Invited Commentary

Ovarian cancer of tubal origin, incessant ovulation and implications for clinical practice

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Abstract: Evidence has been accumulating recently about a tubal origin for the most lethal of ovarian cancers, high-grade serous carcinoma. A tumor originating in the fallopian tube may only fulfill its potential for growth when it is received in the hospitable ovarian environment. Recent studies shed light on the impact of ovulation on the tubal epithelium. The released follicular fluid does not bathe only the surface of the ovary but also the fimbrial end of the fallopian tube. Exposure of the distal tubal epithelial cells to locally elevated inflammatory mediators in the process of ovulation would activate an intrinsic pro-inflammatory response requiring resolution during the ensuing luteal phase. Incessant ovulation may not allow the time needed for the resolution of the inflammatory process. This would result in a sustained pro-inflammatory environment within the distal fallopian tube following each ovulatory event, contributing to an increased propensity for malignant transformation over a woman’s reproductive lifespan.

The tubal origin of ovarian cancer still leaves questions to be answered. But what is known is enough to consider prophylactic salpingectomy as a cancer reduction strategy, while large scale collaborative prospective and retrospective epidemiological studies are being planned. Advances in molecular biology provide promising research leads for interruption of long periods of incessant purposeless ovulation, and for blocking the molecules released in the ovulation-associated inflammatory process, that potentially impact on the pathogenesis of cancer.

Keywords: Ovarian cancer, fallopian tube, incessant ovulation, prophylactic salpingectomy

Evidence has been accumulating recently about a tubal origin for the most lethal of ovarian cancers, high grade serous carcinoma [1]. Meticulous examination of the Fallopian tubes in women genetically predisposed to ovarian cancer and who have undergone prophylactic salpingo-oophorectomy demonstrated dysplastic lesions and tubal intraepithelial carcinomas [2].

The similarity between the tubal epithelium and the ovarian serous carcinoma has long been observed, and it was assumed that the ovarian surface epithelium, sharing the same embryologic origin, can in the process of neoplasia transform into Mullerian type epithelia. A problem has been that no early neoplastic or pre-neoplastic changes or lesions have been definitively observed in the ovary.

That ovarian cancer can have its origin from an extra-ovarian source should not be surprising. Endometriosis has long been known to give rise to ovarian endometrioid carcinoma [3]. That a secondary tumor in the ovary may grow to a large size and metastasize, while the primary tumor is small and localized is not a rare observation. The Kruckenberg tumor has been mistaken for a primary ovarian cancer before its secondary nature has been discovered.

There is no difficulty in understanding how tubal cancer cells may reach the ovary. There is a need, however, to understand why they grow in the ovary, while the fallopian tube primary cancer remains small or limited to the pre-invasive stage. Clinically diagnosed primary tubal carcinoma is very rare [4]. There is a need also to understand the causative factor or factors that lead to tubal epithelial neoplasia.

The seed and the soil

The English surgeon Stephen Paget has been credited with proposing, as far back as 1889, the “seed and soil” theory of metastases, to
explain the predisposition of an organ to be the recipient of specific growths [5]. Paget presented and analyzed 735 fatal cases of breast cancer, complete with autopsy, as well as many other cancer cases from the literature and argued that the distribution of metastases cannot be due to chance or access, concluding that “although the best work in pathology of cancer is done by those who are studying the nature of the seed (the cancer cell), the observations of the properties of the soil (the secondary organ) may also be useful…. When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil.”

Experimental evidence for the role of organ selectivity in the determination of metastatic patterns has also been studied [6]. Using mice, kidney, ovary and lung tissue were grafted under the skin or into the muscle. When mice were injected with melanoma cells, metastases developed in the grafted lung and ovary tissue but not in the renal tissue, thereby showing a distinct preference. The molecular mechanisms that bring seed and soil together to promote tumor growth in a hospitable environment still need unraveling.

The role of the stroma in ovarian tumors is interactive. The stroma sustains and promotes tumor growth [7]. The tumor has also been known to stimulate the stroma cells to differentiate into functioning theca cells with hormone production [8]. Understanding the ovarian environment is needed to explain why a tumor originating in the fallopian tube may only fulfill its potential for growth when it is received in the hospitable ovarian environment.

**Incessant ovulation**

The heterogeneity of ovarian cancers and the complexity of the process of neoplastic change defy the attempt to pinpoint only a single factor for ovarian neoplasia [9].

