Family and genetic testing for hereditary cancer syndromes: Implications for future research

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- ONCOLOGY NURSING FOUNDATION, Breast Cancer Research Award
- MICHIGAN CENTER FOR HEALTH INTERVENTIONS, University of Michigan School of Nursing
- ROBERT WOOD JOHNSON FOUNDATION, Nurse Faculty Scholars
About me....

- 1998 from Greece as a Fulbright scholar to UCSF School of Nursing
  - 13 credits of basic medical genetics/genomics
- 2004 PhD on cognitive/behavioral factors on Breast Cancer Screening
  - Sample of community-dwelling, cancer-free women; 15% family history suggestive of increased breast cancer risk.
    - Overlooked significant risk factors
    - Underestimated breast cancer risk and did not adhere to intensive surveillance
      - Katapodi et al. *Onc Nurs Forum 2009*
- 2006 Assistant Professor to UM School of Nursing
  - High risk women, decision making, genetic testing for HBOC
- 2010 Summer Genetics Institute (SGI), 4-week training program at NIH
  - Foundation in molecular genetics/genomics research for nurses
My research....

- (Breast) Cancer Screening
- Genetic Testing for Hereditary (Breast/Ovarian) Cancer
- Perceived Risk and Decision Making
  - Cognitive Mechanisms
    - Heuristics, Dominance Structure
  - Risk Communication
- Family Processes and Decision Making
  - Communication, Coping and Adaptation
- Methodologist
  - Perceived Risk Measure
  - Decisional Conflict Measure
  - Meta Analysis
  - Heuristic Reasoning Analysis
Breast Cancer

• Most common cancer in women worldwide
  • > 1.2 million women diagnosed in 2006 (WHO, 2007)
  • 2nd leading cause of cancer death among U.S. women (ACS, 2011)

• Three forms of breast cancer
  • Sporadic 70%
  • Familial 20% - 25%
    • strong family history and other indicators of genetic predisposition, unknown mutation
  • Hereditary Breast/Ovarian Cancer (HBOC) 5%-10%
    • known mutations in the BRCA1 and BRCA2 genes (BRCA1/2);
    • other mutations i.e., p53 etc
Hereditary Breast/Ovarian Cancer Syndrome

- BRCA1/2 gene mutations associated with both breast and ovarian cancer

- 75% of families with 3+ cases of breast or ovarian cancer have either a BRCA1 or a BRCA2 mutation

- Risk for breast and ovarian cancer increases
  - 2+ family members with either cancer
  - Breast cancer diagnosis younger than 50 years old
BRCA1 and BRCA2 Genes

• **Breast Cancer susceptibility gene 1**
• **Breast Cancer susceptibility gene 2**
  • Identified in the mid-1990s
  • 2 BRCA1 genes on each **chromosome 17** and
  • 2 BRCA2 genes on each **chromosome 13** (Cancer Genetics, 2006)

• **Tumor suppressor genes**
  • Maintain the stability of the genetic material
    • DNA damage repair
    • DNA breakage
    • Prevent uncontrolled cell growth

• **Germline Mutations**
  • The mutated gene is within germ cells (oocyte or sperm)
  • Transmitted in an **autosomal dominant** fashion
Lifetime Cancer Risks for Mutation Carriers

• 60%–80% lifetime breast cancer risk
  • vs. 12% population risk

• 40%–50% lifetime ovarian cancer risk for BRCA1 carriers
  • vs. 1.8% population risk

• Implications for 3–4 fold elevated risk for pancreatic and prostate cancers, and melanoma
GENETIC TESTING for Hereditary Breast/Ovarian Cancer

Cancer Risk Assessment
- Pedigree Analysis
- Medical/risk factor analysis

Evidence of a Hereditary Cancer Syndrome

Pre-test Counseling for Genetic Testing

Desires Testing???

Unlikely Hereditary Cancer Syndrome

Personalized screening and management guidelines

Yes
Desires Testing

Informed Consent for Genetic Testing

Negative Result

Personalized screening and management guidelines

Positive Result

Intermediate Result

High Risk Cancer Risk Management Guidelines

NO

YES
Breast/Ovarian Cancer
Risk Management Strategies

Mutation Carriers/High Risk Women

- Intensive Surveillance
  - CBEs, mammograms, MRI
  - Transvaginal U/S, CA-125

- Prophylactic Risk Reduction Surgery
  - Mastectomy and/or salpingo-oophorectomy

- Chemoprevention
  - Tamoxifene or Raloxifene

Average/Population Risk Women
(12% or 1 in 8 women)

- Routine Screening
  - CBEs, mammograms, BSE

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**Ripple Effect of Risk**

1\(^o\) - Relative 50% Risk
2\(^o\) - Relative 25% Risk
3\(^o\) - Relative 12.5% Risk

