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The APC I1307K allele conveys a significant increased risk for cancer

Ari Leshno[1], Shiran Shapira[1], Eliezer Liberman[1], Sarah Kraus[1], Miri Sror[1], Amira Harlap-Gat[1], Doran Avivi[1], Lior Galazan[1], Maayan David[1], Nitsan Maharshak[1,2], Serhan Moanis[1], Nadir Arber[1,2] and Menachem Moshkowitz[1,2]

[1] Integrated Cancer Prevention Center, Tel- Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[2] Department of Gastroenterology, Tel- Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

This study is the first attempt to evaluate the association between the *APC* I1307K variant and overall cancer risk. It is unique in both its large sample size and in the reliability of data in the control group. The findings described in this article have major implications in terms of identifying asymptomatic individuals who are at increased risk to harbor cancer and therefore targeted to be enrolled in specific early detection and prevention programs. The prevalence of the *APC* I1307K missense mutation among Ashkenazi Jews is ~6%. Carriers are at an increased risk for colorectal neoplasia. In this study, we examined the association of this variant with non-colorectal cancers. Consecutive 13,013 healthy subjects who underwent screening at the Integrated Cancer Prevention Center between 2006 and 2014 were enrolled. This population was supplemented with 1,611 cancer patients from the same institution. Demographics, medical history, and pathological data were recorded. Mortality data were obtained from the Ministry of Health's registry. The prevalence of *APC* I1307K in cancer patients and healthy subjects was compared. The *APC* I1307K variant was detected in 189 (11.8%) cancer patients compared to 614 (4.7%) healthy subjects, reflecting an adjusted age and sex odds ratio (OR) of 2.53 ($p < 0.0001$). History of two or more cancer types was associated with a positive carrier prevalence (OR = 4.38 $p < 0.0001$). Males had significantly increased carrier prevalence in lung, urologic, pancreatic, and skin cancers. The carrier prevalence among females was significantly higher only in breast and skin cancers. Female carriers developed cancer at a significantly older age compared to non-carriers (average 62.7 years vs. 57.8, respectively, $p = 0.027$), had better survival rates (HR = 0.58, $p = 0.022$) and overall increased longevity (average age of death 78.8 vs. 70.4 years, respectively, $p = 0.003$). In conclusion, the *APC* I1307K variant is a reliable marker for overall cancer risk (OR 2.53). Further studies are needed to evaluate its use for specific cancer types—particularly in males. Female carriers have better prognosis and increased lifespan.

The adenomatous polyposis coli (*APC*) gene is an important tumor suppressor gene whose protein product is a key regulator of β-catenin as well as other pathways critical for cell division and signal transduction.[1,2] Somatic mutations in this gene have been found in more than two-thirds of colorectal neoplasia patients.[3,4] In 1997, Laken *et al.*[1] were the first to report the germ-line missense I1307K polymorphism in the *APC* gene. It is characterized by transition of T to A at nucleotide 3920, converting the wild-type sequence AAAA-TAAA to a homopolymer tract (A8) that is genetically less stable and prone to somatic mutation. Between 5% to 9% of the Ashkenazi Jewish population reportedly carry the *APC* I1307K variant.[5,6] A recent meta-analysis found that Ashkenazi Jews who carried the *APC* I1307K variant were at a significantly increased risk for colorectal neoplasia, with a pooled odds ratio (OR) of 2.17 (95% CI 1.64–2.86).[7]

Several studies evaluated the potential role of the *APC* I1307K polymorphism in non-colorectal carcinomas (CRC), such as prostate,[6,8] ovarian,[9] and breast[9,10] cancers, and reported inconclusive findings. Woodage *et al.*[8] found that *APC* I1307K carriers were more likely to have had any type of cancer (excluding non-melanoma skin cancer) than non-carriers, with an OR of 1.5. Our group demonstrated a tendency towards an increased risk of pancreatic and lung cancers among *APC* I1307K carriers.[11]

This study investigated the overall risk for neoplasia among *APC* I1307K polymorphism carriers in a very large prospective Israeli cohort. The effects of *APC* I1307K carriage state on various clinical parameters, such as age of onset and survival, were evaluated according to gender.

