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STUDIECENTRUM VOOR KERNENERGIE
CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE

Biological effects of radiation: the use of radiopharmaceuticals to kill tumors

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Cancer definition

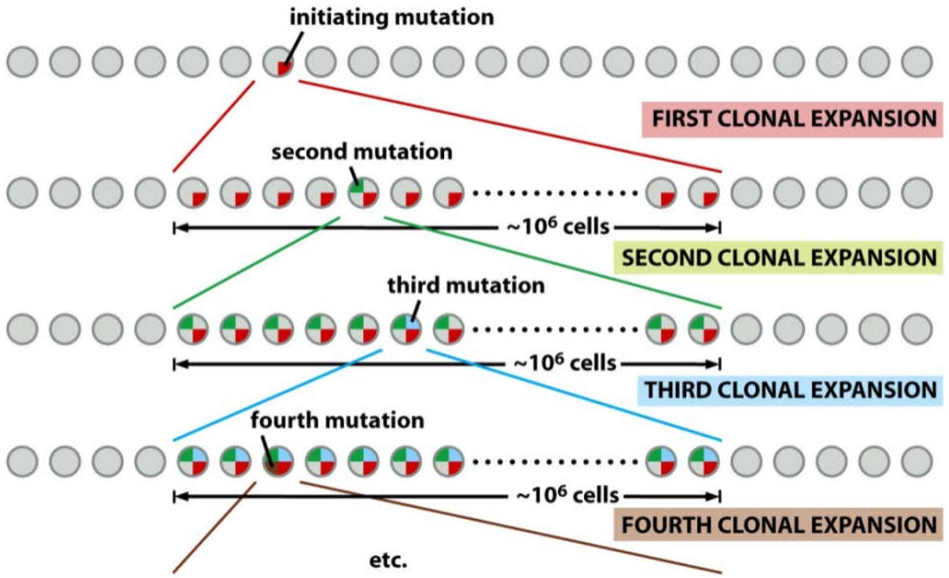
- Many definitions

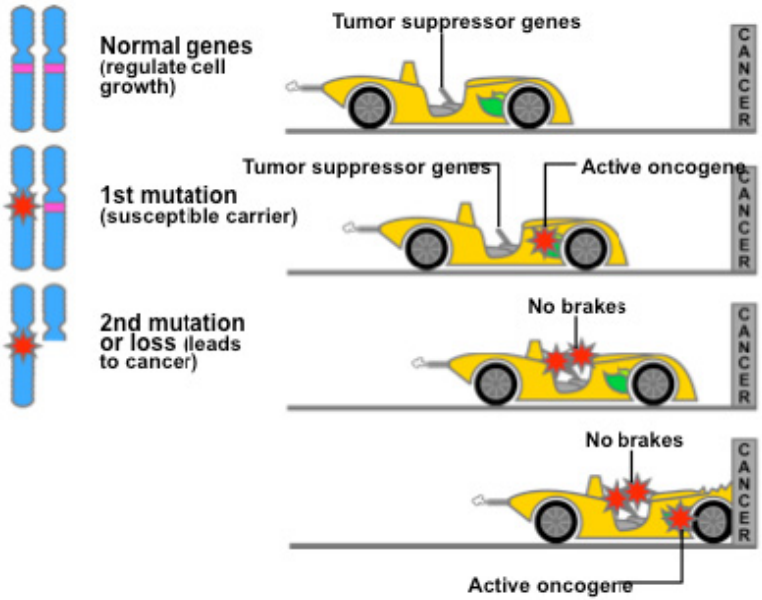
- Definition (used by ASC) :

  - *Cancer is a large group of diseases characterized by the uncontrolled growth and spread of abnormal cells.*
  - *If the spread is not controlled, it can result in death.*

What is/causes cancer?

- Disorder of cells, usually appears as a tumour made up of a mass of cells.
- It is thought that **several mutations** need to occur to give rise to.
- **Mutations** of normal genes :
  - **oncogenes** linked to accelerated cell proliferation
  - **tumour suppressor genes** linked to decreased cell death).
- over 100s forms of cancer





What causes cancer?

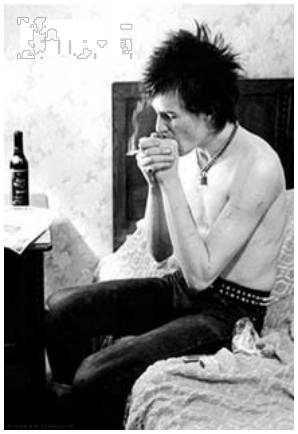
- Cells that are old or not functioning properly normally self destruct and are replaced by new cells.
- However, cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.

Normal Cell

Obeys strict rules
Divides only when told to
Dies rather than misbehaving
Stays close to home

Careful with chromosomes

At least 5 mutations



Cancer Cell

Disobeys rules
Divides at will
Bad behavior doesn't kill
Wanders through body

Careless with chromosomes

Growth pattern

Benign

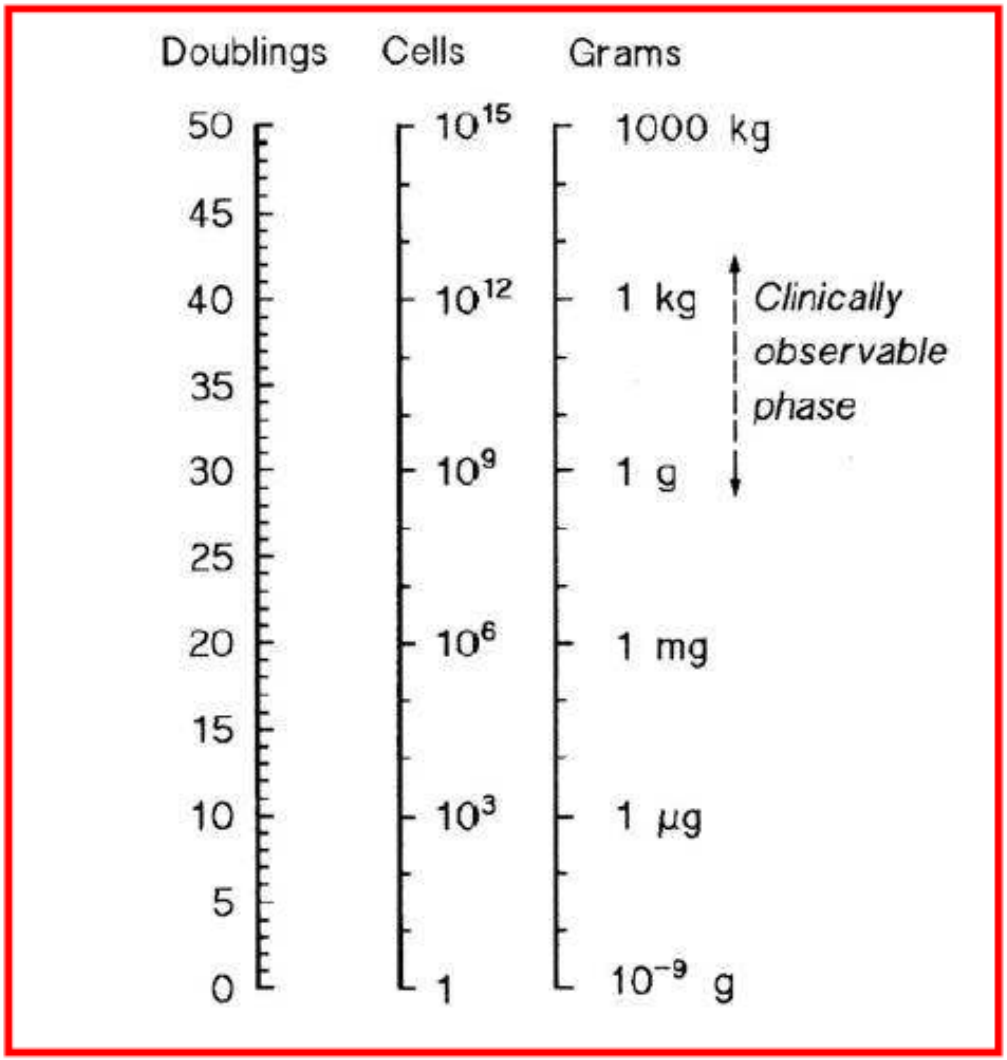
- slow growth
- non-invasive
- encapsulated
- no metastasis

