Royal College of Obstetricians & Gynaecologists

The Distal Fallopian Tube as the Origin of Non-Uterine Pelvic High-Grade Serous Carcinomas

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1. Introduction

Epithelial ovarian cancers (EOCs) are the most common cause of death from gynaecological malignancy in the developed world. EOCs comprise a heterogeneous group of neoplasms including serous (68%), clear cell (13%), endometrioid (9%) and mucinous (3%) pathological subtypes.[1,2] Serous ovarian carcinomas are further divided into low-grade (type I) and high-grade (type II) serous ovarian carcinomas (LGSOC and HGSOC respectively).[3] Most deaths are attributable to HGSOC which is approximately 20 times more common than LGSOC.[4] The lifetime risk of developing EOC is 1 in 70 (1.4%) by 75 years of age,[5] with the main risk factors being advancing age and family history. Approximately 10–25% of ovarian cancers are associated with an identified hereditary genetic abnormality.[6–10] Mutations in the *BRCA1* or *BRCA2* genes are the most common hereditary genetic abnormalities and are associated with a 50% and 25% lifetime risk by the age of 75 years respectively.[11–13] The carcinomas that develop in patients with hereditary *BRCA1* or *BRCA2* mutation are commonly high-grade serous in type.[14]

After the introduction of platinum-based chemotherapy in the late 1980s, there has been little further improvement in survival from EOC. The overall survival at 5 years is 43%. However, if confined to the fallopian tube or ovary, the survival can be as high as 80–95% at 5 years.[15,16] Surgery and chemotherapy remain the main treatment modalities. Screening strategies have had little impact to date because the pathogenesis of EOC has been poorly understood and no precursor lesion has been identified. This article aims to review our understanding of ovarian carcinogenesis, especially HGSOC because it has the potential to change clinical preventive strategies in ovarian cancer significantly.

2. Ovarian cancer pathogenesis

The 'incessant ovulation' theory has for many years been the most accepted hypothesis of EOC carcinogenesis. It proposes that ovulation traumatises the ovarian surface epithelium such that, with time, there is an increasing chance of error occurring during cell replication. Women with a high number of lifetime ovulations are therefore at increased risk of EOC.[17] This was supported by epidemiological studies that suggested nulliparous women, and those with early menarche and late menopause, had an increased risk of EOC. Conversely, women with suppression of ovulation had a lower risk of EOC: for example, multiparous women and users of the combined oral contraceptive pill.[18,19] Other theories include the 'gonadotrophin hypothesis', which suggests that excessive gonadotrophin exposure increases estrogenic stimulation of the ovarian surface epithelium. Gonadotrophin levels increase with advancing age, especially after menopause, which is consistent with the age-specific rates of EOC.[20]

Alternatively, the 'hormonal hypothesis' proposes that excess androgen stimulation of the ovarian surface epithelium leads to an increased risk of cancer, while progesterone stimulation of ovarian surface epithelium is protective.[21] All of these theories are based on epidemiological and circumstantial evidence with little or no direct experimental or pathological evidence.

It is well accepted that most ovarian clear cell and endometrioid carcinomas arise from endometriosis.[22] In the following section, we review evidence that most so-called ovarian high-grade serous carcinomas actually arise from the fimbria of the fallopian tube.

3. The fallopian tube and high-grade serous 'ovarian' cancer

The site of origin of pelvic (fallopian tube, primary peritoneal and ovarian) high-grade serous carcinomas has been the subject of debate for over 60 years. The very poor survival in patients with HGSOC