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Correspondence to: Prof. Nadir Arber, MD, MHA, MSc Head, the Integrated Cancer Prevention Center, Tel-Aviv Sourasky Medical Center, 6th Weizmann St., Tel Aviv 6423906, Israel, Tel: [+972-3-6974968], Fax: +[972-3-6974867], E-mail: nadira@tasmc.health.gov.il

Patients and Methods

Subjects

The study population included 13,119 consecutive subjects who were undergoing annual screening between 2006 and 2014 at the Integrated Cancer Prevention Center (ICPC) in the Tel-Aviv Sourasky Medical Center (TASMC). The ICPC

What's new?
While Ashkenazi Jews who carry the APC I1307K variant are at an increased risk for colorectal neoplasia, the potential role of this polymorphism in non-colorectal carcinomas remains unclear. This study investigates the overall risk for neoplasia among APC I1307K polymorphism carriers in a very large prospective Israeli cohort. The findings suggest that the I1307K variant in the APC gene is a global risk factor for cancer, and mostly in males. Female carriers have a better prognosis, with a relatively increased lifespan. The findings may help identify asymptomatic individuals at increased risk for cancer for enrollment in early detection and prevention programs.

is a unique center that offers comprehensive early cancer detection and prevention services for 11 of the most common cancers including: skin, oral cavity, lung, thyroid, breast, colorectal, ovarian, uterine, cervical, testicular and prostate cancers.[12,13] More information regarding strategy and services provided by the Center can be found on the website (http://www.tasmc.org.il/sites/en/Internalmed/ICPC/Pages/ICPC.aspx). Also Included were 1,505 cancer patients recruited from TASMC's oncology, surgery, gastroenterology, urology, and hematology departments. All subjects completed a detailed questionnaire and provided a blood sample. Data on demographics, symptoms, prior personal and family history of cancer, medications, and histopathological findings were collected and entered into the ICPC computerized database. Mortality data were obtained from the Ministry of Health's registry. In order to ensure that our data are not biased, the association between the *APC* I1307K variant and colorectal neoplasia was also evaluated and compared with previous reports. The endoscopic findings in the database of a subgroup of 5,215 patients (of whom 8.5% were carriers) were reviewed, and the occurrence of adenomatous polyps and CRC was recorded.

All subjects underwent meticulous evaluation by several experienced physicians from various disciplines as we had described elsewhere.[12] The prevalence of the *APC* I1307K mutation was compared between subjects with and those without a past history of any cancer.

The Institutional Review Board (IRB) of the TASMC and the Israeli Ministry of Health approved this study. Written informed consent was obtained from all participants who gave their permission for the anonymous use of their DNA for research purposes.

DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood lymphocytes and amplified by standard PCR. Mutation screening was performed by real-time PCR on a LightCycler. About 200 ng of genomic DNA from each sample was used for all reactions. The *APC* variants were identified using primers designed to detect I1307K as follows.

Determination of the I1307K polymorphism in the APC gene

The *APC* I1307 polymorphism is a substitution of isoleucine (I) (common allele) with lysine (K) (rare allele) at position 1307 of GenBank Accession No. NP_000029.2; SEQ ID NO: 8; which results from the T to A substitution at nucleotide 3977 of NM_000038.3; SEQ ID NO: 7. Genomic DNA was PCR amplified using the following primers: 5′-GAAATAG GATGTAATCAGACG-3′ (forward) and 5′-AGTCTGCTGG ATTTGGTTCTA-3′ (reverse). For real-time PCR, a sensor primer was designed according to the wild-type allele and downstream to it an anchor primer. For the detection of the specific polymorphic nucleotide (T/A at position 3977 of SEQ ID NO: 7), the anchor primer was LC-Red 640-TTTGC AGGGTATTAGCAGAATCTGCTTCCTGTG-ph (SEQ ID NO: 9), and the sensor primer was: CCAATCTTTT CTTT TTTTTCTGC-FL (SEQ ID NO: 10).