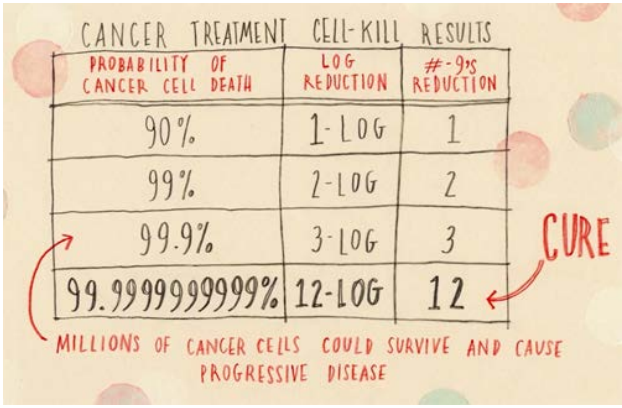
Malignant

- rapid growth
- invasive *
- potential for metastasis

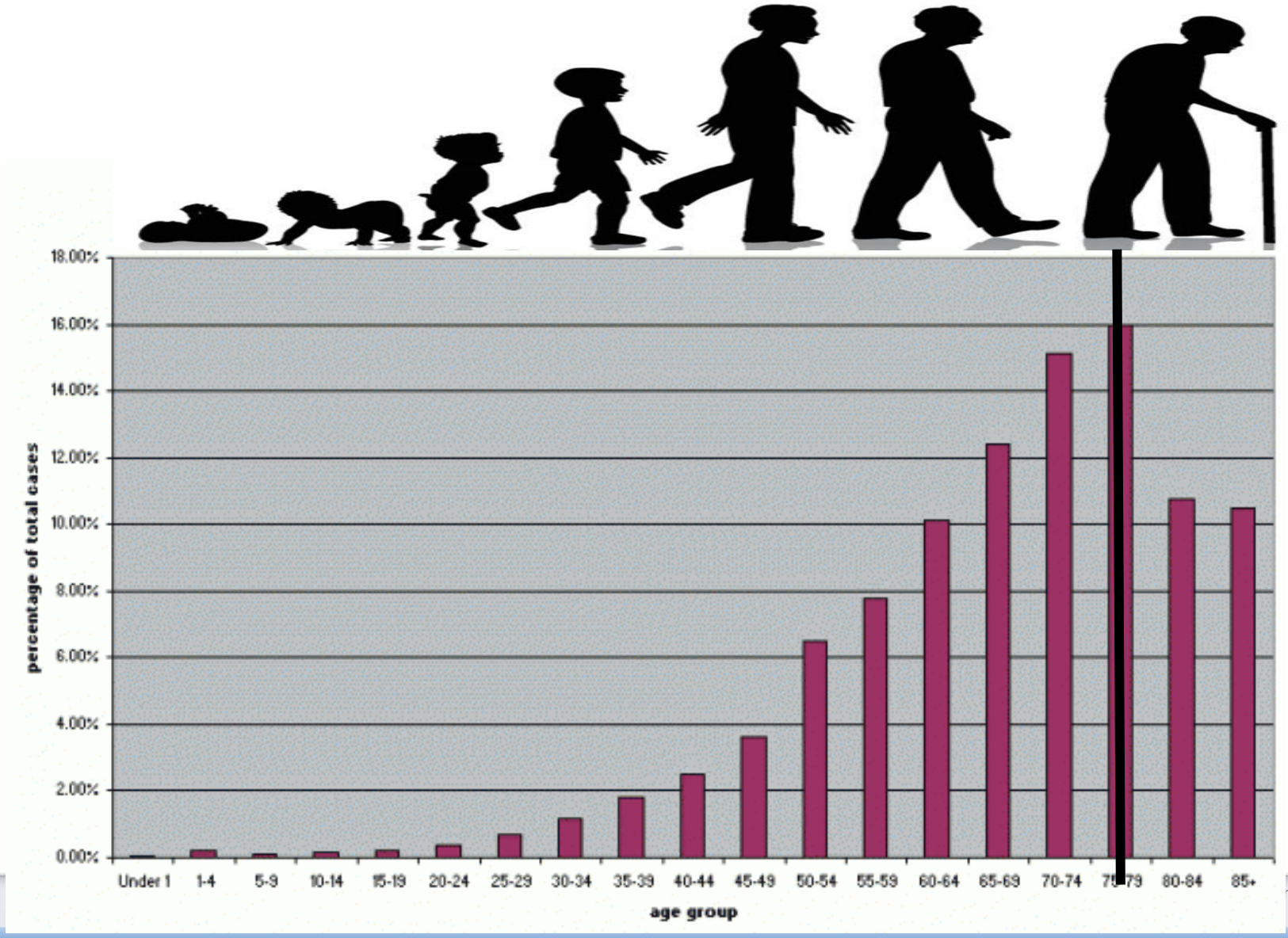
** Ability to spread in healthy surrounding tissues*

Cancer cure = minimum killing of 99,9% cells



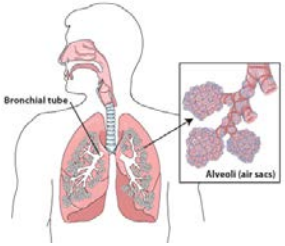


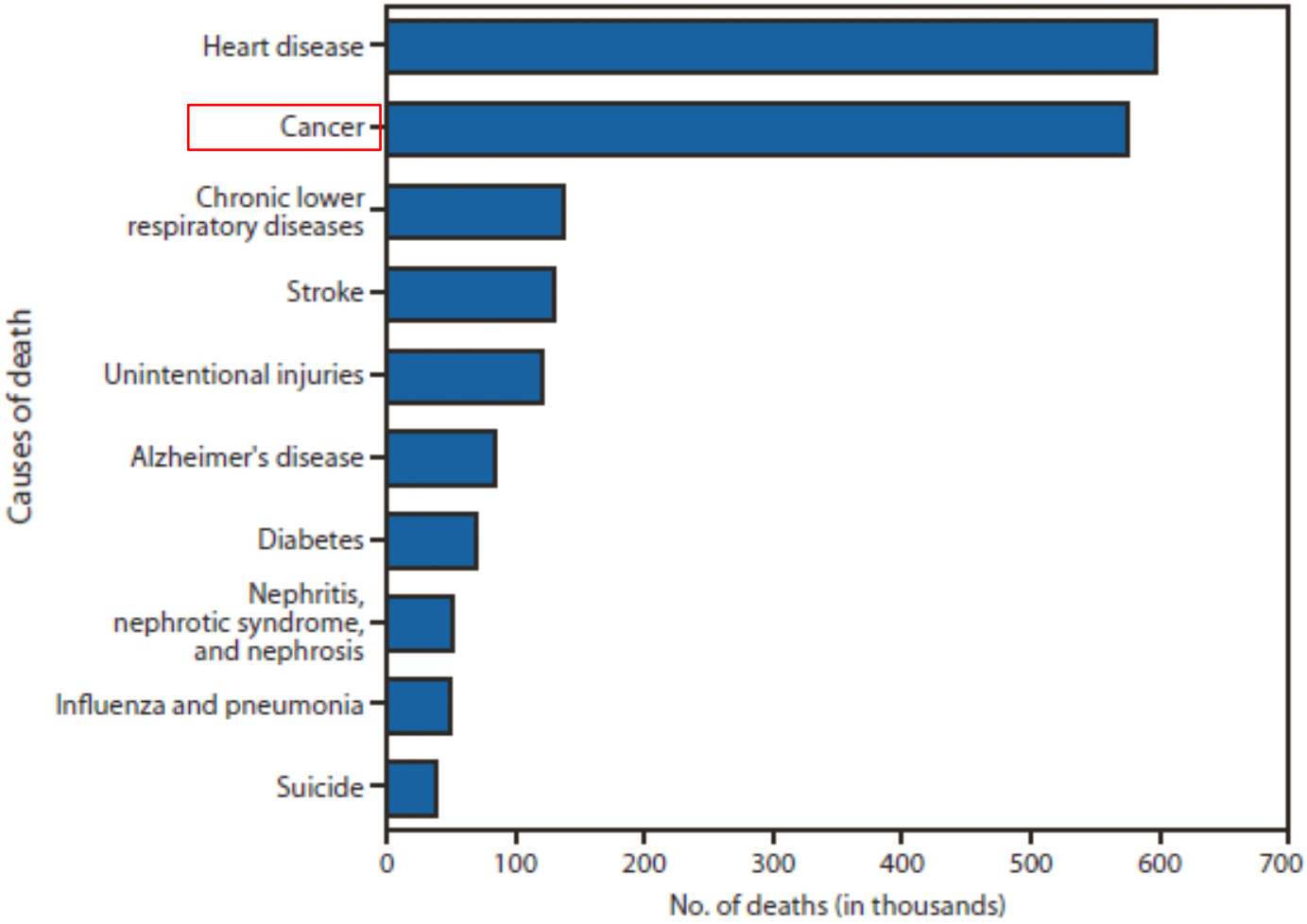
Cancer is directly related to ageing



Cancer= 2nd killer in Western countries

- one of the most common diseases in the developed world
- about 1 in 4 deaths are due to cancer





Worldwide cancer projection

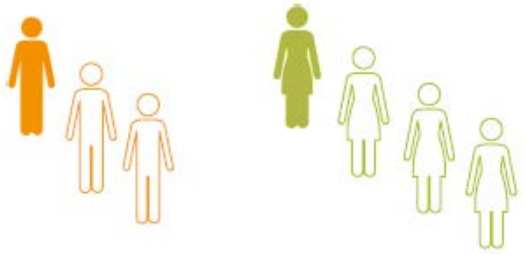
- More than 70% of all cancer deaths occurred in low- and middle-income countries.

- Deaths from cancer worldwide are projected to continue rising because of
  - higher density of populations
  - ageing of the population
  - new diagnostic tools
  - poor medical support in developing countries
  - environment
  - life style

- If trend continues, in 2020, 1st cause of death.

