



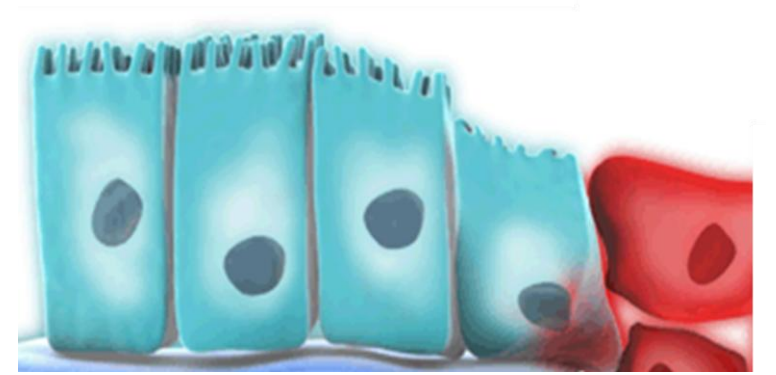
**Ciências
ULisboa**



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

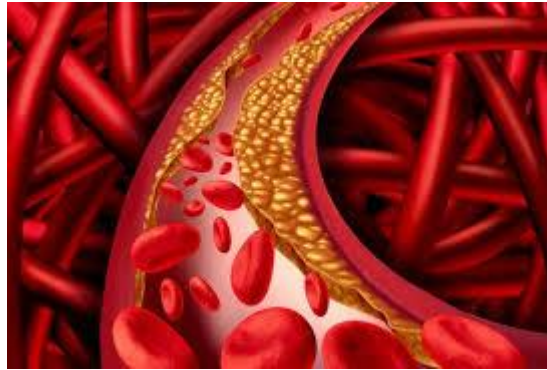
Comparing cancer with other diseases

Cardiovascular disease

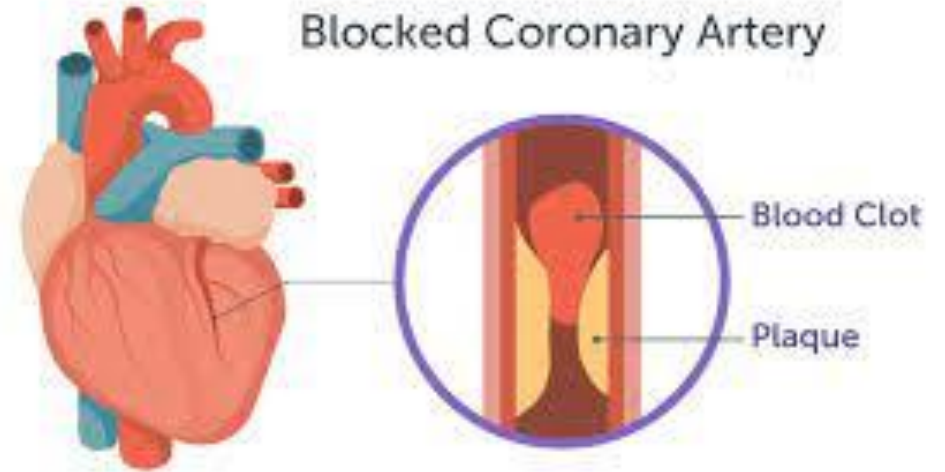
Diabetes

Infectious disease

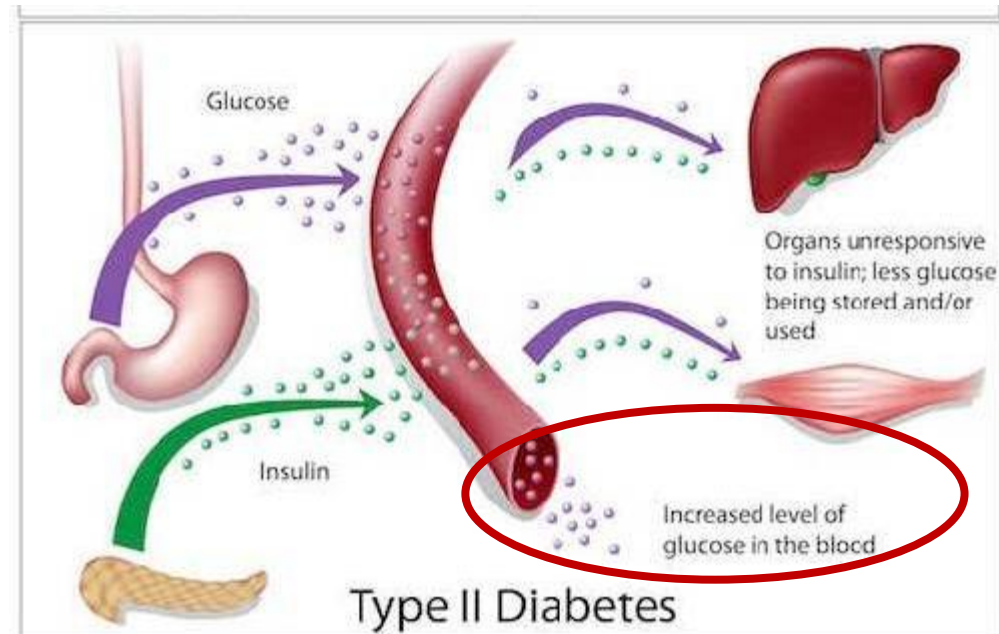
arteriosclerosis



Blocked Coronary Artery



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



Comparing cancer with other diseases

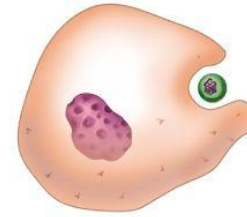
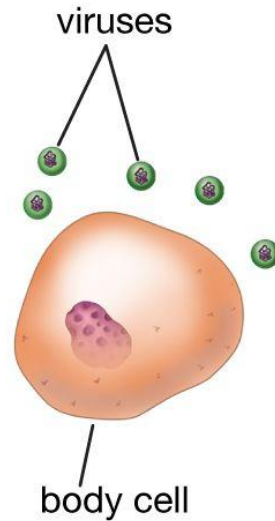
Cardiovascular disease

Diabetes

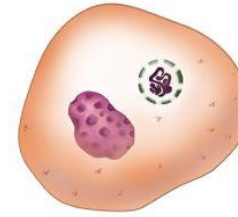
Infectious disease

- body cells
- grow and divide?
- genetic transformation

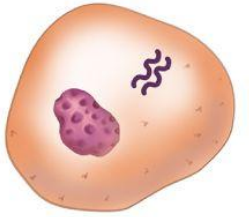
How a virus invades a cell



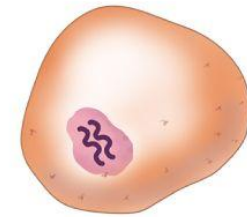
1. A virus enters a cell.



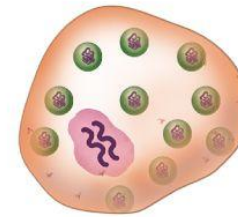
2. Substances in the cell begin to strip off the virus's outer coat of protein.



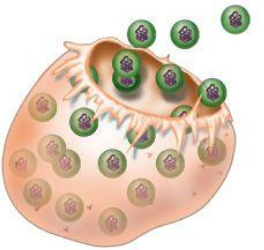
3. The nucleic acid in the center of the virus is released.



