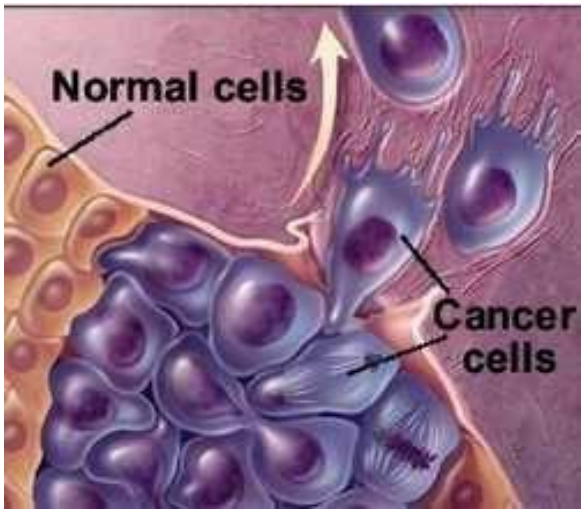
Corso di Laurea in Dietistica

Oncologia

Lezione 2: *Fattori di rischio modificabili*

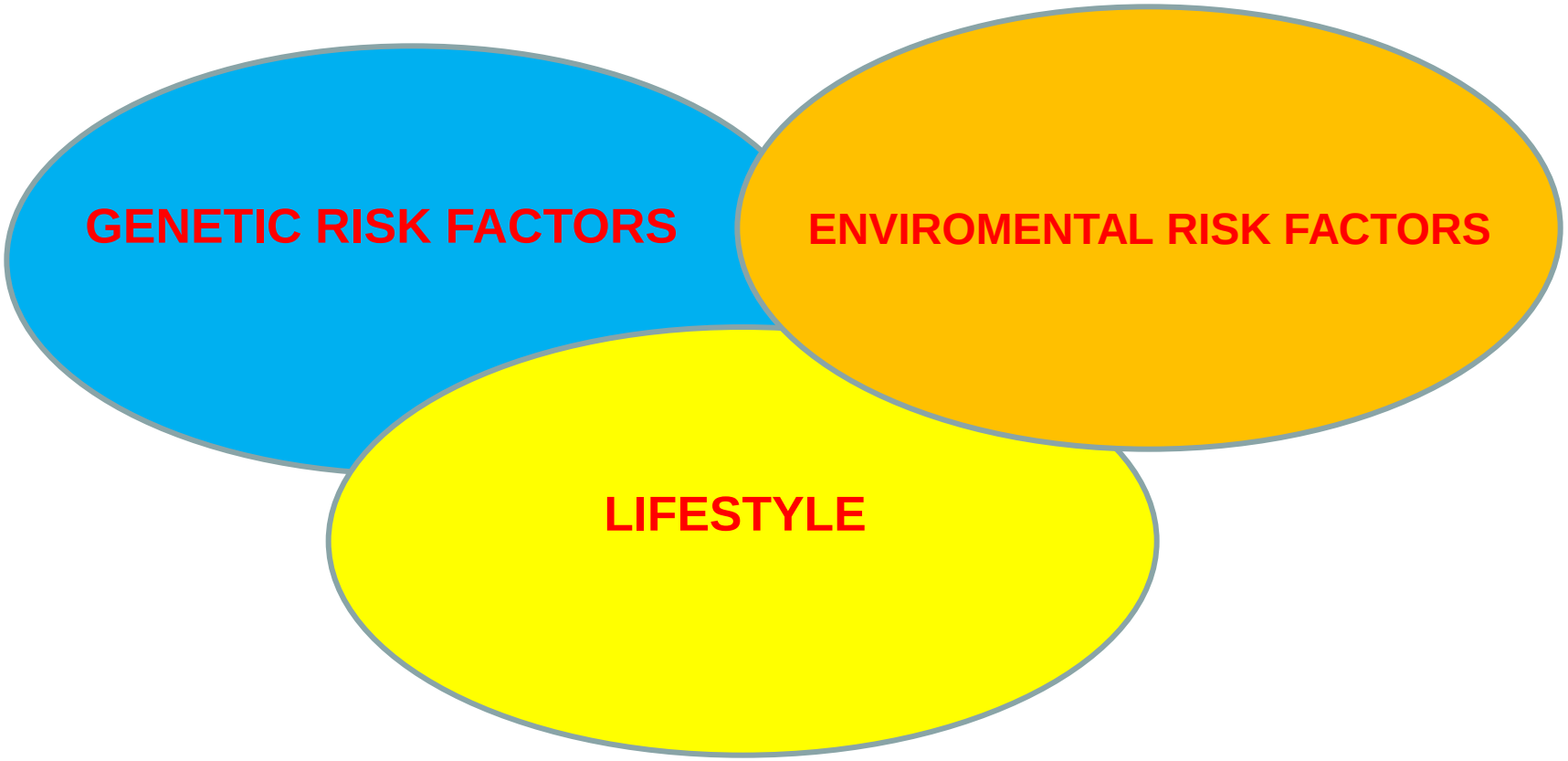
Prof Antonio Frassoldati

TUMORE: una malattia multifattoriale



Eziologia

A risk factor is a condition that can concur to or accelerate the course of a disease



Fattori di rischio ambientale

There are several agency involved in the evaluation of agents' carcinogenic potentiality:

- **IARC** (International Agency for Research on Cancer)
- **CEE** (Economic European Community)
- **CCTN** (National Toxicological Advisory Commission)
- **EPA** (Environmental Protection Agency)
- **NTP** (National Toxicology Program)

Fattori di rischio ambientale

International Agency for Research on Cancer classification based on agents's cancerogenic potentiality:

Group 1:carcinogenic to humans (118 agents)

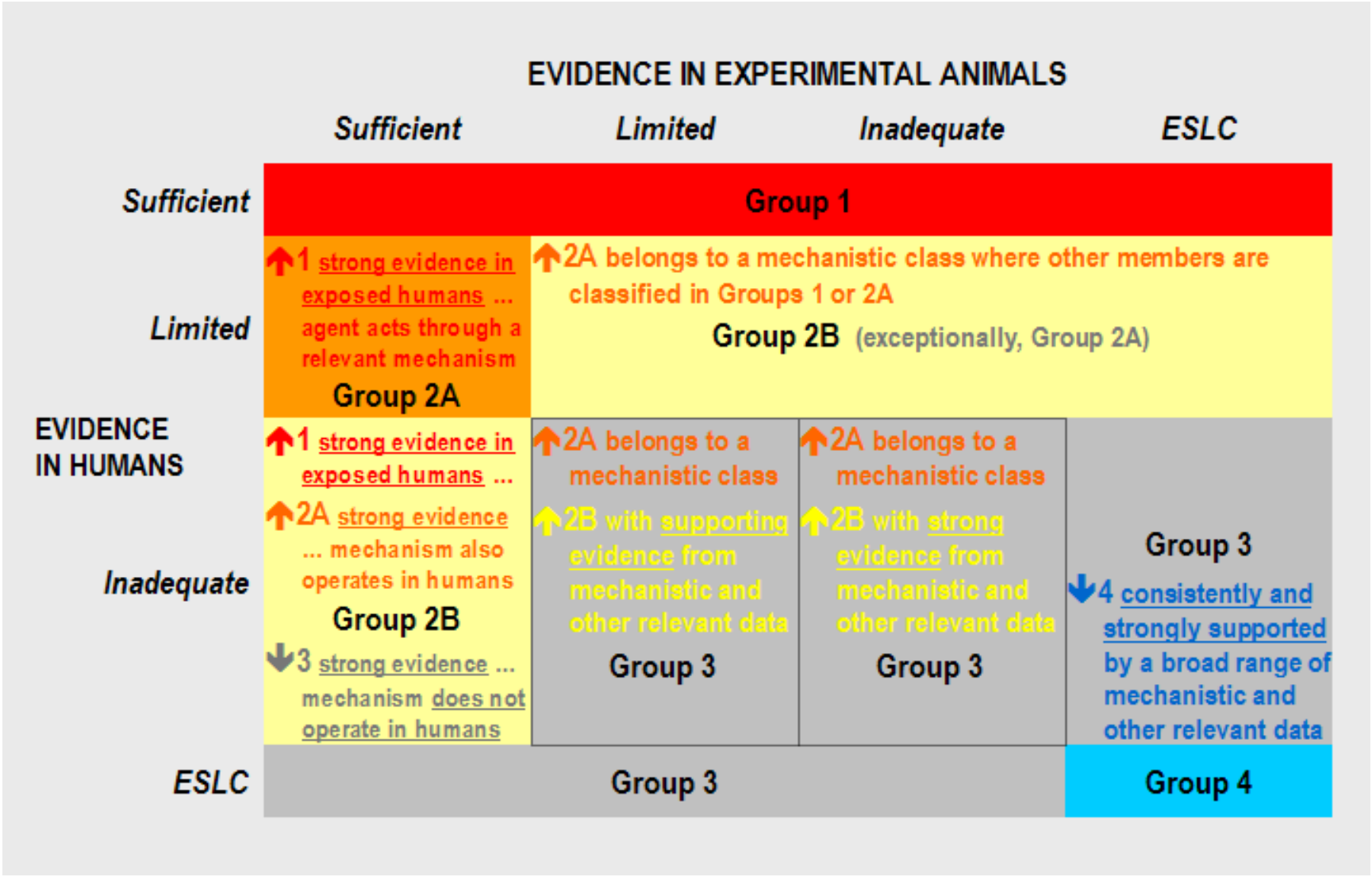
Group 2A:propably carcinogenic to humans (289 agents)

Group2B:possibly carcinogenic to humans (502 agents)

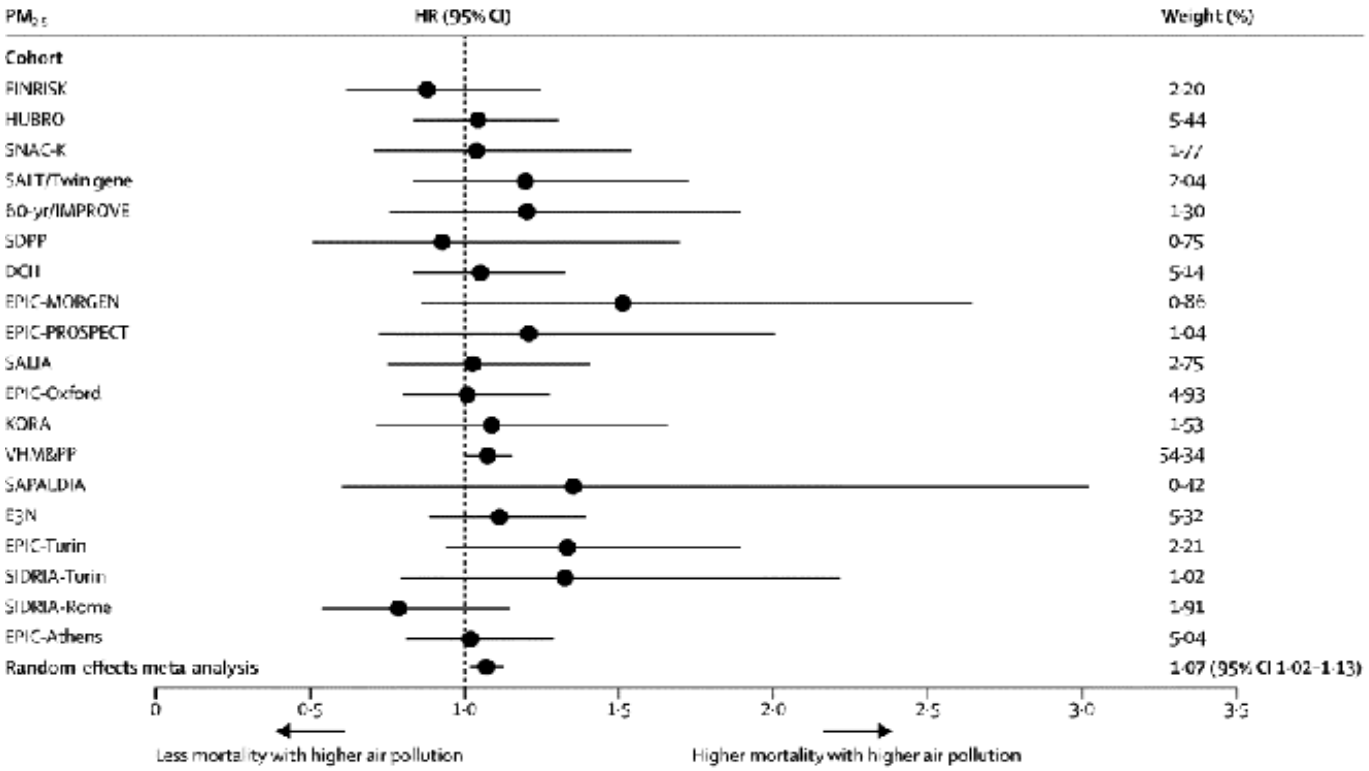
Group 3:not classificable as to its carcinogenicity to humans (502 agents)

Group 4:probably not carcinogenic to humans (1 agent)

Criteri di calssificazione IARC



Enviromental risk factors- enviromental pollution



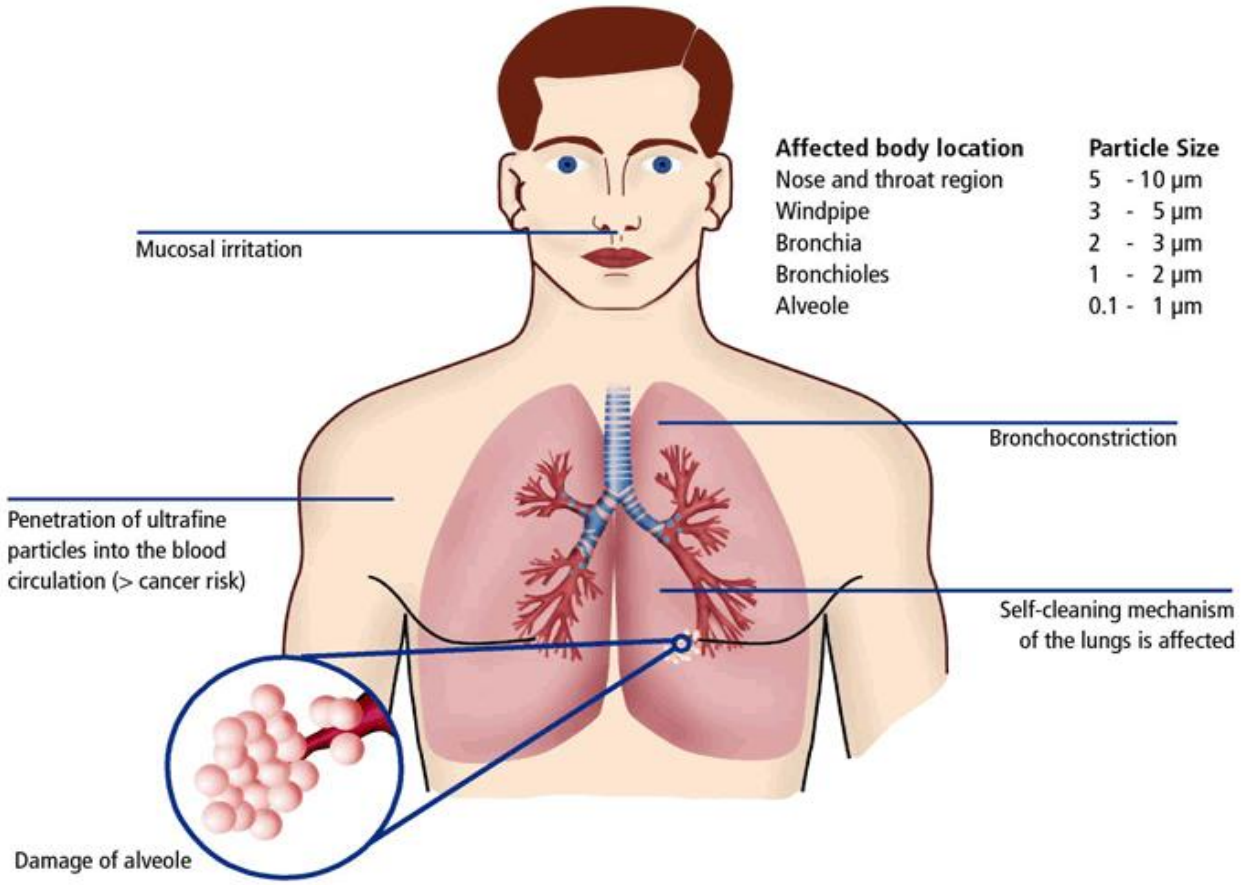
Long-term exposure to fine particulate air pollution was associated with natural-cause mortality, including cancer , even within concentration ranges well below the present European annual mean limit value.A significantly increased hazard ratio (HR) for $PM_{2.5}$ of 1·07 (95% CI 1·02–1·13) per 5 μg/m^3 was recorded

The Lancet 2014

Examples of air pollutants

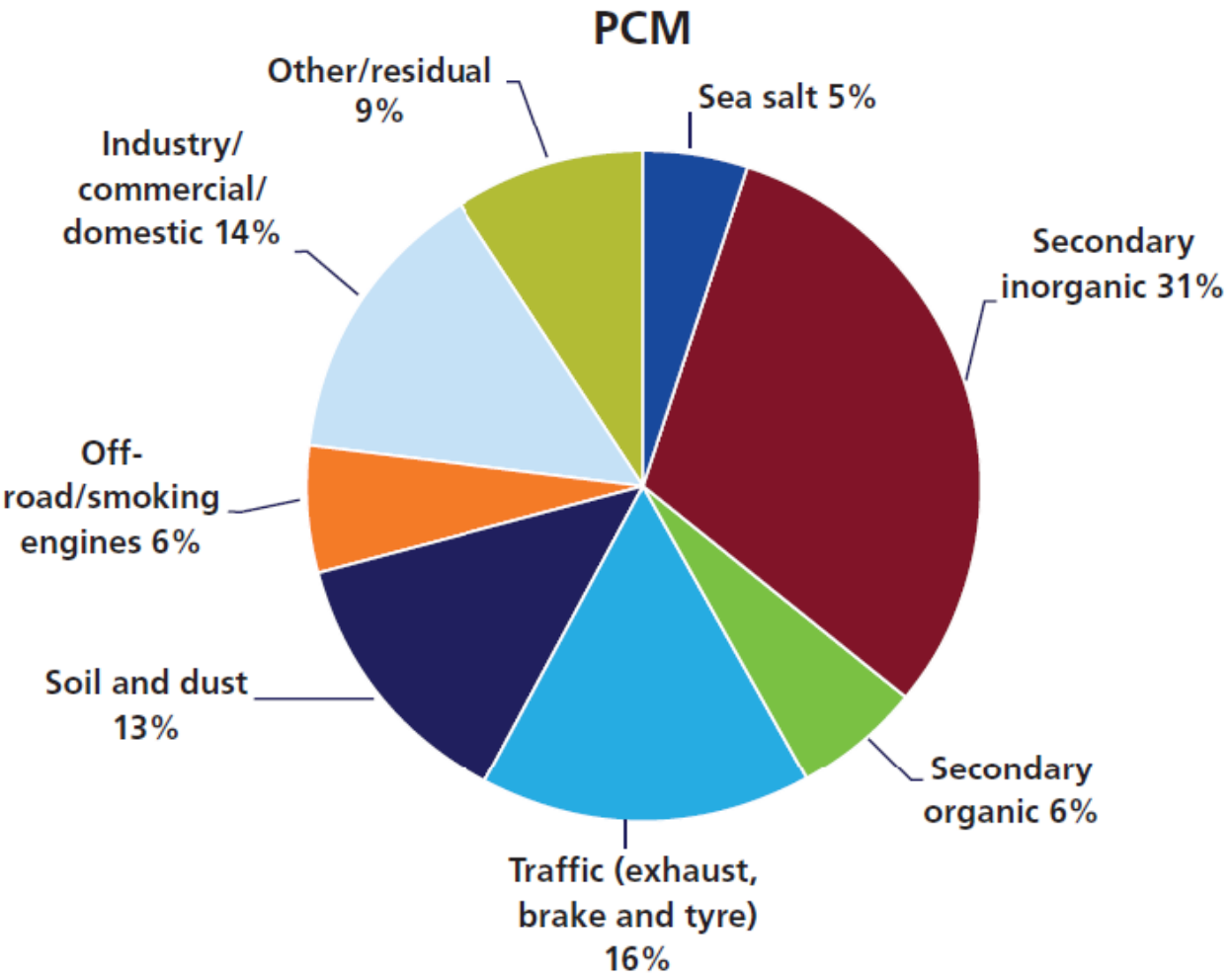
Agent	Overall evaluation of carcinogenicity to humans[a]
Polycyclic aromatic hydrocarbons	Group 2A/2B/3
Nitro-polycyclic aromatic hydrocarbons	Group 3
Bitumen (USA: asphalt)	Group 2B/3
Benzene	Group 1
Asbestos	Group 1
Radon	Group 1
Diesel engine exhaust	Group 2A
Gasoline engine exhaust	Group 2B
Titanium dioxide	Group 3
Sulfur dioxide	Group 3
Trichloroethylene	Group 2A
Carbon black	Group 2B
1,3-Butadiene	Group 2A
Man-made vitreous fibres	Group 2B/3
Styrene	Group 2B
Involuntary smoking	Group 1
Formaldehyde	Group 1

