GRESHAM COLLEGE

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BREAST, UTERINE AND OVARIAN CANCER

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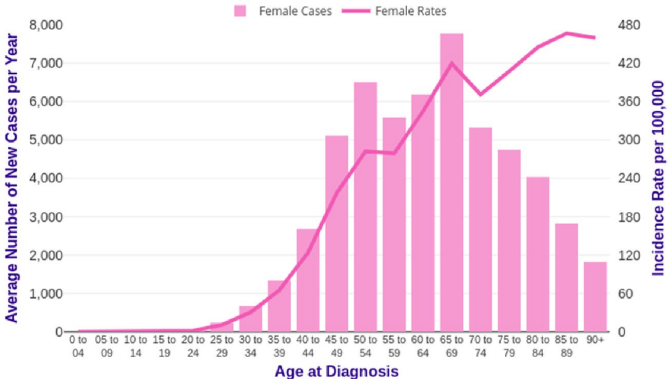
The cancers we are considering in this lecture almost exclusively afflict women. Medical descriptions of women dying of these cancers go back over a thousand years. They have however steadily increased as a proportion of deaths and disability in women as infectious and then cardiovascular deaths have decreased. Cancer remains a major challenge but survival is steadily improving, and treatment is becoming safer and less invasive. Breast cancer is the commonest cancer in women, but uterine and ovarian cancers are also major cancers, being the fourth and sixth most common cancers in women in the UK. The great majority of women diagnosed with breast and uterine/endometrial cancer will be alive and well 10 years later. Advances in ovarian cancer have been slower although the outlook is good if it is caught early. As with all talks in this series this aims to give a broad overview of the diseases, their prevention and treatment, and specific questions about your own health should be discussed with your doctor.

Throughout this lecture and the rest of this series I will be using three terms for a cancer which have implications for its outlook and treatment. These are stage, grade and type. The **stage** of disease is a measure of how large the tumour is and how far it has spread at the point of diagnosis; it is the most important for prognosis for the three cancers we are considering today. The **grade** is how different from normal cells cancer looks under a microscope with more abnormal cells generally being more aggressive and having a worse prognosis. The **type** of cancer is usually based on what kind of cell it arose from in a particular location. If solid cancers are diagnosed at an early stage they can usually be cured with surgery and relatively minimal use of radiotherapy and chemotherapy. Most breast cancer and uterine cancer are diagnosed at an early stage which means there is a high chance of cure whilst majority of ovarian cancer is diagnosed at a later stage.

<u>Breast Cancer</u>

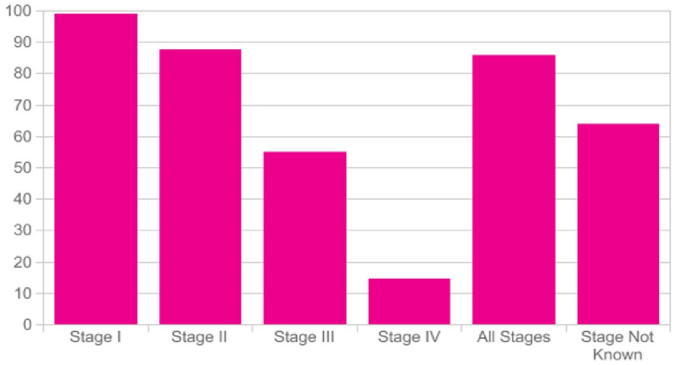
Breast cancer is common; around 1 in 7 women will develop cancer in their lifetime or around 55,000 a year in UK. Most cancer starts in the ducts, with invasive cancer (no special type), most common (70%). Men rarely get breast cancer (about 400 pa in the UK). **Cancer incidence** (cases/100k) peaks in old age (90+) but currently the majority of cases are from late 40s to early 70s (Figure 1, L CRUK data). Breast cancer is the commonest cause of death in women 35 to 49, but still rare. Incidence of breast cancer has been slowly rising over time; around 23% is in theory preventable.

Breast cancer **survival** is steadily improving. 10 year survival in the 1970s was around 40%. Now overall there is 96% survival at 1 year, 87% survival at 5 years and 78% (ie around 4 in 5) at 10 years, and this is likely to continue to improve as medical science continues to advance. The great majority in the UK is diagnosed at Stage I or II. Stage III means >5cm, multiple lymph nodes or local spread. Stage IV is distant spread (metastatic). Stage at diagnosis strongly determines survival. Figure 2 (L, CRUK) shows percentage survival to 5 years by stage at diagnosis. Most breast cancer is found by women noticing lumps or other changes to the



breast. Whist most new lumps are not cancer, persistent new lumps should be checked out with a doctor, especially in older women.

