Ovarian cancer: A researcher's perspective

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Ovarian cancer and research

In this podcast, Dr Caroline Ford chats to James about ovarian cancer from a researcher's perspective. Majority of women (about 75%) receive the ovarian cancer diagnosis when they are at stage III or IV. The symptoms and signs are often non-specific and present late. As a result, this leads to late diagnosis and limited options for therapy. Learn more about what research can do to help with ovarian cancer early intervention in this podcast.

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About Dr Caroline Ford

Dr Caroline Ford leads the Gynaecological Cancer Research Group at the University of New South Wales. Her research aims to understand why gynaecological cancers develop, how and why they spread throughout the body, and how best to treat them. Caroline is also an experienced university lecturer, convening courses on medical research, cancer pathology and personalised medicine. And, she is passionate about science communication and enhancing the health literacy of the wider community. Caroline is a strong advocate for women in science and was recently named an inaugural Superstar of STEM, a national program aimed at giving young women and girls a new generation of role models.

Ovarian cancer: A Researcher's Perspective

With Dr Caroline Ford, Head of the Gynaecological Cancer Research Group at the University of New South Wales, Australia

Introduction

Clinically, ovarian cancer often presents late with non-specific symptoms and signs which ultimately lead to a late diagnosis and limited options for therapy. Most women with ovarian cancer (about 75%) are diagnosed at stage III or IV.

− 1. How might research aid in the early detection of ovarian cancer?

- **Unlike other forms of cancer, there is no early detection test for ovarian cancer**

- Despite this, many women believe a Pap smear screens for ovarian cancer and that an HPV vaccine is protective against ovarian cancer
- The stigma and embarrassment surrounding discussion on women's reproductive organs also needs to be addressed
- The 5year survival rate for stage I and II is 70-90%, whereas that for stages III and IV is less than 20%
- An early detection test for ovarian cancer must be appropriate, sensitive and specific
- Adopting a pan-cancer approach for early detection of low-survival cancers (e.g. pancreatic and ovarian cancer) does not confer high sensitivity or specificity for individual cancers
    - This is problematic because the next step following a positive test is invasive surgery
- The Gynaecological Cancer Research Group is using technology which detects circulating DNA in the bloodstream to look for changes in the genome – looking specifically at methylation of tumour DNA
    - Even small stage tumours release DNA into blood stream
    - This would allow detection before a tumour is visible on USS or before symptoms present

2 How would a biomarker as a diagnostic tool look in a clinical setting?

- This would be an early detection test, a blood test that GPs can perform
- *BRCA1* and *BRCA2*gene mutations predispose to ovarian cancer as well as breast cancer
- Patients with a family history of *BRCA1* or *BRCA2* mutation can be tested and, if positive, may choose to have a prophylactic oophorectomy or salpingo-oopherectomy
- In *BRCA1* mutation patients who have had prophylactic salpingo-oopherectomiesbefore any diagnosis of disease, early changes in the fallopian tubes and a p53 signature have been noted– i.e. early cancer
    - This has radically changed our perspective on 'ovarian' cancer (previously thought to have arisen on the surface epithelium of the ovary) – whether it is organ specific, the cell of origin and how it arises

3. Have advances in molecular profiling been met with more personalisedtreatment options?

- Personalisation of ovarian cancer treatment occurs to a degree but is in its infancy
- There is extreme heterogeneity in ovarian cancer; many studies have demonstrated that amongst the different subtypes of ovarian cancer, the patient populations and prognoses are very different

- Personalised treatment is most applicable to patients with *BRCA1* and *BRCA2* mutations
    - *BRCA1* and *BRCA2* are genes which produce tumour suppressor proteins – important for repair of double-stranded breaks in DNA by the homologous recombination repair pathway
- These patients can receive PARP inhibitors (e.g. olaparib)
    - PARP (poly ADP ribose polymerase) proteins repair single strand breaks in DNA
    - When DNA replicates, the single strand breaks become double stranded breaks and in patients with tumours with *BRCA1* and *BRCA2* mutations, these double stranded breaks cannot be repaired leading to cell death
- However more recent studies have shown it is not only patients with *BRCA1* and *BRCA2* mutations who are sensitive to these agents
- There is good pre-clinical evidence of particular aberrant pathways in different subtypes of ovarian cancer
- There has been a strong movement for international collaboration
    - Ovarian cancer is uncommon and some of its subtypes (e.g. clear cell ovarian cancer) are very rare so studying the treatment of these rarer types can only be done through international trials
- In the next 5 or so years, research will be focused on different signaling pathways, which drug combinations rather than single agents are most effective, and managing resistance to those drugs

4. What are some of the mechanisms of resistance in ovarian cancers?

- Currently, most patients are treated with platinum-based chemotherapies and most patients become resistant to these over a period of time
- One technique cells employ is to become more mesenchymal
    - The epithelial to mesenchymal transition (EMT) is a process whereby upright epithelial cells lose polarity and become elongated and mobile which is important in cancer and metastasis
    - This change also makes cells more impermeable to drugs, as they can hide in the extracellular matrix
    - This mechanism is used across different tumour types so opportunities to target genes involved in this process would be widely applicable
- Recently, resistance to PARP inhibitors has also been observed

5. How does research address some of these challenges?

- Having good models to understand the cancer cells
- Many research groups use patient derived xenografts (PDX) models, where chemo-resistant tumour tissue from patients is implanted into mice and researchers try different drugs in the mice in a laboratory
- The Gynaecological Cancer Research Group uses patient material in a 3D coculture model
    - The omentum from patients is taken and the mesothelial cells and fibroblasts are isolated
    - These are then cocultured with cancer cells within an extracellular matrix
    - Gene expression can then be modulated with knockdowns and knock-ins and fluorescent tags to understand these mechanisms in a controlled laboratory environment

6. How do we best support women living with ovarian cancer?

- There's a strong research focus on survivorship and quality of life – specifically psychosocial effects and patients' decisions surrounding genetic testing
- Because of the location of the cancer, there has to be a discussion about fertility and sexual function
    - Although most women are post-menopausal at diagnosis, many are in their reproductive years
    - Also, for pre-menopausal patients, there are repercussions of surgery, e.g. early menopause
- An understanding of the psychosocial effects is important – many women report feeling a loss of femininity
- From time of diagnosis, patients have access to counsellors and psychologists at hospital clinics
- These issues are most important to patients

Reference

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