Nádory prostaty a prsu

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Reviews

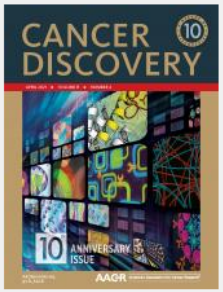
Metastasis-Initiating Cells and Ecosystems

Joan Massagué and Karuna Ganesh

DOI: 10.1158/2159-8290.CD-21-0010 Published April 2021 Check for updates

Abstract

Metastasis is initiated and sustained through therapy by cancer cells with stem-like and immune-evasive properties, termed metastasis-initiating cells (MIC). Recent progress suggests that MICs result from the adoption of a normal regenerative progenitor phenotype by malignant cells, a phenotype with intrinsic programs to survive the stresses of the metastatic process, undergo epithelial–mesenchymal transitions, enter slow-cycling states for dormancy, evade immune surveillance, establish supportive interactions with organ-specific niches, and co-opt systemic factors for growth and recurrence after therapy. Mechanistic understanding of the molecular mediators of MIC phenotypes and host tissue ecosystems could yield cancer therapeutics to improve patient outcomes.



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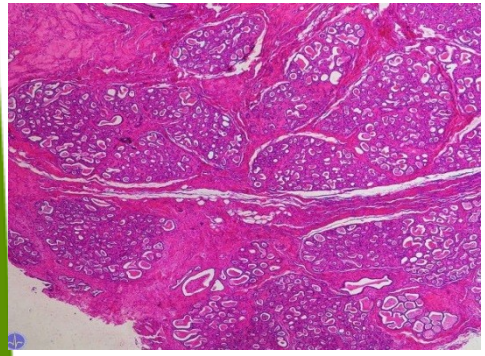
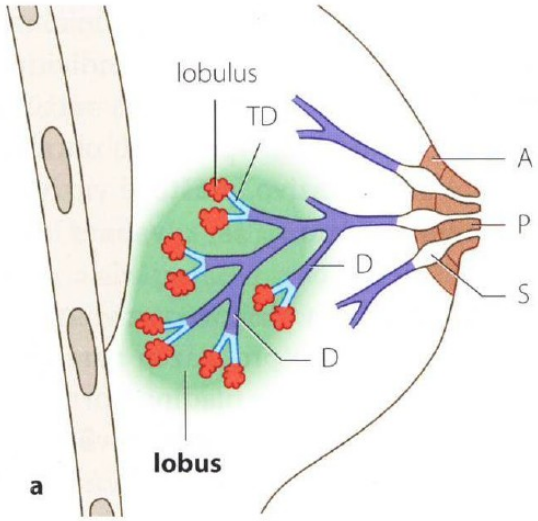
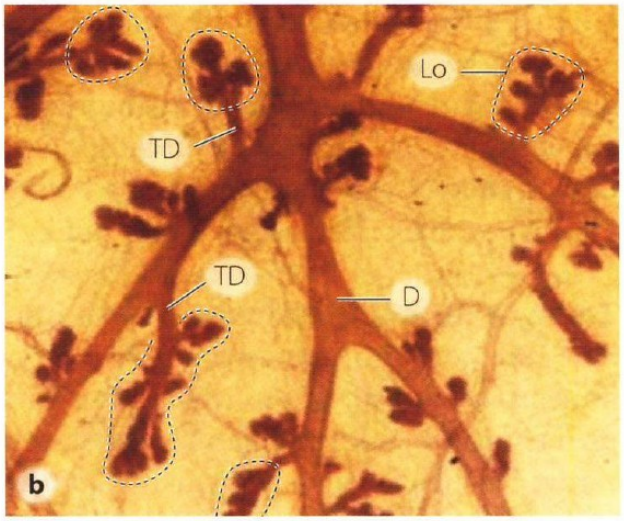
- https://cancerdiscovery.aacrjournals.org/content/11/4/971

MLÉČNÁ ŽLÁZA

- Soubor 15 – 20 tuboaveolárních žláz tvořící laloky - **lobi**
- Každý vývod se rozvětvuje, sekreční oddíly - **lobuly**
- Spolu s tukovou tkání a vazivovým stromatem je podkladem prsu
- K plnému rozvoji dochází v průběhu těhotenství – laktace
  - Intenzivní proliferace **alveolů** na konci interlobulárních vývodů







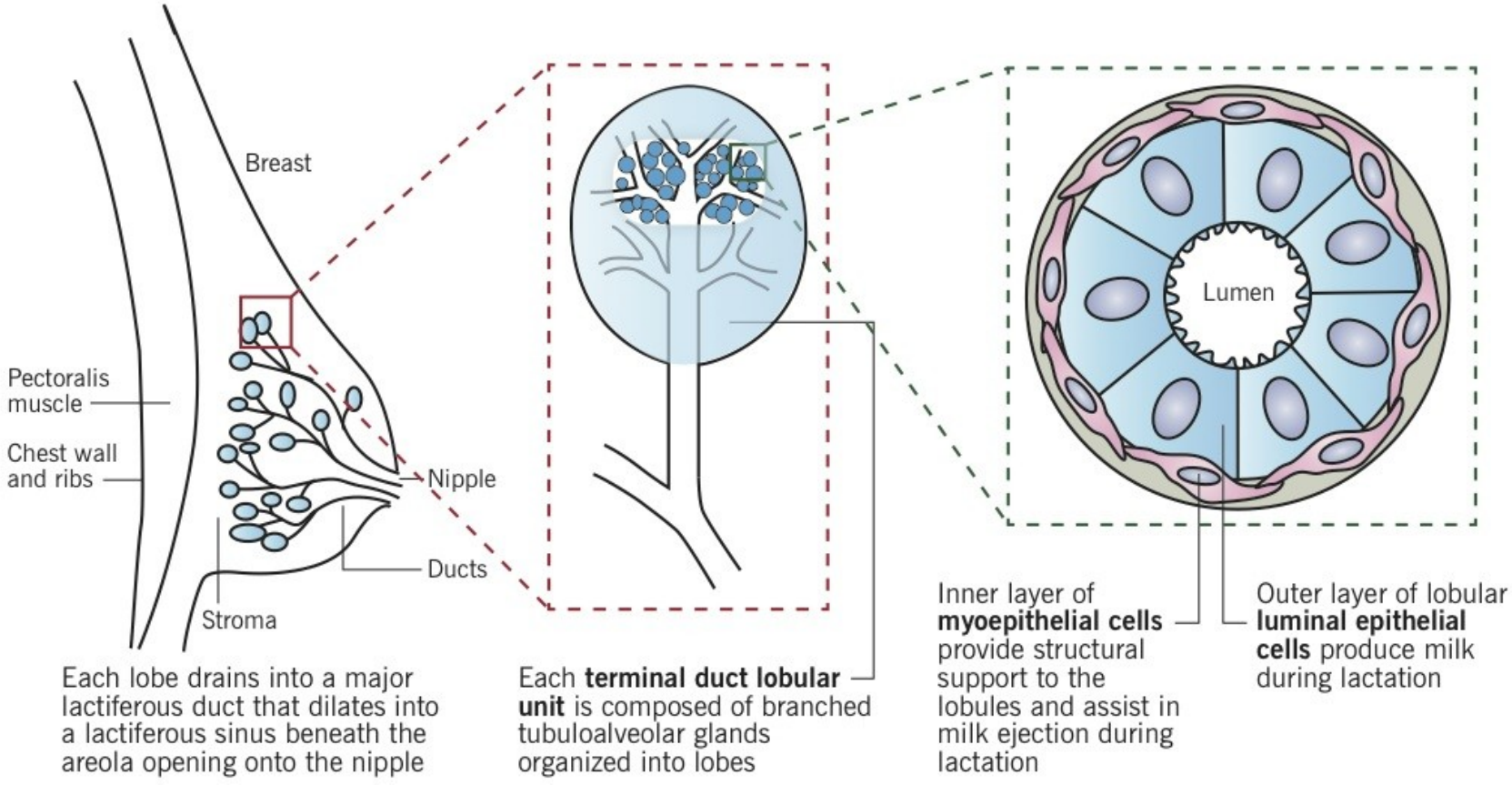
Mechanismy karcinogeneze

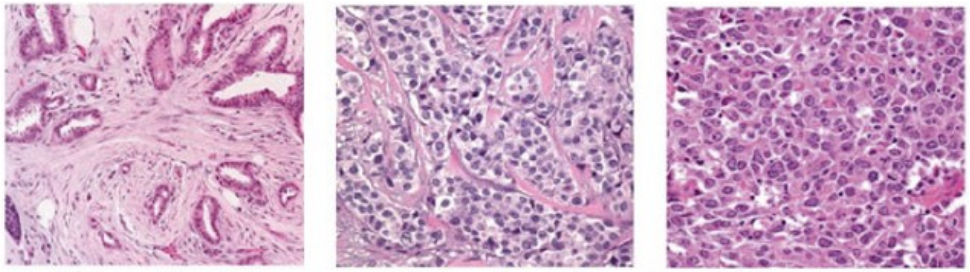
Breast anatomy and histology

Eric Wong

Clin Obstet Gynecol. 2011 Mar;54(1):91-5.

The breast is composed of glandular and stromal tissue. Glandular tissue includes the ducts and lobules. **Stroma** comprises area between lobes.



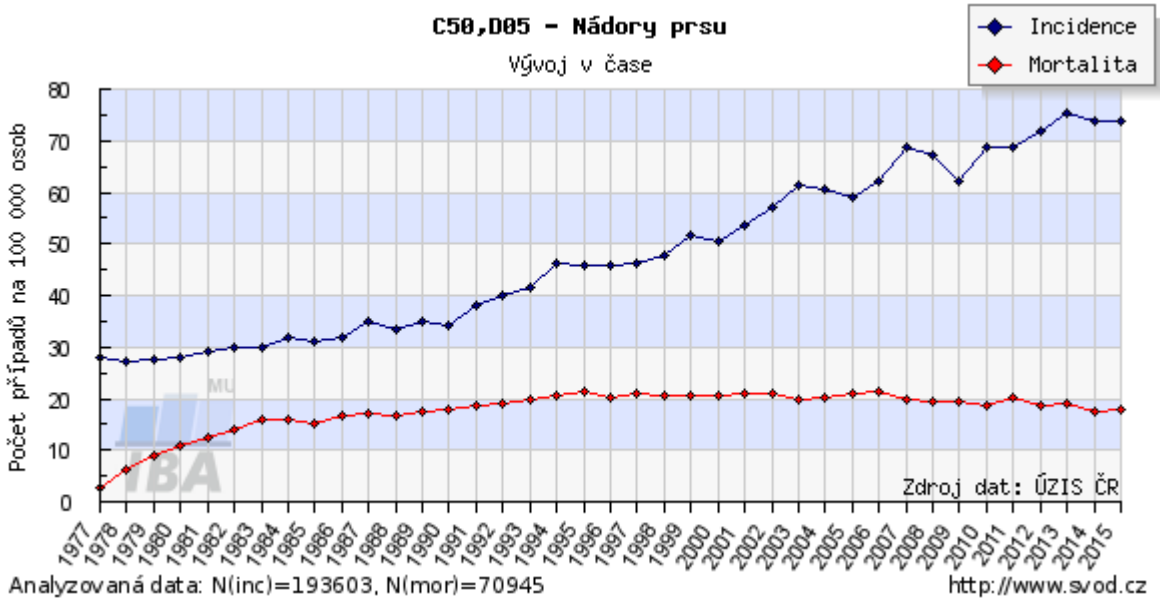


Změny mléčné žlázy spojené s věkem

- Prepuberta
  - Základ duktů vytvořen, lobuly zůstávají nevyvinuty
- Puberta
  - Estrogen a progesteron produkovaný ovárii indukují větvení duktů a vývoj lobulů
- Těhotenství
  - Progesteron a prolaktin indukují kompletní maturaci prsní žlázy
  - Zvýšení počtu a velikosti lobulů
  - Oxytocin indukuje proliferaci a diferenciaci myoepitelialních buněk
  - Po ukončení laktace dochází k apoptóze epitelu a atrofii lobulů
- Menopausa
  - Lobulární a duktální atrofie
  - Zvýšení množství interlobulárního stromatu, fibrózní a tukové tkáně

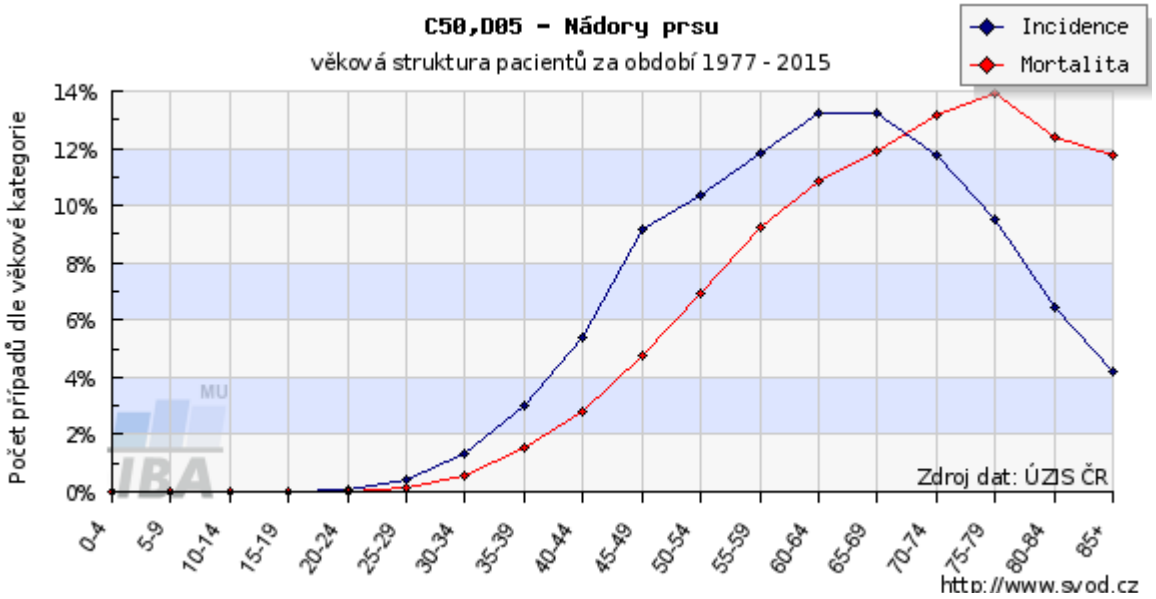
Karcinom prsu

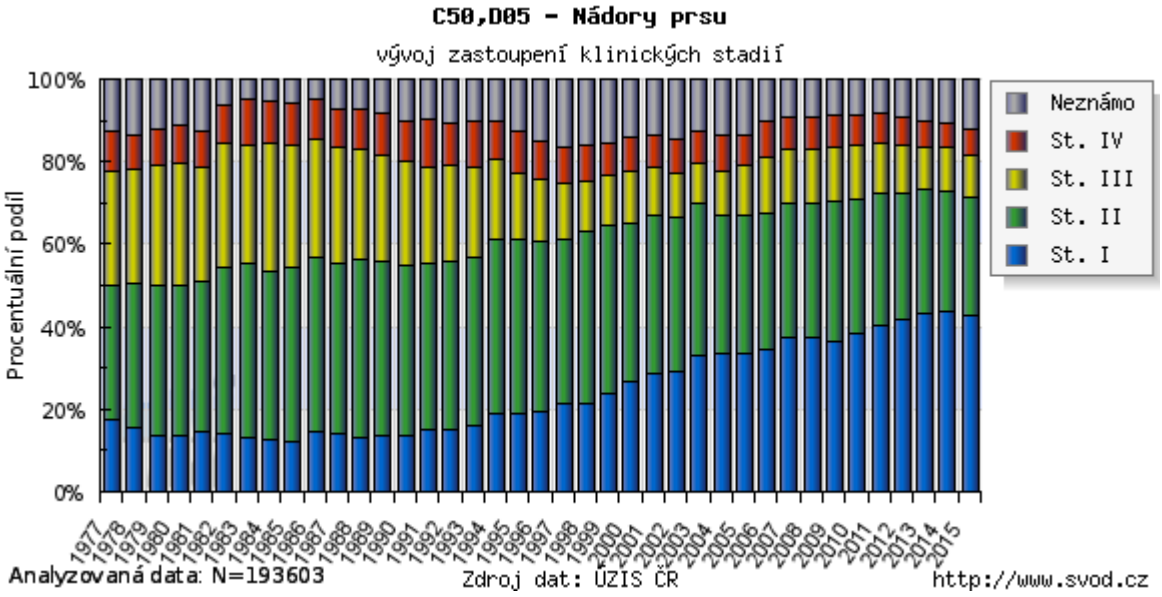
- Druhé nejčastější maligní onemocnění u žen



