Swiss Cancer Predisposition Cascade Screening Consortium for the use and impact of genetic testing in hereditary breast/ovarian cancer and Lynch syndromes: CASCADE Study

Maria C. Katapodi, PhD, RN, FAAN Professor of Nursing Science on behalf of the CASCADE Consortium

FUNDING: FORSCHUNGSFONDS MARCH 2016, OFFICE VICE RECTOR RESEARCH, UNIVERSITY OF BASEL
HEREDITARY BREAST-OVARIAN CANCER SYNDROME (HBOC)

Associated with increased risks for breast, ovarian, prostate, and pancreatic cancers, and melanoma

Involves mainly mutations to tumor suppressor genes

BRCA1 or BRCA2

Tumor suppressor genes

The BRCA1 and BRCA2 genes produce a protein that repairs damaged DNA. Mutations in these genes lead to the accumulation of genetic defects that can allow cells to grow and divide in uncontrollable ways.

COUCH FJ, NATHANSON KL, OFFIT K. SCIENCE.2014
LYNCH SYNDROME (LS PREVIOUS HNPCC)

Inherited condition associated with high risks for colorectal, endometrial and other cancers

Genes belong to DNA mismatch repair (MMR) family, lead to microsatellite instability (MSI)
Test positive in 15% of colorectal and 24% of endometrial tumors
Sensitivity is 77-89% for Lynch Syndrome

MMR proteins missing in tumor tissue - Immunohistochemical (IHC) staining
Absent in 20% of colorectal and 25% of endometrial tumors
Sensitivity is 83% for LS

LE DT ET AL. N ENGL J MED. 2015
HBOC AND LS “RED FLAGS”

Personal health history
Age of cancer onset ≤50 years
Two primary cancers in the same person

Family health history
3+ cases of HBOC- or LS – associated cancers in the same side of the family
Male breast cancer
CURRENT FLOW OF GENETIC INFORMATION FOR HBOC AND LS

Proband is given total responsibility for disseminating results

General lack of knowledge about genetics and cancer

Not an urgent issue

Not everyone lives in area

Lack of communication in the family

No follow-up as to whether relatives pursued genetic counseling and/or testing

HAMPEL ET AL. CASCADE WORKSHOP, BASEL 20-22 SEP 2017
USE OF CANCER GENETIC SERVICES FOR HBOC AND LS IN SWITZERLAND

11% of all Swiss breast cancer patients have genetic testing

25% of breast cancer patients with a strong family history have genetic testing

Lower numbers for LS – 95% of affected individuals do not know they have LS

AYME A, ET AL.. BREAST CANCER RES TREAT. 2014
FEDEWA SA, ET AL., PLOS ONE. 2015
Center Disease Control & Prevention (CDC) Office Public Health Genomics

Tier-1 genetic conditions suitable to promote translational research, linking genetics to public health and epidemiology

- Breast/ovarian or other BRCA-related cancers
- Colorectal cancer associated with Lynch Syndrome (LS)
- Familial hypercholesterolemia

Cascade genetic screening is a public health intervention: Interface of Clinical and Public Health Genomics

Identify relatives of individuals with known mutations and promote systematic familial genetic testing

Khoury MJ, Evans JP. JAMA. 2015
CANCER PREDISPOSITION CASCADE GENETIC SCREENING CONSORTIUM

Multidisciplinary team
Epidemiology, Medicine, Nursing, Psychology, Public Health, Sociology

Multiple clinical sites in three linguistic regions of Switzerland
Basel, Bellinzona, Bern, Geneva, Jura, Lugano, Zurich

Specific Aim 1: Identify HBOC and LS mutation carriers and their close blood relatives and promote cascade genetic screening

Specific Aim 2: Develop web-based interventions designed to increase coping, family communication and support, and decrease decisional conflict
PILOT PHASE OF CASCADE STUDY

1. Feasibility of cancer predisposition cascade genetic screening for HBOC and LS
   ✓ Identify and recruit mutation carriers (HBOC and LS) from clinic-based genetic testing records
   ✓ Identify and recruit close blood relatives (first- and second-degree, and first cousins)
   ✓ Assess willingness to participate in family-based cohort
   ✓ Assess willingness to participate in focus groups (communication barriers, acceptability of web-based and family-based intervention)

2. Design a survey that assesses
   ✓ Barriers and facilitators to using cancer genetic services
   ✓ Gaps in the long-term coordination of cancer surveillance and management of cancer risk
   ✓ Need for interventions that enhance family communication, coping, and quality of life of mutation carriers and relatives
HBOC mutation carriers from Basel

Response rate 53% in two out of three attempts

PROGRESS IN RECRUITMENT OF MUTATION CARRIERS

N=56 MC identified from clinic records

N=5 MC accepted participation

24 invitation letter ...

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DO NOT REPRODUCE
### PROGRESS IN RECRUITMENT OF MUTATION CARRIERS

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<th>Mean and Frequencies</th>
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<td>Age</td>
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<td>Willing to invite % relatives</td>
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Identified 144 relatives
Invited n = 7 mutation carriers to pass on to n = 58 relatives

**PROGRESS IN RECRUITMENT OF RELATIVES**

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<td>Second degree relatives</td>
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<td>First cousins</td>
<td>61</td>
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<td>Minors (&lt;18 years old)</td>
<td>9</td>
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<td>Had cancer diagnosis</td>
<td>18</td>
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<td>Not living in Switzerland</td>
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CHALLENGES

Survey and recruitment material in three languages – culturally appropriate

Ethics Committees – various cantons

Consent form vs. survey of mutation carriers for inviting relatives

Families with uneven size – analytical problems when running data analyses

Identifying relatives when they return a survey

Referring physician

Resources and manpower – keeping tract recruitment process, surveys, reminders
ACKNOWLEDGMENTS

Bürki N, Erlanger T, Heinimann K, Heinzelmann-Schwarz V, Scharfe M, Schoenau E, Urech C

Buehler- Landolt R, Rabaglio M

Chappuis PO, Viassollo V

Caiata- Zufferey, M, Graffeo R, Pagani O.

Swiss TPH

Probst-Hensch N
THANK YOU FOR YOUR ATTENTION