ONCOLOGY: TOPICS

- The nature of cancer
- Multistep carcinogenesis
- Tumor etiology
- Molecular oncology (cf. Cancer Genetic course/module, dr. T. Venesio)
- Tumor-host interaction
- Cancer prevention, early diagnosis and treatment

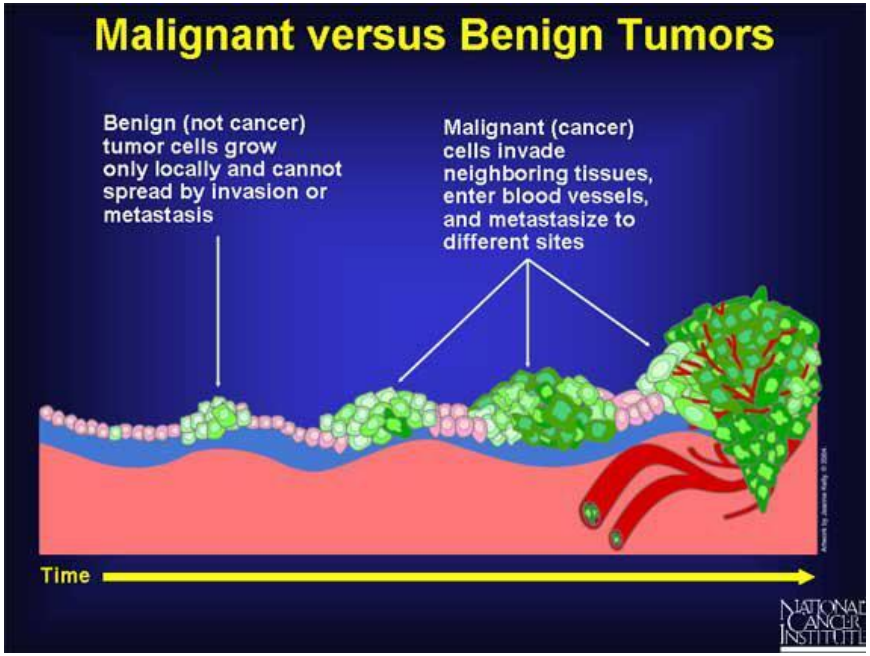
THE NATURE OF CANCER

occurring in vertebrates, invertebrates, plants

first tumor identified 100.000 years ago

originate from normal tissues, able to spread into the whole organism

tumor/neoplasia: benign or malignant (cancer)



TUMORS AS GENETIC DISEASES OF SOMATIC CELLS

TUMORS ARE RARE DISEASES

monoclonality, heterogeneity, progressivity

MONOCLONALITY

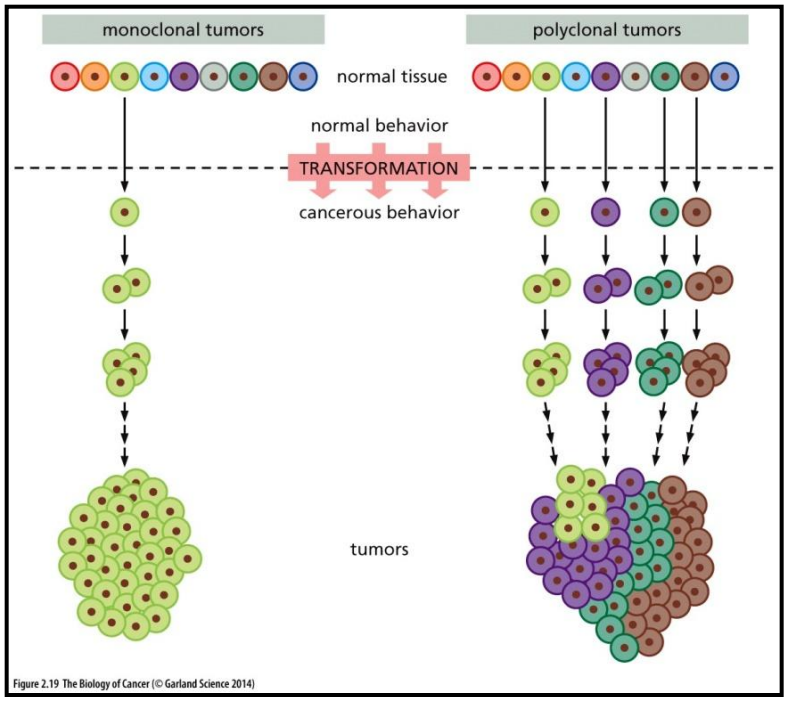
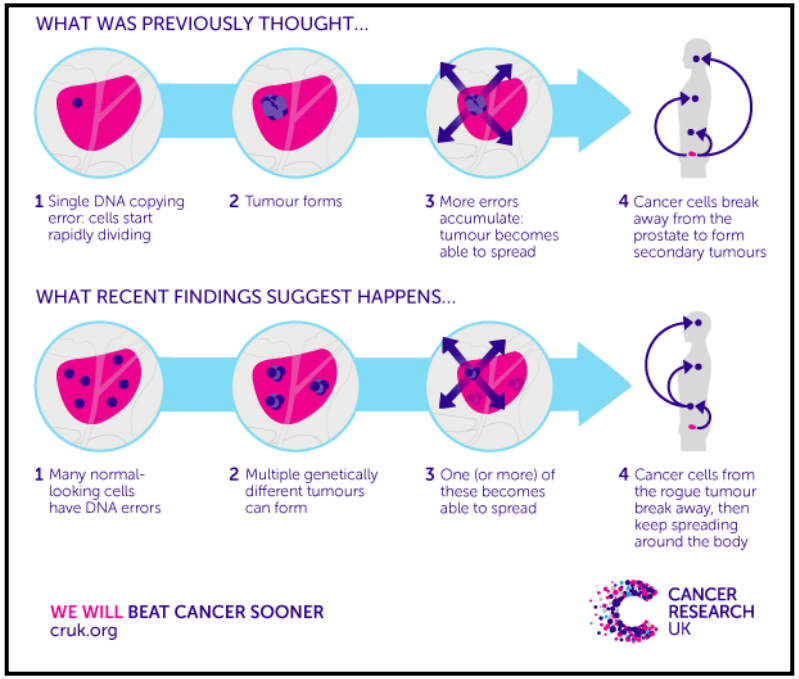


Figure 2.19 The Biology of Cancer (© Garland Science 2014)



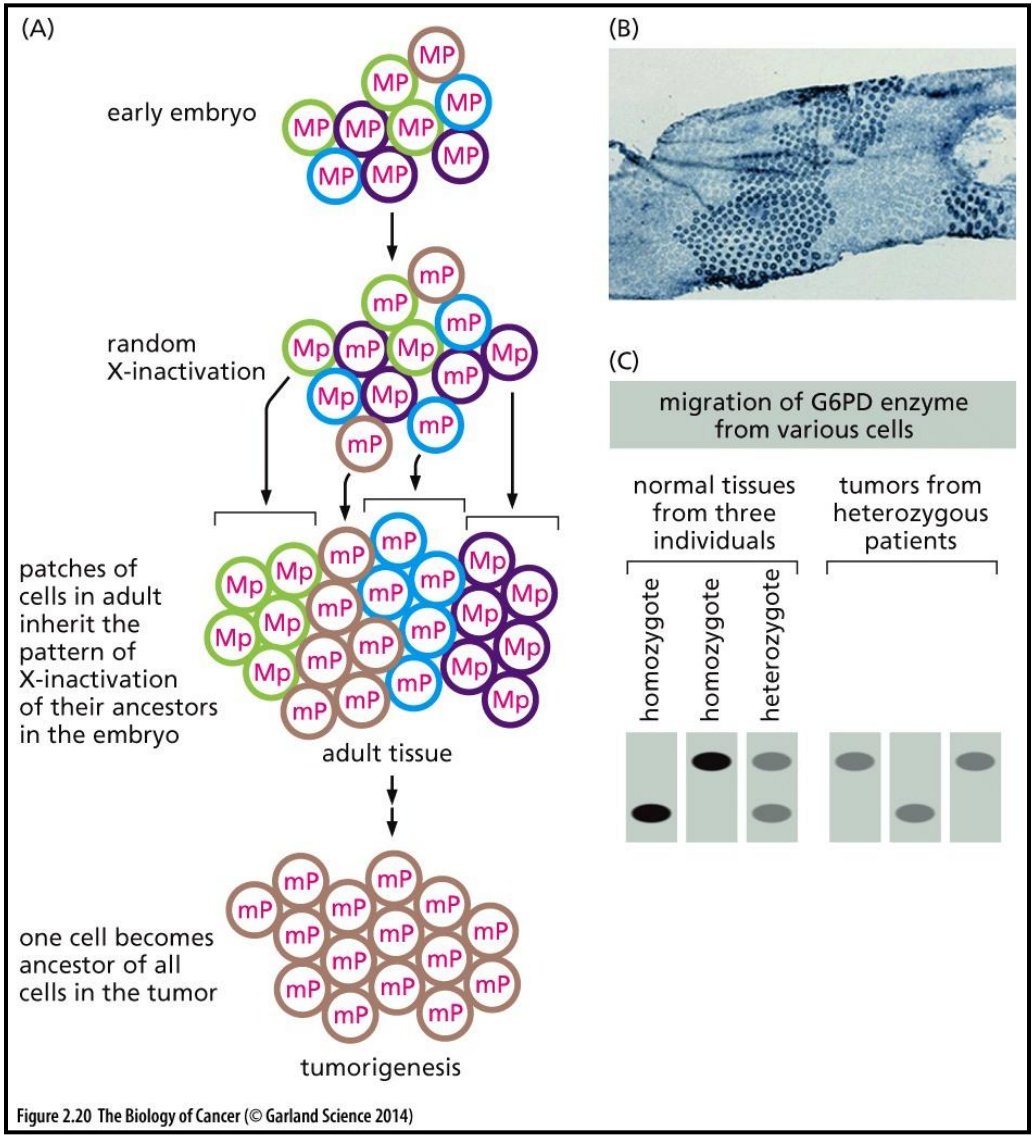
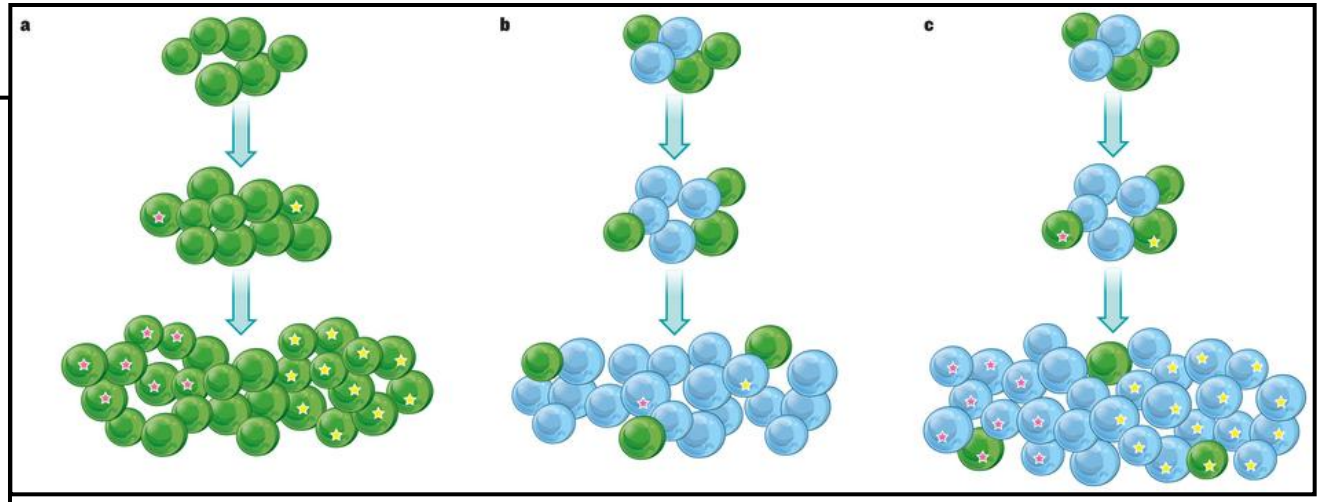