Situation in Belgium

- **In 2013**, 65,847 new cancer diagnoses in Belgium
  - 34,542 in men (53%)
  - 30,945 in women (47%)

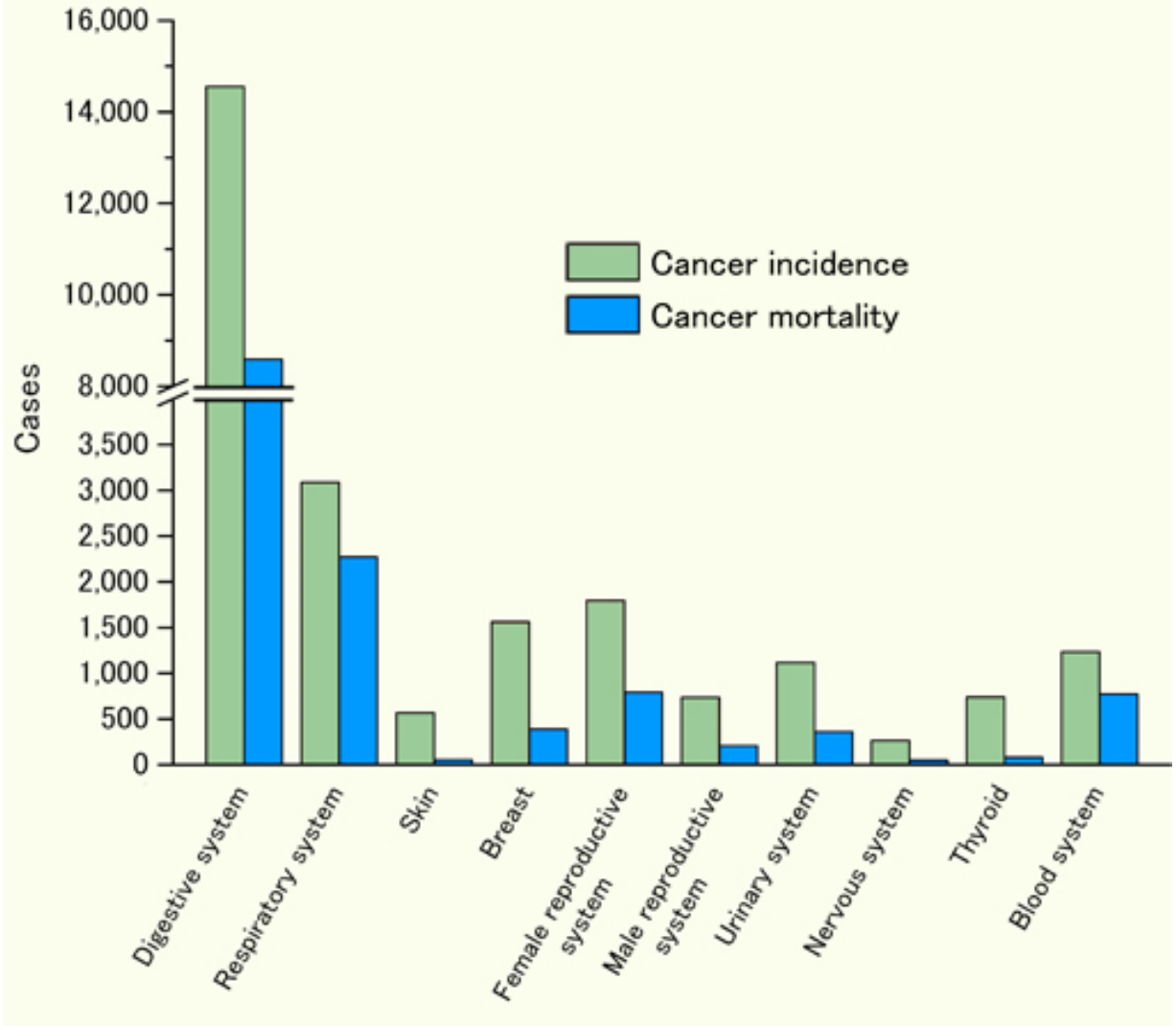


- Before 75th anniversary

- 59% 69% are still alive 5 years after diagnosis
- 3% of the Belgian population is living with cancer or has been diagnosed with cancer in the last 10 years
- 13% of patients with cancer have multiple tumours
- **Estimation for 2025**
  - 12,000 more new diagnoses than in 2013. Estimated total = 78,000
  - In 2025, the risk as high in women as in men (due to smoking habits).
  - This increase of cancers will mainly be due to ageing, growth of the population & new diagnosis.

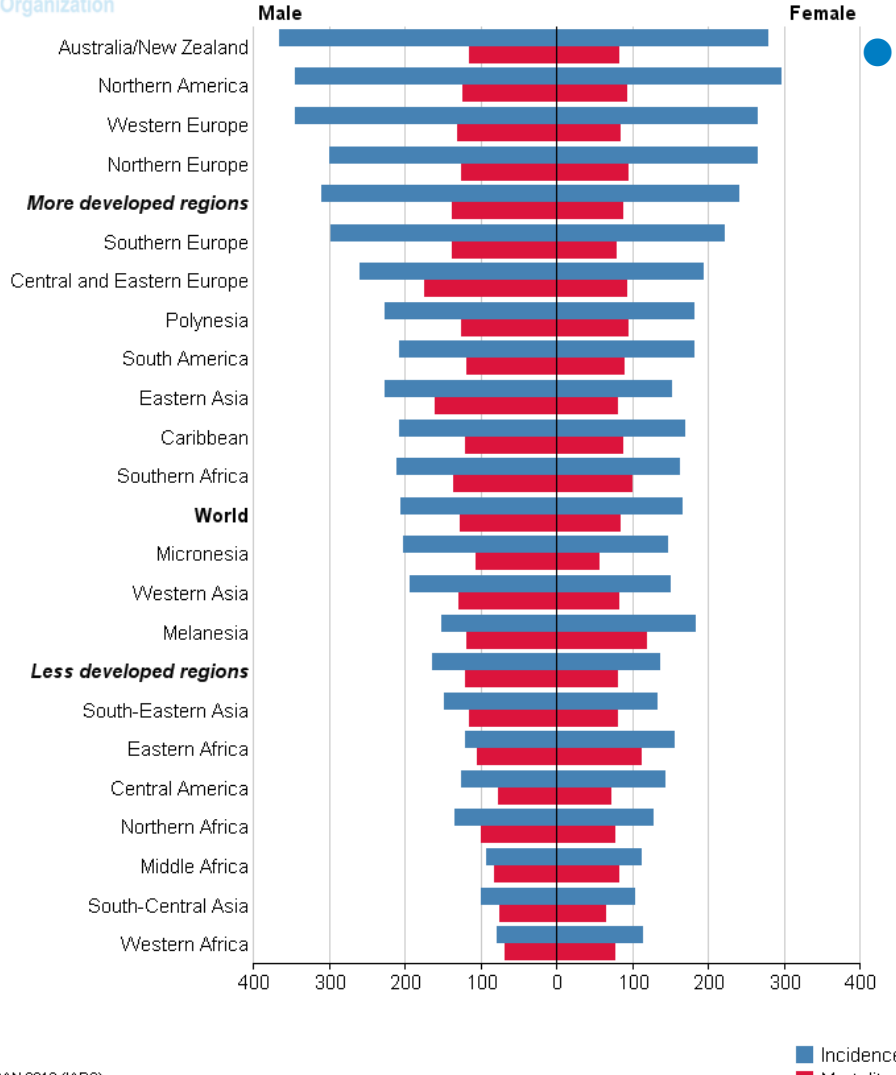
Cancer incidence ≠ cancer mortality

- Cancer with highest incidence = breast (♀) & prostate (♂)
- Cancer with highest mortality = lungs



Worldwide cancer incidence & mortality

International Agency for Research on Cancer
World Health Organization

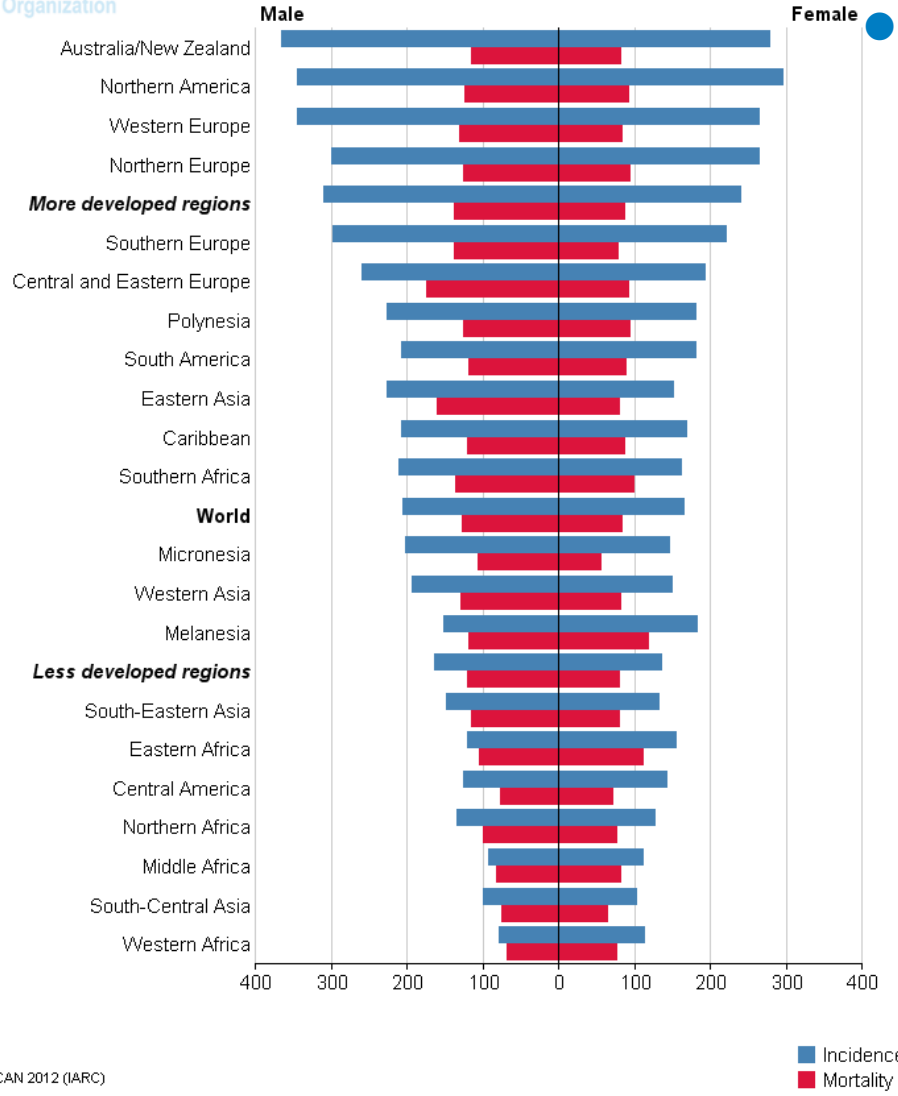


- **CANCER INCIDENCE (2012):**
  - 14.1 million new cancer cases
  - 8.2 million cancer deaths
  - 32.6 million people living with cancer (within 5 years of diagnosis) worldwide.
  - Men: rate 205 per 100,00
  - Women: 165 per 100,000
  - Male incidence rates vary almost 5x across the different regions of the world
    - lowest 79 per 100,000 in Western Africa
    - highest 365 per 100,000 in Australia/New Zealand.
  - Female incidence rates (almost 3x) with rates ranging
    - lowest 103 per 100,000 in South-Central Asia
    - highest 295 per 100,000 in Northern America.