Breast cancer **screening** has been important at helping diagnose early. In the UK it is undertaken between 50



and 70 years. Trials are ongoing to determine if it is effective in 47 49 and 71 73 year olds. Those over 70 can self-refer. In 2017/18 around 2.5 million women were invited for breast screening, around 1.8 million attended (71%). 18,001 cancers were detected of around 54,500 total cancers (33%). UK screening is estimated to save 1 life for every 1,200 women screened, or up to 1,700 lives per year. There is a trend towards lower screening rates in areas of greater deprivation. In all screening there is a tradeoff between tests which are not sensitive enough, so missing cases, and being too sensitive so unnecessary invasive procedures like biopsies are done. Mammography with low-dose X-rays remains the best screening modality. MRI is more sensitive but can lead to more unnecessary procedures (but may be better in dense breasts). Ultrasound is useful for suspicious areas, lumps that do not show up, or to guide biopsy.

Treatment of breast cancer depends on surgery, radiotherapy, hormone therapy and chemotherapy. **Surgery** is the oldest, and remains the most effective, part of breast cancer treatment, especially for early stage disease. A small tumour that has not spread can be cut out and that, for practical purposes, is that. Surgery is still advancing, and there have been major advances in identifying spread to lymph nodes, minimally invasive surgery and breast reconstruction to reduce the psychological and social impact of surgery. For sentinel node sampling radioactive tracer and dye are injected into the tumour to see where it drains. Nodes are sampled and examined to assess need for further operation. This has allowed minimally invasive surgery, which usually has much less physical impact than a mastectomy, with very similar overall survival rates.

Radiotherapy was first used in 1896. It is mainly used mainly after breast conserving surgery to irradiate the area where the lymph glands draining the affected breast are. Radiotherapy kills cancer cells, and cells like mouth, gut or hair cells which also divide rapidly of they are in the beam. Modern advances in radiotherapy include reducing dose and minimising scatter into normal tissue to reduce side effects. Trials clearly support the use of radiotherapy; in 10 801 women, in 17 randomised trials of radiotherapy versus no radiotherapy after breast conserving surgery it reduced the 10 year risk of first recurrence from 35·0% to 19·3%. The side effects of radiotherapy can be overestimated by patients. Severe longer term side effects can occur, but are rare for breast cancer treatment. Short term tiredness, reddening of skin, local swelling are common. As it has effects

on rapidly dividing cells, for breast cancer temporary armpit hair loss is common, sore throat less common. Occasional inflammation of lung or (if it is left breast) heart and skin shrinkage occur. More serious long term side effects occur, but are rare.

To guide further treatment, there are three major subtypes of breast cancer using presence or absence of molecular markers for oestrogen (estrogen (ER)) or progesterone receptors and human epidermal growth factor 2 (ERBB2; formerly HER2). These are hormone receptor positive/ERBB2 negative (70%), ERBB2 (HER2) positive (15%-20%) and triple-negative (tumours lacking all 3 markers; 15%). **Hormone therapy** has been a major advance in breast cancer. Drugs include Tamoxifen, and anti-oestrogen developed as an (unsuccessful) morning after contraceptive. Taking 5 years tamoxifen reduces recurrence and mortality in oestrogen receptor positive (ER+) women; 10 years treatment is a bit better than 5 (15 probably no better than 10). Aromatase inhibitors are better still (reduce by around 30%) in postmenopausal women as they prevent the production of oestrogen in adipose and other peripheral tissue. **Antibodies** also pay a role in some women. HER2+ (human epidermal growth factor receptor 2) is overexpressed in 20-30% of breast cancers. HER2 promotes cell growth. Trastuzumab (Herceptin) monoclonal antibody blocks the receptor, reduces progression and improves survival in HER2+ breast cancer although resistance is a problem.

