DEFINITION of NEOPLASTIC DISEASES

definition, terminology
classification of tumors

local canges 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

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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**

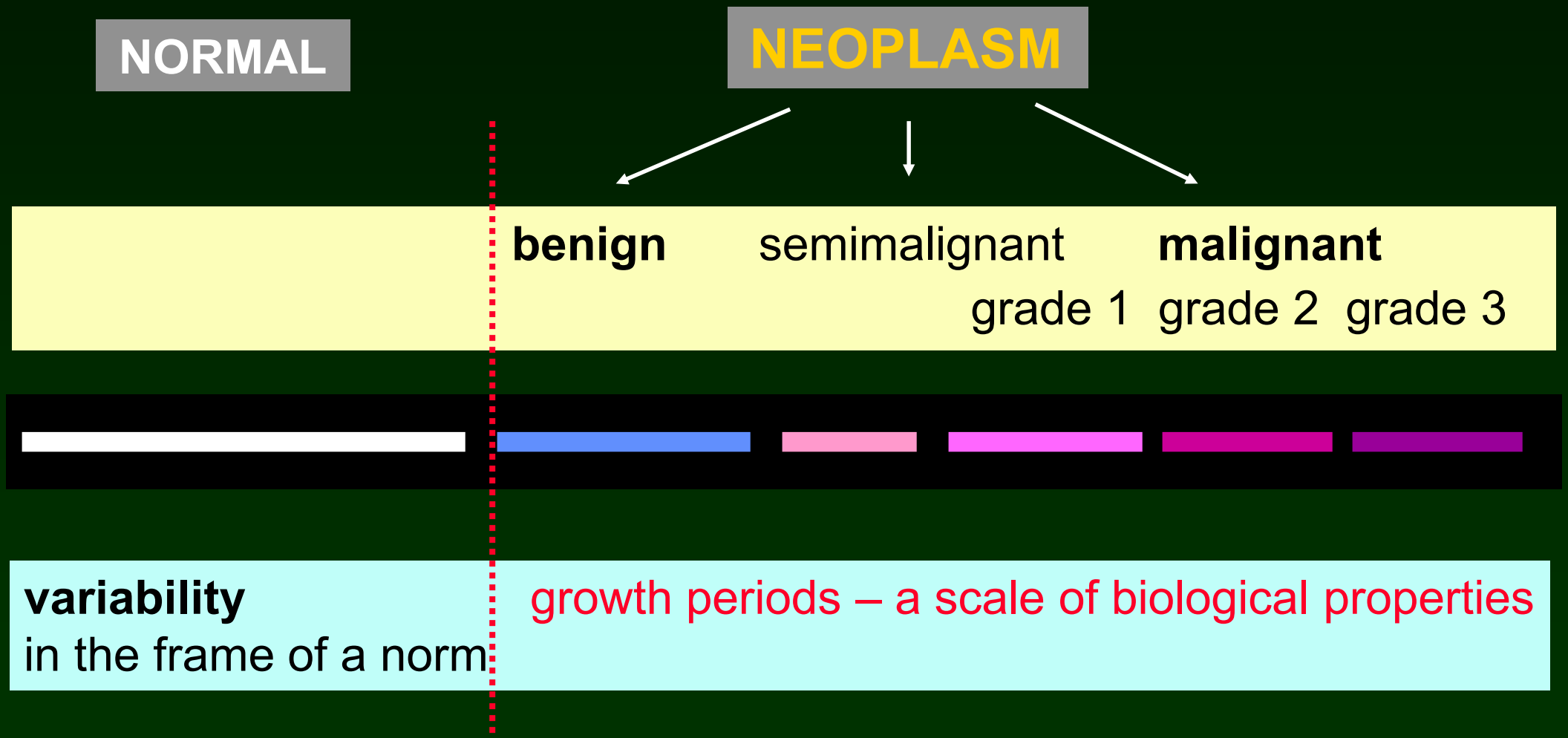
specialized
- **teratoma, seminoma, choriocarcinoma**
- **nefroblastoma, hepatoblastoma**

Classification of tumors

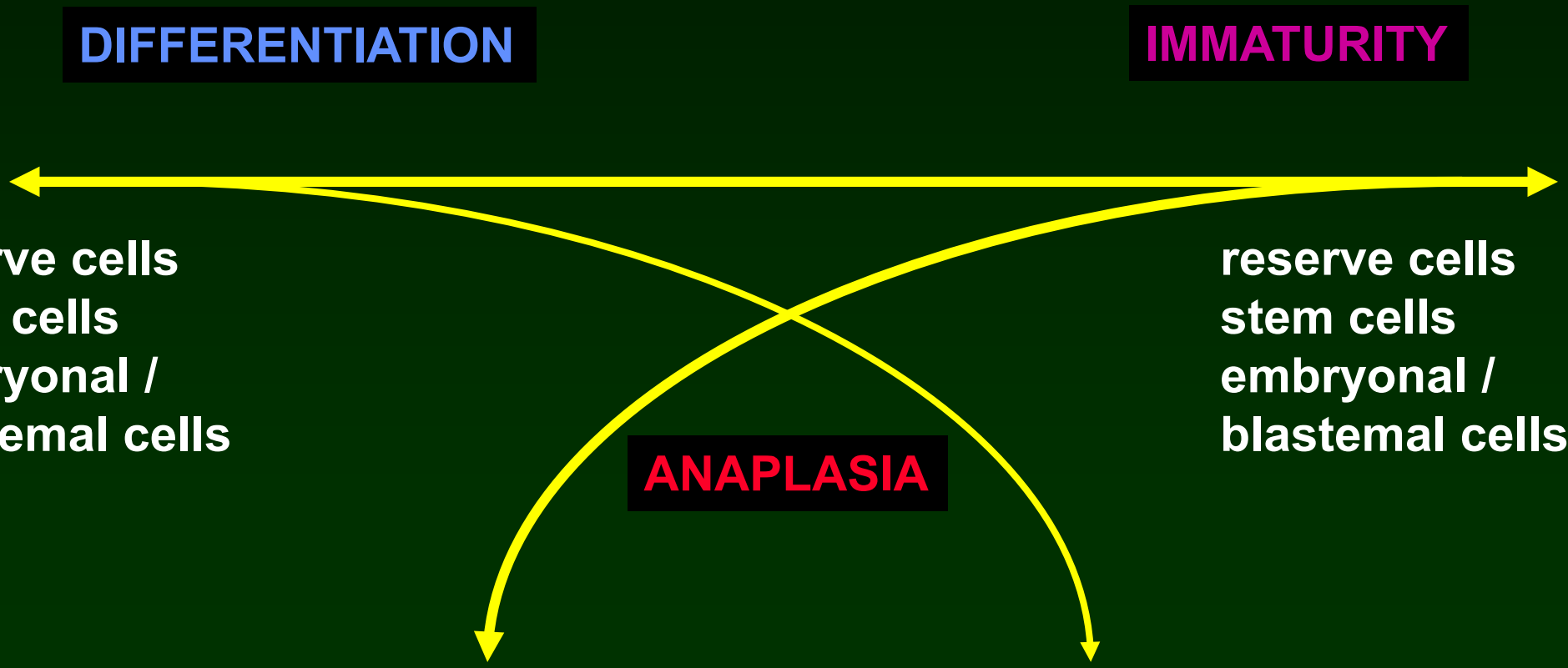
semimalignant

	BENIGN	MALIGNANT
cytology	nearly natural / no atypia	loss of differentiation, anaplasia
structure	„diferentiated“ organoid	loss of diferentiation
growth / boundary	expansive / sharp	infiltrative / invasion + destruction
encapsulation	yes, mostly	usually absent
growth / speed	slow / periods	permanent, variable speed
metastazes	absent	develop regurarly the frekvency / 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



deviation / anaplasia

sarcoma (buttock)

Neoplastic growth - expansive

Neoplastic growth – invasion + destruction

Neoplastic growth – invasion + destruction (ulceration)

Neoplastic growth – invasion + destruction (ulceration)

Judr Synek
BS /20xxxx/2004

Local effects of neoplasia - consequences

„mass effect " + edema, + bleeding	compression, destruction, fracture, vertebral collapse increased intracranial pressure replacement of hemopoesis
obstruction	bronchus – lung collapse, pneumonia billiary ways - jaundice
ulceration	tissue destruction
bleeding	anemia – acute/chronic, aspiration of blood
perforace	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 polycytemia

hemorragic diathesis

thrombophlebitis migrans

thrombotic endocarditis

immunodefficiency

hormonal activity and efects !

