Published OnlineFirst March 23, 2015; DOI: 10.1158/1940-6207.CAPR-15-0072

Commentary

Cancer Prevention Research

The Fallopian Tube: From Back Stage to Center Stage

Mark H. Greene and Phuong L. Mai

Abstract

The recognition that a significant fraction of what historically has been classified as ovarian cancer is, in fact, a malignancy that arises in the fallopian tube mucosa comprises a paradigm shift in our understanding of these neoplasms. New etiologic and management opportunities have been created by this insight, both for women at increased genetic risk of ovarian cancer by virtue of being *BRCA1/2* mutation carriers and, perhaps, for women in the general population as well. *Cancer Prev Res; 8(5); 339–41. ©2015 AACR.*

See related article by Daly et al., p. 342

When each of us began our medical training, and we represent two different generations of physicians, the fallopian tube was a neglected organ, barely mentioned in either the basic science or clinical curriculum. In the context of serous carcinoma of the pelvis, the fallopian tube was literally and figuratively buried in the large abdominal mass that was universally assumed to represent the classical presentation of carcinoma arising in the ovary. Over the years, the notion that the ovarian cancer cell of origin resided in the ovarian surface epithelium (OSE) was challenged by the absence of a clearly defined precursor lesion in either the ovary or the OSE. Furthermore, the occurrence of an intraperitoneal malignancy that looked for all the world like ovarian cancer—designated primary peritoneal carcinoma—in high-risk women who had undergone preventive removal of their ovaries (1) may, in retrospect, have been another inconsistency in the OSE hypothesis, given that it was not routine to remove the fallopian tubes at the time of "prophylactic" oophorectomy when this risk-reducing strategy was conceived (2).

When the *BRCA1* and *BRCA2* genes were identified in 1994 and 1995, respectively, efforts began to more clearly define the associated phenotype in these two syndromes, which were initially viewed as breast/ovarian cancer susceptibility disorders, and fallopian tube cancer was among the additional malignancies that was implicated, at first anecdotally (3–7), and ultimately quantitatively (8, 9). Piek and colleagues provided some of the most convincing histologic and molecular evidence that solidified the conviction that fallopian tube carcinoma was an important constituent of the *BRCA*-associated cancer phenotype (10).

These observations led the investigators who were then developing the National Ovarian Cancer Prevention and Early Detection Study (GOG-0199) to propose that the term "prophylactic oophorectomy" be replaced by the term "risk-reducing salpingo-oophorectomy," (RRSO) to more emphatically convey to both clinicians and patients (i) the growing recognition that the fallopian tube must be removed as an integral part of preventive surgery in women at increased genetic risk of ovarian cancer, and (ii) the fact that a small proportion of women who had undergone surgery to ablate their ovarian cancer risk nonetheless were at residual risk of developing an ovarian cancer–like illness, i.e., primary peritoneal carcinoma (11). This term has since been widely adopted.

From an historical perspective, it may be worth recalling that, when GOG-0199 was being developed 15 years ago, the preventive removal of the ovaries (and tubes) of women at high genetic risk in an effort to mitigate their very high risk of ovarian cancer was being investigated at a limited number of tertiary referral centers in the United States and Europe, but this strategy was viewed with skepticism if not outright alarm in the general medical community, which considered the removal of "healthy ovaries" out of fear regarding what was then a poorly understood genetic disorder as being close to medical heresy. It was not uncommon, at that time, for women from multiple-case breast/ovarian cancer families to have difficulty finding a surgeon who was willing to preventively remove the ovaries and tubes. When GOG-0199 was opened at 150 study sites across the United States and Australia in 2002, with its endorsement of RRSO as a legitimate scientific question warranting research evaluation, the availability of this risk-reduction strategy (removal of both the ovaries and fallopian tubes) began to increase in both the academic and community practice settings. In parallel, the importance of serial sectioning of RRSO-related ovarian and fallopian tube surgical specimens emerged (12–15), as it became clear that small (even microscopic) but clinically important cancers required a special effort for their detection. Not surprisingly, the more extensive the histopathology examination, the more clinically occult neoplasms were detected (16, 17).

In the current issue, Daly and colleagues (18) have provided a comprehensive and timely review of the issues related to RRSO in general, and bilateral salpingectomy (BS) in particular, by compiling recent developments related to the epidemiology and biology of ovarian and fallopian tube cancer, evidence related to the clinical effectiveness of RRSO (including its risks and benefits), and an update related to a new candidate for ovarian

Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland.

