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Breast Cancer: an overview -on molecules, targets, & tumors

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Breast cancer

- Most frequent malignancy in women worldwide
- Curable in 70-80% of patients with early stage, non-metastatic disease
- Advanced, metastatic breast cancer: incurable

- *In thinking about precision medicine: at the molecular level- - **heterogeneous***

Advanced, metastatic breast cancer

- Is treatable
- Numbers of those living with advanced disease not well-documented
  - Cancer registries track diagnosis and deaths, not relapses
- The main goals of treatment are:
  - Prolong survival (Stage IV: 5YS 22% and median is 3 y) and control symptoms
  - Diminish treatment-associated toxicity
  - Maintain or improve quality of life

How to understand better the link between breast cancer, molecular markers, treatment, and outcomes

Breast cancer

- 2018, 2.1 million women were newly diagnosed with breast cancer (1/18 sec)
  - 626,679 women died
- Global incidence of breast cancer: rising by 3.1% annually
  - 641,000 cases in 1980 and increased to >1.6 million in 2010
- Increases regardless of SES
  - Population growth and aging population
- The female population: 49.5% of the global population and larger proportion of the population >60 years of age.

Incidence and outcomes

- Higher in high-income regions (92 per 100,000 in North America) than in lower income regions (27 per 100,000 in middle Africa and eastern Asia)
  - Likely reflects both differences in longevity, risk factors, and the availability of mammography
- Outcomes:
  - High income countries: breast cancer often diagnosed early, prognosis is usually good
  - Low- and middle-income countries, breast cancer often diagnosed later with poorer survival
    - Despite lower incidence overall, poorer survival due to delayed presentation, late stage at diagnosis, and limited access to treatment.

Incidence and age

- Age at diagnosis
  - Presents earlier in Asian women (typically 40–50 years of age) than in their western counterparts (typically 60–70 years of age)
  - In developing countries, women diagnosed with breast cancer are ~10 years younger than those in developed countries.
    - Proportion of patients (<35 years of age) varies from ~10% in developed countries to up to 25% in developing Asian countries

Incidence, biology, and mortality

African and African-American women

- Highest TNBC rates
- Highest rates of poorly differentiated or undifferentiated grade among all subtypes
- Higher rates of metastatic disease
  - Metastatic breast cancer represents 9% of diagnoses among non-Hispanic black women compared with 5–6% of diagnoses in other ethnic groups

Treatment strategies

- Locoregional:
  - Surgery
  - Radiation therapy
- Systemic therapy:
  - Endocrine therapy for hormone receptor-positive disease
  - Chemotherapy
  - Anti-HER2 therapy for HER2-positive disease,
  - Bone stabilizing agents
  - Poly(ADP-ribose) polymerase (PARP) inhibitors for *BRCA* mutation carriers
  - Immunotherapy

Survivorship

- Survival gains (1975–2013): the 5-year cause-specific survival of non-Hispanic white women (19–37%) higher than that of other ethnic groups, particularly non-Hispanic black women (16–26%)
- Causes may be multifactorial:
  - Genetic predisposition, lifestyle, access, bias, environmental factors/exposures


NO
STOPPING
ANY
TIME

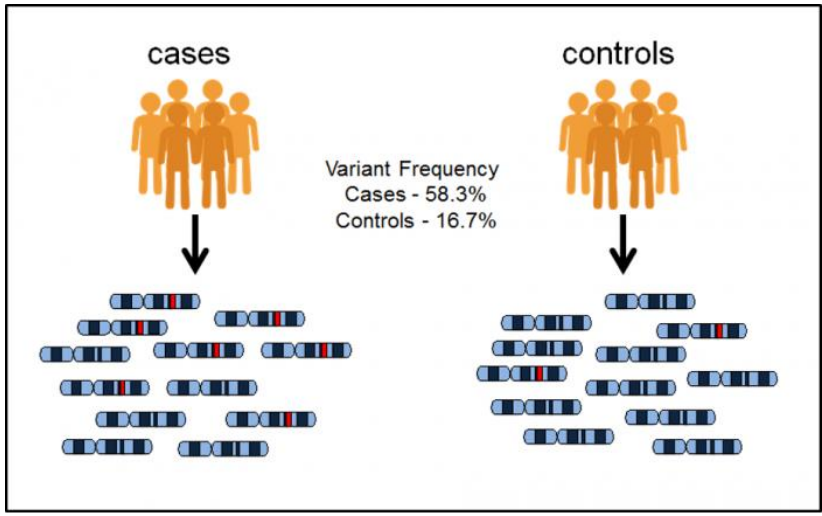
Breast Cancer: carcinogenesis

- Genetic disease: DNA changes lead to cancer

- Deeper understanding into carcinogenesis: how do genetic changes alter cell growth, invasion, and metastases?
  - Most cancers are sporadic in origin
  - Caused by an accumulation of somatic genetic alteration
  - Typical individual breast cancer: may harbor 50-80 different somatic mutations
    - Erroneous DNA replication
    - Exposure to endogenous or exogenous mutages

