Pathology of the Breast

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Fibrocystic changes

Fibrocystic changes

(previously ***fibrous cystic mastopathy***, ***fibrocystic disease***)

- **common process** in women of reproductive age, postmenopausal development is rare
- risk of carcinoma is **not increased**
- clinical significance: differential diagnosis of malignant process *(physical examination, imaging studies, biopsy)*
- caused by hormonal dysbalance *(hyperestrinism, decreased gestagens)*
- protective factor: hormonal contraception

CYSTS

- **different size**
- **epithelial proliferation**
- **apocrine metaplasia**

FIBROSIS

- **chronic inflammation and fibroproduction after the cyst rupture**

ADENOSIS

- **increased number of acini in lobule**
- **intact basal membrane**
- **preserved myoepithelial layer**

Benign epithelial proliferations

- **Sclerosing adenosis**

- acinar proliferation, intact basal membrane and myoepithelial layer
- prominent fibrosis with acinar compression – trabecular formations resembling carcinoma

- **Complex sclerosing lesion (radial scar)**

- star-shaped lesion
- adenosis with central scar and associated intraductal proliferation
- intact basal membrane and myoepithelial layer

- slightly increased risk of invasive carcinoma (1,5 – 2 x)

Intraductal proliferative lesions and precursors of carcinoma

- **Usual Ductal Hyperplasia (UDH)**

  - intraductal epithelial proliferation

  - obliteration of the duct with fenestrations

  - without cytologic atypia

  - slightly increased risk of invasive carcinoma (1,5 x)

- **Atypical Ductal Hyperplasia (ADH)**

  - intradutal epithelial proliferation with cytologic atypia

  - monomorphic cells

  - some lesions are clonal

  - moderately increased risk of invasive carcinoma (4 – 5 x)

- **Ductal Carcinoma In Situ (DCIS)**

  - monomorphic cells and / or cytologic atypia

  - mammographic screening

  - highly increased risk of invasive carcinoma (8 – 10 x)

classification:

- DCIS **comedo-type** (central necrosis and calcification), solid, cribriform, papillar, micropapillar

grading (nuclear atypia + necrosis):

- low grade DCIS *(grade 1)* – without necrosis and atypia
- intermediate grade DCIS *(grade 2)* – with necrosis, without atypia
- high grade DCIS *(grade 3)* – with necrosis and atypia

Lobular proliferative lesions and precursors of carcinoma

- terminology – *low reproducibility, questionable prognostic significance*:

- **Atypical Lobular Hyperplasia (ALH)**

- **Lobular Carcinoma In Situ (LCIS)**

- multicentric (85%) and bilateral (50-70%) (DCIS 10-20%)
- macroscopically discrete, without calcifications, incidental finding
- proliferation of dyscohesive cells in TDLU
- TDLU architecture is preserved

- highly increased risk of invasive carcinoma (7 – 12 x)

