A high frequency of a specific gene mutation in a population founded by a small ancestral group

**Development of a Founder Mutation**

- BRCA Founder Mutations
  - Ashkenazi Jewish (Hungarian and Russian):
    - BRCA1 - 185delAG and 5382insC
    - BRCA2 - 6174delT
  - Icelandic:
    - BRCA1 G5193A
    - BRCA2 999del5
  - Finnish: BRCA1 IVS1-2A=>G
  - Dutch: BRCA1 large deletions
  - Norwegian: BRCA1 1675delA and 1135insA
  - Scottish/Irish: BRCA1 2800delAA

Within these populations carriers share a common haplotype supporting a single ancient mutation rather than mutational hot spots
BRCA1 and BRCA2

- Estimated carriers of a deleterious mutation 1 per 1,000
- Breast cancer risk 35% – 80% by age 80 depending upon study population
- Ovarian cancer risk 20% - 40% by age 80
- Founder mutations have been identified in:
  - Icelanders
  - Ashkenazi
  - Fins
  - African

BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation

- BRCA1
  - 185delAG
    Prevalence = ~1%
  - 5382insC
    Prevalence = ~0.15%

- BRCA2
  - 6174delT
    Prevalence = ~1.5%

Benefits, Risks, and Limitations of BRCA Testing

**Benefits**
- Identifies high-risk individuals
- Identifies non-carriers in families with a known mutation
- Allows early detection and prevention strategies
- May relieve anxiety

**Risks and Limitations**
- Does not detect all mutations
- Continued risk of sporadic cancer
- Efficacy of interventions unproven
- May result in psychosocial or economic harm

Familial Clustering of Cancer

Family history among blood relatives may reflect:
- Presence of a single inherited genetic risk [APC]
- Multiple genetic factors [BRCA + ATM]
- Inheritance of genetic markers of metabolism
- Shared environmental factors with/without inheritance of susceptibility [tobacco smoke]
- Culturally transmitted risk factors [reproductive decisions, hormone use]
Genetic Epidemiology

- Multiple cases in some families may be due to: inherited susceptibility, environmental exposures, lifestyle, reproductive patterns, health behaviors, etc.

- Understanding these causal patterns will assist in defining avenues for prevention and optimum treatment.

- Data and biospecimens from family members are essential for genetic and environmental studies.

- A confidential centralized data repository with DNA samples is required for groundbreaking research.

Factors Affecting Genetic Testing Decisions

- Cost of counseling & testing
- Concerns about health & life insurance
- Confidentiality of test results
- Family dynamics
- Barriers to screening/testing (financial/psychological)
- Clinical decision-making: a burden for mutation carriers
- Unresolved grief
- Survivor guilt among non-carriers
- Patient/physician/counselor communication
Disparities in Genetic Testing

- African American women have been less likely to receive genetic counseling and testing than Caucasian women \( \text{OR} \ 0.3 \ [0.1 - 0.9] \)
- Myriad Genetics: among the first 10,000 individuals tested for BRCA mutations, <10% were from under-represented racial/ethnic subgroups
- Access and knowledge increases use of genetic testing to wealthy, well-insured and medically well informed populations.
- To correct disparities genetic services must be racially and culturally tailored to meet the needs of specific populations
- Federally-funded low cost preventive health programs are needed to provide reliable estimates of inherited risks & genetic penetrance

Hall MJ, Olopade OI. JCO 2006;24:

Disparities in Genetic Testing

Factors potentially contributing to low acceptance of genetic services by some racial/ethnic populations:

- Limited communication among family members restricting awareness of diseases diagnosed among relatives
- Inaccurate personal assessment of disease risk
- Lack of knowledge of inherited risk in predicting future disease
- Inadequate understanding of the value of genetic counseling & testing
- Highly technical genetic services may not be available in local setting
- Distrust of risk reduction interventions coupled with greater reliance on religion

Hall MJ, Olopade OI. JCO 2006;24
Risk Models May Be Inadequate for Some Racial/Ethnic Groups

• Predictive statistical models using family history have been developed primarily with data from white families & may not be applicable to diverse populations

• Models are based upon accurate estimates of population-specific prevalence of high-risk genotypes – data not available for most minority populations due to limited genetic testing

• Heterogeneity within African American and other minority populations may also complicate estimates

Concerns Associated with Genetic Testing

• Fears of genetic discrimination by employer or insurance company

• High cost if self pay considered

• Confidentiality of genetic results in medical records &/or among relatives

• Limited laws protecting genetic information

• Fear of recommended screening methods & their frequency

• Distrust/distaste for preventive medications or surgery

• Potential need for psychological assessment and support not covered by health insurance
Breast-Ovarian Ashkenazi Family
Mother & Daughter with 5382insC

Environment
Exposures
Genetic Factors
Affected

Racial & Ethnic Differences May Impact
Inherited Factors & Environmental Exposures

Manipulation of environmental exposures can modify
risk of developing breast cancer
Paired Sisters Discordant for Breast Cancer
Resource for Gene-Environment Studies

NY Registry: 450 families with one or more discordant sister sets including 120 BRCA carrier families

DNA Repair Capacity in Paired Sisters Discordant for Breast Cancer

% DNA repair capacity of lymphoblastoid cell lines derived from samples donated by 158 case and 154 control sisters from 137 NY Registry families

Conditional logistic regression controlled for potential confounding due to age at blood donation, body mass index, and smoking

Mean repair capacity was lower in sisters with breast cancer compared to unaffected siblings [difference=8.6, 95% CI 4.3, 13.8]

Kennedy et al. JNCI 2005;97:127-32