* Biochemistry *

Cancer

Changes in genes lead to tumor development

Accumulation of mutations

Threshold effect: During the cell cycle, the cell goes through DNA replication and mitosis
mistakes or mutations occur in the cell's genetic code

* الخلل هادا بسبب DNA mismatch & repair genes

There are balances to maintain the rate of new cell growth and cell death, maintained by several genes

1. Tumor suppressors
2. protooncogenes
3. DNA mismatch
4. repair genes

*** Risk factors**

1. Chance → طبيعة العمل تبعته سببته risk
2. Environmental exposures
3. Inherited defect in normal DNA repair system

Irreversible changes → atypical cell with uncontrolled proliferation → tumor

Breast Cancer

Sporadic 80%

Changes in genes after birth
Cause unknown – multifactorial
risk factors age (old)
environmental exposure (رادع)
lifestyle
genetic ما أكتسبها من أهله
Chance
Menarche early
Menopause late
first live birth
postmenopausal obesity
Alcohol
Hormonal replacement therapy
Excessive radiation exposure

more spesific

Familial 10–15%

risk factors in the family
- rare genetic syndrome associated with ↑ cancer
- Unidentified familial susceptibility cancer genes
- Common environment exposures → بشتغلوا بنفس العمل
- Common lifestyle → الأكل والخمور
- Chance → النساء البيض أكثر رضة من السمر

BRCA عندهم الجين لكن مش

Hereditary 5–10%

gene اخر من اله او ايوه

a person born with inherited predisposition to cancer

inherited mutation:

BRCA1 → Ch 17, locus 21
BRCA2 → Ch 13, locus 12.3

يتم فحصهم من دهم صغار على البدري يتم علاجهم

* high risk of developing cancer
* younger age < 50 year

Knudson's "Two-Hit" Hypothesis

- autosomal dominant manner

* At birth → normal or non mutated genes
* Person's lifetime → acquire a hit or mutation in cancer susceptibility gene
* later in life → exposed a 2nd hit or " " " "

Genes involved in hereditary breast Cancer BRCA1, BRCA2

Ch.17 L.21 Ch.13 L.12.3

* Autosomal dominant transmission
* tumor suppressor genes ← بالأساس كانوا
* oncogene خلل فيهم خلالي أياهم
* In male and female

Tumor suppressor genes regulate cell death, maintenance of cell cycle "Caretaker gene" loss of this function called "proto-oncogene"

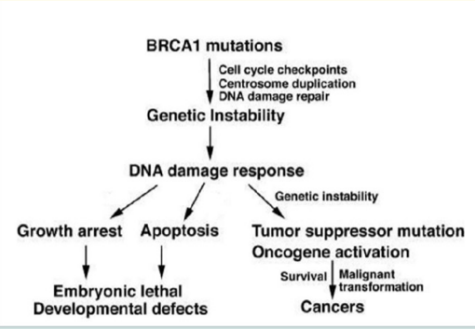
These mutations varies according to ethnicity
age of onset
family history

* Ashkenazi women carry a BRCA mutation 12 - 25%
* African women " " " 0 - 3 %
* Canadian women " " " 13%

نسخة ثانية — نفس المرض → breast cancer, ovarian cancer

⟹ BRCA 1, 2 : Different locus, Different Allele, Same phenotype

BRCA 1: types of mutation
- → Frameshift — تغير مكان ال nucleotide
- → Missense — في nucleotide فقدت
- → Splice-site — منطقة التقاء exon ع entron



BRCA 2: types of mutations
- → frameshift
- → Missense

جايين في الامتحان

* Autosomal Dominant Inheritance
  - → يكفي ظهور جين واحد مريض ليظهر المرض
  - → Men and women transmitted
  - → 50% chance of inheritied mutation
  - → No skipped generation — بتلاقيه بتكرر في كل جيل
  - → High risk in female because it is accosiated with estrogen and organs

Who should be offered referral for genetic counselling or genetic testing?

