# Research in Gynaecological Cancer – a Global Perspective

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UCT Refresher Course 2015

# The ‘War on Cancer’

- **National Cancer Act of 1971**
- The war on cancer began with the National Cancer Act of 1971, a United States federal law
- The act was intended "to amend the Public Health Service Act so as to strengthen the National Cancer Institute in order to more effectively carry out the national effort against cancer"
- It was signed into law by then US President Richard Nixon on December 23, 1971
- $1.5 billion committed to the ‘War’in 1971
- ‘War’ was supposed to mimic ‘….sending a man to the moon’
- Since then over $100 billion have been spent on research in cancer in USA

# National Cancer Institute, USA

- $4.8 billion allocated to NCI in 2013
- Director Harold Vamus Priorities in Cancer research*:
  - Provocative Questions Initiative
    - Why does obesity increase cancer risk?
    - Why are some cancers easily cured with conventional chemotherapy and not others?
  - Support developing countries to develop cancer registries and national cancer plans
  - Study why high rates of certain cancers in some countries e.g gallbladder cancer in Chile
  - Oncogene initiative: find drugs that target cell signalling pathway controlled by RAS (mutations in RAS drive uncontrolled cell growth in one third of all cancers)
  - Support the Cancer Genome Atlas ($375 million) launched 7 years ago, analysis of mutations in 10 000 tumour types covering 20 cancer types
  - Exploring new therapies with genetic tools

*Science 2013, 342:416 - 419

# Global funding and activity of cancer research*

- 2004/5 fiscal year there was a combined spend of 8 billion Euros USA and Europe
- Compared to 3 billion Euros for rest of the world (excluding industry)
- Top 24 pharmaceutical companies spent around 3 billion euros on cancer research in same year
- Per Capita Spends on cancer research 2004/5:

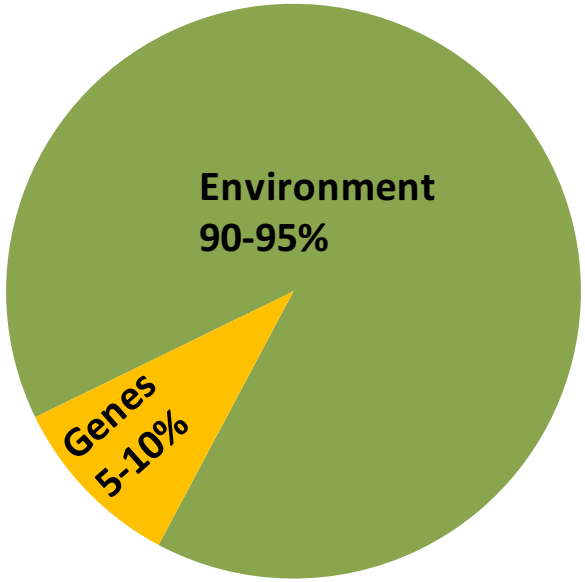
| | Euros |
|---|---|
| UK | 18.5 |
| USA | 17.98 |
| Australia | 7.93 |
| Canada | 8.27 |
| Japan | 7.88 |

*Eckhouse S, et al. Molecular Oncology 2008;2:20 - 32

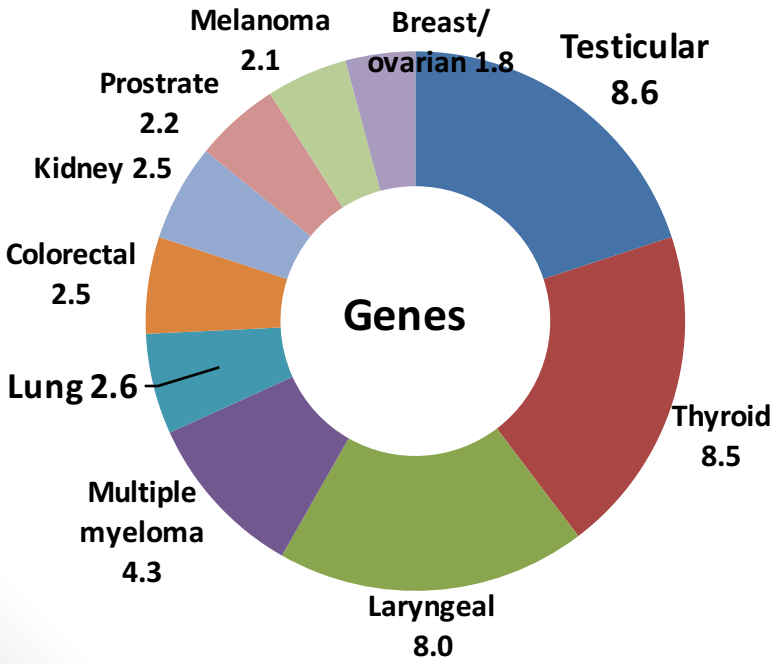
# So what have we learned from $100 billion expenditure?

- Percentage contribution of genetic and environmental factors to development of cancer
- Family risk ratios for selected cancers: defined as the ratio of the observed number of cancer cases among first degree relatives divided by the expected number derived from control relatives
- Percentage contribution of environmental factors to attributable-fraction of cancer deaths
- And more…

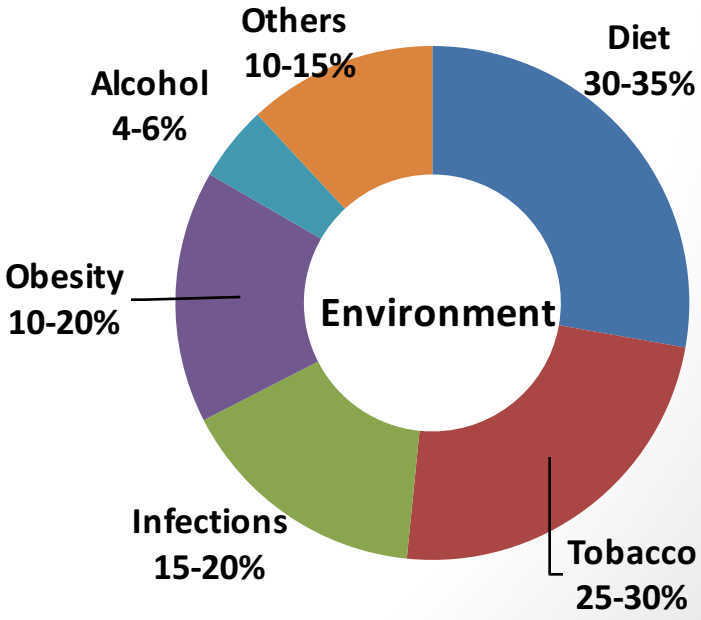
Reproduced from Anand Preetha et al. Pharmaceutical Research 2008;25(9):2097 - 2116

