The I1307K Adenomatous Polyposis Coli Gene Variant Does Not Contribute in the Assessment of the Risk for Colorectal Cancer in Ashkenazi Jews

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Abstract

Ashkenazi Jews with the I1307K adenomatous polyposis coli gene variant were suggested to confer a higher risk for colorectal cancer (CRC). We assessed the clinical importance of this polymorphism in Israeli Jews at average and elevated risk for CRC. Among 1370 consecutive subjects that were examined, 975 Ashkenazi Jews were stratified into those at average risk (no personal or family history of colorectal neoplasia) and those at high risk. DNA was obtained from peripheral leukocytes and amplified by PCR, with primers designed to detect the I1307K variant. Overall, I1307K polymorphism was found in 7.1% (9.1% among Ashkenazi and 1.7% among non-Ashkenazi Jews). The carrier rate was 8.3 and 9.3% in average and high-risk Ashkenazi and 1.7% among non-Ashkenazi Jews. The I1307K polymorphism does not differ between carriers and noncarriers. No interaction on the CRC risk was found between I1307K variant and lifestyle modifiers (such as cigarette smoking, alcohol consumption, high body mass index, low physical activity, and vitamins/antioxidant intake). The I1307K adenomatous polyposis coli gene variant is not an important marker for increased risk for CRC. It confirms previous reports of a slight nonsignificant increase (OR, 1.4) in the risk of CRC in these carriers. There is no interaction effect on the risk of colorectal neoplasia between the I1307K variant and various lifestyle risk factors. The usual recommended screening and surveillance strategies should be used for carriers of this polymorphism.

Introduction

CRC1 is the second leading cause of cancer mortality in the Western world, with a cumulative lifetime risk of ~6% for men and women (1, 2). Although 15–20% of CRC cases occur in the context of a family history of CRC, the specific genetic change in most familial cases is unknown (1–4).

Somatic mutations in the APC gene have been found in more than two-thirds of CR adenomas and cancers. Inactivation of the APC gene appears to be the gatekeeper event for the initiation of CR tumorigenesis, disrupting growth regulatory signals and normal cell-to-cell adhesion. The mutant APC gene decreases the binding of β-catenin and leads to its intracellular accumulation. The β-catenin is translocated to the nucleus, where it binds Tcf-4 to up-regulate target genes, including c-myc, cyclin D1, and the peroxisome proliferator activated nuclear receptor (PPARγ) system (5–7).

In 1997, Laken et al. (4) identified a novel APC gene polymorphism. A specific single base germ-line transition of T to A at nucleotide 3920 of the APC gene causes the substitution of lysine for isoleucine at codon 1307. This alteration produces a small unstable hypermutable region of DNA (a sequence of eight adenines) that may be prone to somatic mutations and thus carcinogenic (4, 6, 8). Laken et al. (4) estimated an overall carrier rate of 6% in Ashkenazi Jews in the United States; worldwide, the carrier rate ranges between 5 and 10% (8–12), including two previous studies from our center (13, 14). Laken et al. (4) also found a prevalence rate of 28% in a small group of 25 Ashkenazi Jewish patients with a personal and family history of CRC. The OR for CRC among carriers of the polymorphism compared with noncarriers has been estimated at 1.3–1.9 (4, 8, 12–15). A recent study from our center has questioned the contribution of this low penetrance variant in the assessment of CRC risk and suggested that it is equivalent to obtaining a family history (14).

In this study of 975 consecutive Ashkenazi Jews at average and increased risk of CRC, there was a nonsignificantly increased OR of 1.4 (95% CI, 0.89–2.3) for CR neoplasia in carriers of the APC gene variant. No significant interaction was

1 The abbreviations used are: CRC, colorectal cancer; APC, adenomatous polyposis coli; CR, colorectal; OR, odds ratio; CI, confidence interval; BMI, body mass index.

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found between lifestyle risk factors and the I1307K variant on the risk of CRC.

Materials and Methods

Study Design. Among 1370 consecutive participants, we identified 975 subjects of Ashkenazi ancestry who attended our prevention and early detection program in the Gastrointestinal Oncology Unit at Tel-Aviv Sourasky Medical Center between October 2000 and February 2002. The setting of our unit includes outpatient clinics in the hospital and in the community. The average risk group consisted of subjects evaluating for a variety of indications that are not associated with CRC risk (e.g., peptic disease, esophageal reflux, irritable bowel syndrome, diverticulosis, fatty liver, cholelithiasis, and so forth) and the average-risk accompanies of the patients.