Conventional **chemotherapy** is used in a minority of women, mainly with later stages. The basic mechanisms of chemotherapy are conceptually simple. They kill any cell that is dividing- cancer cells which divide rapidly are more sensitive and slower to recover. Many of the chemotherapy agents in breast cancer are quite old, and derived from diverse routes. All of them interfere with the process of cell division. Antifolates like methotrexate were derived after the discovery of folate in pregnancy in India 1930s. The nitrogen mustards were from mustard gas (1940s) such as cyclophosphamide. Anthracyclines like Doxorubicin, Epirubicin were derived from an antibiotic produced by Streptomyces bacteria from the soil round Castel del Monte in 1950s. Streptomyces antibiotics also led to mitomycins- Mitomycin-C in Japan, 1950s. Anthracenedione has a basis in plant dyes from fungi- mitoxantrone. Fluorouracil (5FU) was chemically derived in the 1950s. Chemotherapy is understandably a cause of concern for many cancer sufferers, as the side effects are unpleasant, if usually short-term. Chemotherapy has its biggest impact on cells that are rapidly dividing: gut, hair follicles, mouth, skin, bone marrow. This can lead to major nausea, vomiting, swallowing difficulties. Temporary hair loss is common. Immune system suppression leads to an increased risk of infection. Women will want to discuss these in detail with medical professionals before starting treatment to understand the balance of risk and benefit.

Late stage breast cancer treatment and treatment of **metastases** continues to improve. Advances in the best combinations of hormone therapy, radiotherapy and chemotherapy are occurring. New advances in immunotherapy, discussed in my last lecture, are beginning to show results in some women with advanced breast cancer; an example is tumour-infiltrating lymphocytes (TILs). Advanced (late stage) breast cancer will remain a major disease with much higher risk treatment for the foreseeable future however; much better is early diagnosis and better still prevention.

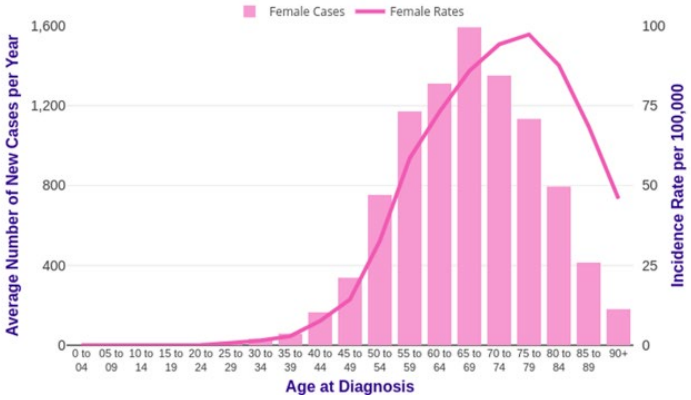
Around 5-15% of breast cancer risk is **genetic / hereditary**. The breast cancer genes, BRCA1 and BRCA2 mutations, are the most important and both increase overall risk and risk of cancer at a lower age. Several less common gene mutations have been identified (PTEN, TP53, STK11, CDH1). Familial risk is a further 15-20%, probably based on several genes ('polygenic risk'). Various approaches have been taken to protecting women with substantially increased risk. Enhanced screening with mammogram or MRI, starting screening earlier in life and being more frequent, prophylactic drugs, and in some (rare) cases mastectomy are considered.

Three potentially modifiable risk factors are significant enough to be worth considering even in a short lecture: alcohol, HRT and obesity. Light **alcohol** drinking has a minimal (not zero) increased risk, but heavier drinking significantly increases risk of breast cancer. In the million women study, it was estimated that by 80 years old breast cancer would occur in 9 out of 100 for those who don't drink at all, 10 out of 100 for two standard drinks a day and 13 out of 100 for six drinks a day. **HRT** (hormone replacement therapy) is a more complex

picture, as there are health benefits from HRT and benefit and risk need to be balanced in discussion with your doctor. There is minimal increased risk for short (<1 year) or previous use, so for women using HRT to deal with the unpleasant symptoms going through the menopause the risk is extremely small. There is a significantly higher risk of breast cancer for longer use, greatest at current use for >10 years. Most risk is, unsurprisingly, in ER+ cancers since oestrogens drive these cancers. Women therefore need to discuss longer HRT use with their doctors, especially if they have a family history of breast cancer. **Obesity** increases risk mainly by increasing production of oestrogens after the menopause. Therefore, again unsurprisingly, obesity is a significant risk for postmenopausal ER+ breast cancer, but not for premenopausal breast cancer. For the same reason postmenopausal obesity is a major risk for uterine cancer.

