Curr Oncol, Vol. 20, pp. 145-147; doi: http://dx.doi.org/10.3747/co.20.1471

COMMENTARY

Salpingectomy to prevent ovarian cancer

A Countercurrents Series[a] *with S.A. Narod* MD

When Pamela Fayerman received a grant of $20,000 from the Canadian Institutes of Health Research in 2012 to pursue health journalism research, she was able to travel throughout Canada to interview experts about a possible new way to prevent ovarian cancer. She was on a fact-finding mission about the wisdom of removing the fallopian tubes of young women to prevent ovarian cancer later on. This surgical procedure has been championed by many, but perhaps most vocally by B.C. pathologist David Huntsman and gynecology colleagues from the west coast.

There were few facts found, but plenty of opinions. The rationale behind the scheme is that most "ovarian" cancers arise in the fimbriated part of the fallopian tube and that the tube can be removed *in toto* while leaving the adjacent ovary intact. Huntsman proposes that, after the operation, the cancer risk might be reduced by as much as 70%. He speculates that if the procedure were to be accepted by patients and to be adopted by doctors, then the potential is there to make a serious dent in the number of new ovarian cancers in British Columbia—perhaps cutting the incidence by as much as 40%.

Is it possible to make an impact on the burden of ovarian cancer in British Columbia by removing fallopian tubes? Let us assume that the risk reduction is, in fact, 70%. Assume that a woman undergoes the operation at age 35—that is, before entering the adult period of risk. Having the operation would then reduce the lifetime risk from 1.4% to 0.4%, or 1 cancer prevented for each 100 operations performed. Not bad, but not a slam dunk.

How many operations are now being done that would not have been done if it weren't for the OVCARE program in British Columbia is uncertain, but I would postulate fewer than 1000 annually. Net gain? Ten cancers prevented, representing 4% of the annual burden in British Columbia of 263 cancers. It is worthwhile to prevent 4% of ovarian cancers, but this prevention does not constitute a revolution. To reach a 40% reduction, it would be necessary to perform 10,000 salpingectomies per year—every year—in British Columbia in a population of 1 million women. That is, 10,000 salpingectomies equal to 100 of 263 cancers prevented annually.

Also, evidence is needed. That is what evidence-based medicine is all about. Biomarkers are not evidence, nor is patient satisfaction. The number of women who undergo the surgery and the number of women who develop cancer have to be counted. It is theoretically possible to confirm the aforesaid hypothesis in a case–control study, but I estimate that the prevalence of the operation in the population would first have to reach about 4%, or 40,000 operations among 1 million B.C. women, though not necessarily in the same year. When the prevalence hits 4%, it would then be possible to detect a 70% reduction in risk with a case–control study of 500 cases and 500 controls. Such a study is not out of reach, but it might take 20 years or more to reach to that level in British Columbia.

Perhaps a cohort study is better, because, for a case–control study, it is best to do all the operations in one province, but in a cohort study, the operations can be spread across the country. The trick would be to find and track 40,000 women with a salpingectomy but no oophorectomy in all the provinces. The incidence of ovarian cancer is about 20 per 100,000 women per year in adult women in Canada, and so a cohort of 40,000 women followed for 5 years would expect to yield 40 cancers if the procedure is ineffectual. If a 70% reduction were to occur, only 12 cancers would be observed. That observation would be pretty good evidence, but to do the operations and to identify all 40,000 women would take a concerted effort of the gynecology community.

As far as I know it is not possible to identify these women passively by running names through provincial computer files, because it is not possible

[a] This guest editorial is part of a series, titled Countercurrents, by Dr. Steven A. Narod. Series Editor: William D. Foulkes MB BS PhD, McGill University, Montreal, QC.

to distinguish a salpingectomy from a salpingo-oophorectomy, or a hysterectomy from a hysterectomy–salpingectomy. In the proposed study, the observed rate would be compared with the population rate to generate a standardized incidence ratio, and so a control group would not be necessary. A multiprovince observational cohort study seems the way to go. Perhaps 40,000 women with salpingectomies is a feasible target ... or perhaps it is too much to expect.