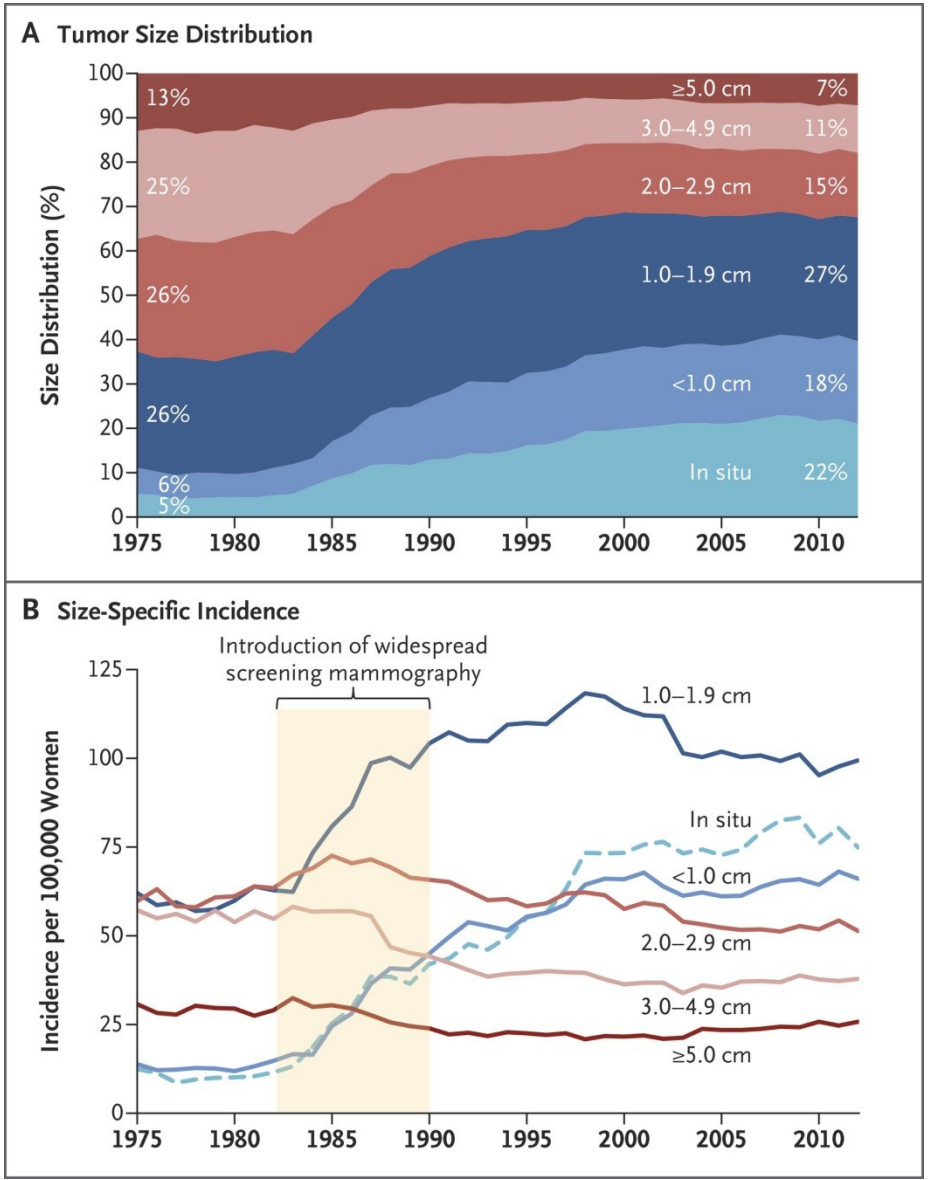
- TNM klasifikace
  - TX – primární nádor nelze hodnotit
  - T0 – bez známek primárního nádoru
  - Tis – Kacinom in situ
  - T1 – nádor ≤ 2 cm
  - T2 – nádor > 2cm, ≤ 5cm
  - T3 – nádor > 5cm
  - T4 – nádor jakékoliv velikosti s přímým šířením do stěny hrudní nebo kůže

Karcinom prsu – věková struktura a zastoupení klinických stádií





Breast-Cancer Tumor-Size Distribution and Size-Specific Incidence among Women 40 Years of Age or Older in the United States, 1975–2012.



Karcinom prsu – rizikové faktory

Age

It's the strongest risk factor for breast cancer, and aging increases your risk.

Genetic alterations

Inherited changes in certain genes (including BRCA and PTEN) affect your risk.

Family history

A breast cancer diagnosis in your mother, sister and/or daughter, especially before age 50.

Dense breast tissue

A high percentage of dense breast tissue can make it more difficult to detect an abnormality on a mammogram.

Reproductive and menstrual history

Having your first menstrual period before age 12, going through menopause after age 55, or having your first full-term pregnancy after age 30 raises your risk.

Body weight

The chance of getting breast cancer is higher for postmenopausal women who are overweight or obese.

Radiation therapy

Undergoing radiation therapy to the chest before age 30 puts you at increased risk.

Menopausal hormonal therapy

Long term combined estrogen and progestin menopausal hormone therapy raises your breast cancer risk.

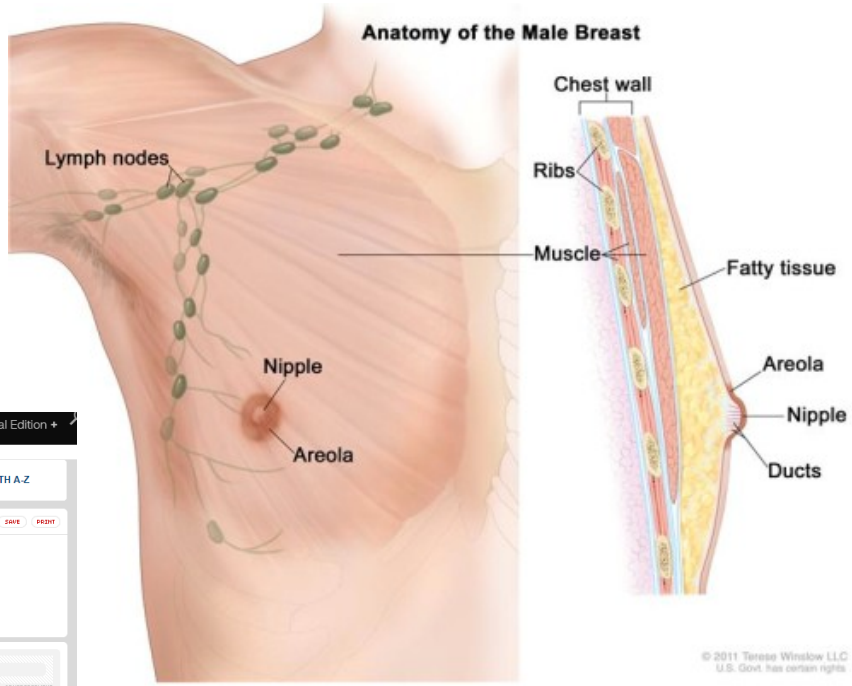
Alcohol

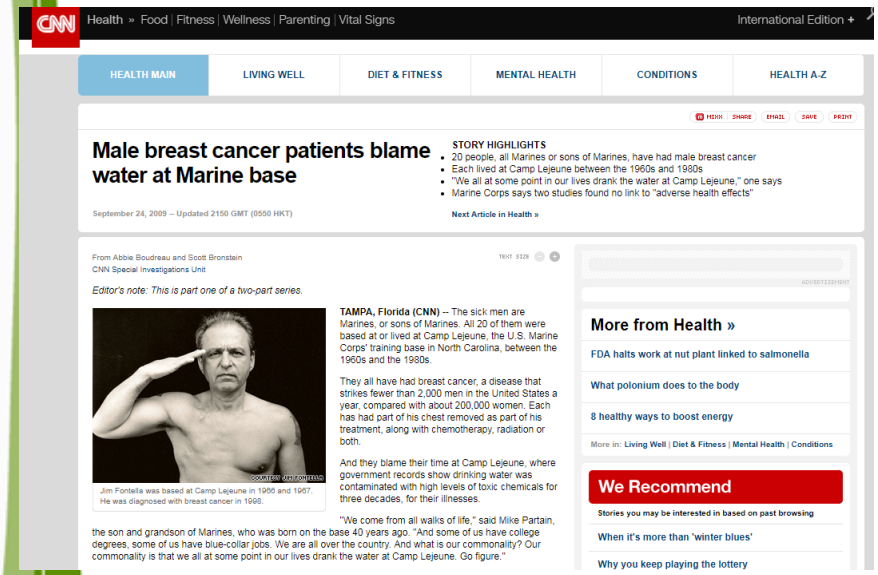
Drinking alcohol frequently may increase breast cancer risk.

http://www.cpmc.org/services/cancer/breast/breast-cancer-risks.pdf

Karcinom prsu – rizikové faktory

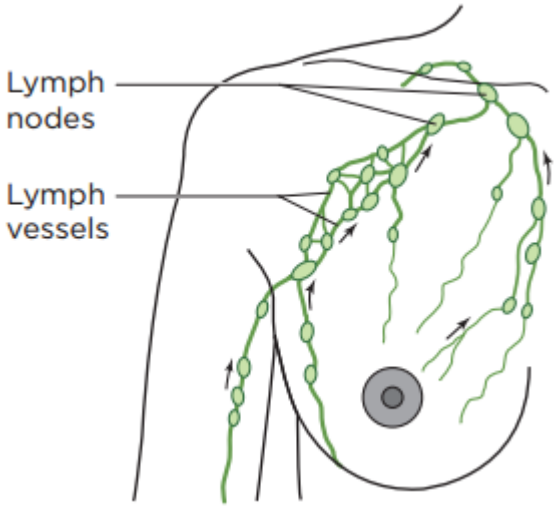
- Hlavní rizikový faktor – pohlaví
- 1 z 8-mi žen onemocnění invazivním adenokarcinomem prsu (USA, ~ 12%)
- 1 z 1000 mužů



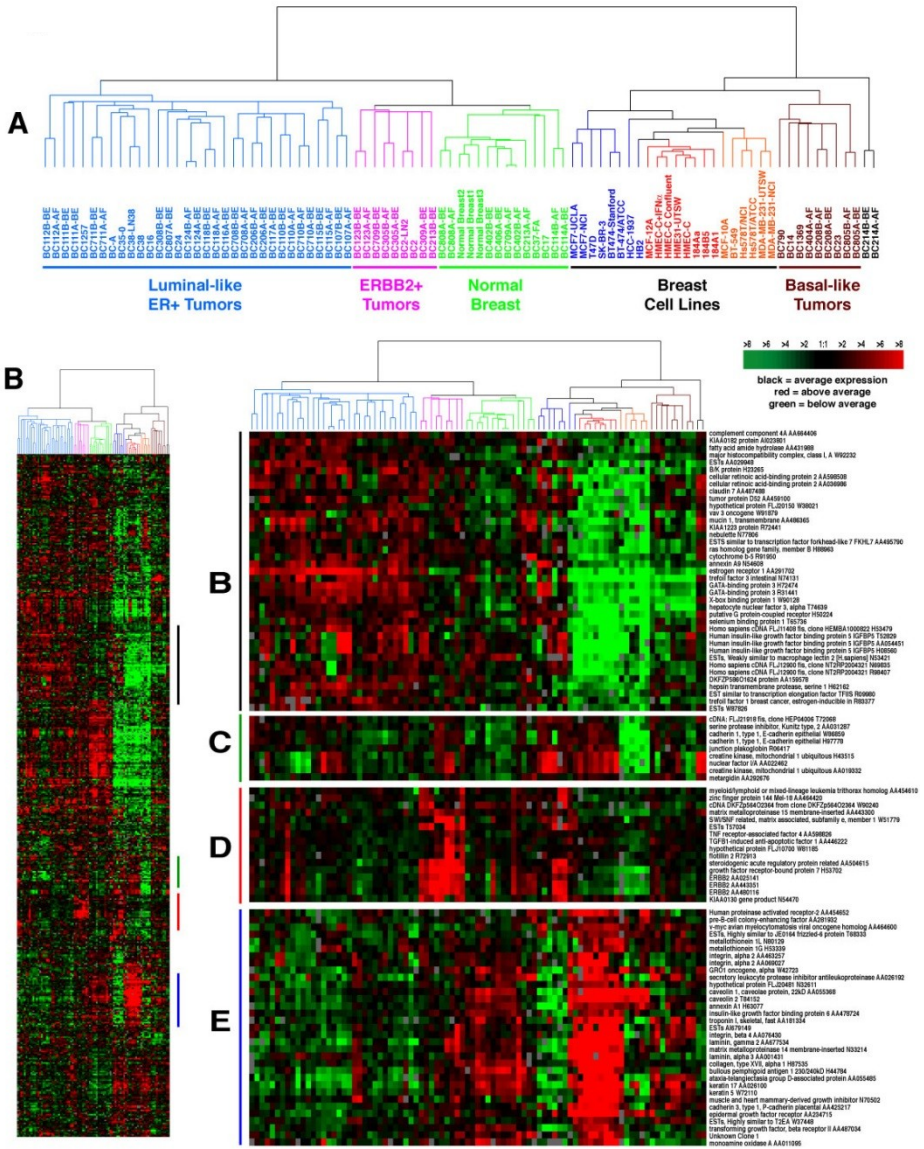


Karcinom prsu – prognostické faktory

- Exprese hormonálních receptorů v nádoru
- Věk
- Klinické stádium
- Postižení axilárních uzlin
- Exprese onkogenu HER2/Neu
- Velikost primárního nádoru
- Histologický typ nádoru a jeho *grade*
- Vaskulární a lymfatická invaze
- Molekulárně genetický profil nádoru
  - Oncotype (21 genů)
  - Mammaprint (70 genů)
  - PAM50 (Prosigna, 50 genů)



Molekulární klasifikace nádorů pomocí profilování genové exprese



letters to nature

Molecular portraits of human breast tumours

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Vol. 96, pp. 9212–9217, August 1999
Genetics

Distinctive gene expression patterns in human mammary epithelial cells and breast cancers

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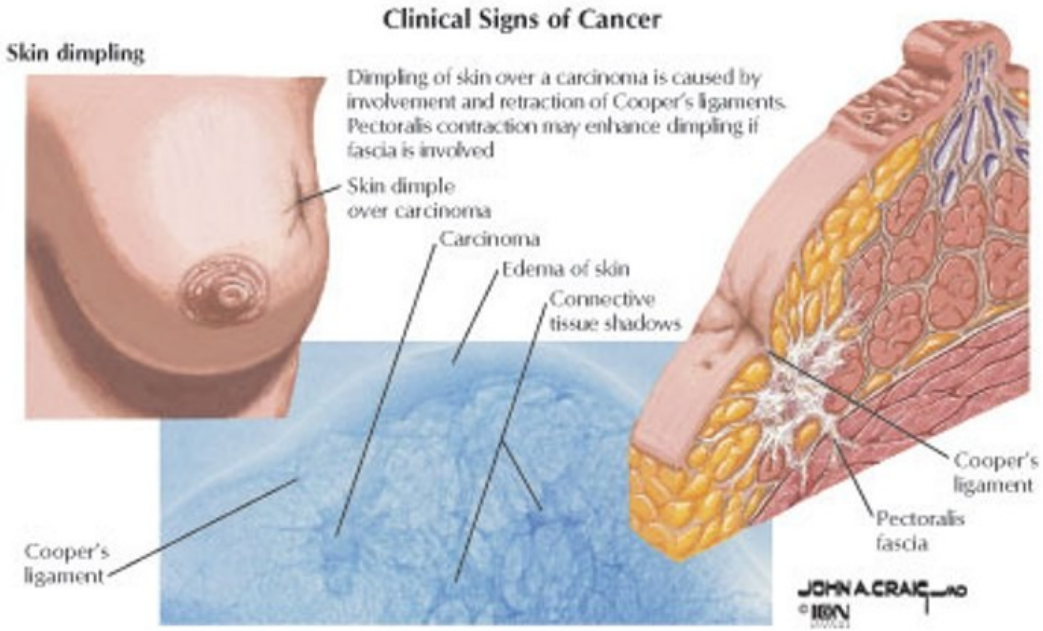
Contributed by David Botstein, June 11, 1999

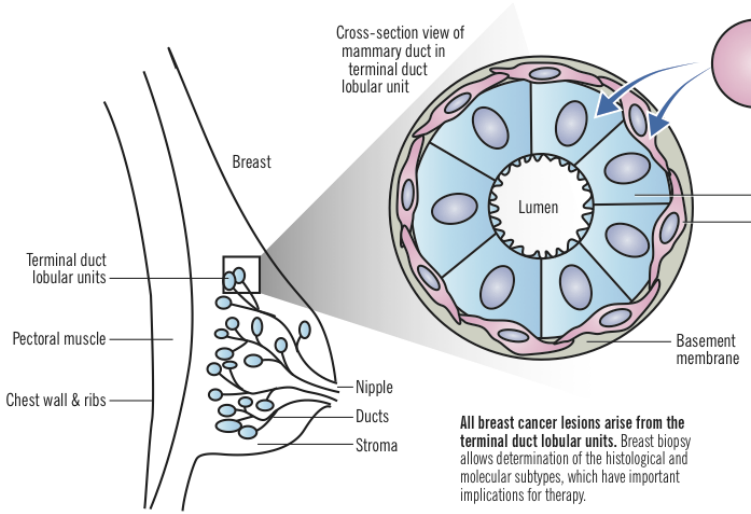
Klinické příznaky

- Primární nádor může být zcela asymptomatický, jindy vede ke změnám prsu
- Nejčastějším příznakem je hmatná rezistence v prsu nebo podpaží
- Metastázování – plíce, játra, kosti



Breast cancer pathogenesis and histologic vs. molecular subtypes

Eric Wong and Jenna Rebelo



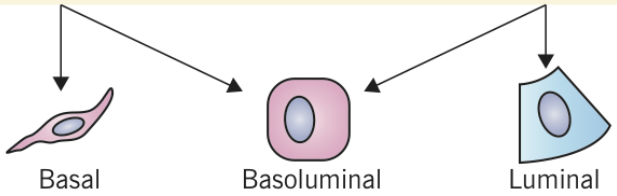
All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

Normal breast stem cells or progenitor cells transform into breast cancer cells. The cancer cells are similar in phenotype to the normal basal and luminal cells of the ductal structure.

