# Why Most Ovarian Cancer isn't Ovarian Cancer And Why that Matters to all women

***Written by Dr Ciarán Ó Riain and Dr James P. Beirne***

The ovaries have long been the focus of attention of much of study of the reproductive system. Despite their small size, the pair of organs that lie on either side of the uterus (womb) play a vital role in hormone production and ovum (egg) production. In addition, they have been home to a variety of benign and malignant types of tumour. Ovarian cancer (OC) represents the 4th most common tumour in women in Ireland. Historically, cases of OC have often been grouped together as one disease for research and clinical trials purposes. However, recent decades have emphasised that OC is not one disease but rather a group of different cancers with different biology, differing response to treatment and differing outcomes for affected women.

Most of what we regard as OC is a particular type known as high grade serous carcinoma (HGSC), accounting for most fatalities. In recent years, evidence has accumulated that most of this common form arise not within the ovary but from its neighbouring organ, the fallopian tube.

In comparison to the amount of study of ovary, the fallopian tube has been relatively ignored. Interest has been limited to its role in transporting the ovum to the uterus and any conditions that inhibit that function or result in a tubal ectopic pregnancy. Tumours of the fallopian tube were considered to be extremely rare.

**Recent Breakthrough**

At the beginning of this century there was a paradigm shift when pathologists examined tissue from women who had elected to have ovaries and tubes removed because they had genetic changes placing them at higher risk of OC. Early features of tumour development are often identified in the tissue of those who carry a genetic predisposition to cancers. Despite extensive examination, a convincing early step in cancer development has never been found in the ovary. Instead, several groups identified subtle microscopic changes in the fallopian tube. The cells lining the finger-like projections at end of the fallopian tube, known as fimbriae, showed changes resembling HGSC.

These findings were labelled serous tubal intraepithelial carcinoma (STIC) and were proposed as a step in development of HGSC. In the intervening years, a wealth of information, including molecular and epidemiological data, has supported the theory that most of what we understand as OC arises in the fallopian tube. Despite some early scepticism, the tubal origin of most HGSC is now widely accepted among those involved in gynaecological cancer care.

**Implications for Diagnosis and Screening**

The discovery that HGSC arises in the fallopian tube may assist in developing more effective diagnostic and screening tools but it has also opened new pathways for prevention.

At the time of clinical detection, HGSC typically has spread to the lining of the peritoneal cavity which contains most of the abdominal organs such as stomach, liver and bowel. This presentation at stage 3 has been cited as a reason for slow progress in improving survival rates over recent decades.

Public awareness around OC has focussed on the value of identifying the tumour when it is confined to the ovary (stage 1). This is understandable because reported survival figures of early OC is much better than advanced disease. This approach poses a problem with the commonest and most aggressive form; HGSC. With its origin in the fallopian tube then ovarian involvement unfortunately represents disease spread from its original site. HGSC spreads throughout the abdominal cavity through shedding of cancerous cells from the end of the fallopian tube that opens into the abdomen beside the ovary. A microscopic tumour on the fallopian tube could easily, and quickly, spread cancerous cells throughout the abdomen. Therefore, the detection of HGSC at an early stage will be extremely challenging, not to mention exceptionally rare, with the current diagnostic modalities available to clinicians today.

Hugely valuable large scale studies exploring the potential role of screening asymptomatic women, employing methods like examining ovaries by radiological imaging and checking blood levels of tumour markers such as CA125, have been performed and have shown that there is no benefit. This is in part due to the fact a microscopic fallopian tube tumour may spread widely before forming an ovarian mass making imaging of limited value for early detection. Likewise, there is potential for cancer spread before stimulating the production of the tumour markers.

Whilst disappointing, rather than aiming for diagnosis at stage 1 (and regarding detection at stage 3 as a failure), a more realistic goal may be to identify women at early stage 3 disease where complete surgical removal is possible. This has one of the greatest effects on the survival. The key to this earlier detection is a widespread awareness of symptoms (as listed in article by Dr. Sharon O'Toole in this issue) along with rapid access to the key diagnostic tools (transvaginal ultrasound and CA125 testing). On a brighter note, ongoing research, utilising the new knowledge of the site of origin of HGSC, is showing the promise of more sensitive, disease-specific blood tests which carry the potential for early diagnosis.