Figure 2.20 The Biology of Cancer (© Garland Science 2014)

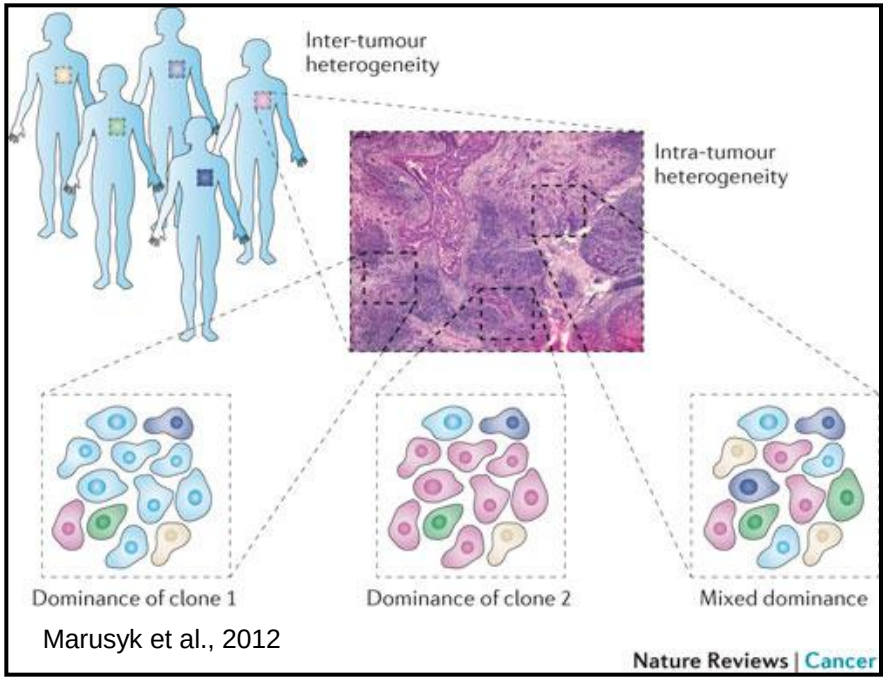
HETEROGENEITY

a, New mutations (different coloured stars) can increase the heterogeneity within tumours as long as the mutations influence cell phenotype or function. **b**, The differentiation of tumorigenic cells into non-tumorigenic progeny creates heterogeneity within tumours. New mutations that occur in non-tumorigenic cells would not be propagated (unless they restore tumorigenic potential). **c**, If mutations occur in tumorigenic cells, then both clonal evolution and the differentiation of tumorigenic cells into non-tumorigenic progeny contribute to tumour heterogeneity. This is probably what occurs in cancers that follow the stem-cell model. This means that phenotypic and functional differences cannot automatically be ascribed to epigenetic differences among tumorigenic and non-tumorigenic cells as genetic heterogeneity may contribute to some of those differences (Meacham & Morrison, 2013)



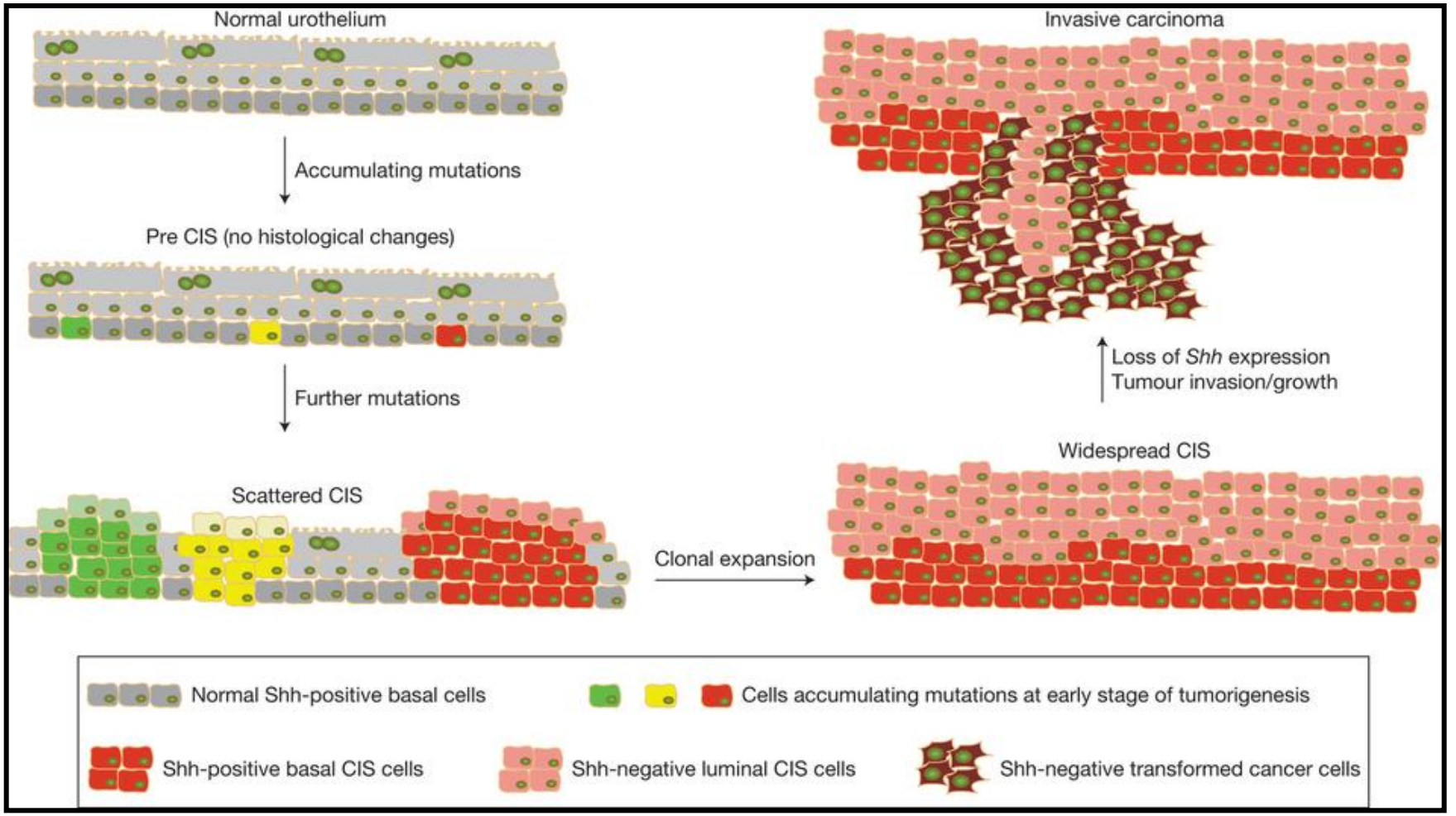
http://www.nature.com/nrc/journal/v12/n5/full/nrc3261.html