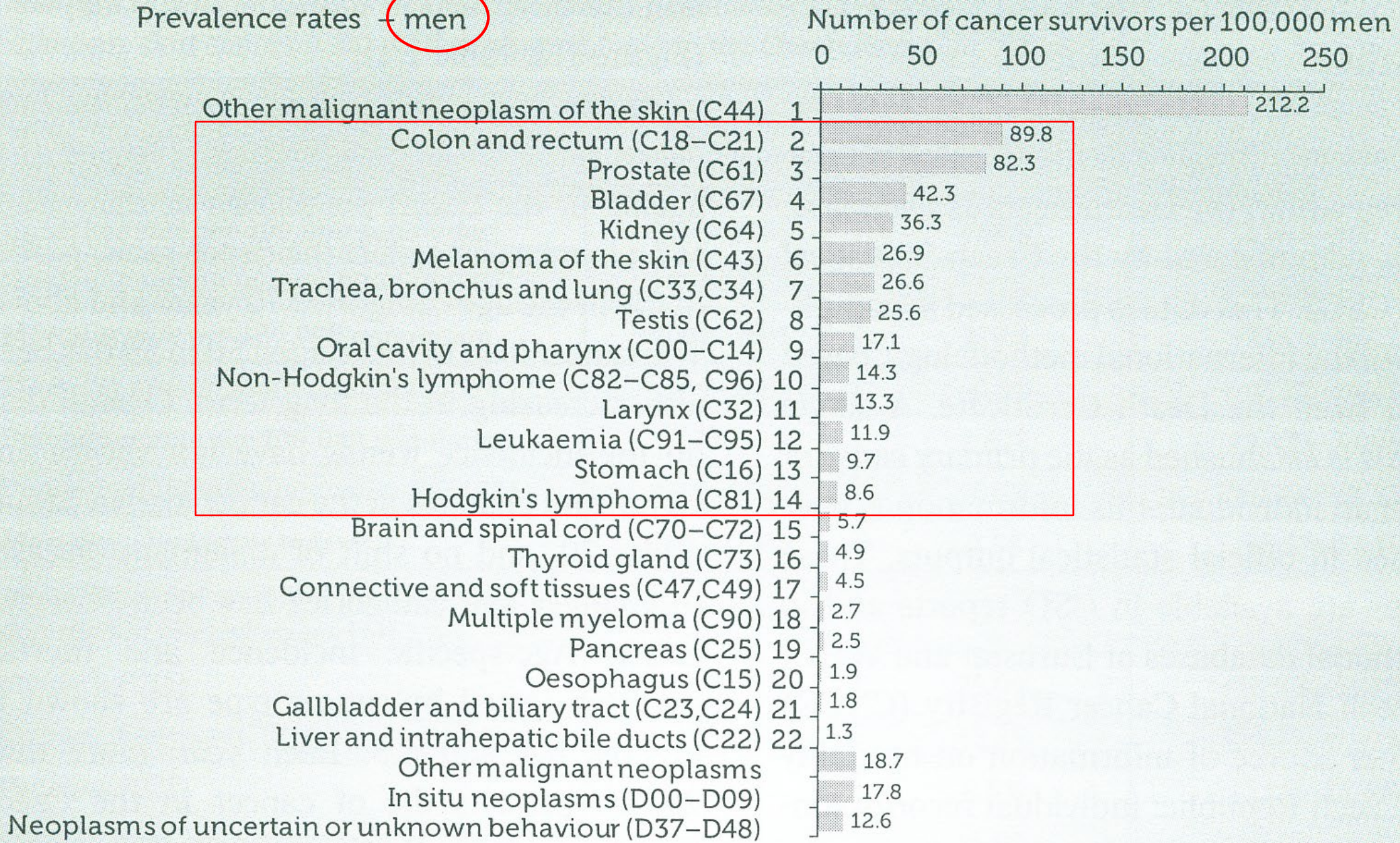
peripheral neuropathy

myopathy

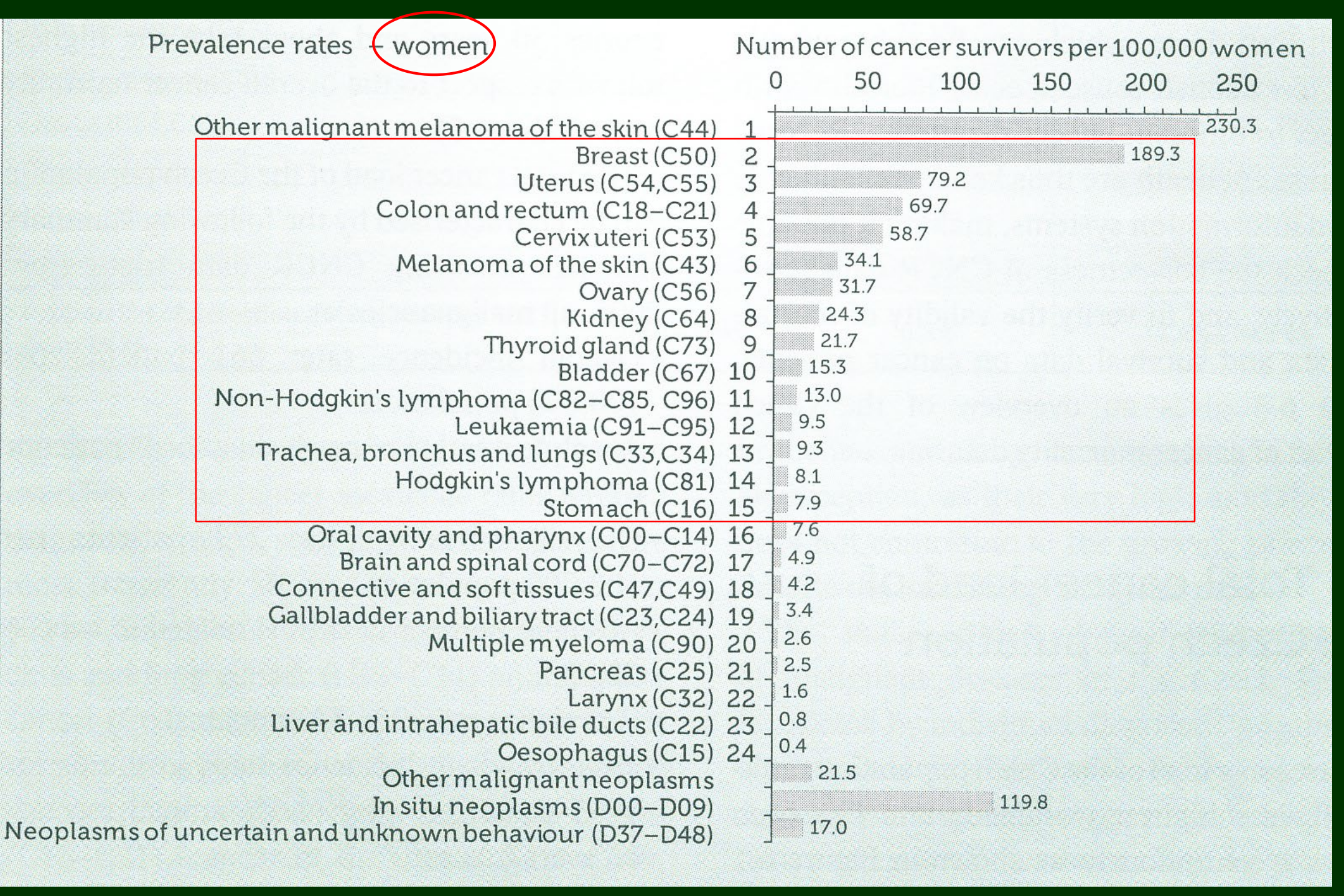
hypercalcemia, hyperuricemia

Incidence of neoplastic diseases

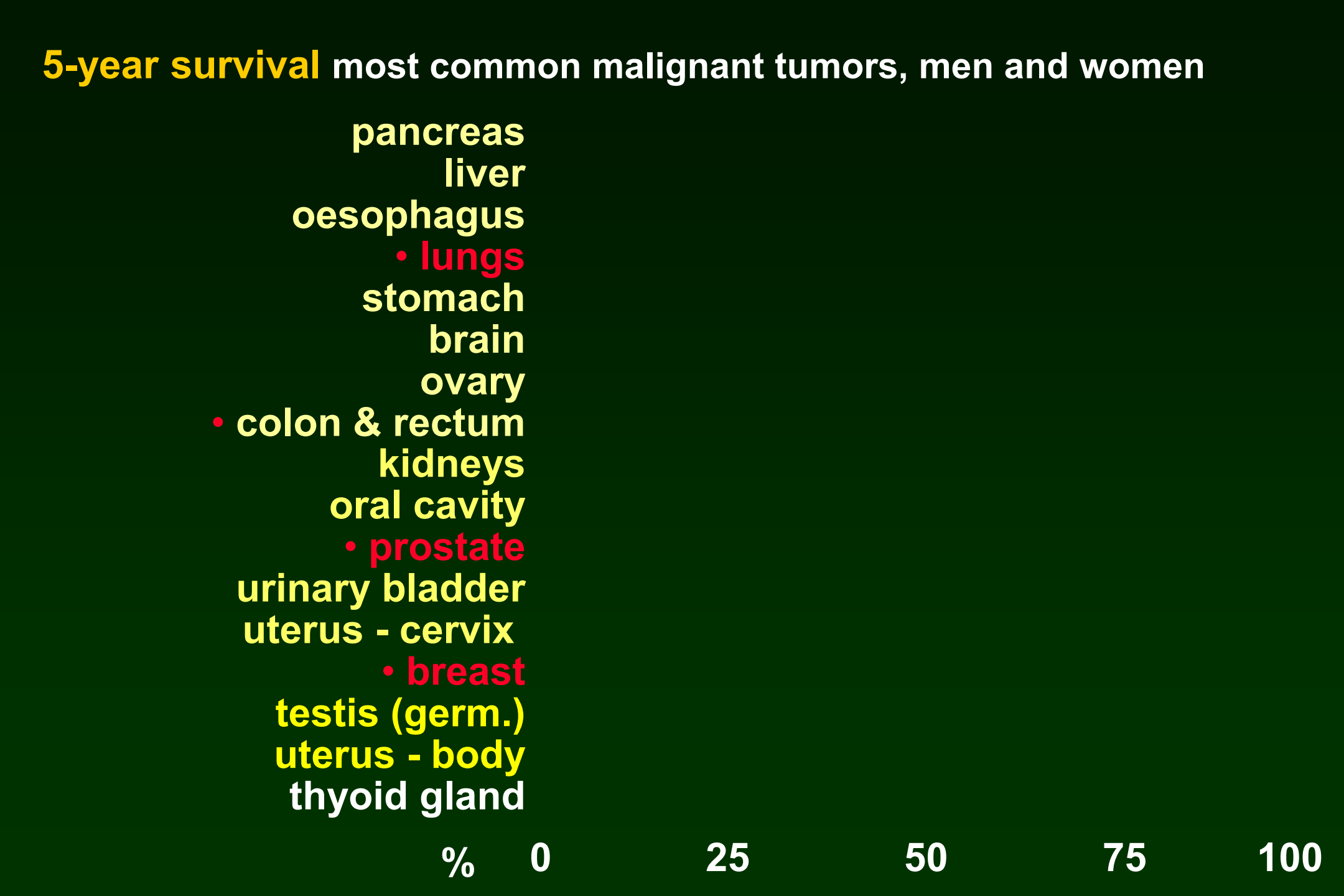
Prevalence rates – men



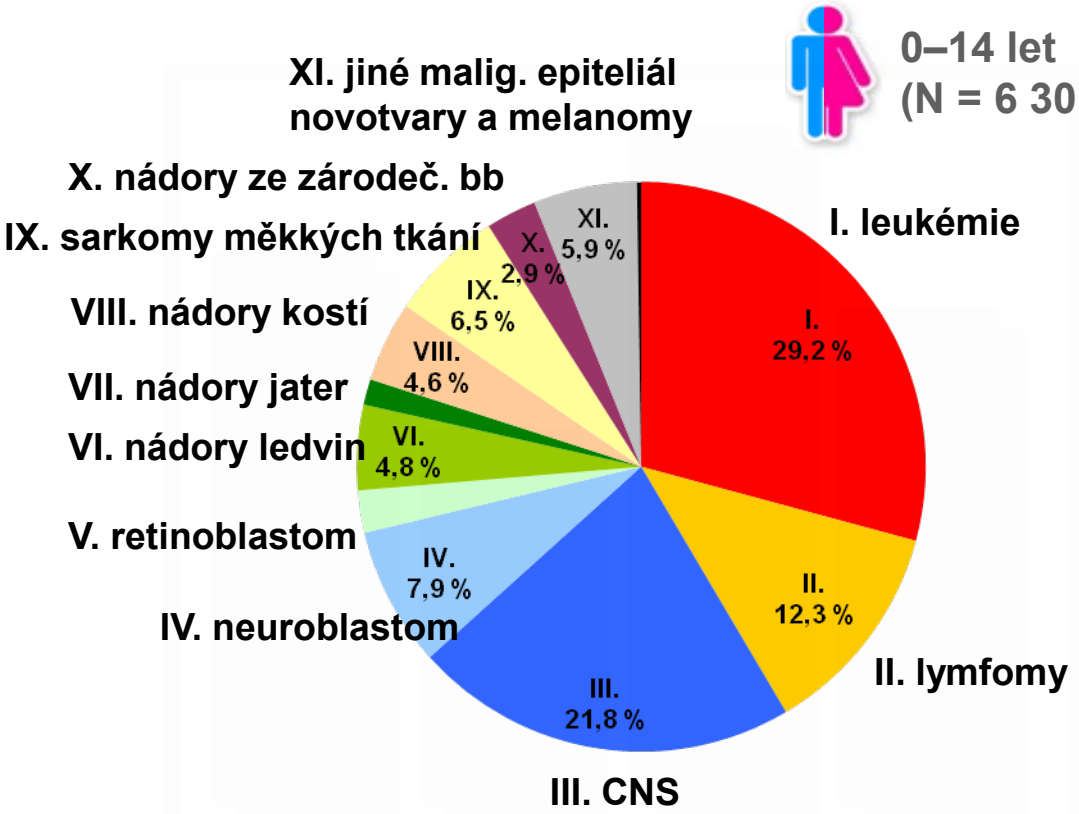
Prevalence rates – women

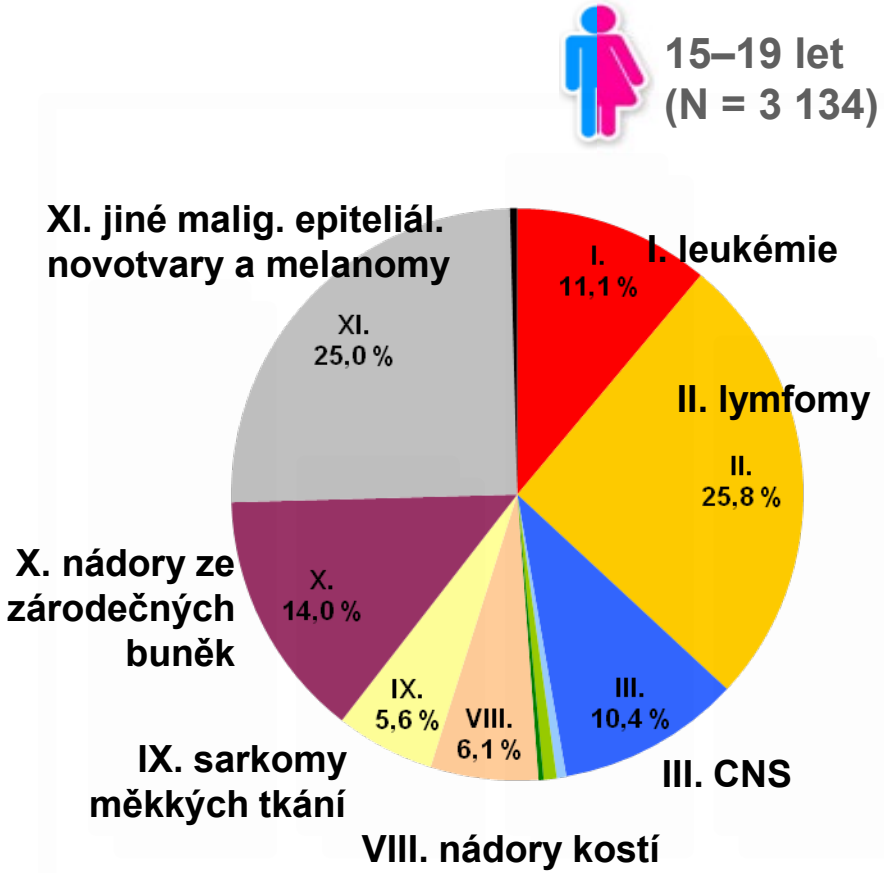


5-year survival most common malignant tumors, men and women



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 II