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**Implications of Tubal Origin for Prevention**

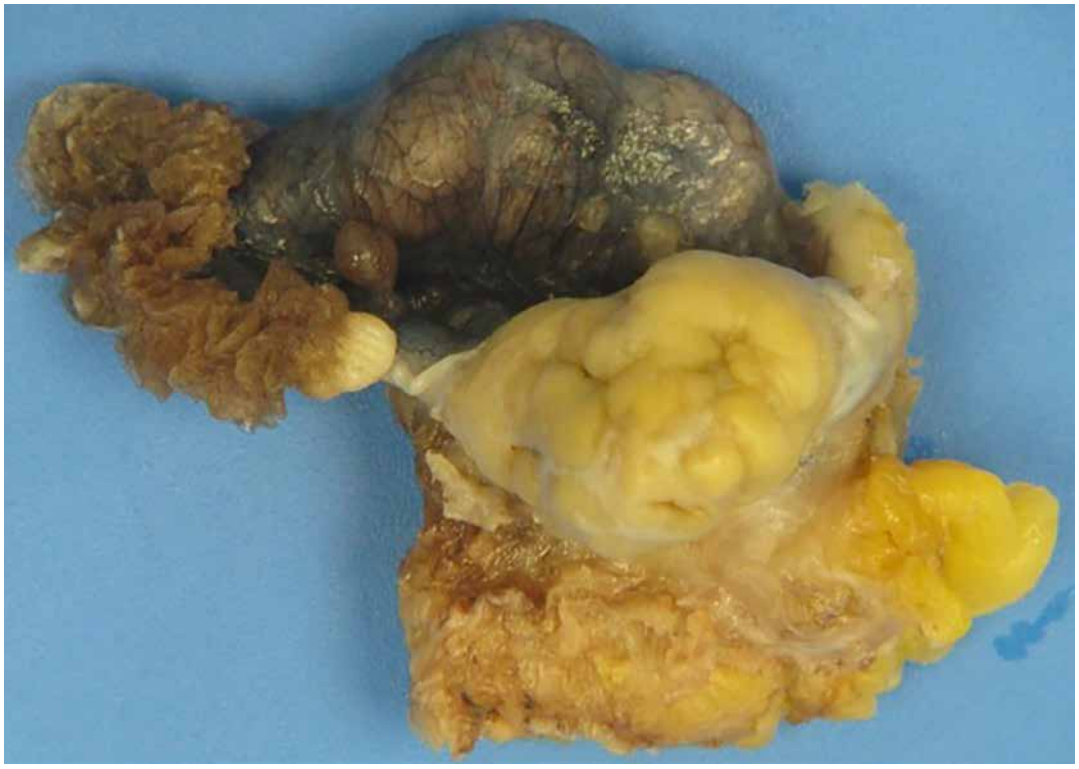
While the discovery has created new research opportunities for diagnostics and targeted therapies, these take time to develop and transfer from the bench to the bedside. However, the implications for primary prevention are much more positive.

The compelling evidence of origin in fallopian tube led some to advocate that fallopian tubes should be surgically removed when the opportunity presented itself.

**Opportunity at Pelvic Surgery**

This procedure (termed opportunistic salpingectomy) could be performed at the time of pelvic surgery in women whose family was complete but who were before the menopause and who wished to retain the benefits of preserving ovary function.

Such opportunities could include hysterectomy for conditions such as fibroids or heavy menstrual bleeding or as an alternative to the traditional methods of ligation (cutting) or clipping of fallopian tubes as a permanent contraceptive method (sterilisation).



Fallopian tube and ovary after surgical removal. The delicate projections at the end of the fallopian tube (top left) are considered to be the site of origin of most 'ovarian cancer'

While the impact for each individual woman will never be known, the potential to impact on a population level is clear. Some North American studies have shown that 20% of women who developed HGSC had had a prior hysterectomy. Each of those could be a potential missed opportunity to intercept a deadly disease.

In debating the merits of the opportunistic salpingectomy (OS) strategy, concerns understandably centred around the safety of the procedure and whether there would be any impact on ovarian function. Reassuringly, studies to date have shown no significant surgical complications and no adverse effect on ovarian function.

Notably, the practice of retaining the fallopian tubes at time of routine hysterectomy has been a historic convention rather than because of any known benefit. Consequently, it has often been associated with various post-operative sequelae, such as dilated fallopian tube masses, sometimes requiring further surgery.

In the last decade opportunistic salpingectomy has increased significantly and has been recommended for consideration by women by several professional gynaecological societies worldwide. A major study by Dr Dianne Miller and colleagues in North America established that the percentage of women undergoing OS at time of hysterectomy had increased by 371% between 2008 and 2013 without any significant increase in peri-operative morbidity or mortality.

**Opportunity at Other Surgery**

Recent years have seen falling hysterectomy rates as improved medical treatment of troublesome symptoms has led to a decreased requirement for hysterectomy in this age cohort. In Northern Ireland, there was nearly a 25% reduction in hysterectomies performed in the largest Health Trust between 2000 and 2010. Thus, the potential impact may be lessened.