Intraductal papillary tumors

- **Peripheral intraductal papilloma**

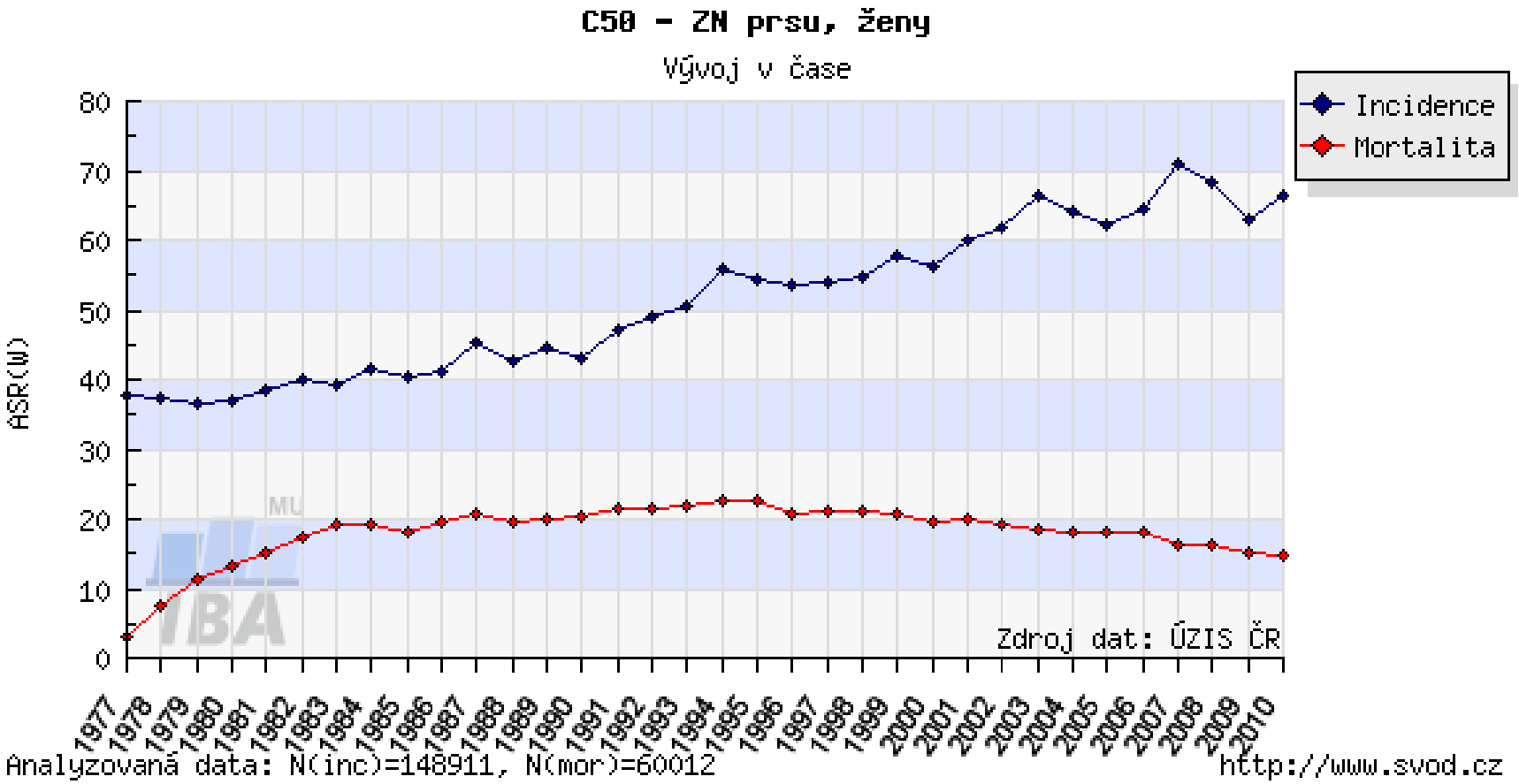
- affects TDLU, multifocal
- microscopic size, clinically asymptomatic
- intraductal papillary proliferation
- associated with UDH, ADH, DCIS
- slightly increased risk of invasive carcinoma (1,5 – 2 x)