GWAS

- Genome wide association studies
  - Hypothesis free methods: identify associations between genetic regions (loci) and diseases
  - Hundreds of somatic breast cancer genes have been identified
  - More cancers need to be sequenced
  - International effort to produce a comprehensive catalog of genetic alterations



https://www.ebi.ac.uk/training/online/course/gwas-catalog-exploring-snp-trait-as

Finding the difference that makes a difference

- Of these mutations, which are oncogenic? Driver mutations?
- Most are “passenger” mutations
  - Harmless or biologically neutral changes

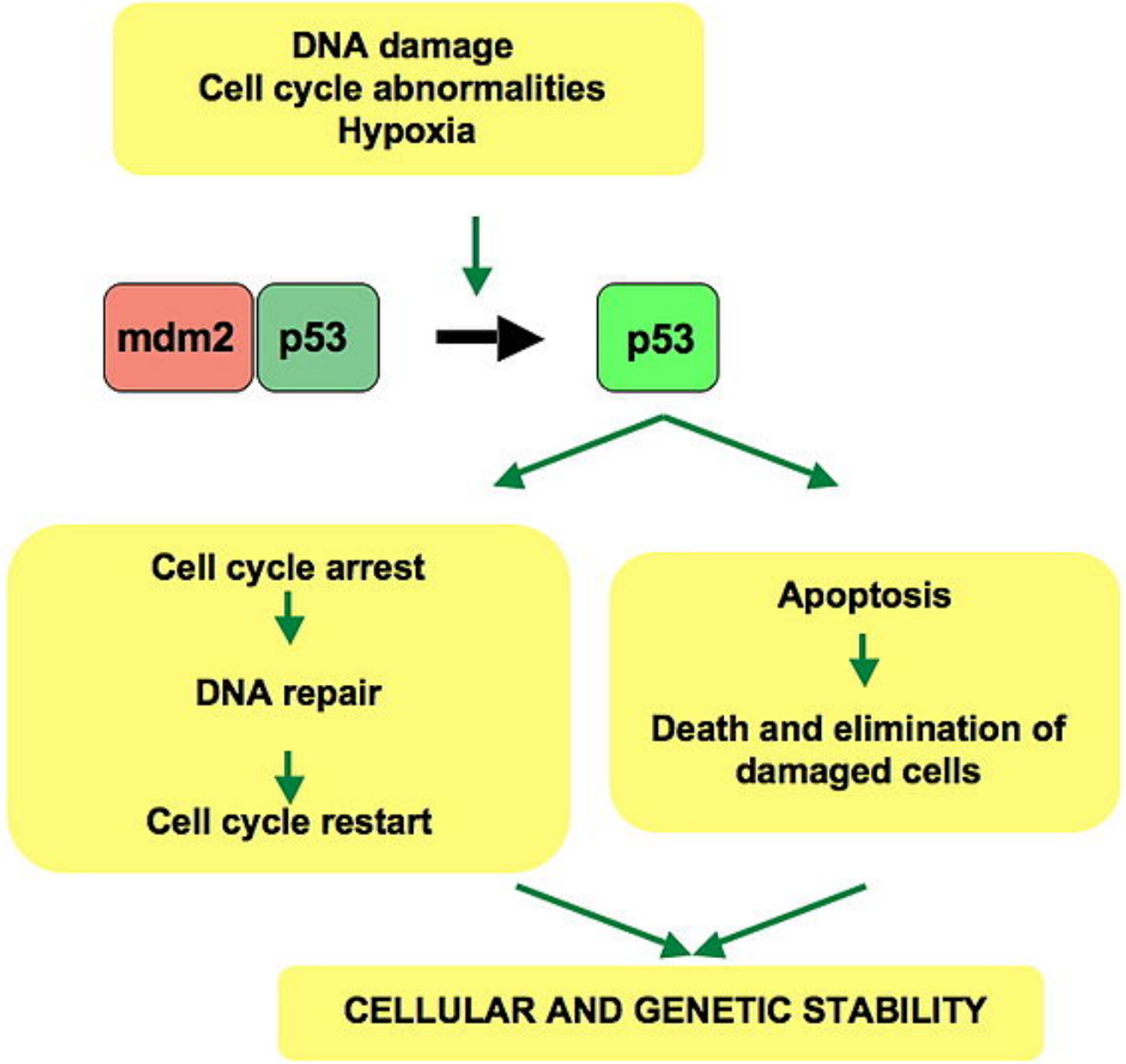
Most common mutations noted in breast cancer