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/congenigal defects: ***germ-line mutations***

acquired mutations: ***somatic mutations***

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

aquired

Basis changes in the genome during the carcinogenesis

zevní faktory

- **chemické**
- **radiační**
- **virové**

endogenní příčiny

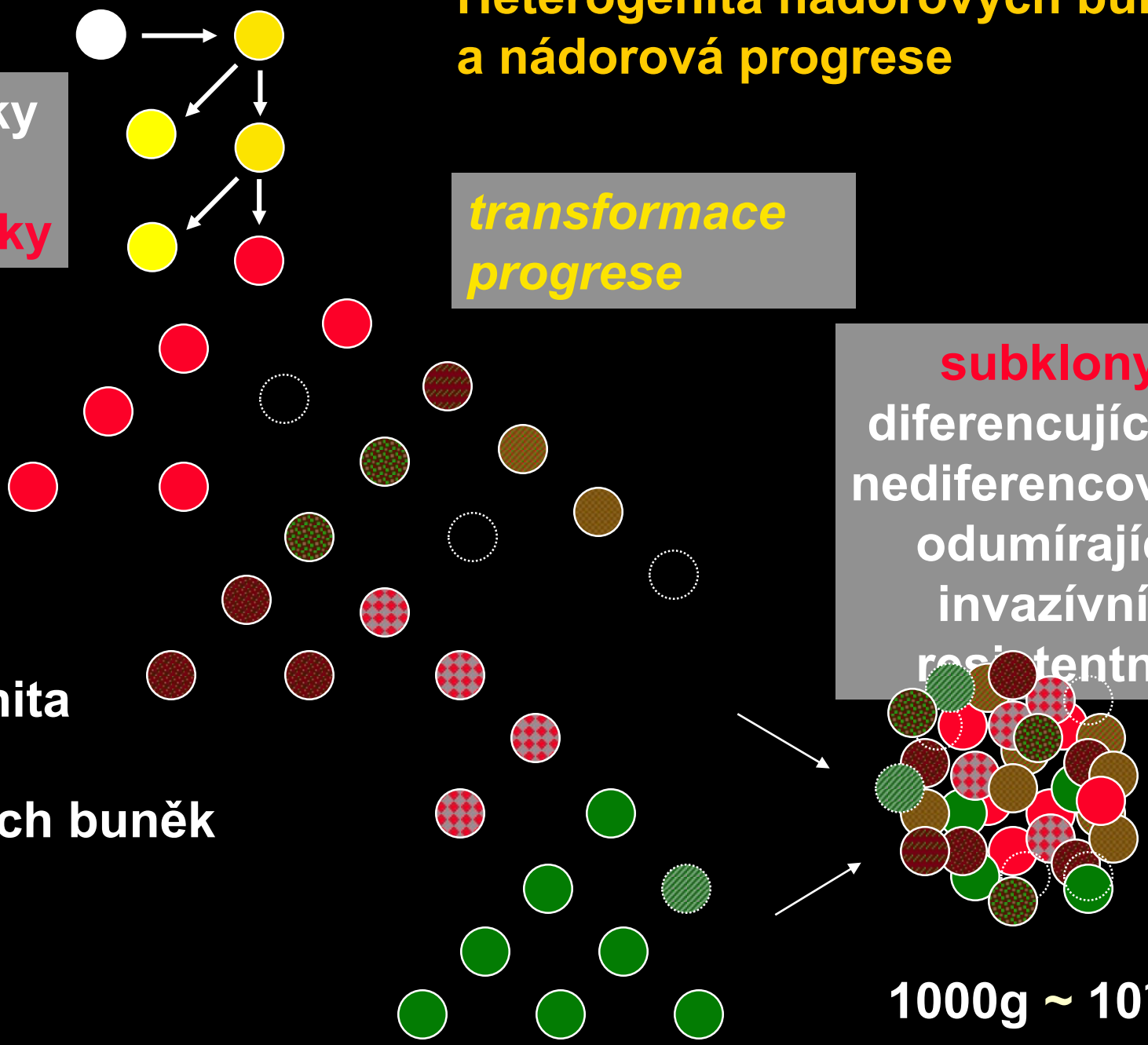
- **spontánní**
- **endogenní mutagenní metabolity** (volné radikály)

