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A new concept in ovarian cancer: how will this change clinical practice?

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The concept that most ovarian malignancies are not derived from the surface epithelium of the ovary itself may have major implications for clinical practice. It will change the way we might think about screening and preventing the disease from occurring in the first place. This is the first article in this new clinic on women's health.

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Ovarian cancer remains the most lethal of all gynaecological cancers, with more than 800 women annually in Australia dying from the disease despite major improvements in the surgical approach and cytotoxic drug treatment. These improvements have together resulted in longer survival of patients with the disease but unfortunately have not impacted on the overall cure rate.

WHERE DOES OVARIAN CANCER BEGIN?

Much of the reason for this gloomy situation stems from the fact that most cases of ovarian cancer present with advanced disease, with only about 20% of cases being diagnosed as stage 1 or stage 2. It was originally thought that a delay in diagnosis contributed substantially to this scenario but a recent Australian study has shown that family doctors are particularly good at interpreting the nonspecific symptoms related to ovarian malignancy, with the diagnosis being made in a timely fashion in more than 90% of cases.[1] This suggests that the disease may not go through the normal logical sequence of progression by commencing in the ovary and then spreading locally and

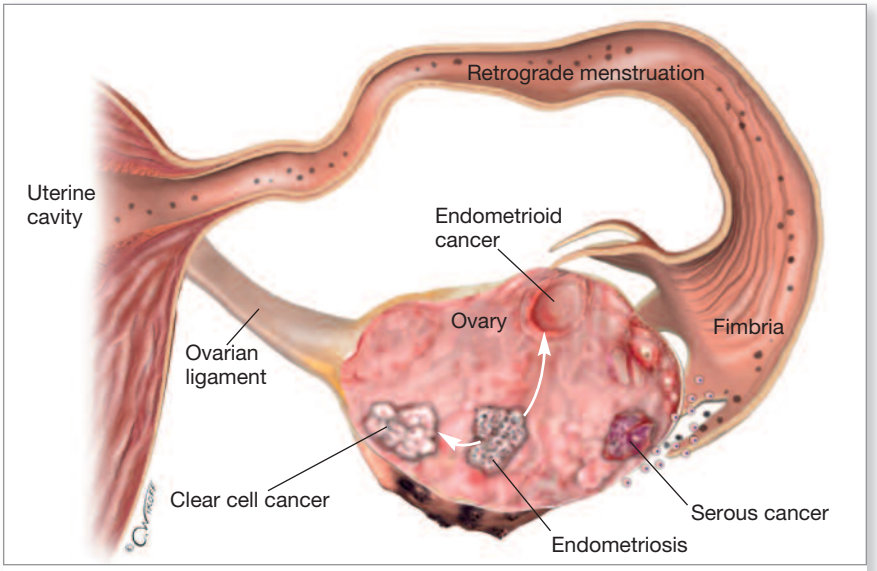

Figure. Origin of serous, endometrioid and clear cell cancers.

eventually into the abdominal cavity, but may start as a field change involving many of the peritoneal surfaces. Furthermore, a study recently published in the *Journal of Clinical Oncology* by the same group from the Queensland Institute of Medical Research and Development has shown that once the woman has symptoms then the time to diagnosis did not affect the stage of disease nor survival.[2]

This late-stage diagnosis has led to the evaluation of potential screening tests before symptoms develop using either measurement of CA125 levels, ultrasound or both. The initial results from studies investigating this are disappointing and it is unlikely that a single test will be effective, certainly in the community at large. We await the results of the UK Collaborative Trial of Ovarian Cancer Screening due for completion next year with interest. This involves 200,000 postmenopausal women, with half being controls and the remainder being screened with annual measurement of CA125 levels or transvaginal ultrasound.

The situation, however, in women with inherited mutations who are at high risk of ovarian cancer may be different. All our thinking about ovarian cancer has been challenged over the past four or five years, with the startling observation that the fallopian tubes in women at high risk of ovarian cancer (mostly who carry *BRCA1* and *BRCA2* mutations) have a very high incidence of carcinoma *in situ*, particularly at the fimbrial end. These *in situ* epithelial lesions of the fallopian tube show gene abnormalities consistent with being early lesions of serous cancer (and are thus termed 'serous tubal *in situ* cancers'). There is a high likelihood that molecular events associated with P53 mutations are the source of 'ovarian malignancy'. Furthermore, gene profiling has shown high-grade serous cancers to be closer to an origin from the epithelium of the fallopian tubes than from the surface of ovarian cells.

