Ciências ULisboa

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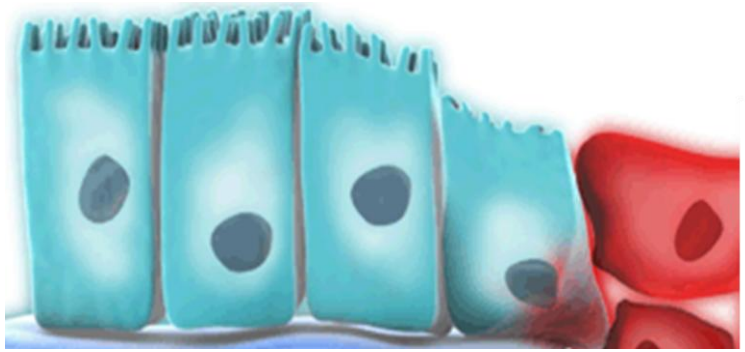
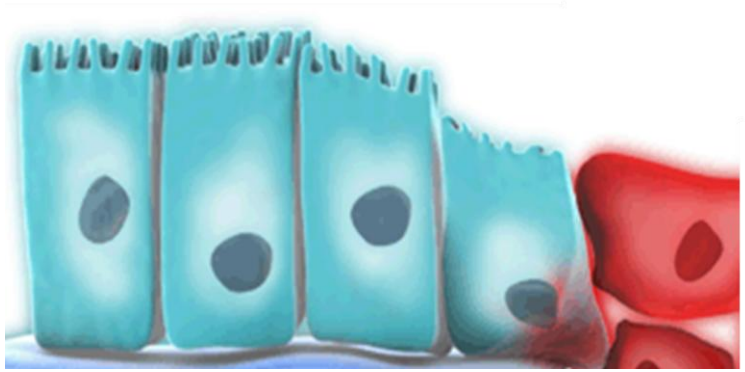


Oncobiology

Margarida Gama-Carvalho (DQB/FCUL) and Peter Jordan (INSA)

Introduction to cancer



What is cancer?

Defining Cancer

- Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

- Cancer is caused by changes to genes that control the way our cells grow and divide.

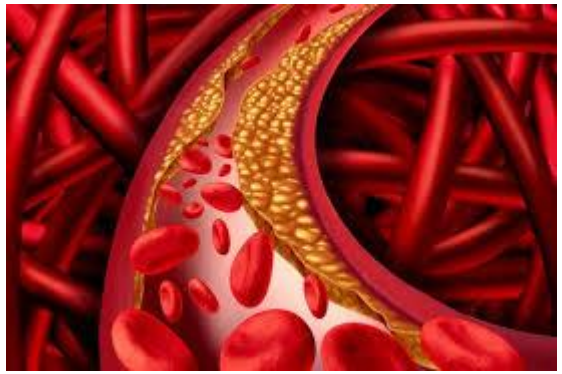
- Cancer is a disease in which a single normal body cell undergoes a genetic transformation into a cancer cell.

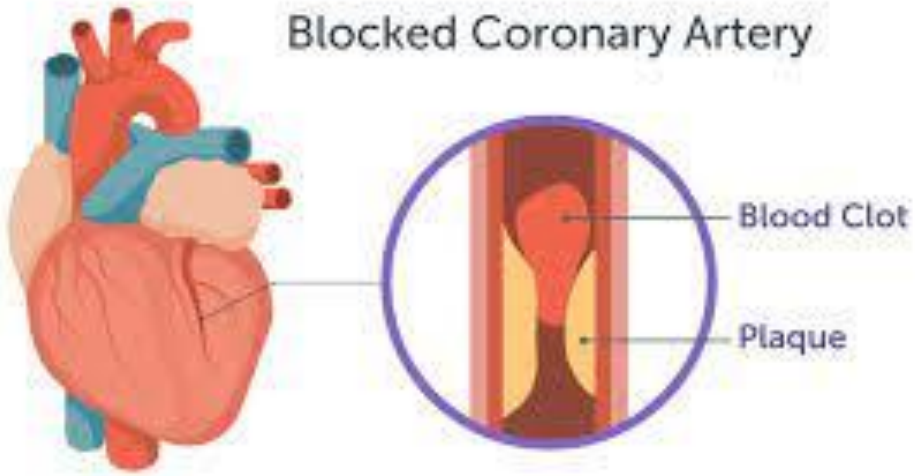
- body cells
- grow and divide
- genetic transformation

Comparing cancer with other diseases

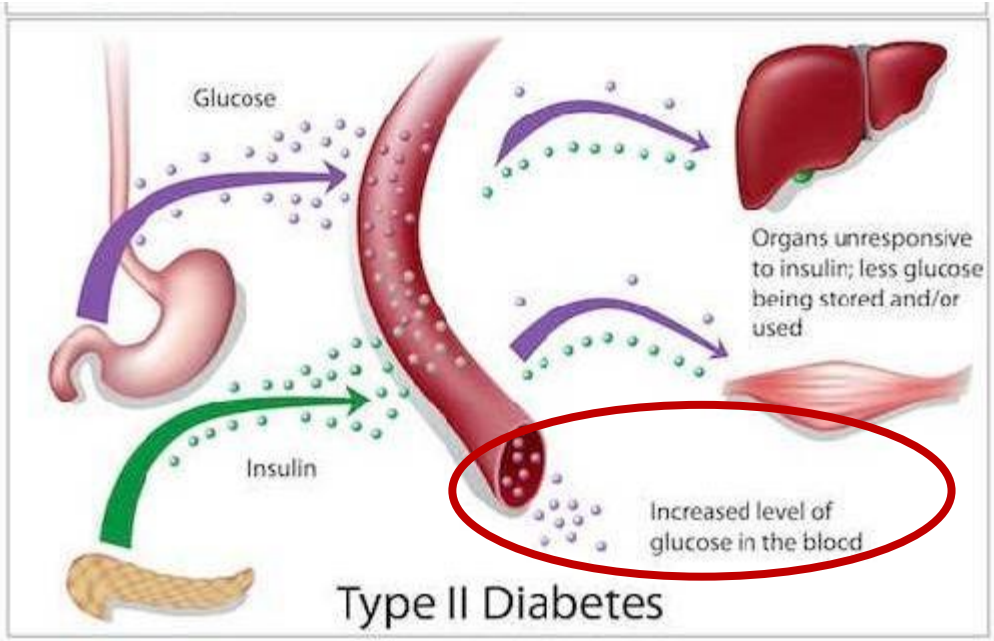
Cardiovascular disease
Diabetes
Infectious disease

artherosclerosis





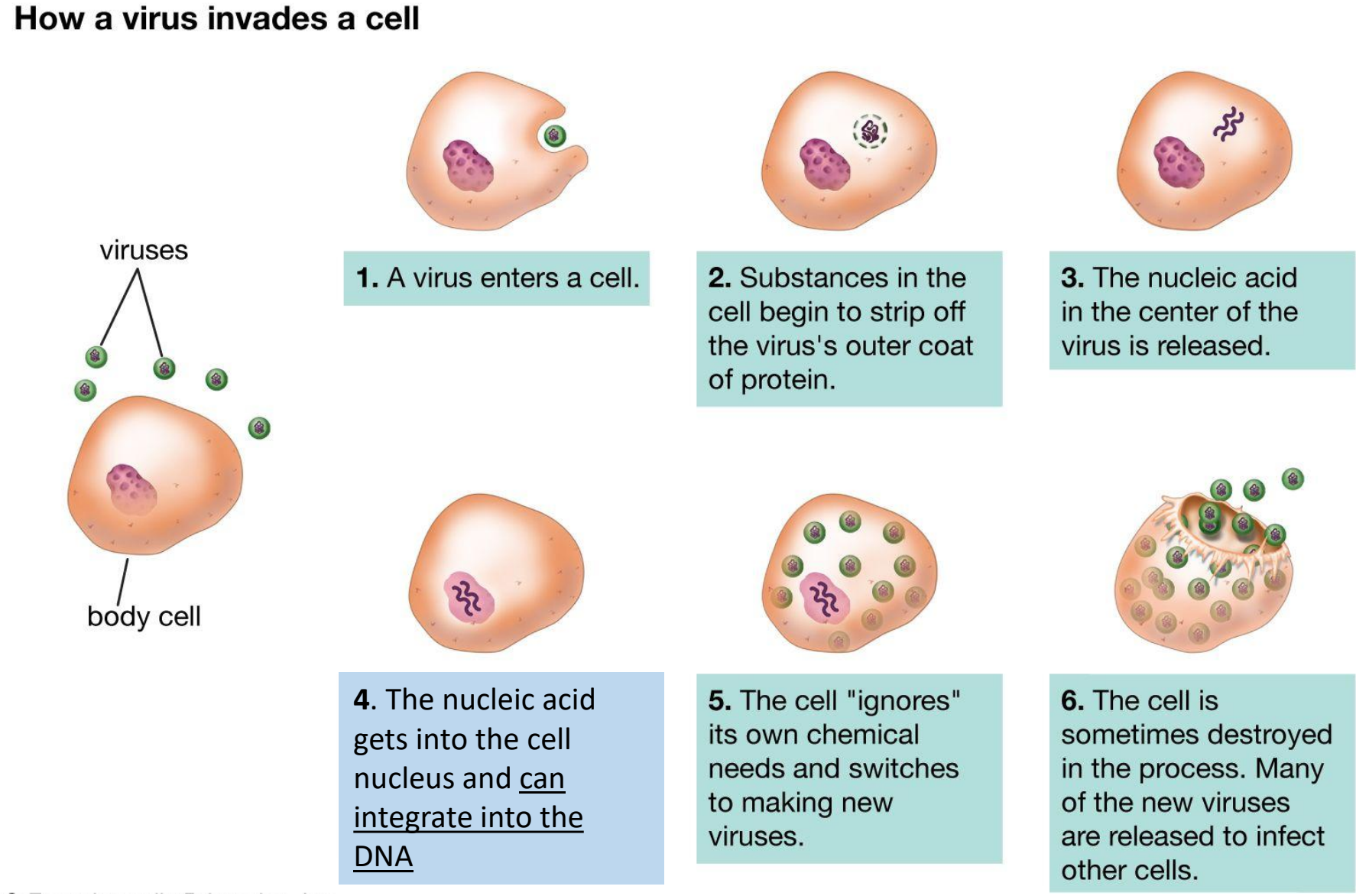
- body cells
- grow and divide?
- genetic transformation?