Statistical analysis

Statistical analyses were performed using IBM SPSS 21.0 software. The 95% confidence interval (CI) and odds ratio (OR) adjusted for age and sex were calculated using logistic regression coefficient for each cancer type.[14] The average age at the onset of malignancy was compared between carriers and non-carriers using the two-tailed Student's *t* test. Cox regression was used to evaluate differences in survival and lifespan. All analyses were done with stratification by gender and age. The p-values were adjusted to multiple testing by the false discovery rate method.[15]

Results

A total of 13,013 (89%) subjects with no personal history of cancer and 1,611 cancer patients (11%) were included in this study (106 of the latter were diagnosed at the ICPC). Table 1 describes the types of malignancies included in the analysis. There was an almost equal number of males (49%) and females (51%), with an average age of 56.6 ± 15.5 years. The *APC* I1307K variant was detected in 803/14,624 (5.5%) individuals. The *APC* I1307K carrier prevalence among subjects with a positive history of any type of malignancy was significantly higher compared to healthy individuals (11.8% and 4.2%, respectively, OR 2.53, 95% CI 2.11–3.04, $p < 0.0001$). The results were almost identical after exclusion of CRC cases (OR 2.54 95% CI 2.03–3.17, $p < 0.0001$). Furthermore, the *APC* I1307K population had a significantly higher prevalence of a past history of two or more cancer types (OR of 4.38 95% CI 2.89–6.97, $p < 0.0001$).

Table 1. Cases of cancer included in the study

Cancer type	Cases diagnosed at the ICPC	Cases from other departments	Total
Bile system	0	4	4
Brain/nervous system	0	10	10
Breast	23	130	153
Endocrine system	9	17	26
Gynecological	7	59	66
Hematologic	0	29	29
Kidneys/urinary tract	0	34	34
Liver	0	10	10
Lung/airways	5	30	35
Other	11	38	49
Pancreas	0	103	103
Prostate	5	135	140
Skin	25	202	227
Gastric	21	831	852
Total	106	1,632	1,738

ICPC, Integrated Cancer Prevention Center.

In accordance to previous studies, the findings in a subgroup of patients who underwent colonoscopy showed that both the adenomatous polyp and the CRC rates were significantly increased among *APC I1307K* carriers compared with non-carriers (adjusted for age and sex OR 1.67, $p < 0.0001$).

Table 2 summarizes the prevalence of *APC I1307K* carriers among individuals with various types of non-colorectal malignancies. Statistically significant increased ORs were found for pancreatic, gastric, breast, kidney, urinary tract, brain, and lung cancers, as well as for melanoma and basal cell carcinoma (BCC) of the skin. There was no significant association with other types of cancers (*e.g.*, esophagus, prostate, ovary, uterus, cervix, hematological, endocrine, and liver). Unlike males, in whom an increased *APC I1307K* carrier prevalence was observed in many cancer types (Table 2), the females had a significantly increased carrier prevalence only for breast (OR 2.84 95% CI 1.74–4.66, $p < 0.0001$) and skin cancers (OR 4.81, 95% CI 2.90–7.97, $p < 0.0001$).

The average age at onset of the different malignancies is depicted in Figure 1. A later onset of cancer was found among carriers (62.84 ± 15.2 years) compared to non-carriers (60.29 ± 15.4 years) in all cancer types except for skin cancer in which an opposite trend was observed (52.11 ± 11.59 years in carriers vs. 61.04 ± 16.67 years in non-carriers). These findings were significant for a number of malignancies among females (*i.e.*, CRC, kidney/urinary tract, and overall non-CRCs) and only in brain cancers among males. The observation of an earlier onset of skin cancers among carriers was significant only in males.

