Gynecology and Minimally Invasive Therapy 5 (2016) 102–105

Contents lists available at ScienceDirect

Gynecology and Minimally Invasive Therapy

journal homepage: www.e-gmit.com

Review article

Salpingectomy and prevention of ovarian carcinoma

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ARTICLE INFO

Article history:
Received 5 November 2013
Received in revised form
11 February 2014
Accepted 20 August 2015
Available online 1 September 2015

Keywords:
BRCA
ovarian cancer
ovarian dysplasia
salpingectomy
serous tubal intraepithelial carcinoma

ABSTRACT

Advanced cases of epithelial, primary peritoneal, and primary tubal malignancies have relative poor prognosis and collectively remain the most deadly of all gynecologic malignancies. Recently, many studies have demonstrated that the fallopian tubes might be the origin of most high grade ovarian and peritoneal serous carcinoma. In this review, we describe the tubal carcinogenic pathway with the precancerous tubal lesions and the impact of salpingectomy for prevention of ovarian carcinoma.

Introduction

To prevent ovarian carcinoma, you have to remove the ovaries and not the adjacent fallopian tubes. This has been challenged in the literature recently. Now the focus of prevention of high grade serous ovarian carcinoma has shifted from the ovary to the fallopian tubes. In view of the recent description of precancerous tubal lesion, the majority of pelvic serous carcinoma (ovarian and peritoneal carcinoma) may arise from the fimbriated end of the fallopian tubes.[1–13] First, this finding could have important implications for the surgical management of prophylactic oophorectomy in groups presenting genetic risk of ovarian cancer. Second, it may be essential for the decision to remove the fallopian tubes at the time of hysterectomy for other type of pelvic surgery for benign conditions and during female sterilization in the general population.

For many epithelial malignancies, the cell of origin is well defined with precursor lesions easily identified. For example, cervical cancer originates from human papilloma virus-infected cells in the cervical transformation zone[14] and adenocarcinoma of the colon originates in dysplastic lesions within the colonic mucosa. In contrast to these tumor types, the origins of epithelial ovarian cancer are not clearly defined. Just as endometriosis has been implicated in the development of some endometrioid ovarian carcinoma,[15] emerging data suggest that the fallopian tube may play a critical role in the origin of what has traditionally been classified as serous ovarian cancer. In this review, we will discuss the proposed mechanism of ovarian carcinogenesis by the tubal epithelium and the emerging role of salpingectomy in the prevention of ovarian cancer.

Ovarian cancer classification and the tubal paradigm

Ovarian cancer is the most lethal gynecologic malignancy. In 2013, it was estimated that there would be >22,000 new diagnoses and >14,000 deaths from the diseases.[16] Although many improvements have been made in surgical techniques and adjuvant treatment, the prognosis of ovarian cancer is poor, with a 5-year survival rate of only 45%.[17] The majority of ovarian cancer is diagnosed in advanced stages, in part because no screening test exists to detect preinvasive or early stage disease.

Epithelial ovarian cancer is divided into its histologic subtypes: serous, mucinous, endometrioid, clear cell, transitional, or any combination of these (mixed). Serous histology is the most common, representing 70% of epithelial ovarian cancer.[18] Serous tumors are aggressive and usually present at advanced stage. Although they respond to surgery and platinum-based chemotherapy, they usually recur. Although ovarian carcinoma is evidently a terrible disease: the life time risk of developing ovarian cancer is 1.8% and the risk for this disease by age 50 years is 1 in 335, rising to about 1 in 65 between the ages of 50 years and 70 years[19] in the general

Conflicts of interest: All authors have no conflict of interest relevant to this article

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http://dx.doi.org/10.1016/j.gmit.2015.08.005

population; the lifetime risk in BRCA1 carriers for ovarian cancer is about 40% and in BRCA2 carriers, the lifetime risk is about 20%.[20] Removing the ovaries cuts those risks by about 80% and annual risk falls from 1% to 0.2% after an oophorectomy.[21]

