



# Preventing ovarian cancer by salpingectomy

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This issue of *Current Oncology* contains four articles<sup>1-4</sup> on the subject of the role of bilateral salpingectomy in preventing high-grade serous ovarian carcinoma. To the uninitiated, that idea may seem counterintuitive. Surely, to prevent ovarian carcinoma, you have to remove the ovaries, and not the adjacent fallopian tubes? Well, maybe not. The four articles, in their various ways, make plain that the focus of prevention in high-grade serous ovarian carcinoma has shifted from the ovary to the fallopian tube. This shift is the result of work in *BRCA1* and *BRCA2* mutation carriers, who are at greatly elevated risk for high-grade serous carcinoma arising in the ovary, fallopian tube, or peritoneum.

## THE ORIGINS OF HIGH-GRADE OVARIAN CARCINOMA

In 2001, Canadian<sup>5</sup> and Dutch<sup>6</sup> gynecology–oncology pathologists demonstrated the occurrence of significant dysplasia in the distal fallopian tube epithelium of *BRCA1/2* carriers undergoing preventive bilateral salpingo-oophorectomy (BSO). That work was later refined and extended by U.S. investigators and others, who particularly focused on the fimbriae as a candidate for the origin of serous ovarian carcinoma in these women<sup>7-9</sup>. Further studies have confirmed that *in situ* serous tubal carcinomas are present in between 60% and 100% of preventive oophorectomy specimens from women with *BRCA1* or *BRCA2* mutations, but also that such disease is seen in the excised fallopian tubes of 30%–60% of women with high-grade serous carcinomas who do not carry *BRCA1/2* mutations<sup>10</sup>. These lesions are associated with—and probably preceded by—subcellular abnormalities, leading in many cases to overexpression of *TP53* in otherwise normal-looking epithelium. Those observations led to the idea that perhaps “ovarian carcinoma” is in some cases a misnomer and that the real culprit is a tubal malignancy. If true, this hypothesis would have important implications for the prevention of ovarian carcinoma

in *BRCA1/2* carriers. Moreover, if high-grade serous ovarian carcinoma arises from the fallopian tube in women not obviously at elevated risk, then salpingectomy might be of relevance to the entire post-reproductive female population.

## THE NUMBERS GAME

The trigger for the suite of articles found in this issue was a Countercurrents piece from Steven Narod. The point of the Countercurrents series is to be provocative, but at the same time insightful. Thus, Narod<sup>1</sup> is critical of the rush to offer salpingectomies on a wider scale than is currently practiced, not because he thinks that the underlying hypothesis—that the tube is the main source of the problem—is inherently wrong, but because some hard numbers are needed to make informed decisions.

This requirement for data is important, because although ovarian carcinoma is evidently a terrible disease, the risk for this disease by age 50 is about 1 in 335, rising to about 1 in 65 between the ages of 50 and 70. The B.C. group lead by Dianne Miller and David Huntsman suggest that bilateral salpingectomy reduces the risk of ovarian carcinoma by 40% (<http://blogs.vancouver.com/2013/02/22/fallopian-tubes-breeding-beds-for-babies-and-ovarian-cancer-should-they-be-removed-for-cancer-prevention-bc-says-yes/>). Given the incidence of the disease, Narod argues that about 100 bilateral salpingectomies have to be performed to prevent 1 case of ovarian carcinoma, or 10,000 salpingectomies annually in British Columbia, to achieve the 40% reduction. That volume translates to 73,500 salpingectomies annually in all of Canada.

Now, assume that all hysterectomies are carried out in premenopausal women. In 2008, about 47,000 hysterectomies were performed in Canada. So, if the hypothesis is correct and if the numbers are accurate, then large numbers of women who do not otherwise “need” a hysterectomy will have to undergo bilateral salpingectomy to achieve a 40%

reduction in disease incidence. That many salpingectomies is more than the “opportunistic removal” put forward by Miller and colleagues<sup>2</sup> in their response to Narod’s Countercurrents piece, in which they argue that a more conservative 20%–30% reduction in incidence might be achieved by removing the distal tube at time of an otherwise routine, but medically indicated, premenopausal hysterectomy. Their contention seems eminently sensible, and it would be hard to see why there would be objections to that approach unless a significant risk of increased intra- or postoperative complications were to be attached (which seems unlikely)<sup>11</sup>.