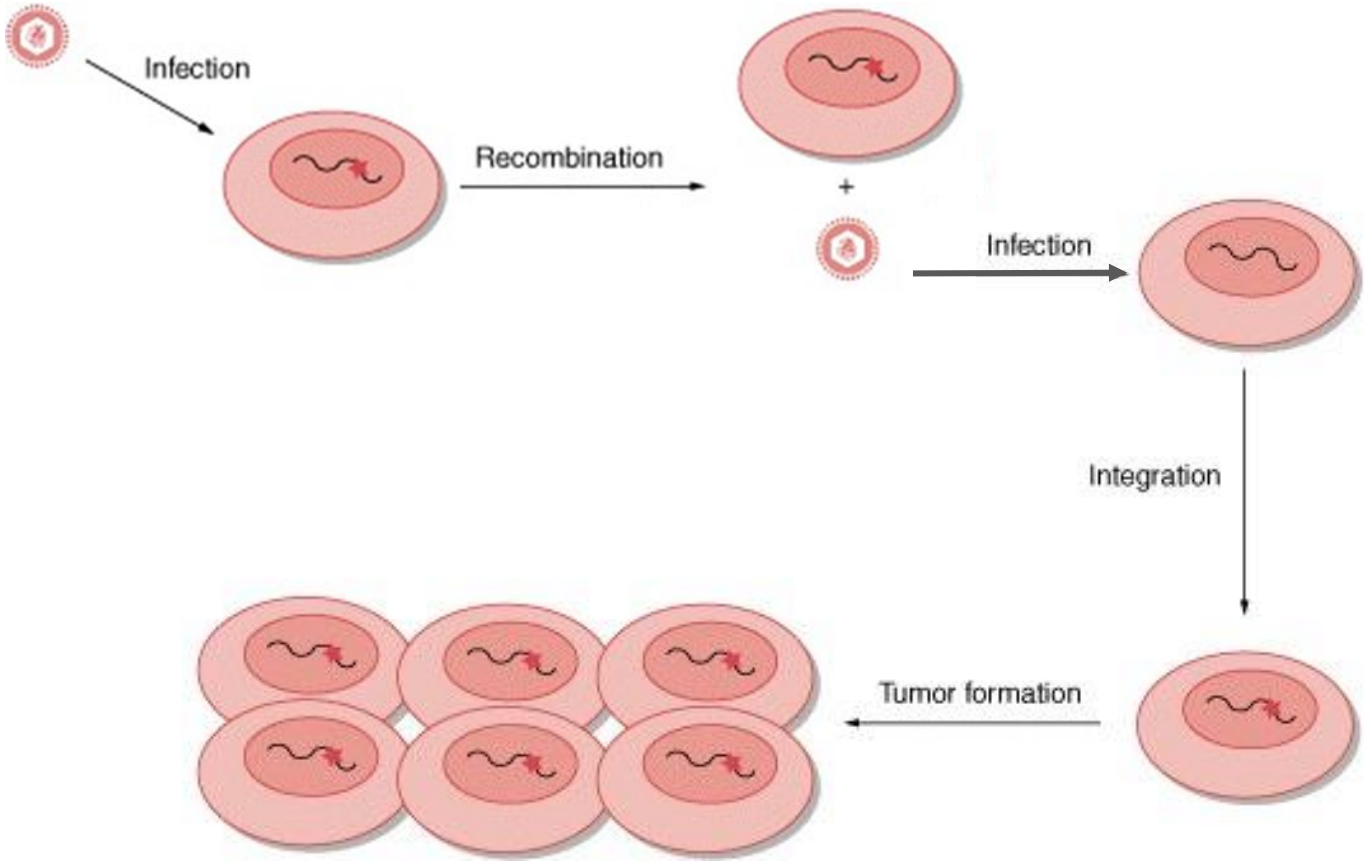
Comparing cancer with other diseases

Cardiovascular disease
Diabetes
Infectious disease

- body cells
- grow and divide?
- genetic transformation



Cancer as an infectious disease caused by tumour viruses?



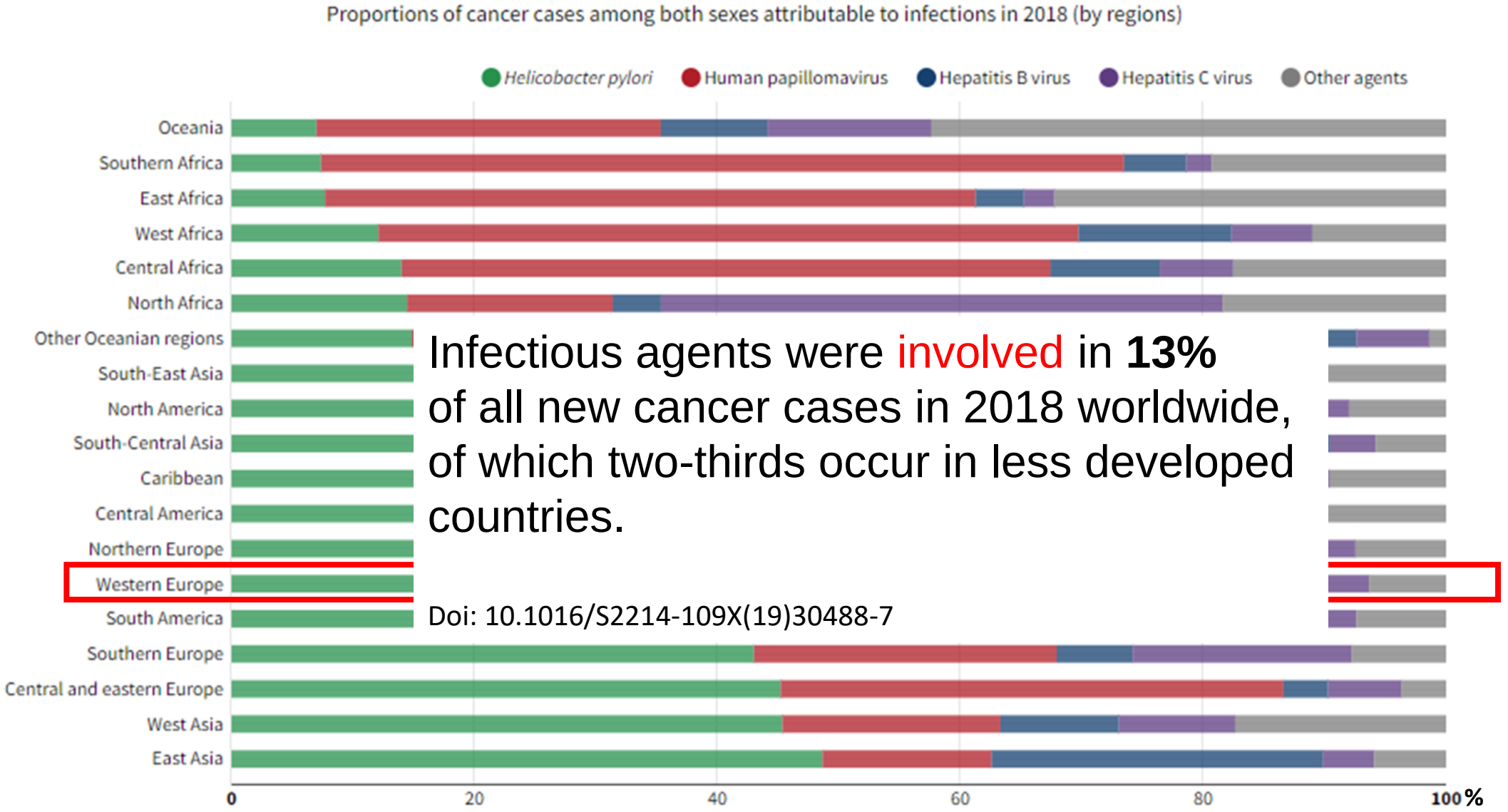
1970-ies:
The study of the an acutely transforming retrovirus **Rous sarcoma virus**, isolated from a chicken sarcoma, revealed that the transforming gene of RSV (designated **v-src**) was not required for viral replication, but was homologous to a host cellular gene (**c-src**), picked up by recombination during the retroviral life cycle (‘oncogene’).

Cancer as an infectious disease?

Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)

International Agency for Research on Cancer
World Health Organization

Cancer as an infectious disease?



Infectious agents were involved in **13%** of all new cancer cases in 2018 worldwide, of which two-thirds occur in less developed countries.

Doi: 10.1016/S2214-109X(19)30488-7

Data source: de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020)
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)

International Agency for Research on Cancer
World Health Organization

Defining Cancer

Genetic changes that can cause cancer occur because:

- damage to DNA is caused by the environment (harmful chemicals in tobacco smoke; irradiation by ultraviolet rays from the sun, etc)

- they were inherited from our parents

- stochastic errors can occur as cells divide

Cancer-related designations

Onco- (greek):	mass, volume
Tumor- (latin):	swelling
Cancer- (greek):	crab

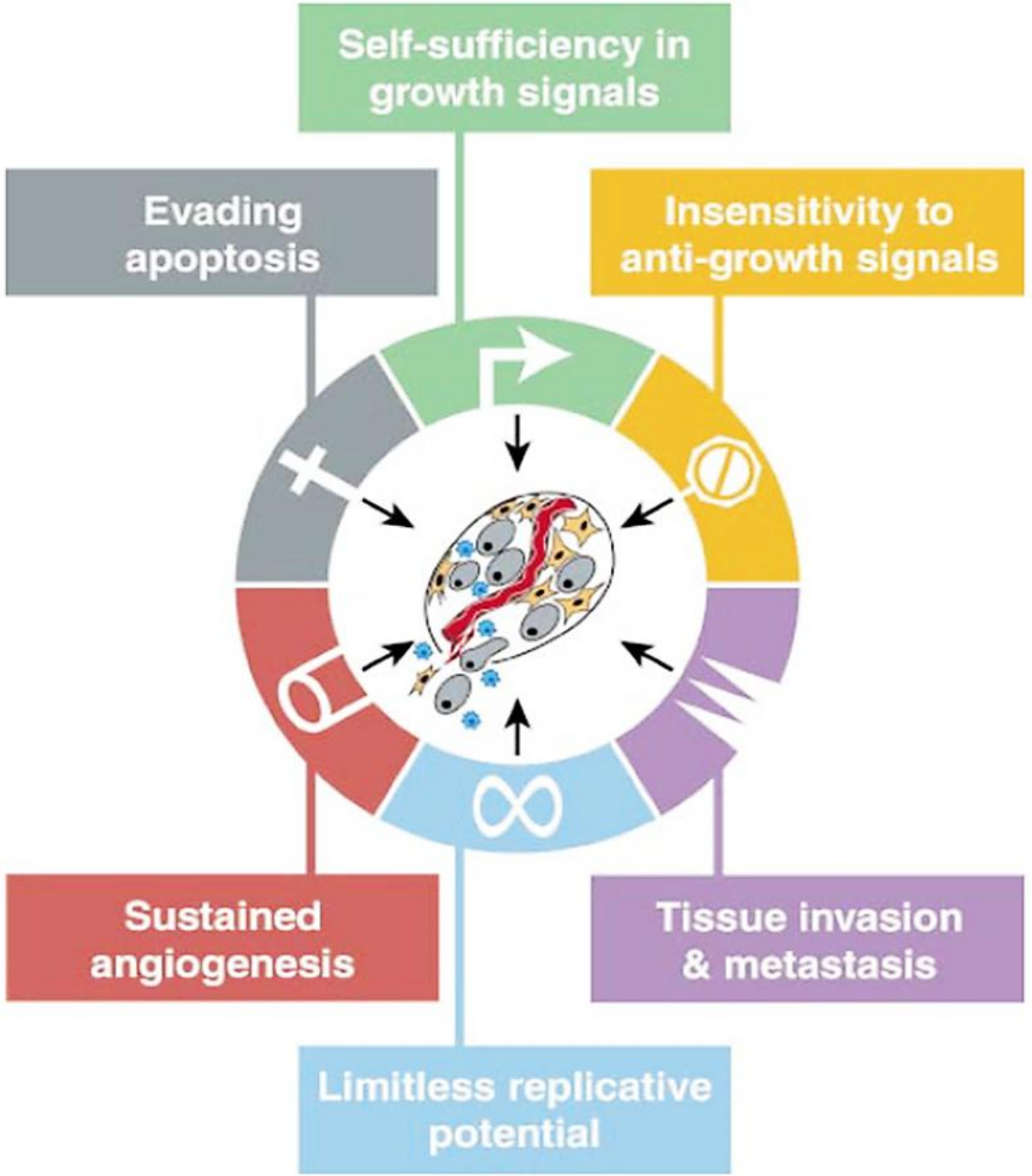
Cancer: a single normal body cell undergoes a genetic transformation into a cancer cell