Basal or myoepithelial cells
- Contractile cells for milk ejection
- *Estrogen receptor* –
- Progesterone receptor –

Luminal or epithelial cells
- Respond to hormonal stimulation for milk production
- *Estrogen receptor* +
- Progesterone receptor +/–

Cancer cell phenotype



Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	**Ductal carcinoma in situ (DCIS)** 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	**Lobular carcinoma in situ (LCIS)** 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	**Invasive ductal carcinoma (IDC)** 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	**Invasive lobular carcinoma (ILC)** 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Molecular subtypes	Triple negative ER–, PR–, HER2–	HER2+	Luminal B	Luminal A
% of breast cancers	15-20%	10-15%	20%	40%
Receptor expression		HER2		ER+/PR+
Histologic grade Level of cell differentiation	High (grade III)			Low (grade I)
Prognosis Correlates to histologic grade	Poor			Good
Response to medical therapy	Chemotherapy	Trastuzumab		Endocrine

Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

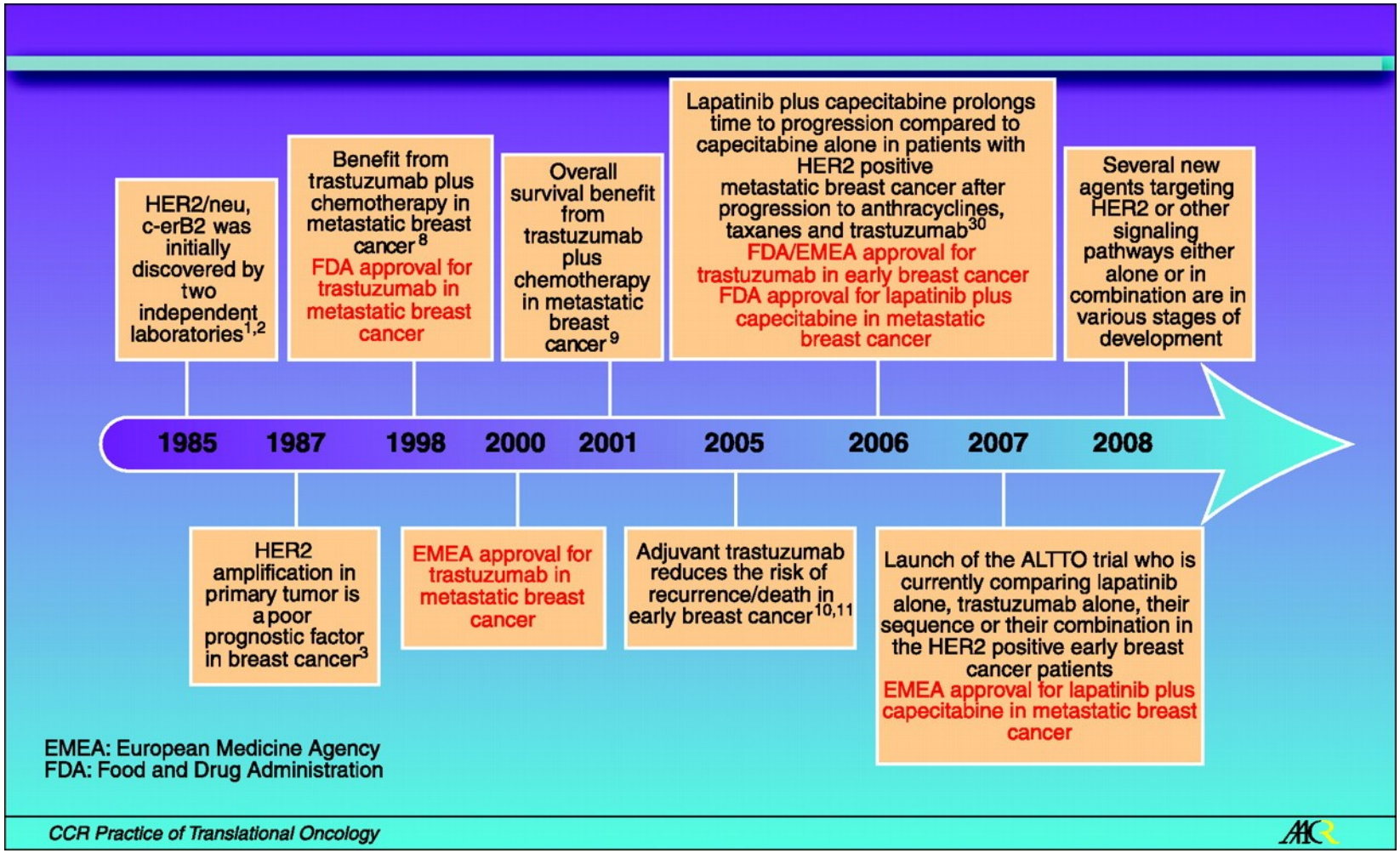
Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

Curr Treat Options Oncol. 2000 Aug;1(3):199-209.
Clin Transl Oncol. 2008 Dec;10(12):777-85.
Nat Clin Pract Oncol. 2007 Sep;4(9):516-25.
Robbins 8E

Léčebný postup

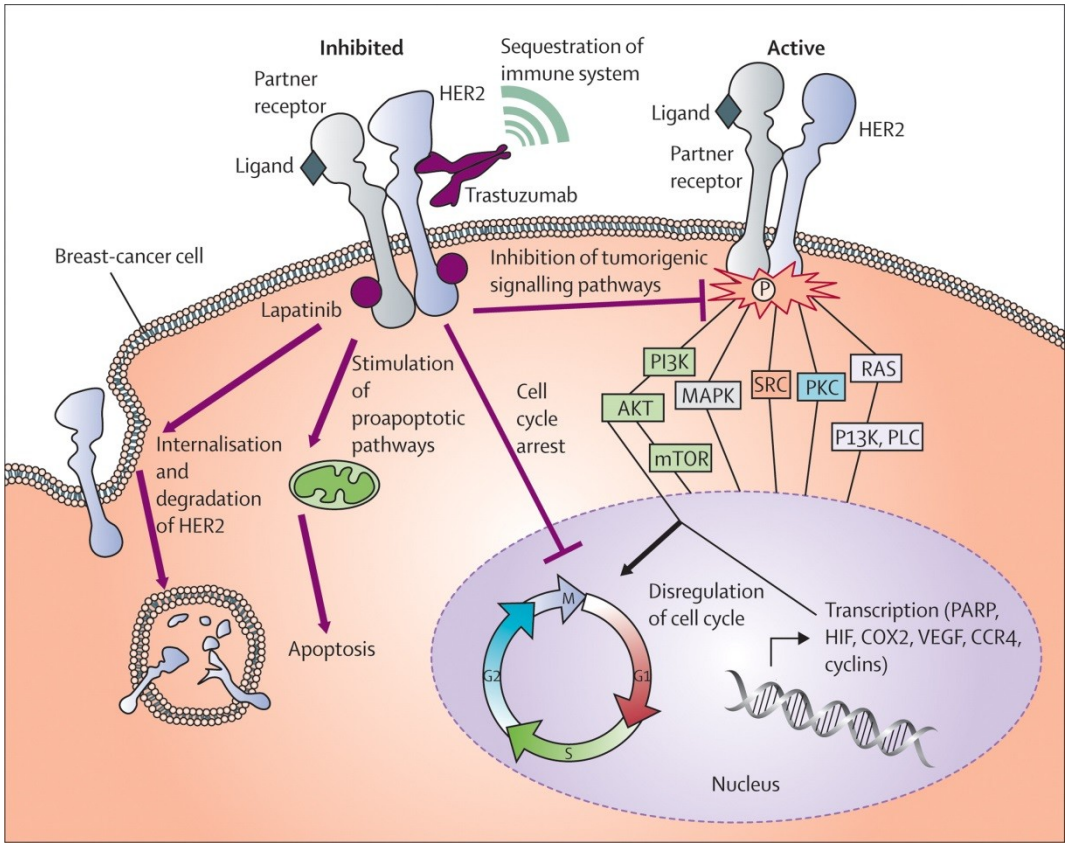
- Chirurgický výkon
- Pooperační systémová léčba
  - Hormonální adjuvantní léčba
    - Premenopauzální pacientky
      - Analoga Luteinizing-hormone-releasing hormone, LHRH
      - Tamoxifen (nesteroidní antiestrogen)
    - Postmenopauzální pacientky
      - Tamoxifen
      - Inhibitory aromatáz
  - Adjuvantní chemoterapie
    - Antracykliny (doxurubicin, epirubicin), taxany (docetaxel)
  - Adjuvantní biologická léčba
    - Transtuzumab – pacientky pozitivní na HER2
      - Vedlejší účínky – neuregulin-1 – vliv na cardiomyocyty - cardiopatie
- Pooperační radioterapie

HER2 jako cíl protinádorové léčby



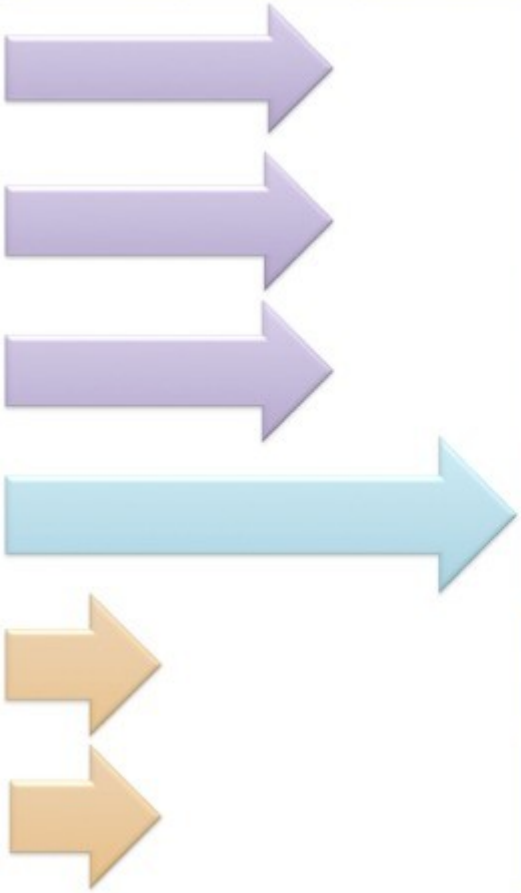
HER2/neu

- Receptor tyrosine-protein kinase erbB-2, CD340
- Rodina epidermal growth factor receptor
- Amplifikace u ~ 30% nádorů prsu



The Lancet Oncology 2009 10, 1179-1187DOI: (10.1016/S1470-2045(09)70315-8)

Vakcína proti rakovině prsu

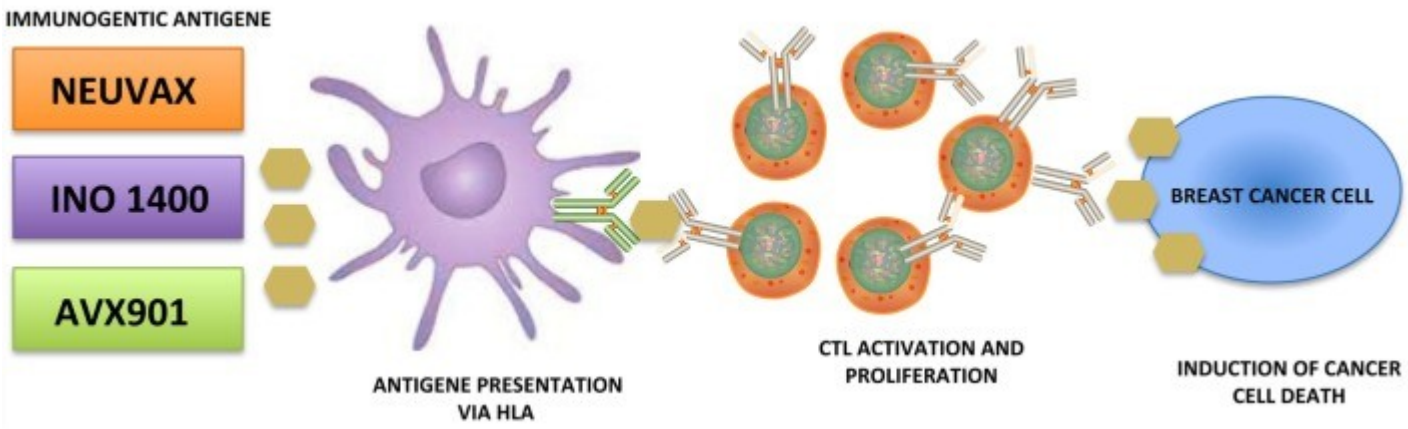


Phase I	Phase II	Phase III	Treatment	Clinical Trials Identifies Number	Recruitmnent Status	Collaborators	Enrollment
			Nelipepimut-S Plus GM-CSF Vaccine	NCT02636582	Ongoing, recruiting participants	National Cancer Institute (NCI)	108
			Combination Immunotherapy With Herceptin and the HER2 Vaccine NeuVax	NCT01570036	Ongoing, recruiting participants	George E. Peoples Genentech, Inc. Galena Biopharma, Inc.	300
			Combination Immunotherapy With NeuVax and Trastuzumab in High-risk HER2+ Breast Cancer Patients (HER3+)	NCT02297698	Ongoing, recruiting participants	Cancer Insight, LLC Genentech, Inc. Galena Biopharma, Inc.	100
			NeuVax Vaccine to Prevent Breast Cancer Recurrence (PRESENT)	NCT01479244	Completed	Galena Biopharma, Inc.	758
			Combination Immunotherapy With AVX901 and trastuzumab	NCT01526473	Ongoing, but not recruiting participants	H. Kim Lyerly Susan G. Komen Breast Cancer Foundation, Duke University	22
			Combination Immunotherapy INO-1400 Alone or in Combination With IL-12 DNA	NCT02960594	Ongoing, recruiting participants	Inovio Pharmaceuticals	54

Front Endocrinol (Lausanne). 2017; 8: 270.
Published online 2017 Oct 13. doi: 10.3389/fendo.2017.00270

Imunoterapie v léčbě karcinomu prsu

- NeuVax – HER2-derived peptide E75
- INO 1400 - virus-like replicon particle (VRP)-HER2
- hTERT DNA



Front Endocrinol (Lausanne). 2017; 8: 270.
Published online 2017 Oct 13. doi: 10.3389/fendo.2017.00270

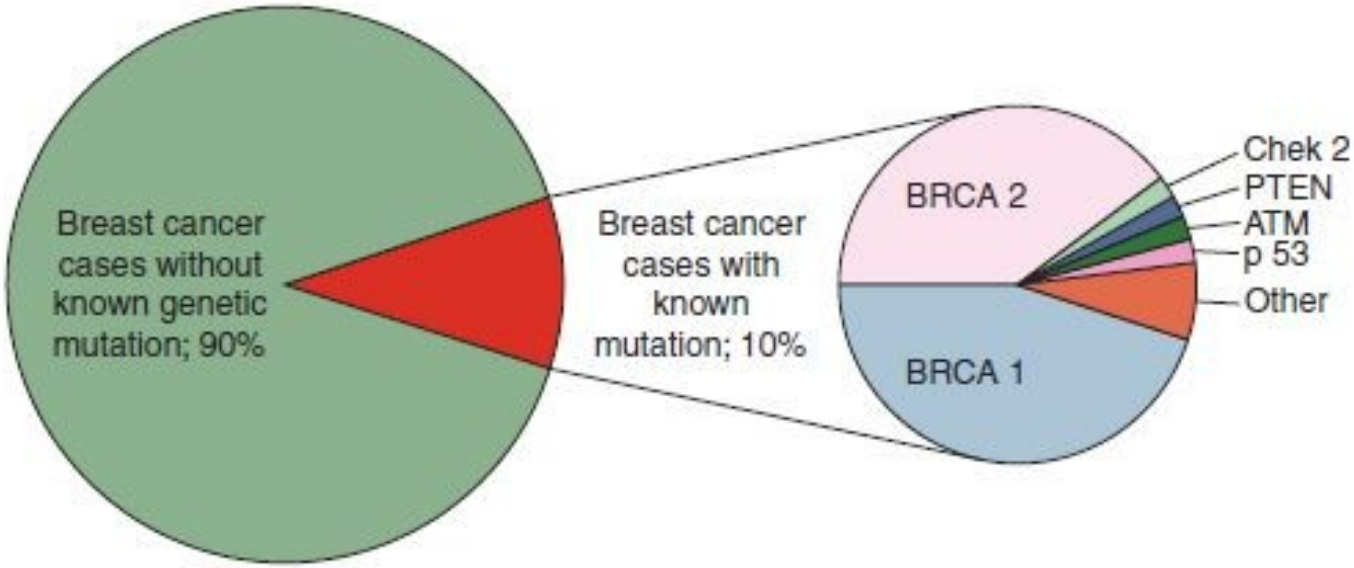


FIGURE 8-2 Percentage of breast cancer cases with a genetic mutation.

