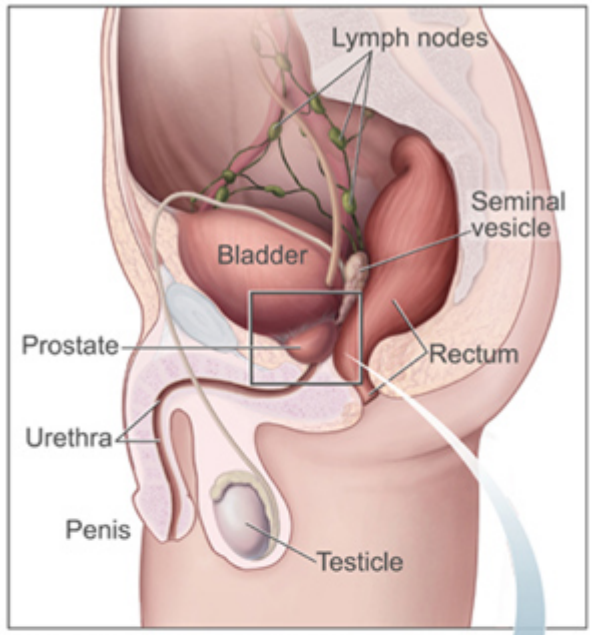
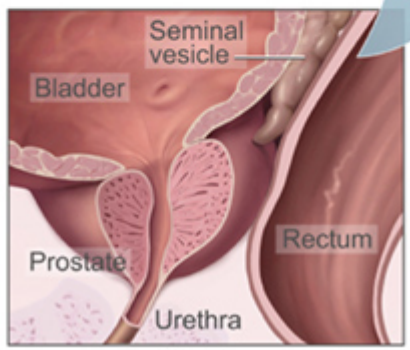
Adenokarcinom prostaty

Předstojná žláza - prostata

- žláznatý - nepárový - orgán velikosti ořechu
- součást mužského reprodukčního systému
- růst a funkce některých jejích buněk je pod kontrolou androgenních hormonů
- podílí se na produkci seminální tekutiny



This shows the prostate and nearby organs.



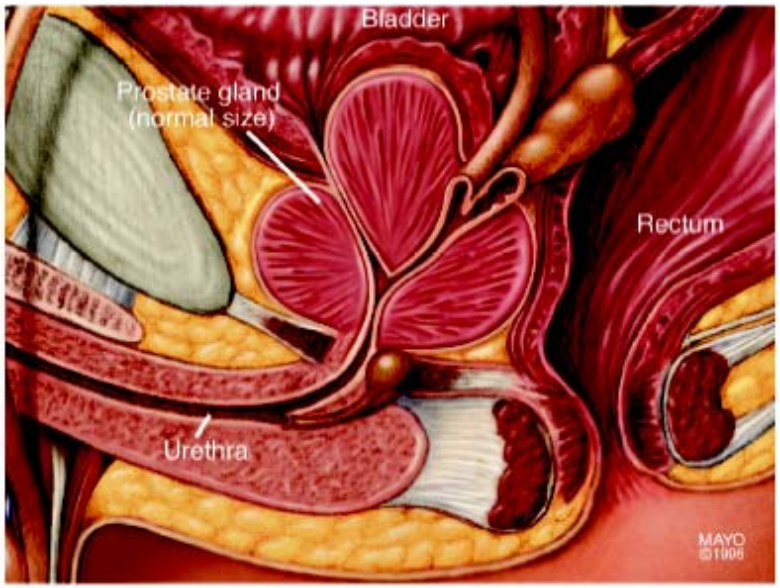
This shows the inside of the prostate, urethra, rectum, and bladder.

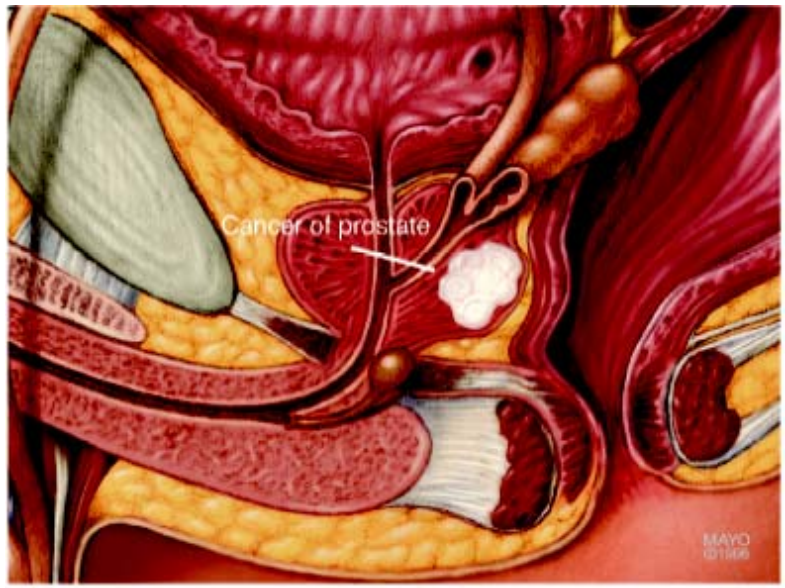
What You Need To Know About™

Prostate Cancer

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Nádorové onemocnění prostaty





Primární nádory: maligní, žlázového původu - adenokarcinomy

Incidence a mortalita

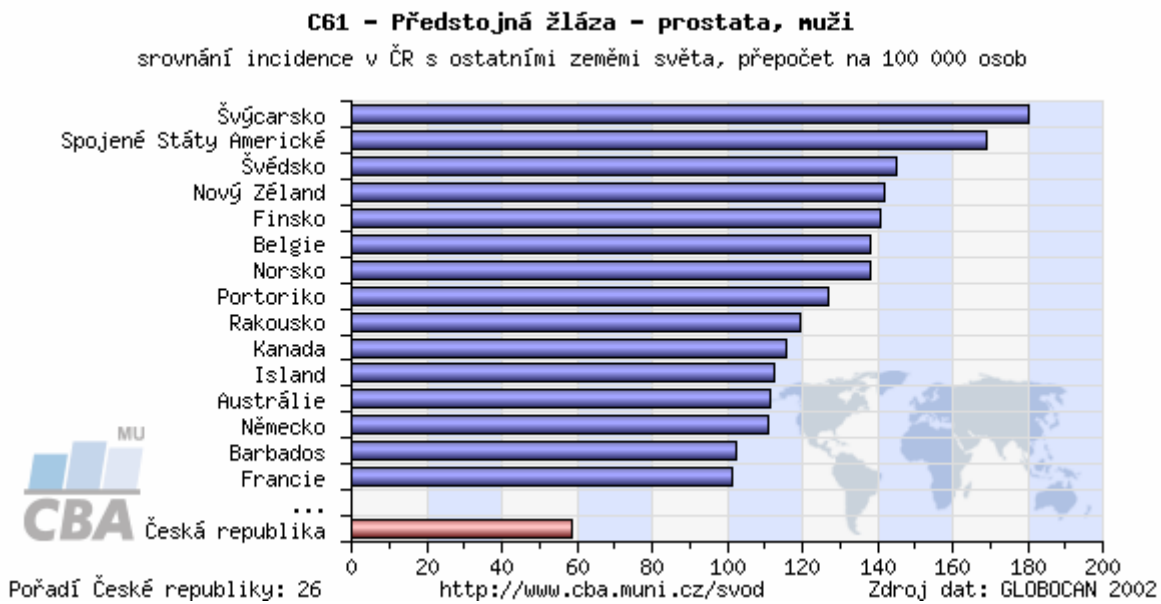
Prostate cancer

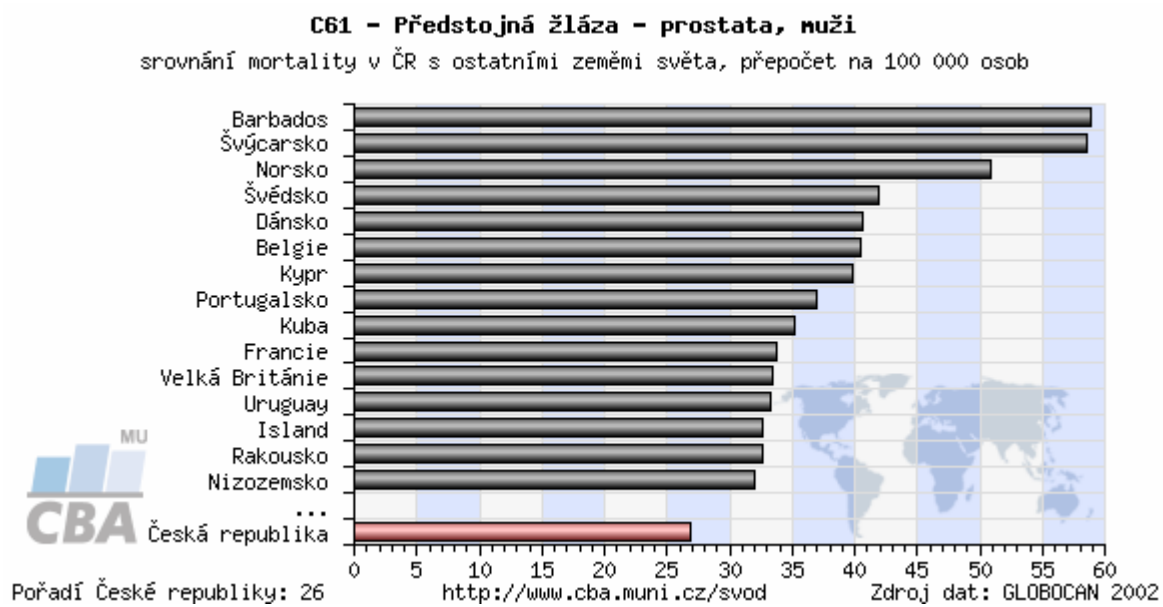
Histologic evidence
Men over age 50 years: 30%
Men over age 80 years: 70%

Clinical Incidence
Incidence: ~190,000 per year in U.S.
Incidence tripled in last 10 years (PSA detection)

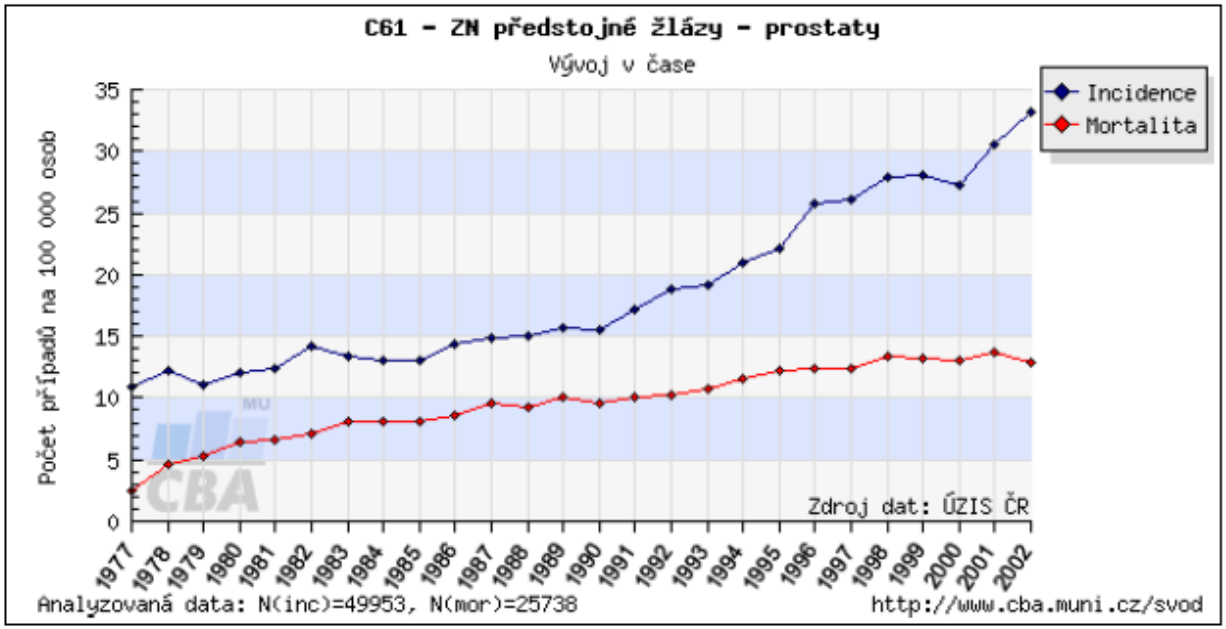
Mortality
Second leading cause of cancer death in men
Mortality: ~ 32,000 deaths per year in U.S.

CENTRUM BIOSTATISTIKY A ANALÝZ MU





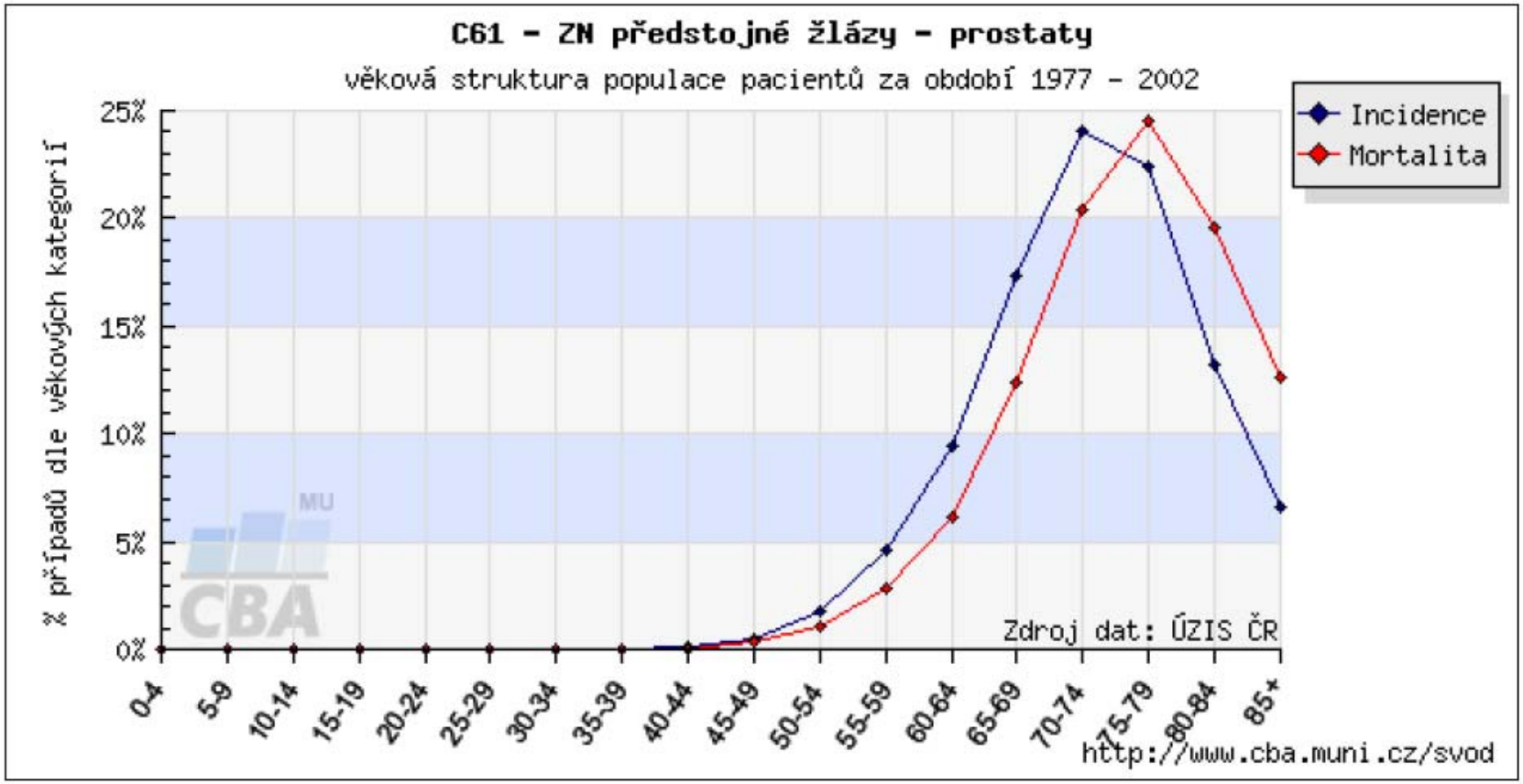
CENTRUM BIOSTATISTIKY A ANALÝZ MU



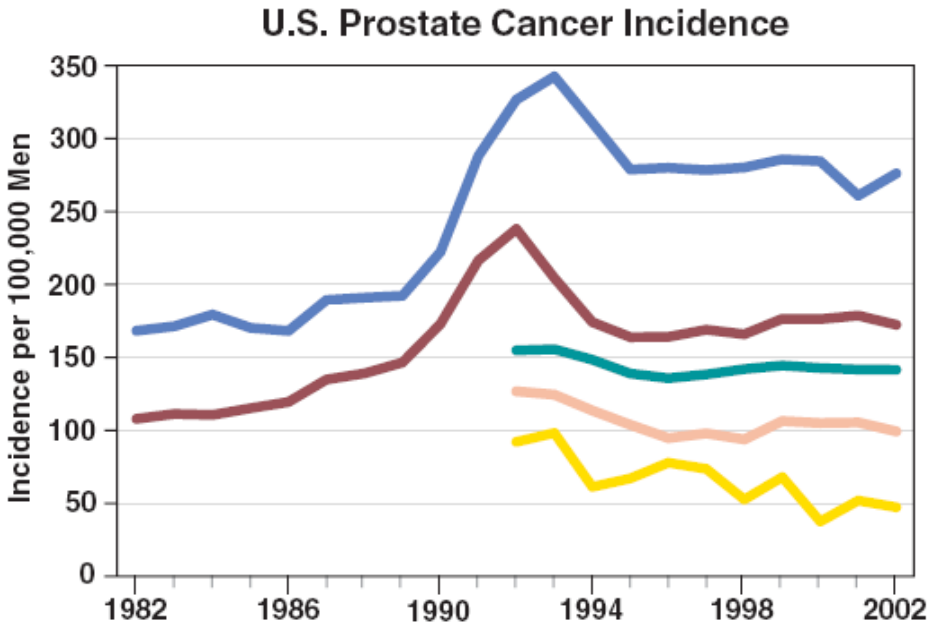
Rok	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Incidence	10.92	12.18	11.12	12.04	12.3	14.19	13.38	13.07	13.1	14.38	14.83	15.07	15.75
Mortalita	2.55	4.65	5.26	6.49	6.55	7.1	8.13	8.14	8.01	8.66	9.56	9.17	10.1

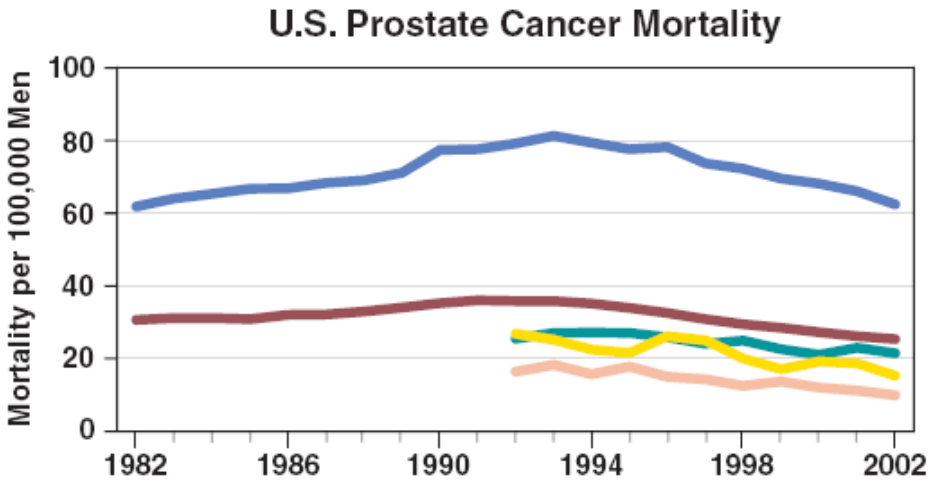
Rok	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Incidence	15.48	17.24	18.88	19.19	20.94	22.06	25.73	26.16	27.91	28.05	27.28	30.48	33.22
Mortalita	9.5	10.1	10.24	10.7	11.48	12.25	12.39	12.46	13.29	13.26	12.98	13.78	12.91

CENTRUM BIOSTATISTIKY A ANALÝZ MU



A Snapshot of Prostate Cancer





Whites
Hispanics*
African Americans
Asians or Pacific Islanders*
American Indians/Alaskan Natives*

*Incidence and mortality data not available for earlier years.

