

DEFINITION of NEOPLASTIC DISEASES

**definition, terminology
classification of tumors**

local changes caused by tumors

**metastasizing
general symptomatology**

Definition of neoplastic diseases

A tumor (neoplasm) represents de novo development and a growth of a clone of cells and a new tissue

The newly formed neoplastic tissue gets out of control of physiological regulation of cell and tissue growth which is tightly balanced in the natural exchange of cells in the regenerative and reparative processes

A tumor does not form any physiological and morphological accessory to the body and therefore, it does not bring any profit to the organism – on the contrary, as a pathological entity it has a deleterious impact on the organism

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The term **neoplasia** must be separated from a general term „**tumor**“ as this term may also mean

- inflammatory edema**
- healing phenomena, eg. a callus**
- inflammatory pseudotumor**

Classification of neoplasia terminology and basic biological properties

mesenchymal

soft tissue tumors

bone tumors

hemopoetic system tumors

leukemia, lymphoma

cell specific

fibroma / fibrosarcoma

osteoma / osteosarcoma

lymphoblastic x lymphocytic

myeloblastic, B and T lymphomas

epithelial

surface epithelia

glangular epithelia

specialized organs

structural, organ and cell specific

papiloma / squamous cell carcinoma

adenoma / adenocarcinoma

adenoma / carcinoma *hepatocellular*

neuroectodermal

CNS

PNS

cell specific

astrocytoma / glioblastoma

neurofibroma, neurinoma / MPNST

embryonal

germinal

organ specific

specialized

teratoma, seminoma, choriocarcinoma

nfroblastoma, hepatoblastoma

Classification of tumors

semimalignant

BENIGN

MALIGNANT

cytology

nearly natural /
no atypia

loss of differentiation, anaplasia

structure

„differentiated“
organoid

loss of differentiation

**growth /
boundary**