4. The nucleic acid gets into the cell nucleus and can integrate into the DNA

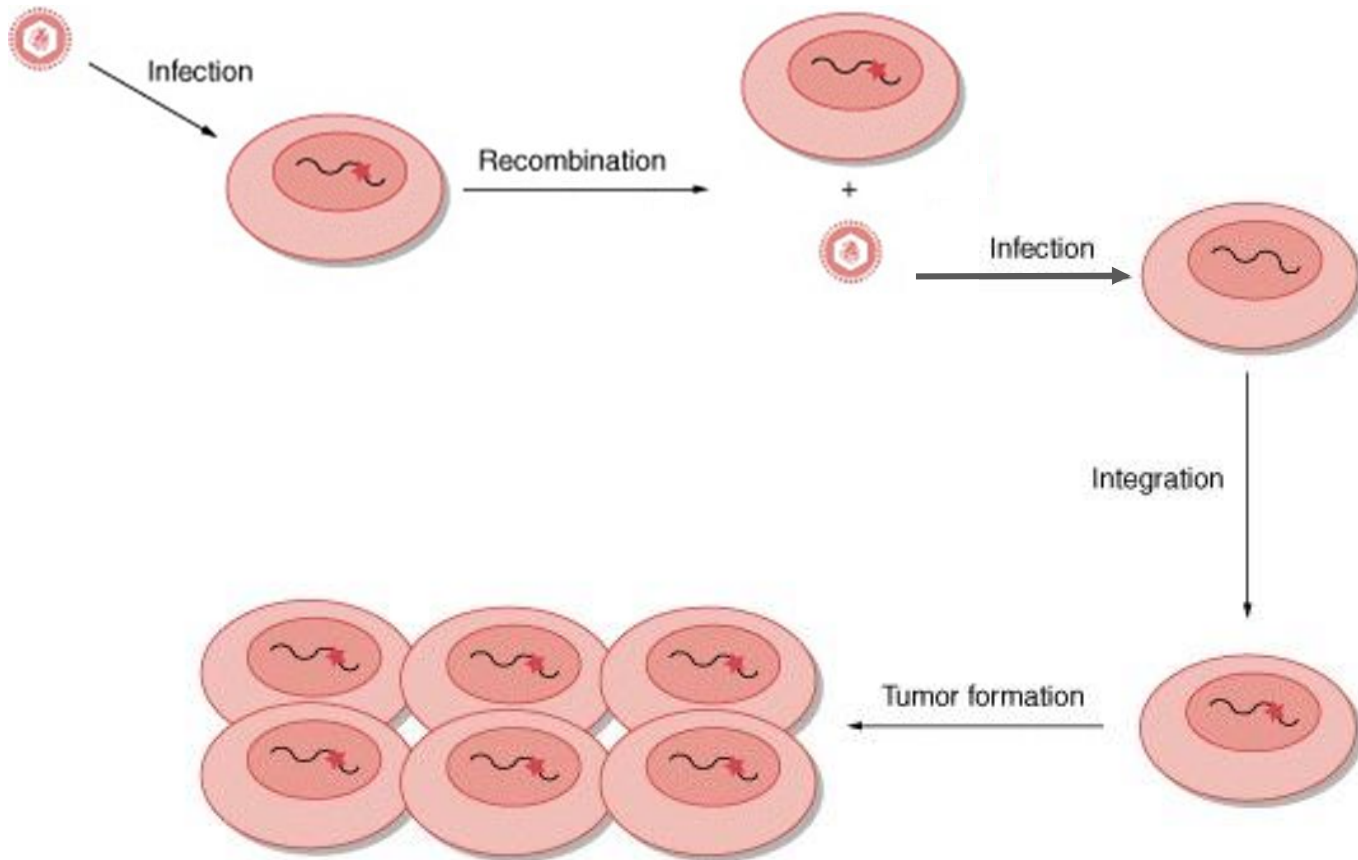


5. The cell "ignores" its own chemical needs and switches to making new viruses.



6. The cell is sometimes destroyed in the process. Many of the new viruses are released to infect other cells.

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?

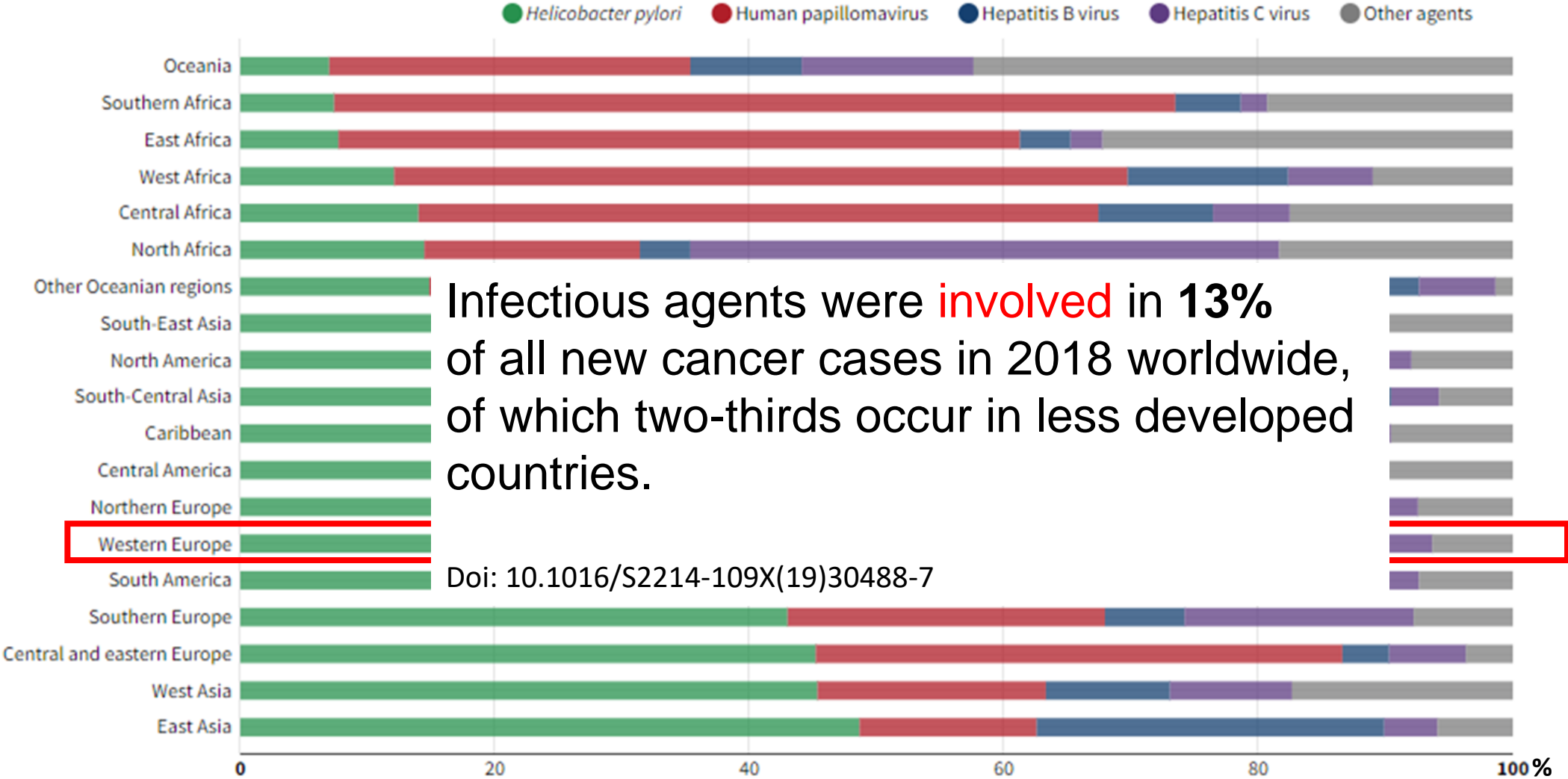
Proportions of cancer cases among both sexes attributable to infections in 2018 (by regions)



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 2022

Cancer as an infectious disease?

Proportions of cancer cases among both sexes attributable to infections in 2018 (by regions)



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 2022

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

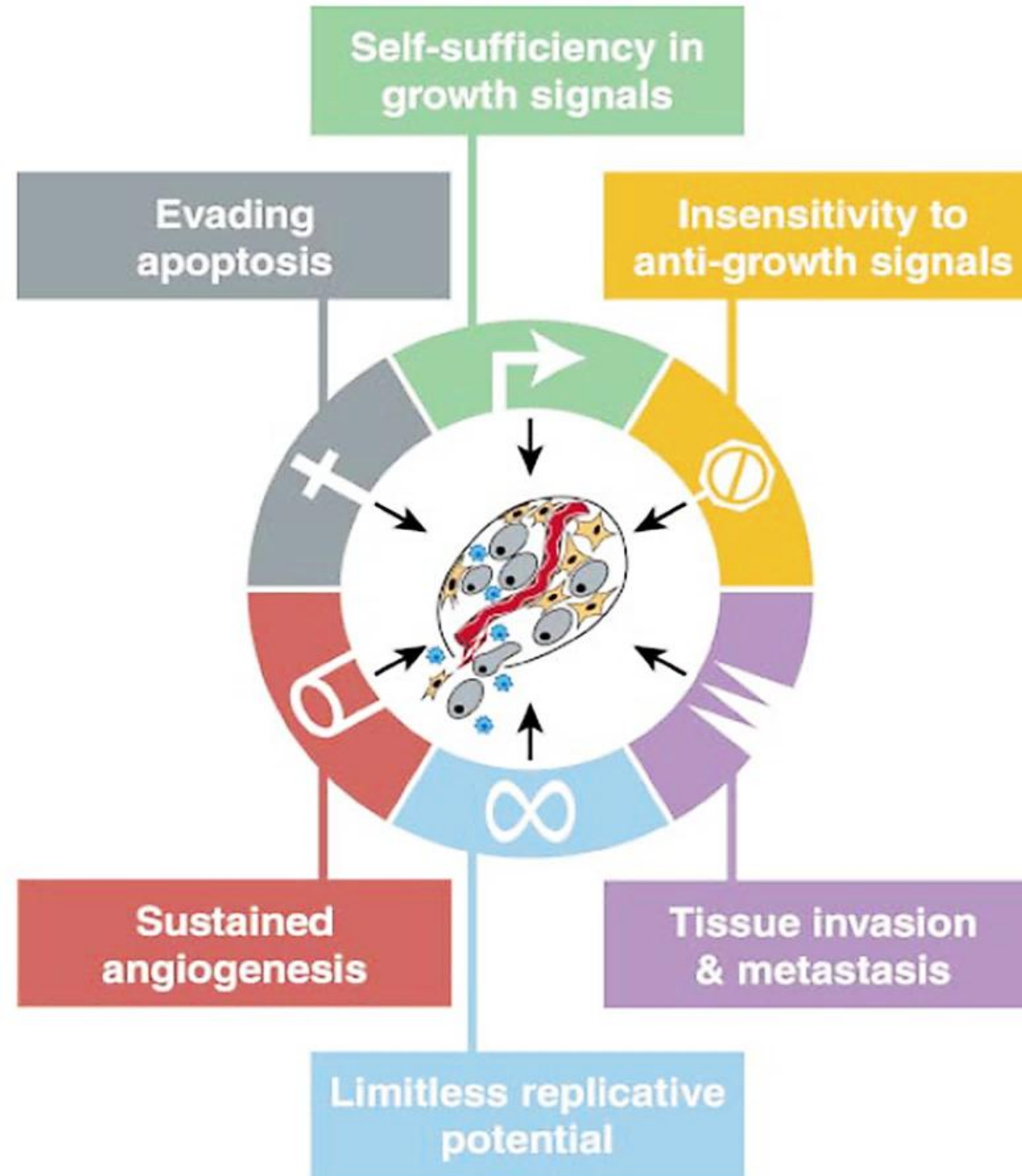
Unlike normal cells, cancer cells do..:

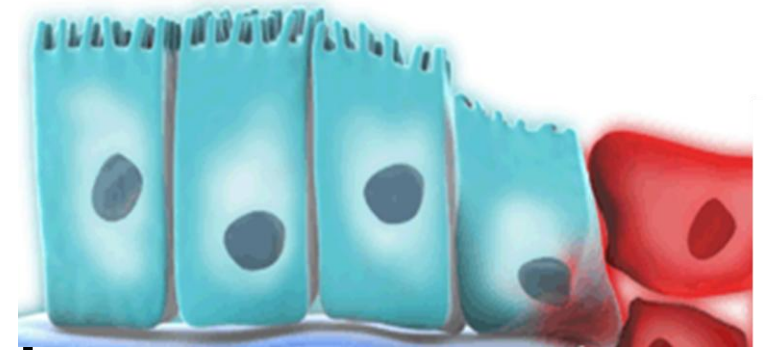
- grow in the absence of growth signals (normal cells only grow when they receive such signals);
- ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis);
- accumulate multiple changes in their chromosomes, such as duplications and 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

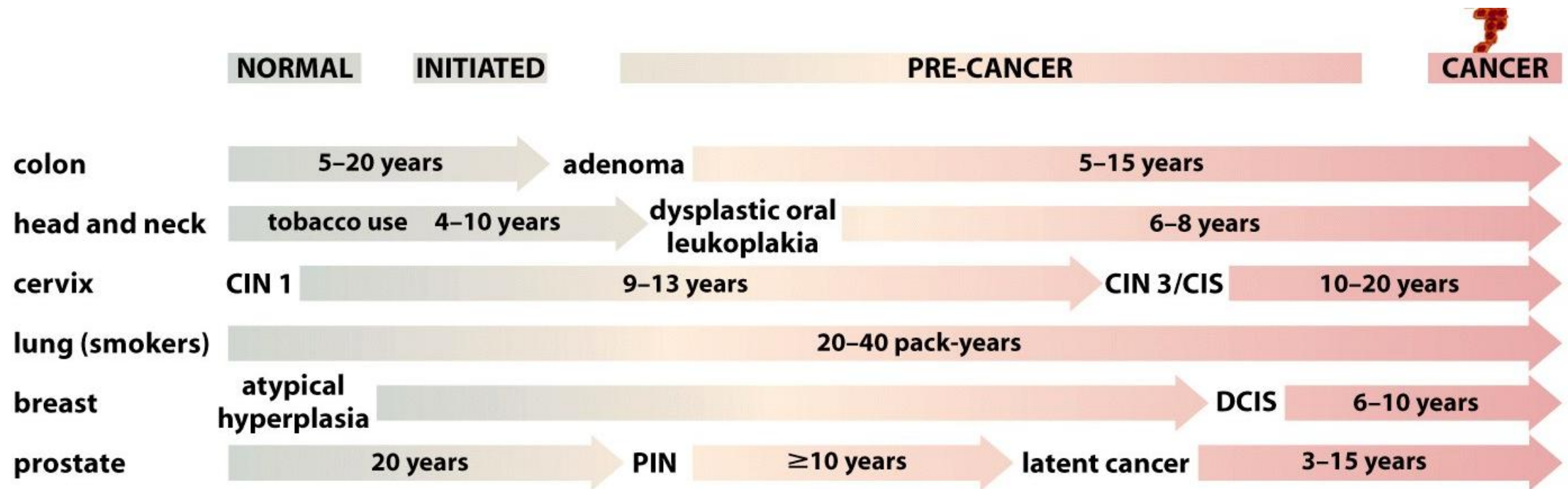
Cell 100, 57–70 (2000)

Hanahan & Weinberg

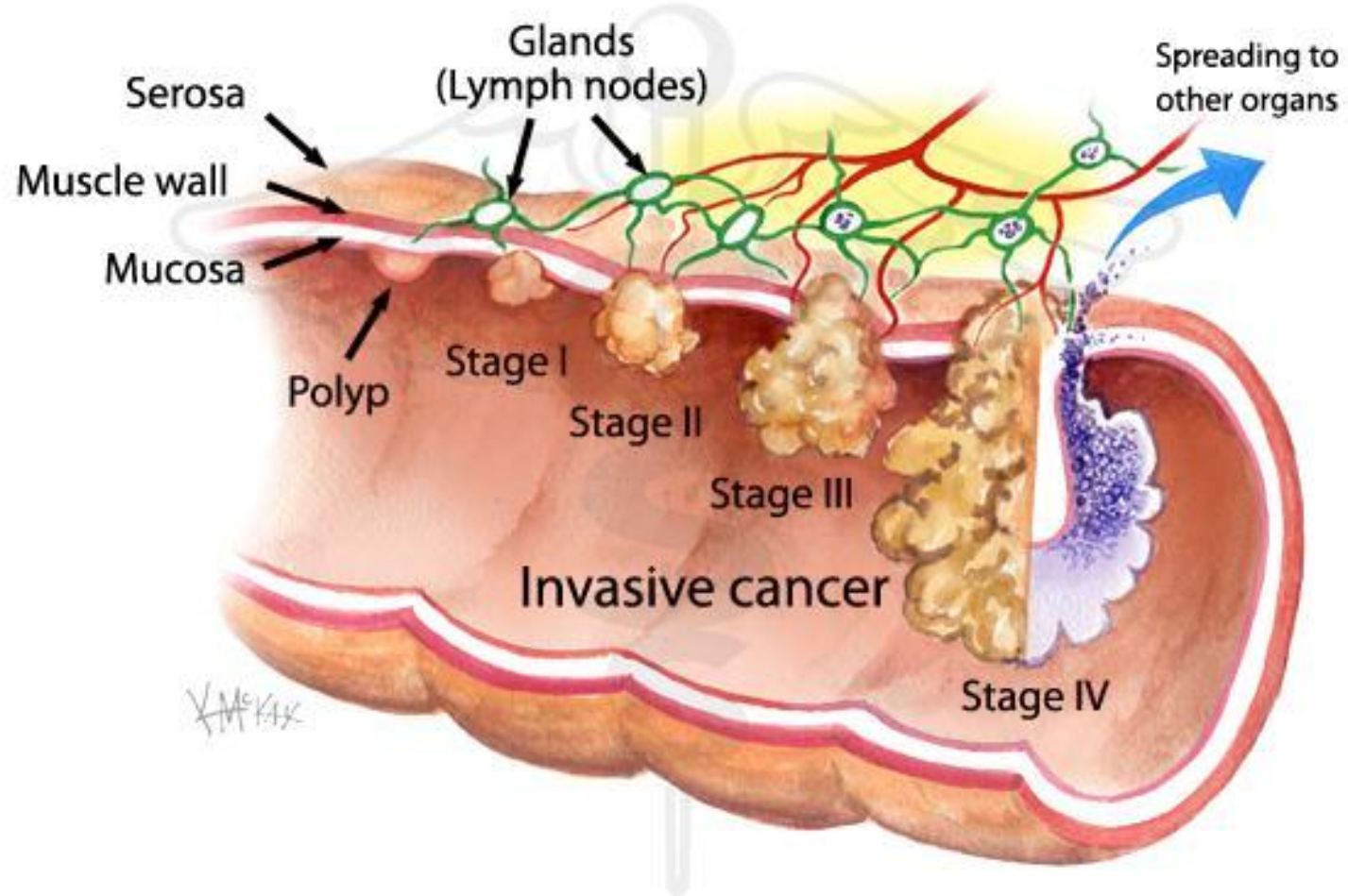




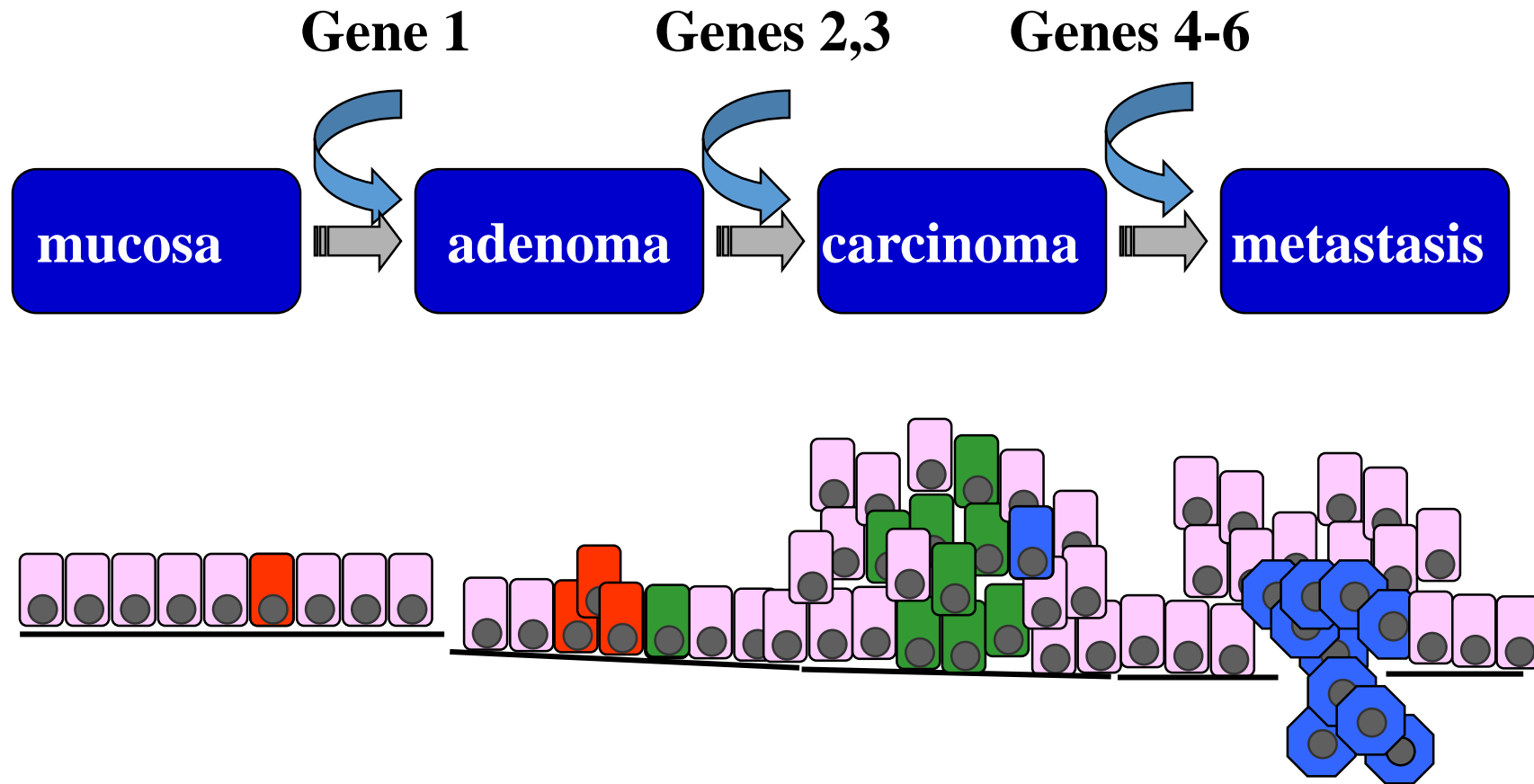
The timing of cancer development



How does cancer develop?

