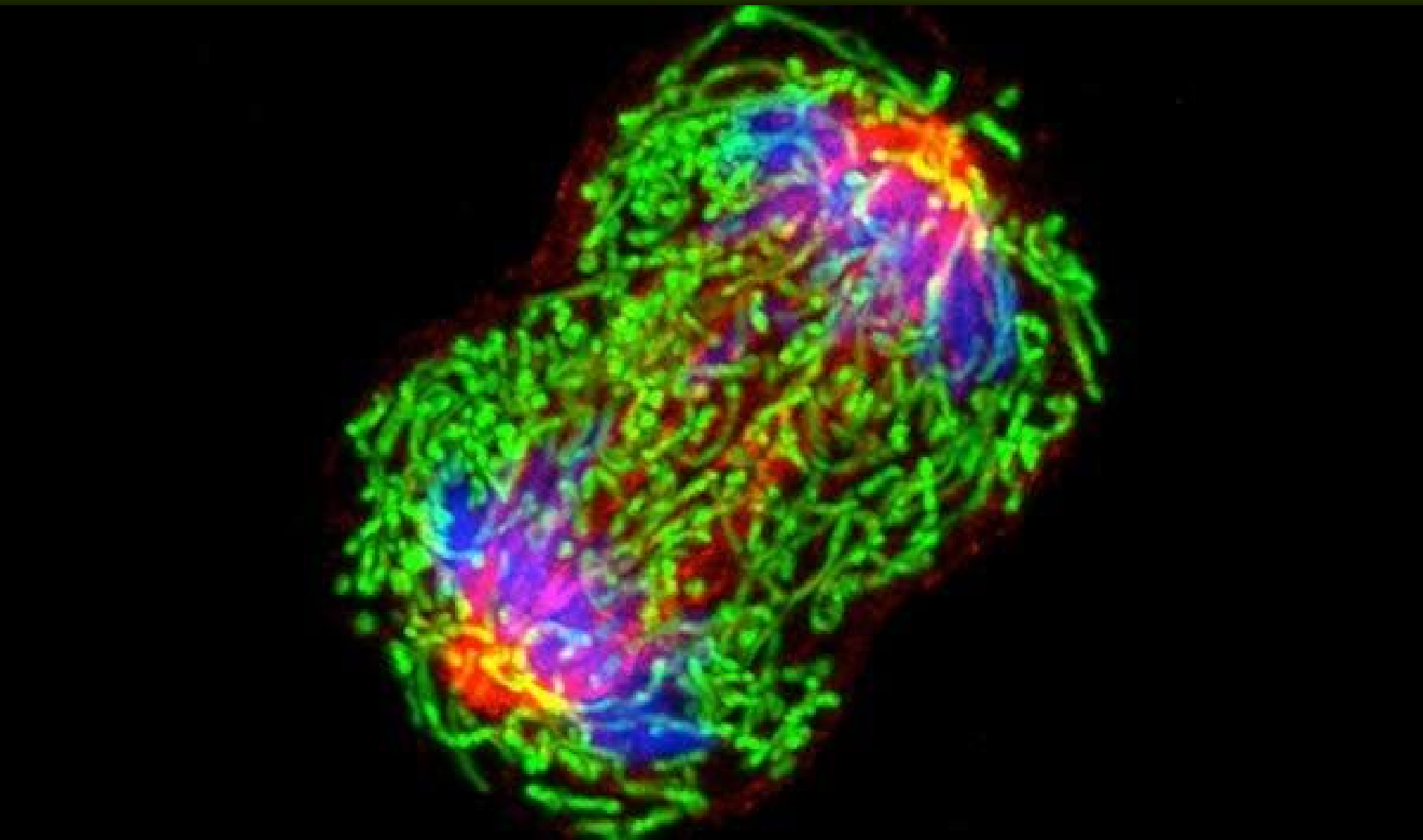
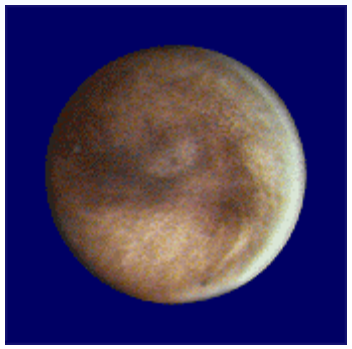
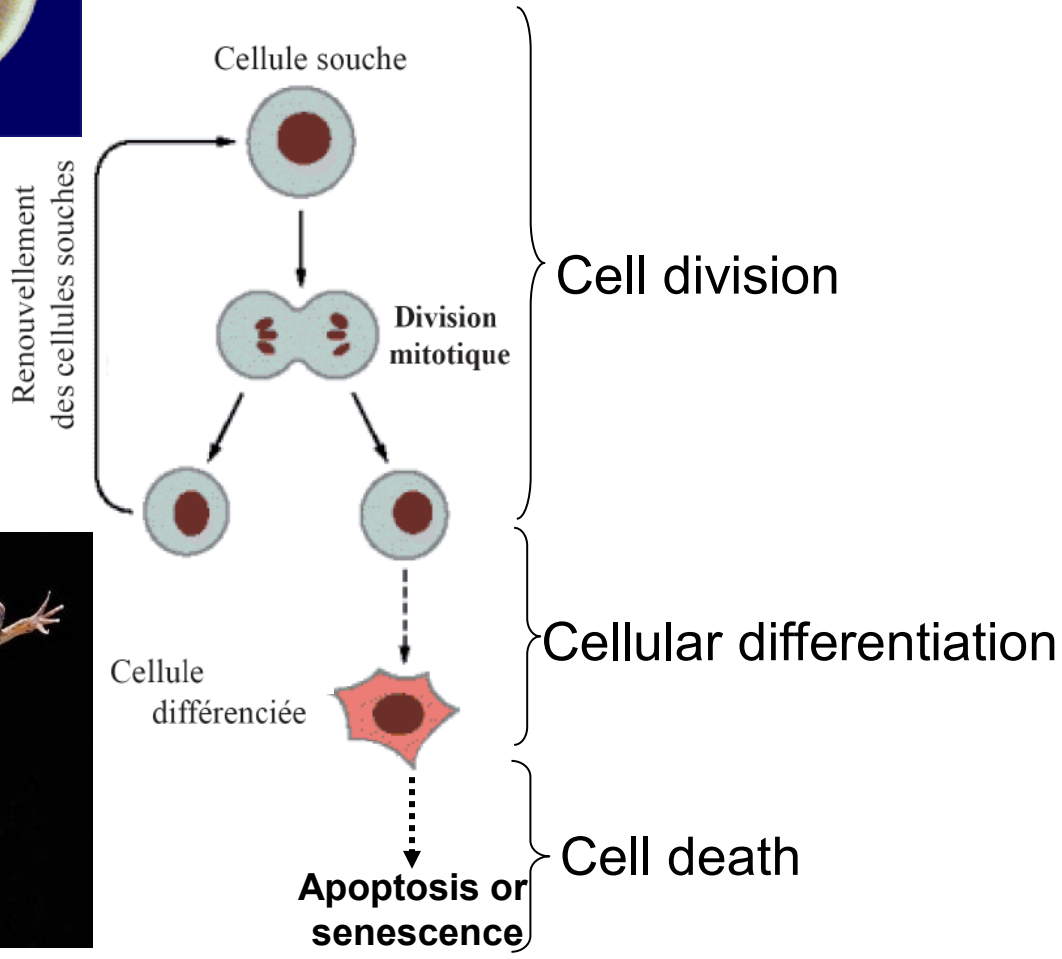
Cancers



Cancer corresponds to a deregulation of the fundamental cell functions



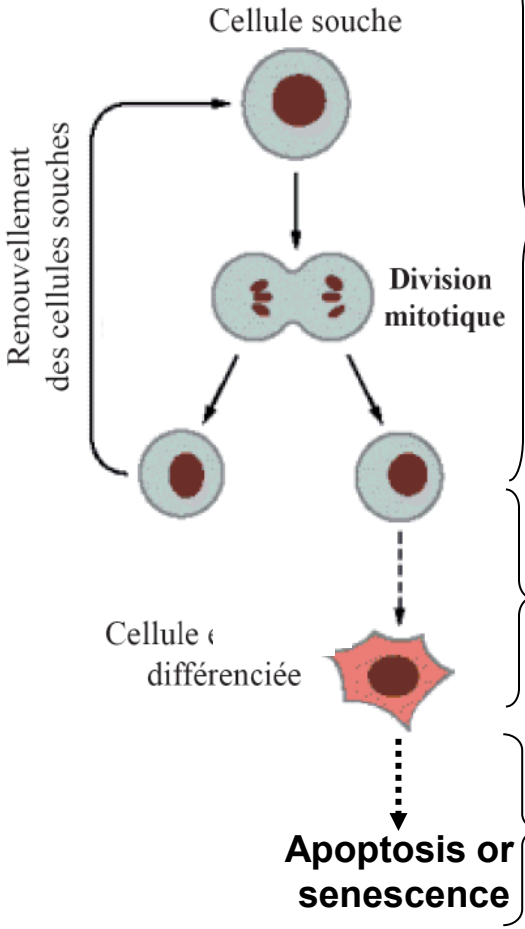


Hormones

Cytokines

Interactions cellular

Cancer corresponds to a deregulation of the fundamental cell functions



Cell division

De-differentiation

Cellular differentiation

Cell death

Development

death

DIVISION

Adult life

Division

death

death

DIVISION

Cancer

Cancer in the world

In 1600-1500 BC, Egyptian "breast ulcers" were cauterized with fire, but the disease was intractable. "A tumor from the God Xenus, you can't do anything about it".

In 2012,
Incidence: newly diagnosed cases
14.1 million new cases of **cancer** worldwide.

Morbidity: the number of sick people
32.6 million people diagnosed with cancer (in the last 5 years)

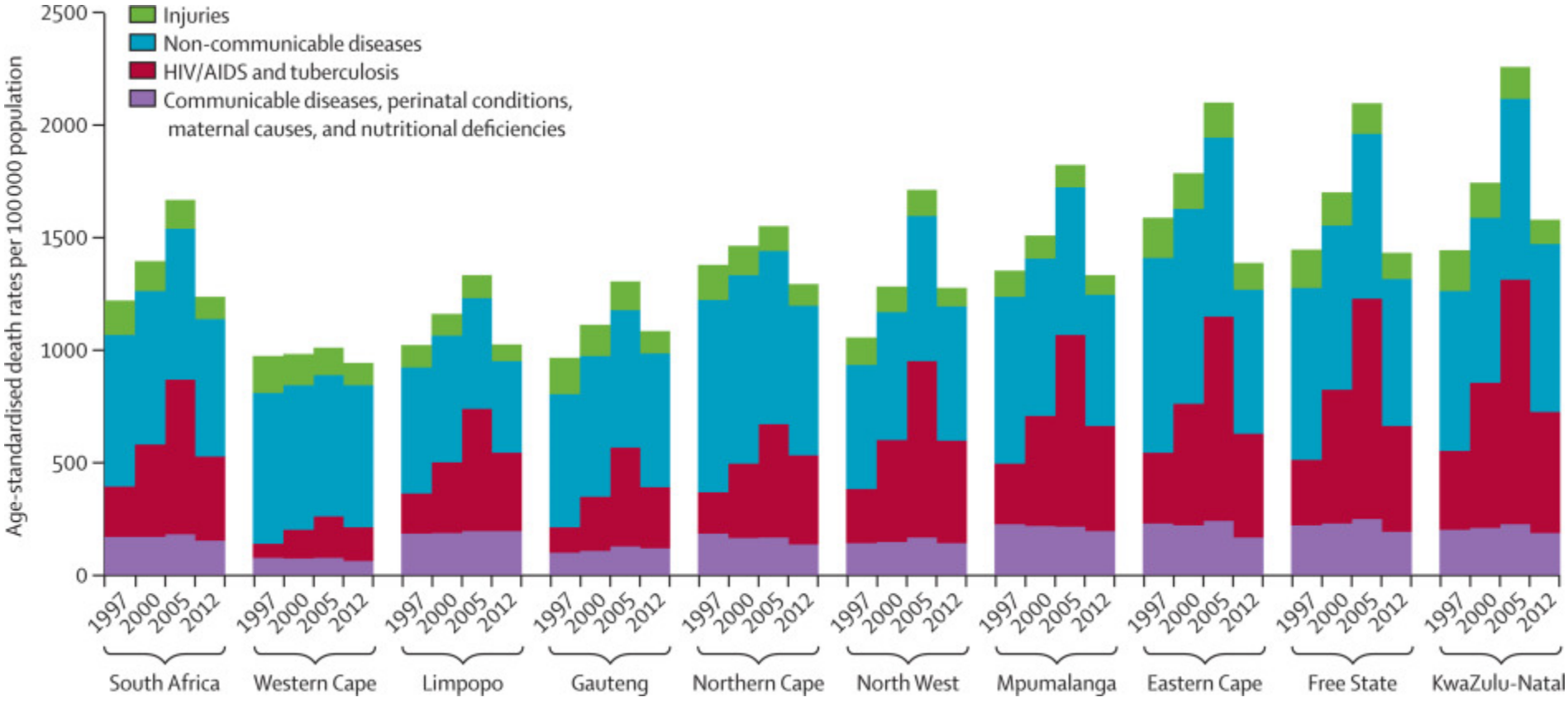
Mortality: deaths directly due to disease
8.2 million deaths from cancer

(http://www-dep.iarc.fr/; http://globocan.iarc.fr/; Globocan data, which compiles data on 28 types of cancer in 184 countries.) and Santé publique France

In 2018,
Incidence: 18.1 million

Mortality: 9.6 million

Cancers in South Africa



Cancer progression in South Africa

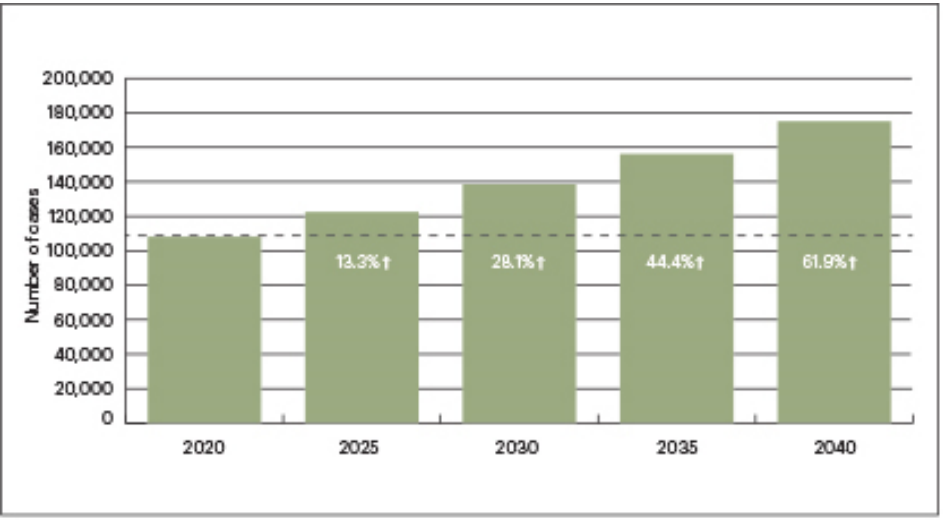


FIGURE 1: Trends in the Incidence of New Cancer Cases in South Africa: 2020–2040.

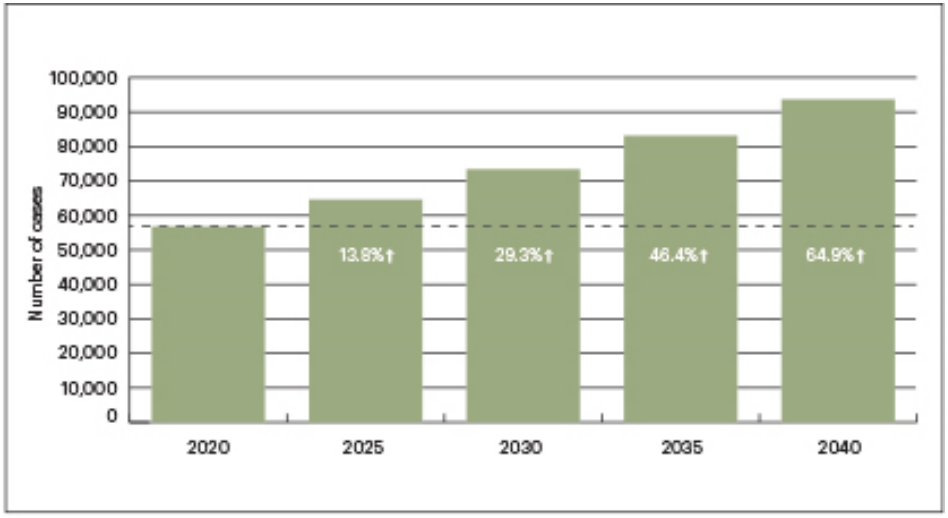
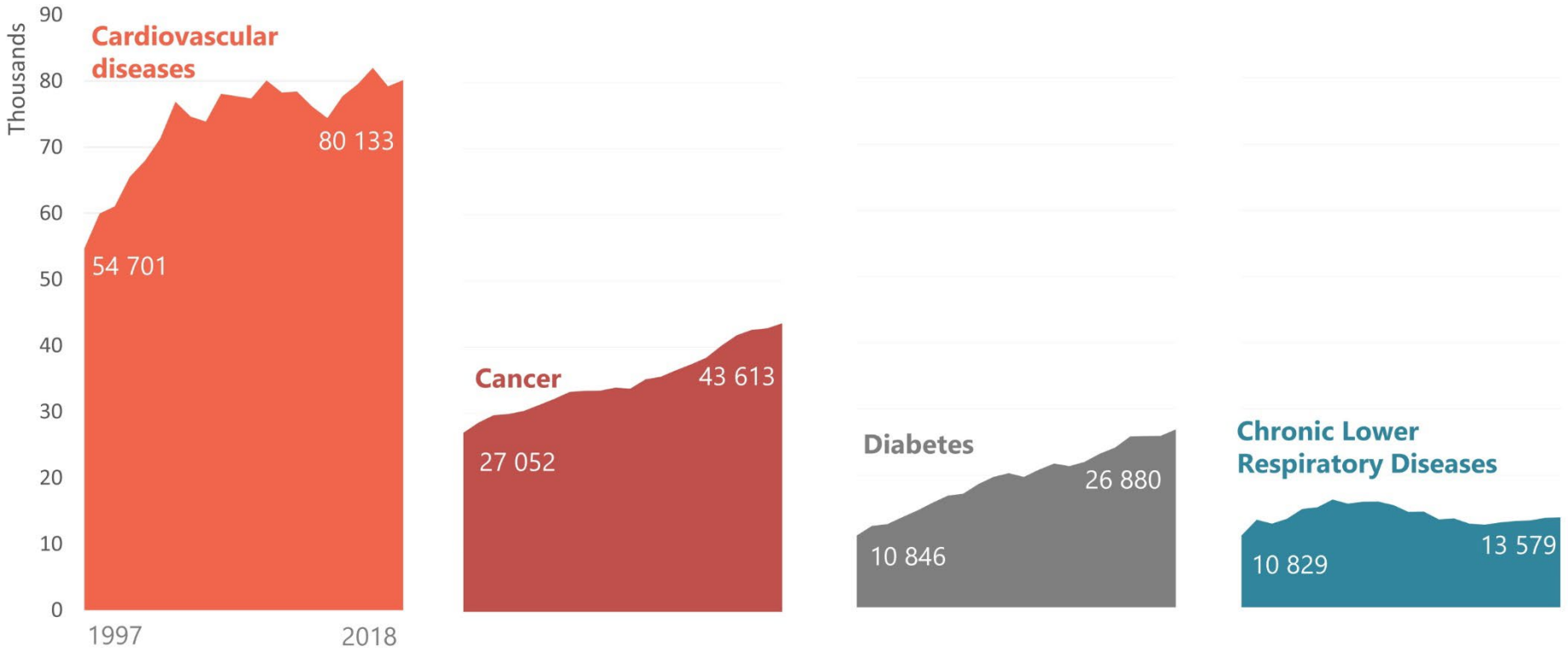


FIGURE 2: Trends in Cancer-Related Mortality in South Africa: 2020–2040.

Cancers in South Africa

Deaths due to noncommunicable diseases, comprising **cardiovascular diseases**, **cancer**, **diabetes** and **chronic lower respiratory diseases** increased by 58,7% over 20 years, from a total of 103 428 in 1997 to 164 205 in 2018.

Deaths due to major noncommunicable diseases over a 20-year period: 1997-2018



Source: Non-communicable diseases in South Africa: Findings from death notifications 2008 – 2018

Rather than talking about cancer, it's more accurate to refer to cancers

Major cancers in South Africa

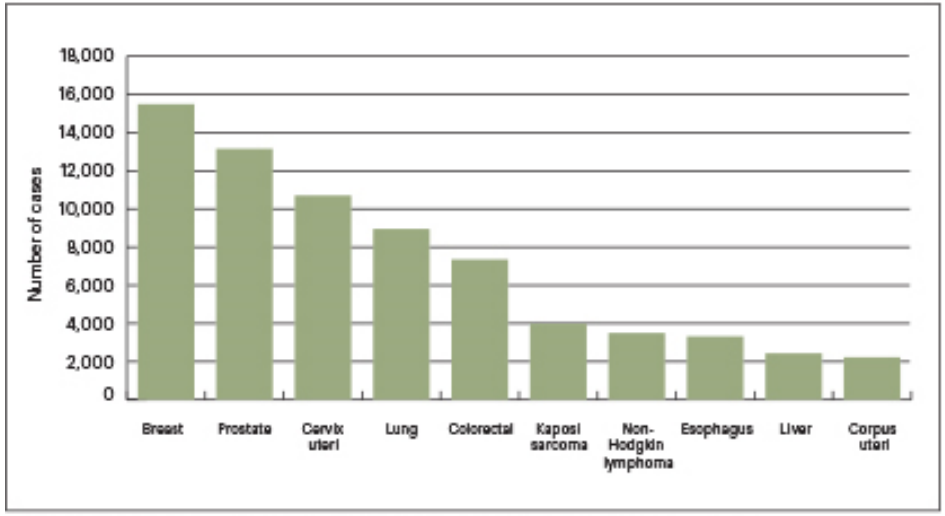


FIGURE 3: Top 10 Cancers by Incidence—Current Rates in South Africa.

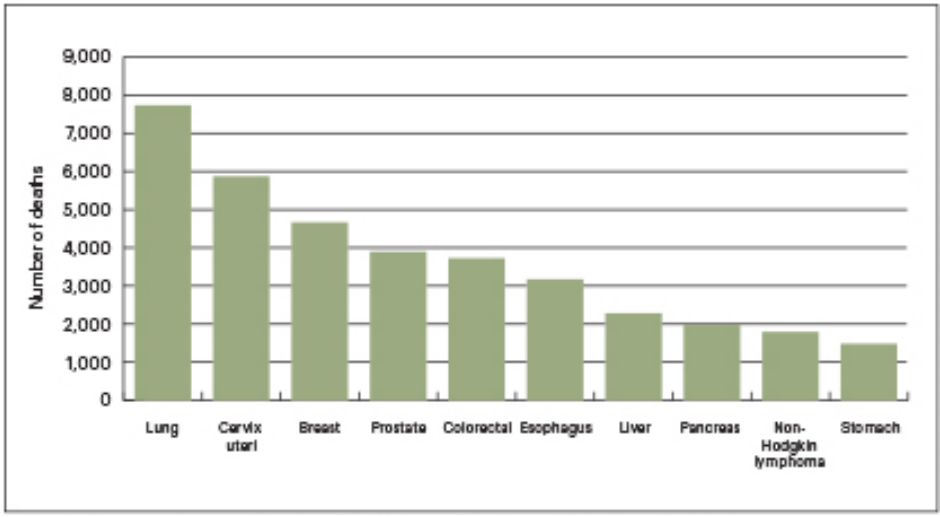
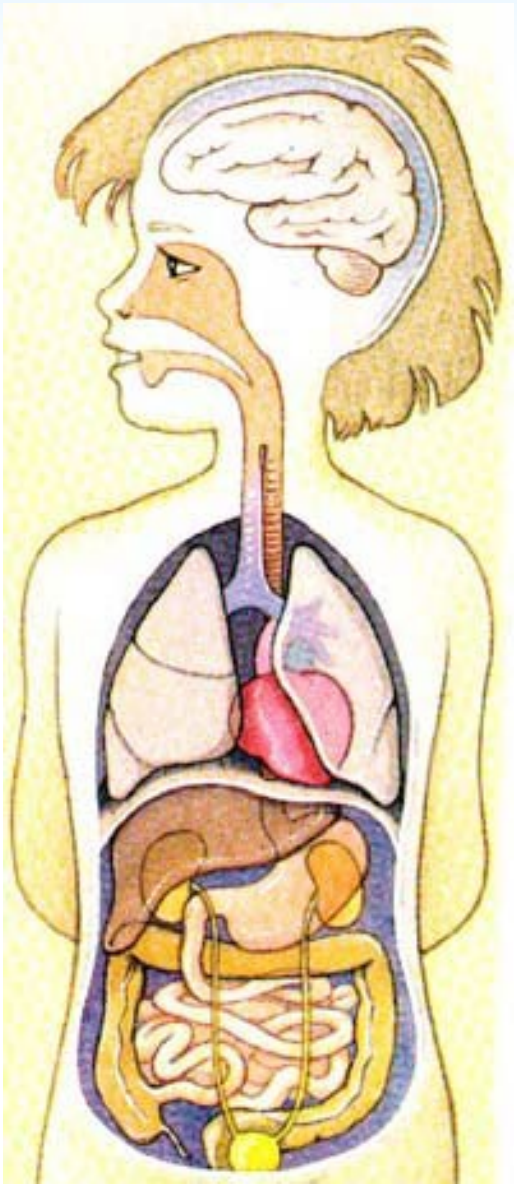


FIGURE 4: Top 10 Cancers by Mortality—Current Rates in South Africa.

Source for Figures 1–4: GLOBOCAN Cancer Today & Cancer Tomorrow. Available at https://gco.iarc.fr. Accessed July 20, 2021.

Cancers differ according to the type of cell from which they emmerge



- Epithelial cells: carcinomas (nearly 85% of cancers)
(lungs, colon, breasts, pancreas, stomach, esophagus, prostate, ovary, etc.).

- Connective tissue or muscle cells: sarcomas (1% of cancers)
(fibrosarcoma, osteosarcoma, angiosarcoma, liposarcoma...)

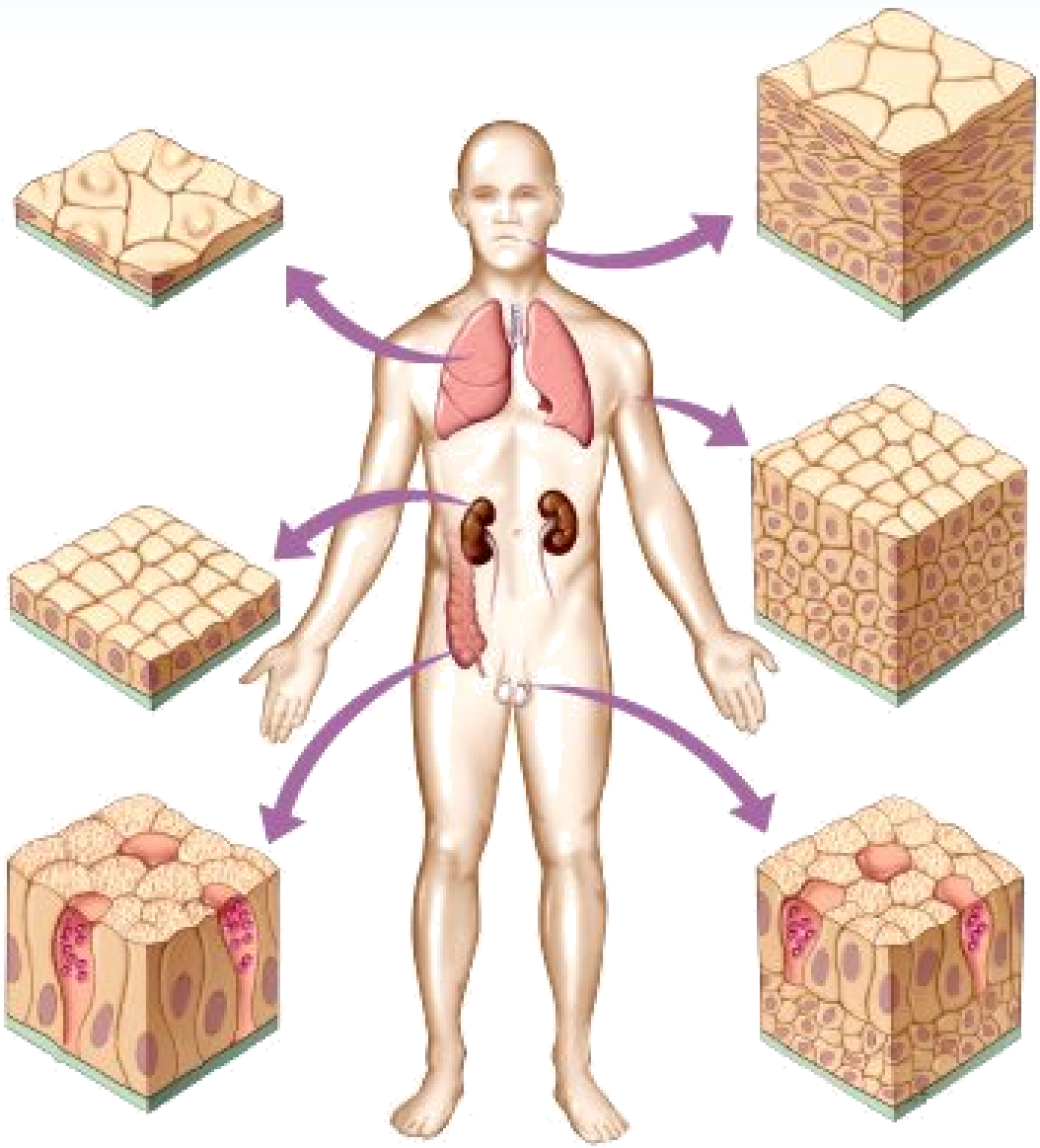
- Immune cells: leukemia (8%)
(myeloid leukemia, lymphocytic leukemia...)

