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Laboratory-Clinic Interface

Fallopian tube tumorigenesis and clinical implications for ovarian cancer risk-reduction

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ABSTRACT

Ovarian cancer remains the leading cause of gynecologic cancer death among American women. Prevention is the only proven approach to reduce the incidence of the disease. Oral contraception, tubal ligation, and risk-reducing salpingo-oophorectomy (rrBSO) for high-risk groups are all established risk reduction strategies. This paradigm is changing as recent biologic studies suggest that many ovarian cancers, especially high-grade serous ovarian cancers, originate in the distal end of the fallopian tube rather than the ovarian surface epithelium. A putative precursor lesion has been identified called the serous tubal intraepithelial carcinoma (STIC). Theoretically, removal of the fallopian tubes alone may prevent these lesions and prevent overt disease. Opportunistic salpingectomy during benign gynecologic surgery appears to be safe and may offer some protection from ovarian cancer without compromising ovarian endocrine function. Despite a lack of evidence for efficacy, several professional societies now recommend this approach for average-risk women. Whether salpingectomy can also serve as a temporizing measure to delay risk-reducing oophorectomy in women with a genetic predisposition to ovarian cancer remains to be seen. Several ongoing non-randomized clinical trials will test the feasibility of this approach. Therefore, the societal impact of increasing salpingectomy rates on ovarian cancer incidence will be an area of intense focus for the next 10–20 years.

Introduction

While ovarian cancer comprises only 2.6% of cancers diagnosed among American women, it is the 5th leading cause of cancer-related death [1]. In 2017, more than 22,000 women were diagnosed with ovarian cancer and more than 14,000 died of the disease [1]. Although cure rates for women presenting with disease confined to the ovary exceed 90%, these women unfortunately represent the minority of cases [2,3]. More than 70% of women present with widely metastatic disease, usually high-grade serous ovarian cancer (HGSOC), where 5-year survival rates average 25–30% [4–6]. Despite significant efforts to diagnose patients earlier in the natural history of the disease, primarily using changes in the serum marker CA-125 and imaging with transvaginal ultrasound, no universal screening approach has been shown to meaningfully reduce ovarian cancer mortality (Table 1) [7–12]. Therefore, prevention remains the most impactful strategy to reduce ovarian cancer deaths [13]. This review summarizes the implications of evolving theories for ovarian cancer pathogenesis as related to the design of ovarian cancer prevention strategies.

Ovarian cancer risk factors

The Society of Gynecologic Oncology and the American College of Obstetricians and Gynecologists recommend risk-reducing bilateral salpingo-oophorectomy (rrBSO) for women with hereditary ovarian cancer syndromes [14]. Between 15 and 20% of ovarian cancer patients carry known pathogenic mutations in the genes *BRCA1* and *BRCA2,* which confer lifetime risks of ovarian cancer of up to 40% and 20%, respectively [15–17]. Currently, rrBSO is recommended at age 35–40 years for *BRCA1* mutation carriers and age 40–45 years for *BRCA2* mutation carriers [14]. Similar recommendations are made for women carrying less common mutations in other members of the DNA homologous repair pathway, such as *BRIP1*, *RAD51C*, and *RAD51D;* however, assigning estimates of lifetime risk for these rare mutations has been difficult [18–20]. Mutations in the DNA mismatch repair proteins associated with Lynch Syndrome, *MLH1*, *PMS2*, *MSH2*, and *MSH6* make up the other large hereditary risk group, conferring a lifetime risk of ovarian cancer of 7–10% [21]. The National Comprehensive Cancer Network (NCCN) suggests that rrBSO can be considered in this population but should be individualized [22]. Table 2 describes

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Table 1
Summary of reported large screening trials for epithelial ovarian cancer.

Study characteristics	UKCTOCS (Jacobs et al. [9])	Normal risk ovarian screening study (NROSS) (Lu et al. [12])	Prostate, lung, colorectal and ovarian cancer screening trial (PLCO) (Buys et al. [10])	UK Pilot (Jacobs et al. [11])
Setting	National Health Service, 13 UK regional centers	United States, 7 health centers	United States, 10 health centers	Community Volunteers, 40 UK primary care practices
Number of study subjects analyzed	202,546	4051	68,557	21,955
Patient population	Post-menopausal women aged 50–74 years old	Post-menopausal women aged 50–74 years old	Women aged 55–74 years old	Post-menopausal women 45 years old and older
Study period	2001–2004	2001–2011	1993–2010	1989–1998
Exclusion criteria	Bilateral oophorectomy, ovarian malignancy, increased risk of familial ovarian cancer, active non-ovarian malignancy	Bilateral oophorectomy, ovarian malignancy, increased risk of familial ovarian cancer, active non-ovarian malignancy	Prior lung, colorectal or ovarian cancer, bilateral oophorectomy	Bilateral oophorectomy, ovarian cancer, any active malignancy
Family history of breast/ovarian cancer	1.6% ovarian, 6.4% breast	NR	17.40%	NR
Primary end point	Ovarian cancer-specific mortality	Ovarian cancer incidence	Ovarian cancer-specific mortality	Ovarian cancer-specific mortality
Control arm	No screening	None	No screening	No screening
Experimental arm(s)	Multimodal screening (MMS) (CA-125 followed by ROCA[a] triaging to TVUS) or TVUS screening alone (USS) annually	Multimodal screening (MMS) (CA-125 followed by ROCA[a] triaging to TVUS)	Baseline CA-125 and TVUS, followed by 3 additional years of TVUS and 5 additional years of CA-125	Annual CA-125 testing with referral to TVUS for CA-125 ≥ 30 U/ml
Median follow-up	11.1 years	NR (0–11 years)	12.4 years	NR (0–8 years)
Outcomes	MMS HR 0.89 (95% CI, 0.74–1.08)[b] USS HR 0.91 (95% CI, 0.76–1.09)	0.9% average annual referral for TVUS Ten overall referrals to surgery with 4 invasive ovarian cancers diagnosed for PPV 40% (95% CI, 12.2–73.8%)	Mortality rate ratio 1.18 (95% CI, 0.82–1.71)	Relative Risk, 0.50 (95% CI, 0.22–1.11)
Clinical trials identifiers	NCT00058032	NCT00539162	NCT00339495 (current)	NR

NR – Not reported.
TVUS – Transvaginal ultrasound.
[a] ROCA – Risk Ovarian Cancer Algorithm.
[b] HR 0.80 (95% CI, 0.60–1.02) excluding prevalent cases or primary peritoneal cancer deaths.