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BRCA1 & BRCA2: CANCER RISK & GENETIC TESTING
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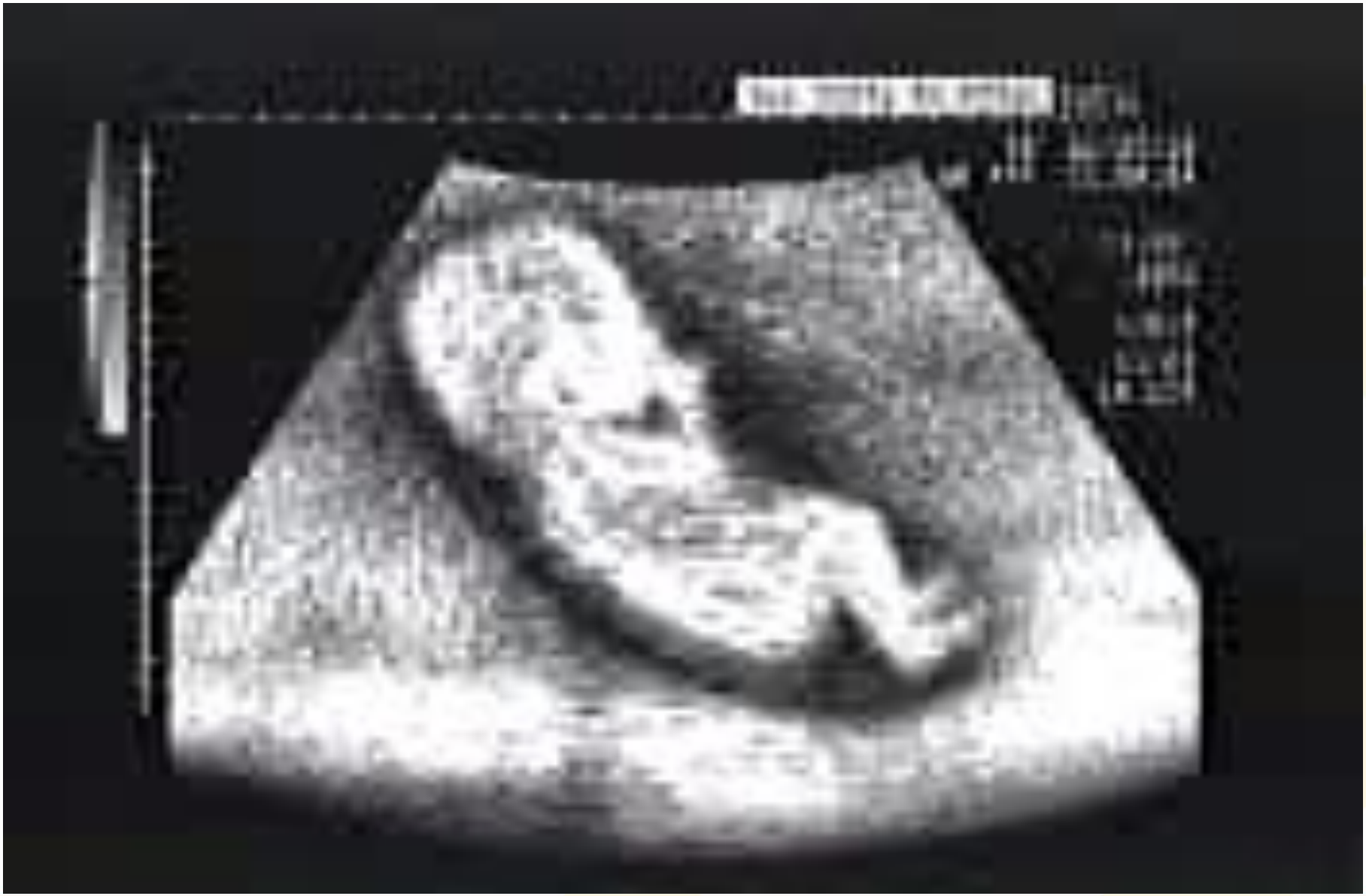


- Familial susceptibility to breast cancer accounts for ~25% of cases.

- High-risk and low- to moderate-risk susceptibility genes.
- *BRCA1*, *BRCA2*, *PTEN*, *TP53*, *LKB1/STK11* and *CDH1* belong to the high-risk breast cancer susceptibility genes.
- A small group of tumors are secondary to mutations in the low- to moderate-risk breast cancer susceptibility genes, such as *CHEK2*, *TGFβ1*, *CASP8* and ATM.

