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Original Research

DNA methylome analysis identifies accelerated epigenetic ageing associated with postmenopausal breast cancer susceptibility

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Abstract ***Aim of the study:*** A vast majority of human malignancies are associated with ageing, and age is a strong predictor of cancer risk. Recently, DNA methylation-based marker of ageing, known as 'epigenetic clock', has been linked with cancer risk factors. This study aimed to evaluate whether the epigenetic clock is associated with breast cancer risk susceptibility and to identify potential epigenetics-based biomarkers for risk stratification.
Methods: Here, we profiled DNA methylation changes in a nested case–control study embedded in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (n = 960) using the Illumina HumanMethylation 450K BeadChip arrays and used the Horvath age estimation method to calculate epigenetic age for these samples. Intrinsic epigenetic age acceleration (IEAA) was estimated as the residuals by regressing epigenetic age on chronological age.
Results: We observed an association between IEAA and breast cancer risk (OR, 1.04; 95% CI, 1.007–1.076, P = 0.016). One unit increase in IEAA was associated with a 4% increased odds of developing breast cancer (OR, 1.04; 95% CI, 1.007–1.076). Stratified analysis based on menopausal status revealed that IEAA was associated with development of postmenopausal breast cancers (OR, 1.07; 95% CI, 1.020–1.11, P = 0.003). In addition, methylome-wide analyses revealed that a higher mean DNA methylation at cytosine-phosphate-guanine (CpG) islands was associated with increased risk of breast cancer development (OR per 1 SD = 1.20; 95 %CI: 1.03–1.40, P = 0.02) whereas mean methylation levels at non-island CpGs were indistinguishable between cancer cases and controls.
Conclusion: Epigenetic age acceleration and CpG island methylation have a weak, but statistically significant, association with breast cancer susceptibility.