expansive / sharp

infiltrative / invasion + destruction

encapsulation

yes, mostly

usually absent

growth / speed

slow / periods

permanent, variable speed

metastazes

absent

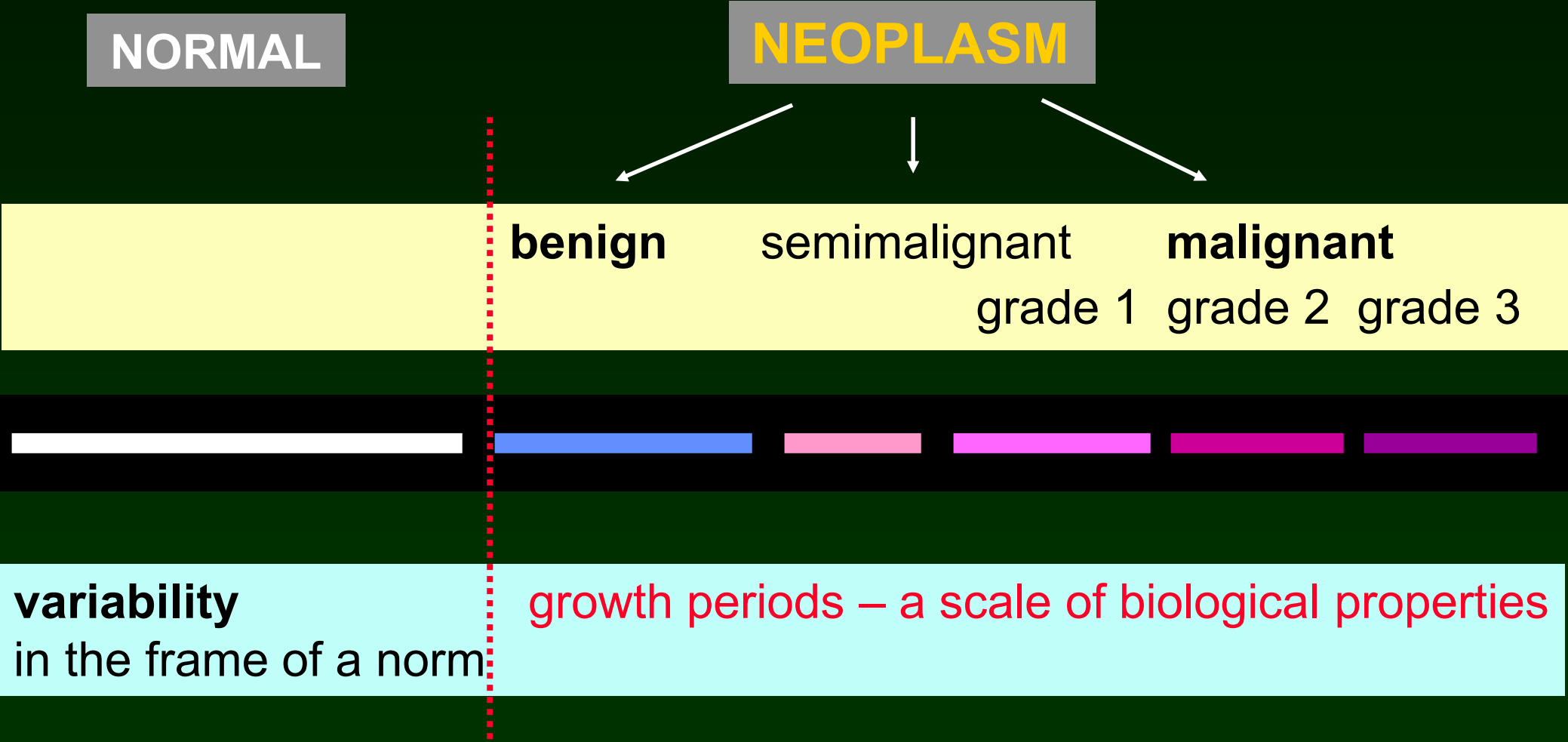
develop regularly

the frequency / numbers variable

solitary x multiple early x late

selective x generalized

Biological properties of tumors – from normal tissues to a malignancy



Cytological / structural deviations of a neoplastic growth

DIFFERENTIATION

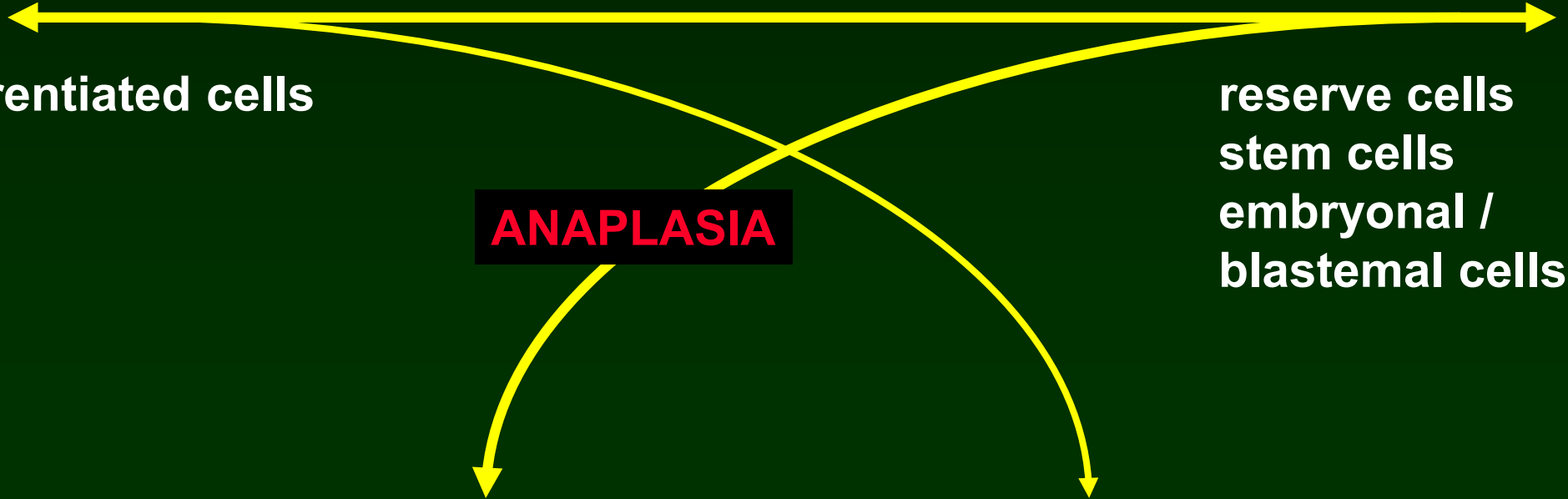
IMMATURITY

differentiated cells

reserve cells
stem cells
embryonal /
blastemal cells

ANAPLASIA

deviation / anaplasia



glioblastoma multiforme

BCSC 1111

sarcoma (buttock)

Neoplastic growth - expansion

• Neoplastic growth - expansion

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• Neoplastic growth - expansion

Neoplastic growth – invasion + destruction

Neoplastic growth – invasion + destruction (ulceration)



Local effects of neoplasia - consequences

„mass effect “

+ edema, + bleeding

compression, destruction,
fracture, vertebral collapse
increased intracranial pressure
replacement of hemopoiesis

obstruction

bronchus – lung collapse, pneumonia
biliary ways - jaundice

ulceration

tissue destruction

bleeding

anemia – acute/chronic, aspiration of blood

perforance

peritonitis, fistulas

inflammation

pleuritis, peritonitis, ulceration

pain

eg. perineural invasion

paresis

eg. n. laryngeus recurrens, n. facialis

brain dysfunction

loss of functions, epilepsy, intracranial hypertension

Distant tumor spread - implantation metastasizing

**Distant tumor spread -
blood stream metastasizing**

Distant tumor spread - lymphatic metastasizing

Important systemic sequelae of neoplastic diseases

CACHEXIA !

anemia x polycythemia

hemorrhagic diathesis

thrombophlebitis migrans

thrombotic endocarditis

immunodeficiency

hormonal activity and effects !

