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EDITORIAL

Opportunistic salpingectomy: the way forward—response to Steven Narod

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> All truths are easy to understand once they are discovered; the point is to discover them.
> — Galileo Galilei

Although stimulated by more profound issues, Galilei's quote could be applied to today's changing understanding of the origin of ovarian carcinoma and how that knowledge might be used to prevent cancer. Louis Dubeau's courageous essay in 1999[1] stimulated pathologists and others to look beyond the ovarian surface epithelium for precursor lesions and the cells of origin for ovarian carcinomas. Since then, researchers such as Christopher Crum of Harvard have provided strong clinical and pathologic evidence that many high-grade serous carcinomas of the ovary arise in the fallopian tube.

In addition to British Columbia's ovarian cancer prevention program, other contributions to this field have been made by Canadians: Dubeau is a McGill graduate, and Patricia Shaw from the University of Toronto has, with collaborators such as Steven Narod, contributed greatly to the understanding of ovarian cancer precursor lesions and the pathologies associated with *BRCA* germline mutations. Indeed, at the first Canadian National Ovarian Cancer meeting in Ottawa more than 10 years ago, Narod surprised most of the audience by declaring that these cancers arise from the fallopian tube.

In no way do we propose or believe that all high-grade serous carcinomas are derived from the fallopian tubes, because plausible biologic and clinical data suggest that a portion might be derived from both sites[2,3]. However, the clinical and pathology studies strongly favour the fallopian tube as the origin in most cases (more than 70% in our estimation). In addition, because the second and third most common types of ovarian carcinoma—namely, clear cell and endometrioid carcinoma—are derived from endometriosis, the fallopian tube is either a source of, or a conduit for, a preponderance of ovarian carcinomas. In British Columbia, we have taken that information and combined it with a robust extension of our hereditary cancer *BRCA* testing program to create a cancer risk reduction strategy that, if fully implemented, could reduce ovarian cancer risk in the population by up to 40%.

Although the attention of a cancer prevention expert of Narod's stature is welcome, his comments seem to be underpinned by some major misunderstandings of our approach and the estimated impact. Our program is not solely focused on women at high risk; rather, it is population-based. We propose opportunistic removal of the fallopian tube as but one part of a double-barreled strategy that involves salpingectomy at the time of gynecologic surgery, paired with referral of all women having high-grade serous ovarian cancers for *BRCA1* and *BRCA2* genetic testing.

Data from our Cheryl Brown Ovarian Cancer Outcomes Unit in British Columbia revealed that almost 20% of women diagnosed with ovarian cancer in the province had undergone a hysterectomy for benign disease in the past. In America, 30% of women will undergo hysterectomy in their lifetime, and in two thirds of them, the ovaries, together with the distal end of the fallopian tube will be left *in situ*. In Canada, the numbers are less, but not by much. Rather than torturing the "number needed to treat" concept, we believe that an opportunity is available to substantially reduce the individual risk of approximately 20% of women if the fallopian tubes are removed at the time of the earlier gynecologic procedure. Almost 50,000 women will undergo hysterectomy every year. A similar number will choose tubal ligation. If we can alter the surgical paradigm, we might conservatively lower the number of high-grade serous cancers by 20%–30%.

In British Columbia, more than 20% of women with high-grade serous cancer will carry a mutation in either *BRCA1* or *BRCA2*[4,5]. By offering genetic testing to all women with high-grade serous cancer, we hope to eventually identify most of the women in our province who are at genetic risk. As a global leader in *BRCA*-associated research, Narod can opine

more eloquently than we on the cancer-risk-reduction potential of genetic testing, with optimal pursuit of carrier testing in family members whenever a mutation is found. However, we estimate that offering surgical "prophylactic" (risk-reducing) surgery to these women will contribute a further 15%–20% decrease in disease incidence.

Importantly, our recommended surgery for risk reduction in known *BRCA* mutation carriers is bilateral salpingo-oophorectomy, which is in line with international standards, and not salpingectomy alone as indicated in Narod's article. But like Narod, we believe that this option needs study in a clinical trial. Thus, the total estimated population risk reduction in ovarian cancer by considering salpingectomy in women in the general population or at low risk, *and* by referring all women with high-grade serous cancers for hereditary testing—thus identifying incident cases and family members who can then undergo risk-reducing surgery—is projected to be in the range of 40% (not 70% as mentioned in Narod's article—70% would be the estimated reduction for an individual woman who has undergone salpingectomy).

The two key components required for the success of this prevention program will be the uptake of salpingectomy in the general-risk population and referral for genetic testing to identify the high-risk population so that risk-reducing bilateral salpingo-oophorectomy can be offered.

By all accounts, the uptake of salpingectomy with hysterectomy in our province has been excellent. We are collecting data on potential morbidity (so far, increased risk has not been measurable)[a], and we will be monitoring our provincial cohort closely. Fortunately, it is possible to use the Canadian Institute for Health Information national databases to differentiate between the procedures performed: for example, salpingectomy versus tubal ligation for permanent sterilization, and hysterectomy with salpingectomy versus hysterectomy with salpingo-oophorectomy. We have already been able to show an impressive increase in salpingectomy in the province of British Columbia.

We strongly agree with Dr. Narod that

- this cancer risk-reduction strategy is low-risk, and yet it is not supported by level 1 evidence.
- conservative estimates of the risk–benefit ratio and the length of time required to see benefit suggest that the most practical and ethical way forward is to proceed with the proviso that this strategy is described as having "potential" rather than "proven" benefit.
- given that we have proceeded without level 1 evidence, it is absolutely imperative that the impact be studied in a robust fashion.

This undertaking will require long-term effort. Because most tubal surgery for contraception and hysterectomies takes place in younger premenopausal women, we project that it might take up to 20 years to potentially realize a change in the incidence of ovarian cancer or a change in the distribution of histologic subtypes of ovarian cancer in British Columbia. However, that long view should not deter us from the endeavor. Also, by combining our efforts with other population-based programs, we can increase the power to detect changes in cancer risk earlier. We would welcome other jurisdictions coming on board with this program.

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest relevant to the present topic to disclose.

REFERENCES

1. Dubeau L. The cell of origin of ovarian epithelial tumors and the ovarian surface epithelium dogma: does the emperor have no clothes? *Gynecol Oncol* 1999;72:437–42.
2. Auersperg N. The origin of ovarian cancers—hypotheses and controversies. *Front Biosci (Schol Ed)* 2013;5:709–19.
3. Flesken–Nikitin A, Hwang CI, Cheng CY, Michurina TV, Enikolopov G, Nikitin AY. Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche. *Nature* 2013;495:1–5.
4. Schrader KA, Hurlburt J, Kalloger SE, *et al*. Germline mutations in *BRCA1* and *BRCA2* in ovarian cancer: utility of a histology-based referral strategy. *Obstet Gynecol* 2012;120:235–40.
5. Alsop K, Fereday S, Meldrum C, *et al*. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation–positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012;30:2654–63.

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[a] McAlpine JN. Personal communication (from review of the Canadian Institute for Health Information data on British Columbia's gynecologic surgery practice and procedure-associated events, 2008–2011). Publication planned for 2013.