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Body mass, age, and the APC I1307K allele in Ashkenazi Jewish prostate cancer patients

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Abstract The I1307K mutation of the adenopolyposis coli gene (APC), located on chromosome 5q21–q22, is associated with an increased risk of cancer in Ashkenazi Jews. In the present study, we analyzed age and body mass of Ashkenazi Jewish prostate cancer patients, with and without the APC I1307K mutation. Participants in our study were found through urology and radiation oncology clinics, and all eligible patients were asked to take part. A familial history was obtained by interview or self-report questionnaire. Histological confirmation of diagnosis was obtained for all subjects. The I1307K allele of the APC gene was detected by amplification of lymphocyte DNA from peripheral blood according to standard polymerase chain reaction (PCR) and dot blot procedures. We studied 135 Ashkenazi Jewish men with prostate cancer. The youngest was 49, the oldest 80, average age 68 ± 6.88 (mean ± SD). The older patients carrying the wild type APC allele tended to have a lower body mass than the younger ones ($r = -.27$, $P = .002$). Of 71 patients under 70 years old, 65 carried the wild type APC allele, and had a body mass index of 28.7 ± 4.23 kg/m^2. The six men under age 70 carrying the I1307K APC allele had a body mass index of 26.87 ± 1.44 kg/m^2. The difference in body mass index of the two groups is significant ($P = .032$, t test for unequal variance). Increased body mass is a prostate cancer risk factor, and hereditary prostate cancer is associated with younger patients. Therefore, our finding, that patients under age 70 carrying the I1307K allele are significantly thinner than those carrying the wild type allele, suggests that the APC I1307K allele is also a prostate cancer risk factor. Our results are in accord with other studies indicating that APC mutations increase the risk of prostate cancer.

1. Introduction

Prostate cancer is the most common malignancy in American men [1]. Though dietary fat plays a role in the development of this cancer [2], and possibly also vasectomy [3], familial history is one of the strongest risk factors [4].

Chromosome 5 abnormalities have been described in some studies of prostate cancer [5–8]. Moreover, there have been multiple reports that the adenopolyposis coli gene (APC), located on chromosome 5q21–q22, is associated with the development of prostate cancer [9–11].

APC is a tumor suppressor gene, and somatic loss occurs in tumors. Laken et al. [12] found a T-to-A germline mutation at APC nucleotide 3920, the I1307K mutation, in 47 of 766 Ashkenazi Jews (6%). Laken et al. [12] reported that the I1307K mutation increased the risk of colorectal cancer, but Petrukhin et al. [13] reported no increased risk in 264 Ashkenazi Jews. In a study of 5,081 Ashkenazi Jews, Woodage et al. [9] reported that the I1307K mutation confers an increased risk of colorectal cancer (odds ratio 1.9) though the increase was not statistically significant ($P = 0.12$).

Woodage et al. [9] did find that the risk of developing any cancer with the I1307K mutation was significantly increased (odds ratio 1.5, $P = .01$). One of the cancers associated with the I1307K mutation was prostate cancer (odds ratio 2.0, $P = .14$).

Woodage et al. [9] postulated that their findings are consistent with impaired function of the APC protein in cancer patients. In addition, Korinek et al. [14], Rubinfeld et al. [15], and Morin et al. [16] have shown that APC can interact with β-catenin, a multi-functional cellular protein, and

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inappropriately activate the transcription factor Tcf4; this process is important in neoplasia.

The relationship of APC to prostate cancer is still controversial. Gao et al. [10] and Phillips et al. [11] reported that APC may be involved in the development of prostate cancer; whereas Suzuki et al. [17] and Watanabe et al. [18] found no such involvement.

In the present study, we analyzed age and body mass of Ashkenazi Jewish prostate cancer patients, with and without the APC I1307K mutation.

2. Methods

Participants in our study were found through urology and radiation oncology clinics, and all eligible patients were asked to take part. A familial history was obtained by interview or self-report questionnaire. Histological confirmation of diagnosis was obtained for all subjects. Ethnic background was confirmed for all subjects by self report or interview. All participants gave informed consent for genetic studies and were not given the option to know their test results. Extensive genetic counseling, covering options for detection and prevention, was available. Although we used mostly sporadic cases of prostate cancer, some germ line mutations would still be expected.

The I1307K allele of the APC gene was detected by amplification of lymphocyte DNA from peripheral blood according to standard polymerase chain reaction (PCR) and dot blot procedures. The following primers for PCR were added to the reaction mixture:

APC primers
5′> G CAG ATT CTG CTA ATA CCC TGC <3′ (forward)
5′> C TTC GCT CAC AGG ATC TTC AGC <3′ (reverse)

Aliquots of amplified DNA were transferred to membranes (Hybond) using a standard protocol [19]. Hybridization was performed for 60 min at 57°C. The following 32p labeled probes were used for dot blot analysis:

5′> GCA GAA ATA AAA GAA AAG 3′< (wild type)
5′> GCA GAA AAA GAA AAG 3′< (I1307K mutant)

Positive and negative controls were included in all runs.