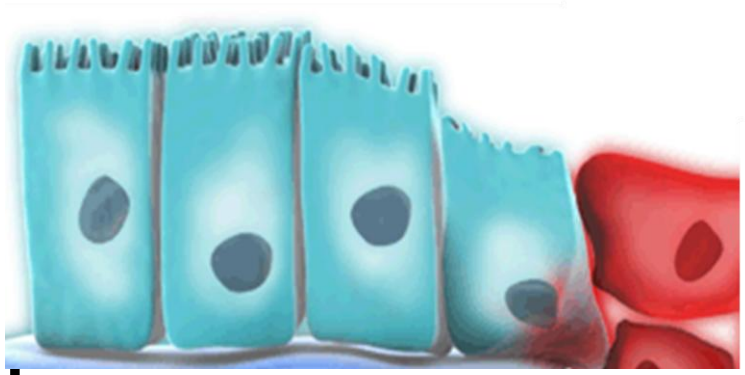
Unlike normal cells, cancer cells do..:

- grow in the absence of growth signals (normal cells only grow when they receive such signals);
- ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis);
- accumulate multiple changes in their chromosomes, such as duplications and deletions of chromosome parts;
- invade into nearby areas and spread to other areas of the body (normal cells stop growing when they encounter other cells, and usually do not move around the body);
- attract blood vessels to grow toward them (for supply with oxygen and nutrients and removal of waste products from tumors);
- 'hide' from the immune system, which normally eliminates damaged or abnormal cells;
- trick surrounding normal cells to help cancer cells stay alive and grow;
- make energy from nutrients in a different way than most normal cells in order to grow more quickly.