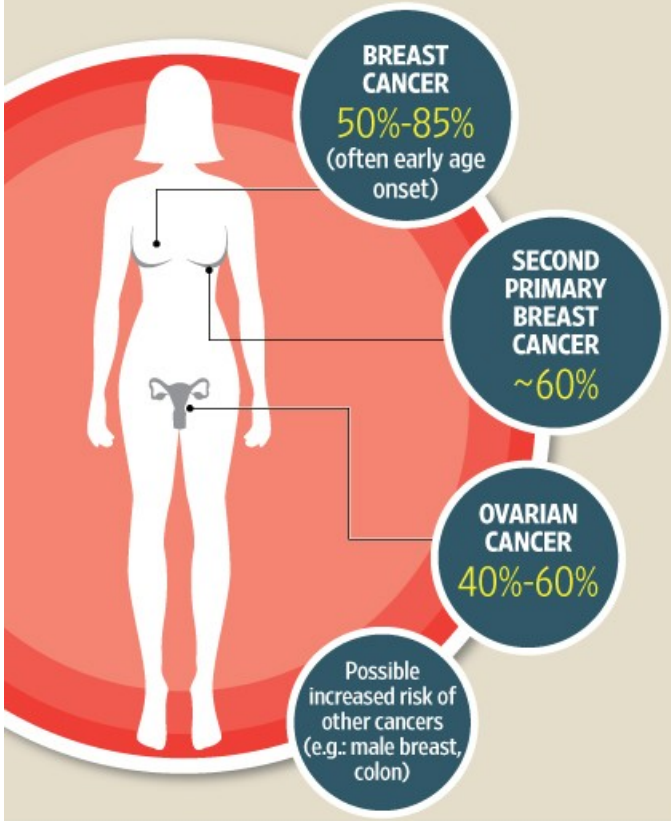
Table 9.1 Inherited risk factors: genes that influence breast cancer risk

Classification	Examples	Magnitude of risk
High penetrance	BRCA1, BRCA2, TP53, PTEN, STK11, LKB1, CDH1	25–85 % lifetime
Intermediate penetrance	CHEK2, ATM, BRIP1, BALB2	Two to threefold increased
Low penetrance	Numerous SNPs from GWAS studies	1.5-fold increased or less

UNDERSTANDING BRCA MUTATIONS

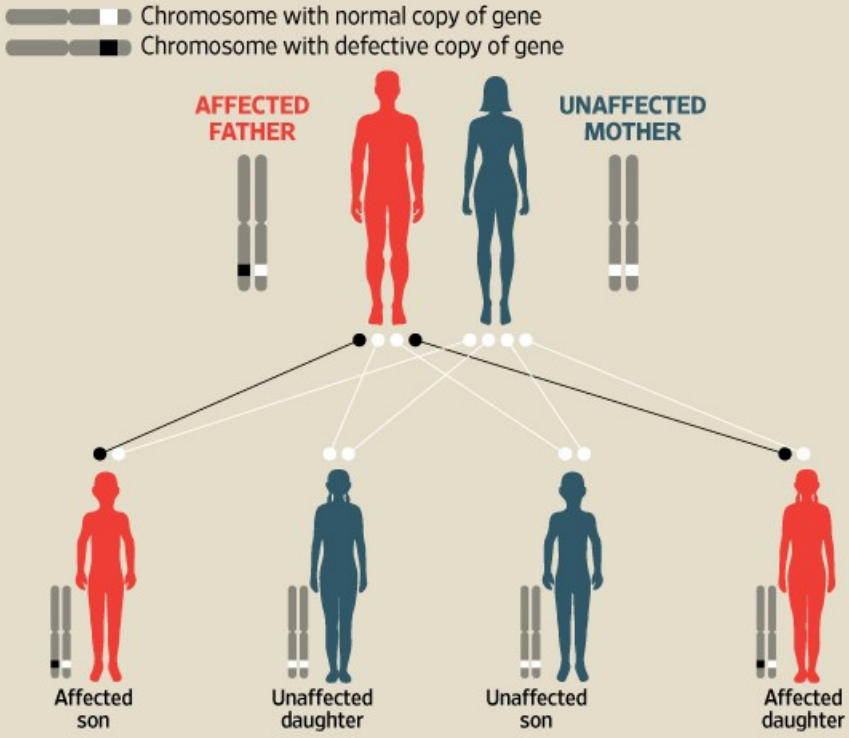
A BRCA gene mutation means a change in either of the two genes—BRCA1 or BRCA2 —that prevents that gene from working properly. When the gene is damaged by mutation, it can increase the risk of cancer

BRCA1- ASSOCIATED CANCERS: **LIFETIME RISK**



AUTOSOMAL DOMINANT INHERITANCE

Each child inherits a normal copy from his/her mother and either a normal or a defective copy from the father



Source: 2009 report by Indian Institute of Science, Bengaluru

BRCA

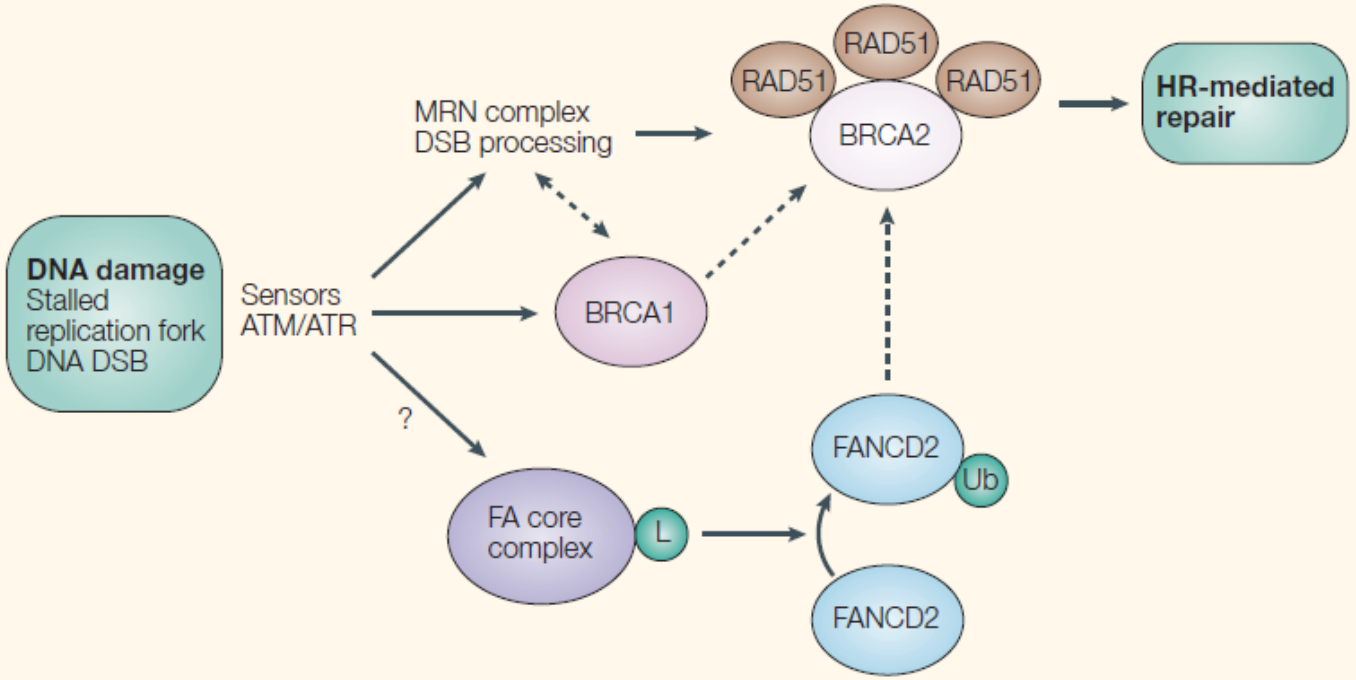


Figure 1 | **The BRCA/Fanconi anaemia DNA-repair pathways.** The BRCA and Fanconi anaemia (FA) proteins function in pathways that repair DNA double-strand breaks (DSBs), stalled replication forks and DNA crosslinks. DNA damage is sensed by protein kinases such as ataxia telangiectasia and Rad3 related (ATR), and ataxia telangiectasia mutated (ATM) that activate the pathways. Five FA proteins (FANCA, FANCC, FANCE, FANCF and FANCG) form a nuclear complex[5], which interacts with FANCL in response to DNA damage leading to mono-ubiquitylation of FANCD2 (REF. 62). Ubiquitylated FANCD2 subsequently co-localizes with both BRCA1 (REF. 63) and BRCA2 (REF. 64) in nuclear foci. Interestingly, homozygous mutations in *BRCA2* also cause FA; BRCA2 is also known as FANCD1 (REF. 54). BRCA2 regulates the RAD51 recombinase that mediates strand invasion and homology-directed repair. For further information, see recent reviews of the mechanistic aspects of these pathways[4,5]. MRN; MRE11–RAD50–NBS1.

Syntetická letalita

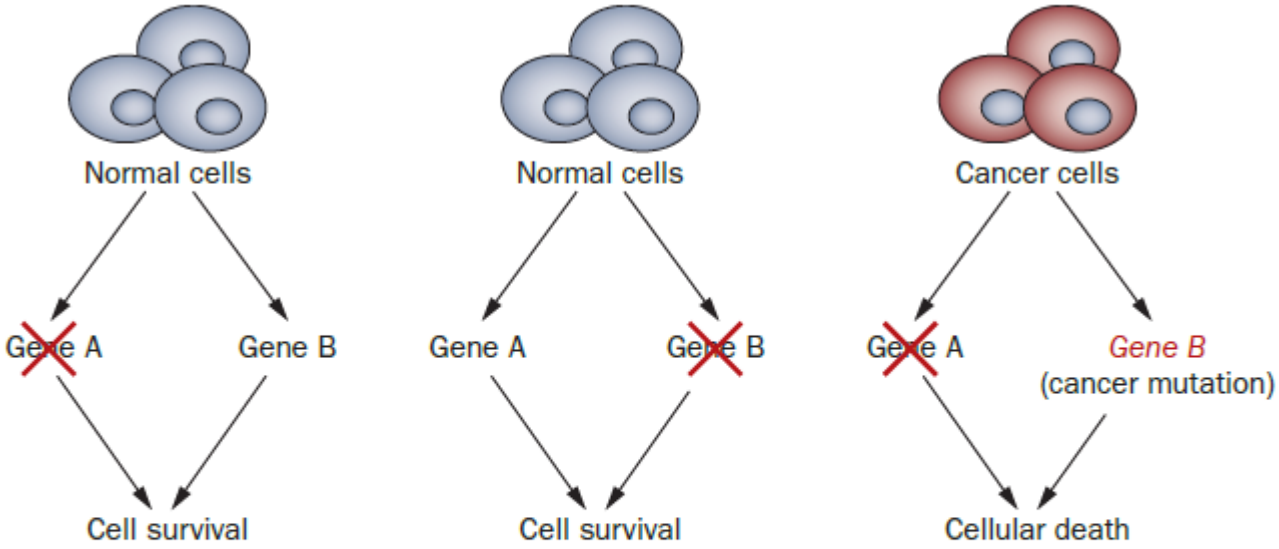
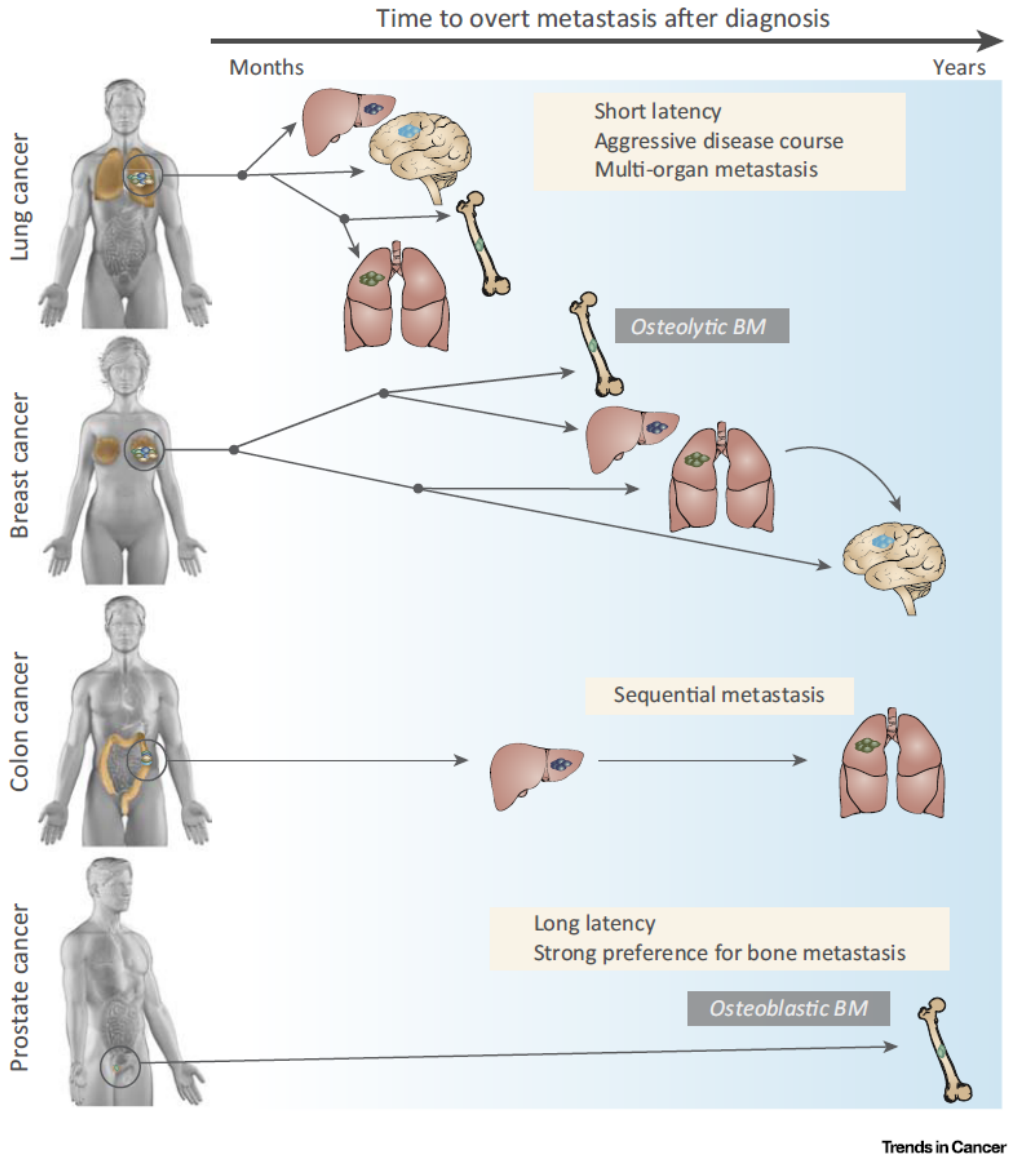


Figure 1 | Synthetic lethality. Loss of either gene A or gene B in normal cells is compensated by the action of the remaining gene. In tumor cells, however, a mutation in one of these genes leaves the cell vulnerable to loss of the other gene by drug inhibition. This approach is the basis of drugs that target synthetic lethal relationships. By contrast, normal tissues are spared any toxic effects.

Diseminace solidních nádorů



Diseminace na nádorů prsu – TNBC vs. non-TNBC

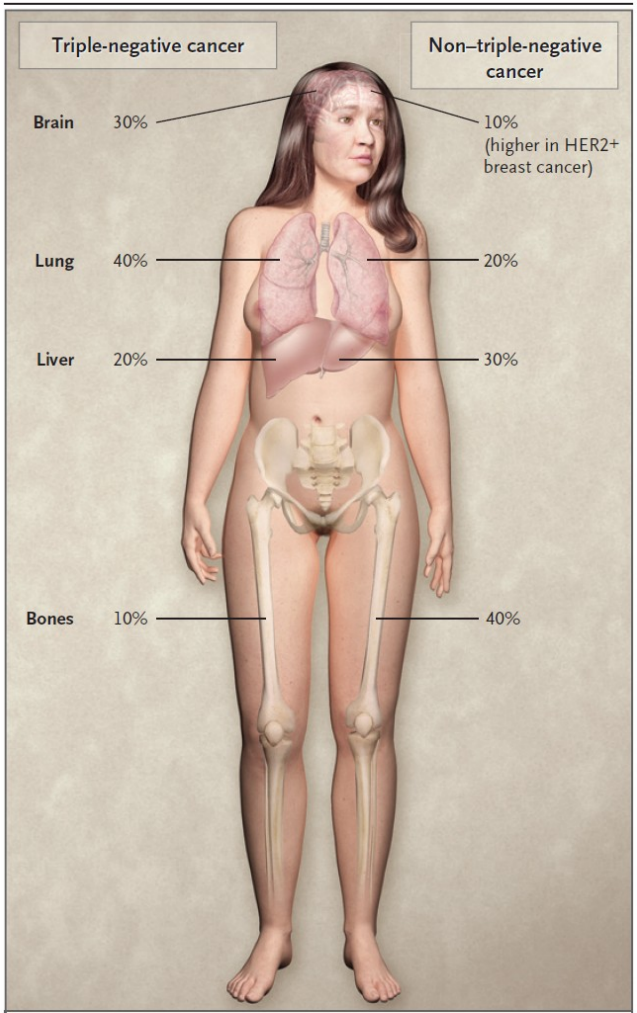
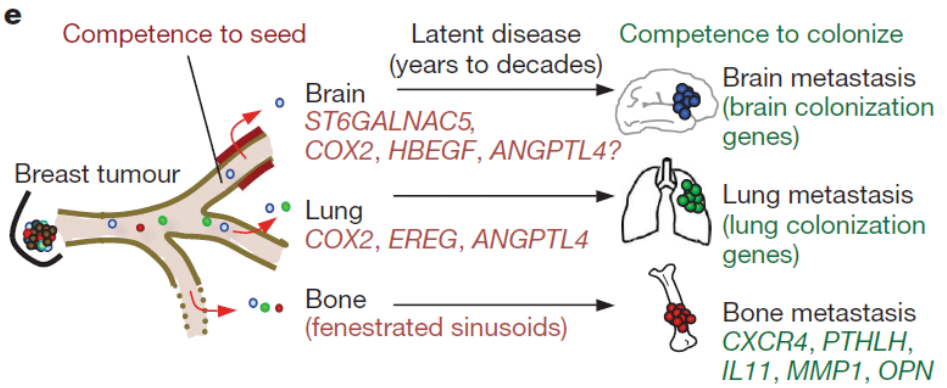


Figure 2. Sites of First Distant Recurrence in Cases of Metastatic Triple-Negative Breast Cancer as Compared with Non–Triple-Negative Breast Cancer.