Enviromental risck factors-enviromental pollution



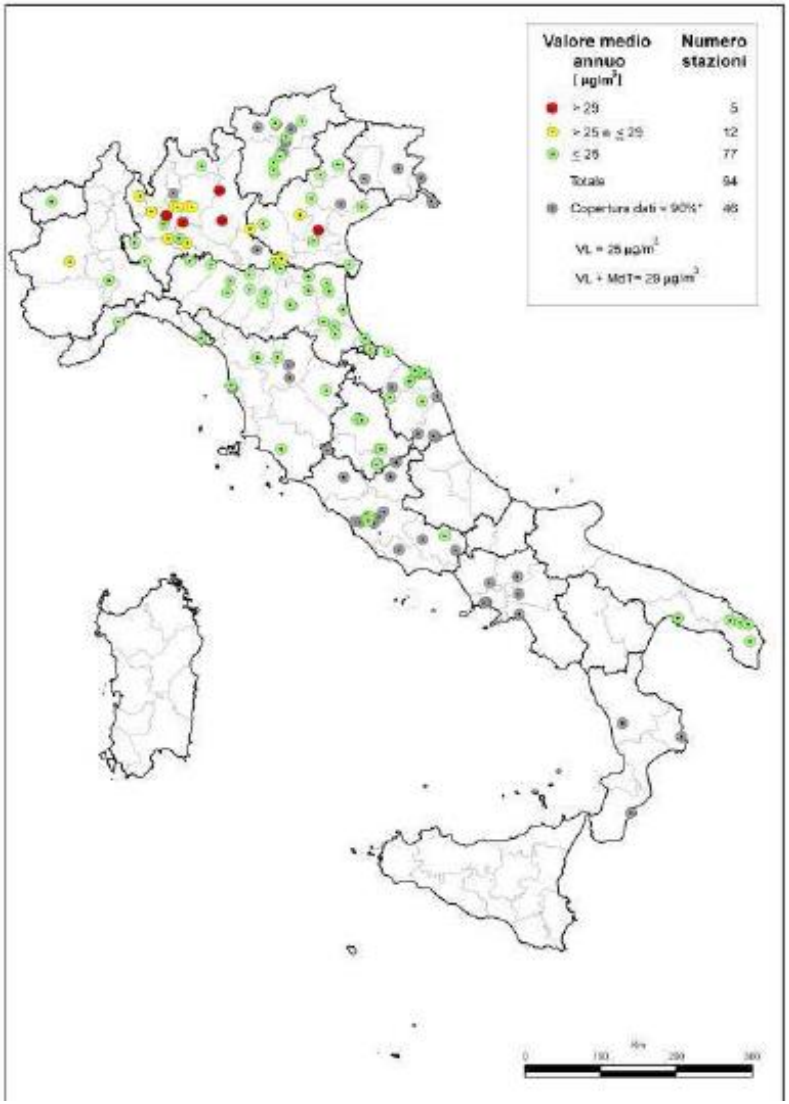
Particulate matter pollutes the environment and damages the health:the smaller the soot particles, the easier these particles find their way through the lungs into the bloodstream and with it in other organs

Sources of $PM_{2.5}$ in UK



Accepted level of $PM_{2.5}$ in Italy

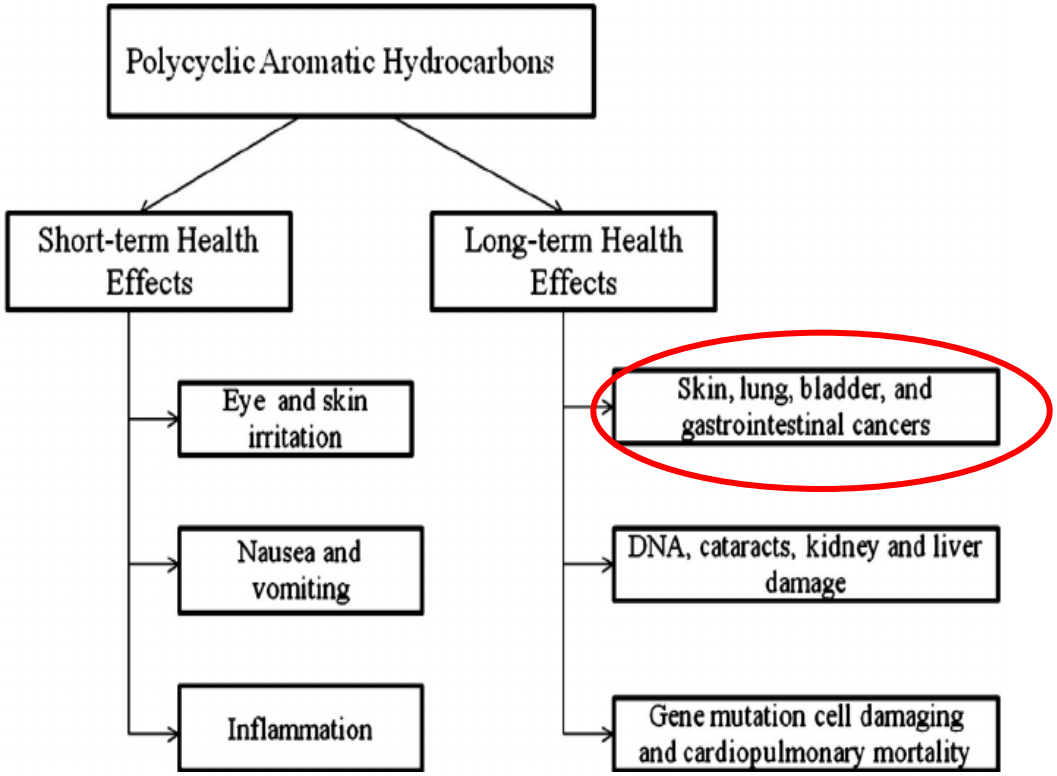
	Periodo di mediazione	Valore limite
Valore limite annuale	Anno civile	25 µg/m^3

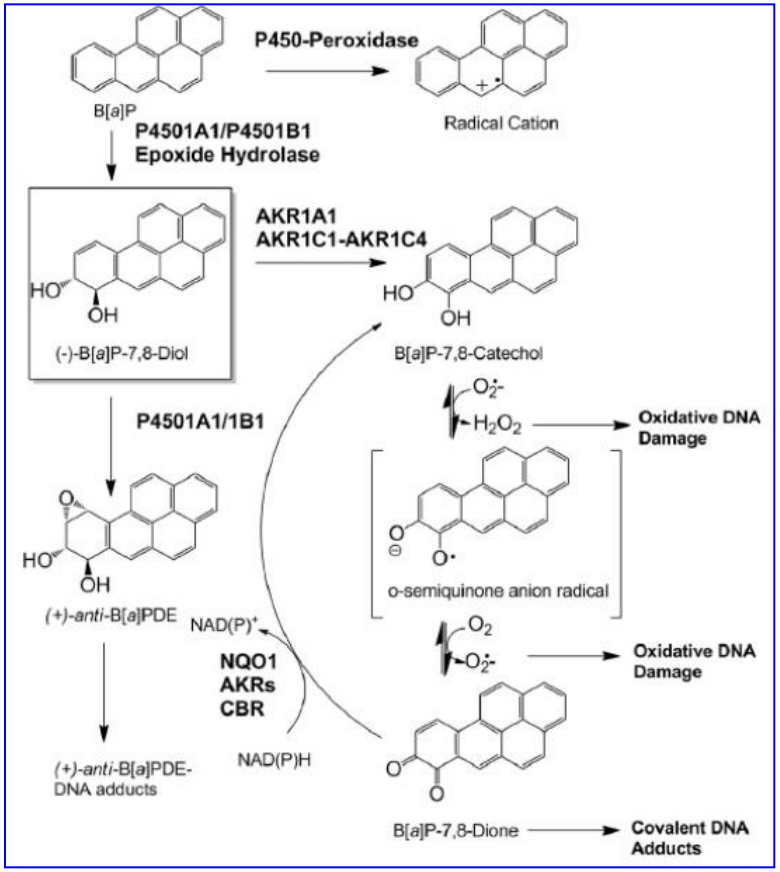


Enviromental risk factors-Chemical Cancerogen

POLYCYCLIC AROMATIC HYDROCARBONS (benzene)

sources: incomplete burning of carbon-conatining materials like oil, wood, garbage or coal. PAH particles bind to ash and can move long distances through the air :some PAHs can dissolve in water or enter groundwater



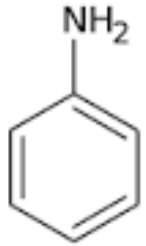


Enviromental risk factors-Chemical Cancerogen

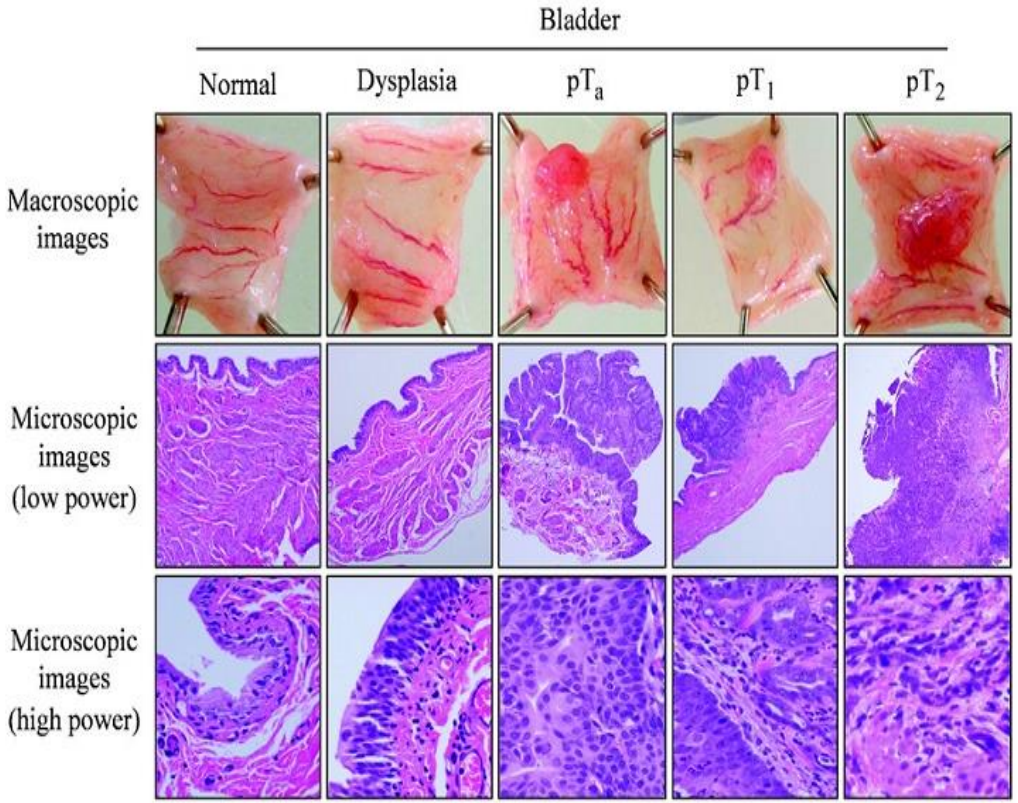
AROMATIC AMINE (anilina, benzidine, naphthylamine)

Risk groups include workers in the following industries: printing,iron foundry, aluminium smelting, industrial painting, gas and tar manufacturing

Strong association with bladder cancer

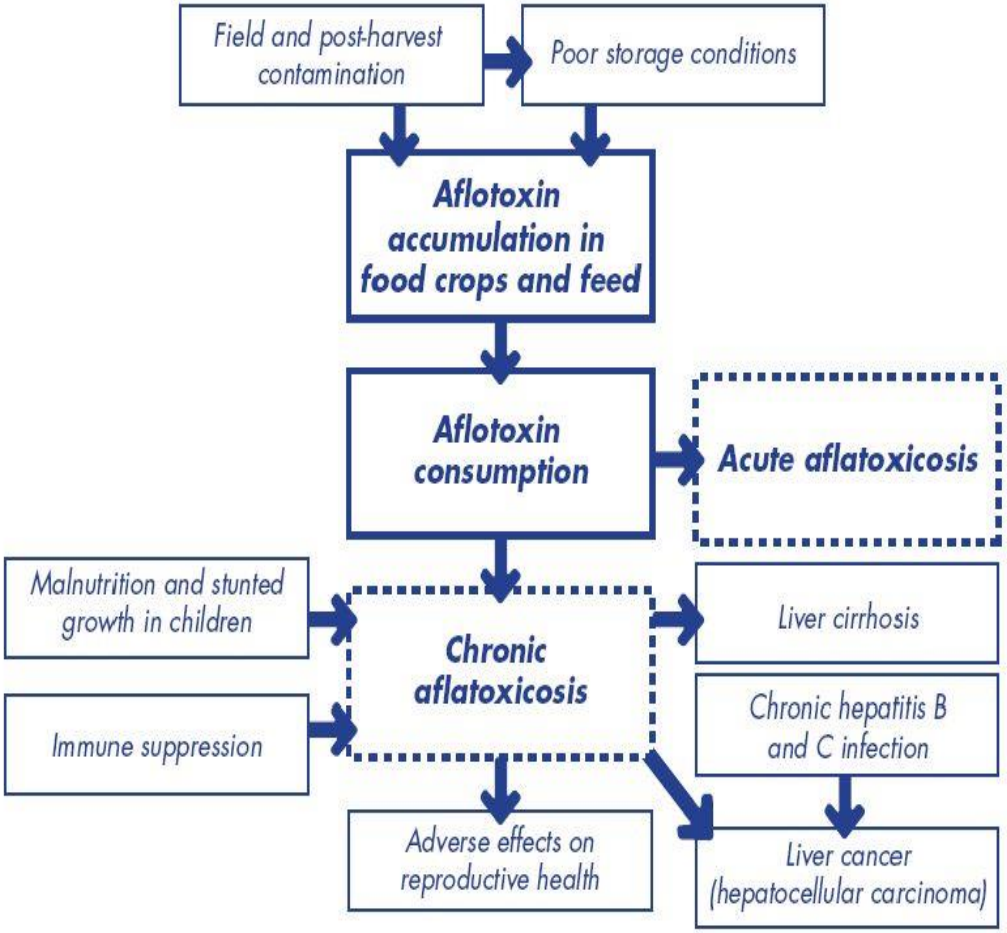


Anilina



Enviromental risk factors-Chemical Cancerogen

AFLATOXINE



Produced by certain molds (Aspergillus flavus and Aspergillus parasiticus)

They are most commonly ingested, but the most toxic type of **aflatoxin B1**, can permeate through the skin

⇑ **RISK LIVER CANCER**

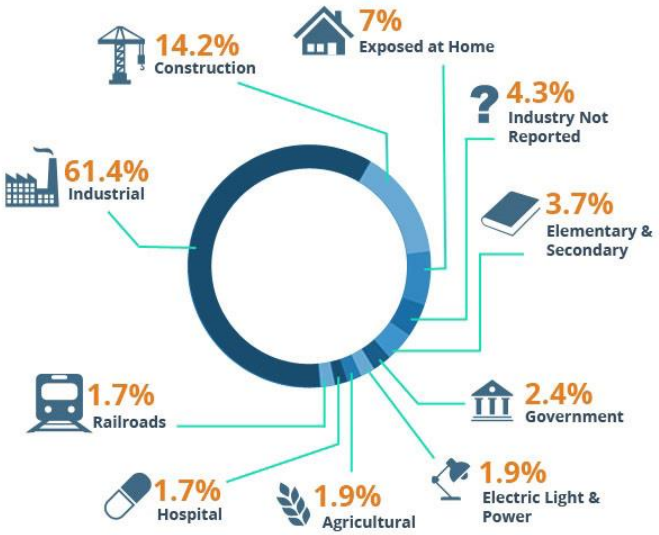
genetic damage observed include formation of DNA and albumin adducts, gene mutations, micronucleus formation, sister chromatid exchange, and mitotic recombination

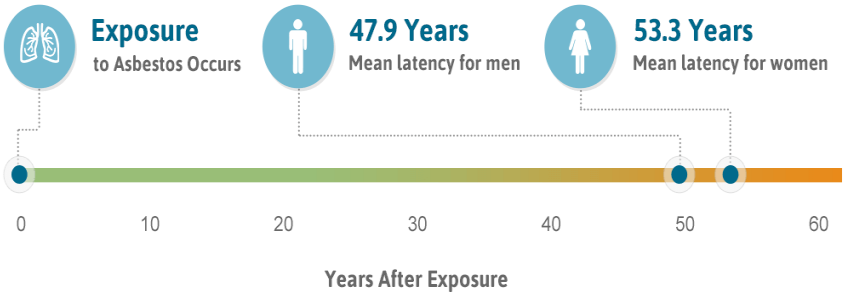
Not destroyed under normal cooking conditions, can be completely destroyed by autoclaving

Enviromental risk factors- Chemical Cancerogen

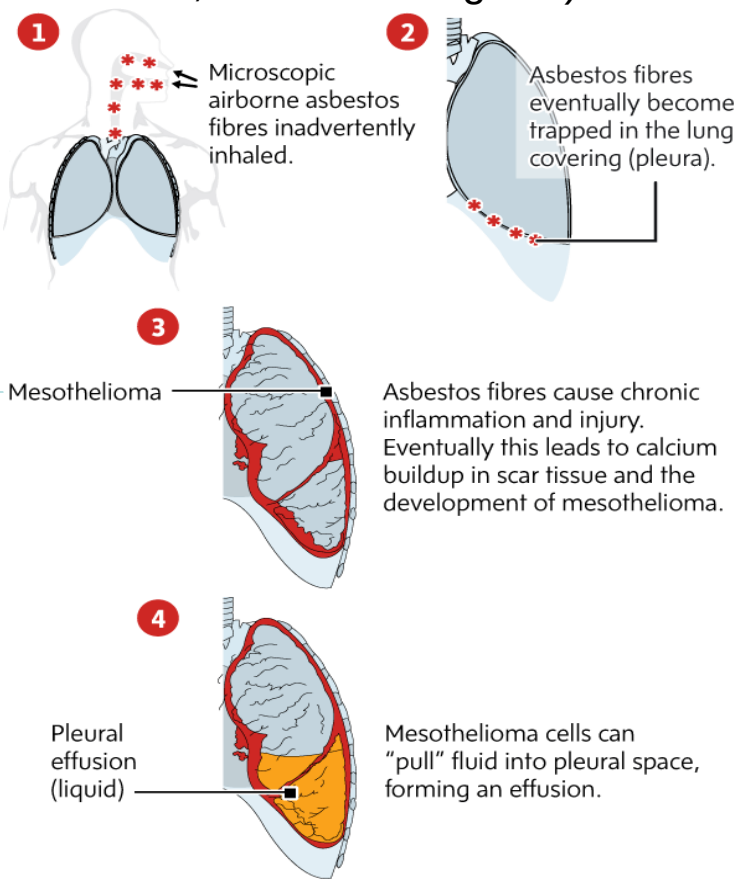
ASBESTOS group of six naturally occurring fibrous silicate minerals, including **chrysotile, actinolite, amosite, anthophyllite, crocidolite, and tremolite.**