http://www.nature.com/nature/journal/v501/n7467/full/nature12624.html



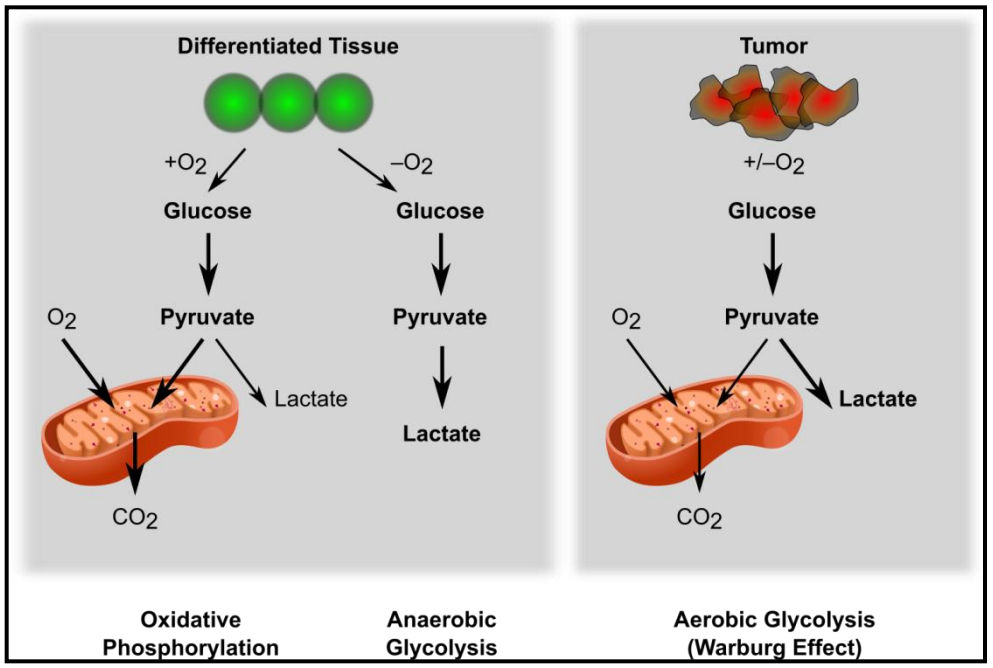
Marusyk et al., 2012

PROGRESSIVITY

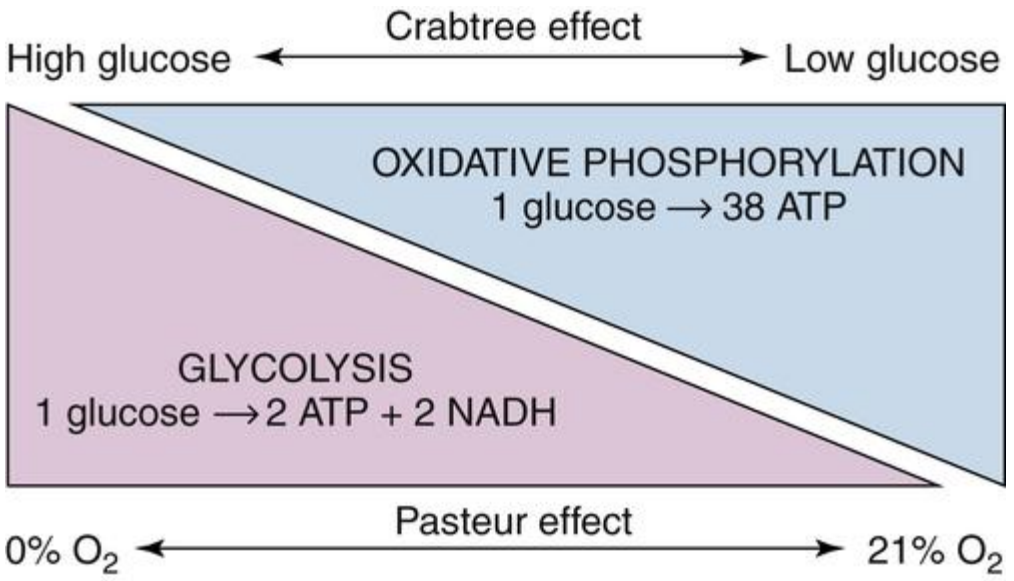


Nitrosamine-induced invasive carcinoma of the mouse bladder arises from basal stem cells that express *Shh* and CK5. Normal basal cells accumulate mutations at early stages of carcinogenesis and initiate clonal expansions to form intermediate CIS lesions, as indicated by green, yellow and red colours. During this process, one or two clones become dominant and expand to repopulate the entire urothelium, generating mono/oligo-clonal CIS (Carcinoma In Situ) lesions. CIS basal cells in one of these lesions then lose expression of *Shh* on establishment of invasive carcinoma (Shin et al., 2014).

GLUCOSE METABOLISM IS MODIFIED IN TUMOR CELLS



Vander Heiden et al., 2009, modified



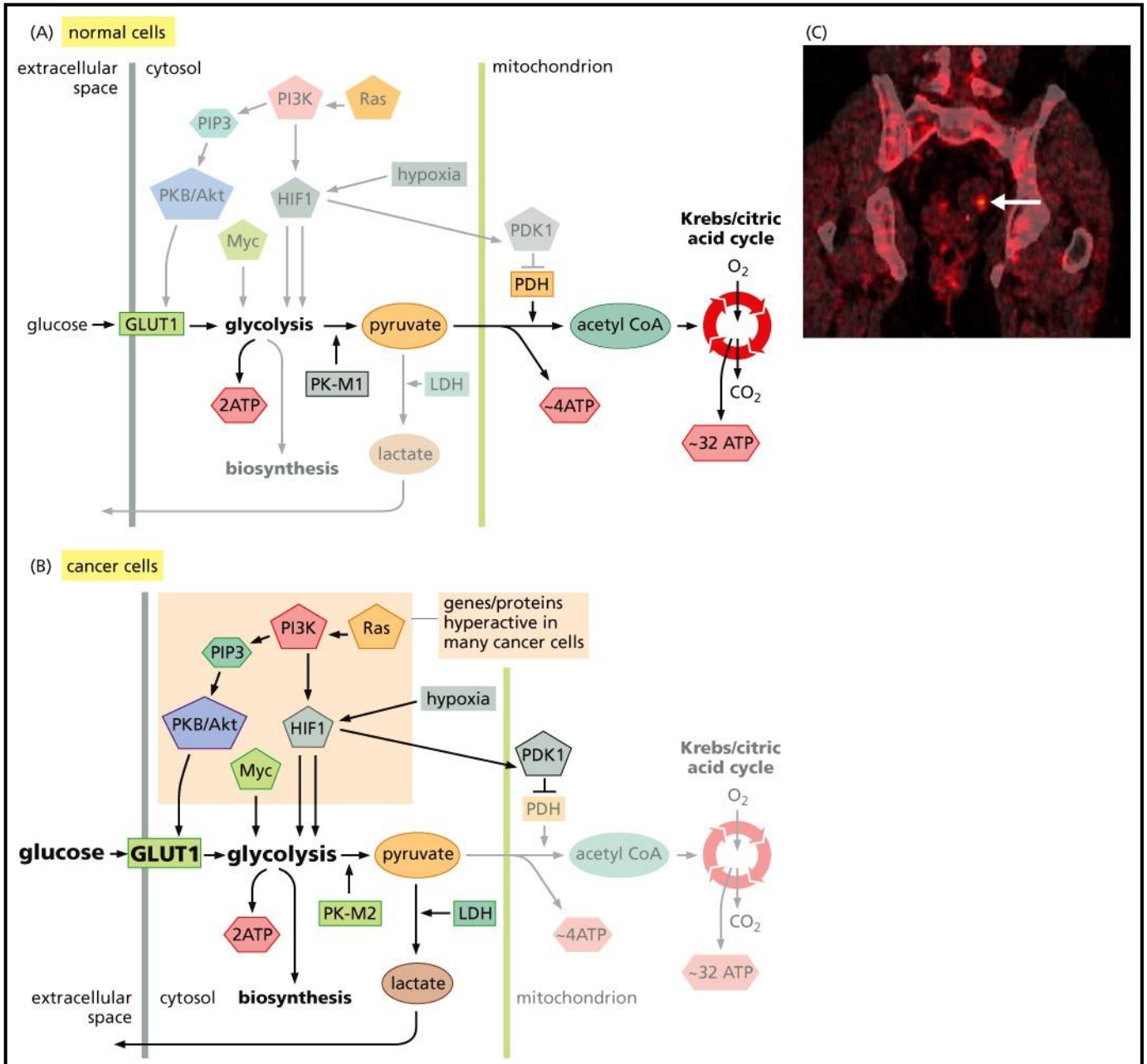


Figure 2.22 The Biology of Cancer (© Garland Science 2014)

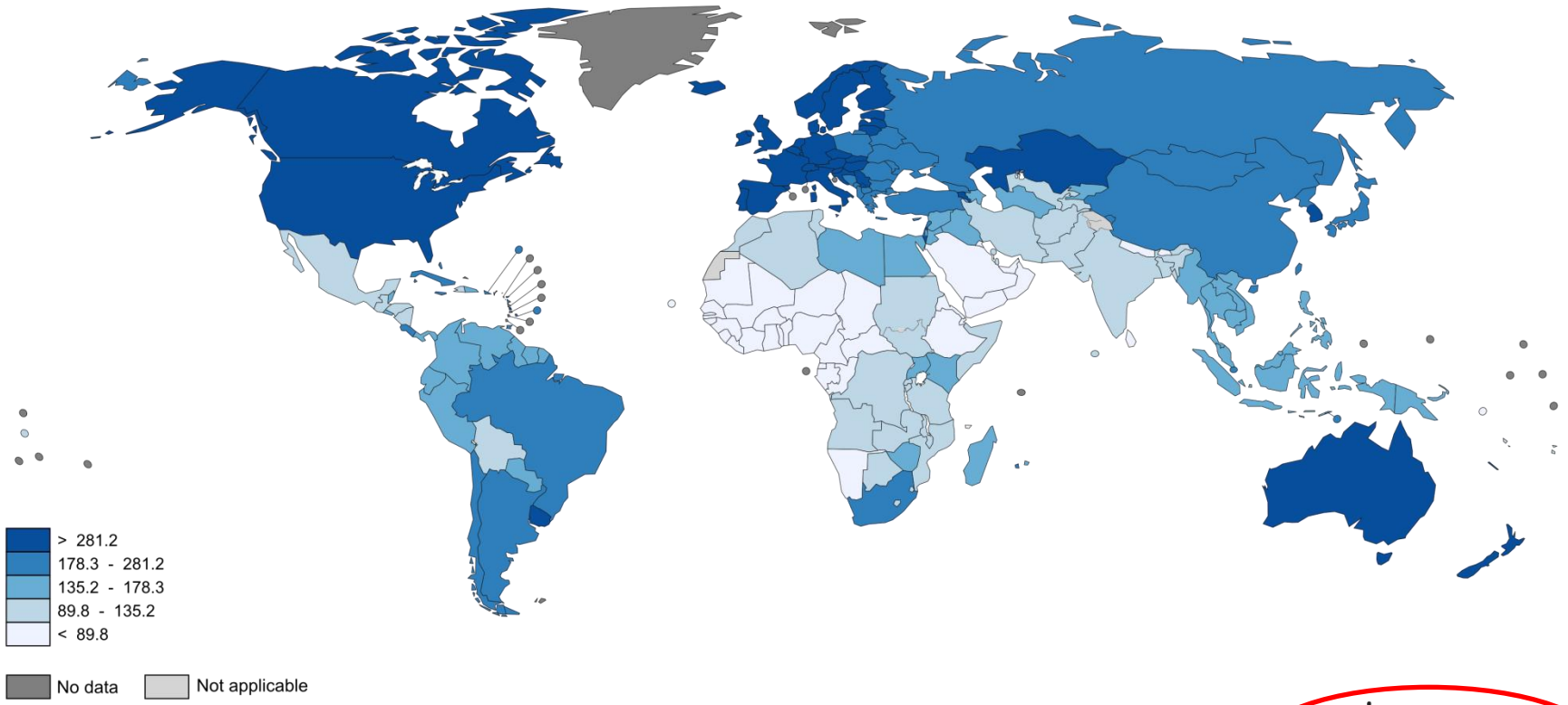
EPIDEMIOLOGY

INCIDENCE number of new cases
(absolute value or fraction of 100.000 people/year)