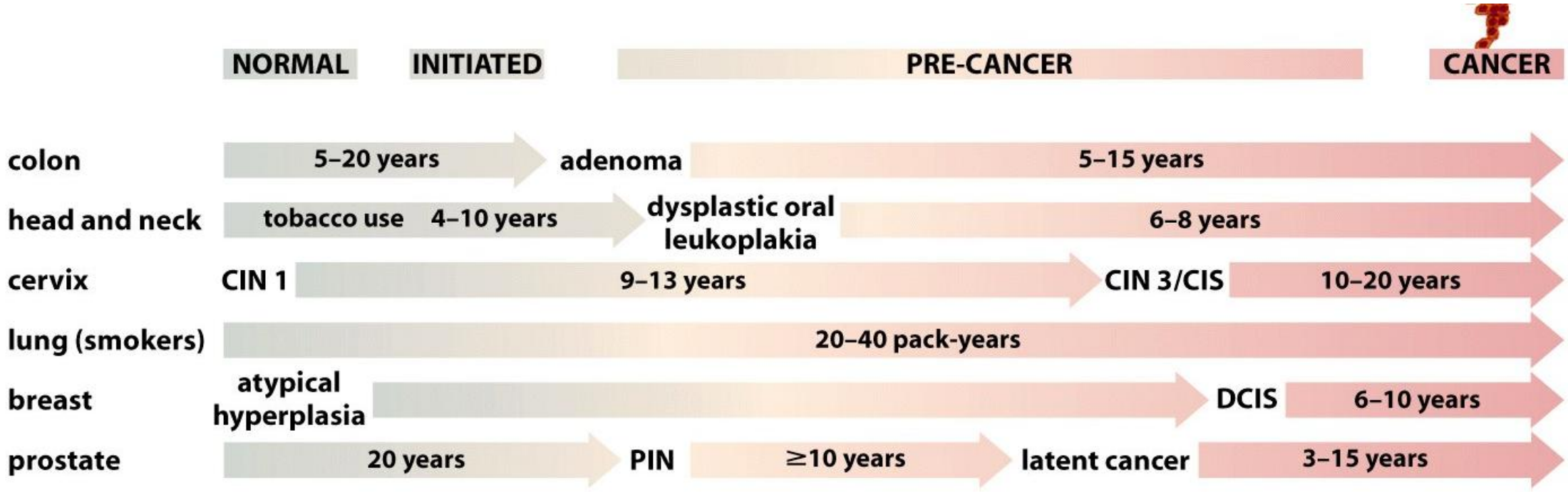
The Hallmarks of Cancer

Cell 100, 57–70 (2000)
Hanahan & Weinberg

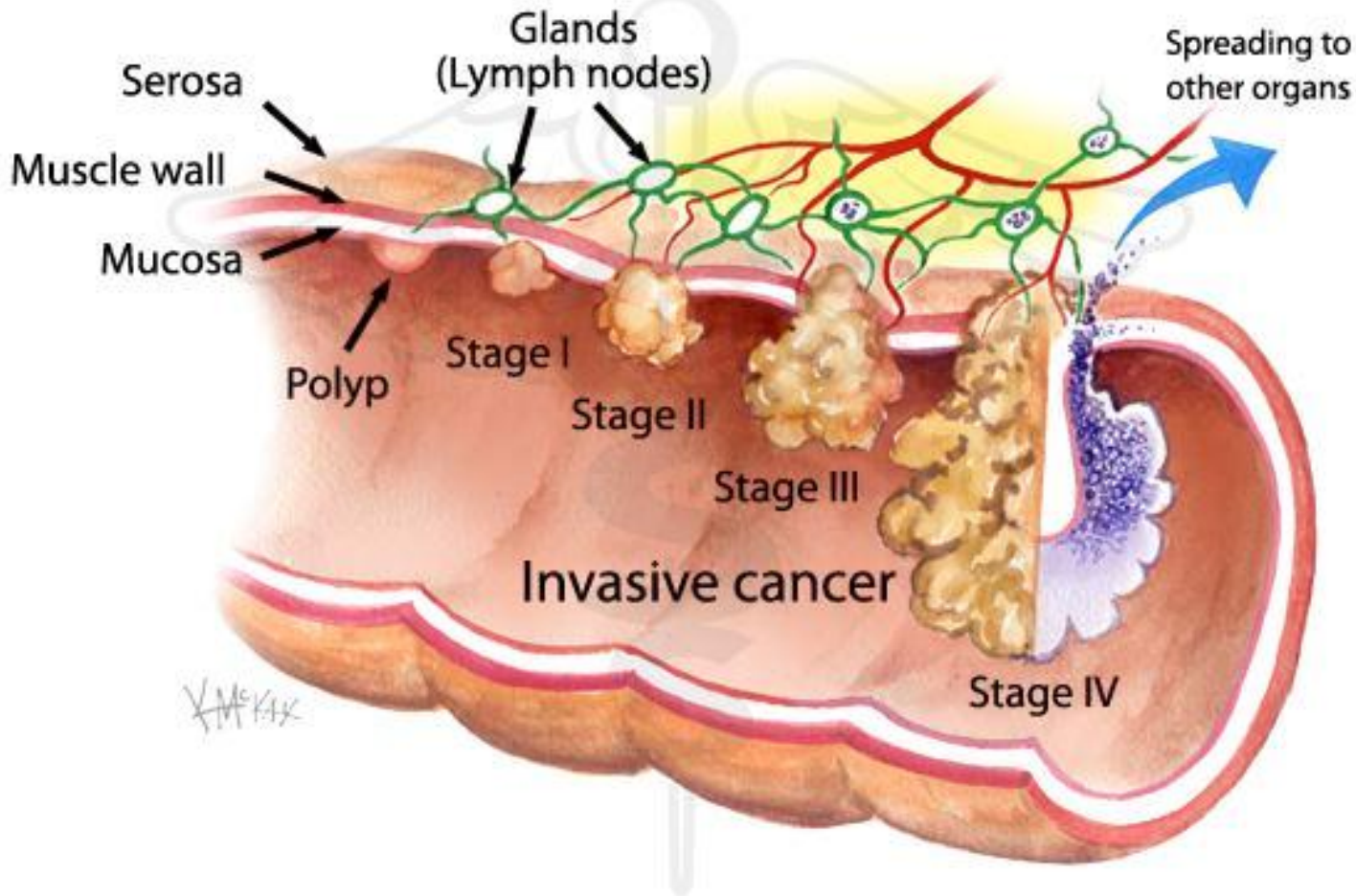




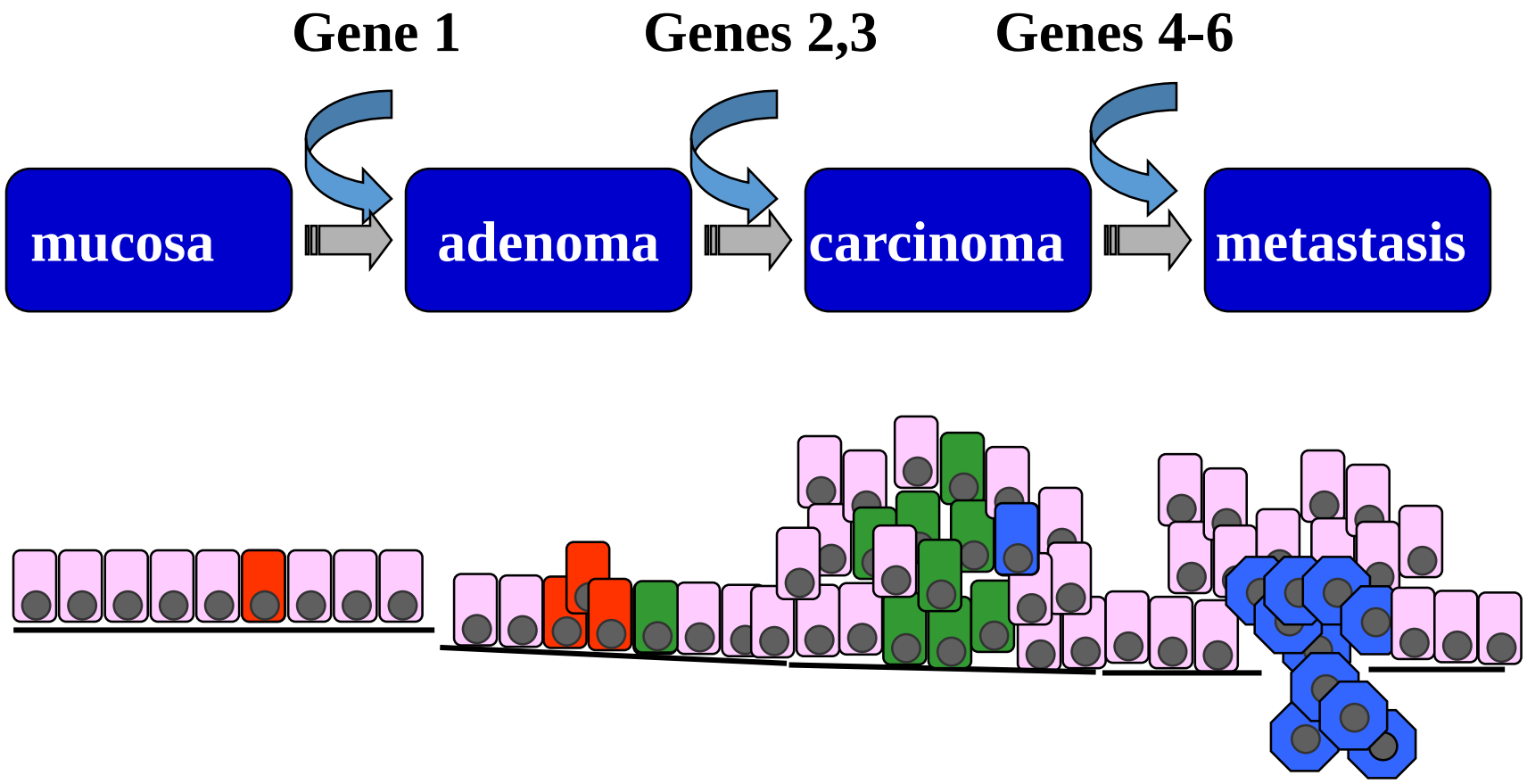
The timing of cancer development



How does cancer develop?

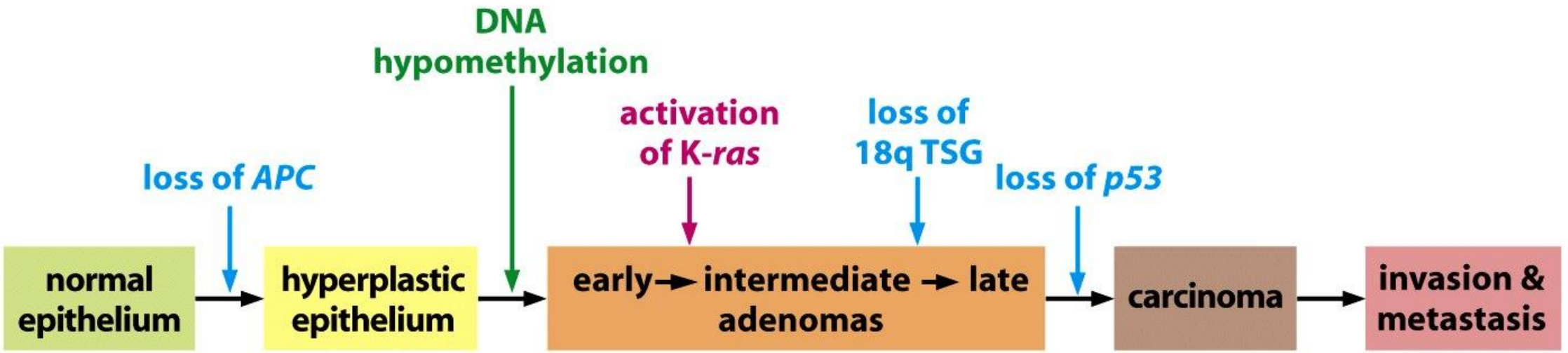


1. The classical model of tumorigenesis through *clonal selection*



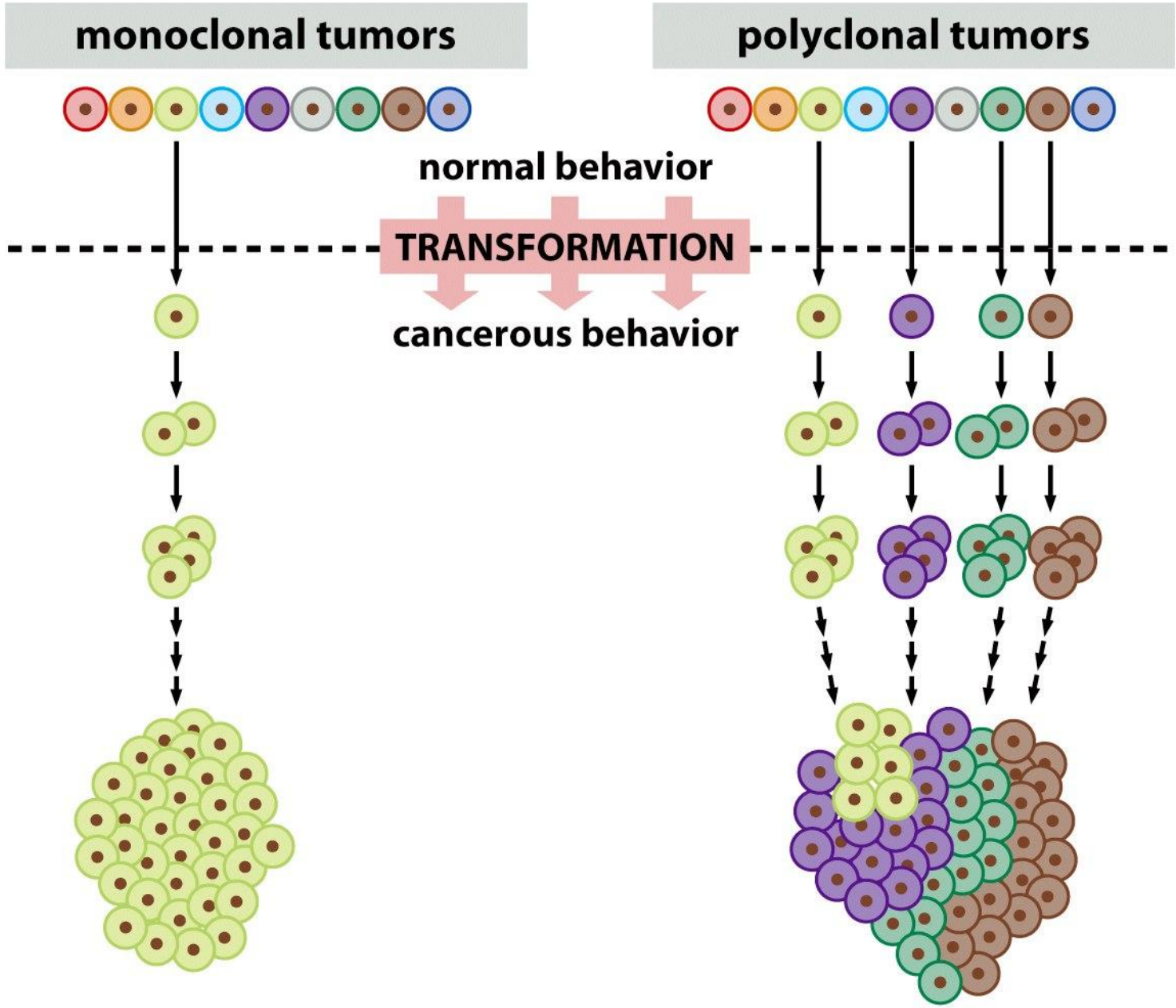
Genetic model: accumulation of genetic changes in a cell

Accumulating genetic changes in a colon cell



Fearon and Vogelstein, A Genetic Model for Colorectal Tumorigenesis, Cell 61, 759-767 (1990)

Figure 11.10 *The Biology of Cancer* (© Garland Science 2007)



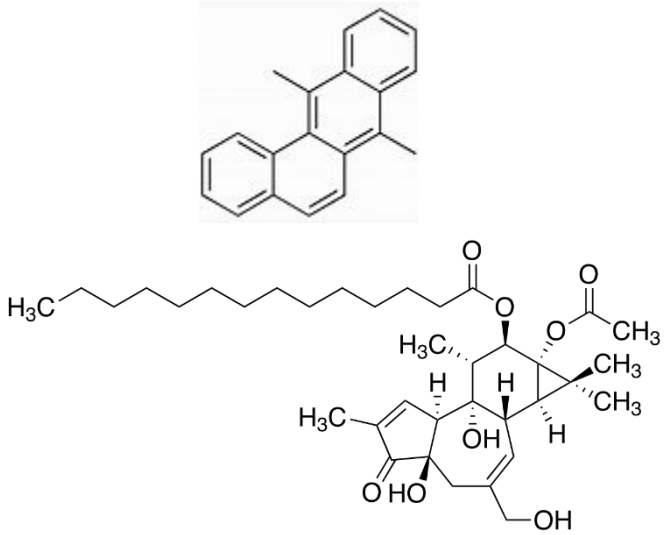
Accumulating genetic changes can occur in parallel, leading to

Tumor heterogeneity

2. The tumorigenesis model from skin carcinogenesis:

Initiation- chemical mutagen
Promotion- signaling stimulator
Progression- irreversible malignant state

Initiator= Carciongen
7,12-dimethyl benz (a)anthracene (DMBA)



Promoter= TPA- 12-O-tetradecanoylphorbol-13-acetate,
a phorbol ester (cell signaling activator)