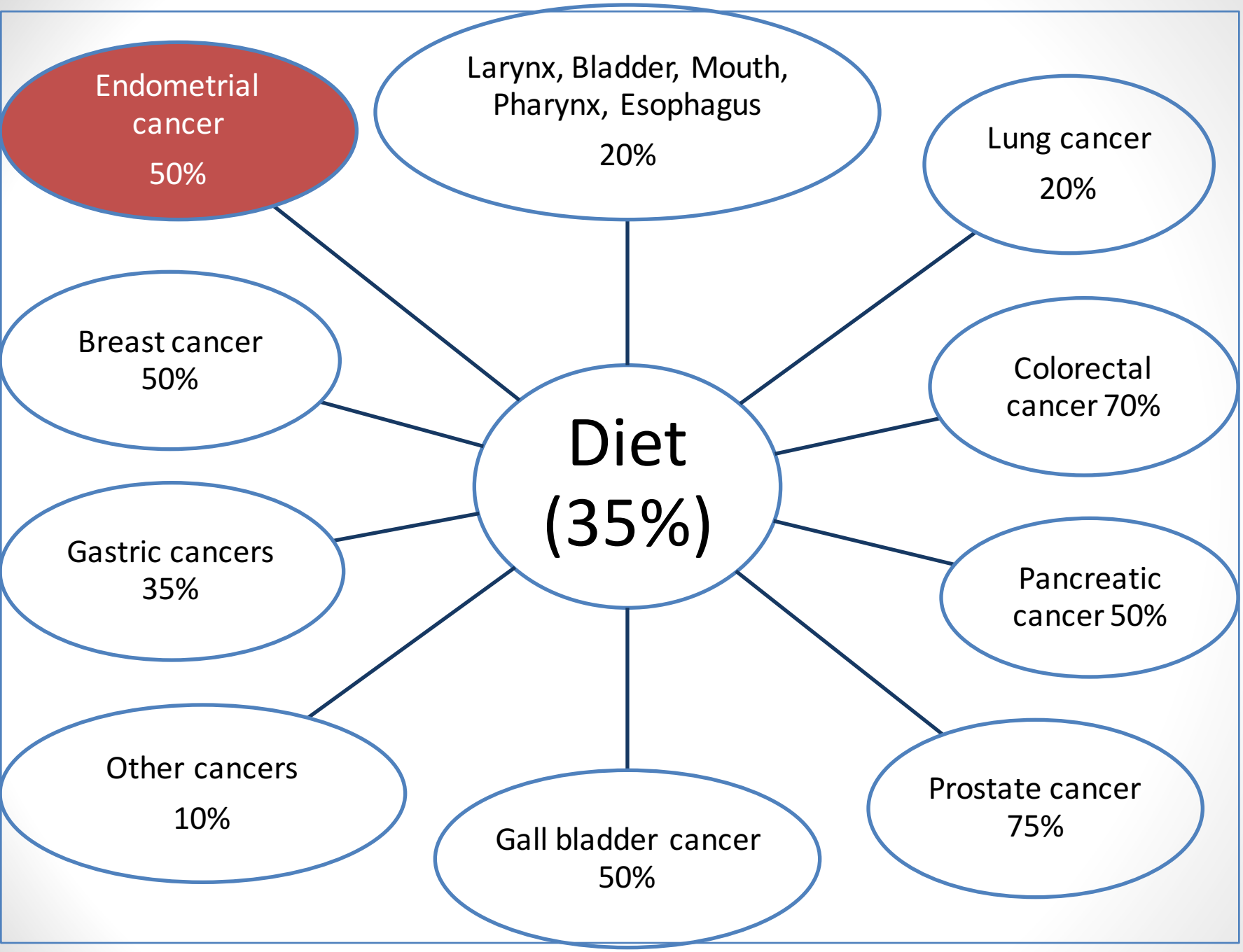


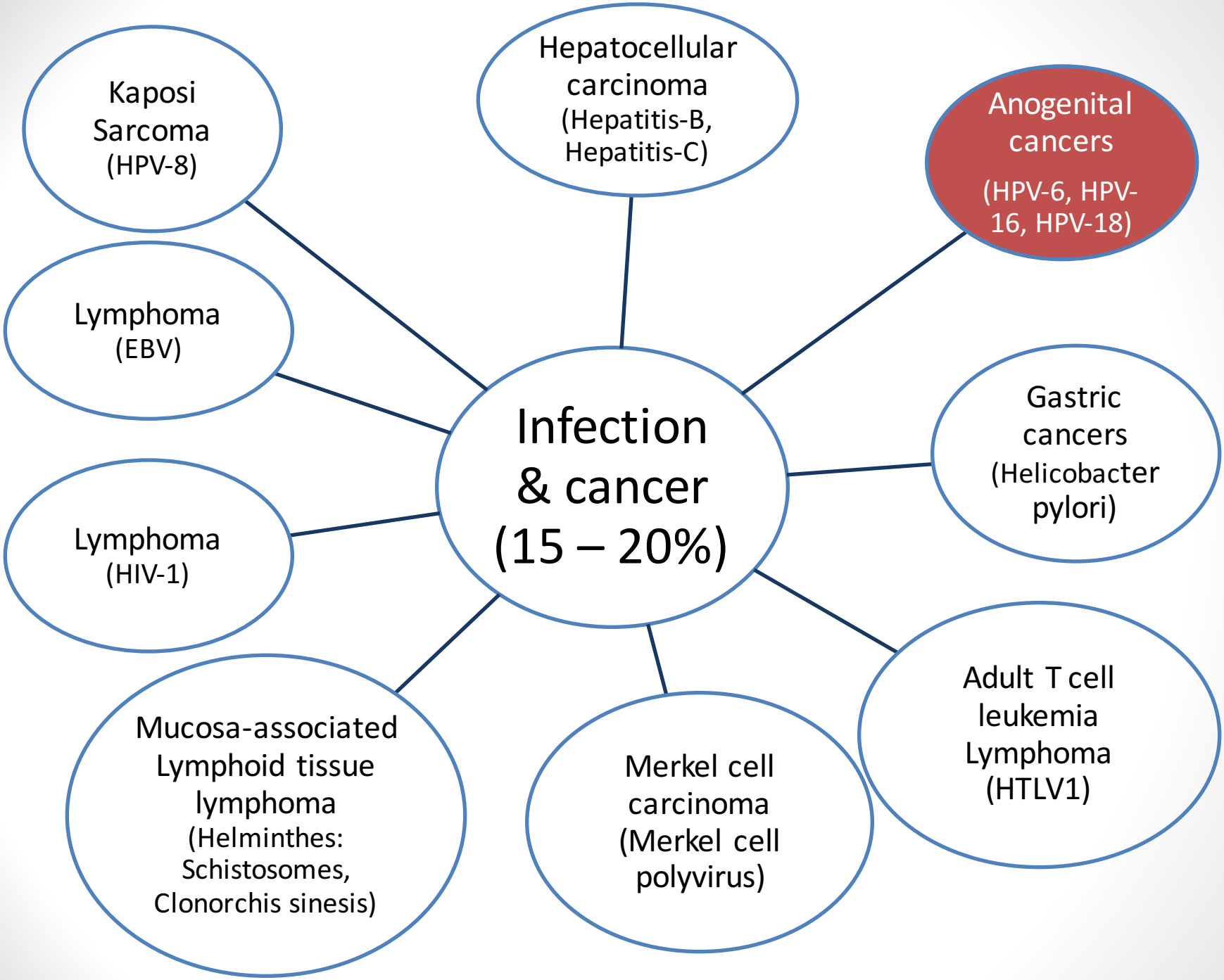

Family risk ratios for selected cancers

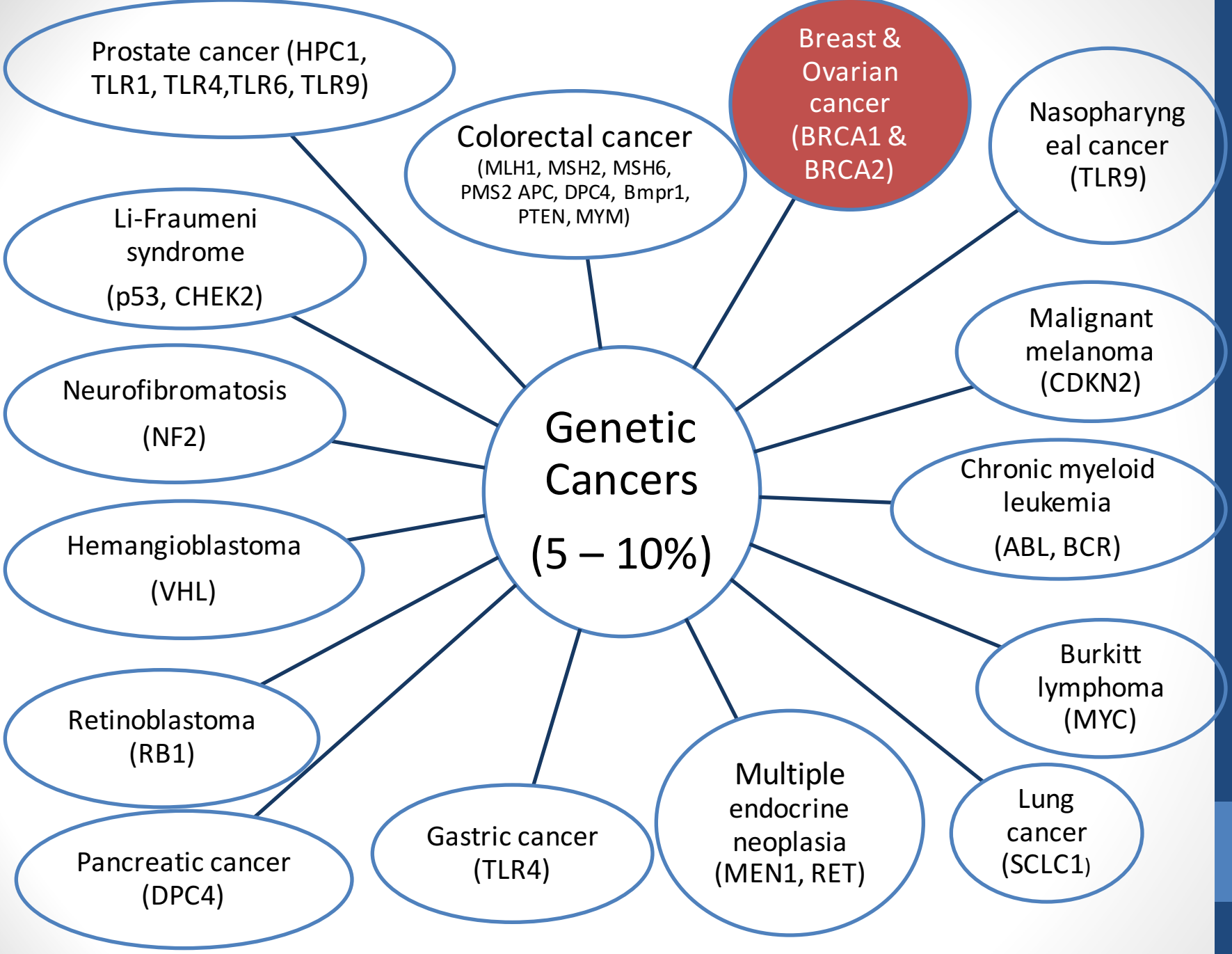