SOURCES:

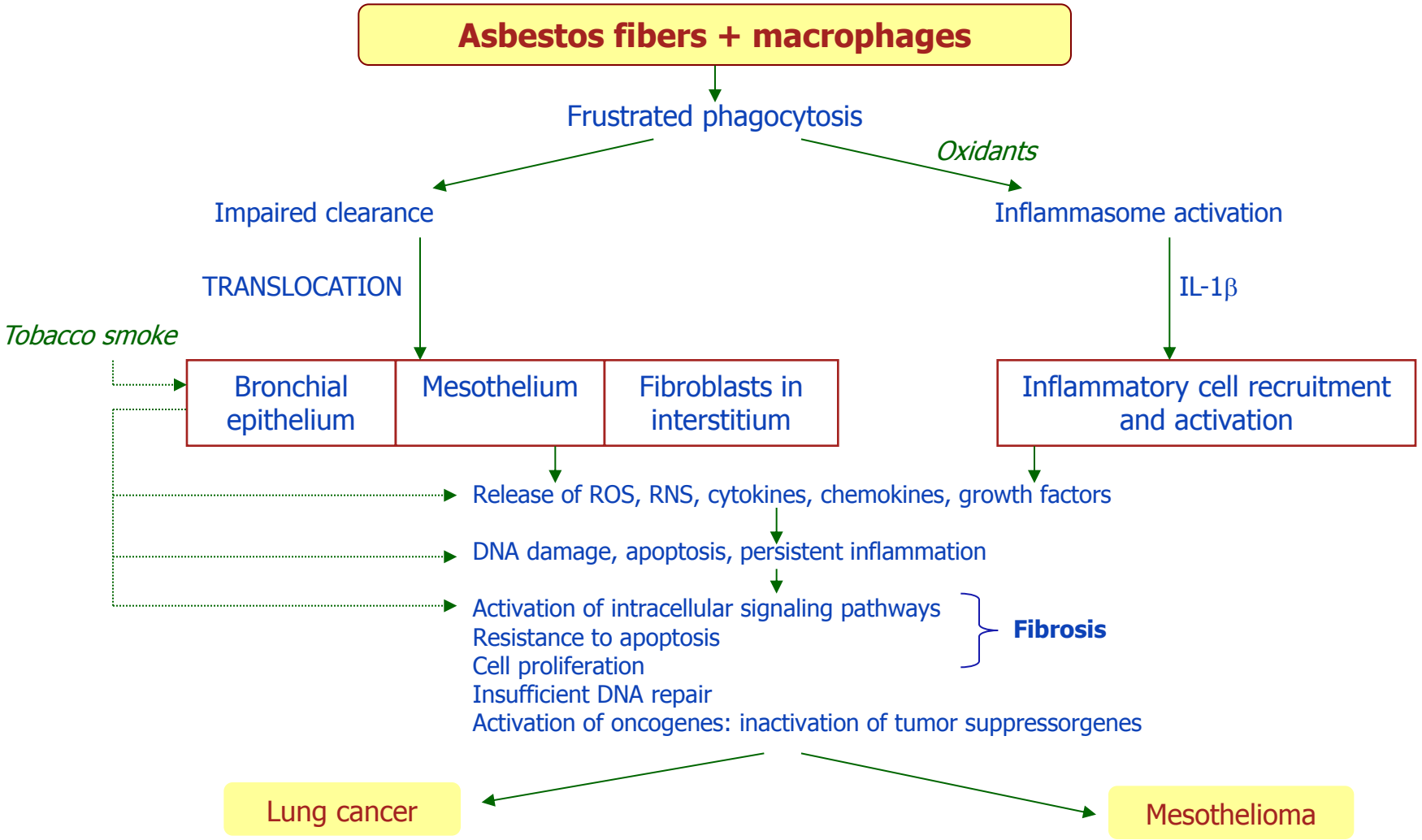




Fiber size important (<1.5 μm in diameter and > 0.8 μm length, due to phagocytosis avoidance, more carcinogenic)



Proposed mechanism for carcinogenicity of asbestos fibers



Adapted from Shukla et al 2003; Kane 2006; Nymark et al 2008

Enviromental risk factors-
Fisical Cancerogen

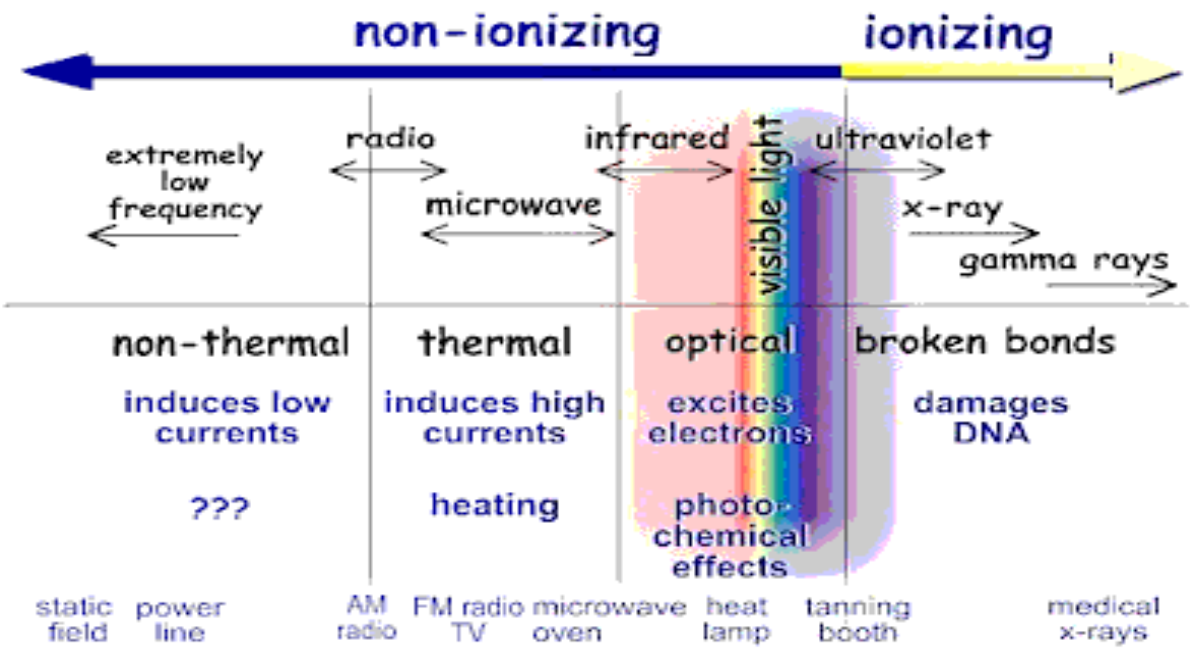
IONIZING RADIATION

•Ionising radiation includes:X-Rays, gamma rays, alpha, beta, protons, neutrons and primary cosmic radiation

•The oncogenic properties of ionizing radiation are related to its mutagenic effects; it causes chromosome breakage, translocations and less frequently , point mutations

•There is also some evidence that non-lethal doses of radiotin may induce genomic instability, favoring carcinogenesis

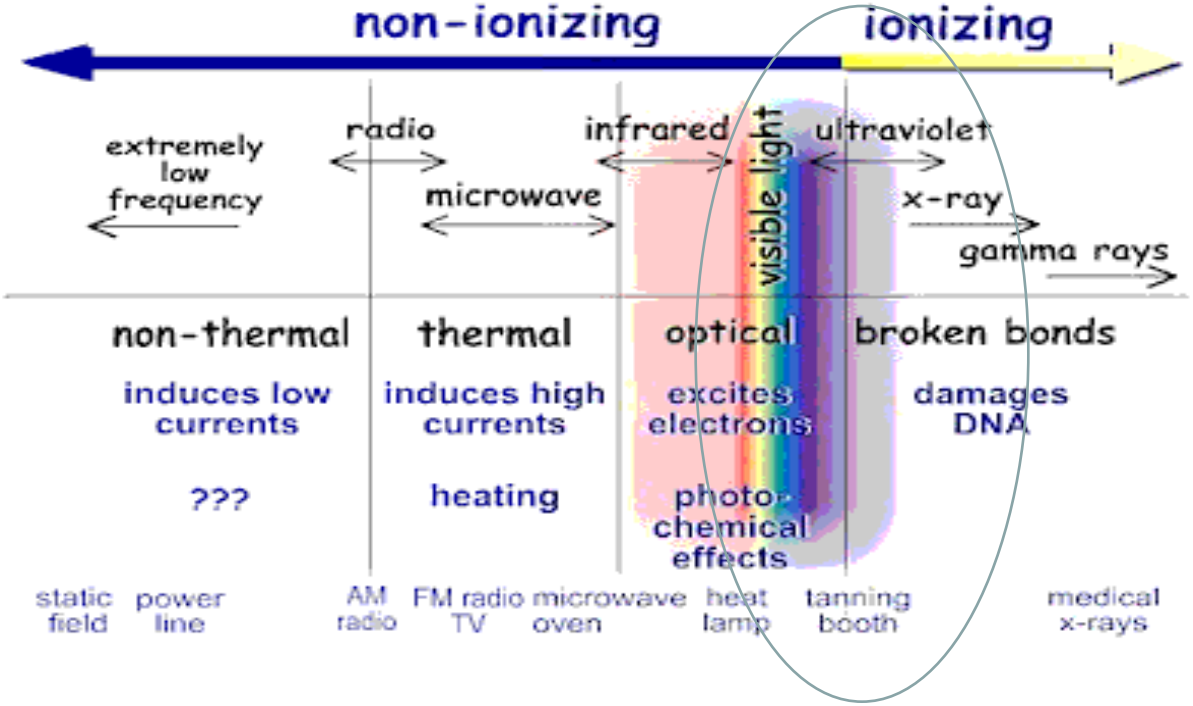
•All forms are carcinogenic with special sensitivity in bone marrow, lung, thyroid



Enviromental risk factors-
Fisical Cancerogen

ULTRAVIOLET LIGHTS

- Strong epidemiologic relationship to squamous cell ca, basal cell ca and melanoma in fair skinned people
- Causes formation of pyrimidine dimmers in the DNA leading to mutations
- This type of DNA damage is repaired y the nucleotide excision repair pathway. With extensive exposure to UV light , the repair systems may be overwhelmed and skin cancer results
- Individual with defects in the enzymes that mediate DNA excision-repair are especiallv susceptible



Enviromental risk factors-Fisical Cancerogen

ULTRAVIOLET LIGHTS-MELANOMA

Enviromental risk factors- Biological Cancerogen

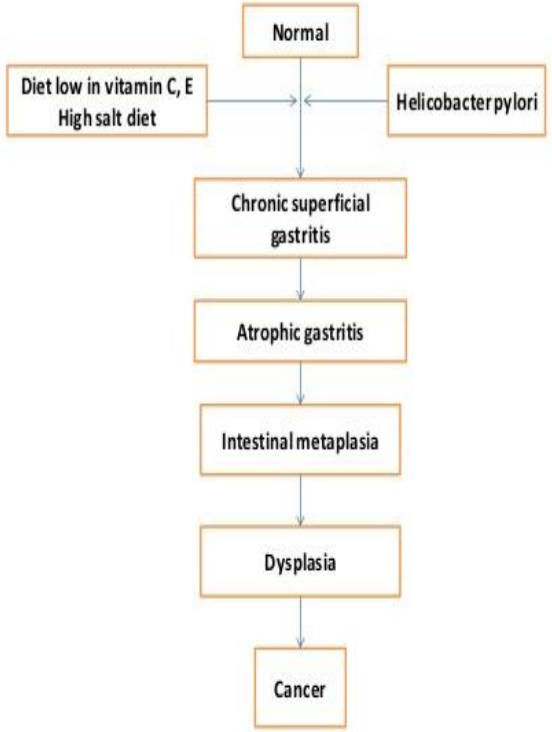
VIRUS

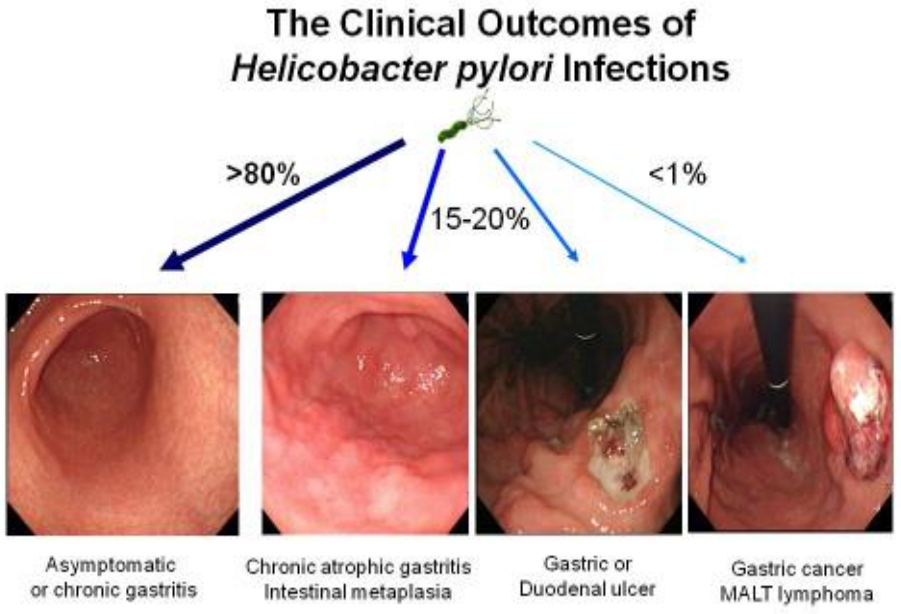
Virus	% of Cancer	Cancer Types
Hepatitis (HBV and HCV)	4.9%	Hepatocellular
Human T-lymphotropic (HTLV)	.03%	Adult T cell leukemia
Human Papillomavirus (HPV)	5.2%	Cervix, Anus, Vulva, Vagina, Oropharynx
Kaposi sarcoma associated herpesvirus (HHV-8)	**0.9%**	**Kaposi sarcoma, multicentic Castleman, primary effusion lymphoma**
Merkel cell polyomavirus	NA	Merkel cell
Epstein-Barr (EBV)	NA	Burkitt, nasopharynx

Enviromental risk factors- Biological Cancerogen

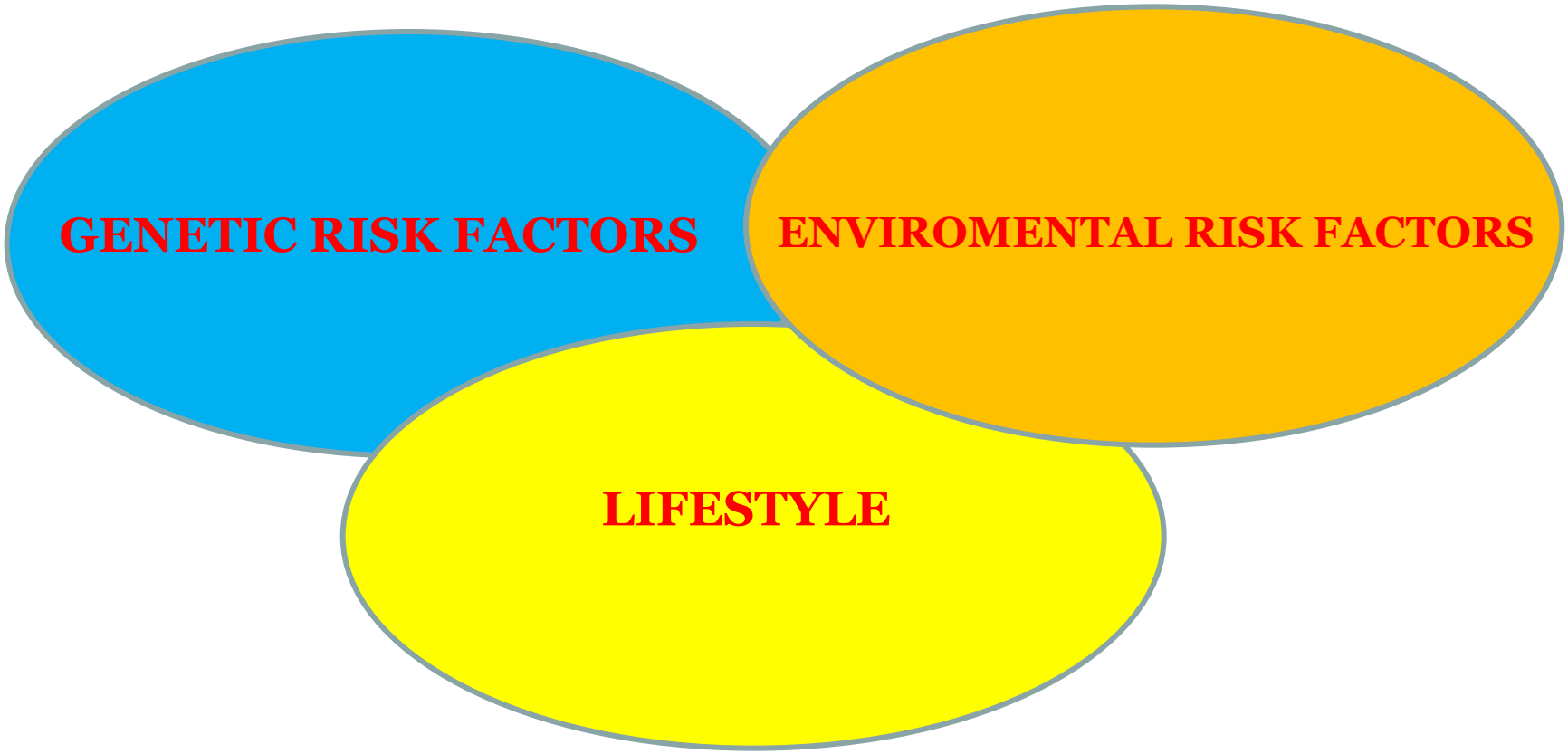
HELICOBACTER PYLORI

Chronic helicobacter pylori infection increases the risk of gastric cancer about threefold when compared to uninfected patients