Heterogenita nádorových buněk a nádorová progrese

normální buňky
indukce
nádorové buňky

transformace progrese

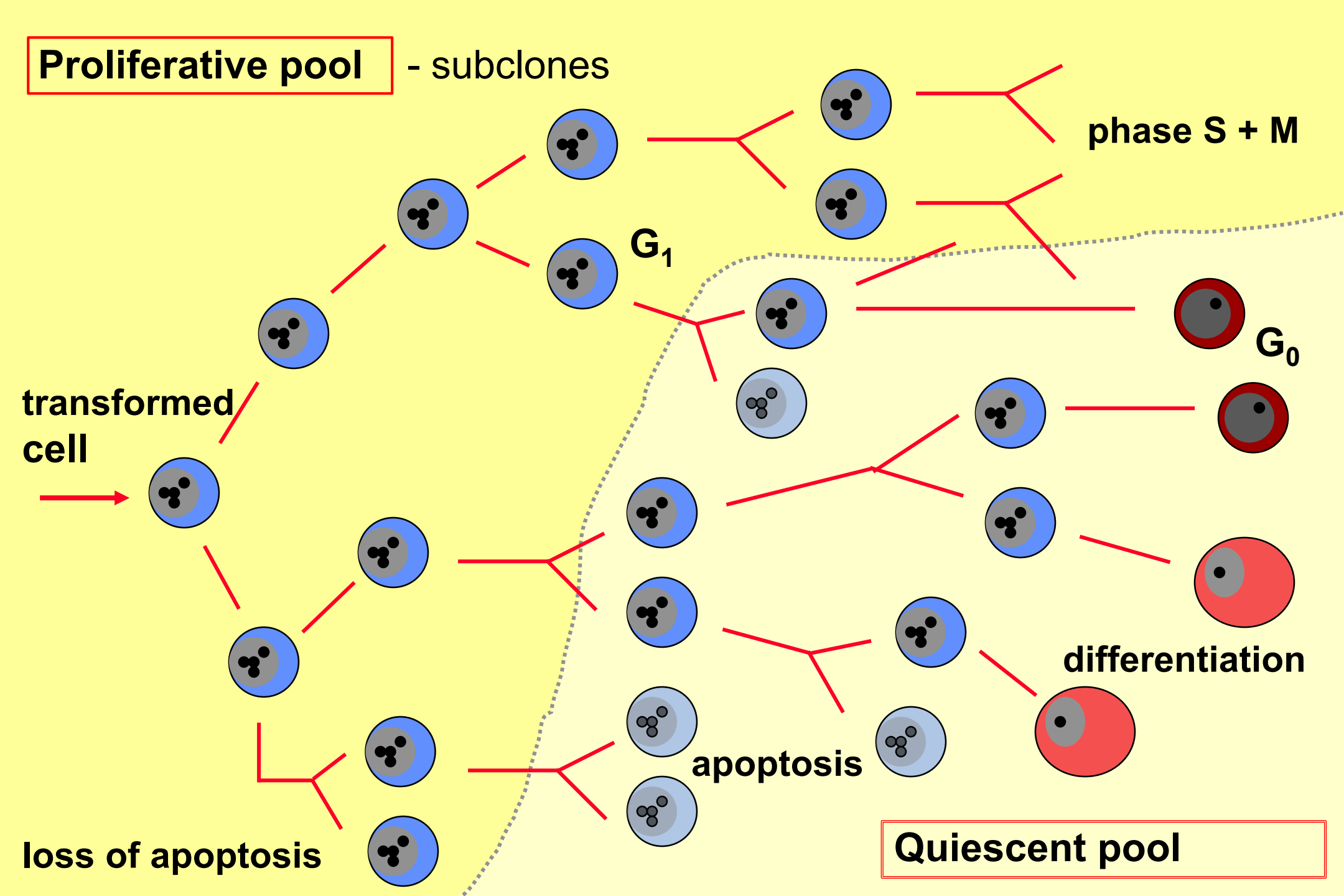
subklony
diferencující se
nediferencované
odumírající
invazívní
rezistentní



heterogenita
populace
nádorových buněk

1g ~ 10^9

1000g ~ 10^{12}


Proliferative pool
- subclones
phase S + M
G_1
G_0
transformed cell
differentiation
apoptosis
loss of apoptosis
Quiescent pool

POZNÁMKY KE VZNIKU NÁDOROVÝCH ONEMOCNĚNÍ II

vícekrokový vznik nádorů

prekancerózy
rodinný výskyt nádorů - dědičné nádory

Acquired preneoplastic processes in malignant neoplasms
PRECANCEROUS lesions

proliferative states
- **inflammatory**
- **regenerative**
- **hyperplastic**

chronic atrophic gastritis
ulcerous collitis
solar keratosis
leukoplakia
pseudoepiteliomatous hyperplasia
hyperplastic nodules in cirrhosis
endometral hyperplasia

- **dysplastic**

cervical → *carcinoma*
bronchial → *carcinoma*
bone marrow → *leukemia*

benign neoplasms

adenoma → *carcinoma*
astrocytoma gr I → *glioblastoma*

Inherited predisposition for neoplastic diseases

- ***inborn syndromes*** **autosomal dominant**

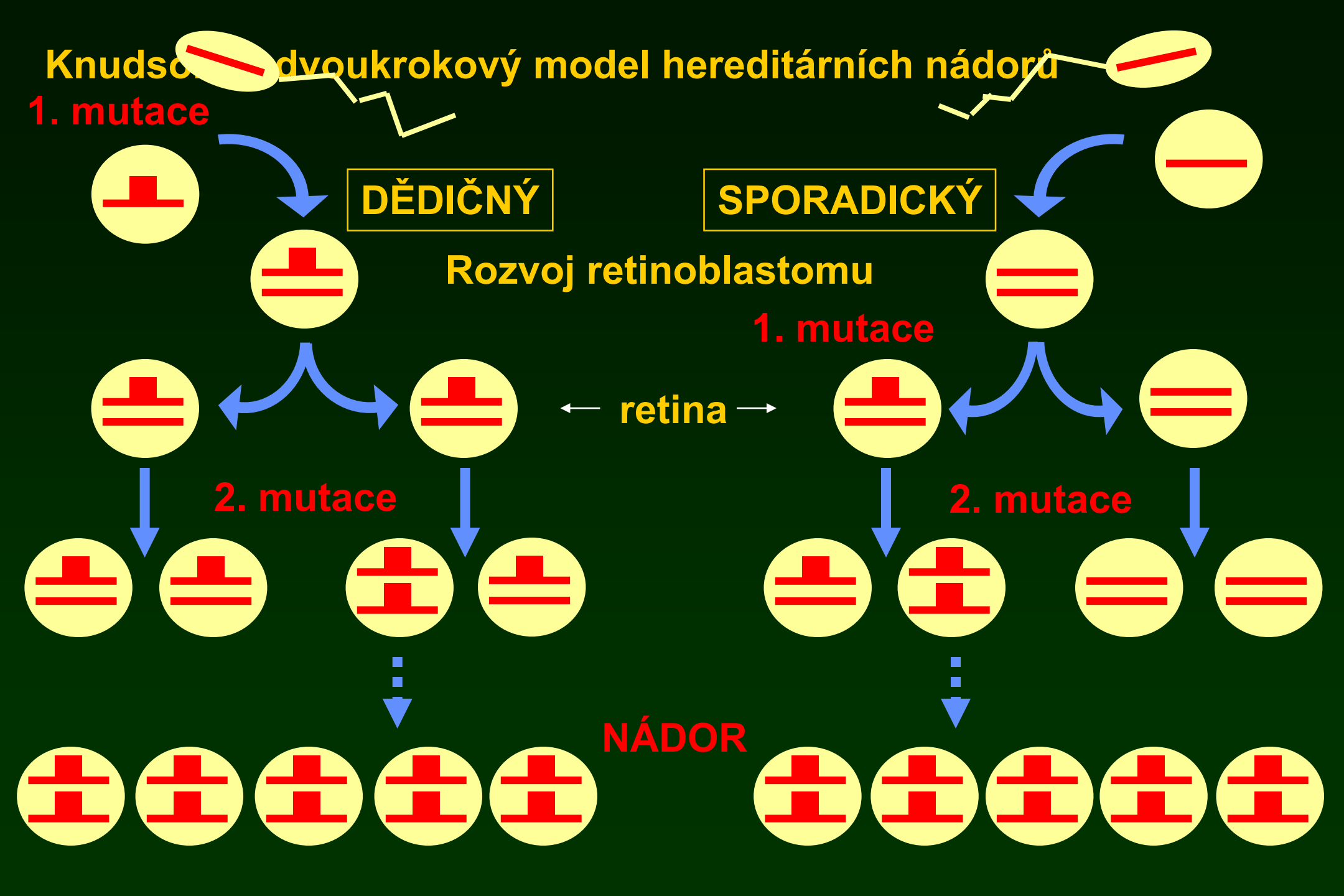
  Familiální retinoblastom
  Familiální adenomatózní polypóza
  Syndromy mnohotné endokrinní neoplázie
  Neurofibromatóza, typ I, typ II
  syndrom Von Hippel-Lindau

