Diseases of the Colon & Rectum

Colorectal Polyps in Carriers of the *APC* I1307K Polymorphism

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PURPOSE: The probability of colorectal cancer is moderately increased among carriers of the *APC* I1307K polymorphism. However, it is not known if endoscopic surveillance of this high-risk group is warranted. The prevalence of polyps and adenomas in specimens of colorectal cancer who are carriers and noncarriers of the *APC* I1307K polymorphism is compared. METHOD: Prevalence of adenomatous polyps in the pathology specimens of the study participants, stratified by their *APC* I1307K polymorphism status, was studied in 900 consecutive cases of colorectal cancer diagnosed in northern Israel between 1998 and 2002, within the framework of a population-based, case-controlled study (MECC Study). RESULTS: The *APC* I1307K mutation was detected in 78 colorectal cancer cases (8.7 percent) of the study population. Prevalence was higher among Ashkenazi Jews (11.2 percent) than among non-Ashkenazi Jews (2.7 percent) or Arabs (3.1 percent). After adjustment for age, *APC* I1307K carriers were significantly more likely than noncarriers to have polyps in their surgical specimen (51.3 percent *vs.* 32.6 percent, $P = 0.002$). Adenomas with a tubular component (either tubular adenomas or tubulovillous adenomas), but not villous adenomas, were significantly more frequent among carriers (37.2 percent *vs.* 23.6 percent, $P = 0.005$). CONCLUSION: Together with former evidence of I1307K being a risk factor for colorectal cancer, these data suggest that colonoscopic surveillance for colorectal adenomas and cancer may be warranted in I1307K carriers, even in the absence of other identifiable risk factors. [Key words: Colorectal cancer; Israel; Epidemiology; *APC* I1307K; Adenoma]

An isoleucine-to-lysine polymorphism at codon 1307 (I1307K) of the *APC* gene creating a hypermutable area and predisposing the development of carcinoma has been identified in 6 to 7 percent of the Ashkenazi Jews.[1] Several studies have confirmed that the magnitude of risk of colorectal cancer conferred by this polymorphism is approximately 1.8 times the risk among noncarriers.[2–8] Some have looked at this polymorphism with regard to other disease groups such as inflammatory bowel disease[9] and multiple adenomas.[10–11] *APC* I1307K does not account for the increased risk of colorectal cancer in patients with inflammatory bowel disease, but it appears to be

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overrepresented among individuals with multiple adenomas.

High-risk groups have been shown to benefit from enhanced colorectal surveillance,[12] and thus it would be useful to evaluate the potential for screening I1307K carriers. A strong relationship between *APC* I1307K and colorectal adenomas would provide a rationale for considering enhanced surveillance within this group, especially if the adenomas demonstrated advanced histologic features suggesting further pathogenetic evolution of these clonal colorectal proliferations. Thus, additional studies of *APC* I1307K and adenomas are warranted.

The current report studies the prevalence of adenomas in I1307K carriers to evaluate if routine endoscopic surveillance may be of value for this group.

MATERIALS AND METHODS

Cases from the Molecular Epidemiology of Colorectal Cancer (MECC) study, an institutional review board (IRB)-approved, ongoing, population-based, case-controlled study in northern Israel, were included. All cases were diagnosed between 1998 and 2002 with invasive cancer of the colon or rectum and underwent a surgical procedure, usually a hemicolectomy. Study tools used after the patient signed an informed consent, include full interview, blood sample, tumor blocks, and frozen tumors. All eligible cases were evaluated for the presence of the I1307K polymorphism in the *APC* gene. *APC* I1307K carriers were identified by allele-specific oligohybridization as previously described.[13] Histologic diagnosis of invasive colorectal cancer was independently confirmed by a single external GI pathologist (JKG). Pathology reports were reviewed for any mention of polyps or adenomas in the surgical specimen. The number of polyps and their histologic characteristics (hyperplastic, tubular, tubulovillous, villous) were recorded. All pathology reports from the five participating hospitals were written by a single pathologist in each hospital. Two of the five involved hospital pathologists read more than 70 percent of the slides in this study. The interpreting pathologist was usually not the same pathologist who received and described the surgical specimen. All pathologists and the data extractors were blinded as to the *APC* I1307K carrier status of the case.

Age-adjusted prevalence rates and 95 percent confidence intervals of polyps in the various demographic groups were calculated (using the age distribution of all Jews in the study as the standard population) and compared using Z-test. Comparisons of proportion with polyps between carriers and noncarriers were conducted using the chi-squared test. Univariate analysis of variance (ANOVA) was used for testing differences in mean number of polyps, adjusted for age. Level of significance for all tests was set at $P \leq 0.05$. Data analysis was performed using SPSS V. 11.5 (SPSS Inc., Chicago, IL).