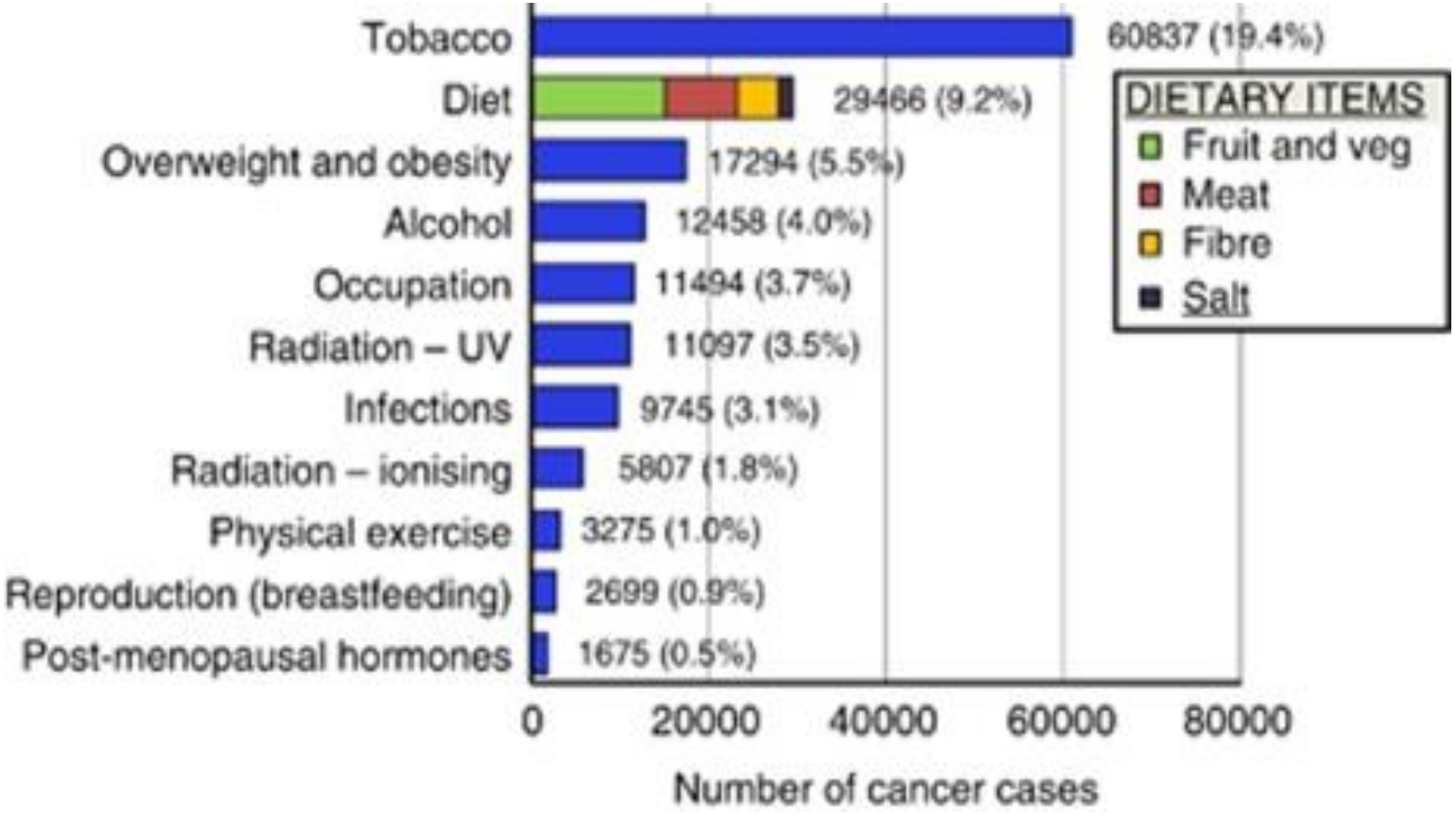
Cancer Etiopathogenesis



THE LEVELS OF PREVENTION

	PRIMARY Prevention	**SECONDARY** Prevention	**TERTIARY** Prevention
Definition	An intervention implemented before there is evidence of a disease or injury	An intervention implemented after a disease has begun, but before it is symptomatic.	An intervention implemented after a disease or injury is established
Intent	Reduce or eliminate causative risk factors (risk reduction)	Early identification (through screening) and treatment	Prevent sequelae (stop bad things from getting worse)

Cancer Etiopathogenesis

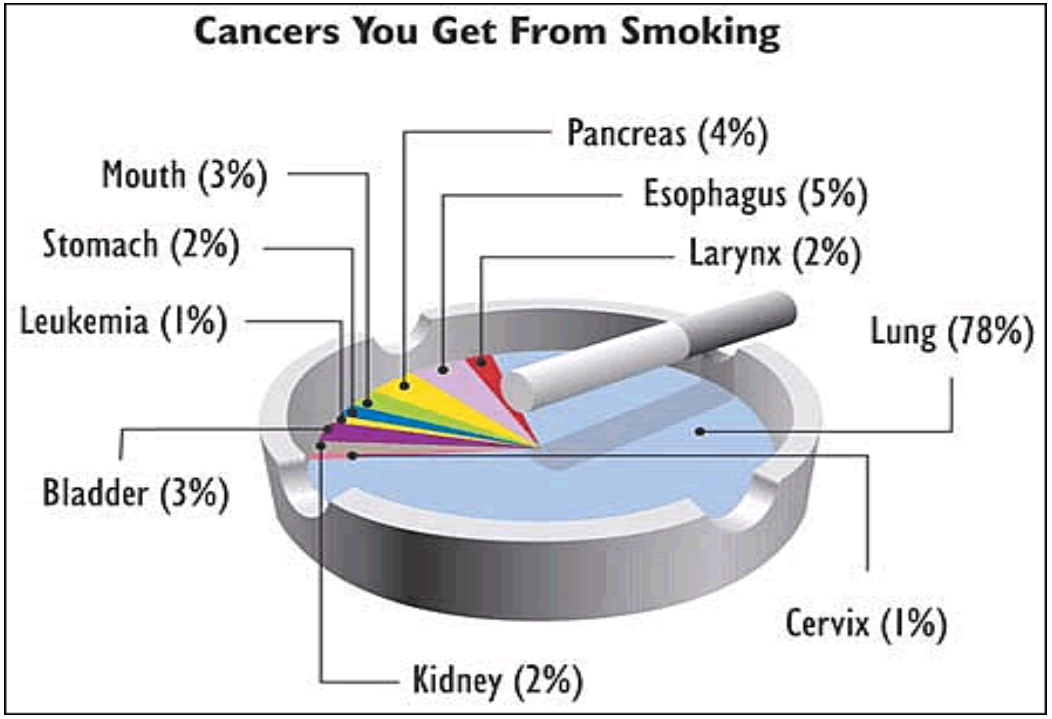


Number and percentage of cancer cases attributable to different exposures

Br J Cancer. 2011 Dec 6; 105(Suppl 2): S77–S81

TOBACCO SMOKING

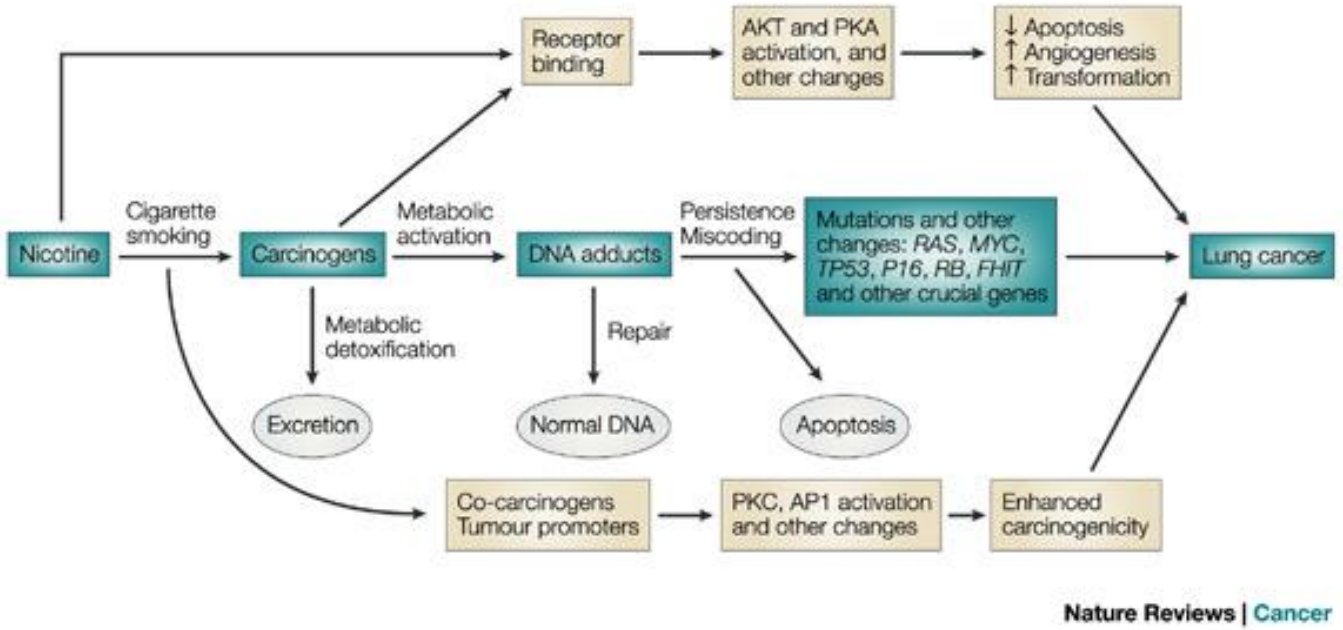
- Smoking contributes to approximately 30% of all cancers in the developed world:



- Growing evidence also ties smoking to an elevated risk of liver and prostate cancer

TOBACCO SMOKING

Tobacco likely acts on multiple stages of carcinogenesis; it not only delivers a lot of *carcinogens* but also causes *irritation* and i*nflammation* and interferes with the body's natural protective barriers:



SEDENTARY LIFESTYLE

Sedentary lifestyle is linked to most **major chronic diseases**, including type II diabetes, osteoporosis, stroke, cardiovascular disease, and **cancer**

- Inactivity **increases the risk of colon and breast cancer** and likely **endometrial** cancer as well (International Agency for Research on Cancer, 2002)

- The impact on colon cancer risk is especially striking; high levels of physical activity may reduce the risk of colon cancer by as much as 50%

- Growing evidence suggests that lack of physical activity also may be associated with an elevated risk of **lung** and **prostate cancer**

- Overall, sedentary lifestyle has been linked **to 5% of deaths from cancer**

SEDENTARY LIFESTYLE

- Several mechanisms have been proposed to explain the dose–response relationship observed between activity and cancer risk:

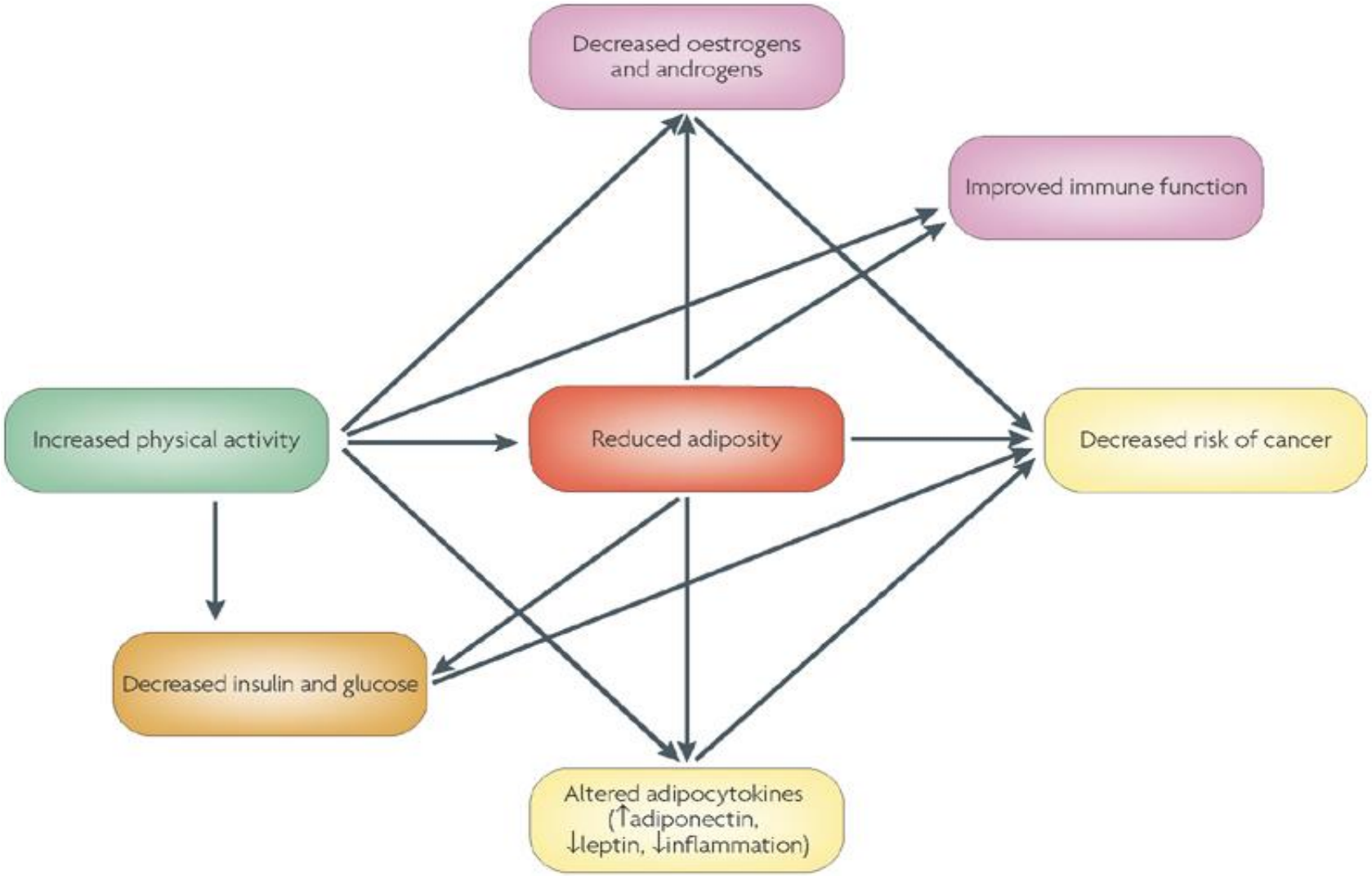
  -physical activity **may reduce** circulating levels of *insulin, hormones, and other growth factors*

  -physical activity may also alter **prostaglandin** *levels* and ***improve immune*** *function*

- Fortunately, the **negative effects** of a sedentary lifestyle **are reversible**

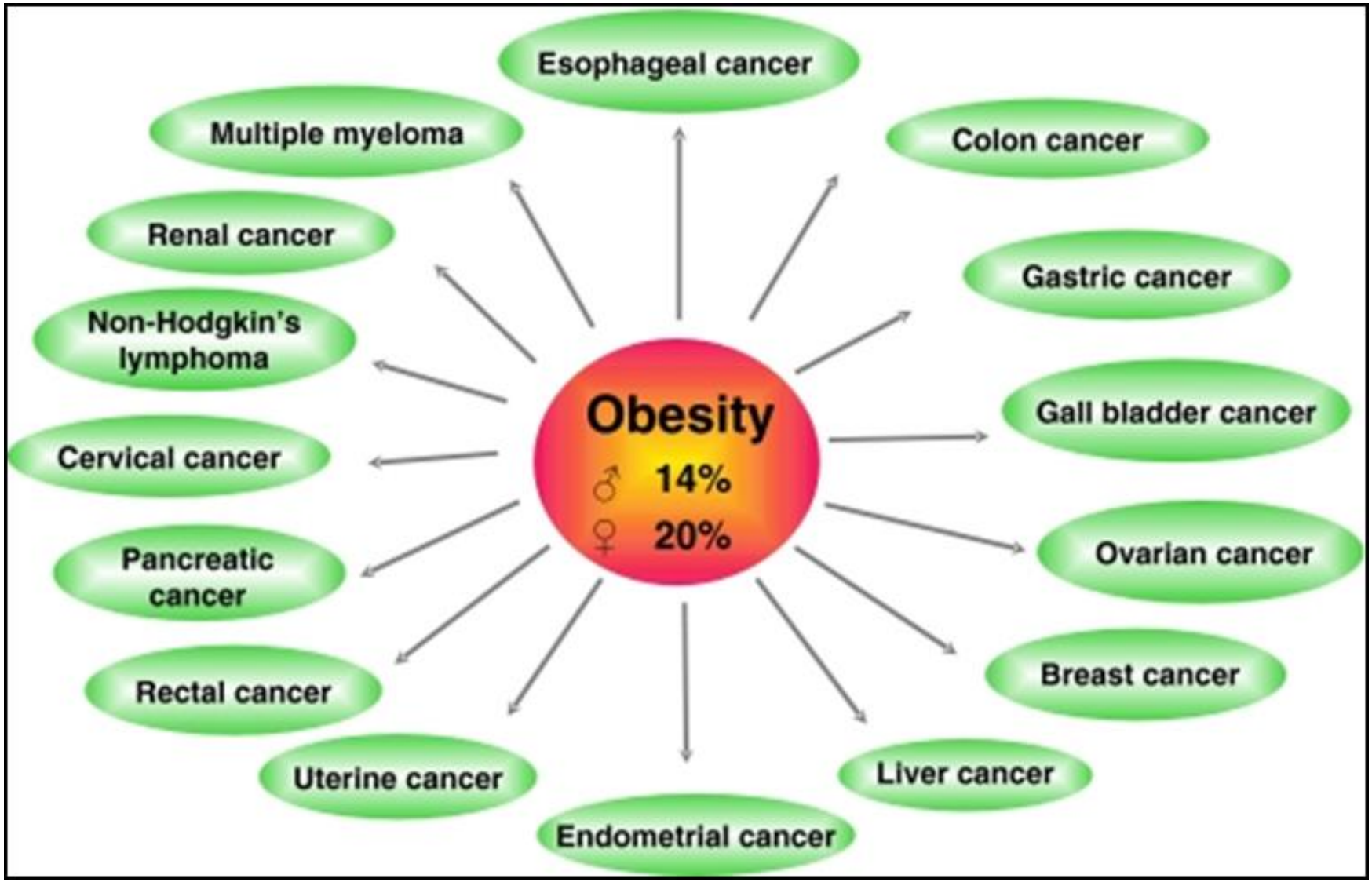
- Beyond individual behaviour choice, changes are needed at the family, community, and organisational levels to create an environment that is safe for and conducive to physical activity

PHYSICAL ACTIVITY

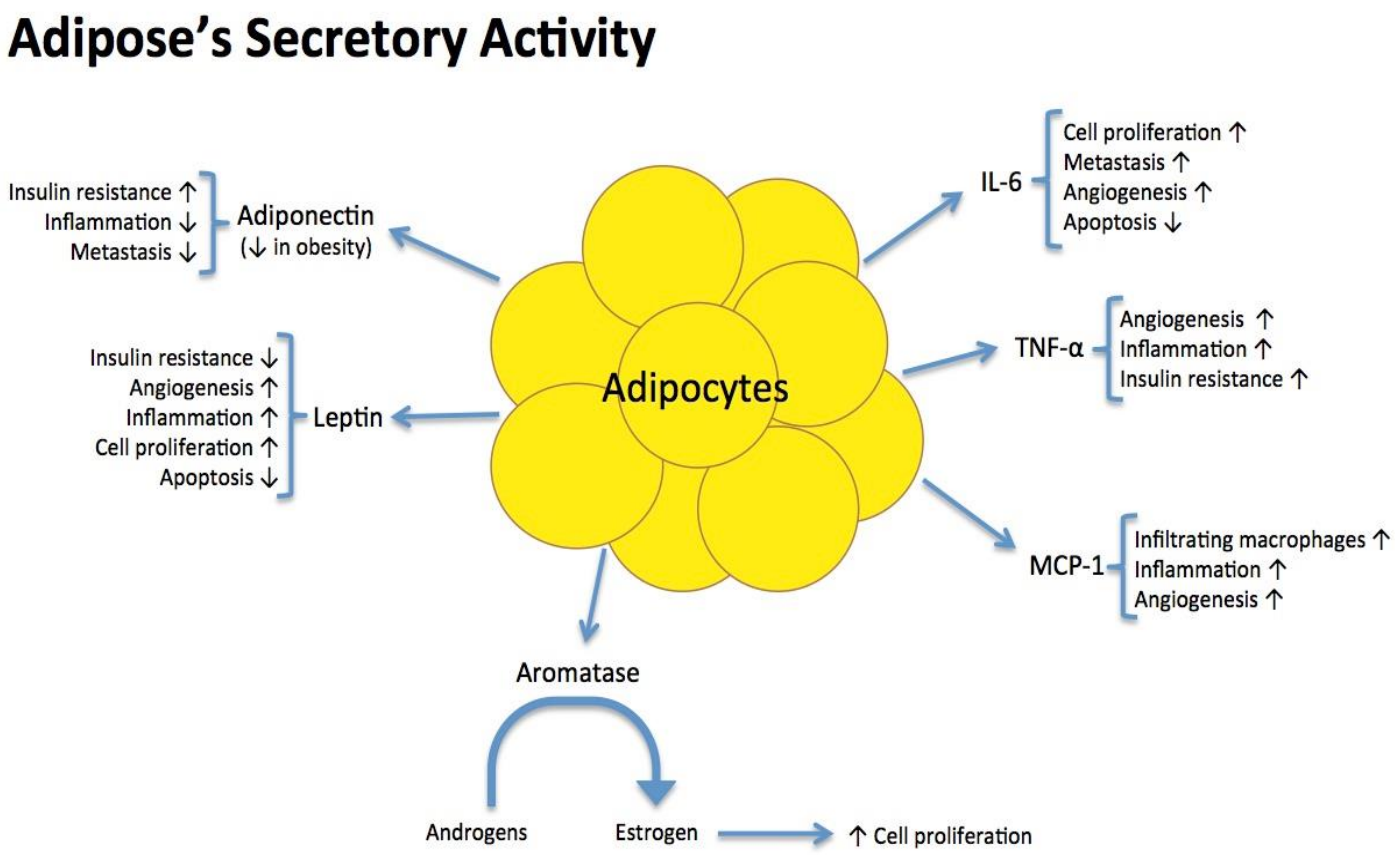


Nature Reviews | Cancer

OBESITY


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

OBESITY-FAT AS A SECRETORY ORGAN



It may help to think of **fat deposits** as another **hormone-producing gland** in the endocrine system:fat cells actively release molecules called ***adipokines*** that can have negative effects on the rest of the body in terms of cancer development and progression