- **Central intraductal papilloma**

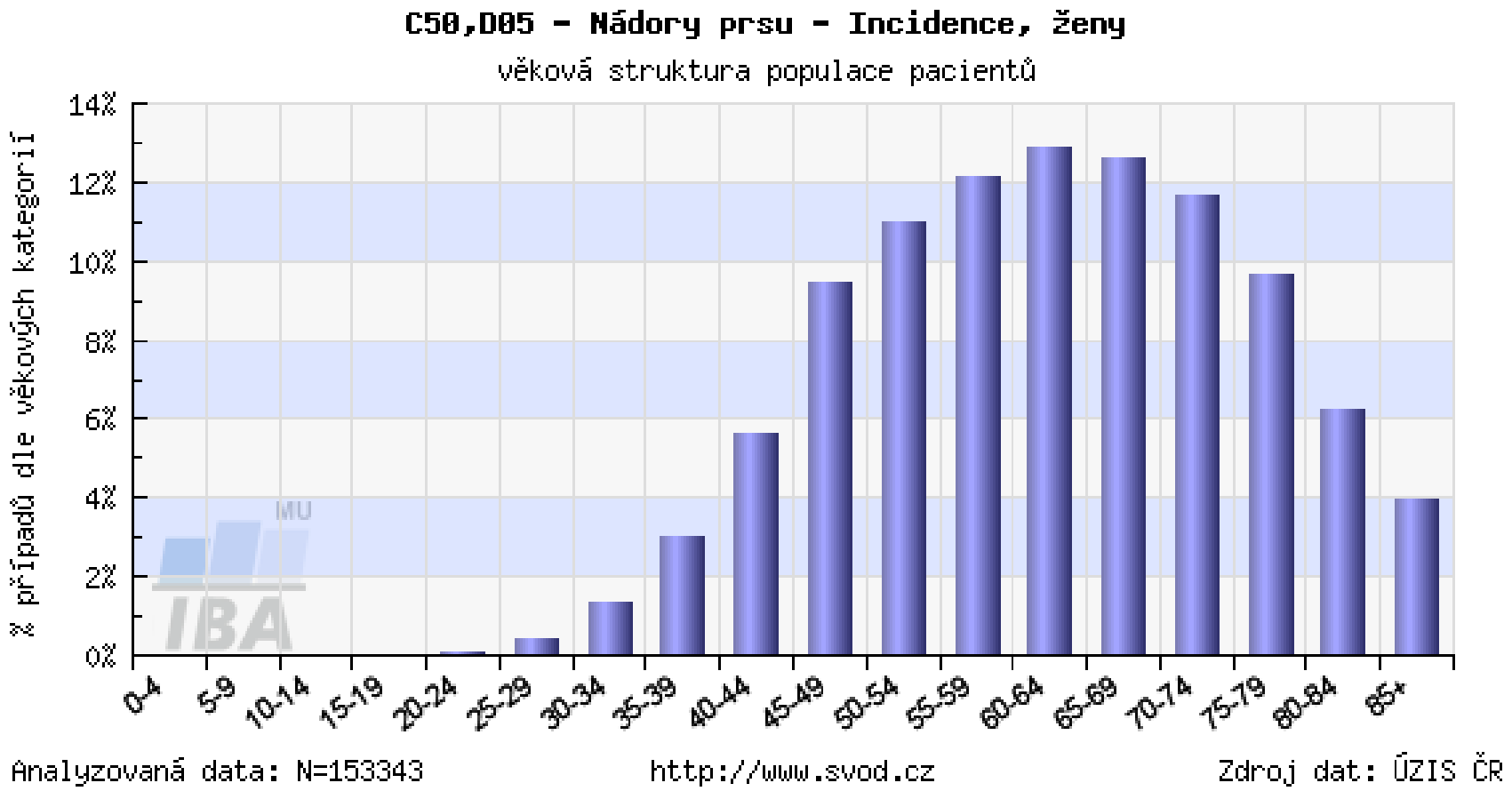
- solitary lesion in larger ducts
- serous or hemorrhagic discharge from nipple
- NOT precursor of papillary carcinoma