RESULTS

This interim analysis pertains to 900 cases of colorectal cancer diagnosed in northern Israel within a framework of a population-based, case-controlled study. Of these, 78 cases (8.7 percent) were found to carry the I1307K polymorphism. Much higher prevalence of the polymorphism was noted among Jews (9.3 percent) than among colorectal cancer cases of Arab descent (3.1 percent). Ashkenazi Jews with colorectal cancer had a much higher prevalence (11.2 percent) than non-Ashkenazi Jewish cases (2.7 percent) (Table 1).

Prevalence of Polyps

APC I1307K carriers were significantly more likely than noncarriers to have any polyps in their surgical specimen after age-adjustment (51.3 percent *vs.* 33.6 percent, $P = 0.03$). The higher prevalence of any polyps was found in Ashkenazi and non-Ashkenazi Jewish carriers alike (Table 2). This excess was noted in males and females and also in Arab patients, although

Table 1.
Prevalence of I1307K Polymorphism Among MECC Study Cases with Colorectal Cancer

	Number of Cases	*APC* I1307K Carriers	% Positive
Jews	817	76	**9.3**
Ashkenazi	633	71	11.2
Males	331	35	10.6
Females	302	36	11.9
Non-Ashkenazi	184	5	2.7
Males	94	4	4.3
Females	90	1	1.1
Arabs	65	2	3.1
Males	*36*	*1*	*2.8*
Females	*29*	*1*	*3.4*
Non-Jewish / Non-Arab	14	0	0
Total	896	78	**8.7**

MECC = Molecular Epidemiology of Colorectal Cancer.

Table 2.
Age-Adjusted Prevalence of Polyps of All Types Among Carriers and Noncarriers of the *APC* I1307K Mutation

	Number of Cases	Proportion with Polyps in I1307K Positive Cases	Age-Adjusted Rate in I1307k Positive Cases	Proportion with Polyps in I1307K Negative Cases	Age-Adjusted Rate in I1307k Negative Cases	Significance of Difference in Age-Adjusted Rates *P*-Value
Jews	817	51.3% 39/76	49.7 (33.7,65.8)	33.6% 249/741	33.7 (29.5,37.9)	0.03
Ashkenazi	633	47.9% 34/71	46.0 (30.1,61.8)	33.3% 187/562	32.6 (27.9,37.4)	(0.06)
Males	331	51.4% 18/35	46.8 (24.3,69.3)	35.8% 106/296	34.4 (27.8,41.1)	(0.15)
Females	302	44.4% 16/36	43.2 (21.1,65.4)	30.5% 81/266	29.9 (23.3,36.5)	(0.13)
Non-Ashkenazi	184	100.0% 5/5	55.4 (0,155.3)	34.6% 62/179	20.8 (11.0,30.6)	(0.25)
Males	94	100.0% 4/4	55.4 (0,115.5)	40.0% 36/90	42.5 (28.1,57.0)	(0.34)
Females	90	100.0% 1/1	40.6 (0,120.4)	29.2% 26/89	31.8 (18.2,45.5)	(0.42)
Total (Jews and non-Jews)	896	51.3% 40/78	49.9 (34.2,65.8)	32.6% 268/822	25.8 (22.3,29.4)	0.002

it did not reach statistical significance in these subgroups (data not shown).

Number and Type of Polyps

The mean number of polyps per surgical specimen (excluding those where no polyps were found) did not differ significantly between *APC* I1307K carriers and noncarriers, in either Ashkenazi Jews (2.47 *vs.* 2.75) or non-Ashkenazi Jews (2.60 *vs.* 2.31), when tested in a model, which included age.

Among the adenomas, villous adenomas were not found to differ significantly in prevalence between the carriers and noncarriers, but adenomas with a tubular component (either tubular adenomas or tubulovillous adenomas) were significantly more frequent among all carriers and Jewish carriers, mostly attributed to their higher prevalence in non-Ashkenazi Jews (Table 3).

No differences were appreciated when analyses were restricted to cancers arising in the colon rather than in the colon and rectum combined.