The tubal theory[1–10] is based on the following findings: with meticulous and thorough histopathologic analysis of specimens from prophylactic adexectomy for BRCA genetic mutation, between 4% and 17% occult cancers were revealed, 57–100% of which were located in the distal portion of the tubes.[3–8] These occult intraepithelial cancerous lesions are termed serous tubal intraepithelial carcinomas (STICs).They are characterized by epithelial stratification, nuclear atypia with an increase in the nuclear cytoplasmic ratio, loss of nuclear polarity, nuclear pleomorphism, and loss of ciliated cells.[21]

Earlier benign lesions are called serous tubal intraepithelial (STILs) or tubal intraepithelial lesions in transition. STICs and STILs are most frequently located at the fimbriated end of the fallopian tubes.[11–13] As we will discuss below, the question arises about whether fimbriectomy should be proposed instead of salpingectomy in prophylactic strategies.

Studies at the molecular level indicate that STICs and high grade serous ovarian or peritoneal carcinoma are clonally related and STICs are not metastases from ovarian carcinoma.[22]

Recently, another precursor has been described and it is termed secretory cell out growth (SCOUT), which is distributed throughout the fallopian tubes,[22–25] and finally would provide argument in favor of salpingectomy instead of fimbriectomy.

All these histopathologic terms (STICs, STILs, and SCOUT) should now be familiar to clinicians and surgeons because they are, and will continue to be, increasingly present in pathologic reports. All the fallopian tubes removed during permanent contraception should be sent for histological studies, which will help later in patients' management.

Last but not least, Kim et al[26] recently provided experimental evidence of the tubal origin using a mouse model; they showed that a high grade serous ovarian cancer could also arise from the fallopian tubes. Moreover, removal of the fallopian tube prevented cancer initiation, whereas bilateral ovariectomy had no effect.[26]

Several series of sporadic serous ovarian cancer and primary serous peritoneal cancers have been analyzed, and STICs were only present in about 30–60% of cases.[27–29] In cases where STICs were absent, ovarian cancer can arise from the ovary itself and a precancerous lesion named ovarian epithelial dysplasia has been described.[30–33] Ovarian dysplasia is defined by cytologic and architectural abnormalities: surface papillomatosis, epithelial pseudo stratification, inclusion cysts, nuclear pleomorphism, and epithelial invagination.[34]

Some other theories have been discussed such as the secondary mullerian system theory proposed by Lauchlan[35] and the unifying hypothesis proposed by Ausperg[36] in which ovarian cancer may arise from the transitional epithelium between the ovarian surface epithelium and the fimbrial epithelium of the oviduct. It is possible that the tubal pathway would be preponderant, particularly in cases of associated genetic risk, whereas the ovarian and tubal pathways could coexist in sporadic ovarian cancer.[37,38]

Salpingectomy and implications for prevention

Effective cancer screening programs typically require identification of either a precursor lesion or an early stage malignancy. This is demonstrated most notably in colon, cervix, and breast cancer screening. Unfortunately, without a clear precursor lesion or biomarker, ovarian cancer screening has thus far been unsuccessful in identifying preinvasive or early stage disease. A large trial studying ultrasonography and serum cancer antigen (CA)125 for ovarian cancer screening in asymptomatic women was unable to demonstrate efficacy in detecting early stage disease.[39] Modification to this approach may demonstrate efficacy either following CA125 overtime rather than at a single point[40] or by triaging patients to ultrasound only if the CA125 is consistently elevated.[41] Models have predicted that tubal intraepithelial carcinoma and early stage disease are likely to be present for at least 4 years before becoming widely metastatic.[42]

Due to the role of the fallopian tube in epithelial ovarian cancer, approaches to gynecologic surgery have already begun to shift. With the understanding that ovarian carcinogenesis probably begins in the fallopian tube, prevention strategies such as salpingectomy with ovarian conservation are increasingly being studied to determine whether they will effectively reduce the burden of ovarian cancer while allowing women to preserve ovarian function.

