Early signatures of cancer evolution from cell-free DNA methylation profiling in pre-diagnosis biologics

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Cell-free DNA (cfDNA) has been highlighted as a promising biomarker for early cancer detection owing to the capability of non-invasively detecting DNA methylation signatures and mutations concordant with the originating tumour in blood. While many studies have been able to demonstrate the capability of utilizing plasma cfDNA biomarkers to distinguish cancer patients from healthy individuals, most of these findings have profiled from individuals with late-stage or established cancers that were detected through conventional screening or from clinical follow-up following onset of symptoms. Evaluating the clinical utility of emerging biomarkers for early disease detection requires application of new technologies to biologics collected from asymptomatic individuals prior to diagnosis. By leveraging biologics collected in the Ontario Health Study longitudinal population cohort, genome-wide cfDNA methylome profiling was performed on blood plasma of incident breast and prostate cancer cases collected up to nine years prior to diagnosis, in addition to matched cancer-free controls. Across both cancer types, observed cfDNA differentially methylated regions (DMRs) in discovery cohort samples were significantly enriched for regulatory elements particularly in promoter and enhancer regions. Notably, target genes of these regions were highly associated with gene sets involved in tumour growth and survival, inflammation, and various metabolic processes. Building on these insights, predictive models trained and tuned using cfDNA DMRs identified from discovery set samples were evaluated in held-out test data. Across both breast and prostate cancers, cfDNA DMRs were highly predictive of early cancer up to eight years prior to diagnosis, even capable of identifying individuals with early breast cancers despite a negative mammogram screen prior to blood collection. Furthermore, cfDNA methylome signatures were also capable of stratifying individuals at high and low risk of developing cancers, highlighting an alternative application of cfDNA biomarkers. Collectively, this work provides further insights into the signatures of early cancer evolution through cfDNA methylome analysis. By interrogating pre-diagnosis biologics, I highlight potential biological processes driving early cancer development and demonstrate potential applications from early detection and risk stratification, to identifying potential molecular targets for early cancer prevention.