GLOBOCAN 2012 (IARC)

Worldwide cancer incidence & mortality

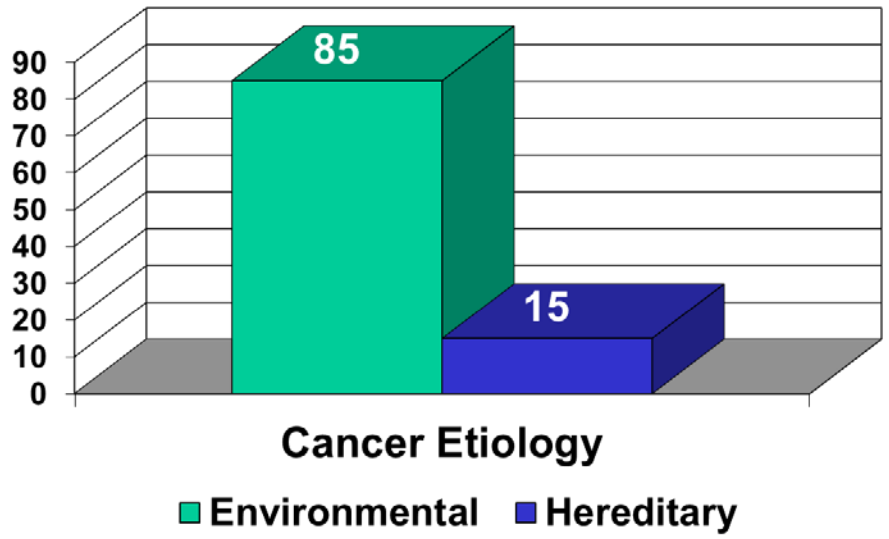
International Agency for Research on Cancer
World Health Organization



GLOBOCAN 2012 (IARC)

- **CANCER MORTALITY (2012):**
  - Less regional variability than for incidence
  - Men: 15% higher in more developed than in less developed countries
  - Women: 8% higher in more developed than in less developed countries
  - Men: rate 205 per 100,00
  - Women: 165 per 100,000
  - Male mortality rates
    - lowest 69 (79 incidence) per 100,000 in Western Africa
    - highest 173 per 100,000 in Central & Eastern Europe
  - Female mortality rates
    - lowest 72(103 incidence) per 100,000 in South-Central Asia
    - highest 119 per 100,000 in Melanesia and 111 in eastern Africa

Environmental *vs.* hereditary cancer causes



- Poor medical support
- Tobacco use
- Alcohol use
- Dietary factors, including insufficient fruit and vegetable intake
- Overweight and obesity
- Physical inactivity
- Chronic infections from bacteria and viruses
- Environmental (sun) and occupational risks

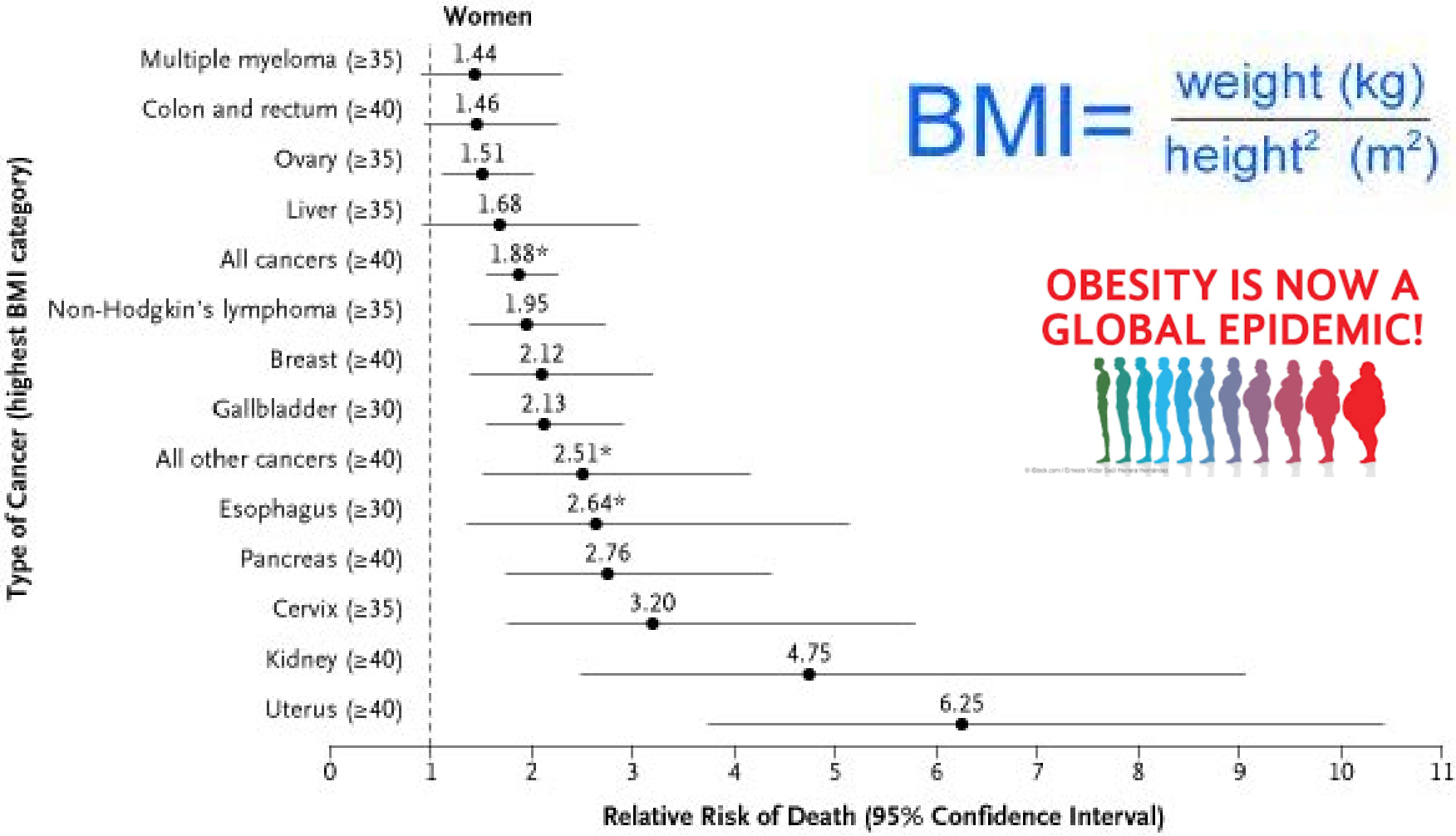
Cancers are also related to infectious agents

- **BACTERIA:**
  - *H. pylori* --> gastric cancer

- **VIRUS** (**accounts for 1/7 cancers**)

  - **Human Papilloma Virus (HPV)** --> cervix, vulva, vagina, anus, penis + head and neck (tongue and tonsils) cancers.
  - **Hepatitis B/C virus** --> liver cancer
  - **Epstein Bar virus (EBV)** --> leukemia, Hodgkin's disease, cervical cancer, and Burkitt's lymphoma, nasopharyngeal cancer
  - **HIV** --> Kaposi sarcoma and non-Hodgkin lymphoma