Uterine Cancer

Uterine cancer is also known as womb cancer. Most (>3/4) is endometrial cancer. There are 9,500 cases of uterine cancer a year in the UK, the 4th most common cancer in women. The great majority (90%) are diagnosed in Stage 1 due to bleeding, either abnormal bleeding premenopausal, or (much more commonly) postmenopausal bleeding. It is important to stress most bleeding post menopause (90%) is not cancer, but it should be investigated. 95% of women with Stage 1 survive for >5 years. Around 78% of all patients survive >10 years.



The great majority of uterine cancer is postmenopausal (Figure 3, CRUK data). The mainstay of treatment for Stage 1 and Stage 2 uterine cancer is **surgery**, and for most women this is all the treatment they need. For Stage 1 disease a total hysterectomy with womb, cervix; often bilateral salpingo-oophorectomy including fallopian tubes and ovaries. One or both ovaries may be left in pre-menopausal women. Surgery is more extensive in Stage 2 (radical hysterectomy), including lymph nodes. It may be done by laparoscopic (keyhole) surgery which improves recovery times. Some high-grade or rarer types of cancer (eg clear cell, 2%) may need chemotherapy or radiotherapy in Stage 1 or 2, but it is a minority. **Radiotherapy** may be brachytherapy, delivered locally rather than external beam to minimise the scatter of radiotherapy to healthy tissues. The general effects of radiotherapy and chemotherapy are similar to breast cancer, but radiotherapy will also cause some (usually temporary) local effects the radiotherapy team will need to explain depending on site.

In Stage 3 and even more Stage 4 the relative importance of surgery decreases, and of chemotherapy, hormone therapy and radiotherapy increases. Common drugs used in current conventional **chemotherapy** is Paclitaxel (Taxol) first isolated in 1971 from the Pacific yew, and the Carboplatin, cisplatin class. Cisplatin was discovered in 1845 (Peyrone's salt); its cancer-fighting properties derived indirectly from finding that using platinum electrodes inhibited *E. coli* growth. Doxorubicin and cyclophosphamide may also be used as for breast cancer.

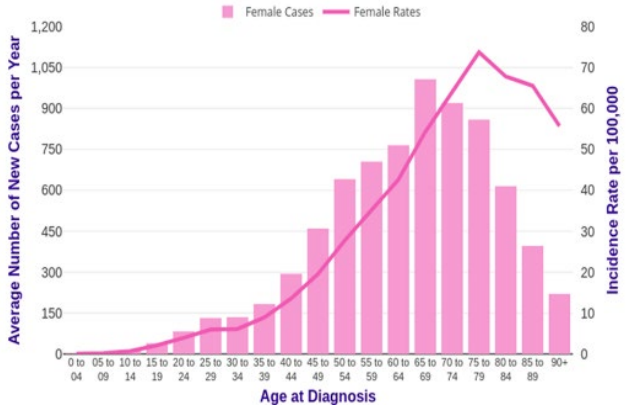
In contrast to breast cancer, currently **hormone therapy** is normally only used in advanced cancer. Progesterone and oestrogen are the two major hormones of the female cycle. Around 25% of advanced endometrial cancers respond to progesterone. A rare cancer, endometrial stromal sarcoma, responds well to hormone treatment.

Most of the **risk factors and protective factors** for uterine cancer are associated with hormonal balance. When oestrogen is higher, especially relative to progesterone, the risk is higher. Obesity is a significant risk

factor because of the ability of adipose tissue to generate oestrogens post-menopausally. Oestrogen-only HRT is higher risk, whilst the combined oral contraceptive protective. Pregnancy decreases risk, probably due to lower oestrogen. Polycystic ovary syndrome also increases risk. Type I and II diabetes appear to be a risk factor, whilst exercise is (as with so many diseases) protective.

Ovarian Cancer

There are around 7,500 cases a year in the UK. Incidence is broadly flat, and there is no deprivation gradient. It is more common in white women than those with Asian or African heritage. Outlook is good in Stage 1 disease without spread: 90% survival at 5 years. Surgery is the mainstay. The major problem in ovarian cancer is that a high proportion (>50%) is diagnosed in Stage 3 or 4, where the outlook is not as good. The symptoms are usually minor and non-specific until advanced.