Based on epidemiologic data about human ovarian cancer and data from comparative animal oncology the author advanced in 1971 the hypothesis of incessant ovulation as a causative factor in epithelial ovarian cancer [10]. The hypothesis predicted that oral hormonal contraceptives, which act largely by suppressing ovulation, will have a protective role against ovarian cancer. It was only later that large epidemiological studies lent support to the hypothesis and demonstrated this protective role [11]. Incessant ovulation is a new phenomenon in the modern woman. The woman hunter gatherer may experience only about 50 ovulations in her lifetime. During most of her reproductive years she is either pregnant or lactating. The modern woman may have about 500 ovulations. Incessant concealed ovulation was an ingenious evolutionary mechanism in nature to make sex perpetually available, encourage the pair bond and sustain paternal investment in the offspring [12].

Ovulation is a unique process of a hormonally induced physiological injury in the human body. The process of repeated trauma and repair provided a plausible explanation for a supposed vulnerability of the ovarian surface epithelium for neoplastic change. Our understanding of the process of ovulation, thanks to advances in molecular biology, has now moved from the simplistic mechanistic distended ovarian follicle reaching the ovarian surface, and rupturing to release the ovum [13]. Ovulation is recognized as an acute localized inflammatory process involving complex molecular interactions and resulting in the release not only of the ovum but of follicular fluid rich in potentially oncogenic factors. The released follicular fluid does not bathe only the surface of the ovary but also the fimbrial end of the fallopian tube. It is this fimbrial part of the fallopian tube that is vulnerable to neoplasia.

**Impact of ovulation on the tubal epithelium**

Recent studies shed light on the impact of ovulation on the tubal epithelium.

The composition of the follicular fluid has been studied for its implications in the pathogenesis of ovarian cancer [14]. Mature human follicles release about 5 ml of follicular fluid. Follicular fluid can contain as much as 1,000 fold higher levels of estrogen and progesterone than the serum. Other constituents include fatty acids, inflammatory factors, reactive oxygen species, and growth factors. They have a physiologic window; being required in the process of embryo formation, but the accumulation of these potentially anti-apoptotic and mutagenic components may play a role in ovarian cancer pathogenesis.
Exposure of fallopian tube epithelium to pooled follicular fluid, in an ex-vivo model, was found to mimic carcinogenic changes in precursor lesions of ovarian serous carcinoma [15]. The follicular fluid stimulated inflammatory and DNA repair pathways, resulted in the up-regulation of pro-angiogenic and pro-inflammatory interleukin 8, and led to double stranded DNA breaks.

To determine which components of the ovulation process contributed to DNA damage in the fallopian tube, an immortalized baboon tubal epithelial cell and a three-dimensional organ culture system for mouse oviduct and baboon fallopian tubes were developed [16]. Tubal epithelial cells did not proliferate or display increased DNA damage in response to gonadotropins or estradiol alone in vitro. Oxidative stress generated by treatment with hydrogen peroxide or macrophage-conditioned medium increased DNA damage in tubal epithelial cells in culture. It was postulated that ovulation may impact the tubal epithelium by generating DNA damage and stimulating macrophage infiltration but does not increase proliferation through gonadotropin signaling.

The vulnerability of the fimbrial tubal epithelium to oncogenic insults may also be augmented by the fact that it presents a transitional zone between two types of epithelia, the peritoneal mesothelium and the secretory tubal epithelium. The junction between two types of epithelia in the human body is noted to be an area vulnerable to malignant change. The squamo-columnar junction of the uterine cervix is such an example.

The role of inflammation in pathogenesis of certain cancers is now well established [17]. It is plausible that exposure of the distal fallopian tube epithelial cells to locally elevated inflammatory mediators following ovulation would activate an intrinsic pro-inflammatory response requiring resolution during the ensuing luteal phase. Incessant ovulation may not allow the time needed for the resolution of the inflammatory process.

Observations of differential inflammatory gene expression in luteal phase fallopian tube epithelial samples suggested that epithelia from a proportion of BRCA1 mutation carriers have an altered ability to resolve the local pro-inflammatory environment associated with ovulation. This would result in a sustained pro-inflammatory environment within the distal fallopian tube following each ovulatory event, contributing to an increased propensity for malignant transformation over a woman's reproductive lifespan [18].

**Does ovulation play a role in facilitating migration of malignant cells?**

A study utilizing *in vitro*, *ex vivo*, and *in vivo* models to recapitulate the process of extra-ovarian malignant cells migrating to the ovaries and forming tumors, provided experimental evidence to support that ovulation, by disrupting the ovarian surface epithelium and releasing chemokines/cytokines, promotes the migration and adhesion of malignant cells to the ovary [19]. The study identified the granulosa cell-secreted stromal cell derived factor SDF-1 as a main chemo-attractant that recruits malignant cells towards the ovary. SDF-1 regulates a variety of physiological processes including spermatozoa chemotaxis to the ovulation site. In addition, the ruptured ovarian surface epithelium upon ovulation may create an access for extra-ovarian malignant cells to home in the ovary. It is also plausible that the exposed ovarian stromal extracellular matrix provides an optimal scaffold for the extra-ovarian malignant cells to adhere. In the *ex vivo* model, cancer cells specifically adhered to the areas of ruptured follicles. It was proposed that blocking “attraction” or “stromal scaffold” may inhibit cancer cell adhesion to ovary.