MORTALITY absolute value or fraction of 100.000 people/year

PREVALENCE ill people number in a specific time-point

Estimated Cancer Incidence Worldwide in 2012: Men

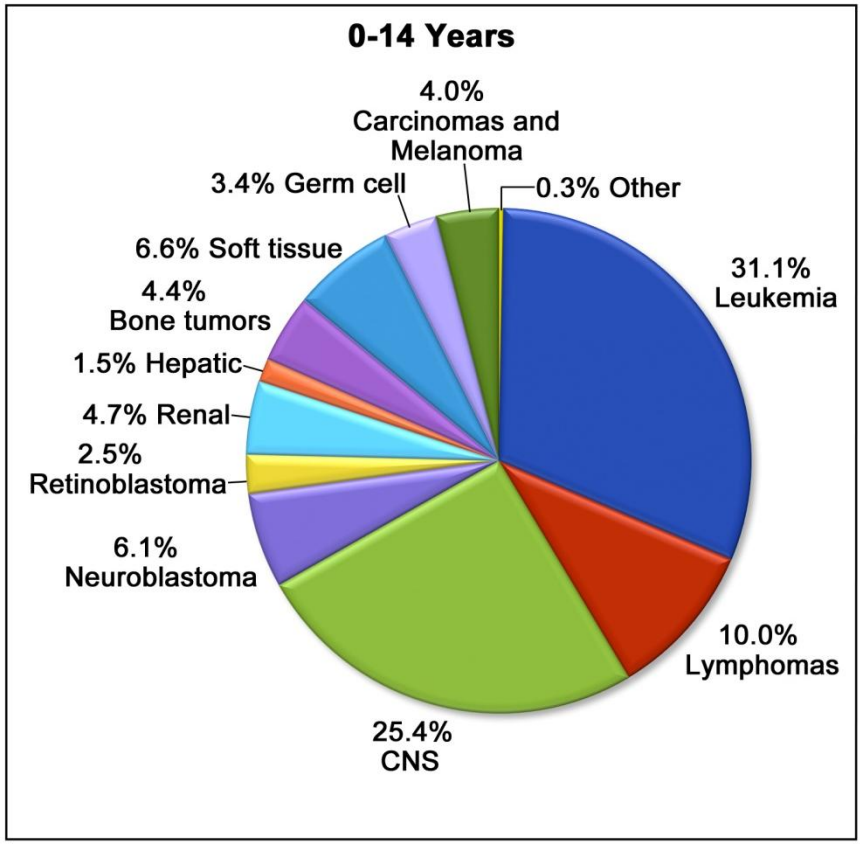


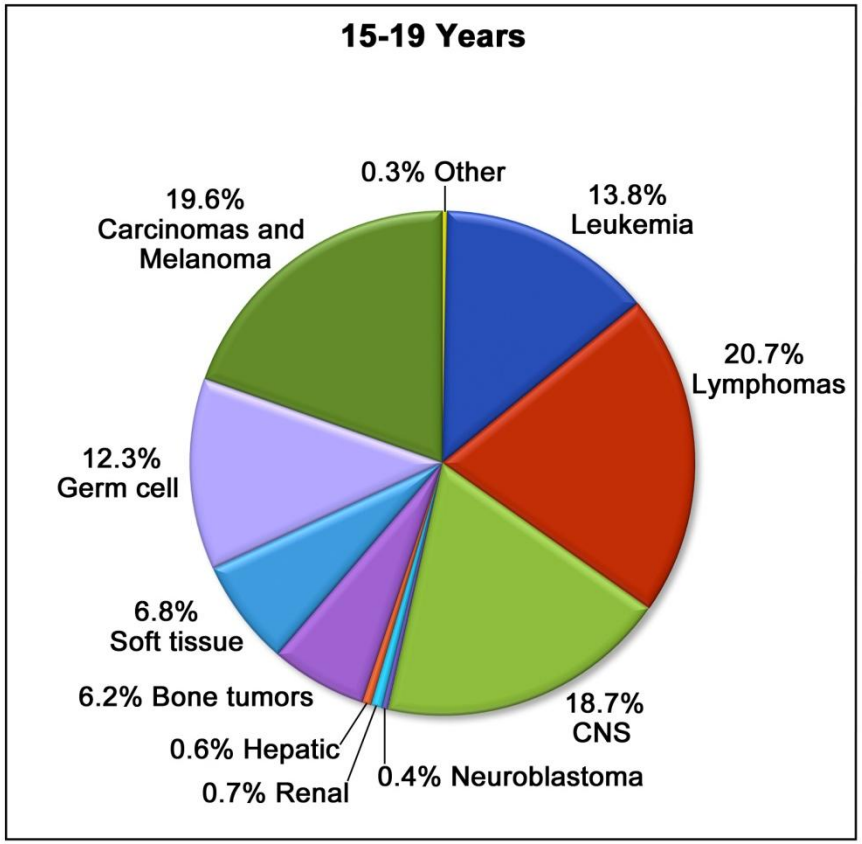
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients 0-19 Years of Age (SEER 2005-2009)





Surveillance Epidemiology and End Results (SEER) program

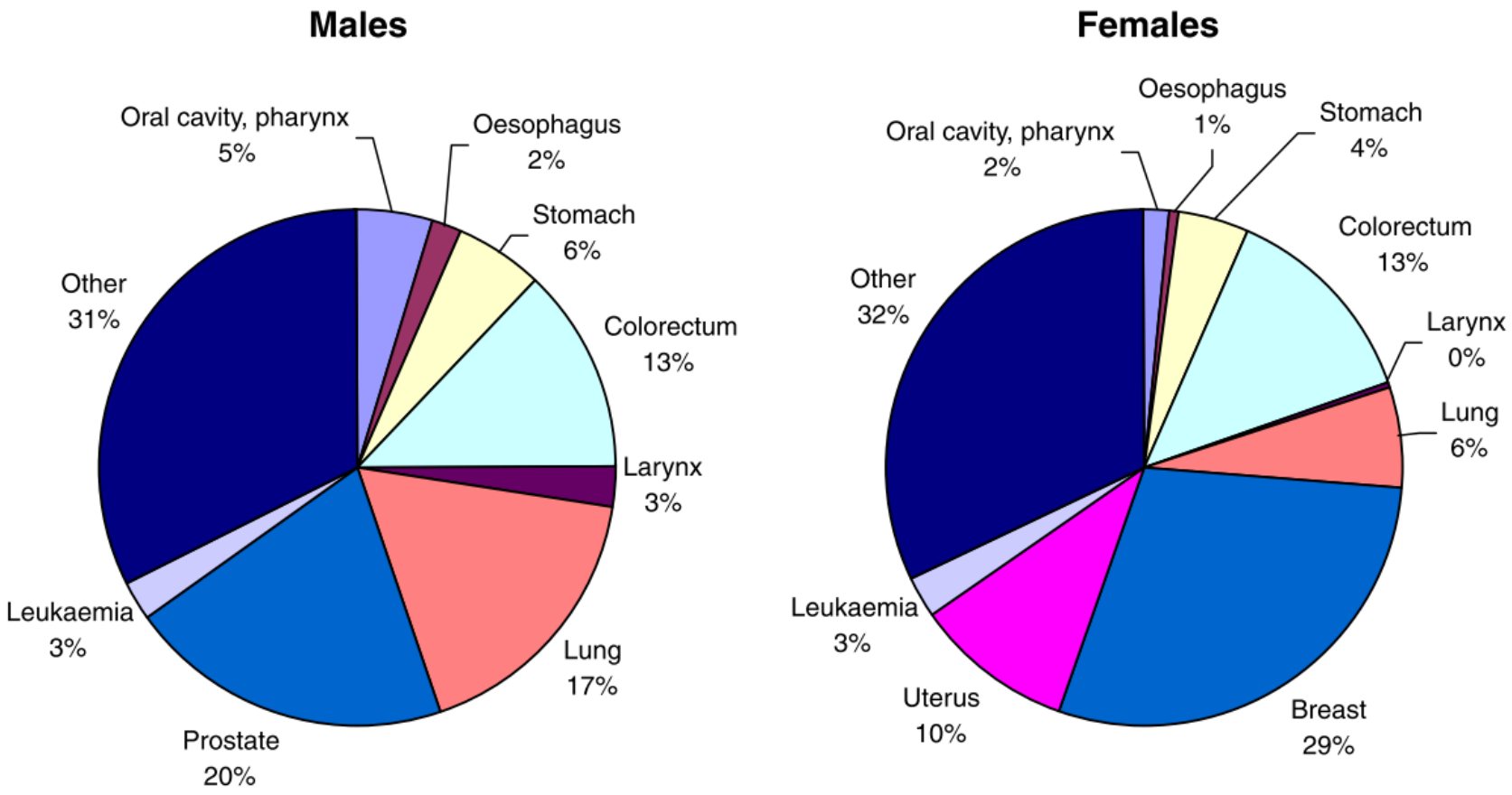
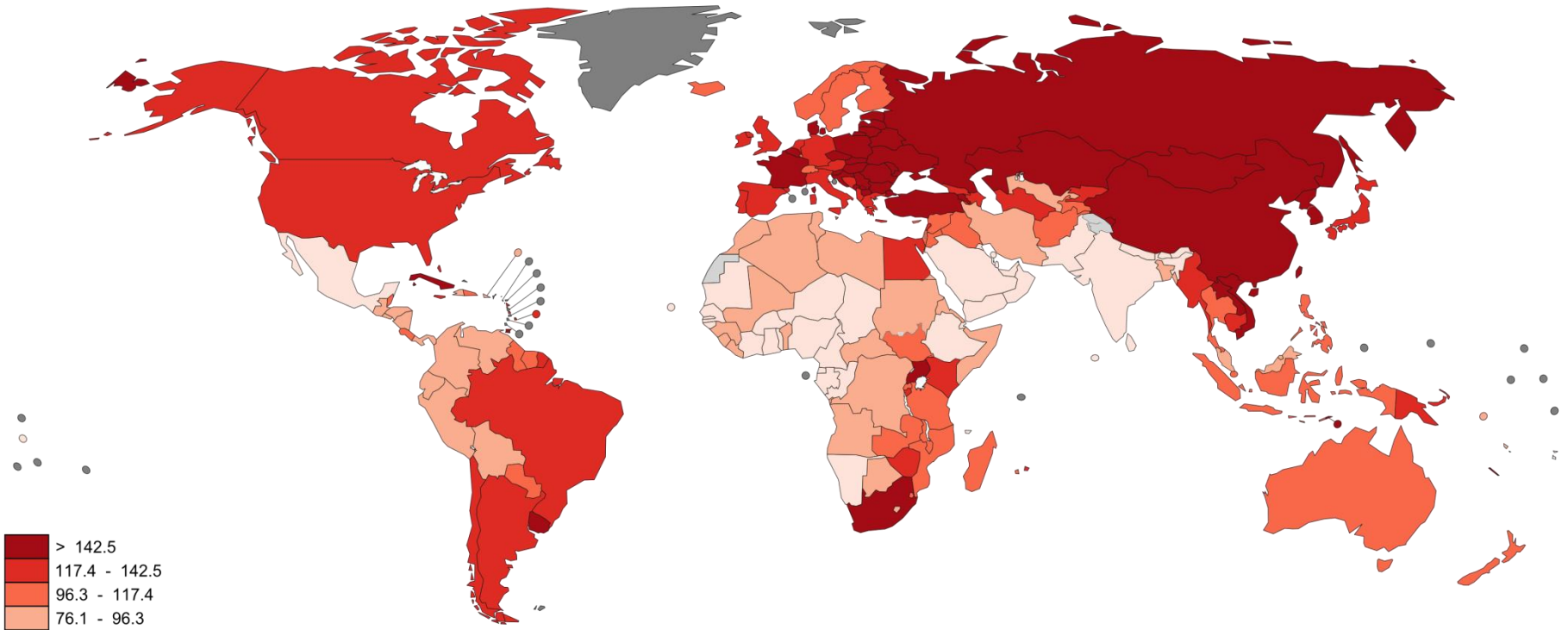