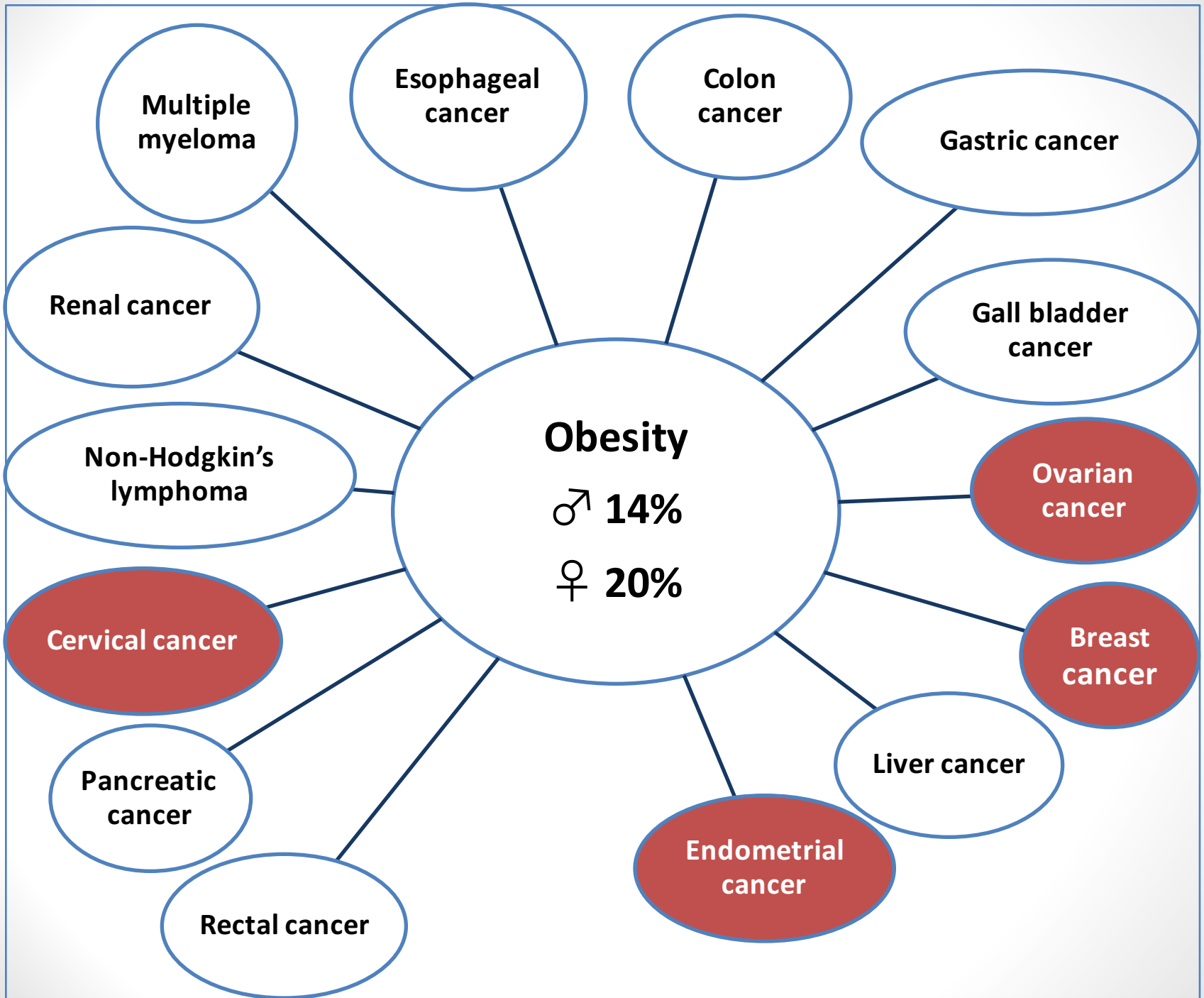

Percentage contribution of each environmental factor



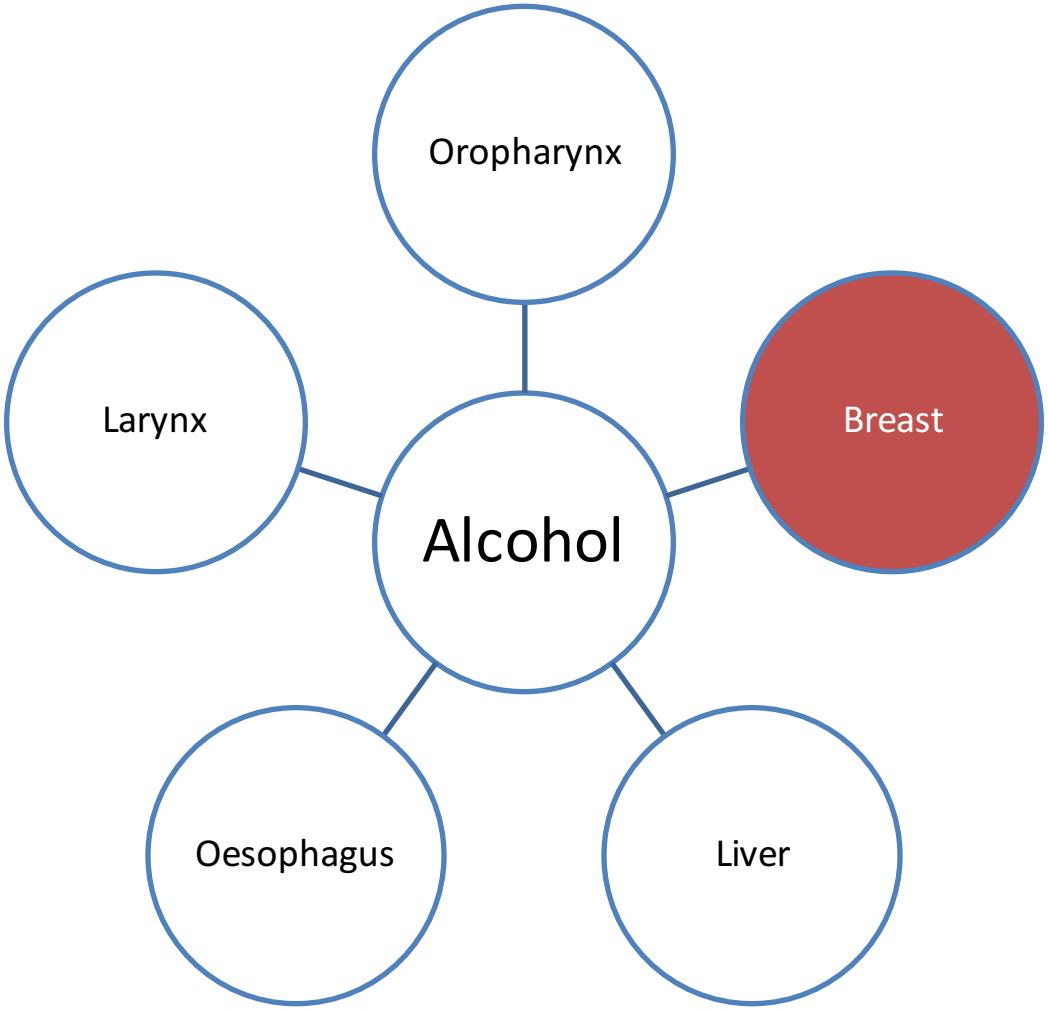

Endometrial cancer
50%
Larynx, Bladder, Mouth, Pharynx, Esophagus
20%
Lung cancer
20%
Breast cancer
50%
Diet
(35%)
Colorectal cancer 70%
Gastric cancers
35%
Pancreatic cancer 50%
Other cancers
10%
Gall bladder cancer
50%
Prostate cancer
75%