- TP53
- CDH1
- P13K (phosphatidylinositol 3-kinase)
- Cyclin D
- PTEN
- AKT
- Other mutations: <5%,
  - Wide variability in phenotypes, tumor behavior, response to therapy
  - Large number of mutations may drive tumor progression through specific cell signaling pathways

Molecular alterations

- *TP53* (41%), *PIK3CA* (30%), *MYC* (20%), *PTEN* (16%), *CCND1* (16%), *ERBB2* (13%), *FGFR1* (11%) and *GATA3* (10%)
- Encode cell-cycle modulators that are:
  - repressed (for example, p53)
  - activated (for example, cyclin D1)
  - inhibit oncogenic pathways that are activated (MYC, HER2 and FGFR1)
  - inhibit tumor suppressors (PTEN)

sustain proliferation and/or inhibit apoptosis



https://en.wikipedia.org/wiki/P53

Cell cycle pathways

- Interferon signaling
- Cell cycle checkpoint
- BRCA 1/2 related DNA repair
- P53
- AKT
- RAS
- P13K
- Transforming growth factor-B signaling
- Notch
- Epidermal growth factor receptor
- FGF
- ERBB2

Particular regions of the genome may be more commonly amplified

- Example:
  - 17q12 amplification harbors the Her2 oncogene
  - Leads to a more aggressive tumor phenotype
  - Target for: trastuzumab, pertuzumab, lapatinib
  - Knocking down coamplified genes in this region: results in decreased cell proliferation and increased apoptosis

