Genetics of Oncology

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CREOG Objectives

- Describe the clinical relevance of viral oncogenes
- Describe the role of aneuploidy in the pathogenesis of neoplasia
- Describe the inheritance patterns for malignancies of the pelvic organs and breast
- Describe the indications for screening for BRCA1 and BRCA2
- Describe the cell replication cycle and identify the phases of the cycle most sensitive to radiation and chemotherapy
Cell Cycle

- Gap1 (G1) > Synthesis (S) > Gap 2 (G2) > Division
- G1- preparation for DNA replication
- S- DNA synthesis occurs, DNA content doubles
- G2- Resting Period
- Division- Mitosis
Mitosis

- Daughter cells receive identical copies of parental cells’ genome
- Prophase
- Metaphase
- Anaphase
- Telophase
Meiosis

- Diploid complement (2n=46) is divided into haploid (n=23)
- Meiosis I and Meiosis II
Chemotherapy

- Most drugs are effective in destroying cancer cells because they interfere, through various mechanisms
- Synthesis or function of nucleic acids
Radiation Therapy

- Disrupt the atomic or molecular structure
- DNA is the critical target, additional targets include cell membranes and microtubules
- Damage to DNA occurs during synthesis of DNA by loss or change of a base, rupture of hydrogen bonds, dimerization, crosslink formation, single or double strand breaks.
Oncogenes

- Altered forms of normal cellular genes called proto-oncogenes that can lead to cancer
- Regulators of normal cell growth and differentiation
- Examples: c-src, c-erbB, c-ras
Oncogenes

- Mutations can result in overproduction of a normal protein or an aberrant protein that is overactive.
- Proto-oncogenes must be activated to express their oncogenic potential.
- May occur by: Point Mutations, Insertional Mutagenesis, or Gene Amplification.
Viral Oncogenes

- Proto-oncogenes must be activated to express their oncogenic potential.
- Retroviruses can induce cancers because it harbors an altered version of cellular proto-oncogene.
- Alternation of just one of the proto-oncogenes could cause malignant transformation in cell cultures.
Tumor Suppressor Genes

- Tumor Suppressor Genes function to prevent malignant transformation
- Usually act in a recessive fashion
- Tumors develop in cells in which both normal copies have been inactivated or lost.
- One normal allele is sufficient to prevent neoplastic transformation.
Two-Hit Model

- Both alleles must be affected for tumor to occur
- Aneuploidy- lacking the expected number of chromosomes
- Inactivation mutations, absent gene transcription, chromosomal rearrangement and nondisjunction, gene conversion, imprinting, or mitotic recombination
Inheritance patterns

- Cervical, Vagina, Vulva, Fallopian Tubes - no familial tendencies detected
- Endometrial- most cases sporadic, however rare cases are due to HNPCC is autosomal dominant disorder with increased CA in uterus, ovary, colon, kidney, ureters, breast, prostate, lung, bladder, larynx, bone or brain
- Ovarian- HNPCC, BRCA1 and BRCA2
BRCA1 and BRCA2

- 1971 “Breast-ovarian cancer syndrome”
- Early-onset familial ca linked to long arm of chromosome 17
- 75-90% of inherited breast and ovarian ca
- Can be identified by linkage analysis
BRCA1 Structure and Function

- on 17q21- RNA mainly expressed in the testis and thymus, and at lower levels in the breast and ovary
- Function unknown, but may act to regulate transcription of genes involved in cellular proliferation
- Possibly a tumor suppressor gene
BRCA2 Structure and Function

- On 13q12-13- most highly expressed in testis and thymus, lower levels in breast and ovary
- Function unknown
- May respond better to radiation therapy than BRCA1
BRCA1 and BRCA2

- Both are unusually large genes and rich in adenine-thymine base pairs
- More than 200 different mutations have been described
- Mutations are widely dispersed, but several nations and ethnic groups then to have their own common mutations; Ashkenazi Jews, Belgium and Holland, Sweden and Denmark
Risk of CA with BRCA1 and BRCA2

- Initial estimates as high as 87 percent, but these numbers were from high-risk families studied in research protocols.
- In less biased samples, risk of breast CA in carriers is 33-56% (noncarriers 4.5-13%); Ovarian CA 7-16% (noncarriers 0.4-1.6%)
- No difference between BRCA1 and BRCA2
In other words...

- BRCA1- 3% of all US breast CA, 4.4% of all US ovarian CA
- In woman less than 40: 10% of Breast, 17.5% of ovarian
- BRCA2 numbers are similar, but tend to have younger onset
- Role in sporadic CAs remain unclear
Proposed Strategies for Carriers

- Monthly breast-self exam by age 18
- Semi-annual or annual clinician exams
- Annual Mammography starting at 25 (controversial)
- CA-125, TVUSG, Pelvic exams- not cost effective, may be useful for early detection in young women who want to maintain fertility
- Annual fecal occult blood, Flex Sig from age 50
Controversy

- Prophylactic Mastectomy – cancer after prophylactic mastectomy has been well documented (1-19%)
- Prophylactic oophorectomy- insufficient data, may have slight risk of breast ca, but not well documented; risks of premature menopause
- Chemoprophylaxis with antiestrogens and OCPs currently in trials
BRCA Screening

Serious concerns have been raised about our ability to identify appropriate patients for genetic testing.

Patients from high-penetrance families can be identified easily, but testing all women would produce low yield of positive results.

Different mutations would be missed in different populations.
Genetic Screening

- ASCO (1996) recommended that testing be performed only in certified laboratories and only in those patients with a reasonable likelihood of being positive and for whom the test would result in alteration of their medical management.

- NAPBC supported the above, but only to individuals who agree to join peer-reviewed, approved research protocols.
More controversy

- Biologic uncertainties
- Potential discrimination
- Financial and Psychological exploitation of the public
- Difficulty incorporating into clinical practice
- Patients’ rights to information
- Misuse of information by insurance, job
Warning

- ASCO warns of the danger of the creation of a “genetic underclass” who might be virtually uninsurable and unemployable.
- Psychological counseling should be included as a part of a multidisciplinary team in genetic testing.
- Psychological reactions have ranged from guilt and depression after a positive test to survivor guilt in the case of a negative result.
Even More Controversy

- Debate as to whether parents have authority to consent their children for testing.
- May stigmatize and otherwise “normal” child the rest of his life.
- Currently accepted that parents should not be free to have their children screened for late onset genetic diseases.
Conclusions

- Current knowledge regarding the interpretation and management of the results derived from genetic testing is still limited and continually changing.
- We must create safeguards to ensure that benefits of testing exceed the risk.
- No current recommendations for screening the general public.
- Genetics in Obstetrics and Gynecology, Simpson and Elias, 2003
- Genetics in Medicine, Nussbaum et al, 2001
- Clinical Oncology, Murphy et al, 1995
- BRCA1 and BRCA2 Gene Mutations: Decision-Making Dilemmas Concerning Testing and Management; Fasouliotis and Schenker, 2000