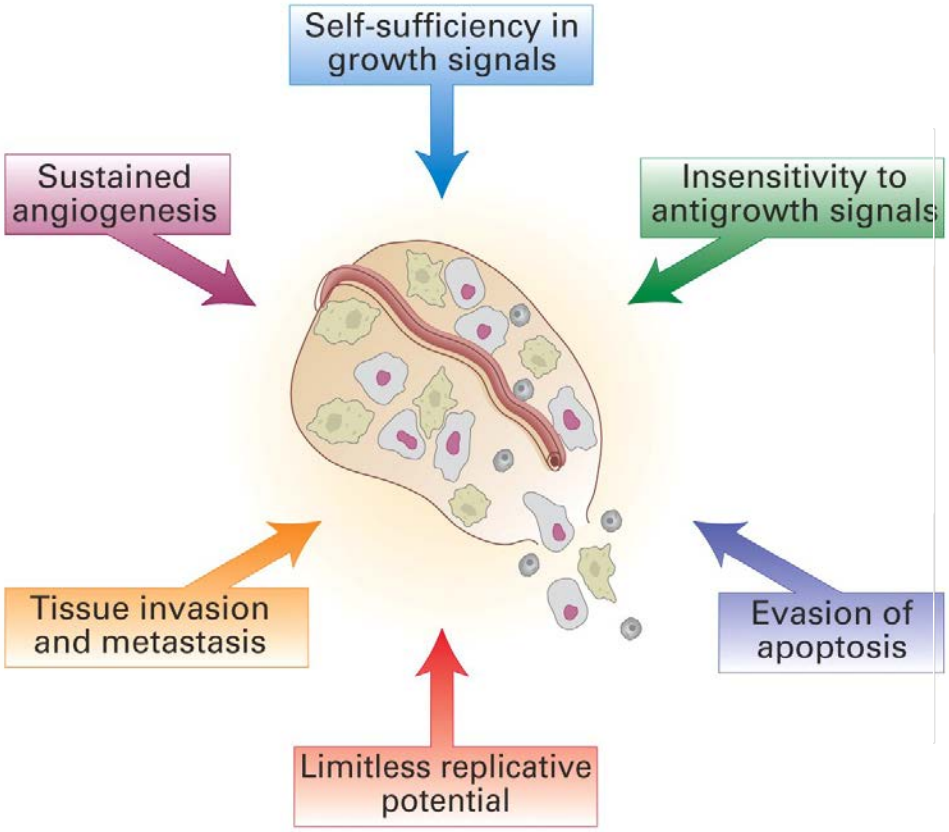
Obesity and cancer

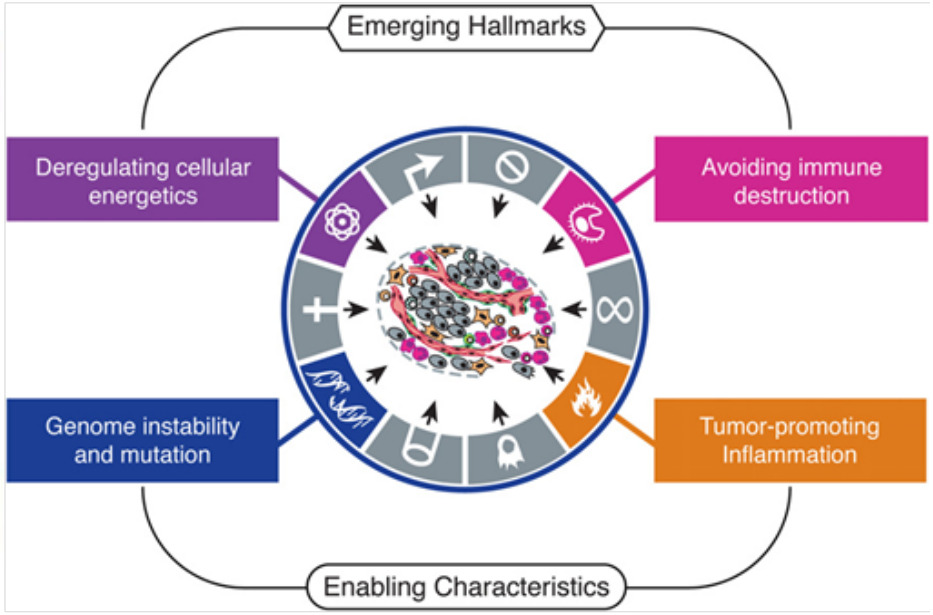


$$BMI = \frac{\text{weight (kg)}}{\text{height}^2\ (\text{m}^2)}$$

OBESITY IS NOW A GLOBAL EPIDEMIC!

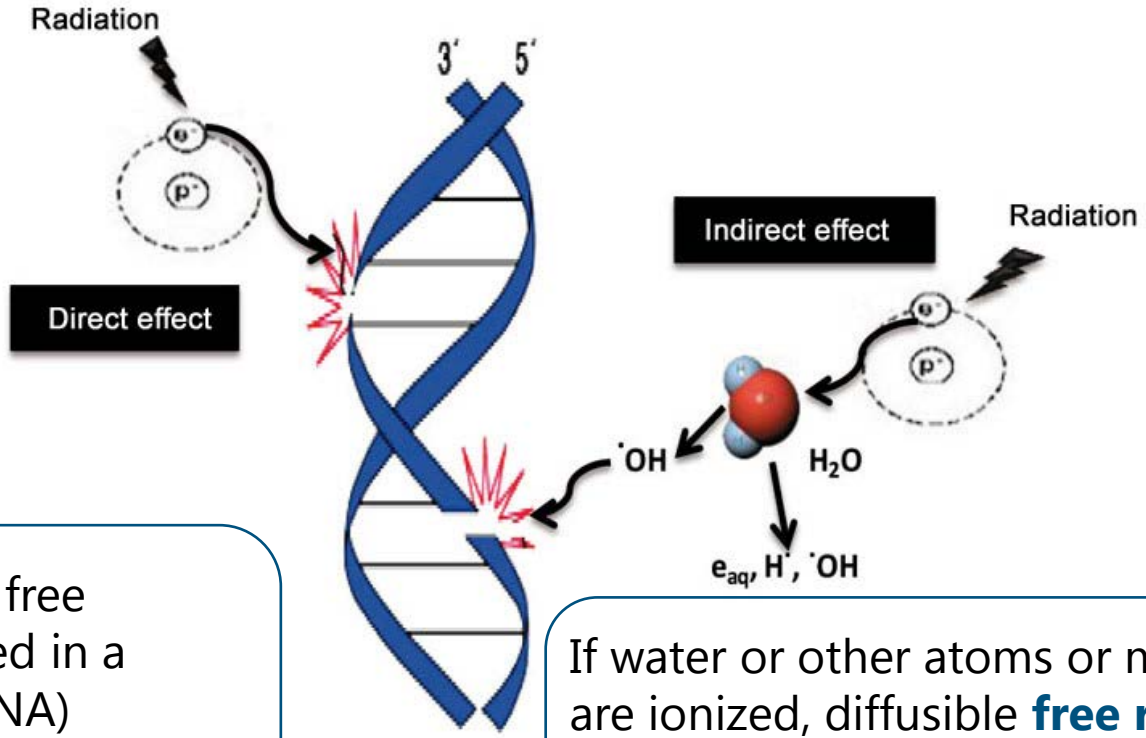
10 hallmarks of cancer





Biological effects of radiation

- Direct and indirect effects
- Both actions will produce reactive species that will interact and damage DNA.



If the **ion pairs** and free radicals are produced in a biological target (DNA) then - **this is direct action**

If water or other atoms or molecules are ionized, diffusible **free radicals** can act as intermediaries to cause damage - **this is indirect action** (75% hydroxyl radicals (OH·)

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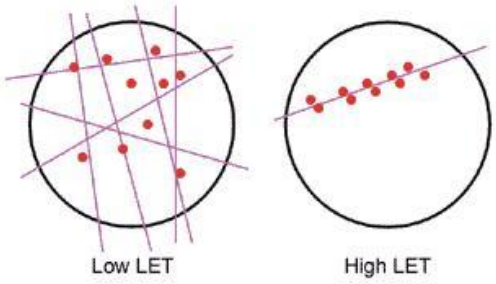
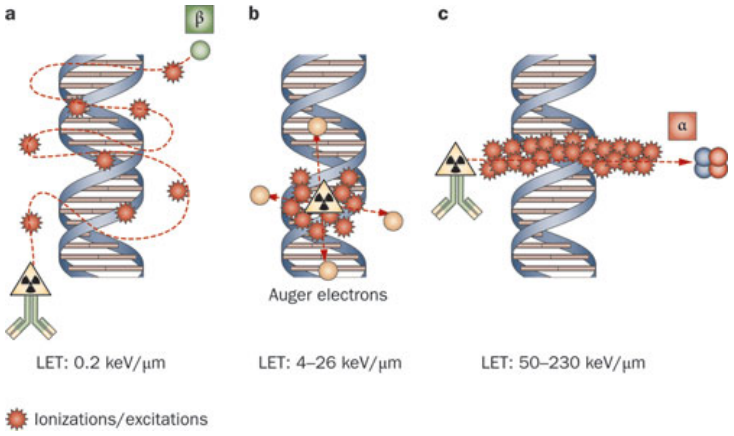
Damage in DNA

- Low-LET radiation = produce localized clusters of ionizations within single electron track
- High-LET radiation = somewhat larger number of ionizations that are closer together
- Direct action of radiation is dominant process for high–LET, such as neutrons or α-particles
- For low-LET radiation, direct action represents about 20%, and indirect action is about 80%.