peripheral neuropathy

myopathy

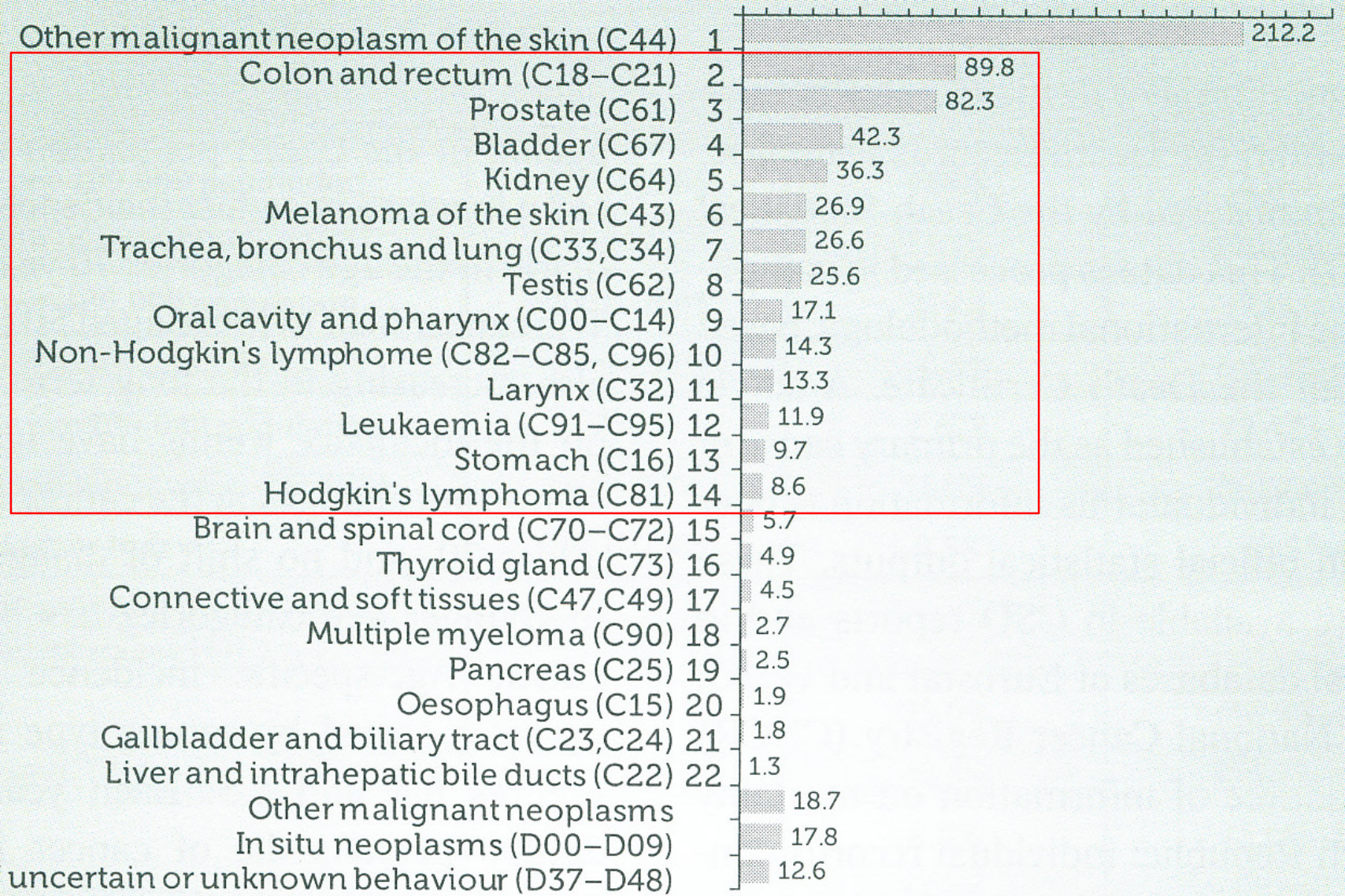
hypercalcemia, hyperuricemia

Incidence of neoplastic diseases

Prevalence rates - men

Number of cancer survivors per 100,000 men

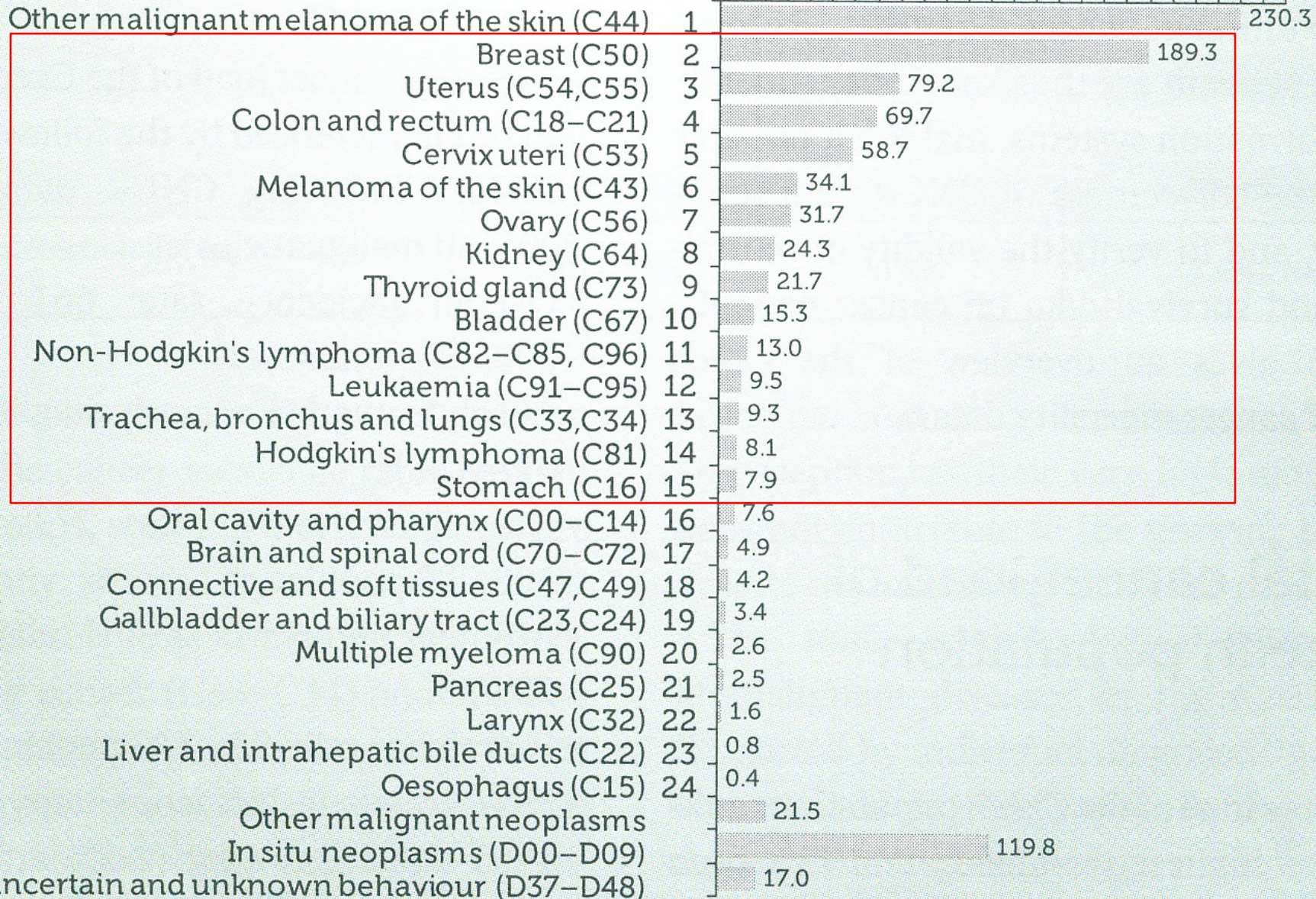
0 50 100 150 200 250



Prevalence rates - women

Number of cancer survivors per 100,000 women

0 50 100 150 200 250



Tumors in children and adolescences, ÚZIS, KDHO

Notes to the pathogenesis of neoplastic diseases I

A neoplasm = a disease of the genome & proteome

„impairment“ of the genomic / proteomic segment
which is responsible
for a physiological homeostasis
of cells