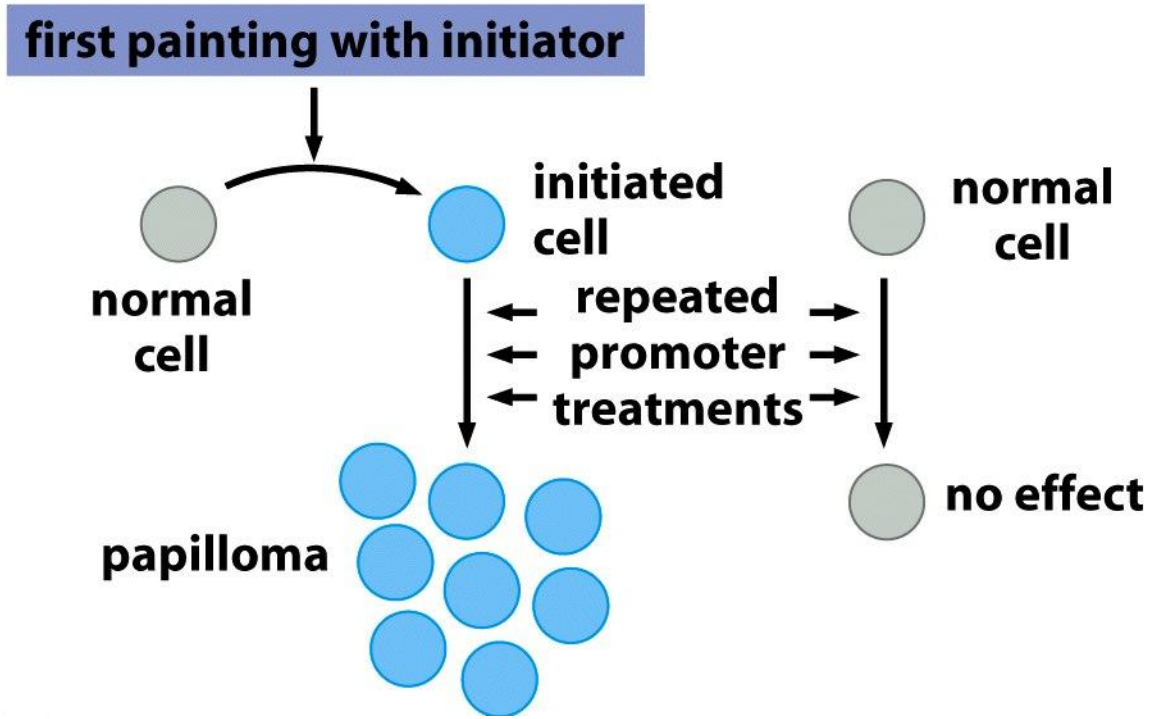


Figure 11.29 part 1 of 2 *The Biology of Cancer* (© Garland Science 2007)

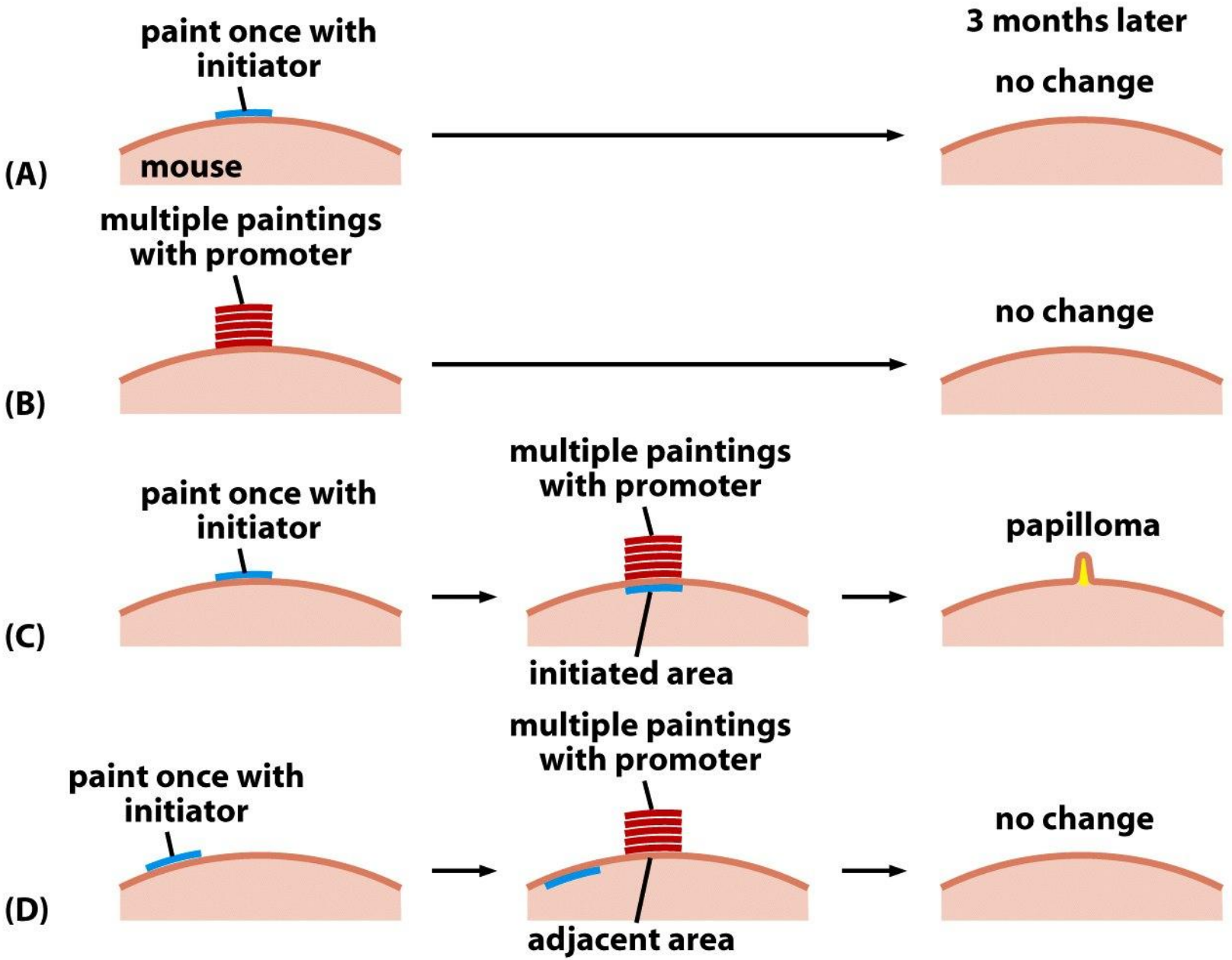


Figure 11.28 part 1 of 2 *The Biology of Cancer* (© Garland Science 2007)

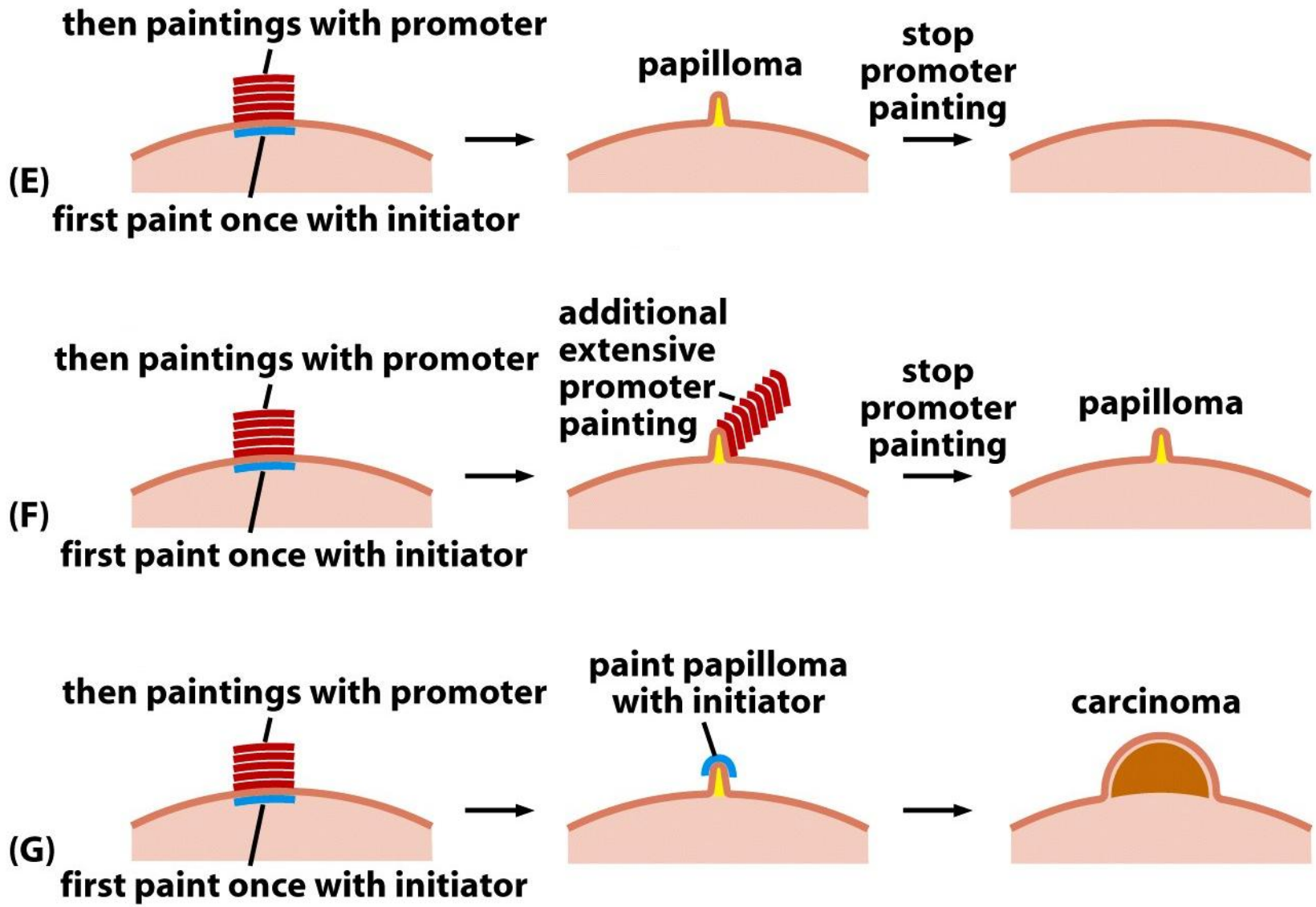


Figure 11.28 part 2 of 2 *The Biology of Cancer* (© Garland Science 2007)

Infectious agents were involved in **13%** of all new cancer cases worldwide

Table 11.3 Known or suspected human tumor promoters and their sites of action

Agent or process	Cancer site
Hormones	
Estrogen	endometrium
Estrogen and progesterone	breast
Ovulation	ovary
Testosterone	prostate
Drugs	
Oral contraceptives, anabolic steroids	liver
Analgesics	renal pelvis
Diuretics	kidney
Infectious agents	
Hepatitis B/C viruses	liver
Schistosoma haematobium—blood fluke	bladder
Schistosoma japonicum—blood fluke	colon
Clonorchis sinensis—liver fluke	biliary tract
Helicobacter pylori—bacterium	stomach
Malarial parasites	B cell
Tuberculosis bacillus	lung
Chemical agents	
Betel nut, lime	oral cavity
Chewing tobacco	oral cavity
Bile	small intestine
Salt	stomach
Acid reflux	esophagus
Physical or mechanical trauma	
Asbestos	mesothelium, lung
Gallstones	gallbladder
Coarsely ground corn	stomach
Head injury	meninges
Chronic irritation/inflammation	
Tropical ulcers	skin
Chronic ulcerative colitis	colon
Chronic cystitis	bladder
Chronic pancreatitis	pancreas

Adapted in part from S. Preston-Martin, M.C. Pike, R.K. Ross et al., *Cancer Res.* 50:7415–7421, 1990.

