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Breast cancer risk assessment combined with a polygenic risk score in the general population for personalized screening

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Abstract:
Background: Polygenic risk scores (PRS) composed of single nucleotide polymorphisms (SNPs) known to increase breast cancer risk could improve the performance of existing breast cancer risk prediction tools. However, data is still limited on the feasibility of risk assessment including PRS in the general population of women undergoing routine screening mammography.**Patients and Methods:** Women, aged 40 or older and not previously identified as high risk, underwent a complete breast cancer assessment, including a questionnaire on personal and family history, mammogram with evaluation of breast density using DenSeeMammo®, and saliva-based testing of 76 SNPs. The PRS was calculated using published per-allele odds ratio corresponding to the SNP associations with breast cancer. We analyzed whether the addition of PRS in eligible women modified risk classification. PRS was not used for risk assessment in non-Caucasian women, but was calculated for comparison between ethnicities.**Results:** A total of 140 Caucasian women underwent a breast cancer assessment and 130 were eligible for MammoRisk® assessment, with a median age of 51 (38-71). With MammoRisk without PRS: 26 (20%) were found to have moderate risk (5-year risk <1%), 71 (55%) intermediate risk (between 1 and 1.67%), and 33 (25%) high risk (≥1.67%). When PRS was performed and integrated into MammoRisk score, 34 (26%) were found to have moderate risk, 45 (35%) intermediate risk, and 51 (39%) high risk. The use of PRS changed the risk classification in 57 women (44%), 32 (25%) to a higher category and 25 (19%) to a lower category. When PRS was assessed for women of sub-Saharan African origin (n=36) using allele frequencies and odd-ratio observed in Caucasian populations, mean PRS was much higher (mean=1.89, [0.65-5.33], median = 1.65 ; n=36) than in the group of Caucasian women (mean=0.97 [0.33-3.05], median = 1.02 ; n=130), which would overestimate the PRS and the risk of developing breast cancer in women of African origin. **Conclusions:** The use of PRS changed the risk classification in a large subset of women. Results of ongoing large-scale studies will inform on the benefits of personalized risk-based screening compared to annual

screening (Wisdom [NCT02620852], MyPEBS [NCT03672331]). As current PRSs have been developed and validated in women of European ancestry, population-specific PRSs need to be developed with data from ongoing large-scale genome-wide association studies for improved risk assessment in women of other ethnicities (Confluence Project, Nigerian Breast Cancer Study).

Number of women by risk category

	W/O PRS	With PRS
Moderate	26	34
Intermediate	71	45
High	33	51

Number of women with change in risk category when using PRS

Intermediate to Moderate	16
Moderate to Intermediate	5
High to Intremediate	9
Moderate to High	3
Intermediate to high	24

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Author Disclosure Information:

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