Diagnostika a prognóza

- Prostate Specific Antigen (PSA)

One of the first serological biomarkers (lack of tumour specificity)
"more we know the less we understand"

- Digital Rectal Examination

- Transrectal ultrasound

- Biopsy and Tumour grading and staging

(BRCA1, BRCA2, PTEN, MYC, E-cadherin, apoptotic genes, proliferation - related genes)

TNM staging

American Joint Committee on Cancer

http://www.cancerstaging.org/

AJCC Cancer Staging Manual, Sixth Edition

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

Primary Tumor (T)

Clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

Primary Tumor (T)

Clinical

T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

Primary Tumor (T)

Clinical

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

**Note:* Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

***Note:* Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Pathologic

pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)

Prostate

(Sarcomas and transitional cell carcinomas are not included.)

*Distant Metastasis (M)**

MX	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

STAGE GROUPING

Stage I	Tla	N0	M0	G1
Stage II	Tla	N0	M0	G2, 3–4
	Tlb	N0	M0	Any G
	Tlc	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Stages 1 and 2
(Cancer that is only in the prostate gland, PSA)

Between 65 - 98% with stage 1 and 2 prostate cancer will live for more than five years after they are diagnosed.

Stage 3
(Cancer cells have spread outside the covering (capsule) of the prostate gland to tissues around the prostate but not to the lymph nodes.)

About 60% diagnosed with stage 3 prostate cancer will live for more than five years after diagnosis.

Stage 4
(Cancer cells have spread (metastasized) to lymph nodes (near or far from the prostate gland) or to organs and tissues far away from the prostate such as the bone, liver, or lungs.)

About 20 -30% have cancer spread to another part of their body when they are diagnosed with prostate cancer.

About 30% men with advanced prostate cancer will live for more than five years after diagnosis.

On average, men in this situation can expect their cancer to respond to treatment for about 12 to 18 months. Average survival after that is about another two years.

www.cancerhelp.org.uk, www.phoenix5.org/staging.html

Future Diagnostic tools

- Gene Chip Analysis (prostate specific genes)
- Proteomic (tissue, serum, urine)

➔specific ~ “fingerprint”
~ “signature”

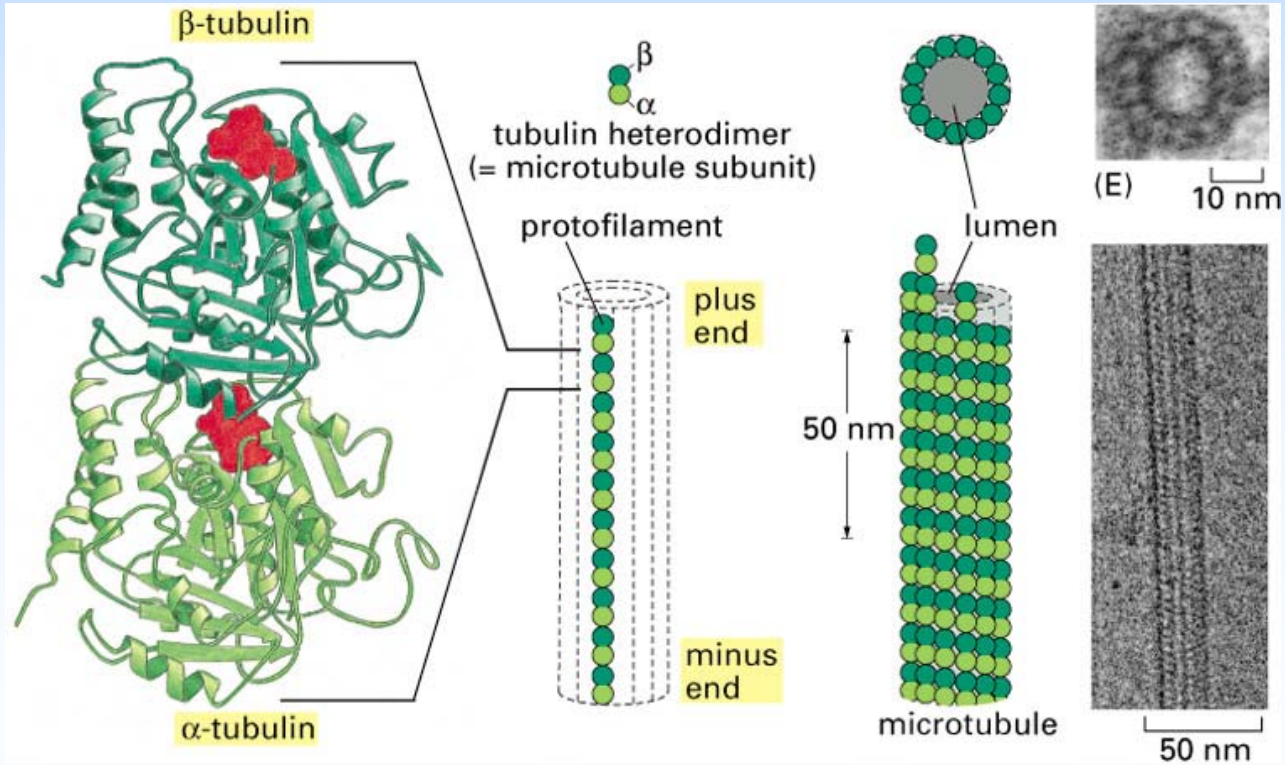
Profil posttranslačních modifikací α-tubulinu jako možný „fingerprint“ nádorů prostaty.

Souček, K. *et al.*, 2006

Microtubules - key components of cytoskeleton

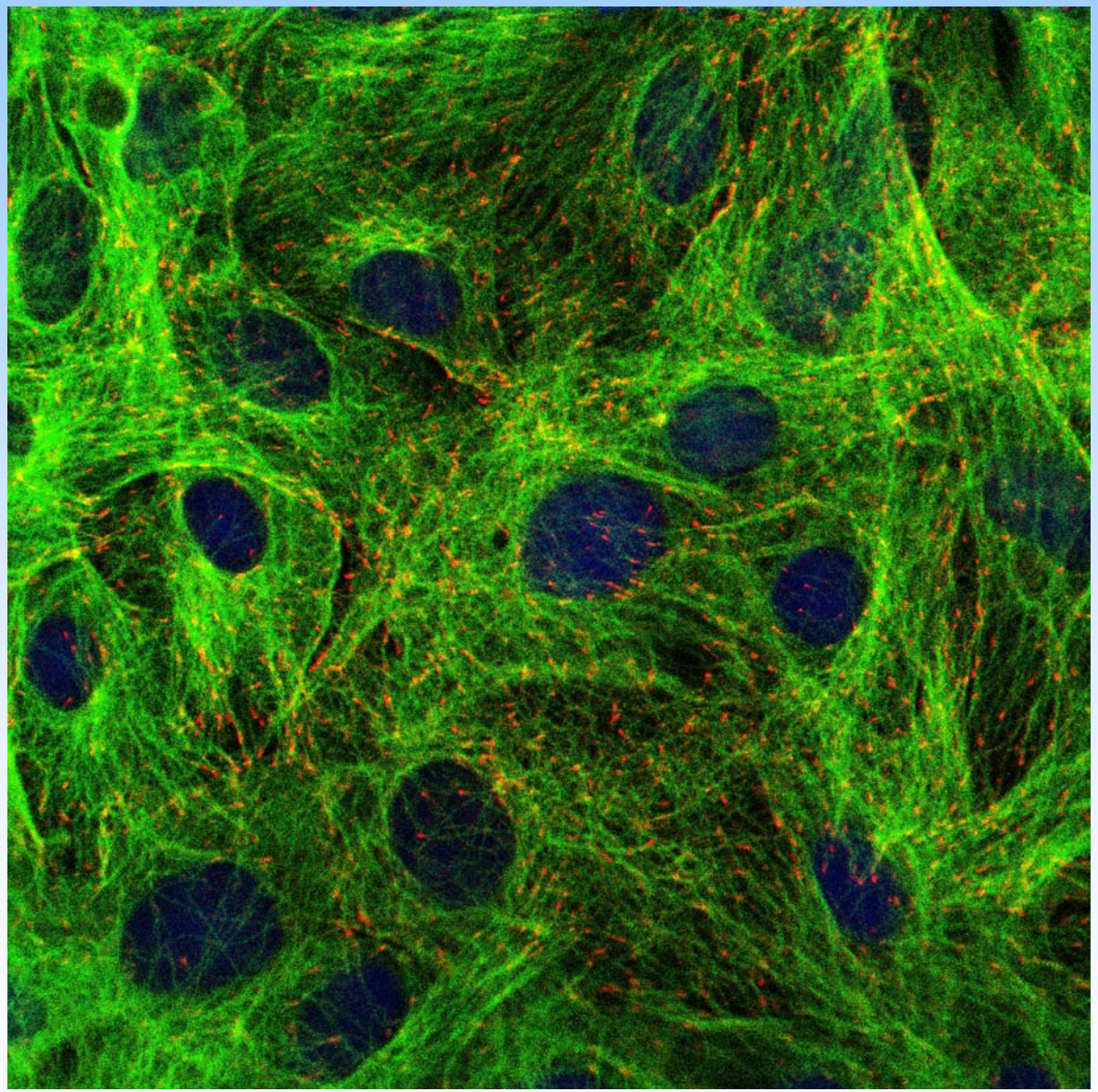
α-tubulin and β-tubulin heterodimers
Highly dynamic polymers

Functional diversity
-binding of regulatory proteins (MAPs)
-expression of isotypes (6 forms of α-tubulin and 7 forms of β-tubulin)
-post-translational modifications



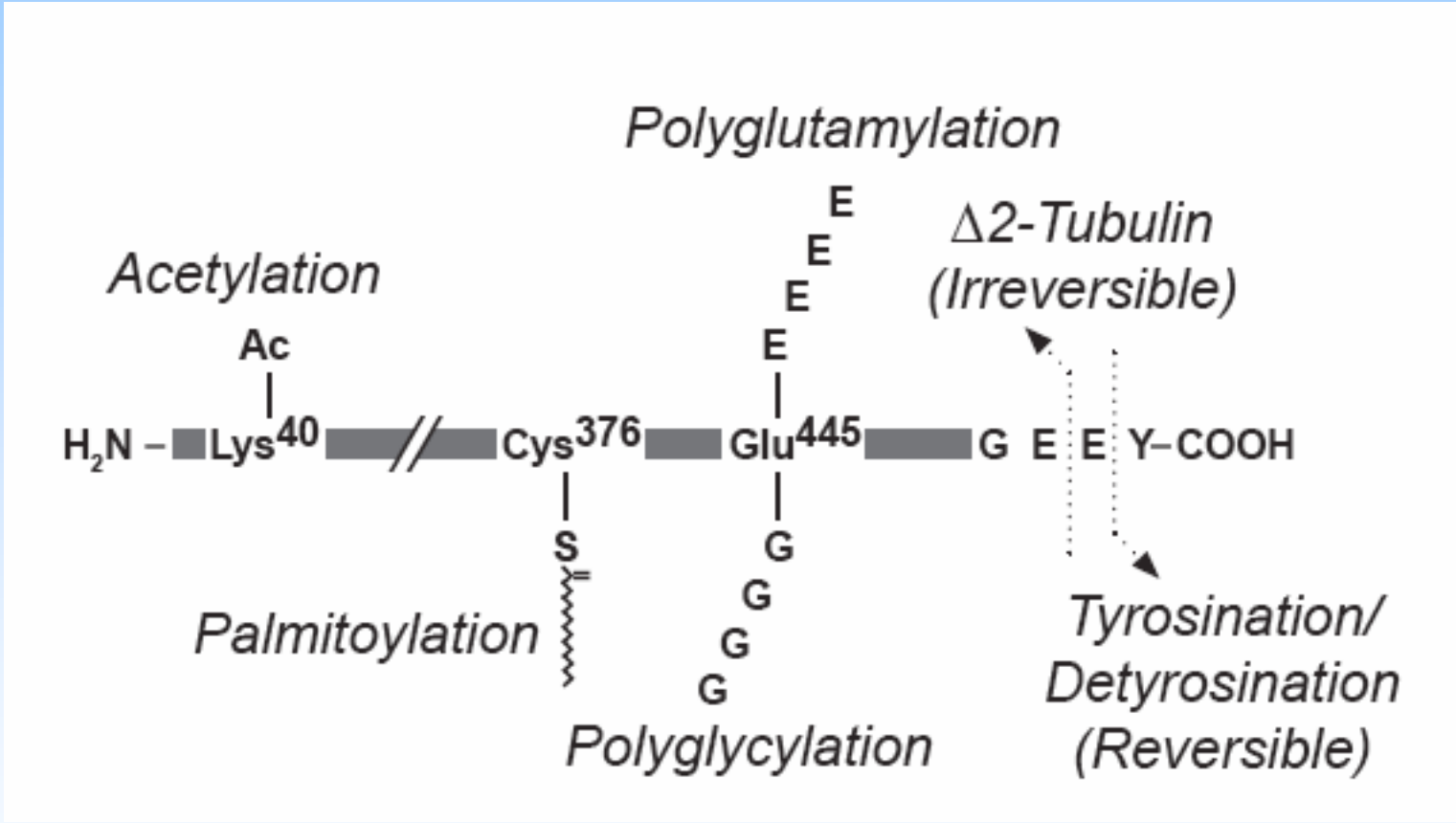
Molecular Biology of the Cell (4th Ed.)

Rat Vascular Smooth Muscle Cells
EB1 and α-Tubulin staining



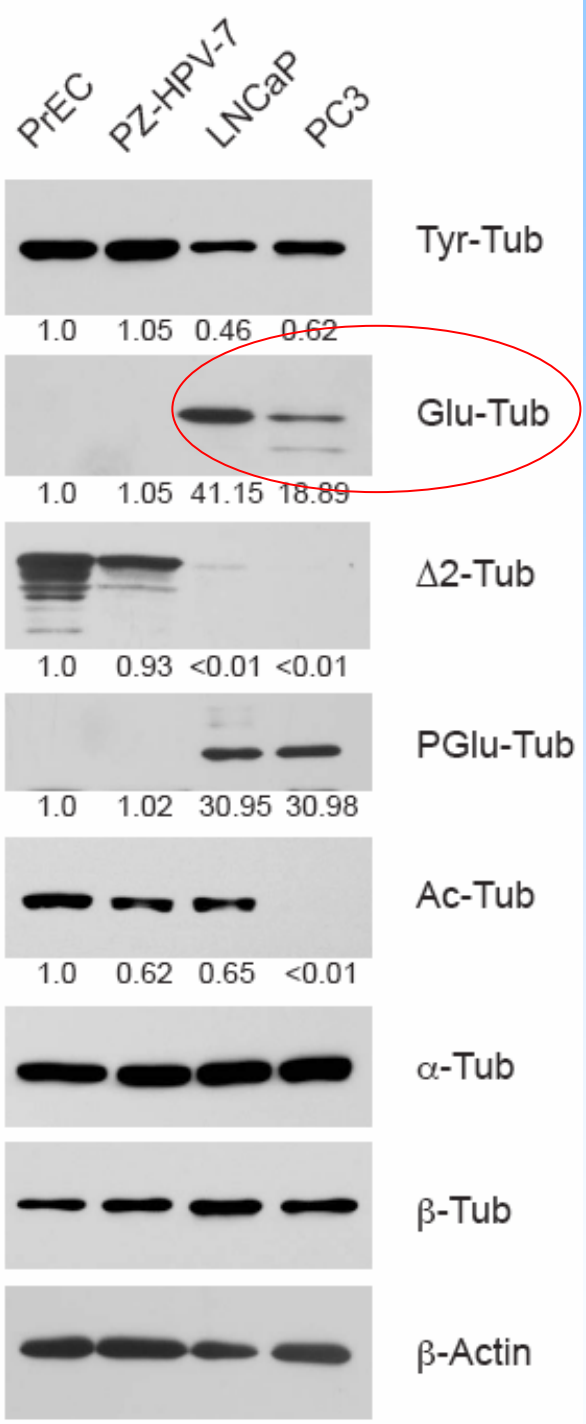
Anh D.Phung
2005

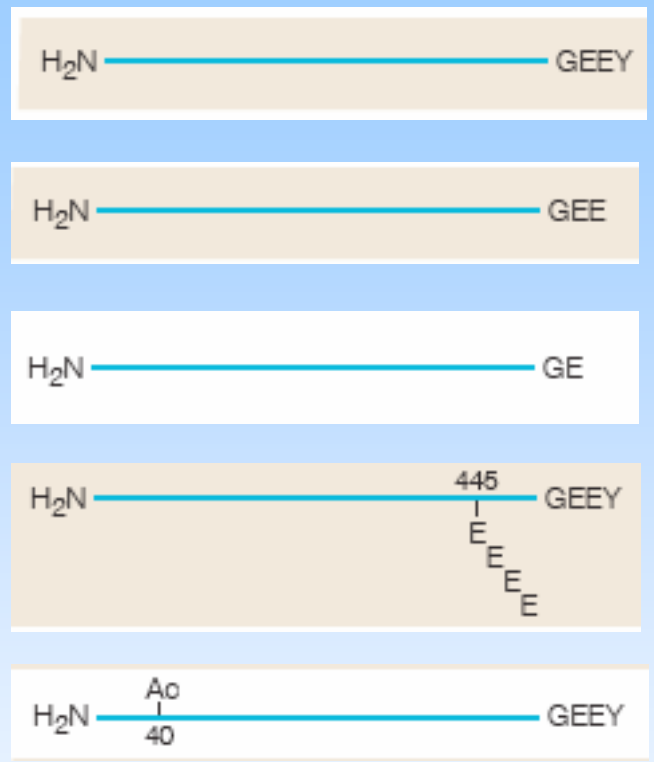
Post-translational modifications of tubulin



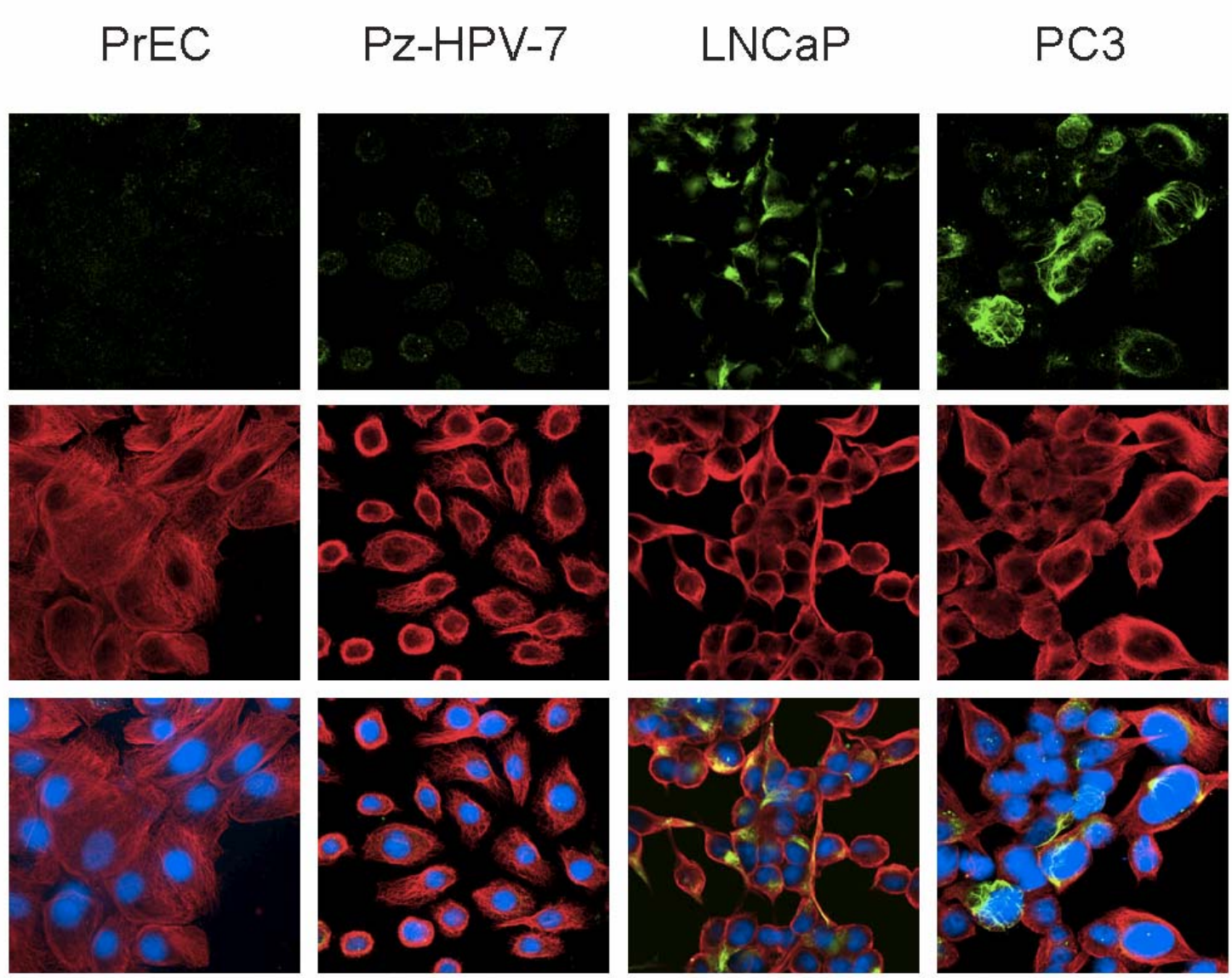
Souček, K. *et al.*, 2006

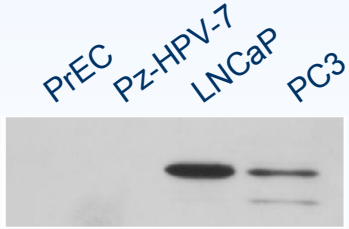
Post-translational modification of α-Tubulin in prostate epithelial cells





