PEDIGREE MODELING DEMONSTRATES THAT FAMILY HISTORY PERFORMS POORLY FOR THE IDENTIFICATION OF WOMEN WITH INHERITED RISKS FOR BREAST CANCER

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BACKGROUND

- Women with an estimated >20% lifetime risk of breast cancer are candidates for more aggressive clinical management, including screening at younger ages, at more frequent intervals, and with more sensitive technologies i.e. breast MRI.
- We utilized pedigree simulation to test the hypothesis that the majority of patients carrying pathogenic variants (PVs) of moderate to high penetrance in breast cancer-associated genes cannot be identified by family history analysis.
- In this study a qualifying family history was considered a 24% lifetime breast cancer risk as determined by the Claus model.[1]

METHODS

FIGURE 1. PEDIGREE MODELS

Three-generational pedigrees were simulated with 2 or 5 offspring per generation. Simulated pedigrees were one-sided and limited to either the maternal or paternal side segregating the disease allele.

The proband (III-1) is indicated by an arrow. The proband was assumed to be a 40-year old female carrying one copy of an autosomal dominant PV (+).

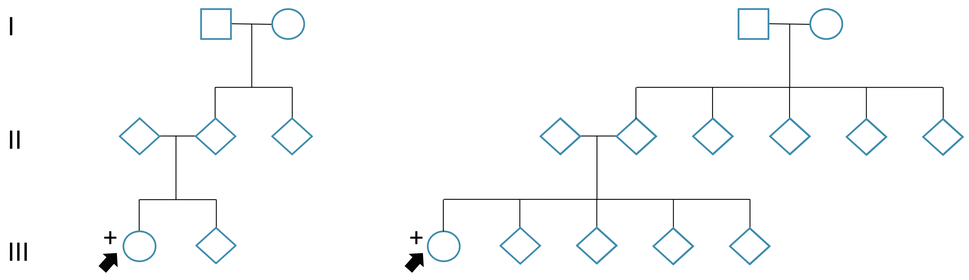
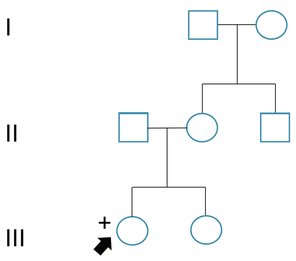


FIGURE 2. PEDIGREE SIMULATION AND RISK ASSESSMENT PROCESS

Step 1. Pedigree Simulation

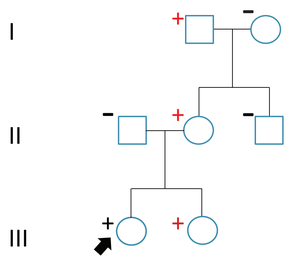
1000 pedigrees were simulated for each structure in Figure 1 using the SIMLA[2] program.



Step 2. Disease Locus Simulation

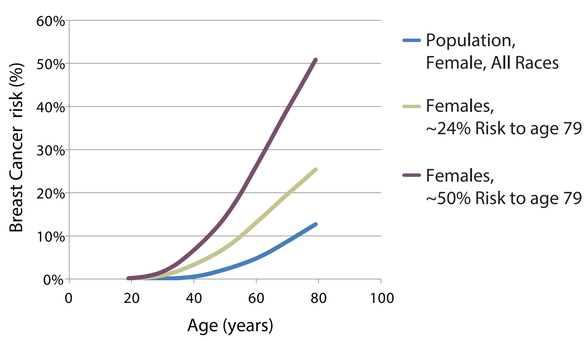
For each pedigree, a biallelic disease locus (-/+) was simulated according to Mendelian inheritance using the SLINK program.[3]

The possibility of *de novo* mutation was excluded.



Step 3. Breast Cancer Risk

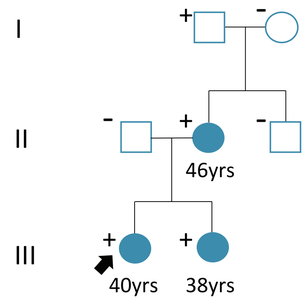
Breast cancer risk curves for a moderate (~24% risk to age 79) and highly (~50% risk to age 79) penetrant PV were extrapolated from SEER breast cancer incidence data.[4]



Step 4. Affection Status

For each pedigree, Breast Cancer affection status and age at diagnosis (for positive cases) were simulated using either the moderate or high penetrance model in Step 3 with the following assumptions:

1. All males are unaffected.
2. Generation I and II females are >70 years of age, but may have a breast cancer diagnosis prior to their present age.
3. Generation III females (including the proband) are between 40-49 years of age, but may have a breast cancer diagnosis prior to their present age.