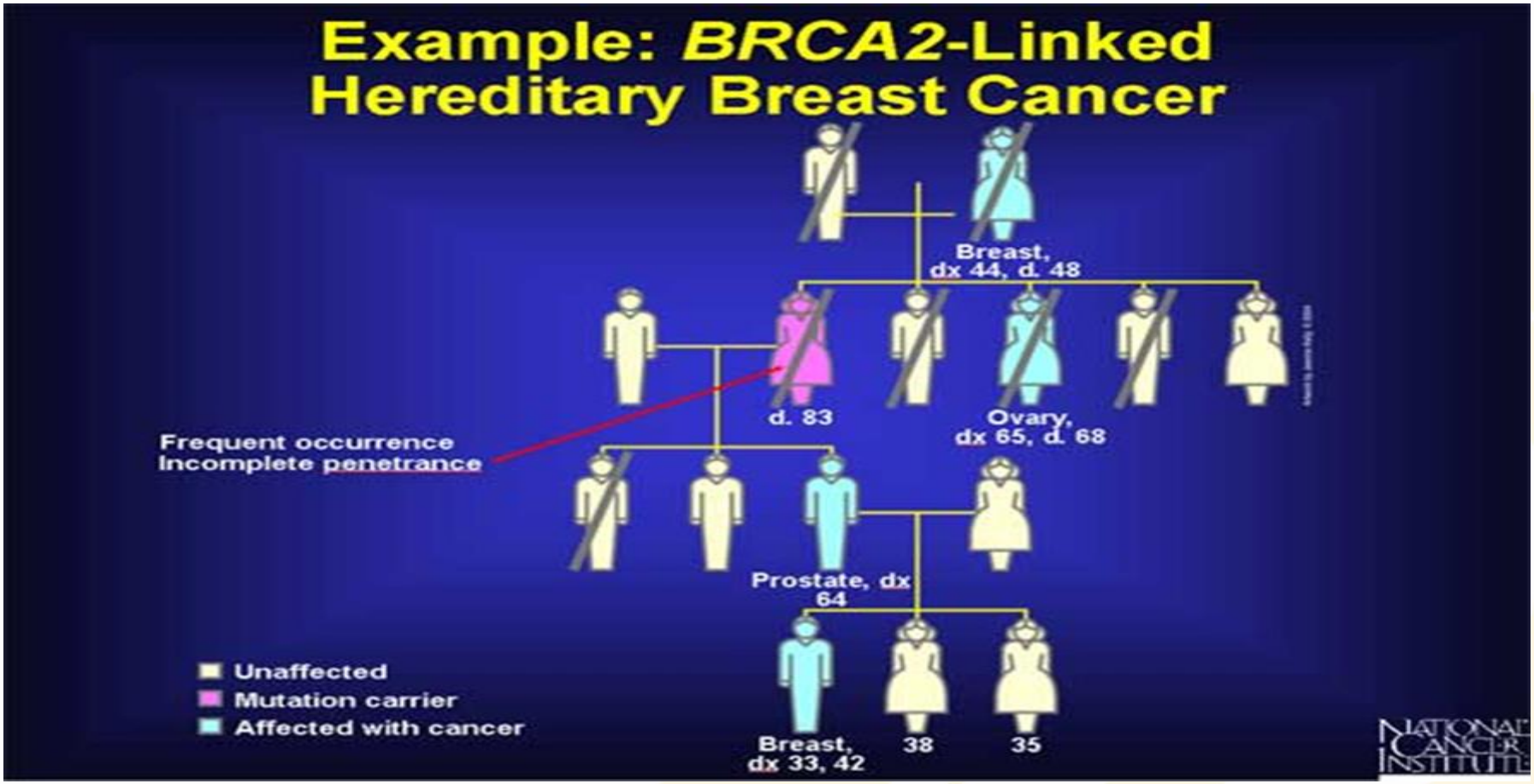
- Germline mutations in 2 genes, BRCA1 and BRCA2, discovered by Mary-Claire King, PhD have been associated with an increased risk for breast cancer and ovarian cancer.

- Estimated that 5.3% of breast cancers occurring in women under forty years and 1.1% of breast cancers in women from 50 to 70 years are due to mutations in either of these.

- Both genes are considered to be tumor suppressor genes that play a role in DNA repair and mammary stem cell differentiation

- Specific BRCA mutations (founder mutations) are clustered among certain ethnic groups, such as Ashkenazi Jews among families in the Netherlands, Iceland & Sweden.