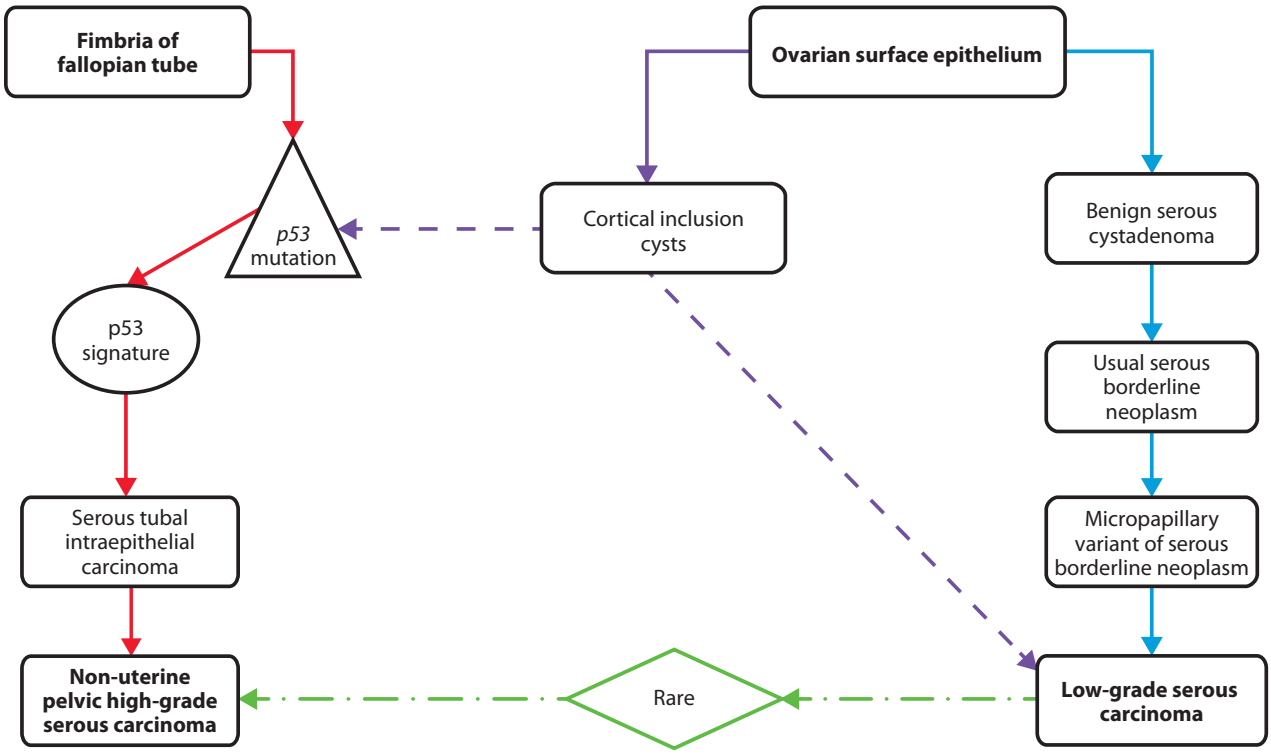
necessitates a drive to identify the site of origin and develop new strategies for the prevention of this disease. There has been a rapidly increasing body of evidence supporting the fallopian tube as the site of origin of HGSOC. In fact, a review article by Crum et al.[23] states the association between the fallopian tube and HGSOC as 'indisputable'.

Much of the initial evidence came from the study of prophylactic specimens in women at high risk of developing pelvic serous carcinomas. Twenty years ago, a screening trial attempting to detect early ovarian cancers in the general population using assays of CA125 found that the ratio of fallopian tube to ovarian cancers was 25 times higher than expected. This raised the possibility that the fallopian tube may be involved early in the disease process of high-grade serous cancers (HGSCs).[24] In 2006, Finch et al.[25] published clinical and pathological findings of prophylactic salpingo-oophorectomy specimens from 159 *BRCA1* and *BRCA2* carriers. Seven (4.4%) occult fallopian tube cancers were identified in these women, in the absence of symptoms. These and other observations have led to increased pathological scrutiny of fallopian tubes in prophylactic specimens from high-risk women. Medeiros et al.[26] published a pilot study of 13 *BRCA*-positive women undergoing prophylactic bilateral salpingo-oophorectomy. The authors outlined a protocol for sectioning and examining the fallopian tube extensively, especially the fimbrial end, and found that the fimbriae were the most common site of serous adenocarcinoma in *BRCA*-positive women. The same group published a further study of 122 *BRCA*-positive women undergoing prophylactic surgery, identifying seven cancers on extensive histological examination of the fallopian tube and ovary. All originated from the fimbrial end of the fallopian tube.[27]

