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Clinical Cancer Research

Letter to the Editor

KRAS-LCS6 Genotype as a Prognostic Marker in Early-Stage CRC–Letter

Bríd M. Ryan, Ana I. Robles, and Curtis C. Harris

In their recently published study (1), Smits and colleagues reported an association between rs61764370 and colorectal cancer (CRC) survival of early-stage tumors. Similarly, in our study of 678 (441 controls and 237 cases; Table 1), we found that rs61764370 was also associated with a reduced risk of mortality, albeit in late-stage tumors [$HR_{TG/GG\ vs.\ TT}$, 0.38; 95% confidence interval (CI), 0.16–0.88; $n = 124$] (Fig. 1 and Table 2). Neither study found an association with risk (Table 1).

There are some key differences between the two studies that could explain the differential findings. The first of these relates to the ethnicity of the cohorts. Our study was based upon both African Americans and European Americans, whereas that of Smits and colleagues focused on a European population. While we lose power upon stratification, we still observe the same association in European Americans and survival of late-stage tumors ($HR_{TG/GG\ vs.\ TT}$, 0.46; 95% CI, 0.18–1.16; $n = 78$).

We believe a more likely explanation lies in the differences between *KRAS* mutation status among the two cohorts. In our study, 70% of the cancers with a *KRAS* mutation were diagnosed as either stage III or IV. In Smits and colleagues, only 33.5% of stage III and 43.5% of stage IV tumors were *KRAS*-mutant. We also noted that there were no deaths among patients who carried rs61764370 and whose tumors were mutant for KRAS. This could therefore suggest that the presence of *KRAS* mutation is a more important factor in determining the relationship between rs61764370 and survival than stage. In addition, it helps to explain the differences between the studies' findings and clarify why our association was primarily seen in late-stage tumors.

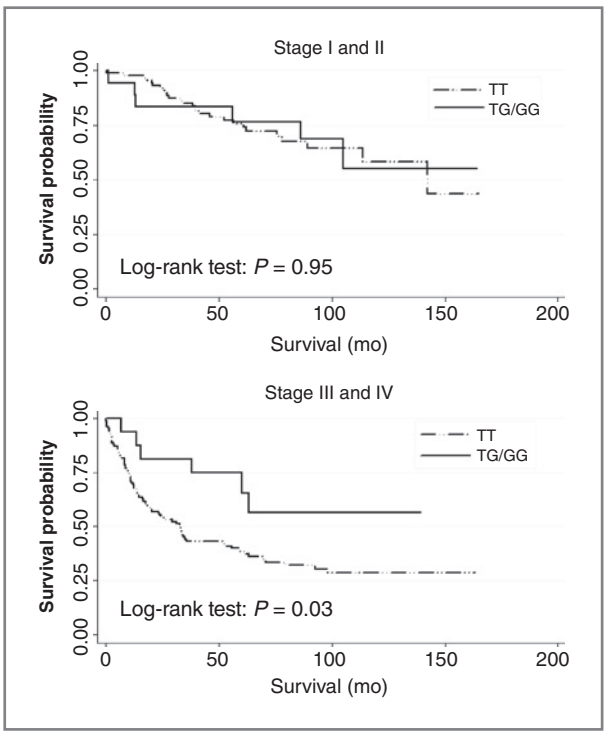

Figure 1. rs61764370 and survival in colorectal cancer stratified by stage.

Table 1. Risk of colorectal cancer

Stratification	Genotype	Cases, *n* (%)	Controls, *n* (%)	Univariable [OR (95% CI)]	*P*
All	TT	375 (85.0)	202 (85.2)	Reference	
	TG/GG	66 (15.0)	35 (14.8)	0.98 (0.63–1.53)	0.945
African Americans	TT	172 (91.0)	88 (94.6)	Reference	
	TG/GG	17 (9.0)	5 (5.4)	0.57 (0.21–1.61)	0.292
European Americans	TT	203 (80.6)	114 (79.2)	Reference	
	TG/GG	49 (19.4)	30 (20.8)	1.09 (0.66–1.81)	0.739

Another possible difference that could confound these reports is the predictive properties of the rs61764370 single-nucleotide polymorphism (SNP). Zhang and colleagues previously reported that the variant G allele predicts

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Table 2. Survival of patients with colorectal cancer

Gene	Genotype	HR	(95% CI)[a]	*P*[a]
Stage I & II	TT	Reference		
	TG/GG	0.96	(0.40–2.36)	0.938
Stage III & IV	TT	Reference		
	TG/GG	**0.38**	**(0.17–0.92)**	**0.025**

[a]Adjusted for age and gender (Cox regression model).

response to single-agent cetuximab monotherapy in refractory CRCs, particularly in patients whose tumors are KRAS wild-type (2). Intriguingly, Graziano and colleagues reported that the same genotype was predictive of *poor* outcome in patients treated with both cetuximab and irinotecan (3). Collectively, these results suggest that both *KRAS* mutation status and therapy modulate the impact of this SNP. Smits and colleagues did not describe the treatment details of their cohort, and where data are available, our cohort primarily received 5-fluorouracil. Collectively, we find that this SNP is not predictive of risk. Rather, an association with survival has again emerged. However, larger studies that take KRAS, BRAF, and treatment status (1–5) into account are needed to more accurately and completely define the role of this SNP in CRCs and its potential to contribute to individualized and personalized treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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