Understanding the impact of ovulation on the fallopian tube epithelium adds to the plausibility of a tubal origin for ovarian serous carcinoma. Understanding the molecular mechanisms involved may provide possible future research leads for cancer chemoprevention.

**Implications for clinical practice**

The tubal origin of ovarian cancer still leaves many questions to be answered [1]. But what is known is enough to consider prophylactic salpingectomy as a cancer reduction strategy. Providing the scientific evidence for a protective effect takes time and necessitates large controlled prospective or retrospective studies. One large-scale population-based cohort study using data from the Swedish Cancer Registry...
on women with previous surgery reported a significantly lower risk for ovarian cancer among women with previous salpingectomy compared with the unexposed population [20]. More studies are needed.

With ovarian cancer ranking as one of the leading causes of cancer deaths among women, and with lack of progress in early detection, we cannot afford not to act and to wait for the definite evidence. Absence of evidence is not evidence of absence. In fact, evidence will not be obtained unless prophylactic salpingectomies are more widely performed to allow the evidence to accumulate.

Prophylactic salpingectomy has been recommended in two clinical situations: as an opportunistic procedure and as an elective procedure. ACOG recommended that the surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy [21]. When counseling women about sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception, as well as a potential benefit for ovarian cancer prevention [22]. RCOG recommended that all women who have completed their families should be carefully considered for prophylactic removal of the fallopian tubes with conservation of ovaries at the time of gynecological or other intraperitoneal surgery [23].

Elective bilateral salpingectomy, with delayed oophorectomy, was recommended in premenopausal women with an identified BRCA mutation, could overcome the quality of life issues associated with bilateral oophorectomy, with minimal loss of the benefit to life expectancy [23].

The histological precursors of cancer arise in the fimbrial portion of the fallopian tube. It is imperative that entire lateral portion of the tube, including the fimbria ovarica is removed when prophylactic salpingectomy is performed.

Primum non nocere

In the current state of knowledge, the potential benefit of prophylactic salpingectomy is justified so long that we hold the principle of “first do no harm”. A population-based retrospective cohort study to assess the perioperative safety of bilateral salpingectomy as an ovarian cancer risk-reduction strategy in low-risk women confirmed the feasibility and safety of the procedure [24]. Minimal additional surgical time was required and there were no significant risks of hospital readmission or blood transfusions. Adding opportunistic salpingectomy to benign hysterectomy is unlikely to aggravate any impairment of the blood supply to the ovary. No short term effect on ovarian reserve, as measured by Anti-Mullerian Hormone levels, was reported following salpingectomy during laparoscopic hysterectomy in a pilot randomized controlled trial [25].

Irreversibility may be a concern when substituting salpingectomy for female sterilization. However, sterilization reversal by salpingoplasty carries the risks of re-operation, failure and ectopic pregnancy, and in vitro fertilization is now a reasonable alternative.

Potential impact of prophylactic salpingectomy

The potential impact of prophylactic salpingectomy on sporadic ovarian cancer prevention will depend on two factors. The first is the willingness of obstetrician/gynecologists to incorporate opportunistic salpingectomy in their surgical practice, in the current absence of definite scientific evidence for its potential protective role. The second is the incidence of the opportunities for prophylactic salpingectomy in medical practice. On the first factor, there is evidence from at least two surveys in British Columbia and in Ireland of the increasing uptake of the procedure [24, 26].

Changing trends in medical practice may influence the incidence of the opportune procedures. The incidence of hysterectomy may decrease with the availability of alternatives such as the levonorgestrel IUD and endometrial ablation. The need for tubal sterilization may be less with the availability of effective long acting reversible contraceptive methods. The increasing rate of Caesarean delivery may, however, provide more opportunities for tubal sterilization.

The potential impact of prophylactic salpingectomy on hereditary ovarian cancer will depend on the feasibility for screening for BRCA muta-
tions among women with a family history of ovarian or breast cancer as well as on willingness of properly counseled women to go for the procedure in absence of definite scientific evidence.

The future

The challenge of ovarian cancer prevention still stands. Research is needed to document the protective effect of prophylactic salpingectomy through well designed large scale collaborative prospective and retrospective epidemiological studies. Advances in molecular biology provide promising research leads for interruption of long periods of incessant purposeless ovulation, through suppression of ovarian follicle rupture without interfering with follicular development and subsequent luteinization [11], and for blocking the molecules released in the ovulation-associated inflammatory process, that potentially impact on the ovarian epithelial carcinogenesis [17].

Disclosure of conflict of interest

None.

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References


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