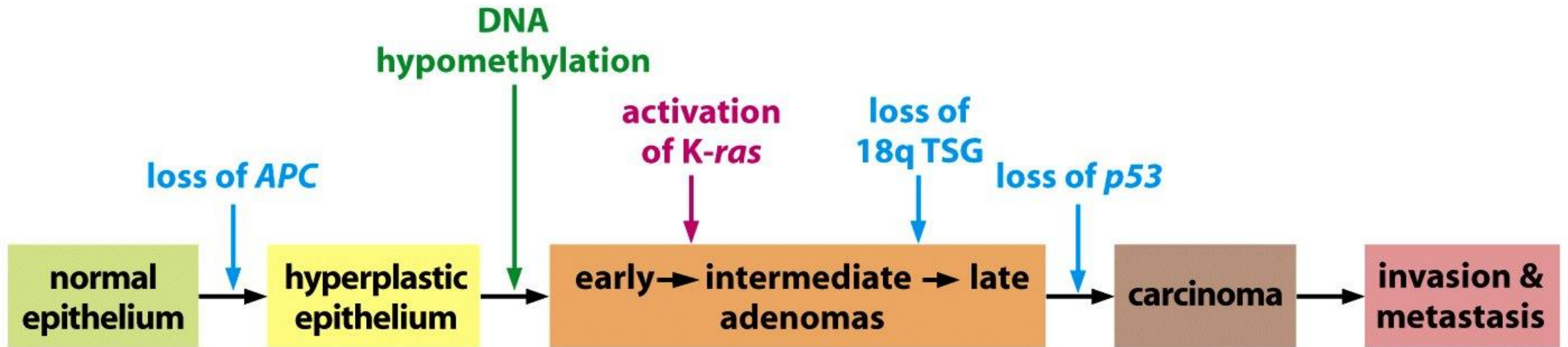


1. The classical model of tumorigenesis through *clonal selection*

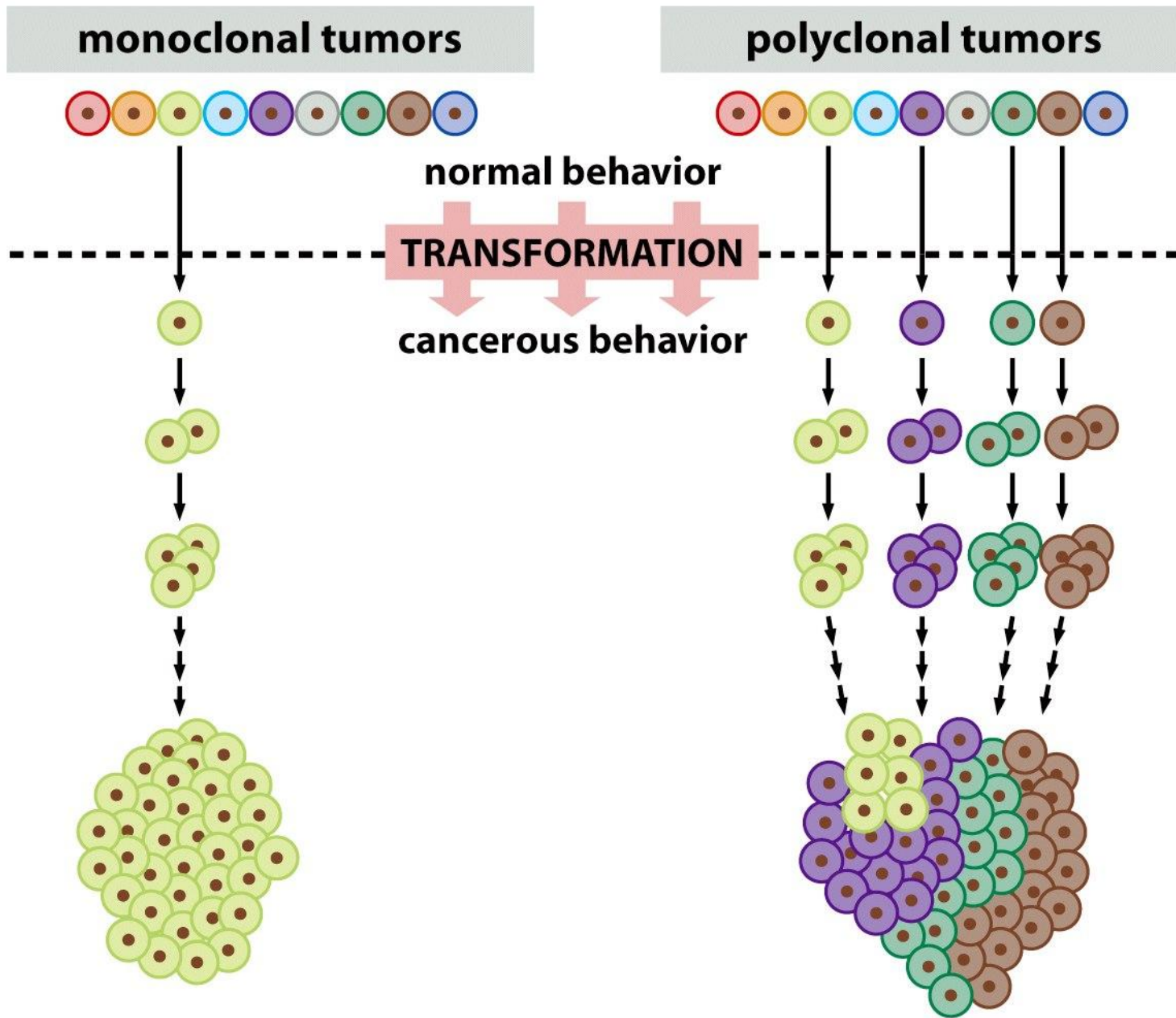


Genetic model: accumulation of genetic changes in a cell

Accumulating genetic changes in a colon cell



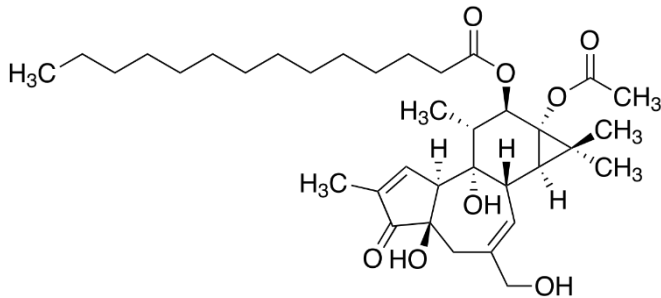
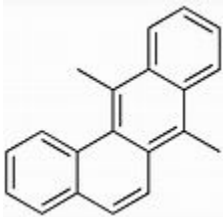
Fearon and Vogelstein, A Genetic Model for Colorectal Tumorigenesis, Cell 61, 759-767 (1990)



2. The tumorigenesis model from skin carcinogenesis:

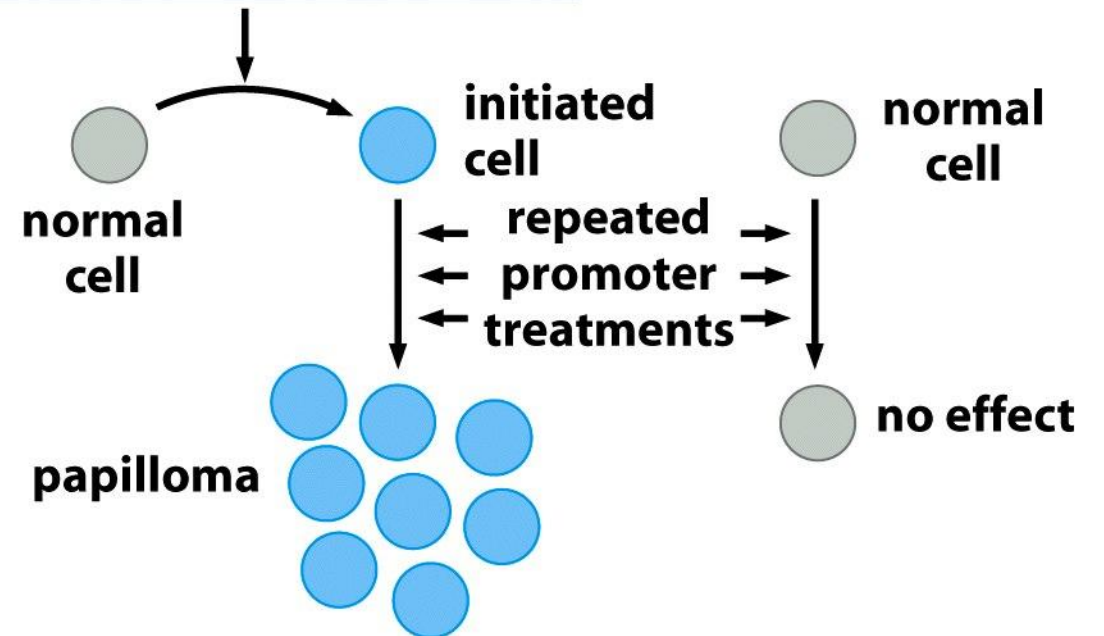
Initiation- chemical mutagen
Promotion- signaling stimulator
Progression- irreversible malignant state