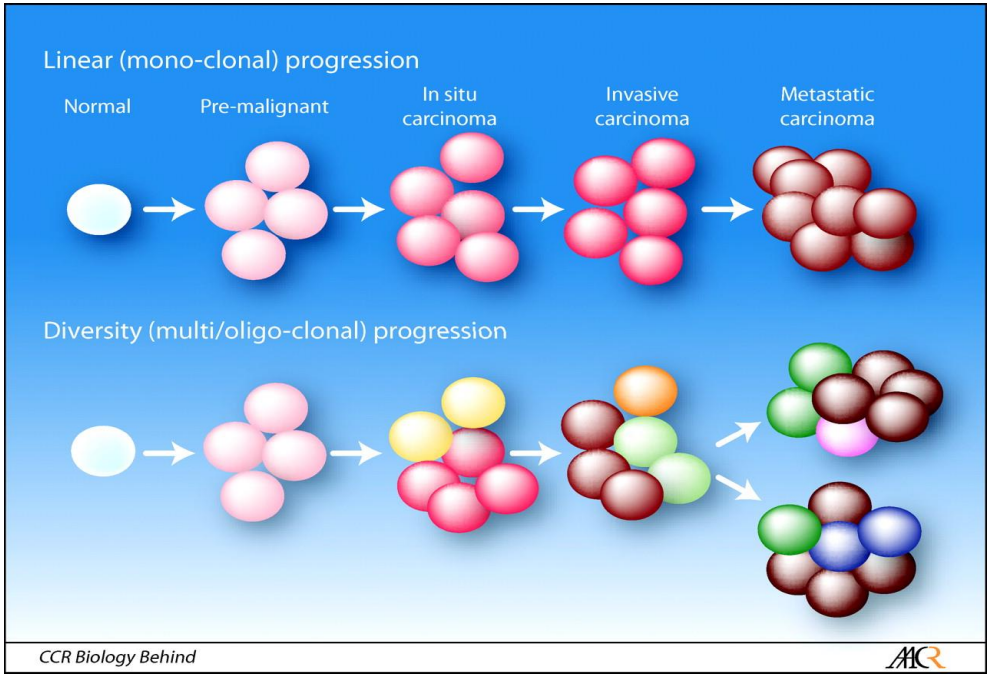
2000: classification of breast cancer

- From a focus on histology and tumor burden to biology

Breast cancer initiation: the 1st step

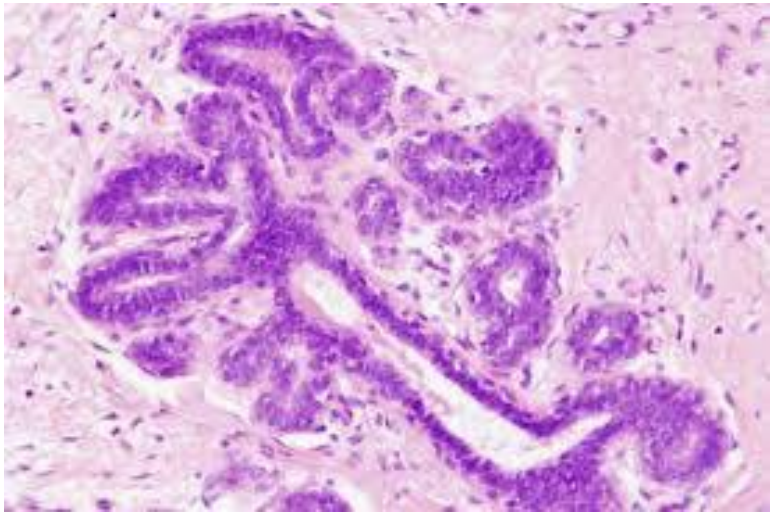
The exact mechanism is unknown

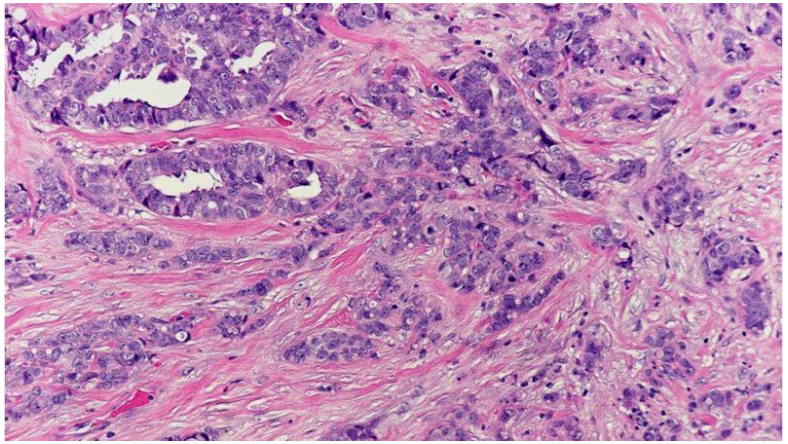
- Much effort has been made to molecularly characterize breast cancer and delineate its formation and progression
- At the cell of origin level:
  - the cancer stem cell model: precursor cancer cells initiate and sustain progression
  - the clonal evolution model: mutations accumulate, epigenetic changes in tumor cells occur and the 'fittest' cells survive



Breast cancer initiation

- At the morphological level: continuum of lesions and genetic modifications from normal glands to cancer





