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Cancer Prone Disease Section

Mini Review

Hereditary breast cancer

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Identity

Alias: Site-specific breast cancer; Familiar breast-ovarian cancer

Note: Hereditary or familiar form of breast cancerwith a familiar background.

Inheritance

Follows an autosomal dominant pattern.
5-10 % of all breast cancers have hereditary background.
Hereditary susceptibility for breast cancer has been counted to be 30-40 % of BRCA1 (see below, gene section), 10-30 % of BRCA2, less than 1 % of Tp 53, less than 1 % of PTEN and one third of unknown mutations; frequency of BRCA1 mutation is around 0.2 % in general population, 200 carriers among 100 000 individuals.

Clinics

Note

Hereditary breast cancer is a heterogenous entity including several clinical variants.

Phenotype and clinics

"Site specific breast cancer" is characterized by the predominance of breast cancer, while "hereditary breast-ovarian cancer" has neoplasms in both organs.
BRCA1 mutation carrier (chromosome 17q12-21) has early age at onset, and lifetime risk for breast cancer 50 % - 85 % and ovarian cancer 15 %-45 %; about 500 different mutations have been reported; possible increased risk of prostate cancer and colon cancer.
BRCA2 (chromosome 13q12-13) mutation carrier has risk for breast cancer 30 %-85 %; about 300 different mutations have been reported; it is also associated for male breast cancer (6 %) and ovarian breast cancer (10% -20%); increased risk of prostate, laryngeal cancer and pancreatic cancer.
Other genetic conditions associated with increased breast cancer risk are:
Li-Fraumeni syndroma (p53 mutation on chromosome 17p13) is characterized by very early onset of neoplasms, including soft tissue sarcoma, osteosarcoma, brain tumours, leukemia, lung cancer, laryngeal cancer and adrenocorteal cancer.; lifetime risk for cancer: about 90 % for women and 70 % for men.
Cowden syndroma (PTEN, 10q23) is a rare type of autosomal dominant inherited condition of multiple hamartomas with increased risk of bilateral breast cancers and thyroid tumours.
Muir-Torre Syndroma (MSH2, MLH1), with also cancers of the gastro intestinal (GI)-tract, skin, genito urinary (Gu)-system.
Peutz-Jeghers Syndroma, with also abnormal melarin deposits, GI-polyposis, cancers of the GI-tract, uterus, ovary and testis.
Ataxia-teleangiectasia (linked to chromosome 11q21) autosomal recessive disorder with many clinical signs including increased risk for breast cancer; homozygous AT carriers have around 100-fold risk of cancer.
One third of familiar breast cancers with hereditary background is still unknown; recent findings indicated that genotyping "BRCA3" locus at 13q and "BRCA2" locus at 2q may lead identifing the next mutations.
Breast cancers of BRCA1 and, to lesser extent BRCA2 carriers differ from those of sporadic breast cancers: more high-grade tumours, pleomorphism, a higher mitotic count, less tubule formation, more often steroid receptor negative, DNA-aneuploid and more often higher s-phase fractions.

Treatment

Prophylactic bilateral mastectomy (reduces the risk of about 90 %) and/or ovarian ablation. Chemoprevention (antiestrogens, aromataze inhibitors, retinoids) mainly in clinical trials (tamoxifen may reduce the risk about 45 %).
Early detection of cancers by screening mammograms (ultrasound) yearly, palpation, transvaginal ultrasound.

Prognosis

Prognosis is more dependent on extent of the disease at diagnosis than on the hereditary susceptibility.

Genes involved and proteins

NOTE: see also breast cancer.

BRCA1

Location: 17q21

DNA/RNA
Description: 22 coding exons spanning over 70 kb of genomic DNA the BRCA1 mRNA has a size of 7.8 kb.

Protein
Description: the corresponding protein has 1863 amino acids, and 190-220 kDa.
Expression: wide.
Function: involved in DNA replication, repair transcriptional activation, cell cycle progression.

Mutations
Germinal: more than 500 sequence variations of the germline level have been reported.

BRCA2

Location: 13q12-13

DNA/RNA
Description: gene spanning more than 17 kb of genomic DNA; the coding sequence comprisons 26 exons (10 254 nucleotides).

Protein
Description: the corresponding protein has 3 418 amino acid residives (384 kDa).

Mutations
Germinal: more than 300 unique germ-line mutations have been reported.

P53

Location: 17p13

DNA/RNA
Description: 11 exons.

Protein
Function: gene p53 encodes an ubiquitous nuclear protein involved in the control of genome integrity by preventing cells dividing before DNA damage is repaired.

PTEN

Location: 10q23

DNA/RNA
Description: 9 exons.

Protein
Description: the PTEN protein (also called MMA1) is an evolutionary conserved dual-extensive similarity with the cyto-skeletal protein tensin
Function: tumour suppression since bi allealic inactivations, inactivating germline mutations are responsible for a cancer prone síndrome.

Mutations
Germinal: heterozygeous germline mutations are responsible for the Cowden disease.

LKB1

Location: 19p13

DNA/RNA
Description: 10 exons spanning 23 kb.

Protein
Description: 433 amino acids.
Expression: wide.
Function: serine/threonine kinase; tumor suppressor gene.
Homology: Heterozygous mutations are responsible for the Peutz-Jeghers síndrome.

ATM

Location: 11q22-23

DNA/RNA
Description: 66 exons spanning 184 kb.

Protein
Description: 3056 amino acids, 350 kDa.
Function: at the cell cycle checkpoint; induces G1 phase arrest.

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