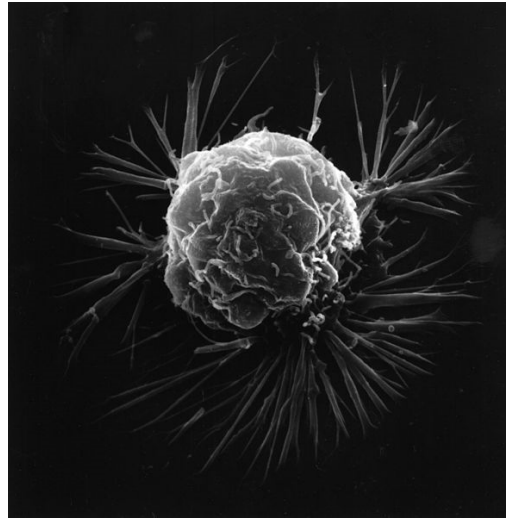


Breast, uterine and ovarian cancer.



Christopher Whitty  
Gresham College 2019.

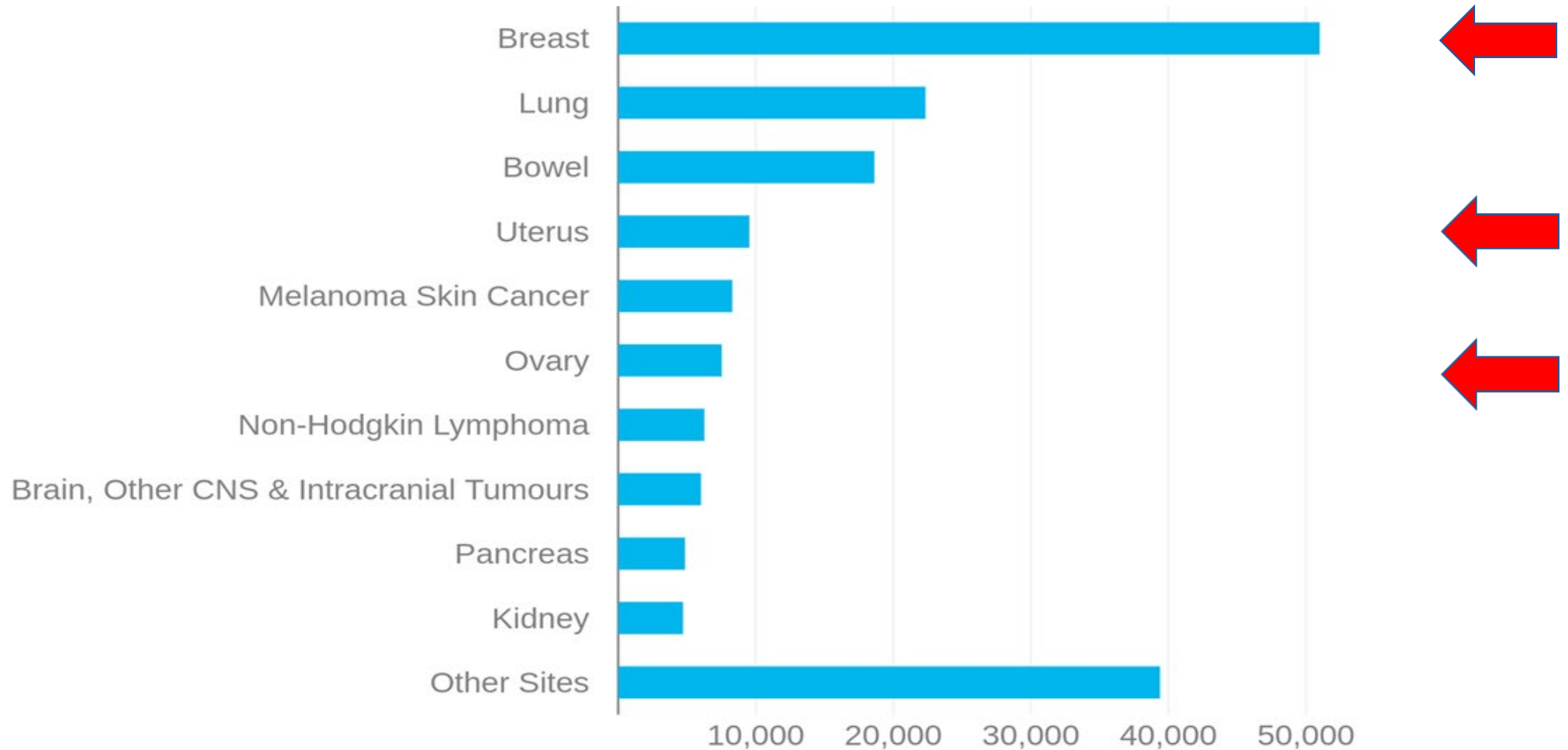
# Descriptions of women dying of cancer are as old as recorded medical history.

- The proportion of deaths caused by cancer steadily increased as infectious and then cardiovascular deaths decreased.
- Survival from cancer has steadily improved.
- Treatment has become safer.



Empress Theodora C500-548

Breast cancer the commonest cancer in women in the UK, around 54,500 cases a year (31% of all female cancers). Uterine is 4<sup>th</sup>, 9500 cases, ovarian 6<sup>th</sup> most common 7500 cases a year. *CRUK 2019.*



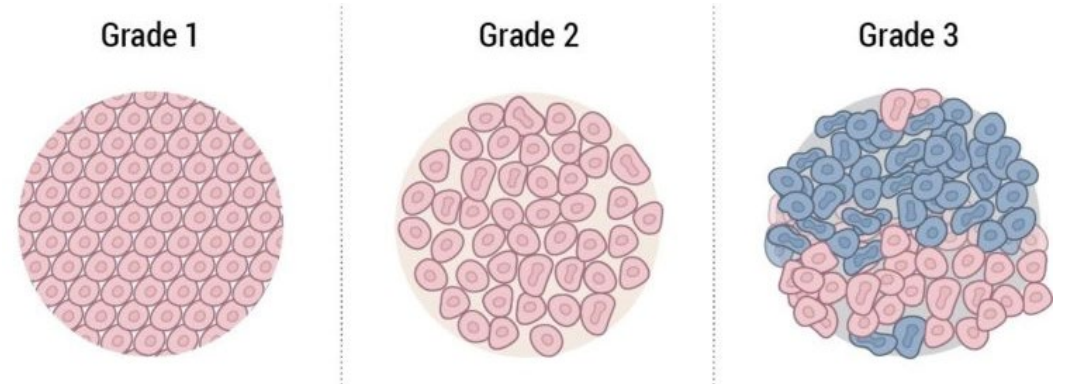
## Stage, grade and type of cancers.

**Stage:** size and degree of spread.  
Usually Stage 1 to Stage 4.

**Grade:** appearance of the cells.

- Grade 1 – cancer cells resemble normal cells, aren't growing rapidly
- Grade 2 – cancer cells don't look like normal cells and are growing faster than normal cells
- Grade 3 – cancer cells look more abnormal; may grow or spread more aggressively.

**Type.** Several types in one organ,  
usually from the cell they arise from.



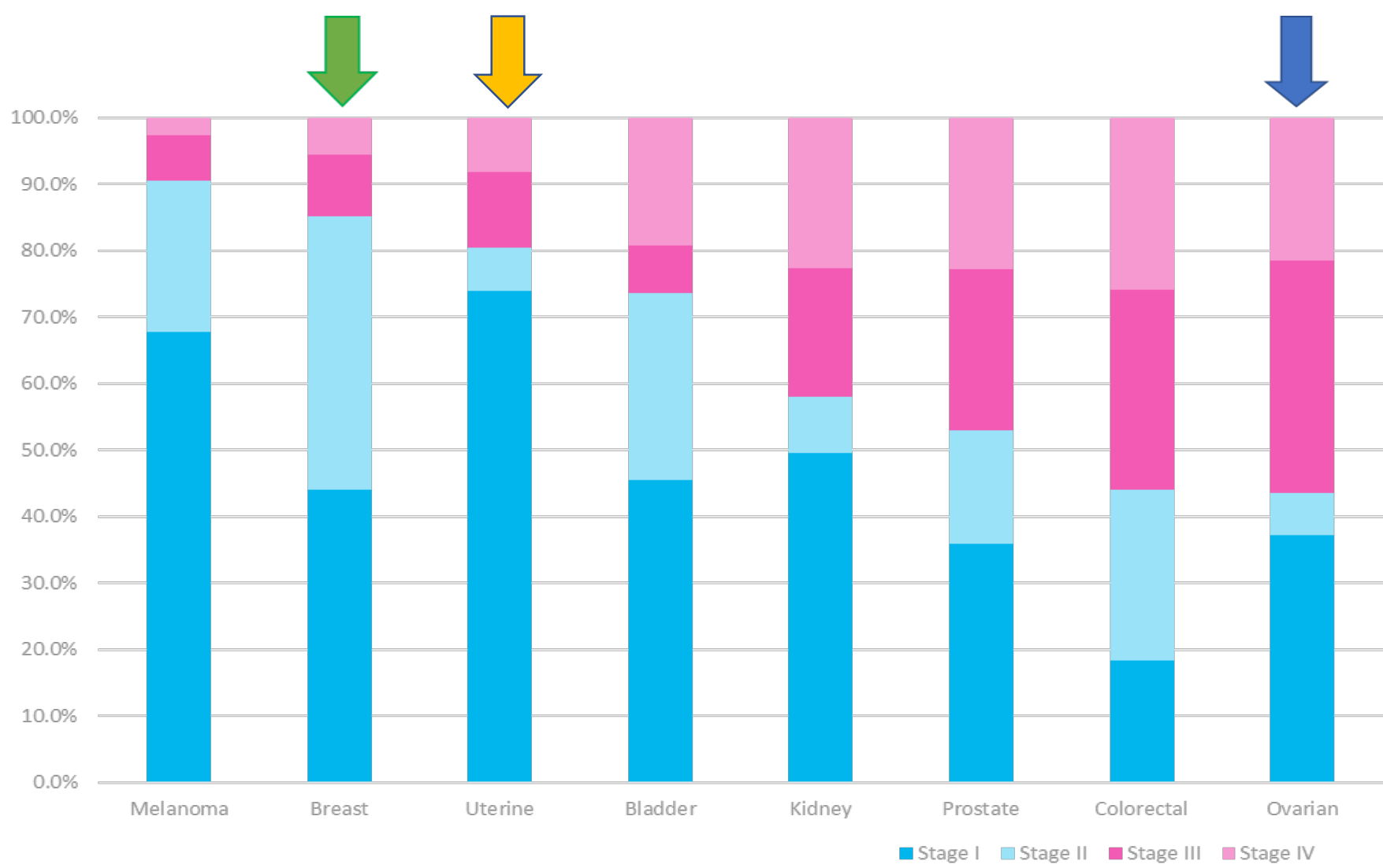


# Early diagnosis key. Proportion diagnosed by stage, England 2017.

Breast, uterine, ovary. (CRUK).

100%

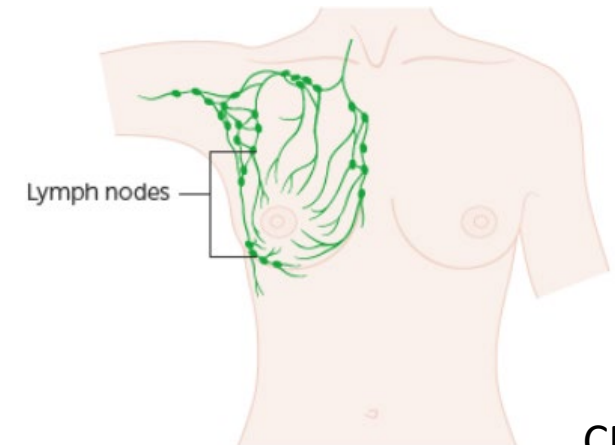
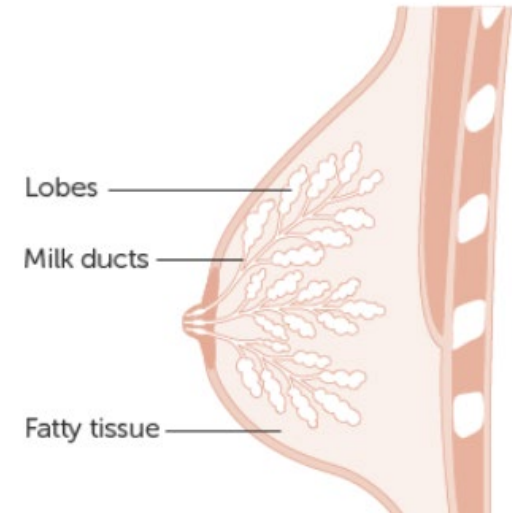
50%



■ Stage I ■ Stage II ■ Stage III ■ Stage IV

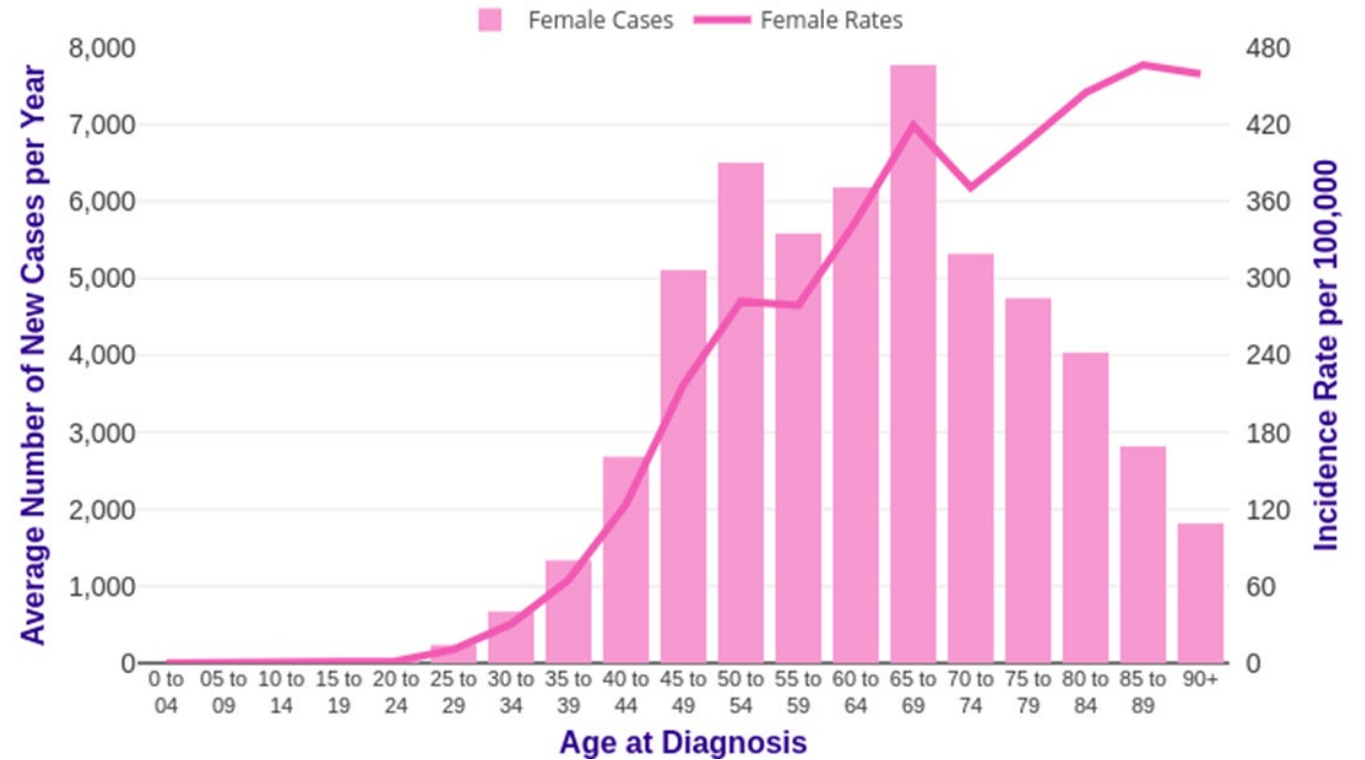
# Breast cancer.

- 1 in 7 women will develop cancer in their lifetime. Around 54,500 a year in UK.
- Most cancer starts in the ducts.
- Invasive cancer (no special type), most common (70%). Lobular cancer around 15%.
- Treatment the same.
- It may be localised to the breast tissue, or spread to the lymph nodes.
- Men rarely get breast cancer (about 400 pa).