The percentages shown are approximate percentages of women with a first distant recurrence among women in whom metastases develop. Data are from Dent et al.,[47] Rodríguez-Pinilla et al.,[48] and Liedtke et al.[49]



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LETTERS

Genes that mediate breast cancer metastasis to the brain

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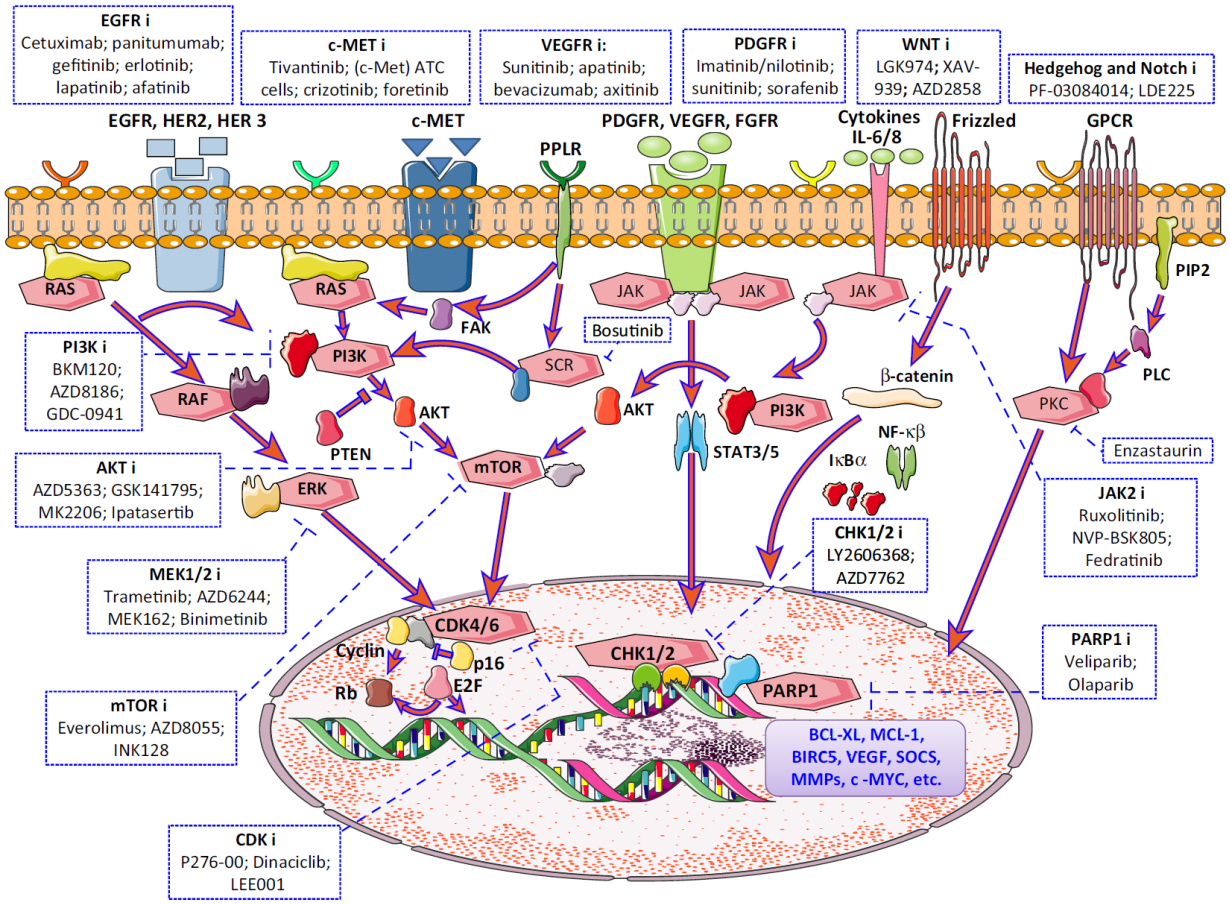
TNBC

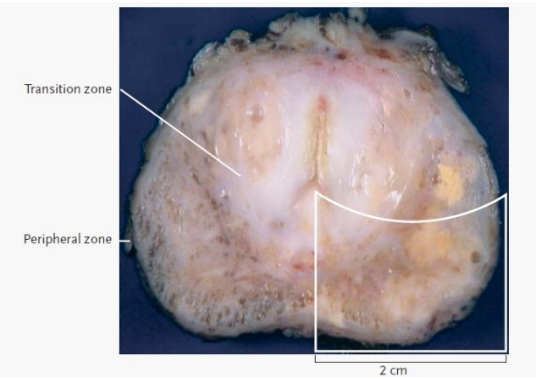
- 15-20% ze všech diagnostikovaných nádorů prsu
- Heterogenní onemocnění, 4-6 molekulárních subtypů
- Řada uvažovaných cílů pro terapii (proliferace, DDR, buněčný cyklus, přežívání

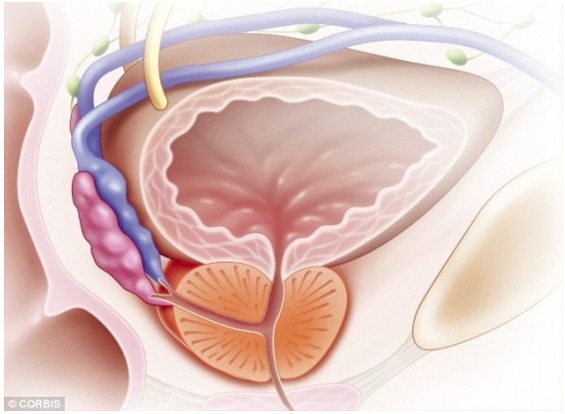


Trends in Pharmacological Sciences

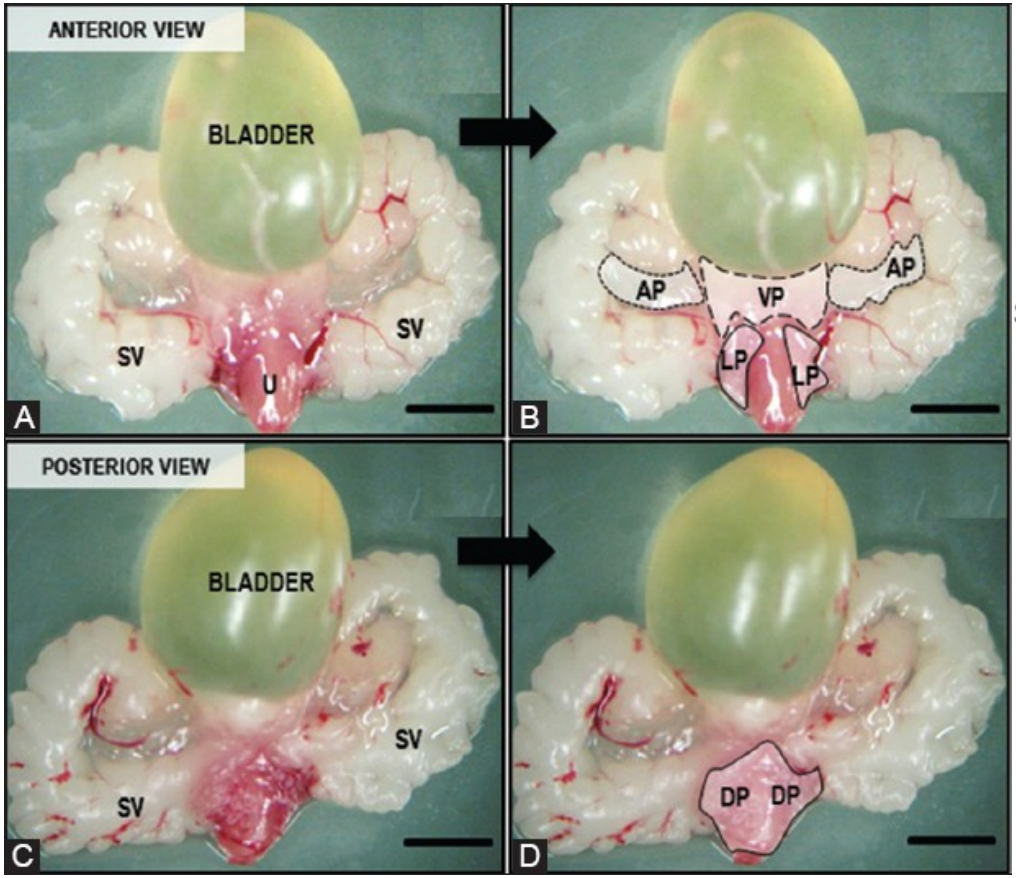
PROSTATA

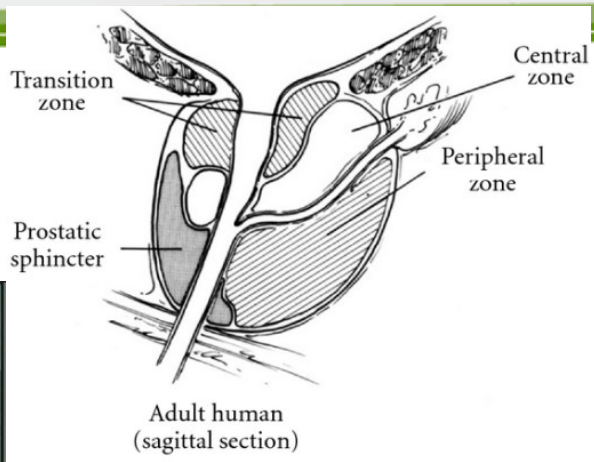
- parenchymatozní orgán, lumen žlázek je složeno v slizniční řasy (vystlány 1vrst.-dvouřadým kubickým až cyl. epitelem)
- 30-50 rozvětvených tuboalveolární žlázek uložených ve vazivově-svalovém stromatu; vývody ústí na colliculus seminalis uretry
- žlázky mají jako podklad **fibromuskulární stroma**
  - **trojí lokalizace: slizniční , podslizniční, hlavní**
- **sekret:** hojně bílkovin, kapénky lipidů, kyselá fosfatáza (klin.významná), pH lehce kyselé, kyselina citronová, fibrinolyzin, prostaglandiny; ve vyšším věku konkrementy prostaty (corpora amylacea)



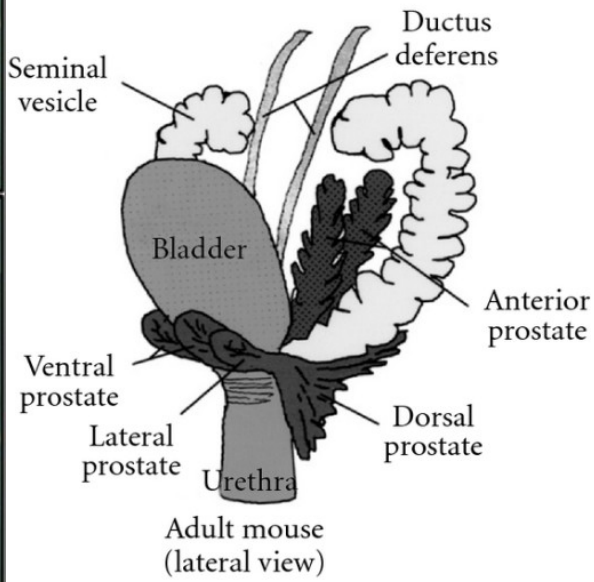


Prostata člověk vs. myš



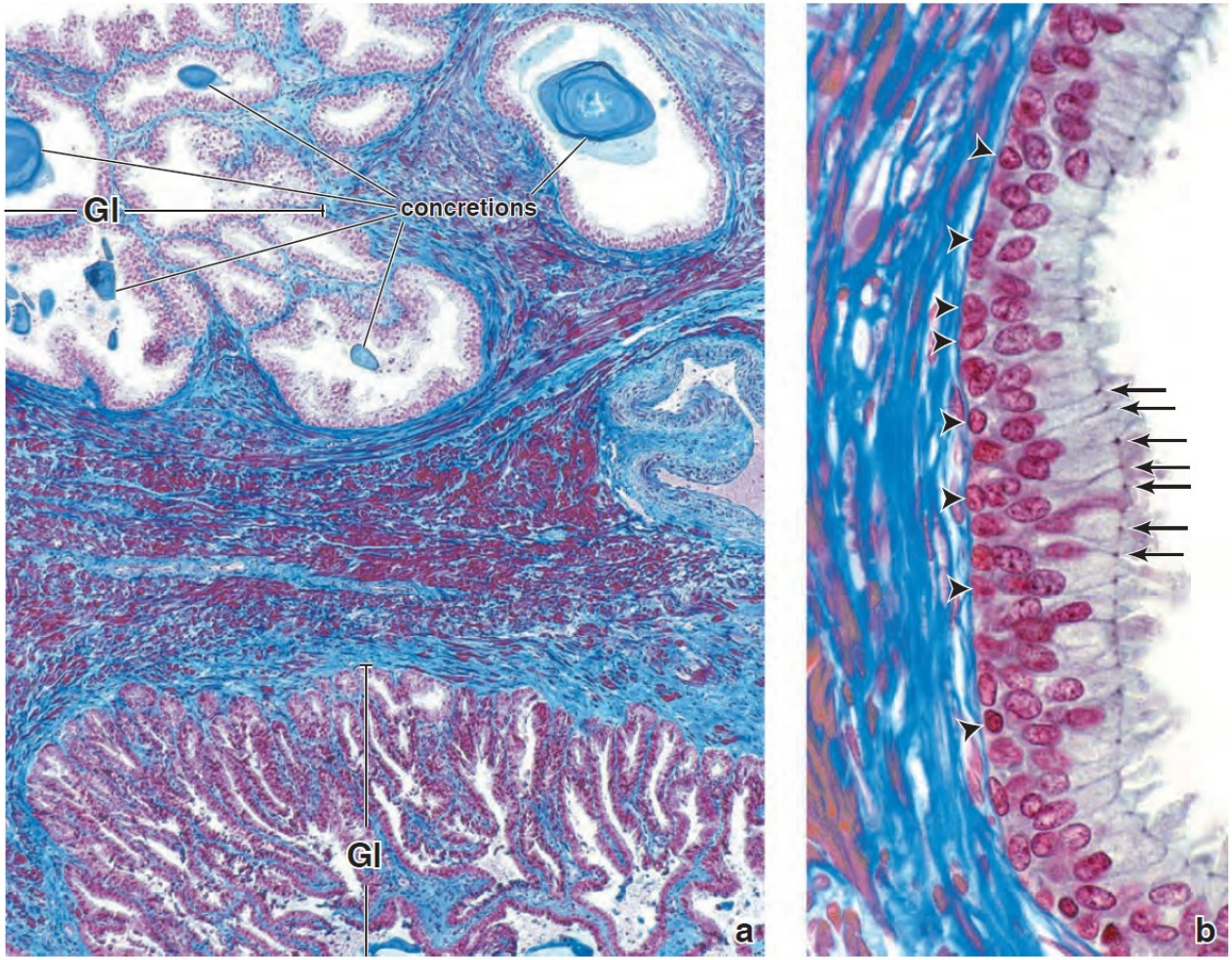


(a)