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



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

first painting with initiator



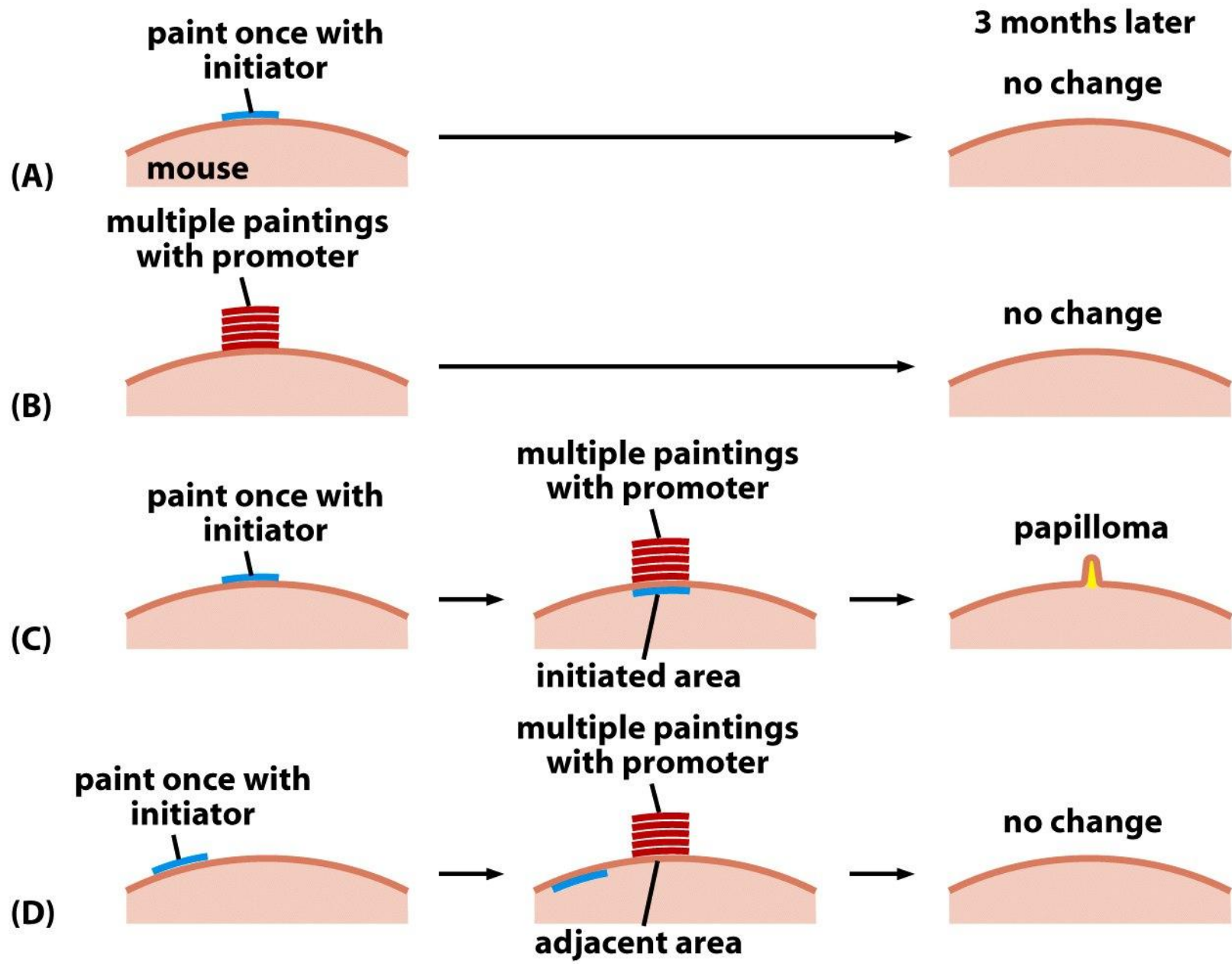


Figure 11.28 part 1 of 2 *The Biology of Cancer* (© Garland Science 2007)

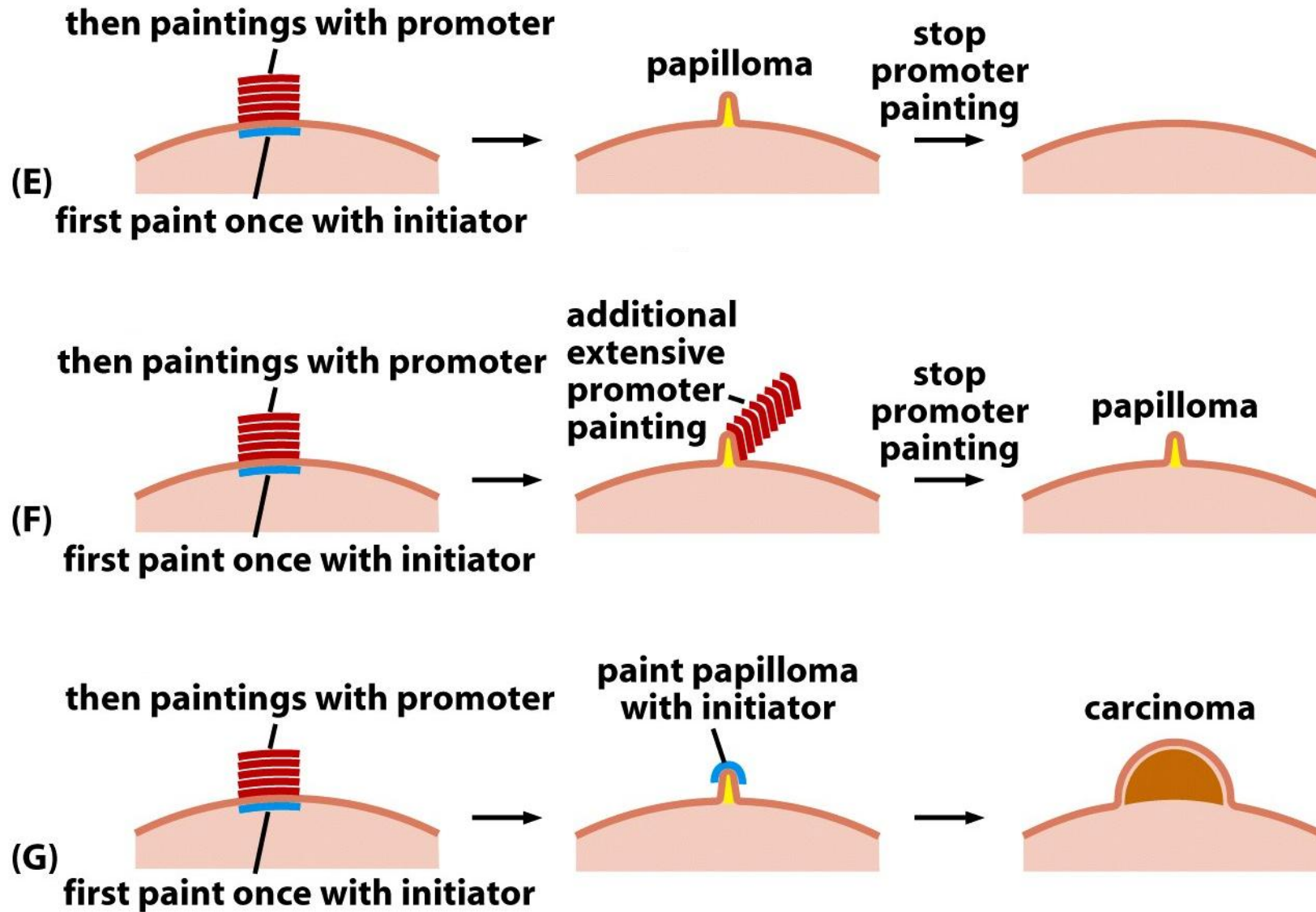


Figure 11.28 part 2 of 2 *The Biology of Cancer* (© Garland Science 2007)

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
<i>Schistosoma haematobium</i> —blood fluke	bladder
<i>Schistosoma japonicum</i> —blood fluke	colon
<i>Clonorchis sinensis</i> —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

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

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:

Thyroid- ~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

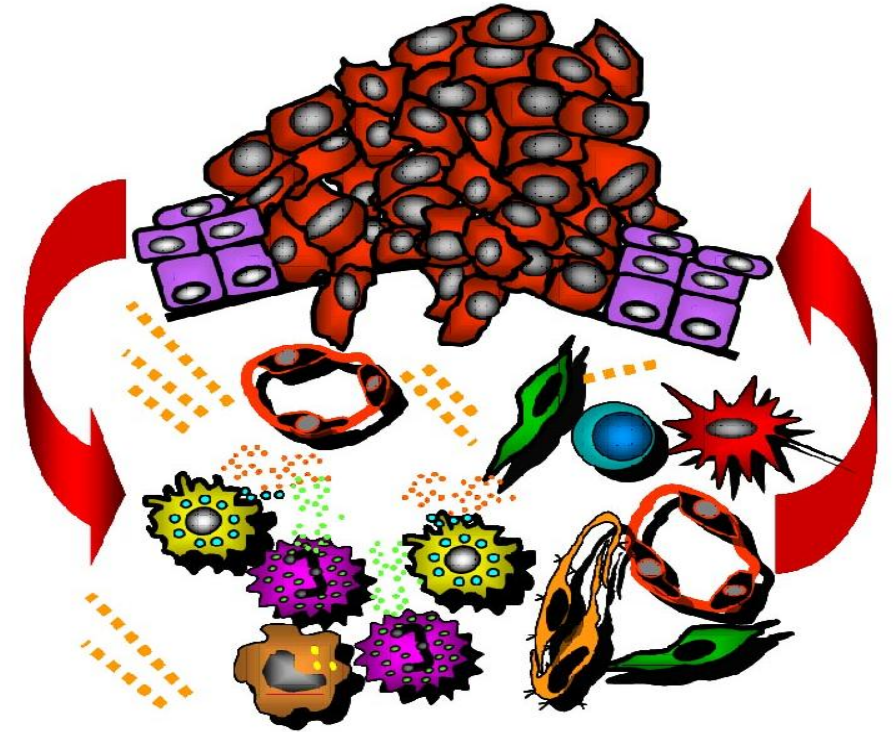
gene mutations in tumor cell

3.2:

Tumors like wounds that do not heal

(pathologist R. Virchow 1863):

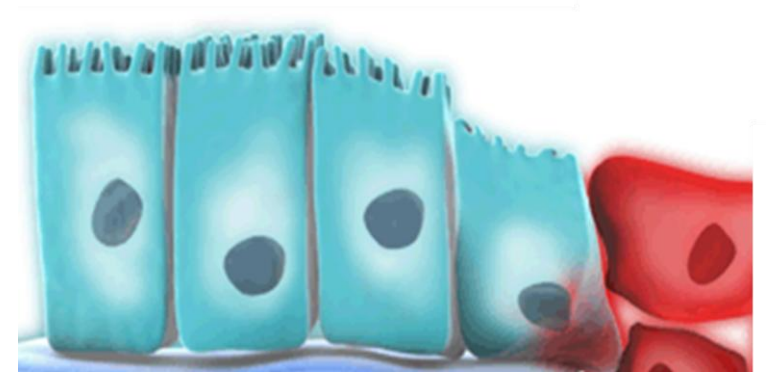
- Infiltration with macrophages and lymphocytes
- Vasodilation
- Organ dysfunction and oxidative stress
- Tissue remodeling and fibrosis



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/)
<https://gco.iarc.fr/>

International Association of Cancer Registries (IACR) - WHO



HOME

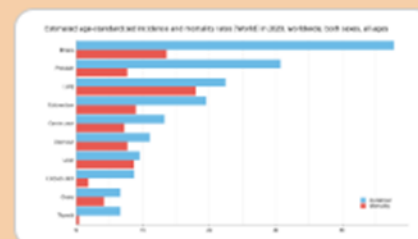
ABOUT THE GCO

PROJECTS

ABOUT US

HELP

CANCER TODAY



Region	Cancer Type	ASIR	ASMR
World	Colorectal cancer	18.0	12.0
World	Prostate cancer	15.0	10.0
World	Stomach cancer	10.0	8.0
World	Bladder cancer	5.0	4.0
World	Other	10.0	7.0

 **CANCER TODAY**

CANCER OVER TIME

CANCER TOMORROW

CANCER CAUSES

CANCER SURVIVAL

CANCER @CSU

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

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world.¹ According to estimates from the World Health Organization (WHO) in 2019,² cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries (Fig. 1). Cancer's rising prominence as a leading cause of death partly reflects marked declines in mortality rates of stroke and coronary heart disease, relative to cancer, in many

Distribution of Cases and...
sex, the area of the pie...
GLOBOCAN 2020.

Figure 4 shows the top...
and women, combined...
both sexes combined, t...
cancer cases and >70%...
diagnosed cancer (11.7%...
prostate (7.3%), and sto...
death (18.0% of the tota...
(7.7%), and female brea...
cancer and the leading...
cancer for incidence an...
the most commonly dia...
colorectal and lung can...

es (including NMSC, except basal cell...
ease from the corresponding 19.3...
timated in 2020 remain constant (Fig...
g in low HDI countries (95%) and in...
burden, the high HDI countries are...
ence, with 4.1 million new cases more...
due to the growth and aging of the...
creasing prevalence of risk factors in



Open in figure viewer | PowerPoint

(Sexes Combined) in 2040 According to the

Figure 7

Incidence and Mortality Age-standardized Rates in High/Very High Human Development Index (HDI)

Open in figure viewer | PowerPoint

Figure 1

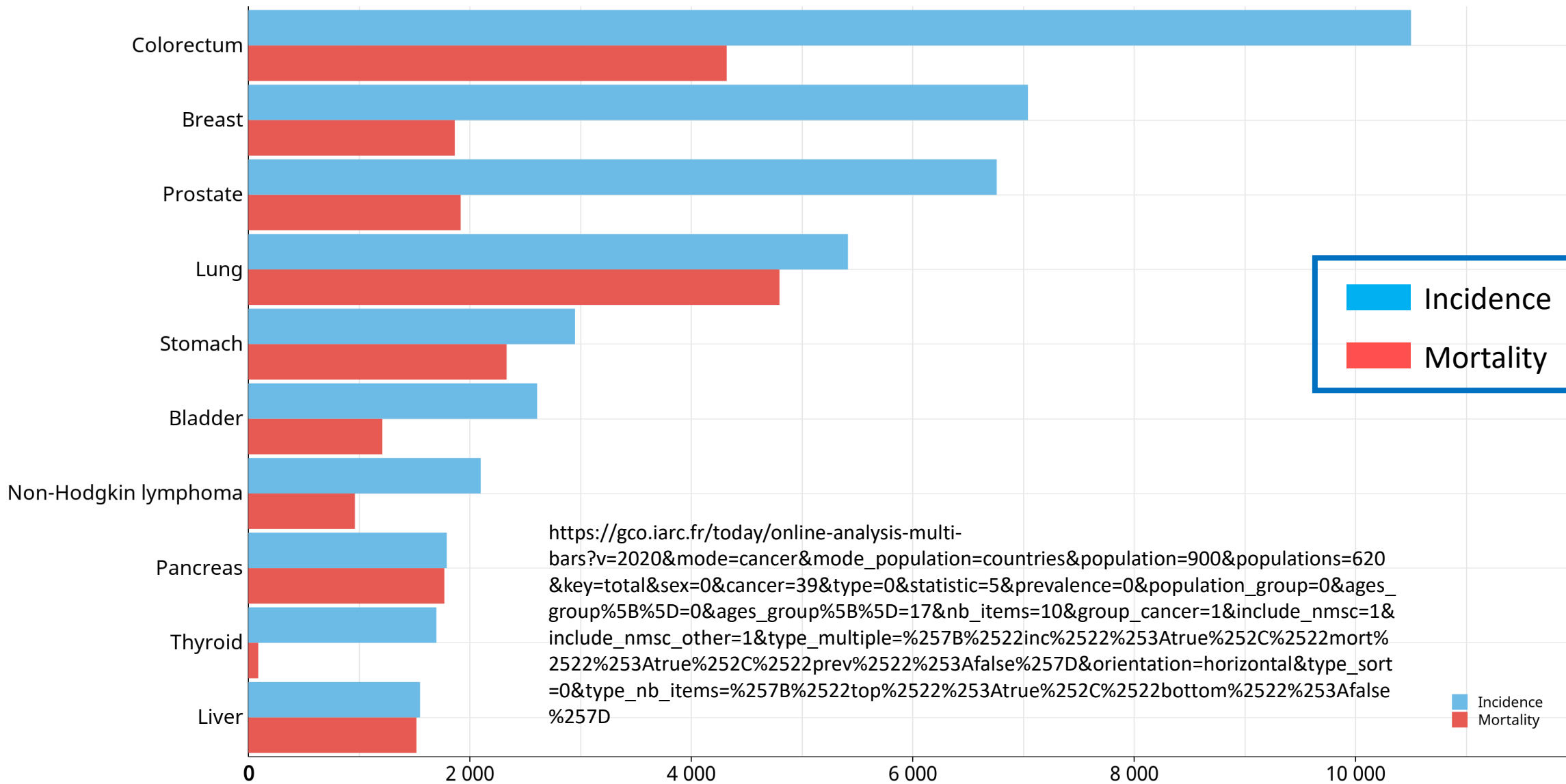
Cause of Death at Ages <70 Y...
are included in the legend

Overall, cancer incidence and mortal...
reflects...
distribution...
risk factors for cancer, several o...
socioeconomic development.³⁻⁵ The extent to which the position of cancer as a cause of premature death reflects national levels of social and economic development can be seen by comparing the countries of Europe and Europe with the more developed countries of the Americas