# Breast cancer incidence.

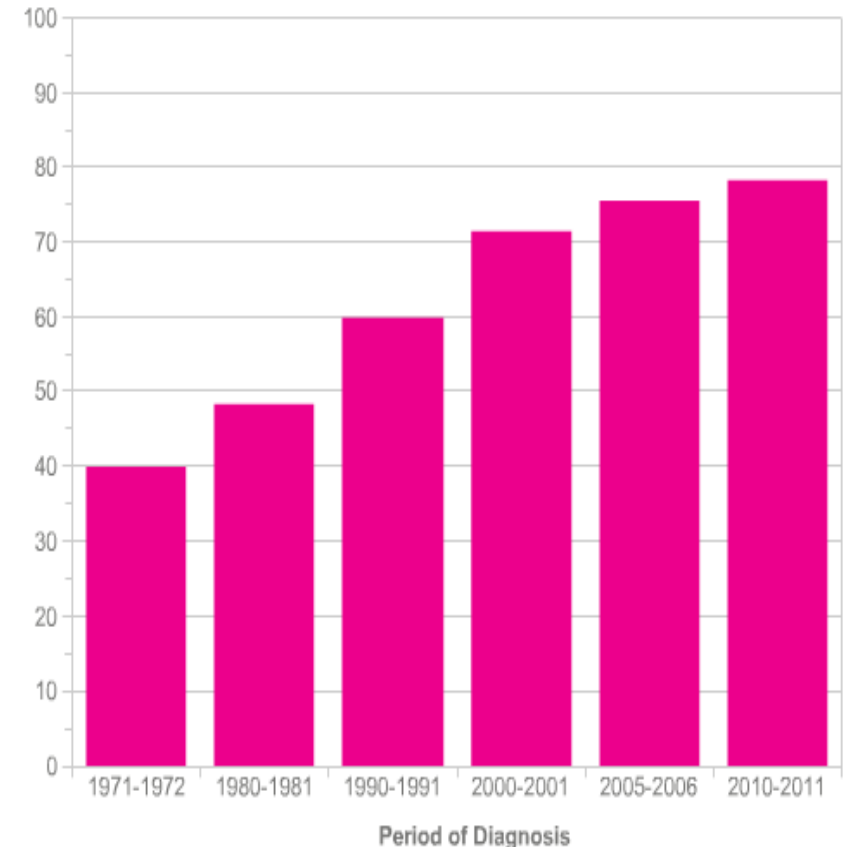
- Cancer incidence (cases/100k) peaks in old age (90+).
- But the majority of cases from late 40s to early 70s.
- The commonest cause of death in women 35-49, but still rare.
- Incidence slowly rising over time.
- Around 23% preventable.



30 50 70

# Cancer survival breast cancer.

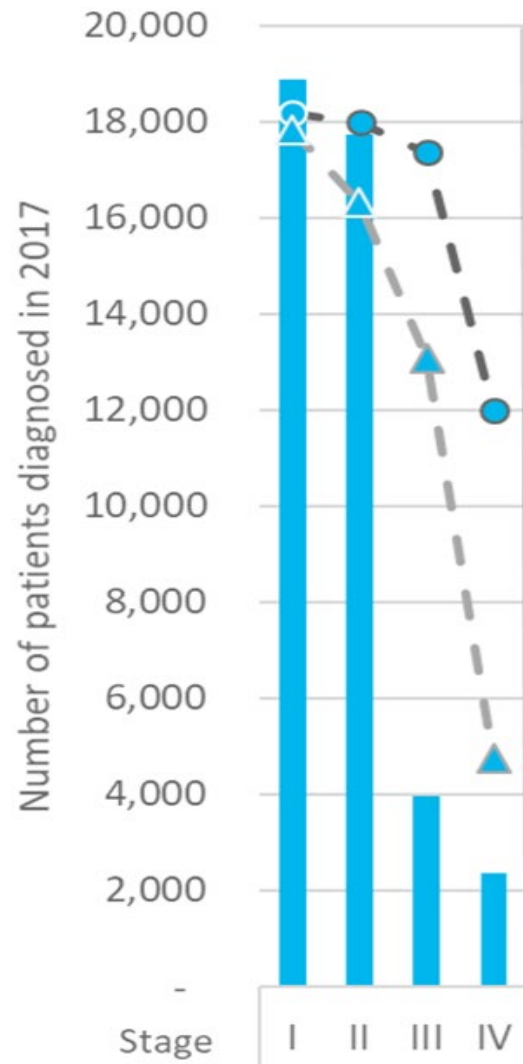
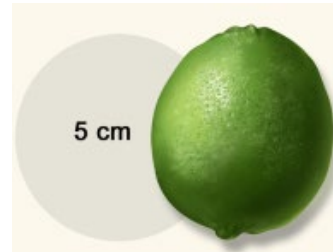
- Cancer survival steadily improving.
- 10 year survival since 1970s. Started at around 40%.
- Overall, 96% survival at 1 year, 87% survival at 5 years, **78% at 10 years.**



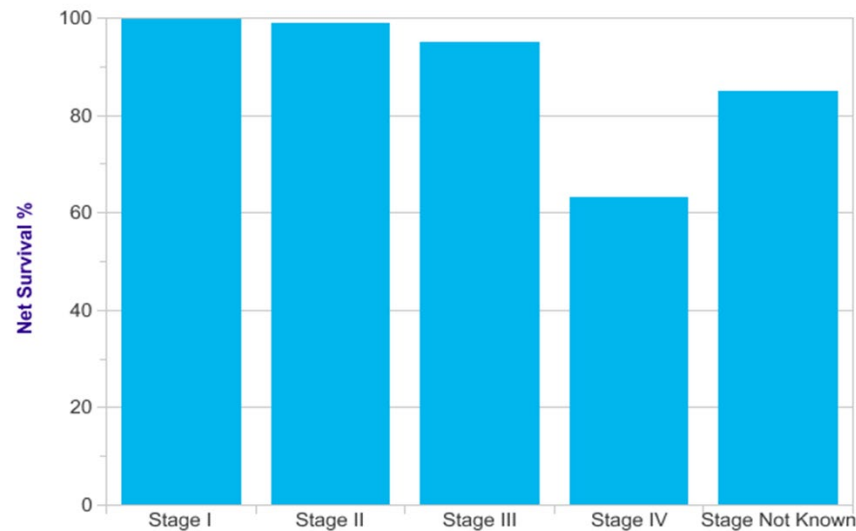


# Survival strongly determined by stage.

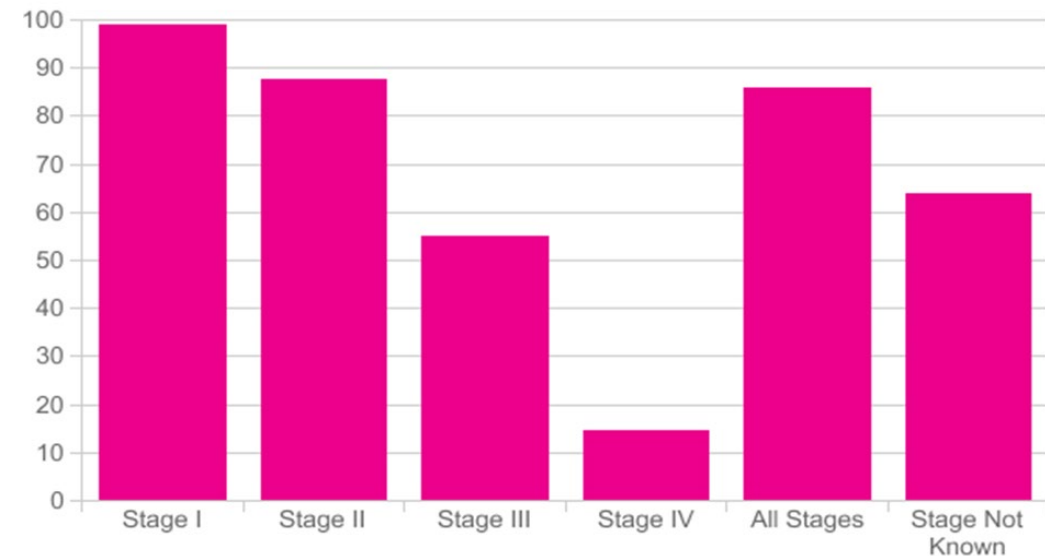
The great majority in UK diagnosed at Stage I or II.  
Stage III >5cm, multiple lymph nodes or local spread.  
Stage IV is distant spread (metastatic).



2017



1 year survival by stage, 2014.

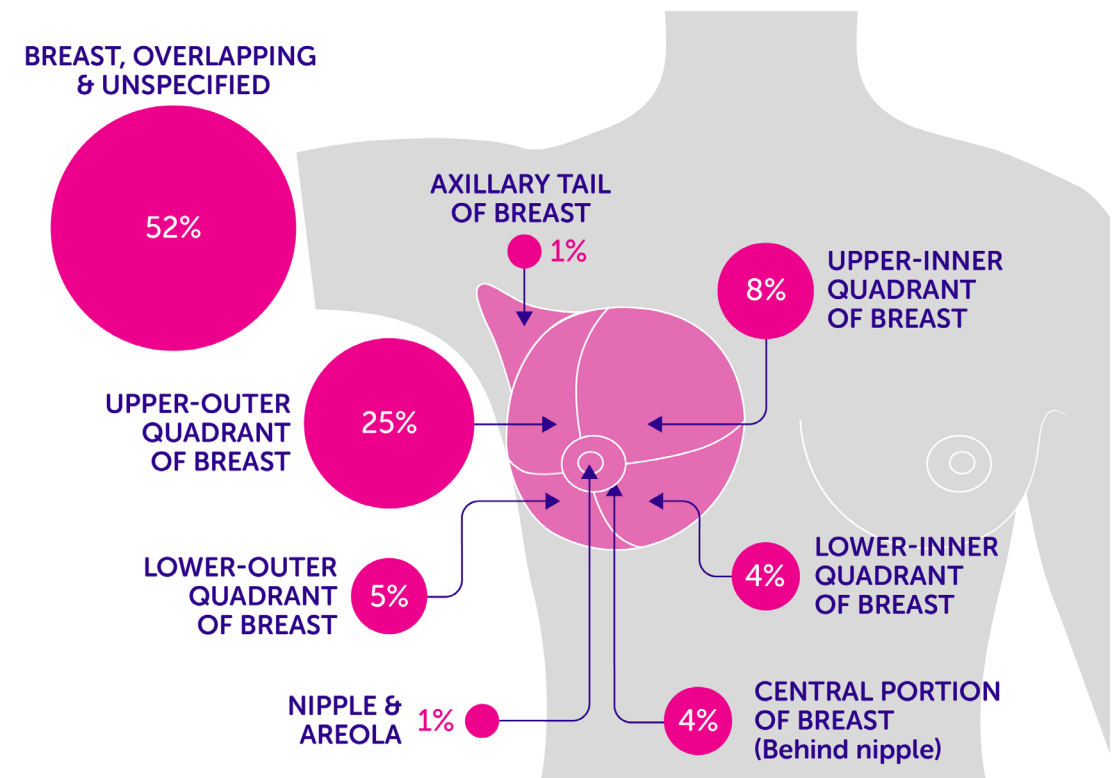


5 year survival by stage 2002-6.

# Most cancers diagnosed by a woman finding an abnormality.

- Lumps.
- Changes to the skin over the breast.
- Changes to the nipple or discharge.
- Most lumps are NOT breast cancer.

## INVASIVE BREAST CANCER CASES: PERCENTAGE DISTRIBUTION BY ANATOMICAL SITE

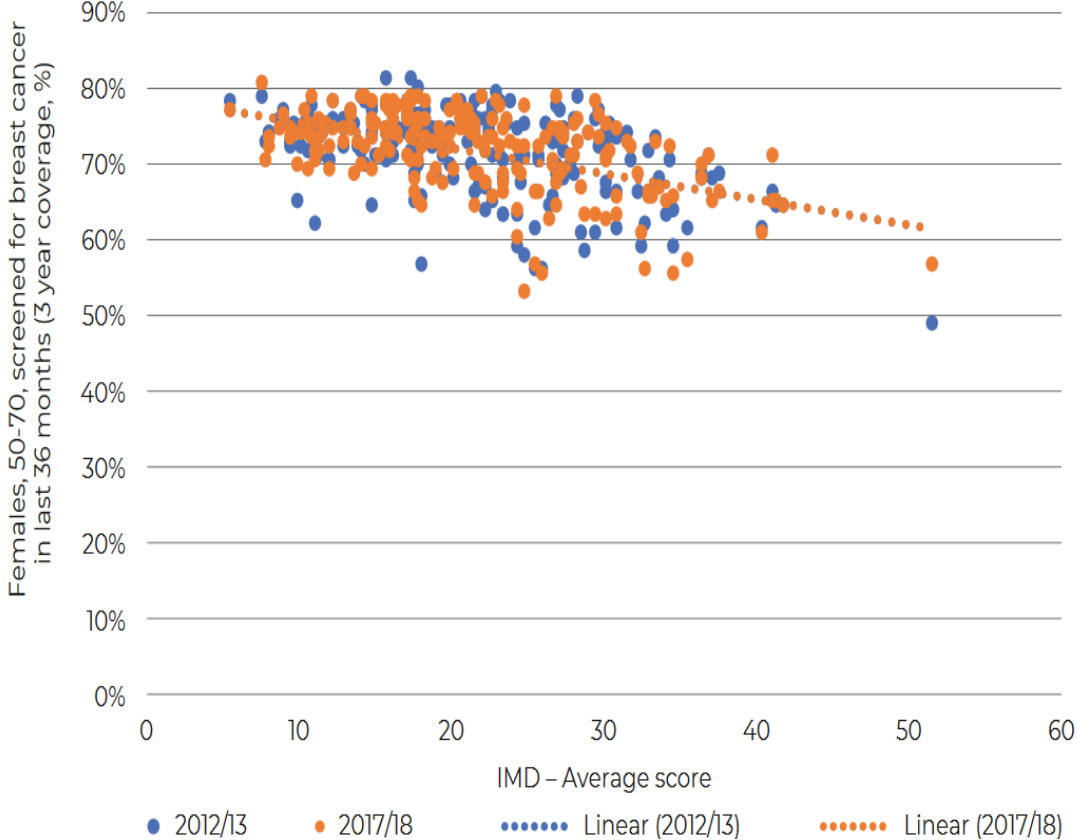
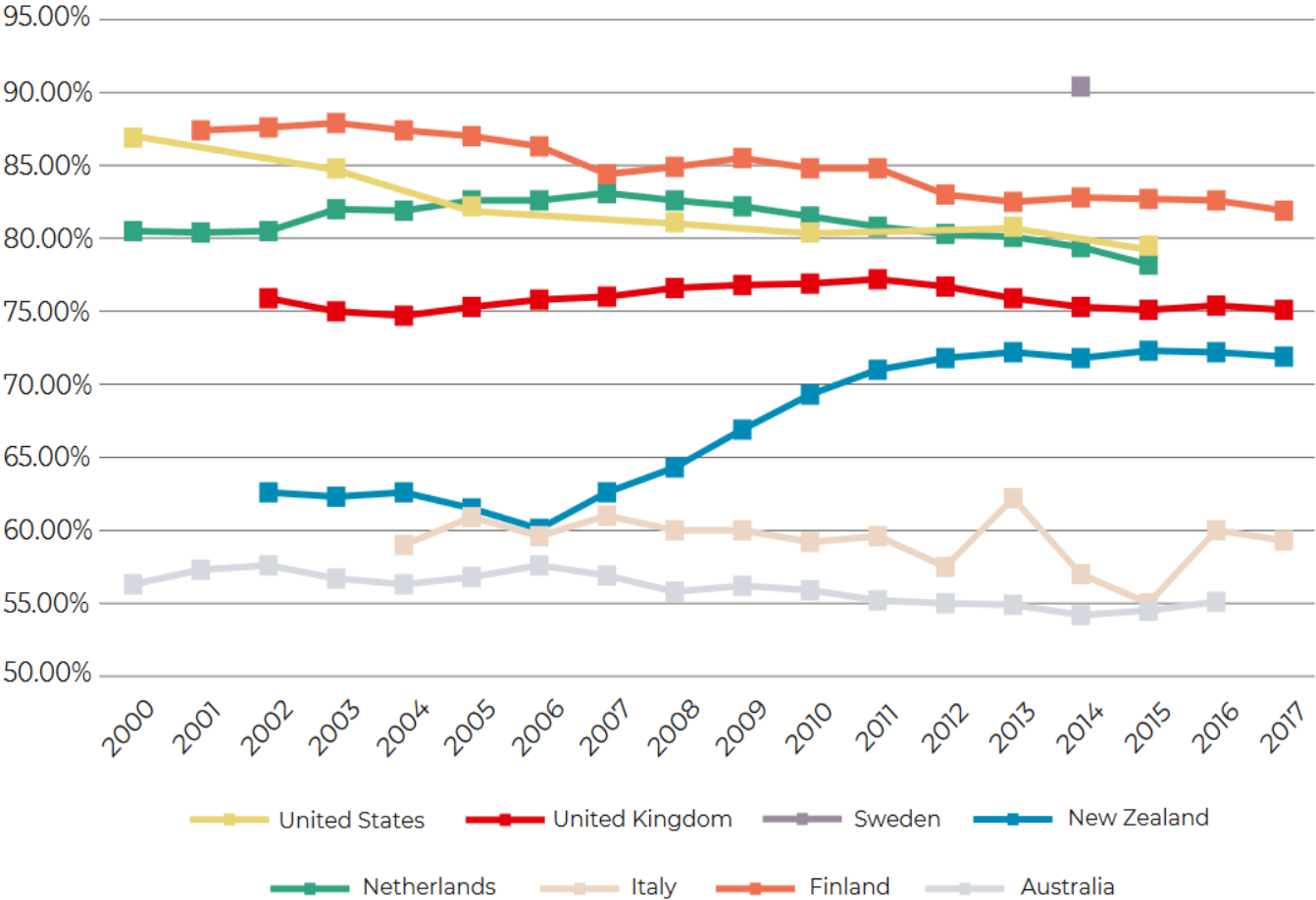


## Breast screening.

- In UK 50-70 years.
- Trials in 47-49 and 71-73 year olds.
- Those over 70 can self-refer.
- 2017/18 around 2.5 million women invited for breast screening, around 1.8 million attended (71%).
- 18,001 cancers were detected of around 54,500 (33%).
- Estimated to save 1 life for every 1,200 women screened, or up to 1,700 lives per year.