However, the opportunity to potentially impact on this cancer may not be confined only to pelvic surgery. The possibility of performing OS at time of removal of gallbladder (cholecystectomy) has been suggested. While this may seem outlandish at first, the rationale is reasonable and given that thousands of such operations are performed each year, the impact on population risk may be considerable. Gallbladder removal is one of the most frequent surgical procedures. In Northern Ireland there was an estimated 2300 cholecystectomies per annum in 2012, having risen from less than 500 per year in 1995. It is also often performed in the group whose families are complete but are before menopause and wish to retain ovaries.

A recent Austrian study (Dr. Gordana Tomasch and colleagues) offering OS to women over 45 years of age undergoing laparoscopic (keyhole) cholecystectomy showed 60% acceptance rate amongst women. Salpingectomy was only performed where the fallopian tubes were clearly visualised and accessible. The additional operating time was 13 minutes on average and no surgical complications were reported in the 98 women who had surgery. The authors noted that while their study showed the potential feasibility of this approach, nonetheless significant logistical challenges would need to be overcome to make this approach feasible in a routine surgical setting including training of general surgeons or coordination with gynaecological surgeons.

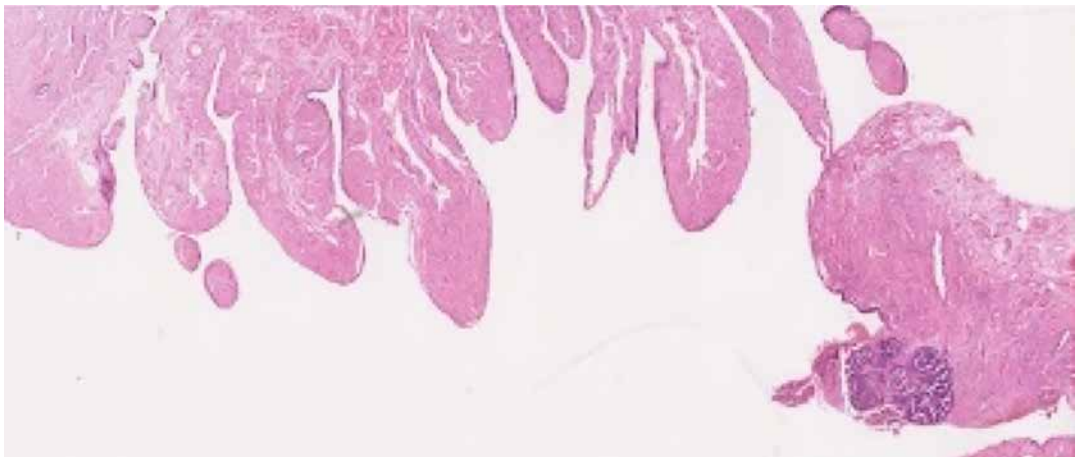
**Impact of Opportunistic Salpingectomy**

Given the effort involved in OS, it is reasonable to ask what the benefit will be and whether there is evidence that it works to reduce the incidence of HGSC. To date there is no prospective study that has shown an effect. Such studies would take decades to come to fruition as the intent of the procedure is to remove the potential source of tumour many years before it would typically develop into HGSC. Given the lifetime frequency of less than 2% of women it would also take vast numbers to definitively show an effect at the population level.

The Vancouver group who have pioneered OS have argued that they “choose to act” now given the strong logical rationale for OS and the reassuring data on safety. They undertook a national educational initiative amongst clinicians in 2010 and a subsequent observational study displayed a significant increase in salpingectomy with hysterectomy, and as the sole method of tubal sterilisation, without any elevation in peri-operative adverse events. With rates of OS increasing significantly, it is clear that OS is an acceptable procedure for women and there has been no groundswell of safety concerns despite being performed for a decade in many centres.

**Prevention in the High-Risk Group**

The discovery that most OC is in fact cancer of fallopian tube origin also has implications for women who have inherited genetic mutations that place them at increased risk of this cancer. Women with BRCA mutations



Microscopic image of the finger-like projections of the fallopian tube. A very early tumour is seen (bottom right)

have increased lifetime risk of breast cancer and HGSC with an estimated risk of 59% and 11 – 27% for HGSC in those with BRCA1 and BRCA2 mutations respectively.

Such women have traditionally been offered surgery in their mid-thirties (BRCA1) and early forties (BRCA2) to reduce risk of developing cancer in future. This surgery involves removal of both fallopian tubes and ovaries (risk reducing bilateral salpingo-oophorectomy - RRBSO). This reduces risk of HGSC to less than 1% and has some effect on the risk of developing breast cancer.

However, undertaking this procedure is a difficult decision given the drawbacks, given that removal of ovaries not only leads to a loss of fertility but also to a 'surgical menopause'. This causes symptoms of menopause, which can be quite debilitating, and an increased risk of osteoporosis (brittle bones), heart disease and stroke. Whilst these can be mitigated by hormone replacement therapy, it is not always feasible for all women and considerable pre-operative counselling and post-operative support is required. Thus, women are faced with a very difficult decision balancing all these factors.