- 1 – cell division
- 2 – inhibition of division
- 3 – differentiation of cells
- 4 – a natural cell death

principal changes – non-lethal changes in the genome
with a progressive genetic instability

Notes to the pathogenesis of neoplastic diseases

Principal changes – non-lethal changes in the genome

**clonal expansion
subclones**

local consequences of the tumor growth

metastasizing

general impact of tumor growth and progression

Basis changes in the genome during the carcinogenesis

non-lethal genomic changes due to mutations  **hereditary**
acquired

caused by:

hereditary/congenital defects:

germ-line mutations

acquired mutations:

somatic mutations

non-lethal genomic impairment of a **functional character** - deregulations
acquired

Basis changes in the genome during the carcinogenesis

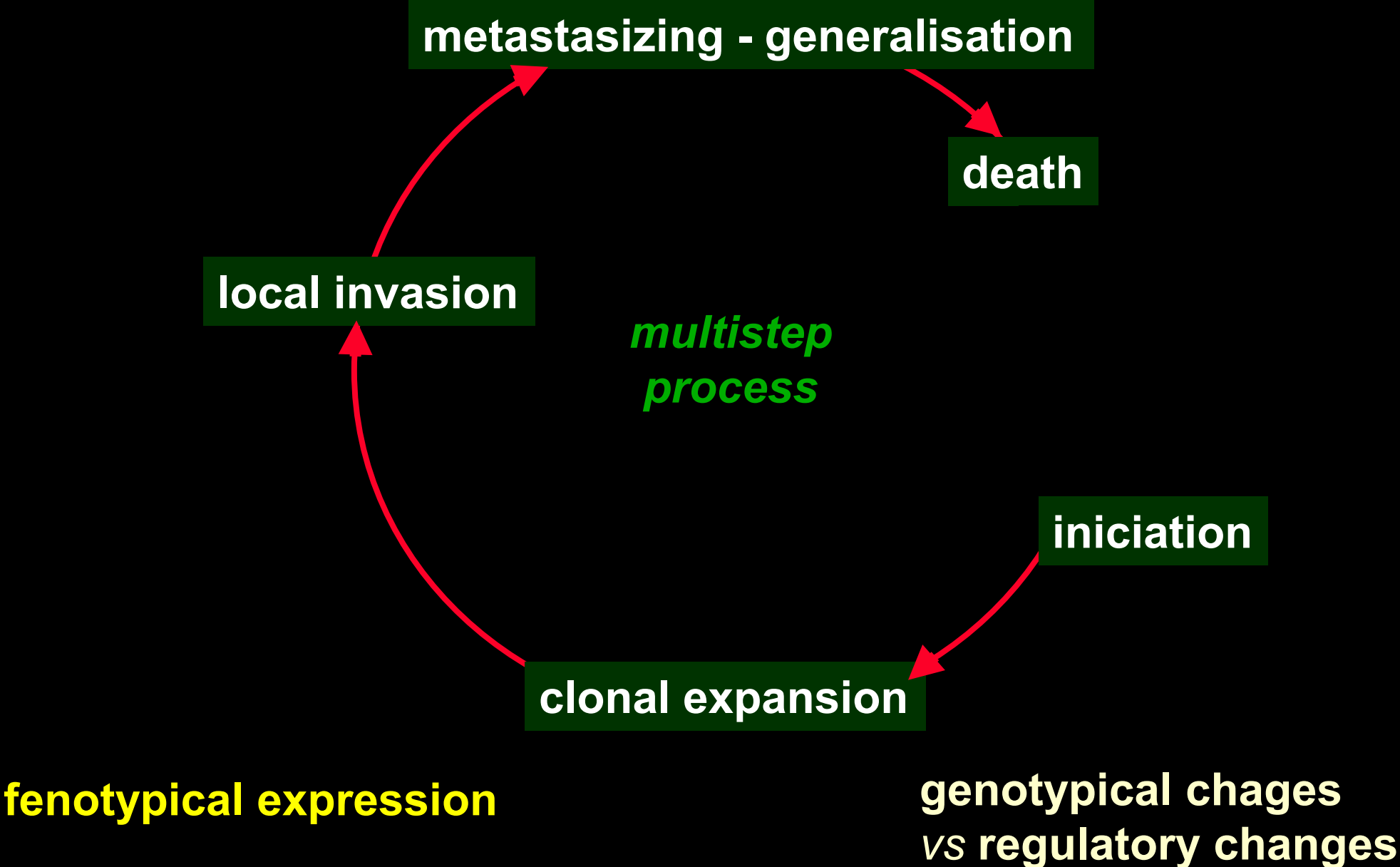
extrinsic factors

- chemical
- radiation
- viral

endogenous causes

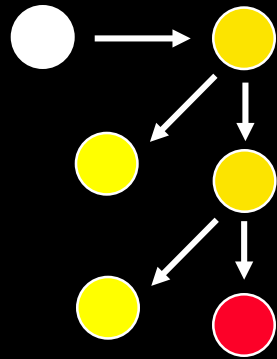
- spontaneous
- endogenic
mutagenous metabolites
(free radicals)

