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Association of Chromosomal Instability, Microsatellite Instability and CPG Island Methylator Phenotype with Postcolonoscopy Colorectal Cancer in a Population Based Study

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Background and aim: Over 50% of the postcolonoscopy colorectal cancers (PCCRCs) (i.e. CRC diagnosed after a colonoscopy that excluded cancer) originate from missed precursor lesions. The biologic pathway of these lesions is unclear. We hypothesized that PCCRCs originate from subtle appearing non-polypoid (NP) adenomas and sessile serrated lesions (SSLs). In a population based study, we examined the occurrence of chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) in PCCRCs and prevalent CRCs.

Methods: We identified all PCCRCs diagnosed from 2001 to 2010 in a large gastroenterology practice from the Netherlands. PCCRCs were defined as cancers occurring within 5 years after a complete index colonoscopy. Only missed and newly developed PCCRC were included. Whole genome DNA copy number changes and mutation status of genes commonly affected in CRC (APC, KRAS, BRAF, FBXW7, PIK3CA, NRAS, SMAD4 and TP53) were examined by shallow whole-genome sequencing and targeted sequencing, respectively, using Illumina next generation sequencing platforms. MSI and CIMP status were examined using the pentaplex marker panel from Promega and the Weisenberger CIMP panel using methylation-specific PCR, respectively. Results were adjusted for age and gender.

Results: In total, 120 PCCRCs and 100 prevalent CRCs were examined. Regarding DNA copy number alterations, PCCRCs contain less often 18q ($p<0.001$) deletions than prevalent CRCs. Furthermore, PCCRCs contain less frequently APC ($p=0.04$), NRAS ($p=0.03$), and TP53 mutations ($p=0.02$) than prevalent CRCs. In contrast, MSI ($p=0.01$), CIMP ($p=0.03$) and BRAF mutations ($p=0.05$) were more frequent in PCCRCs than in prevalent CRCs.

Conclusion: Both CIN and MSI pathways are associated with the occurrence of PCCRC. The molecular profiles support the hypothesis that NP adenomas and SSLs are at the origin of PCCRCs.