Initiation – promotion -progression in human tissues

Autopsies on car accident victims

show the presence of small tumor foci (<1 mm) in:

Thyroide- ~100 % (cancer rate = 0,1 %)
Breast- 39 % at age 40 (rate= 1 %)
Prostate- 34 % at age 40 (rate= 1 %)

The majority of healthy individuals may carry small pre-cancerous foci ("in situ tumors")…
…but only a fraction progress to cancer.

What distinguishes the non-cancer individuals?

Bissell and Hines (2011): Why don´t we get more cancer? Nat Med 17, 320-29

3. Alternative views on tumorigenesis

3.1:

*milieu intérieur (*Claude Bernard)

the interior environment of the body

versus

the germ theory by Louis Pasteur (1860-70)

→ strengthening the body condition to fight off the disease

versus killing the pathogen

Analogous considerations concerning the role of

tumor microenvironment

versus

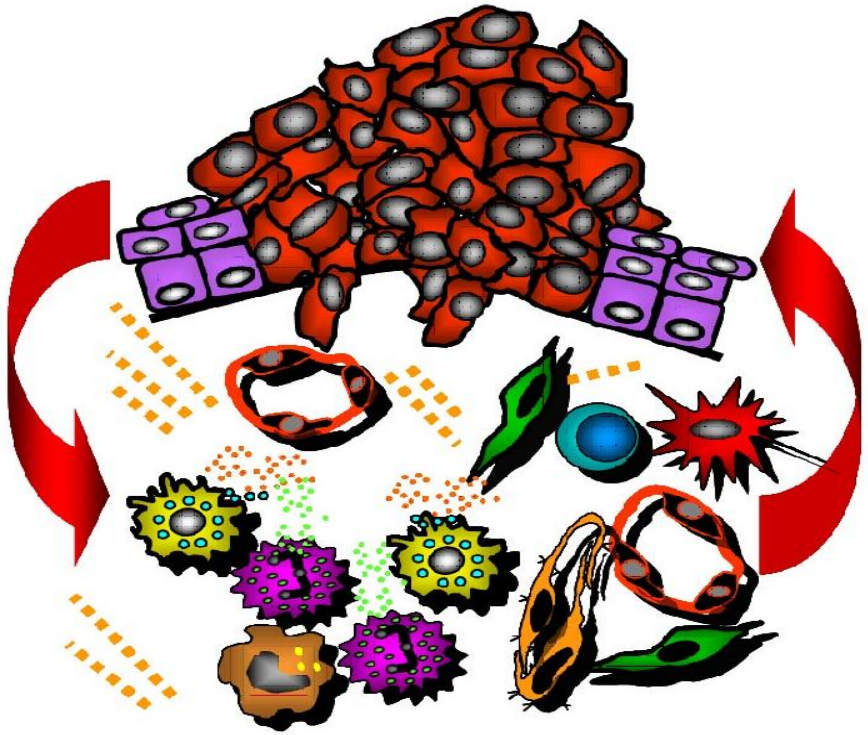
gene mutations in tumor cell

3.2:

Tumors like wounds that do not heal

(pathologist R. Virchow 1863):

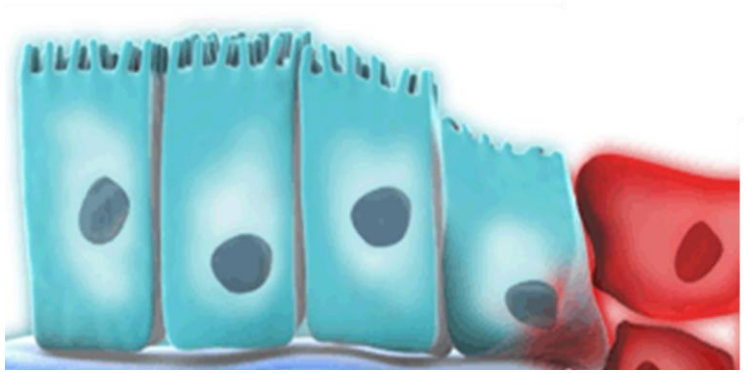
- Infiltration with macrophages and lymphocytes
- Vasodilation
- Organ dysfunction and oxidative stress
- Tissue remodeling and fibrosis



3.3:

Stephen Paget 1889:

proposal that metastasis depends on cross-talk between selected cancer cells **(the 'seeds')** and specific organ microenvironments **(the 'soil')**



Epidemiologic data on cancer

Global Cancer Observatory (iarc.fr)
https://gco.iarc.fr/

International Association of Cancer Registries (IACR) - WHO

International Agency for Research on Cancer

World Health Organization

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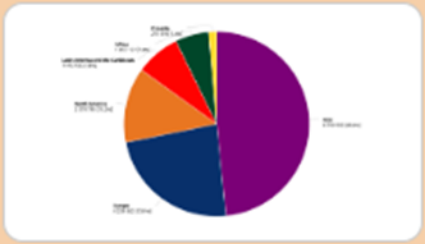
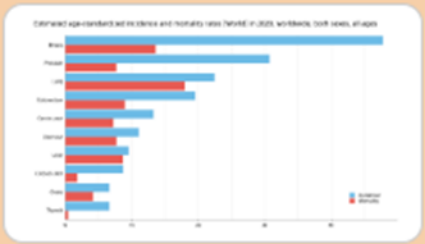
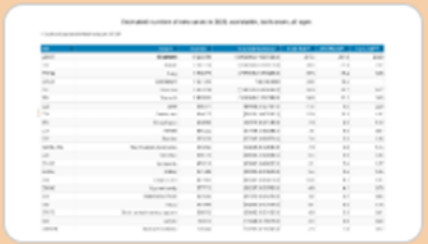
CANCER TODAY







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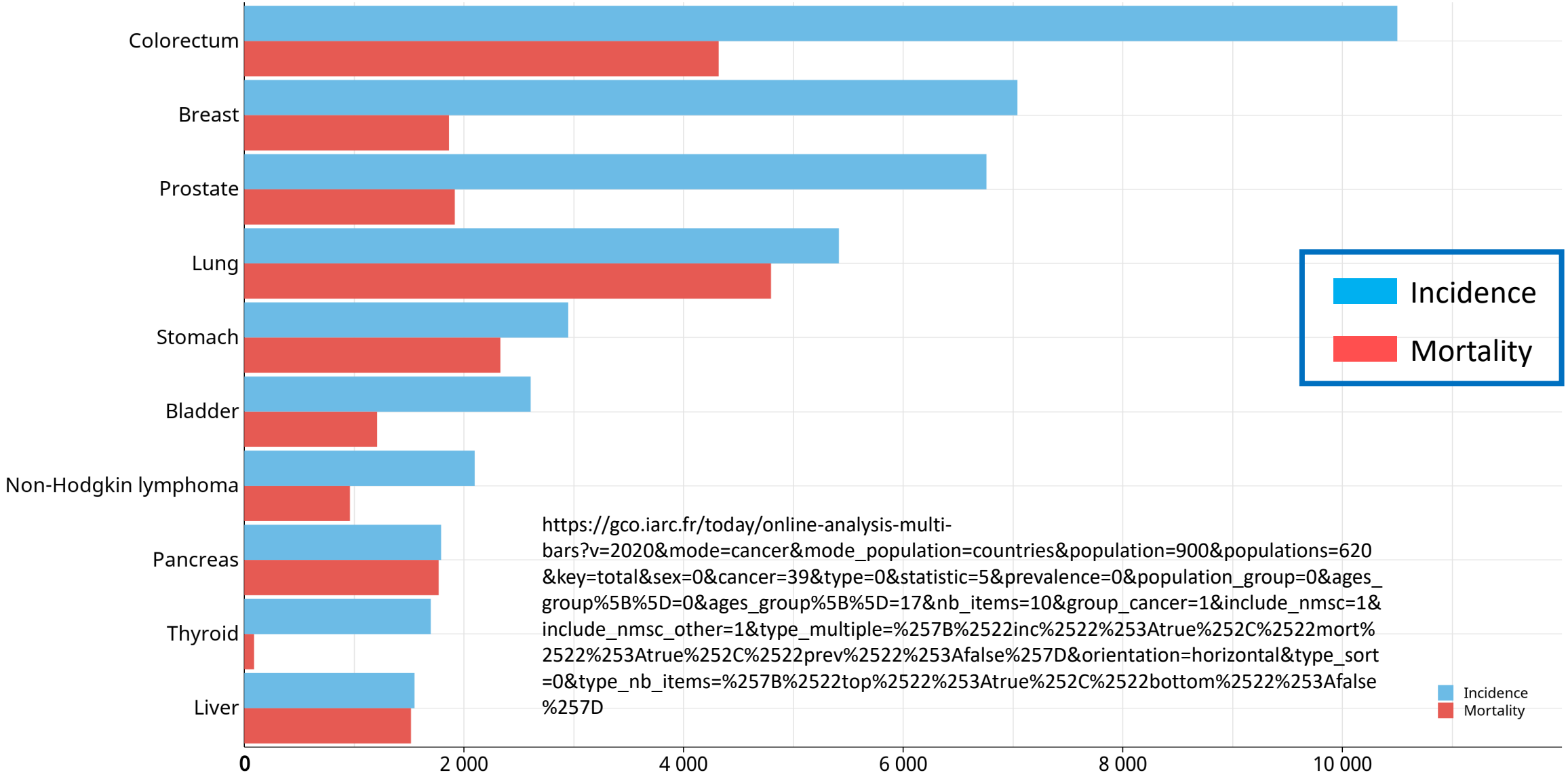
CANCER TODAY
Data visualization tools for exploring the global cancer burden in 2020
Multi bars
Pie chart
Dual bars
Maps
Tree map
Scatter plot
Table
Sunburst
Introduction

Estimated number of incident cases and deaths Portugal, both sexes, all ages 2020



