

Common Genetic Variation May Affect Colorectal Cancer Incidence and Prognosis

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Recent genome-wide association studies have shown the importance of common genetic variation in mediating the risk of colorectal cancer by identifying at least 16 germline single-nucleotide polymorphisms (SNPs) that are significantly associated with disease incidence. To examine whether this common genetic variation could also play a role in disease prognosis, postdoctoral fellow Amanda Phipps and colleagues from the Public Health Sciences Division recently examined whether the 16 previously identified SNPs associated with colorectal cancer incidence were also associated with overall and disease-specific mortality in a sample of 2611 cases of invasive colorectal cancer pooled from five separate prospective cohort studies.

In their meta-analysis of overall survival, adjusted for sex and age at diagnosis, most of the SNPs previously associated with risk of incident colorectal cancer showed no association with survival (after Bonferroni adjustment for multiple comparisons). However, a significant association was detected with SNP rs4939827 (18q21, *SMAD7*), such that each copy of the minor allele (G) was associated with a 16% increased risk of all-cause mortality (Hazard Ratio (HR): 1.16, 95% Confidence Interval (CI): 1.06-1.27; $p=0.002$), a finding that was similar across all five individual studies. Rs4939827 was also associated with poorer disease-specific survival (HR: 1.17, 95% CI: 1.05-1.30, $p=.005$), although this association was only of borderline statistical significance after adjustment for multiple comparisons.

Phipps and colleagues found no apparent difference in the association between rs4939827 and survival according to smoking status, body mass index or the use of anti-inflammatory medications. Adjusting for stage at diagnosis modestly attenuated the association with overall survival (HR: 1.13, 95% CI: 1.01-1.30, $p=.005$), while there was a non-significant difference according to family history (HR: 1.01, 95% CI: 0.69-1.46 vs. HR: 1.18, 95% CI: 1.05-1.32 for patients with and without a family history of colorectal cancer, respectively).

Interestingly, the study's findings appear contrary to previously reported associations of rs4939827 with decreased risk of incident colorectal cancer. Because Rs4939827 is located on an intronic region of *SMAD7*, a downstream inhibitor of transforming growth factor- β 1 (TGF- β 1), the current study authors postulate that the apparent contradiction may be owed to the pleiotropic function of the

TGF- β 1 pathway, which functions as a tumor suppressor in normal epithelium but can nevertheless promote metastasis in established tumors. Although the functionality of rs4939827 is currently unknown, it is plausible that a variant in *SMAD7* that contributes to up-regulation of TGF- β 1 could result in lower cancer risk but poorer post-diagnosis survival.

This study provides support for the role of genetic variation in survival after a colorectal cancer diagnosis, specifically the minor allele in rs4939827. However, the common genetic variants most strongly associated with survival are likely to be distinct from those that underlie initial tumor development.

[Phipps AI, Newcomb PA, Garcia-Albeniz X, Hutter CM, White E, Fuchs CS, Hazra A, Ogino S, Nan H, Ma J, Campbell PT, Figueiredo JC, Peters U, Chan AT.](#) (2012). Association between colorectal cancer susceptibility loci and survival time after diagnosis with colorectal cancer. *Gastroenterology*. 143(1):51-54.e4.

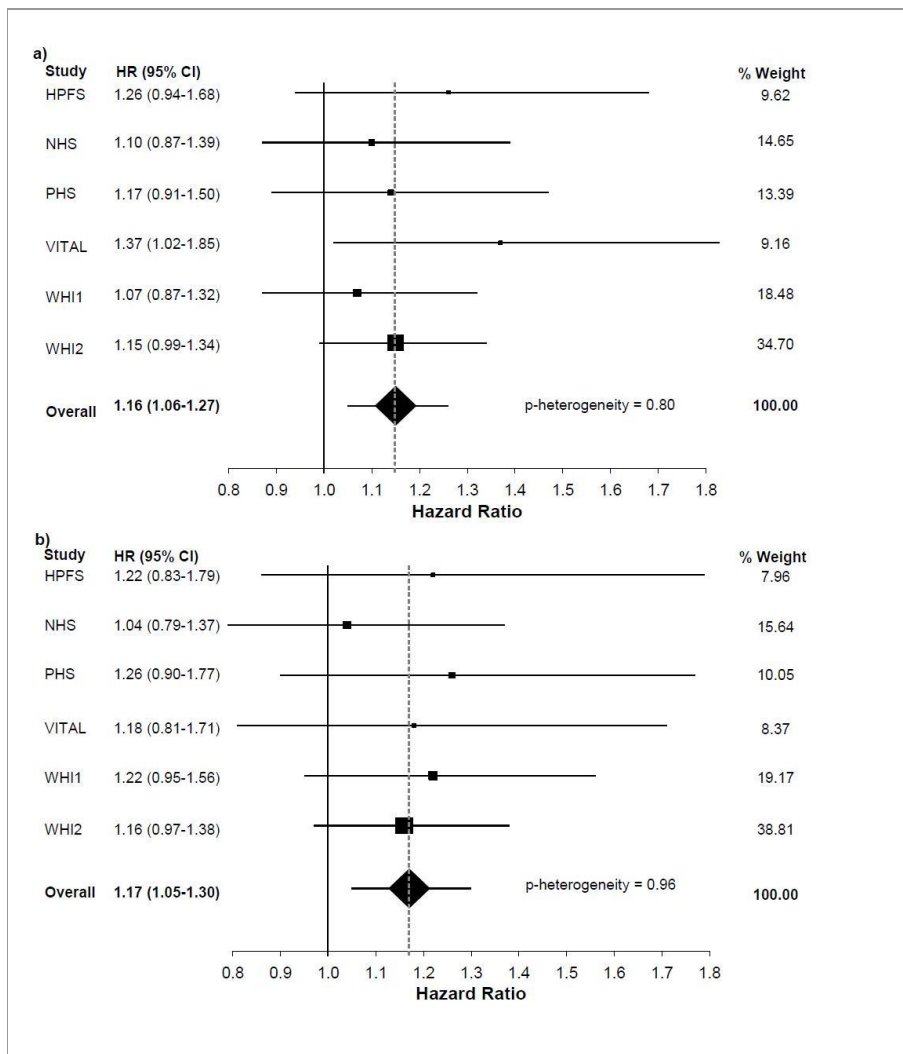


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Figure. Association between dose of rs4939827 minor allele and a) overall survival and b) colorectal cancer-specific survival by study population, adjusted for age at diagnosis and sex. HPFS=Health Professionals Follow-Up Study; NHS=Nurses' Health Study; PHS=Physicians' Health Study; VITAL= VITamins and Lifestyle Study; WHI=Women's Health Initiative.