Step 5. Claus Eligibility

Determine Claus model[1] eligibility of each pedigree.

CLAUS Positive ✓

Why Pedigree Simulations?

1. Ascertaining 1000's of complete 3-generational breast cancer families is not feasible.
2. It is even more difficult to ascertain families harboring a pathogenic variant (PV) in the absence of family history.
3. Modeling allows us to assess family units of defined size and assess impact.

RESULTS

- Analyses of simulated pedigrees indicate that <9% of female probands carrying a pathogenic mutation, conveying a ~24% risk of breast cancer, would receive modified clinical risk management based only on Claus model risk assessment (Figure 3A).
- Analyses of simulated pedigrees indicate that <25% of female probands, carrying a pathogenic mutation conveying a ~50% risk of breast cancer, would receive modified clinical risk management based only on Claus model risk assessment (Figure 3B).
- Detection rates decreased with smaller sibship size, reduced penetrance, and PVs segregating with the paternal lineage.

FIGURE 3A. CLAUS RISK MODEL ELIGIBILITY: RESULTS OF 1000 SIMULATIONS FOR ~24% LIFETIME RISK

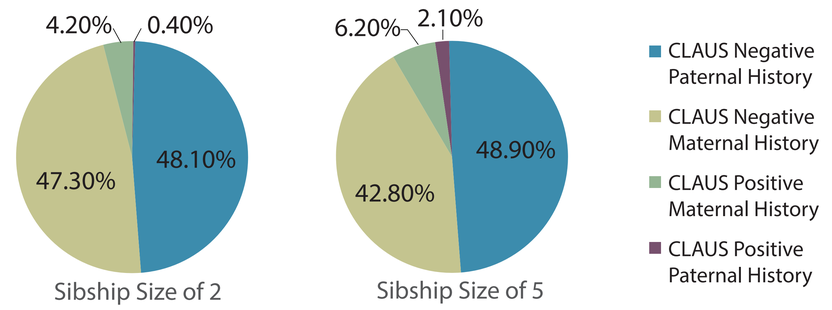
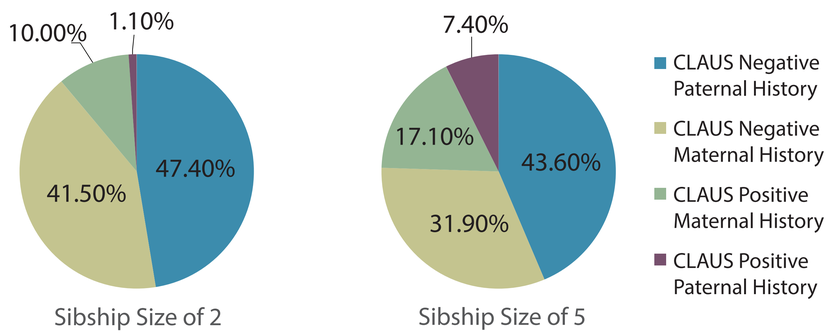


FIGURE 3B. CLAUS RISK MODEL ELIGIBILITY: RESULTS OF 1000 SIMULATIONS FOR ~50% LIFETIME RISK



CONCLUSIONS

- Pedigree simulation demonstrates that family history analysis alone fails to identify the majority of patients carrying PVs in breast cancer risk genes.
- Simulated analysis of pathogenic mutations of high or moderate penetrance failed to identify >75% and >91% of appropriate patients, respectively.
- Genetic testing is critical for identifying women who are candidates for modified medical management under current professional society guidelines.
- Although questions remain about the feasibility of population screening, this study demonstrates a potential benefit of broad pan-cancer testing over family history based cancer-specific testing for patients who have been targeted for evaluation of inherited cancer risk.
- Clinical diagnostic testing of actual patient samples confirms the results of this pedigree simulation approach.[5]

REFERENCES

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2. Schmidt M. *Stat Appl Genet Mol Biol*. 2005;4:Article15.
3. Ott J. *Proc Natl Acad Sci USA* 1989;86:4175-4178.
4. Surveillance, Epidemiology and End Results Program, National Cancer Institute (seer.cancer.gov) Dec 10, 2013.
5. Rosenthal et al. Detection of Pathogenic Mutations in Moderate Penetrance Breast Cancer Genes Significantly Increases the Number of Patients Identified as Candidates for Increased Screening, ASHG 2014.

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