Numbers

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

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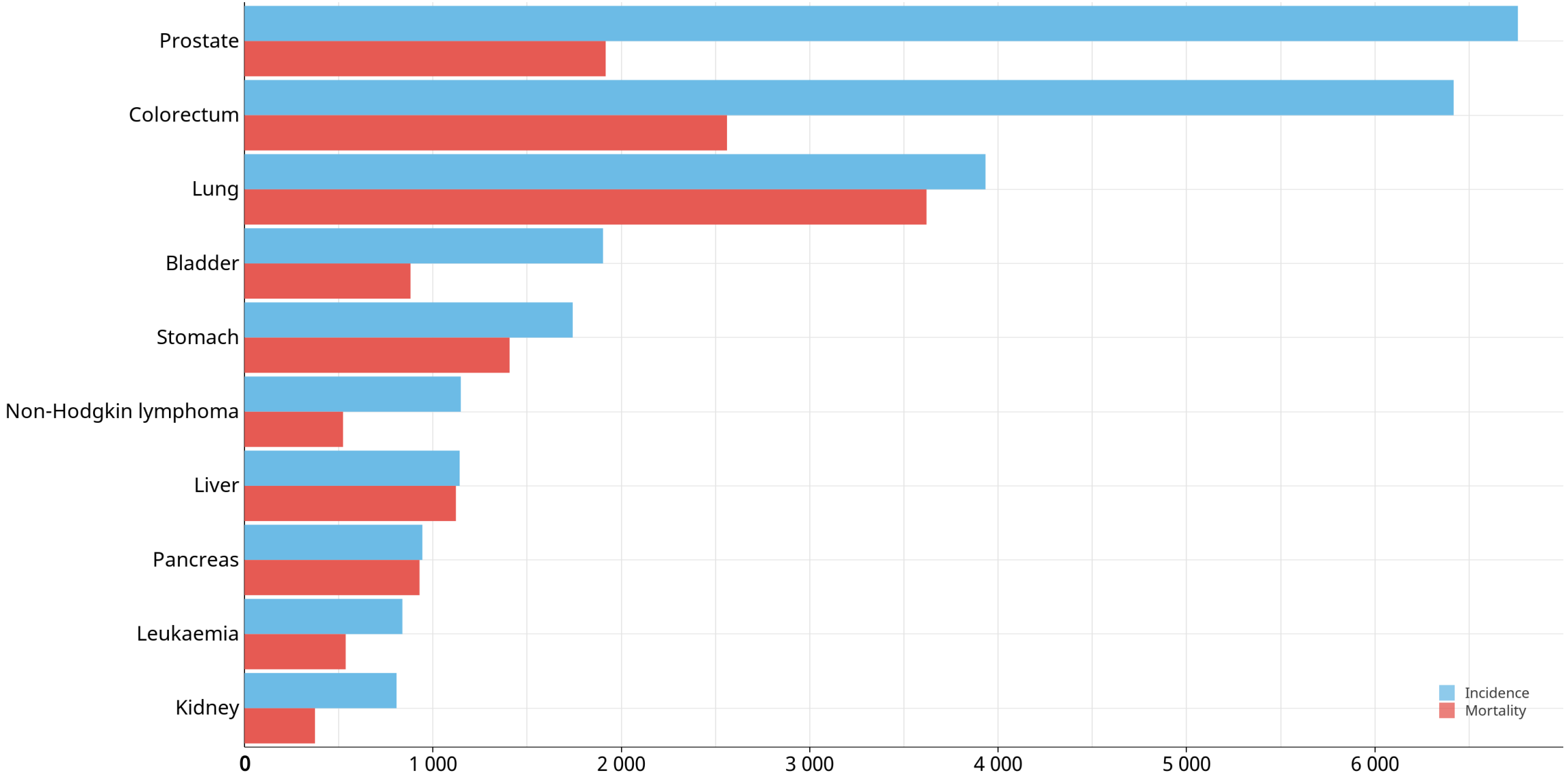
Estimated number of incident cases and deaths Portugal, males, all ages

2020

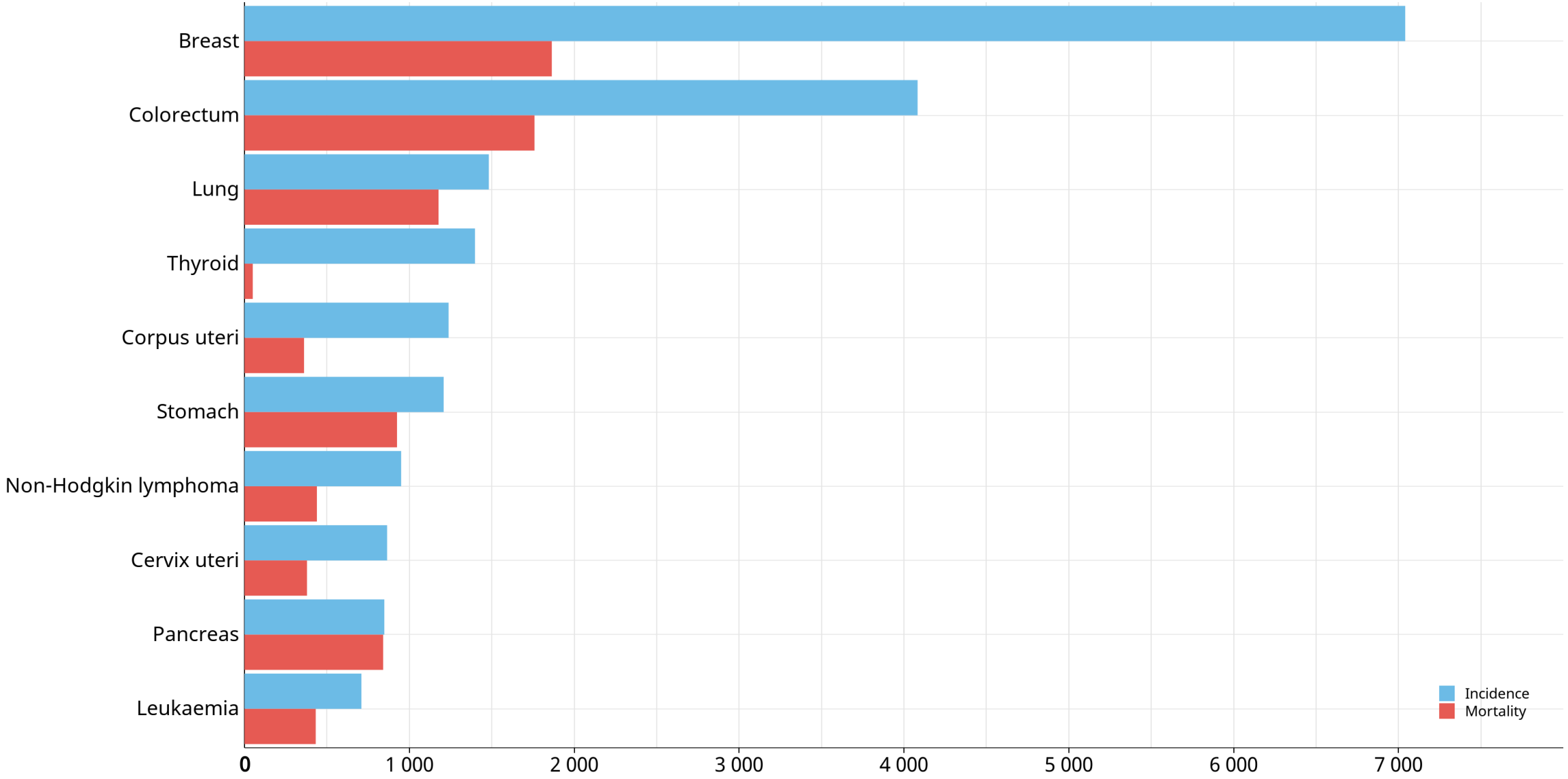


Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Estimated number of incident cases and deaths Portugal, females, all ages