http://www.breastpathology.info/Normal-Structure.html

https://pathology.jhu.edu/breast/types-of-breast-cancer/

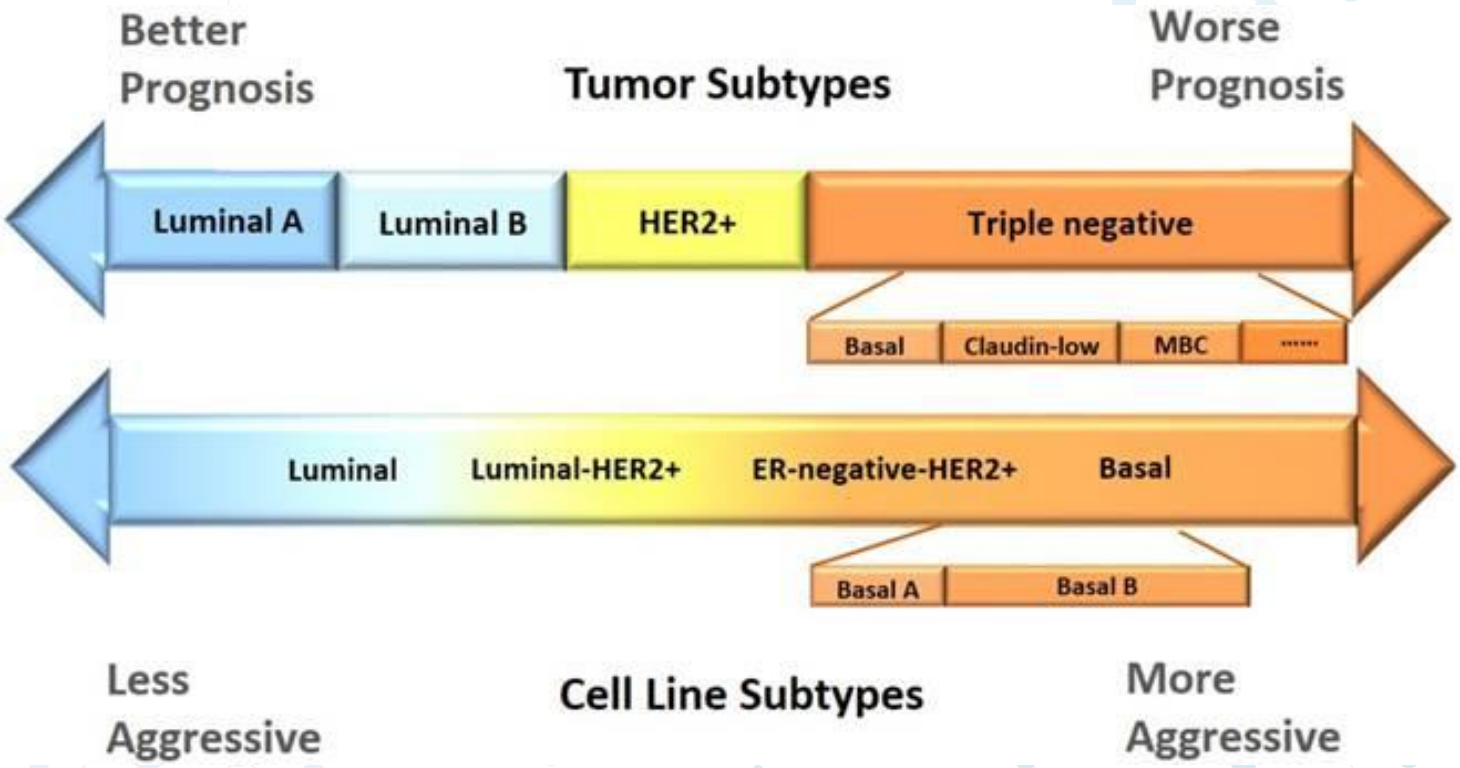
Breast cancer initiation

- At the molecular level, breast cancer evolution along two molecular pathways:
  - ER expression
  - Tumor grade and proliferation

Intrinsic classification

	Luminal A	Luminal B	Her-2/neu	Basal-like
Gene expression pattern	Expression(LMW) cytokeratins, and high expression of HR's and associated genes	Expression (LMW) cytokeratins, and moderate to weak expression of HR's and associated genes.	**High expression of Her-2/neu** . Low expression of ER and associated genes.	High expression of basal epithelial genes, basal cytokeratins. **Low expression of ER and Her-2/neu** associated genes.
Clinical	~ **50%** of invasive breast cancer	~**20%** of invasive breast cancers	~15% of invasive breast cancers	~15% of invasive breast cancers
ER/PR status	**ER/PR positive**	**ER/PR positive**	ER/PR negative	Most ER/PR negative
Her-2/neu status	Her-2/neu negative	Her-2/neu expression variable (+/-)	Her-2/neu positive (by definition)	Her-2/neu negative**("triple negative")**
Biological features		High proliferation than luminal A	High proliferation	High proliferation

https://www.slideshare.net/dhanya89/molecular-profiling-of-breast-cancer



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Journal of Cancer 08: 3131 image No. 001

Molecular alterations

- Most breast cancers are caused by multiple, low-penetrant mutations that act cumulatively.
  - Luminal A tumors have a high prevalence of *PIK3CA* mutations (49%)
  - Basal-like tumors have a high prevalence of *TP53* mutations (84%)
    - TNBC: different molecular drivers by subtype
  - Metastatic stage: specific predictive alterations, such as *PIK3CA* mutations, can be detected non-invasively in the plasma in circulating tumor DNA rather than on tumor biopsy

