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COMMENTARY

Fallopian tube removal: "STIC-ing" it to ovarian cancer: what is the utility of prophylactic tubal removal?

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BACKGROUND

Ovarian cancer and associated fallopian tube and primary peritoneal cancers fall under a continuum of malignancies arising from the mullerian tract. They are collectively called "ovarian cancers," and they affect approximately 22,400 women in the United States, causing more than 14,000 deaths annually[1]. Clinically, these cancers are generally treated similarly, and most treatment and clinical trial protocols include patients with any of the entities. Importantly, although improved 5-year survivals have been observed over the years, the cure rate for patients who present with advanced ovarian cancer has not appreciably increased, underscoring the importance of primary prevention for this disease.

Deciphering the pathogenesis of ovarian cancer has been challenging, because this cancer appears to be a spectrum of distinct molecular diseases. Table I details the two ovarian cancer types that have recently been characterized[2,3]. These types emerged from numerous investigations, but even this classification system is likely an oversimplification of complex causes and diverse transformative genetic changes requisite for ovarian tumorigenesis.

Serous ovarian cancers represent the most common of the epithelial histologic subtypes. These tumours have been postulated to arise, in significant proportion, from fallopian tube epithelium. They reportedly form a continuum, beginning initially with *p53* mutational signatures, progressing to serous tubal intraepithelial carcinomas (STICs) that are then followed by invasion and spread to the ovarian surface, finally reaching other portions of the peritoneal cavity[4]. The first associations between the fallopian tube and these cancers were confirmed in patients with known *BRCA* mutations who were undergoing risk-reduction surgery. In one series, 6% of patients were found to have occult malignancies, most of which were associated with either an invasive or pre-invasive lesion in the distal fallopian tube[5].

The exact percentage of ovarian tumours arising from the tube is unknown. Some estimates set the association at up to half of these tumours, but recent reports have estimated a much higher proportion. Przybycin *et al.* determined the frequency of STIC in 114 non-uterine gynecologic cancers and determined that STIC was confirmed in 59% of the high-grade serous tumours, with 92% of the lesions found in the fimbriated portion of the tube and the remaining 8% in the ampullary region[6]. Furthermore, these investigators reported that when high-grade serous carcinomas conventionally classified as ovarian, peritoneal, and tubal in origin were re-classified using a supplemental STIC criterion to define a case as tubal in origin, the original distribution of 70%, 17%, and 13% was modified to 28%, 8%, and 64% respectively[6].

Gao and colleagues looked at 116 consecutive cases of STIC and found that 92% were associated with high-grade serous tumours[7]. Tang *et al.* found a lower incidence of 19% STIC in 32 high-grade serous tumours[8]. Many other reports have shown intermediate incidences of STIC precursors associated with high-grade serous tumours.

MODELLING A BENEFIT OF TUBAL REMOVAL

The importance of identifying the true incidence of the putative precursor tumours is important in trying to formulate effective screening and prevention programs. As can be seen from the foregoing studies, the range of STIC precursors varies widely: from nearly 20% to 90% is reported and likely depends on patient selection and the protocol used for the pathologic interrogation of the tubes. If 60%–70% of epithelial tumours are assumed to be of high-grade serous histology, and if the true incidence of STIC precursors is as high as 50%–60%, then more than 9000 cases of ovarian cancer would be prevented with bilateral tubal removal. Even if the most conservative numbers were to be applied, then more than 3000 cases would be projected to be prevented. This magnitude

TABLE I Characterization of ovarian cancer

Characteristic	*Ovarian cancer*	
	Type I	*Type II*
Histology	Low-grade serous Clear cell Low grade endometrioid Mucinous Transitional Borderline	High-grade serous High-grade endometrioid Undifferentiated
Common genetic defects	*ARID1A* *BRAF* B-Catenin *KRAS* *PTEN* *MAPK* *MEK*	*p53* *BRCA* (mutation or promoter methylation) *AKT* *NOTCH3* *PAX2* *PAX8* *PIK3CA* *WT1*
Proportion of cancers (%)	20–25	75–80
Primary tissue of origin	Ovarian surface epithelium	Fallopian tube
Pathway to cancer	Cortical inclusion cysts or tuboperitoneal nest transformations or endometriosis	*p53* Mutation in distal fallopian tube to STIC to invasive carcinoma
Clinical behavior	Slower growing Indolent to aggressive	Rapidly growing Aggressive

STIC = serous tubal intraepithelial carcinoma.

of effect would certainly be sizable, considering the impact of past preventive interventions.

