Associations of genetically predicted metabolites with mammographic breast density and breast cancer risk in premenopausal women

Ghazaleh Pourali, MD[1], Linshuoshuo Lyu, MS[2], Xingyi Guo, PhD[2], Adetunji T. Toriola, MD, PhD, MPH[1]

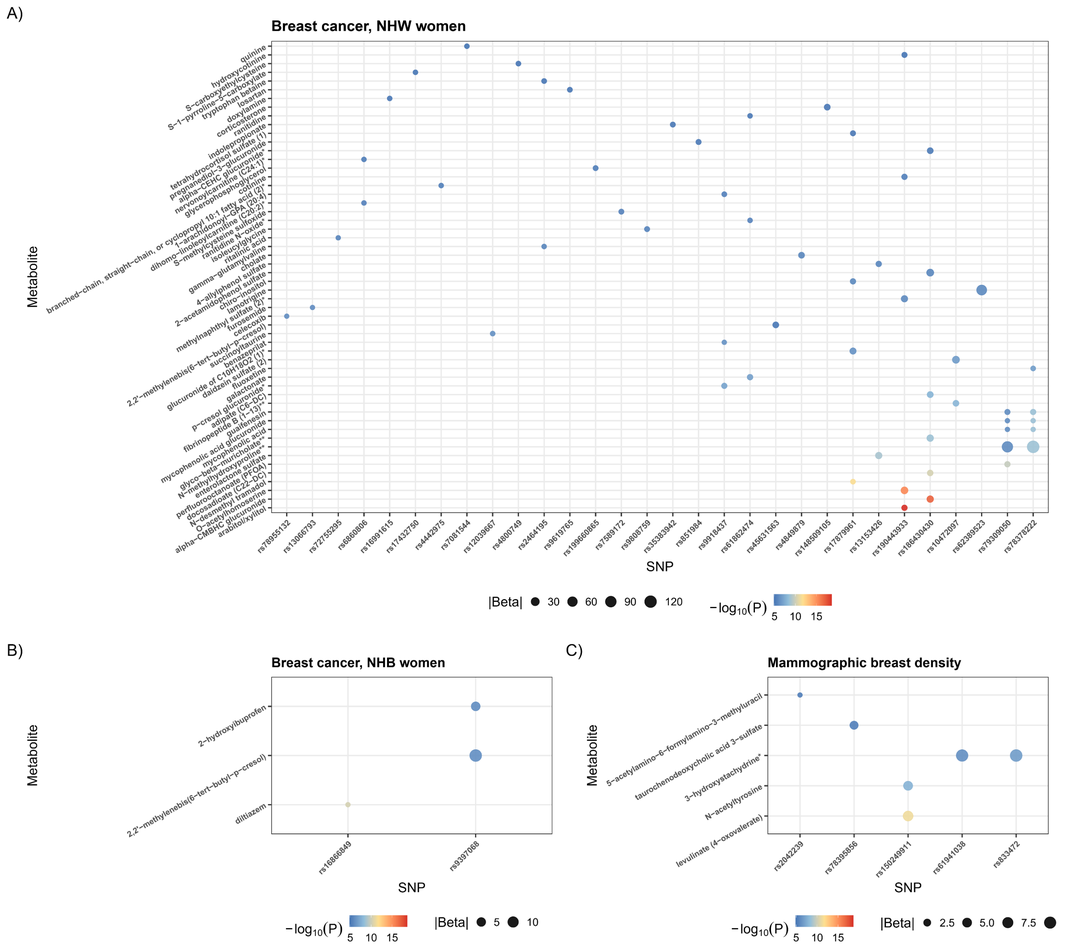
1. Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, USA.
2. Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA.

Introduction

- Genome-wide association studies (GWAS) have identified genetic loci associated with mammographic breast density (MBD) and breast cancer risk, but the mechanisms underlying these associations remain unclear.
- Metabolite quantitative trait loci (mQTL) analyses can map genetic loci associated with metabolites, offering insight into mechanisms involved in risk, but there is limited data on how genetically predicted metabolites are associated with MBD and breast cancer risk in premenopausal women.
- To address this, we performed mQTL analyses in non-Hispanic White (NHW) and non-Hispanic Black (NHB) women and examined their overlap with established GWAS loci for MBD and breast cancer.

Methods and Materials

- **Study population:** 494 NHW and 163 NHB women who had screening mammograms at Washington University in St. Louis.
- **Metabolomics profiling:** At Metabolon®, identified 1,074 metabolites. Metabolite data were batch-normalized, metabolites with >10% missingness were excluded, and remaining missing values were imputed.
- **Genotyping:** Infinium microarray, Illumina, covered 2,028,571 loci.
- **mQTL mapping:** Linear regression in PLINK 2.0, stratified by race and adjusted for age, body mass index, alcohol use, oral contraceptive use, and first five genotype principal components. Significant mQTLs (FDR-p<0.05) were compared to GWAS loci for breast cancer, two fine mapping studies, and GWAS of MBD.



Results

- In NHW women, 30 mQTLs were associated with 54 metabolites overlapping breast cancer GWAS loci. These metabolites were in xenobiotic pathways (e.g., anti-inflammatory/ immunosuppressant drugs, chemicals, tobacco metabolites), lipid metabolism (fatty acids, corticosteroids, bile acids), and amino acid metabolism (tryptophan, methionine/cysteine, tyrosine).
- In NHB women, 2 mQTLs were associated with 3 metabolites overlapping breast cancer GWAS loci, including drug and chemical metabolites.
- For MBD, NHW women had 5 mQTLs associated with 5 metabolites overlapping MBD GWAS loci. Key metabolites mapped to tyrosine metabolism, xanthine metabolism, bile acid metabolism, and plant/food components.

Figure 1. mQTL associations that overlap with: A) breast cancer GWAS loci in NHW women; B) breast cancer GWAS loci in NHB women; C) mammographic breast density GWAS loci in NHW women.

Conclusions

Our novel study identified genetic loci associated with metabolites that overlap with established MBD and breast cancer risk loci with differences in NHW and NHB women. These findings suggest biological mechanisms of genetic risk and provide a basis to prioritize metabolites and pathways for targeted prevention.

Contact

Ghazaleh Pourali and **Adetunji T. Toriola**
Division of Public Health Sciences, Department of Surgery
Washington University School of Medicine
St. Louis, Missouri, USA.
Email: pourali@wustl.edu; a.toriola@wustl.edu

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