A significant protective effect was found for female carriers with any type of cancer (Fig. 2a), and it remained significant after exclusion of the CRC cases (Fig. 2b). There was no significant HR in males or for a specific type of cancer in females.

Notably, there was a trend towards a longer lifespan in carriers compared to non-carriers (HR = 0.795 95% CI 0.63–1.00, $p = 0.054$). After stratification by past history of any malignancy (Fig. 3), female carriers diagnosed with cancer were found to have lived significantly longer than non-carrier female cancer patients (HR 0.48, 95% CI 0.29–0.79, $p = 0.004$). There was no comparable protective effect for males.

Discussion

The I1307K allele in the *APC* gene is a risk factor for colorectal neoplasia, particularly in Ashkenazi Jews. The current study, the largest of its kind thus far, revealed that this single nucleotide polymorphism (SNP) is an important predictor of overall neoplasia, with an OR of over 2.5, and particularly in males. A similar observation was previously made only by Woodage *et al.*[8]

There is ample evidence showing that the disruption of the Wnt/β-catenin pathway through *APC* mutations plays an important role in the multi-step process of carcinogenesis. *APC* mutations have been found in various extra-intestinal tumors, including those of the breast,[16] lung,[17] pancreas,[18] gastric,[19] kidney,[20] and skin,[21] albeit at rates significantly lower than in CRC.

The I1307K variant is a hypermutable site on the exon of the *APC* gene. It has eight adenine in a row (A8) that may be prone to slippage of DNA/RNA polymerase and/or miss-pairing during DNA and RNA replication.[1] In a recent study, Zauber *et al.*[22] found that this variant is associated with the insertion of an additional adenine (A9), which produces a frame shift with definite functional consequences. Such genetic changes might result in abnormal function of the *APC* gene that disrupts the Wnt/β-catenine pathway and causes a widespread organ effect. Few studies have thus far examined the association between the *APC* I1307K variant and specific extra-intestinal forms of cancer. Redston *et al.*[10] reported an OR of 1.5 for breast cancer among *APC* I1307K carriers (95% CI = 1.2–2.0), and Woodage *et al.*[8] reported that *APC* I1307K carriers were more likely to have first-degree relatives who had had breast cancer than were non-carriers. Other studies, however, failed to show such an association.[9,23] Similarly no increased risk was seen for ovarian or prostate cancer in *APC* I1307K carriers.[24,25]

In a previous small sample study, we had found a trend toward an increased prevalence of lung cancer among *APC* I1307K carriers which did not reach a level of significance.[11] A significant association between lung cancer and positive carriage state was observed in the current study (OR 4.08 95% CI 2.08–11.09, $p < 0.0001$). Moreover, this is the first report to describe an association of this SNP with kidney, gastric, pancreatic, and skin cancers. Larger studies are