- Nervous system cells: neuroectodermal tumors (2%)
(gliomas, neuroblastomas, schwanomas, meningiomas...)

- Others (5%)

Among cancers of the same cell type, there are also many variations.

Carcinomas can affect any epithelial tissue in the body



Cancers of the colon, breast, pancreas, stomach, esophagus, prostate, lung, ovary, endometrium, skin, pharynx, larynx, uterus, bladder, kidney, liver...

Course outline

I- An example of cancer: colorectal cancer

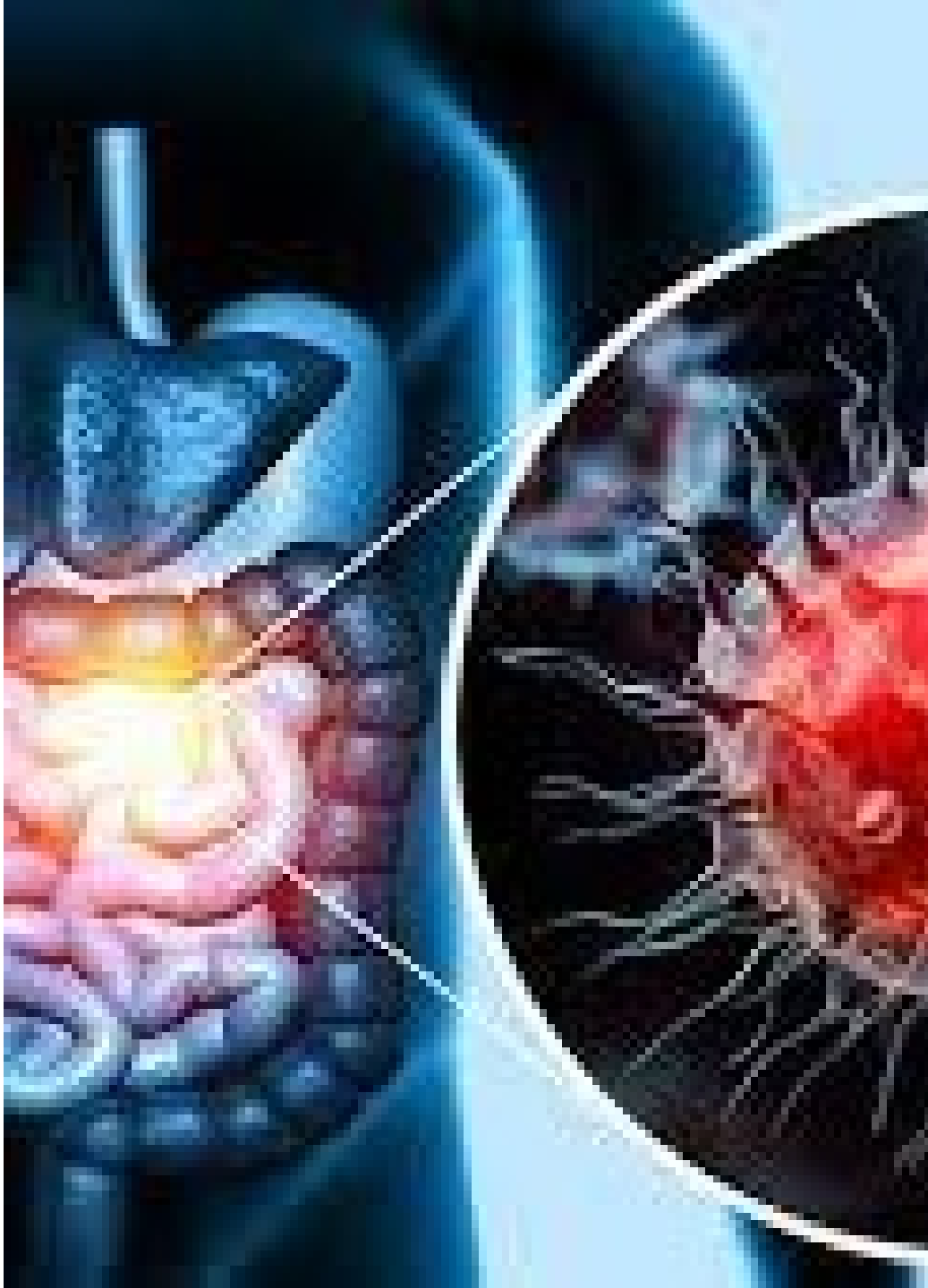
II- Tumor formation and evolution

III- Molecular mechanisms of oncogenesis

IV- Prevention, screening and treatment

I- An example of cancer: colorectal cancer

- Presentation
- Epidemiology
- Risk factors

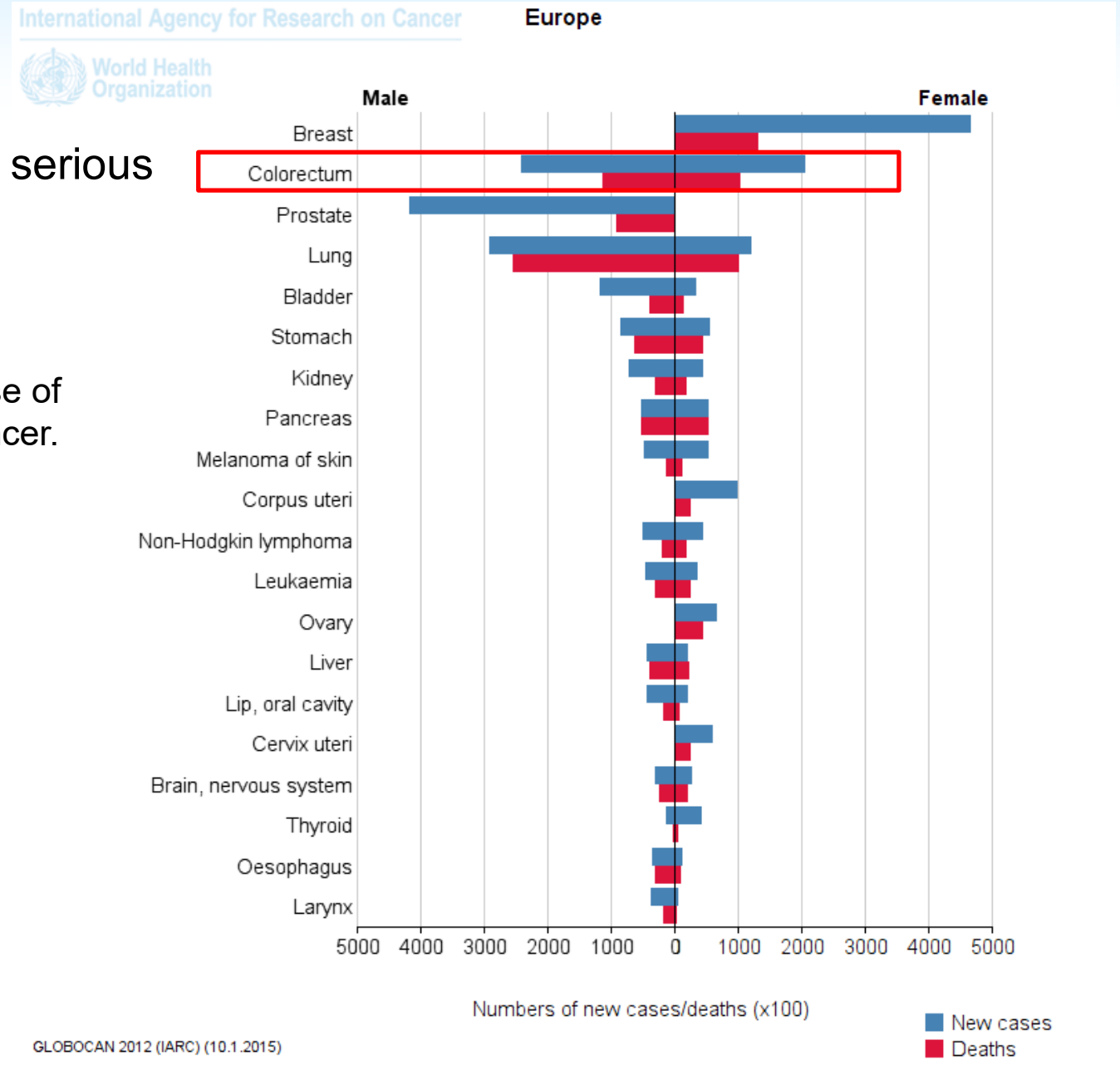


Colorectal cancers are particularly common.

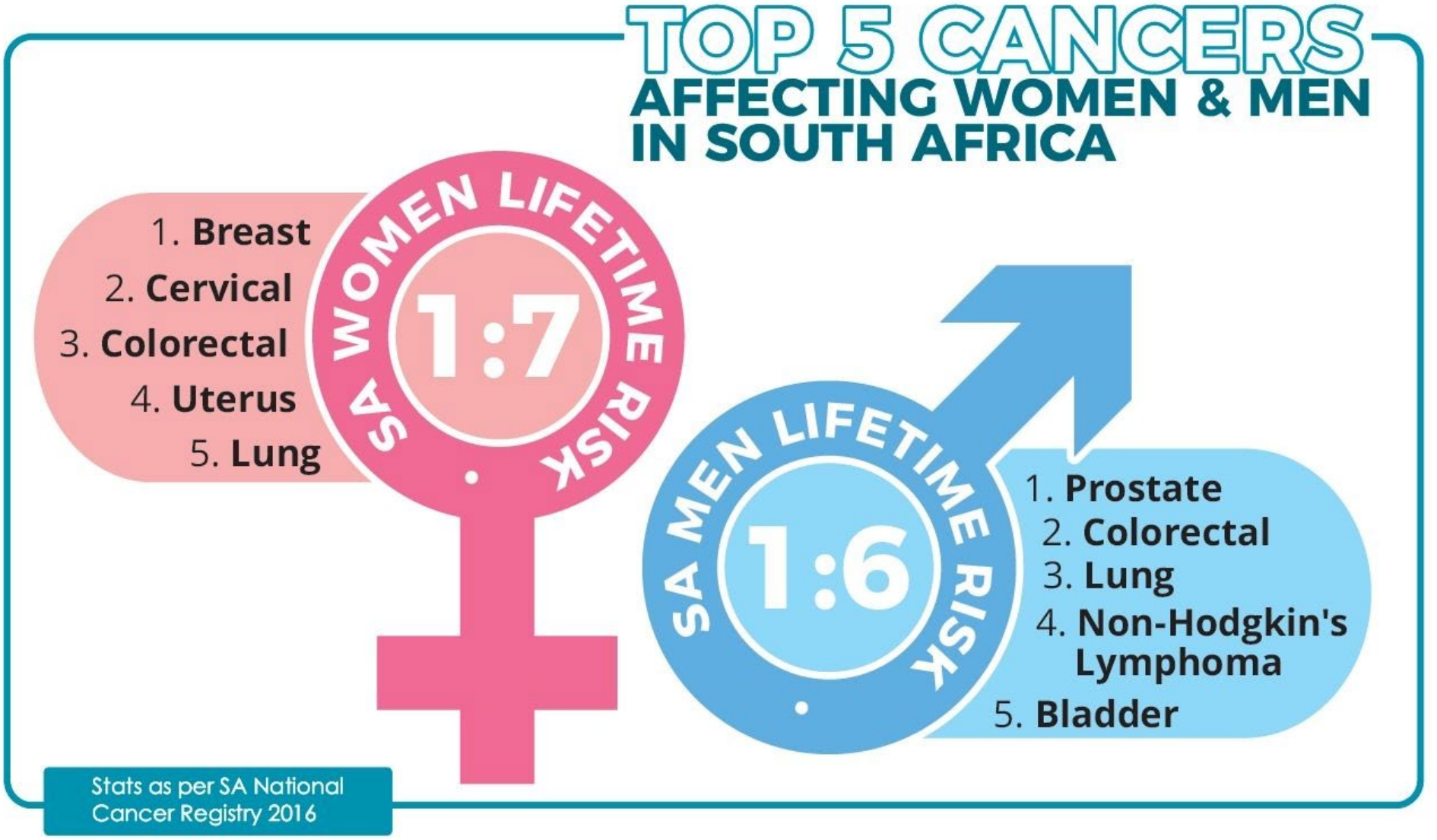
Colorectal cancers are serious cancers.

- 56% 5-year survival rate
- 79% at 1 year.

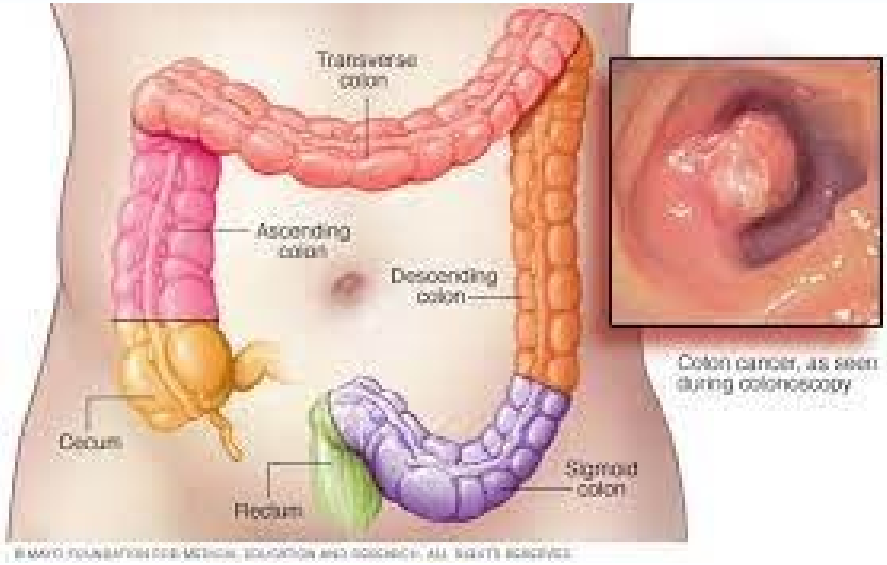
It is the second leading cause of cancer deaths after lung cancer.

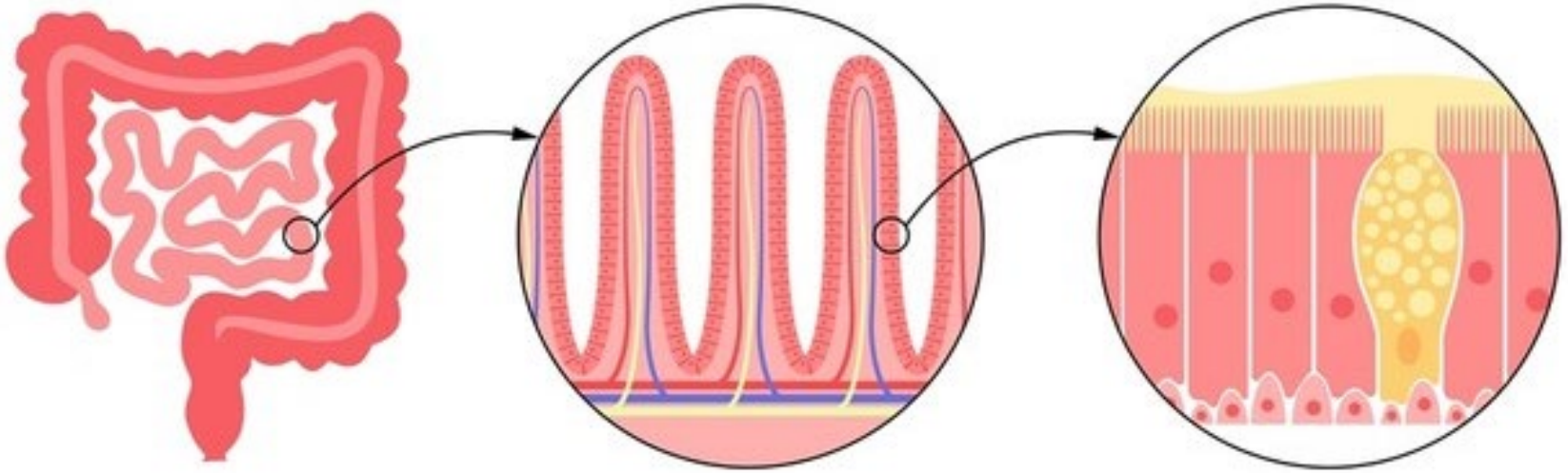


Colon Cancer in one of the major cancer in South Africa



Colorectal cancer affects the epithelial cells of the colon





CRCs may be favoured by environmental factors

- Food-related factors

Diets high in animal fats and cholesterol and low in plant fiber are thought to promote colon cancer.

- Smoking

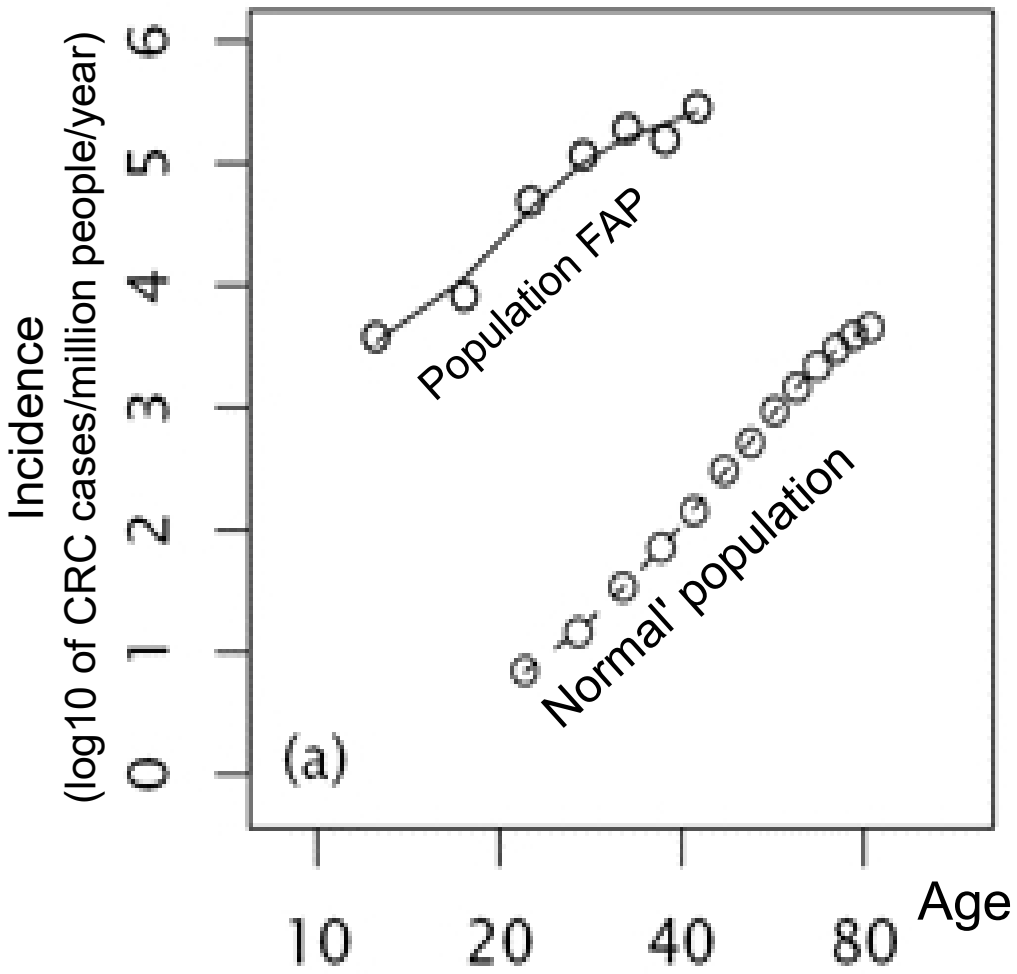
The risk of developing colon or rectal cancer is increased in subjects who have smoked more than 20 packet-years.

- Chronic colonic pathologies

CRCs may be genetic in origin

Over 5% of CRCs are due to a hereditary predisposition.

- Adenomatous polyposis family (FAP).
- Colorectal cancer syndrome hereditary non-polyposis (HNPCC) or Lynch syndrome



- These diseases are genetically transmitted.
- People with the disease have a very high risk of CRC.

Conclusions I

I- An example of cancer: colorectal cancer

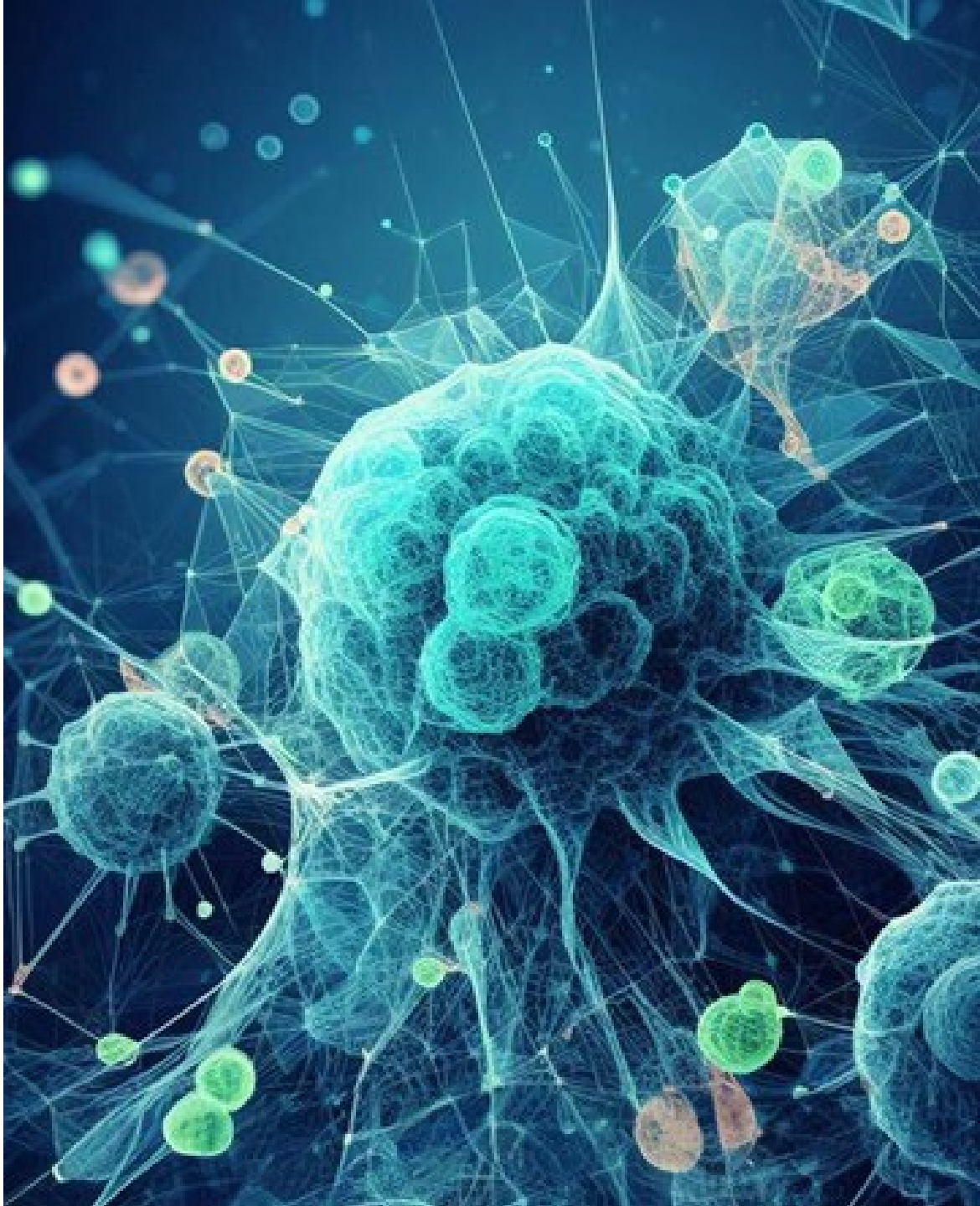
- Epidemiology

- Cancer is one of the world's leading causes of death.
- CRC is a carcinoma arising from the epithelial cells of the colon.
- CRC is one of the most common cancers.
- CRCs, like most cancers, are on the increase.
- Mortality due to CRC has fallen slightly.

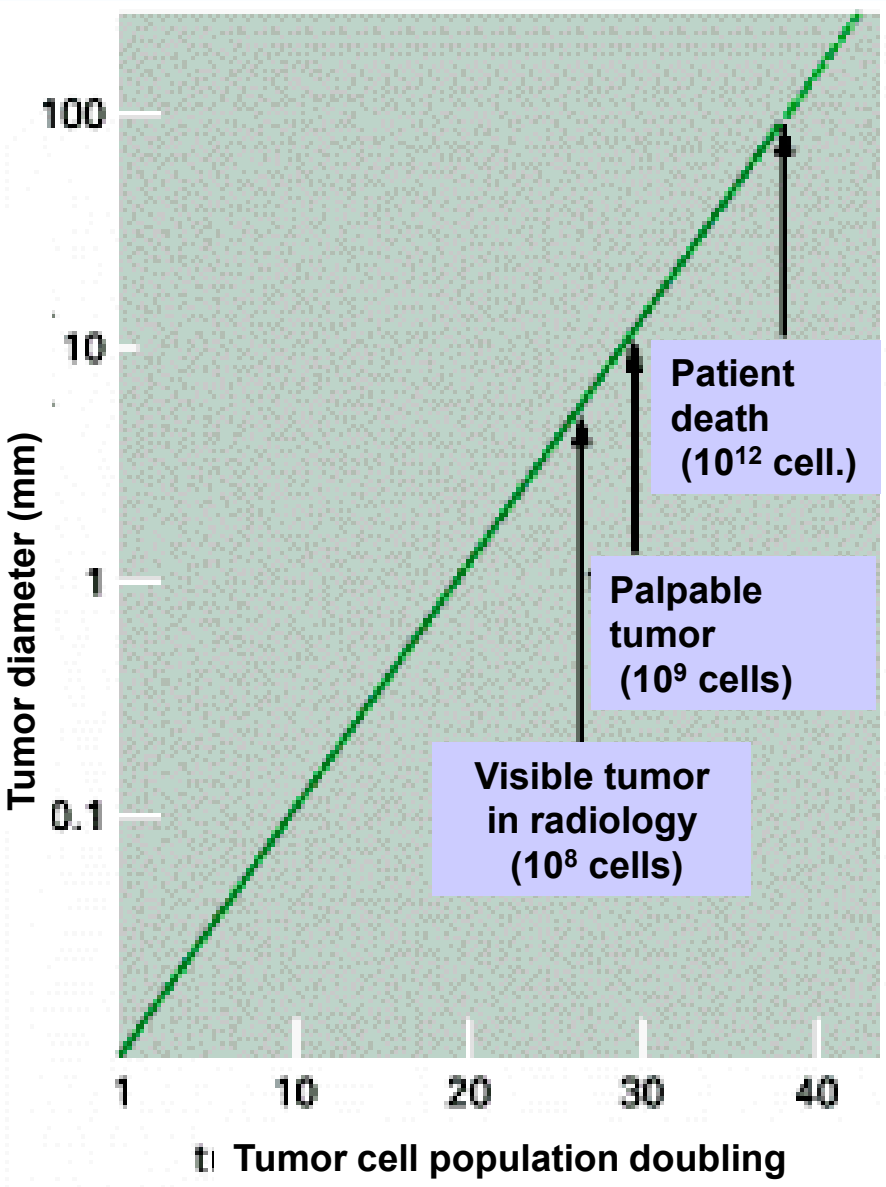
- Risk factors

- CRCs are favored by certain environmental factors, particularly diet.
- Some CCRs are genetic in origin.