Intrinsic classification: summary

- Luminal A and somewhat Luminal B: The first pathway —the low-grade-like pathway — is characterized by gain of 1q, loss 16q, infrequent amplification of 17q12 and the majority of genes associated with the ER phenotype, diploid or near diploid karyotypes and low tumor grade.
- Her2: amplification of 17q12 (encoding HER2) and an expression signature of genes involved in the cell cycle and cellular proliferation
- Basal-like: high-grade-like pathway — loss of 13q, gain of chromosomal region 11q13, and an expression signature of genes involved in the cell cycle and cellular proliferation
  - TNBC fall into this pathway

Hormone receptors and breast cancer

- The major risk factor for sporadic breast cancer is hormone exposure
- Estrogen is a promoter of breast cancer: binds the ER located in the nucleus
- Hormones stimulate breast development during puberty, menstrual cycles and pregnancy (the only period when the organ is functional)

Estrogen

- Critical to breast cancer initiation

Historical interlude

- Breast cancer described approximately 3000 BCE (!)
  - Egyptian papyrus texts (The Edwin Smith Surgical Papyrus): earliest historical record
  - Imhotep: Egyptian physician-architect-practiced medicine and designed step pyramids
  - Described 8 case of ailments of the breast: one describes a tumor in a male where the description is non-infectious and where treatment is considered futile

Hippocrates

- Greek term: “karkinoma”-malignant, unceasing growth
- Description:
  - Hard tumors appear in the breast, become increasingly firm, contain no pus, and spread to other parts of the body
  - As the disease progresses, the patient develops bitter taste, refuses food, develops pain that shoots from the breast to the neck and shoulder blades, com- plains of thirst, and becomes emaciated.
  - From this point death was certain.
  - No treatment advised because treatment was futile and shortened the patient’s life.

Medicine in the Roman Empire

- Breasts of women: sites for cancer.
- Celsus, in manuscript, *De Medicina*, defined four stages for breast cancer
  1. Cacoethes (early): excise
  2. Carcinoma without skin ulceration
  3. Carcinoma with ulceration
  4. “Thymium”: advanced exophytic and sometimes bleeding lesion, suggesting the flowers of thyme

Surgery in the Alexandrian School: 300 BCE

- Leonides, a surgeon of the Alexandrian School, described surgical removal of breast cancers
- With the patient supine he cut into the sound part of the breast and used a technique of alternately cutting and cauterizing with hot irons to control bleeding.
- The resection was carried through normal tissues wide of the tumor and customized to the extent of involvement.
- The operation concluded with a general cauterization to destroy any residual disease.
- Poultices then applied to the wound to promote healing.
- Excision used selectively for tumors in the upper part of the breast of limited extent
- No surgery if the whole breast was hardened or if the tumor was fixed to the chest wall.
- First to record that breast cancers spread to the axilla.

Complete and thorough excision of breast malignancies has been a cardinal principle of surgery since the time of Leonides.

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1800s: the estrogen connection

- Thomas William Nunn reported regression of breast cancer in a woman 6 months after she attained menopause
- Albert Schinzinger, German surgeon, suggested oophorectomy as a treatment for breast cancer
- George Thomas Beatson (Lancet 1896) reported on 3 patients with breast cancer treated with bilateral oophorectomy
  - One patient survived 4 years post op

Breast cancer

- First targeted therapy: estrogen as target

The menstrual cycle and breast cancer

- During the menstrual cycles: cycling of estrogen and progesterone enhances cell proliferation and may cause DNA damage accumulation
- As this process repeats with each cycle, a defective repair process can occur, leading to mutations in pre-malignant, and then in malignant, cells
  - Estrogen stimulates cell growth and proliferation that support cancer development
  - The ER can modulate gene expression by interacting with estrogen response elements located in the promoter region of specific genes
  - Extracellular signals can stimulate the expression and activation of the ER in the absence of estrogen
  - The ER can interact directly with proteins, such as growth factor receptors, to enhance gene expression related to cell proliferation and survival

Hormone blockade

- Treatment to block the effects of estrogen
- Tamoxifen: competes with estrogen for the ER
  - Estrogen-like effects on the bone, prevent osteoporosis
- Aromatase inhibitors (AIs): block the production of estrogen
  - As AIs interact with bone, can cause osteoporosis (as menopause does)

Her2

- *ERBB2*: amplified in 13–15% of breast cancers-activates the HER2 pathway
- HER2 is part of the epidermal growth factor receptor family
- HER2 signaling activates proliferation, cell survival, metastasis and adhesion through different pathways such as the RAS pathway and the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mitogen-activated protein kinase (MAPK) pathway
- Targeting HER2 has proven to be effective in HER2-positive breast cancers that are defined by protein overexpression or gene amplification

