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Atopic allergic conditions and pancreatic cancer risk: results from the Multiethnic Cohort Study

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Abstract

Previous case-control studies have suggested that atopic allergic conditions (AACs) are inversely associated with pancreatic cancer, but this relationship has not been supported in many prospective settings. In this study, we investigated the influence of AACs (asthma, hay fever, or allergy) and the treatment of these conditions on pancreatic cancer risk among participants of the Multiethnic Cohort Study (MEC). AACs and antihistamine use were assessed via a baseline questionnaire when participants joined the MEC in 1993–1996. Risk ratios (RRs) and 95% confidence intervals (CIs) for pancreatic cancer incidence by AACs and antihistamines were calculated using Cox regression, adjusting for age, sex, ethnicity, education, smoking status, family history of pancreatic cancer, body mass index, diabetes, and alcohol intake. We further evaluated associations among subgroups defined by age, sex, ethnicity, follow-up time and known pancreatic cancer risk factors. During an average 16-year follow-up, 1,455 incident cases of pancreatic cancer were identified among 187,226 white, African American, Latino, Japanese American and Native Hawaiian men and women. AACs (RR 1.00, 95% CI 0.88–1.12) and antihistamines (RR 0.92, 95% CI 0.78–1.07) were not clearly associated with pancreatic cancer incidence. While these associations were also null for most subgroups, we did observe protective associations of AACs (RR 0.74, 95% CI 0.56–0.98) and antihistamines (RR 0.66, 95% CI 0.45–0.96) among the oldest participants (70+). Our results, in agreement with past prospective studies, suggest that AACs are not associated with pancreatic cancer in general, but the observed protective associations among the oldest age group may warrant future investigation.

Keywords

allergies; atopic allergic conditions; antihistamines; pancreatic cancer

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INTRODUCTION

Pancreatic cancer is considered one of the most lethal cancers in the United States. It is presently the third leading cause of cancer-related mortality and is projected to become the second most common cancer death by 2030.[1,2] Despite improvements in survival over the past decades, its current 5-year survival rate of 8% is still the lowest among all cancers.[1] In light of these poor outcomes, more efforts are needed to understand the etiology and to combat the burden of this disease.

As pancreatic cancer has been related to inflammation,[3] the role of the immune system in this malignancy has been of major interest in epidemiologic research. Specifically, researchers have evaluated the influence of atopic allergic conditions (AACs) on pancreatic cancer in a number of retrospective studies.[4,5] In a recent meta-analysis of fourteen case-control studies with a total of 5,550 cases, summary estimates revealed inverse associations for history of asthma, nasal allergies and skin allergies with pancreatic cancer risk.[4] While most of the individual studies in the meta-analysis showed reduced risks for nasal allergies, there was less agreement across the studies for skin allergies and asthma.[4] Asthma has also been assessed in several registry-based retrospective cohorts from Finland and Sweden, which also have yielded conflicting results.[6–8]

In contrast, there has been a scarcity of prospective evidence regarding this relationship. To date, there have only been four prospective cohorts examining AACs and pancreatic cancer, all of which have had findings inconsistent with those of the case-control studies.[9–12] Three out of the four cohorts observed null associations between pancreatic cancer and conditions such as asthma, hay fever, and dermal reactions,[9–11] while the fourth cohort study observed an increased risk for asthma but a null association for skin allergies.[12] These four cohorts, however, were conducted in mainly Caucasian populations. The two larger cohorts were also conducted among special populations of 34,000 Seventh-Day Adventists and 29,000 male smokers from Finland.[10,12] Moreover, none of these cohorts evaluated whether allergy-treating medications were related to pancreatic cancer incidence.

Given the current literature, the influence of AACs and the treatment for such conditions on pancreatic cancer risk has not been prospectively investigated in a large heterogeneous population or within particular ethnic groups. The objective of our current study was to fill this gap in knowledge by assessing these relationships among white, African American, Latino, Japanese American and Native Hawaiian men and women of the prospective Multiethnic Cohort Study (MEC). Further, we sought to evaluate whether the impact of AACs and allergy medications varied across individuals with and without known pancreatic cancer risk factors.