ALCOHOL CONSUMPTION

- Alcohol consumption can increase a person's **risk** of developing cancers of the *mouth, pharynx, larynx, esophagus, colorectum* (particularly for men) and *breast*

- Researchers have identified multiple ways that alcohol may increase the risk of cancer, including:

  -metabolizing ethanol in alcoholic drinks to **acetaldehyde**, which can damage both DNA and proteins

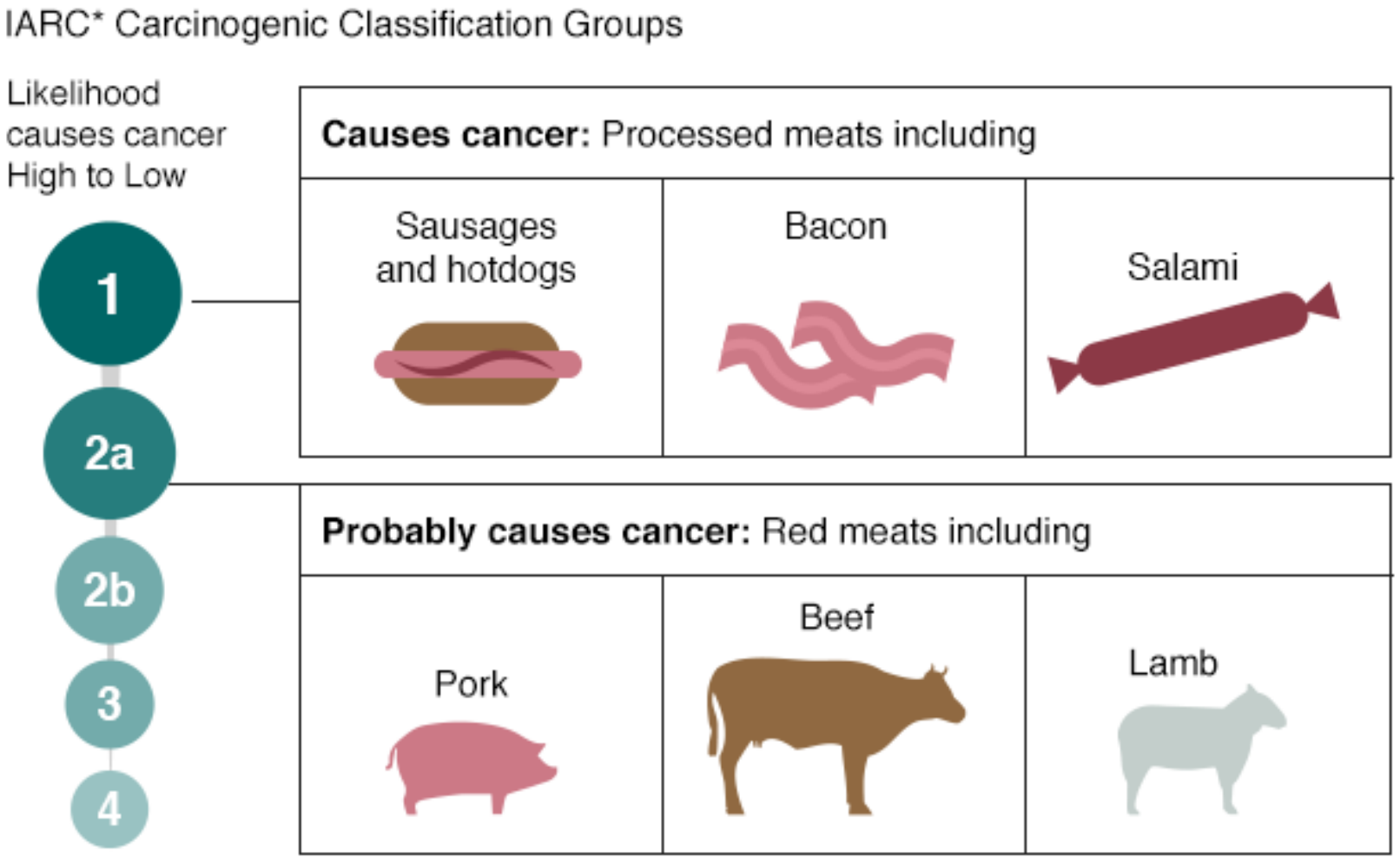
  -generating **ROS** which can damage DNA, proteins, and lipids through oxidation

  -**impairing** the body's ability to break down and **absorb a variety of nutrients** that may be associated with cancer risk

  -increasing blood levels of **estrogen**

  -presence of **carcinogenic contaminants** that are introduced during fermentation and production, such as *nitrosamines, asbestos fibers, phenols, and hydrocarbons*.

DIET AND CANCER



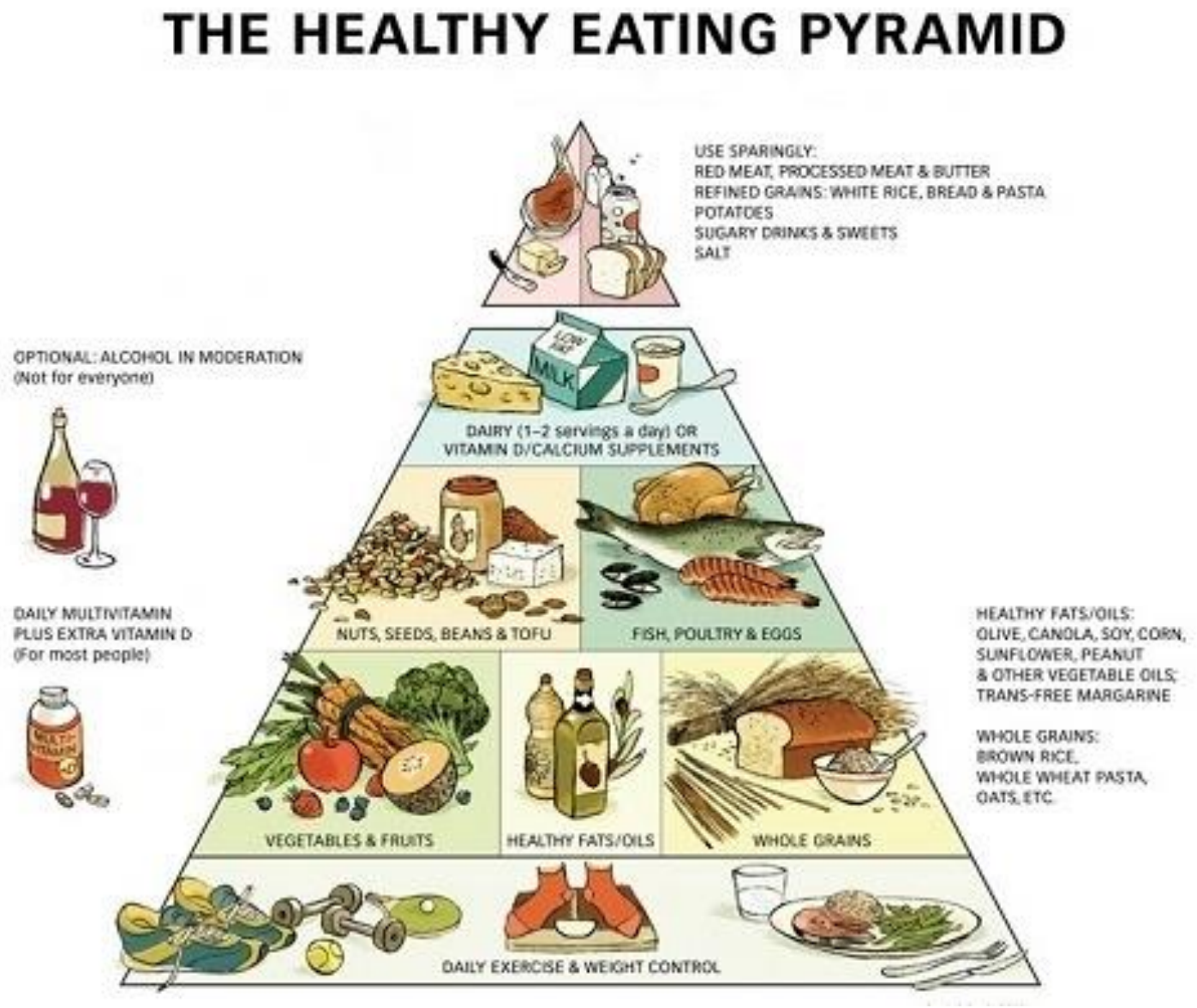
The **IARC** classifies processed meat as a cause of cancer, and red meat as a probable cause of cancer

DIET AND CANCER

- Around a quarter of **bowel cancer** cases in men, and around a sixth in women, are *linked to eating red or processed meat.*
- **Bowel cancer** risk increases by nearly a **fifth (17%) for every 100g of red meat eaten per day**, and by a similar amount (18%) for every **50g of processed meat** eaten per day
- There is also some evidence linking red meat to **pancreatic cancer**, breast cancer and prostate cancer, and processed meat to stomach cancer
- The biological reasons for the link between red and processed meat and cancer are still unclear, but it is likely that chemicals found in red and processed meat play a part :

  - ***haem***
  - ***nitrites and nitrates***
  - ***heterocyclic amines & polycyclic aromatic hydrocarbons***

DIET AND CANCER



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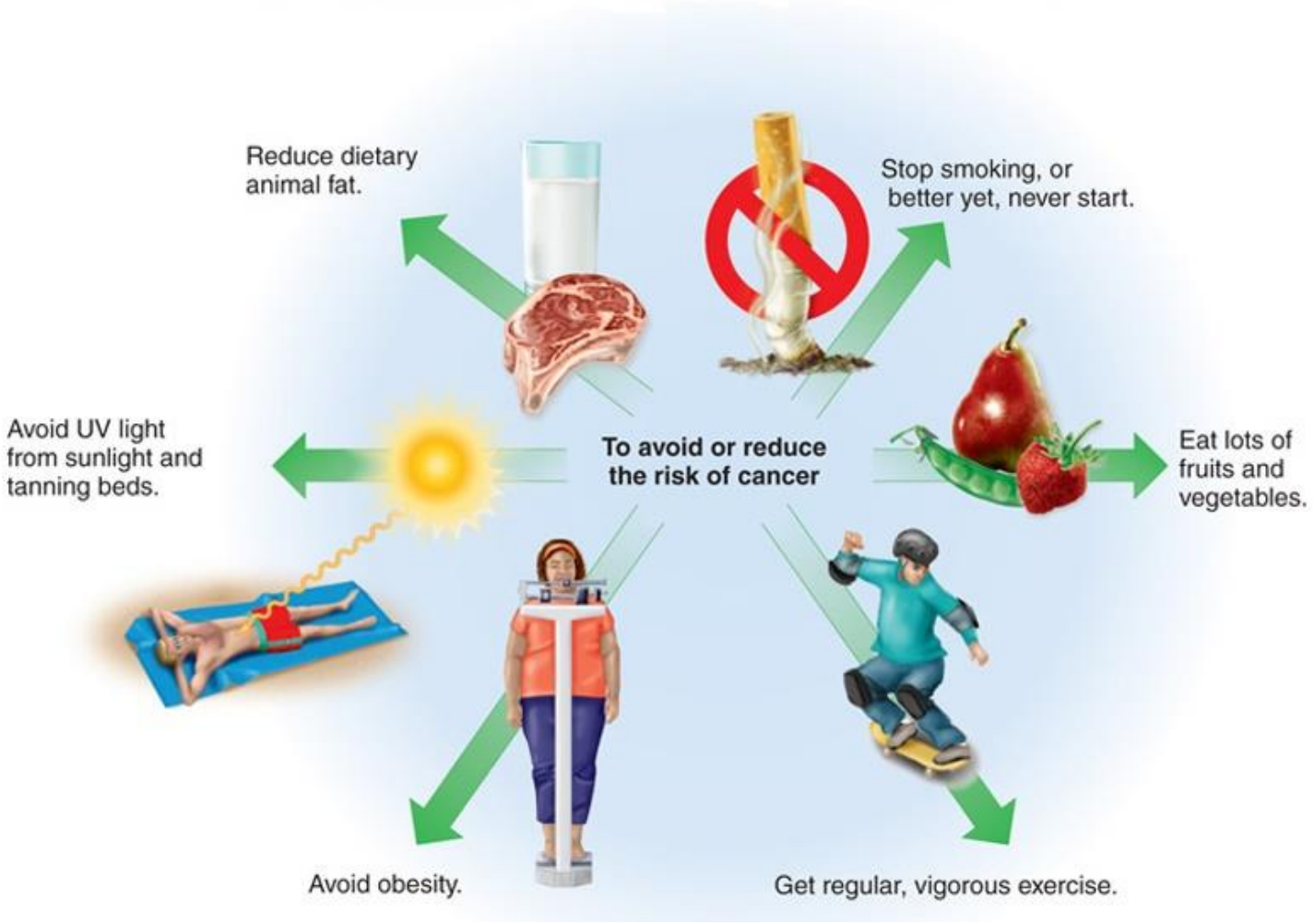
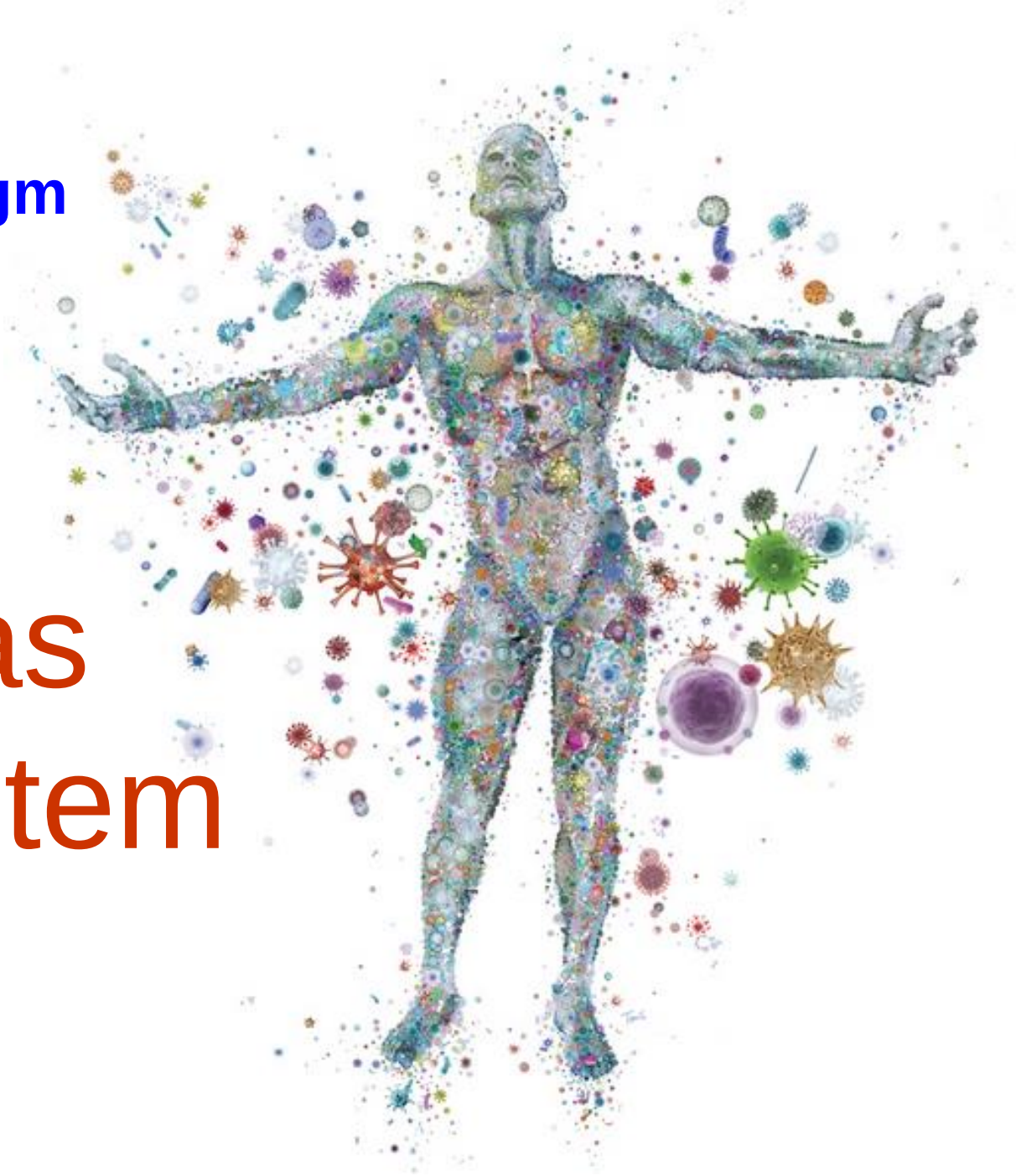
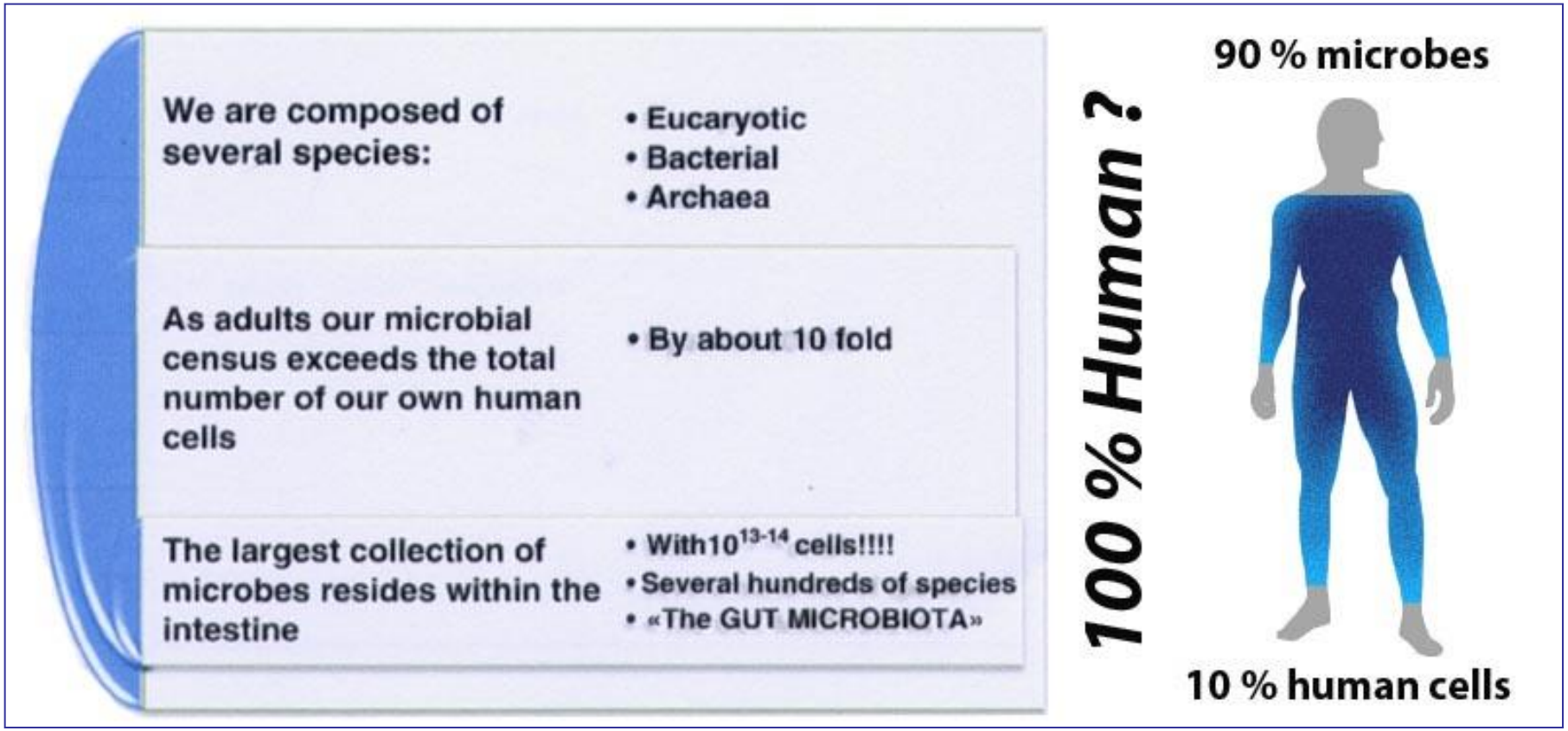

Reduce dietary animal fat.
Stop smoking, or better yet, never start.
Avoid UV light from sunlight and tanning beds.
To avoid or reduce the risk of cancer
Eat lots of fruits and vegetables.
Avoid obesity.
Get regular, vigorous exercise.