Basic changes in the genome during cancerogenesis



Heterogeneity of neoplastic cells and a neoplastic progression

normal cells
induction
neoplastic cells



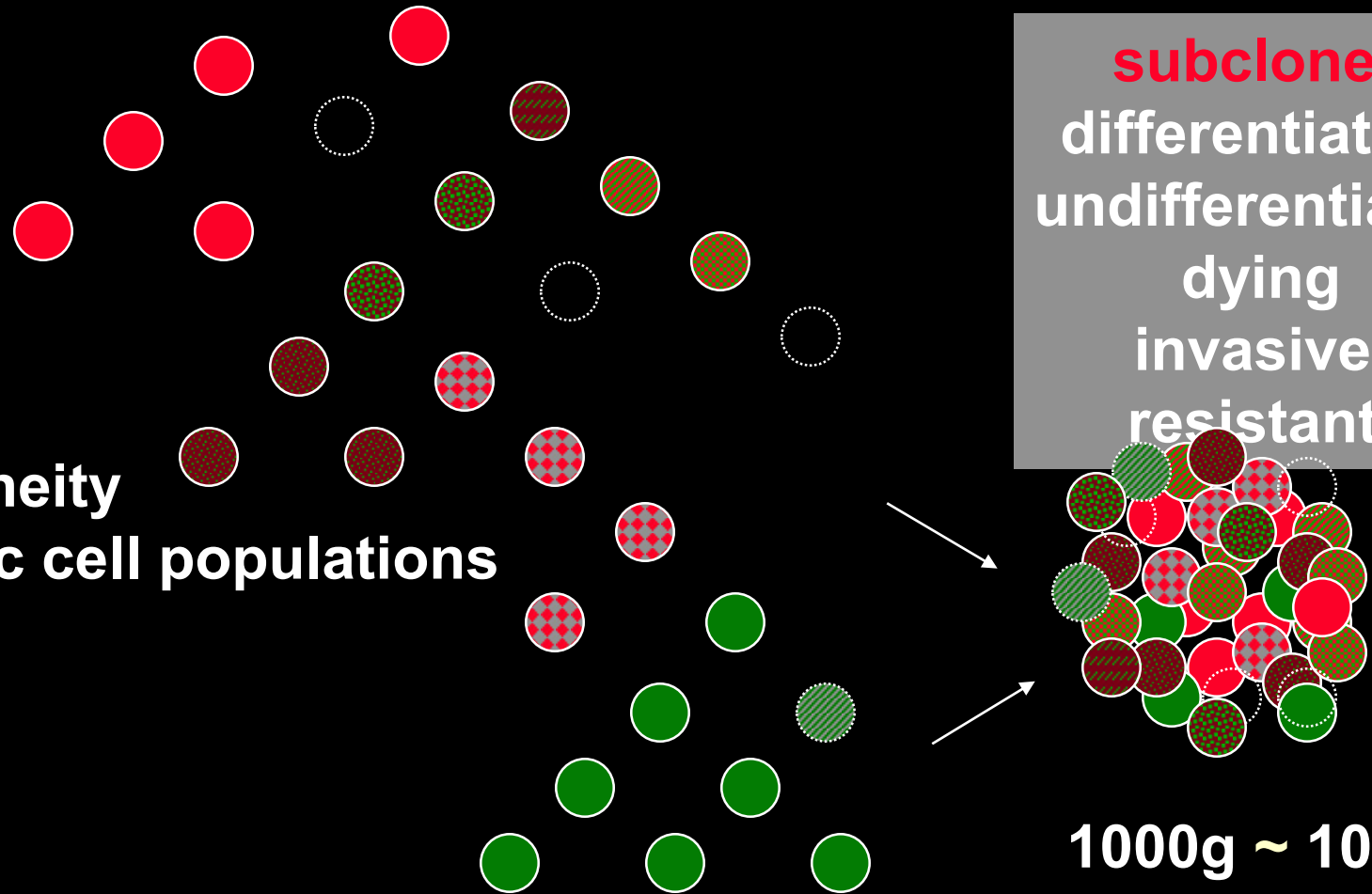
transformation
progression

subclones
differentiating
undifferentiated
dying
invasive
resistant

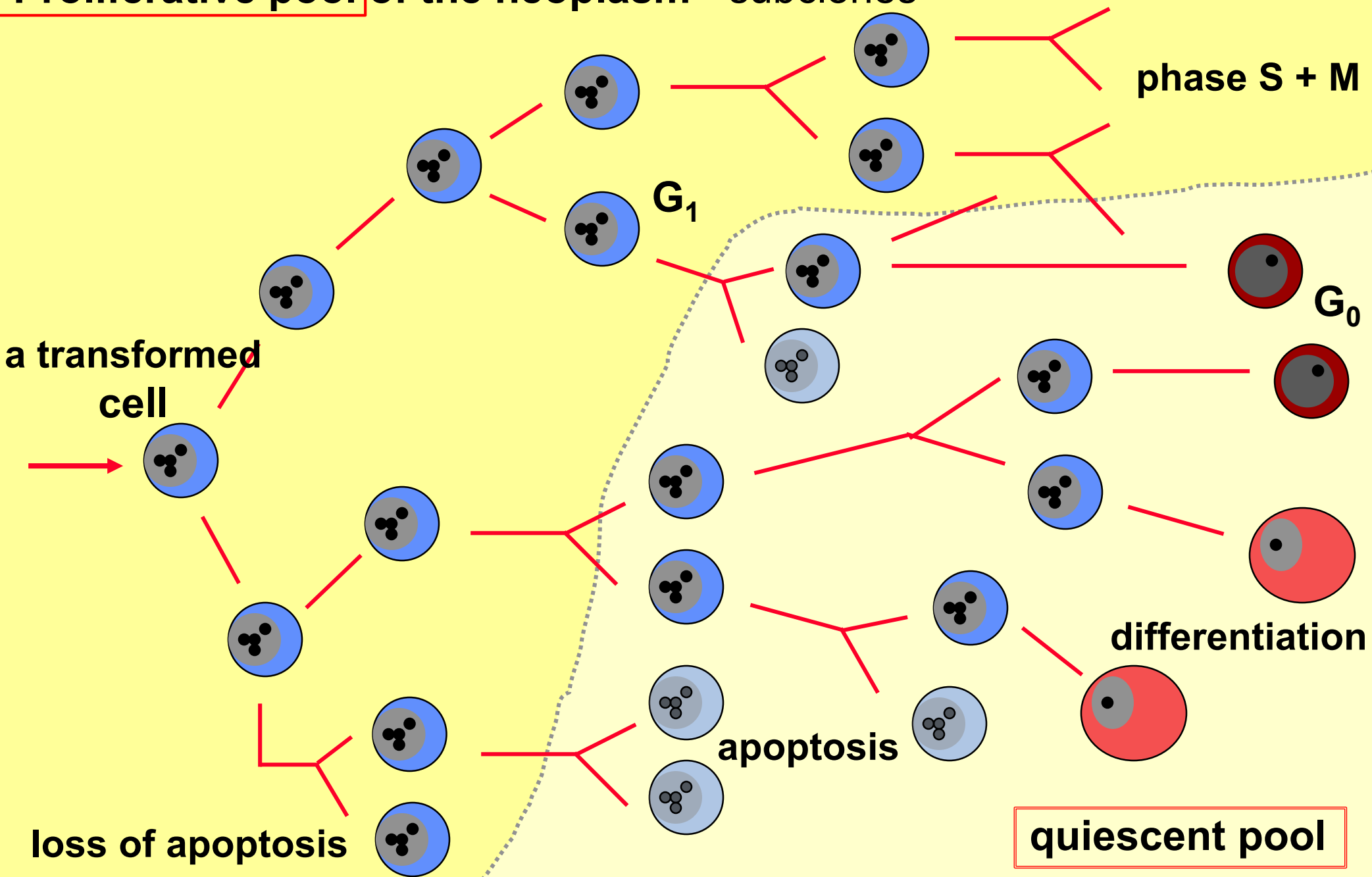
heterogeneity
neoplastic cell populations