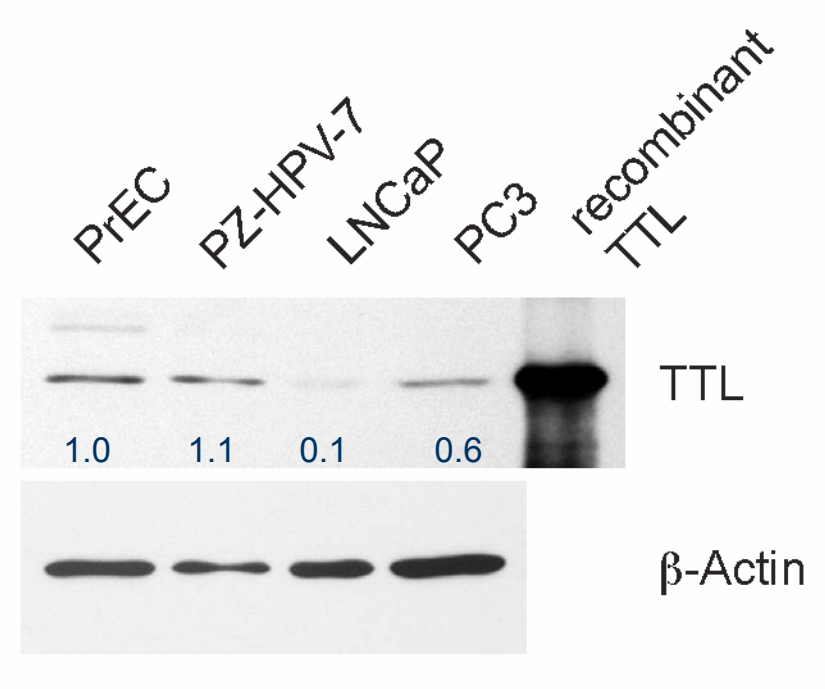
Souček, K. *et al.*, 2006

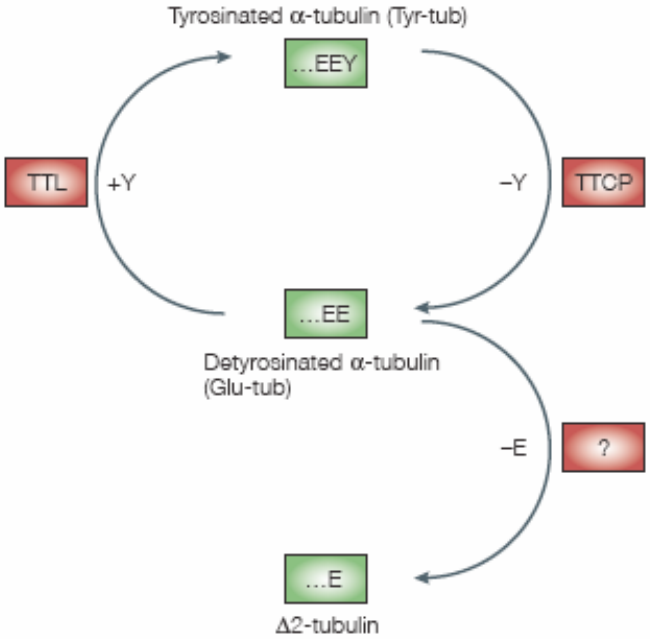


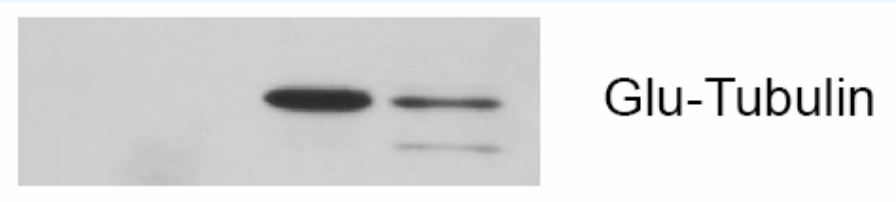


Souček, K. *et al.*, 2006

tubulin tyrosine ligase expression in prostate epithelial cells

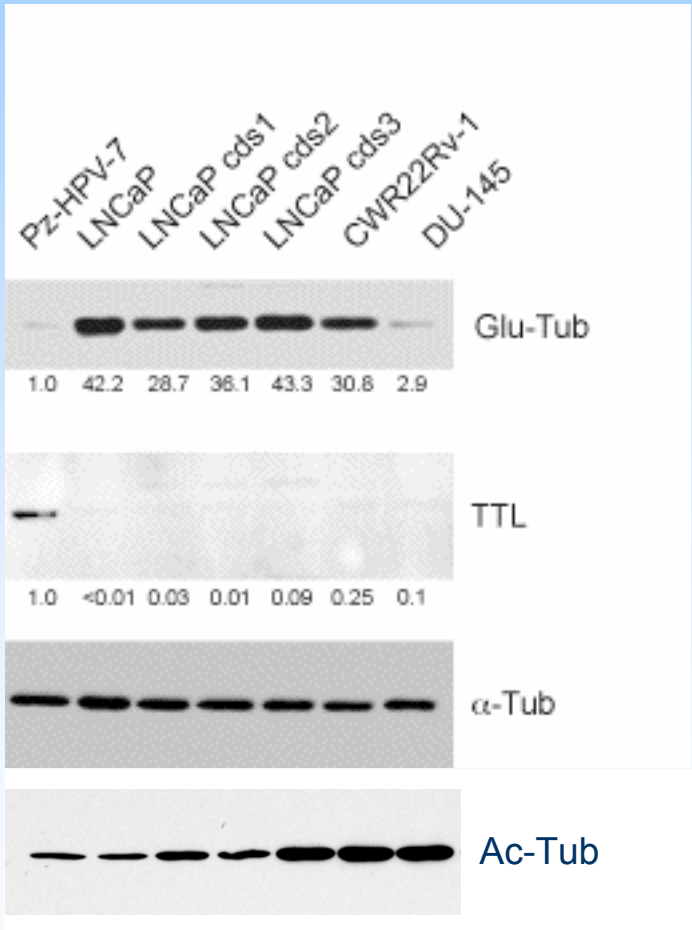






Souček, K. *et al.*, 2006

Glu-Tubulin and Tubulin - Tyrosine Ligase expression in prostate epithelial cells - proof of the concept



Souček, K. *et al.*, 2006

SUMMARY

- Normal and prostate cancer cells display distinct molecular profiles of α-Tubulin posttranslational modifications
- Low expression of tubulin tyrosine ligase is characteristic also for prostate cancer cells
- Different profile of post-translation modifications α-Tubulin in various prostate epithelial cell lines show the possibility to distinguish the stages of cancer disease and has the potential to establish a novel tool to diagnose and treat prostate cancer.

Souček, K. *et al.*, 2006

Léčba nádorů prostaty

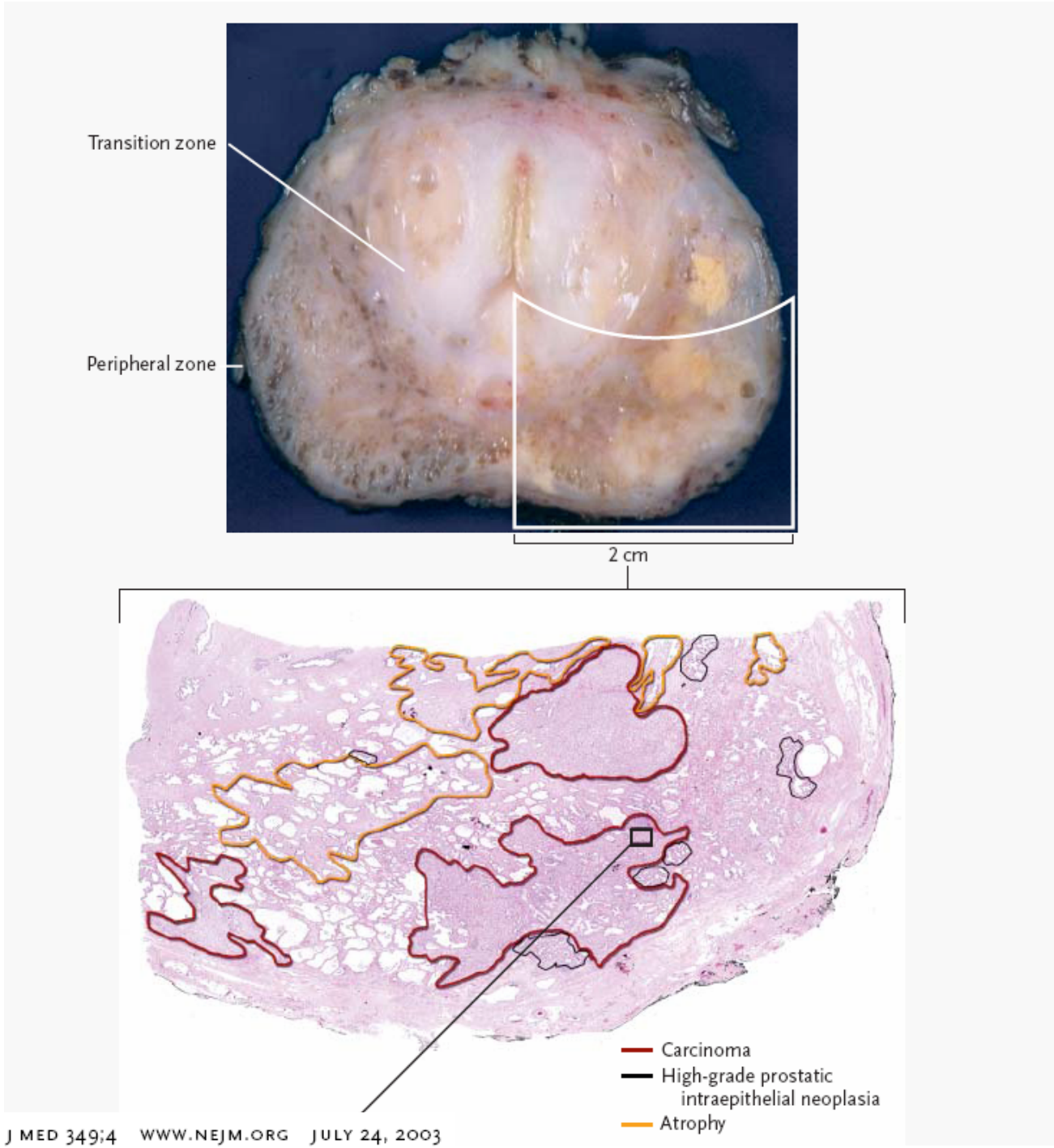
- **Surgery**
  Radical prostatectomy
  Resection
  Cryosurgery

- **Radiotherapy**
  External, internal

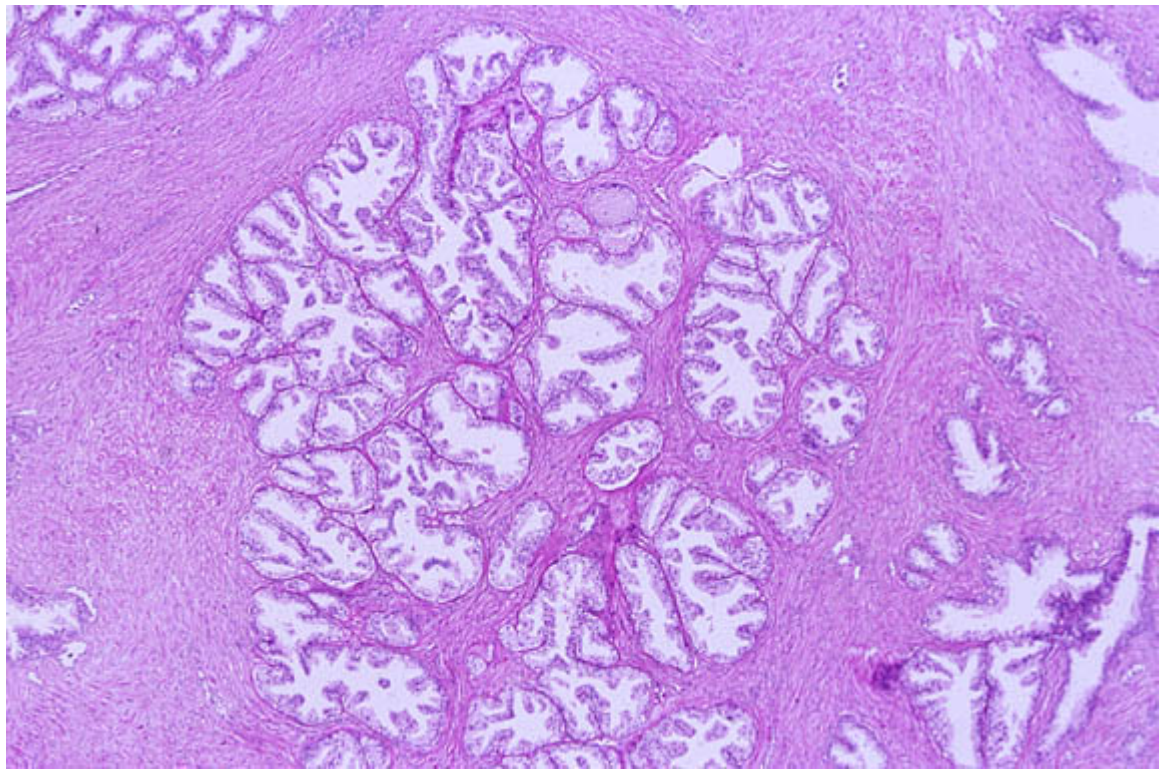
- **Hormonal (androgen deprivation) therapy**
  Castration - surgical
  - medical

- **Chemotherapy in androgen-independent cancer**
  -Docetaxel / Estramustine (Calcitriol)
  - Satraplatin, Mitoxantrone/Predisone

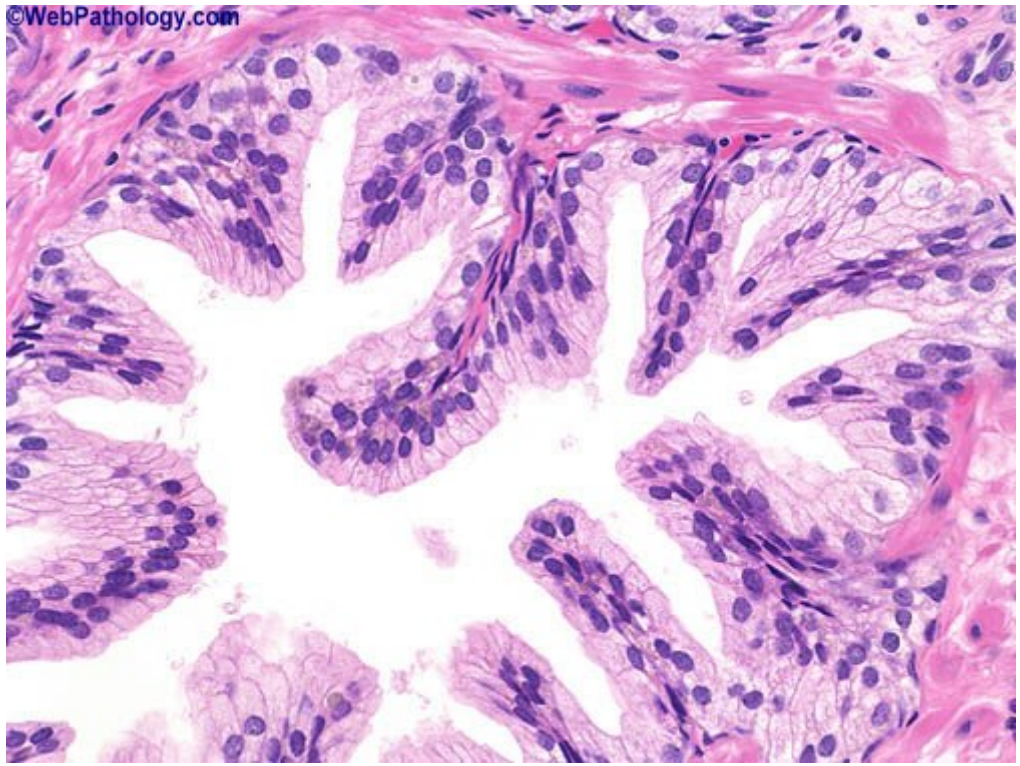
Patologie nádorového onemocnění prostaty


Transition zone
Peripheral zone
2 cm
Carcinoma
High-grade prostatic intraepithelial neoplasia
Atrophy

Histologie prostaty– normální



Histologie prostaty– normální



The normal prostatic epithelium – 5 interrelated cell types:

- stem cells
- basal epithelial cells
- transitamplifying cells
- neuroendocrine cells
- secretory luminalepithelial cells

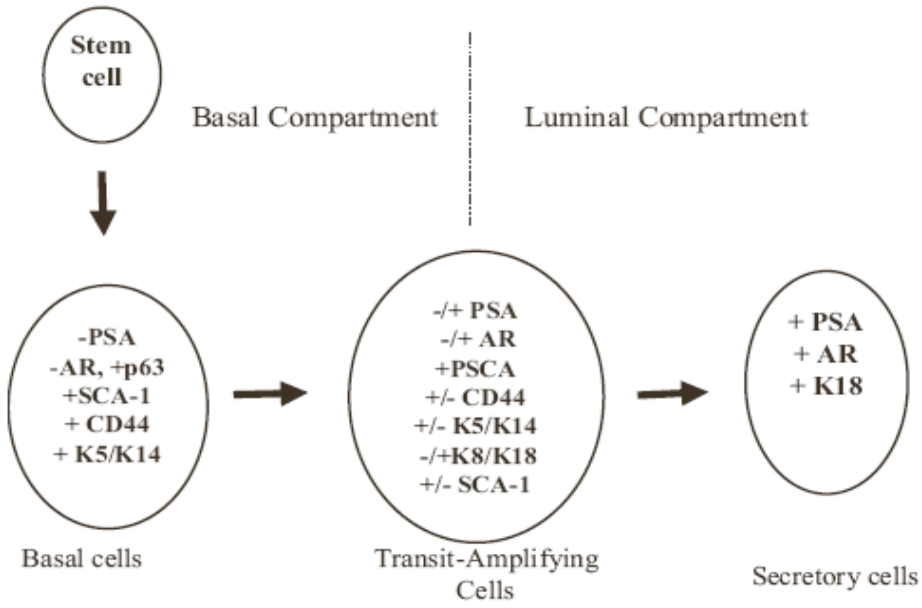
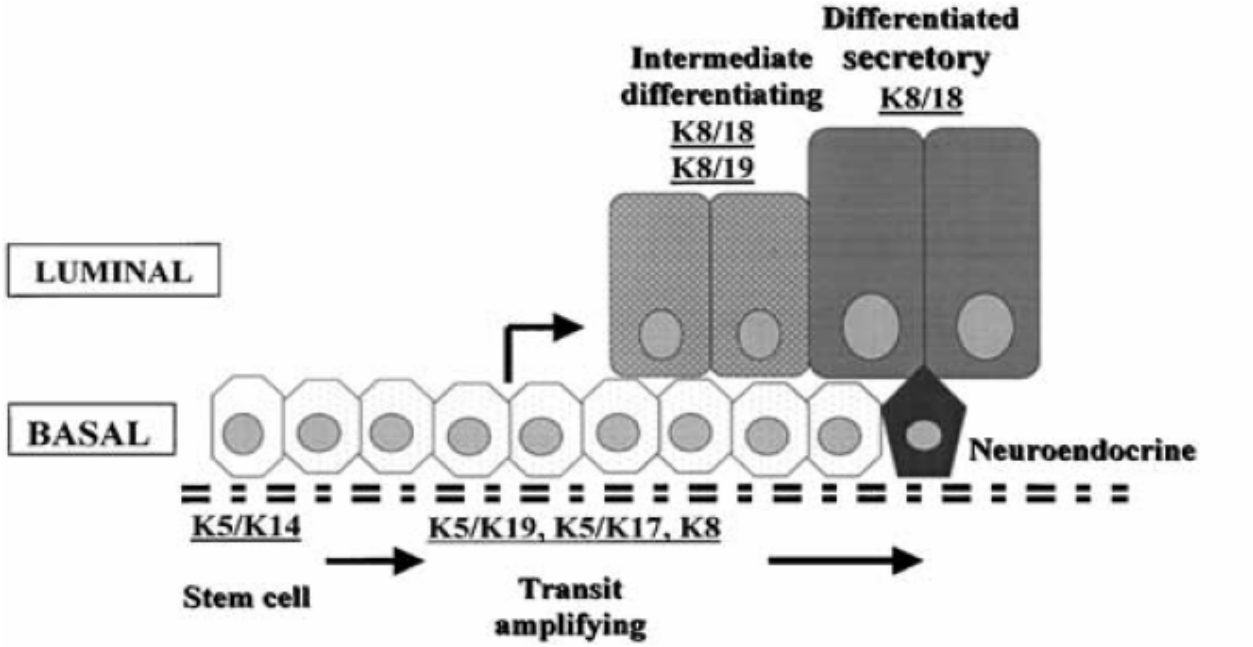