We have over time moved from a view that ovarian cancer is one single disease to the view that it is a disease composed of a diverse group of cancers (serous, endometrioid, mucinous, clear cell and transitional [Brenner] cancers), which were classified originally based on their distinct morphological features but now more on their molecular and genetic features. However, the normal ovary does not contain constituents that in any way resemble these cellular types. Ovarian cancer can now be classified into two groups, type I and type II (see Table showing the differences between these two types). Type 1 ovarian cancer is thought to be associated with a substantially better prognosis than type 2 cancer, the latter of which is more common and has a different origin, presentation and molecular profile. We now view ovarian

TABLE. CLASSIFICATIONS FOR OVARIAN CANCER

Classifications	Type 1	Type 2
Histology	Low-grade serous Endometrioid Clear cell Mucinous	High-grade serous Undifferentiated cancers Carcinosarcomas
Precursors	Borderline serous Endometriosis Transitional cells Perhaps benign tumours	Intraepithelial cancer in the fallopian tube
Clinical	Indolent Localised	Aggressive widespread
Mutations	*KRAS, BRAF, PTEN, ERB-B2, PIK3CA, CTNNB1*	*P53*

cancer as arising from the epithelium of the fallopian tube (serous cancers; see Figure) and endometrium (endometrioid and clear cell cancers), and possibly from the transitional-type epithelial nests at the tubal-mesothelial junction (mucinous and transitional [Brenner] cancers).

IMPLICATIONS FOR CLINICAL PRACTICE

The concept that most ovarian malignancies are in fact not derived from the surface epithelium of the ovary itself has major implications for the way in which we view ovarian cancer and also how we might think about screening for the disease or preventing it from occurring in the first place. It should also lead to a more molecular approach to new drug therapies given the molecular changes in the various tumour types, hopefully improving outcomes for women who present with advanced intraperitoneal malignancies.

Prevention

It is not quite clear why ovulation inhibition (e.g. use of oral contraceptives, pregnancy and breastfeeding) is associated with a substantial reduction in the risk of ovarian cancer if it is tubal in origin. It has been suggested that ovulatory cytokines produced locally or during inflammation might influence the *in situ* changes at the fimbrial ends of the fallopian tubes and precipitate transition from *in situ* to invasive malignancy.

We, therefore, need to continue to support the benefits of inhibiting ovulation in women but in the future gynaecologists will need to consider removal of the fallopian tubes or at least the distal end of the fallopian tubes at every opportunity once childbearing is complete. Salpingectomy should be discussed with patients before they undergo surgery for benign reasons, such as for uterovaginal prolapse or uterine fibroids. Furthermore, when discussing sterilisation with the patient, the use of occlusive methods is probably not the ideal choice given the current information available and bilateral salpingectomy should be the approach of choice, certainly if prevention of ovarian cancer is important to the individual woman.

For women at high risk of ovarian cancer, including mutation carriers, then we have to start thinking about whether prophylactic ovarian removal is indeed necessary if the fallopian tube is the source of the disease. It may be possible to eventually counsel young women who are still premenopausal that having children early followed by bilateral salpingectomy is a good option. Prophylactic oophorectomy following the menopause may then be considered. This approach will need strict evaluation with good longitudinal studies to ensure safety, given the fact that we already know prophylactic bilateral salpingo-oophorectomy does lead to a substantial reduction in the incidence and death rate from both ovarian and breast cancers.[3]

Screening

We will also need to rethink our screening strategies and look for potential proteins that are tubal related or molecular markers of tubal origin rather than ovarian origin. The fact that the fallopian tubes may be the source of the disease may clearly explain why ovarian screening has been ineffective as has the use of ovarian biomarkers such as CA125.

SUMMARY

Alterations in the way we view the origin and different subtypes of ovarian cancer are exciting. They provide a more rational way forward in exploring new ways of screening and new options for the treatment of women with ovarian cancer. Finally, some light at the end of the tunnel on this terrible disease! MT

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COMPETING INTERESTS: None.

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