Immune involvement

- Breast cancer develops in a complex microenvironment:
  - benign cell types and an extracellular matrix which provides mechanical support for the tumor and enables cellular interaction
  - most abundant cell type: cancer-associated fibroblasts
  - and cells of leukocyte lineage: lymphocytes, macrophages and myeloid-derived stromal cells - involved in the immune response
- Immunogenicity of breast cancer varies between the molecular subtypes:
  - highest in TNBC and HER2-positive tumors
  - Lower in luminal A and luminal B subtypes
- Response to neoadjuvant treatment and prognosis: positively influenced by the amount of tumor-infiltrating lymphocytes, which reflects the intensity of the immune response within the tumor bed.

Immune microenvironment

- The immune microenvironment influences the development and progression of breast cancer
  - In the early phase of carcinogenesis, the immune microenvironment exerts mostly anti-tumor action
    - cytokine milieu
    - activated $CD8^+$ and $CD4^+$ T cells.
  - Once a tumor becomes invasive, the microenvironment cell composition, including cancer-associated fibroblasts and cytokine content, are tumor-promoting, ‘hacked’ by breast cancer cells


Beware
of Baboons
No Picnics

Tumor biology and tumor behavior

- The intrinsic classification helps predict tumor behavior
  - Luminal A tumors tend to relapse late (after 5 years of first presentation) and have a tropism for bone and lymph nodes (as do luminal B, HER2-negative tumors).
  - TNBCs are prone to early recurrences (within 2–3 years of first presentation) and tend to form visceral (lung) and brain metastases.
  - HER2-positive breast cancers: better prognosis with anti-Her2 treatment

Genomic risk

- The main question in luminal (hormone-receptor-positive, HER2-negative) early breast cancer (LN neg) is which patients need chemotherapy (neoadjuvant or adjuvant) in addition to endocrine therapy.
- Genetic signature studies (OncotypeDx): low genomic risk score – low benefit for chemotherapy

Tumor biology and metastatic disease

- Breast cancer diagnosed as metastatic de novo: 25–28% of metastatic breast cancers
- Proportion varies with the age at diagnosis
  - 5.1% for women <40 yo
  - 34.3% if aged >75 years (data from France)
- Metastatic relapse may be influenced by: age, diagnosed through screening, quality of initial local treatment (access to medication, radiation, and clinical trials).
- Proportion of patients who experience metastatic recurrence: 20–30%.

Tumor molecular evolution

- The majority (~80%) of the driver alterations of the primary breast cancer are conserved in the metastatic sites
- Different metastatic sites may harbor ‘private’ mutations, new drivers: leads to sub-clonal diversification and discrepancies between the biology of breast cancers at different metastatic sites within an individual patient
- Such alterations occur late, and some alterations are subsequent to treatment pressure

Tumor molecular evolution and metastases

- During metastatic development, the different malignant deposits exhibit linear, parallel or polyclonal evolutionary pathways from the primary tumor, showing different genetic and epigenetic evolution.
  - This process is highly complex and still poorly understood
- Liquid biopsy with an evaluation of circulating tumor DNA profiles can reflect the clonal heterogeneity, but may lack sensitivity
- Sub-clonal diversification may explain the discrepancies observed between primary breast cancers and metastatic breast cancer for the expression of ER (~20% discordance), PR (~33% discordance) and HER2 (~8% discordance)
  - Molecular targets are more frequently lost than newly acquired (for instance, 13% of HER2-positive primary tumors generate HER2-negative metastases whereas only 5% of HER2-negative primary tumors generate HER2-positive metastases which affects treatment strategies.

Systemic therapies

- **Systemic therapy is guided by biology**
- Relative distribution of subtypes in the metastatic setting is similar to that in the early setting
- Biopsy and assessment of receptor status (ER and HER2 in particular; PR is less relevant in the metastatic setting) at least once during the course of advanced breast cancer, preferentially at first metastasis, can verify histology and assess potential changes in tumor biology from the primary tumor
- Multigene panels have not yet been proven useful in the metastatic setting in clinical trials and are only research tools
- Circulating tumor markers (CA 15-3: most important protein marker) should not initiate a change in therapy; progression must be confirmed by imaging

Treatment: luminal-like metastatic breast ca

- Endocrine-based therapy to endocrine resistance: unless there is rapid progression or visceral crisis (severe organ dysfunction)
- For premenopausal patients, ovarian suppression:
  - Tamoxifen
  - Ovarian ablation plus: 2 trials-show improvements in decreased relapse (5-8%) with OS benefit 1-4% in high risk women
    - *Premature menopause is associated with long-term mortality risks and women often experience significant menopausal symptoms that impact on quality of life. These considerations should play a role in the treatment selection of those patients who may benefit from adjuvant OA.*
- For postmenopausal patients, first-line endocrine therapy can be an aromatase inhibitor, fulvestrant, or tamoxifen, depending on the adjuvant endocrine therapy received and the duration of DFS.