Infection & cancer (15 – 20%)
Kaposi Sarcoma (HPV-8)
Hepatocellular carcinoma (Hepatitis-B, Hepatitis-C)
Anogenital cancers (HPV-6, HPV-16, HPV-18)
Lymphoma (EBV)
Gastric cancers (Helicobacter pylori)
Lymphoma (HIV-1)
Mucosa-associated Lymphoid tissue lymphoma (Helminthes: Schistosomes, Clonorchis sinesis)
Merkel cell carcinoma (Merkel cell polyvirus)
Adult T cell leukemia Lymphoma (HTLV1)

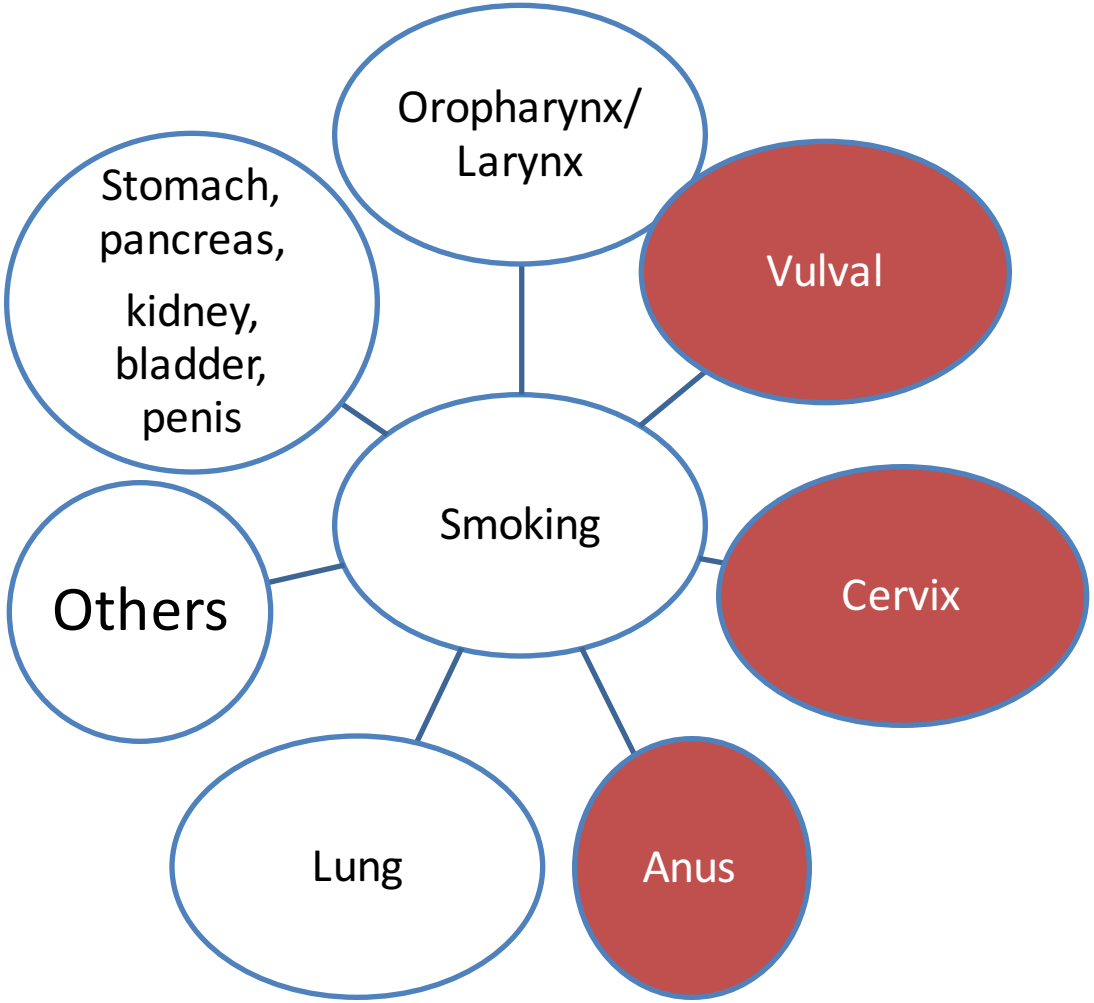

Genetic Cancers
(5 – 10%)
Prostate cancer (HPC1, TLR1, TLR4,TLR6, TLR9)
Colorectal cancer (MLH1, MSH2, MSH6, PMS2 APC, DPC4, Bmpr1, PTEN, MYM)
Breast & Ovarian cancer (BRCA1 & BRCA2)
Nasopharyngeal cancer (TLR9)
Li-Fraumeni syndrome (p53, CHEK2)
Malignant melanoma (CDKN2)
Neurofibromatosis (NF2)
Chronic myeloid leukemia (ABL, BCR)
Hemangioblastoma (VHL)
Burkitt lymphoma (MYC)
Retinoblastoma (RB1)
Lung cancer (SCLC1)
Multiple endocrine neoplasia (MEN1, RET)
Gastric cancer (TLR4)
Pancreatic cancer (DPC4)


Obesity
♂ 14%
♀ 20%
Multiple myeloma
Esophageal cancer
Colon cancer
Gastric cancer
Renal cancer
Gall bladder cancer
Non-Hodgkin's lymphoma
Ovarian cancer
Cervical cancer
Breast cancer
Pancreatic cancer
Liver cancer
Endometrial cancer
Rectal cancer

# Cancers linked to alcohol



# Cancers linked to smoking



# Overall incidence of cancer

- Globocan 2012 (www.iarc.fr/ globocan)
- Incidence of all cancers excluding non-melanoma skin cancers in men and women
  - 14 090 149
  - ASIR 182.3/100 000
- Deaths
  - 8 202 030
  - ASMR 102.4/100 000
- Top five cancers in women:
  - Breast
  - Colorectal
  - Lung
  - Cervix
  - Stomach

# Quality of life

- Historically the most neglected aspect of oncological research
- Now recognised that QOL should be critically evaluated in all oncological research
- In gynaecological cancer the use of radical surgery, multiple types and cycles of chemotherapy and radiation can have devastating effects on women, their quality of life, their families and communities
- The desire to live or keep our patients alive regardless of the price is becoming increasingly problematic with the development of new and novel therapies and an aggressive research agenda

# Quality of life

- Major crises occur when:
  - The ‘war’ metaphor creates its own dynamic of fear and acquiescence to medical intervention
  - Failure to respond to treatment becomes a personal failure
  - Create false hope by shifting to new and experimental chemotherapeutic regimens – hope, loss, hope, loss cycle
  - Continue treating women without hope of cure with toxic regimens and failure to deal with patient’s need to live ‘no matter what’
  - Fail to share bad news with integrity, honesty and frankness
  - Fail to respect the innate intelligence and insight of our patients
  - Fail to listen to their stories…….what ails you the most?