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

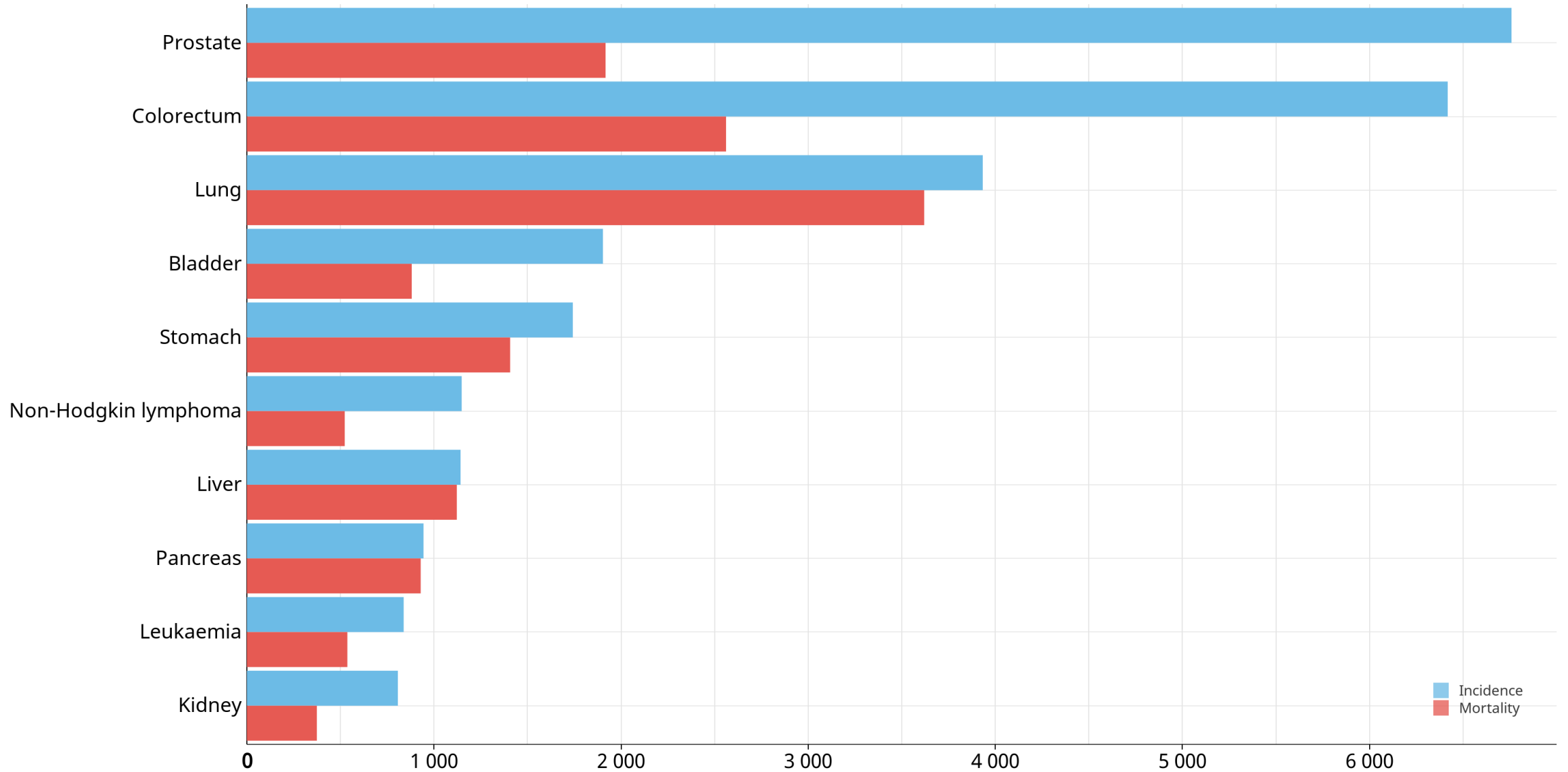
2020



https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=620&key=total&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Atrue%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D

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

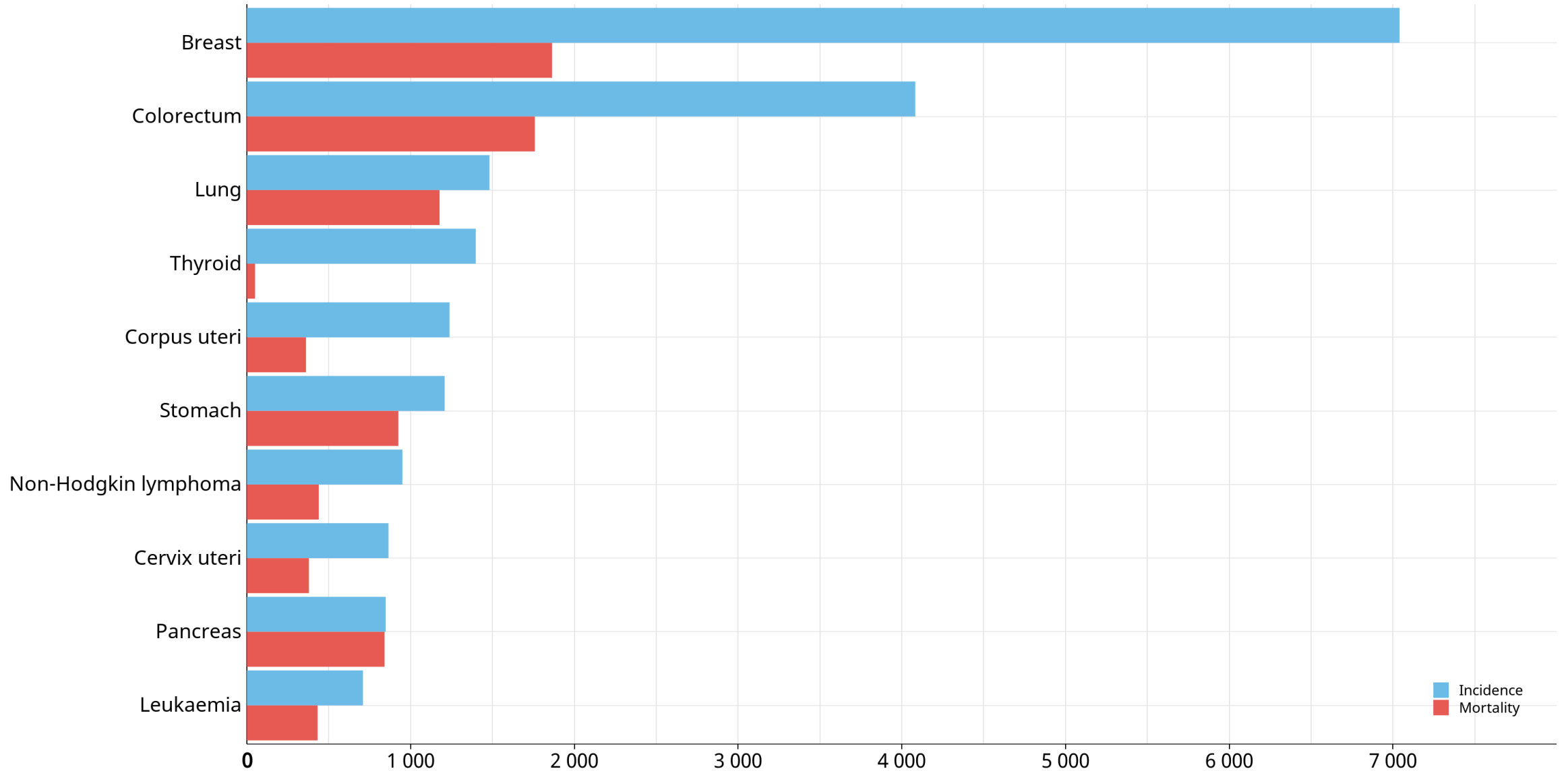
2020



Incidence
Mortality

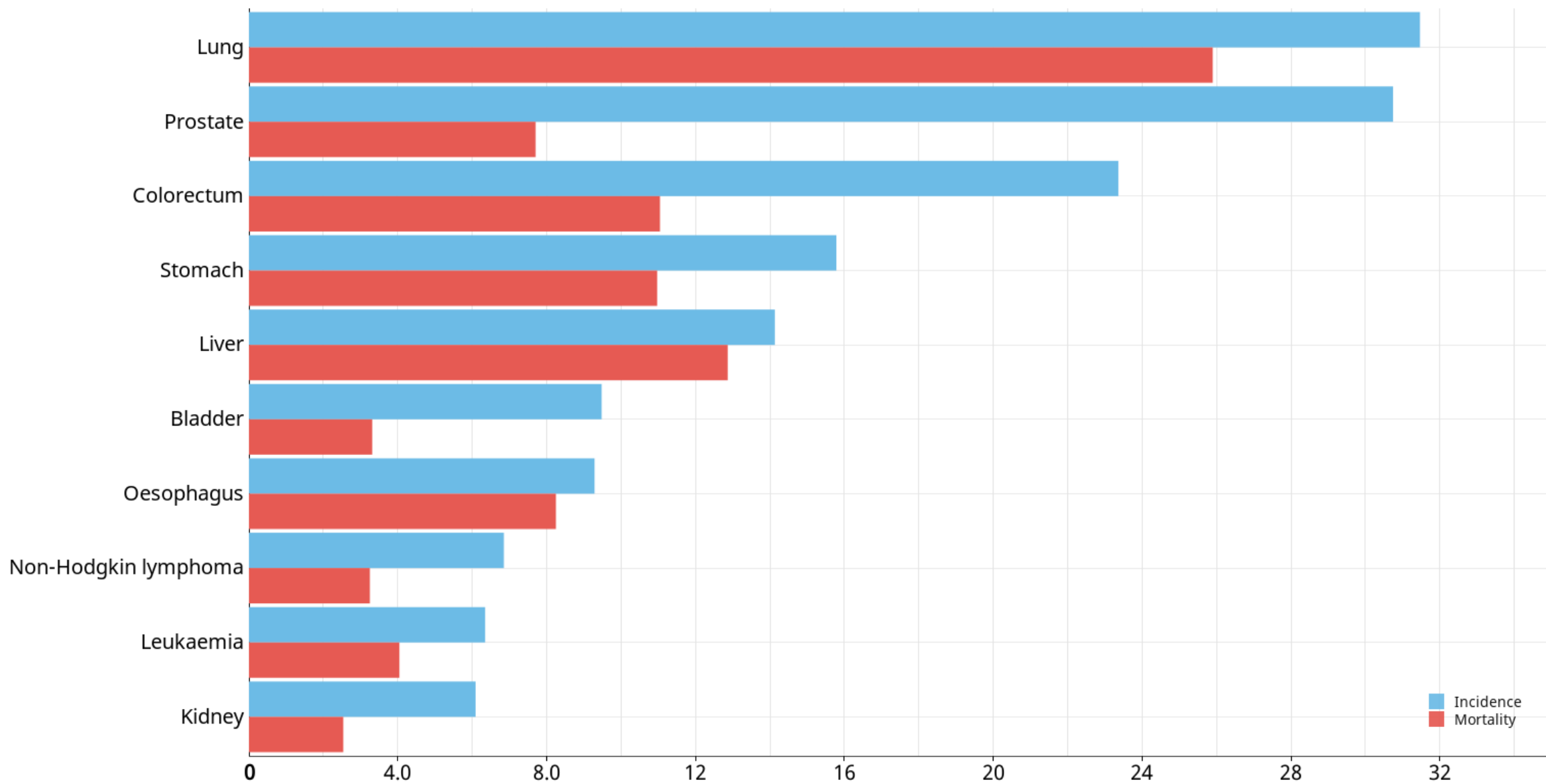
Estimated number of incident cases and deaths Portugal, females, all ages