Why wait for endocrine resistance?

- Mechanistic target of rapamycin (mTOR) inhibitor everolimus improves PFS by ±5 months but not overall survival
- CDK4/6 inhibitors improve PFS (±10 months in the first line and ±5 months in the second line).
  - PFS benefit may translate to overall survival benefit
  - The MONALEESA-7 study in premenopausal patients showed a significant prolongation of overall survival for first-line use of a CDK4/6 (ribociclib) in combination with ovarian suppression and an aromatase inhibitor or tamoxifen compared with endocrine therapy alone (HR 0.71; 95% CI, 0.54–0.95, $P = 0.00973$). At 42 months, 70% of patients were still alive in the ribociclib group compared with only 46% in the control group.
  - In view of additional cardiac toxicity with tamoxifen, ribociclib is only approved with an aromatase inhibitor (plus GnRH) in this setting.

Optimal sequence of therapies in metastatic disease is unknown.

Chemotherapy and MBC

- Sequential use of monochemotherapy is recommended
- Combination chemotherapy is generally reserved for situations of visceral crisis or rapidly progressive disease
- The duration of each regimen and the number of cycles should also be individualized, and chemotherapy should be continued until disease progression or unacceptable toxicity
- Optimal sequence is unknown.

Her2 positive advanced breast cancer

- For HER2-positive advanced breast cancer (ER-positive or ER-negative): use anti-HER2 agents
- In patients previously untreated with trastuzumab:
  - dual HER2-blockade with trastuzumab and pertuzumab plus chemotherapy (usually taxane)
- In patients previously treated with adjuvant trastuzumab
  - dual HER2-blockade with trastuzumab and pertuzumab plus chemotherapy (usually taxane)
  - trastuzumab (in countries without access to pertuzumab) plus chemotherapy

Her2 positive advanced breast cancer

- For HER2-positive, ER-positive disease
  - endocrine therapy and anti-HER2 agents: initial and maintenance tx
- Second-line options:
  - T-DM1
  - trastuzumab plus another chemotherapy
  - trastuzumab plus lapatinib (a tyrosine kinase inhibitor that interrupts the HER2 and epidermal growth factor receptor pathways)
    - trastuzumab plus chemotherapy: superior to lapatinib plus chemo
- Sequential monochemotherapy should be used
- The optimal sequence of all available options is unknown.

Triple negative metastatic breast cancer

- For TNBC, there are no different or specific chemotherapy recommendations for patients without *BRCA* mutations
- For *BRCA*-associated advanced TNBC:
  - A platinum agent
  - A PARP inhibitor (olaparib or talazoparib)
- In TN MBC with >1% PD-L1 (programmed cell death 1 ligand 1) immune cell staining, nab-paclitaxel plus atezolizumab has shown significantly superior PFS compared with nab-paclitaxel alone in the first-line setting:
  - overall survival advantage (7–10 months) seems evident in the PD-L1 immune cell-staining subgroup,

Treatment strategies

- Future therapeutic concepts
  - Individualization of therapy
  - Treatment de-escalation and escalation based on tumor biology and early therapy response.
  - Improve global access to therapeutic advances

Future Directions

- In the adjuvant and metastatic setting, goals of treatment
  - Decrease unnecessary toxicities from overtreatment without compromising outcome
- Epidemiological data suggest that contemporary adjuvant systemic therapies exert evolutionary pressures on the tumors

Future Directions: an example

- In invasive lobular cancers, matched-pair analysis of primary tumors and their corresponding metastases revealed acquisition of several genomic alterations (such as mutations in *CDH1*, *ESR1*, *ARID1A*, *ERBB2*, *GATA3*, *IGF1R*, *MAP3K1* and *PIK3CA)* at a frequency of 5–11% in metastatic disease that could be associated with disease progression and development of endocrine resistance
  - Some of these alterations will become relevant to choosing specific targeted therapies.

Thank you!

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