PENETRANCE



* Probability of developing breast /ovarian cancer in women with BRCA1 /BRCA2 mutation
* Published reports of penetrance describe estimates of BRCA1 and BRCA2 mutations ranging from 35% to 84% for breast cancer and 10% to 50% for ovarian cancer, calculated to age 70 years, for non–Ashkenazi Jewish women or those unselected for ethnicity.

Hereditary Breast Ovarian Cancer Syndrome

An autosomal dominant pattern of inheritance (vertical transmission through either the mother or father's side of the family)

Clinical Diagnosis: If >1of the following features are present in a family

1. Early-age-onset (age <50 years) breast cancer including invasive and in situ (DCIS) breast cancers.

2a. 2 breast primaries OR breast +ovarian/fallopian tube/primary peritoneal cancer in a single individual, OR,

2b.>2breast primaries OR breast + ovarian/fallopian tube/primary peritoneal cancers in close relatives(s) from the same side of the family.

3. Populations at risk (e.g., Ashkenazi Jewish).

4. Member of a family with a known BRCA1 or BRCA2 mutation.

5. Any male breast cancer.

6. Ovarian/fallopian tube/primary peritoneal cancer at any age.

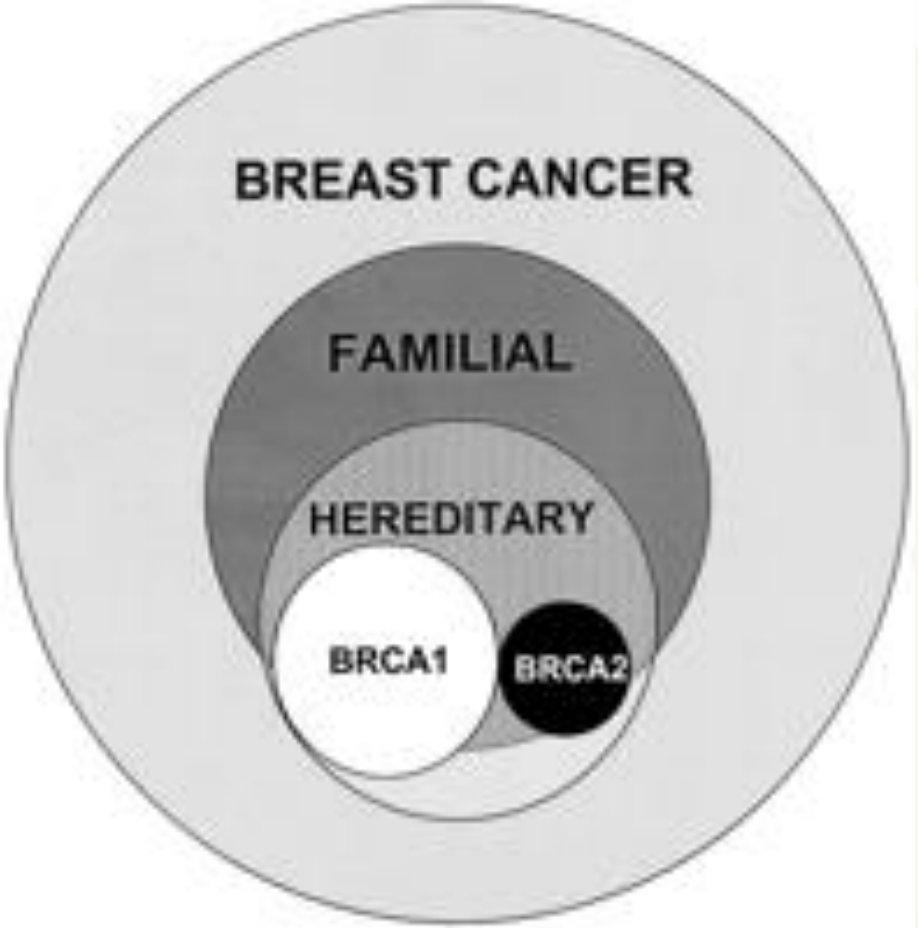
National Comprehensive Cancer Network 2010

PREVALENCE

- Hereditary breast and ovarian cancer (HBOC) resulting from mutations in BRCA1 and BRCA2 is the most common form of both hereditary breast and ovarian cancers

- Occurs in all ethnic and racial populations.