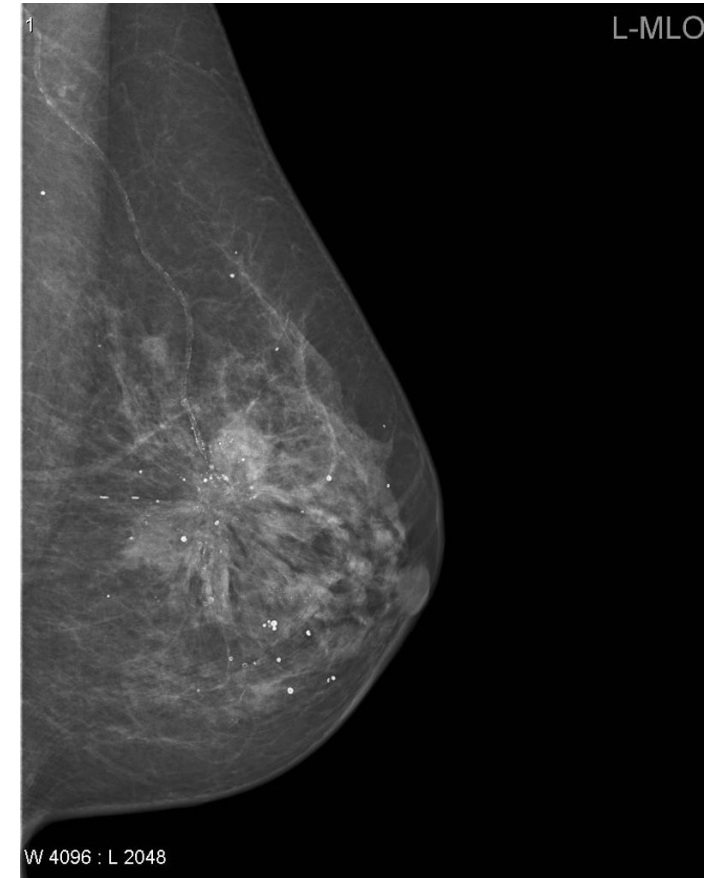
# Breast screening coverage by country (L), and in UK relationship with Index of Multiple Deprivation (CCG). *(Richards Review, 2019).*





# Imaging for breast cancer: mammogram, MRI, ultrasound.

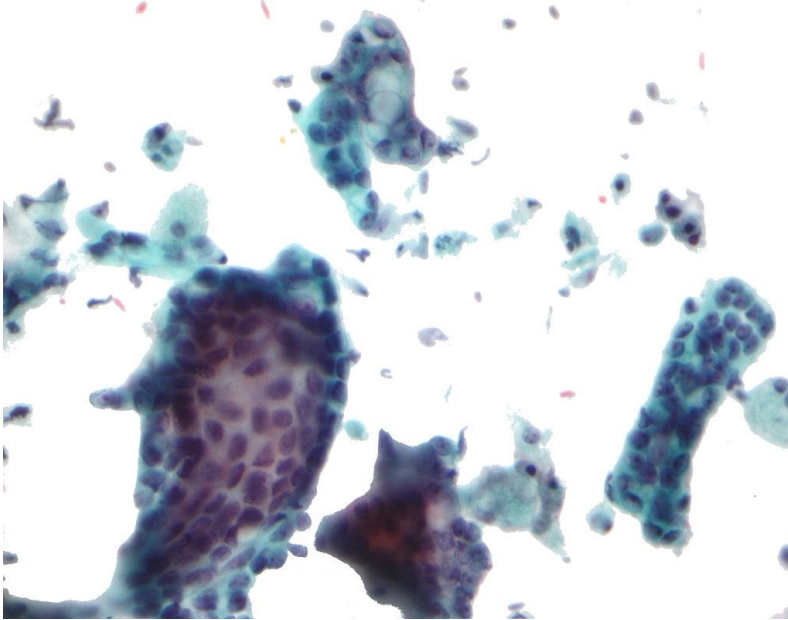
- Mammography remains the best screening modality.
- MRI more sensitive but can lead to more unnecessary procedures. Better in dense breasts.
- Ultrasound useful for suspicious areas, lumps that do not show up, or to guide biopsy.



Courtesy Dr Henry Knipe,  
Radiopaedia.org

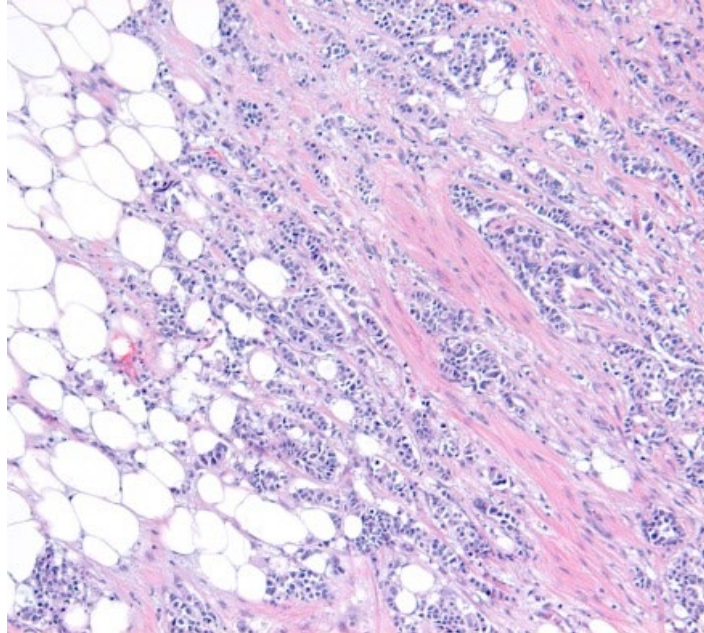
# Fine needle aspiration and biopsy.

FNA.



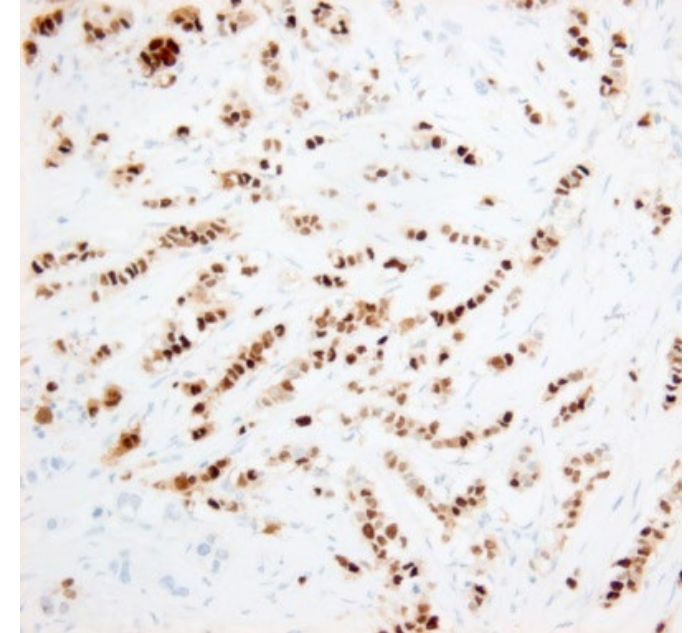
*FNA ductal carcinoma. Nephron Wiki.*

H&E histology.

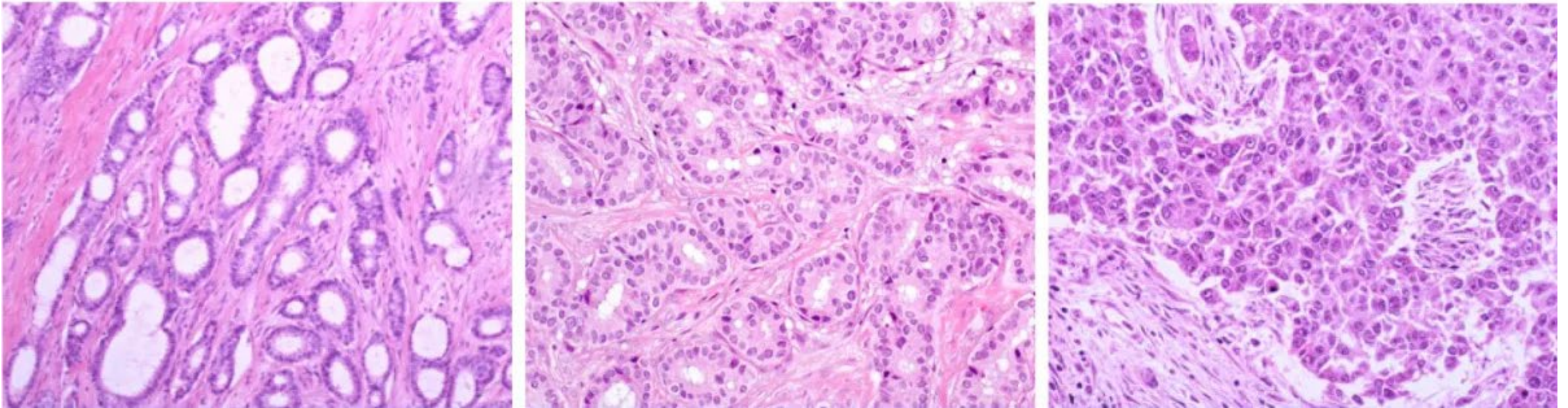


*Dr Ala Enno, Liverpool Hospital. Cancer Council Australia*

IHC ER+. Can also be PR+.  
Hormone receptors.



Grade 1-3. The more similar the cancer cells are to normal the lower the grade. 1 (L)-3 (R).



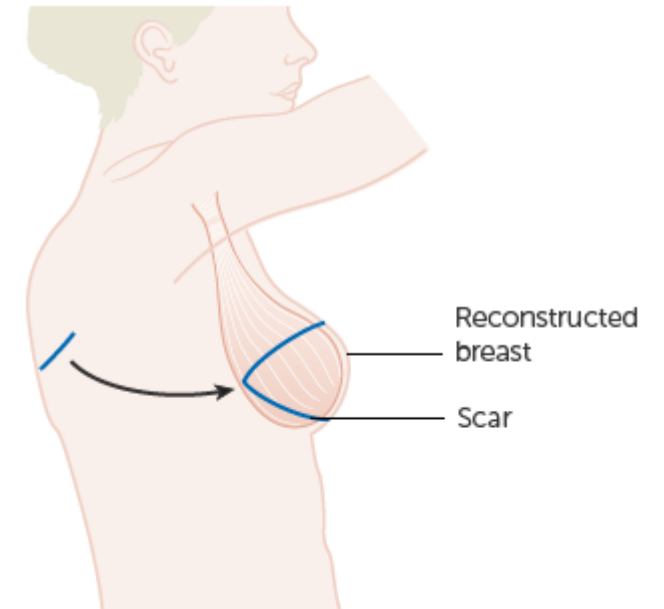
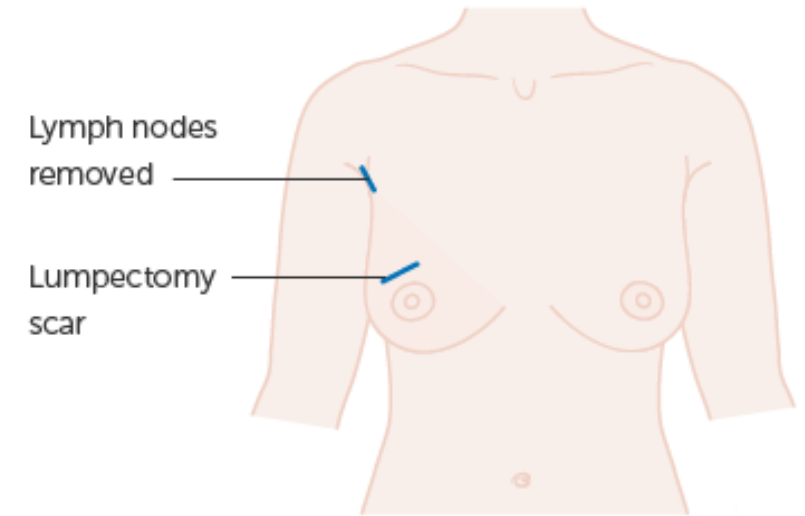


## Surgery.

- Surgery is the oldest, and still most effective, part of breast cancer treatment.

Major advances in:

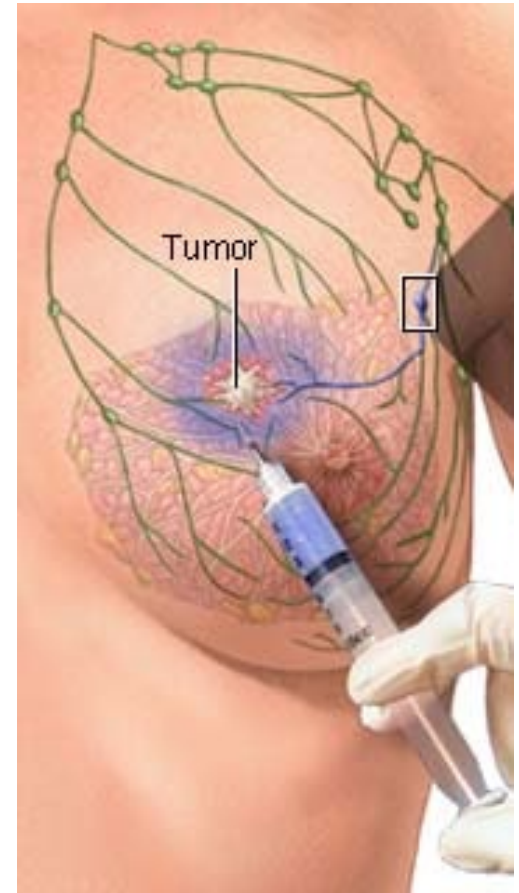
- Identifying spread to lymph nodes.
- Minimally invasive surgery.
- Breast reconstruction.