Fig. 1 – Distribution of new cancer cases in Europe by gender, 2006 Source: Ferlay et al.[2]

http://healthcare-economist.com/2013/09/05/cancer-incidence-and-deaths-in-europe/

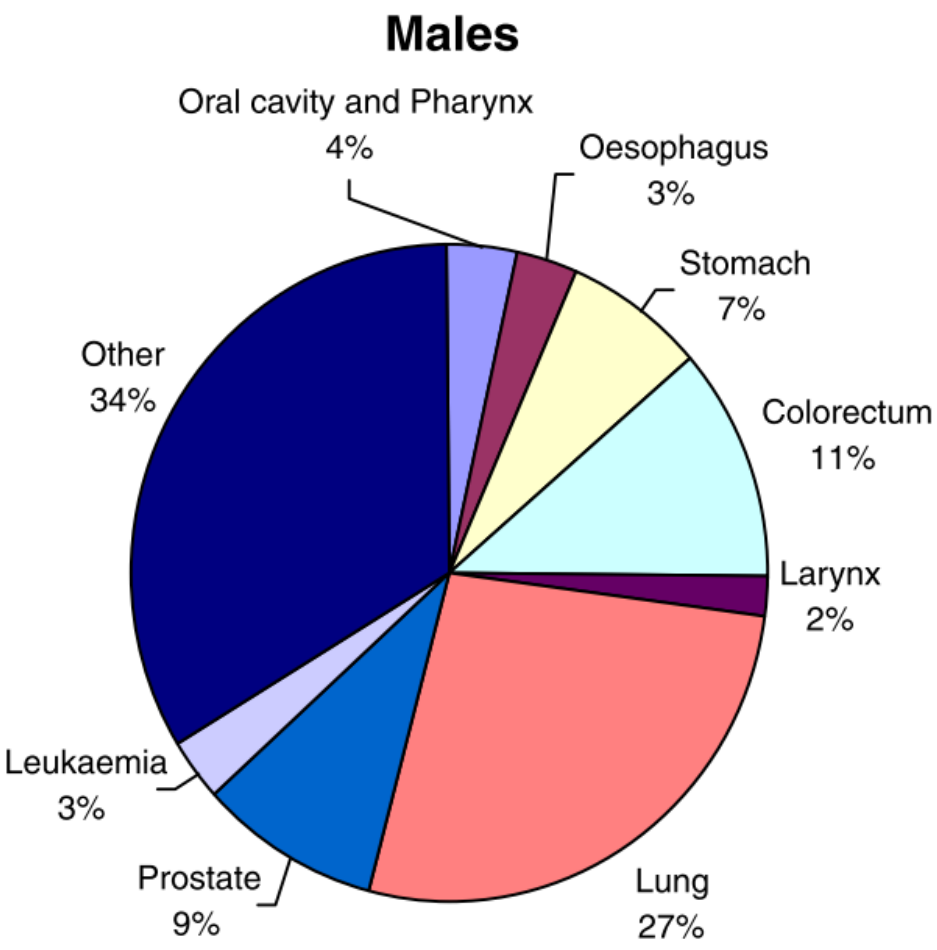
Estimated Cancer Mortality Worldwide in 2012: Men



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization



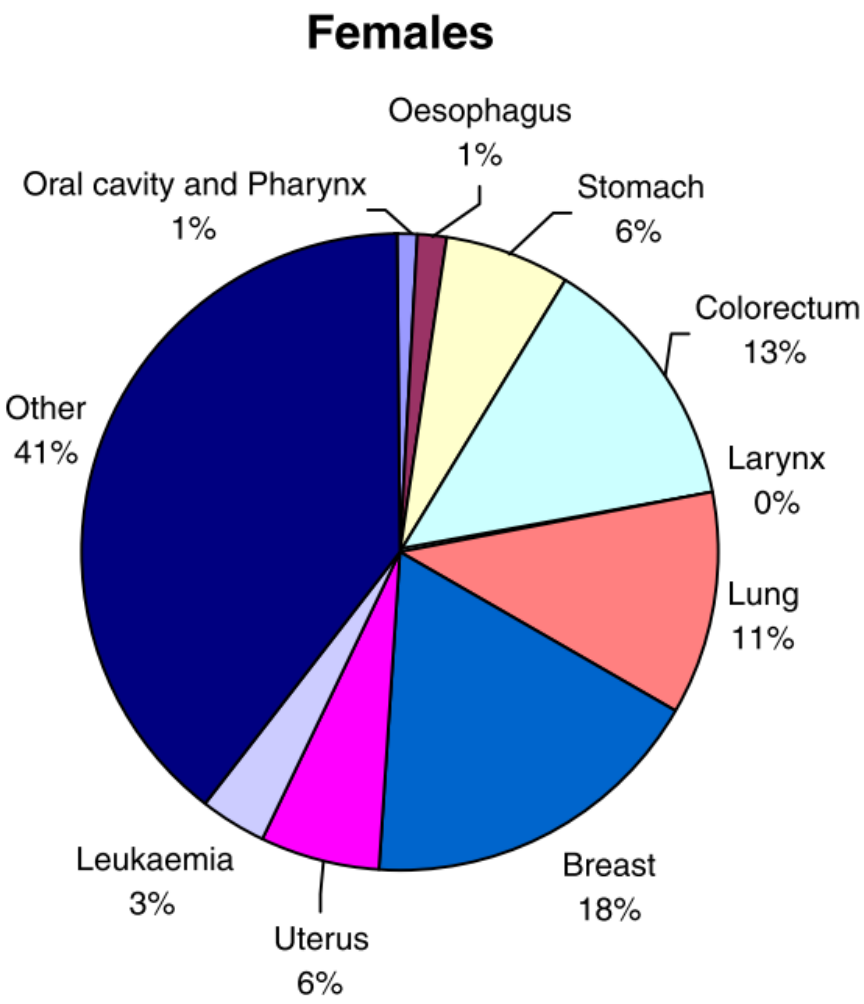
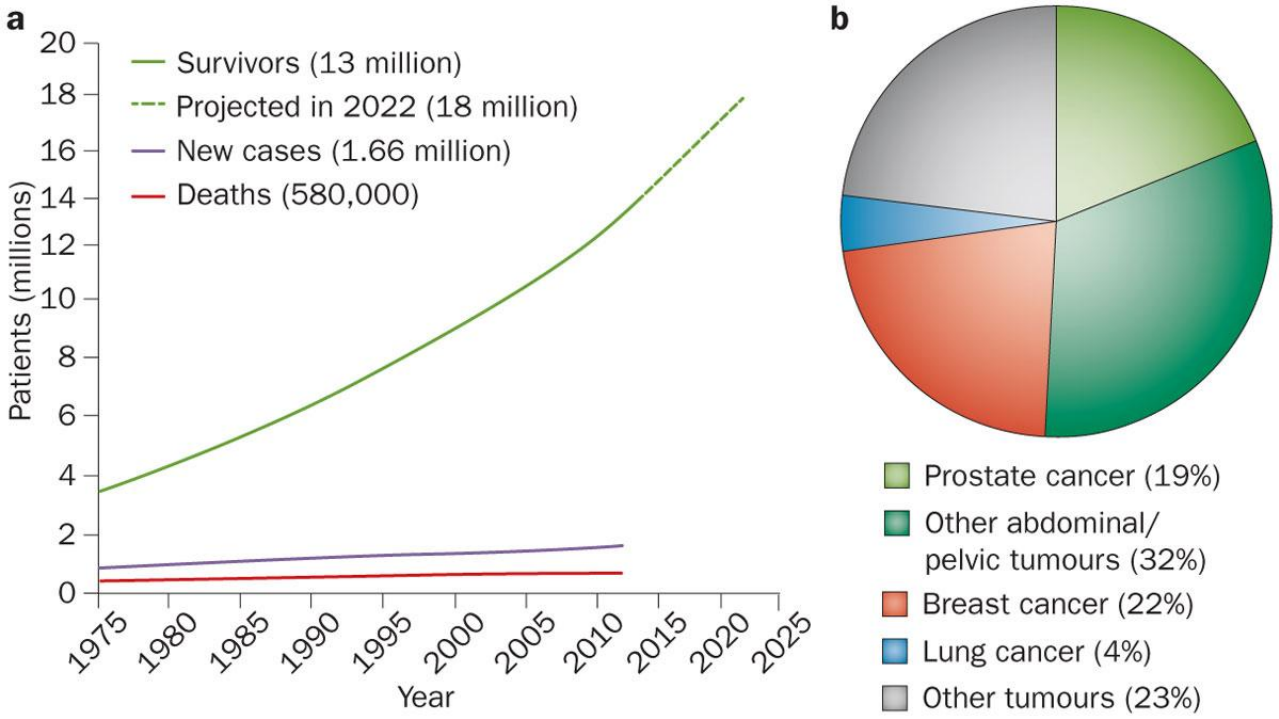