II- Tumor formation and evolution

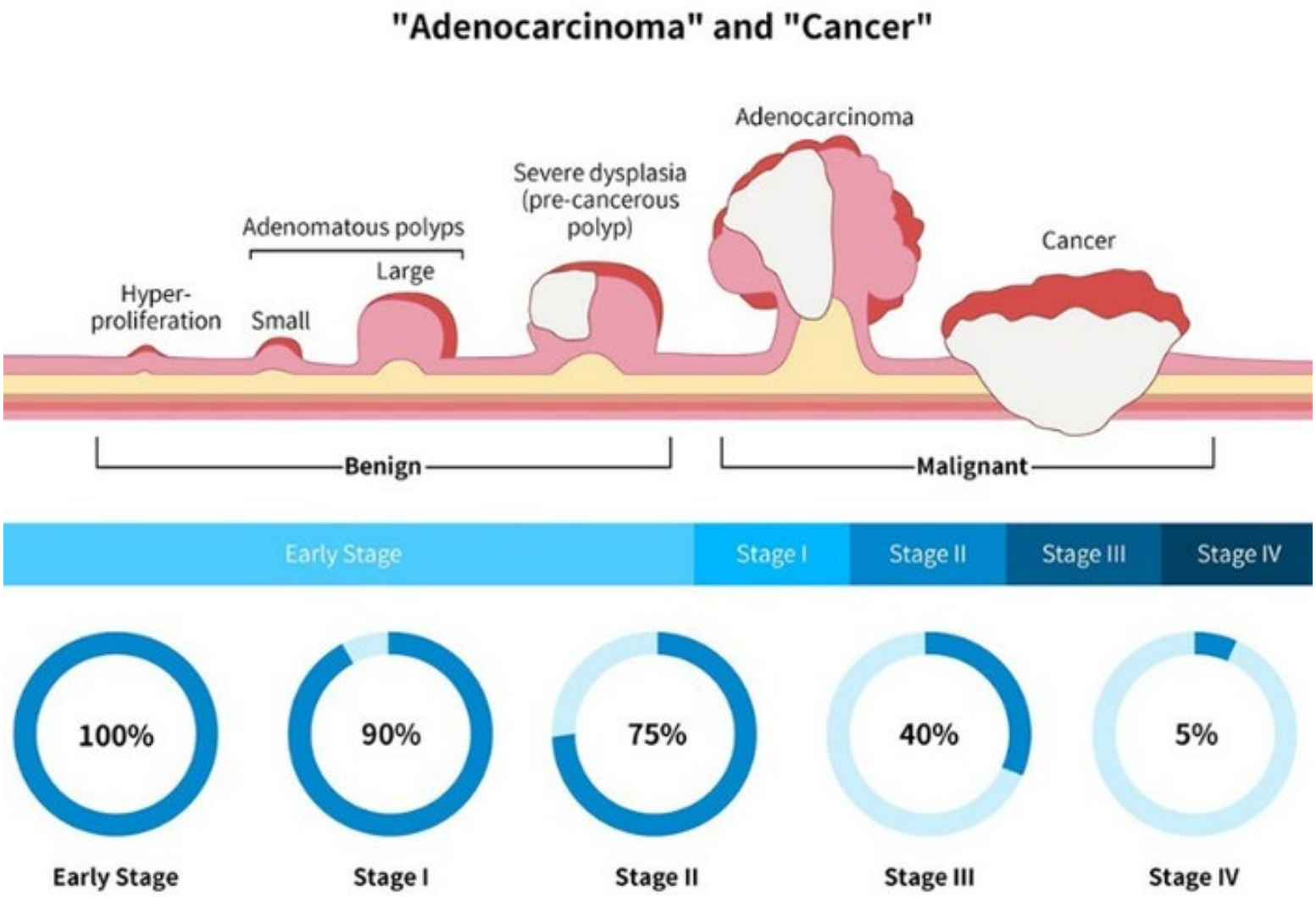


Cancer development is an initially slow process



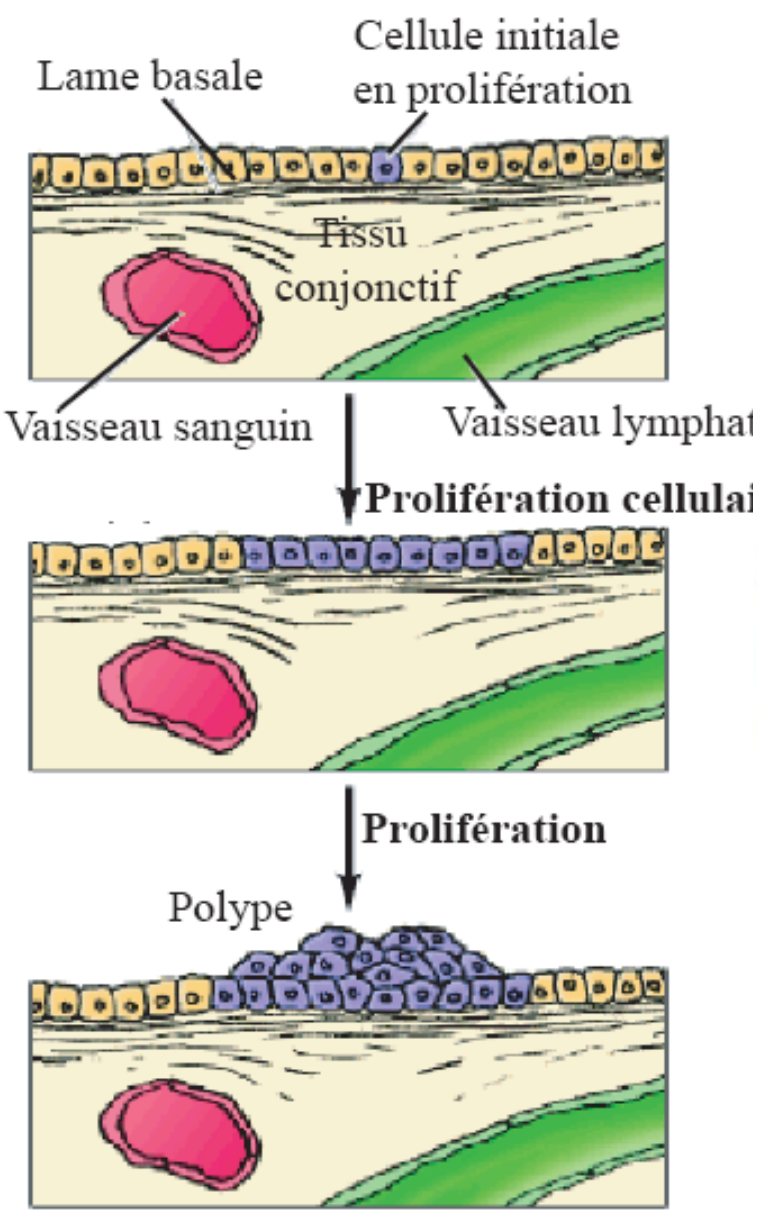
Oncogenesis takes place in several stages

- Tumors emerge from healthy tissue.

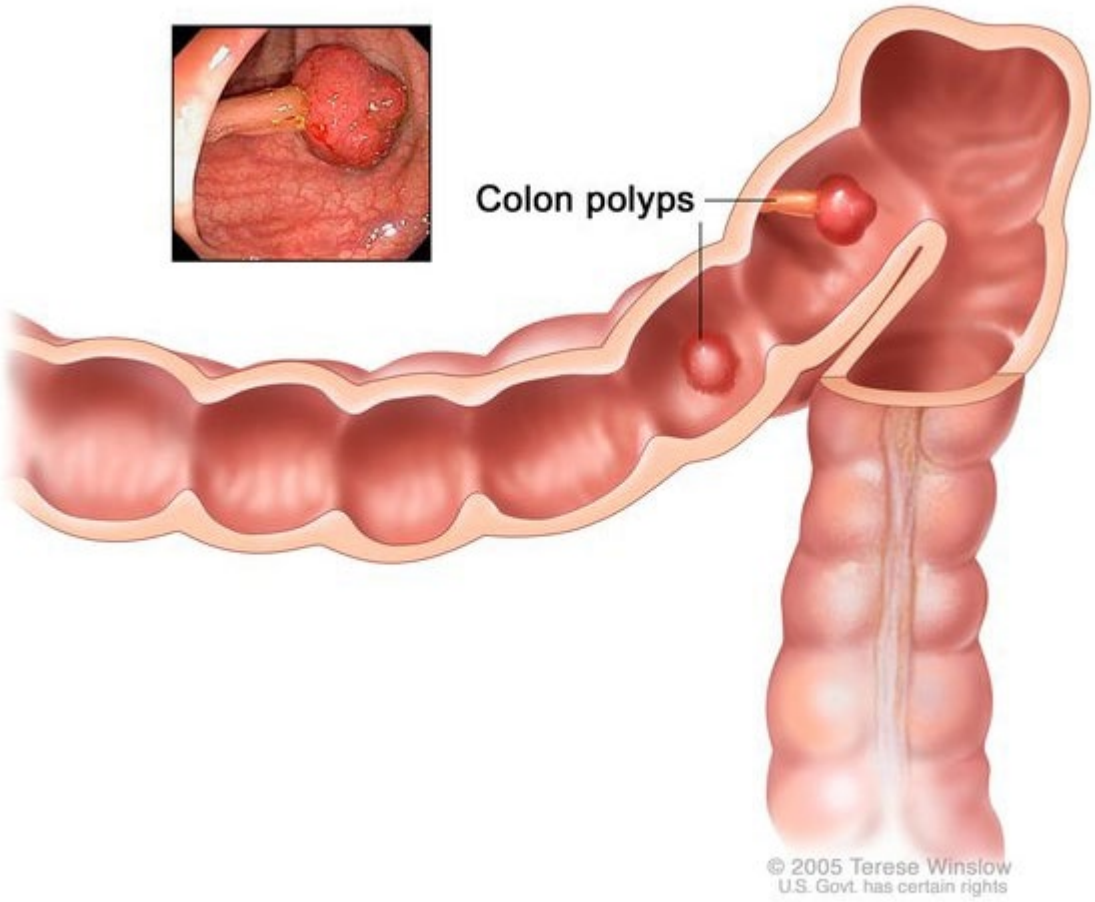


- Tumors are initially benign before becoming malignant (cancer).

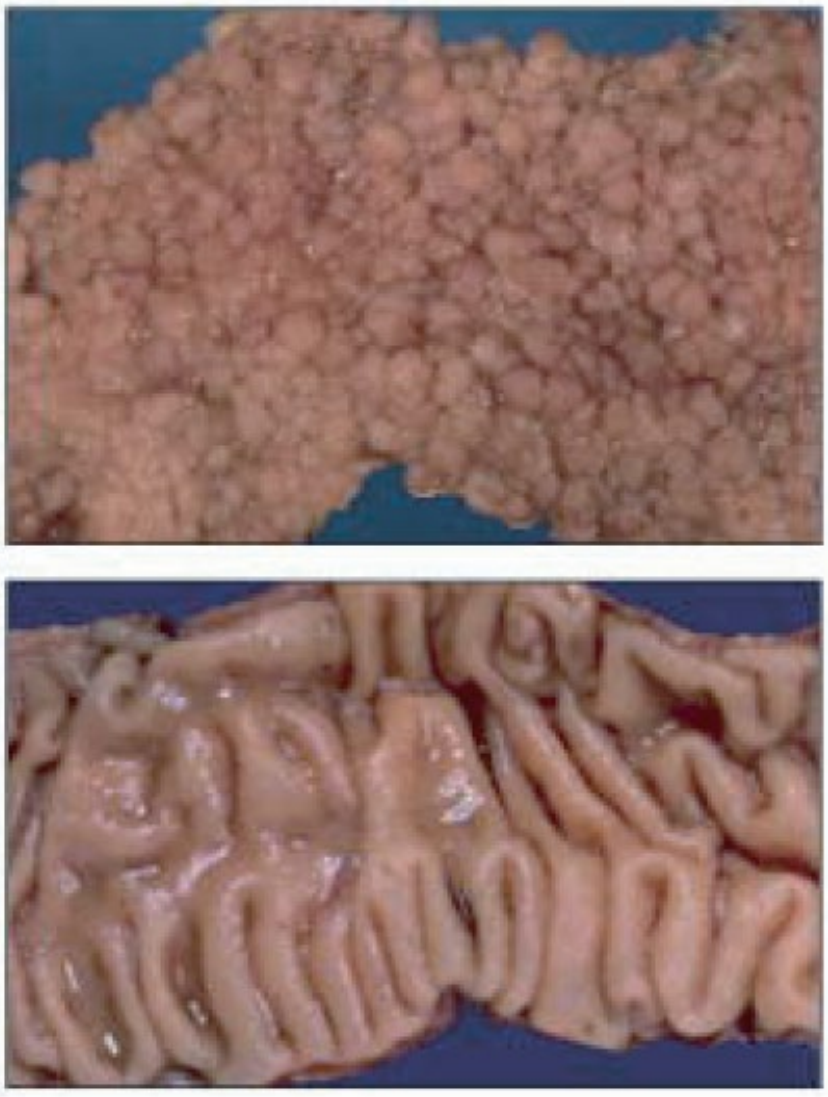
Benign tumors are formed by cell multiplication



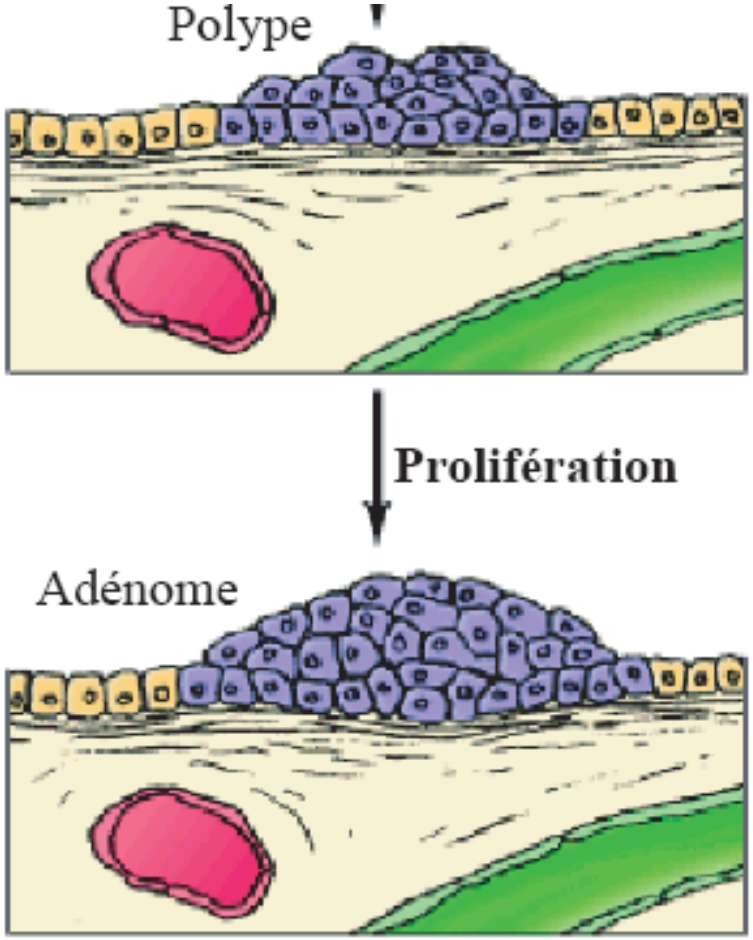
- Colorectal tumours start from polyps in the intestinal wall

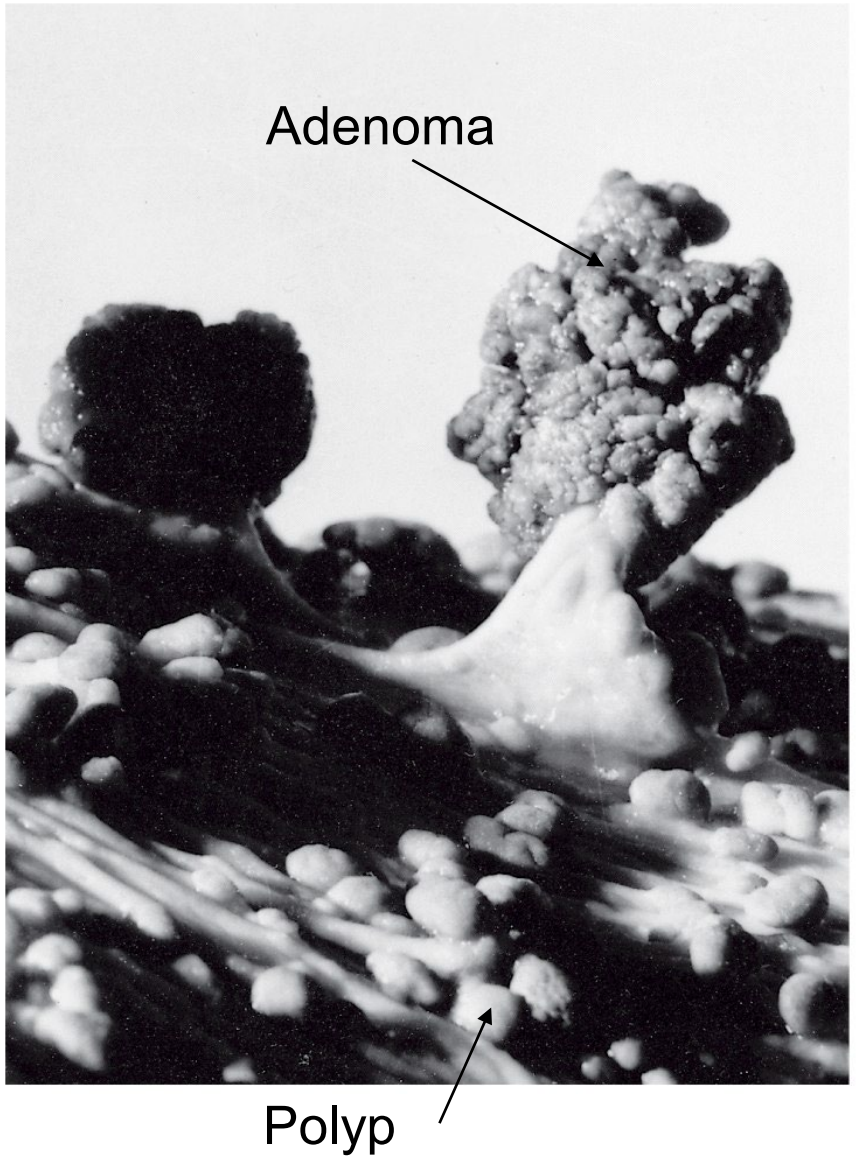


In cases of Familial Adenomatous Polyposis (FAP), polyps are extremely numerous

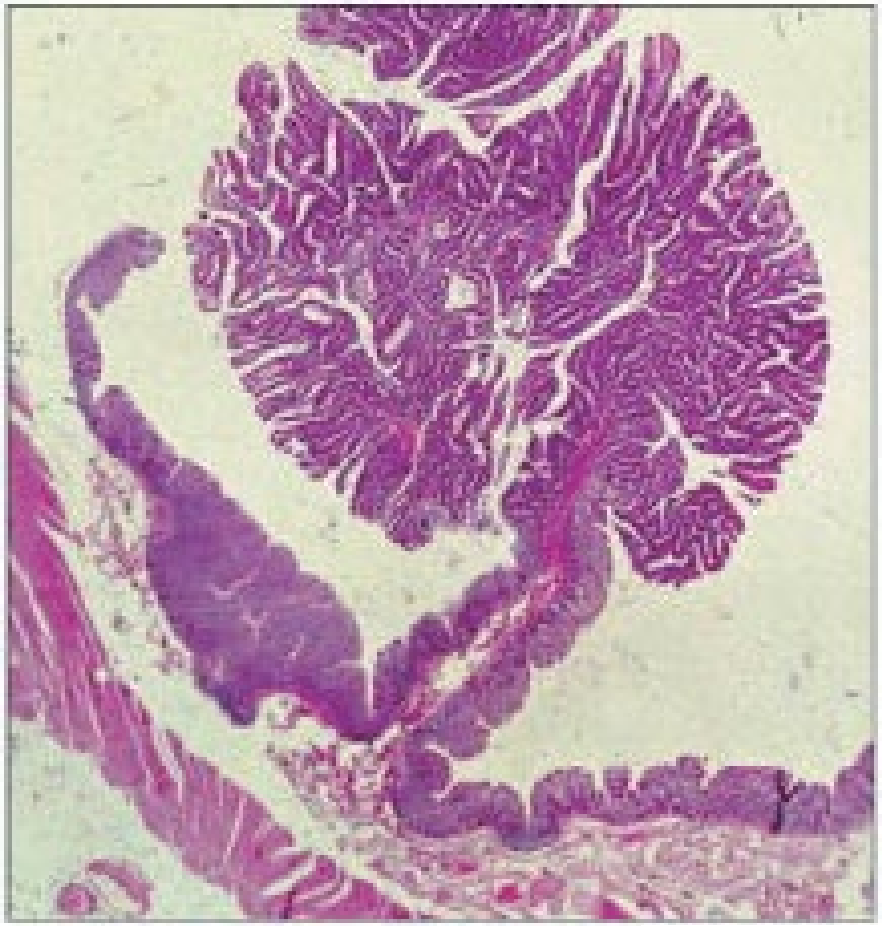


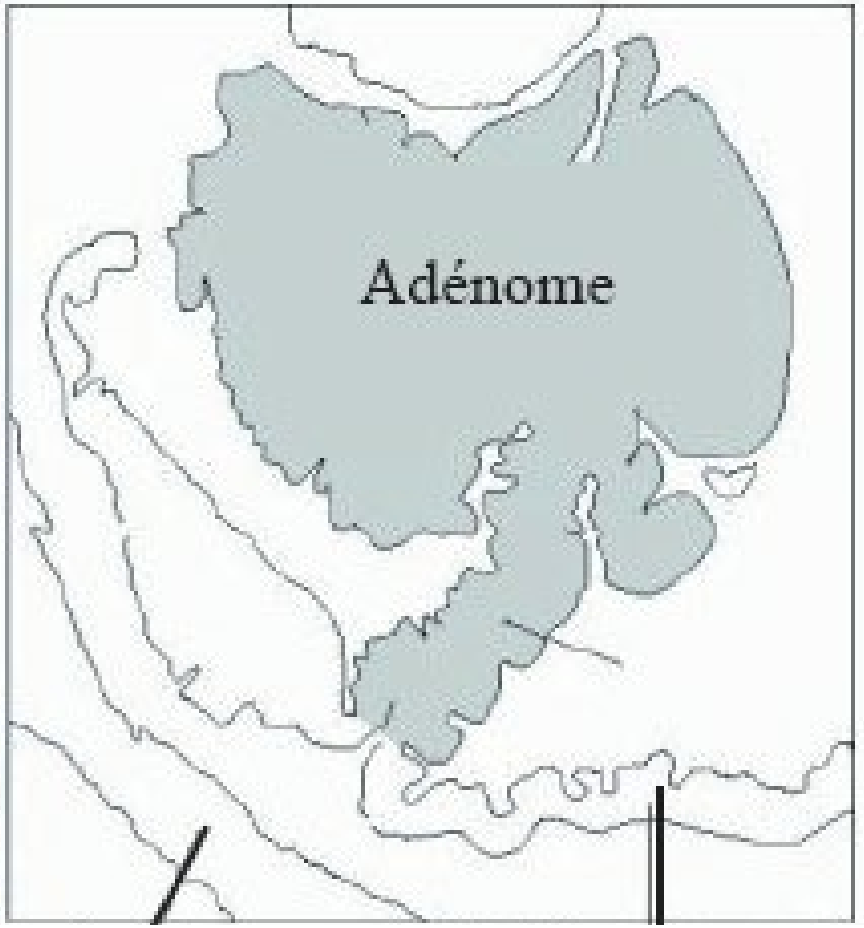
Polyps grow and form adenomas





Polyps grow and form adenomas

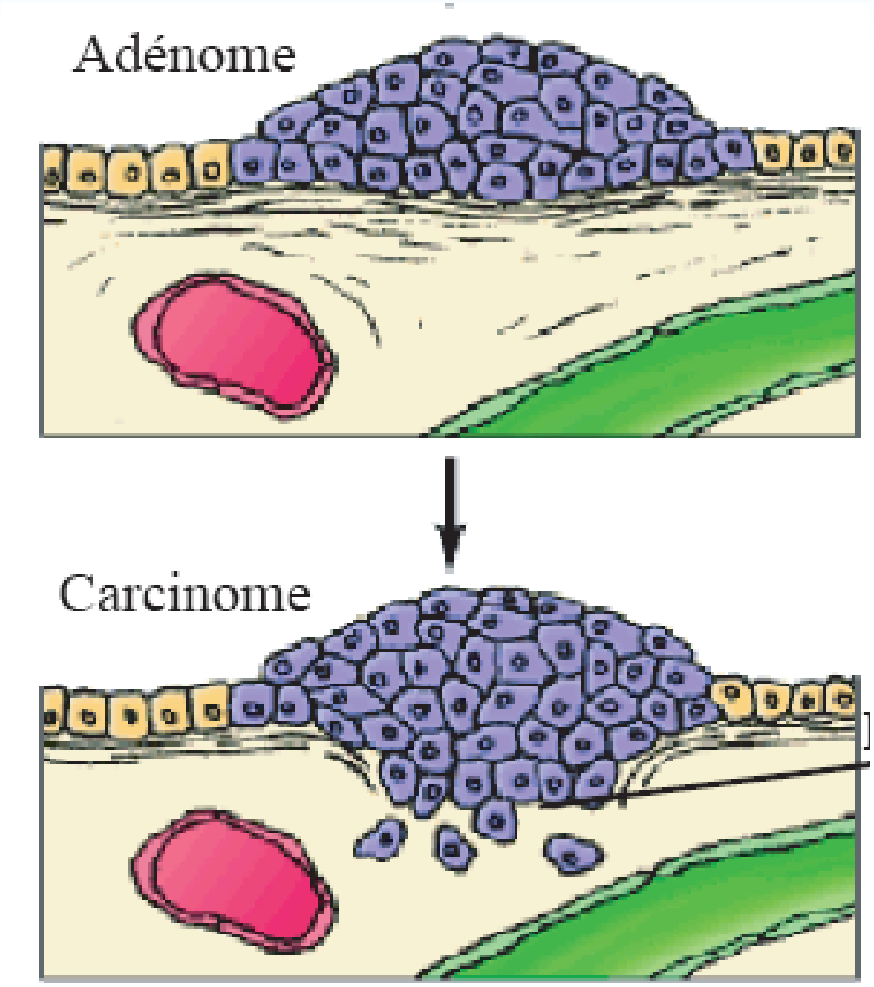


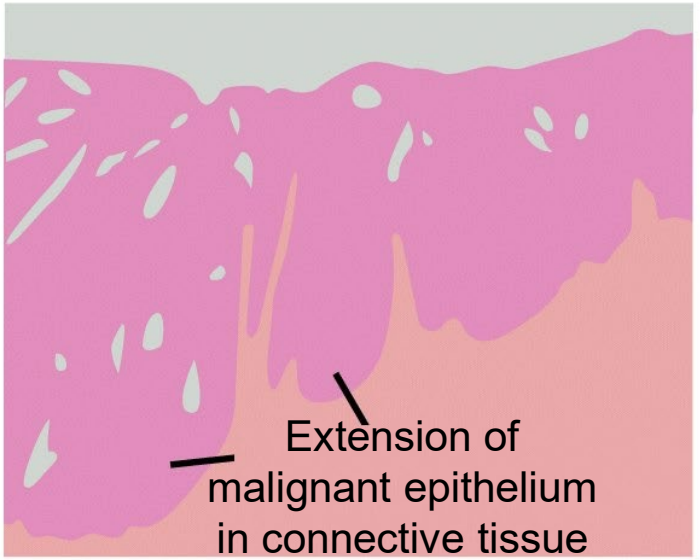


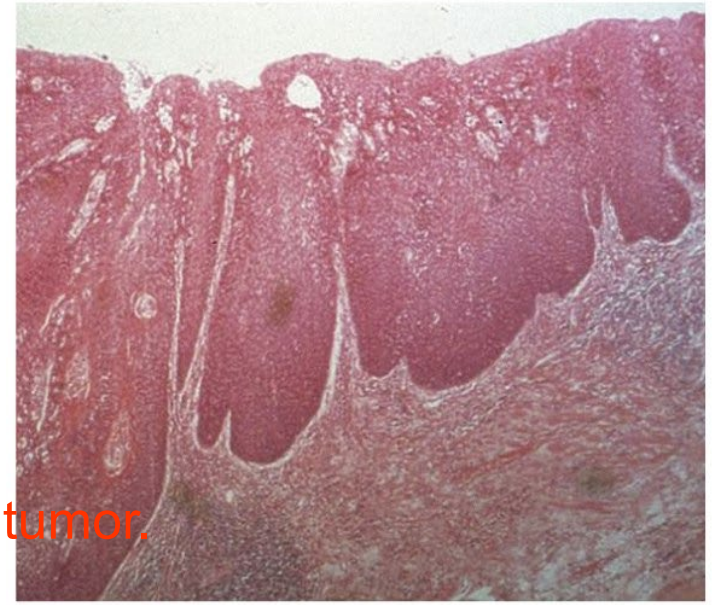
Underlying muscle

normal epithelium

Adenoma becomes carcinoma when it invades neighboring tissues

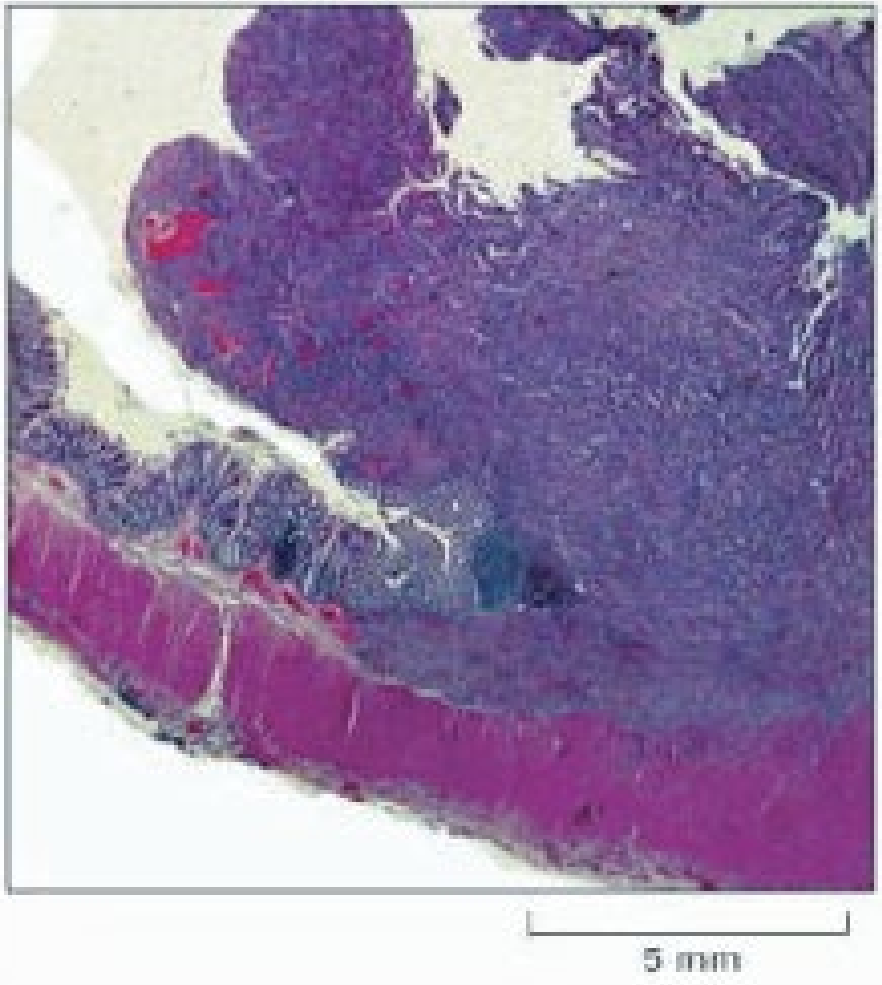






The adenoma becomes a carcinoma, a malignant tumor.