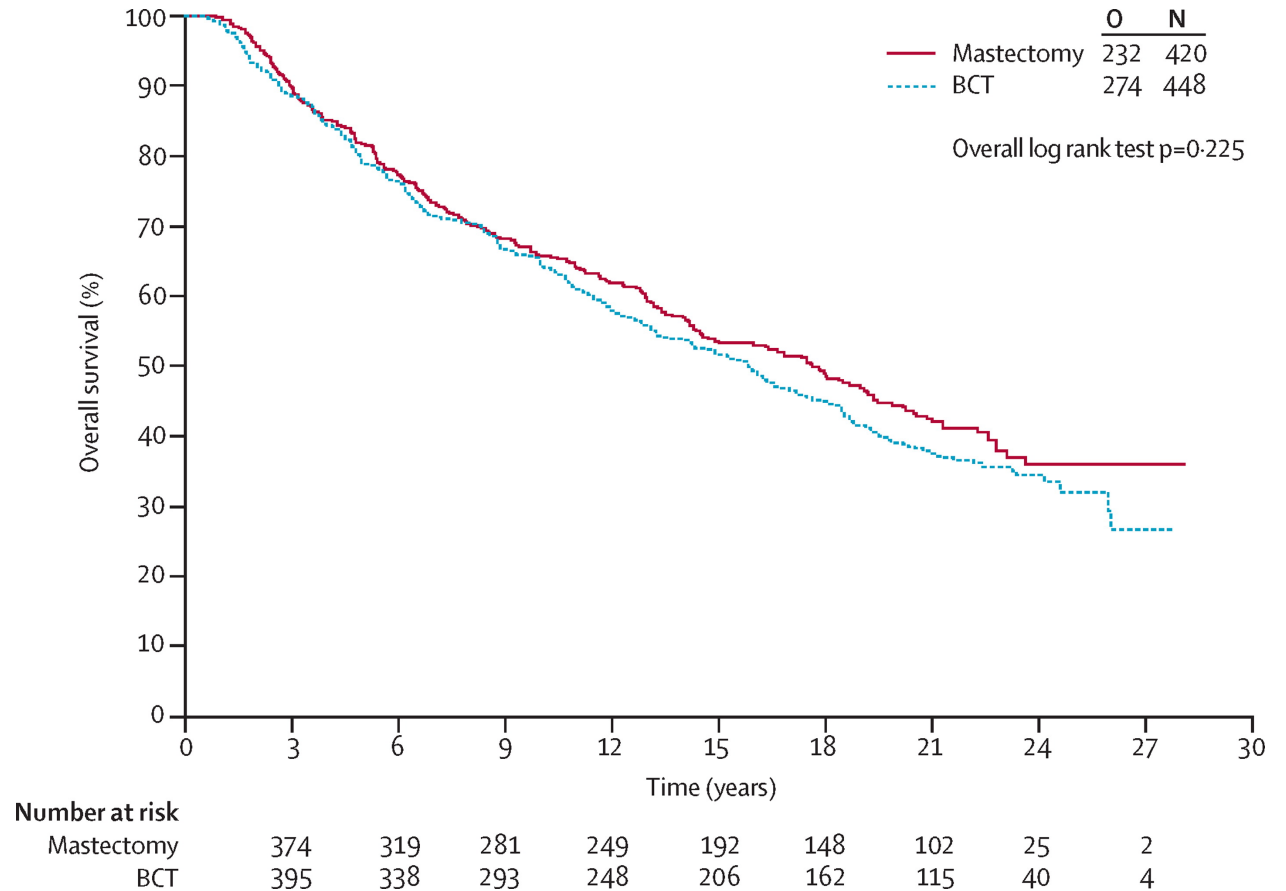
## Identifying who needs further node clearance and treatment.

- Sentinel node sampling.
- Radioactive tracer and dye injected into the tumour.
- Nodes sampled and examined to assess need for further operation.
- Recently further refined for breast: RD-100i OSNA test for cytokeratin-19 (CK19) gene (NICE).
- 45 minutes so can be done during the operation.



# Less surgery often as good as more for survival.

- Mastectomy v breast-conserving surgery for breast cancer over 27 years.
- The difference is minimal in appropriate patients.
- Overall survival rates would now be much better.



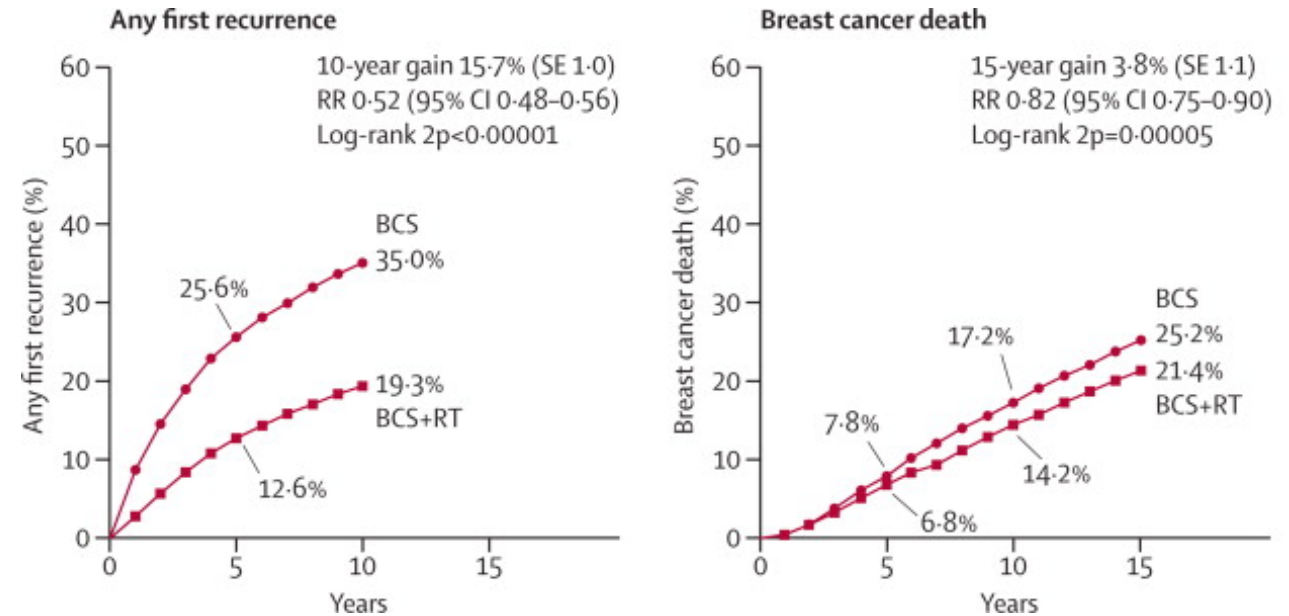
# Radiotherapy for breast cancer.

- Radiotherapy first used in 1896.
- Kills rapidly dividing cells.
- Mainly after breast-conserving surgery.
- Kills which divide rapidly. Cancer cells, and mouth, gut, hair cells divide rapidly.
- Modern advances in radiotherapy include reducing dose, minimising scatter into normal tissue.



# Radiotherapy after breast-conserving surgery.

- 10 801 women, 17 randomised trials of radiotherapy versus no radiotherapy after breast-conserving surgery.
- Radiotherapy reduced the 10-year risk first recurrence from 35.0% to 19.3%.
- Reduced the 15-year risk of breast cancer death from 25.2% to 21.4%.
- Outcomes would now be better.



*Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 2011.*



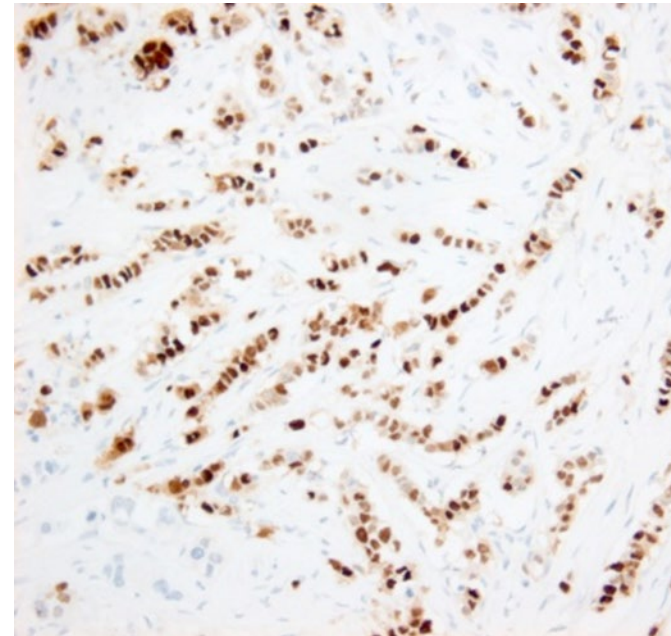
## Side effects of local breast radiotherapy.

- Short term tiredness, reddening of skin, local swelling are common.
- Effects on rapidly dividing cells. For breast cancer armpit hair loss common and temporary, sore throat less commonly.
- Occasional inflammation of lung or (if of left) heart, usually temporary.
- Skin shrinkage.
- Serious long term side effects occur, but rare.

EFFECT	INCIDENCE % of women
Long term	
Second cancer	<1
Myocardial infarction	<1
Pneumonitis	<1
Lymphedema (after nodal irradiation)	
Mild to moderate	6–10
Severe	1–5
Brachial plexopathy (after nodal irradiation)	<1
Skin (breast or chest wall)	
Mild shrinkage or induration	10–50
Severe shrinkage or induration	6–10
Short term	
Skin (breast or chest wall)	
Hyperpigmentation, dry desquamation, or erythema	>50
Moist desquamation	6–10
Mild fatigue	>50
Mild myelosuppression	>50

# Three subtypes of breast cancer with therapeutic importance.

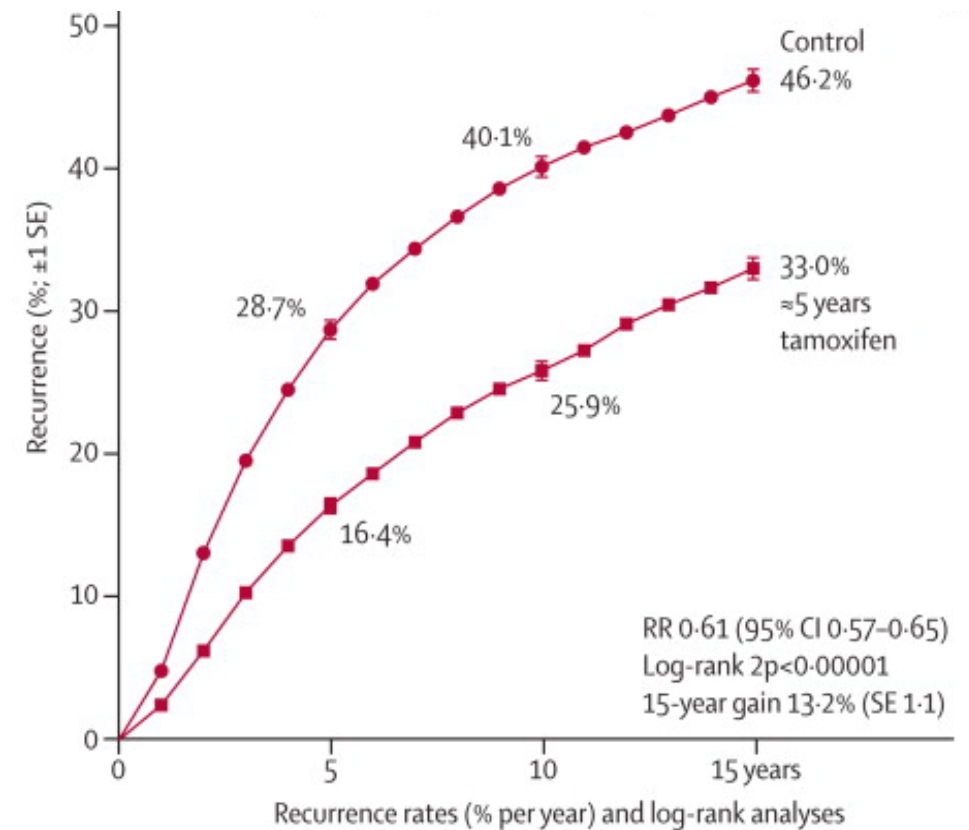
- Use presence or absence of molecular markers for **oestrogen** (estrogen) or **progesterone** receptors and **human epidermal growth factor 2** (ERBB2; formerly HER2).
- Hormone receptor positive/ERBB2 negative (70%).
- ERBB2 (HER2) positive (15%-20%)
- Triple-negative (lacking all 3 markers; 15%).



## Hormonal treatments in ER+ breast cancer.

- **Tamoxifen**: anti-oestrogen developed as an (unsuccessful) morning after contraceptive.
- 5 years tamoxifen reduces recurrence and mortality in hormone receptor ER+ women (recurrence by about 50%).
- 10 years a bit better than 5 (15 probably no better than 10).
- **Aromatase inhibitors** better still (reduce by around 30%) in postmenopausal women.
- May be combined with **CDK4/6-selective inhibitors**, especially in advanced cancer.

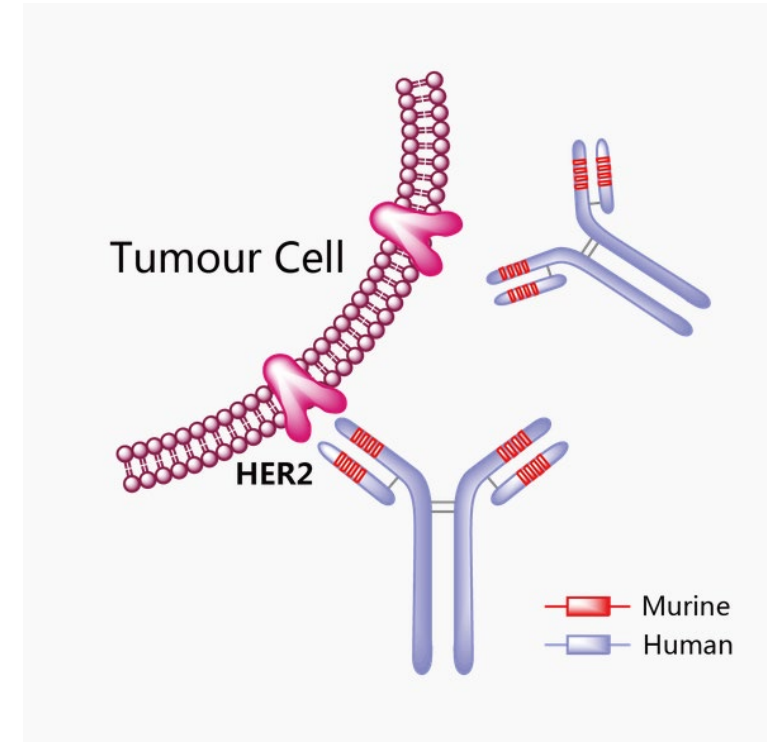
### Tamoxifen 5 years recurrence



EBCTCG, Lancet

## Antibody treatment for ERBB2 (HER2+) cancer.

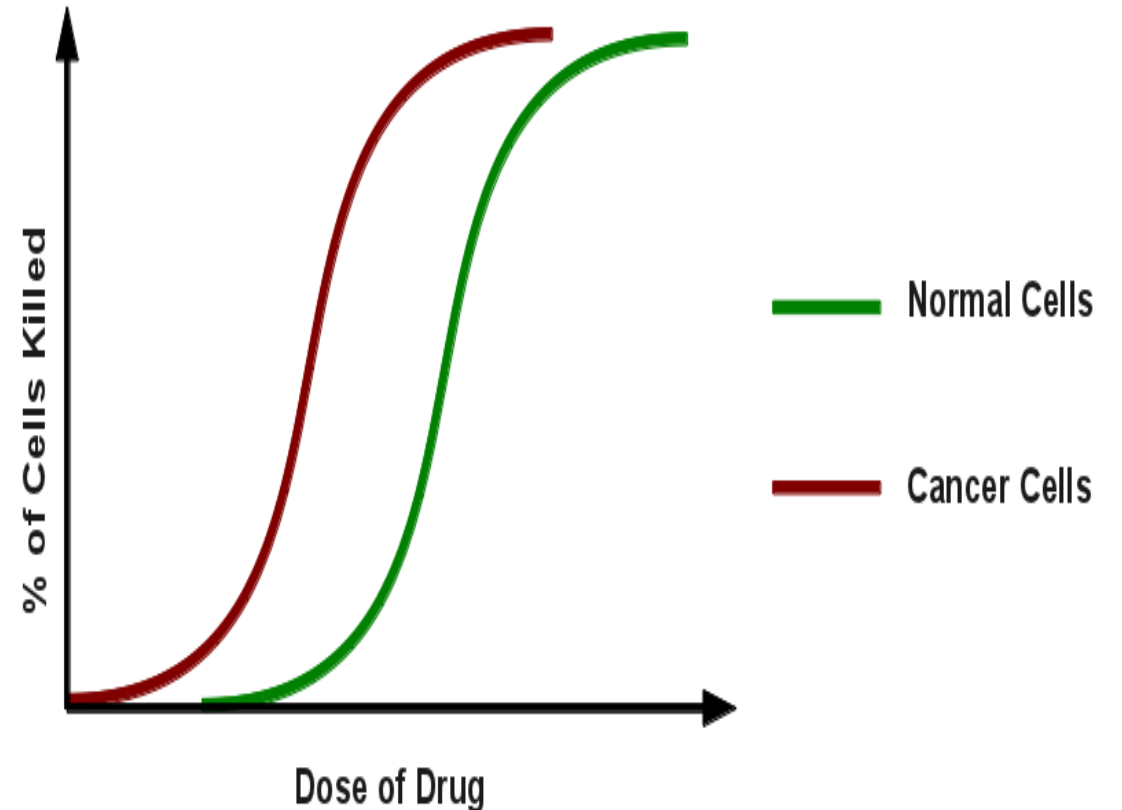
- ERBB2 (HER2+) (human epidermal growth factor receptor 2). Overexpressed in 20-30% of breast cancers.
- ERBB2 promotes cell growth.
- Trastuzumab (Herceptin) monoclonal antibody blocks the receptor.
- Trastuzumab reduces progression and improves survival in ERBB2 breast cancer.
- Resistance a problem.