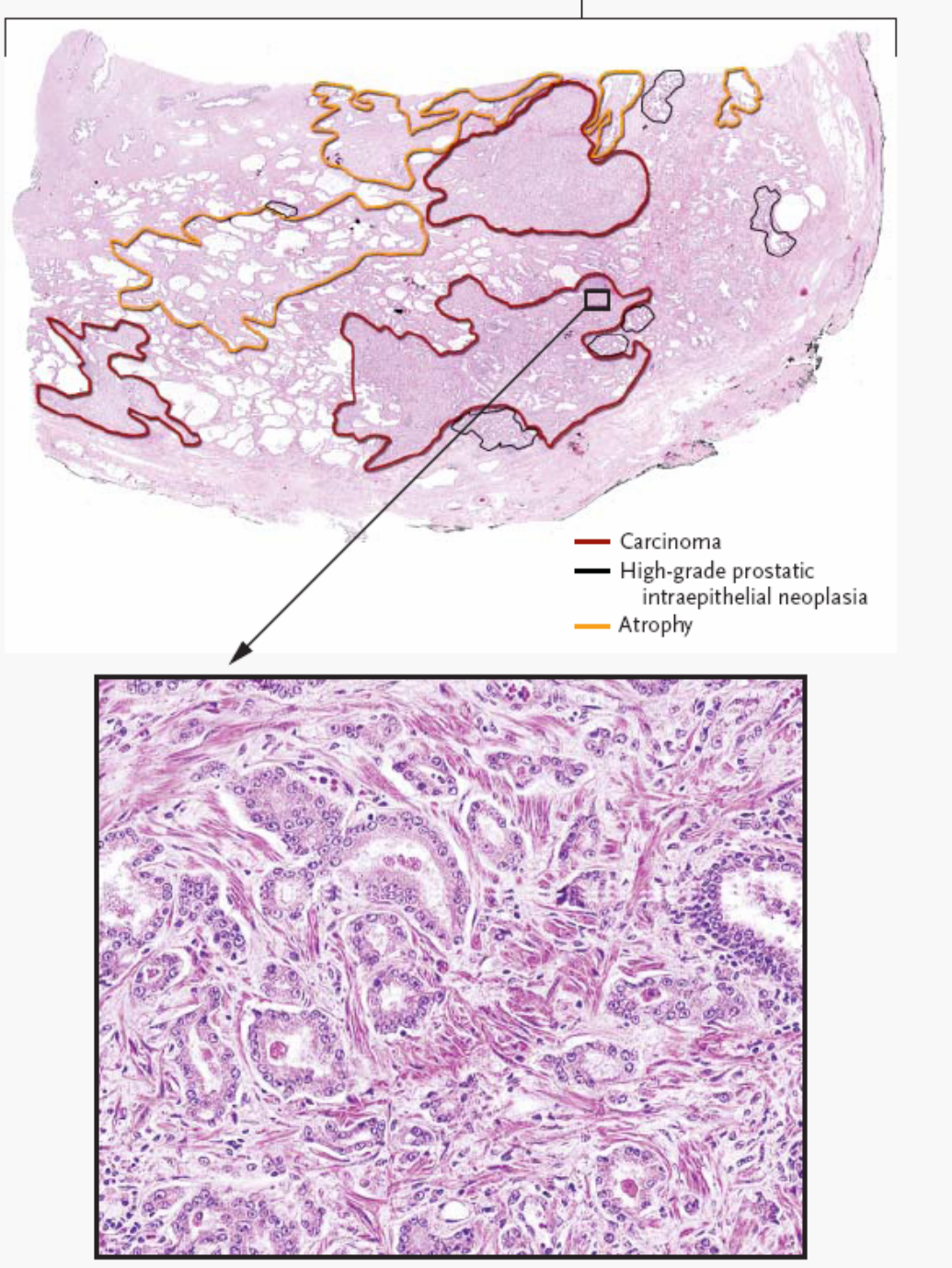
Fig. 1. Postulated model and markers of prostate epithelial development. AR, androgen receptor; PSA, prostate-specific antigen; PSCA, prostate stem cell antigen; SCA, stem cell antigen.

Lam, J.S. *et al.*, 2006

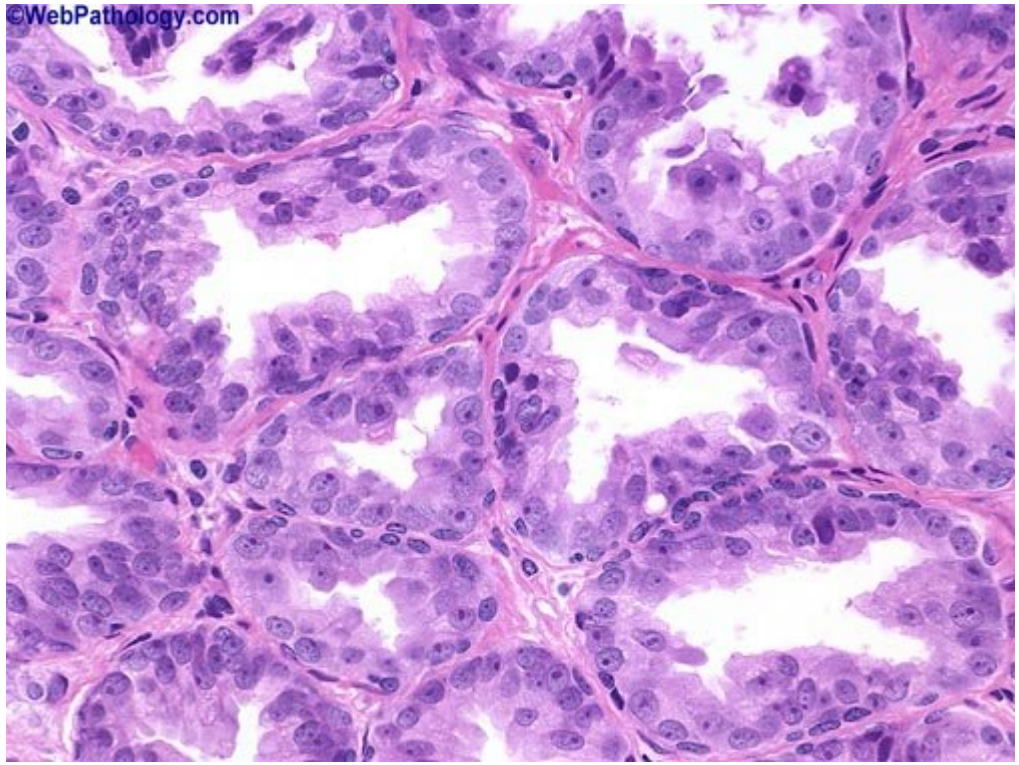
Hypotetický model diferenciace prostatického epitelu



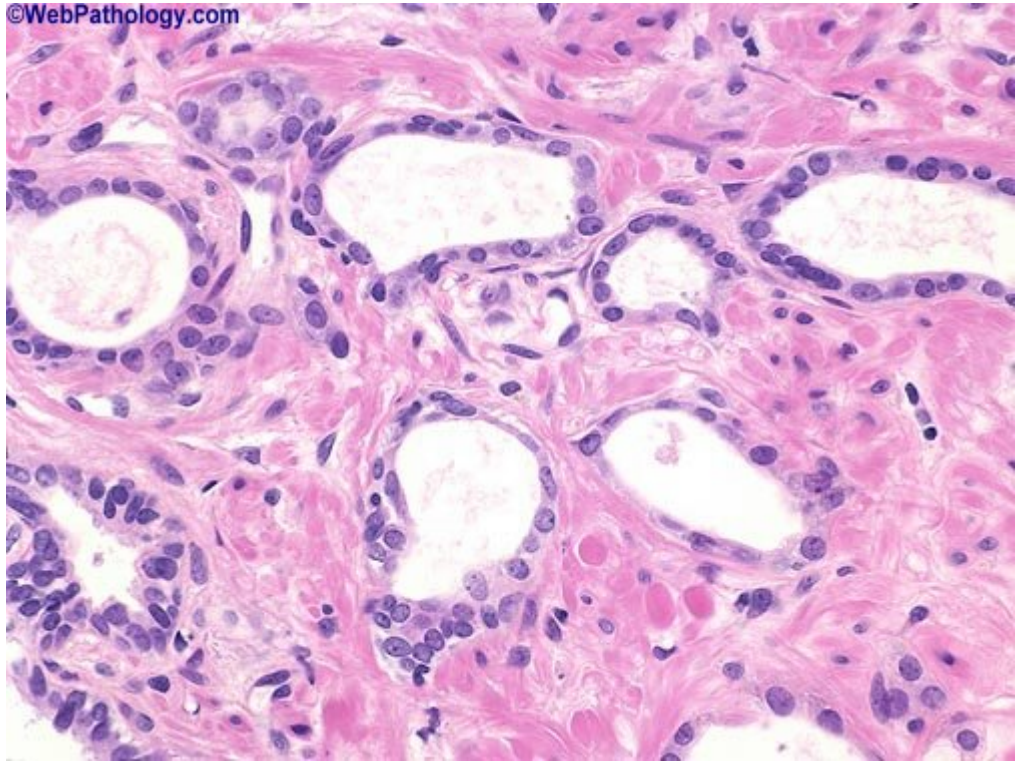
Hudson, D.L. *et al*, 2004


Carcinoma
High-grade prostatic intraepithelial neoplasia
Atrophy

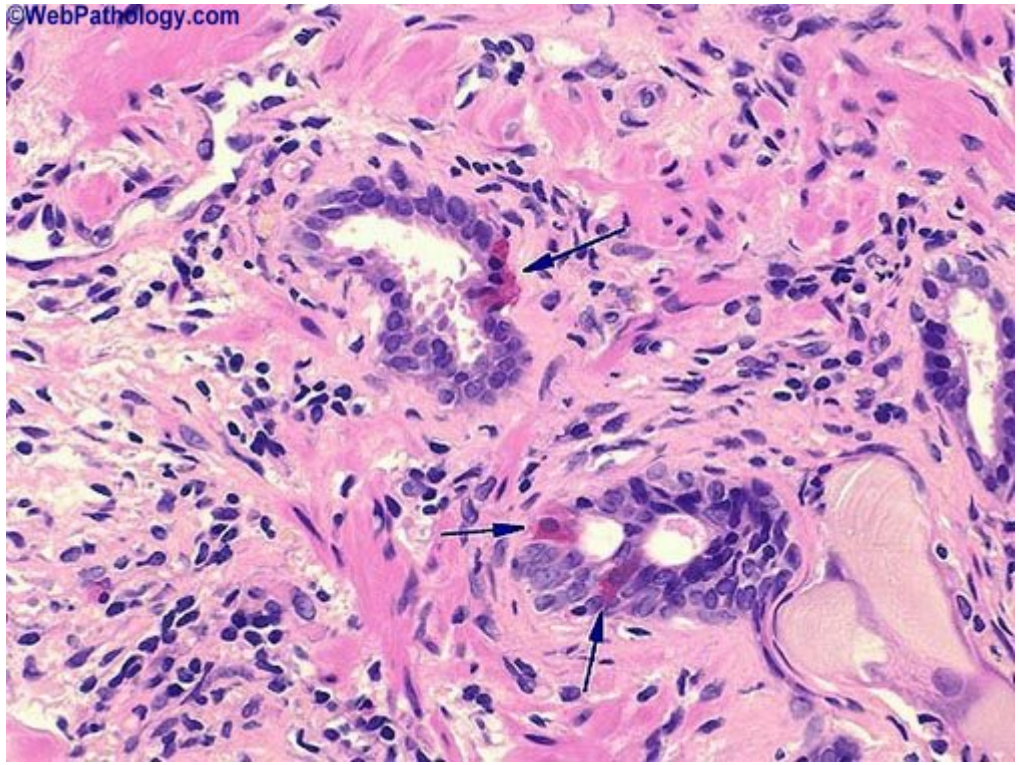
Histologie prostaty – intraepiteliální neoplasie



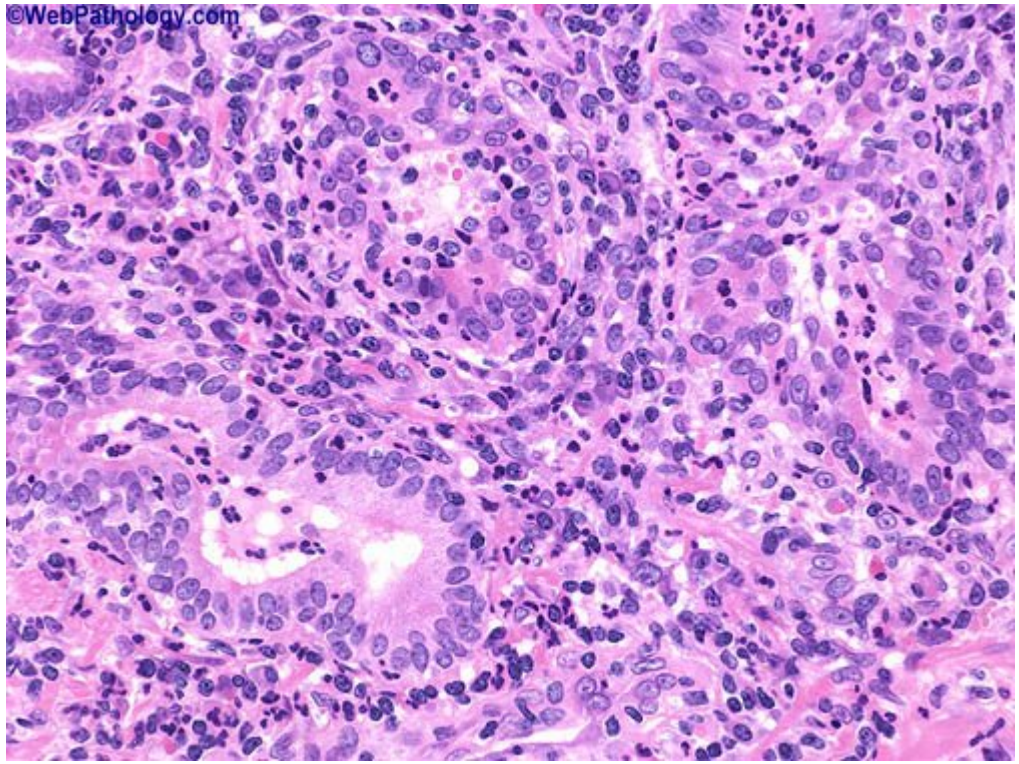
Histologie prostaty– atrofie



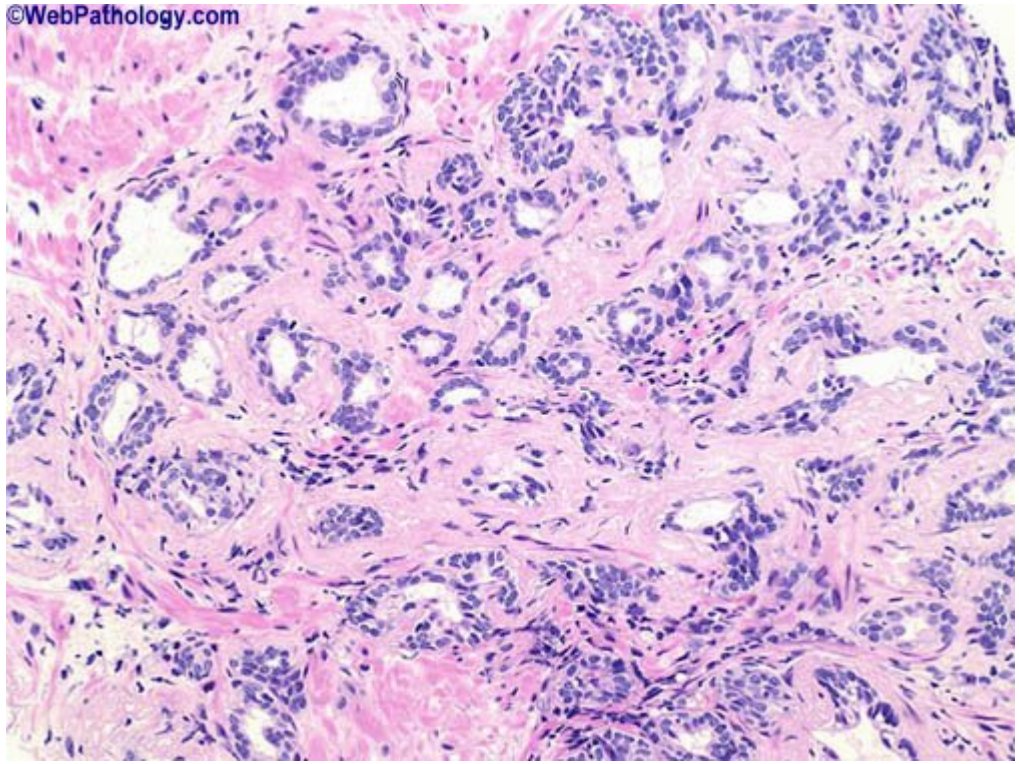
Histologie prostaty– atrofie/neuroendokrinní diferenciace



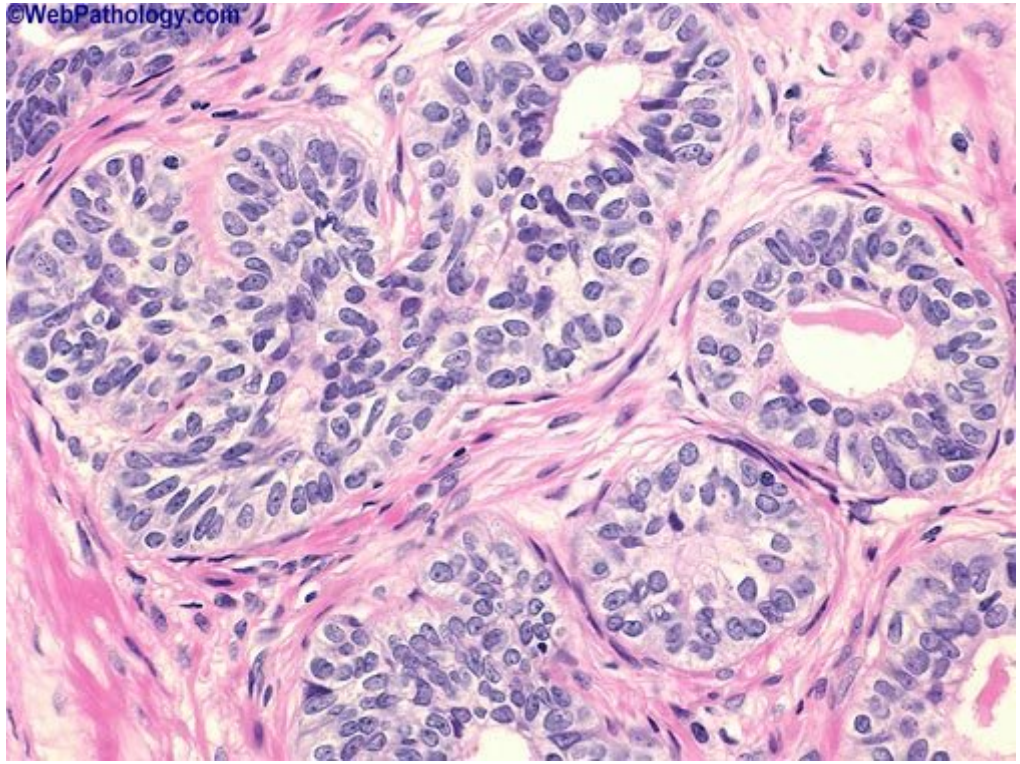
Histologie prostaty– normální/zánět



Histologie prostaty– hyperplazie (post-atrofická)