Fig. 2 – Distribution of cancer deaths in Europe by gender, 2006 Source: Ferlay et al.[2]

http://healthcare-economist.com/2013/09/05/cancer-incidence-and-deaths-in-europe/

Figure 1 Cancer survivors and cancer prevalence rates in the USA



Hauer-Jensen, M. *et al.* (2014) Radiation enteropathy—pathogenesis, treatment and prevention
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2014.46

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

TUMOR CLASSIFICATION : based on tissue of origin

CARCINOMA: from epithelial tissues (≅ 80% of human tumors)

Table 2.1 Carcinomas

Tissue sites of more common types of adenocarcinoma	Tissue sites of more common types of squamous cell carcinoma	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		

Table 2.1 The Biology of Cancer (© Garland Science 2014)

SARCOMA: from connective tissues

Table 2.2 Various types of more common sarcomas

Type of tumor	Presumed cell lineage of founding cell
Osteosarcoma	osteoblast (bone-forming cell)
Liposarcoma	adipocyte (fat cell)
Leiomyosarcoma	smooth muscle cell (e.g., in gut)
Rhabdomyosarcoma	striated/skeletal muscle cell
Malignant fibrous histiocytoma	adipocyte/muscle cell
Fibrosarcoma	fibroblast (connective tissue cell)
Angiosarcoma	endothelial cells (lining of blood vessels)
Chondrosarcoma	chondrocyte (cartilage-forming cell)

Table 2.2 The Biology of Cancer (© Garland Science 2014)

HEMATOPOIETIC malignancies

Table 2.3 Various types of more common hematopoietic malignancies

Acute lymphocytic leukemia (ALL)
Acute myelogenous leukemia (AML)
Chronic myelogenous leukemia (CML)
Chronic lymphocytic leukemia (CLL)
Multiple myeloma (MM)
Non-Hodgkin's lymphoma[a] (NHL)
Hodgkin's lymphoma (HL)

[a]The non-Hodgkin's lymphoma types, also known as lymphocytic lymphomas, can be placed in as many as 15–20 distinct subcategories, depending upon classification system.

Malignancies of the nervous system: glioma, glioblastoma, neuroblastoma, medulloblastoma, etc.

SOME EXCEPTIONS: melanoma (neural crest), small cell lung carcinoma (microcitoma, neuroectodermal cells?)
teratoma (germ cell precursors?)

TUMOR CLASSIFICATION : clinical/histological

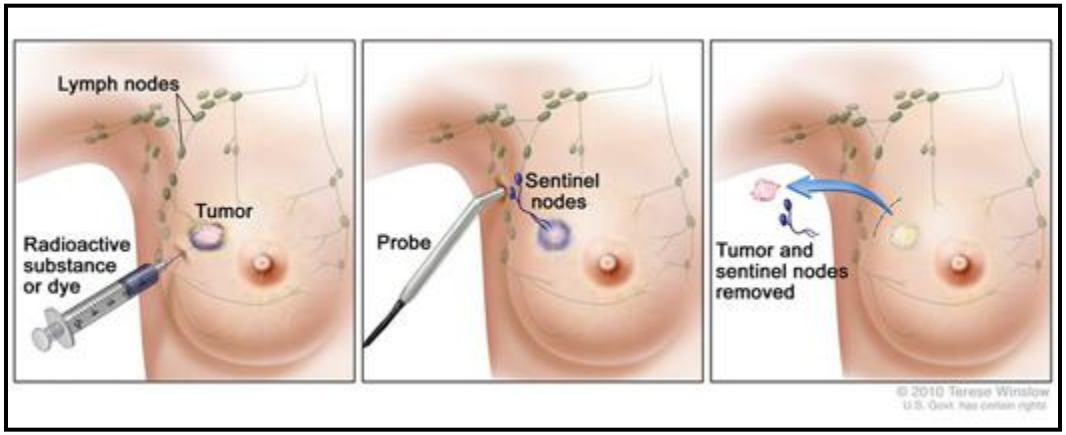
TNM: clinical classification
T = tumor
N = lymph nodes
M = metastasis

Grading: histological classification
grade of differentiation

TNM Classification (American Joint Commission on Cancer)				Dukes' Classification
Stages	T	N	M	Stages
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	B1
Stage II	T3	N0	M0	B2
	T4	N0	M0	B2
Stage III	T1, T2	N1 or N2	M0	C1
	T3, T4	N1 or N2	M0	C2
Stage IV	Any T	Any N	M1	D

http://breastcancerhelp.net/do-you-know-what-is-tnm-breast-cancer-staging/

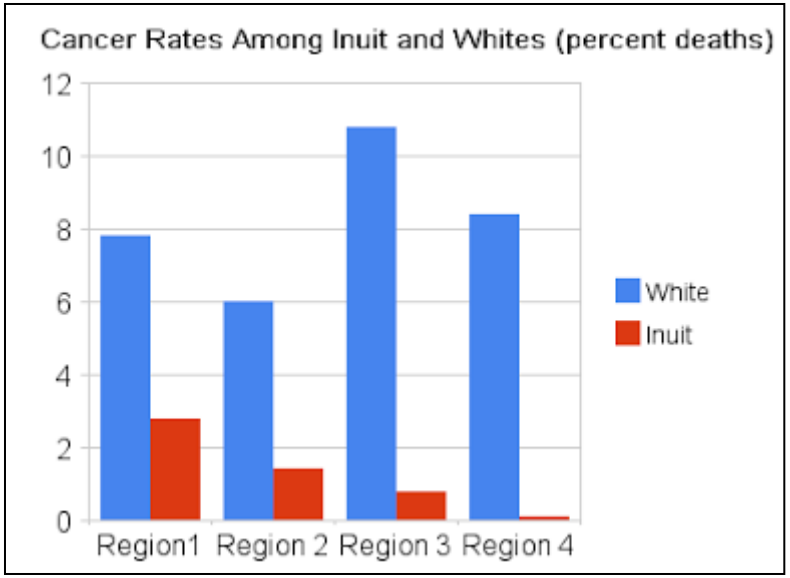
SENTINEL LYMPH NODE: international standard from 2003



Sentinel lymph node biopsy of the breast. A radioactive substance and/or blue dye is injected near the tumor (first panel). The injected material is located visually and/or with a device that detects radioactivity (middle panel). The sentinel node(s) (the first lymph node(s) to take up the material) is (are) removed and checked for cancer cells (last panel).

https://www.cancer.gov/about-cancer/diagnosis-staging/staging/sentinel-node-biopsy-fact-sheet

LIFESTYLE AND CANCER



Top six causes of all cancers in men and women

Risk factors of the 158,700 cancers diagnosed in men and 155,600 cancers diagnosed in women each year

Ranking		Risk factor %		Risk factor %
1	Tobacco	23	Tobacco	15.6
2	Lack of fruit & vegetables	6.1	Overweight	6.9
3	Occupational hazard	4.9	Infection	3.7
4	Alcohol	4.6	Exposure to sun & sunbeds	3.6
5	Overweight	4.1	Lack of fruit & vegetables	3.4
6	Exposure to sun & sunbeds	3.5	Alcohol	3.3

Source: Cancer Research UK

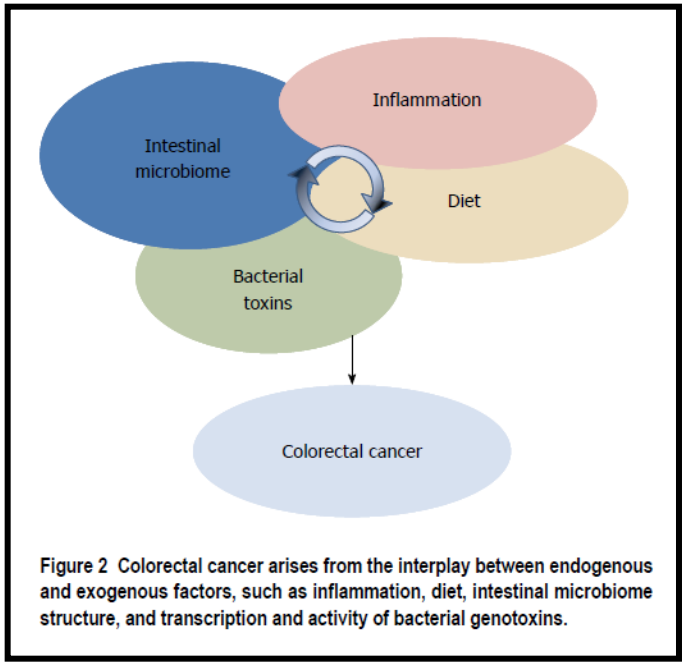


Figure 2 Colorectal cancer arises from the interplay between endogenous and exogenous factors, such as inflammation, diet, intestinal microbiome structure, and transcription and activity of bacterial genotoxins.