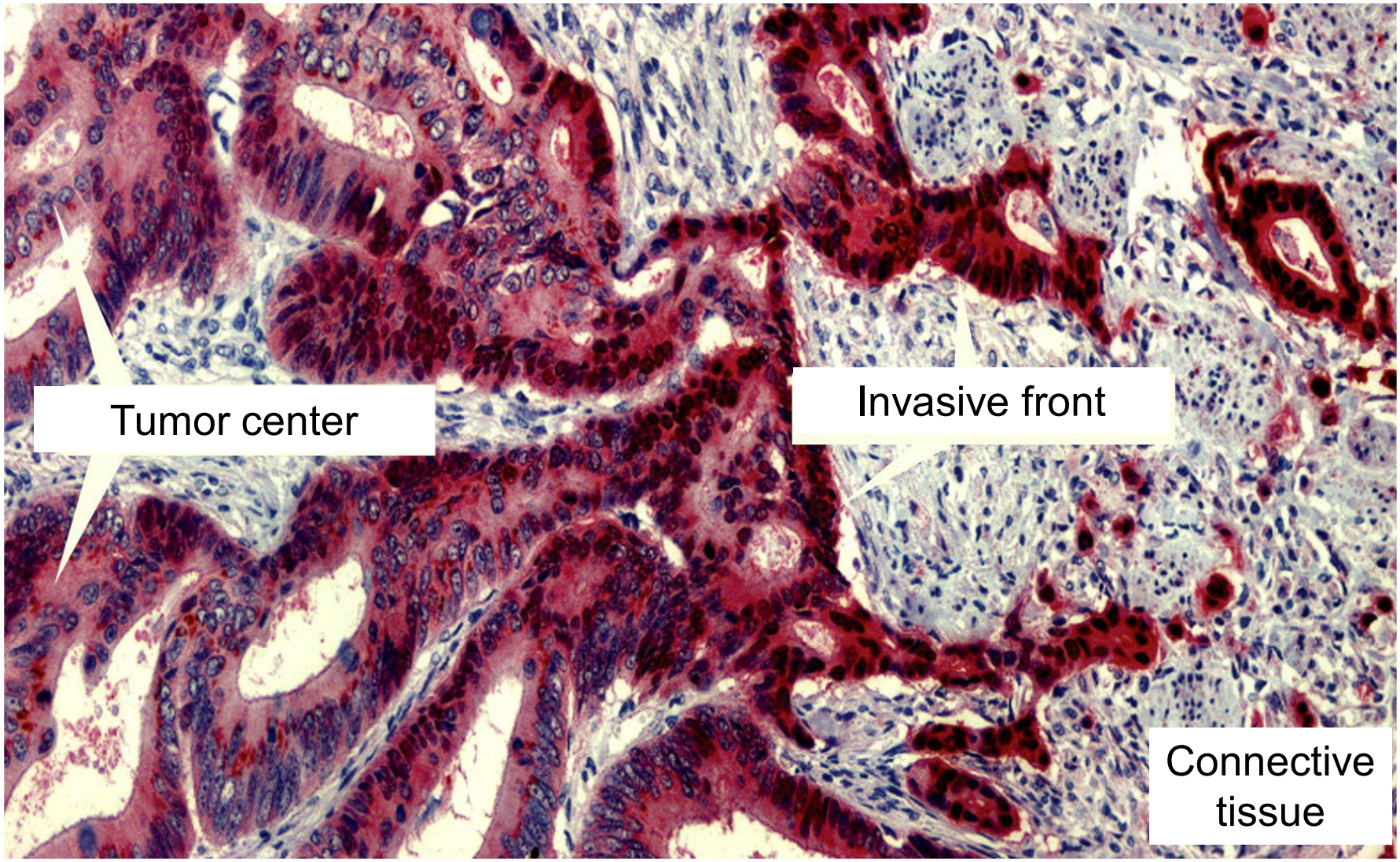
To invade connective tissue, tumor cells must cross the basal lamina.



Normal epithelium

Disruption of the basal lamina

Tumor cells must migrate within connective tissue



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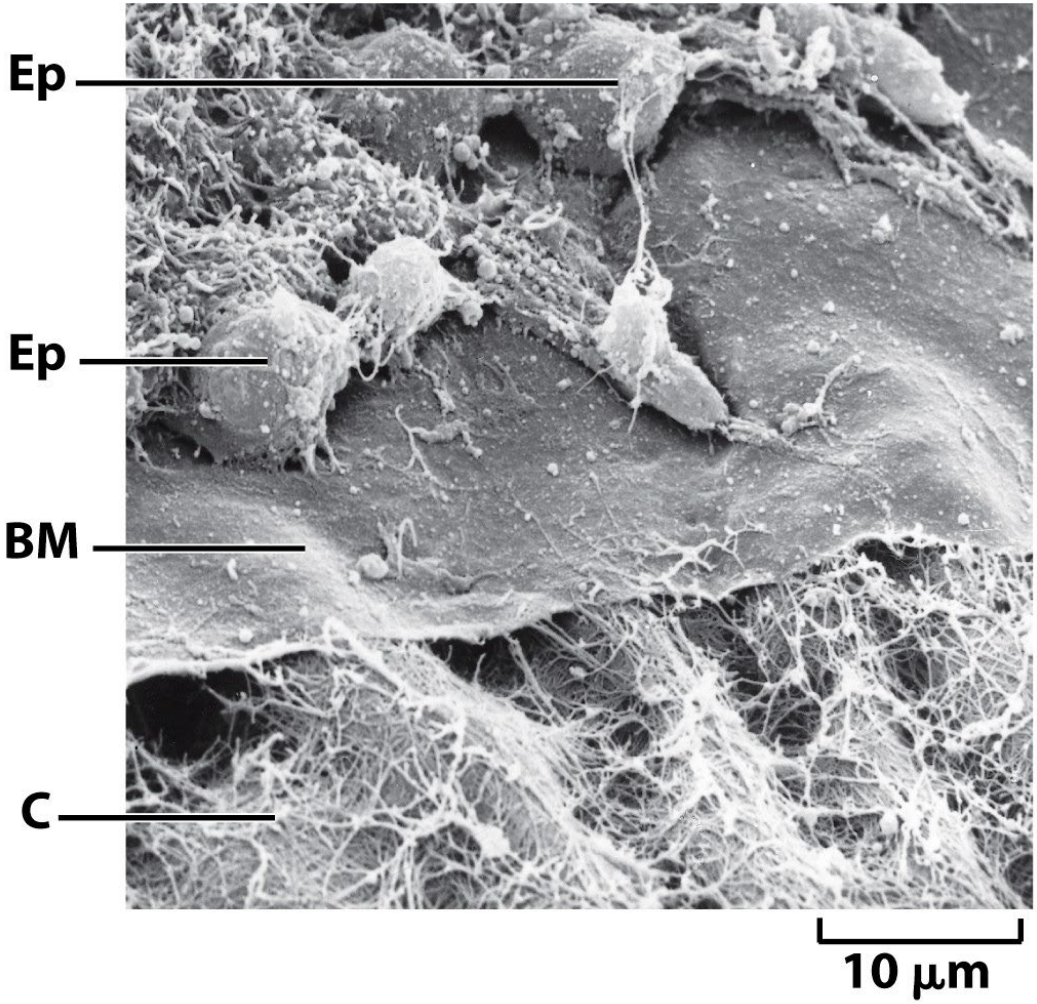
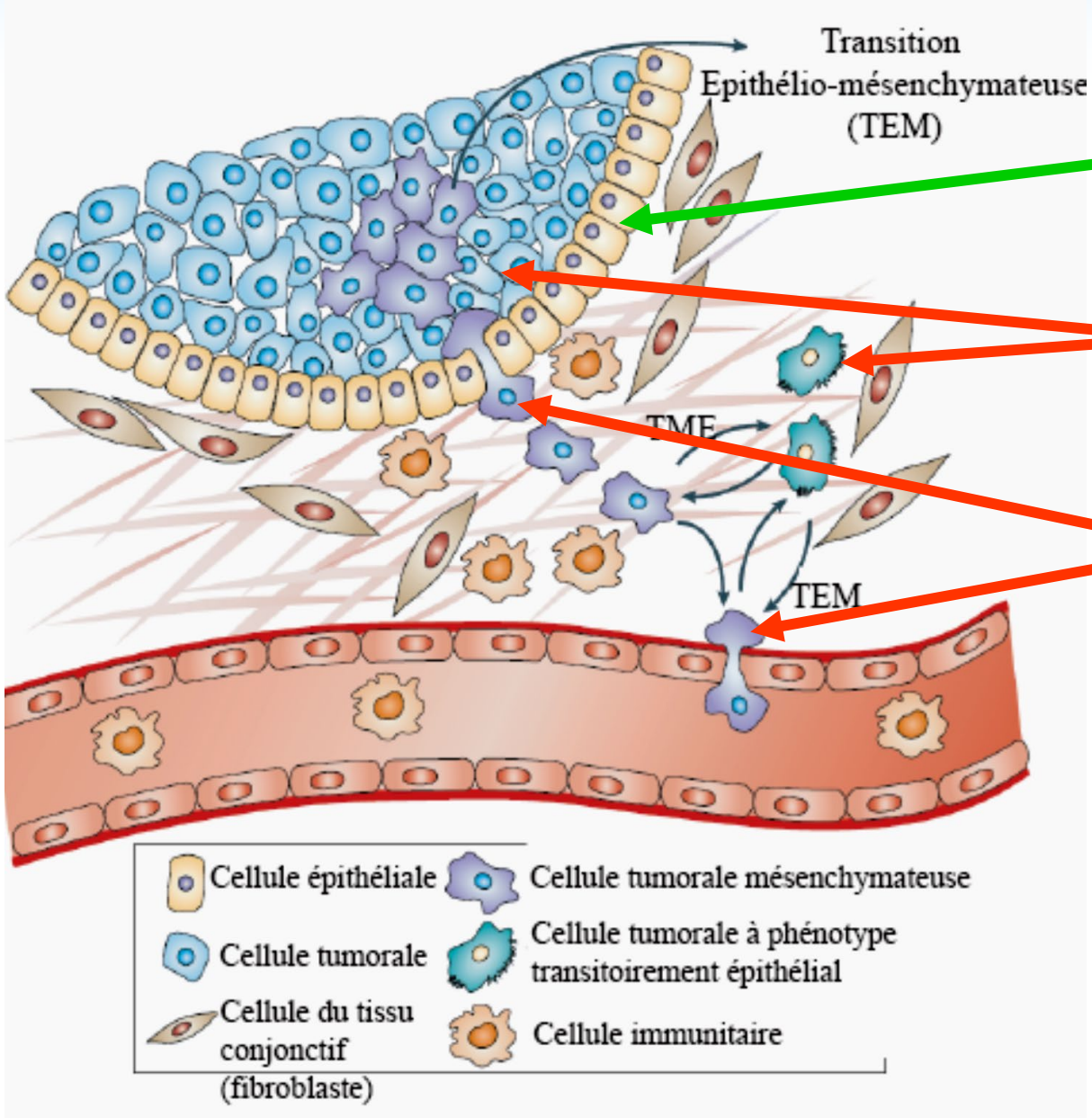


Cells undergo epithelial-mesenchymal transition (EMT)

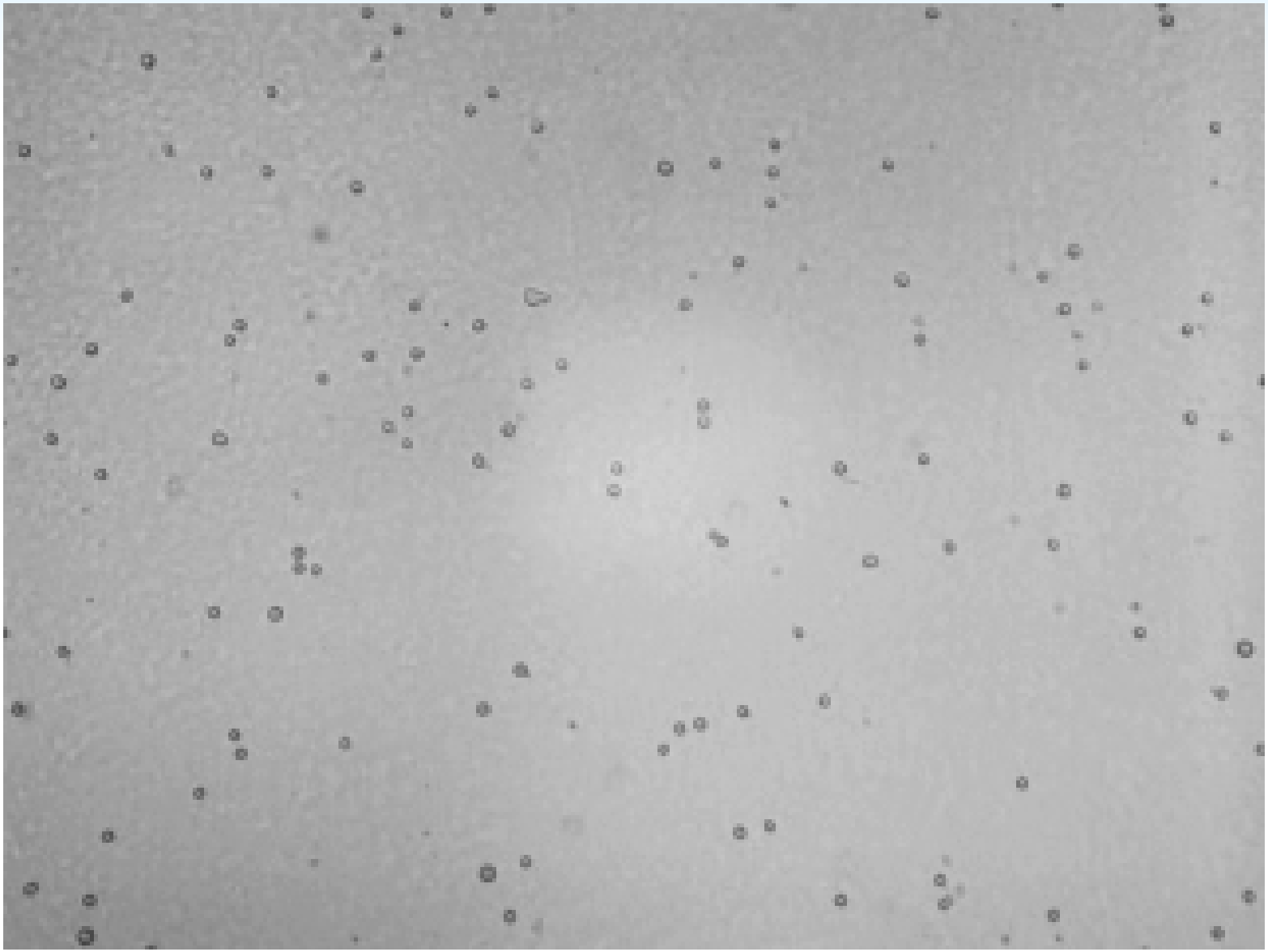


Epithelial cells

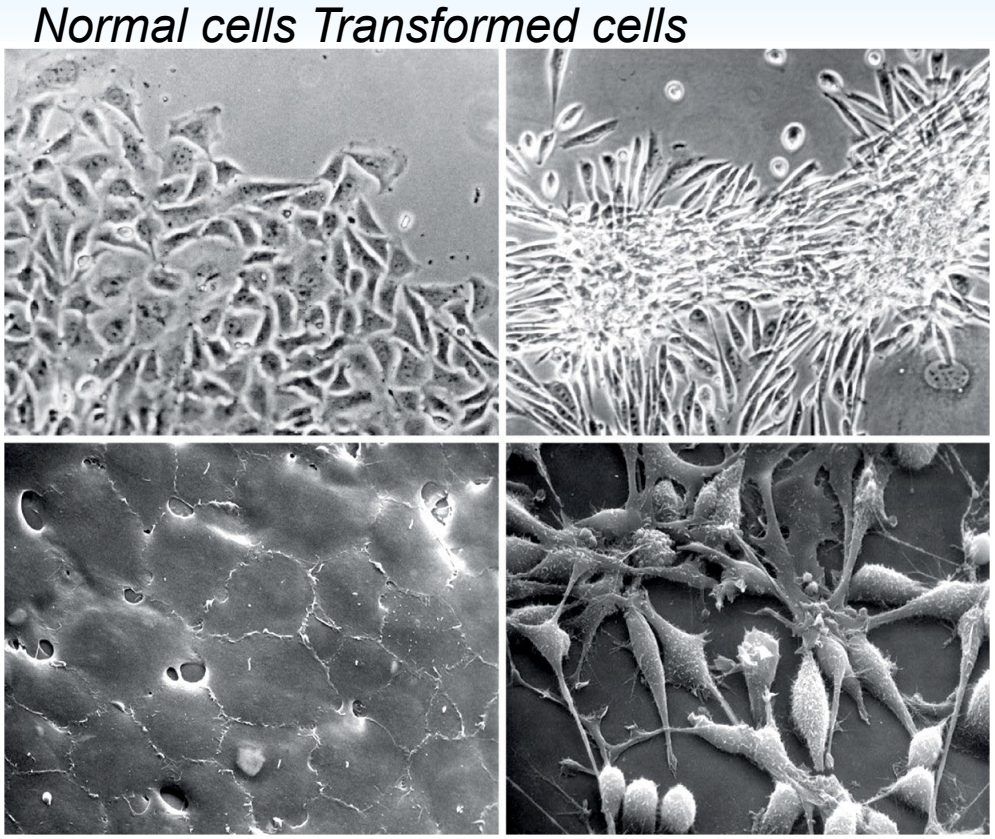
Tumor cells epithelial

Tumor cells with a mesenchymal phenotype

During the Epithelial-Mesenchymal Transition cells lose their epithelial characteristics



During the Epithelial-Mesenchymal Transition cells de-differentiate



Changes associated with TEM :

Loss of :

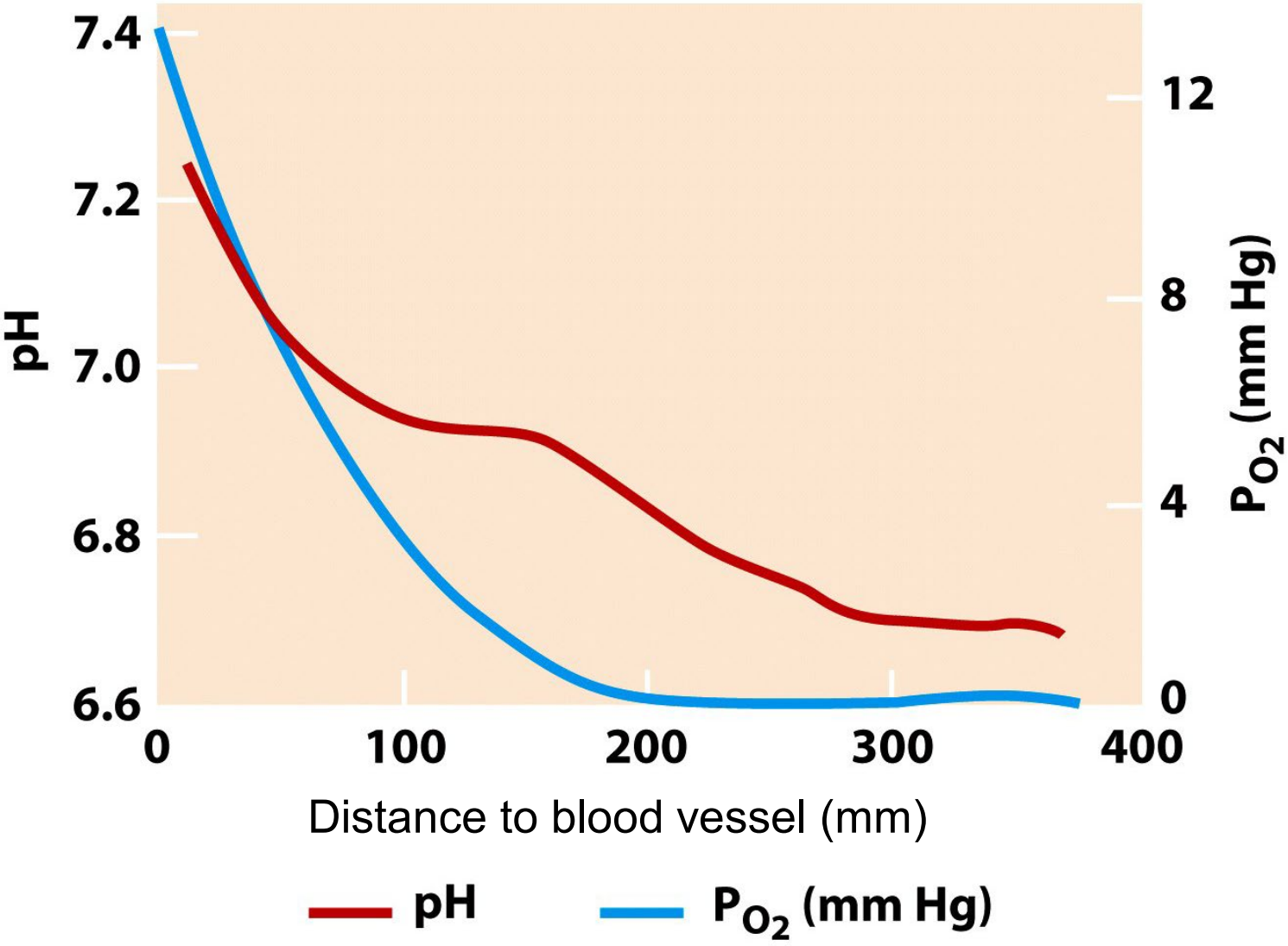
- adhesion to epithelial tissue
- epithelial polarity
- cytokeratin (*intermediate filament specific to epithelial cells)*
- E-cadherin *(junctional protein) adherent epithelial cells)*

Acquisition of :

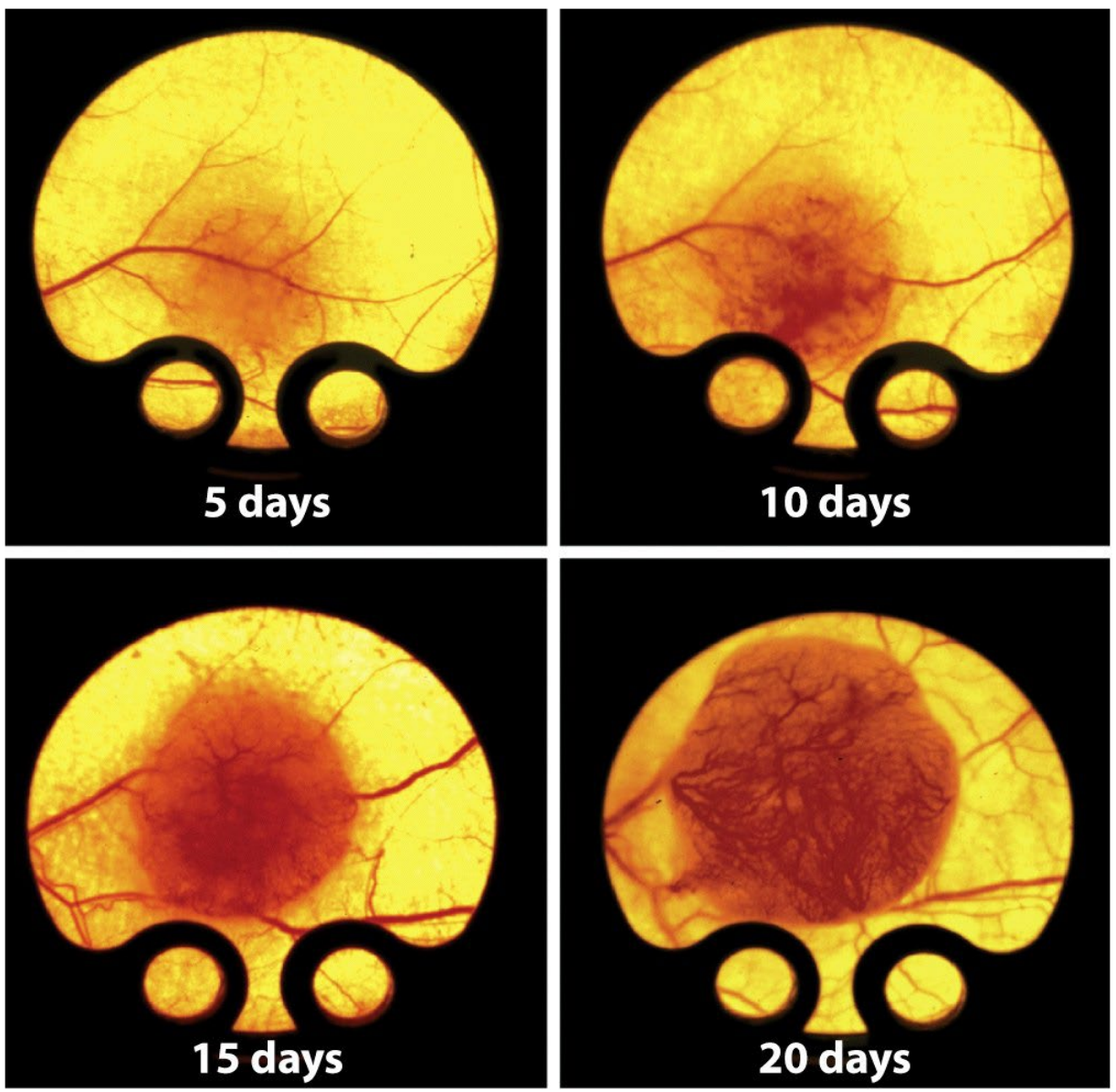
- migration and invasion capabilities
- mesenchymal cell proteins (fibroblasts)
  (vimentin, intermediate filaments of mesenchymal cells; N-cadherin...)
- proteases to break down the extracellular matrix
- growth factor receptors
- mesenchymal cell morphology