Changing paradigm

Man as echosystem

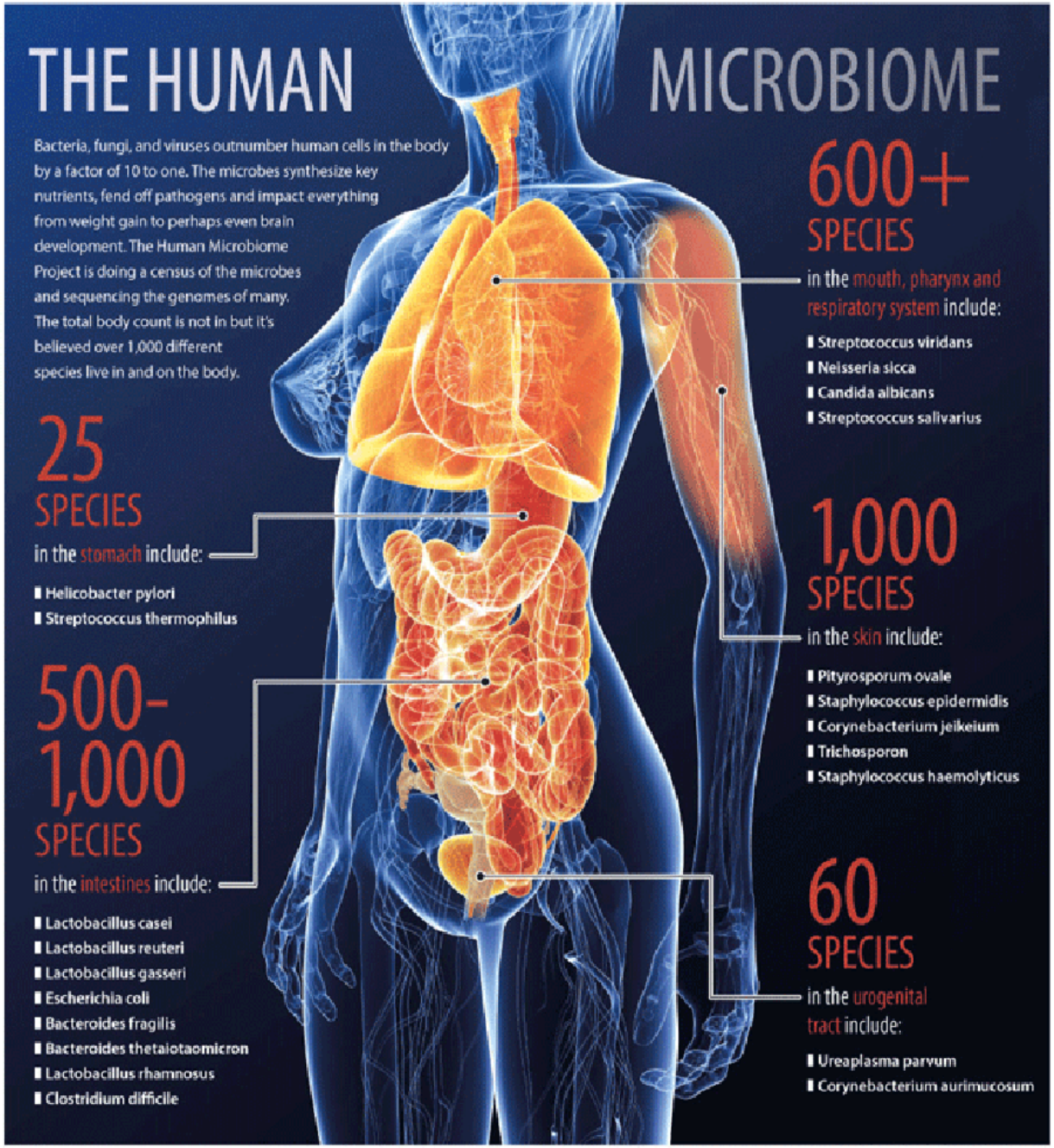


A different way in considering our body

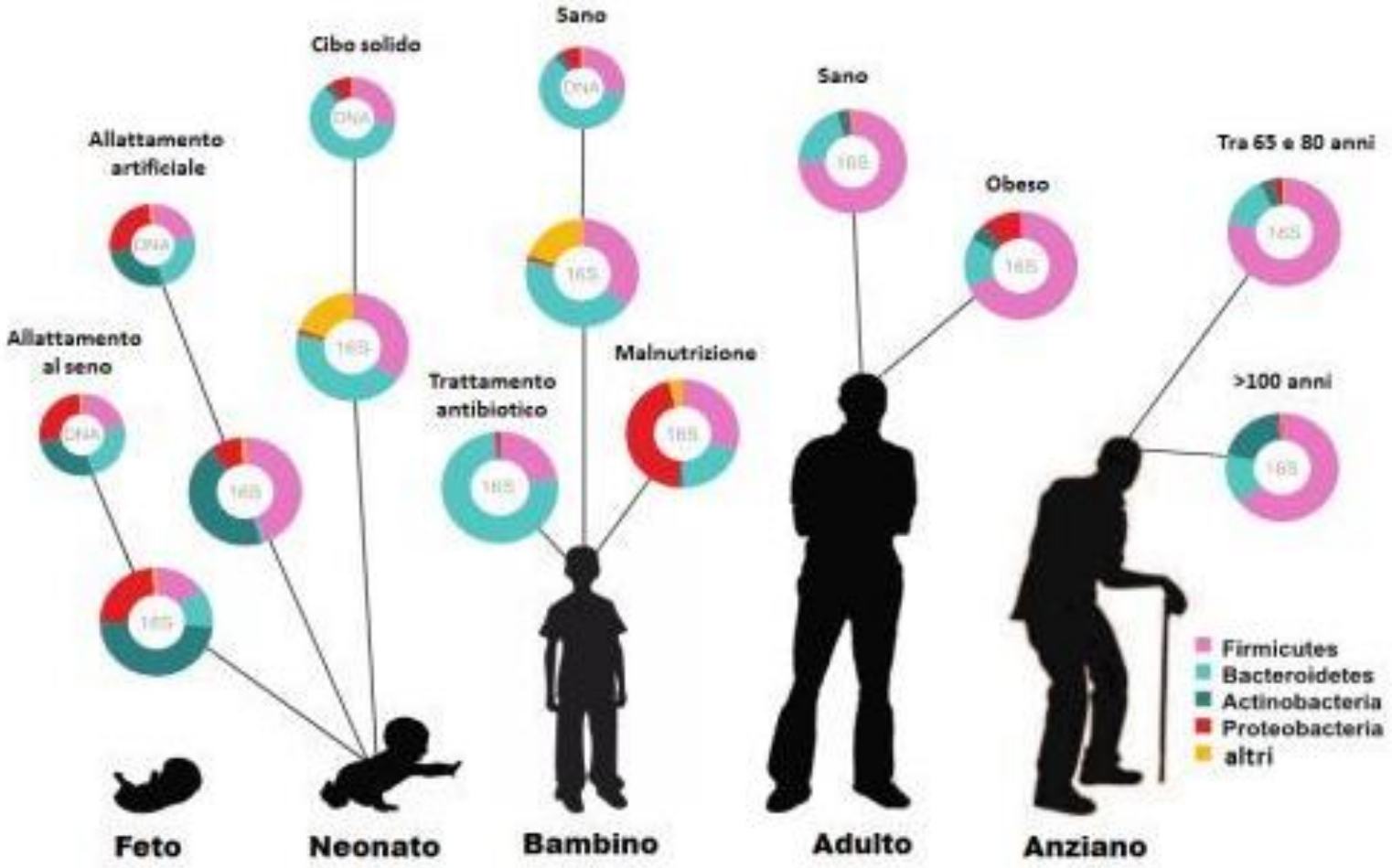


- An Echosystem is a community of organisms that live whithin an enviroment, getting mutual beneficial effects.

The human microbiome is the collective genome of all bacteria, archaea, fungi, protists, and viruses found in and on the human body



The microbiota composition changes with time



Intestinal microbiota is the most important

There are more than
3 MILLION
MICROBIAL GENES
in our gut microbiota

150 TIMES
more genes than in the
HUMAN GENOME[1]

The composition of
GUT MICROBIOTA
IS UNIQUE
to each individual,
just like our
FINGERPRINTS[1]

APPROXIMATE
WEIGHT OF THE TOTAL
GUT
MICROBIOTA[1]

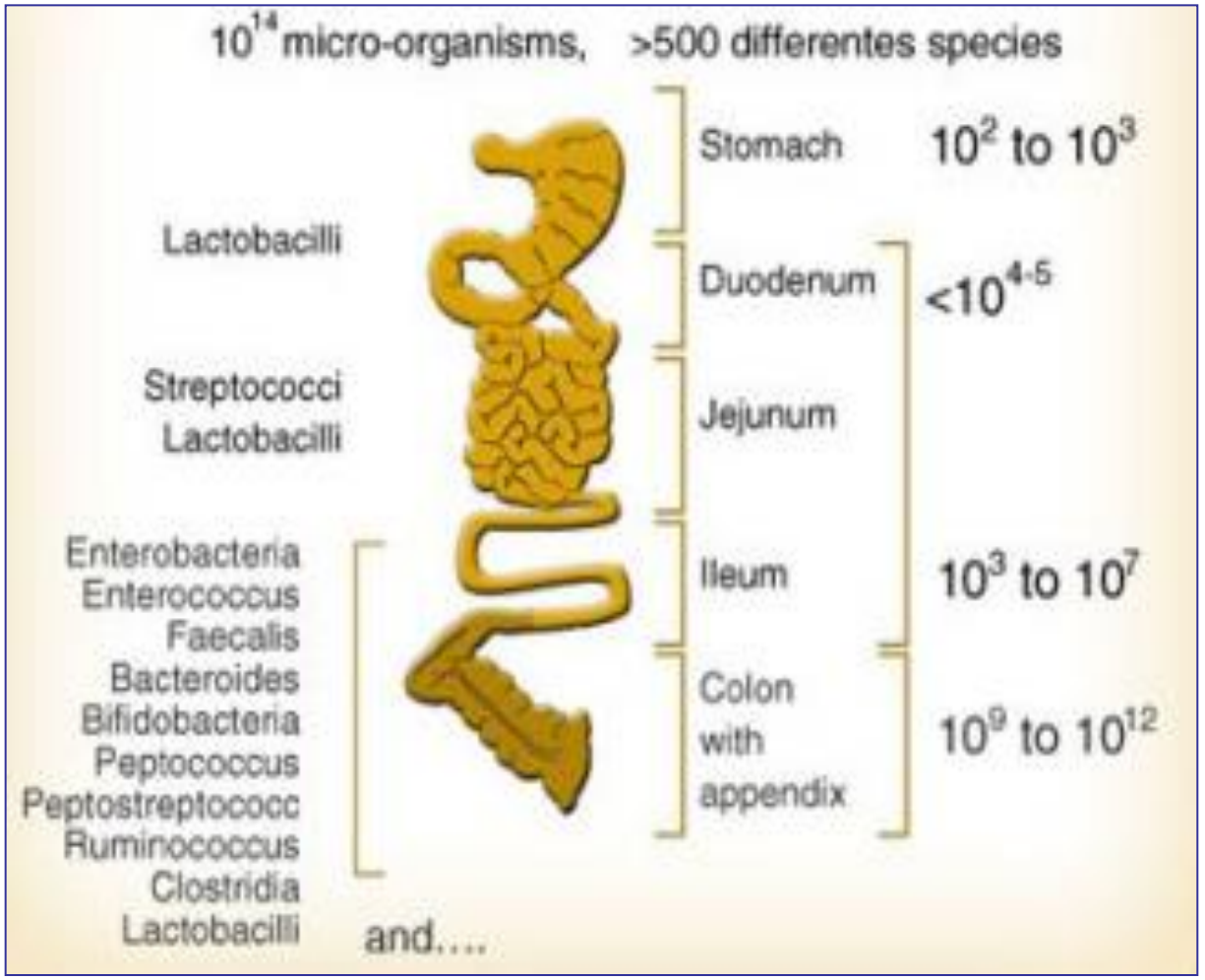
OUR GUT MICROBIOTA EVOLVES THROUGHOUT OUR ENTIRE LIFE
and is the result of a variety of influences:[1-2]

Main bacteria present in the intestinal microbiota

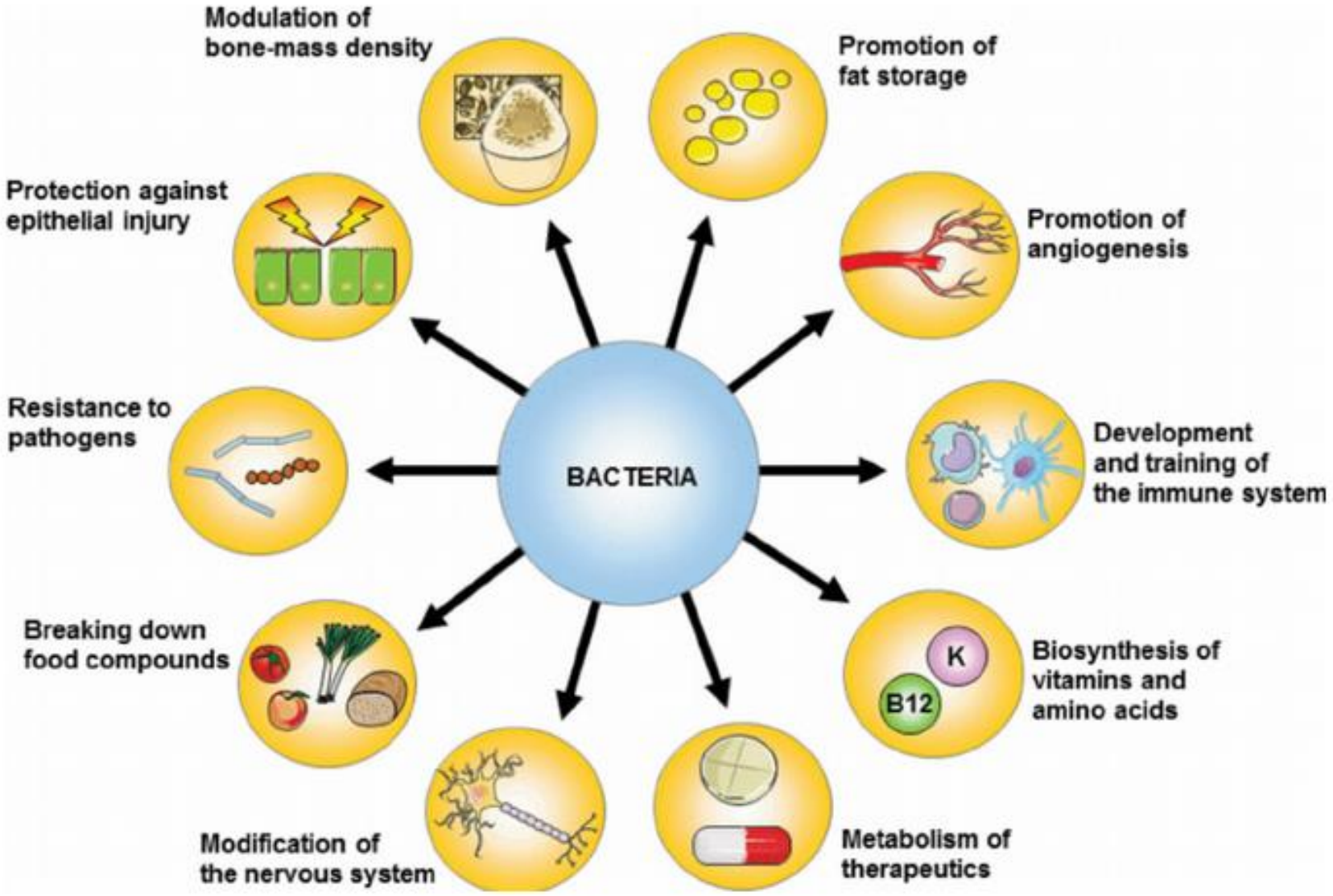
Intestinal flora comprises 3 main types of bacteria:
- *Firmicutes* (30%-50%),
- *Bacteroidi* (20%-40%)
- *Actinobacteri* (1%-10%).