Candela et al., 2014

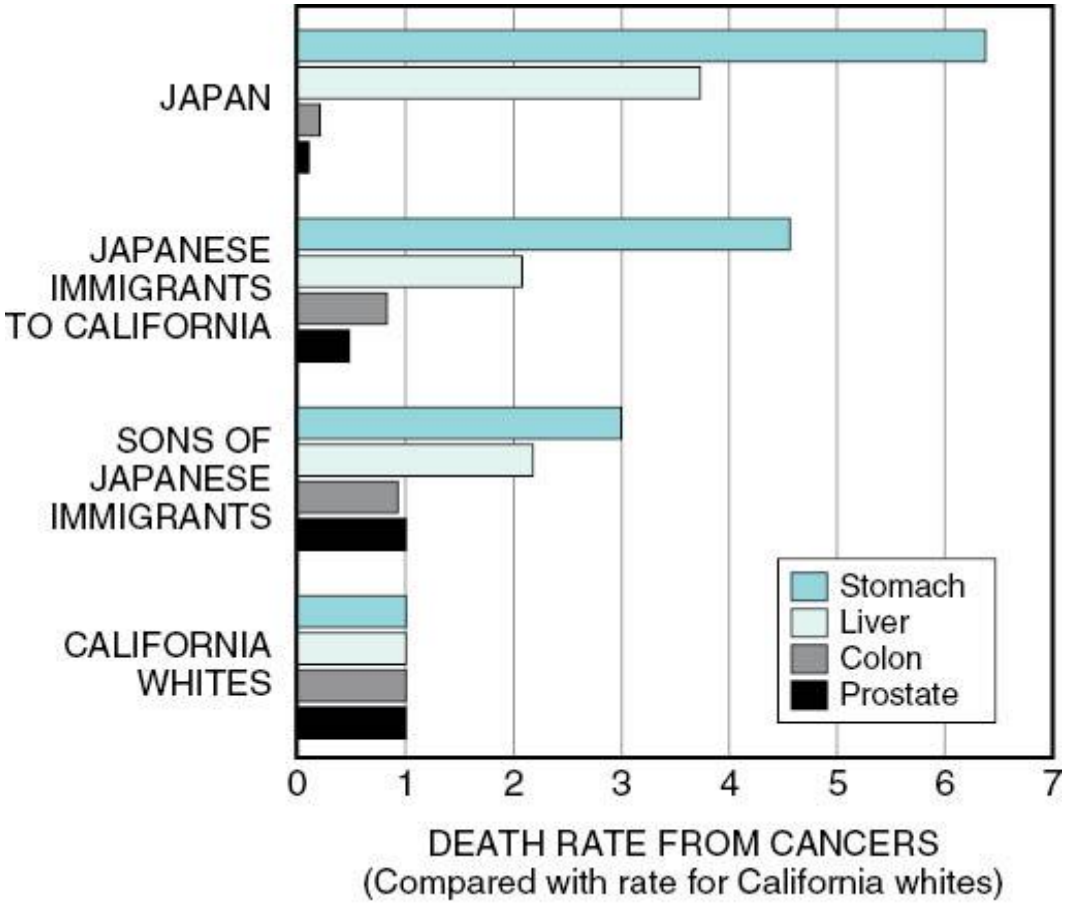


FIGURE 7–22 The change in incidence of various cancers with migration from Japan to the United States provides evidence that the occurrence of cancers is related to components of the environment that differ in the two countries. The incidence of each kind of cancer is expressed as the ratio of the death rate in the population being considered to that in a hypothetical population of California whites with the same age distribution; the death rates for whites are thus defined as 1. The death rates among immigrants and immigrants' sons tend consistently toward California norms.

(From Cairns J: The cancer problem. In Readings from Scientific American—Cancer Biology. New York, WH Freeman, 1986, p 13.)

NUTRITION AND CANCER: EPIGENETIC EFFECTS

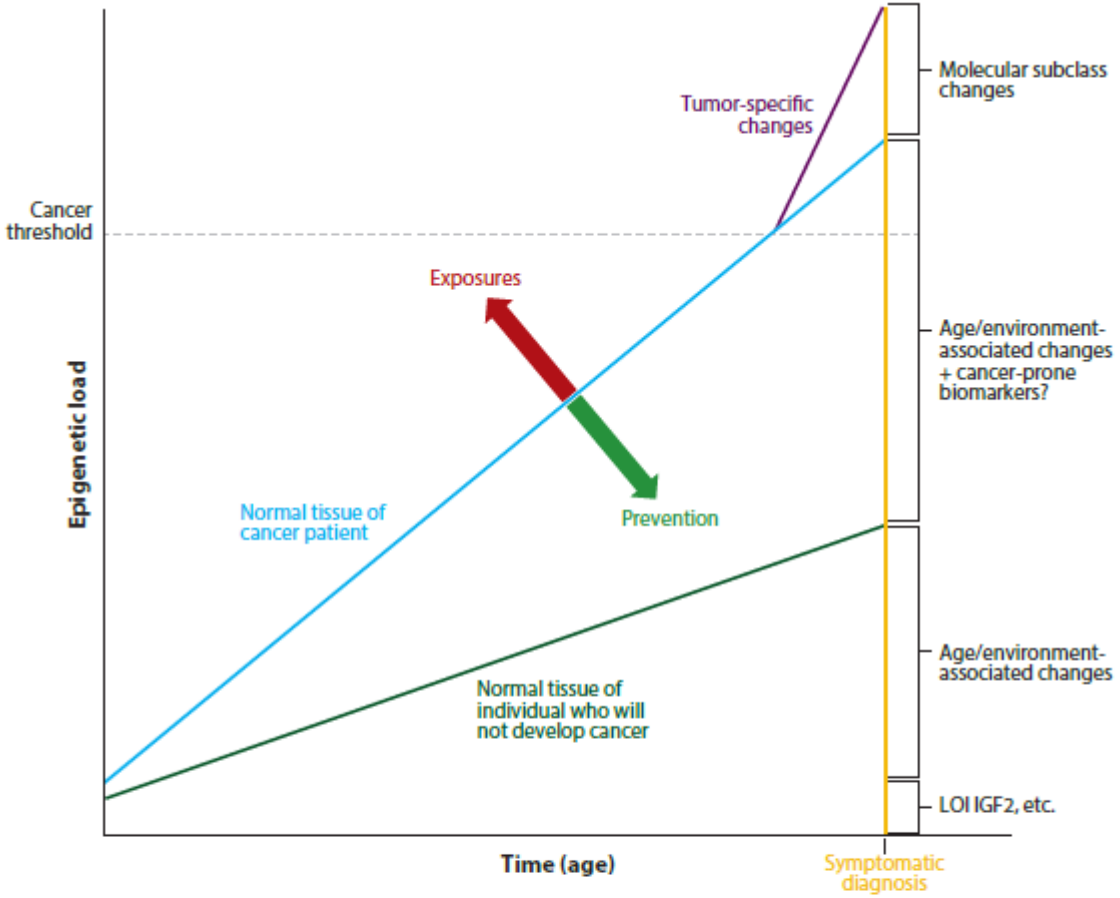


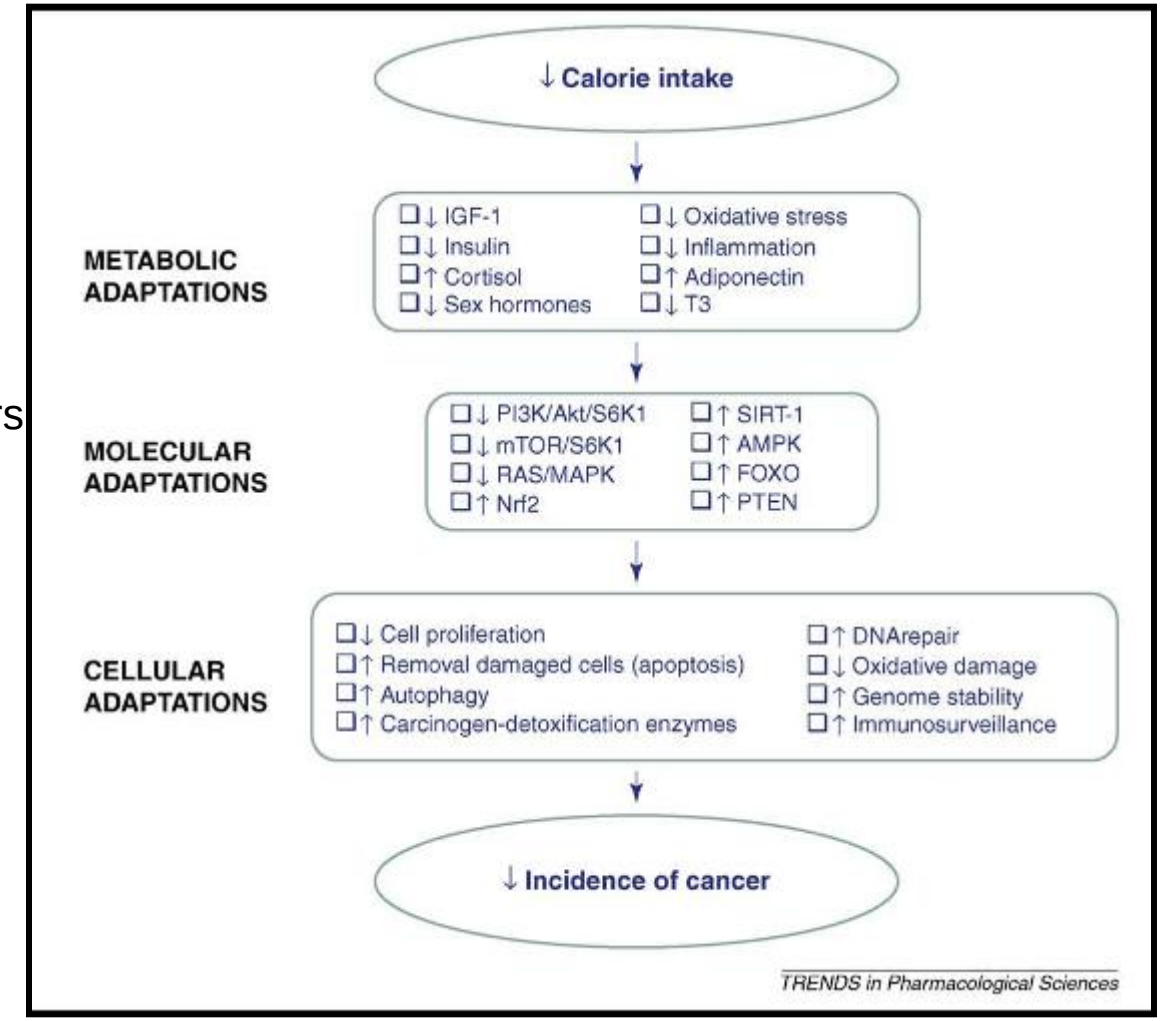
Figure 2

The molecular fossil record hypothesis for age- and environment-related epigenetic modifications and their relationship to cancer. Each individual is assumed to have been born with some level of epigenetic (and genetic) risk for cancer [e.g., loss of imprinting (LOI) at *IGF2*]. As individuals age, age-related (e.g., methylation loss through stem cell divisions, spontaneous deamination) and environmental exposure-related (e.g., folate supplementation, inflammation; see **Figure 1**) alterations occur, increasing epigenetic load. Individuals who accumulate epigenetic load at a slower rate are unlikely to develop cancer, whereas others accumulate changes at a rate sufficient to cross the threshold required for tumor promotion. Dietary factors may increase (exposures) or decrease (prevention) the rate of accumulation of epigenetic load.