Large tumors require vascularization

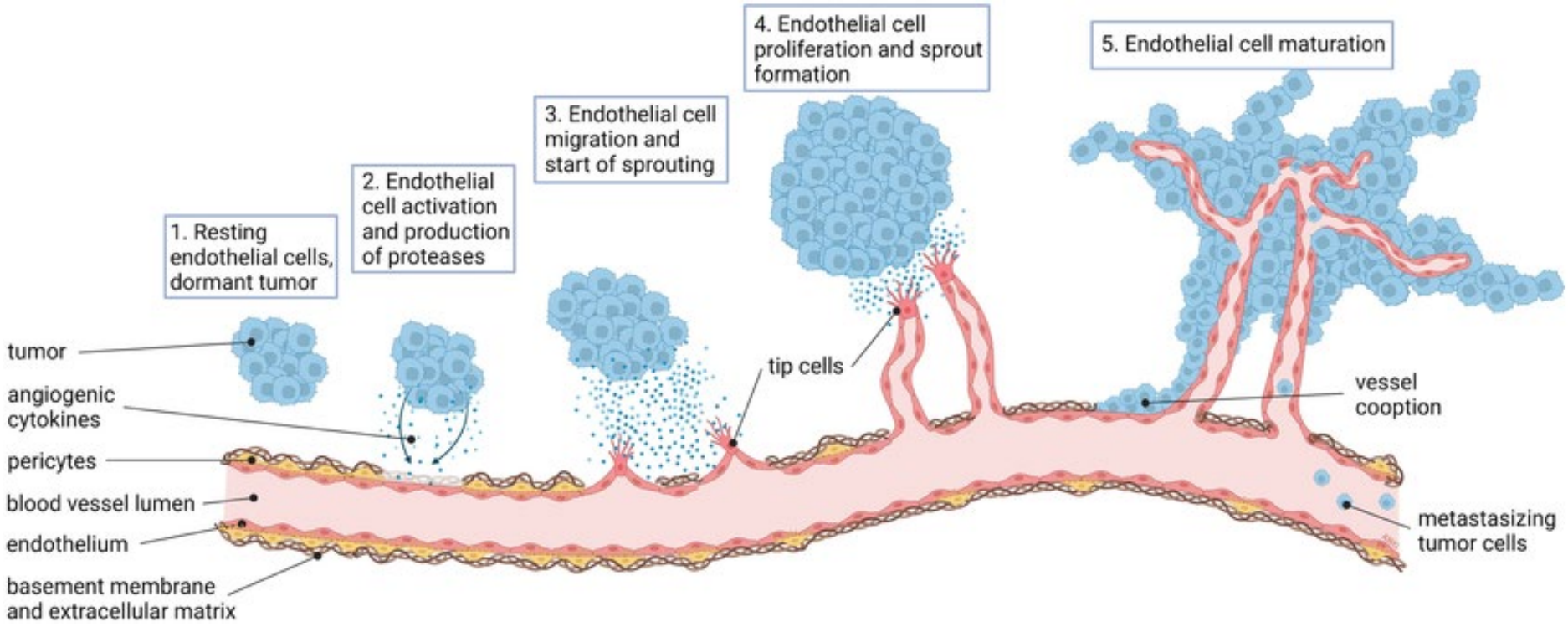
- In the absence of vascularization, oxygen supply is too low. Tumors cannot grow



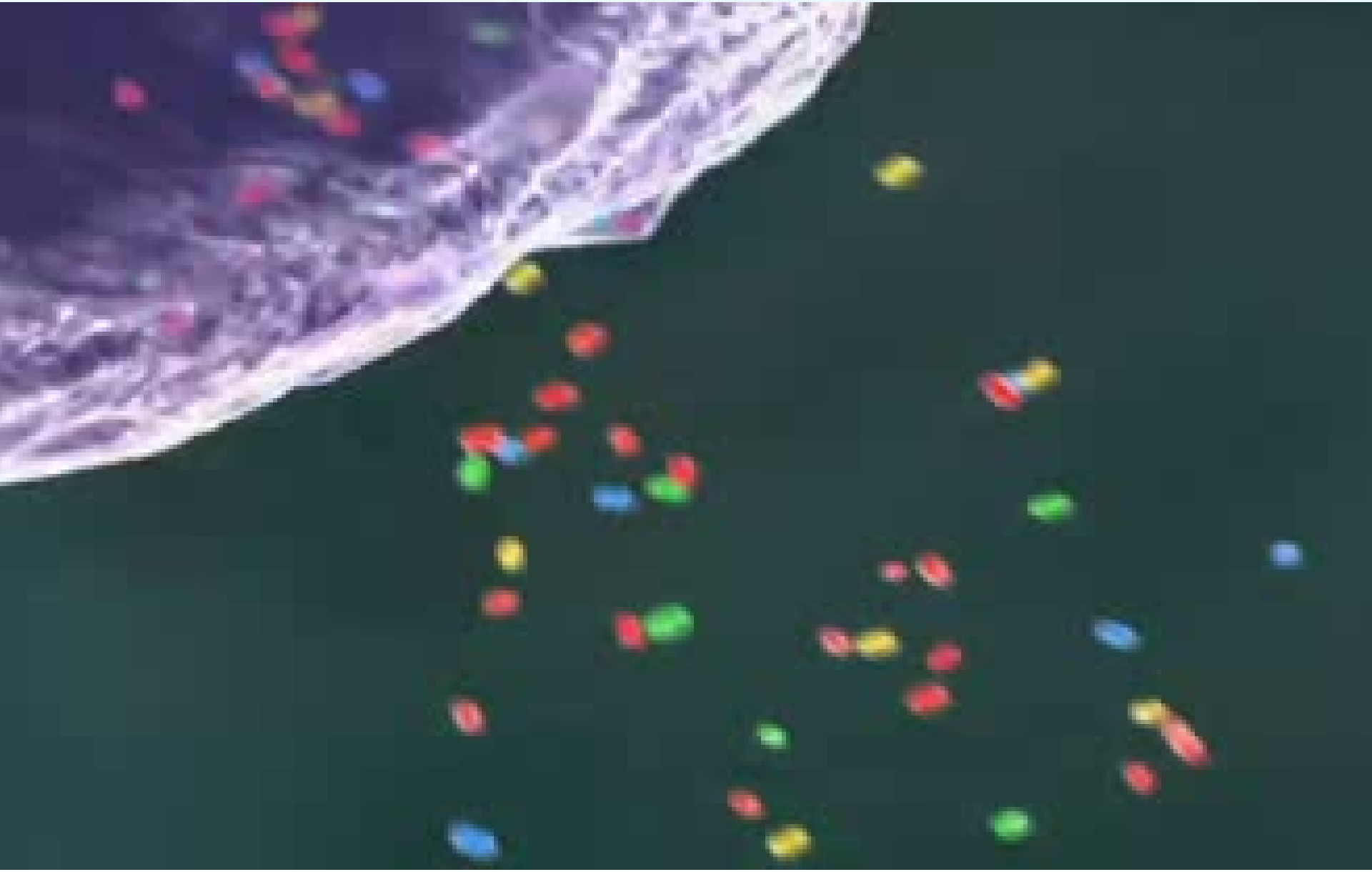
Tumor cells induce the formation of new blood vessels



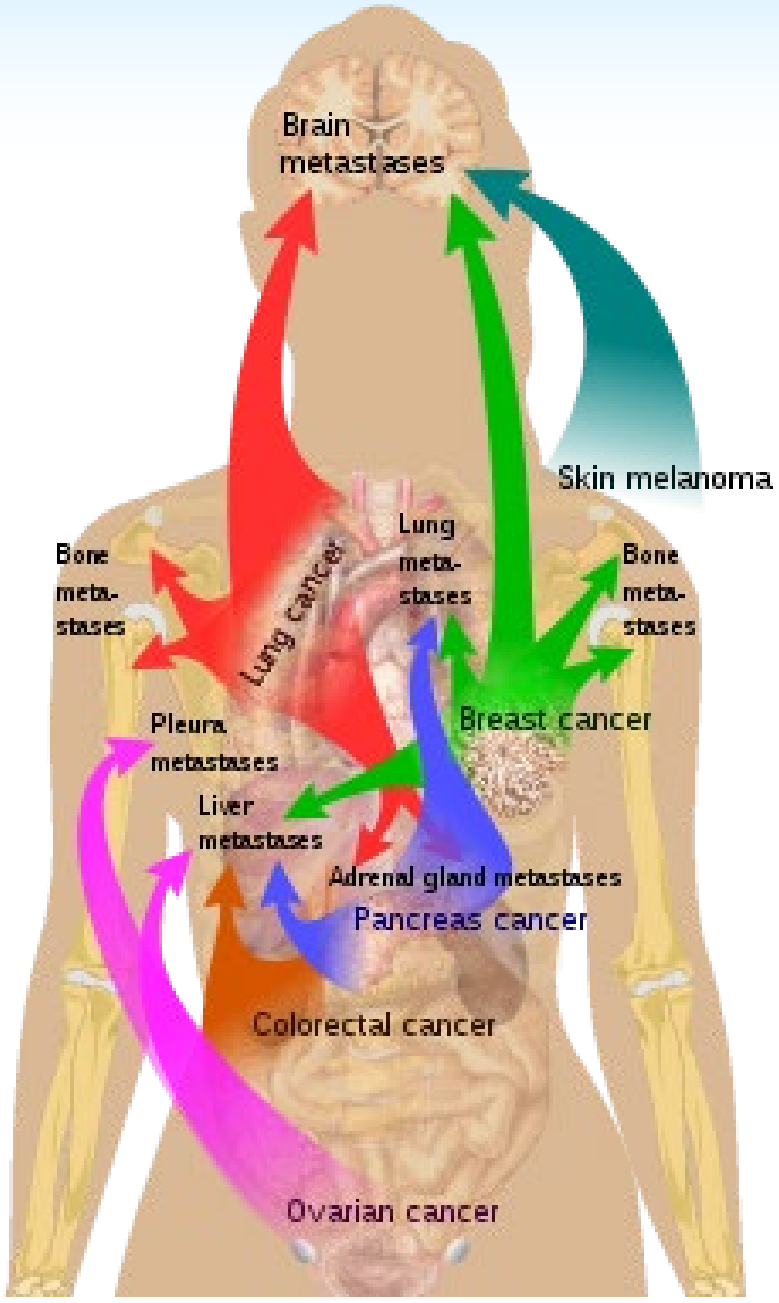
Tumor cells induce the formation of new blood vessels: the angiogenic switch



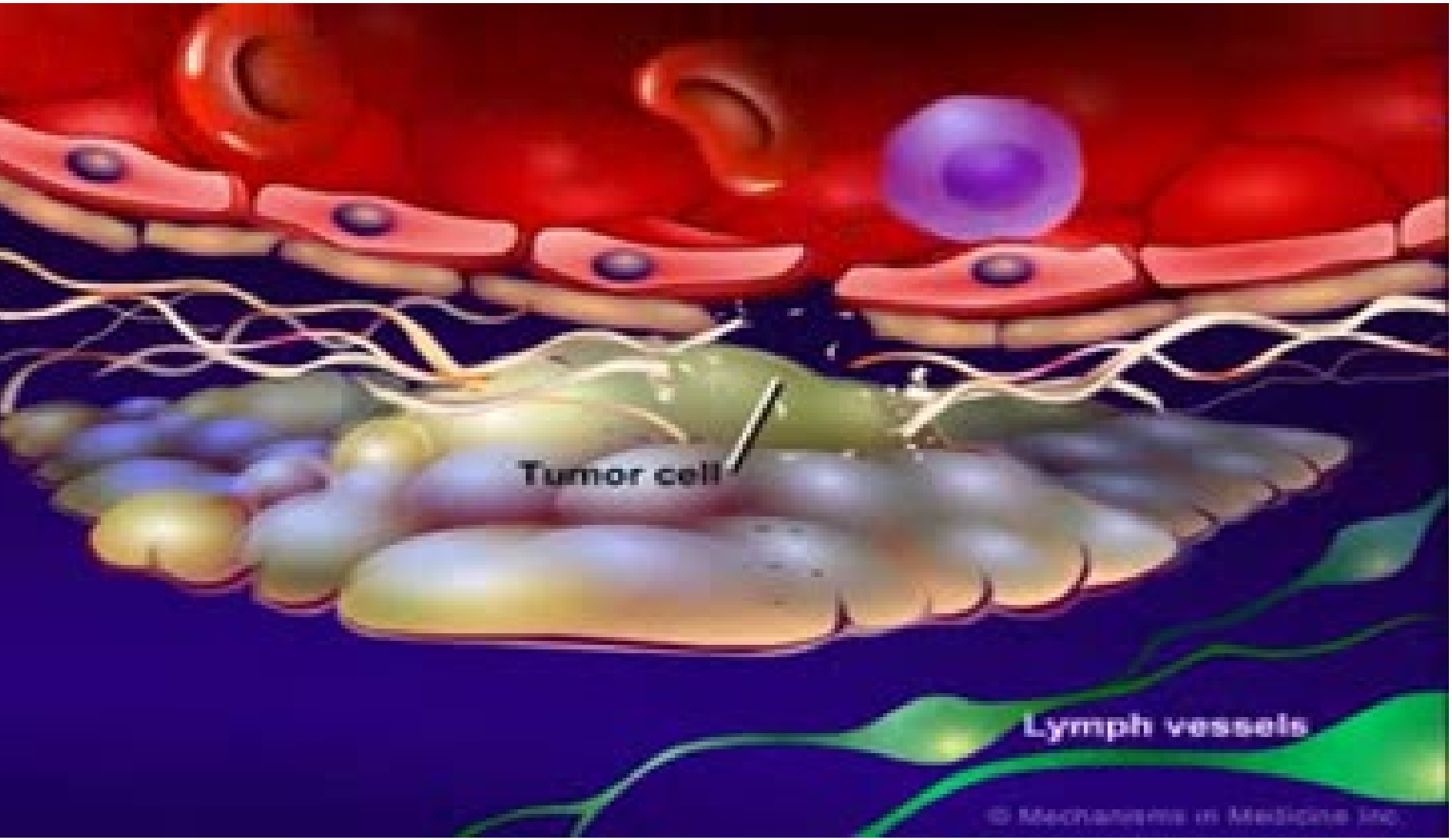
Tumor cells induce the formation of new blood vessels



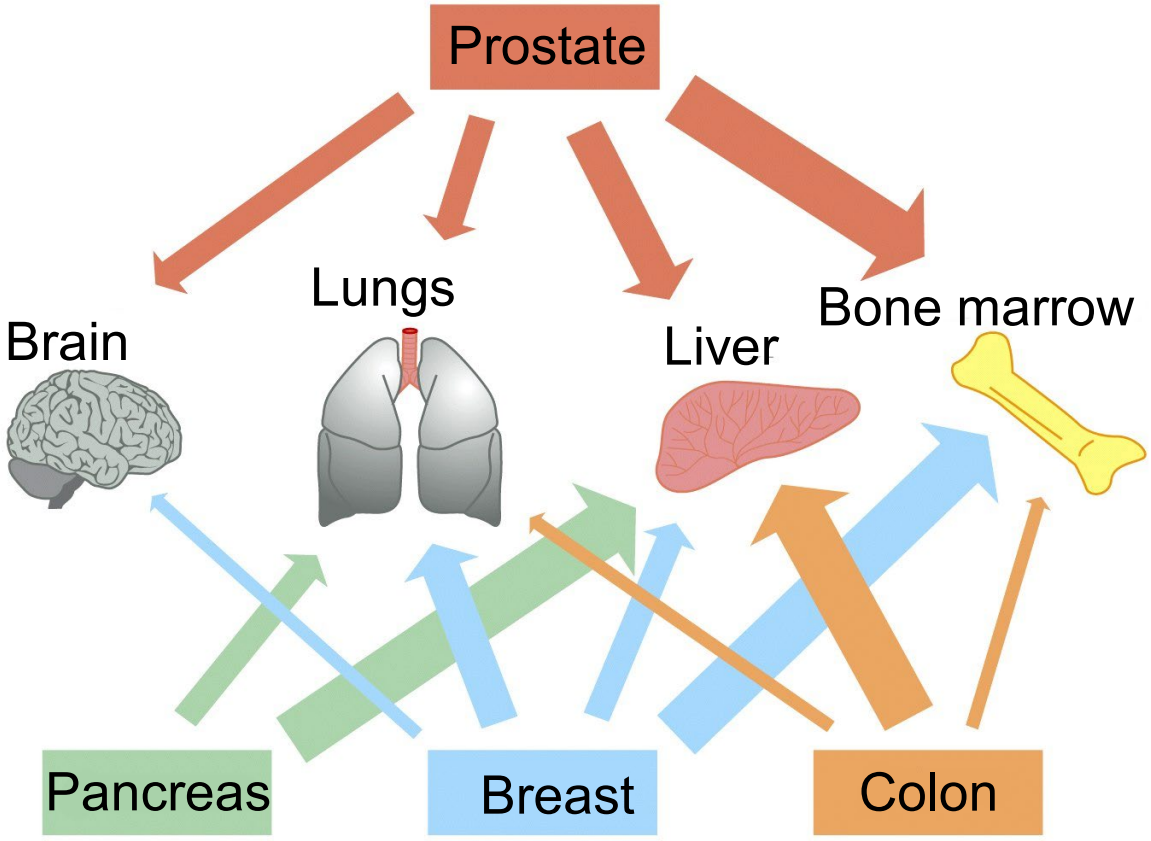
Carcinomas can form secondary tumors in other organs



Carcinomas can form secondary tumors in other organs of the body

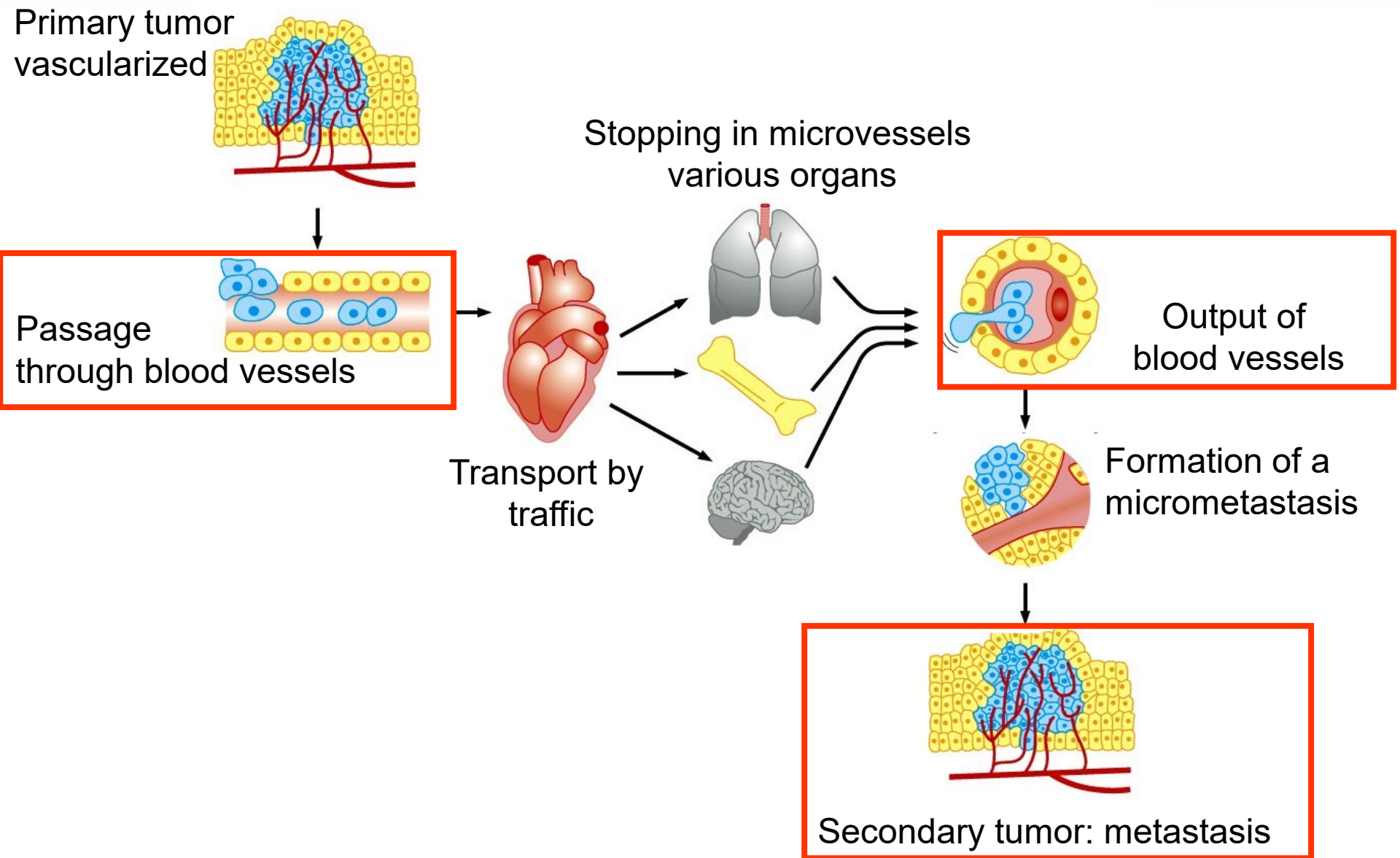


Metastases form in different organs depending on the nature of the primary tumour.

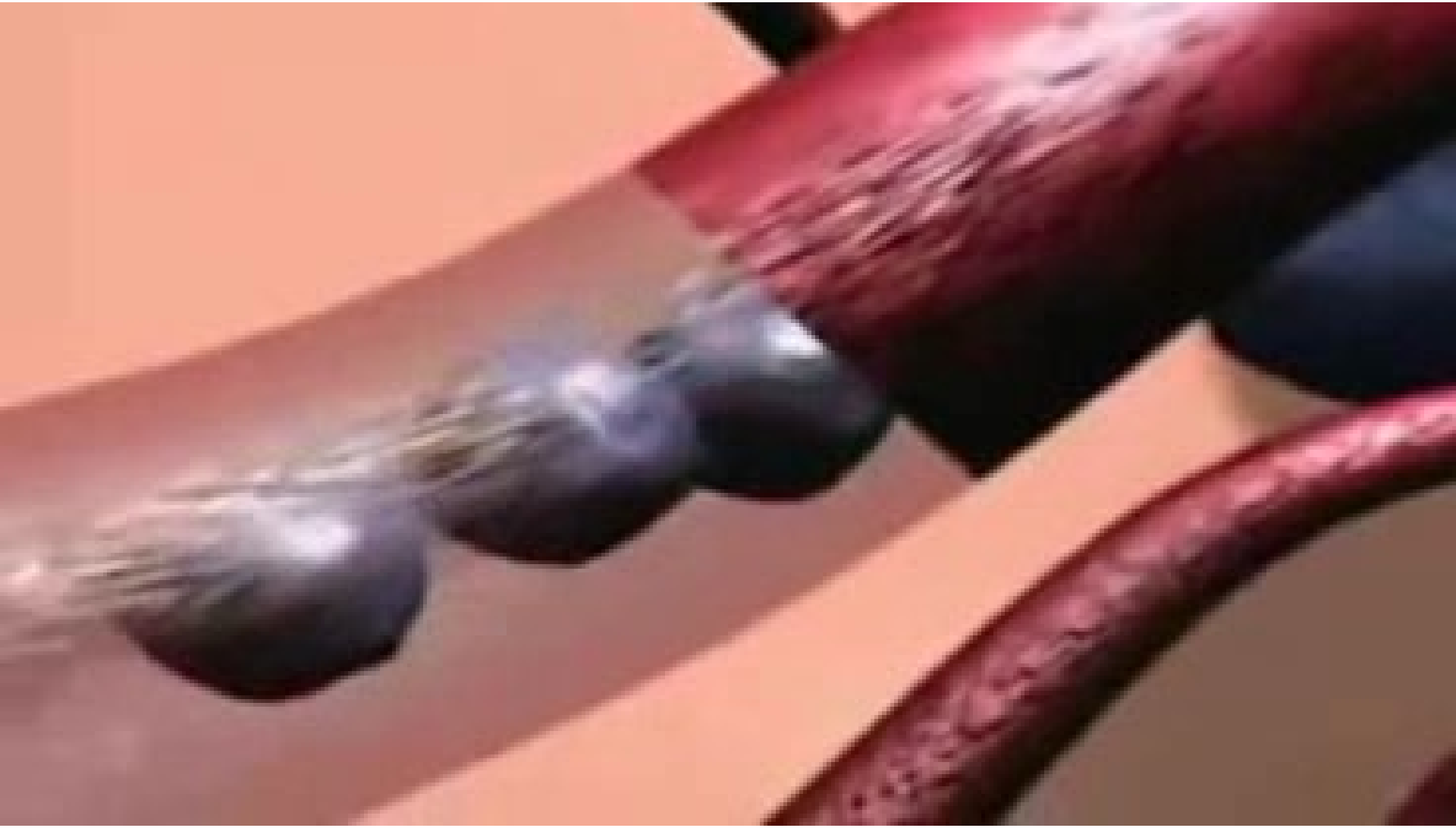


Metastases colon cancer in the liver

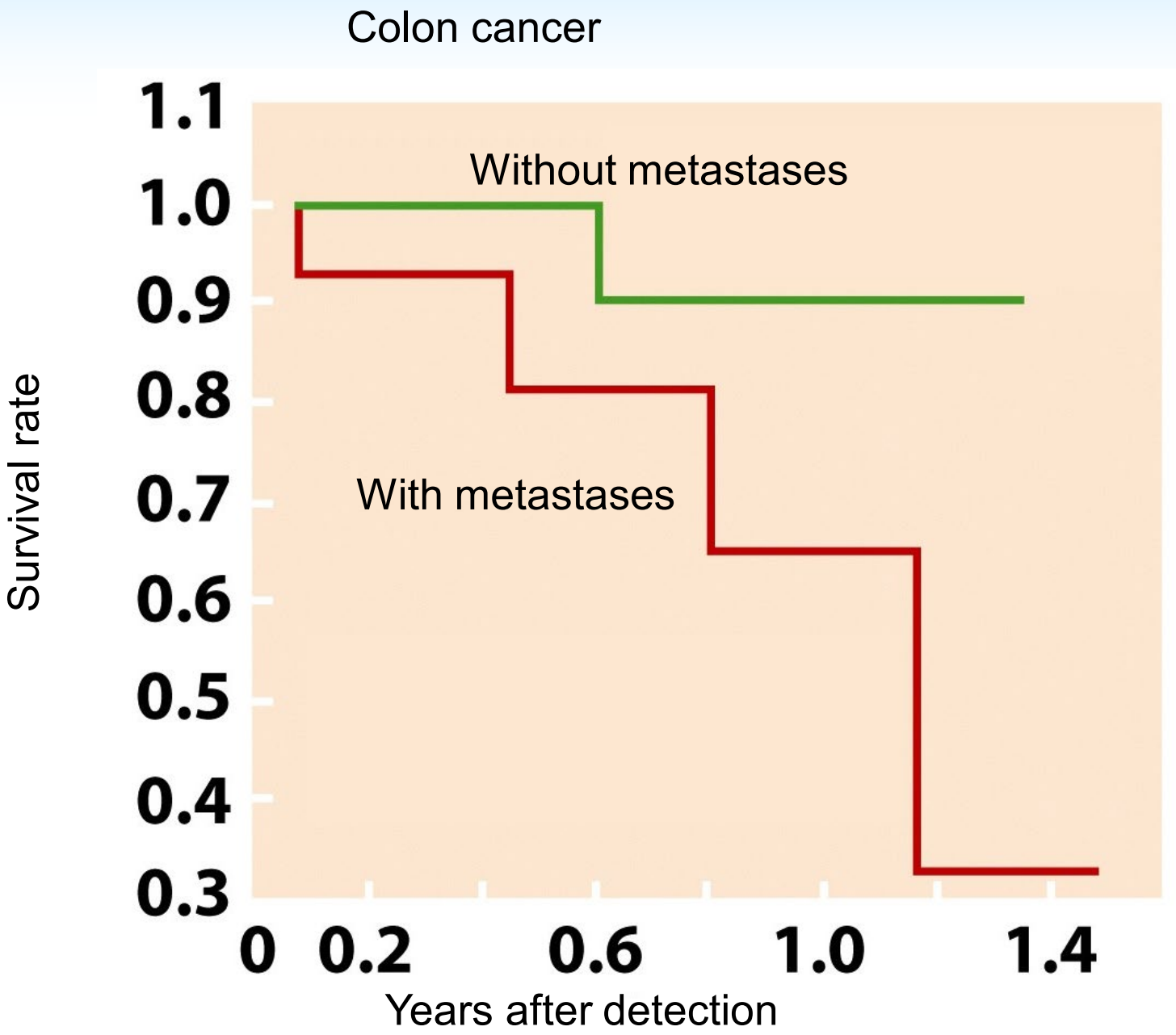
The metastatic cascade: Cells pass into the bloodstream to form metastases



Cells pass into the bloodstream to form metastases



Metastases are largely responsible for mortality



Conclusions II

II- Tumor formation and evolution

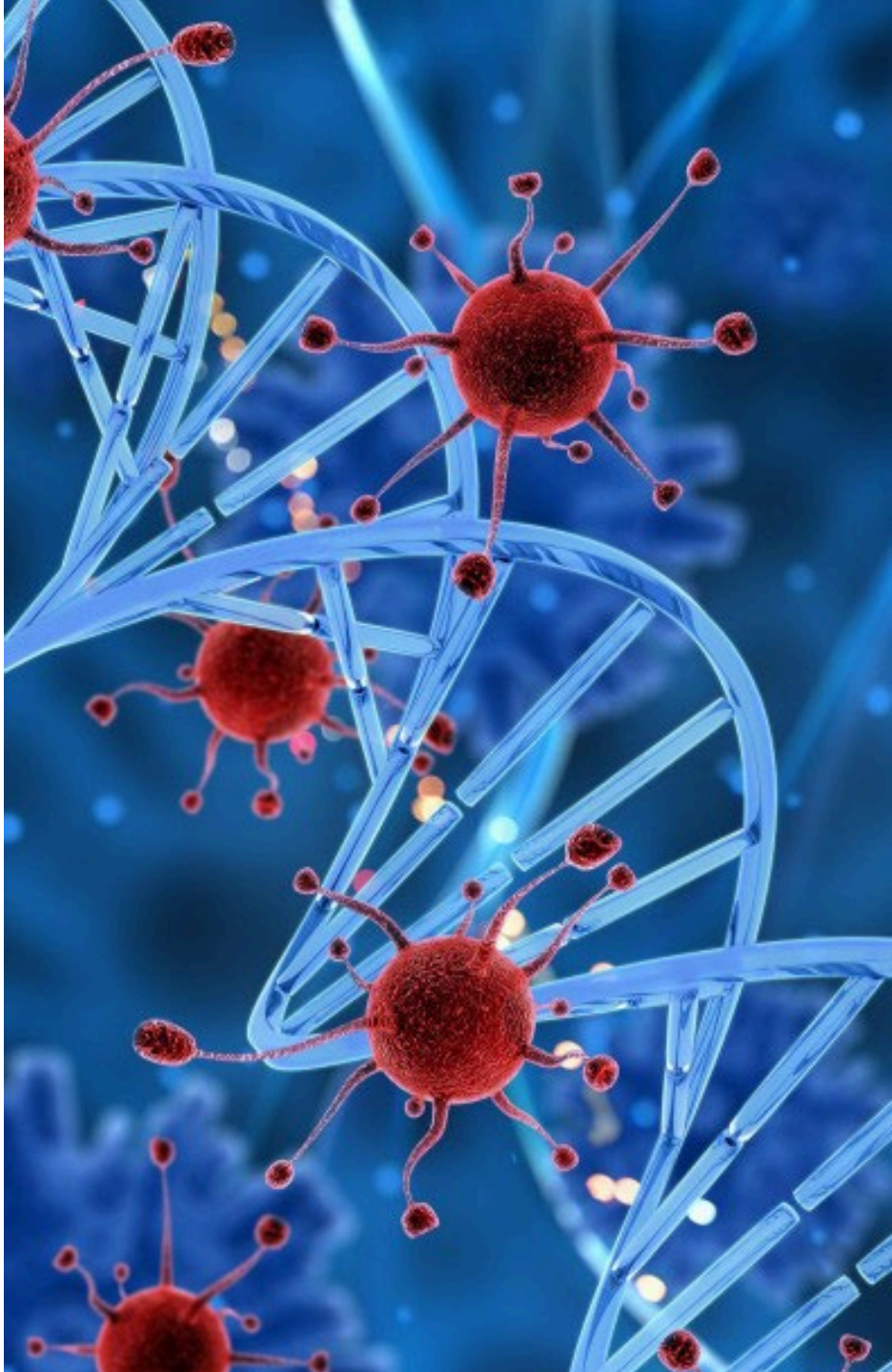
- Cancer development is a slow process.