**Legal framework:** issues of privacy and confidentiality

**FAMILIAL VS. INDIVIDUAL PRIVACY**

- UNESCO’s International Declaration on Human Genetic Data
- Human Genome Organization (HUGO)
- Ethical Legal and Social Issues (ELSI) Committee
- WHO
- UK’s Nuffield Council
Communication of genetic information among family members is not utilized effectively

Genetic testing among unaffected, high-risk relatives is <45%

Women with Hereditary Cancer (Mutation Carriers)
- Distressed, cancer diagnosis and mutation status
- 50% communicate test results to 1° - Relatives, usually females
- No sense of moral obligation to communicate to distant relatives
- Requested assistance from healthcare providers

- Relatives
  - Distressed, risk and lack of genetic counseling
  - Uninformed decision not to seek genetic testing

- Familial Environment
  - Lack of effective family communication
  - Relationships and role conflicts
  - Viewed as parental obligation
Hereditary cancer risk, family functioning, and decision-making

- Examine the influence of illness appraisals of HBOC and family functioning on women’s decisions to pursue genetic testing
- Explore if family functioning moderates the relationship between illness appraisals and decisions to pursue genetic testing

Figure 1. Theoretical Framework
Methods

• **SETTING**
  • University of Michigan Comprehensive Cancer Center
    • Breast and Ovarian Cancer Risk Evaluation (BOCRE) Clinic
    • Cancer Genetics Clinic

• **DESIGN**
  • Descriptive, Cross-sectional, Cohort study
    • 2 RELATED COHORTS OF HIGH RISK WOMEN
    • WOMEN WHO PURSUED GENETIC TESTING FOR HBOC (PROBANDS)
    • ONE OF THEIR FEMALE RELATIVES
      • a priori >10% risk of carrying a genetic mutation; did NOT pursue genetic testing
      • Self-administered questionnaire, validated instruments

• **SAMPLE**
  • 172 matched dyads Proband – Relative
  • On average 30 months post genetic testing
### Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Probands (n=172)</th>
<th>Relatives (=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>51±11 (Range: 22-83)</td>
<td>48±16 (Range: 18-81)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt; Bachelor’s degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Bachelor’s degree</td>
<td></td>
<td></td>
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<tr>
<td><strong>Personal History of Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast (Invasive, LCIS, DCIS)</td>
<td></td>
<td></td>
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<tr>
<td>Ovarian</td>
<td></td>
<td></td>
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<tr>
<td>Other Cancer</td>
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<td></td>
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<tr>
<td><strong>Surgery</strong></td>
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<td></td>
</tr>
<tr>
<td>Breast (Lumpectomy, Mastectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
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<tr>
<td>Oophorectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Hysterectomy, Surgery on Cervix)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive Mutation Status (BRCA1, BRCA2)</strong></td>
<td></td>
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<tr>
<td><strong>Known Mutation in Other Family Members</strong></td>
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</tbody>
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**Statistical Analyses**

- **Computer program SAS v.9**

- **Conditional Logistic Regression Analyses**
  - Matched pairs of observations – Proband/Relative
  - Dichotomous Outcome: Genetic Testing Yes/No

- **3 steps analysis**
  - Univariate Analyses
    - Each variable as independent predictor
  - Multivariate Analyses
    - Significant predictors examined simultaneously
  - Moderator Analysis
Univariate Conditional logistic regression analysis of predictors of HBOC genetic testing

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Wald Confidence Limits</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.00 - 1.03</td>
<td>0.06</td>
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<tr>
<td>Income</td>
<td>1.00</td>
<td>0.99 - 1.00</td>
<td>0.96</td>
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<tr>
<td>Education</td>
<td>1.23</td>
<td>1.04 - 1.45</td>
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<tr>
<td>Personal History of Cancer</td>
<td>5.12</td>
<td>3.14 - 8.35</td>
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<tr>
<td>Perceived Risk HBOC</td>
<td>1.45</td>
<td>1.21 - 1.73</td>
<td>&lt;0.05</td>
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<tr>
<td>Perceived Cause HBOC</td>
<td>1.65</td>
<td>1.38 - 1.96</td>
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<tr>
<td>Perceived Severity HBOC</td>
<td>0.49</td>
<td>0.35 - 0.67</td>
<td>&lt;0.05</td>
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<tr>
<td>Perceived Controllability HBOC</td>
<td>0.72</td>
<td>0.55 - 0.94</td>
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<tr>
<td>Psychological Distress HBOC</td>
<td>1.12</td>
<td>1.01 - 1.24</td>
<td>0.03</td>
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<tr>
<td>Family Relationships</td>
<td>1.19</td>
<td>0.68 - 2.08</td>
<td>0.54</td>
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<tr>
<td>Family Problem Solving Communication Index</td>
<td>1.11</td>
<td>0.74 - 1.65</td>
<td>0.62</td>
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<tr>
<td>Family Hardiness Index</td>
<td>0.36</td>
<td>0.15 - 0.84</td>
<td>0.02</td>
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<tr>
<td>Perceived Utility of Genetic Testing</td>
<td>2.30</td>
<td>1.68 - 3.15</td>
<td>&lt;0.05</td>
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</table>
**Multivariate Conditional logistic regression analysis of predictors of HBOC genetic testing**