Corresponding Author: Mark H. Greene, Clinical Genetics Branch, National Cancer Institute, NIH, 9609 Medical Center Drive, Room 6E-454, Rockville, MD 20850-9772. Phone: 240-276-7242; Fax: 240-276-7836; E-mail: greenem@mail.nih.gov

doi: 10.1158/1940-6207.CAPR-15-0072

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cancer risk reduction, BS with ovarian retention (BSOR). This latter strategy has its origins in the recognition that a substantial fraction of what has historically been classified as "ovarian cancer" actually originates in the fallopian tube. They provide an excellent summary of the literature related to this etiologic paradigm shift, including supportive preclinical data from several mouse models of fallopian tube carcinogenesis.

Despite the proven RRSO benefit relative to both reduced cancer incidence and improved disease-specific and overall survival (19, 20), a significant fraction of premenopausal *BRCA* mutation carriers who have completed child-bearing continue to opt for ineffective ovarian cancer screening rather than risk-reducing surgery. Fears regarding the morbidity associated with premature menopause comprise a major deterrent to electing RRSO. Given our new (albeit incomplete) understanding of the role played by the fallopian tube in ovarian carcinogenesis, it was suggested that—at least theoretically—removal of the fallopian tubes while temporarily retaining the ovaries might represent a viable management option for premenopausal mutation carriers who were not prepared to enter surgical menopause (21). To the extent that "ovarian cancer" is actually fallopian tube cancer, BSOR might eliminate that risk while patients get closer to menopause, and become more willing to have their ovaries removed as well. That report reviewed the pros and cons of this management strategy and concluded that a clinical trial was warranted to assess the acceptability and morbidity of BSOR before it could be recommended for routine clinical practice. Despite that cautionary note, anecdotal reports began to surface that some patients and providers were already exercising this option, and a recent survey conducted by Facing Our Risk of Cancer Empowered (FORCE), the patient advocacy group that represents the interests of women with hereditary breast/ovarian cancer, indicated that there was strong interest in BSOR among high-risk women (22).

Daly and colleagues (18) have summarized the subsequent literature regarding this procedure, including an updated summary of its potential risks and benefits. They, too, recommended performing a clinical trial to further evaluate this strategy. In addition to the benefits they cite, it is worth noting that the BSOR procedure provides an early opportunity to directly inspect, evaluate, and sample (if necessary) the peritoneal cavity while the salpingectomy is being performed. It is likely that an occasional occult malignancy will be detected during that operation, providing a presymptomatic diagnosis for some women. A significant fraction of the clinically occult tumors that are discovered at the time of RRSO are of early stage, and perhaps more amenable to long-term disease control or even cure.

The final noteworthy feature of Daly and colleagues' (18) review is its bringing to the attention of a wider clinical audience the innovative work being done by the obstetrics/gynecology community in British Columbia (BC) regarding the possibility of extending BS beyond high-risk women to women in the general population who are undergoing hysterectomy for benign indications or who are contemplating tubal ligation for permanent sterilization (23). They performed a population-based retrospective cohort of women in BC undergoing BS in conjunction with those two surgical procedures, after deploying an educational initiative aimed at making clinicians aware of the potential cancer prevention opportunity afforded by this approach. They report dramatic increases in the proportion of women undergoing BS, in addition to, or instead of, their planned surgical procedure, with minimal additional surgical time, no excess risk of rehospitalization or blood transfusion, and a sharp increase in the proportion of hysterectomies being performed laparoscopically. They concluded that this approach was both feasible and safe.

These investigators have also performed a cost–benefit analysis, which suggests that salpingectomy added to hysterectomy or substituted for tubal ligation were cost-effective alternatives to standard therapy. They estimated that use of BS in this fashion would reduce the risk of ovarian cancer by 38% and 29% when used with hysterectomy or instead of tubal ligation, respectively (24). They conclude that "opportunistic salpingectomy should be considered for all women undergoing these surgical procedures."

As logical and appealing as this strategy might be, its utility cannot be generalized to the management of women at increased genetic risk of ovarian cancer. A cooperative group-based trial targeting *BRCA1/2* mutation carriers is being actively planned, with the goals of determining the acceptability of BSOR among patients and their providers, assessing the impact of salpingectomy on ovarian function, and evaluating the impact of salpingectomy on quality of life. It remains our view that BSOR is an investigational procedure that should not be routinely implemented in high-risk women until its risks and benefits are more clearly defined. Recognizing the importance of the fallopian tube in ovarian carcinogenesis has provided us with invaluable etiologic and clinical leads that promise to refine and improve both the prevention and management of ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.H. Greene
Writing, review, and/or revision of the manuscript: M.H. Greene, P.L. Mai
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.H. Greene

Grant Support

This study was supported by the Intramural Research Program, National Cancer Institute, NIH.

Received February 17, 2015; accepted March 11, 2015; published OnlineFirst March 23, 2015.

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Published OnlineFirst March 23, 2015; DOI: 10.1158/1940-6207.CAPR-15-0072

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Cancer Prev Res 2015;8:339-341. Published OnlineFirst March 23, 2015.