Sapienza and Issa, 2016

CALORIC RESTRICTION AND CANCER

Moreschi, 1909:
caloric restriction inhibits the growth of experimental tumors



Mechanisms for cancer prevention by CR. CR causes several key metabolic/hormonal adaptations that alter the expression of several genes and signaling pathways (upregulation of certain genes/signaling pathways and downregulation of others as indicated by the arrows), which produce major cellular adaptations (e.g. a reduction in cell proliferation, increased removal of damaged organelles or cells via autophagy or apoptosis, upregulation of DNA repair systems and genomic stability) that result in a reduced cancer incidence (see the text). T3 = triiodothyronine; PI3K = phosphatidylinositol-3 kinase; AKT = kinase AKT, also known as protein kinase B; S6K1 = ribosomal S6 protein kinase 1; mTOR = mammalian target of rapamycin; MAPK = mitogen-activated protein kinase; NRF2 = transcription factors NF-E2-related factor 2; SIRT-1 = silent mating type information regulation 2 homolog 1; AMPK = adenosine monophosphate (AMP)-activated protein kinase; FOXO = Forkhead transcription factors; PTEN = phosphatase and tensin homolog (Longo and Fontana, 2010).

MODULATORS OF CARCINOGENESIS

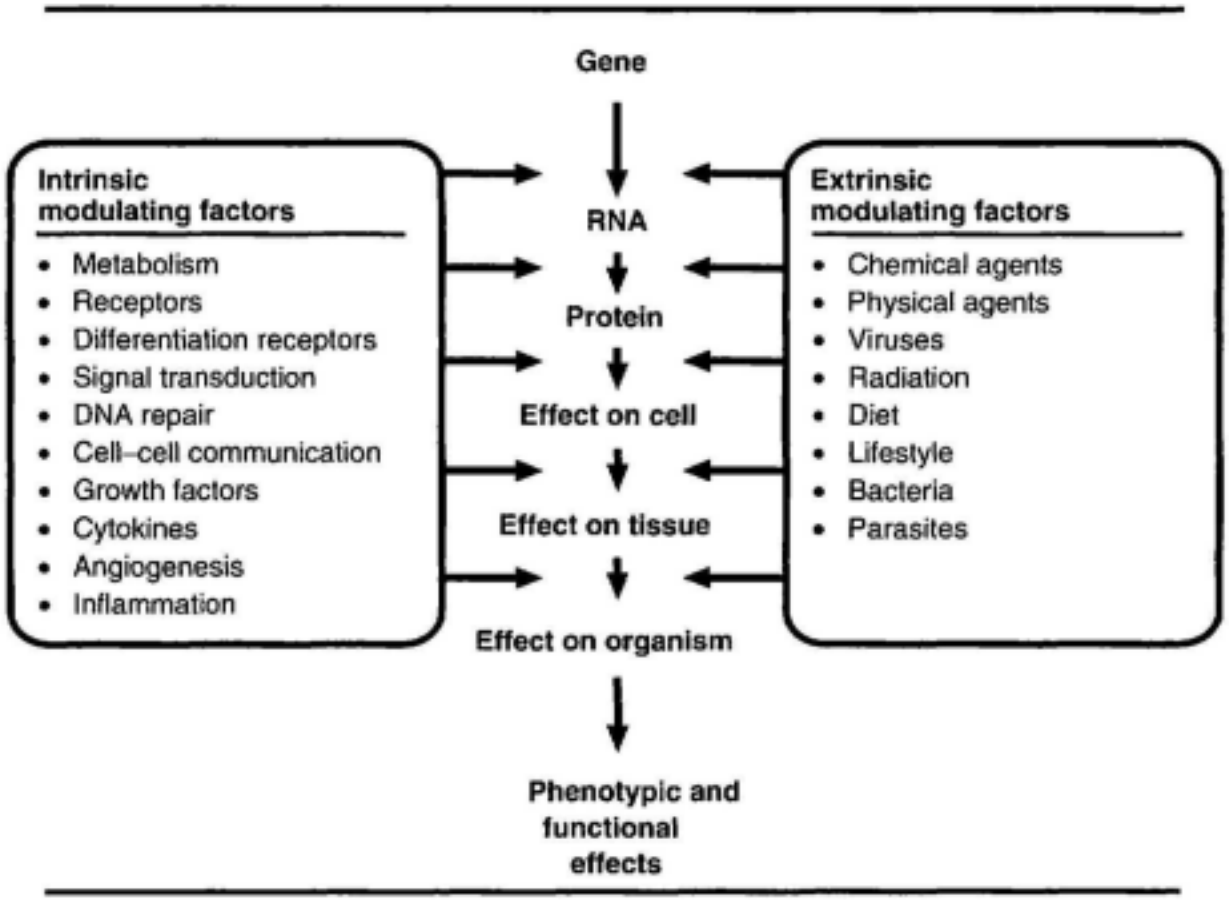
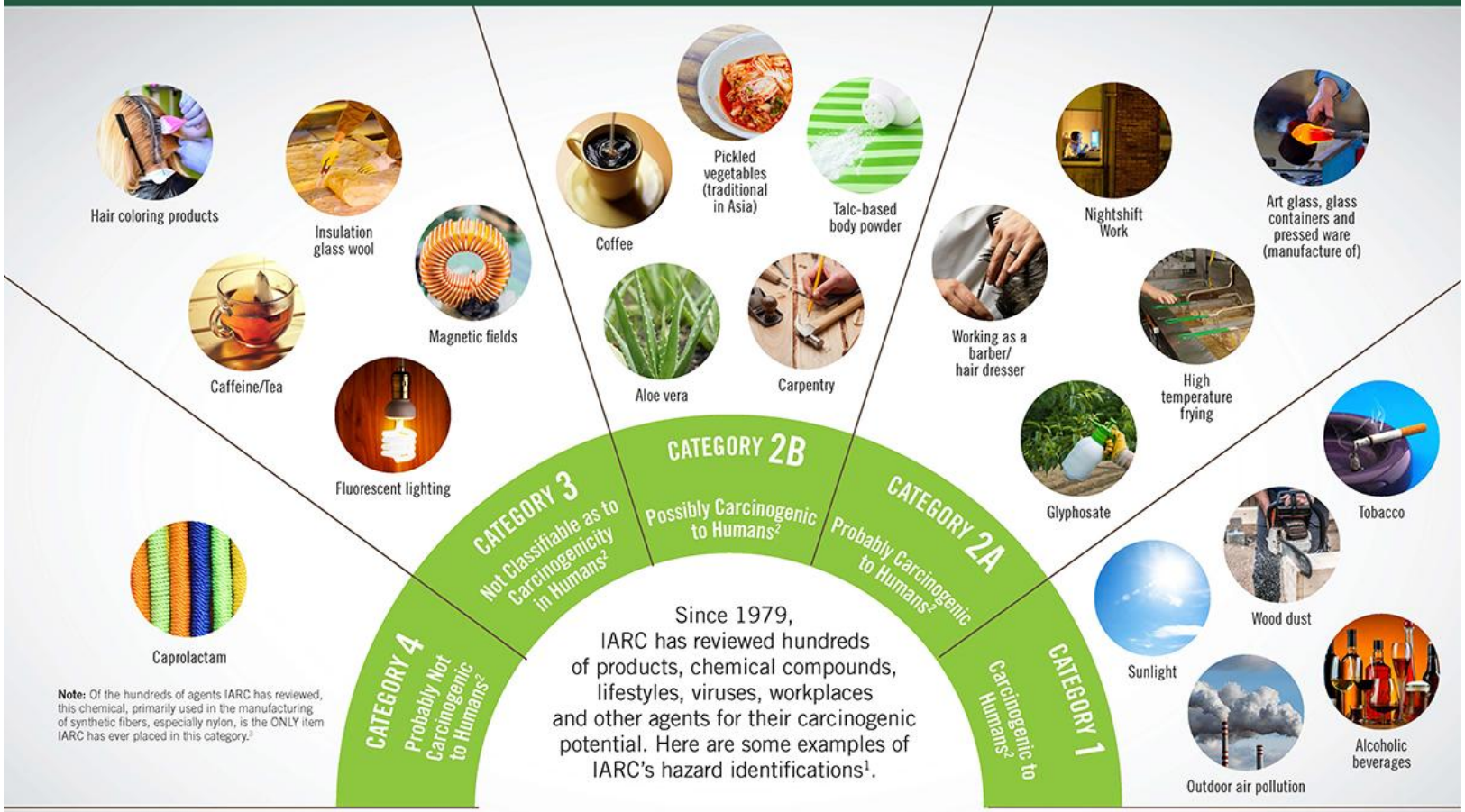


Figure 6 Intrinsic and extrinsic factors modulating specific gene expression and its effect on tissue phenotype and function.

http://focusontoxpath.com/carcinogenesis/

Examples of International Agency for Research on Cancer (IARC) Carcinogenic Classifications

gmo answers



Note: Of the hundreds of agents IARC has reviewed, this chemical, primarily used in the manufacturing of synthetic fibers, especially nylon, is the ONLY item IARC has ever placed in this category.[3]

Since 1979, IARC has reviewed hundreds of products, chemical compounds, lifestyles, viruses, workplaces and other agents for their carcinogenic potential. Here are some examples of IARC's hazard identifications[1].

[1] http://www.24d.reviews/IARC-and-24D.php
[2] http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf
[3] http://www.epa.gov/ttnatw01/hlthef/caprolac.html