Table 2. Comparison of APC I1307K prevalence among extra colonic cancer patients

Cancer type	Total number of cases	I1307K carriers Total = 803 *n*, (% of cases)	Overall OR[1] (95% CI)	Males OR[1] (95% CI)	Females OR[1] (95% CI)
Brain/nervous system	10	3 (33.3)	8.34[4] (2.15–32.35)	12.74[3] (2.12–76.60)	4.90 (0.55–44.11)
Breast	153	20 (13.1)	2.82[4] (1.72–4.61)	-	2.84[4] (1.74–4.66)
Gastric	91	10 (11.0)	2.39[4] (1.23–4.66)	3.93[3] (1.72–8.99)	1.25 (0.38–4.05)
Kidneys/urinary tract	34	6 (17.6)	4.26[4] (1.74–10.42)	4.50[3] (1.49–13.57)	4.11 (0.88–19.21)
Lung/airways	35	7 (20.0)	4.08[4] (2.08–11.09)	7.31[4] (2.58–20.77)	2.77 (0.63–12.29)
Pancreas	103	13 (12.6)	2.79[4] (1.54–5.05)	3.71[3] (1.71–8.03)	1.93 (0.75–4.93)
Skin					
BCC	90	18 (20.0)	5.02[4] (2.96–8.52)	3.25[3] (1.44–7.36)	7.90[4] (3.86–16.14)
Melanoma	118	17 (14.4)	3.29[4] (1.95–5.54)	2.98† (1.40–6.34)	3.68[4] (1.79–7.57)
All types	227	40 (17.6)	4.25[4] (2.98–6.07)	3.86[4] (2.34–6.37)	4.81[4] (2.90–7.97)
Any type of neoplasm	1,611	189 (11.8)	2.53‡ (2.11–3.04)	2.88[4] (2.08–4.00)	2.33[4] (1.72–3.15)
Any type of non-CRC	976	113 (11.6)	2.54[4] (2.03–3.17)	2.89‡ (2.22–3.77)	2.28[4] (1.77–2.94)
≥2 cancer types	146	27 (18.5)	4.48[4] (2.89–6.97) 1.80[2] (1.14–2.84)	4.73[4] (2.54–8.81) 1.59[2] (0.843–3.01)	4.60[4] (2.45–8.65) 2.19[2] (1.13–4.21)
Controls (no history of malignancy)	13,013	614 (4.7)	-	-	-

A p values <0.0054 is considered significant according to the false discovery rate method.
[1]Compared to healthy controls.
[2]Compared to patients with one type of malignancy.
[3]$p < 0.001$.
[4]$p < 0.0001$.
OR, odds ratio; CI,confidence interval; BCC, basal cell carcinoma; CRC, colorectal carcinoma.

obviously warranted in order to confirm and validate this association in Jews as well as in other ethnic groups.

Only a few previous studies have investigated the association between *APC* I1307K, cancer risk and gender. In the current study, male carriers exhibited an increased risk for several types of cancer (pancreas, lung, kidney, urinary tract, skin, and gastric), while female carriers showed an increased prevalence of only breast and skin cancers. This finding is consistent with the general observation that the overall cancer prevalence and mortality rates are higher among males compared to females.[26] Environmental exposure, such as smoking and alcohol consumption, seem to dominate overall gender-related cancer risk, however, genetic factors probably contribute to some extent to this gender disparity.[27]

Gender-related variability was also observed regarding age of disease onset and longer survival. Carriers generally developed cancer at an older age, although this difference was significant mostly for females. Skin cancers were the exception, with an earlier age of onset for carriers, although this was statistically significant only for males. In addition, female carriers of the *APC* I1307K variant who were diagnosed with cancer had better longer survival rates (HR = 0.6 95% CI 0.39–0.92, $p = 0.018$) and an increased lifespan (HR = 0.48 95% CI 0.294–0.792, $p = 0.003$) than non-carriers. Although the actual mechanism responsible for the observed increased lifespan solely for females is unknown, the older age at disease onset and the increased risk only for malignancies that have a relatively good prognosis (*e.g.*, breast and skin cancers) might explain the better prognosis and overall higher survival rates.

There are several examples of gene-related cancer predispositions, and it is currently estimated that around 3% of cancers are due to mutations in such genes.[28] The fact that *APC* I1307K carriers had organ-wide cancer predisposition