- There are several stages in the formation and development of a cancer:
  - formation then growth of a benign tumor (polyp then adenoma).
  - formation of a malignant tumor (carcinoma).
  - increased tumor vascularization.
  - metastasis.

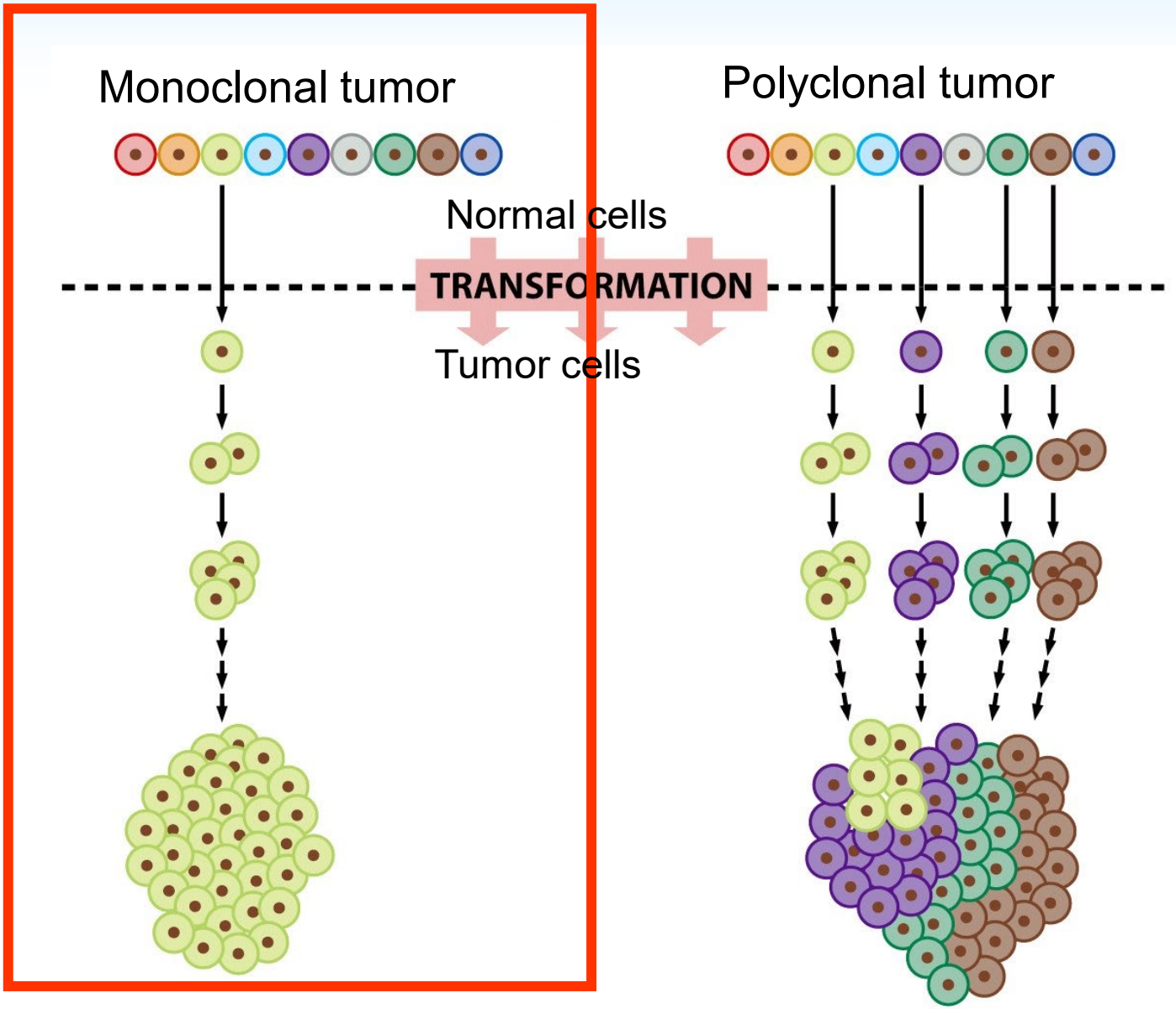
- A tumor is malignant (cancerous) when it :
  - grows significantly : cell division
  - invades surrounding tissue : cell MIGRATION

- Cancers are made up of 'transformed' cells that :
  - divide abnormally and indefinitely ('immortal' cells).
  - have de-differentiated.
  - migrate through the extracellular matrix and invade neighboring tissues.

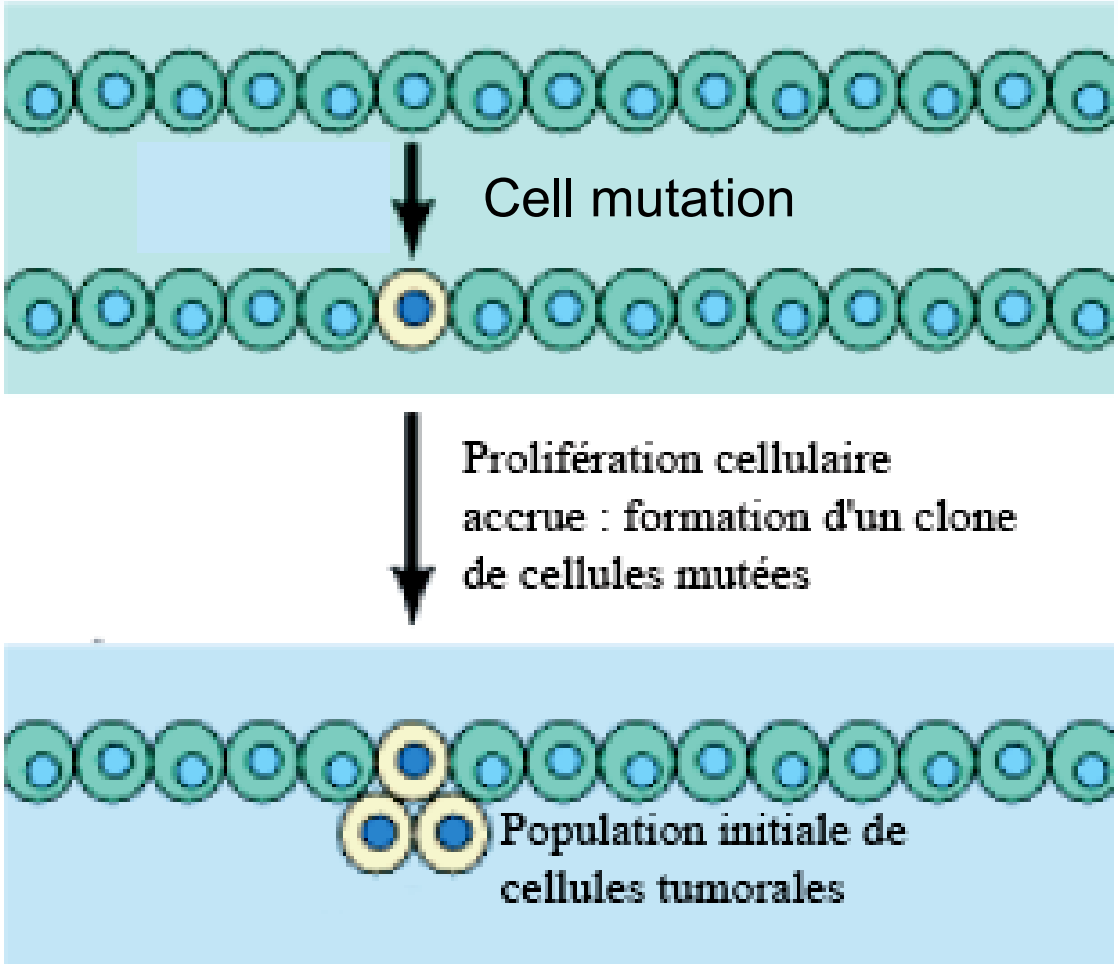
III- Molecular mechanisms of oncogenesis



Tumors start by multiplying a single initial cell

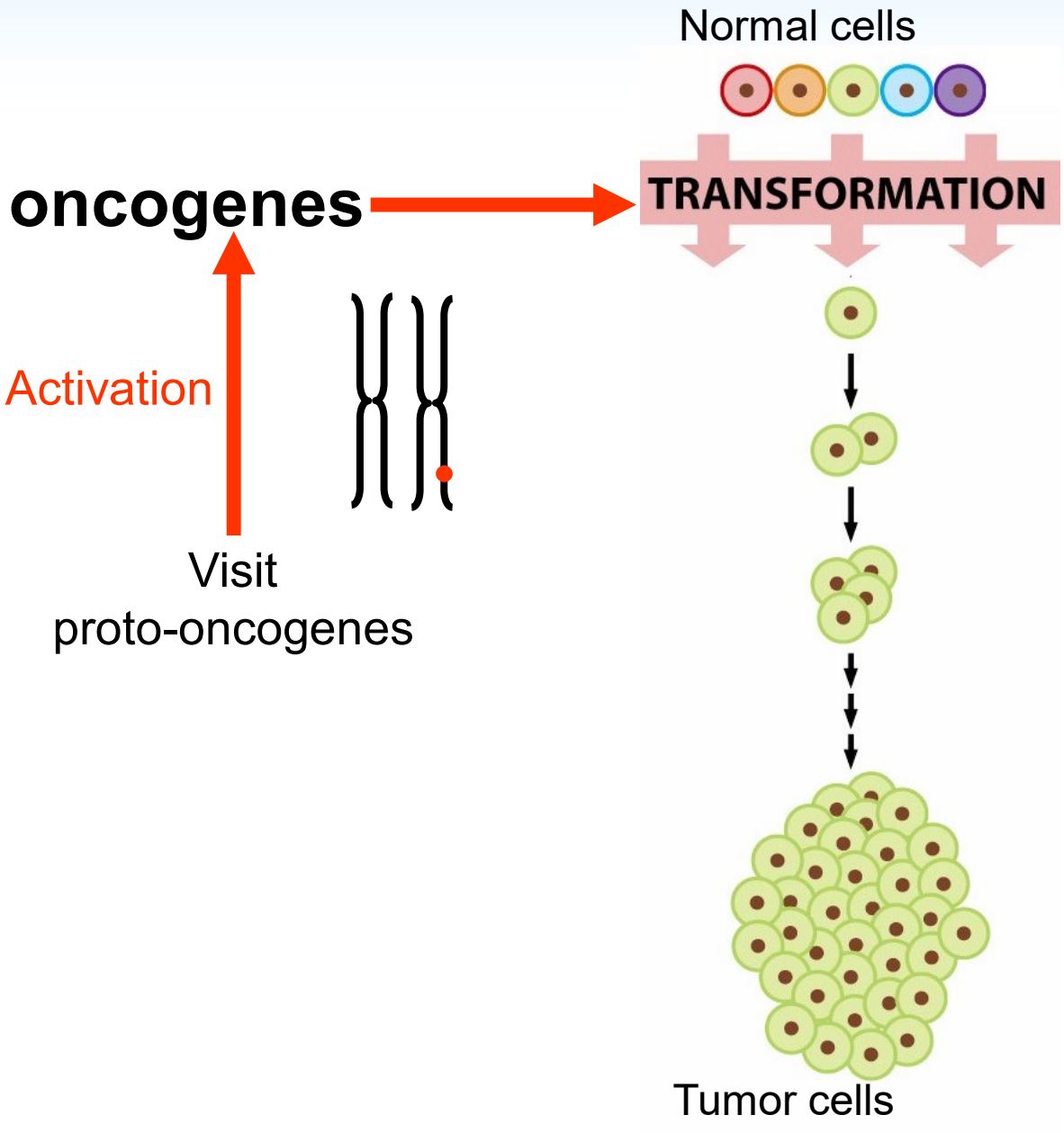


Cellular transformation is the result of alterations to the genome



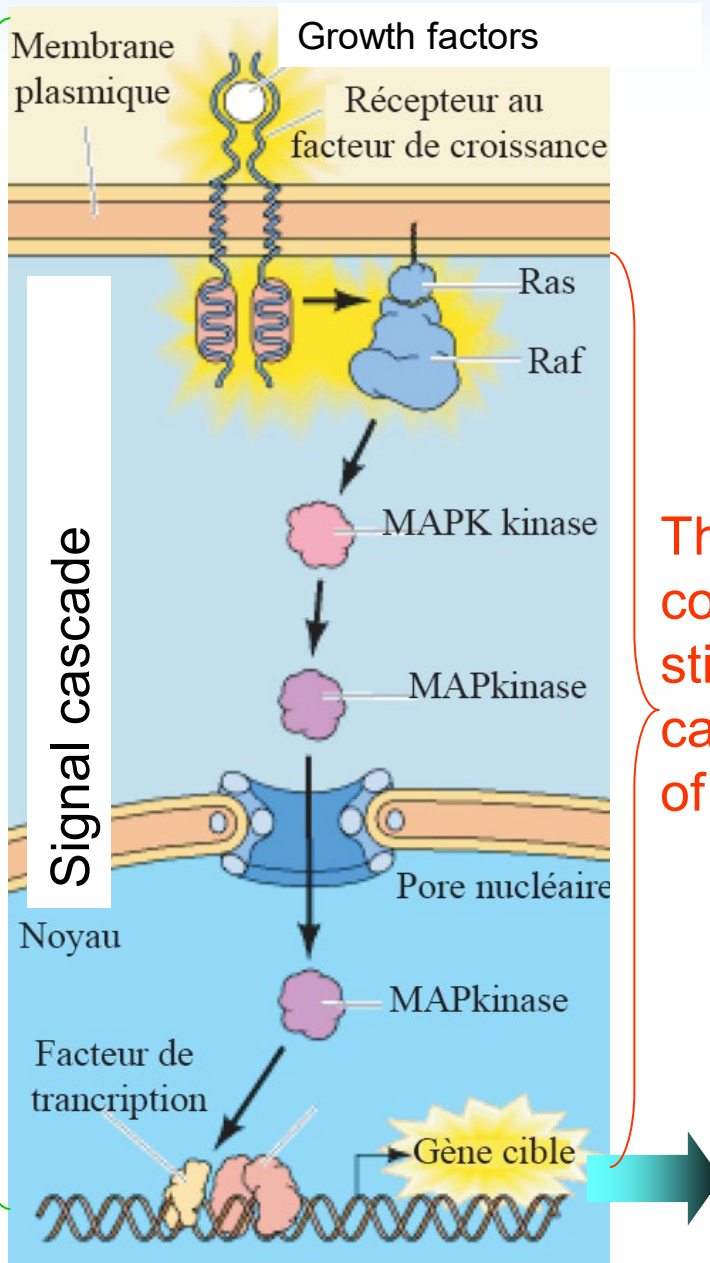
- Which gene(s) are mutated?
- Is a single mutation enough to form a tumor?
- Why do mutations occur?

Two categories of genes may be involved in oncogenesis



Oncogenic form of Ras activates transcription and cell division

Normally, Ras participates in the signalling cascade induced by growth factor receptors.



The Ras oncogene is constitutively active: stimulates the signalling cascade in the absence of growth factors

↑ Transcription

↑ Cell division

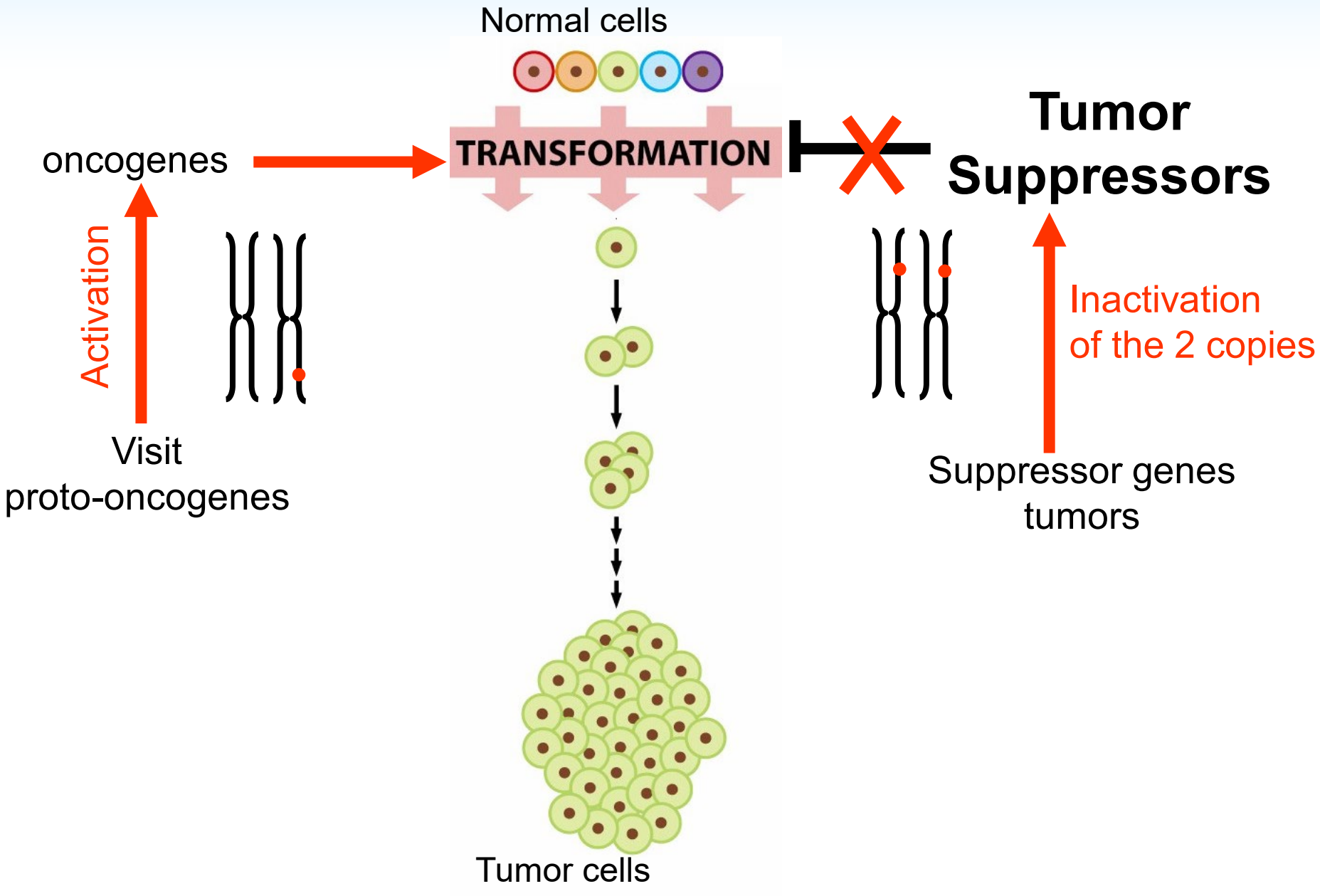
Many oncogenes exist

Oncogenes are frequently
- growth factor receptors,
- elements of the signalling cascades downstream of these receptors
- transcription factors

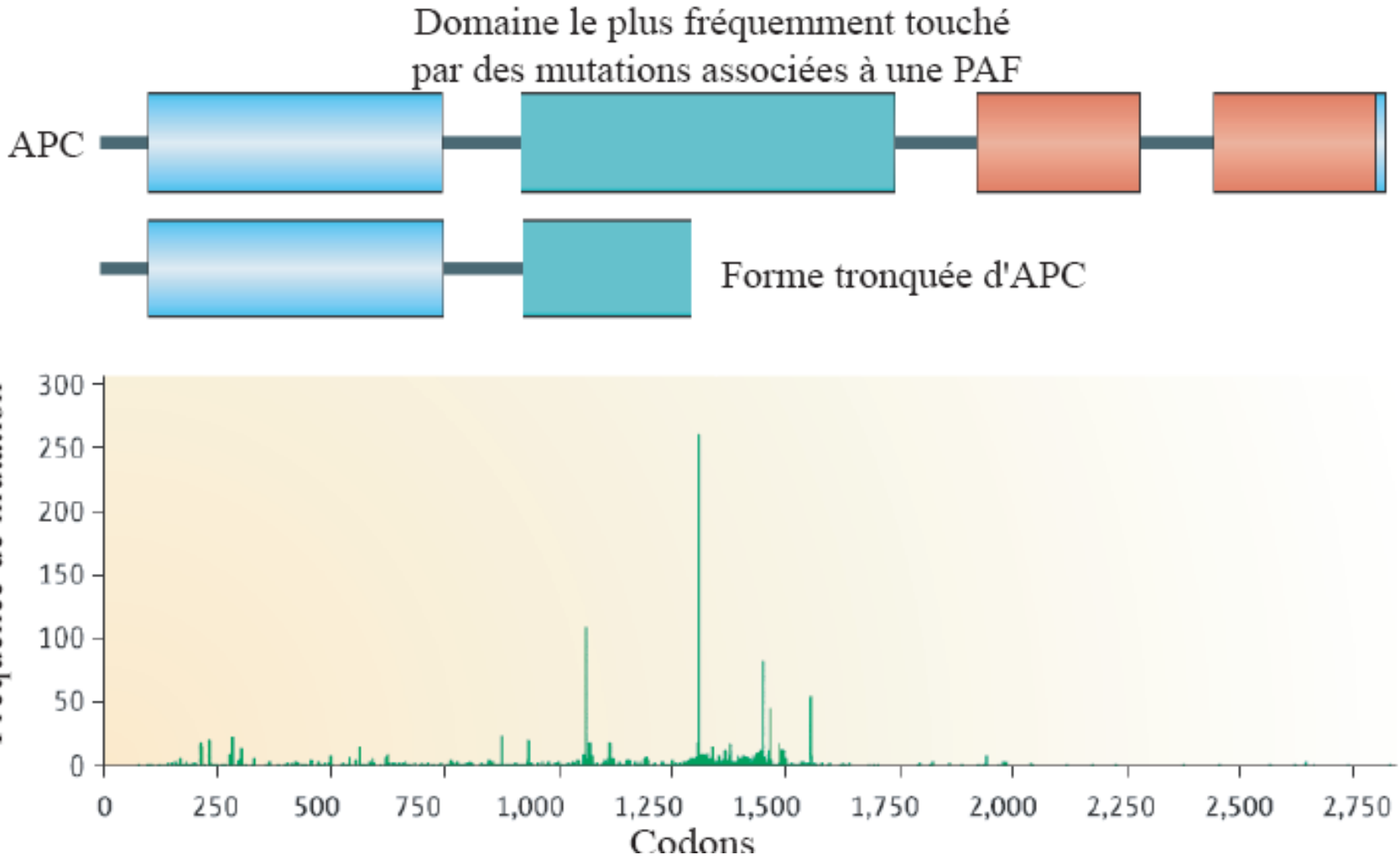
Name of the human oncogene	Location chromosomal protein	Cancers	Nature of protein
erbB1	7q12–13	glioblastomas (50%); squamous cell carcinomas (10–20%)	RTK
cab1–erbB2–grb7	17q12	gastric, ovarian, breast carcinomas (10–25%)	RTK, adaptor protein
k-sam	7q26	gastric, breast carcinomas (10–20%)	RTK
FGF-R1	8p12	breast carcinomas (10%)	RTK
met	7q31	gastric carcinomas (20%)	RTK
K-*ras*	6p12	lung, ovarian, bladder carcinomas (5–10%)	small G protein
N-*ras*	1p13	head and neck cancers (30%)	
c-*myc*	8q24	various leukemias, carcinomas (10–50%)	TF
L-*myc*	1p32	lung carcinomas (10%)	TF
N-*myc–DDX1*	2p24–25	neuroblastomas, lung carcinomas (30%)	TF
akt-1	14q32–33	gastric cancers (20%)	ser/thr kinase
cyclin D1–exp1–hst1–ems1	(11q13)	breast and squamous cell carcinomas (40–50%)	G1 cyclin
cdk4–mdm2–sas–gli	12q13	sarcomas (40%)	CDK, p53 antagonist
cyclin E	19q12	gastric cancers (15%)	cyclin
akt2	(19q13)	pancreatic, ovarian cancers (30%)	ser/thr kinase
AIB1, BTAK	(20q12–13)	breast cancers (15%)	receptor co-activator
cdk6	(19q21–22)	gliomas (5%)	CDK
myb	6q23-24	colon carcinoma, leukemias	TF
ets-1	11q23	lymphoma	TF
gli	12q13	glioblastomas	TF
FGFR2	10q26	breast carcinomas	RTK

RTK: receptor tyrosine kinase (growth factor receptor); TF: transcription factor

Two categories of genes may be involved in oncogenesis



The APC tumor suppressor is mutated in Familial Adenomatous Polyposis (FAP).