# Models for quality of care

- Multi-disciplinarity key to better outcomes
- Team should represent care for all aspects of patient experience of life threatening illness
- Holistic care recognises that the patient is a lot more than her cancer
- Presumption is dangerous
- Patient should be given the opportunity to be integrally involved in her care, to articulate her needs, fears, aspirations, support required, identify partners in her journey
- Use of complementary or other health systems should be allowed and acknowledged – particularly important in developing countries
- We can only prepare our patients for the 'cancer journey' (called entry into tumortown by Christopher Hitchens), if we are able to really listen to their experiences

# Research issues in site specific gynaecological cancers

# Research priorities Vulval cancer

- **Reduction in surgical morbidity**
- Surgical complications*
  - Review of English literature from 1965 – 2012, 35 studies included
  - 11 prospective, remainder retrospective
  - 5 year survival with negative IFL 96% compared to 80% with 1 or 2 positive nodes and drops to 12% if more than 2 nodes
  - Knowledge of nodal status is important

- Complications following inguinofemoral lymphadenectomy (IGFL)
- Lymphedema 14 – 48% patients
  - Major risk factors include:
    - Obesity
    - Number of LNs removed
    - Extent of surgery
    - Post-operative infection
    - Radiation
    - Post-operative DVT

*Wills A, Obermair A. Gynecol Oncol 2013; 131:467- 479

# Other Surgical Complications

- Lymphocoele formation
- Wound complications (infection, cellulitis, wound breakdown)
- Sexual dysfunction
- Psychosocial disorders
- Urinary incontinence, vaginal prolapse

# Sentinal lymph node biopsy in vulval cancer*

- Groningen International Study on Sentinal Nodes in Vulval cancer (GROINSS-V) included 403 women with unifocal vulval cancer stage 1 or II, tumour size < 4 cms, stromal invasion > 1 mm and clinically negative nodes
- SLN negative women, IGF dissection omitted (n= 259)
- Groin recurrences occurred in 2.3% of women, with median follow-up of 35 months
- Overall disease specific survival was 97% at 3 years, with substantial reduction in morbidity but no increase in oncological morbidity
- Lymphedema was reported in 1.9% in SLN group compared to 25.2% who underwent full IGF dissection

*der Zee AGJ van et al. J Clin Oncol 2008;26(6):884 - 9

# SLN dissection

- GOG – 173 study*
- 772 groin dissections in 452 patients
- All patients had SLN biopsy followed by systematic IGFL
- Nodes positive in 132 women, including 11 patients with false negative nodes with false negative predictive value of 3.7%
- Women with tumours < 4 cms had < 2% risk of false negative nodes
- These and other studies suggest that SLN dissection is oncologically safe and associated with significant decrease in morbidity

*Levenback CF et al. J Clin Oncol 2012;30(31):3786 - 91

# Relationship vulval cancer to HPV infection

- Incidence rates of vulval cancer and VIN increasing
- Warty and basaloid types of vulval cancer associated with infection with HPV
- Types associated with chronic dermatoses, eg LS et A are not associated with HPV and occur in older women
- 2012 USA study using archival material reported HPV detection in 121/176 (68.8%) of invasive cancers and 66/68 (97.1%) of VIN lesions*
- HPV 16 was present in 48.6% of invasive cases and 80.9% of VIN 3 cases
- Prevalence of HPV by squamous cell subtype:
  - Keratinising 49.1%
  - Nonkeratinising 85.7%
  - Basaloid 92.3%
  - Warty 78.2%
  - Warty/basaloid 100%

*Gargano JW et al. J Low Genital Tract Disease 2012;16(4):471- 79

# Relationship vulval cancer and HPV infection

- De Sanjose et al* collected histologically confirmed cases of VIN (n = 587) and invasive cancer (n = 1709) from 39 countries
- HPV detected 86.7% VIN cases and 28.6% of invasive cases
- HPV 16 commonest type detected in both VIN and invasive cases
- Other types associated with vulval cancer include HPV 33, 18 and 45
- P16 INK4a was performed to determine whether at tumour was HPV driven or not: 87.6% of HPV DNA positive tumours were also p16 INK4a positive