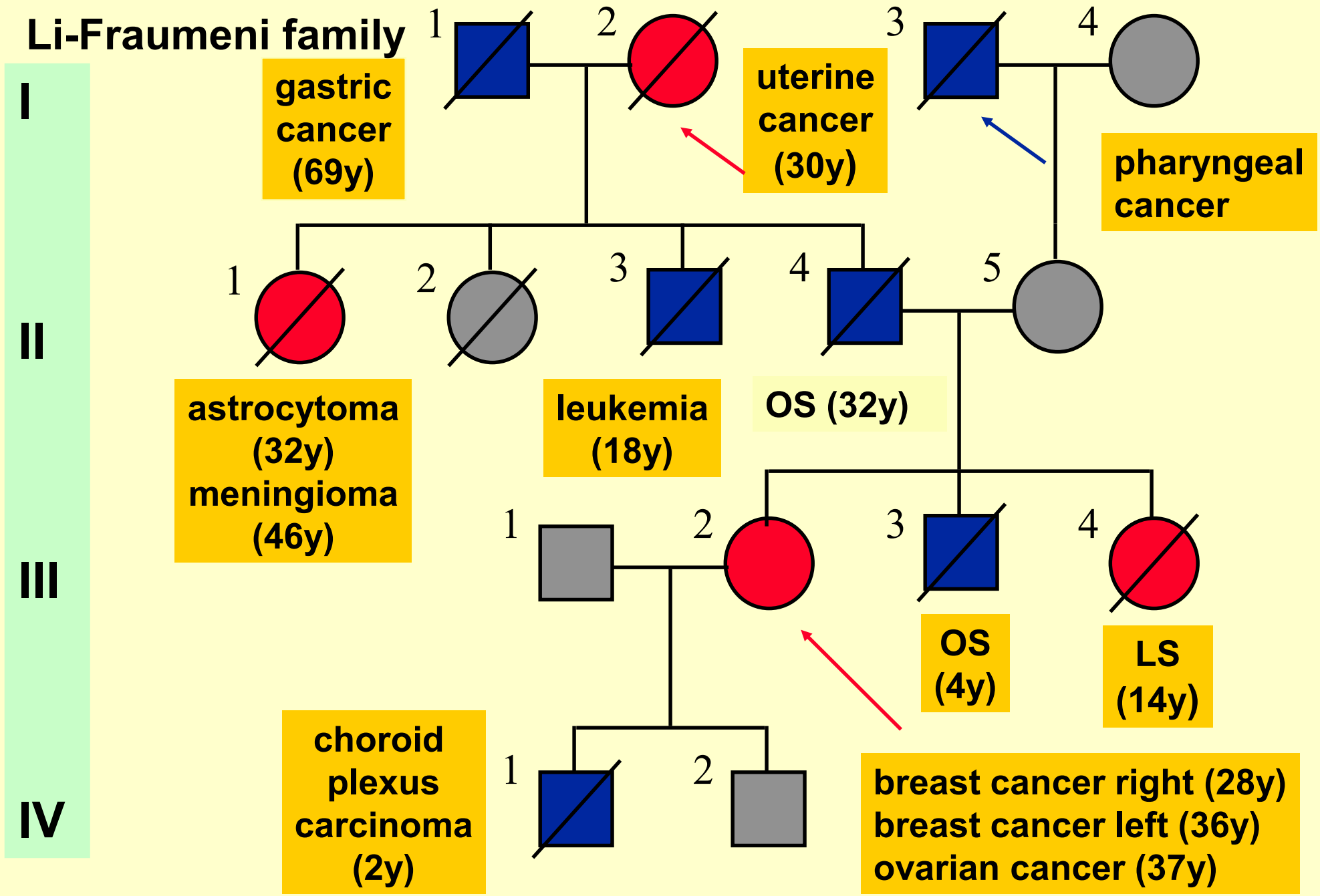
- ***Vrozené syndromy*** **autosomal recessive**

  Li-Fraumeni syndrome
  Breast carcinomas

- ***Syndromes with defects of DNA*** **reparation autosomálně recesivní**

  Lynchův syndrome
  Bloom syndrome
  Ataxia teleangiectasia
  Nijmegen breakage syndrome
  Fankoni anemia
  Xeroderma pigmentosum


Knudsonův dvoukrokový model hereditárních nádorů
1. mutace
DĚDIČNÝ
SPORADICKÝ
Rozvoj retinoblastomu
1. mutace
retina
2. mutace
2. mutace
NÁDOR

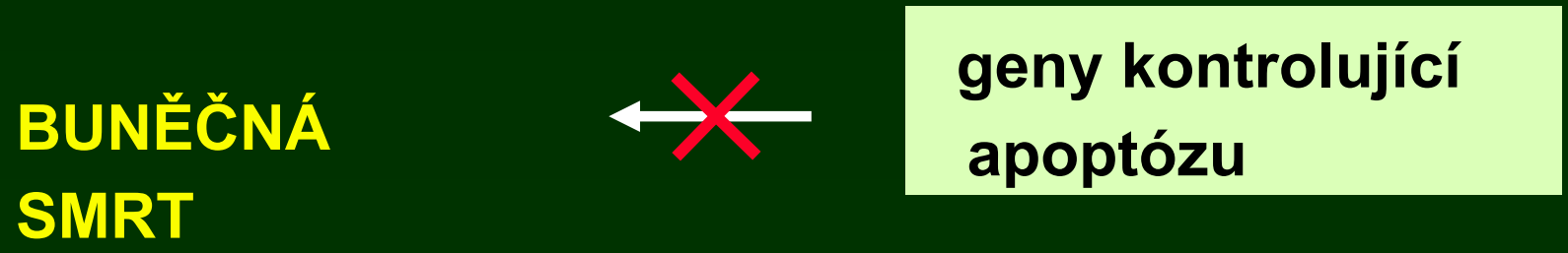

Li-Fraumeni family
I
II
III
IV
1
2
3
4
gastric cancer (69y)
uterine cancer (30y)
pharyngeal cancer
1
2
3
4
5
astrocytoma (32y) meningioma (46y)
leukemia (18y)
OS (32y)
1
2
3
4
OS (4y)
LS (14y)
choroid plexus carcinoma (2y)
1
2
breast cancer right (28y)
breast cancer left (36y)
ovarian cancer (37y)

POZNÁMKY KE VZNIKU NÁDOROVÝCH ONEMOCNĚNÍ III

Skupiny genů participujících na rozvoji nádorových onemocnění

poškozená regulace buněk

druhy regulačních genů:



Aktivace proto-onkogenů a ztráta funkce supresorových genů

změny v genech → strukturální
změny v genech → regulační

Aktivace proto-onkogenů → c-onkogeny, v-onkogeny

- inserční mutagenese — *Rous sarcoma v-src, HTLV-1*
- translokace — *t(8;14)* c-*myc* / *IgH* → *ML Burkitt*
- bodové mutace — *12q* *p21^{ras}* → *ca pankreatu*
- amplifikace — *2p23-24* n-*myc* → *neuroblastoma*

Ztráta funkce supresorových genů

- bodové mutace — *17p13* *p53* → *různé nádory*
- delece — *13q14* *Rb* → *retinoblastom*
- inserce — *18q* DCC → kolorektální ca

