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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

1000 pedigrees were simulated for each structure in Figure 1 using the SIMLA2 program.

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 1. Pedigree Simulation

Step 2. Disease Locus Simulation

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

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.