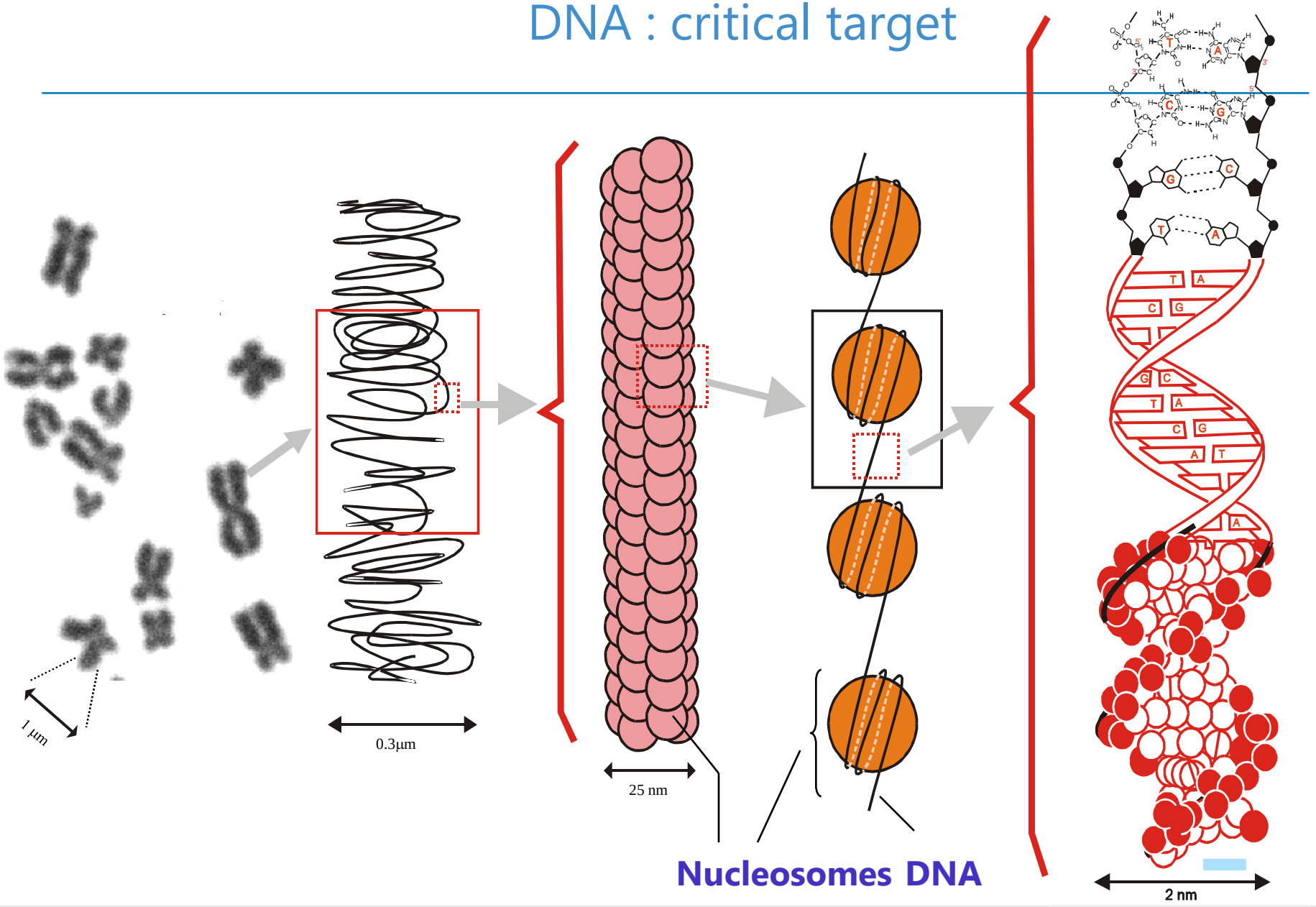
Both examples produce the same total number of ionizations, thus represent the same dose, but with different effects by Low LET and High LET



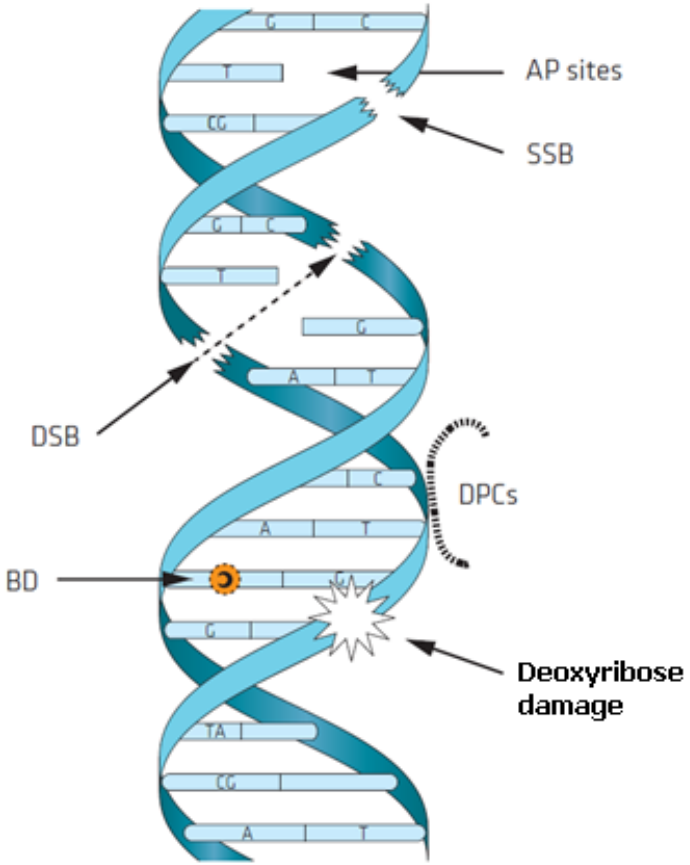
Sequence of events by which ionizing radiation affects living systems

Time	Event
10-18 s	Absorption of Ionizing Radiation
10-16 s	Physical Events
	Ionization
	Excitation
10-12 s	Physicochemical Events
	Free radical formation
	Breakage of chemical bonds
10-12 – 10-6 s	Chemical Events
	Reactions of radicals
Minutes to hours	Biochemical/Cellular Processes
	Repair
	Division delay
	Chromosome damage
	Loss of reproductive capacity
Days to months	Tissue Damage
	Central Nervous System, Gastro-Intestinal,
	Bone marrow syndromes
	Late tissue damage
	Birth defects from in utero exposure
Years	Late Somatic Effects
	Cataracts
	Carcinogenesis
Generations	Genetic Effects

DNA : critical target



Types of DNA lesions



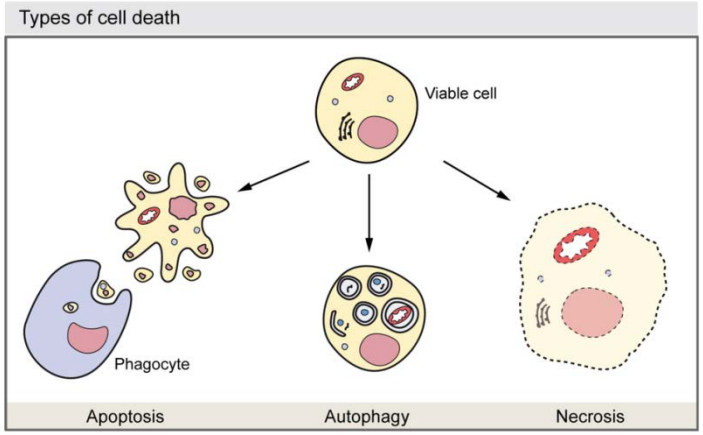
Estimation of numbers of radiation - induced different types of DNA lesions after 1 Gy irradiation with low-LET radiation *(UNSCEAR)*

Damage type	Amount of damage
Base Damage (BD)	1000 - 2000
Deoxyribose damage	1200
SSBs	1000
AP sites	250
DSBs	40
DPCs	150

* DPC: DNA protein crosslinks

Cell death mechanisms

- **APOPTOSIS (cell suicide)** = programmed (I-131, Xe-33, Ir-192, Sr-89, W-188)
- **NECROSIS (cell explosion)**= results from trauma or injury (I-131, W-188, Sr-89)
- **AUTOPHAGY (auto cell digestion)** = due to nutrient deficiency(Nobel prize 2016 to Yoshinori Ohsumi)
- **MITOTIC CATASTROPHE** = inappropriate entry into mitosis
- **ANOIKIS** = cell detachment from tissue and degradation

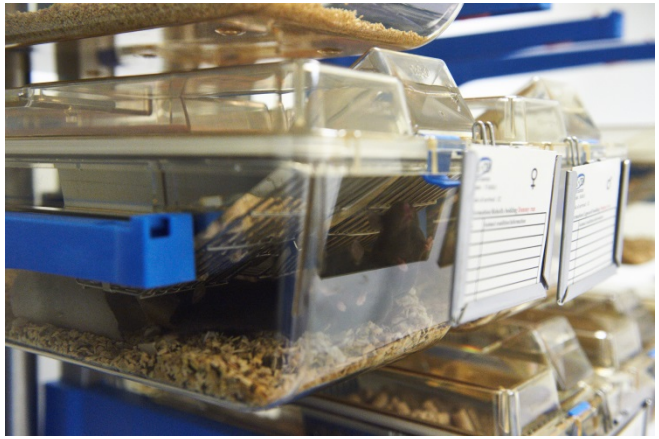


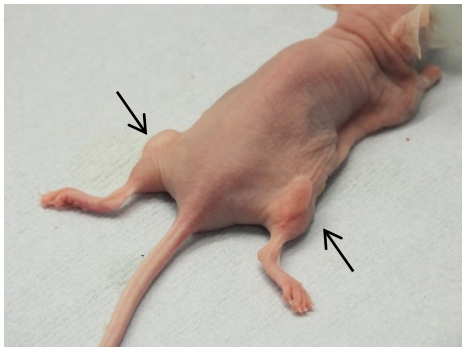
- **OTHER FORMS: CORNIFICATION (cell death to the eyes)**

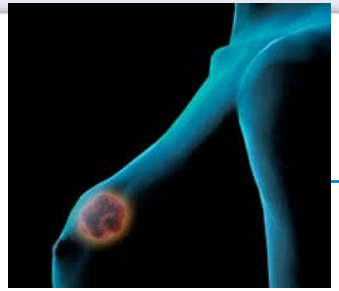
PYROPTOSIS (wrong killing from immune system); **FERROPTOSIS** (iron dependent cell death); **NECROPTOSIS/APONECROSIS** (combined apoptosis and necrosis); **ERYPTOSIS** (suicidal erythrocyte death)

Cancer research in radiobiology

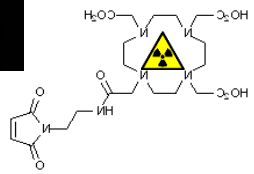
Cancer studies within SCK•CEN animal facility