Cytogenetické změny v nádorových buňkách

chomosomální materiál

bez ztrát →
- translokace
- inverze

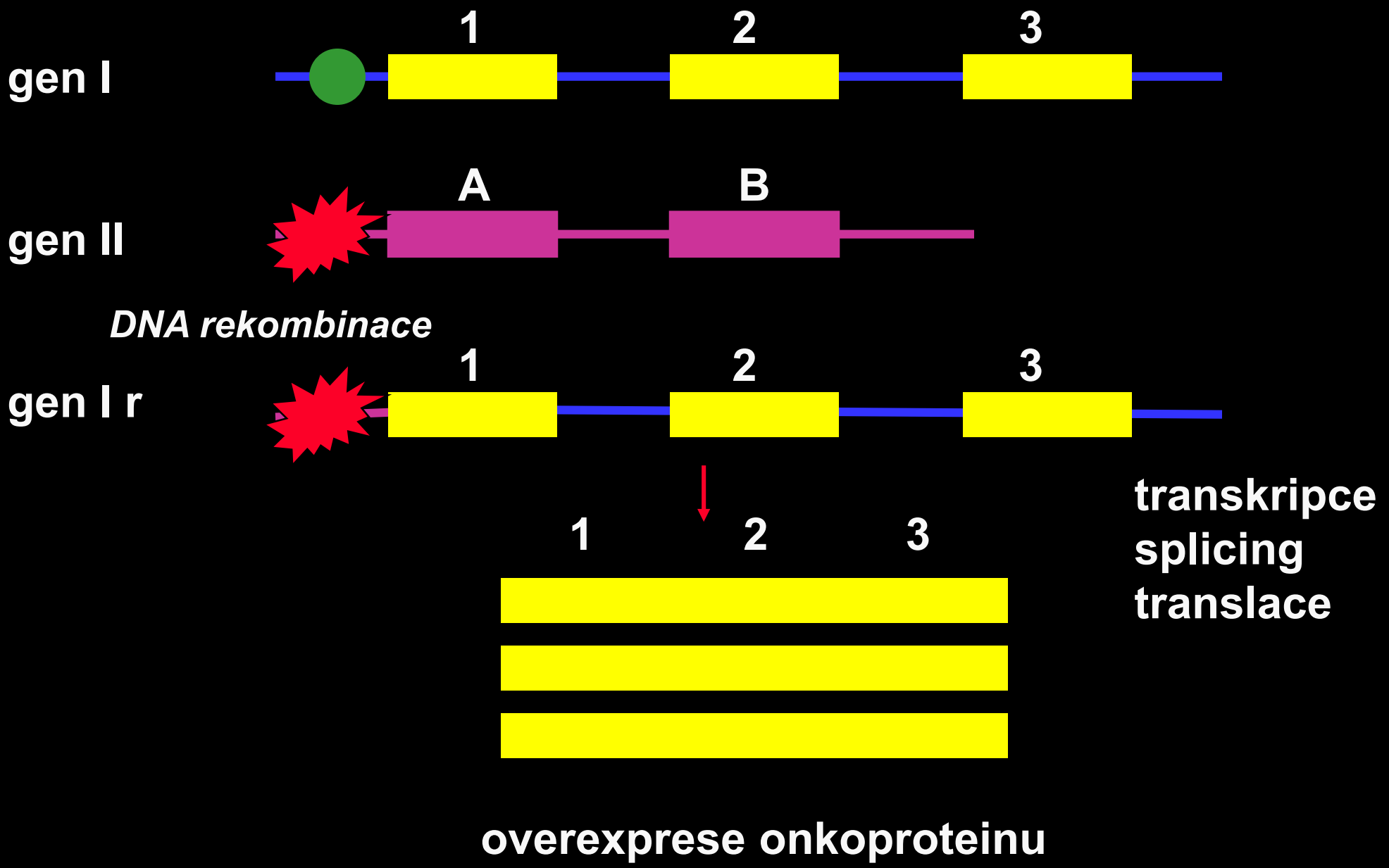
se ztrátou →
- delece
- monosomie

se zmnožením →
- duplikace
- amplifikace
- trisomie
- polysomie

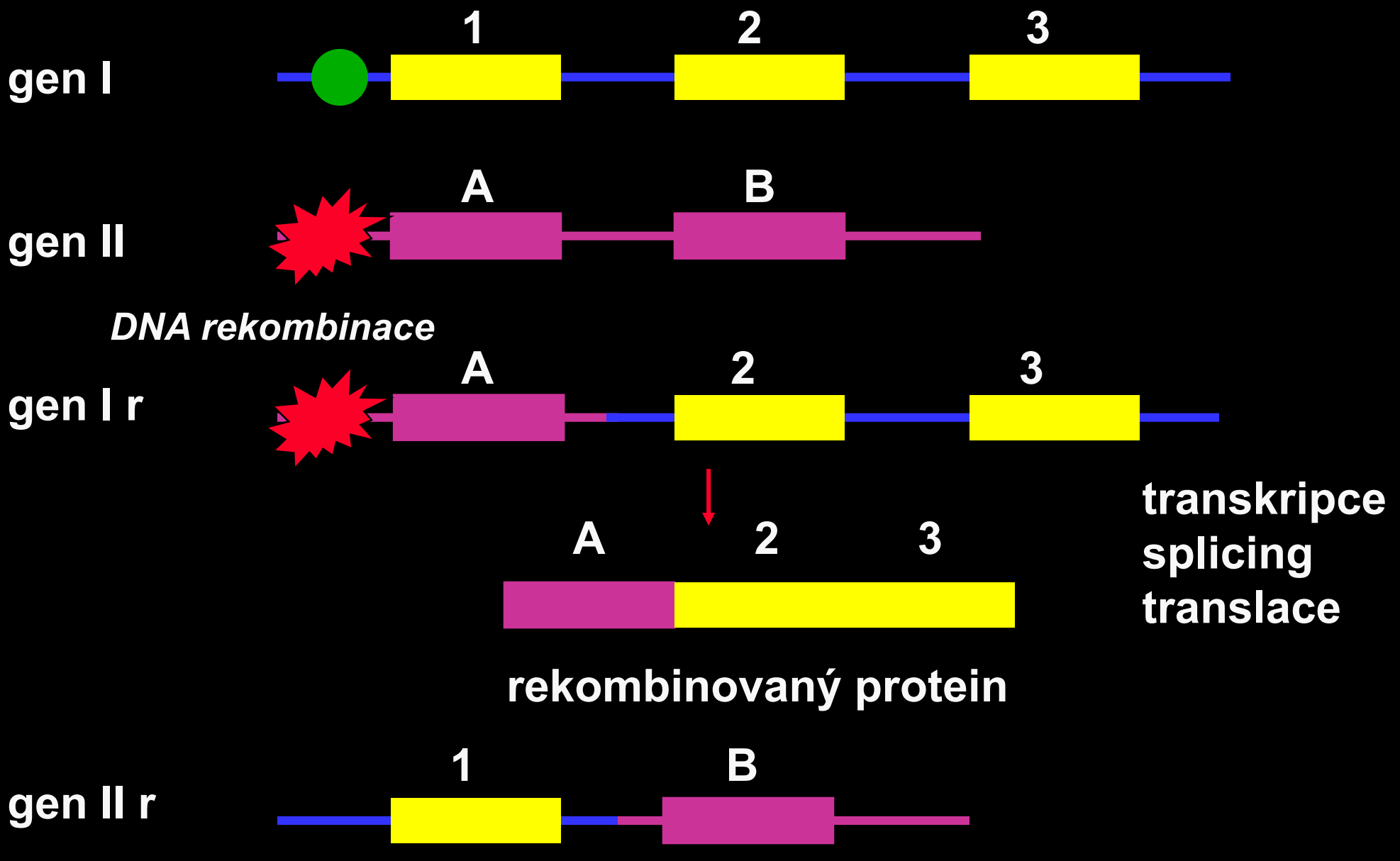
specifické	x	nespecifické
náhodné	x	nenáhodné
primární	x	sekundární

INSERČNÍ a TRANSLOKAČNÍ MUTAGENEZE

Rekombinace DNA a overexprese onkoproteinu



Rekombinace protoonkogenů a vznik onkoproteinu



CHROMOSOMÁLNÍ TRANSLOKACE

a GENOVÉ PŘESTAVBY

translokace

příklady

- nádory měkkých tkání

translokace

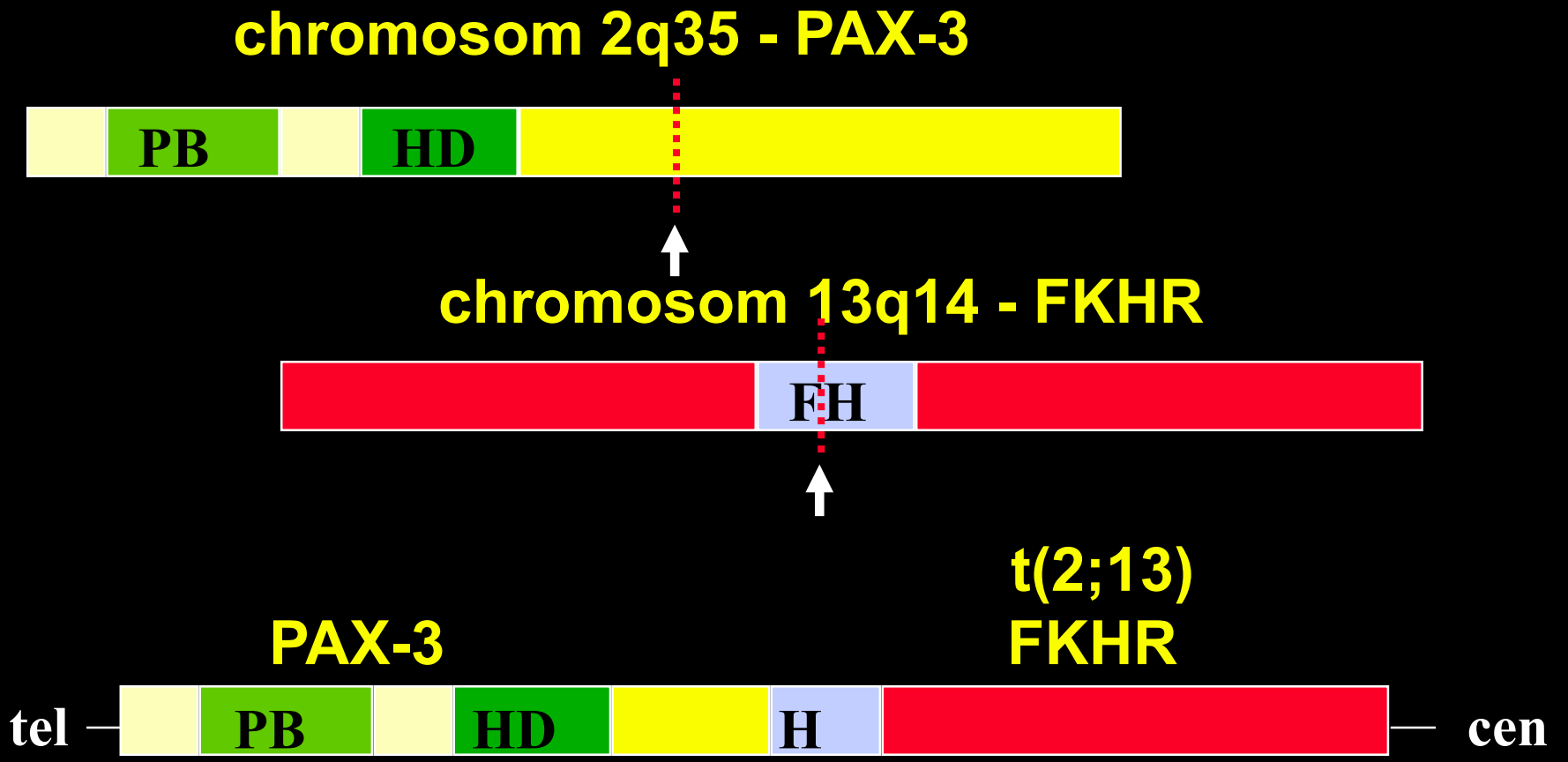
klíčový „vedoucí“ gen - různí „sparing partneři“

stejný typ nádoru

alveolární rabdomyosarkom (A RMS)

t(2;13)(q35;q14)
PAX3 – FKHR
t(1;13)(p36;q14)
PAX7 – FKHR

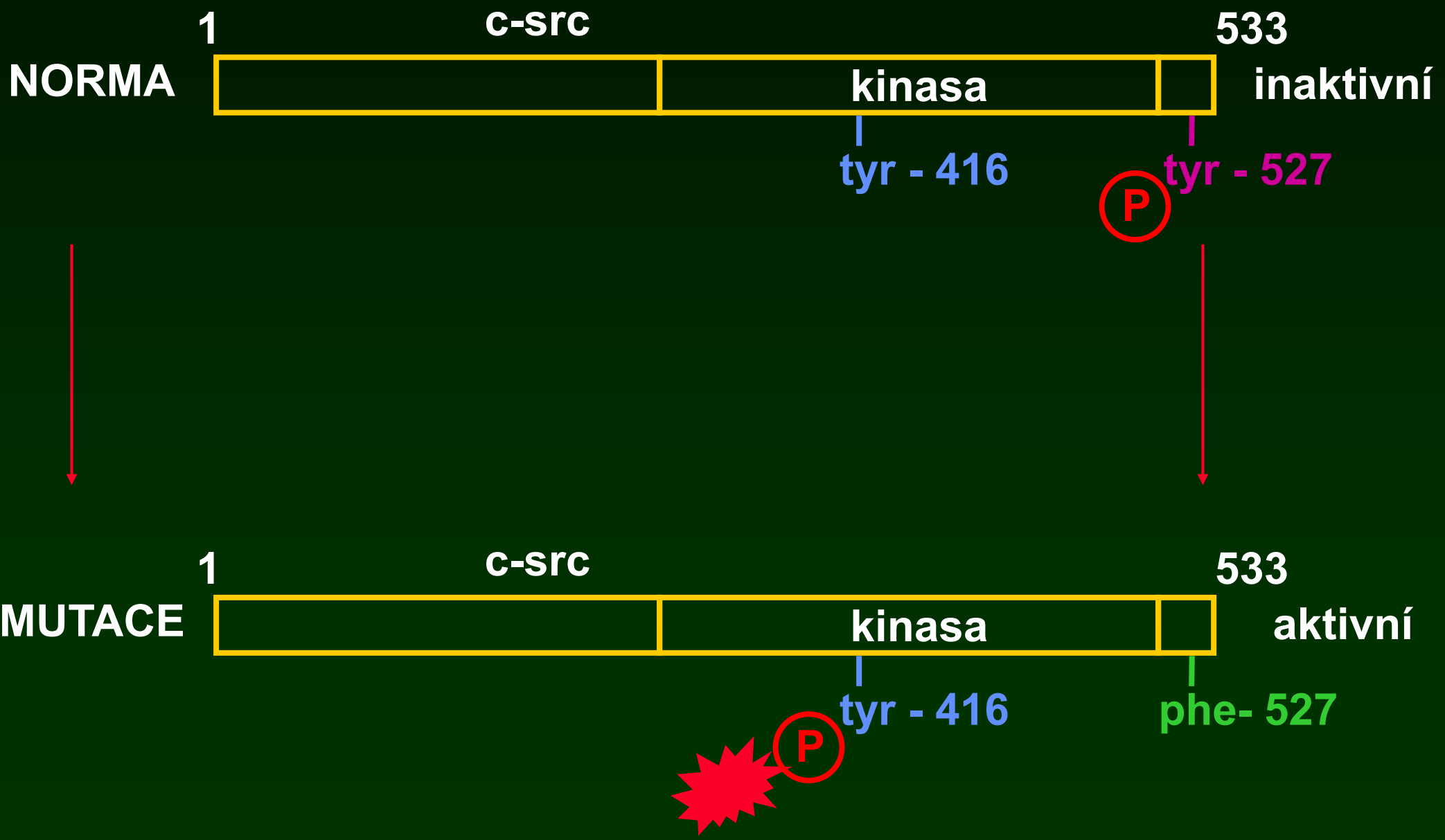
Schema vzniku chimerického produktu u A RMS