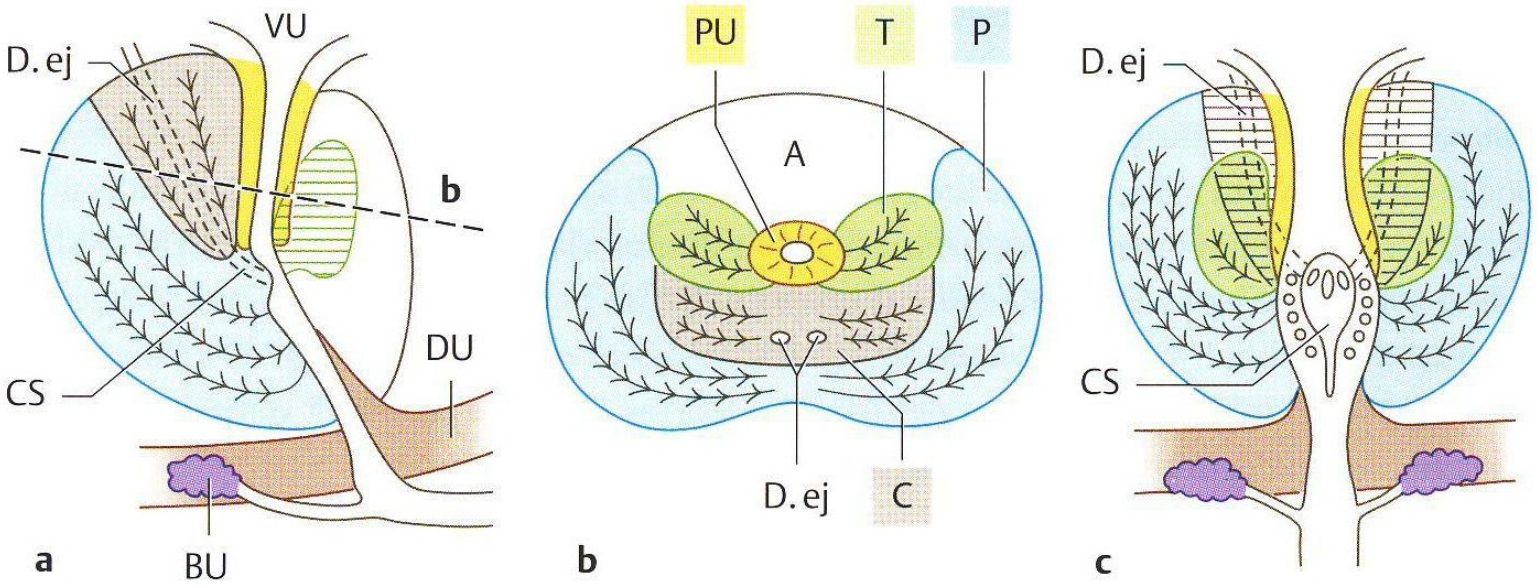


(b)

Prostata - člověk



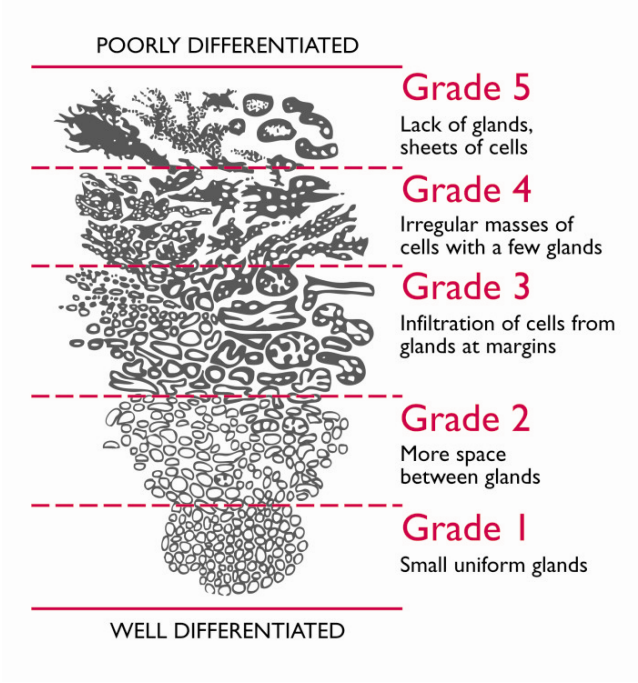
Členění prostaty člověka



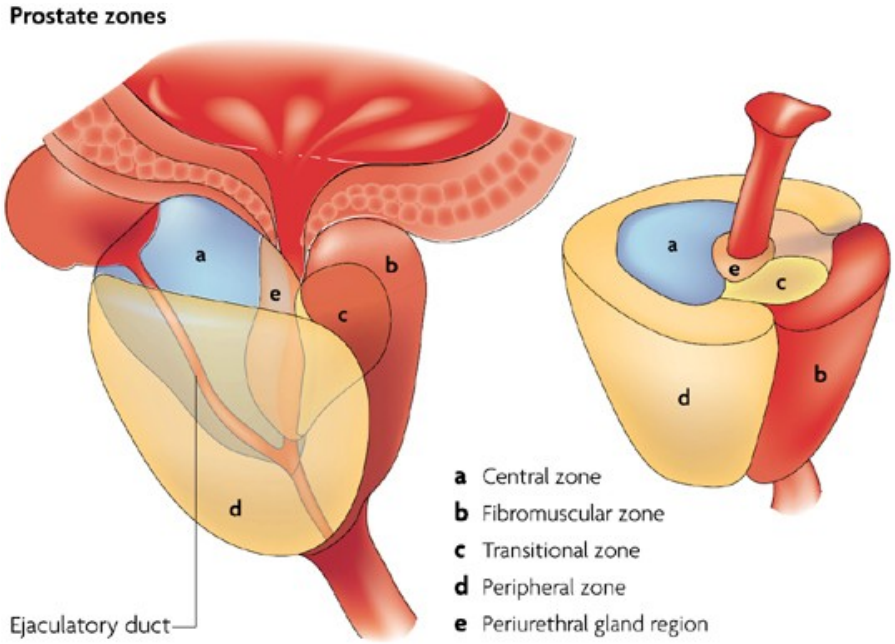
- Zóna centrální (C), periferní (P), přechodová (T), periutherální (PU), přední, nežlaznatá (A)

Karcinom prostaty

- Třetí nejčastější nádorové onemocnění u mužů
  - Diagnostikován u 20% mužů, u 3% příčinou úmrtí (USA)
- 95% - adenokarcinom
- Heterogenní, multifokální charakter
  - Gleasonovo skóre – zohledňuje stupeň diferenciace
- TNM klasifikace
  - TX – primární nádor nelze hodnotit
  - T0 – bez známek primárního nádoru
  - T1 – nezjistitelný klinicky, palpačně ani zobrazovací metodou
  - T2 nádor omezený na prostatu
  - T3 nádor se šíří přes pouzdro prostaty
  - NX, N0, N1 – zasažení regionálních mízních uzlin
  - MX, M1 – vzdálené metastázi
  - Stádia - I – IV (př. III – T3 N0 M0)



Zonální predispozice k onemocnění prostaty

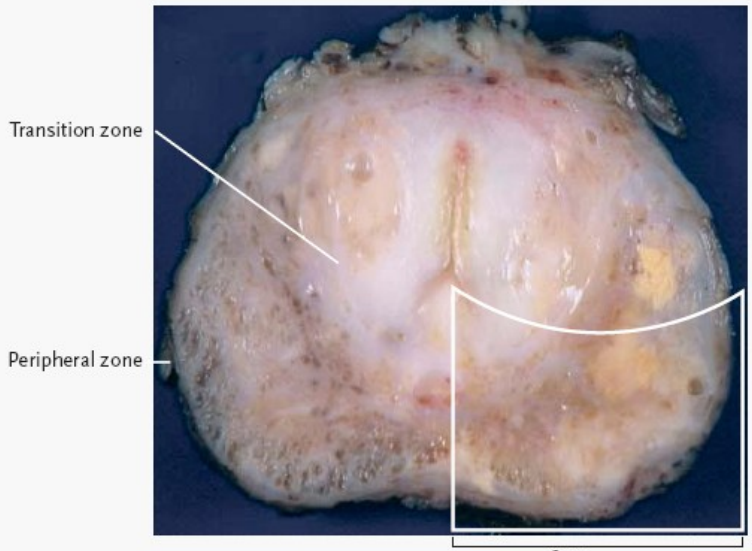


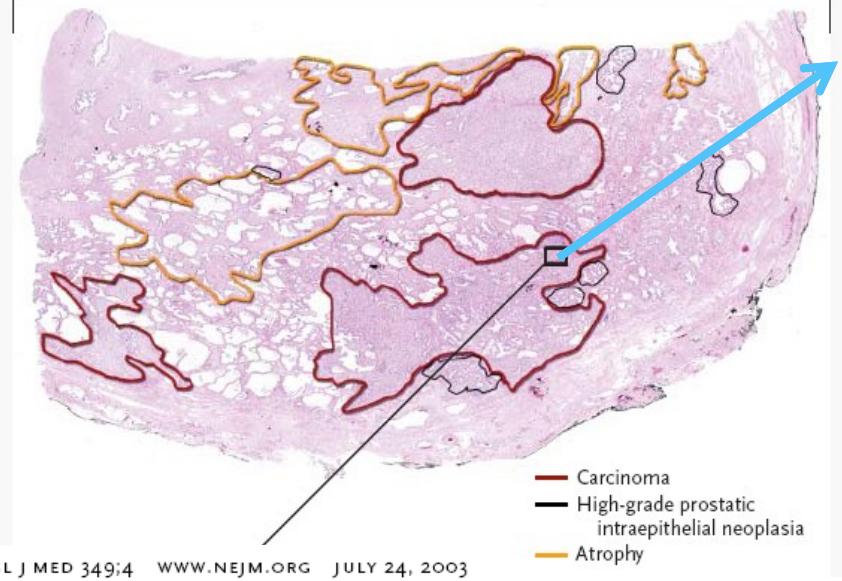
	Prostate zone		
	Peripheral	Transition	Central
Focal atrophy			
Acute inflammation			
Chronic inflammation			
Benign prostatic hyperplasia			
High-grade PIN			
Carcinoma			

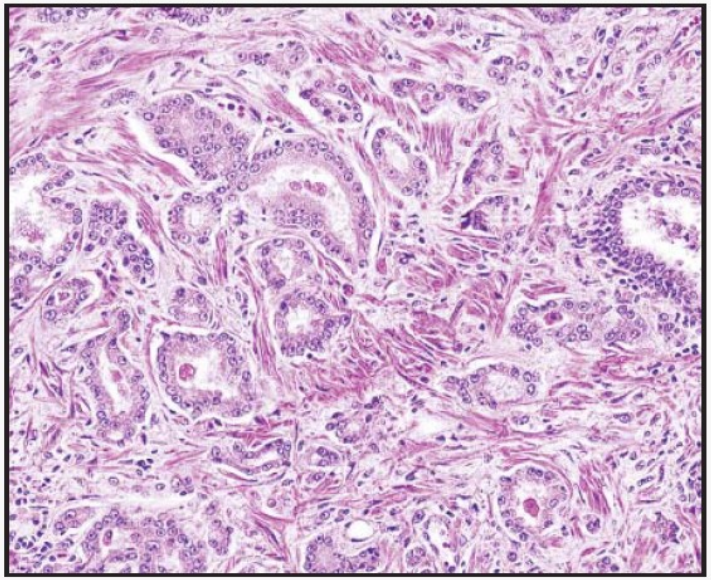
High prevalence
Medium-high prevalence
Low prevalence
None

Nature Reviews | Cancer

Mechanismy karcinogeneze

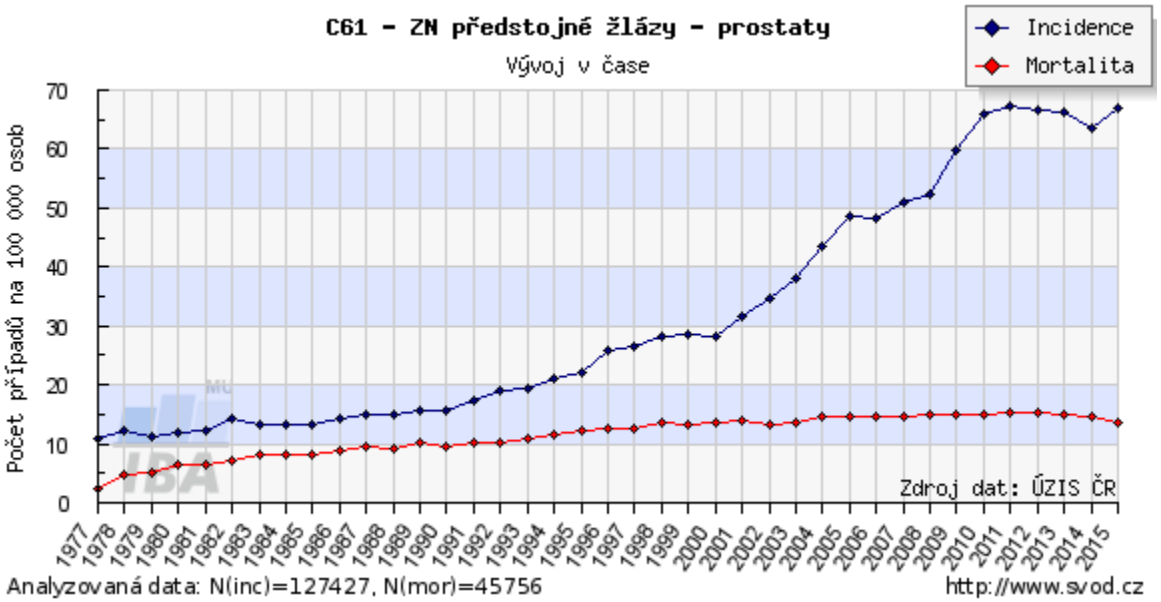


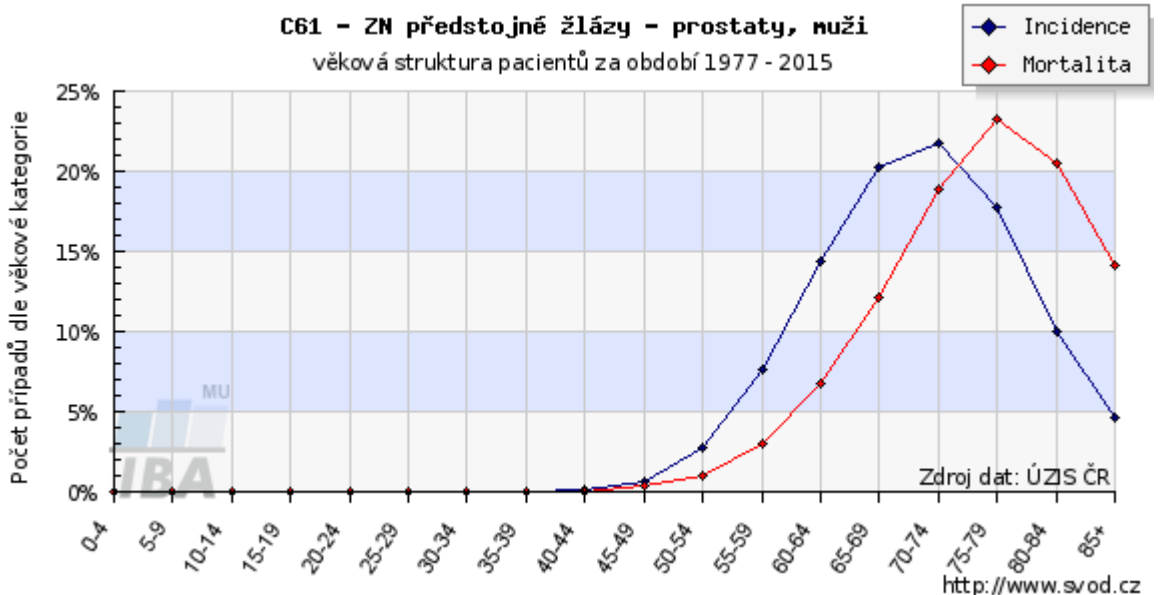




N ENGL J MED 349;4 WWW.NEJM.ORG JULY 24, 2003

Karcinom prostaty - incidence



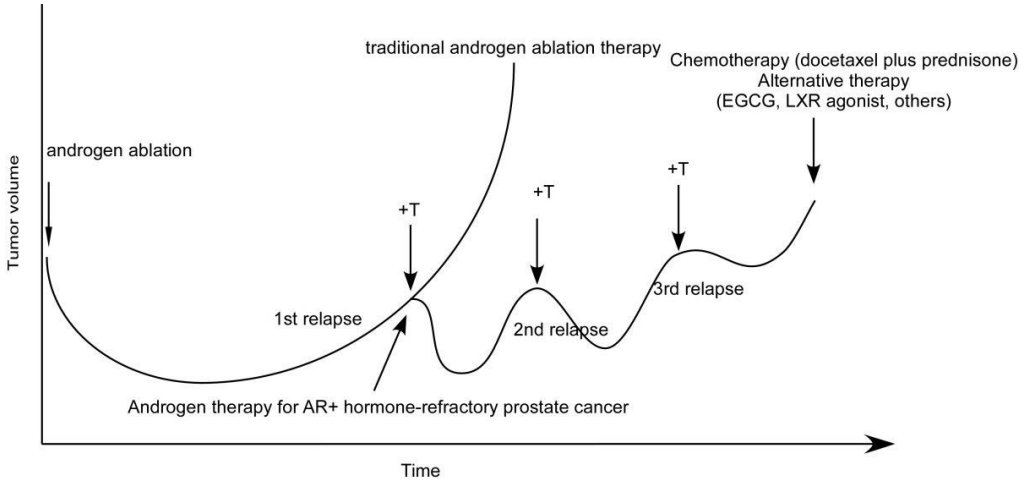


Karcinom prostaty – rizikové faktory, prognóza

- Riziko
  - Hladina DHT (etnický původ)
  - Věk
  - Rodinná anamnéza (15%, mutace BRCA1, BRCA2)
  - Stravovací návyky
- Prognóza
  - TNM, Gleasonovo skóre, Prostate Specific Antigen (PSA) – nízké < 10ng/ml, vysoké > 20ng/ml
- Klinické příznaky
  - 75% nádorů bez příznaku, krev v moči a ejakulátu, poruchy močení, metastázování do kostí
- Diagnostika
  - Biopsie, PSA, sonografie, MRI, scintigrafie skeletu