2020



Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

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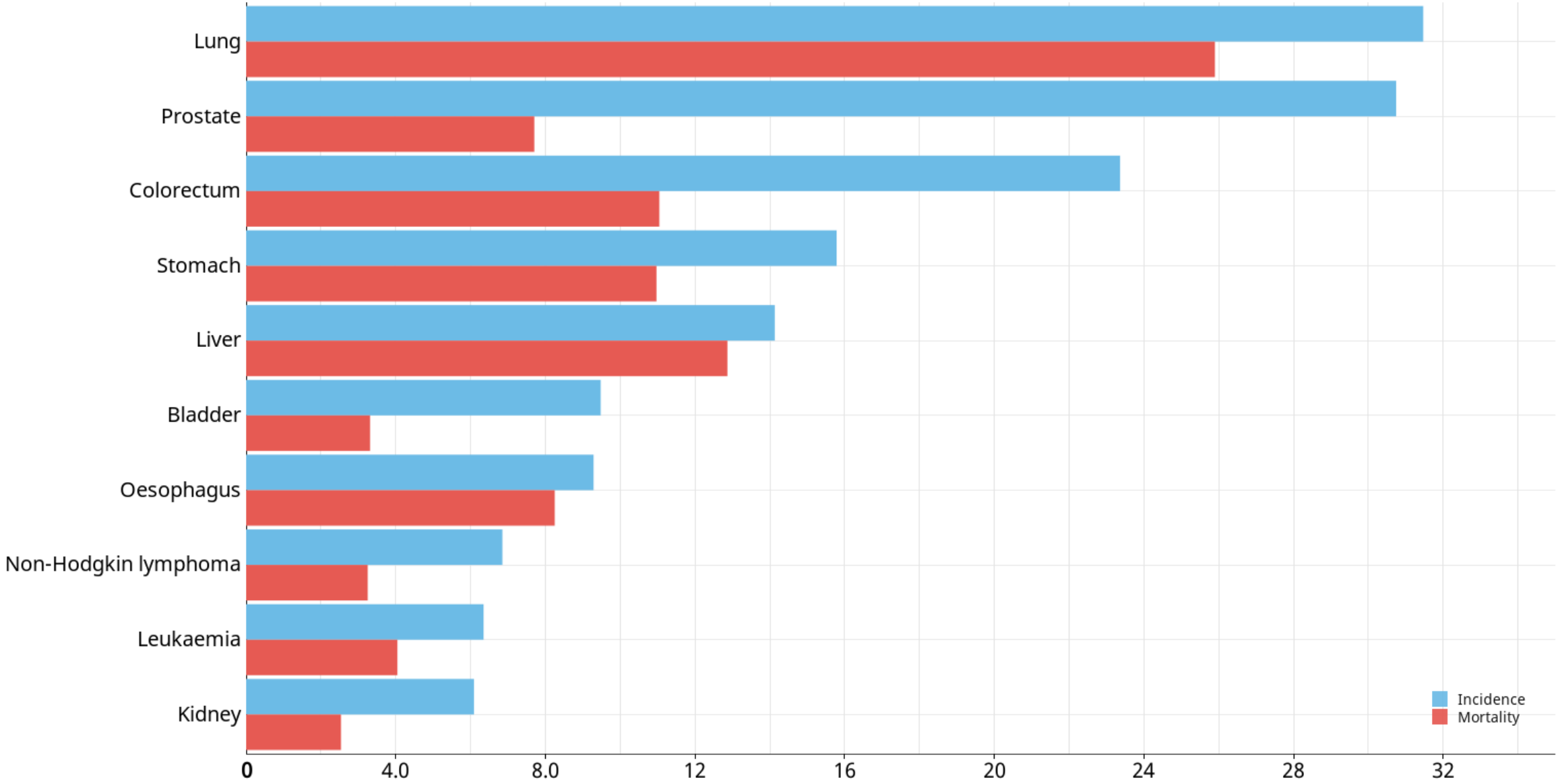
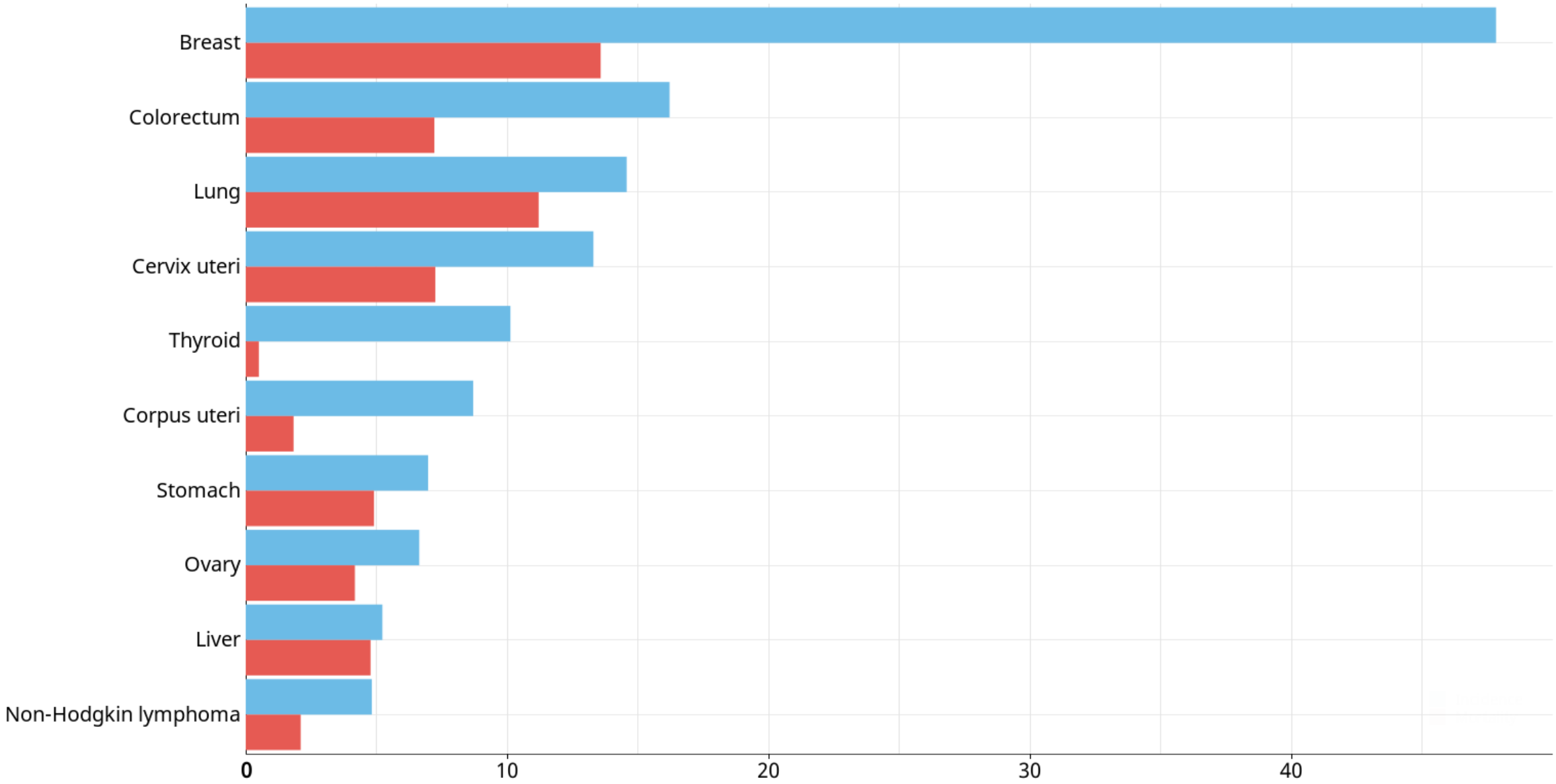
Estimated age-standardized incidence and mortality rates (World) in 2020, worldwide, males, all ages



Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Estimated age-standardized incidence and mortality rates (World) in 2020, worldwide, females, all ages



Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

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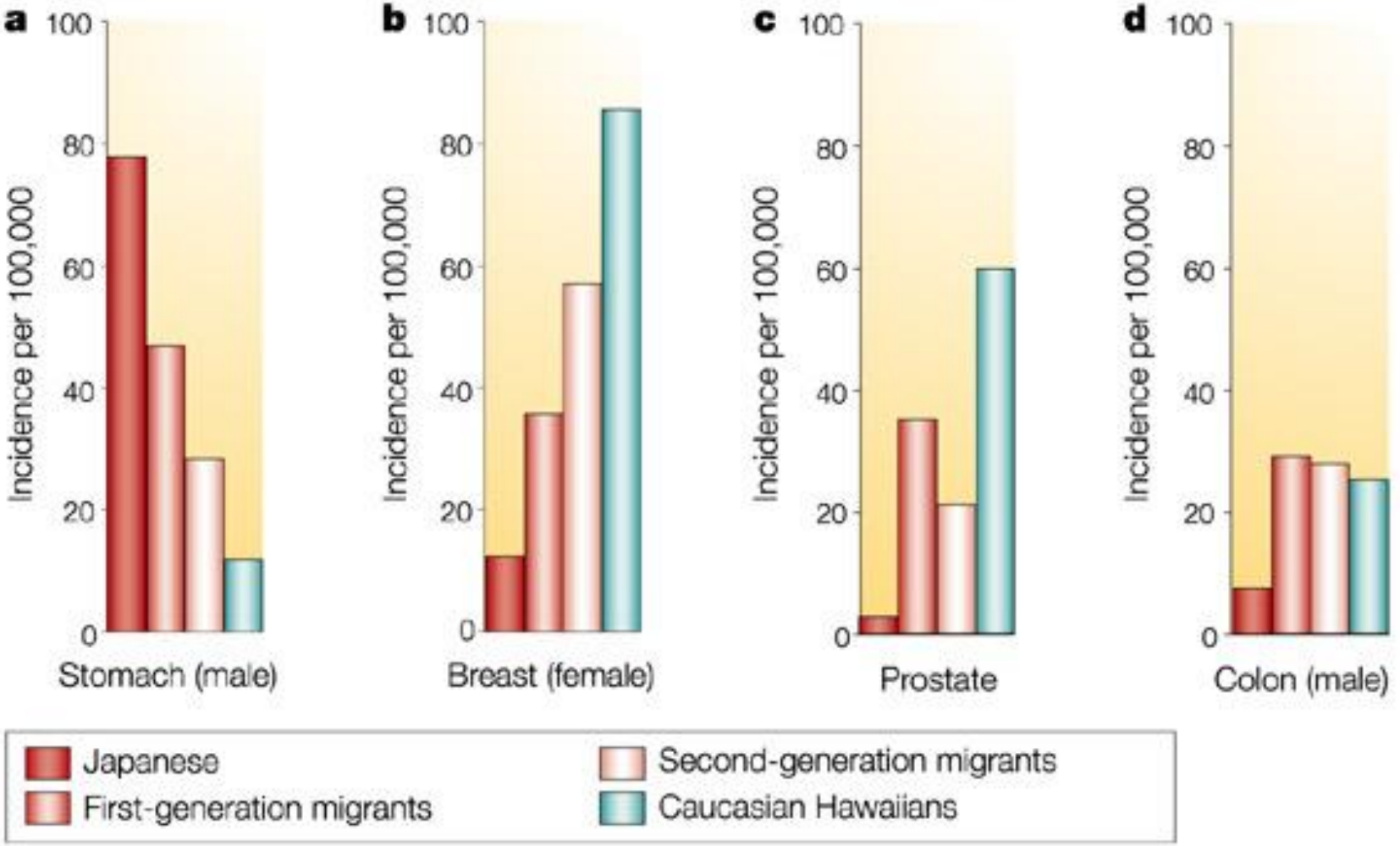
Epidemiologic data on cancer:
Migrant studies
Reveal the effects of life-style and environmental factors

Incidence of cancer in Japanese migrants in Hawaii



Nature Reviews | Cancer

Nature Reviews Cancer 4, 519-527 (July 2004)

Epidemiologic data on cancer: Life-style and environmental effects

Table 2.7 Known or suspected causes of human cancers

Environmental and lifestyle factors known or suspected to be etiologic for human cancers in the United States[a]	
Type	**% of total cases[b]**
Cancers due to occupational exposures	1–2
Lifestyle cancers	
Tobacco-related (sites: e.g., lung, bladder, kidney)	34
Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)	5
Diet (high fat, lower fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)	37
Tobacco and alcohol (sites: mouth, throat)	2

Specific carcinogenic agents implicated in the causation of certain cancers[c]	
Cancer	**Exposure**
Scrotal carcinomas	chimney smoke condensates
Liver angiosarcoma	vinyl chloride
Acute leukemias	benzene
Nasal adenocarcinoma	hardwood dust
Osteosarcoma	radium
Skin carcinoma	arsenic
Mesothelioma	asbestos
Vaginal carcinoma	diethylstilbestrol
Oral carcinoma	snuff

First environmental carcinogen, 1775

[a]Adapted from Cancer Facts and Figures, American Cancer Society, 1990.
[b]A large number of cancers are thought to be provoked by a diet high in calories acting in combination with many of these lifestyle factors.
[c]Adapted from S. Wilson, L. Jones, C. Coussens and K. Hanna, eds., Cancer and the Environment: Gene-Environment Interaction, Washington, DC: National Academy Press, 2002.

Cell-type of origin and cancer designations

epithelial cell-derived cancer = carcinoma

Table 2.1 Carcinomas

(A) Tissue sites of more common types of adenocarcinoma	(B) Tissue sites of more common types of squamous cell carcinoma	(C) Other types of carcinoma
lung	skin	small-cell lung carcinoma
colon	nasal cavity	large-cell lung carcinoma
breast	oropharynx	hepatocellular carcinoma
pancreas	larynx	renal cell carcinoma
stomach	lung	transitional-cell carcinoma (of urinary bladder)
esophagus	esophagus	
prostate	cervix	
endometrium		
ovary		

mesenchymal / connective tissue cell-derived = sarcoma
hematopoietic cell-derived = lymphoma, leukemia
neuroectodermal cell-derived = glioblastoma, astrocytoma, neuroblastoma, ..

video