*Pharmacodia*

# Cytotoxic chemotherapy mechanisms.

- The basic mechanisms of conventional chemotherapy simple.
- Kill any cell that is dividing- cancer cells more sensitive and slower to recover.
- Good effect depends on the cancer. Rapidly dividing = more effective.





## Chemotherapy- from many routes.

- Antifolates, after discovery of folate in pregnancy in India 1930s. **Methotrexate**.
- Nitrogen mustards from mustard gas (1940s). **Cyclophosphamide**.
- Anthracyclines derived from antibiotic produced by *Streptomyces* bacteria from the soil round Castel del Monte in 1950s. **Doxorubicin, Epirubicin**.
- *Streptomyces* antibiotics also led to mitomycins- **Mitomycin-C** in Japan, 1950s.
- Anthracenedione with a basis in plant dyes from fungi- **mitoxantrone**.



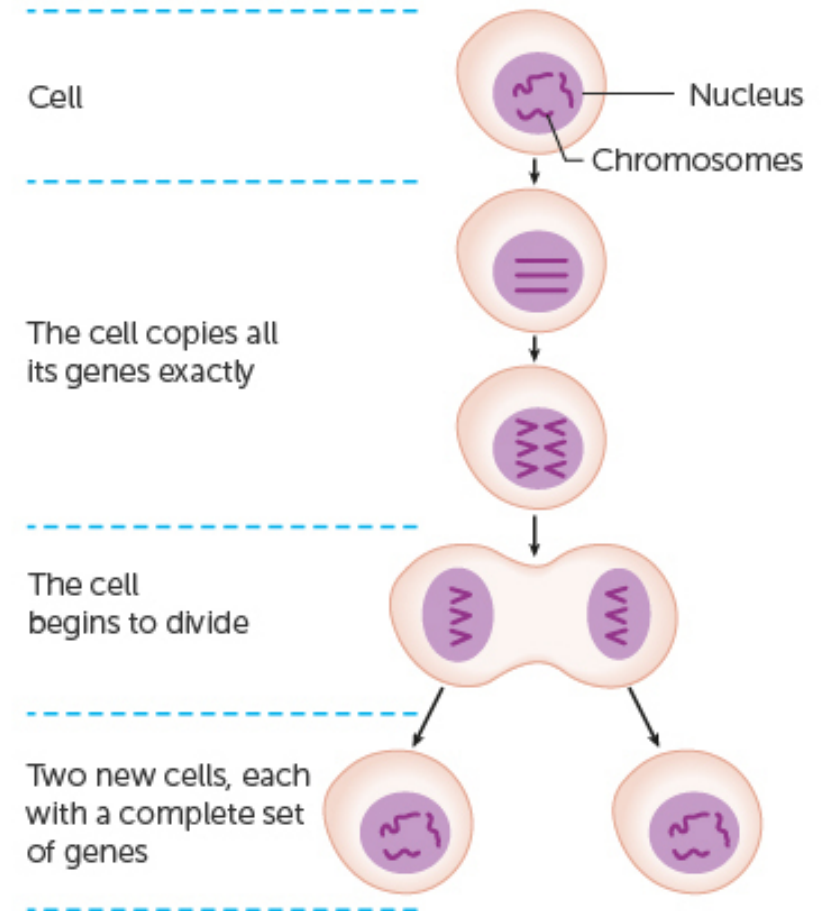
## Chemotherapy 2

- **Paclitaxel** (Taxol) first isolated in 1971 from the Pacific yew.
- **Carboplatin, cisplatin**. Cisplatin discovered in 1845 (Peyrone's salt). Cancer-fighting properties derived from finding that using platinum electrodes inhibited *E. coli* growth.
- **Fluorouracil** (5FU), chemically derived in the 1950s.



# Many mechanisms of chemotherapy. Interfere with dividing cells.

- Alkylating agents like **cyclophosphamide** damage DNA.
- Antimetabolites like **methotrexate** interfere with synthesis of DNA, RNA.
- Antitumour antibiotics like **doxorubicin**, **epirubicin**, and also **5FU** attack enzymes which assist in DNA replication.
- **Mitomycin-C** a powerful DNA crosslinker.



## Side effects of chemotherapy.

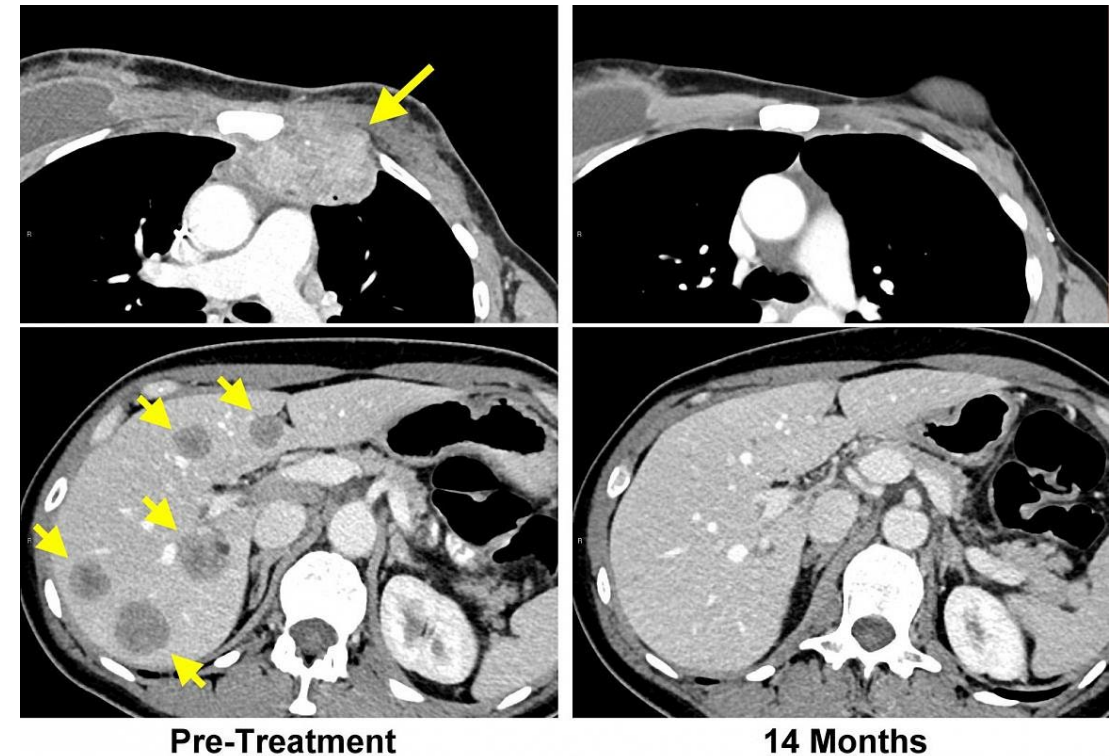
- Biggest impact on cells that are rapidly dividing: gut, hair follicles, mouth, skin, bone marrow.
- Nausea, vomiting, swallowing.
- Hair loss.
- Immune system.



*Macmillan Cancer Support*

# We continue to improve management of advanced metastatic breast cancer.

- Improvements in best combinations of hormone therapy, radiotherapy and chemotherapy.
- New advances in immunotherapy.
- An example is tumour-infiltrating lymphocytes (TILs), National Cancer Institute, right.
- Much better is early diagnosis.
- Better still prevention.

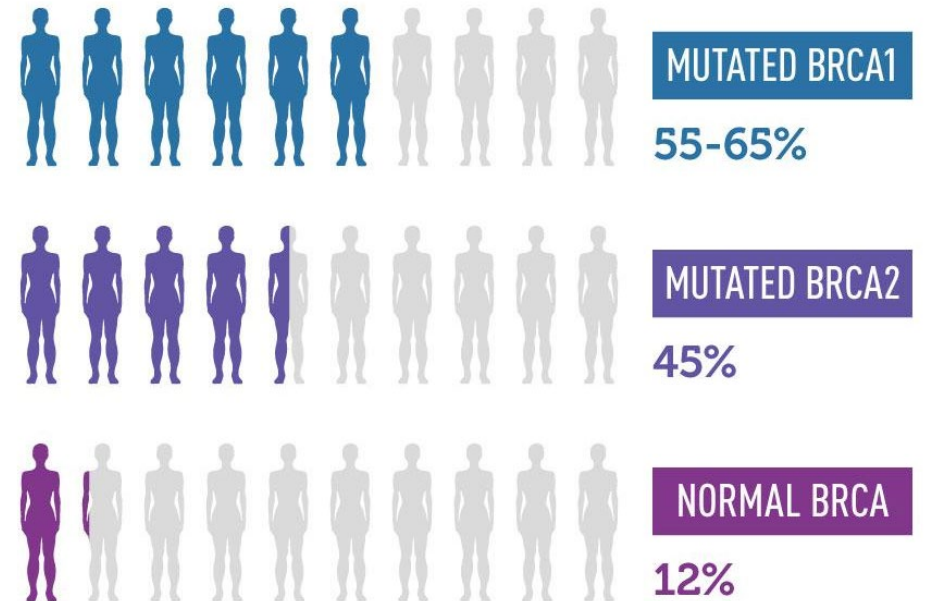


*Rosenberg S, NCI 2018*



## Identified genetic risk.

- 5-15% breast cancer risk hereditary. Also may be linked to ovarian cancer.
- Breast cancer genes, BRCA1 and BRCA2 mutations most important.
- Increase risk and at a lower age.
- Several less common gene mutations identified (PTEN, TP53, STK11, CDH1).
- Familial a further 15-20%. Polygenic risk.
- Enhanced screening, drugs, mastectomy?
- May have yearly mammogram or MRI.



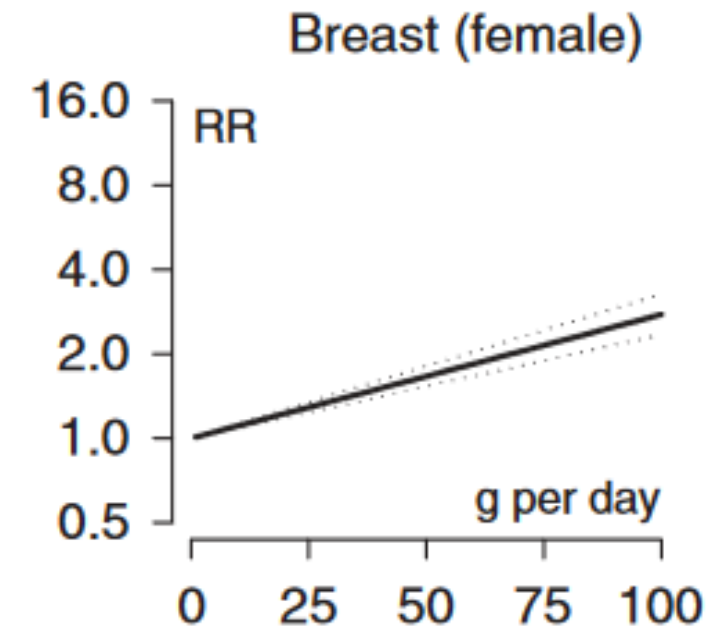
US National Cancer Institute. Risk by age 70.

## Alcohol and breast cancer: around 8% of UK cases.

- UK 'unit' 8g alcohol. A large glass of wine around 25g.
- Light <12.5g/day, heavy >50g/day.
- RR 1.04 for light
- 1.2 for moderate
- 1.6 for heavy alcohol.

Million women study, by 80 years:

- 9 out of 100 for those who don't drink at all
- 10 out of 100 for two drinks a day
- 13 out of 100 for six drinks a day.

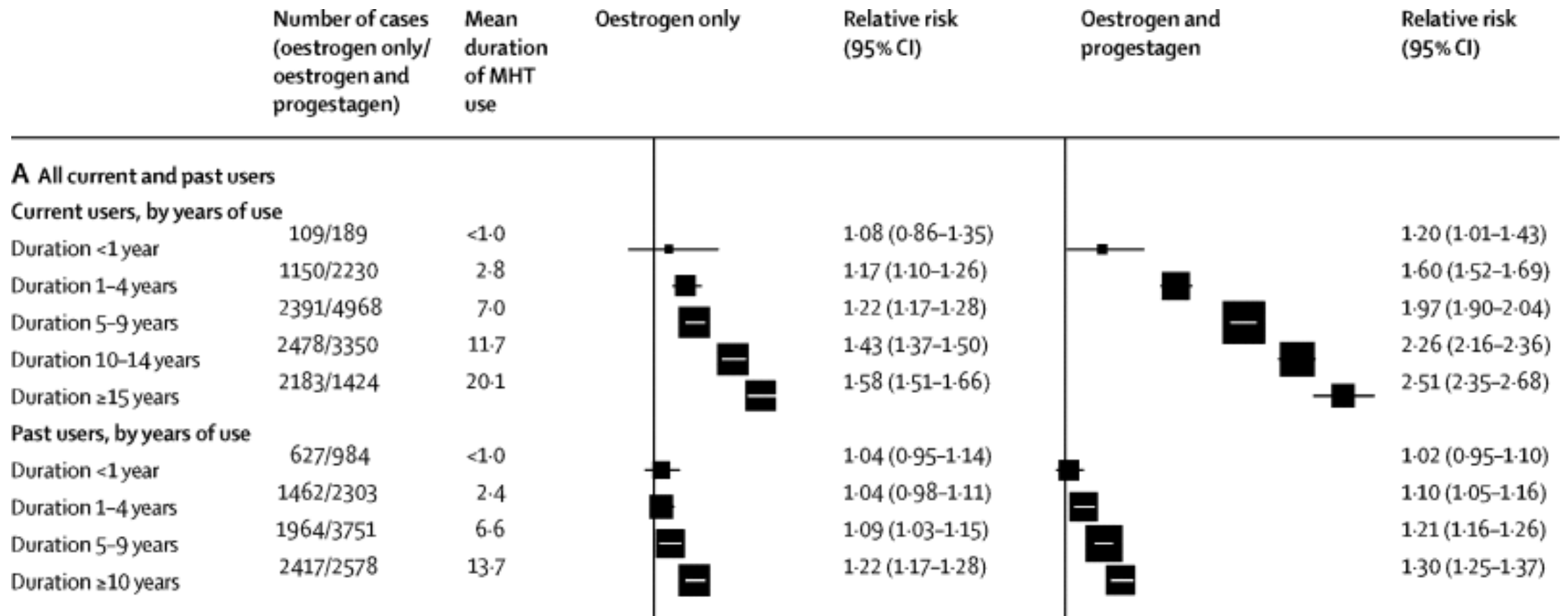


# HRT (hormone replacement therapy).

Minimal increased risk for short or previous use.

Higher risk for longer use, greatest at current >10 years.

Most risk is in ER+ cancers.