1g ~ 10⁹

1000g ~ 10¹²



Proliferative pool of the neoplasm - subclones



phase S + M

G₁

G₀

a transformed cell

differentiation

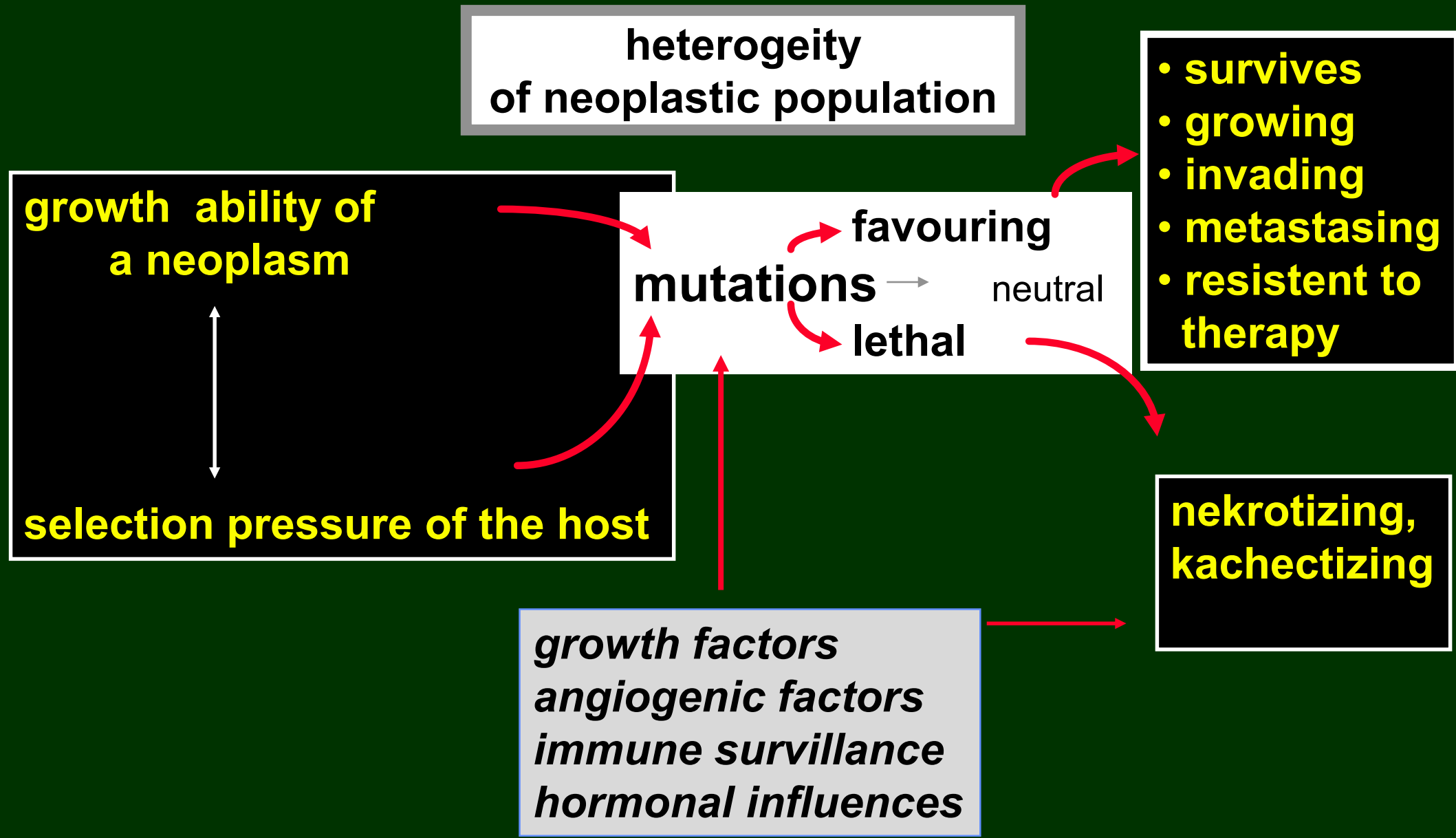
apoptosis

loss of apoptosis

quiescent pool

Proliferative pool

Notes to biology of neoplastic growth – summary of clonal expansion



Notes to the pathogenesis of neoplastic diseases

multistep process in the neoplastic development

precancerous diseases

Acquired preneoplastic lesions transforming to malignant neoplasms PREKANCEROSES

proliferative lesions
- inflammatory
- regenerative
- hyperplastic

- dysplastic

benign neoplasms



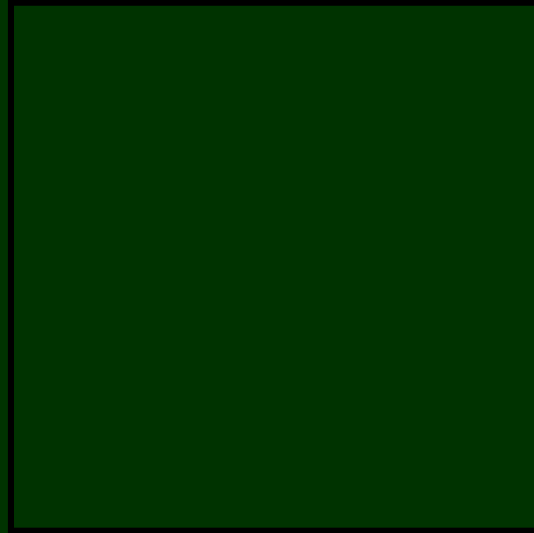
chronic atrophic gastritis
ulcerous colitis
solar keratosis
leukoplakia
pseudoepitheliomatous hyperplasia
hyperplastic nodules in cirrhosis
endometrial hyperplasia