1. Multiple cases of breast or ovarian cancer in family
2. Breast cancer diagnosed at age < 35
3. Family member with both breast and ovarian cancers
4. Ashkenazi Jewish + relatives with breast or ovarian cancer

نسبة الميلانين عالية

STK11 / LKB1 gene

* Ch. 19 locus 13.3
* Serine / Theronine Kinase 11 "liver kinase B1"
* regulates energy metabolism and tumor suppressor regulate cell cycle
* multible mutations cause "Peutz-Jeghes syndrome" → autosomal dominant and characterized by mucocutaneous melanin pigmentation and gastrointestinal polyposis and ↑risk of breast and cervix cancers

في الوجه والشفة

TP53 gene

* Control cell death "apoptosis"
* Ch 17
* Mutation in it Cause breast cancer → BRCA لكنه غير اساسي مقارنة مع

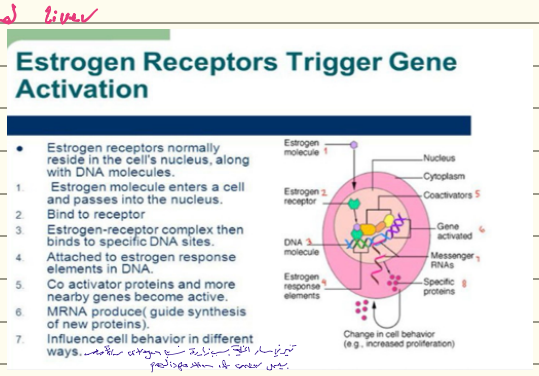
ERBB2 gene

Epidermal growth factor receptor

* Ch. 17
* Encodes tyrosine Kinase → regulate polypeptide growth factors, cytokines and hormones
* Mutation in it Cause poor prognosis in breast cancer سرد نوع
* ⊖ effect of estrogen receptor → cytotoxic لا يستجيب الى العلاج بالاستروجين
* يتم تحويله إلى العمليات على طول لانه بصل lymph node

Estrogens: responsible for sexual characteristics and reproduction

* most prevalent are estradiol and estrone
* Produced and secreted by ovaries, adipose tissue, adrenal glands and liver
* Target tissue are breast and uterus
* Estrogen receptors are intracellular in the nucleus
* Estrogen in liver ↓LDL & ↑HDL, postmenopause ↑LDL, ↓HDL (obese)
  - LDL: bad Cholestrol, release Cholestrol to arteries, create plaque
  - HDL: inhibit formation of plaque and direct it to liver



* It's effect

Beneficial E.	Harmful E.
Breast milk production	Breast ↑ cancer risk
Liver & Heart controls Cholesterol	
uterus prepares for fetus	uterus ↑ cancer risk
Bone Preserves Strength	

* Antiestrogen Tamoxifen → blocking estrogen from binding to these receptors for breast cancer not for ovary cancer

* SERMs selective estrogen receptor modulators → Stimulation or inhibition of estrogen receptors in different tissue, ihibit breast cells proliferation but stimulate uterine endometrial proliferation لذلك يستخدم في علاج breast cancer ولا يستخدم لعلاج endometrial c

* Estrogen receptor
  - ⊕ effect treated with tamoxifen in breast cancer
  - ⊖ effect not treated with " in uterus cancer

* يتم علاج cancer بـ hormonal therapy ناجح بال Chemotherapy , Surgery
* A cancer caused by estrogen defect is an aggressive cancer
* the charachtarstic of breast cancer lump, thickening, swelling, skin irritation or nipple discharge

Temoxifen [Nolvadex] الاسم التجاري

good effect	bad effect
- Reduces breast cancer risk	↑ uterine cancer risk
- ↓ LDL	↑ blood clot risk
- Strengthens bones	
- ↓ blood Cholesterol	
- Prevention of heart disease	

Done ♡ Yara Kassah