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Evaluation of the impact of lifestyle parameters on global DNA methylation and hydroxymethylation in a French cohort

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Cancer development and progression are intimately linked with epigenetic alterations. Of these, DNA methylation on cytosine, a repressive mark inhibiting transcription, have been widely studied. Cytosine hydroxymethylation has received less attention, although perturbations of this mark have also been associated with cancer. Most studies investigate DNA methylation alterations at the level of individual loci, thought to reflect potential alterations in gene expression. Another view upon DNA methylation can be obtained while looking at global methylation levels genome wide, thereby reflecting potential alterations of the mechanisms driving DNA methylation.

In this study, we use an UHPLC-MS/MS method for the quantification of methylated and hydroxymethylated cytosine. The method was validated using the bioanalytical method guideline of European medicines agency. Quality control samples were periodically injected to check the robustness of the results. Global DNA was obtained from neutrophils in a population of 551 individuals affiliated to the French agricultural social protection, previously included in the EPIBIO97 study and biobank. Enrolment for this cohort began in 1997 and included 42.2% of women. Their age ranges from 17 to 76 years old with a mean of 44.4. Their BMI ranges from 18.1 to 44.1 with a mean of 25.4. 33.7% of them had already smoked at inclusion while 66.3% never did.

The blood samples were accompanied with data from questionnaires regarding individual health parameters, life habits and agricultural work exposures. Using statistical analysis, we linked epigenetic marker levels with several of these life habit parameters to assess their effects on epigenetic biomarkers. Using this method, we highlighted an increase of global methylation in women. We observed a decrease of methylation and hydroxymethylation correlated with higher BMI. Older people were associated with a decrease of hydroxymethylation level.

Finally, smokers were associated with lower hydroxymethylation level. These results were already described in region specific analysis of DNA. This study brings a more global approach of these parameters with a number of samples rarely studied in the literature. As a follow-up of the present results, DNA hydroxymethylation and methylation will be analysed in line of agricultural exposures of the studied population; to further explore the link between agricultural occupational exposures and risk of cancer.

Keywords:

Methylation; Hydroxymethylation; Global DNA; UHPLC-MS/MS; Agricultural cohort.