Closer histological examination of the fallopian tubes in high-risk women and women with sporadic HGSOC has also led to the discovery of potential precursor lesions for high-grade pelvic serous cancers.[28] At a molecular level, HGSOC differs from LGSOC. LGSOC is associated in two-thirds of cases with *KRAS* or *BRAF* mutations. *HER2* (*ERBB2*) mutations may also occur but there is no association with *p53* mutations. In contrast, HGSOC has an extremely high rate of *p53* mutations (approaching 100%), somatic *BRCA* mutations and an absence of *KRAS*, *BRAF* or *HER2* mutations.[3,9,29] HGSOC is therefore characterised by *p53* mutation as well as dysfunction in *BRCA1* and *BRCA2*.[29] Staining for p53 reveals foci of intense p53 overexpression, known as 'p53 signatures', in morphologically normal fallopian tubes; p53 signatures are found in many fallopian tubes and are not restricted to patients with *BRCA1* or *BRCA2* mutation. Histological lesions believed to be precursors of high-grade serous carcinomas have also been identified; these are known as serous tubal intraepithelial carcinoma (STIC) lesions.[30] These STIC lesions show identical *p53* mutations to the adjacent HGSOC, suggesting a link between STIC and HGSOC.[31] Identical *p53* mutations have also been demonstrated in p53 signatures, suggesting that these represent an early event in the pathogenesis of HGSOC. Adult epithelial stem cells are imperative for cell repair through mechanisms including clonal growth and self-renewal. These processes make the cells susceptible to DNA damage and subsequent malignant change. The distal fallopian tube has been shown to contain double the amount of stem-like epithelial cells compared to the proximal end and therefore may play a role in initiating neoplastic transformation, even in the presence of BRCA1/BRCA2 DNA repair proteins.[32,33] Exposure of the distal fallopian tube to locally elevated levels of inflammatory cytokines could contribute to the development of precursor lesions and eventual malignant transformation of these cells.[34,35]

It has been proposed that there are two distinct pathways in 'ovarian cancer' carcinogenesis. The first involves the incorporation of müllerian epithelium into the ovary with the formation of endosalpingiosis, cortical inclusions or endometriosis. This müllerian epithelium could derive from the fallopian tube through exfoliation of tubal cells or tubal ovarian adhesions, or be secondary to müllerian metaplasia of ovarian surface epithelium. This incorporated müllerian epithelium may give rise to benign and borderline serous tumours, low-grade serous adenocarcinomas, endometrioid or clear cell tumours but rarely HGSOC. The second pathway involves malignant transformation of the distal fallopian tube mucosa through p53 signatures and the development of STIC. These STIC lesions may invade locally into the underlying tubal wall, exfoliate onto the surface of the ovary or into the peritoneal cavity, or a combination of these possibilities. This exfoliation into the peritoneal cavity could explain the clinical finding of widespread peritoneal HGSOC in the absence of a significant volume of invasive disease in the fallopian tube or ovary[36] (Figure 1).

Figure 1. Pathway of HGSOC



The current World Health Organization (WHO) criteria for defining the origin of pelvic serous carcinomas are the tumour distribution and the presence or absence of a precursor lesion.[37] The precursor lesions include an intraepithelial carcinoma or a predisposing lesion, such as an endometriotic cyst, cystadenoma or borderline tumour. The presence of coexisting intraepithelial carcinoma is a prerequisite for a diagnosis of primary tubal carcinoma. However, finding a coexisting intraepithelial carcinoma in ovarian or peritoneal serous carcinomas is rare. Thus, most pathologists classify peritoneal and ovarian serous cancers according to tumour distribution. Large ovarian tumours with parenchymal involvement are usually designated as ovarian primaries, while advanced tumours with little or no ovarian involvement/mass are designated as peritoneal primaries. In other words, because these tumours are classified without identifying a defined precursor, their classification is subject to error.