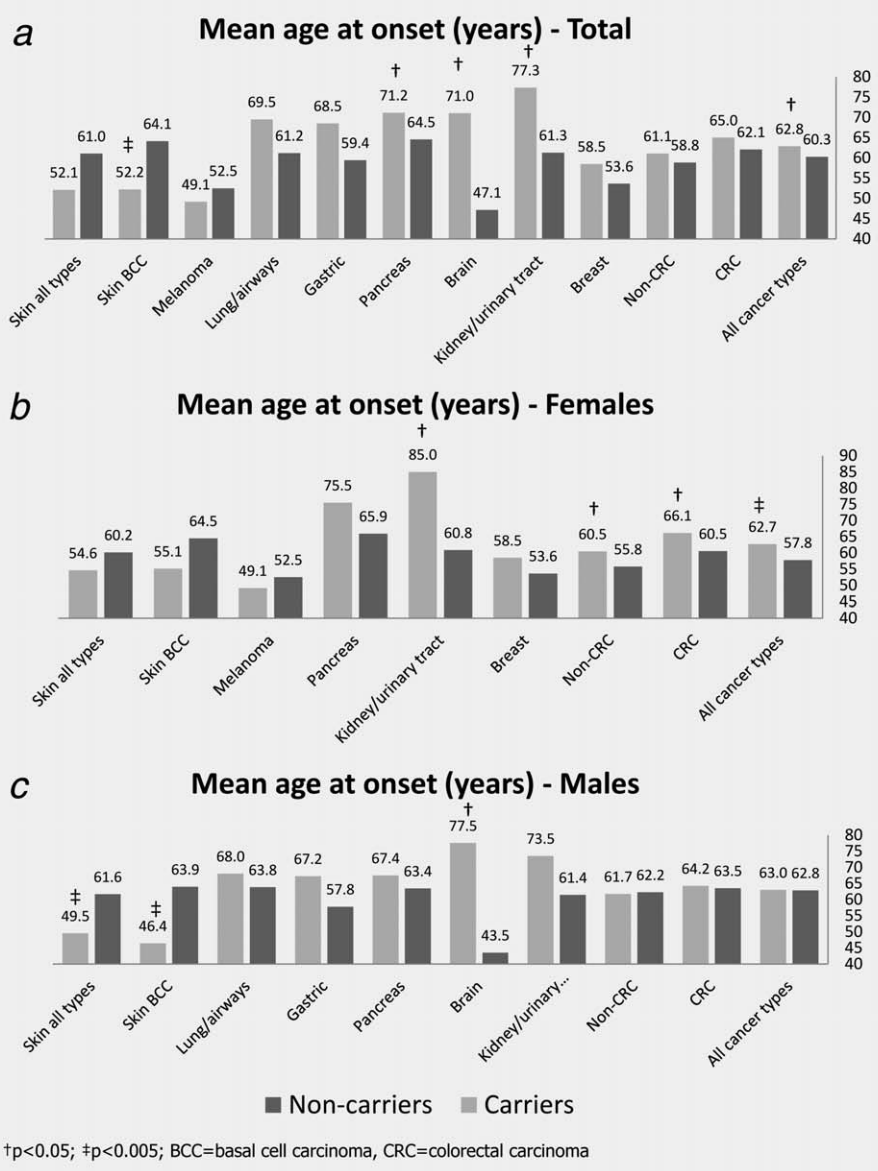

Figure 1. Comparison of mean age of onset of cancer. (*a*) Overall mean age of onset. (*b*) Mean age of onset in females. (*c*) Mean age of onset in males.

on the one hand and an older age at cancer onset with better survival on the other might be due to different pathways of cancer development and progression. A similar phenomenon was observed among *BRCA* carriers who are prone to breast, ovarian, gastric, colon, pancreatic, and prostate cancers.[29] Despite the increased risk for the development of cancer, studies have shown that BRCA-associated ovarian and fallopian tube cancers had a survival advantage over those with sporadic disease, suggesting that an underlying tumor biology contributes to disease outcome.[30] The gender disparity described herein could be due to several contributing factors, such as sex hormones, environmental causes, and epigenetics.[31] Specifically, the differences in skin cancer might be explained by previously described gender-linked differences in the composition of the skin.[32]

Although the *APC* gene is an autosomal gene, previous studies have shown that autosomal genes can have different effects on males and females. For example, vascular endothelial growth factor increased the risk of lung cancer only in males,[33] while an apolipoprotein E gene polymorphism was found to increase the risk of pancreatic cancer only in females.[34] Dorak and Karpuzoglu[27] have summarized several such examples and relate the differences to diversity between males and females in gene regulation. Although the actual mechanism remains unclear, it seems that any genetic variant has the potential to yield a gender-specific association.