BODOVÉ MUTACE
DELECE

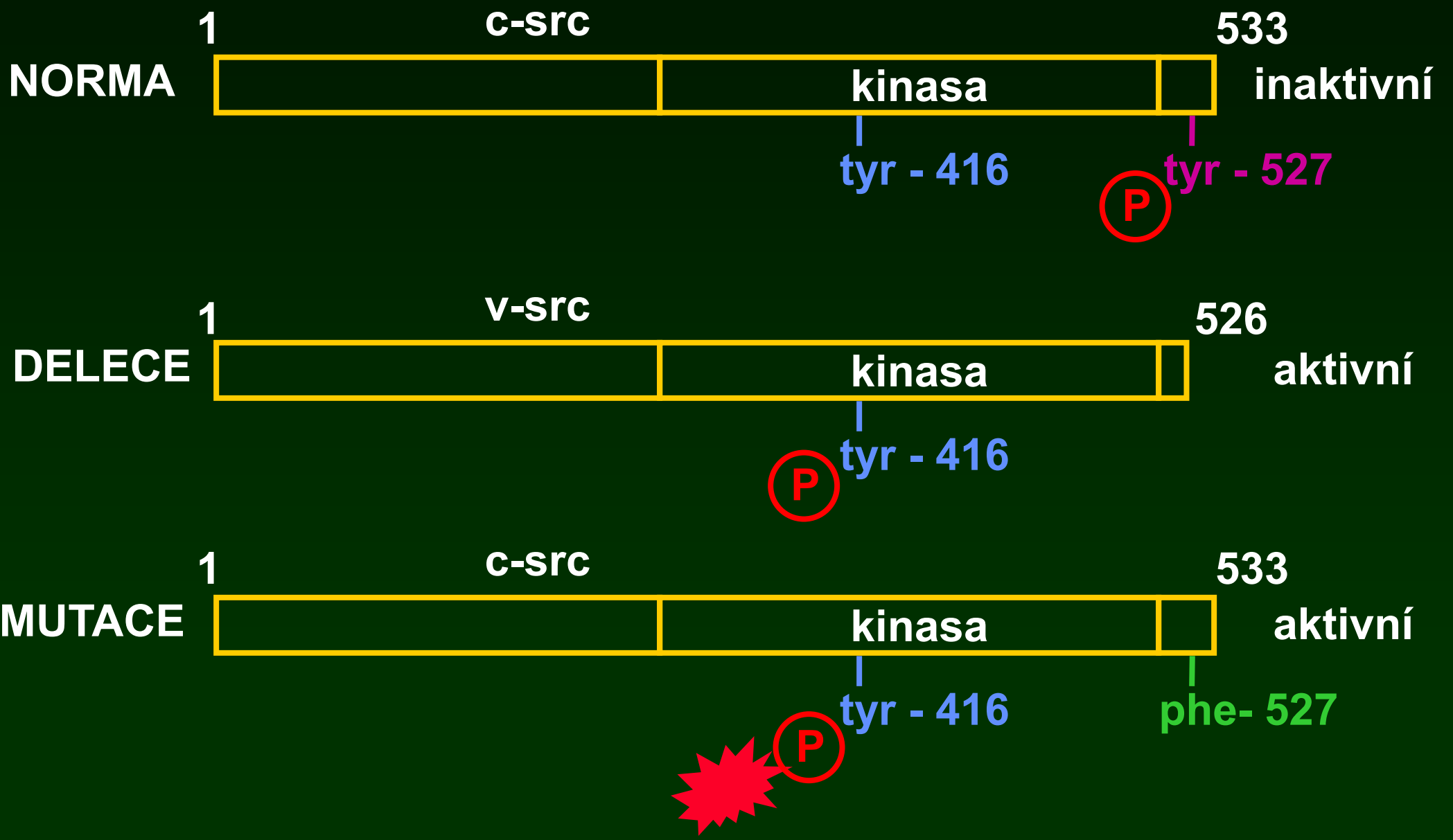
Bodové mutace

Regulace src kinasy



Bodové mutace

Regulace src kinasy



AMPLIFIKACE DNA

skupiny genů - proteinů
participujících na

řízení buňky

a na

nádorové transformaci

Proteiny řídící růst a diferenciaci buňky

I. růstové faktory
II. receptory pro růstové faktory
III. proteiny přenášející signály
IV. transkripční faktory
V. pro- a anti- apoptotické proteiny
VI. proteiny kontrolující buněčný cyklus (nádorové supresory)
VII. proteiny opravující DNA
VIII. miRNA

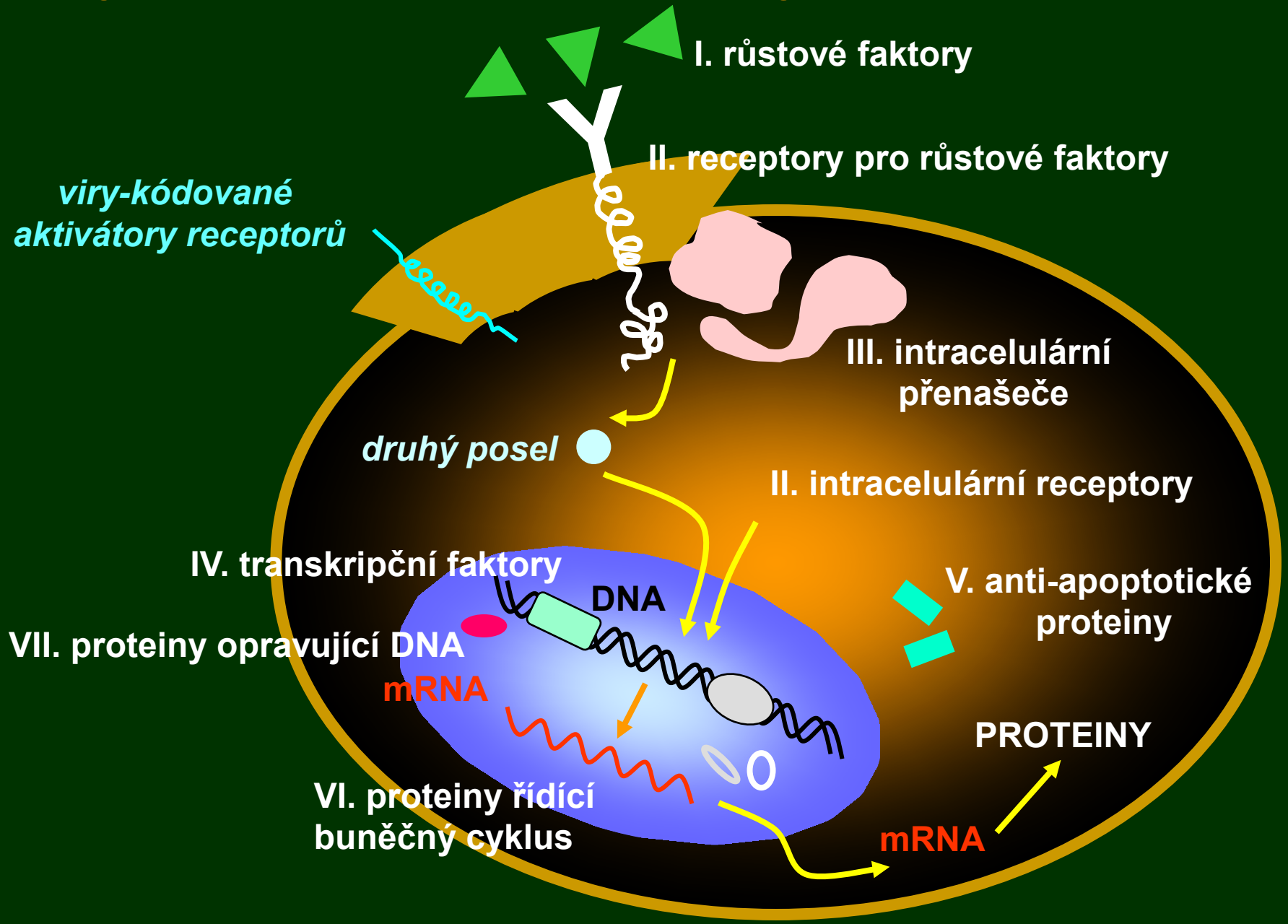
Mutace genů mění strukturu nebo expresi proteinů:

I.- IV. třídy vznik dominantně aktivních onkogenů

V.-VI. třídy uvolnění buňky z řízení a přežívání
(z mutantní buňky se stane buňka nádorová)

