

Genome-wide Association Studies Meet Chemoprevention

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A disappointment of genome-wide association studies (GWASs) applied to colorectal and other cancer risk has been the challenge of translating the observed small effects of individual genetic variants to immediate clinical application. The lackluster impact has in many ways detracted from the promise of GWASs, which includes a genetic strategy to gain some insight on component traits of complex adult-onset diseases in man. In this issue of the Journal (1), Nan et al. remind us of the potential of GWASs to advance our understanding of the genetic basis of colorectal cancer prevention, providing observational and functional evidence for an aspirin-response allelic variant.

The T variant at rs6983267 on 8q24 is a weakly protective allele for colorectal cancer discovered in the conduct of GWASs (2–4). This locus resides in an apparent enhancer domain for *MYC* (5), and deletion of the region in mice has been associated with resistance to APC^{min}-induced intestinal tumorigenesis (6) by decreasing TCF7L2 interaction with CTNNB1 (TCF4/β-catenin)-mediated transactivation of the *MYC* oncogene (5). Separately, the protective effect of aspirin for colorectal cancer is, in part, mediated by the ability of aspirin to block prostaglandin E₂/EP2 receptor-mediated stabilization of CTNNB1 (7,8). Based on the consistent effects of aspirin alone and the rs6983267 variant alone, Nan et al. (1) tested the joint effect of the rs6983267 genotype and aspirin use on the risk of colorectal cancer in a nested case-control study, pooling subjects from the Nurses' Health Study (n = 472 case patients; n = 1013 control subjects) and the Health Professionals Follow-up Study (n = 368 case patients; n = 1686 control subjects). Carriage of the low-risk T variant among regular users of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) confers half the risk of colorectal cancer when compared with nonaspirin users of the same genotype. Although increased dose and duration of aspirin use appear to enhance the protective effect of NSAIDs in TT/TG carriers, the protective effect of aspirin in these subjects is present even at modest doses. However, there is no overall protective effect of regular aspirin use on colorectal cancer among GG carriers, and longer duration of aspirin use was associated with a non-statistically significant decrease in risk, suggesting no benefit of aspirin in the non-T genetic background.

Important to this work is the functional demonstration by the authors that TCF7L2 demonstrates lower binding to the T allele 6983267 relative to the G allele in cell line studies in the presence of aspirin and does so in a dose-dependent manner. The findings from the binding studies strengthen the observed differential effect of aspirin by genotype in the human studies, favoring

the hypothesis that the benefit of aspirin, and other NSAIDs, is specific to a subset of the population. This study adds to the emerging evidence that genetic variation at 8q24 is functionally relevant as a risk variant. This study also strengthens the emerging hypothesis that the antitumorigenic effect of aspirin and other NSAIDs is partly mediated by a disrupting effect on the transactivation of *MYC*. This is shown in this study as the benefit of aspirin limited to the T carriers (responsive genotype), for which the lower risk of colorectal cancer in this background is largely limited to tumors driven by nuclear CTNNB1 that overexpress the *MYC* oncogene.

Collectively, the work of Nan et al. (1) provides compelling evidence that aspirin interacts with the genetic background at rs6983267 to influence the risk of colorectal cancer and that the effect is mechanistically coupled to the ability of the region to bind the CTNNB1/TCF7L2 complex and transactivate the *MYC* oncogene. In the GG background, regular aspirin appears less efficacious, supporting evidence that those with the GG genotype have a more constitutively active enhancer function for *MYC* expression. Importantly, the non-statistically significant reduction in risk with long-duration aspirin use in this background suggests that higher dosing or long use is necessary to achieve benefit in the GG background. These questions can and should be addressed quickly in randomized controlled trials of NSAIDs.

These findings are of interest for cancers where *MYC* oncogenesis is implicated and possibly explain the identification of polymorphisms on 8q24 as susceptibility loci in other cancers (9). Thus, considering analyses of NSAIDs and 8q24 genotypes in *MYC*-driven tumors, as opposed to lumping tumors together based on their tissue of origin, is certainly warranted.

Although the impact of this study on identifying individuals most likely to benefit from the regular use of NSAIDs for cancer prevention is clear, there is an additional attribute of this work that is worth highlighting. This study is an excellent example of the joining of discovery efforts, mechanistic studies, and prior clinical knowledge in the conception of a testable and biologically rational hypothesis—or the logical but essential next step. This study is timely for the readership because it represents the promise of the GWAS era for the field of cancer prevention, highlights the importance of environmental factors such as aspirin as important modifiers of trait expression, and offers new genotype-based strategies on which to advance NSAIDs for chemoprevention from evidence to actual patient-level cancer risk reduction.

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Obesity That Makes Kidney Cancer More Likely but Helps Fight It More Strongly

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Kidney tumors, including renal cell carcinoma, are among the top three most common genitourinary cancers and are ranked as the seventh and ninth most malignant disease in men and women, respectively (1). In the United States each year some 65 000 people are diagnosed with a kidney cancer, and 13 000 annual deaths are attributed to this malignancy (2). Over the past two decades the incidence rate of kidney tumors has risen substantially (3). Whereas more frequent abdominal imaging in recent years may have played an important role for the higher diagnostic ascertainment of renal masses, there appears to be a true rise stemming from higher prevalence of the risk factors of kidney malignancies among Americans, in particular the higher rate of obesity. According to observational studies, almost half of all kidney tumors are linked to obesity (ie, body mass index [BMI] >30 kg/m²), and renal cancer risk is 20% to 35% higher for every 5 kg/m² of higher BMI (4). This association is no surprise given the role of obesity as the chief culprit in a diverse array of portentous and fatal conditions from malignancies to cardiovascular and renal diseases, with the prevailing commonality of a high death risk among these conditions.

Despite the presumably true role of obesity in the development of many chronic disease states, such as cancer, and acute devastating illnesses, such as coronary events, once these conditions have emerged, being obese appear to counterintuitively provide protective advantages and even survival benefits (5). Notwithstanding the disparaging impact of obesity on health and disease, emerging data suggest the existence of an obesity paradox, in that higher BMI may protect against worse outcomes in many acute and chronic

disease states. The seemingly counterintuitive association between higher BMI and greater survival was first observed in patients with end-stage kidney disease undergoing maintenance hemodialysis treatment (6). Recent observational studies have also suggested a consistent obesity paradox in patients with heart failure (7) and those with malignancies (8), as well as among geriatric populations (9). These provocative observations have also been referred to as “reverse epidemiology” of cardiovascular risk factors when also considering data on lipid paradox and hypertension paradox (ie, survival advantages of higher lipid concentrations or higher blood pressure values among dialysis or heart failure patients) (7). Similarly, in a recent study among more than half a million patients with incident acute myocardial infarction without prior cardiovascular disease, in-hospital mortality was inversely associated with the number of coronary heart disease risk factors, including hypertension, smoking, dyslipidemia, diabetes, and family history of coronary heart disease (10). Although the biologic plausibility of the obesity paradox has remained unclear, the consistency of the data is remarkable, leaving little doubt that these observational data are beyond statistical confounding.

In this issue of the Journal, Hakimi et al. (11) examined a contemporary cohort of 2119 patients with clear cell renal cell carcinoma who underwent partial or total nephrectomy over 17 years (ie, from 1995 to 2012). Interestingly there were three seemingly counterintuitive findings consistent with the obesity paradox: First, compared with normal-weight patients, overweight (BMI 25 to <30 kg/m²) and obese (BMI >30 kg/m²) patients had 39% and 35%