cervical	→	<i>carcinoma</i>
bronchial	→	<i>carcinoma</i>
bone marrow	→	<i>leukemia</i>

adenoma	→	<i>carcinoma</i>
<i>colorectal</i>		
astrocytoma gr I	→	<i>glioblastoma</i>

Multistep genesis of neoplasms: bronchial metaplasia - dysplasia

Multistep genesis of neoplasms: adenoma – carcinoma sequence



Notes to the pathogenesis of neoplastic diseases

multistep process in the neoplastic development

familial occurrence of neoplasia – hereditary neoplasms

Congenital predispositions to „cancer“ pathogenesis

- *Inborn syndromes*

Familial retinoblastoma

Familial adenomatous polyposis, FAP

Syndromes of multiple endocrine neoplasia

Neurofibromatosis - type I, type II

syndrom Von Hippel-Lindau

Li-Fraumeni syndrome

Breast and ovarian carcinomas

summer semester

- *Syndromes with a defect of DNA reparation* autosomal recessive

Lynch syndrome

Bloom syndrome

Ataxia teleangiectasia

Nijmegen breakage syndrome

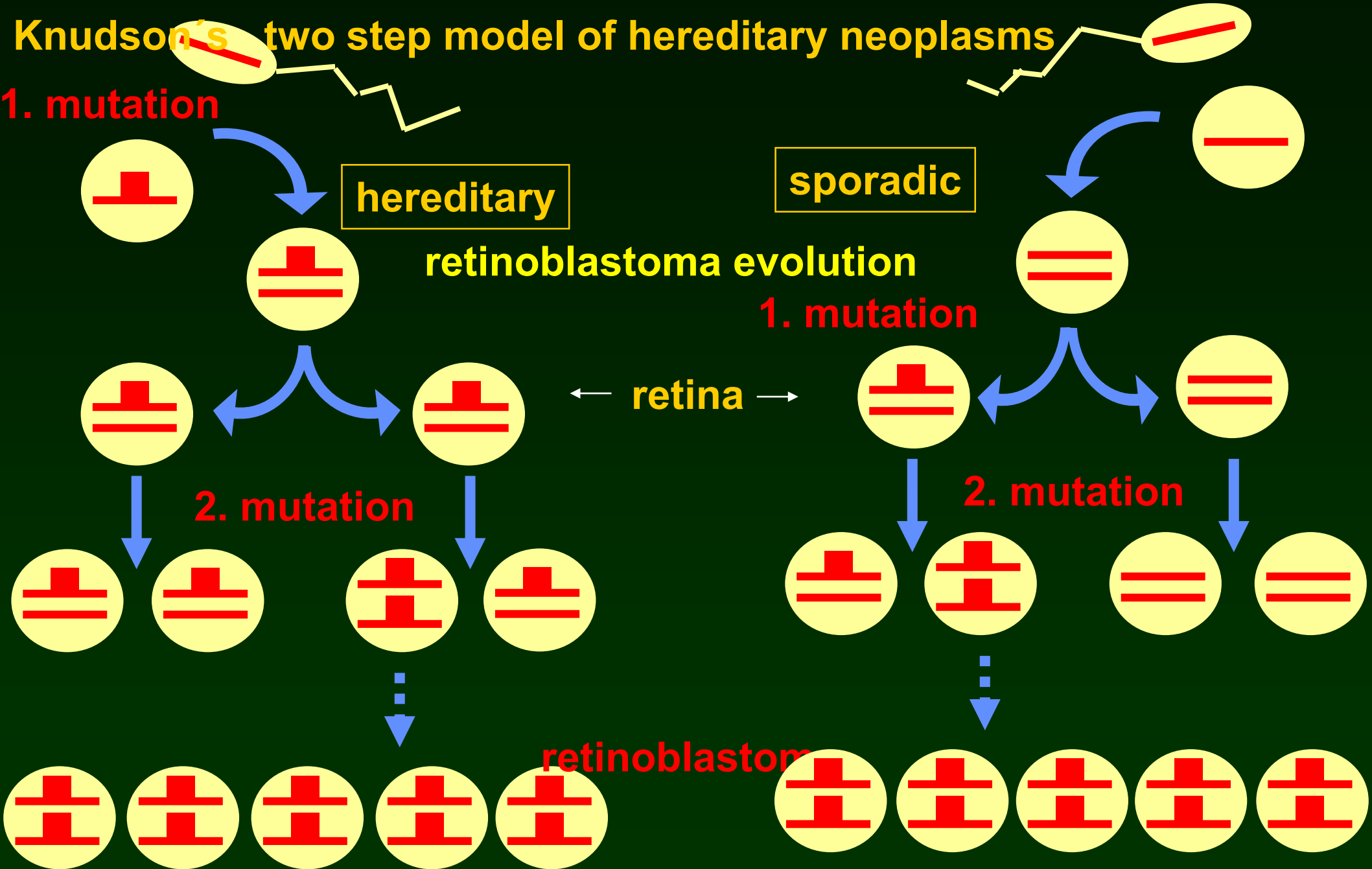
Fankoni anemia

Xeroderma pigmentosum

summer semester, some of which

Knudson's two step model of hereditary neoplasms

1. mutation



hereditary

sporadic

retinoblastoma evolution

1. mutation

retina

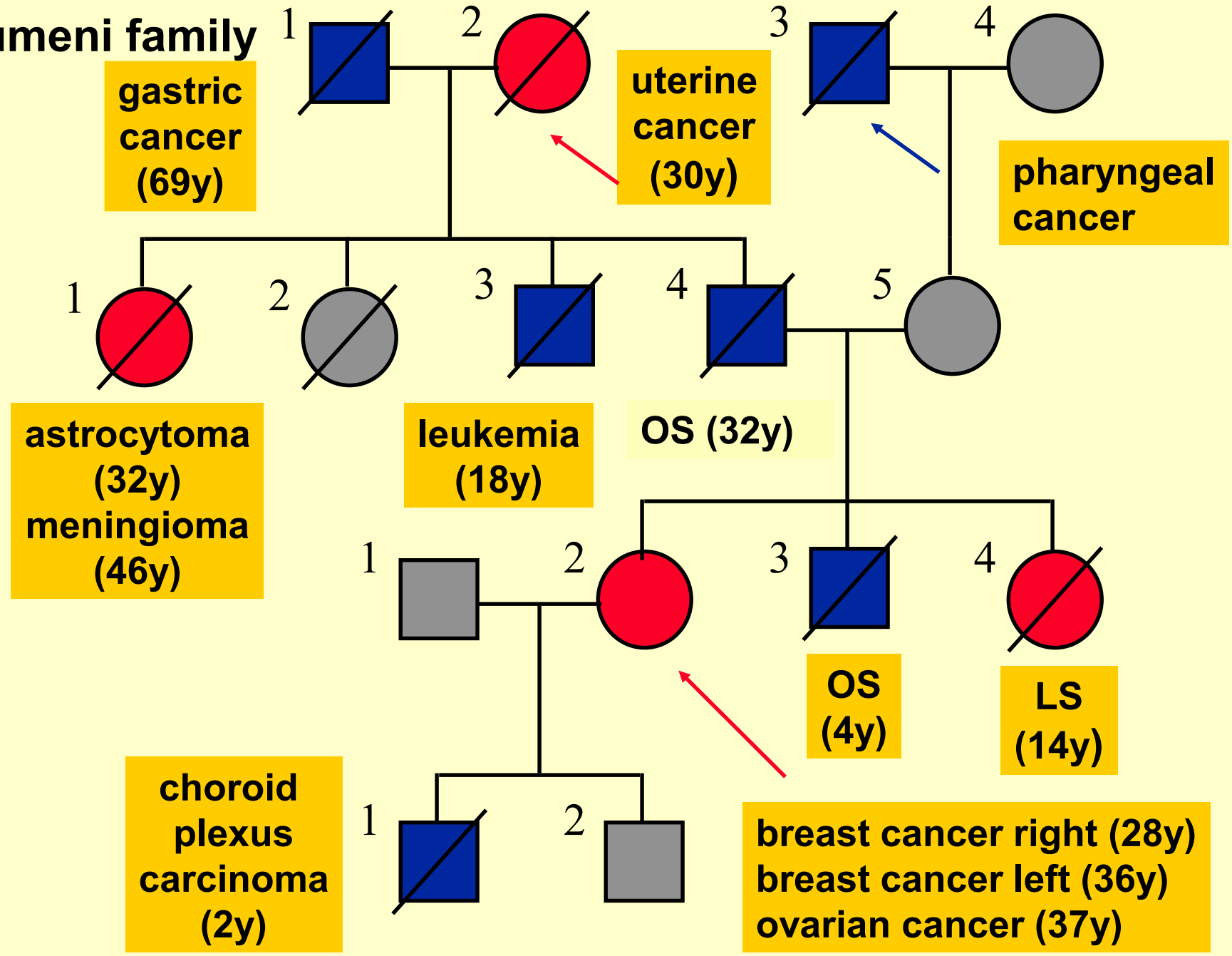
2. mutation

2. mutation

retinoblastoma

Li-Fraumeni family

I
II
III
IV



Notes to the pathogenesis of neoplastic diseases

**genetic changes in the genome leading
to evolution of tumors**

Groups of genes participation on the evolution of tumors

damaged cell regulation

types of regulatory genes:

supressor
genes

***PROLIFERATION
DIFFERENTIATION***

proto-oncogenes

repair control genes