Invasive carcinomas

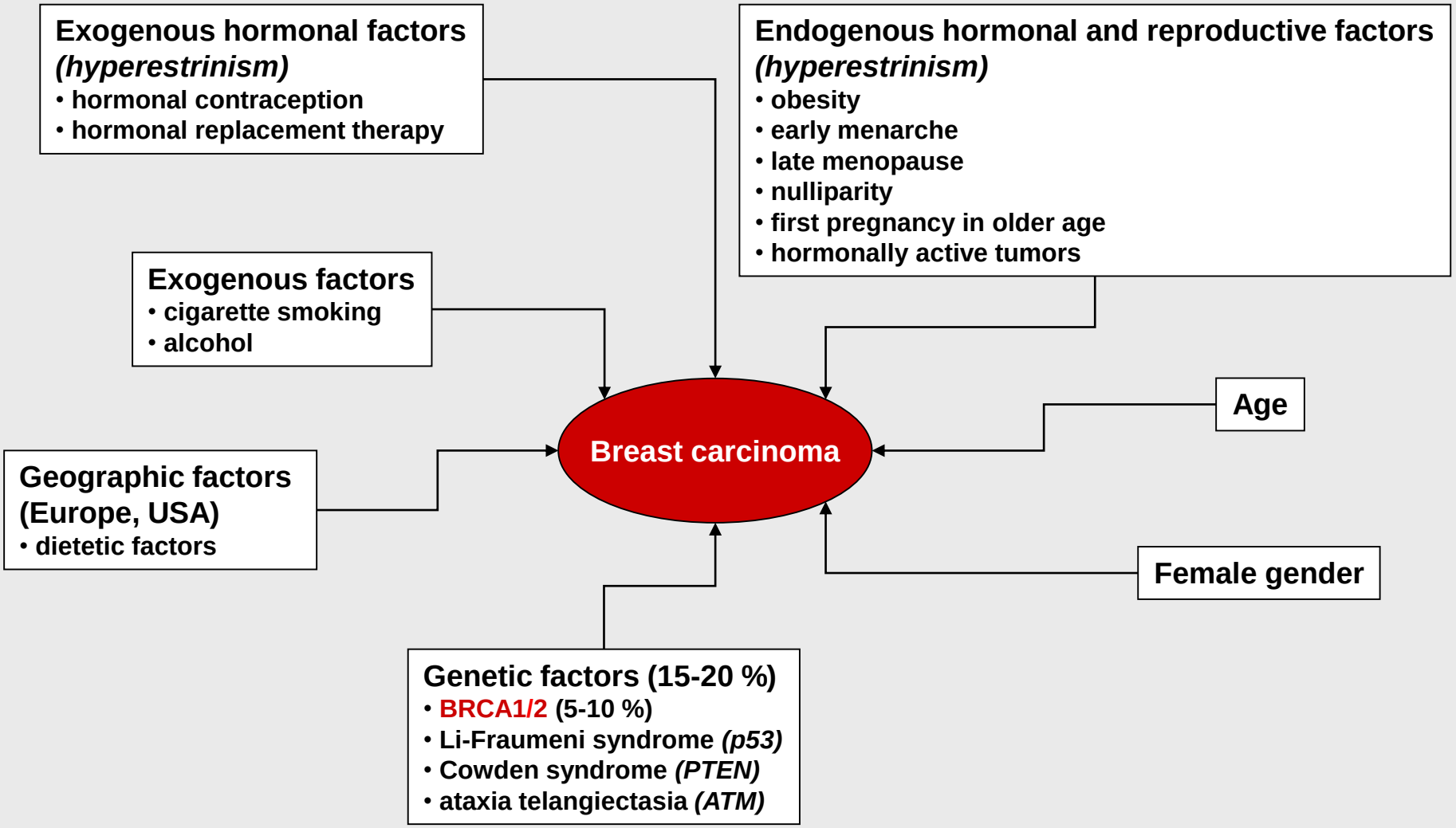
Incidence and mortality



Age distribution



Etiology


Exogenous hormonal factors
(hyperestrinism)
• hormonal contraception
• hormonal replacement therapy
Endogenous hormonal and reproductive factors
(hyperestrinism)
• obesity
• early menarche
• late menopause
• nulliparity
• first pregnancy in older age
• hormonally active tumors
Exogenous factors
• cigarette smoking
• alcohol
Age
Breast carcinoma
Geographic factors
(Europe, USA)
• dietetic factors
Female gender
Genetic factors (15-20 %)
• BRCA1/2 (5-10 %)
• Li-Fraumeni syndrome (p53)
• Cowden syndrome (PTEN)
• ataxia telangiectasia (ATM)

BRCA1/2 syndrome

Hereditary breast and ovarian cancer syndrome

- triple negative invasive ductal carcinomas
- medullary carcinomas

- prophylactic mastectomy
- prophylactic salpingo-oophorektomy

The role of pathology

Histopathologic / cytologic evaluation of tissue:

- **biologic behavior** of lesion

- **histologic type** of tumor

- **tumor grade** (prognostic significance)

- **predictive factors** (targeted therapy)
(estrogen and progesterone receptors, overexpression c-erb-B2)

- **tumor stage** (TNM) and **surgical margins**

Non-surgical biopsy / cytology

FNA (Fine Needle Aspiration)

CNB (Core Needle Biopsy)

Surgical biopsy

- **Incisional biopsy**

  - part of the tumor

- **Excisional biopsy**

  - conservative surgery:

  - segmentectomy
  - kvadrantectomy
  - lumpectomy

  - radical surgery:

  - modified radical mastectomy

SLN (Sentinel Lymph Node)