Patients were classified as being at high risk or average risk using standard criteria based on the personal or family history of CR neoplasia (1, 2, 6, 16). The high-risk group included patients having at least one of the following: (a) personal history of CRC; (b) personal history of CR adenoma; and (c) family history of CR adenoma or carcinoma in one first degree relative < 70 years or two family relatives at any age. The high-risk group was further stratified into five strata, according to these criteria (Table 1). Patients were classified according to their most advanced lesion. The rate of I1307K carriers was assessed in each of the following categories: family history of CR neoplasia; personal history of CR neoplasia (no FH); personal CRC (no FH); personal adenoma (no CRC or FH); and combined personal and family history of CR neoplasia. Exclusion criteria included: (a) hereditary nonpolyposis colon cancer according to the revised Amsterdam criteria (1, 6); (b) familial adenomatous polyposis; (c) Peutz-Jeghers or Juvenile polyposis syndromes; and (d) inflammatory bowel disease (ulcerative colitis or Crohn’s disease).

The majority of our study participants, 87% (n = 848), underwent a complete colonoscopy in the last decade. The small group of unscreened subjects were all young, asymptomatic, without a family history of cancer who confer a very low risk of neoplasia in whom colonoscopy was not justified.

All participants completed a questionnaire and provided a blood sample. The Institutional Review Board of the Tel-Aviv Sourasky Medical Center and the Israeli Ministry of Health approved this study. Written informed consent was obtained from all participants. Test results remained anonymous to preserve confidentiality.

Detection of I1307K APC Variant. DNA was extracted from peripheral blood leukocytes and amplified by standard PCR. The APC variant was identified using primers designed to detect the I1307K variant. The variant fragment length is 130 bp, whereas the wild-type allele was 105 + 25 bp. The specific oligonucleotide method that was used by Laken et al. (4), with complete identity between the two methods.

Questionnaires. A lifestyle habits questionnaire, including well-established risk factors for CR neoplasia (cigarette smoking, alcohol consumption, BMI, physical activity, and vitamins and antioxidant intake) was administered to all participants. The standardized questionnaire was previously used and validated in epidemiological studies (17). The patients were stratified according to the I1307K status and the lifestyle parameters to identify a possible interaction on the risk of CR neoplasia.

Statistical Analysis. Database management and all statistical analyses were performed with SPSS software version 11. Multiple logistic regression analysis was used to examine the relation of the I1307K APC gene variant to CRC or adenomas in terms of OR with adjustment for the following confounding variables: age; gender; family history of CR neoplasia; and lifestyle habits (cigarette smoking, alcohol consumption, BMI, physical activity, and vitamins and antioxidant intake). The 95% CI of OR was estimated by using the SE of a logistic regression coefficient for each indicator variable (18, 19). The final variables used in the logistic regression model were determined by a backward elimination algorithm. The prevalence of the APC variant and the incidence and characteristics of CR neoplasia were calculated using the x² test and Fisher’s exact test. We used t test to compare the means of continuous variables.

According to previous publications, we estimated the proportion of patients with CR neoplasia in the population as 36% (16) and the OR for carriers of APC as 1.4. The sample size

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<table>
<thead>
<tr>
<th>Average risk</th>
<th>No. of subjects</th>
<th>% of I1307K carriers</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No personal or FH of CR neoplasia</td>
<td>204</td>
<td>8.33</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal and/or family history (FH) of CR neoplasia</td>
<td>771</td>
<td>9.34</td>
<td>0.65</td>
</tr>
<tr>
<td>Personal CR neoplasia (no FH)</td>
<td>242</td>
<td>11.52</td>
<td>0.26</td>
</tr>
<tr>
<td>Personal CRC (no FH)</td>
<td>113</td>
<td>10.62</td>
<td>0.49</td>
</tr>
<tr>
<td>Personal adenoma (no CRC or FH)</td>
<td>129</td>
<td>12.40</td>
<td>0.23</td>
</tr>
<tr>
<td>Combined personal and family history of CR neoplasia</td>
<td>154</td>
<td>9.15</td>
<td>0.78</td>
</tr>
<tr>
<td>Family history (no personal history) of CR neoplasia</td>
<td>375</td>
<td>8.00</td>
<td>0.88</td>
</tr>
</tbody>
</table>

* P for comparing the rate of I1307K carriers in each stratum with the average risk group.

FH, family history.

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Fig. 1. The I1307K APC gene variant was identified using primers designed to detect the I1307K. The variant fragment length is 130 bp, whereas the wild-type allele was 105 + 25 bp. MW, molecular weight; Lanes 1–5 and 7, wild type APC gene; Lane 6, I1307K APC gene variant; Lane 8, positive control; Lane 9, H2O negative control.
required to detect a difference between the carrier and noncarrier groups with 85% power ($\beta = 15\%$) and $\alpha = 5\%$ was estimated as 951 patients (18, 19).

**Results**

Among the 1370 participants, the carrier rate of the I1307K polymorphism was 9.1% in Ashkenazi Jews ($n = 975$), 1.7% in non-Ashkenazi Jews ($n = 180$), and 2.3% in a group of mixed or uncertain ethnicity ($n = 215$).