METHODS

Study population

The Multiethnic Cohort Study was established in 1993–1996 to study cancer and chronic disease etiology among individuals living in California (mostly Los Angeles County) and Hawaii. It consists of roughly 215,000 participants ages 45–75 of five primary ethnic

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groups: white, African American, Latino, Japanese American and Native Hawaiian.[13] Upon enrollment, cohort members completed a 26-page baseline questionnaire, which included questions on demographics, lifestyle factors, personal medical conditions and family history of cancer.

Cohort members were excluded if they were not in the five main ethnic groups, had a previous history of pancreatic cancer prior to cohort entry, or were missing information on AAC status and pancreatic cancer risk factors (e.g. smoking, diabetes). The present study follows individuals from the date of the baseline questionnaire to pancreatic cancer diagnosis, death, or the closure date of follow-up on December 31, 2012. Incident, invasive pancreatic cancer cases were identified by annual linkage with the statewide Surveillance, Epidemiology, and End Results (SEER) registries of Hawaii and California. Mortality information was obtained through linkage with states' death certificate files and the National Death Index.

Exposure Assessment

Participants were asked to self-report on the baseline questionnaire whether a physician had ever informed them that they had "asthma, hay fever, skin allergy, food allergy or any other allergy," asked as a single combined exposure on the baseline questionnaire. In addition, participants were asked whether they had used any antihistamine medications ("allergy pills or shots") for "at least two times per week for one month or longer" and the duration at which they used these medications.

History of AACs was assessed as a binary exposure. Antihistamine medication was analyzed as ever use and duration of use (none, ≤5 years, >5 years). We also combined these exposures to create an index of allergy severity (no AACs, AACs with no medication use, AACs with medication use).

Statistical Analyses

Baseline characteristics were compared across individuals with and without AACs using a t-test for age and chi-square tests for all other variables. Pancreatic cancer incidence rates, truncated to ages 45–95, were computed within the MEC, age standardized by 5-year age groups to the United States Census 2000 standard population.

The influence of AACs and antihistamine use on pancreatic cancer incidence was evaluated using Cox proportional hazards regression models with time since baseline as the time metric. We used separate models to evaluate the associations between each of our exposures of interest (history of AACs, ever use of antihistamine, duration of antihistamine use, and allergy severity) and pancreatic cancer. We fit minimally adjusted models that included age at cohort entry, sex, and race/ethnicity (white, African American, Latino, Japanese American, Native Hawaiian) as strata variables, as well as fully adjusted models that also included smoking status (never, past, current), family history of pancreatic cancer, diabetes, education (≤12 years, some college/vocational, college graduate), alcohol intake (none, <24, 24–48, >48 g/day), and body mass index (BMI) (<25, 25–30, ≥30 kg/m^2) as covariates. We also ran models with continuous measurements for alcohol intake and BMI and observed no

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change in the results; thus only findings from models with categorical groupings for these variables are presented. Individuals were censored at death or end of follow-up.

To assess effect modification of the associations of AACs or ever use of antihistamine medication on pancreatic cancer, we ran additional models among subgroups defined by age group (<50, 50–54, 55–59, 60–64, 65–69, 70+), sex, ethnicity, follow-up time since baseline (<5 years, ≥5 years), and known/potential pancreatic cancer risk factors (cigarette smoking, family history of pancreatic cancer, diabetes, alcohol use, BMI). We tested for heterogeneity by fitting a separate model with a cross-product term for the exposure (history of AACs or ever use of antihistamine medication) and the stratifying variable. The proportional hazards assumption was assessed using Schoenfeld residuals while model fit was evaluated using Martingale and deviance residuals.[14] All analyses were conducted using SAS 9.3 (Cary, NC) and reported P values are two-sided.

RESULTS

After exclusions, the present study consisted of 187,226 total individuals (females N=101,845, males N=85,381). The mean age at cohort entry was 59.9 (standard deviation 8.8). Japanese American (28.7%), whites (25.0%), and Latinos (22.2%) were the most represented ethnicity groups, followed by African Americans (16.8%) and Native Hawaiians (7.3%). During an average follow-up period of 16.2 years, 1,455 incident cases were identified among participants at risk.