2020

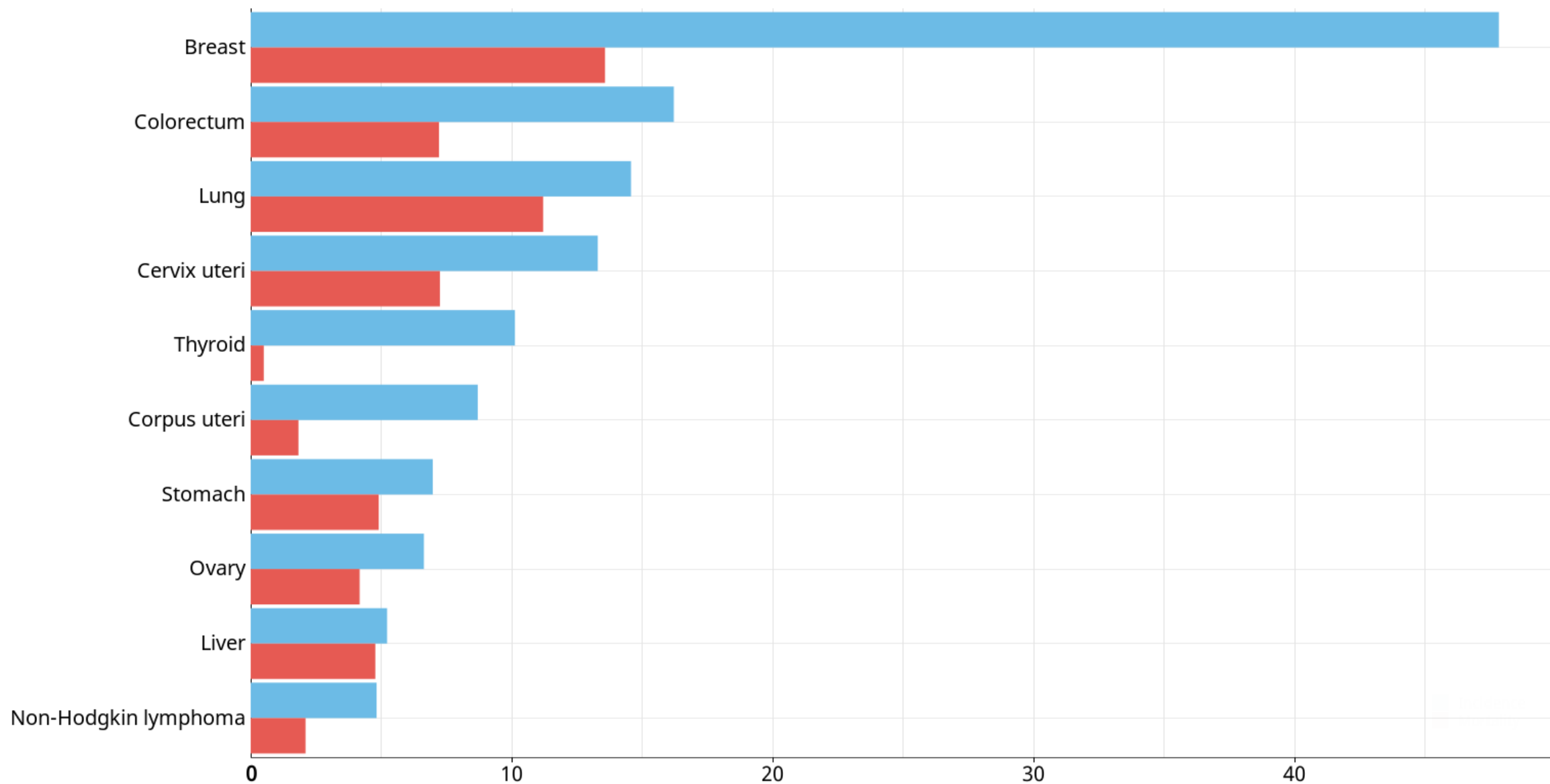


Incidence
Mortality

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



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



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

Incidence of cancer in Japanese migrants in Hawaii

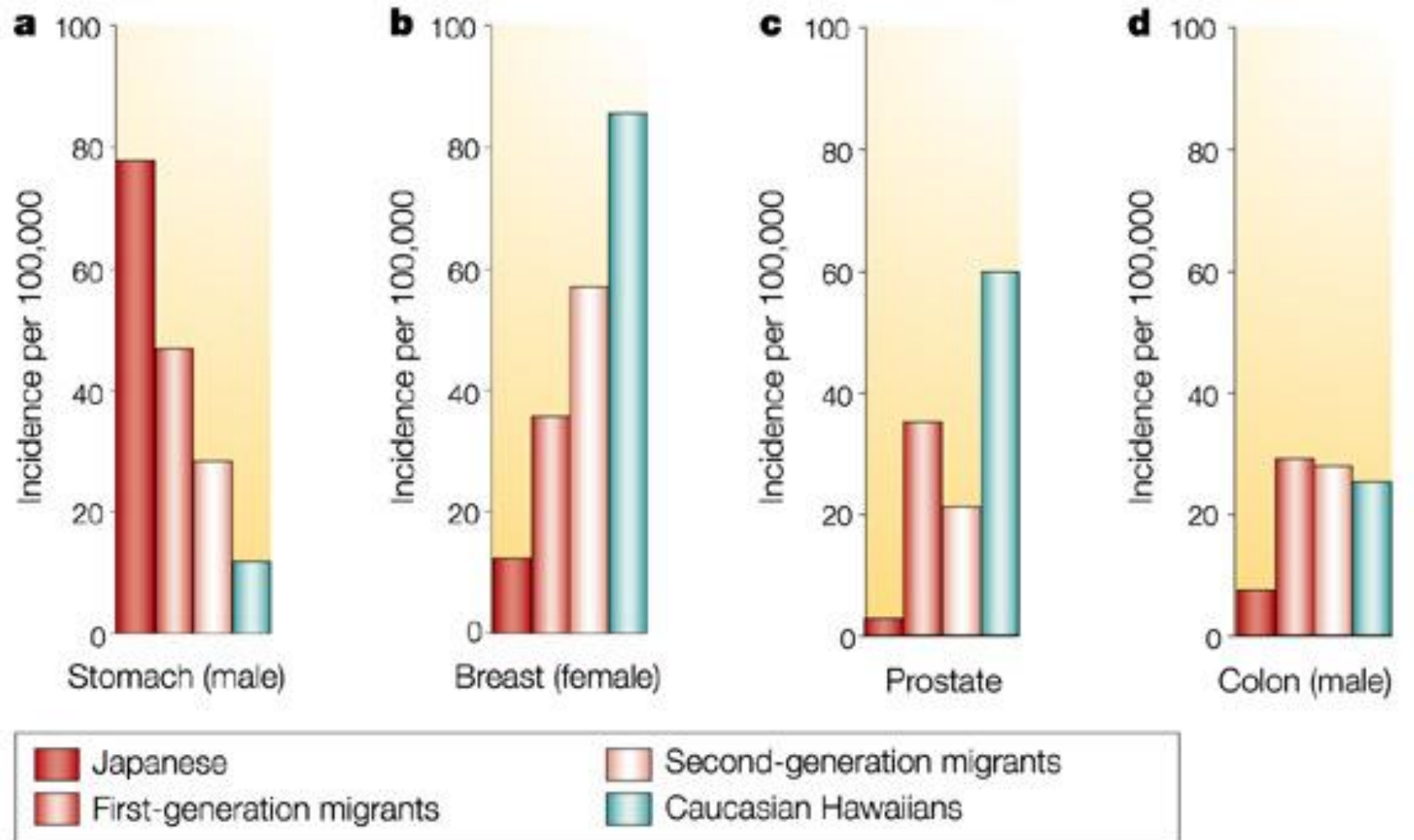


Table 2.7 Known or suspected causes of human cancers

Epidemiologic data on cancer:
Life-style and environmental effects

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

^aAdapted from Cancer Facts and Figures, American Cancer Society, 1990.

^bA large number of cancers are thought to be provoked by a diet high in calories acting in combination with many of these lifestyle factors.

^cAdapted 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 colon breast pancreas stomach esophagus prostate endometrium ovary	skin nasal cavity oropharynx larynx lung esophagus cervix	small-cell lung carcinoma large-cell lung carcinoma hepatocellular carcinoma renal cell carcinoma transitional-cell carcinoma (of urinary bladder)

mesenchymal / connective tissue cell-derived = sarcoma

hematopoietic cell-derived = lymphoma, leukemia

neuroectodermal cell-derived = glioblastoma, astrocytoma, neuroblastoma, ..

video