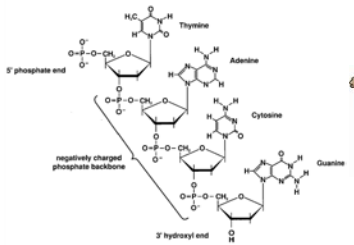




Development of radiopharmaceuticals
Breast cancer



Radiochemistry



VHH

Molecular vehicles:

Aptamers (oligonucleotide)

Bifunctional chelator

Gallium-68

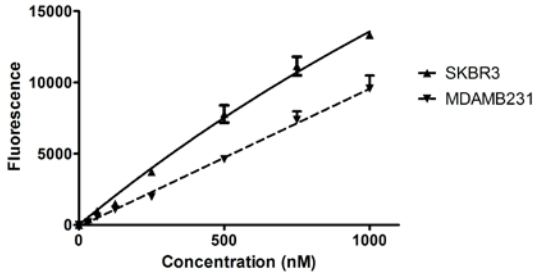
Nanobodies

Bifunctional chelator

Lu-177

Biology *in vitro*

Binding affinity of aptamer by flow cytometry

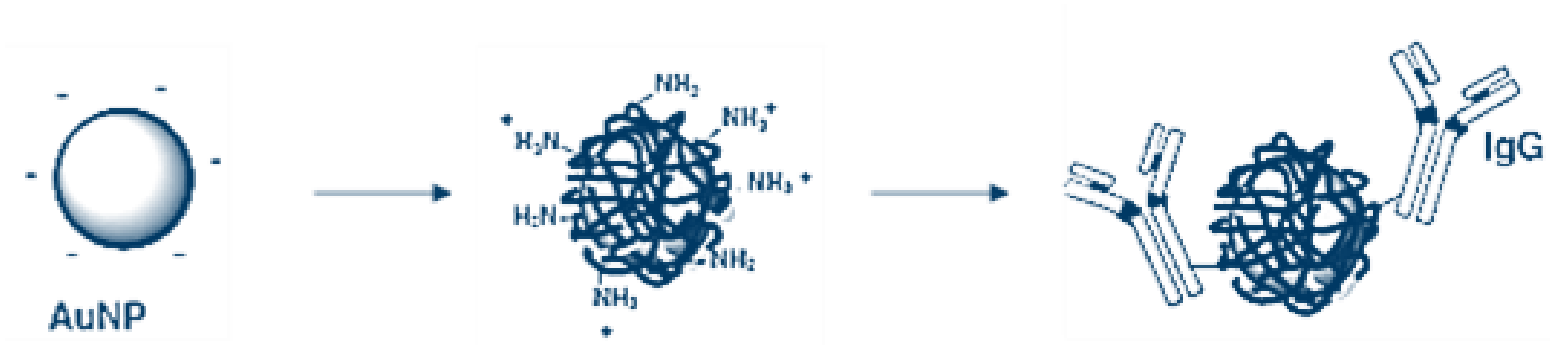


Biology *in vivo*

Vrije Universiteit Brussel

Gold nanoparticles

- "Gold nanoparticles for cancer therapy and diagnosis"
- Gold has radiosensitizing effects



- Study of healthy tissue cytotoxicity and radioactive doping
- Collaboration UNamur & SCK•CEN RDB, RCA

BHTC
Belgian Hadron Therapy Centre
Private Stichting-Fondation Privée

Hadron therapy research at SCK•CEN

- Belgian Hadron therapy Consortium (BHTC)
  - 7 University hospitals, the Foundation against Cancer and SCK•CEN
  - Supported by the Federal Public Service
    - Feasibility study ‘Application of hadron therapy in Belgium’
    - Action 30 of the Belgian Cancer plan
  - SCK•CEN contribution: Radiobiology and Dosimetry

federale overheidsdienst
VOLKSGEZONDHEID,
VEILIGHEID VAN DE VOEDSELKETEN
EN LEEFMILIEU

GANIL
GRAND ACCELERATEUR NATIONAL D'IONS LOURDS
LABORATOIRE COMMUN DSM/CEA-IN2P3/CNRS

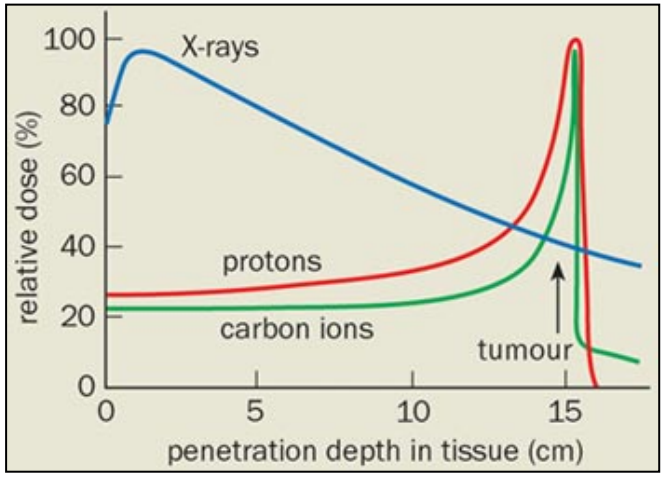
UNIVERSITÉ DE NAMUR

UCL
Université catholique de Louvain

KU LEUVEN

Conventional versus hadron therapy

- Conventional = high energy photons
- Advanced = accelerated particle beams

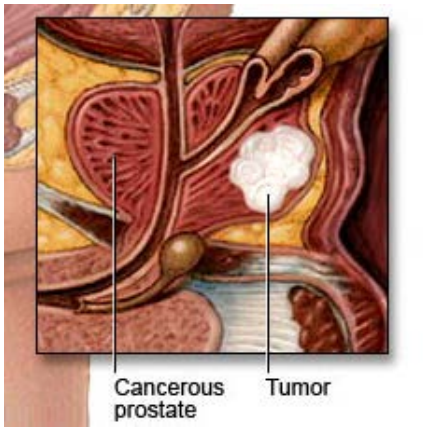


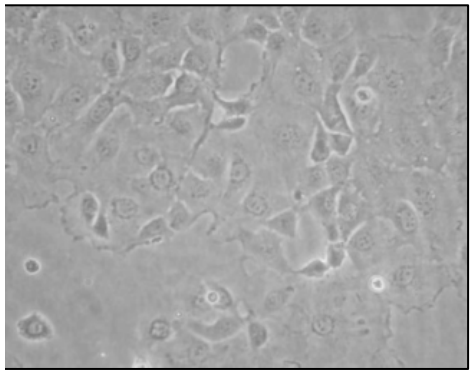
  - Protons and carbon ions
  - Superior physical and biological properties

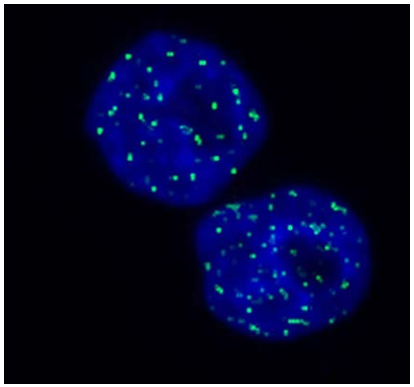
    - Precise localization of radiation dose
    - Useful for (radioresistant) tumours at critical locations and pediatric tumors
    - Clinical trials: good local tumour control and survival rates

Hadron therapy radiobiological research

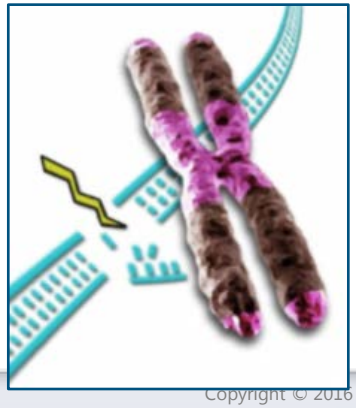
Aim: *in vitro* response of **prostate and colon** cancer cells to carbon/proton irradiation



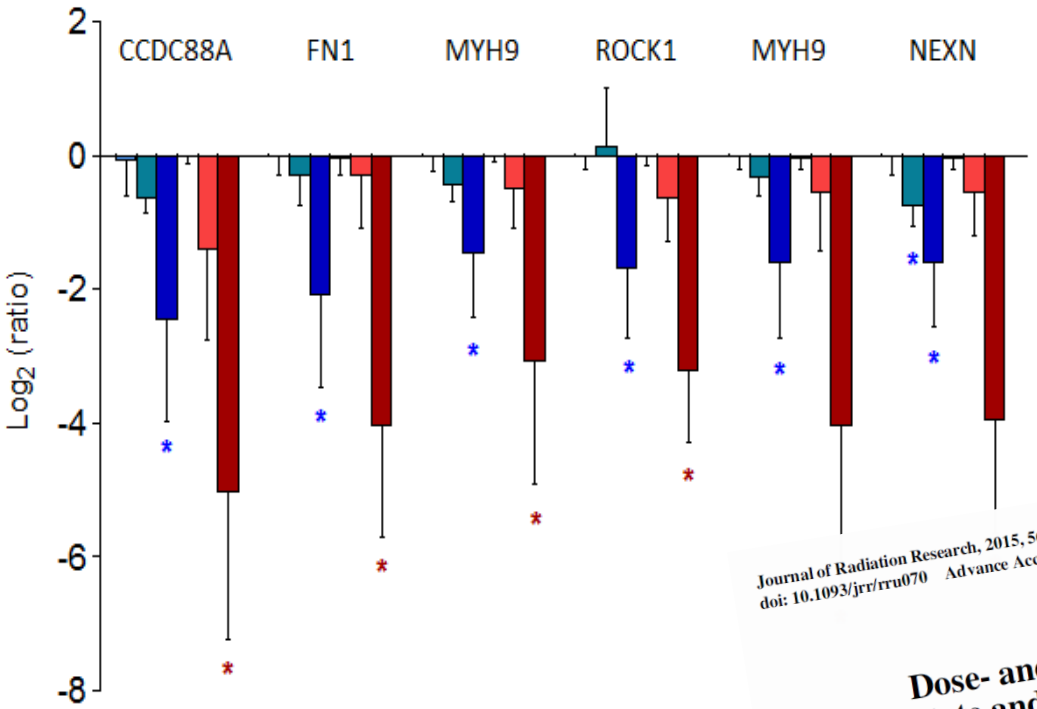




- Endpoints: cell survival & DNA damage
- Gene expression profiling
- Motility



Motility genes highly inhibited after C irradiation



Journal of Radiation Research, 2015, 56, 11–21
doi: 10.1093/jrr/rru070 Advance Access Publication 4 September 2014