DNA REPARATION

genes controlling
apoptosis and other types
of cell death



CELL DEATH

INSERTION and TRANSLOCATION / INVERSION MUTAGENESIS

CHROMOSOMAL TRANSLOCATION
and GENE REARRANGEMENTS

translocation

examples

- soft tissue tumors

POINT MUTATIONS DELETIONS

AMPLIFICATION OF DNA

**groups of genes – proteins, miRNAs
participating on**

regulations of cells

and

progression to neoplastic disease

Proteins regulating growth and differentiation of cells

- I. growth factors
- II. receptors of growth factors
- III. signal transducing proteins
- IV. transcription factors
- V. pro- and anti- apoptotic proteins
- VI. proteins controlling cell cycle (tumor suppressors)
- VII. DNA repair proteins
- VIII. miRNA

Mutations of genes changes structure or expression of proteins:

I.- IV. class dominant oncogenes

V.-VI. class escape of cells from regulation and survival

VII. class increase the likelihood of mutations of other classes

I. growth factors

II. receptors of growth factors

III. intracellular transducers

ras proteins

mTOR

the mammalian target of rapamycin signaling pathway

integrates signals from

- intracellular
- extracellular
space

serves as a

- central regulator of cell**
 - metabolism
 - growth
 - proliferation
 - survival

**mTOR
targeted by**

everolimus (Afinitor)
sirolims (Rapamune)
temsirolimus (Torisel)

**in
breast carcinoma
neuroendocrine carcinoma
pancreatic carcinoma
renal cell carcinoma
subependymal giant cell astrocytoma
and other diseases**

multistep carcinogenesis

Multistep genesis of neoplasms, example - Burkitt lymphoma (BL) - colorectal carcinoma