One of the strengths of this prospective study is the large control group and the efforts that were made to ensure that it contained only individuals who were deemed as being healthy after undergoing extensive clinical and laboratory

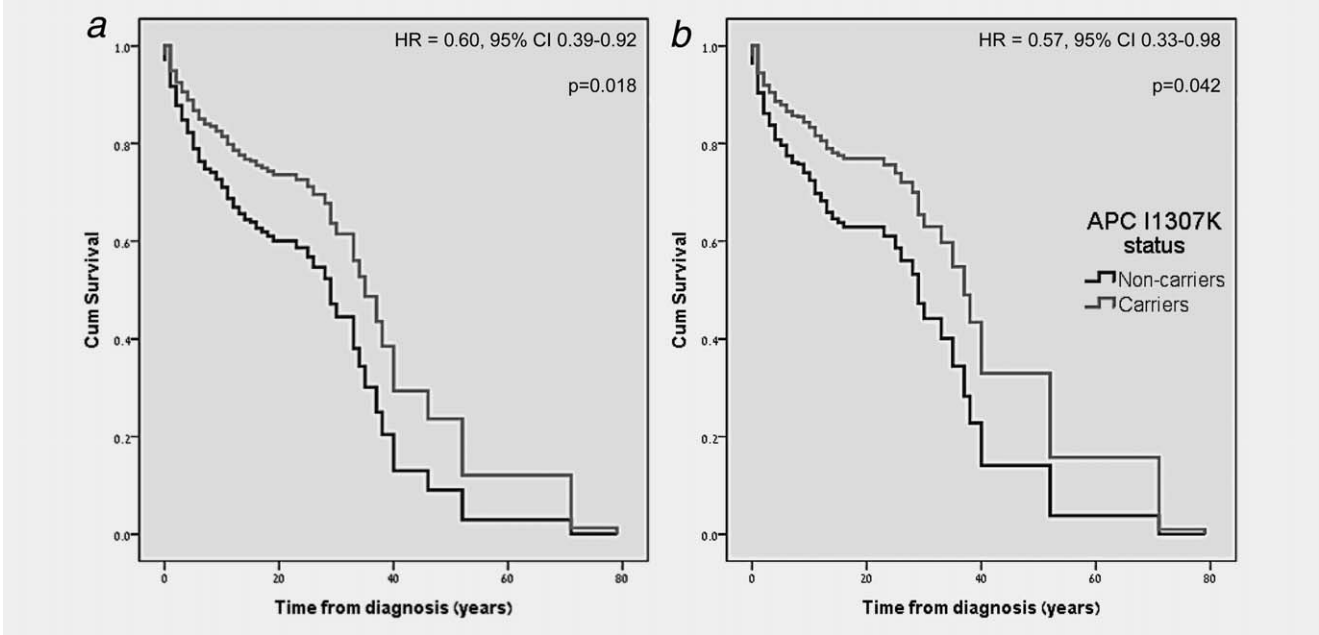

Figure 2. Survival analysis from the time of diagnosis of cancer. (*a*) Survival after diagnosis in all cancer types in females. (*b*) Survival after diagnosis in non-colorectal cancers (non-CRC) in females.