Dose- and time-dependent gene expression alterations in prostate and colon cancer cells after *in vitro* exposure to carbon ion and X-irradiation

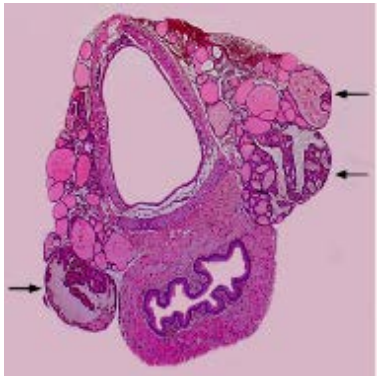
SUETENS[1,2], Marjan MOREELS[1], Roel QUINTENS[1], Els SOORS[1], Jasmine BUSET[1], Kevin TABURY[1], Vincent GREGOIRE[2] and Sarah BAATOUT[1,4,*]

Carbon ion irradiation of the human prostate cancer cell line PC3: A whole genome microarray study

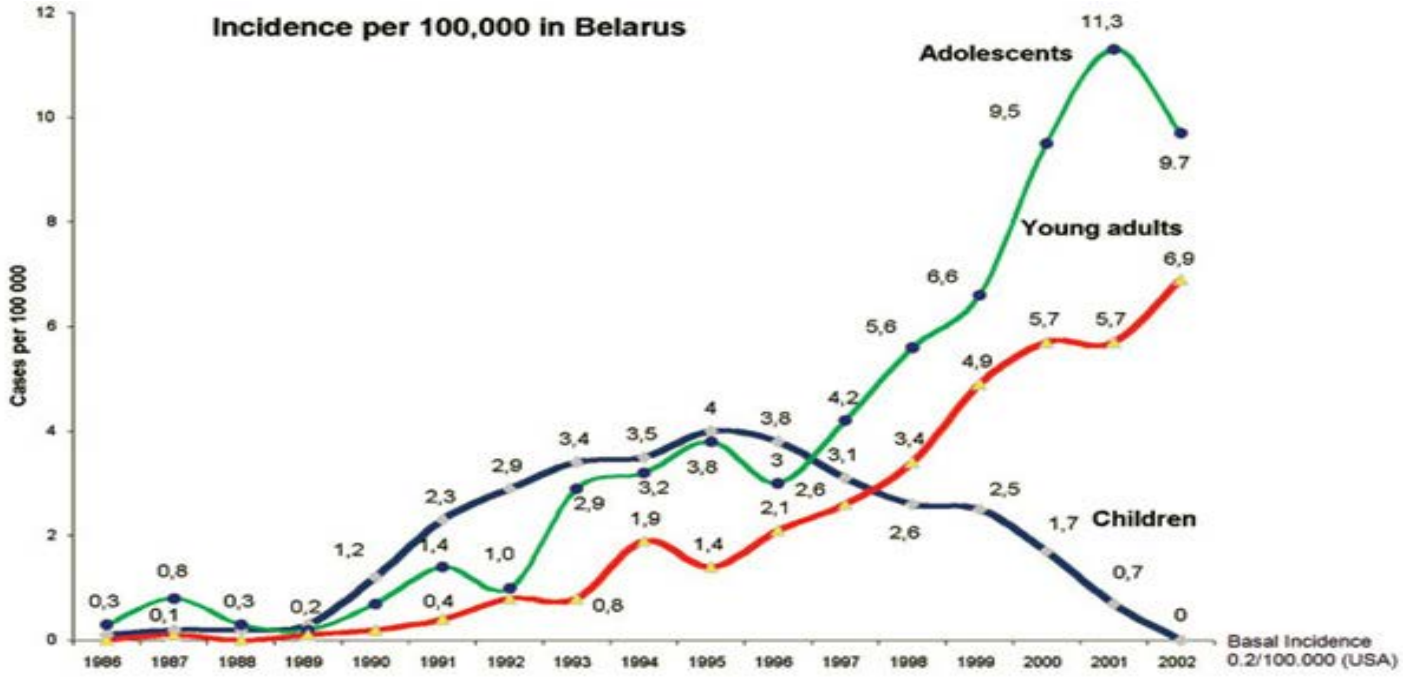
OLOGY 44: 1056-1072, 2014

ANNELIES SUETENS[1,3], MARJAN MOREELS[1], ROEL QUINTENS[1], SABINA CHIRIOTTI[2,3], KEVIN TABURY[1], ARLETTE MICHAUX[1], VINCENT GRÉGOIRE[3] and SARAH BAATOUT[1,4]

Biomarkers of thyroid cancer

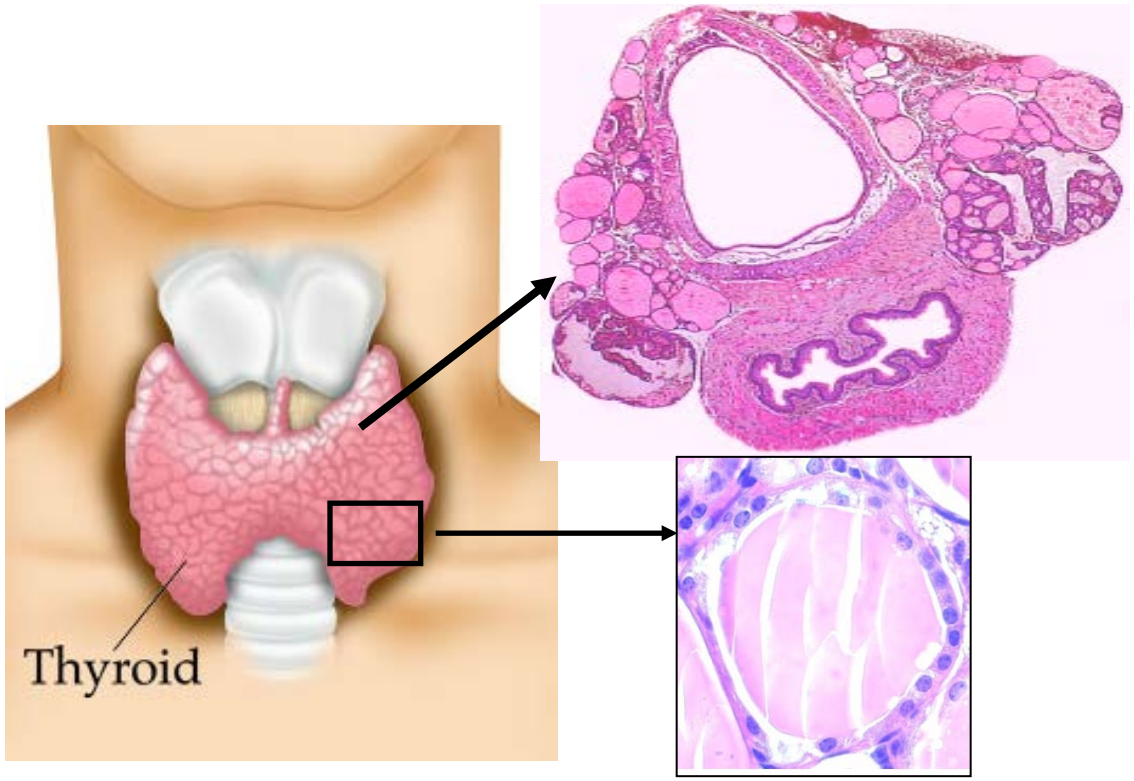


- After the 1986 **Chernobyl** disaster, large amounts of **radioactive iodine** were released.
- Increase in cases of papillary thyroid carcinoma in children in subsequent years in Belarus, the Ukraine and Russia.



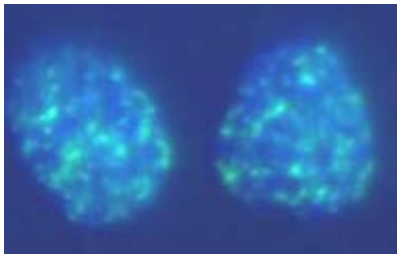
Genetic components of thyroid cancer risk at low doses

Histology



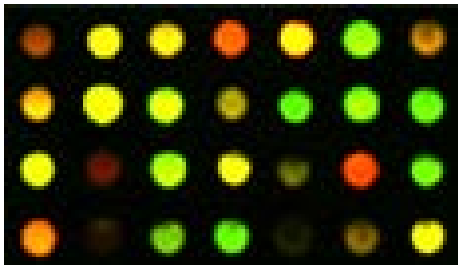
Histological section of the thyroid. On the bottom, a magnification of one thyroid follicle

Microscopy



Human thyroid cancer cells. Green dots show molecules (γ-H2AX) involved in DNA damage response after irradiation

Molecular Biology



Gene expression. Red: genes repressed, green: genes overexpressed and yellow: genes equally expressed

Thank you for your attention

Better treatment and radiation protection empowered by better fundamental/applied research and education

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