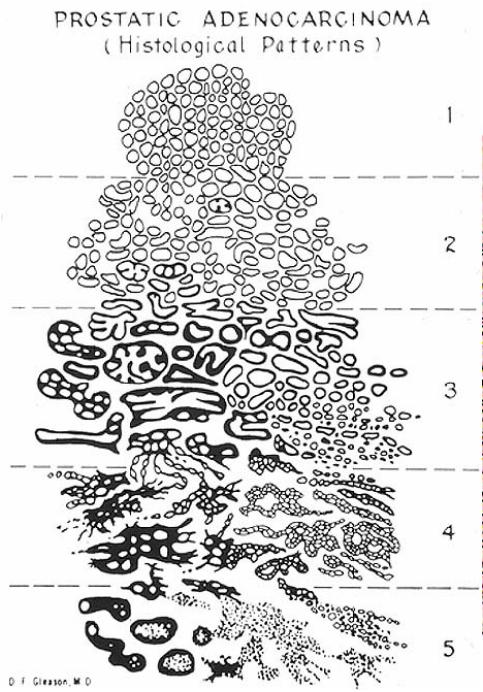


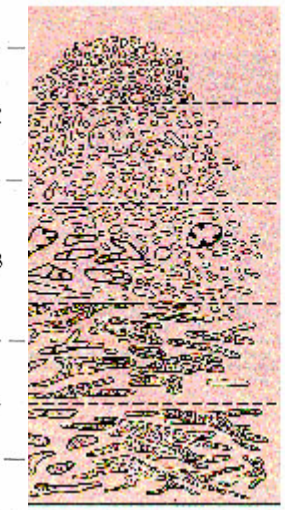
Histologie prostaty– hyperplazie



WebPathology.com

Gleason's Pattern





Gleason's Pattern

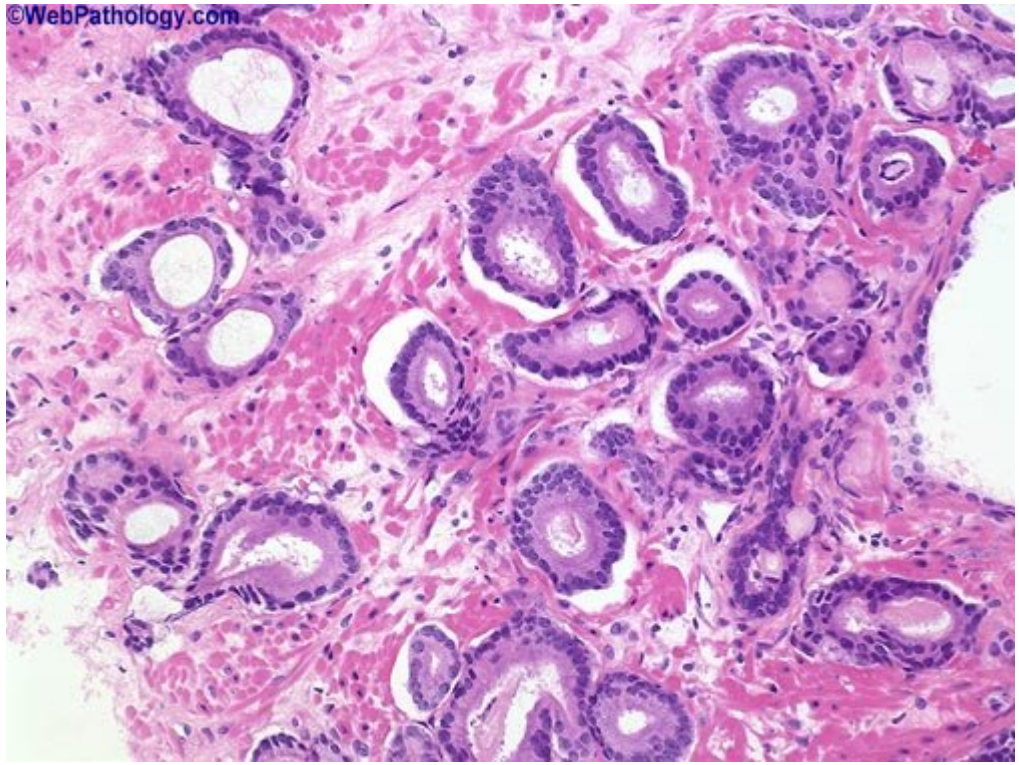
1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Well differentiated

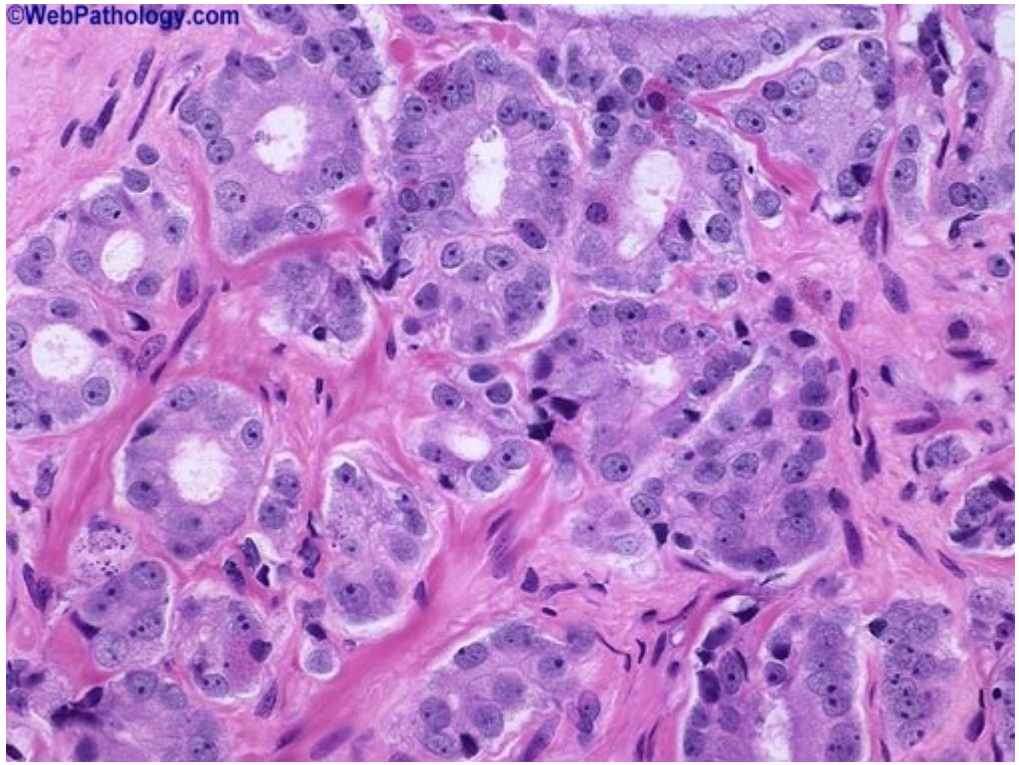
Moderately differentiated

Poorly diff./ Anaplastic

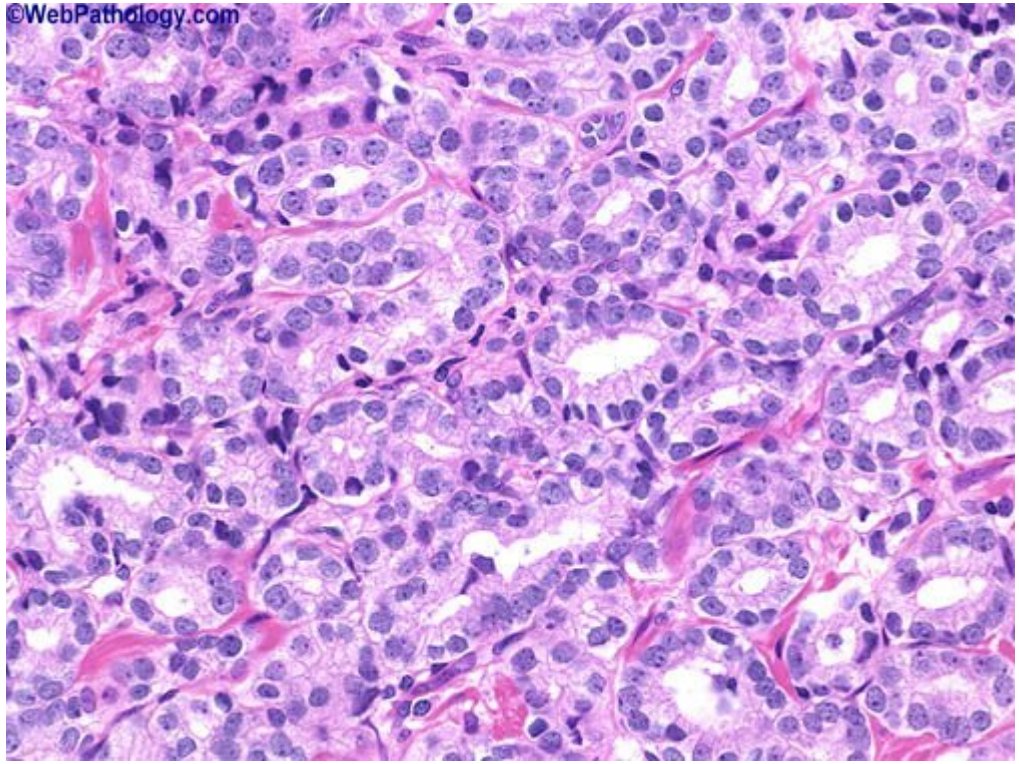
Histologie prostaty– adenokarcinom (Gleason Pattern 2)



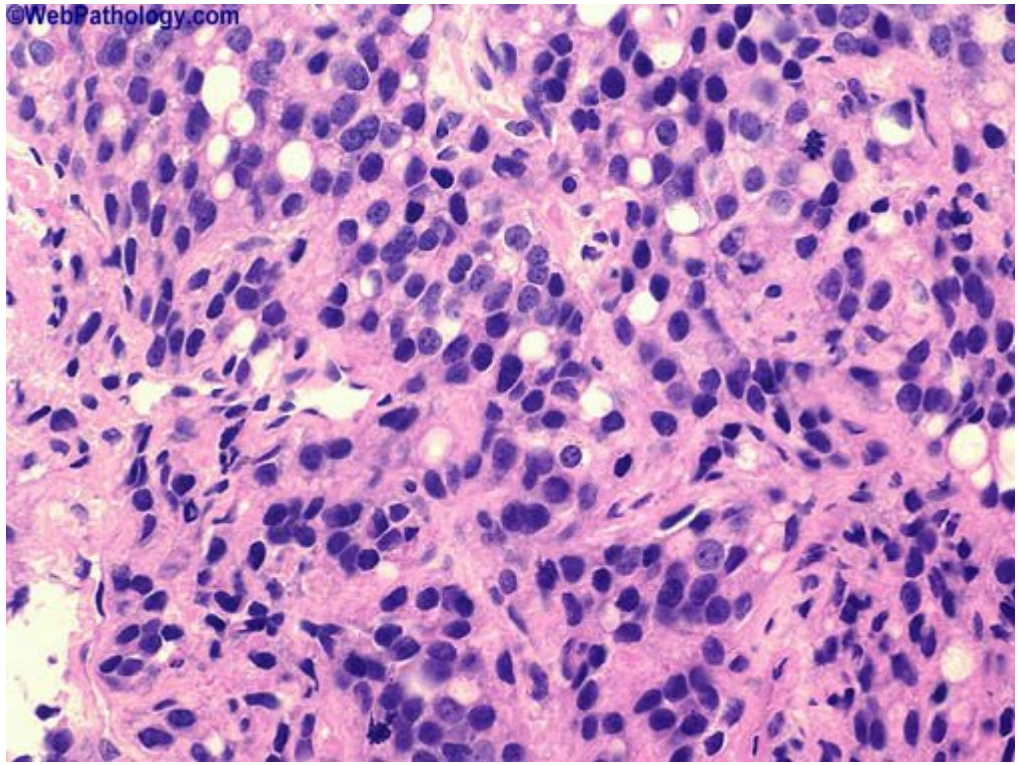
Histologie prostaty– adenokarcinom (Gleason Pattern 3)



Histologie prostaty– adenokarcinom (Gleason Pattern 3-4)



Histologie prostaty– adenokarcinom (Gleason Pattern 5)



Faktory ovlivňující riziko rakoviny prostaty

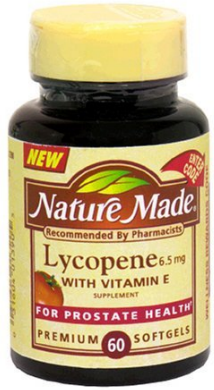
- etnický původ
- věk a rodinná historie
- dieta
- polymorfismus AR
- metabolismus vitaminu D
- životní styl (?)
- životní prostředí (?)

Složky diety zvyšující riziko rakoviny prostaty

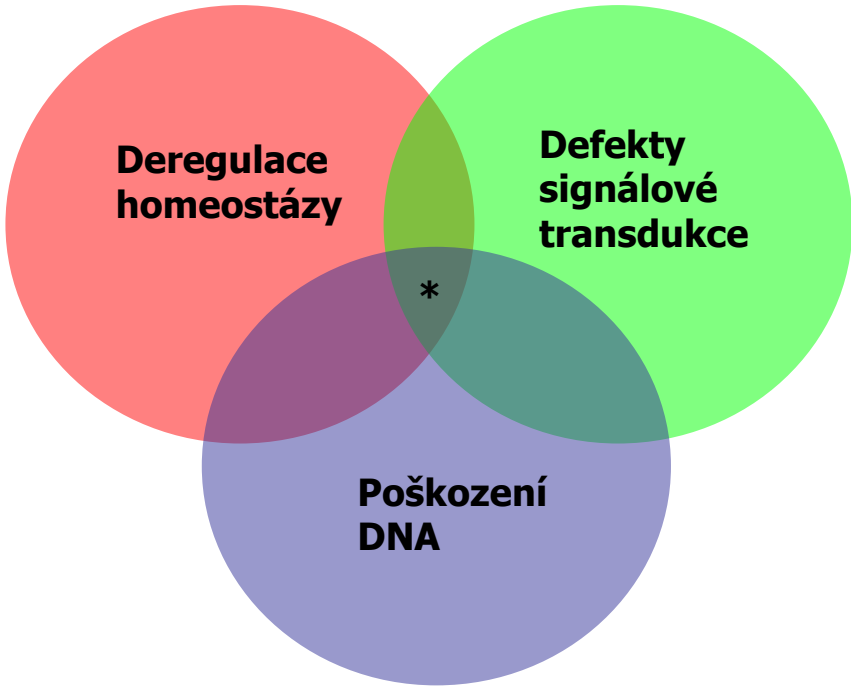
- tuky (celkový příjem)
- n-6 PUFAs (prozánětlivé metabolity)
- vápník (?) (zvýšený příiem snižuje metabolismus vitamínu D)

Chemopreventivní složky diety

- n-3 PUFAs (protizánětlivé metabolity)
- selen (indukuje enzymy-antioxidanty)
- phytoestrogeny (isoflavony, sójové proteiny)
- zelený čaj (polyfenoly)
- vitamin E (antioxidant)
- lycopene (antioxidant)



Mechanismus



*únik z pod kontroly reparačních mechanismů → Iniciace, Promoce, Progrese → rakovina