Is, then, the new approach being adopted in British Columbia and across Canada?

In this issue of *Current Oncology*, Sandoval *et al.*<sup>3</sup> report interesting statistics on this very subject. They included in their analysis hospitalizations from 2006 to 2011 for Canadian women 15 years of age and older who underwent a hysterectomy in an acute-care hospital or day surgery setting. They found that bilateral salpingectomies performed at the same time as hysterectomy increased to 11% from 1% over the duration of the study. Not surprisingly, the highest rates in 2011 were seen in British Columbia: 38.5%. Will that increase be enough to reveal a comparative difference in ovarian cancer incidence rates across Canadian provinces? If the hypothesized 40% reduction is correct, then a comparison will be sufficient to show incidence and possibly mortality differences within a few decades.

## TO TRIAL OR NOT TO TRIAL?

In 2011, at Centre Oscar Lambret in Lille, Eric Leblanc and colleagues started a national trial (search for NCT01608074 at <http://clinicaltrials.gov>) of *BRCA1/2* mutation carriers more than 35 years of age who have completed childbearing. Bilateral salpingectomy is the primary form of ovarian cancer prevention being offered. The trial has three notable features:

- Women are allowed to enter the trial even if they have had breast cancer.
- Entrants have to be “unprepared” to undergo bilateral oophorectomy (although it is not clear what “unprepared” means in this context).
- The study is not due to be completed until 2019.

Is this study premature, or is it overdue? Are there alternatives to a trial?

Narod argues that a large observational study in *BRCA1/2* carriers might answer the question—but that it will still take 10 years to reach an answer. An international registry of such cases is needed. Perhaps Canada can take a lead here and move toward the answer more quickly.

## EXPERT OPINION

In the absence of hard data, there is always expert opinion to call upon, and the current issue also features an opinion piece from U.S. authors. Herzog and Dinkelspiel<sup>4</sup> from Columbia University are generally supportive of a shift to initial bilateral salpingectomy in *BRCA1/2* carriers, but rightly argue that data are needed before such an important change in standard practice is to be seriously considered. They also advocate for population-based studies to establish the generalizability of findings in *BRCA1/2* carriers to the entire female population—a substantial undertaking. At least it seems that bilateral salpingectomy is as safe as BSO in low-risk women<sup>11</sup>.

A group of ovarian cancer experts, meeting at the 2011 Helene Harris Memorial Trust 12th International Forum on Ovarian Cancer, decided that it was premature to recommend that only the fallopian tube be removed in high-risk women, such as *BRCA1/2* mutation carriers<sup>12</sup>. But the B.C. group are, of course, not arguing that the ovaries be left in place until menopause. They are advocating a two-stage procedure, separated by 10 years, which, according to their Markov Monte Carlo simulation model, will give the best outcome (when compared with bilateral salpingectomy alone at age 40 years and early BSO at age 40 years), adjusted for quality-of-life measures<sup>13</sup>.

All such models are highly dependent on the variables entered and how they are compared. In his Countercurrents article, Narod argues that oophorectomy offers highly significant breast cancer risk reduction to *BRCA1/2* mutation carriers who have not had a bilateral preventive mastectomy, and so interpretation of the results depends to a certain extent the value placed on each of the variables. That is the limitation of expert opinion—and everyone is entitled to an opinion.