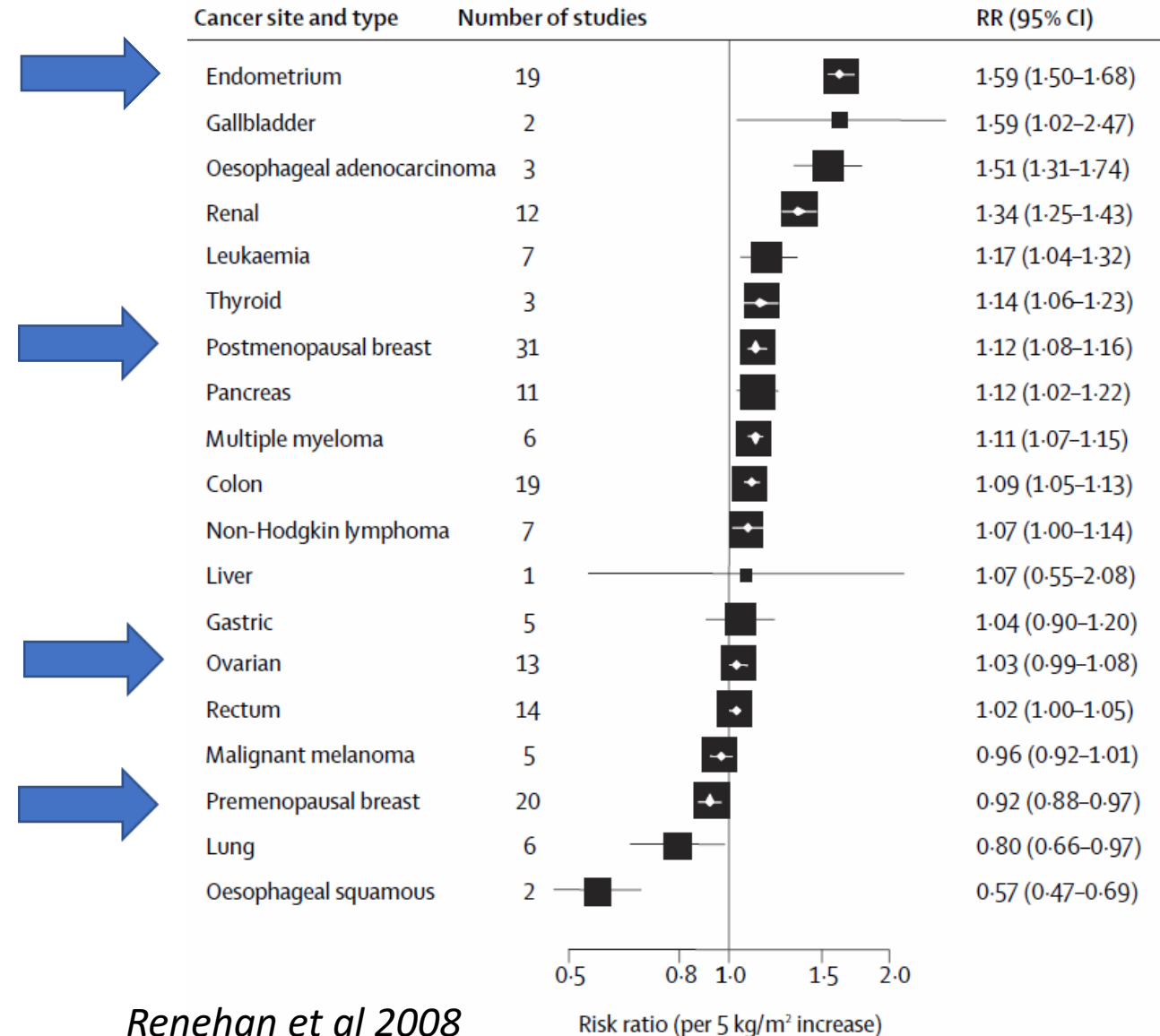


# Association between cancer and BMI in women.

- Associations between 5 kg/m<sup>2</sup> increase in BMI and:
- Endometrial (uterine) RR 1.6
- Postmenopausal breast RR 1.12.

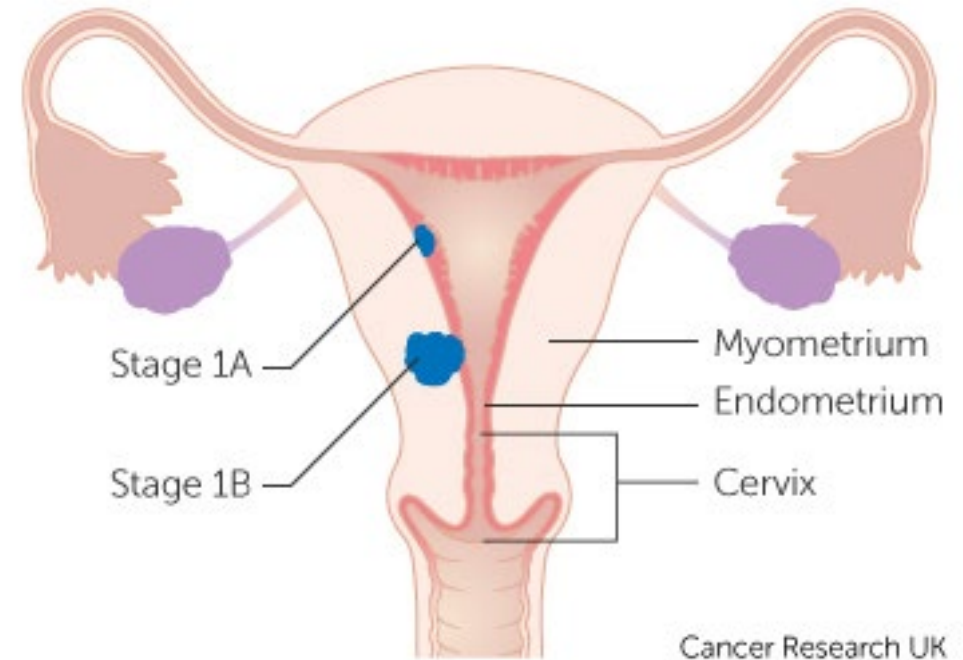
A modest risk for postmenopausal breast cancer- but breast cancer is common. Estimated 8% of cases.

Obesity/overweight is a significant risk for uterine/endometrial cancer- around 30% of cases.



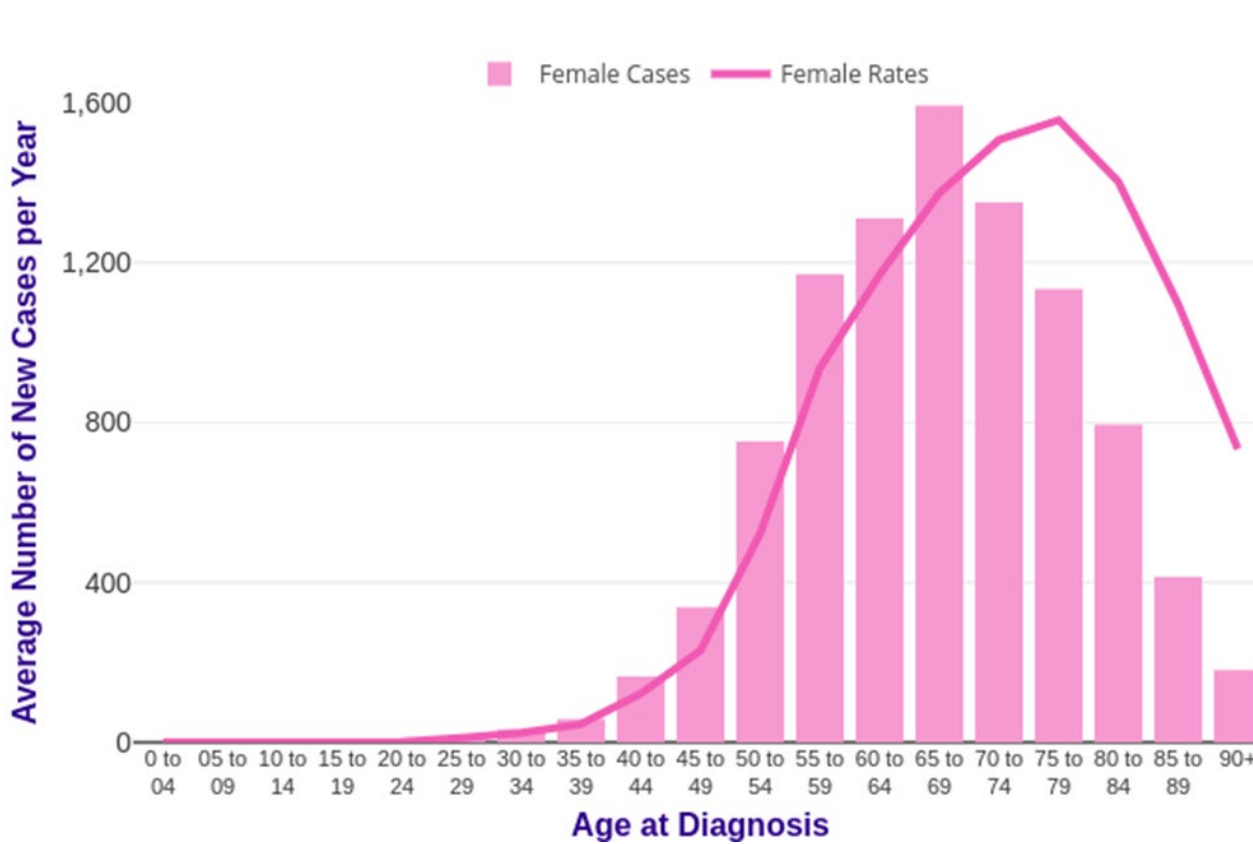
## Uterine cancer.

- Also known as womb cancer. Most (>3/4) is endometrial cancer.
- 9,500 a year in the UK. 4<sup>th</sup> most common cancer in women.
- The great majority (90%) diagnosed in Stage 1 due to bleeding.
- Most bleeding post menopause (90%) not cancer.
- Occasionally pain.
- 95% of women with Stage 1 survive for >5 years. Around 78% of all patients survive >10 years.



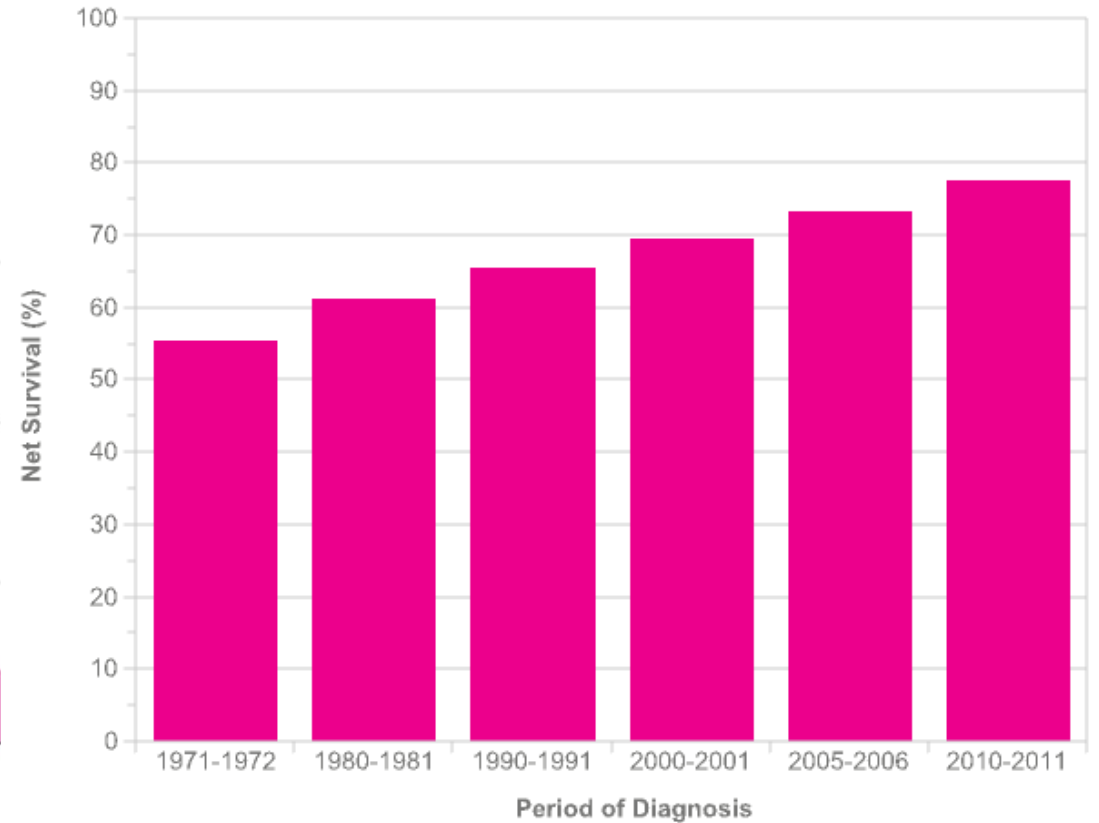


Peak age late 60s to late 70s. Survival has been improving.  
Incidence increased by 57% in UK from 1993-1995 to 2014-2016.



50

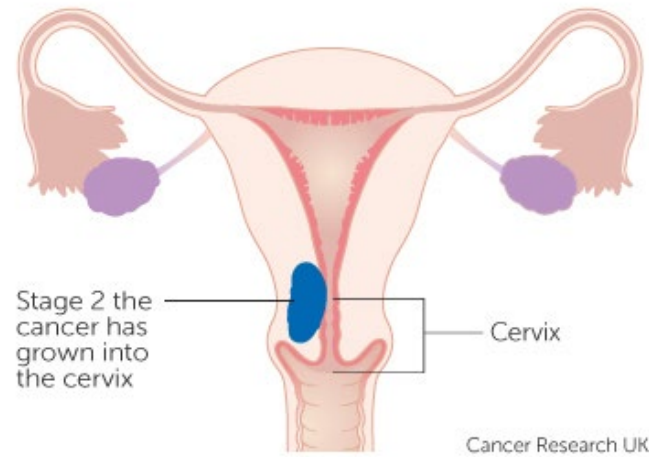
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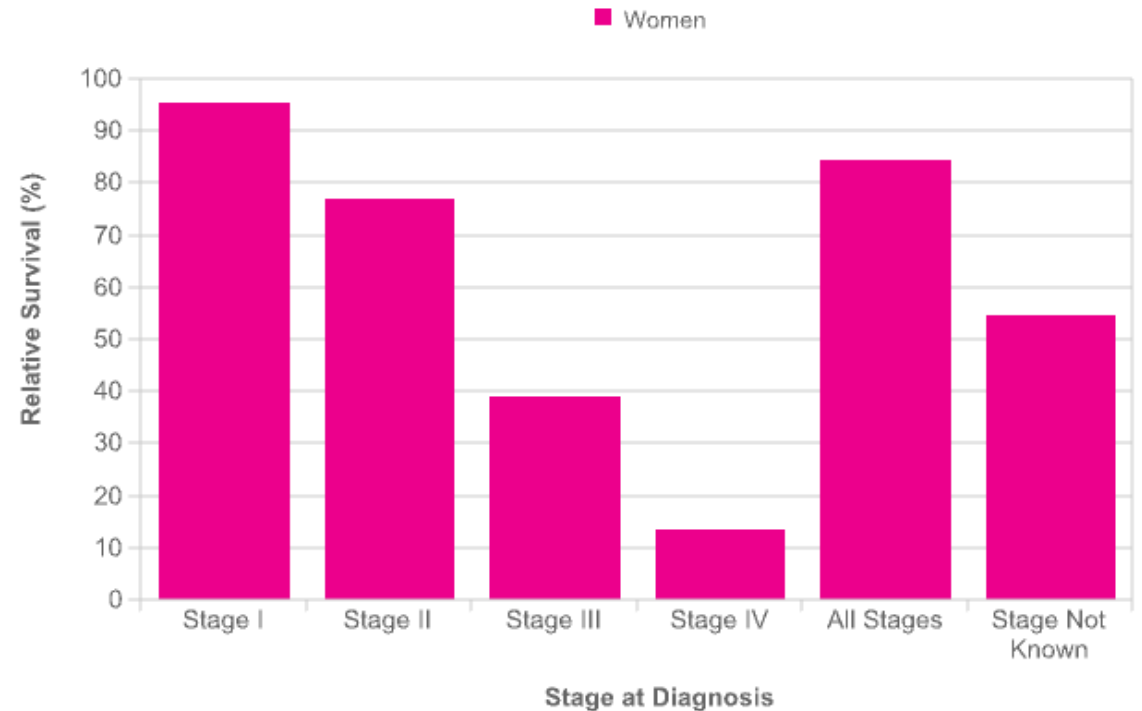
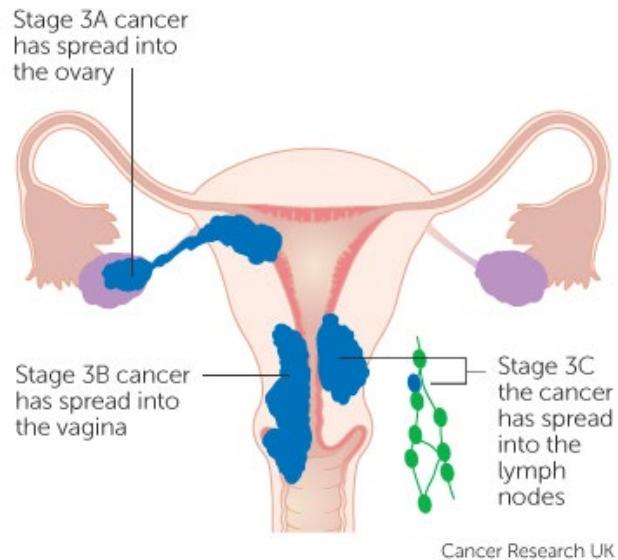
10 year survival 1971-2011

# Stage, grade and type affect treatment and outlook.

## Stage 2



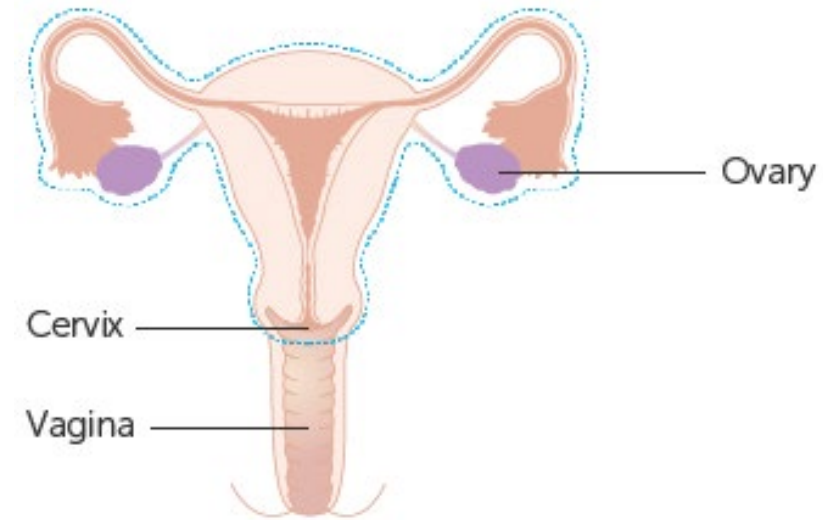
## Stage 3



5 year survival.

