilization methods on utero-ovarian Doppler blood flow and serum levels of ovarian hormones. *Eur J Obstet Gynecol Reprod Biol.* 2005; 122:112–7. [PubMed: 16154047]
11. Kelekci S, Yilmaz B, Yakut Y, Yasar L, Savan K, Sonmez S. Hormonal and ovarian stromal blood supply changes after laparoscopic tubal sterilization: a prospective controlled study. *Contraception.* 2006; 73:279–83. [PubMed: 16472571]
12. Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev.* 2008; 17:139–46. [PubMed: 18287871]
13. Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the *GSTM1*, *GSTT1*, and *NAT2* genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:2436–44. [PubMed: 18768514]
14. Powell CB, Kenley E, Chen L-M, et al. Risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol.* 2005; 23:127–132. [PubMed: 15625367]
15. Carlson JW, Miron A, Jarboe EA, et al. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. *J Clin Oncol.* 2008; 26:4160–4165. [PubMed: 18757330]
16. Agoff SN, Mendelin JE, Grieco VS, Garcia RL. Unexpected gynecologic neoplasms in patients with proven or suspected *BRCA-1* or *-2* mutations: implications for gross examination, cytology, and clinical follow-up. *Am J Surg Pathol.* 2002; 26:171–8. [PubMed: 11812938]
17. Carcangiu ML, Peissel B, Pasini B, Spatti G, Radice P, Manoukian S. Incidental carcinomas in prophylactic specimens in *BRCA1* and *BRCA2* germ-line mutation carriers, with emphasis on fallopian tube lesions: report of 6 cases and review of the literature. *Am J Surg Pathol.* 2006; 30:1222–1230. [PubMed: 17001151]
18. Colgan TJ, Murphy J, Cole DEC, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with *BRCA* germline mutation status. *Am J Surg Pathol.* 2001; 25:1283–1289. [PubMed: 11688463]
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. *Gynecol Oncol.* 2006; 100:58–64. [PubMed: 16137750]
20. Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley P. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. *Gynecol Oncol.* 2002; 87:52–56. [PubMed: 12468342]
21. Lu KH, Garber JE, Cramer DW, et al. Occult ovarian tumors in women with *BRCA1* or *BRCA2* mutations undergoing prophylactic oophorectomy. *J Clin Oncol.* 2000; 18:2728–2732. [PubMed: 10894872]

22. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol.* 2006; 30:230–6. [PubMed: 16434898]
23. Folkins AK, Jarboe EA, Saleemuddin A, et al. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. *Gynecol Oncol.* 2008; 109:168–73. [PubMed: 18342932]
24. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. *Am J Obstet Gynecol.* 2004; 191:718–32. [PubMed: 15467531]
25. Piek JM, Verheijen RH, Menko FH, et al. Expression of differentiation and proliferation related proteins in epithelium of prophylactically removed ovaries from women with a hereditary female adnexal cancer predisposition. *Histopathology.* 2003; 43:26–32. [PubMed: 12823709]
26. Piek JMJ, Diest PJv, Zweemer RP, et al. Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. *J Pathol.* 2001; 195:451–456. [PubMed: 11745677]
27. Drapkin R, Crum CP, Hecht JL. Expression of candidate tumor markers in ovarian carcinoma and benign ovary: evidence for a link between epithelial phenotype and neoplasia. *Hum Pathol.* 2004; 35:1014–21. [PubMed: 15297969]
28. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol.* 2007; 31:161–9. [PubMed: 17255760]
29. Folkins AK, Jarboe EA, Roh MH, Crum CP. Precursors to pelvic serous carcinoma and their clinical implications. *Gynecol Oncol.* 2009; 113:391–6. [PubMed: 19237187]
30. Olivier RI, van Beurden M, Lubsen MAC, et al. Clinical outcome of prophylactic oophorectomy in *BRCA1/BRCA2* mutation carriers and events during follow-up. *Br J Cancer.* 2004; 90:1492–7. [PubMed: 15083174]
31. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in *BRCA*-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol.* 2007; 25:3985–3990. [PubMed: 17761984]
32. Hermesen BBJ, Diest PJv, Berkhof J, et al. Low prevalence of (pre) malignant lesions in the breast and high prevalence in the ovary and Fallopian tube in women at hereditary high risk of breast and ovarian cancer. *Int J Cancer.* 2006; 119:1412–1418. [PubMed: 16615107]
33. Laki F, Kirova YM, This P, et al. Prophylactic salpingo-oophorectomy in a series of 89 women carrying a *BRCA1* or a *BRCA2* mutation. *Cancer.* 2007; 109:1784–1790. [PubMed: 17351952]
34. Lamb JD, Garcia RL, Goff BA, Paley PJ, Swisher EM. Predictors of occult neoplasia in women undergoing risk-reducing salpingo-oophorectomy. *Am J Obstet Gynecol.* 2006; 194:1702–1709. [PubMed: 16731090]
35. Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:594–604. [PubMed: 18349277]
36. Beattie MS, Crawford B, Lin F, Vittinghoff E, Ziegler J. Uptake, time course, and predictors of risk-reducing surgeries in *BRCA* carriers. *Genet Test.* 2009; 13:1–6.
37. Kram V, Peretz T, Sagi M. Acceptance of preventive surgeries by Israeli women who had undergone *BRCA* testing. *Familial Cancer.* 2006; 5:327–335. [PubMed: 16724248]
38. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, et al. International variation in rates of uptake of preventive options in *BRCA1* and *BRCA2* mutation carriers. *Int J Cancer.* 2008; 122:2017–2022. [PubMed: 18196574]
39. Schmeler KM, Sun CC, Bodurka DC, et al. Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with *BRCA* mutations. *Obstet Gynecol.* 2006; 108:515–520. [PubMed: 16946209]
40. Risch HA, McLaughlin JR, Cole DEC, 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. [PubMed: 11179017]

41. Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol*. 2007; 25:1329–33. [PubMed: 17416853]
42. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struwing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of *BRCA1* mutation carriers. *J Clin Oncol*. 2005; 23:8629–8635. [PubMed: 16314625]
43. Eisen A, Lubinski J, Klijn J, 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]
44. Peterson HB, Jeng G, Folger SG, et al. The risk of menstrual abnormalities after tubal sterilization. *N Engl J Med*. 2000; 343:1681–1687. [PubMed: 11106717]