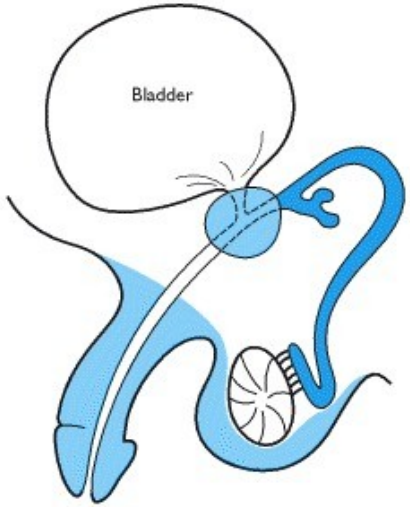
Léčebný postup

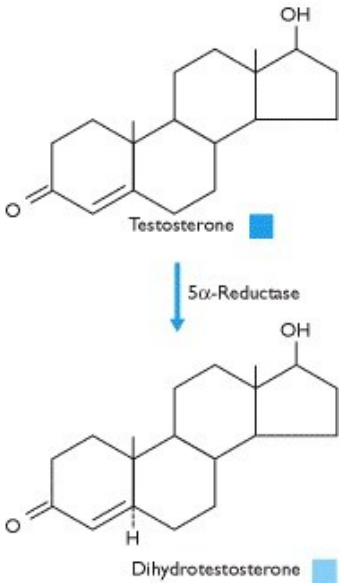
- Nemocní s velmi nízkým rizikem
  - Terapie v případě výhledu přežití > 20 let
  - jinak pouze observace
- Nemocní s nízkým rizikem
  - v případě výhledu přežití do 10 let
    - observace
  - v případě výhledu přežití > 10 let
    - radikální prostatektomie
    - Radikální ozáření
- Nemocní se středním rizikem
  - v případě výhledu přežití do 10 let
    - observace
  - v případě výhledu přežití > 10 let
    - radikální prostatektomie
    - Radikální ozáření
    - Krátkodobá **androgen deprivation therapy (ADT)**
- Nemocní s vysokým rizikem
  - v případě výhledu přežití do 5 let
    - observace
  - v případě výhledu přežití > 5 let
    - radikální prostatektomie
    - Radikální ozáření
    - androgen deprivation therapy (ADT)



Hlavní místa syntézy mužských pohlavních hormonů:

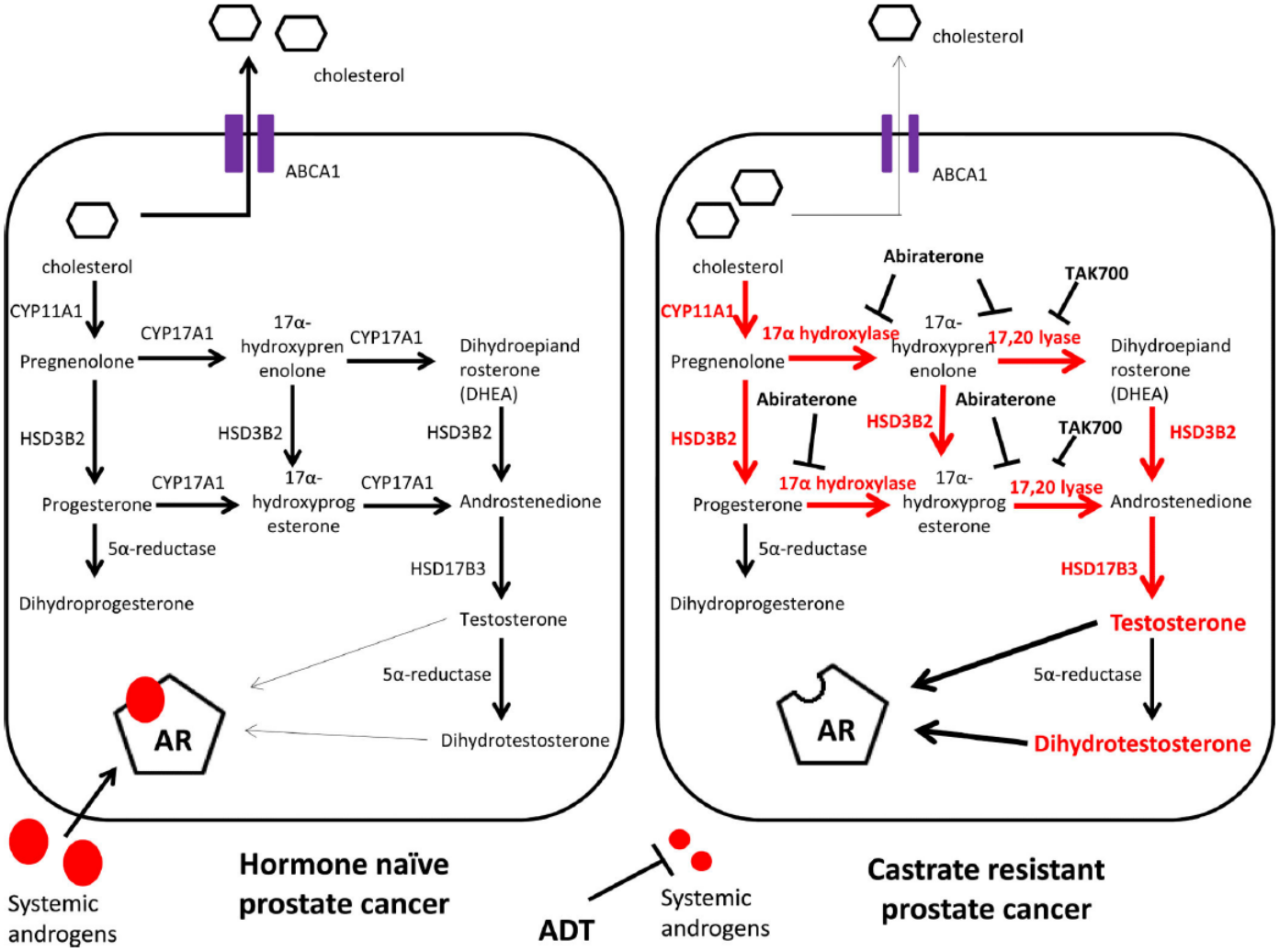
Muž (%)	Varlata	Nadledvinky	Konverze ve tkáních
Testosterone	95	<1	<5
5α-DHT	20	<1	80
Androstenedione	20	<1	90
DHEA	2	<1	98
DHEA-S	<10	90	-





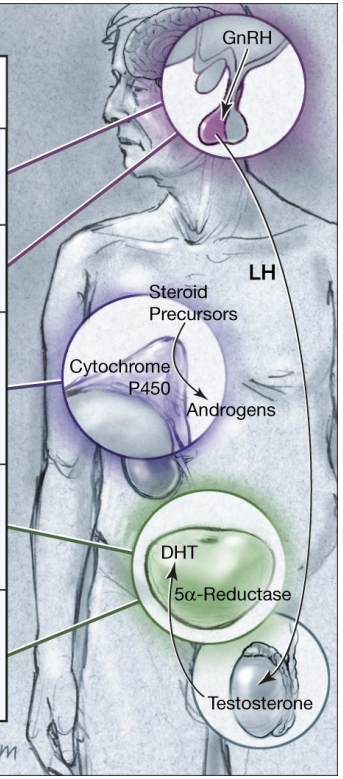
Endocrinology: An Integrated Approach, Nussey S and Whitehead S., 2001.

Biosyntéza androgenů

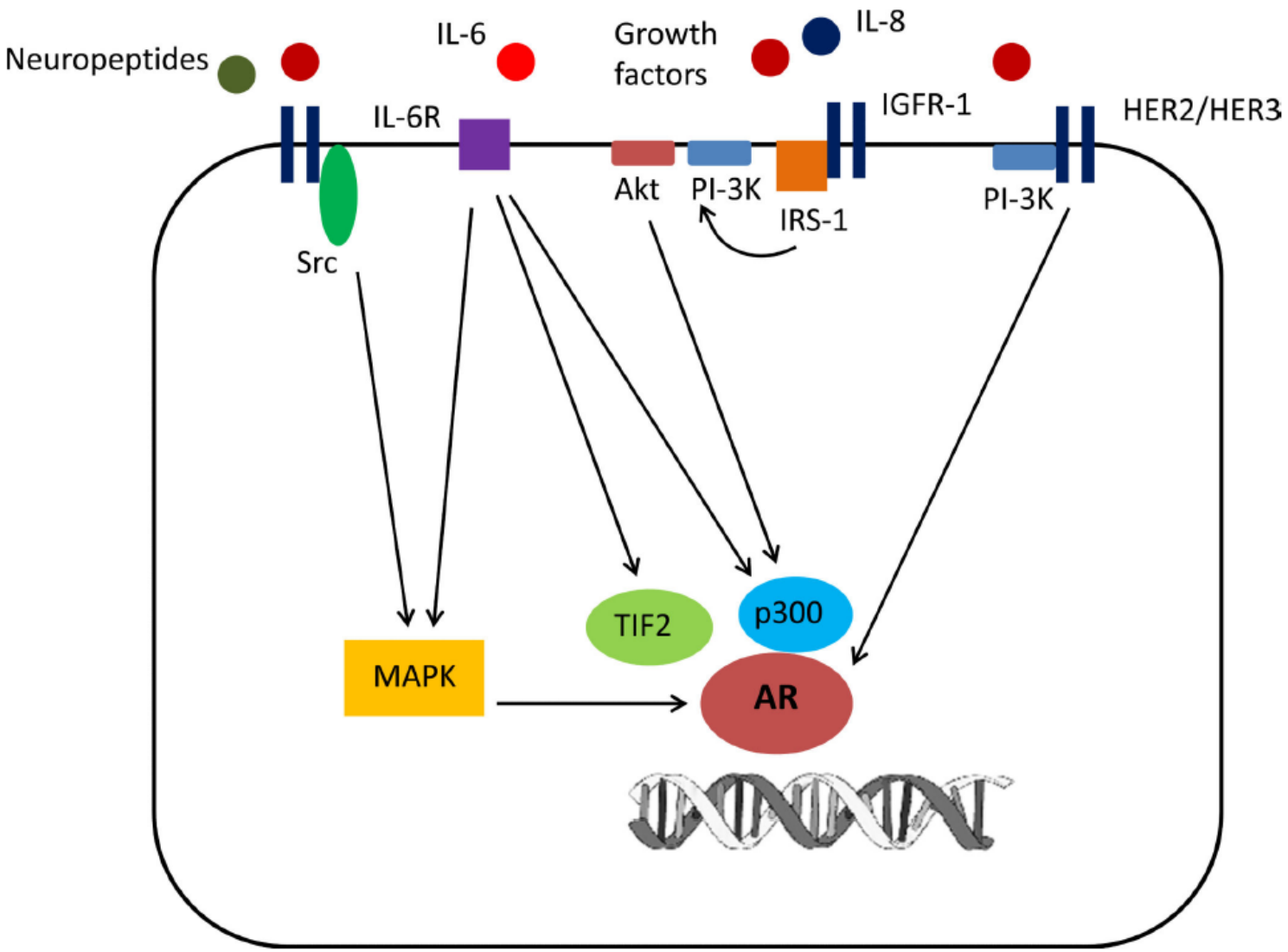


Mechanismy karcinogeneze

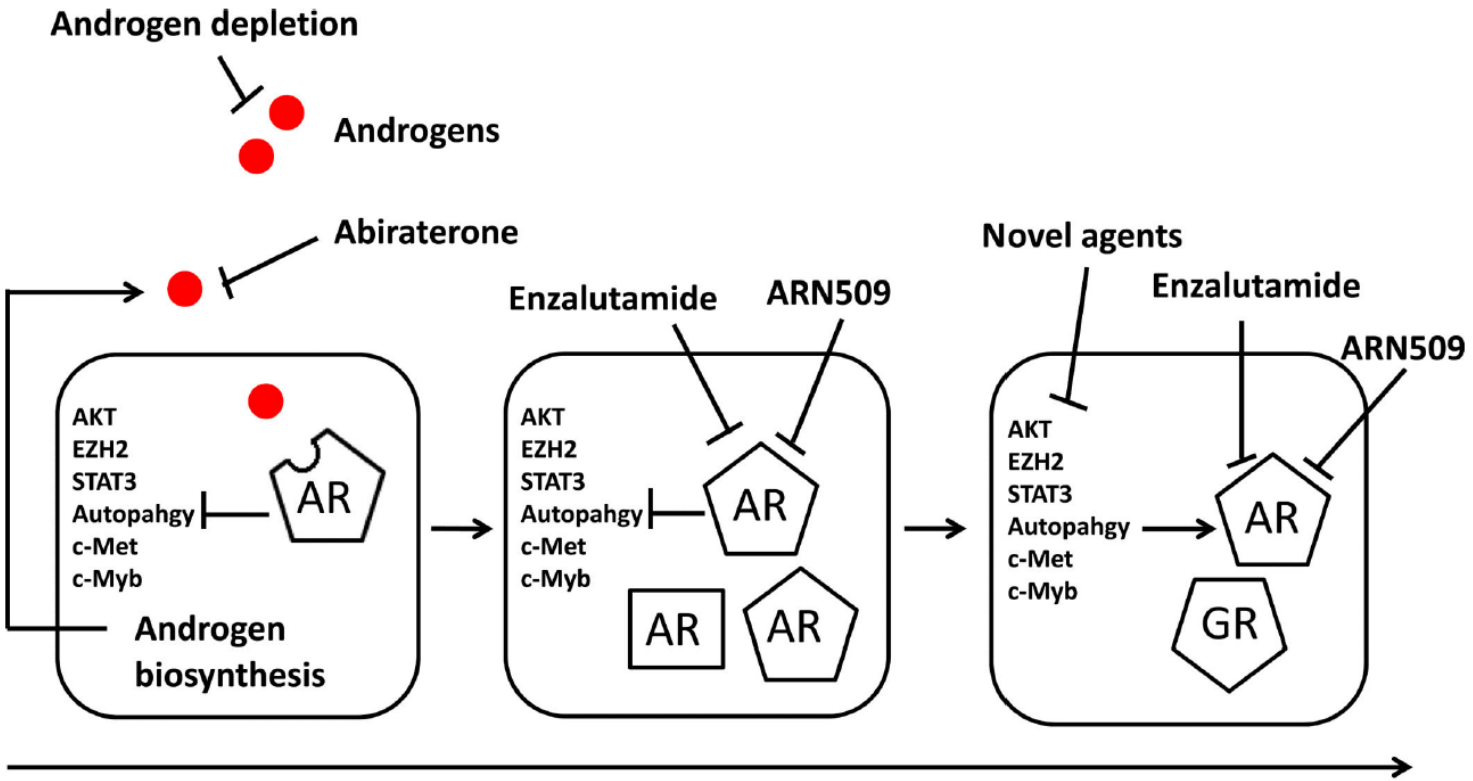
Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gondatropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix*	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5α-Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase	No Defined Role in Standard Care of Prostate Cancer