Molekulární patogeneze rakoviny prostaty

Geny jejichž somatické změny jsou spojené s rakovinou prostaty

- GSTP1 *(hypermetylace, snížená exprese)*

Glutathion S-transferasa

- NKX3.1 *(ztráta alely, snížená exprese)*

Potenciální „gatekeeper“ gen, supresor transkripce PSA

- PTEN *(ztráta alely, mutace, snížená funkce a exprese)*

Phosphatase with tensin homology, nádorový supresor

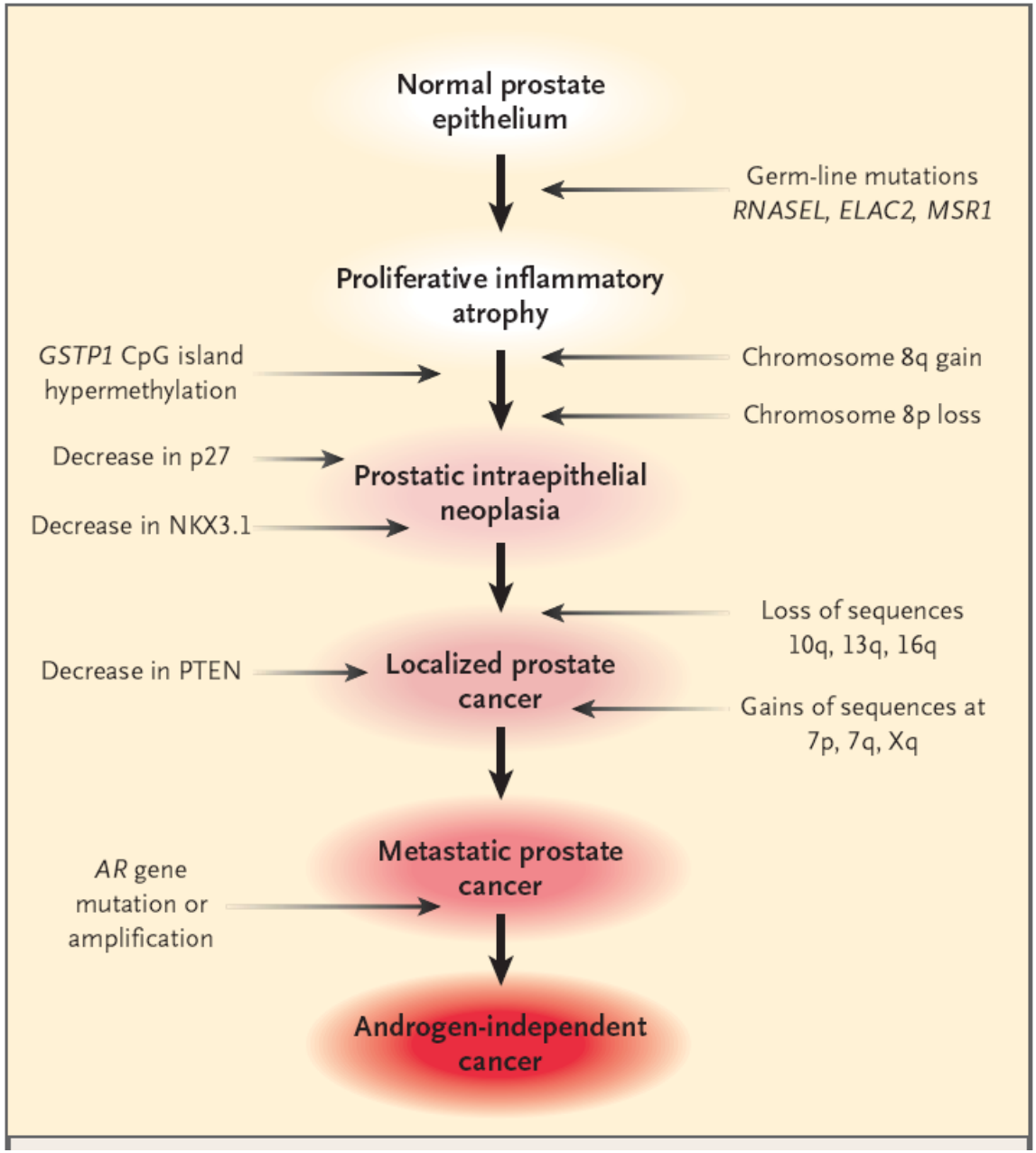
- p27 *(ztráta alely, snížená exprese)*

CDKN1B – cyclin-dependent kinase inhibitor

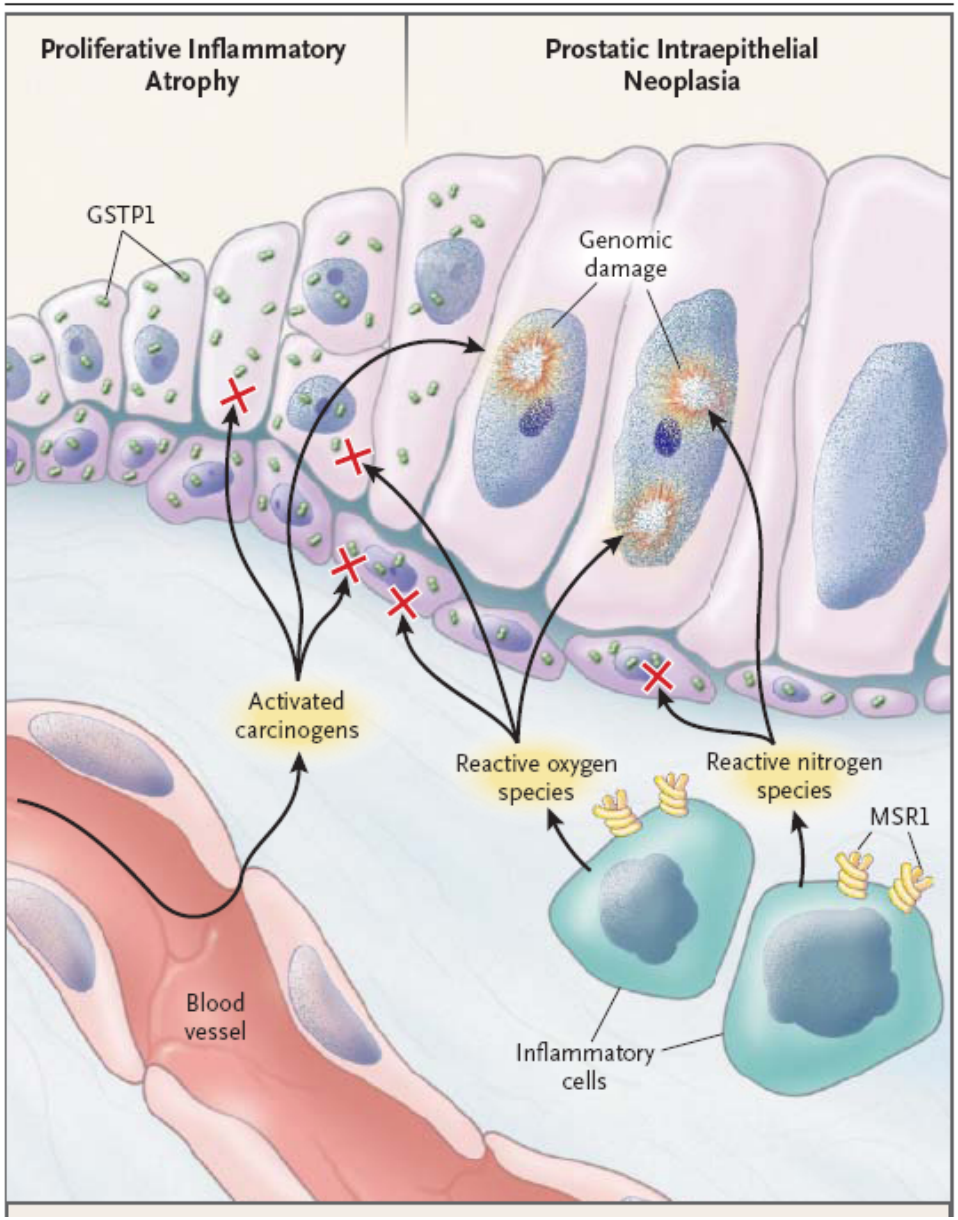
- androgenní receptor *(amplifikace, zvýšená exprese, změněná funkce)*

jaderný receptor, transkripční faktor

Molekulární patogeneze rakoviny prostaty

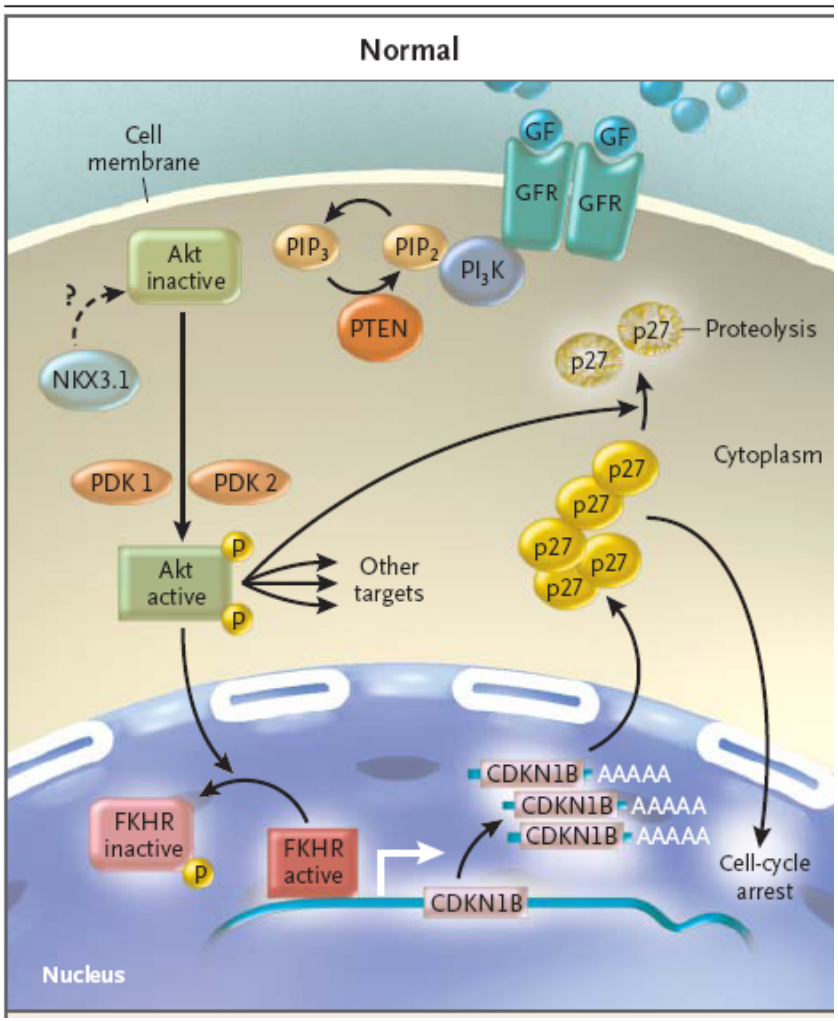


N Engl J Med 2003;349:366-81.

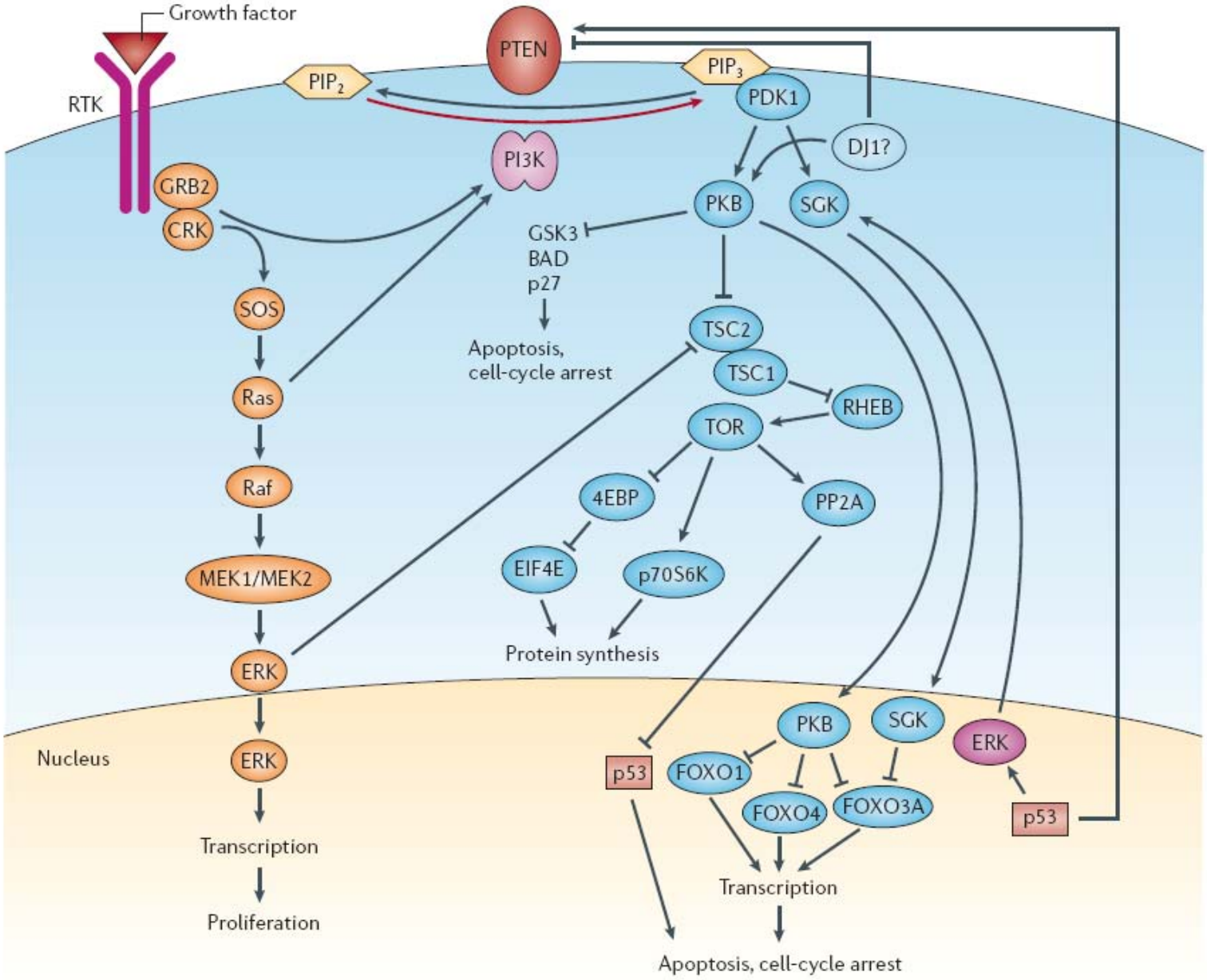


N Engl J Med 2003;349:366-81.

Molekulární změny během patogeneze rakoviny prostaty



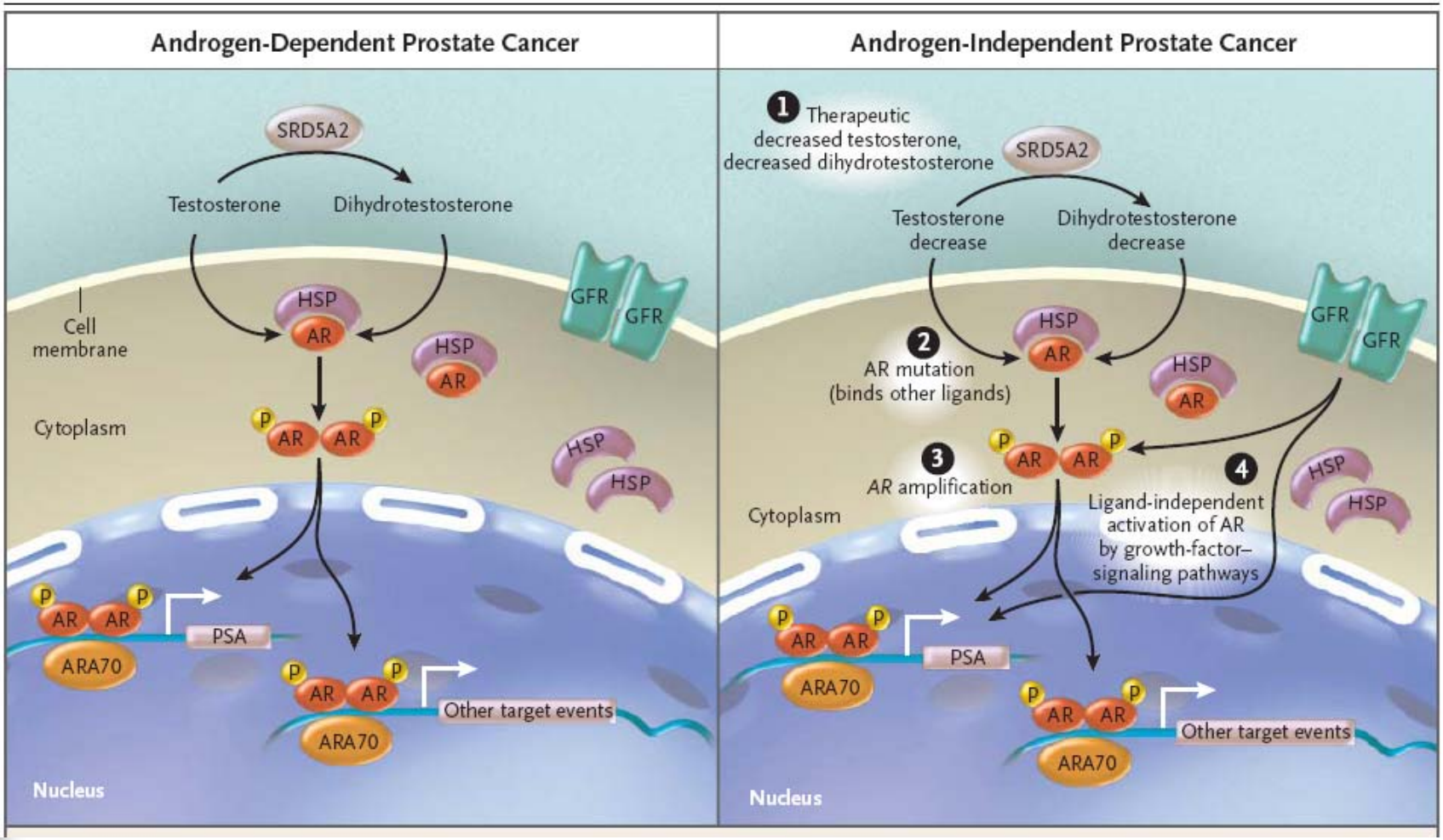
N Engl J Med 2003;349:366-81.



Cully, M. *et al*., 2006

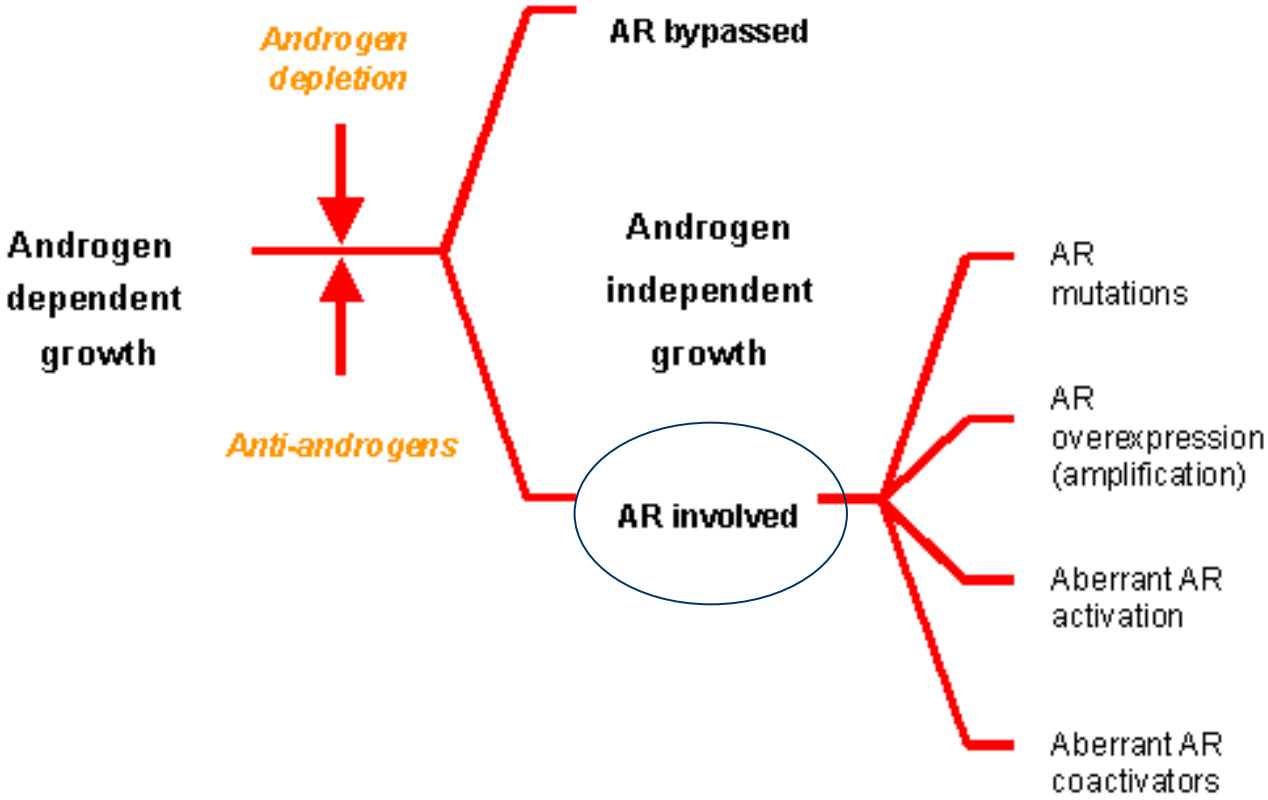
Androgenní receptor

Progrese androgen nezávislého adenokarcinomu prostaty



N Engl J Med 2003;349:366-81.

PROGRESSIVE GROWTH OF PROSTATE CANCER



www2.eur.nl/fgg/pathol/research/trapman/androgen_receptor.htm

ANDROGEN RECEPTOR GENE MUTATIONS DATABASE

Curator: Dr. Bruce Gottlieb
Lady Davis Institute for Medical Research
3755 Cote Ste Catherine Rd. Montreal, Quebec H3T 1E2, Canada

Telephone:514-340-8260
FAX: 514-340-7502
E-Mail: bruce.gottlieb@mcgill.ca
Internet: http:// www.mcgill.ca/androgendb/

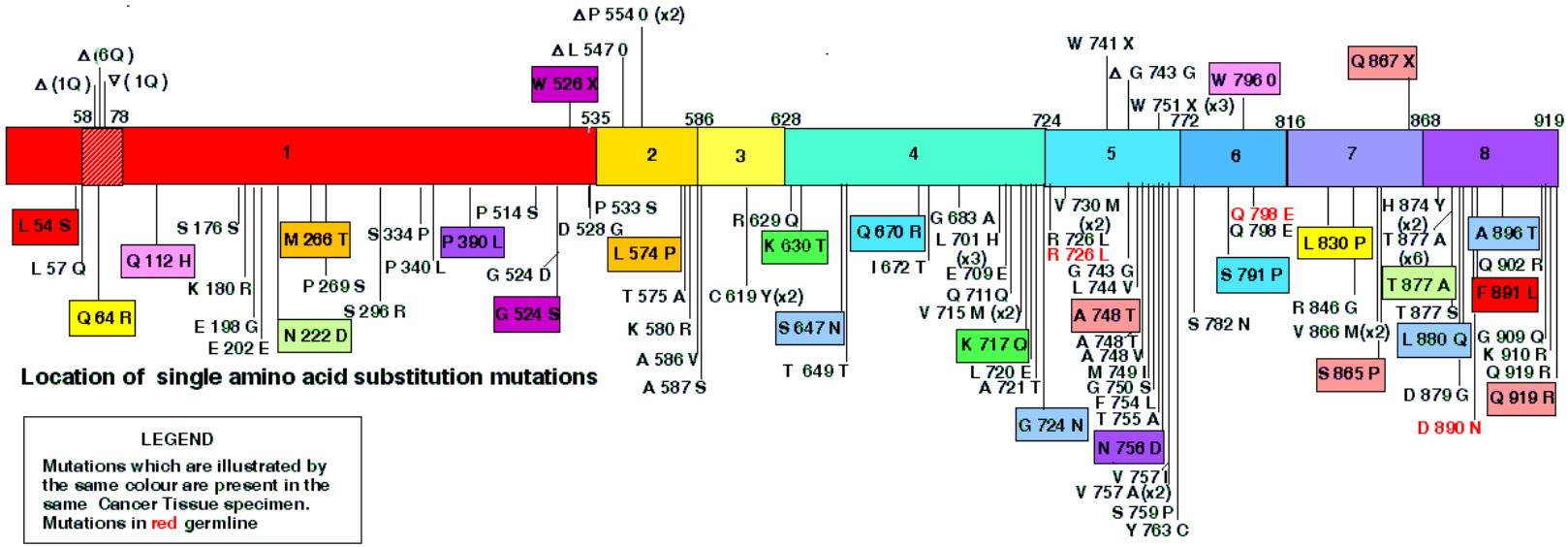
Date of this version: 06-12-2005

Somatic mutation - orange.
Mutations showing variable expressivity - green.
Normal phenotypes - blue.