Histologic types

Carcinoma in situ	
Ductal carcinoma in situ (DCIS)	80 %
Lobular carcinoma in situ (LCIS)	20 %
Invasive carcinoma	
Ductal carcinoma Invasive carcinoma of no special type (NST)	80 %
Lobular carcinoma	10 %
Tubular carcinoma	5 %
Mucinous carcinoma	2 %
Medullary carcinoma	2 %
Papillary carcinoma	1 %
Metaplastic carcinoma	rare

- **Invasive ductal carcinoma**

- prominent stromal fibrosis
- retraction of soft tissues, nipple and skin
- calcifications
- *E-cadherin* positive (IHC)

- **Invasive lobular carcinoma**

- bilateral (20%) and multicentric
- diffuse invasive growth (difficult detection by physical examination and mammography)
- metastatic spred on serous surfaces, in ovaries, uterus, bone marrow, meninges …
- *E-cadherin* negative (IHC)

- **Medullary carcinoma**
  - younger age, BRCA1/2 mutations
  - well circumscribed, better prognosis than IDC
  - prominent atypia, syncytial growth, lymphocytic infiltration
- **Mucinous carcinoma**
  - older age, slow growth, good prognosis
  - abundant extracellular mucin
- **Tubular carcinoma**
  - younger age
  - well differentiated, good prognosis
- **Papillary carcinoma**
  - good prognosis
- **Metaplastic carcinoma**
  - sarcomatoid component
  - poor prognosis

Invasive carcinoma of the breast

- left breast more frequently, upper outer quadrant
- 5-10 % synchronous or metachtonous contralateral carcinoma
- **signs of local progression:** firm fixed solid mass, infiltration of soft tissues, skin or chest wall, restraction of skin and/or nipple, secretions from nipple, ulceration
- **grading (1-3):** combined score *(Elston – Ellis) – extent of tubular formations, level of nuclear atypia and number of mitotic figures* (/10 HPF)
- **LVSI:** lymphedema (peau d'orange), **inflammatory carcinoma**
- **lymphogenic spread** in axillary lymph nodes (level I, II and III) – **sentinel lymph node**
- **pleural and pericardial dissemination**
- **hematogenic spread** (lungs, bones, liver, brain …)
- **mammographic screening**

Prognostic factors

- **lymph node metastases - TNM**
- **local progression (skin, chest wall) - TNM**
- **tumor size - TNM**
- **histologic type**

- tubular, mucinous, medullary and papillary carcinomas have better prognosis than IDC

- **grade**
- **LVSI**

- **positivity of estrogen and progesterone receptors**

- antihormobnal therapy (tamoxifen) – better prognosis

- ***c-erb-B2 (HER-2/neu)* overexpression** **(Human Epidermal growth factor Receptor 2)**

- monoclonal antibodies (trastuzumab - Herceptin)

- **triple negative tumors** (10-20 %) – ER, PR and c-erb-B2 negative

- BRCA 1/2 syndrome

Fibroepithelial tumors

- **fibroadenoma**

- common benign tumor, young women (under 30 years of age)
- well circumscribed, movable
- slightly increased risk of subsequent invasive carcinoma

- **phyllodes tumor** (older term **cystosarcoma phyllodes**)

- older women
- resemble fibroadenoma
  (higher cellularity and proliferation of stromal component)

- *benign* (local progression)
- *borderline*
- *malignant* (sarcomatous overgrowth, hematogenous spread)

Other tumors

- **hemangioma**
- **lipoma**
- **leiomyoma** (nipple area)
- **fibromatosis** (desmoid tumor)
- **angiosarcoma**
  - ***primary*** (de novo)
  - ***secondary*** (after mastectomy – lymhedema and/or radiotherapy)
- **liposarcoma**
- **leiomyosarcoma**
- **lymphoma** (DLBCL, ALL, MALT, BL)

Nipple tumors

- **Nipple adenoma**

- tubular architecture
- palpable mass
- serous or hemorhagic discharge

- **Paget's disease**

- intraepithelial migration of tumor cells from DCIS or IDC into the skin of the nipple and areola
- eczematous appearance, retraction of the nipple, ulceration
- dif. dg.: melanoma (mucicarmine stain, IHC)

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