Among Ashkenazi Jews, I1307K was detected in 8.3% and 9.3% of those at average and overall increased risk, respectively ($P = 0.65$). In stratification of the high-risk group, there was no significant difference in the variant rate between patients with a personal history of CR neoplasia (11.52%) and those with a combined personal and family history of CR neoplasia (9.15%; Table 1).

The carriers and noncarriers were demographically comparable. The rate of male/female gender was 56/44% in the carriers and 51/49% in the noncarriers. The mean age of carriers and noncarriers and the mean age at which CR neoplasia developed did not differ significantly ($P = 0.142$–0.421; Table 2).

Overall, the OR for CRC or adenoma in carriers of this polymorphism was 1.43 (95% CI, 0.89–2.30; Table 3), adjusted for lifestyle parameters. Among carriers, an OR of 1.02 for CRC and an OR of 1.57 for adenoma without CRC were detected (95% CI, 0.54–1.93 and 95% CI, 0.94–2.64, respectively; Table 3).

The size and histology of adenomas and the site and stage of CRC in carriers did not significantly differ from noncarriers (Table 2). In I1307K carriers, the OR for harboring more than two adenomas was higher, although nonsignificant (OR, 2; 95% CI, 0.94–4.44).

After stratification, we did not find an interaction on the risk of CR neoplasia between the I1307K and lifestyle parameters (alcohol consumption, low physical activity, vitamins, and antioxidant intake; Table 3). There was an interaction between I1307K variant and BMI > 30 or cigarette smoking, although it did not reach statistical significance (Table 3).

**Discussion**

This large study confirms previous reports of only a slight nonsignificant increase in the prevalence of the I1307K APC variant among Jews of Ashkenazi ancestry who are at increased risk for CRC (4, 8–15).

The rate of I1307K variant in high-risk subjects and the OR of neoplasia in carriers are controversial (4, 8, 11, 12, 15). The inconsistency results from a relatively small number of subjects and lacking of adequate control groups of average risk (4, 8, 11, 12). In other studies, patients with familial cancer syndromes (such as hereditary nonpolyposis colon cancer and familial adenomatous polyposis) were not excluded or separated from other high-risk subjects (4, 8, 11, 12, 15). Also, the definition of asymptomatic subjects was less certain (4, 8, 10, 12–15). Many average risk patients did not undergo colonoscopy and up to 36% may harbor an asymptomatic lesion (16). The clinical data were retrieved retrospectively from medical records or from mailed questionnaires (4, 11, 12).

The participants in the current study were part of an early detection program. Therefore, they were carefully interviewed face-to-face by skillful interviewers (Y. D. and Y. K.), closely
followed, and most importantly, the vast majority (87%) of them underwent at least one colonoscopy in the last decade. The remaining were subjects who did not meet the acceptable criteria for screening colonoscopy (e.g., average risk asymptomatic individuals under the age of 50 years). These patients confer a very low risk of CR neoplasia and therefore could be considered as average risk.

Furthermore, when the data were reanalyzed after the exclusion of unscreened persons, similar statistical results were found.

Subjects with familial cancer syndromes or inflammatory bowel disease were excluded. Therefore, our study cohort is more accurately defined and more generalizable as compared with most other published cohorts.

This large cohort did not identify, based on phenotypic characteristics, any subgroup of carriers that harbors a significantly increased OR of CR neoplasia. The demographic and clinical features of carriers and noncarriers are similar; the presence of I1307K variant does not appear to affect the natural history or progression into CR neoplasia. The detection of more than two adenomas was more likely in I1307K carriers, although it did not reach statistical significance (OR, 2; 95% CI, 0.94–4.44).

The mean age of neoplasia did not significantly differ in the I1307K carriers as compared with noncarriers (Table 2). Stratification of the study cohort did not reveal other confounders or modifiers and, in particular, demographic features and lifestyle factors. An interaction, although nonsignificant, was found between I1307K variant and high BMI (OR, 6.7; 95% CI, 0.68–67) or cigarette smoking (OR, 4.3; 95% CI, 0.74–25). This intriguing association needs additional assessment in a larger size of cohort.

Subjects with the I1307K variant carry a nonsignificant OR of 1.4 (95% CI, 0.89–2.3) for CR neoplasia. This polymorphism does not seem to add considerably more risk points to the already known CRC risk of the individuals, as determined by the personal and family history of CR neoplasia (which confer a relative risk of up to 2–3; Refs. 1–2).

It is suggested that the I1307K/APC gene variant is not an important clinical marker for determining the risk of CRC. In our center, we offer colonoscopy once every 5–10 years for individuals at average risk as per guidelines (1, 16). In average-risk carriers of the variant, there is no support for an intensified screening program. At the same time, high-risk patients should be offered the appropriate intensive screening and surveillance program, regardless of their I1307K variant state.

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