Accession # / Phenotype	Mutation type	Pathogenicity proven Exon / Domain	CpG hot spot	Position Amino acid / Base	Change Amino acid / Base	Exon 1 tracts Poly Gln #	Poly Gly #	Androgen Binding Thermolabile Bmax	Kd	k	Comments	Sex of rearing	External Genitalia	Family history	Reference
0001 PAIS	Substitut	1 Nterm	*	002 4	Glu⇒Lys GAA⇒AAA					high	20-50 % reduction in mutant protein	Male	Ambiguous	pos	Choong et al; J Clin Invest. 98: 1423-1431, 1996
0624 CAIS	Deletion	1 Nterm		039 117	Pro⇒0 CCC⇒						In frame deletion of 3nt. removing proline				Jung et al; Human Genetics 222, 2004
0002 CAIS	Insertion	1 Nterm		051	Gly⇒0 GGAC⇒			zero			1 nt del causing frameshift & stop in Codon 180 1 aff sib	Female	Normal	pos	Boehmer et al; J Clin Endocrinol & Metab 86: 4151-4160, 2001
0003 Prostate cancer	Substitut	1 Nterm		054 523	Leu⇒Ser TTG⇒TCG						Also Phe891 Leu (TTT to CTT) mut. Somatic mutation	Male	Normal		Tilley et al; Clinical Cancer Res. 2: 277-285, 1996
0004 Laryngeal cancer	Deletion	1 Nterm		057 	⇒ ⇒						30 nt. deletion Somatic mutation	Male	Normal		Urushibara et al; 10th. Int. Cong. Endocrinol Abstr. P3-706, 1996
0005 Prostate cancer	Substitut	1 Nterm		057 532	Leu⇒Gln CTG⇒CAG						Somatic mutation	Male	Normal		Tilley et al; Clinical Cancer Res. 2: 277-285, 1996
0612 MAIS ?	Substitut	1 Nterm		058 535	Gln⇒Leu CAG⇒CTG						2 out of 62 patients with male infertility	Male	Normal		Lund et al; Fertility and Sterility 79(suppl 3): 1647-148, 2003
0411 Mental Retard.	Deletion	1 Nterm		058 	⇒ ⇒	8		normal	normal		3 affected siblings - normal CAG = 23	Male	Normal	pos	Kooy et al; Am J Med Genet. 85: 389-393, 1999
0006 Kennedy Syndrome	Insertion	1 Nterm		058-078 	⇒ ⇒	> 40					Expansion of polyglutamine repeat	Male	Normal		LaSpada et al; Nature 352:77, 1991
0007 Prostate cancer	Deletion	1 Nterm		058-078 	⇒ ⇒	18					Contraction of poly Gln repeats (24 to 18) Somatic mutation	Male	Normal		Schoenberg et al; Bioch. & Biophys Res Comm 198: 74-80 1994
0324 Prostate cancer	Deletion	1 Nterm		058-078 	⇒ ⇒	22					Deletion of 1polyGln repeat (23-22) Somatic mutation	Male	Normal		Watanabe et al; Jpn J Clin Oncol 27: 389-393, 1997
0325 Prostate cancer	Insertion	1 Nterm		058-078 	⇒ ⇒	22					Insertion of 1polyGln repeat (21-22) in 2 diff patients.Som mut	Male	Normal		Watanabe et al; Jpn J Clin Oncol 27: 389-393, 1997
0495 Prostate cancer	Deletion	1 Nterm		058-078 	⇒ ⇒	18					Contraction of poly Gln repeats (20 to 18) Somatic mutation	Male	Normal		Wallin et al; J Pathology 189: 559-653, 1999
0692 CAIS	Substitut	1 Nterm		059	Gln⇒Stop CAG⇒TAG			zero				Female	Normal		Holterhus et al; J Mol Med 2005
0008 CAIS	Substitut	1 Nterm	*	060 540	Gln⇒Stop CAG⇒TAG			low	normal	high	Normal upregulation.	Female	Normal	neg	Zoppi et al; J Clin Inv 19: 1105, 1993
0671 CAIS	Substitut	1 Nterm	*	060 540	Gln⇒Stop CAG⇒TAG						bilateral inguinal hernia.	Female	Normal		Bouvattier et al: J Clin Endorinol & Metab 87: 29-32, 2002
0409 CAIS	Insertion or deletion	1 Nterm		060 542	Gln⇒Gln CAG⇒CAAG						either 1nt. insert or 2nt. del. -frameshift & stop in codon 80	Female	Normal	pos	Zhu et al; J Clin Endocrinol & Metab 84: 1590-1594, 1999
0009 Prostate cancer	Substitut	1 Nterm		064 550	Gln⇒Arg CAG⇒CGG						Also Leu830Pro (CTT to CCT) mut. Somatic mutation	Male	Normal		Tilley et al; Clinical Cancer Res. 2: 277-285, 1996
0416 CAIS	Insertion	1 Nterm		085 617	Gln⇒Gln CAG⇒CAAG	25		zero			1nt. insertion causing frameshift and stop in codon 91	Female	Normal		Gottlieb et al; Hum Mutat. 14: 527-539, 1999
0672 CAIS	Substitut	1 Nterm		088 624	Gln⇒Stop CAG⇒TAG						bilateral inguinal hernia.	Female	Normal		Bouvattier et al: J Clin Endorinol & Metab 87: 29-32, 2002
0529 CWR22R Prost. CA Cell line	Substitut	1 Nterm		91 635	Glu⇒Asp ⇒	27	19				AR indep.+Leu57Gln & His 874Tyr mut. + Duplication of exon 3	Male	Normal		Chelraki et al. The Prostate 47: 66-75, 2001
0417 CAIS	Deletion	1 Nterm		102 668	Pro⇒Pro CCAC⇒CCG	12	25	zero			1 nt. deletion causing frameshift and stop in codon 172	Female	Normal	neg	Gottlieb et al; Hum Mutat. 14: 527-539, 1999

ANDROGEN RECEPTOR GENE MUTATIONS IN PROSTATE CANCER 30-7-03

Location of mutations introducing premature termination of codons or deletion of 1-6 bp

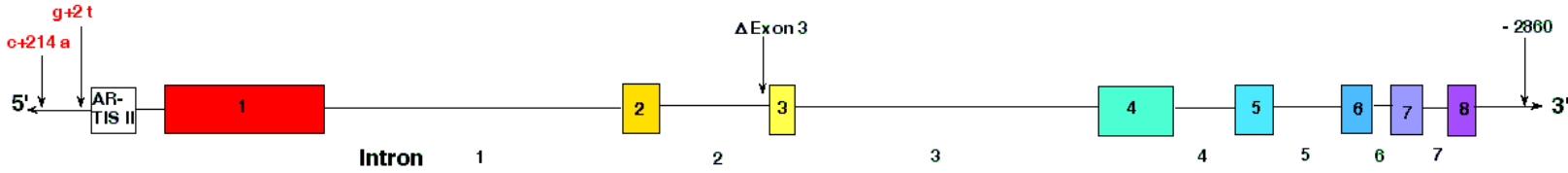


Location of single amino acid substitution mutations

LEGEND

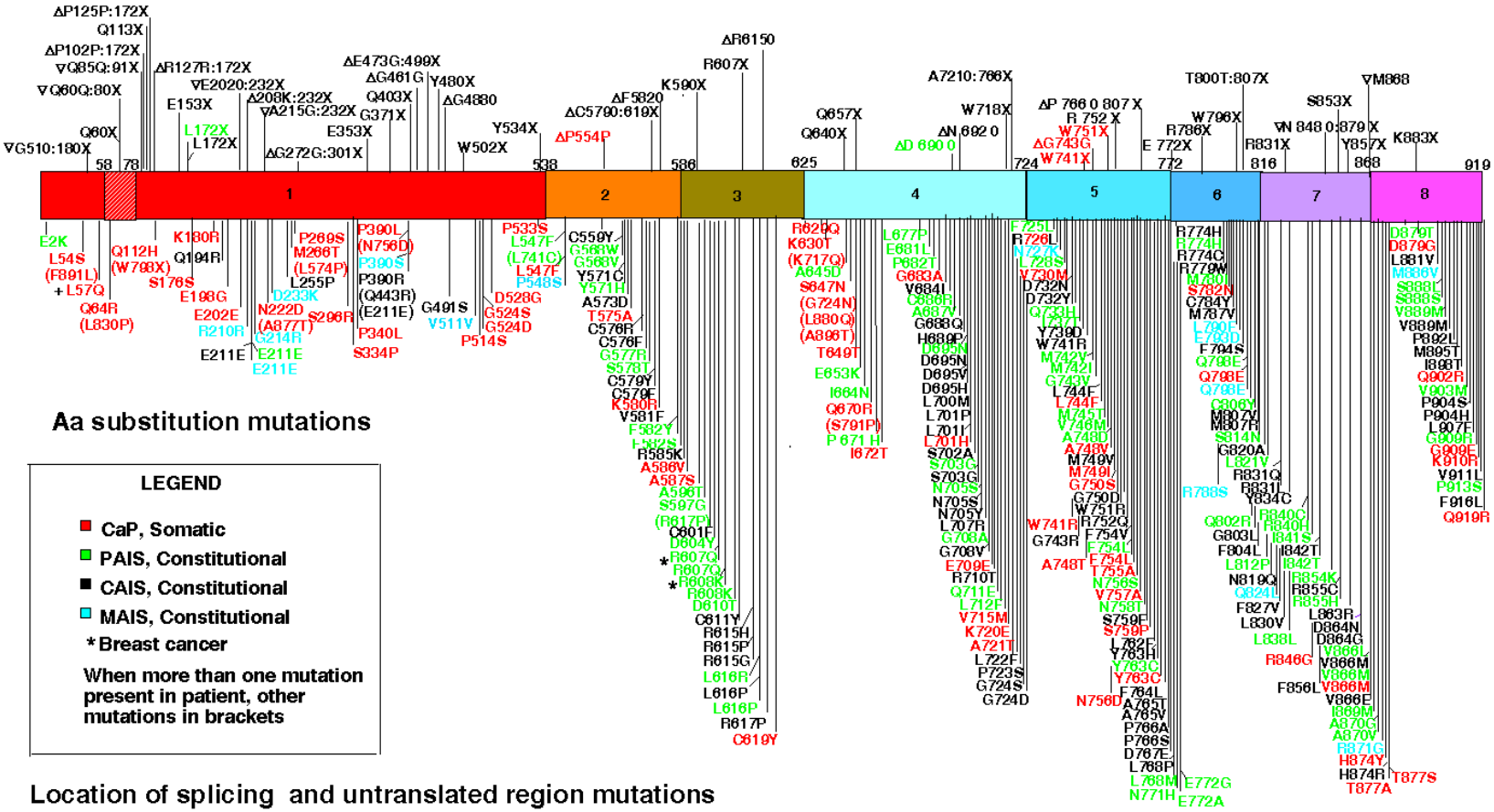
Mutations which are illustrated by the same colour are present in the same Cancer Tissue specimen.
Mutations in red germline

Location of splicing and untranslated region mutations



ANDROGEN RECEPTOR GENE MUTATIONS, 30-7-03

Premature termination mutations or 1-6 bp Δ or ∇



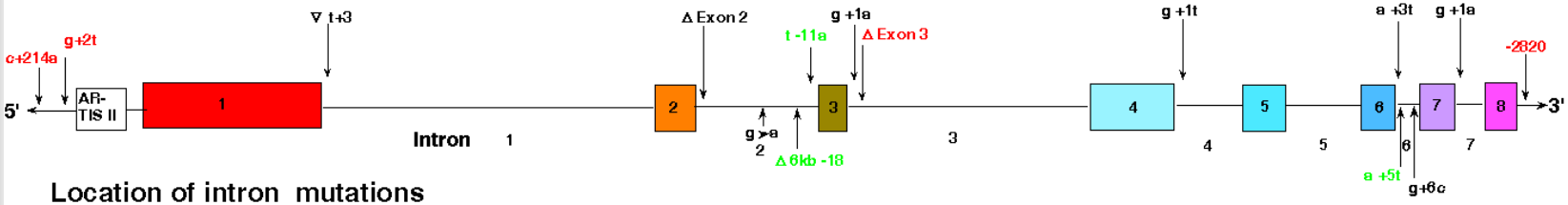
Aa substitution mutations

LEGEND

- CaP, Somatic
- PAIS, Constitutional
- CAIS, Constitutional
- MAIS, Constitutional
- *Breast cancer

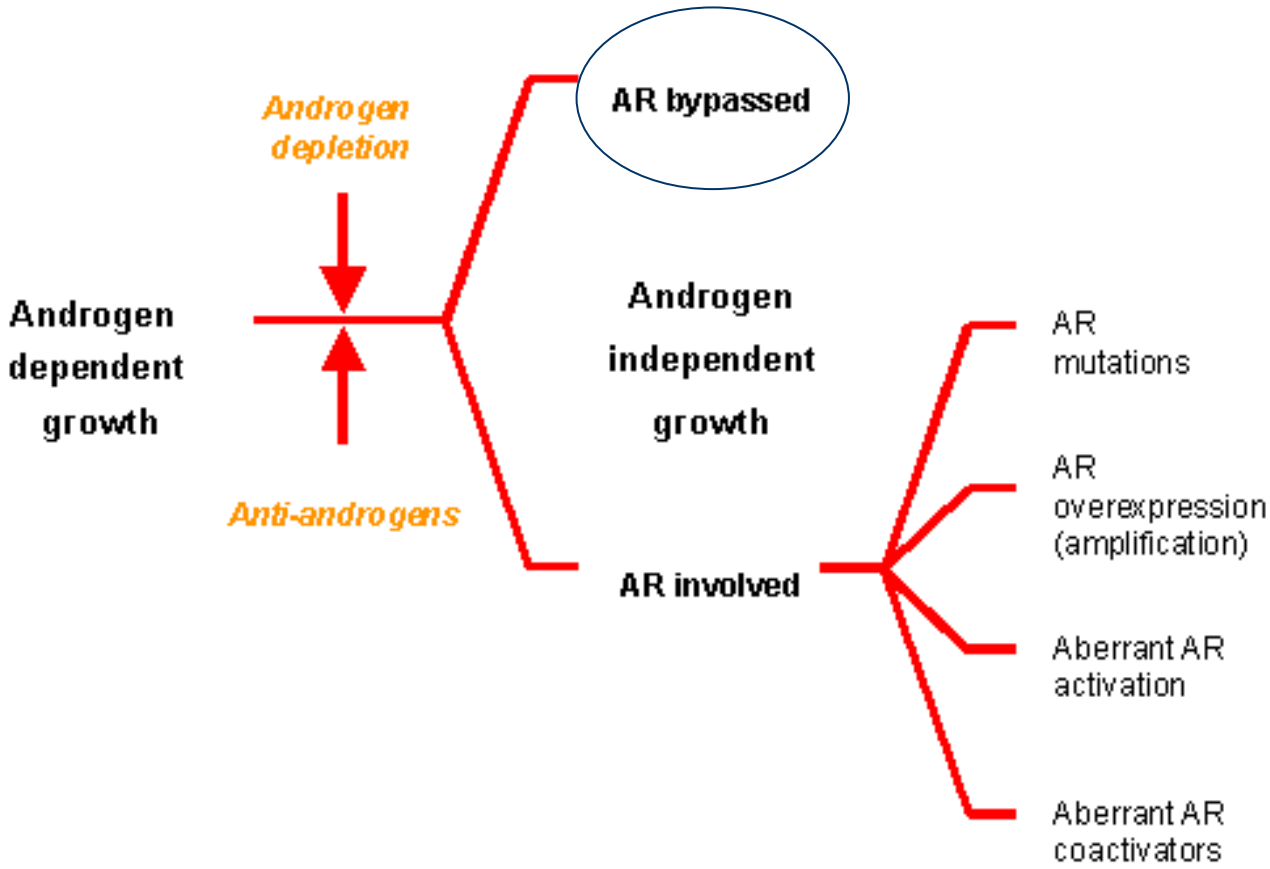
When more than one mutation present in patient, other mutations in brackets

Location of splicing and untranslated region mutations



Location of intron mutations

PROGRESSIVE GROWTH OF PROSTATE CANCER



www2.eur.nl/fgg/pathol/research/trapman/androgen_receptor.htm

Neuroendokrinní diferenciace

The Prostatic Neuroendocrine Cell

- Prostatic neuroendocrine cells are intraglandular and intraductal hybrid epithelial/ neural/ endocrine cells which express/ secrete serotonin and numerous peptides/ neuropeptides.

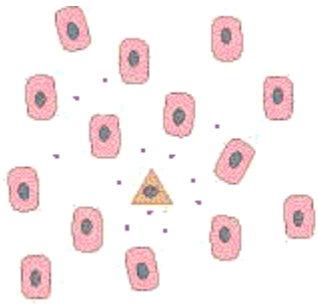
Prostate Neuroendocrine Cell Products

- Chromogranins
- **Serotonin**
- Gastrin releasing peptide **(bombesin**)
- Calcitonin gene family
- Somatostatin
- Parathyroid hormone-related protein
- Neuropeptide Y
- **Vascular endothelial growth factor (VEGF)**
- Cholecystokinin
- Proadrenomedullin N-terminal peptide
- TSH-like peptide
- Histamine

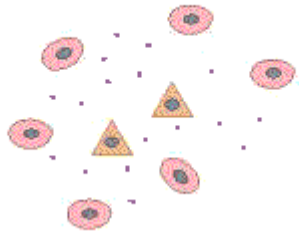
Prostate Neuroendocrine Receptors (normal prostate and/or cancer)

* Gastrin releasing peptide (GRPR)
* Serotonin (5HT1a)
* Somatostatin (SST 1-5)
* Calcitonin (hCTR-2)
* Cholecystokinin (CCK-a)
* Neuropeptide Y (NPY1 and NPY2)