Among anaerobi *Eubacteri*, *Bifidobacteri, Fusobacteri*, *Peptostreptococchi* e *Atopobium* are the most represented

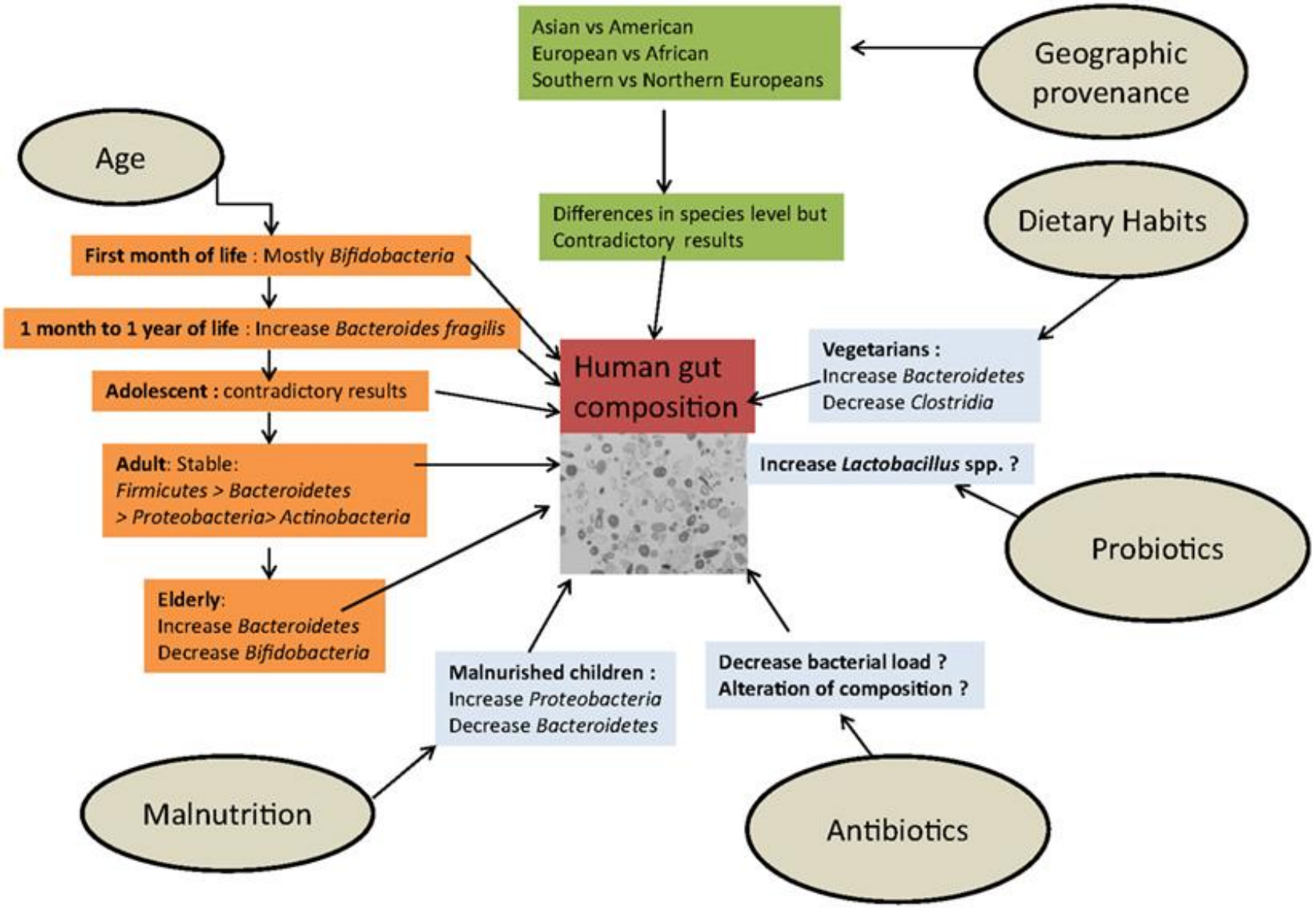
Lactobacilli, *Enterococchi*, *Streptococchi and Enterobacteri are less reprented*

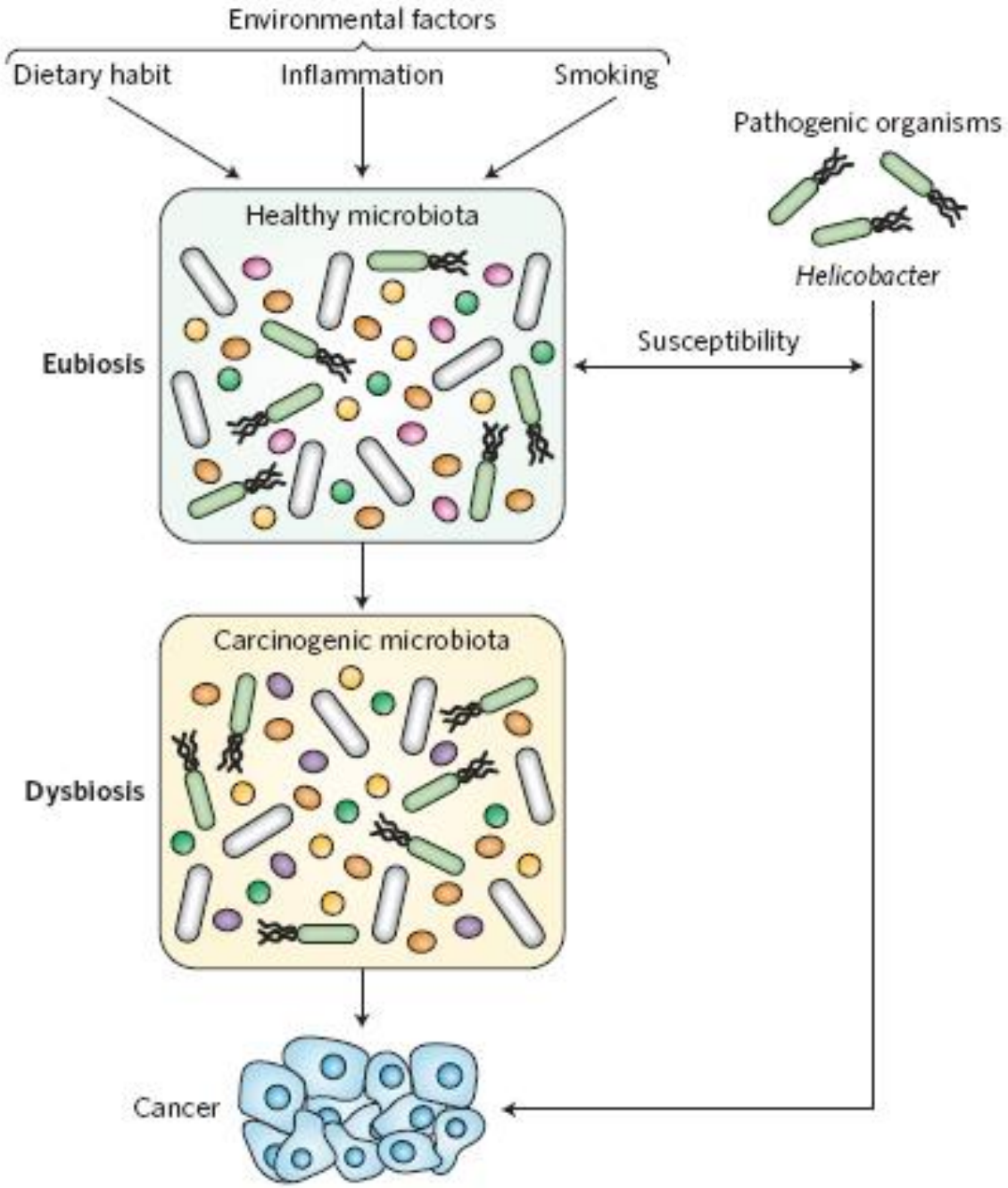


Le funzioni del microbiota



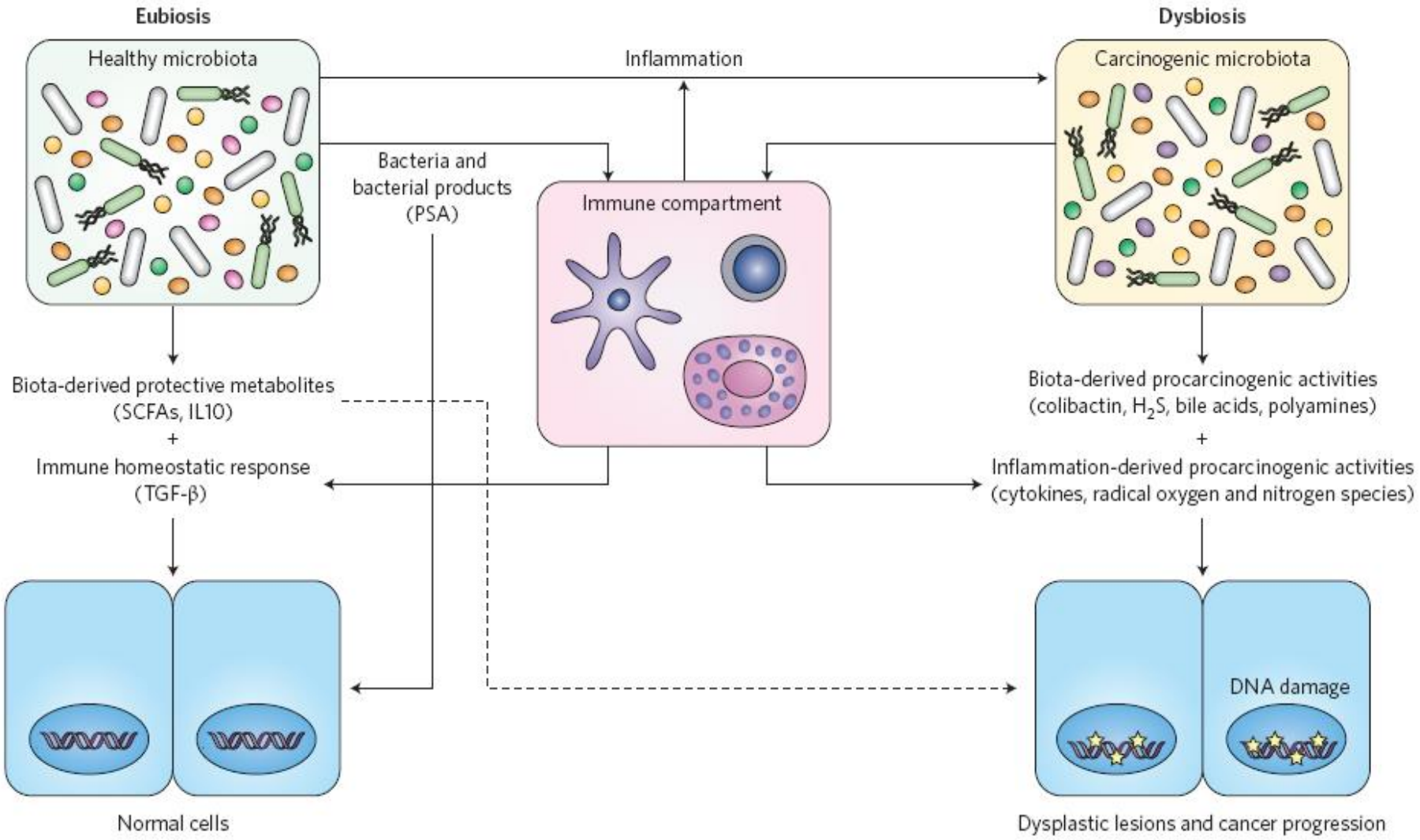
What influences the microbiota?





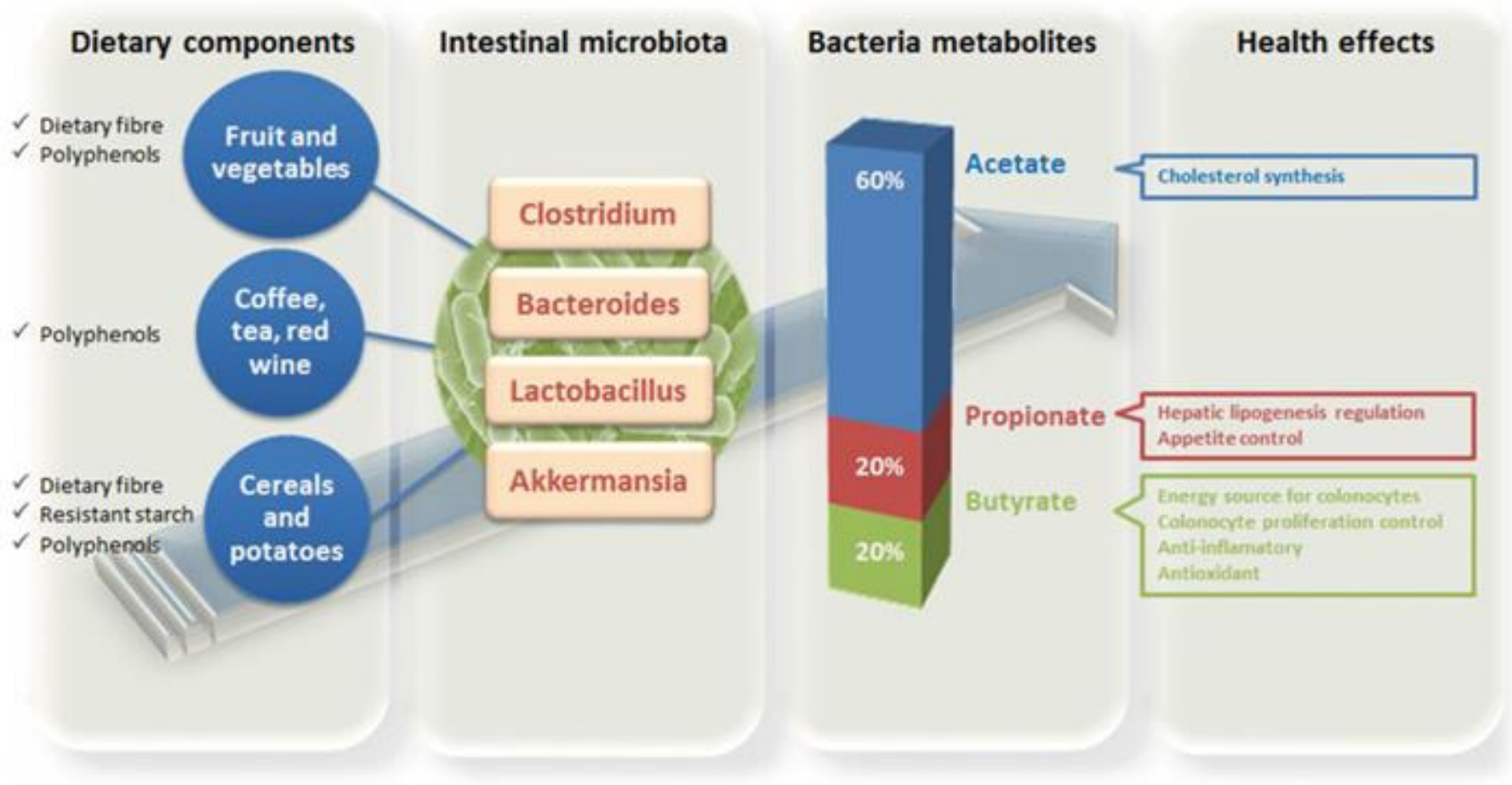
Enviromental factors can induce changes in the microbiota composition, that can increase tumor susceptibility

Interaction between microbiota and immune system can favor the onset of cancer

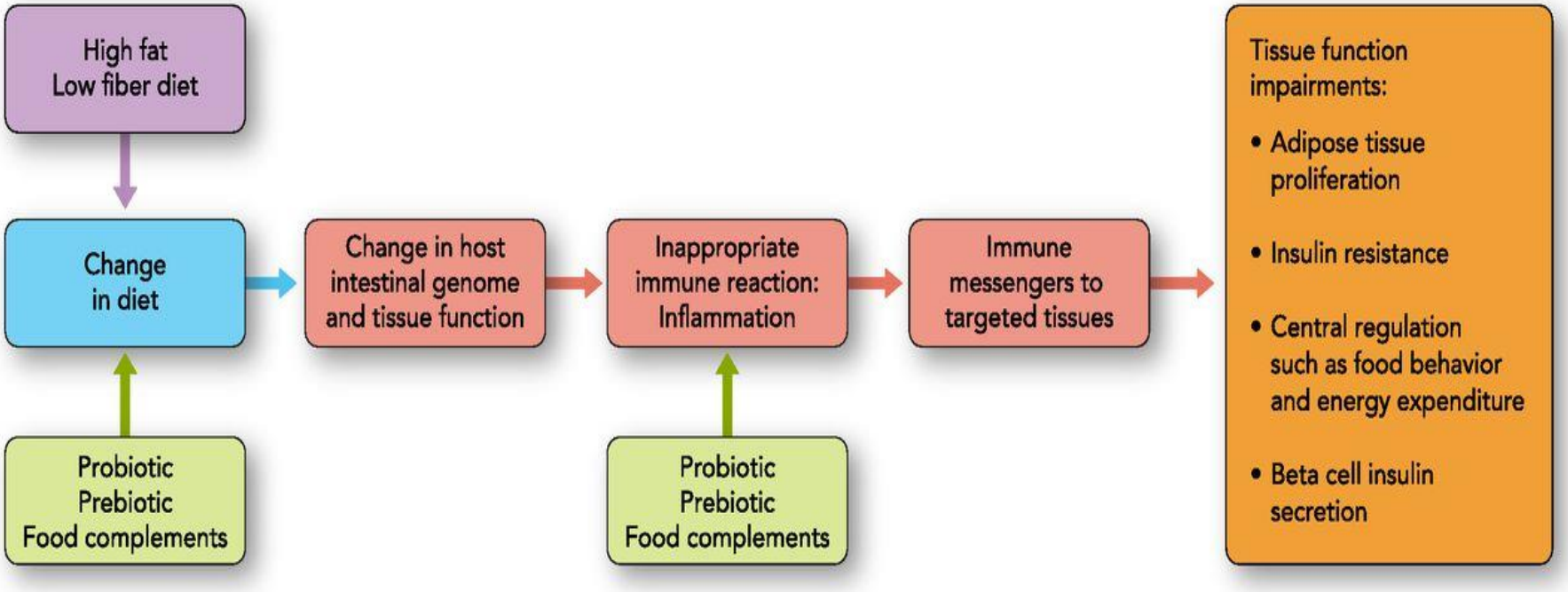


SCFA: short chain fatty acid; PSA Polysaccaride A

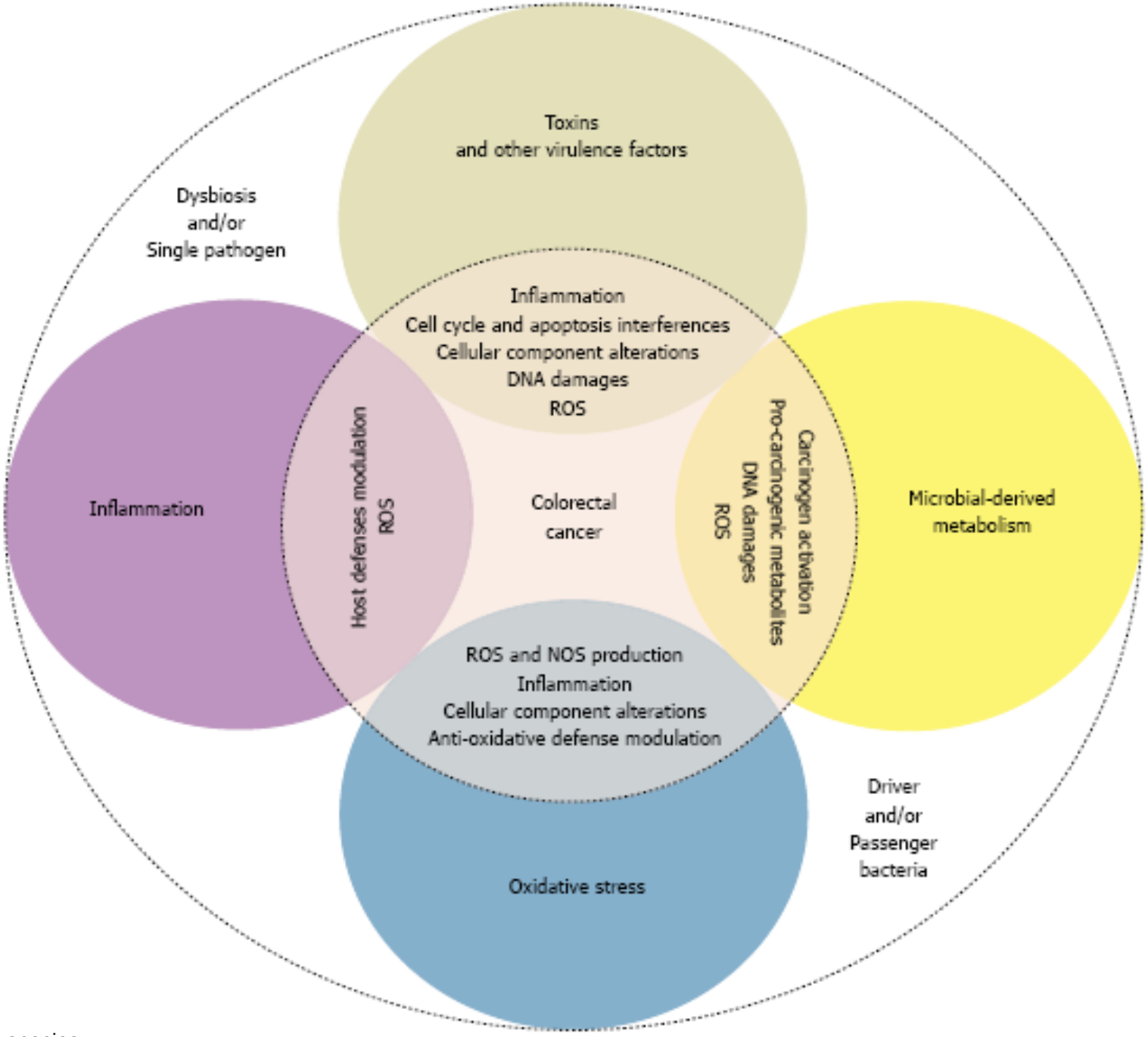
Effects on health due to the metabolic activity of intestinal microbiota



