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**Title:** NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer

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**Body:** Background: Combination of metabolomics and epidemiological approaches opens new perspectives for ground-breaking discoveries. The aim of the present study was to investigate for the first time whether plasma non-targeted metabolomic profiles, established from a simple blood draw from healthy women, could contribute to predict the risk of developing breast cancer within the following decade and to better understand the etiology of this complex disease.

Methods: A prospective nested case-control study was set up in the SU.VI.MAX cohort, including 206 breast cancer cases diagnosed during a 13y follow-up, and 396 matched controls. Non-targeted NMR metabolomic profiles were established from baseline plasma samples. Multivariable conditional logistic regression models were computed for each individual NMR variable and for combinations of variables derived by principal component analysis.

Results: Several metabolomic variables from 1D NMR spectroscopy were associated with breast cancer risk. Women characterized by higher fasting plasma levels of valine, lysine, arginine, glutamine, creatine, creatinine, and glucose and lower plasma levels of lipoproteins, lipids, glycoproteins, acetone, glycerol-derived compounds and unsaturated lipids had a higher risk of developing breast cancer. P-values ranged from 0.00007 ( $OR_{T3vsT1}=0.37[0.23-0.61]$  for glycerol-derived compounds) to 0.04 ( $OR_{T3vsT1}=1.61[1.02-2.55]$  for glutamine).

Conclusion: This study highlighted associations between baseline NMR plasma metabolomic signatures and long-term breast cancer risk. These results provide interesting insights to better understand complex mechanisms involved in breast carcinogenesis and evoke plasma metabolic disorders favorable for carcinogenesis initiation. This study may contribute to develop screening strategies for the identification of at-risk women for breast cancer well before symptoms appear.