The discovery of the tubal origin has led to further considerations. If the risk is predominantly related to the fallopian tubes could removal of fallopian tubes alone decrease the cancer risk while preserving the benefits of retaining the ovaries.

This has created the possibility of a two-step procedure for those in this high risk group. The first step would involve removal of fallopian tubes. This could be in the early thirties and when the family complete (or earlier if the woman understood the implications of reduction in fertility potential). Ovaries would then be removed closer to the natural age of menopause, thus preserving years of benefits of ovarian hormones and reducing the risks of premature menopause.

While OS in the population at large is a low risk change in practice once shown to be safely performed, the stakes are higher for those in these high risk groups. Fortunately, a prospective clinical trial is studying the impact of delayed oophorectomy. In the United Kingdom's PROTECTOR study, women at high risk of tubal/ovarian cancer will be offered three options for treatment; risk reducing early salpingectomy and delayed oophorectomy, standard surgery (oophorectomy and salpingectomy at same time), or no surgical operation.

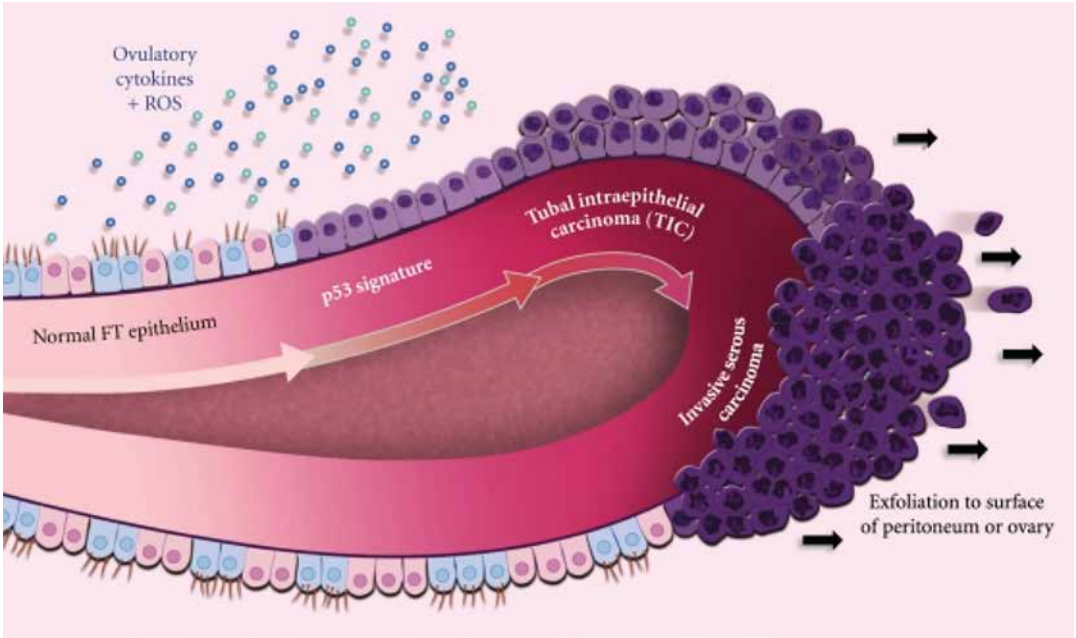
The study assesses women's views and the impact of this approach to prevent OC on sexual function, hormone levels, quality of life and overall satisfaction. The results of this trial are likely to have considerable impact on the care of women at high risk of OC.

**Shared Decision Making**

The rapid pace of change in or understanding of tubal/ovarian cancer in recent years means that there are many considerations for women considering opportunistic salpingectomy at time of abdominal or pelvic surgery and for those women at high risk considering a two-step approach to prevention. There are still many uncertainties and caveats. It will be crucial to provide as truly an informed choice as possible in decision making for women. This will require clinicians to provide up-to-date information to each woman, who may judge their decision based on their own individual perception of risk. In particular for the high risk group considering two stage surgery, the relative values they may place on cancer prevention versus the long term sequelae of premature menopause will inform individual decisions.

**Time for a New Name?**

While the term 'ovarian cancer' is well established in the public mind, perhaps such complex decisions would be better guided and supported by increasing awareness that not all OC is the same. It may now be prudent to undertake a public health campaign to establish clarity that ovarian cancer is a number of different diseases with various sites of origin, which behave differently and require different treatment and prevention strategies. Beginning with education regarding the implications of the fallopian tubal origin of the commonest and most aggressive form, HGSC, would be a good place to start.




Proposed model of tumour development in fallopian tube and spread to ovary and abdominal cavity (from Karst and Drapkin, Journal of Oncology 2010 Article ID 932371)