Alternativní onkogenní dráhy regulující postranslační modifikace AR

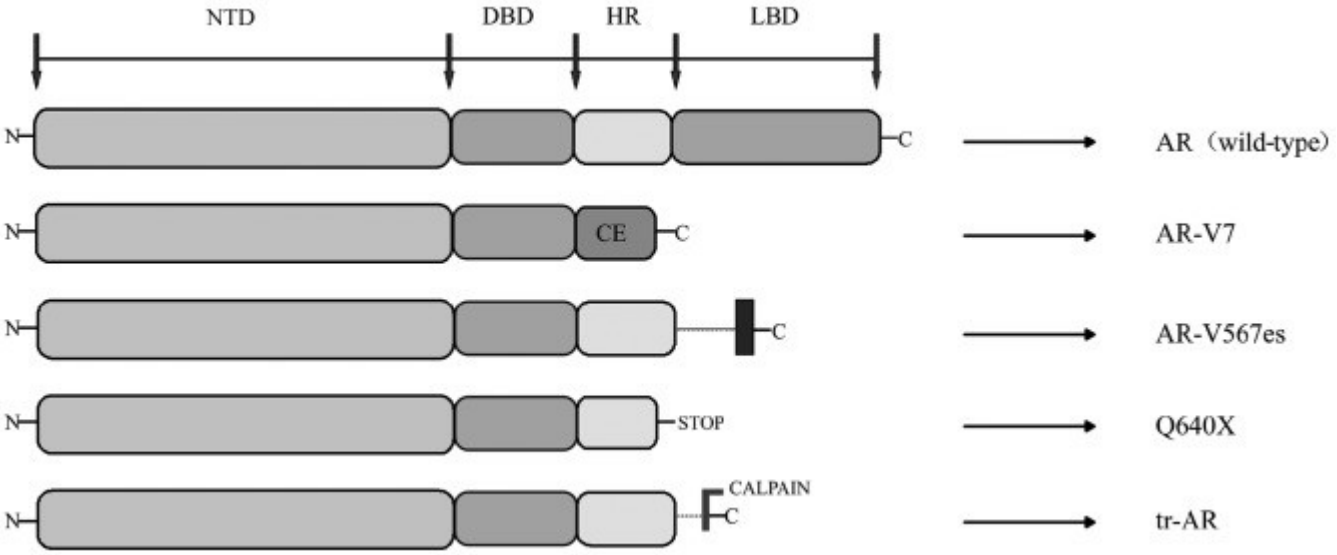


Progrese karcinomu prostaty



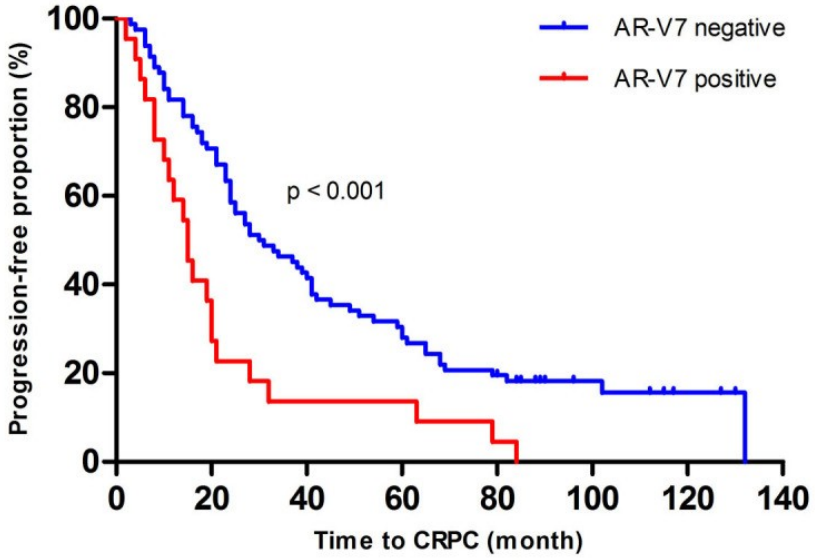
- Androgen biosynthesis at the tumor microenvironment
- AR mutations
- AR amplifications
- AR variants
- GR upregulation
- Alternative oncogenic signaling induction

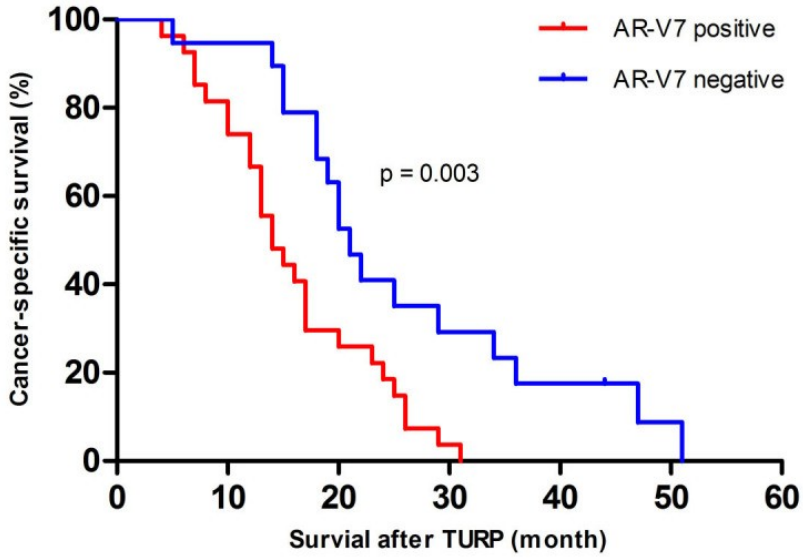
AR a jeho varianty



AR, full length AR wild type; AR-V7, product of alternative splicing, CE; ARv567es, product of altered splicing, exon 5, 6 and 7 skipped during splicing; Q640X, AR with a nonsense mutation leading to a tr-AR of 640 aa; enzymatically cleaved by calpain. AR, androgen receptor; DBD, DNA-binding domain; LBD, ligand-binding domain; PCa, prostate cancer; CE, cryptic exon; tr-AR, truncated AR; AR-V, AR splice variants; NTD, N-terminal domain; HR, hinge region.

Role AR-A7 v rozvoji rezistentního karcinomu prostaty





Vakcína proti karcinomu prostaty

- sipuleucel-T (Provenge) - vakcína pro léčbu karcinomu prostaty (od roku 2010)
- Imunogen – prostatic specific phosphatase
- Využití v terapii pokročilého onemocnění – rezistentního na anti-androgenní léčbu
- 100 000 USD/patient
- Další v testech – např. POSTVAC, rekombinantní poxvirus exprimující PSA

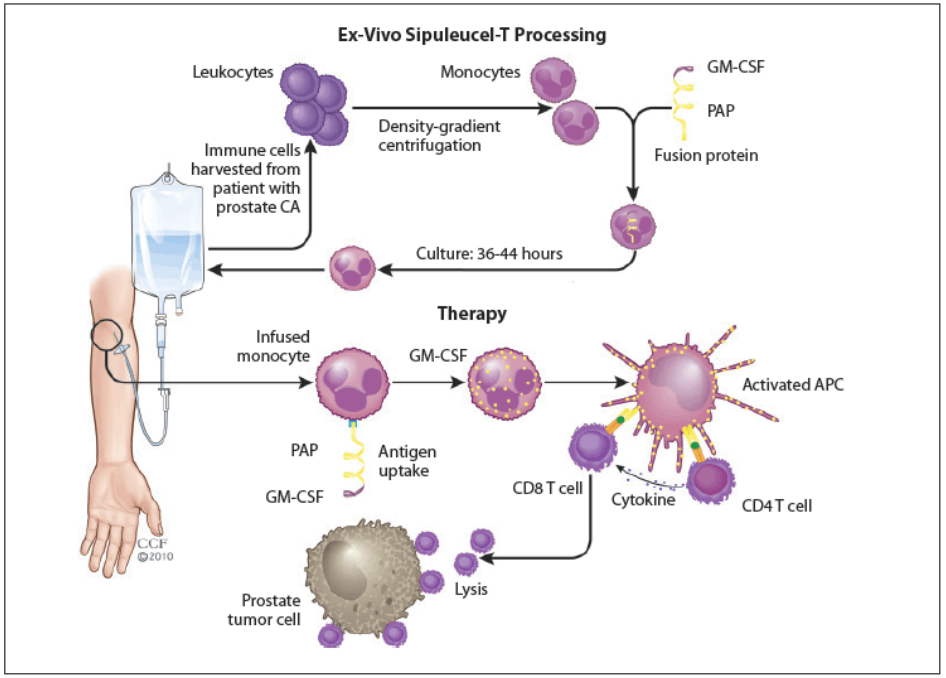
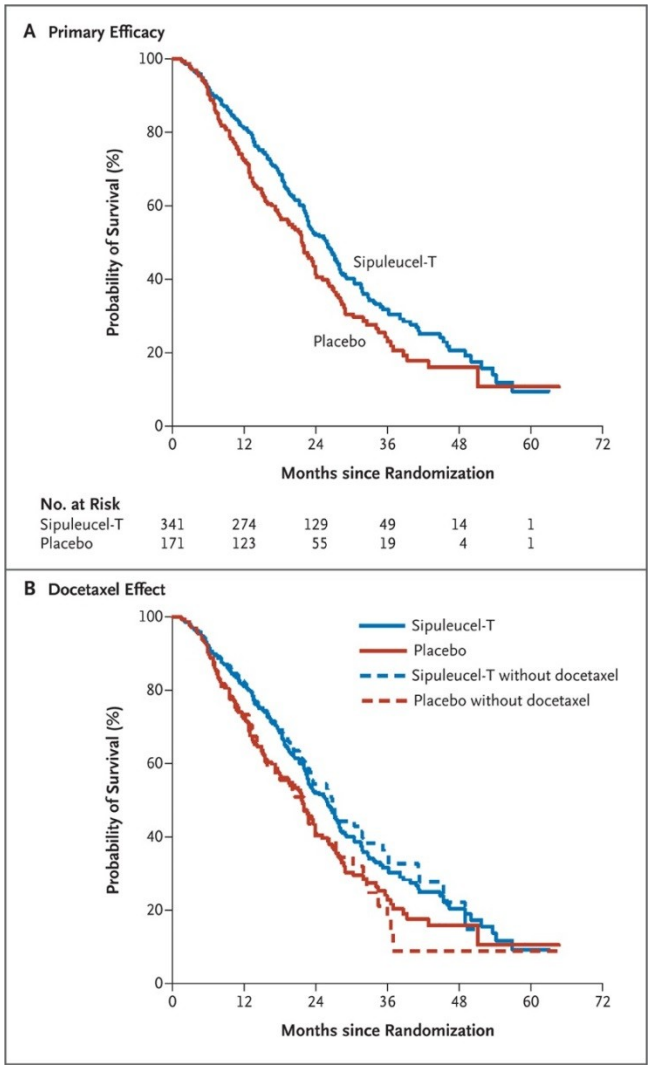


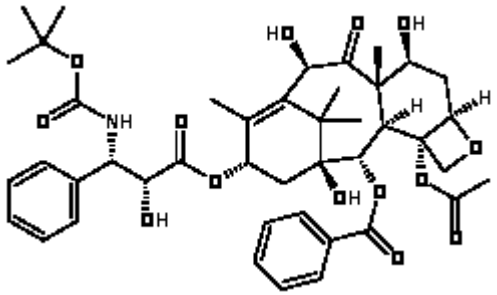
Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient's dendritic cells and then pulsing these ex vivo with a recombinant fusion protein made of prostatic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM-CSF); and (2) infusing the cultured cells into the patient, where the PAP–GM-CSF-loaded antigen-presenting cells induce the proliferation of T-cells that recognize and target prostate tumor cells. APC = antigen-presenting cell.

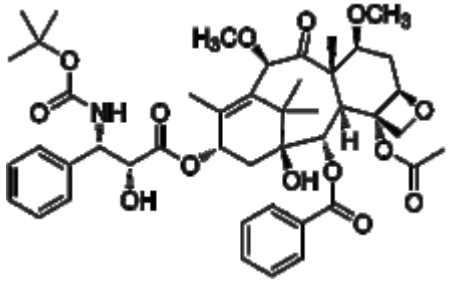
sipuleucel-T (Provenge)

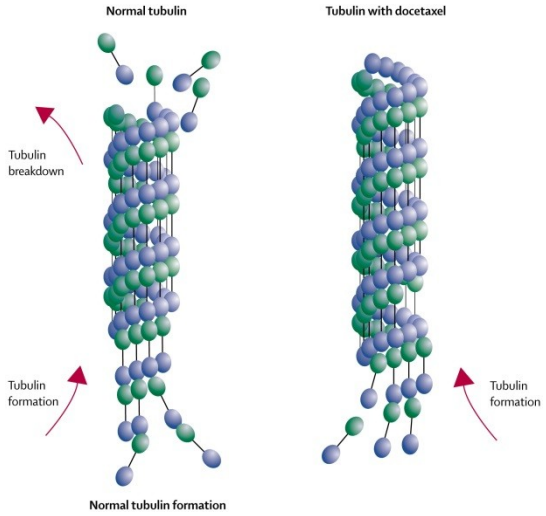


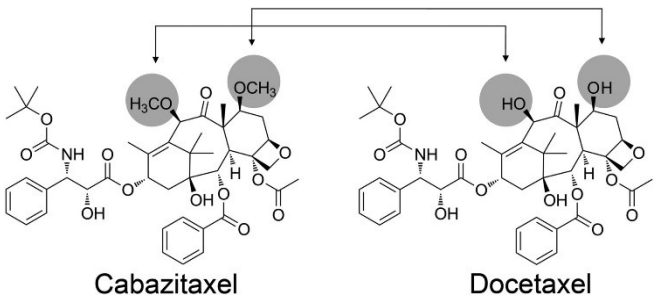
Chemoterapie pokročilého adenokarcinomu prostaty

- Docetaxel (Taxotere)
  - Semi-syntetický analog paclitaxelu
  - Stabilizuje mikrotubuly
  - Benefit ~ 5 měsíců
  - rezistence
- Cabazitaxel (Jevtana)

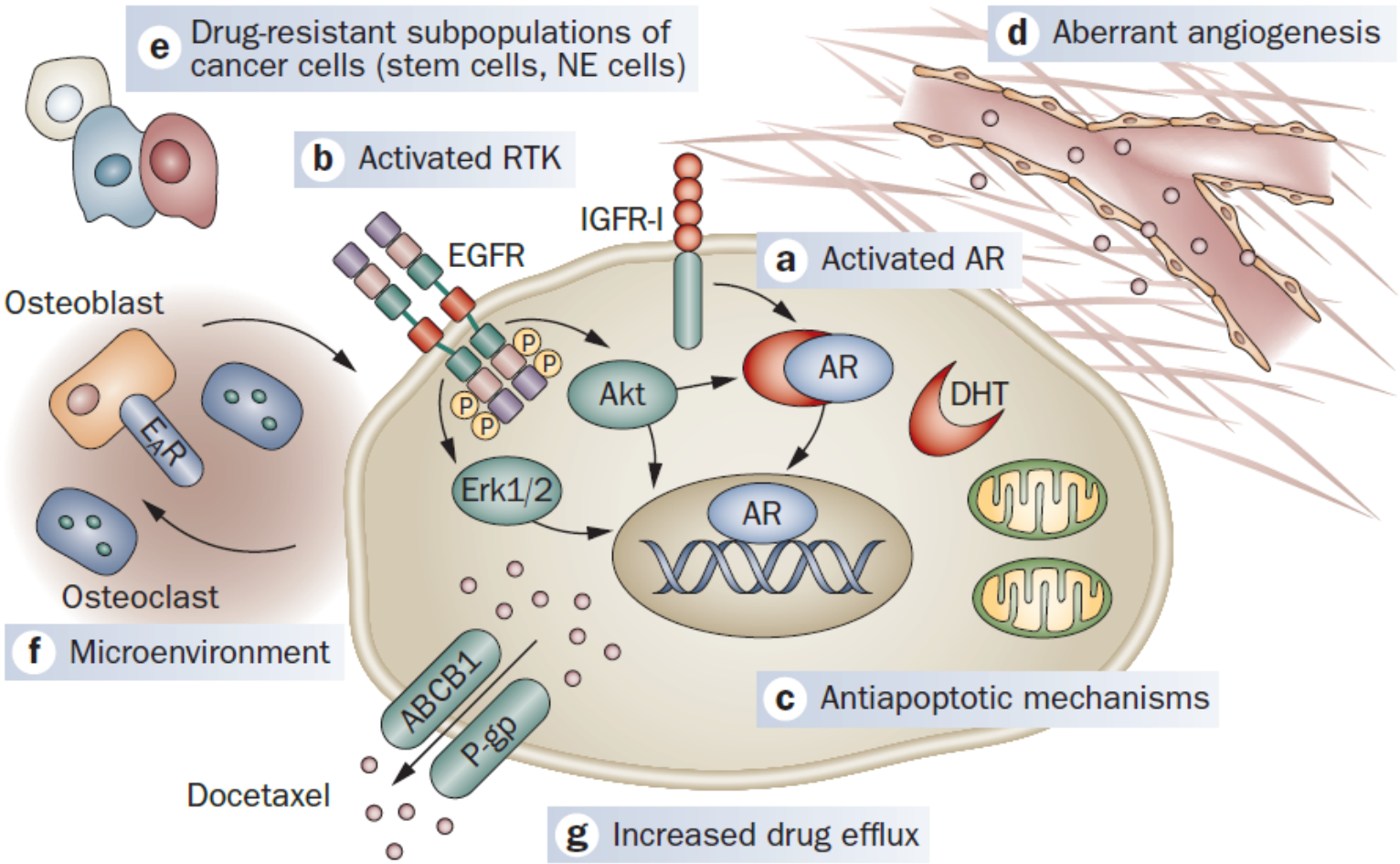








Mechanismy docetaxelové rezistence



Shrnutí

- Nádory prsu
  - Hormonálně dependentní – lze relativně šetrně léčit
  - TNBC – neexistuje cílená léčba
  - Dlouhé období dormance
  - ? mechanismus aktivace a vzniku makrometastáz
  - Zásadní otázky:
    - Jaké nádory léčit?
      - Lepší biomarkery a prediktory
    - Koho a jak často vyšetřovat mamogramem?
    - Jaké jsou skutečné možnosti imunoterapie?
    - Jaké jsou faktory rizika?
- Nádory prostaty
  - AR cílená terapie končí rozvojem rezistentního, metastazujícího onemocnění
  - Zásadní otázky:
    - Co způsobuje nádorové onemocnění prostaty?
    - Je testování hladiny PSA vhodnou metodou pro screening?
    - Je bezpečné neléčit nádory prostaty?
    - Je možná léčba pokročilého karcinomu prostaty?