If removal of the tubes is considered at benign hysterectomy (historically performed in up to 30% of women in the United States, with half having their tubes and ovaries conserved at the time of removal), then a large number of ovarian cases would again be prevented[9]. Alternatively, if tubal resection instead of bilateral tubal ligation were to be performed, then the effect would again be substantial in terms of estimated risk reduction.

SHOULD BILATERAL SALPINGECTOMY WITH OVARIAN RETENTION BE THE NEW STANDARD FOR OVARIAN CANCER RISK REDUCTION?

Certainly the case can be made for bilateral salpingectomy with ovarian retention (BSOR), considering the substantial reduction in projected tumour incidence. Greene and colleagues proposed that BSOR be performed for patients with *BRCA* mutations, because that intervention likely reduces the cancer incidence, but does not confer the negative consequences of oophorectomy, especially in premenopausal patients[10]. Kwon *et al.* reported improved quality-adjusted life expectancy with salpingectomy followed by delayed oophorectomy for risk reduction in patients with *BRCA* mutations. The procedure also showed favorable cost effectiveness, making offering it a reasonable alternative to prophylactic bilateral salpingo-oophorectomy in patients who elect not to undergo bilateral salpingo-oophorectomy[11]. The criteria could certainly be widened beyond just *BRCA* patients to the general population, but the potential negative effects would have to be considered. Table II enumerates the relative risks and benefits of applying a BSOR strategy. Clearly the most critical factor is a formal cost-effectiveness analysis.

TABLE II Relative risks and benefits of a strategy of bilateral salpingectomy with ovarian retention (BSOR)

Factor	*BSOR strategy*	
	Advantage	*Disadvantage*
Ovarian cancer incidence	Substantial decrease likely	Will not prevent all cases Unclear as to true risk reduction
Consequences of premenopausal oophorectomy[a]	Largely avoids	None unless blood supply to ovary is surgically compromised
Psychological impact	Less stressful than BSO	Still limits fertility
Complications	Low	Has some surgical and perioperative complications
Surgical logistics	Easily performed by scope with modern energy devices	Oophorectomy timing unclear
Financial	None, unless proven to prevent cancers	Cost of procedure and indirect costs

[a] Shorter life expectancy, cardiovascular disease, dementia, parkinsonism, osteoporosis, depression, anxiety[12,13].
BSO = bilateral salpingo-oophorectomy.

CRITICAL NEXT STEPS

The concept of endorsing BSOR is seemingly easy from a theoretical perspective. The problem with BSOR advocacy is multifaceted, however. Myriad questions require clarification before widespread adoption of BSOR.

Defining Patient Population

Certainly individuals with *BRCA* mutations (in whom the incidence of ovarian cancer is so high) seem to be a reasonable place to start. The ideal patients would be those who are motivated to avoid the all-cause morbidity and mortality of premenopausal castration. The second group would be patients considering tubal ligation. It has been unclear if other factors reported with tubal ligations are protective in ovarian cancer reduction. Widening the patient population further to women undergoing hysterectomies or other surgeries would require more data. A current trial is recruiting participants undergoing hysterectomy for benign disease for randomization to salpingectomy or to ovarian and tubal conservation, but long-term outcomes data will take years to mature (search for NCT01628432 at http://clinicaltrials.gov/).

Obtaining Metrics

The impact of BSOR has to be translated from theoretical modelling to actual measurable risk reduction. A registry or interventional prospective trial would be ideal. Extending from such studies would be economic impact analyses that would define how widespread BSOR should best penetrate the general population.

Defining Protective Effect

Clearly, as noted from the narrative so far, the degree of protection in large part depends on the fidelity of the linkage between STIC and high-grade serous tumours. Not all STICs result in invasive cancers, and not all serous tumours have a tubal origin. Better studies using novel methods to determine *p53* signatures and the presence of alternative causative pathways will be needed. Those alternative pathways include secretory cell outgrowths ("SCOUTS") in the fallopian tube that are associated with altered *PAX2* expression[14].

Clinical investigation and further molecular pathogenesis refinement will be required to answer those critical questions, but the opportunity for cancer prevention with punch warrants strong consideration of BSOR. The time for initiating population-based studies is now.

CONFLICT OF INTEREST DISCLOSURES

The authors have no conflicts of interest relative to this subject matter to disclose.

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