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Epigenetic age acceleration and colorectal cancer in an ageing population cohort

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Motivation and Aim: Ageing is one of the most important risk factor of colorectal cancer (CRC) [1], and its contribution largely depends on 'biological age' which reflects an individual rate of health decline. The measure of 'epigenetic age' (EA) based on DNA methylation (DNAm), is considered as ageing biomarker. We investigated the relationship between acceleration of six markers of the epigenetic age acceleration (EAA) and incident colorectal cancer during a 16-year follow-up in a nested case-control study from a population cohort of middle and older age in Russia.

Methods and Algorithms: A random population sample (Novosibirsk) was examined at baseline in 2003/05 (men, women, 45–69, n=9360) and followed up for 16 years. In a nested case-control design, we randomly selected 35 cases of CRC from an entire set of incident colorectal cancer (154), and 354 matched controls. The assessment of DNAm was conducted on Illumina EPIC850k Beadchip. Six baseline EA measures (Horvath, Hannum, PhenoAge, Skin and Blood (SB), BLUP, Elastic Net (EN)) were calculated, along with their respective EAA [2].

Results: DNAm ages calculated by Horvath's, Skin and Blood, BLUP and EN clocks were close to participants' chronological age (CA); the corresponding mean (SD) difference were -4.66 (5.25), -0.07 (4.08), 4.19 (3.16) and 0.30 (3.29). Hannum and PhenoAge EAs were less close to CA. The mean EAAs for four markers were significantly higher in CRC cases compared to control 3.91 (5.45) vs. -0.43(4.53), p<0.001; 2.15 (3.41) vs. -0.24(4.10) p<0.001; 2.29 (4.73) vs. -0.22(5.69), p-0.005; 1.83 (2.41) vs. -0.11(2.90) p<0.001 for Horvath, Hannum, PhenoAge, and BLUP, correspondingly. In multivariable adjusted logistic regression, the odds ratios (ORs) for CRC risk per decile increase in EAA ranged from 1.20 (95 % CI: 1.04-1.39) to 1.44 (95 % CI: 1.21-1.76) for Horvath, Hannum, PhenoAge, and BLUP measures. Conversely, the SB and EN EAA measures showed borderline inverse associations with CRC and had ORs of 0.86-0.87 (95 % CI: 0.76-0.99). Tertile analysis reinforced a positive association between CRC risk and four EAA measures (Horvath, Hannum, PhenoAge, BLUP) and a modest inverse relationship with EN EAA

Conclusion: In this case-control study based on a population cohort of middle and elderly age, we found a direct association between incident CRC and four markers of accelerated baseline epigenetic age (Horvath, Hannum, PhenoAge, and BLUP). In contrast, two markers showed a negative or no association. These results warrant further exploration in larger cohorts [3] and may have implications for CRC risk assessment and prevention.

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