VII. třídy zvýšení pravděpodobnosti mutací jiných tříd

Proteiny řídící růst a diferenciaci buňky

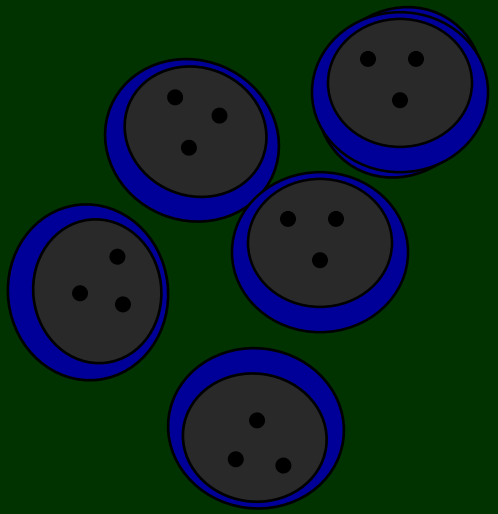


mnohokroková kancerogeneze

Vícekroková genese nádorů - Burkittův lymfom (BL)

první krok

EBV



potenciální imortalizace B-lymfocytů, regulované BCGF

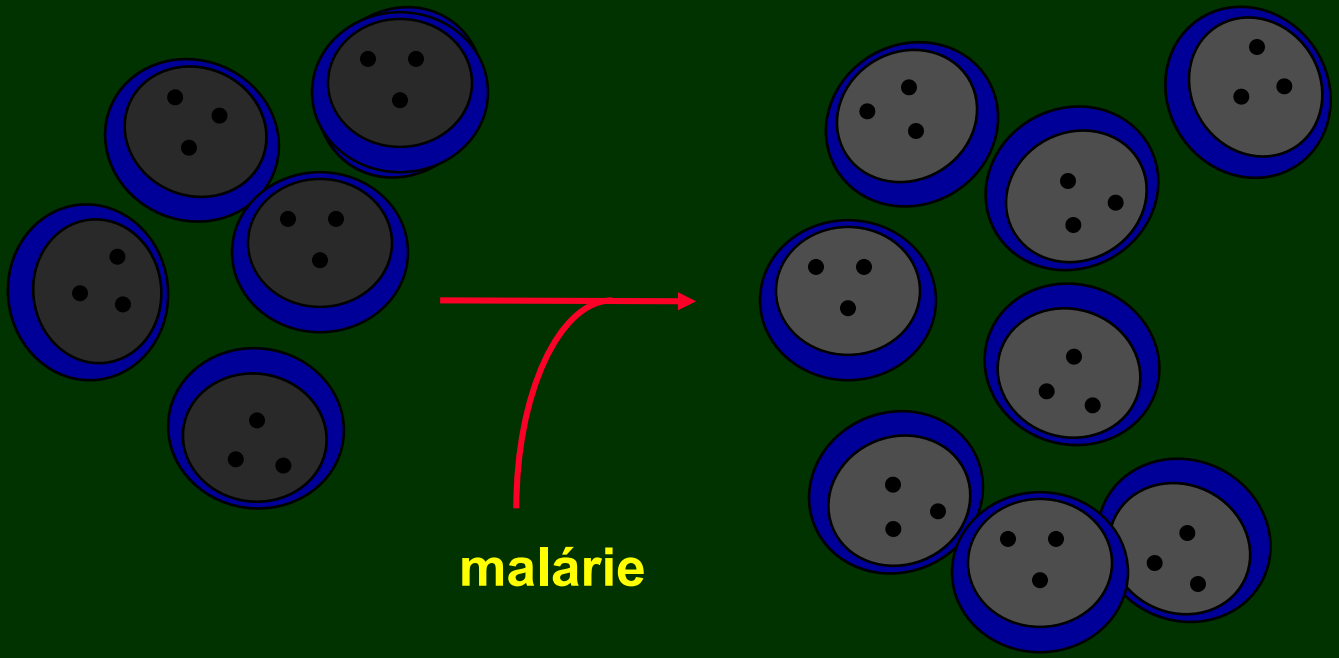
Vícekroková genese nádorů - Burkittův lymfom (BL)

první krok

EBV

druhý krok

t(8;14)

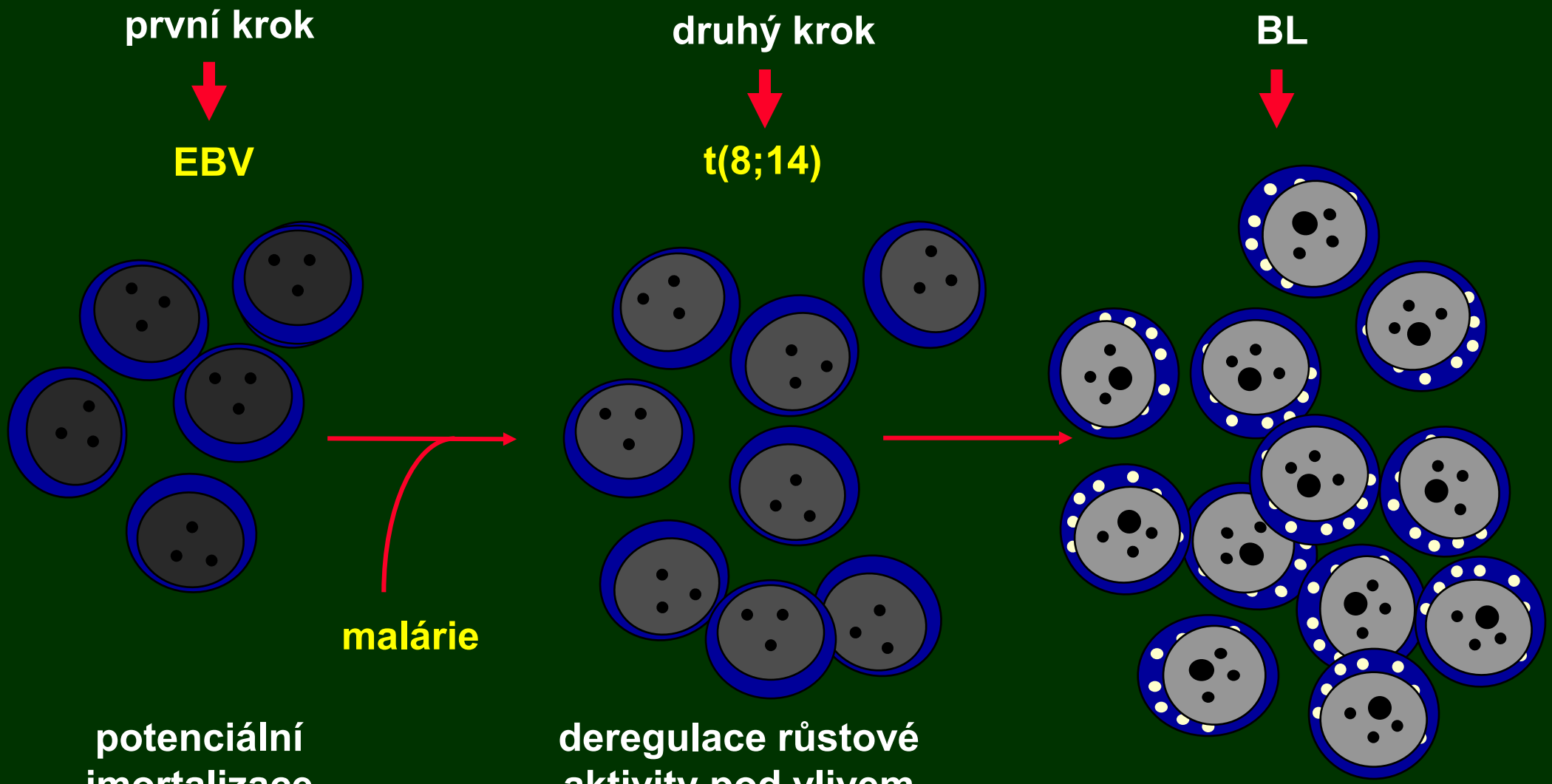


malárie

potenciální imortalizace B-lymfocytů, regulované BCGF

deregulace růstové aktivity pod vlivem c-*myc* , neregulovatelné BCGF

Vícekroková genese nádorů - Burkittův lymfom (BL)



Key genes in biological processes associated with colorectal adenoma to carcinoma progression

Gene set (FDR value)	Carcinoma vs adenoma	Gene Symbol	*P*-value (Wilcoxon signed rank test)
Ontology gene-sets			
Regulation of mitosis (FDR = 0.02)	Upregulated	–	–
Mitosis (FDR = 0.02)	Upregulated	*AURKA*	1.28E-08
		PLK1	3.67E-07
		SSSCA1	1.56E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
Cell cycle phase (FDR = 0.02)	Upregulated	*AURKA*	1.28E-08
		PLK1	3.67E-07
		SSSCA1	1.56E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
		POLD1	1.22E-06
Mitotic cell cycle (FDR = 0.02)	Upregulated	*AURKA*	1.28E-08
		SSSCA1	1.56E-07
		PLK1	3.67E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
		POLD1	1.22E-06
Cell cycle process (FDR = 0.02)	Upregulated	*AURKA*	1.28E-08
		PLK1	3.67E-07
		SSSCA1	1.56E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
		POLD1	1.22E-06
M-phase (FDR = 0.02)	Upregulated	*AURKA*	1.28E-08
		SSSCA1	1.56E-07
		PLK1	3.67E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
Collagen (FDR = 0.03)	Upregulated	*LUM*	1.22E-06
M-phase of mitotic cell cycle (FDR = 0.03)	Upregulated	*AURKA*	1.28E-08
		SSSCA1	1.56E-07
		PLK1	3.67E-07
		TPX2	5.53E-06
		SMC1A	2.00E-06
Chromosomal part (FDR = 0.06)	Upregulated	*RFC3*	4.12E-06
		SMC1A	2.00E-06
		POLD1	1.22E-06
Chromatin binding (FDR = 0.06)	Upregulated	*SUV39H1*	4.45E-07
		SMC1A	2.00E-06
Chromosome segregation (FDR = 0.07)	Upregulated	*SMC1A*	2.00E-06
Chromosome pericentric region (FDR = 0.07)	Upregulated	*SMC1A*	2.00E-06

Molecular Mechanisms of Cancer