3. Results

We studied 135 Ashkenazi men with prostate cancer. The youngest was 49, the oldest 80, average age 68 ± 6.88 (mean ± SD). There were 26 men with a familial history of prostate cancer. Ten of these had a father with prostate cancer, and three had a brother with prostate cancer.

Ten patients of the 135 studied (7.4%) carried the I1307K allele. All were heterozygotes. Using the data in our study, we are unable to make a definitive comment on the relative risk of prostate cancer associated with the I1307K allele, as we did not include controls without cancer. However, based on the 6% incidence of the I1307K allele that Laken et al. [12] found in the general population of Ashkenazi Jews, we postulate that the 7.4% incidence of the mutation we found in Ashkenazi Jews with prostate cancer suggests that the APC I1307K mutation increases the risk of this cancer.

Only one patient with a first-degree familial history of prostate cancer had the I1307K allele. This patient had both a father and a paternal uncle with prostate cancer, and was 70 years old when his own cancer was diagnosed.

Age, body mass, and APC genotype of all patients studied are displayed in Fig. 1. The older patients carrying the wild type APC allele tended to have a lower body mass than the younger ones ($r = -.27$, $P = .002$).

Of 71 patients under 70 years old, 65 carried the wild type APC allele, and had a body mass index of 28.7 ± 4.23 kg/m^2. The six men under age 70 carrying the I1307K APC allele had a body mass index of 26.87 ± 1.44 kg/m^2. The difference in body mass index of the two groups is significant ($P = .032$, t test for unequal variance).

4. Conclusions

One would expect the older men carrying the wild type APC allele to have a lower body mass than younger ones. Increased body mass and age are both well documented prostate cancer risk factors [20,21]. Older men, more prone to prostate cancer, presumably do not need as much body mass to develop the disease. Hereditary prostate cancer is most common in younger patients [22–28]. Moreover, in a study of CAG polymorphic repeats in the androgen receptor

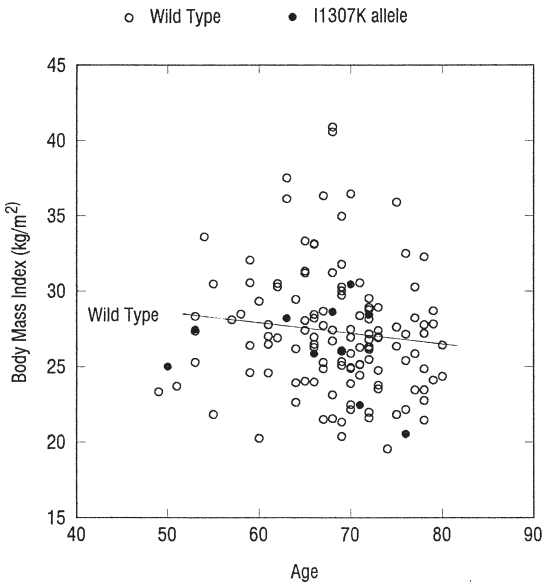

Fig. 1. Age, body mass index, and APC genotype (wild type or I1307K) of 135 Ashkenazi Jewish prostate cancer patients in this study. The older patients carrying the wild type APC allele tended to have a lower body mass than the younger ones, as indicated by the downward slope of the wild type regression line ($r = -.27$, $P = .002$).

gene, Stanford et al. [20] found that men with 16 or less CAG repeats, who were young and relatively thin, had a significant elevation of prostate cancer risk, when compared to men with more than 16 repeats. Our finding, that patients under age 70 carrying the APC I1307K allele are significantly thinner than those carrying the wild type allele, suggests that the I1307K allele is a prostate cancer risk factor, comparable to 16 or less androgen receptor CAG repeats.

Our results are thus in accord with the findings of Woodage et al. [9], Gao et al. [10], and Phillips et al. [11], and suggest that the APC I1307K allele increases the risk of prostate cancer. It would be worthwhile to include control Ashkenazi Jewish men without prostate cancer in a future study, in order to determine the increase in prostate cancer risk associated with the I1307K allele. One could then make a more exact assessment of risk than Woodage et al. [9] estimated, since the risk factors of age and body mass could be included in the risk calculation.

It would also be worthwhile in a larger study to analyze the relationship of the APC I1307K allele to tumor stage at diagnosis and to biochemical recurrence, as indicated by rising PSA after definitive treatment. Should the I1307K allele be an independent predictor of more aggressive disease, it could serve as a useful clinical tool in the management of prostate cancer.

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