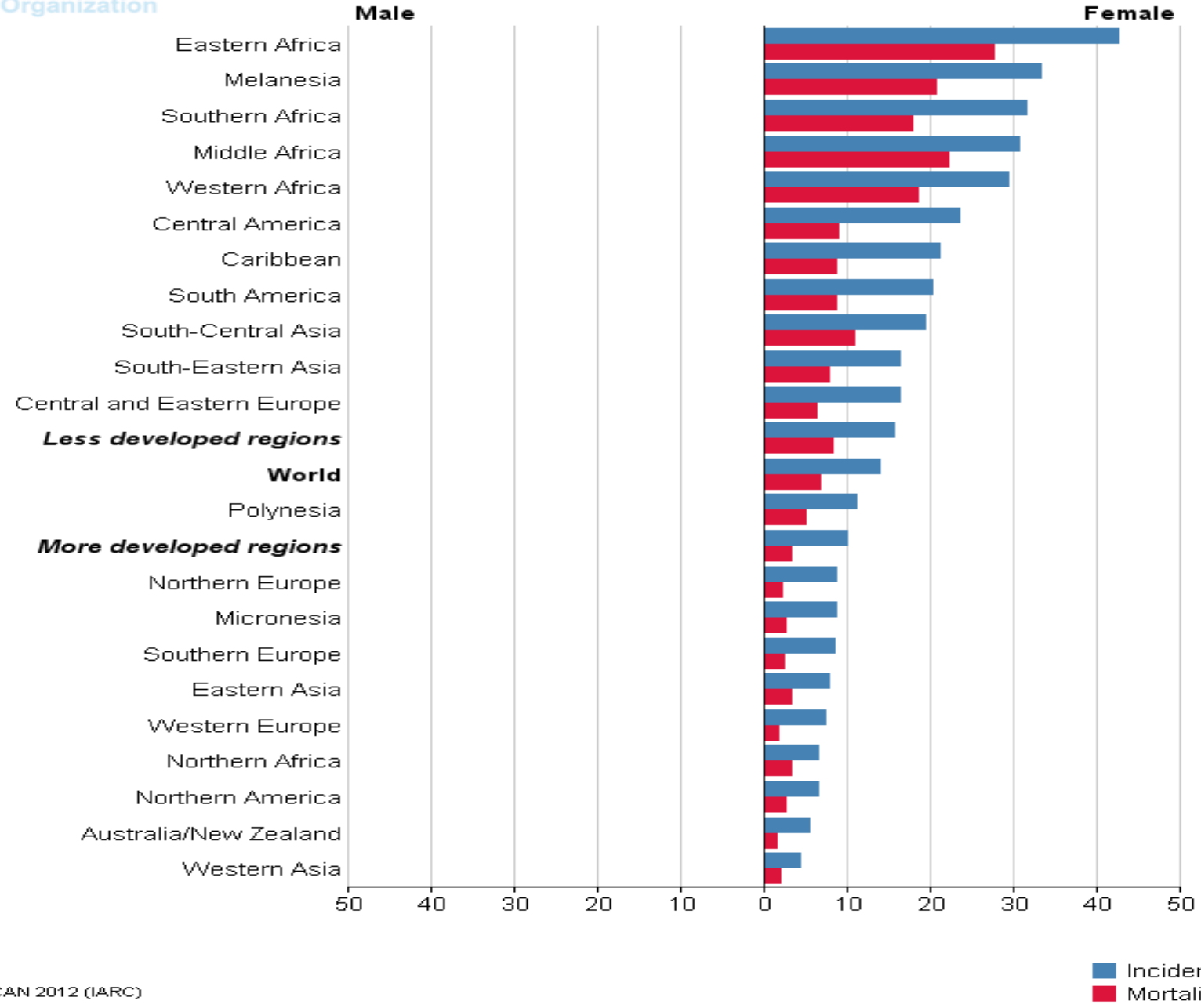
*De Sanjose et al. European Journal of Cancer 2013;49:3450 - 3461

# Relationship between vulval cancer, HPV and HIV infection

- Increase incidence in HIV infected women
- Poorly documented
- High incidence of inoperability, lymph node involvement at presentation, poorer outcomes in terms of response to surgery and chemoradiation
- Occurs in younger women
- Risks of mutilating surgery
- Is vulval cancer preventable?
  - Role of therapeutic vaccination
  - Impact of prophylactic vaccination
  - Role of immunotherapy

# Cervical Cancer

- Cervical cancer is the fourth most common cancer in women,
- Estimated 528,000 new cases in 2012 (Globocan 2012)
- High-risk regions, with estimated ASRs over 30 per 100,000, include:
  - Eastern Africa (42.7)
  - Melanesia (33.3)
  - Southern (31.5) and Middle (30.6) Africa.
  - Rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4).
- There were an estimated 266,000 deaths from cervical cancer worldwide in 2012
- 87% cervical cancer deaths occur in the less developed regions
- Mortality varies 18-fold between the different regions of the world




GLOBOCAN 2012 (IARC)

# Cervical cancer in developing countries

**Negative side**

- Lack of prevention
- Lack of access to diagnosis and treatment with late stage presentation
- Lack of palliative care
- High incidence to mortality ratios
- Poor training and lack of requisite skills

**Positive side**

- Alternative strategies to cytology
- Vaccination
- Increasing placement of radiation facilities and focus on supporting access to diagnostic services
- Increasing recognition that cancer is a public health problem in poor countries
- State of cancer services in poor countries is recognised as NOT ok!

# Cervical cancer research issues

- Role of lymphadenectomy in locally advanced disease
- Role of sentinel nodes
- Fertility sparing surgery
- Chemotherapy
- Targeted therapies

# New chemotherapy in locally advanced cervical cancer

- Concurrent chemoradiation led to significant improvements in survival over radiation alone
- Overexpression of vascular endothelial growth factor (VEGF) is common in cervical cancer and is associated with poorer outcome
- GOG evaluated single-agent bevacizumab, 15mg/kg every 21 days in patients with recurrent or metastatic disease and showed that 24% of patients had no progression over 6 months+
- Followed by trial by RTOG 0417 of the efficacy of bevacizumab in combination with definitive radiation therapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma*

+ Monk BJ et al. J Clin Oncol 2009;27:1069 – 1074
*Schefter T et al. Int J Radiation Oncol Biol Phys 2014;88(1):101 - 105

# Angiogenesis

- Bevacizumab (BVB) is a humanised anti-VEGF monoclonal antibody that binds with an affinity comparable with that of the original antibody
- A randomised phase 3 clinical trial showed that compared to chemotherapy alone, chemotherapy plus BVB significantly increased OS from 13.3 months to 17.0 months (hazard ratio 0.71 [98% CI: O.54 – 0.95; p=0.004]) in patients with advanced cervical cancer (GOG 240)*

# Angiogenesis

- The triplet regimes used in the study, a phase 3 randomised trial, were both associated with a 6% incidence of fistula and 8% incidence of TE (compared to <1% and 1% for either regime without BVB, respectively)
- The drug was however approved for the treatment of advanced cervical cancer by the FDA
- It is critical in women with advanced cervical cancer that QOL be measured to balance treatment toxicities and, particularly in view of poor prognosis for women with advanced cervical cancer

# Ovarian cancer

- Rationale for subtyping:
  - Different histological subtypes differ with respect to:
    - Genetic risk factors
    - Precursor lesions
    - Patterns of Spread
    - Molecular events during oncogenesis
    - Response to chemotherapy
    - Survival
- Targeted therapies
  - Specifically target tumour cells and/or microenvironment by exploiting specific molecular abnormalities in the tumour
- Molecular pathogenesis
  - Divides epithelial ovarian cancer into:
    - Type I (low grade serous, low grade endometrial, clear cell and mucinous and Brenner cancers)
    - Type II tumours (high grade serous, high grade endometrioid, carcinosarcomas and undifferentiated cancers)