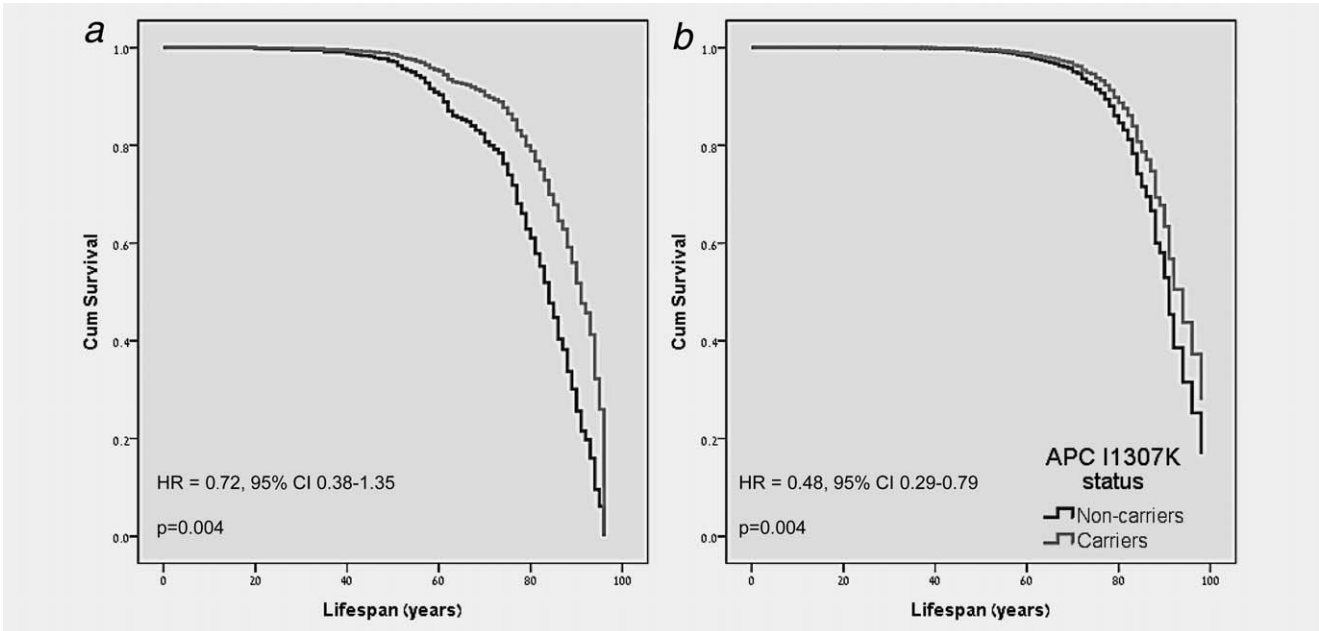

Figure 3. Comparison of overall lifespan. (*a*) Lifespan of females with no past history of cancer. (*b*) Lifespan of females with a past history of cancer of any type.

evaluations. As such, the current results may be more accurate and reliable than other series in which the control group included asymptomatic subjects that underwent less meticulous evaluations than the current study population.

One of the limitations of the study is the variation of the number of cancer cases by type and gender. Although the low case number of females with kidney and urinary tract cancer compared to males might account for the difference in the statistical significance of the risk, the same cannot be said for lung, gastric or pancreatic cancer, in which the incidence was similar for males and females. We were able to establish an association between *APC* I1307K and cancer-specific risk. However, since the OR might be influenced by sample size, it is impossible to accurately compare risks, and further large-scale studies on I1307K cancer-specific risk are needed. Zauber *et al.*[22] searched for somatic mutations in

colorectal tumors from *APC* I1307K carriers and found an association for further somatic changes with definite functional consequences. Unfortunately, we had no pathologic samples that could be used for evaluation of somatic slippage.

In conclusion, the findings that were derived from this large study cohort suggest that the I1307K variant in the *APC* gene is a global risk factor for cancer, with an OR of over 2.5, and mostly in males. Female carriers have better prognosis, with a relatively increased lifespan. The results of this study confirm the association between the *APC* I1307K variant and colorectal neoplasia. They also indicate that this variant is associated with several extra-colonic and extra-intestinal tumors, including those of the brain, lung, urinary tract and pancreas, as well as melanoma and BCC of the skin. Genetic screening would help identify carriers of this polymorphism and enable physicians to recommend the appropriate cancer screening tests. Further studies are needed to assess the relationship between the presence of the *APC* I1307K variant and the course of disease, such as age at onset, severity, and rate of survival. Meanwhile, it is suggested that this SNP be considered as part of the routine evaluation of healthy Ashkenazi Jews, and that the accumulated data may contribute to the design of a specific screening program in this population.

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