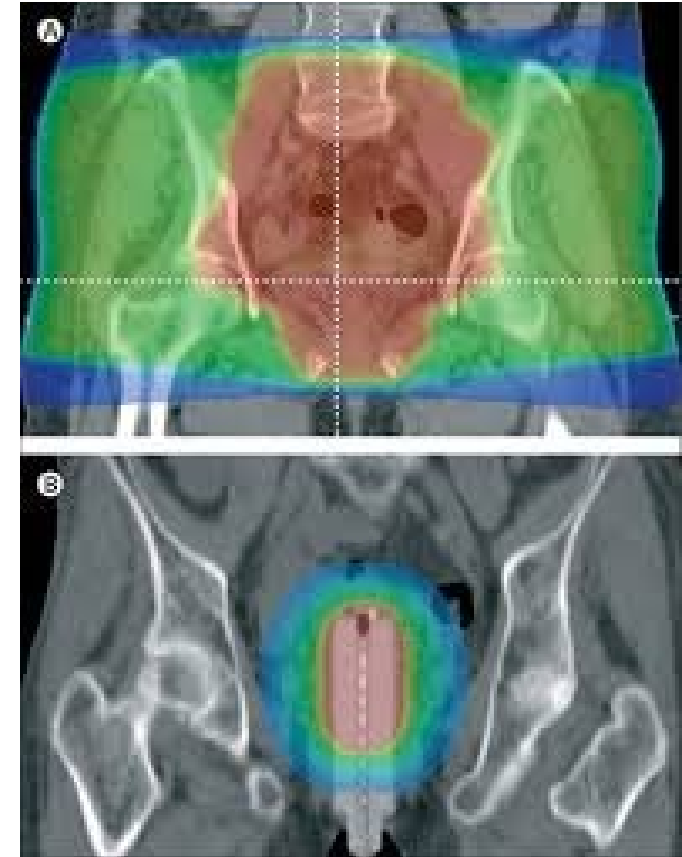
## Surgery.

- The mainstay of treatment for Stage 1 and Stage 2 cancer.
- For most women this is all the treatment they need.
- Stage 1 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.
- More extensive in Stage 2 (radical hysterectomy), including lymph nodes.
- May be done by laparoscopic (keyhole) surgery.



# Chemotherapy and radiotherapy.

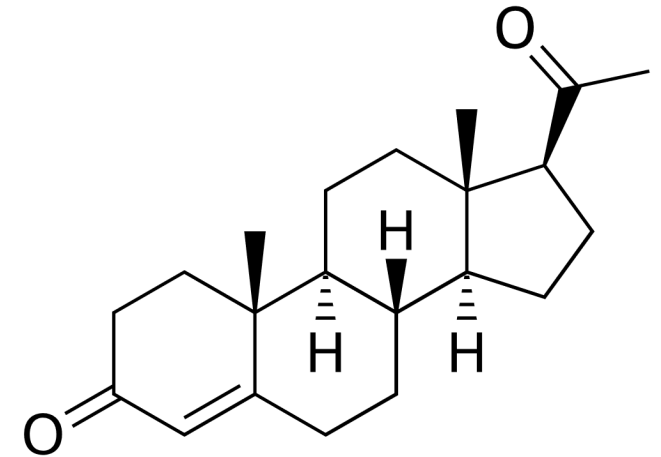
- Some high-grade or rarer types of cancer (eg clear cell, 2%) may need chemotherapy or radiotherapy in Stage 1 or 2, but a minority.
- May be brachytherapy, delivered locally rather than external beam.
- In Stage 3 and even more Stage 4 the relative importance of surgery decreases, and of chemotherapy, hormone therapy and radiotherapy increases.
- Chemotherapy similar drugs to breast cancer.



Kitchener and Powell, Lancet 2010.

## Hormone therapy.

- Currently hormone therapy 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 type, endometrial stromal sarcoma, responds well to hormone treatment.





## Risk factors for uterine cancer.

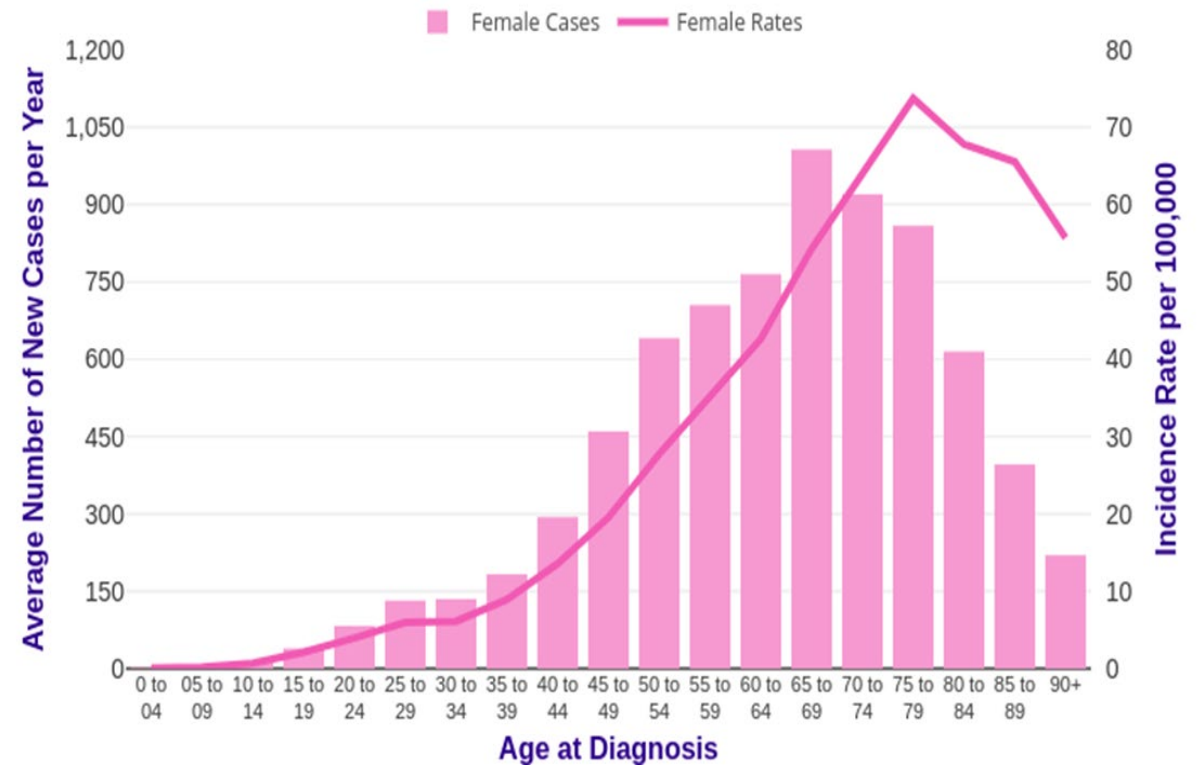
- When oestrogen higher, especially relative to progesterone.
- Obesity a significant risk factor.
- Oestrogen-only HRT.
- Combined oral contraceptive protective.
- Pregnancy decreases risk, probably due to lower oestrogen.
- Polycystic ovary syndrome.
- Type I and II diabetes.
- Exercise is protective.



Gustav Klimt 1903

## Ovarian cancer. Risk factors, and age.

- Older age the major risk factor.
- Family history. If mother or sister diagnosed with ovarian cancer have around 3x the risk.
- BRCA1, BRCA2, Lynch syndrome.
- Slight increased risk diabetes, overweight, extended HRT.
- Oral contraceptive, pregnancy, breastfeeding slightly decrease risk.

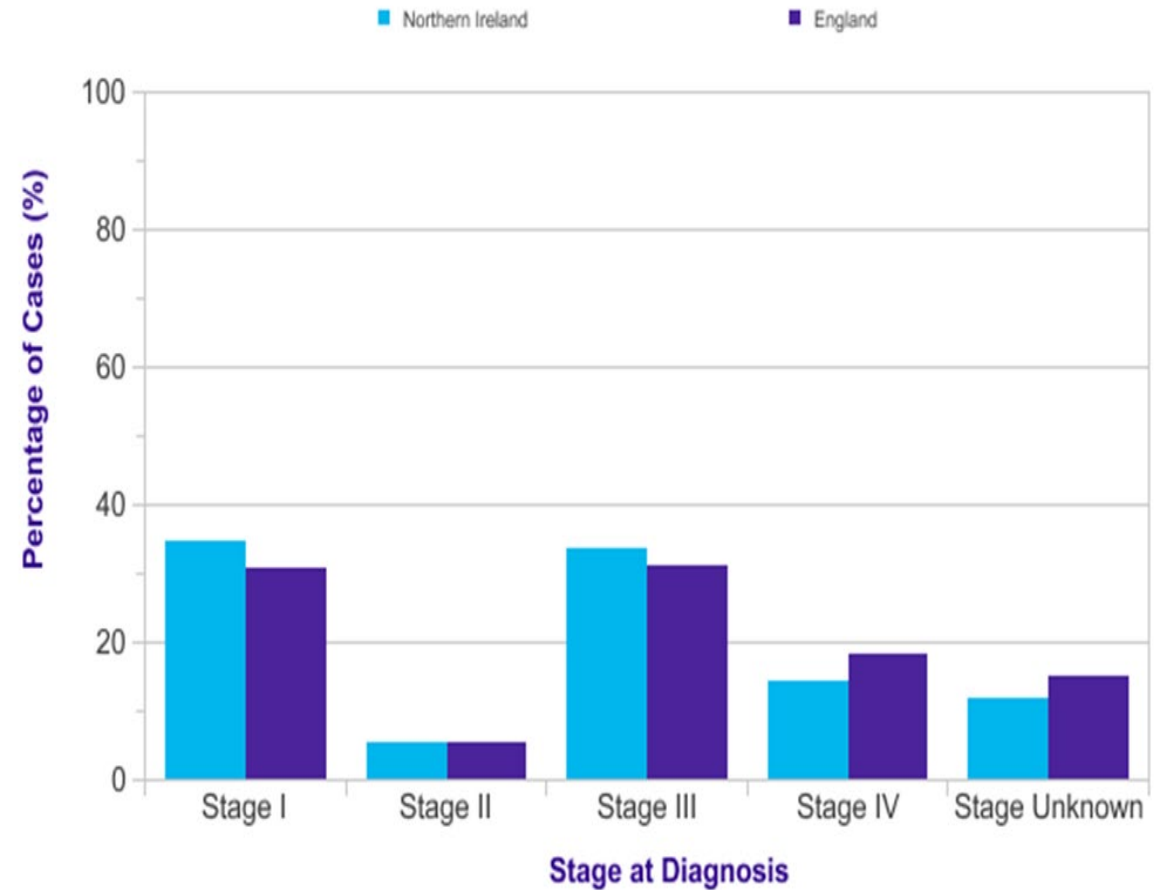


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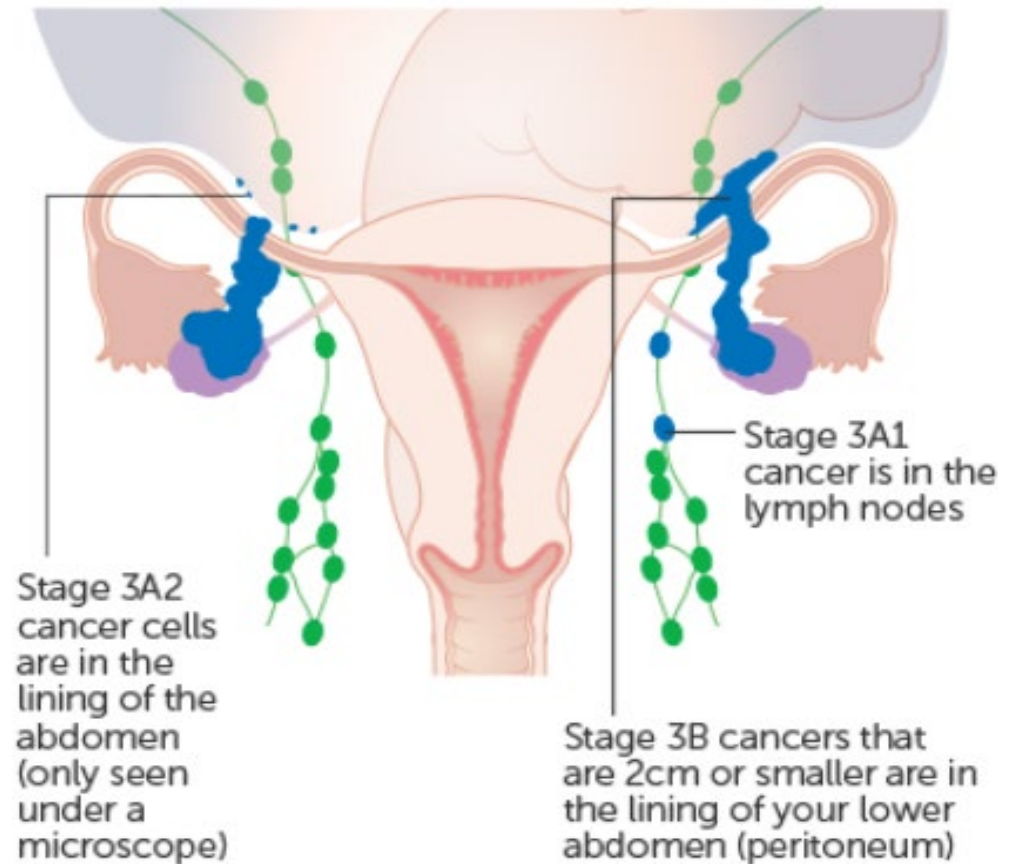
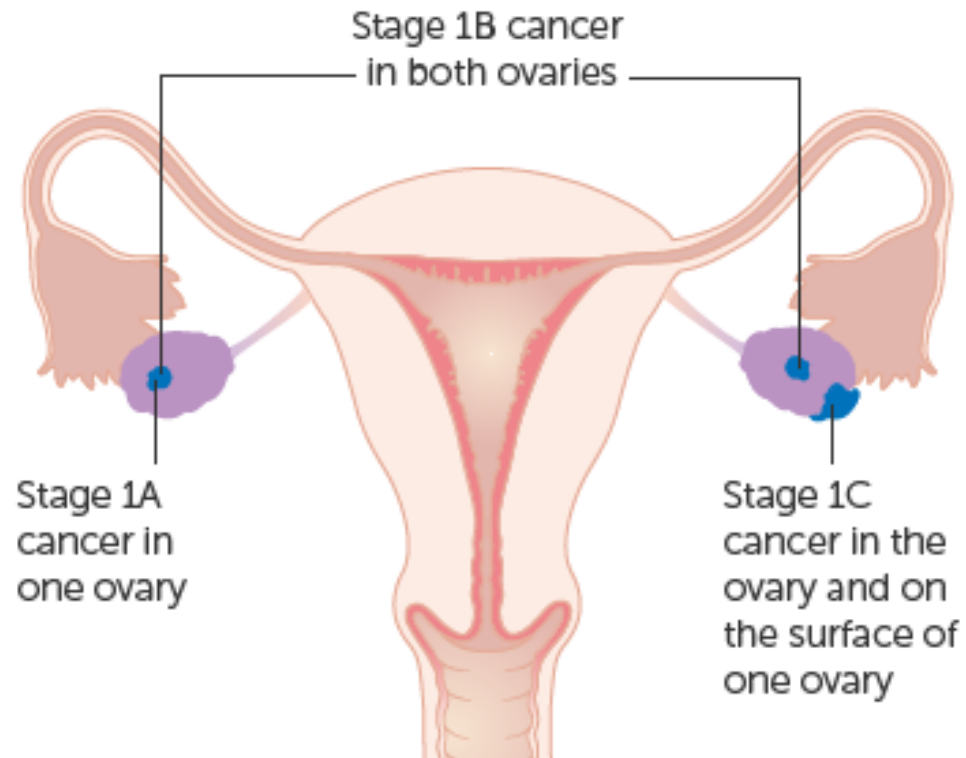
80

# Ovarian cancer.

- Around 7,500 cases a year in the UK.
- Incidence broadly flat. No deprivation gradient. More common in white women than those with Asian or African heritage.
- The major problem in ovarian cancer is that a high proportion (>50%) is diagnosed in Stage 3 or 4.
- Outlook good in Stage 1: 90% survival at 5 years. Surgery mainstay.
- The symptoms are usually minor and non-specific until advanced.