# Sub-types of EOC*

- HGSC have abnormalities of BRCA 1 and 2 and TP53 mutation or deletion resulting in loss of ability to repair DNA double-stranded breaks resulting in chromosomal instability
  - Most HGSC respond to platinum/taxane chemotherapy, albeit most will recur
- In contract, LGCS exhibit BRAF or KRAS mutations and do not show chromosomal instability nor are they associated with BRCA mutations
  - Do not respond to conventional chemotherapy however, few studies as only recently recognised as an entity
- KRAS mutations are common in mucinous carcinomas and HER 2 is amplified in 15 – 20%
  - Studies suggest mucinous tumours less responsive to standard chemotherapy and in those women with HER2 amplification trastuzumab may prove effective although no clinical studies

*Gilks C, Prat J. Human Pathology 2009;40:1213- 1223

# Targeted therapies in ovarian cancer

- Angiogenesis is a critical factor in cancer growth and metastasis with VEGF and its receptors playing a pivotal role
- VEGF actions are mediated by binding to tyrosine kinase receptors – this results in receptor dimerisation, phosphorylation and activation of signalling cascades resulting in endothelial cell survival, proliferation, invasion and migration
- Bevacizumab (IV administered humanised monoclonal antibody) binds and neutralises VEGF
- Tyrosine kinase inhibitors (TKI) inhibit the activity of VEGF receptors and block downstream signalling pathways
- Examples of TKI include vandetanib, sunitinib and pazopanib

# Phase III trials of bevacizumab

- Data still immature
  - OCEANS trial – platinum sensitive patients
  - AURELIA trial – platinum resistant patients
  - Dose dense chemotherapy with bevacizumab ongoing trials
- Unanswered questions include:
  - Use frontline or recurrence?
  - Single agent or in combination?
  - Dose, duration, continuation beyond progression
  - Cost-effectiveness and impact on QOL
- TKIs – 5 ongoing trials
  - Data to date indicate improved PFS but not OS
- Up to now, no USA FDA indication for anti-angiogenesis therapy in ovarian cancer due to failure to show improved OS and use of PFS as endpoint not considered acceptable

# Molecular Pathogenesis*

- Type 1 ovarian tumours
  - Indolent, present early stage
  - Specific mutations include KRAS, BRAF, ERBB2, CTNNB1, PTEN, PIK3CA etc which target specific cell signalling pathways
  - Rarely harbour TP53 mutations and are genetically stable
- Type II tumours
  - Aggressive, present at advanced stage
  - High frequency of TP53 mutations and altered expression of BRCA either by mutation or promoter methylation
  - Genetically highly unstable

*Kurman RJ, Shih I. Human Pathology 2011;42:918 - 931

# Molecular pathogenesis

- New thinking
  - Fallopian tube epithelium is source of LGSC and HGSC rather than ovarian surface epithelium
- Clear cell and endometrioid ovarian cancers arise from endometriosis
  - and since endometriosis is believed to arise from retrograde menstruation, these tumors can be regarded as involving the ovary secondarily
- Most mucinous tumours of the ovary are secondary and primary cancers of the ovary are rare: approx. 3% of all EOCs
  - Possible that arise from microscopic transitional cell nests at the tubal-peritoneal junction along with Brenner tumours
- Only true primary ovarian cancers are gonadal stromal and germ cell tumours, analogous to testicular tumours

# Which women with ovarian cancer should be offered genetic testing?

- Most studies have indicated that germline BRCA1 and BRCA2 mutations occur in 5 – 10% of all ovarian cancers
- Genetic testing offered on grounds of family history
- Germ-line BRCA mutations associated with longer survival after ovarian cancer diagnosis and favourable response to platinum plus activity of PARP inhibitors have suggested a re-look at criteria for genetic testing
- Recent Australian study* evaluated a prospectively ascertained population based cohort of 1 001 Australian women diagnosed with ovarian cancer to measure mutation frequency

*Alsop K et al. J Clin Oncol June 18, 2012

# Which women with ovarian cancer should be offered genetic testing?

- Pathogenic BRCA1/2 mutations were identified in 14.1% of patients (n = 141)
- 88/141 were in BRCA1
- Women with pathogenic mutations were more likely to be diagnosed with advanced stage
- Higher proportion of women with HGSC carried pathogenic mutations (22.6%; 98/433 patients)
- 44% of mutation carriers had no significant family history
- Multivariate analysis BRCA1/2 mutation status was an independent predictor of better OS and PFS, after adjusting for age, stage and debulking as well as response to platinum at recurrence
- Authors propose that women are *routinely* referred for genetic counselling and testing early in disease as the outcome may influence treatment strategies

# Should we be removing Fallopian tubes in women having surgery for benign gynaecological disease?

- Growing evidence that HGSC may originate in the fallopian tubes
- No population based data to quantify the risk-benefit ratio and not yet proven that this approach will reduce incidence of ovarian cancer
- No described harms of bilateral salpingectomy and few studies have indicated no real impact on ovarian reserve
- Decision should be individualised and women extensively counselled pre-operatively regarding either bilateral salpingectomies or BSO
- BSO may be associated increased mortality due to coronary heart disease, osteoporosis related fracture, dementia, depression and anxiety (but literature contradictory)

# Developing countries

- Everything centres around infrastructure
  - Range from death notification to collection of statistics
  - Defining the extent of the problem to allow for appropriate resource allocation and policy formulation
  - Creation of National Cancer Control Programmes and Cancer Registeries
  - Investment in PREVENTION of Cancer should be starting point
  - Parallel Investment in health care and understanding that healthier nations bring healthier development
  - Divert resources from corruption to investment in people:
    - Training health care professionals
    - Creating diagnostic services
    - Early detection
    - Access to treatment and follow up

# Conclusions

- Cancer care and research must take into account three factors:
  - The patient as a whole person
  - The biology and treatment of the disease
  - The health care professional
- Requires transversal co-operation with a wide range of professionals who currently tend to work in silos
  - Molecular biologists, pathologists, pharmacologists, basic scientists should be interacting with social scientists, sexual health specialists, social workers , palliative care specialists, health care advocates, politicians, epidemiologists…..
  - The list is endless….
- The locus of cancer incidence will shift to the developing world in the next 20 – 30 years
- Are we ready?