- Prevalence of BRCA1/2 mutations 1:400 to 1:800

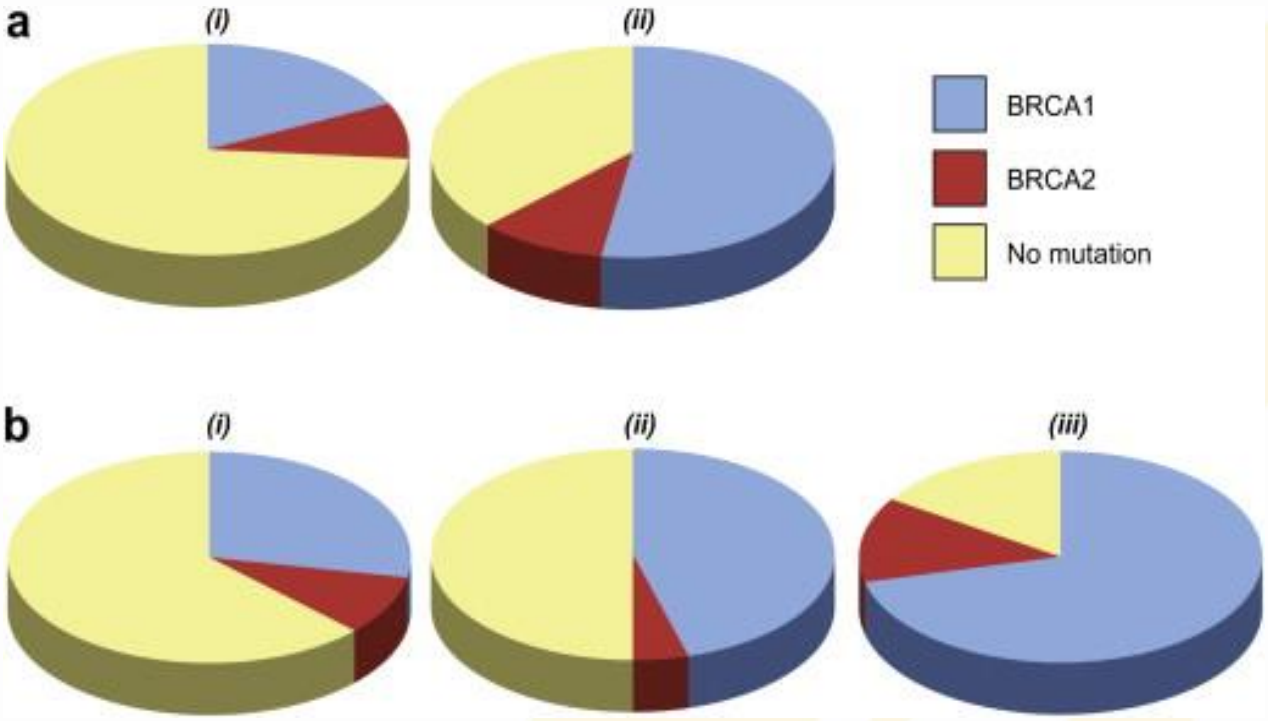


<u>Situations that may lower the threshold of suspicion for HBOC</u>

- ❖ Families with a limited family structure
- ❖ Oophorectomy at a young age in family members (reduces the risk)
- ❖ Presence of adoption in the lineage
- ❖ Populations at risk of having a BRCA1 or BRCA2 mutation

Contribution of BRCA1 &2 to Ovarian Cancer-

Ramus *et al*



Families with BRCA1 (blue), BRCA2 (red) and no detectable mutation (yellow). (a) Families with mutations with increasing number of ovarian cancer cases i) 2 ovarian cancer cases only, ii) 3 or more ovarian cancer cases only. (b) Families with mutations with increasing number of breast cancer cases i) 2 or more ovary and no breast cancer, ii) 2 or more ovary and one breast cancer case, iii) 2 or more ovary and 2 or more breast cancer cases.

GUIDELINES FOR TESTING

1. U.S. PREVENTIVE SERVICES TASK FORCE

- ✓ The U.S. Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2).
- ✓ The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing.
- ✓ These recommendations apply to women who have not received a diagnosis of breast or ovarian cancer.
- ✓ They do not apply to women with a family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; these women should be referred for genetic counseling.
- ✓ These recommendations do not apply to men.

2. AMERICAN COLLEGE OF MEDICAL GENETICS

Recommends risk assessment and genetic counseling before testing for BRCA1/BRCA2 mutations in individuals at increased risk, based on a personal or family history of breast cancer, ovarian cancer, or both

3. NATIONAL COMPREHENSIVE CANCER NETWORK

Recommends offering genetic susceptibility testing (after risk assessment and counseling) to individuals who meet the criteria for hereditary breast or ovarian cancer or both.

Ann Intern Med 2005;143:355-61