## TUBE OPPORTUNITIES

Interestingly, tubal ligation seems to reduce the risk for ovarian carcinoma<sup>14</sup>, but given that this procedure usually leaves the fimbriae intact, it is difficult to see how the procedure prevents ovarian carcinoma if the origin is truly in the fimbriae. It has been argued that the ovarian cancer risk reduction is achieved by altering ovarian function or by providing a barrier (the ligation) to ascending cancer cells or carcinogens<sup>15</sup>. Whatever the mechanism, salpingectomy might presumably be a viable contraceptive option for women who currently undergo tubal ligation for that purpose, with the added benefit of preventing at least some cases of ovarian carcinoma.

In a recent twist, van Diest’s group<sup>16</sup> reported disseminated intra-abdominal high-grade serous

carcinoma after a serous tubal *in situ* carcinoma arose in the fallopian tube of a *BRCA1* carrier. Perhaps intraluminal shedding is an under-recognized metastatic route for these very early malignancies. A recent study in Montreal attempted to use a symptom score to identify early-stage ovarian carcinomas in postmenopausal women. The study was only partially successful in that regard, but 7 of 9 high-grade serous cancers were found to have originated in the fallopian tube<sup>17</sup>, further advancing the cause of those who feel that investigators should turn to the tube for answers. The *BRCA1/2* status of the studied women was not generally available, and so the question of how many “non-Mendelian” high-grade ovarian carcinomas actually arise in the fallopian tube remains a critical unanswered question. Doubters remain unconvinced<sup>18</sup>, and they have reason for skepticism.

## OTHER ORIGINS

Early work from Bell and Scully<sup>19</sup> demonstrated that some high-grade serous carcinomas do arise from the surface of the ovary. Murine models also support such a view<sup>20,21</sup>, although other models suggest a tubal origin<sup>22</sup>. Because the rate of peritoneal cancer in *BRCA1/2* carriers who have undergone BSO is about 0.2% annually<sup>23</sup>, it is fairly clear that other peritoneal tissues are vulnerable to loss of *BRCA1/2* functions. An early opinion<sup>24</sup> suggested that these extra-ovarian yet Müllerian origins for so-called ovarian cancer are actually very common (the secondary Müllerian system can be widely distributed within the peritoneum), but an important role for this system does not fit with a tubal origin for these cancers. A modification of that view, incorporating an additional tubal component, has now been advanced<sup>25</sup>. Other hypotheses have been proposed, most notably Auersperg’s attempt to unify an ovarian surface epithelial origin with a tubal origin<sup>26</sup>. Instead of seeing the two structures as distinct (which they appear to be under the light microscope), she has argued that there is no real embryologic boundary between the fimbriae and the ovarian surface epithelium. Perhaps the distribution of expression of the housekeeping gene *PAX8* holds the key<sup>27</sup>; especially given that *PAX8* is expressed in inclusion cysts within the ovary and that some of the epithelial linings of those cysts may originate in the fimbriae.

## EARLY DIAGNOSIS OR PREVENTION?

Early diagnosis of ovarian cancer by symptomatology, serology, or sound waves has proved to be difficult. Nevertheless, some researchers have focused their energies on using modern molecular means to detect these cancers early. Even the humble Pap smear has been “genomified.” Early data suggest that genomic Pap smears can detect ovarian carcinoma in nearly 50% of affected women<sup>28</sup>, an observation

that is all the more likely to be repeatable in a larger study if the origin of these tumours really is in the fallopian tube, especially given that 100% of endometrial cancers were detected using the same methods.

## CONCLUSIONS

The idea that the fallopian tube, and not the ovary itself, is the site of origin of most so-called ovarian carcinomas has gathered momentum over the last several years and has now reached a point at which clinicians and scientists are prepared to take action. The question is not whether clinical exploration of this conceptual change should proceed, but how to proceed. I do not believe that a trial is a feasible option, despite good intentions. But a prospective observational study, if conducted nationally (or, preferably, internationally), could answer the key questions discussed in the suite of articles presented here. I hope that the authors will start to plan such studies—in *BRCA1/2* carriers and in the general population.

## CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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