Older age is the major **risk factor** for ovarian cancer (Fig 4, CRUK data). Family history is also important. If mother or sister are diagnosed with ovarian cancer a woman has around 3x the risk than when there is no family history, and BRCA1, BRCA2, Lynch syndrome significantly increase the risk. There is a slight increased risk with diabetes, overweight, extended HRT. Oral contraceptive use, pregnancy, and breastfeeding slightly decrease risk.

Since late diagnosis is the major issue with ovarian cancer a lot of effort has gone into earlier diagnosis, with only modest impact to date. Two common modalities for detecting ovarian cancer earlier; the blood test CA125, and ultrasound (generally transvaginal) have been considered for **screening**. A recent large UK trial of 202 638 women aged 50–74 randomised to yearly CA125 blood test+ultrasound, yearly ultrasound, or neither. Of these, 0·29% of women in the combined group, 0·30% in the USS group, and 0·34% in the no screening group had died of ovarian cancer at median 11 years (Ian Jacobs et al, Lancet 2016). This was not significant and is consistent with previous large studies. We therefore probably need to get better tests before screening will be worthwhile.

Women therefore need to take account of symptoms, which can be vague. New symptoms 12 or more times in a year, especially after age 50, including feeling constantly bloated, a swollen abdomen, discomfort in abdomen or pelvic area, feeling full quickly when eating, or loss of appetite and needing to pass urine more often than normal are all worth taking seriously, and discussing with a doctor. Most women with these symptoms will **not** have cancer.

Whilst surgery will be curative in the great majority of Stage 1 disease, **chemotherapy** is considered in Stage 1c or above, or in high grade cancers. Carboplatin +/- Paclitaxel (used also in uterine cancer) are the mainstays of treatment, but Gemcitabine, originally developed as an antiviral, Etoposide derived from wild mandrake, and Topotecan derived from bark of Camptotheca (Happy) tree in Tibet and southern China are also used in conventional chemotherapy. Side effects are similar to chemotherapy agents discussed above.

Survival from ovarian cancer is improving for higher stages, albeit slowly. It is already very good (over 90% 5 year survival) for early disease. UK ten-year survival for ovarian cancer overall doubled from 18% to 35% since 1970s. But it is still poor compared to breast and uterine cancer, and late diagnosis is the main reason. Ovarian cancer is therefore a major target for earlier diagnostic methods and new treatments in later disease. Immunotherapy, discussed in the last lecture, is being tested in ovarian cancer with some promising early results but it is not yet in standard treatment.

Conclusions

It is likely that over time cancers we currently treat as a single cancer type will increasingly be seen as several subtypes with differentiation on the basis of genotyping. They will have different prognosis and treatment. Whilst this is likely to be less important in early breast, uterine and ovarian cancers where surgery +/- localised radiotherapy is highly effective, it is going to be important in later disease to guide chemo- and immune-therapy.

This lecture has discussed the remarkably improved outlook for the major cancers which are almost exclusive to women (breast cancer in men, and transsexual people the exceptions). For **breast cancer** screening, early surgery, radiotherapy and hormone therapy have changed the outlook. 78% 10 year survival is the current standard, and is likely to continue to improve.

Uterine cancer is generally diagnosed early, at which stage outlook is good. It also has 78% 10 year survival.

Ovarian cancer already has good outlook with early diagnosis, but most is diagnosed late, and whist survival is improving it is slowly.

Cervical cancer was discussed in the last lecture on infection-associated cancer, and is another major cancer of women. Screening has reduced mortality significantly and HPV vaccination will substantially reduce incidence over time in the UK and globally.

Finally I would like to pay tribute to the many thousands of women who have taken part in the trials and studies which have made these and future advances possible, and the scientists, including many leading women scientists who have provided the underpinning research to make these improvements possible.

Further Reading

The Cancer Research UK (CRUK) website has some excellent data on these diseases, and the NHS website and other cancer charities have very good information for patients. I would highlight for

Breast cancer: CRUK https://www.cancerresearchuk.org/about-cancer/breast-cancer

Uterine cancer: CRUK https://www.cancerresearchuk.org/about-cancer/womb-cancer

Ovarian cancer: CRUK https://www.cancerresearchuk.org/about-cancer/ovarian-cancer

For more technical recent reviews (generally needing a medical library)

Waks AG, Winer EP. Breast Cancer Treatment: A Review. *JAMA*. 2019 Jan 22;321(3):288-300.

Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. *Lancet*. 2019 Mar 23;393:1240-1253.