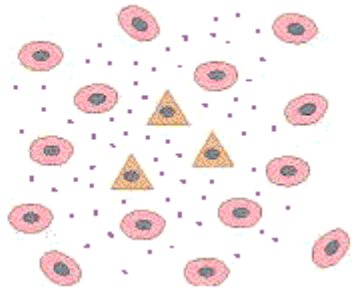
Neuroendocrine cells in cancer



Androgen Dependent Cancer

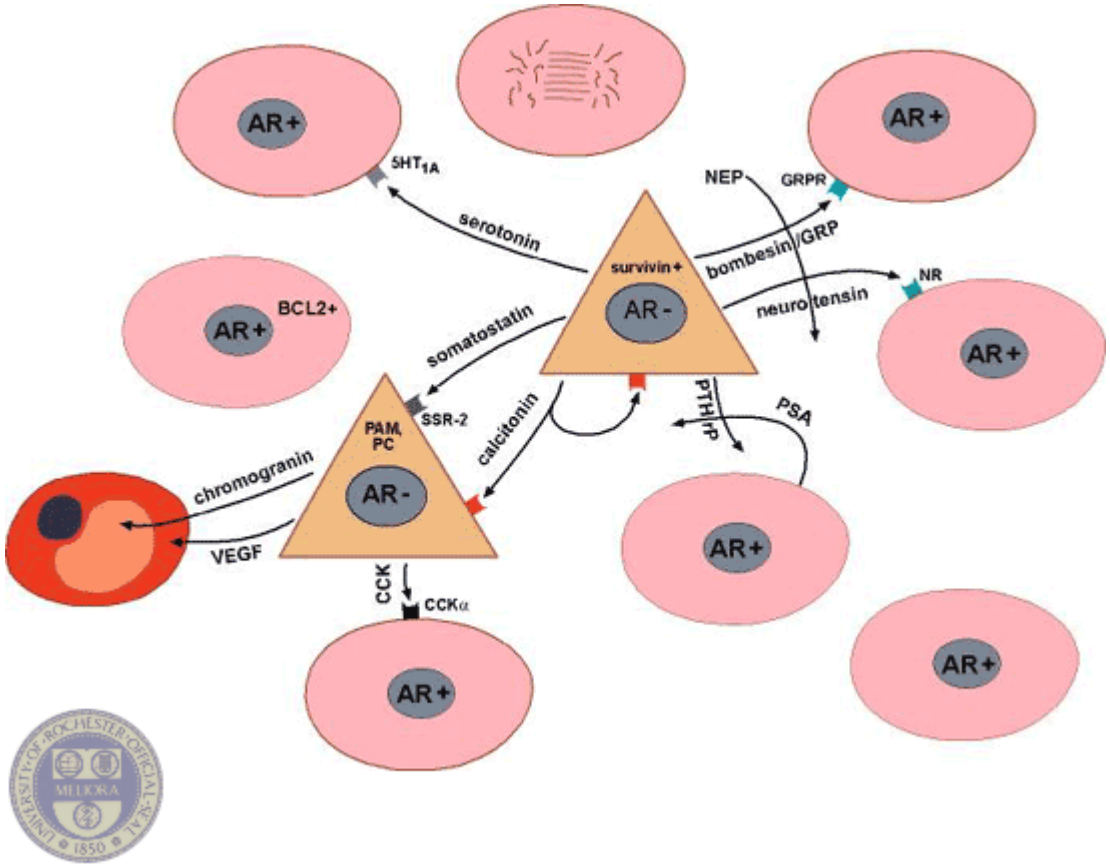


Androgen Deprived Cancer

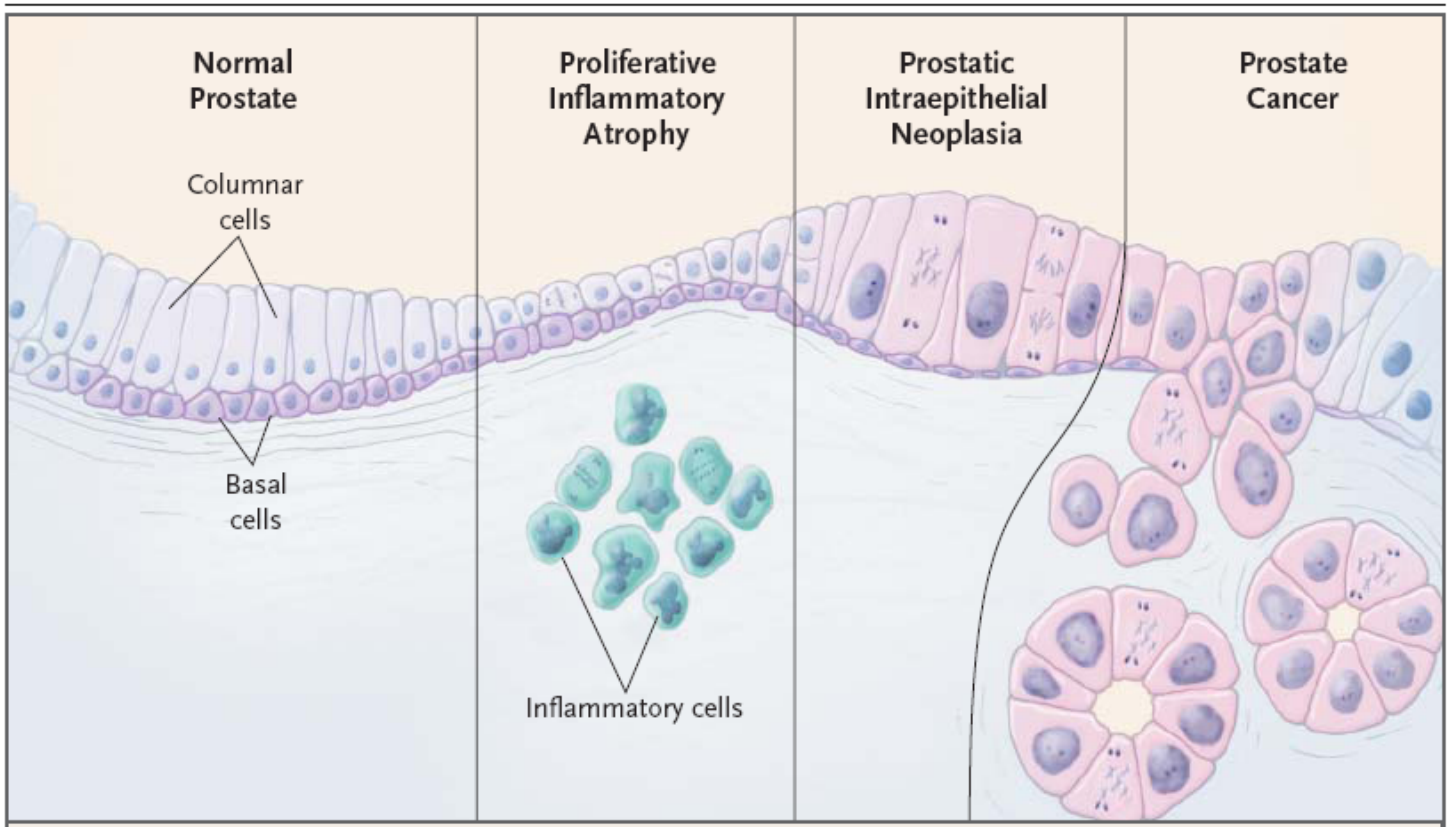


Androgen Independent Cancer

Neuroendocrine cells in prostate



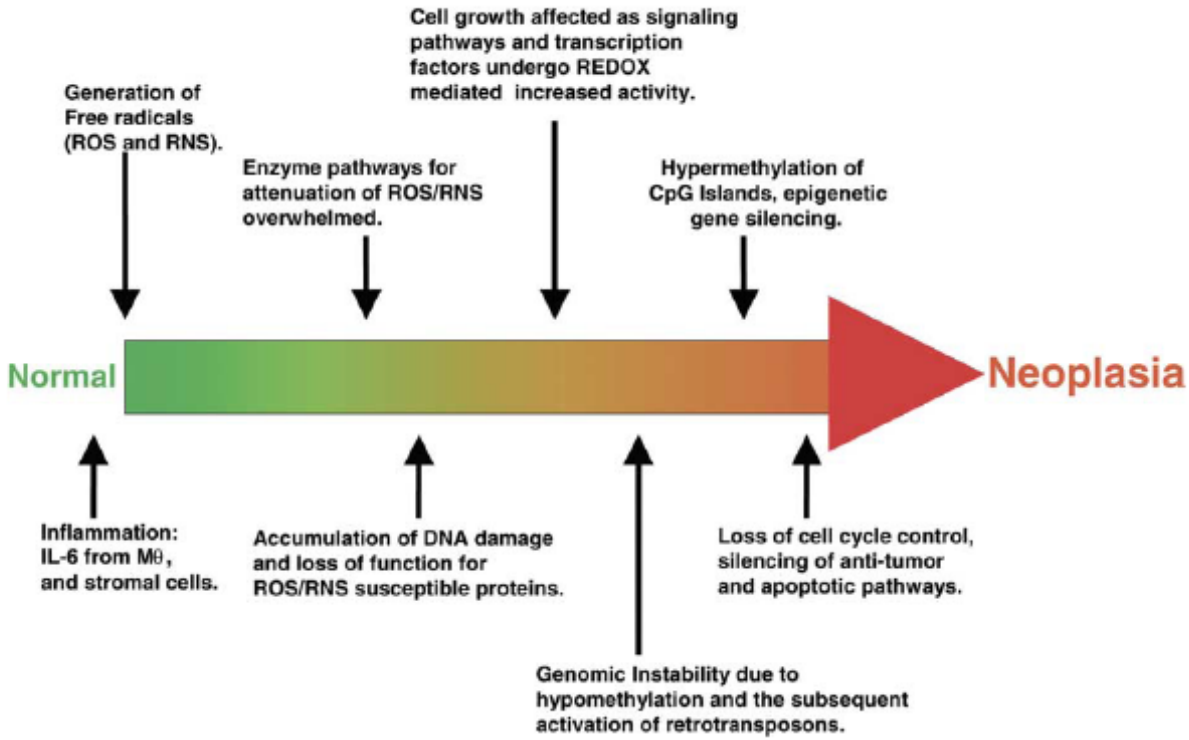
Zánět jako podpůrný faktor pro vznik nádoru prostaty



N Engl J Med 2003;349:366-81.

IL-6

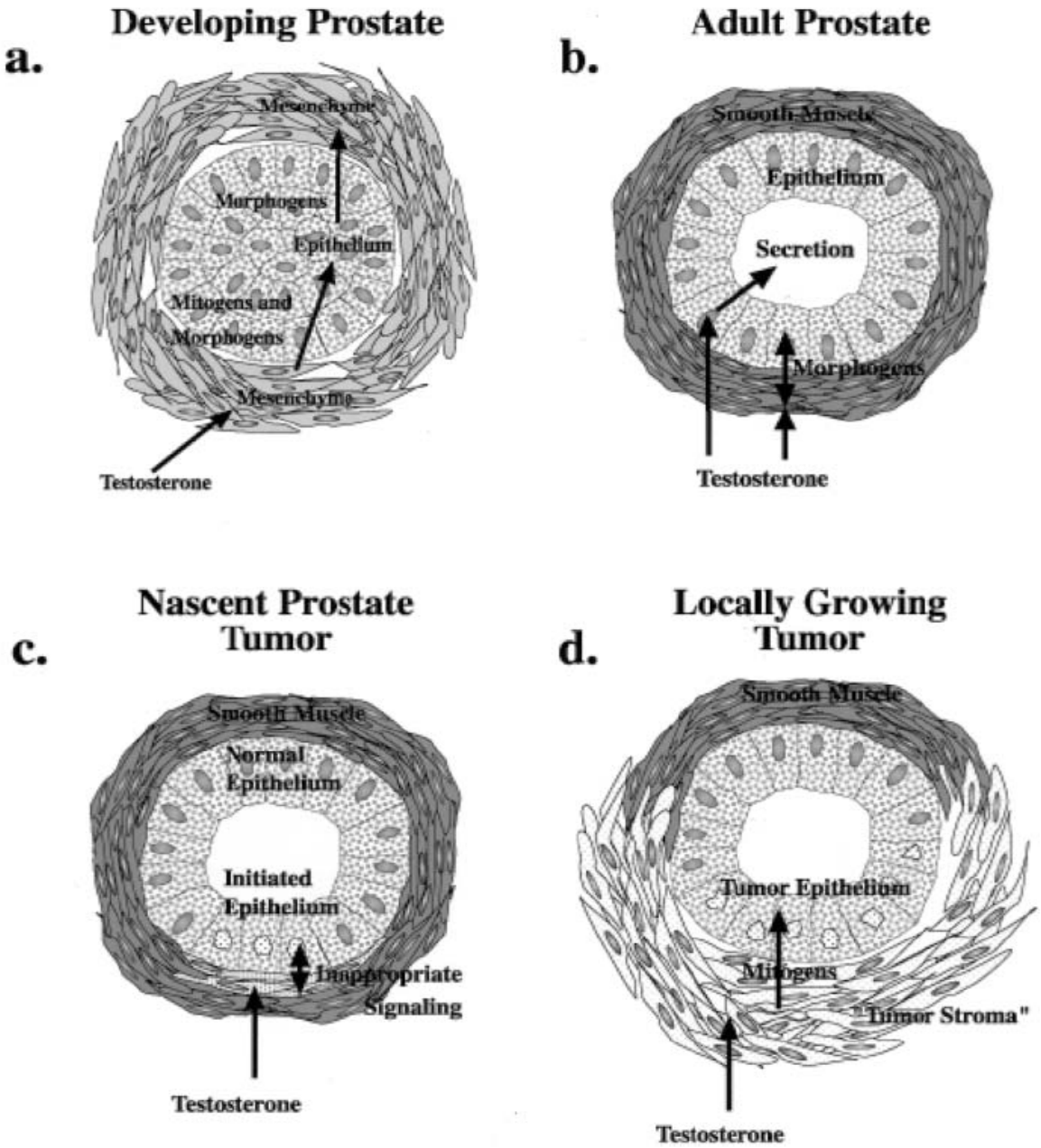
- Pleiotropic cytokine
- Pro-inflammatory



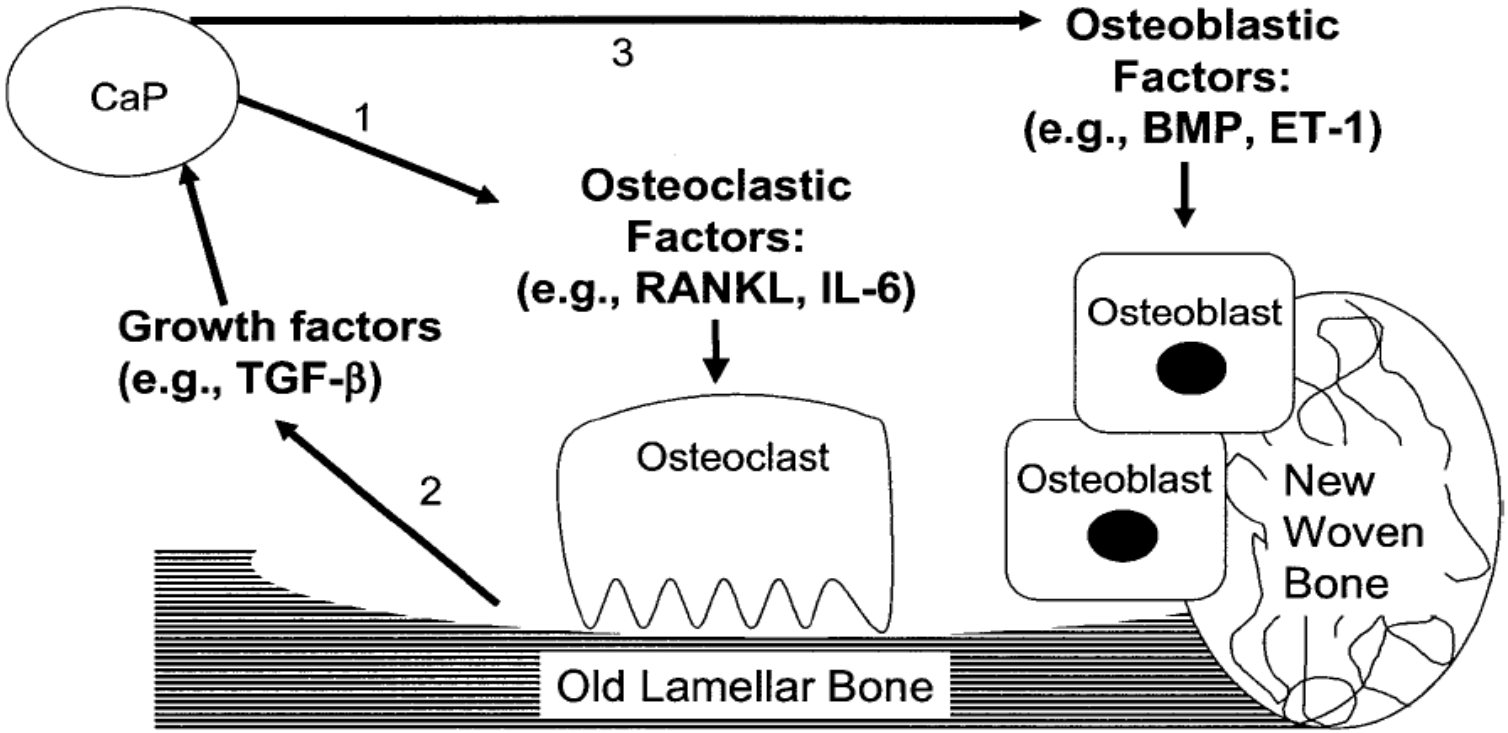
Rakovina není onemocnění jednoho buněčného typu !!!

Vzájemné mezibuněčné interakce a ovlivňování „mikroprostředí“ nádoru jsou klíčové pro rozvoj rakoviny.

Interakce mezi epitelem a stroma prostaty



Cunha, G.R. *et al.*, 2002



Keller E.T. *et al.*, 2004

Výzkum nádorového onemocnění prostaty a experimentální modely

in vitro

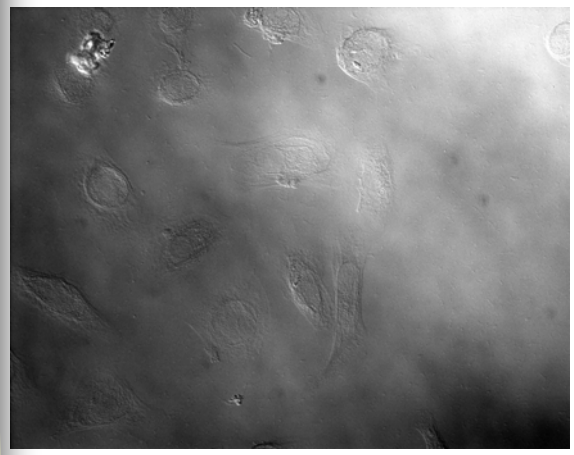
- *primární linie epitelu, stromatu*
- *nádorové linie ze sekundárních nádorů*

in vivo

- *transgenní myší kmeny (TRAMP)*
- *myší xenografy*
- *psy*

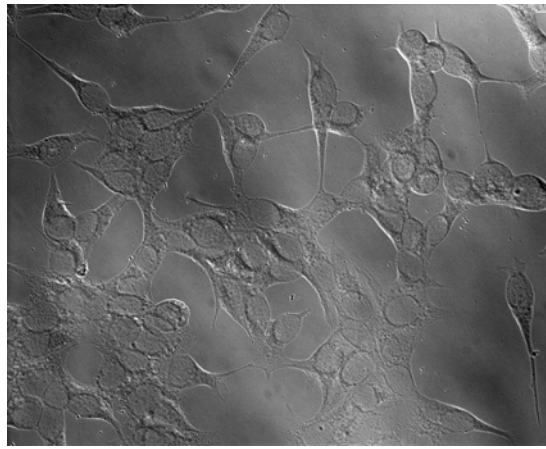
PrEC

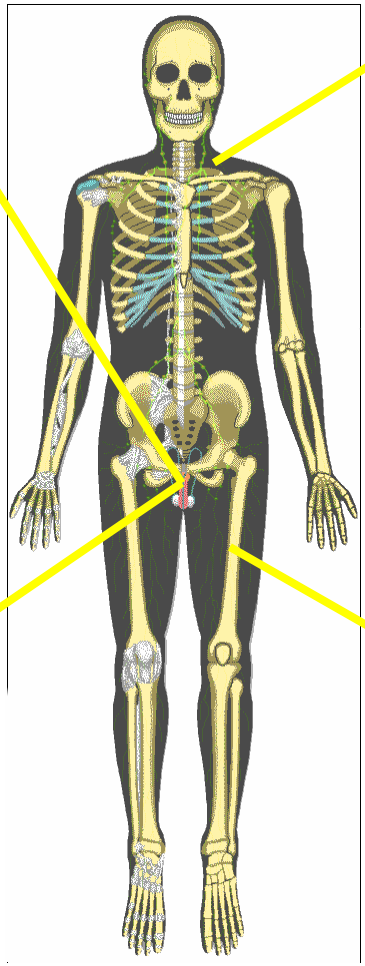
normal prostate epithelial cells



LNCaP

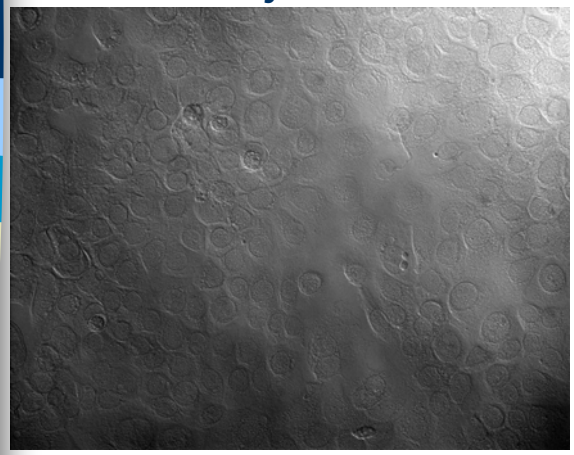
Supraclavicular lymph node prostate carcinoma





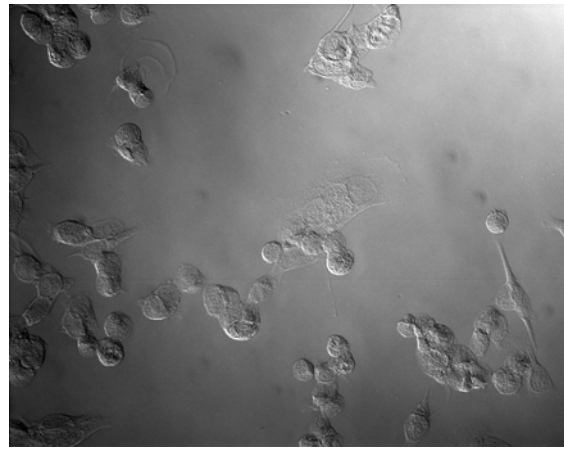
Pz-HPV-7

epithelial cells from peripheral zone of prostate transformed by HPV-18



PC3

Bone metastasis of a grade IV prostatic adenocarcinoma



Výzkum nádorového onemocnění prostaty a experimentální modely

Otázky na které musíme najít odpověď:

- *Jaká je souvislost mezi benigní hyperplazií a rozvojem adenokarcinomu?*
- *Je rakovina prostaty “stem cell cancer”?*
- *Jaká je skutečná úloha karcinogenů, androgenů a estrogenů?*
- *Jak je možné ovlivnit přechod k androgen nezávislému adenokarcinomu?*
- *Jaká je účinná chemoprevence?*
- *Jak účinně léčit pokročilá stádia onemocnění?*
- *….*