DISCUSSION

APC I1307K polymorphism is a common risk factor for colorectal cancer in the Jewish population, and it also increases the risk for colorectal adenomas. Although originally described in Ashkenazi Jews, we have demonstrated that approximately 3 percent of non-Ashkenazi Jews and 3 percent of Arab populations also carry this polymorphism.[14] This estimate is higher than previous reports of a prevalence of less than 2 percent in non-Ashkenazi Jewish populations.[3,15] Another small study reported that this polymorphism was not found in any Arabs or non-Ashkenazi Jews with colorectal cancer other than in Jews from Yemen in which the mutation prevalence was reported to be extremely high.[4]

Our study identified a higher prevalence of adenomas among carriers of *APC* I1307K with colorectal cancer; this is in line with a previous study that reported an elevated frequency of this polymorphism in Ashkenazi Jews with adenomatous polyps but not with hyperplastic polyps.[10] Hyperplastic polyps were rarely mentioned in our pathology reports of cancer specimen, but this does not necessarily reflect a true lack of these polyps. While we found more adenomas with a tubular component, the phenotypic features of the adenomas in another study of Ashkenazi Jews were indistinguishable between I1307K carriers and noncarriers. Our data suggesting that tubular and tubulovillous adenomas are overrepresented among *APC* I1307K carriers is driven by differences that were appreciated predominantly in non-Ashkenazi Jews and should be replicated in additional studies. The accuracy of our findings relies on information provided by the pathologist and not on colonoscopy findings. Such data are dependent on the size of the

Table 3.
Proportion With Adenomas, by Histologic Type Among Carriers of the *APC* I1307K Polymorphism

Type of Adenoma	Carriers	Noncarriers	*P*-Value
All Jews			
Tubular	25.0 19/76	15.7 116/741	0.04
Tubulovillous	11.8 9/76	8.4 62/741	(0.31)
Villous	5.3 4/76	4.2 31/741	(0.66)
Any tubular component	35.5 27/76	22.0 163/741	0.008
Any villous component	17.1 13/76	11.9 88/741	(0.19)
Ashkenazi Jews			
Tubular	19.7 14/71	15.3 86/562	(0.34)
Tubulovillous	12.7 9/71	8.0 45/562	(0.18)
Villous	4.2 3/71	4.6 26/562	(1.00)
Any tubular component	31.0 22/71	21.2 119/562	0.06
Any villous component	16.9 12/71	12.1 68/562	(0.25)
Non-Ashkenazi Jews			
Tubular	100.0 5/5	16.8 30/179	<0.001
Tubulovillous	0.0 0/5	9.5 17/179	(1.00)
Villous	20.0 1/5	2.8 5/179	(0.15)
Any tubular component	100.0 5/5	24.6 44/179	0.001
Any villous component	20.0 1/5	11.2 20/179	(0.46)
Total (Jews and non-Jews)			
Tubular	25.6 20/78	15.6 128/822	0.02
Tubulovillous	11.5 9/78	8.0 66/822	(0.28)
Villous	5.1 4/78	4.0 33/822	(0.55)
Any tubular component	37.2 29/78	23.6 194/822	0.005
Any villous component	16.7 13/78	12.0 99/822	(0.17)

resected sample, assumed to be similar between cases because it usually stemmed from hemicolectomy.

The literature provides equivocal evidence regarding the relationship of *APC* I1307K to colorectal adenomas. A community survey of 189 Ashkenazi Jews with a personal or family history of colorectal cancer who underwent a single colonoscopic evaluation did not find any significant differences in polyp size, multiplicity, location, or degree of villosity between carriers and noncarriers.[16] In contrast, *APC* I1307K mutations and *APC* E1317Q were commonly found in a study of patients with multiple colorectal adenomas, leading the authors to recommend screening patients with these mutations.[11] The study of 183 Ashkenazi patients with polyps reported by Syngal *et al.* demonstrated that *APC* I1307K was more common in Ashkenazi Jewish patients with adenomas than in patients with hyperplastic polyps.[10] This polymorphism was similarly overrepresented in the 72 Ashkenazi patients with adenomas reported by Gryfe *et al.* in their large cohort of unselected Ashkenazi Jewish subjects with adenomatous polyps and/or colorectal cancer. The authors concluded that the *APC* I1307K variant leads to increased adenoma formation.[2]

Together with reproducible evidence that *APC* I1307K is a risk factor for colorectal cancer, our data suggest that colonoscopic surveillance for colorectal adenomas and cancer may be warranted in I1307K carriers, even in the absence of other identifiable risk factors. Colonoscopic screening for adenomas in this genetic subgroup carries a higher potential for colorectal cancer prevention than in an average risk population. Given the size of the APCI1307K carrier Jewish population, such screening could potentially translate into a meaningful effect on colorectal cancer incidence.

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