A prospective study of duration of smoking cessation and colorectal cancer risk by epigenetic-related tumor classification

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Abstrak

The effect of duration of cigarette smoking cessation on colorectal cancer risk by molecular subtypes remains unclear. Using duplication-method Cox proportional-hazards regression analyses, we examined associations between duration of smoking cessation and colorectal cancer risk according to status of CpG island methylator phenotype (CIMP), microsatellite instability, v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation, or DNA methyltransferase-3B (DNMT3B) expression. Follow-up of 134,204 individuals in 2 US nationwide prospective cohorts (Nurses' Health Study (1980-2008) and Health Professionals Follow-up Study (1986-2008)) resulted in 1,260 incident rectal and colon cancers with available molecular data. Compared with current smoking, 10-19, 20-39, and ≥40 years of smoking cessation were associated with a lower risk of CIMP-high colorectal cancer, with multivariate hazard ratios (95% confidence intervals) of 0.53 (0.29, 0.95), 0.52 (0.32, 0.85), and 0.50 (0.27, 0.94), respectively (Ptrend = 0.001), but not with the risk of CIMP-low/CIMP-negative cancer (Ptrend = 0.25) (Pheterogeneity = 0.02, between CIMP-high and CIMP-low/CIMP-negative cancer risks). Differential associations between smoking cessation and cancer risks by microsatellite instability (Pheterogeneity = 0.02), DNMT3B expression (Pheterogeneity = 0.03), and BRAF (Pheterogeneity = 0.10) status appeared to be driven by the associations of CIMP-high cancer with microsatellite instability-high, DNMT3B-positive, and BRAF-mutated cancers. These molecular pathological epidemiology data suggest a protective effect of smoking cessation on a DNA methylation-related carcinogenesis pathway leading to CIMP-high colorectal cancer.