In high-risk women with an identified *BRCA* mutation, bilateral salpingo-oophorectomy offers the greatest risk reduction for ovarian cancer[38] and significant risk reduction for breast cancer. The identification of the fallopian tube as the origin of high-grade pelvic serous carcinomas, and its associated precursor lesion, has the potential to have significant clinical impact on the reduction of mortality associated with this disease. A study of ovarian cancers in British Columbia, Canada, showed that 20% of patients diagnosed with ovarian cancer had previous gynaecological surgery and 10–15% had previous tubal ligation.[39] The implication was that if the fallopian tubes of these patients had been removed at the time of their initial surgery, 30% of the ovarian cancers could have been prevented. Opportunistic removal of the fallopian tubes at hysterectomy or sterilisation has minimal additional surgical risk to the patient, although we do accept that there is currently no large published study that quantifies this risk. There is a small study comparing 79 patients who underwent total laparoscopic hysterectomy (TLH) with bilateral salpingectomy with 79 women who underwent TLH without salpingectomy. There was no significance difference in operative time, fall in haemoglobin, hospital stay, return to normal activity or complication rate between the two groups.[40]

In 2010, an educational initiative was launched in British Columbia, Canada, to shift the surgical paradigm and promote opportunistic bilateral salpingectomy at the time of hysterectomy for benign gynaecological disease and at sterilisation. McAlpine et al. recently published the data from this

initiative, demonstrating an increased uptake for opportunistic salpingectomy without any increase in operative risk or perioperative complications.[41] In November 2012, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) issued a guideline on 'Managing the Adnexae at the Time of Hysterectomy for Benign Gynaecological Disease', which recommended that consideration be given to bilateral salpingectomy at the time of benign hysterectomy.[42] More recently, in November 2013, the Society of Gynecologic Oncology (SGO) in the USA released a practice statement suggesting that women at low risk of ovarian cancer, within the general population, consider opportunistic salpingectomy at the time of pelvic or intra-abdominal surgery.[43] Although evidence is currently lacking, 'if we wait until we have the evidence before we offer the operation [...], then we will never have the evidence'.[44] A recent publication by Kim et al.[45] identified that non-uterine HGSC developed in the fallopian tube of mice rather than the ovary, with similar molecular changes to the human. They also identified subsequent spread to the ovaries and peritoneal cavity. The study additionally demonstrated that if the fallopian tubes alone were removed (ovaries left intact), the mice failed to develop HGSCs.

4. Opinion

Although the majority of 'ovarian' carcinomas are of serous histological subtype, the heterogeneous group that make up EOCs are all frequently included in clinical and molecular research. However, we now know that they differ not only in morphology, but in their origins of carcinogenesis, particularly, and most importantly, at a molecular level. This has a significant impact on clinical outcomes, particularly in their response to chemotherapy. It is therefore appropriate and necessary to study high-grade serous pelvic carcinomas as a distinct group and adopt stricter inclusion criteria to this histological subgroup.

In high-risk women with an identified *BRCA* mutation, bilateral salpingo-oophorectomy offers the greatest risk reduction for ovarian cancer and significant risk reduction for breast cancer. However, bilateral salpingectomy with delayed oophorectomy may be a cost-effective strategy that could overcome the quality of life issues associated with bilateral oophorectomy in premenopausal women, with minimal loss of the benefit to life expectancy.[46,47] Currently there is no evidence from randomised controlled trials with respect to the effectiveness of bilateral salpingectomy alone in preventing ovarian cancer in high- or low-risk women. Although such evidence is the gold standard and should be encouraged, ongoing epidemiological studies are likely to add strength to the current translational research evidence and change surgical practice.

It is therefore our opinion that women who are not at high risk for *BRCA* mutation and have completed their families should be carefully considered for prophylactic removal of the fallopian tubes with conservation of ovaries at the time of gynaecological or other intraperitoneal surgery.

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