Max-rescaled R-Square = 0.62

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<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
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<th>p-value</th>
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<td>Perceived Cause HBOC</td>
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<td>Family Hardiness Index</td>
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<tr>
<td>Perceived Utility of Genetic Testing</td>
<td>1.97</td>
<td>1.26 - 3.08</td>
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<tr>
<th>Interaction</th>
<th>Estimate</th>
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<td>Perceived Cause * Family Communication</td>
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<td>0.06</td>
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Decisional Conflict about Genetic Testing for HBOC

• What was the level of decisional conflict in women who pursued genetic testing and their at-risk relatives who did not?

• What factors influenced decisional conflict in these two groups of women?
## Decisional Conflict about Genetic Testing for HBOC

<table>
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<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>t-test</th>
<th>df</th>
<th>p</th>
<th>95% CI Mean Difference</th>
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<td><strong>Decisional Conflict</strong></td>
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<tr>
<td>Probands</td>
<td>3.61</td>
<td>0.69</td>
<td>10.67</td>
<td>338</td>
<td>&lt;0.001</td>
<td>0.59 – 0.85</td>
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<tr>
<td>Relatives</td>
<td>4.33</td>
<td>0.53</td>
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<td></td>
<td>0.08</td>
<td>-0.07</td>
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<td>0.15</td>
<td>0.02</td>
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<tr>
<td>Relatives</td>
<td>0.03</td>
<td>0.02</td>
<td>0.11</td>
<td>-0.20*</td>
<td>-0.19*</td>
<td>-0.16*</td>
<td>0.03</td>
<td>0.16</td>
<td>0.04</td>
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Decisional Conflict about Genetic Testing for HBOC

Probands

Relatives

Family Environment

Common Family Environment
Limitations

• **Self-report**
  • Personal Ca Dx, Hx Surgery, and results of genetic testing for probands and family members

• **Control over recruitment**
  • Eligible female relatives

• **Cross sectional design**
  • Limited opportunity to examine illness representations and family functioning during the time that the actual decision to pursue genetic testing was made

• **Relatives of True Negatives?**
Discussion

Decision Making for Genetic Testing for HBOC

- **Personal Ca Dx (Probands)**
  - Prompts referrals from health providers

- **Perceived fewer barriers and more benefits (Probands)**
  - Perceived utility increases after genetic counseling session

- **Perceived greater severity of HBOC (Relatives)**
  - Likely overestimate consequences of disease
  - Decreases decisional conflict

- **Family hardiness – family cohesion, ability to cope and overcome life’s adverse events**
  - Individual and family adjustments to the disease

- **Family communication**
  - Increases knowledge about risk factors and modes of gene inheritance
  - Increases decisional conflict
Future Directions

• **Enhance informed decision-making and optimal risk management**
  - Be proactive in identifying high-risk individuals
  - Promote optimal decisions and risk management
  - Decrease decisional conflict

• **Enhance family communication**
  - Family communication increases knowledge
  - Family/ Social support reduces distress; increases coping
Future Directions: Project 1

• **Develop a family-based intervention:**
  - Accurate appraisal of threat
  - Decisional conflict about genetic testing
  - Family communication
  - Problem-based coping and risk management

• **Test the effect of family-based intervention:**
  - Decrease decisional conflict
  - Increase use of genetic testing
  - Increase coping and optimal risk management

**Funding:**

*Robert Wood Johnson Foundation – Nurse Faculty Scholars*
**Future Directions: Project 2**

- **Public Health Approach to:**
  - Identify high-risk individuals
  - Promote optimal decisions and risk management
  - Enhance family communication

- **Multidisciplinary Team:**
  - Michigan Prevention Research Center (PRC/MI)
  - University of Michigan (UM) Schools of Nursing, Public Health, and Medicine
  - Michigan Department of Community Health (MDCH)
  - Michigan Cancer Consortium (MCC)

- **Aims:**
  - Identify and survey YBCS about breast cancer screening
  - Identify and survey YBCS’ high-risk relatives about breast cancer screening
  - Implement an evidence-based intervention for breast cancer screening

*Funding: CDC*
Future Directions: Project 3

• **Evidence-based Approach:**
  • Decision aids that address individual- and intra-familial decision-making processes
  • Decision aid characteristics efficacious in increasing use of genetic testing and risk management

• **Aims:**
  • *Meta-Analysis and Moderation Analysis*

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