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Abstract

Genetic Risk Factors Modulate the Association between Physical Activity and Colorectal Cancer †

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Abstract: Physical activity (PA) is an established protective factor for colorectal cancer (CRC). However, the mechanisms underlying this relationship are less understood, and it is not known if the association is modified by genetic variants. To investigate this possibility, we conducted a genome-wide gene–PA interaction analysis. Using logistic regression and two-step and joint tests, we analyzed the interactions between common genetic variants across the genome and self-reported PA (categorized as active vs. inactive and as study- and sex-specific quartiles) in relation to CRC risk. PA had an overall protective effect on CRC, showing a 15% risk reduction among active vs. inactive participants (OR = 0.85; 95% CI = 0.81–0.90). The two-step GxE method identified an interaction between rs4779584, an intergenic variant located between the GREM1 and SCG5 genes, and PA for CRC risk ($p = 2.6 \times 10^{-8}$). Stratification by genotype at this locus showed a significant reduction in CRC risk by 20% in active vs. inactive participants with the CC genotype (OR = 0.80; 95% CI = 0.75–0.85), but no significant PA–CRC association was observed among CT or TT carriers. When PA was modeled as quartiles, the 1-d.f. GxE test identified that rs56906466, an intergenic variant near the KCNG1 gene, modified the association between PA and CRC ($p = 3.5 \times 10^{-8}$). Stratification at this locus showed that increase in PA (highest vs. lowest quartile) was associated with a lower CRC risk solely among TT carriers (OR = 0.77; 95% CI = 0.72–0.82). In summary, these results identified two genetic variants that modified the association between PA and CRC risk. One of them, related to GREM1 and SCG5, suggests that the bone morphogenetic protein-related, inflammatory and/or insulin signaling pathways may be associated with the protective influence of PA on colorectal carcinogenesis.

Keywords: physical activity; gene-environment interaction; colorectal cancer; GWAS

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