Numerous tumor suppressors have been identified

Gene	chromosome	cancer sporadic	cancer familial	function protein
RUNX3	1p36	—	gastric carcinoma	TF co-factor
HRPT2	1q25–32	parathyroid tumors, jaw fibromas	parathyroid tumors	chromatin protein
FH	1q42.3	familial leiomyomatosis[a]	—	fumarate hydratase
FHIT	3p14.2	—	many types	diadenosine triphosphate hydrolase
RASSF1A	3p21.3	—	many types	multiple functions
TGFBR2	3p2.2	HNPCC	colon, gastric, pancreatic carcinomas	TGF-β receptor
VHL	3p25	von Hippel–Lindau syndrome	renal cell carcinoma	ubiquitylation of HIF
hCDC4	4q32	—	endometrial carcinoma	ubiquitin ligase
APC	5p21	familial adenomatous polyposis coli	colorectal, pancreatic, and stomach carcinomas; prostate carcinoma	β-catenin degradation
NKX3.1	8p21	—	prostate carcinoma	homeobox TF
p16^{INK4A}[b]	9p21	familial melanoma	many types	CDK inhibitor
p14^{ARF}[c]	9p21	—	all types	p53 stabilizer
PTC	9q22.3	nevoid basal cell carcinoma syndrome	medulloblastomas	receptor for hedgehog GF
TSC1	9q34	tuberous sclerosis	—	inhibitor of mTOR[f]
BMPR1	10q21–22	juvenile polyposis	—	BMP receptor
PTEN[d]	10q23.3	Cowden's disease, breast and gastrointestinal carcinomas	glioblastoma; prostate, breast, and thyroid carcinomas	PIP_3 phosphatase
WT1	11p13	Wilms tumor	Wilms tumor	TF
MEN1	11p13	multiple endocrine neoplasia	—	histone modification, transcriptional repressor
BWS/CDKN1C	11p15.5	Beckwith–Wiedemann syndrome	—	$p57^{Kip2}$ CDK inhibitor
SDHD	11q23	familial paraganglioma	pheochromocytoma	mitochondrial protein[e]
RB	13q14	retinoblastoma, osteosarcoma	retinoblastoma; sarcomas; bladder, breast, esophageal, and lung carcinomas	transcriptional repression; control of E2Fs
TSC2	16p13	tuberous sclerosis	—	inhibitor of mTOR[f]
CBP	16p13.3	Rubinstein–Taybi	AML[g]	TF co-activator
CYLD	16q12–13	cylindromatosis	—	deubiquitinating enzyme
CDH1	16q22.1	familial gastric carcinoma	invasive cancers	cell–cell adhesion
BHD	17p11.2	Birt–Hogg–Dube syndrome	kidney carcinomas, hamartomas	unknown
TP53	17p13.1	Li–Fraumeni syndrome	many types	TF
NF1	17q11.2	neurofibromatosis type 1	colon carcinoma, astrocytoma	Ras-GAP
BECN1	17q21.3	—	breast, ovarian, prostate	autophagy
PRKAR1A	17.q22–24	multiple endocrine neoplasia[h]	multiple endocrine tumors	subunit of PKA
DPC4[i]	18q21.1	juvenile polyposis	pancreatic and colon carcinomas	TGF-β TF
LKB1/STK11	19p13.3	Peutz–Jegher syndrome	hamartomatous colonic polyps	serine/threonine kinase
RUNX1	21q22.12	familial platelet disorder	AML	TF
SNF5[j]	22q11.2	rhabdoid predisposition syndrome	malignant rhabdoid tumors	chromosome remodeling
NF2	22q12.2	neurofibroma-position syndrome	schwannoma, meningioma; ependymoma	cytoskeleton–membrane linkage

A single mutation is not enough to induce a tumor

- There are around 10^{16} cell divisions in the course of a human being's life.
- spontaneous mutations occur at a rate of 10^{-6} mutations/gene/division

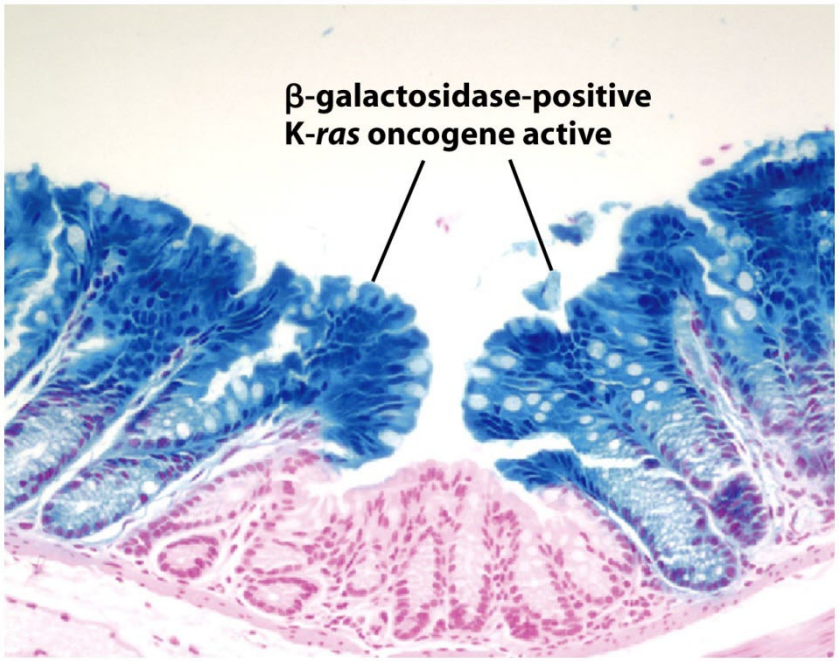
Each gene therefore has around 10^{10} 'chances' of acquiring a mutation during an individual's lifetime.

→ Why do cancers occur so rarely?

A single mutation is not enough to induce a tumor

The Ras oncogene is found in many cancers

Type of tumor	% of tumors carrying a point mutation in the Ras gene
Pancreas	90
Thyroid	60
Colorectal	45
Lung	35
Leukemia	30
Liver	30
Melanoma	15
Bladder	10
Kidney	10

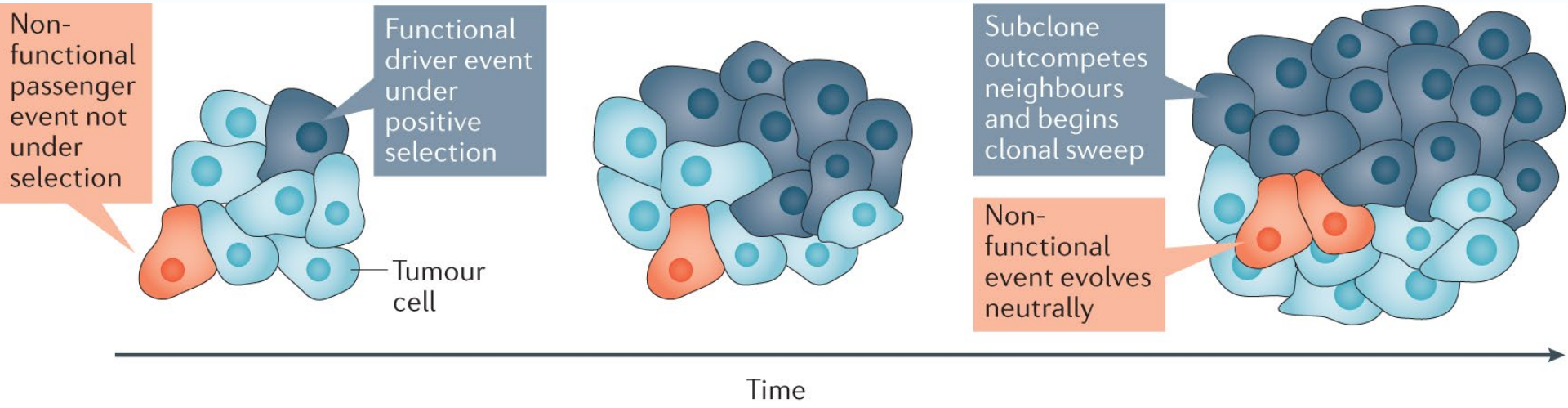


Expression of the K-Ras oncogene is not sufficient to induce cancer

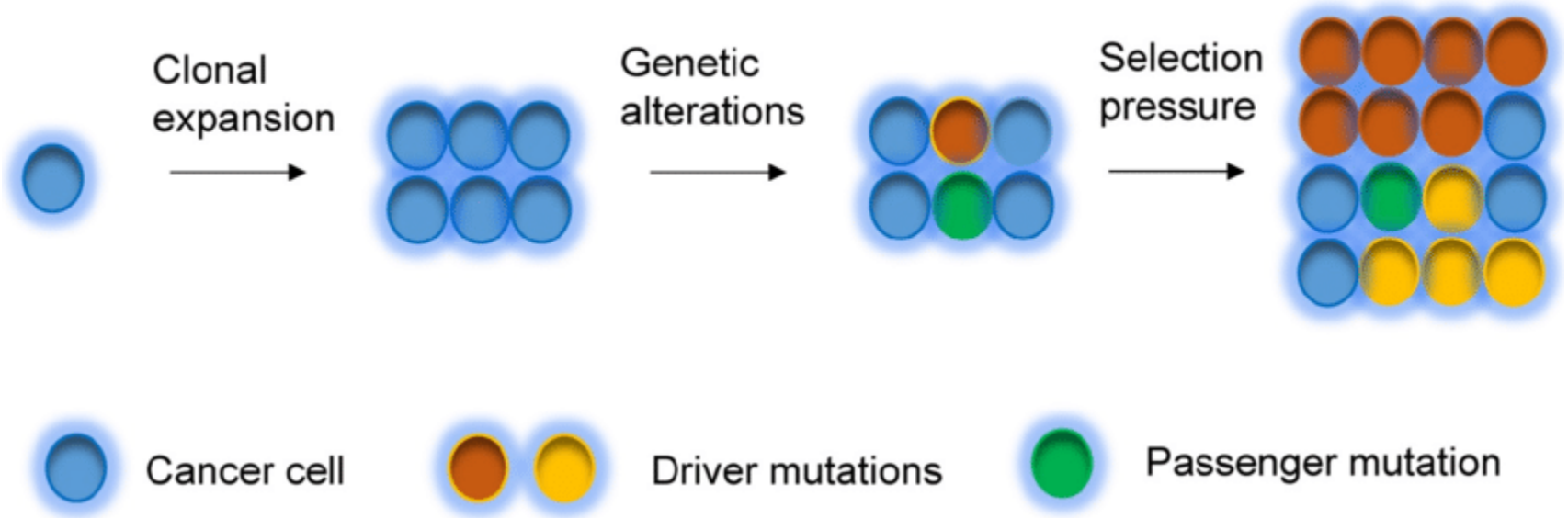
- It takes several successive oncogenic events in the same cell for a tumor to develop

- There are protective mechanisms against tumor formation

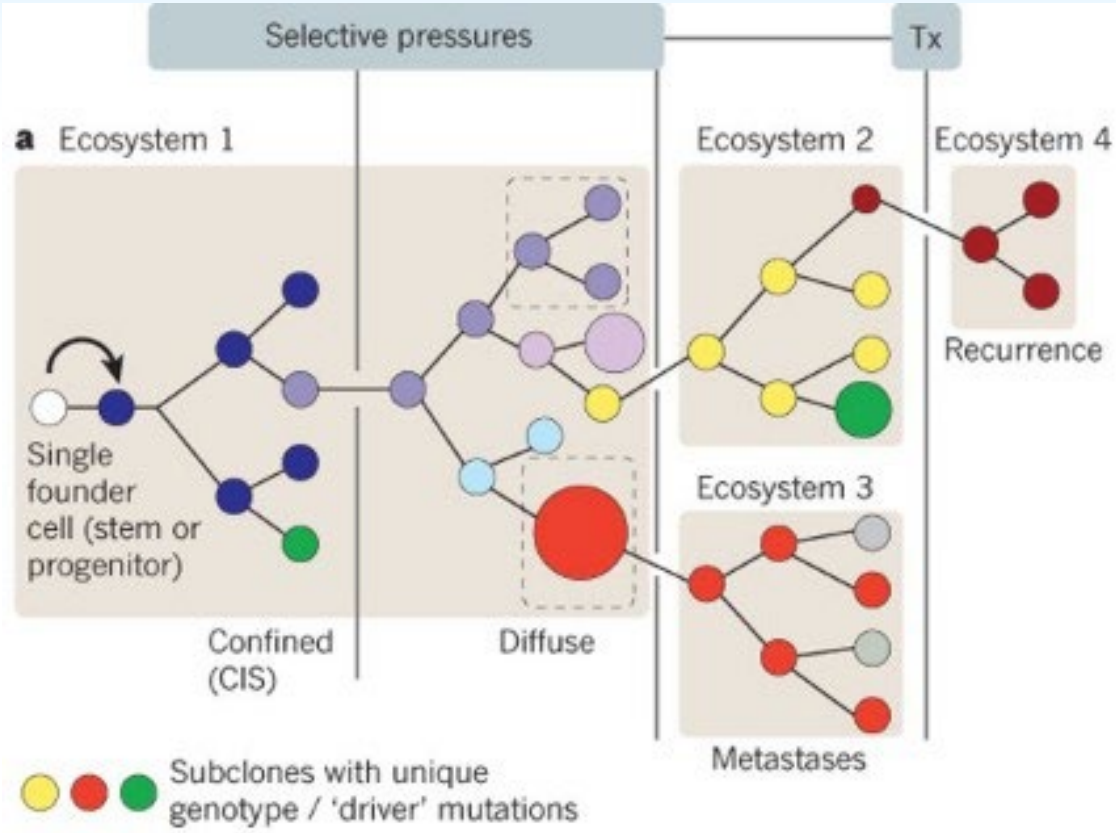
Cellular transformation is the result of multiple alterations to the genome: clonal selection

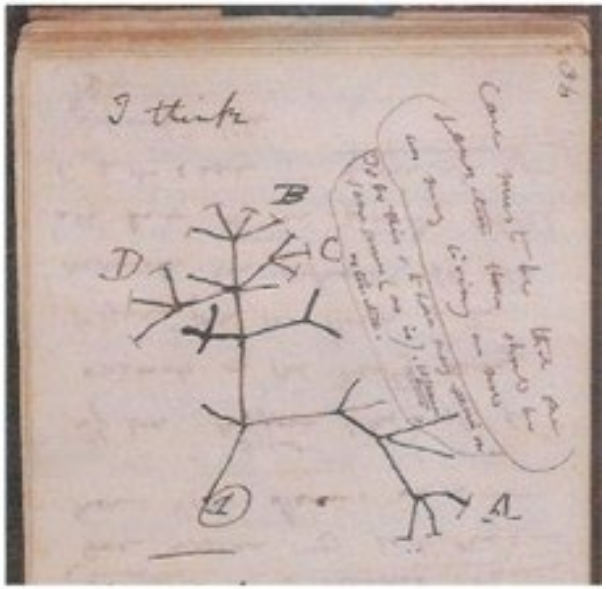


Tumor cells undergo several successive cycles mutation-selection



Mutations are acquired progressively as the tumor evolves

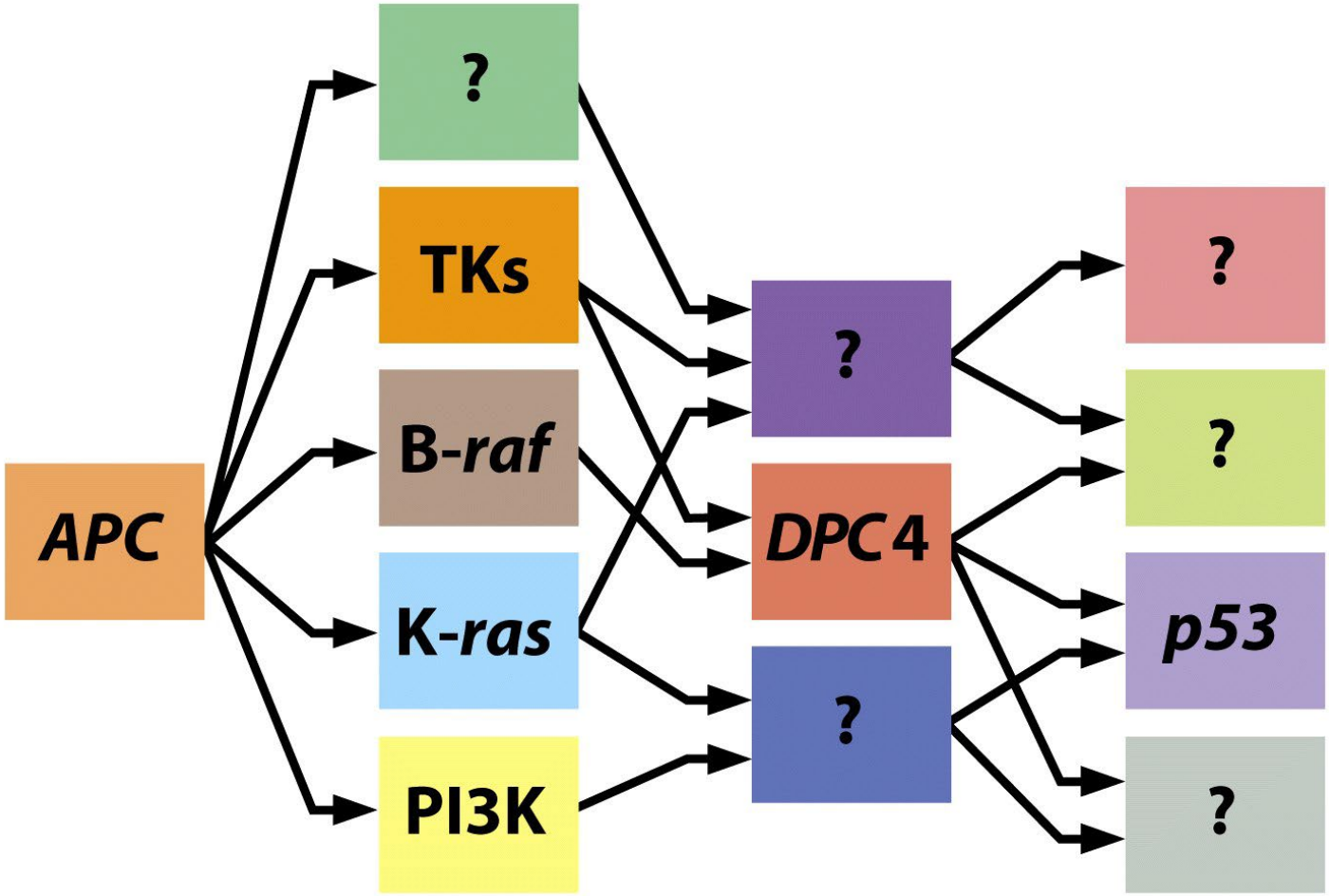




The accumulation of mutations enables cells to acquire new properties:

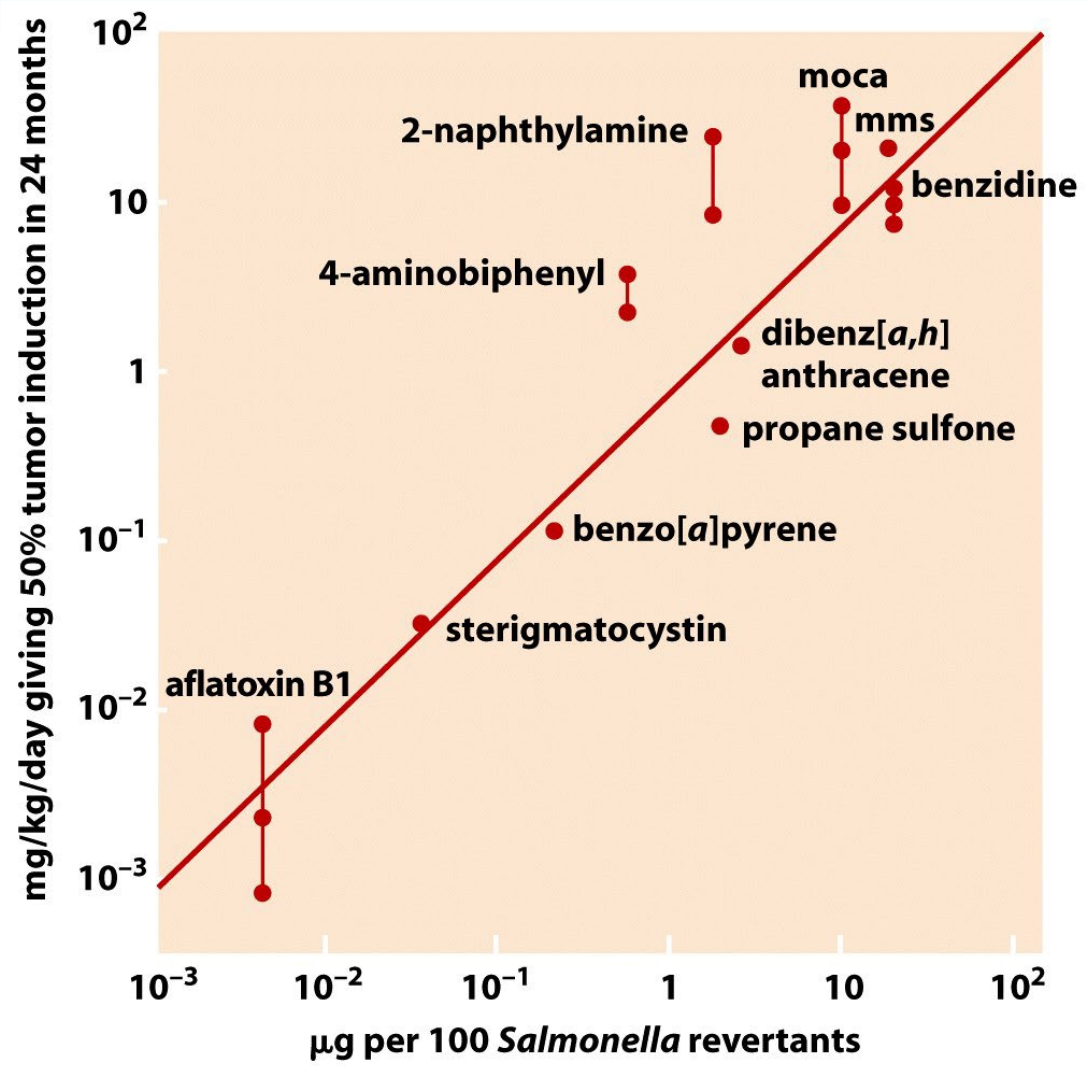
- they are able to survive and multiply in the absence of growth factors
- they are insensitive to the triggering of apoptosis
- they become immortal
- they are able to leave their initial environment and invade adjacent tissues
- they become genetically and genomically unstable

Mutations can accumulate in different orders in different tumors



Mutations can be caused by exposure to mutagenic compounds

Mutagenic compounds are carcinogenic.



Mutations in DNA repair genes are responsible for the emergence of certain cancers

Disease	Sensitivity	Susceptibility to certain cancers
Ataxia telangiectasia	Irradiation γ	Lymphomas
Bloom's syndrome	Alkylating agents	Carcinomas, leukemias, lymphomas
Cockayne's syndrome	UV irradiation	
Fanconi's anemia	Bridging agents	Leukemia
Hereditary nonpolyposis colorectal cancer	UV irradiation, chemical mutagens	Colon, ovaries
Xeroderma pigmentosum	UV irradiation, chemical mutagens	Skin carcinomas and melanomas

Some viruses can cause cancer

Virus	family	target cells	Human cancer
EBV	Herpesviridae	B cells	Burkitt's lymphoma
		oropharyngeal epithelial cells	nasopharyngeal carcinoma
		lymphoid	lymphoma[b]
HTLV-I	Retroviridae	T cells	non-Hodgkin's lymphoma
HHV-8[d]	Herpesviridae	endothelial cells	Kaposi's sarcoma, body cavity lymphoma
HBV	Hepadnaviridae	hepatocytes	hepatocellular carcinoma
HCV	Flaviviridae	hepatocytes	hepatocellular carcinoma
HPV	Papovaviridae	cervical epithelial	cervical carcinoma
JCV[e]	Papovaviridae	central nervous system	astrocytoma, glioblastoma

Conclusions III

III- Molecular mechanisms of oncogenesis

• Cellular transformation results from the accumulation of mutations in key genes: oncogenes and tumor suppressors.

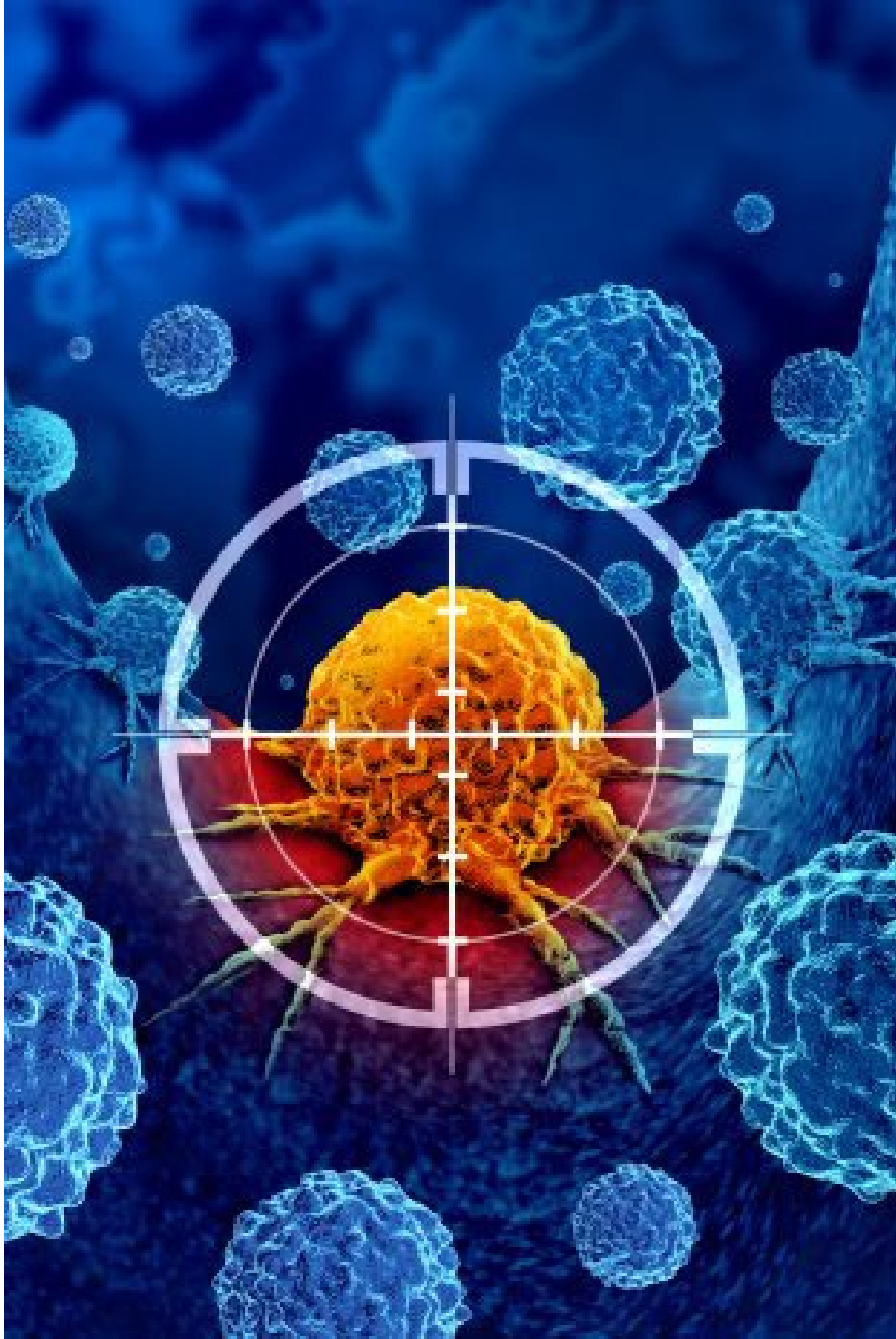
• Oncogenes result from the activation (mutation, transcriptional activation, etc.) of a proto-oncogene.

• Both copies of the tumor suppressor genes must be inactivated.

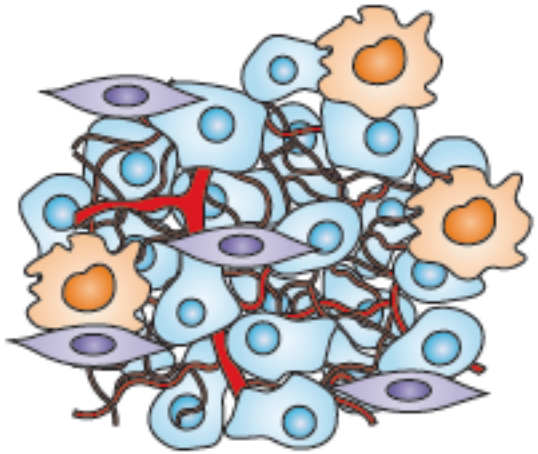
• Multiple mutations gradually accumulate within tumor cells, enabling them to acquire their many properties.

• Mutations are the consequence of exposure to mutagenic products, mutations in certain genes that guard genome integrity, alterations in gene expression, and viral infections.

IV- Prevention, screening and treatment



Cancer prevention



Preventing colon cancer.

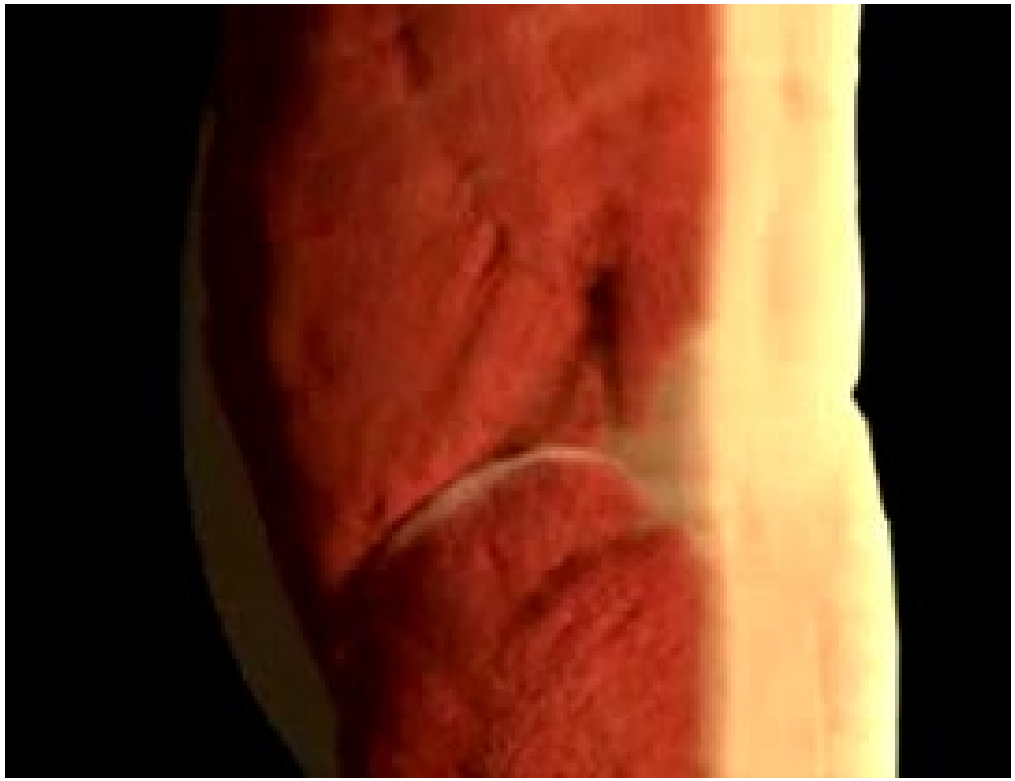
• Recommendations are limited to dietary advice: increase vegetable consumption, reduce overall calorie intake and increase physical activity.