Risk-reducing surgery for patients with BRCA mutations currently includes complete excision of the ovaries and fallopian tubes with serial sectioning. With careful excision and close evaluation, rates of occult preinvasive or invasive tubal malignancies in this population may be as high at 10%.[3]

Surgical implications may extend beyond prophylactic surgery for high-risk patients. In the USA, >600,000 hysterectomies are performed each year and about 55% of hysterectomies are accompanied by bilateral salpingo-oophorectomies (BSO) and about one-third of all 60-year-old women have had a hysterectomy.[43] There has been considerable debate about the risks and benefits of performing a BSO at the time of hysterectomy. The risk of epithelial ovarian cancer is reduced, but this comes at the expense of the potential risks of cardiovascular disease, osteoporosis, and even cognitive impairment seen with early surgical menopause.[44] In a large analysis of >20,000 patients from the Nurses' Health Study, all-cause mortality as well as cancer mortality increased in women who received a BSO.[45] The authors concluded that with an expected life span of 35 years after surgery, for every nine BSOs performed there was one additional early death.[45] It has been demonstrated that if salpingectomy is performed with great care by preserving blood vessel integrity in the proximity of the ovarian hilum and in the context of the mesosalpinx, patients will not have negative effects on their ovarian function.[46] There were no perioperative complications associated with the procedure attributable to salpingectomy alone.[46]

With the risk associated with BSO at the time of hysterectomy for benign disease, it is becoming more apparent that it may be clinically prudent to leave the ovaries in place for prolonged hormone exposure. However, because the postreproductive fallopian tube serves little biologic purpose, it may be sensible to perform only a salpingectomy at the time of surgery. Although no prospective data support this practice, it follows rationally that this has the potential to reduce the risk of serous carcinoma with little or no increased morbidity.[47] Given that an estimated 80–90% of BRCA-related ovarian cancers originate in the fallopian tube, consideration might also be given to performing risk reduction salpingectomy, especially in young people, to conserve ovarian function.[48] The patient then may have more time to complete childbearing with the help of *in vitro* fertilization and does not have to suffer the consequences of surgical menopause. This approach has no impact on breast cancer but could be combined with intensive breast surveillance and chemoprevention.

It has long been noted that bilateral tubal ligation confers some protection against developing ovarian cancer. Specifically, in a meta-analysis of 13 studies, there was a 34% risk reduction in the development of endometrioid and serous epithelial ovarian cancers.[49] It is unlikely that tubal ligation surgically removes areas of STICs found at the fimbriated end of the tube; however, this has not yet been evaluated.

The surgical procedure

The preferred approach for salpingectomy remains minimally invasive surgery (laparoscopy or robotic surgery).[50–52] The surgical procedure should be preceded by meticulous and complete inspection of the whole abdominopelvic cavity. Pelvic washings should take place systematically, especially in the case of patients with BRCA mutations[53] and there is no advantage to fimbriectomy alone because SCOUT lesions can occur anywhere in the tube. During laparoscopy, it is important to use bipolar electrocoagulation carefully, because diathermy-induced injury in the fallopian tubes affects the detection of STICs.[54–56]

Future perspectives

In the near future, there may be opportunities to sample the preinvasive lesions in the fallopian tubes by use of *in situ* and real time optical imaging technologies. Confocal microlaparoscopy or robotics in real time will help the surgeon in the near future to decide whether salpingectomy is needed or not.[34] McAlpine et al[57] managed to identify STICs in a preliminary report with autofluorescence imaging.

Conclusions

Epithelial ovarian, primary peritoneal and primary tubal carcinomas are complex and heterogeneous groups of malignancies that remain the most deadly of all gynecologic malignancies. Ongoing research has confirmed there is no one single site or cell type from which these cancers arise. A majority of serous ovarian carcinomas appear to have preinvasive lesions in the distal fallopian tubes and this recent finding has shifted the paradigm of ovarian carcinoma carcinogenesis. Complete bilateral salpingectomy as a risk-reducing strategy in patients with BRCA mutations is an approach worthy of further investigation and it may be reasonable to consider salpingectomy for all patients undergoing hysterectomy for benign reasons, and for general populations who seek permanent contraception. For instance, the Gynecologic Oncology of Canada[58] already recommends bilateral salpingectomy for patients undergoing hysterectomy or requesting permanent contraception. As we move forward, new research is still needed to provide insight into the carcinogenesis and interaction between the tubes and ovaries and molecular studies may someday find more effective screening strategies.[59,60]

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