What about high-risk women? Other than *BRCA1* and *BRCA2* mutation, no good risk factors for ovarian cancer have been identified. Oral contraceptives, childbearing, and breastfeeding are all protective, but cannot be used to classify high-risk patients[1]. Hormone replacement therapy (HRT) is too weak a risk factor[2], and once the *BRCA* carriers are removed, a family history of ovarian cancer is no longer very important[3]. Many promises have been made about single nucleotide polymorphism profiling and personalized risk, but no practical test has emerged, and the buzz has all but fizzled out now that whole-exome sequencing is available to double the bet. In a *BRCA1* carrier, the lifetime risk of ovarian cancer is about 40%, and in a *BRCA2* carrier, the lifetime risk is about 20%[4]. Removing the ovaries cuts those risks by about 80% (some women still get peritoneal cancer)[5]. The annual risk of cancer falls from 1% to 0.2% after an oophorectomy[5]. About half the cancers in *BRCA1* carriers occur before the age of menopause (Metcalfe KA, Kim–Sing C, Ghadirian P, *et al.* Recommendations of health care providers for reducing cancer risk among *BRCA1* and *BRCA2* mutation carriers. Submitted), and so it is not prudent to wait until age 50 do the oophorectomy. At Women's College Hospital, we recommend it be done at age 35.

The proposed alternative is to do a salpingectomy first (at age 35) and then to follow with an oophorectomy at age 50, presumably to prevent the acute and chronic symptoms of acute surgical menopause. Many menopausal symptoms can be managed with HRT, and HRT does not seem to increase the risk of breast cancer[6]. If women wish to preserve their ovaries because they are afraid to take HRT, they should be reassured about the alternative.

The two drawbacks to the foregoing approach are that the degree of protection offered by salpingectomy alone (compared with oophorectomy) is not known and that women will forego prevention against breast cancer[7,8]. I think that this approach is reasonable for women who have not had breast cancer and who have had a bilateral preventive mastectomy, but I would not recommend it for a patient with intact breasts—the protection against breast cancer offered by oophorectomy in *BRCA1* and *BRCA2* carriers is far too great to ignore[7,8]. And that protection also persists after menopause[8]. Moreover, evidence is emerging that oophorectomy is associated with a reduction in deaths in breast cancer patients with a *BRCA1* mutation (Huzarski T, Byrski T, Gronwald J, *et al.* Ten year survival in *BRCA1*-negative and *BRCA1*-positive breast cancer patients. Submitted; Valentini A, Lubinski J, Byrski T, *et al.* The impact of pregnancy on breast cancer survival in women who carry a *BRCA1* or *BRCA2* mutation. Submitted). I now recommend oophorectomy to all women with breast cancer and a *BRCA1* mutation soon after diagnosis.

For a woman with a bilateral mastectomy and no prior breast cancer, salpingectomy is not a bad idea, but again, this question is difficult to study. A clinical trial in women who decline oophorectomy has been proposed. I personally think that the situation of randomizing women to a study if they decline the best management is a difficult one ethically. If the trial were not available, would they be equally likely to decline the oophorectomy? I don't believe that the study has to be randomized. The effects of mastectomy on breast cancer and of oophorectomy on breast and ovarian cancer have been studied in *BRCA1* and *BRCA2* carriers using purely observational approaches[5,6–8], and there is no reason that the same approach should not work with salpingectomy. I calculate that, in a cohort of 500 women with a mutation receiving a salpingectomy followed for 10 years, an answer to the question can be expected. If salpingectomy doesn't prevent cancer, 50 cases will occur, and if the surgery is as good as oophorectomy, the cases will be 10 in number.

In conclusion, I think that the proposal for preventing ovarian cancer through salpingectomy is a good one, but that the research agenda needs to be thought through. Different issues arise for women at average risk and for women with *BRCA* mutations; however, in both cases, a prospective cohort study of women who are having the operation is the most promising approach. If women are already having these operations, it would be a missed opportunity not to capture the relevant information for future review. One thing is for sure: If we wait until we have the evidence before we offer the operation (as several of Feyerman's interviewees soberly opine), then we will never have the evidence.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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