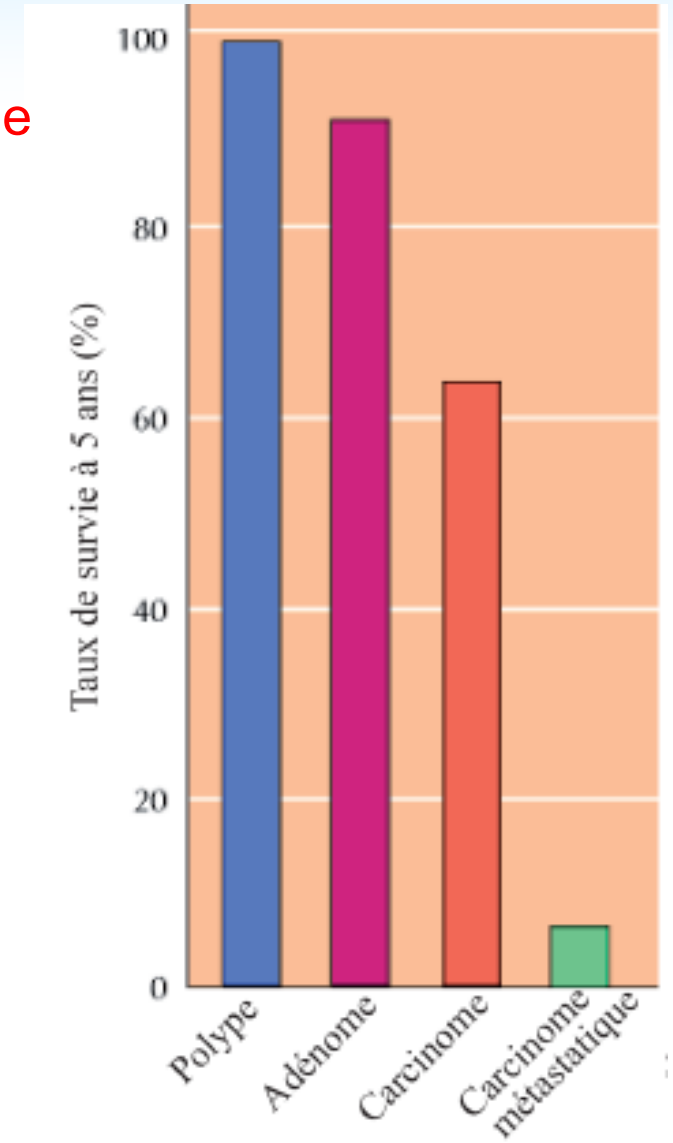
Prevention :
Limit risk factors!

Risk factors :
Obese or overweight
Insufficient consumption of fruit and vegetables
Lack of exercise
Smoking
Alcohol consumption
Pollution exposure
Exposure to UV rays
Chronic infections (viruses) ...

It's important to detect cancers as early as possible

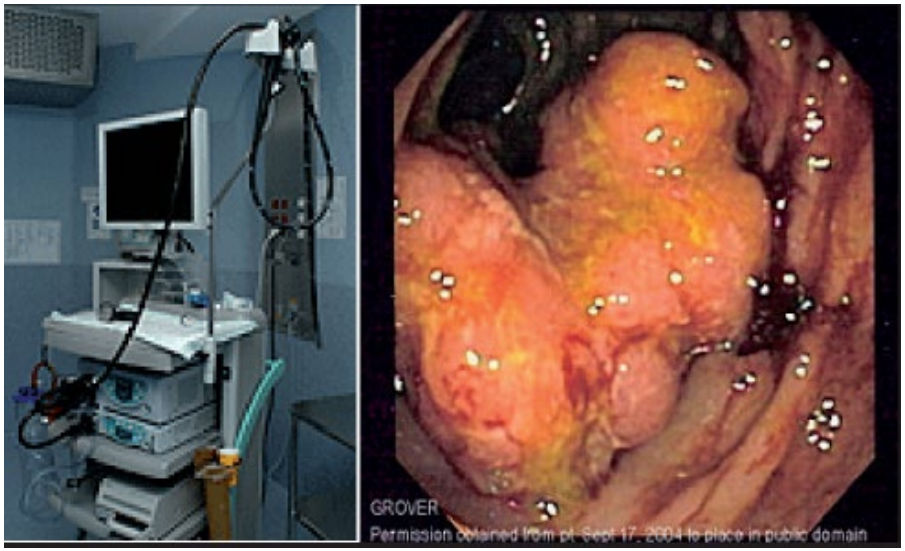
Treatment of precancerous lesions reduces the risk of colon cancer



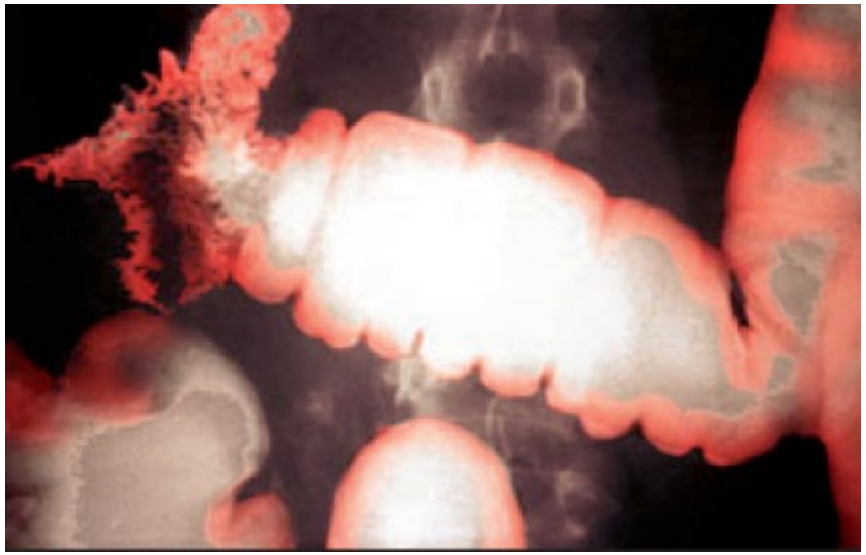


Development stage
at the time of detection

A number of screening techniques are now available

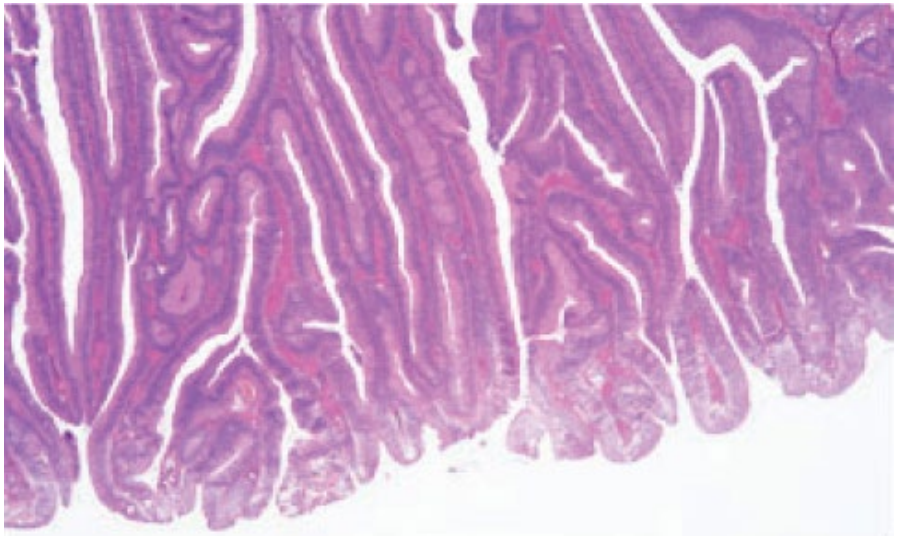


Colonoscopy



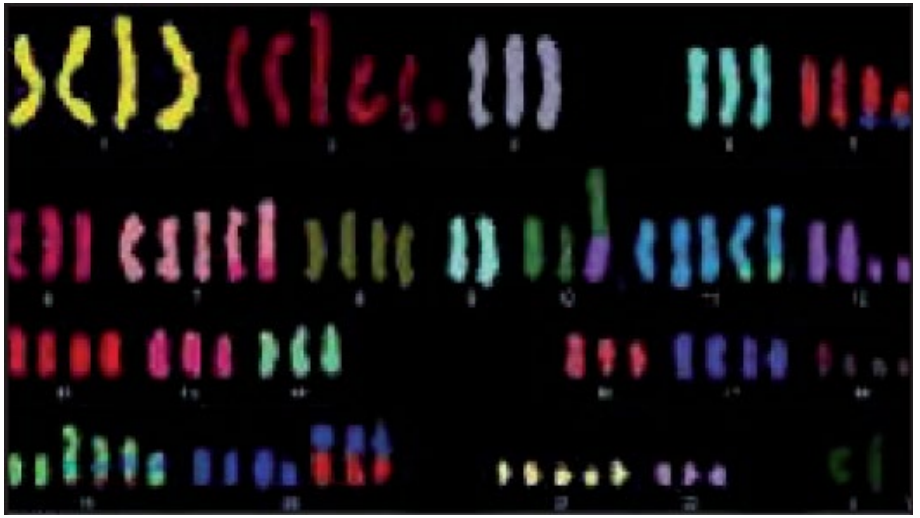
Radiology

A number of screening techniques are now available



Histology after surgery

Genetic analysis



Conventional treatments eliminate the primary tumor primary

SURGERY

Curative excision aims **to** cure the patient. It is based on the eradication of all cancerous tissue.

RADIOTHERAPY

Aims to destroy residual neoplastic cells in the tumor bed after surgical excision.

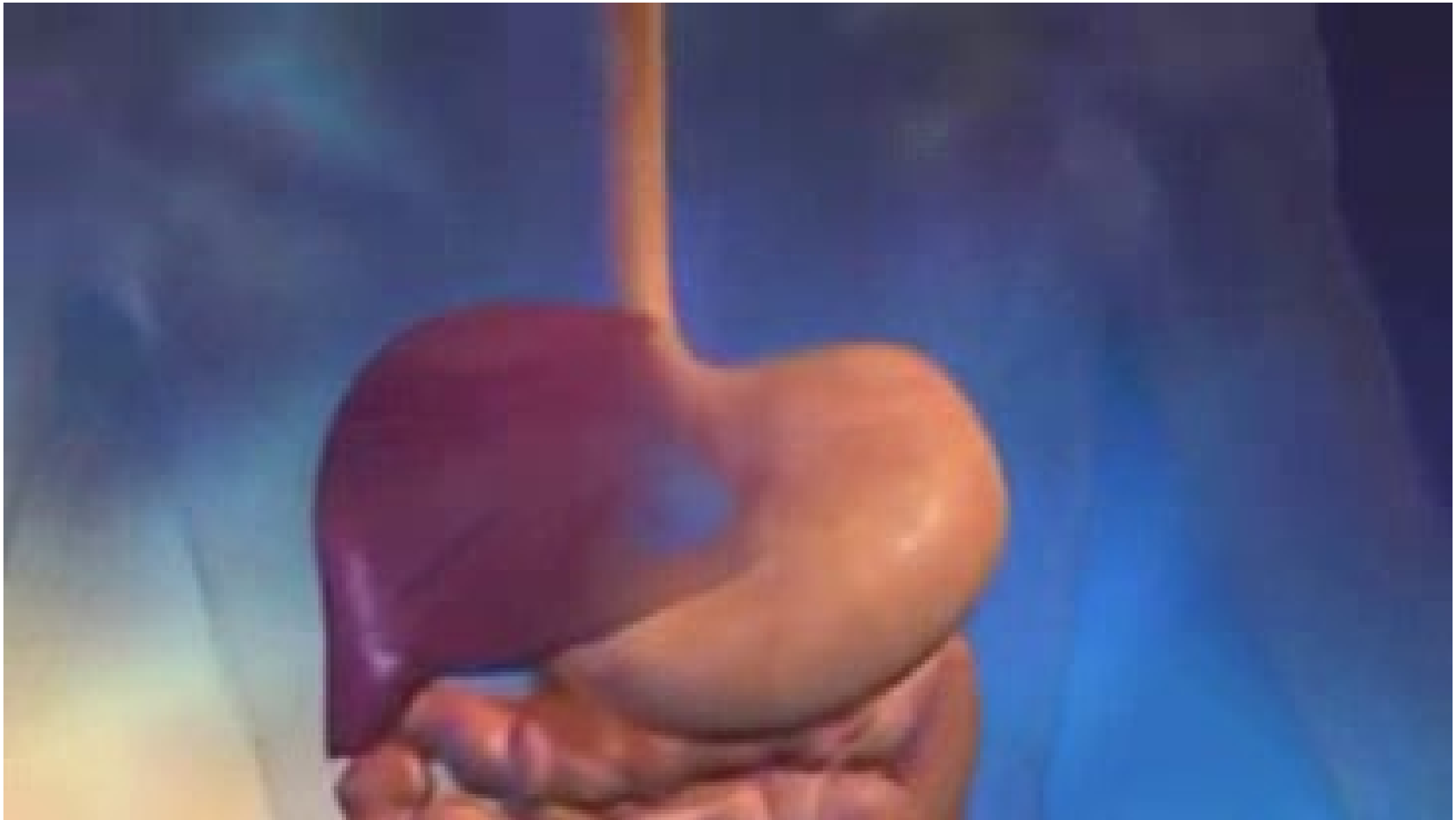
It is indicated for tumors extending beyond the colonic wall,
in the event of incomplete exeresis or local recurrence.

Various treatments can be used as adjuvants to surgery or as systemic therapy

CHEMOTHERAPY

It aims to inhibit cell multiplication:

- nucleic acid synthesis inhibitors.
- replication inhibitors.



Various treatments can be used as adjuvants to surgery or as systemic therapy

CHEMOTHERAPY

It aims to inhibit cell multiplication:

- nucleic acid synthesis inhibitors.
- replication inhibitors.
- cell division inhibitors.

HORMONE THERAPY

It interferes with tumor cell responses to hormones in hormone-dependent tumors (breast, prostate...).

BIOTHERAPY

A more specific treatment that acts on more than just tumor cells.

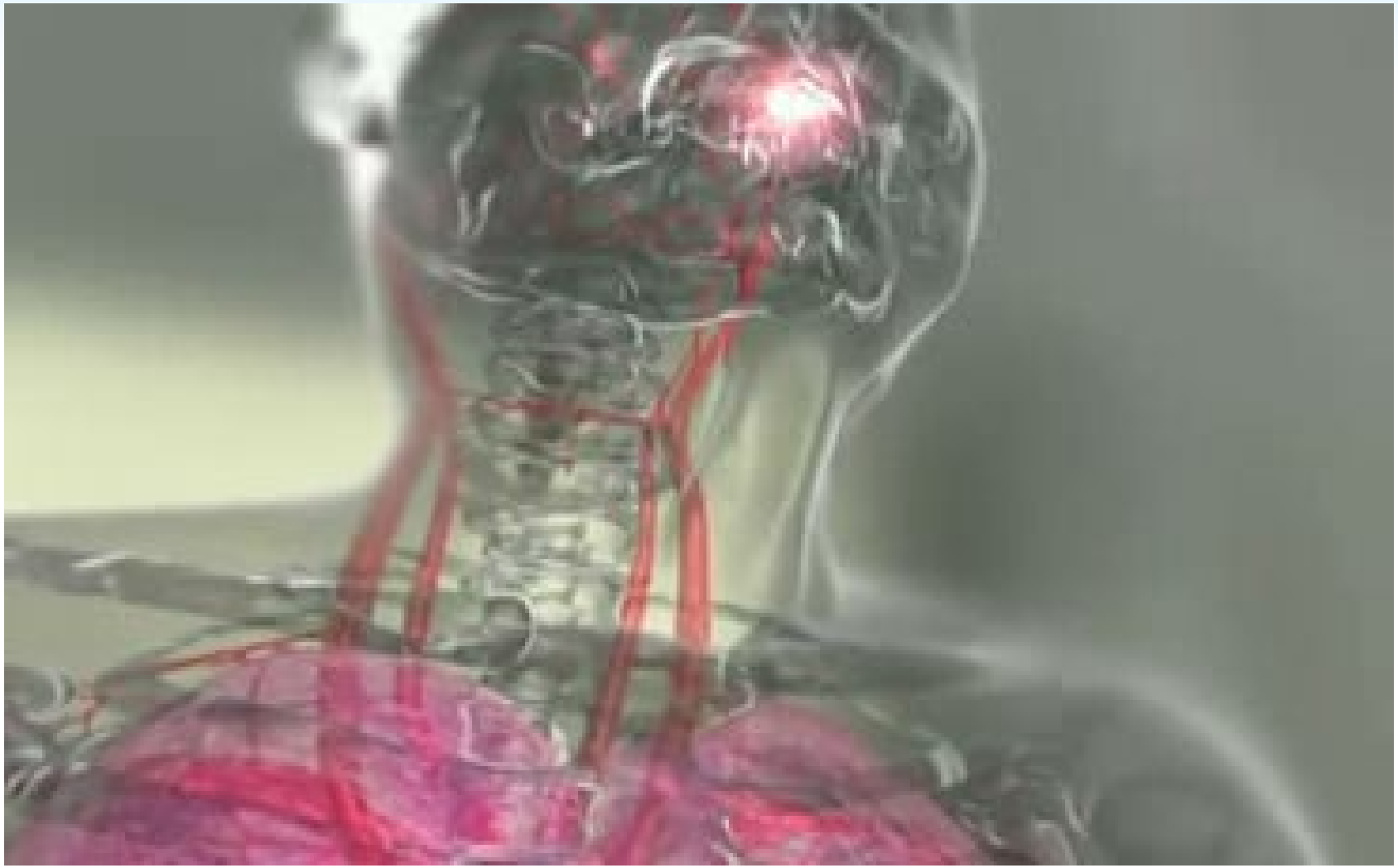
It acts on :

- immunity mechanisms.
- tumor vascularization. (Avastin, anti-VEGF mAc)
- altered signaling pathways (Cetuximab, mAc anti EGF Rec)
- cell invasion.

Various treatments can be used as adjuvants to surgery or as systemic therapy

- immunity mechanisms (immunotherapy).

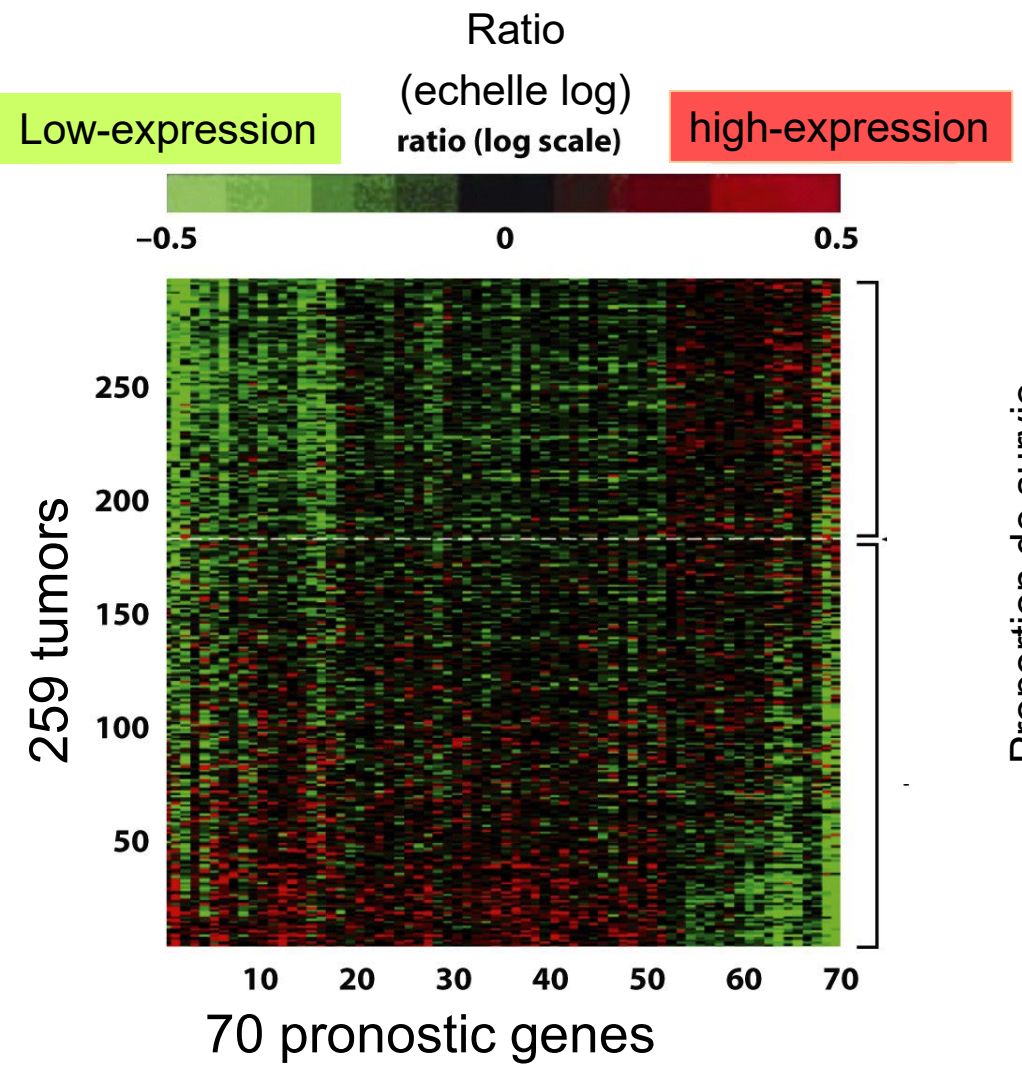
Various treatments can be used as adjuvants to surgery or as systemic therapy

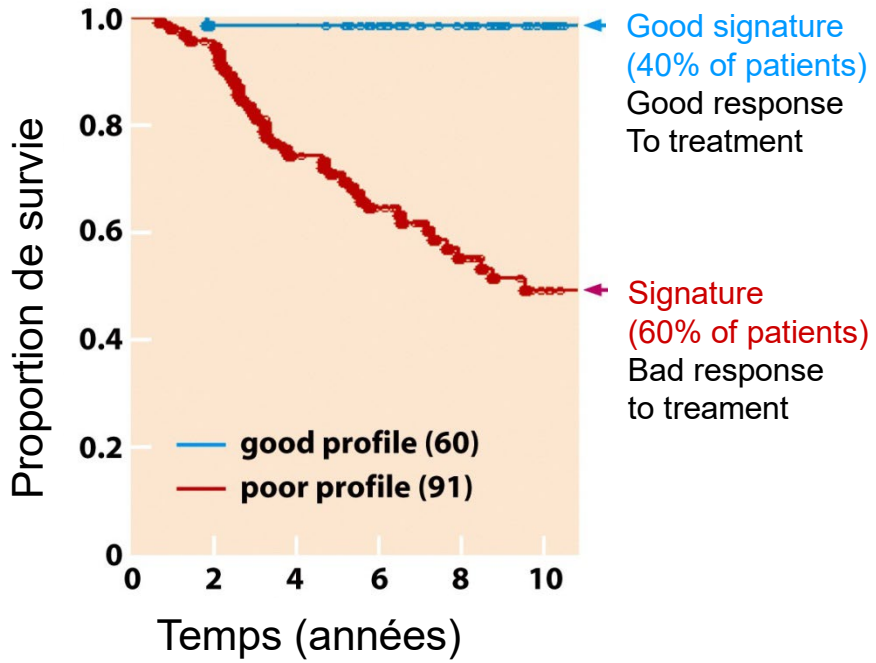


- tumor vascularization. (Avastin, anti-VEGF mAc)
- altered signaling pathways (Cetuximab, mAc anti EGF Rec)
- cell invasion.

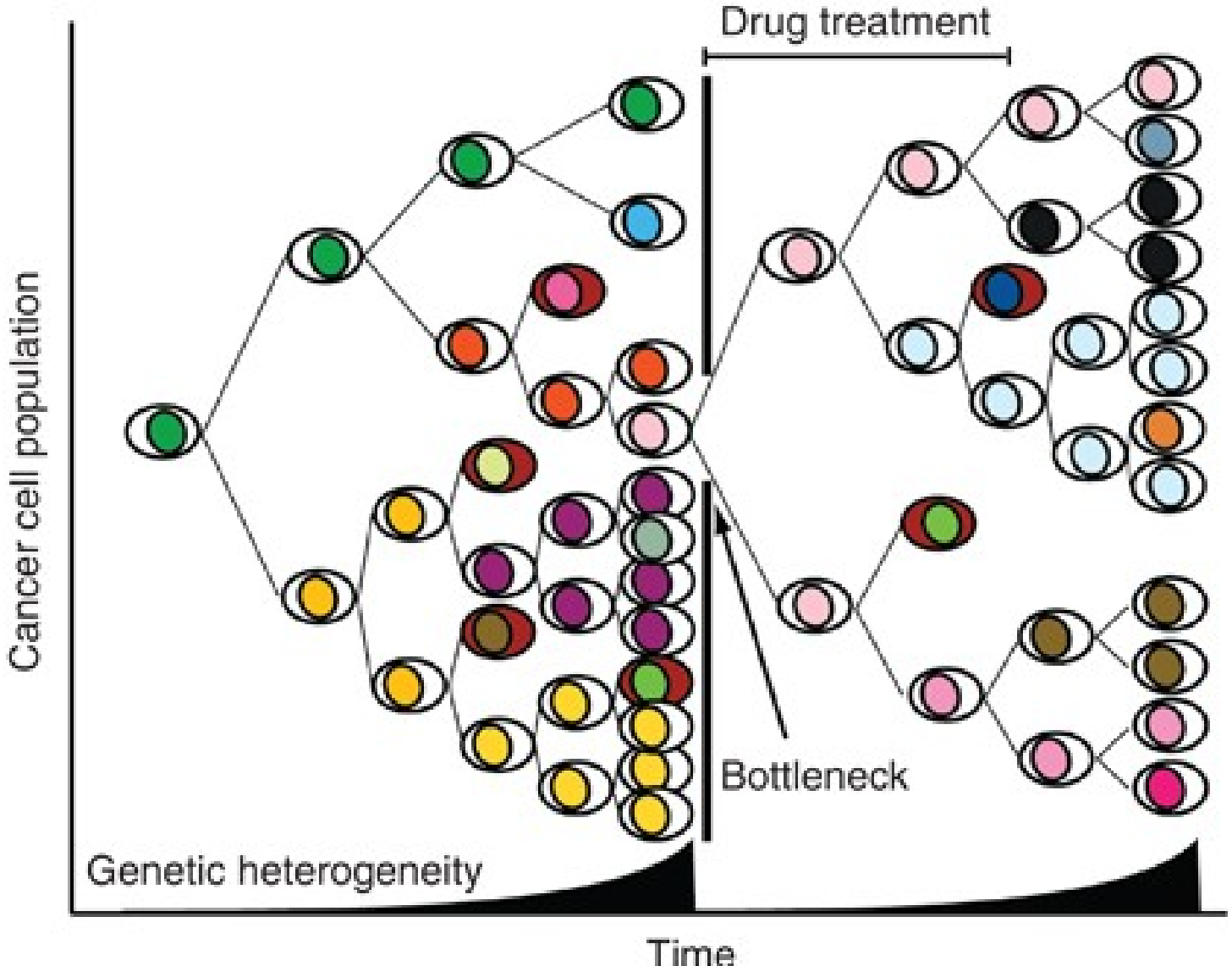
Evaluate inter-tumoral genetic heterogeneity to improve treatment

Tumor genetic profile → Appropriate treatment





Genetic intra-tumoral heterogeneity remains a major reason for resistance



Conclusions IV

IV- Prevention, screening and treatment

- Prevention methods are still poorly defined.
- Early, systematic screening is an effective way of combating certain cancers.
- Cancer treatment may require a combination of approaches: surgery, radiotherapy, chemotherapy, hormone therapy...
- Improvements in cancer diagnosis should enable the development of more specific treatments.