Effects of high-fat containing diet

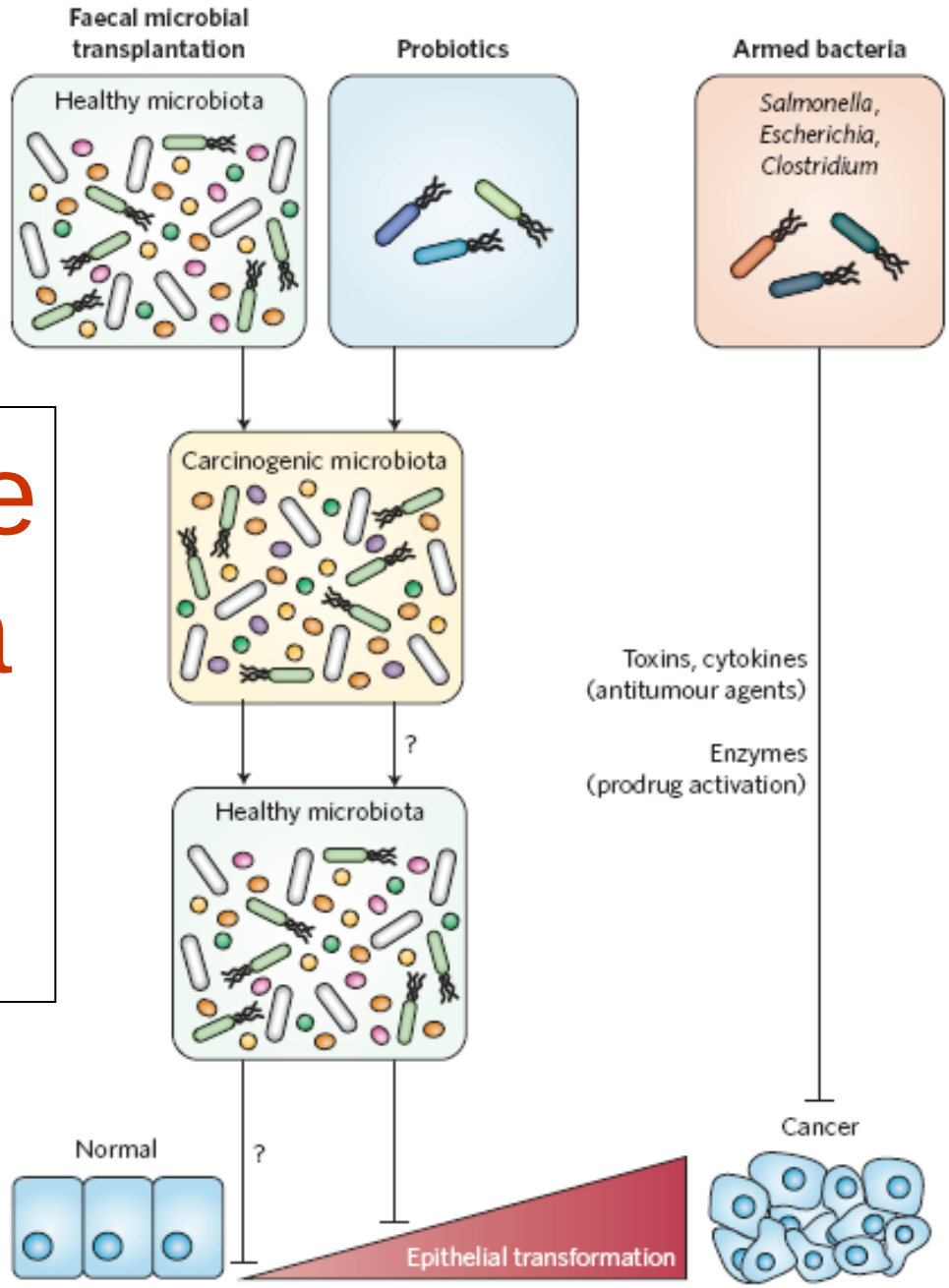


Potential relationschips between microbiota and cancer



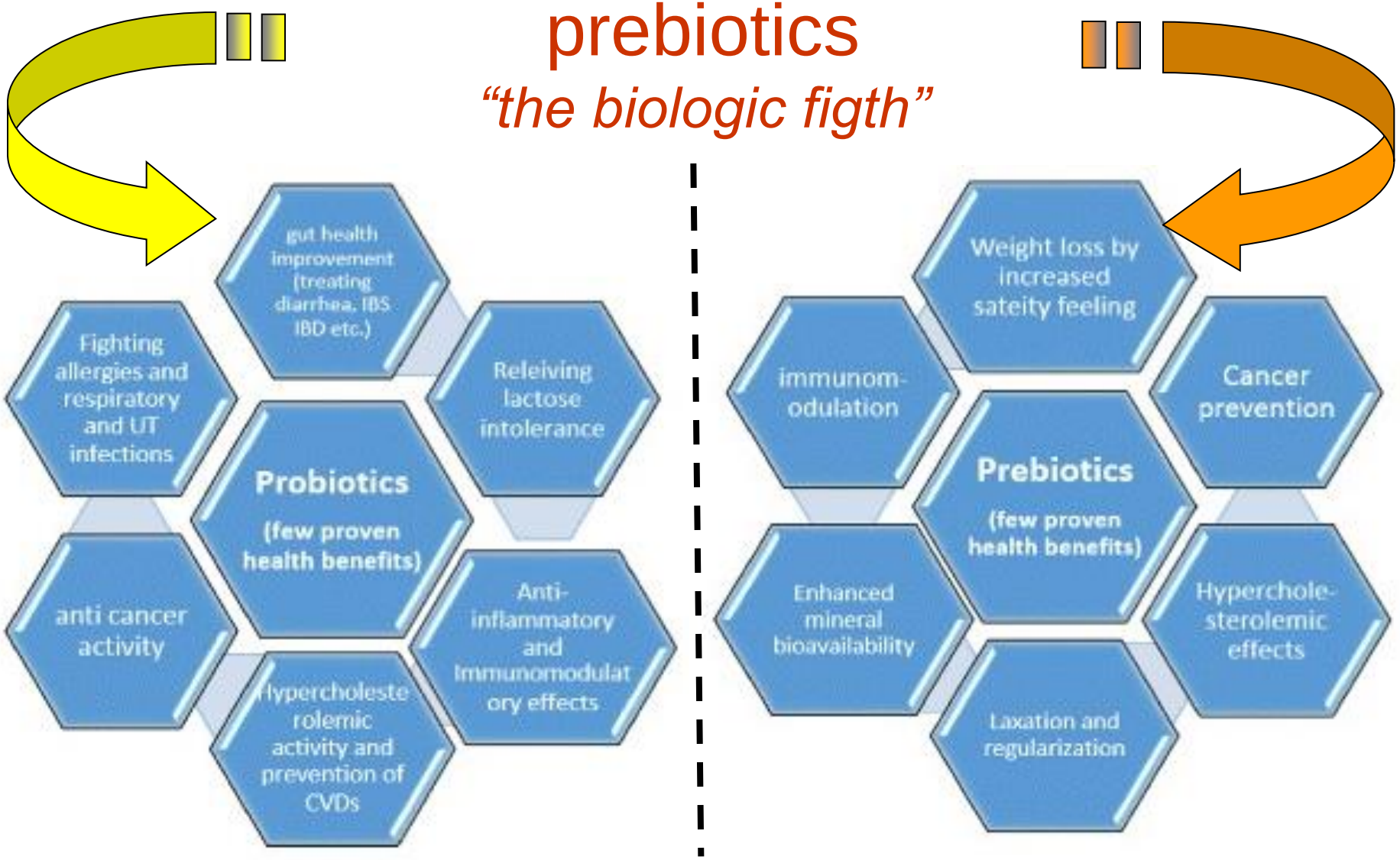
ROS: reactive oxygen species

A possible role for microbiota in the cancer therapy



Probiotics and prebiotics

"the biologic figth"



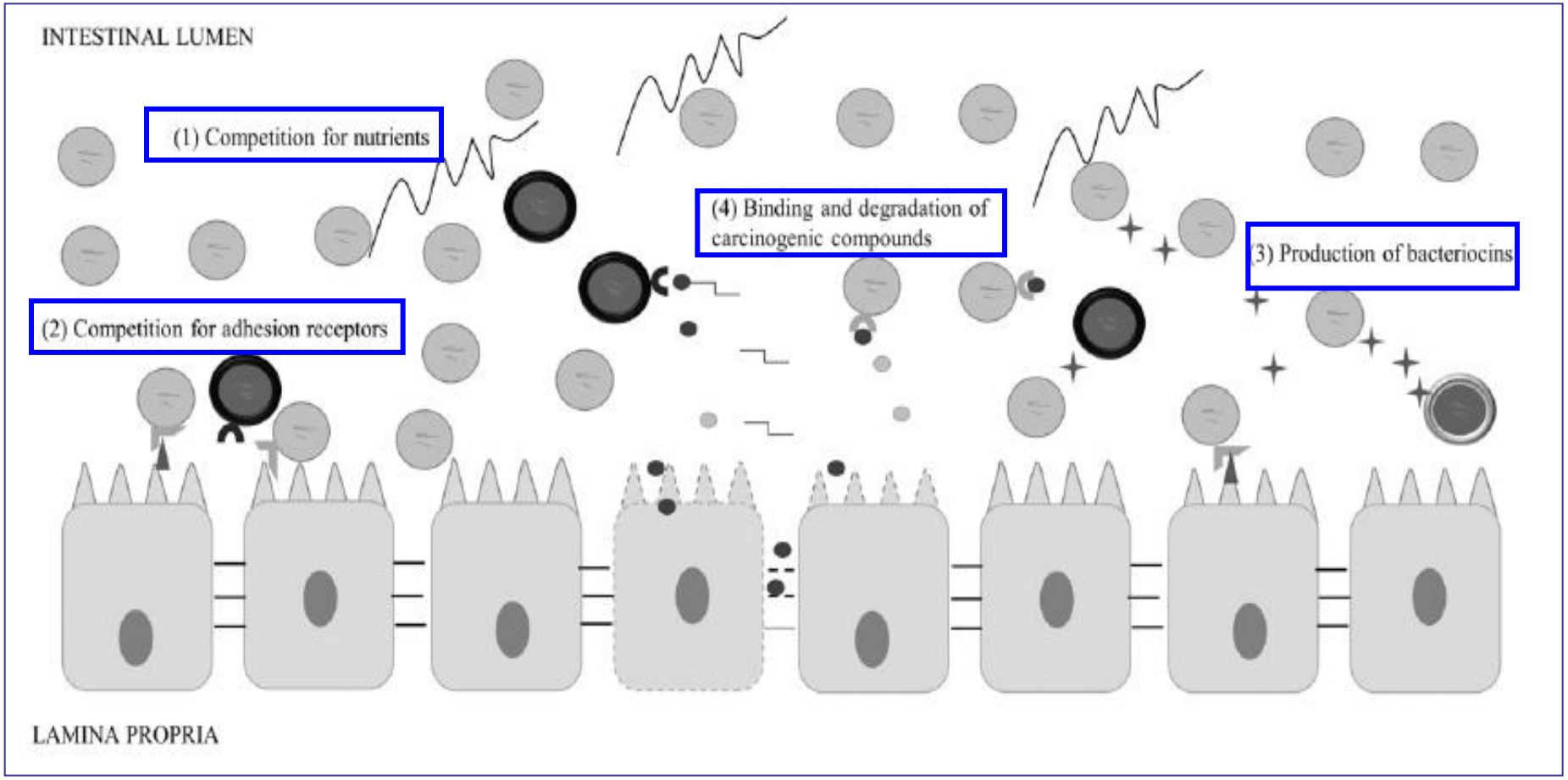
Probiotics: live bacteria in diary products

Prebiotics: specialised fibers with beneficial effects on good bacteria in the gut

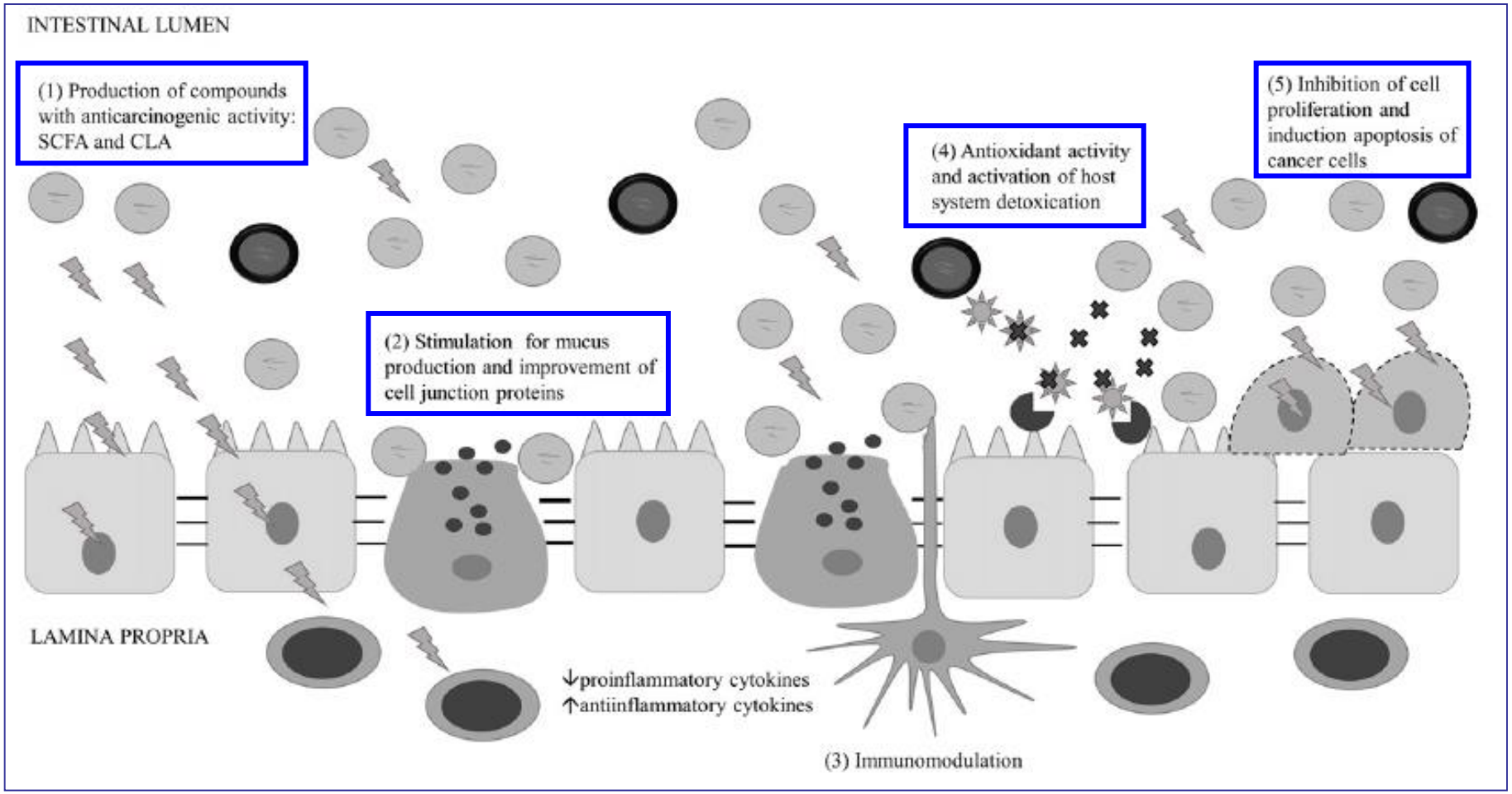
Possible preventive role of probiotics

Probiotics	Effects	Potential mechanisms
Bacillus polyfermenticus SCD	↓ Cell proliferation	?
Bifidobacterium adolescentis SPM0212	↓ Cell proliferation	?
L. plantarum LA11 and *S. thermophilus* VM46	↓ DNA damage	?
L. rhamnosus GG and *B latis* Bb12	↑ Apoptosis	Activation of the apoptosis through the mitochondrial pathway: ↑ BAX translocation, cytochrome c release, and caspase-9 and -3 cleavage
Saccharomyces boulardii	↓ Cell proliferation and colony formation ↑ Apoptosis	Inactivation of the EGFR-Mek-Erk pathway signaling
Bacillus polyfermenticus	↓ Cell proliferation Did not induce apoptosis.	Inhibited the ErbBs 2 and 3 receptors' expression and their downstream molecules including the cyclin D1 and its transcriptional regulator E2F-1
Bacillus polyfermenticus	Did not affect cell colony formation of normal colonocytes ↓ Cell colony formation in cancer cells	Inhibited the ErbBs 2 and 3 receptors' expression and theirs downstream molecules including the cyclin D1 and its transcriptional regulator E2F-1 Antioxidant and SCFA activities

A regular use of probiotics can regulate the instinal microbiota



Other possible effects of probiotics



CLA: conjugated linoleic acid

Bacterial metabolites exerting a preventive effect on cancer growth

Whole food	Dietary component	Bacterial metabolite	Potential mechanism(s) of chemoprevention
Fruits, vegetables, grains	Fiber	Butyrate	- Energy source for colonocytes - HDAC inhibitor (cell cycle, apoptosis) - Ligand for GPRs - Anti-inflammatory effects
Berries, walnuts, pomegranates	Ellagic acid	Urolithins	- Alters estrogenic activities - Inhibits COX-2 and inflammation
Soy-based products	Daidzein	Equol	- Binds to estrogen receptors (ER) and regulates their function - Antioxidant

Bacterial metabolites exerting a preventive effect on cancer growth

Whole food	Dietary component	Bacterial metabolite	Potential mechanism(s) of chemoprevention
Cruciferous vegetables (e.g., broccoli)	Glucosinolates	Isothiocyanates	- Bacterial thioglucosidases convert glucosinolates to isothiocyanates in cooked vegetables - Inactivate carcinogens - HDAC inhibitor (cell cycle, apoptosis) - Anti-inflammatory effects
Vegetable oils	Linoleic acid	Conjugated linoleic acid	- Ratio of omega-3 and omega-6 PUFAs - Anti-inflammatory effects - Inhibition of angiogenesis to minimize tumor vascularization

HDAC: Hystone deacethilase inhibitors; PUFA: poly unsatured fatty acid