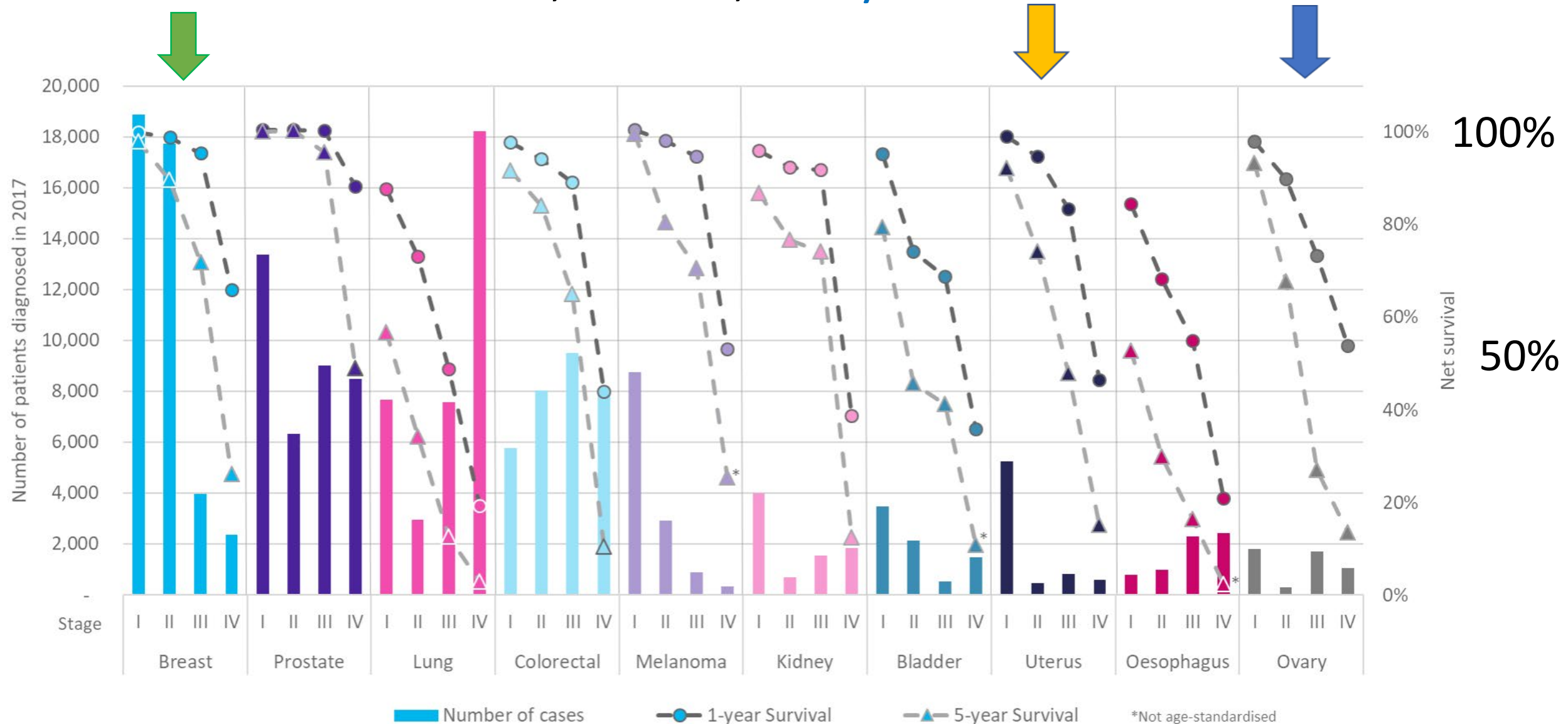


## Stage 1 (L) and Stage 3 (R) ovarian cancer.



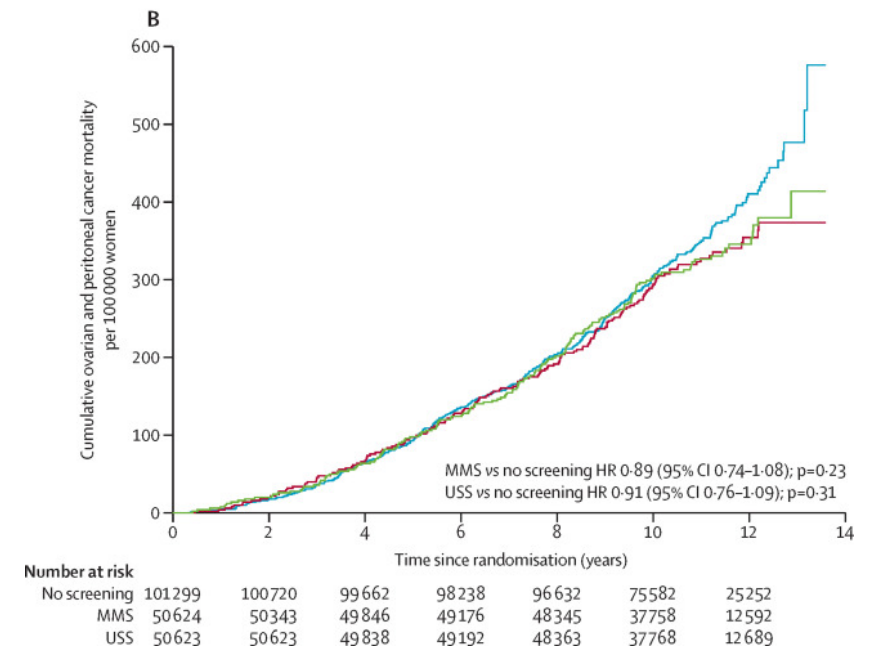
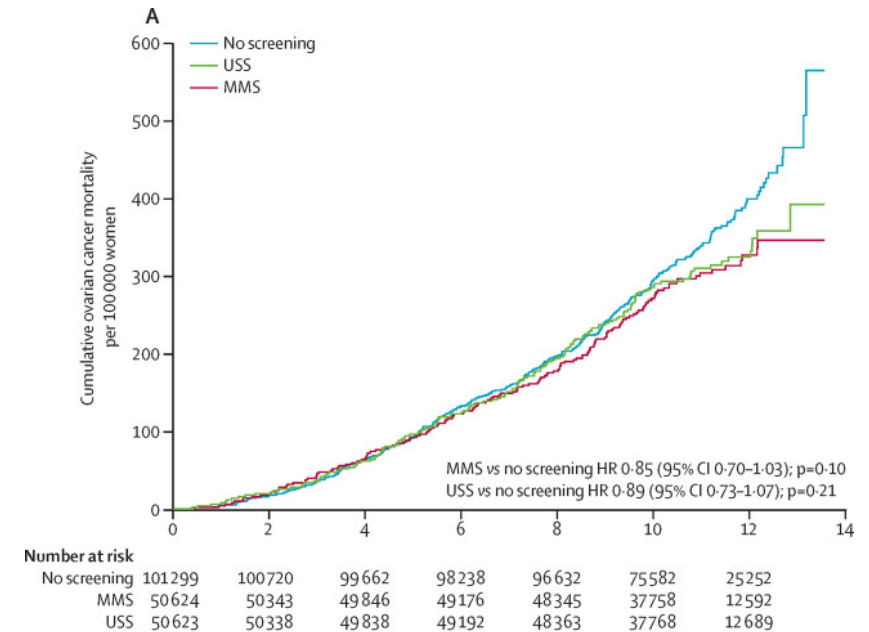
# Incidence of cases by stage, with 1 and 5 year survival (to 2018).

Breast, uterine, ovary. (CRUK/PHE 2019)



# Early diagnosis of ovarian cancer.

- Blood test- CA125.
- Ultrasound, generally transvaginal.
- Large UK trial of 202 638 women aged 50–74 randomised to yearly blood test and ultrasound, yearly ultrasound, or neither.
- 0.29% 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.
- Not significant. Consistent with other large studies. *Jacobs I et al Lancet 2016*





# Symptoms of ovarian cancer. Most women with these do not have cancer, but should discuss with GP.

New symptoms 12 or more times a year, especially after age 50:

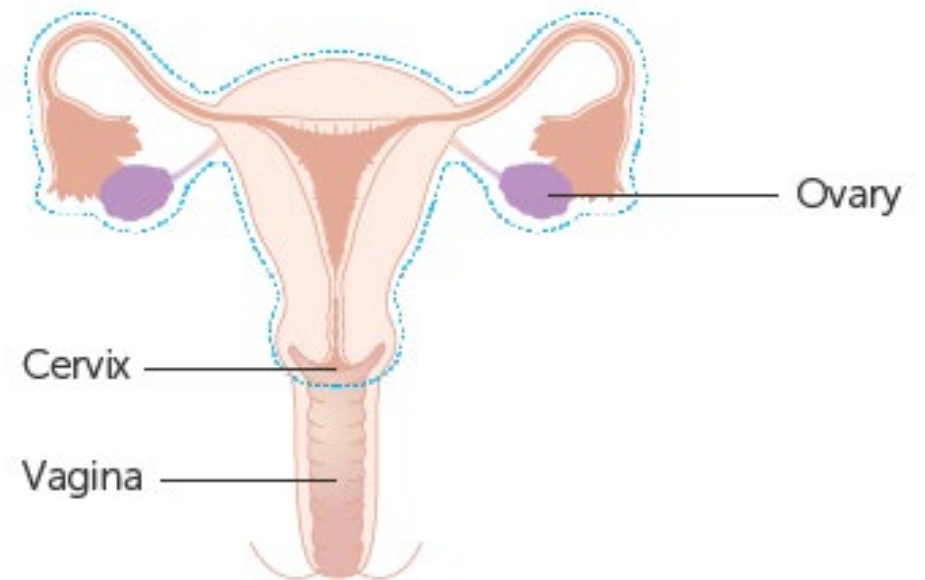
- feeling constantly bloated
- a swollen abdomen
- discomfort in abdomen or pelvic area
- feeling full quickly when eating, or loss of appetite
- needing to pass urine more often than normal

Worried about the symptoms of ovarian cancer?



## Surgery for ovarian cancer.

- In early (Stage 1) ovarian cancer surgery curative in most cases.
- In postmenopausal women both ovaries and fallopian tubes, and the womb including the cervix.
- In very early cancer in some premenopausal women wanting to have children only the ovary.
- In advanced cancer may have debulking surgery.



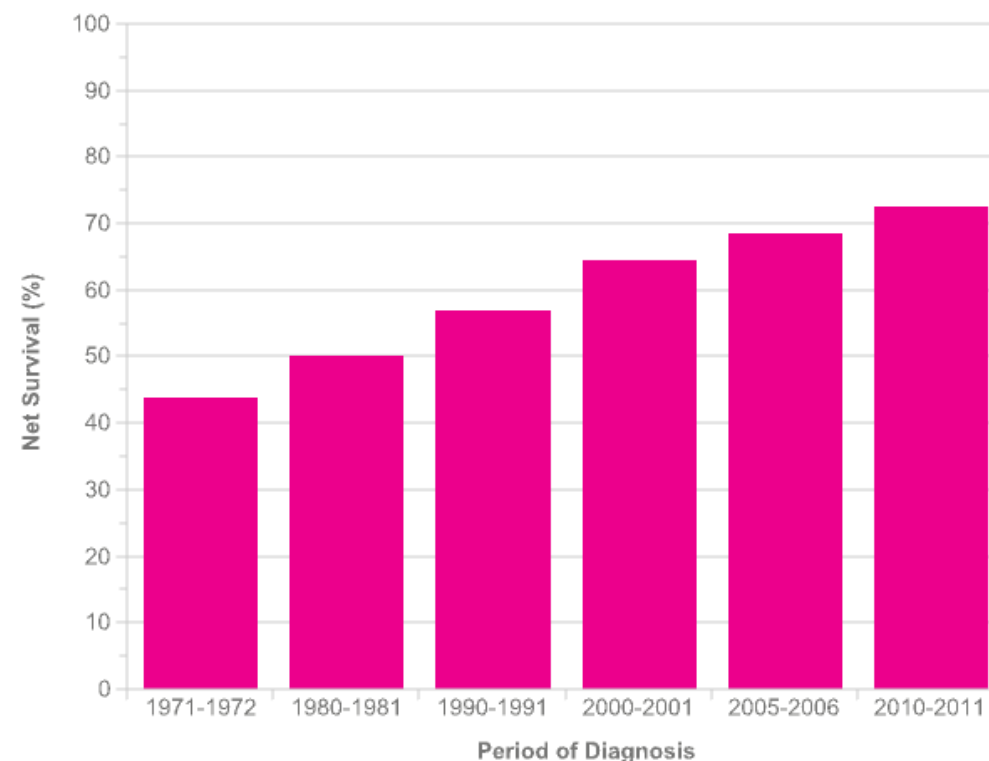
# Chemotherapy for ovarian cancer.

- Mainly Stage 1c or above, or high grade.
- Carboplatin +/-
- Paclitaxel.
- **Gemcitabine**. Originally developed as an antiviral.
- **Etoposide**. Originally derived from wild mandrake.
- **Topotecan**. Derived from bark of Camptotheca tree in Tibet and southern China.



## Trends over time for ovarian cancer survival.

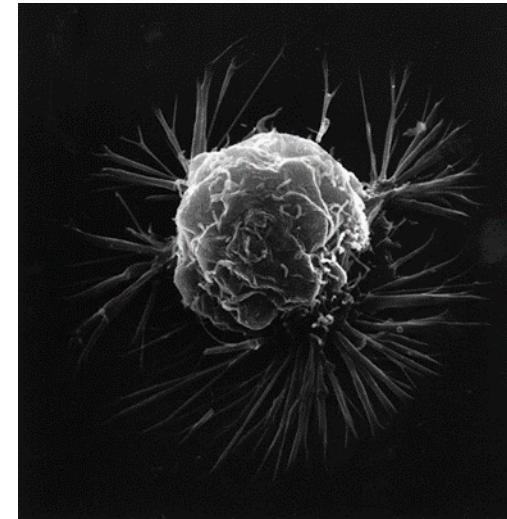
- Survival from ovarian cancer is improving for higher stages.
- Already very good (over 90% 5 year survival) for early disease.
- UK ten-year survival overall doubled from 18% to 35% since 1970s.
- But still poor compared to breast and uterine cancer.
- A major target for earlier diagnosis, new treatments.
- Immunotherapy being tested in ovarian cancer. Promising early results.



1 year survival.

Increasingly we will have subtypes.

- What we currently treat as a single cancer type will increasingly be seen as several subtypes.
- Differentiation on the basis of genotype of cancer.
- Important in later disease.
- They will have different prognosis and treatment.



## Cancers (almost) exclusively affecting women.

- **Breast cancer.** Screening, early surgery, radiotherapy and hormone therapy have changed the outlook. 78% 10 year survival.
- **Uterine cancer** generally diagnosed early, at which stage outlook is good. Also 78% 10 year survival.
- **Ovarian cancer.** Good outlook with early diagnosis, but most diagnosed late.
- **Cervical cancer.** Screening has reduced mortality significantly. HPV vaccination will substantially reduce incidence.



Marie Curie, Rosalind Franklin  
(who died of ovarian cancer).