Roughly one quarter of individuals reported a history of AACs (N=49,696, 26.5%). Age-standardized pancreatic cancer incidence rates (left truncated at age 45) were lower in those with AACs (44.8 cases per 100,000) than in those without AACs (50.2 cases per 100,000) (Table 1). Demographic characteristics and risk factors differed across individuals with and without AACs. Those who reported having AACs tended to be younger, female, and white and were more likely to have a family history of pancreatic cancer and more years of education. Additionally, these individuals were less commonly diabetics, current smokers, or heavy alcohol drinkers (Table 1). Antihistamine medication use was reported in 28,413 (15.2%) participants. Among these individuals, 15,405 (54.2%) used antihistamines for five or less years. In regards to allergy severity, 15.0% of participants reported having AACs without antihistamine use and 10.7% reported a history of both AACs and medication use (Table 1).

In our models minimally adjusted for age, sex and race, we detected no significant associations between AACs, antihistamine use, or allergy severity with pancreatic cancer (Table 2). However, we found a borderline protective association for those who had used antihistamines for five or less years (RR 0.81, 95% CI 0.65–1.00) compared to those who did not use any medications. All of the aforementioned associations were quite similar and non-significant after including the remaining covariates in our fully adjusted models. Again, we observed a borderline reduced risk for individuals with five or less years of antihistamine use (RR 0.82, 95% CI 0.66–1.01) compared to those without any history of medication use (Table 2).

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The null associations for AACs and ever use of antihistamines were present across all stratified analyses, except within the oldest individuals (age 70+) in the cohort (Tables 3 & 4). Among individuals who were 70 or older at cohort entry, those who had a history of AACs had a 26% reduced risk (RR 0.74, 95% CI 0.56–0.98) while those who used antihistamines had a 34% reduced risk (RR 0.66, 95% CI 0.45–0.96) of pancreatic cancer. In addition, AACs had a borderline protective association among those who were followed for less than five years (RR 0.76, 95% CI 0.56–1.04). There were no associations of AACs and antihistamines within any of the other subgroups stratified by sex, ethnicity, BMI, family history of pancreatic cancer, smoking, diabetes, and alcohol use (Table 3 & 4).

DISCUSSION

In this prospective cohort study, we investigated the influence of atopic allergic conditions and antihistamine medication use on pancreatic cancer risk in a population of white, African American, Latino, Japanese American and Native Hawaiian individuals. After adjusting for covariates, we observed no significant association between any prior history of AACs, antihistamine use, or allergy severity with the incidence of pancreatic cancer. The null associations for AACs and antihistamine medication were consistent across subgroups defined by sex, ethnicity, follow-up time, BMI, family history, smoking status, diabetes and alcohol use. However, we did observe protective associations among those who were aged 70+ at cohort entry. While these findings may have resulted from censoring due to death, further evaluations of AACs and antihistamines on pancreatic cancer risk among older individuals might be worthwhile.

Four previous prospective cohorts have studied the association of AACs and pancreatic cancer. In these studies, the number of pancreatic cancer cases ranged between 4 and 172 and the resulting RR's ranged from 0.59 to 2.16.[9–11] Thus, the null findings in these cohorts may have been attributed to insufficient statistical power. Though the largest number of cases came from the 29,000 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, the results from this study cannot be easily extrapolated to the general population given the specificity of the study participants.[12] These cohort members were also at a higher baseline risk for pancreatic cancer given their shared smoking history.[15] Our results in the MEC agree with the null results of these past studies and, with nearly 1,500 cases from an ethnically diverse population, provide more convincing evidence of a null association between overall allergies and pancreatic cancer.

On the other hand, our findings conflict with the protective associations found in several case-control studies. This discrepancy may be due to differences in the participant selection across prospective and retrospective study designs. For instance, many of the case-control studies excluded a large proportion of cases due to death, refusal and non-response. Among the seven case-control studies that reported a decreased cancer risk for any allergic condition, nearly all were unable to recruit over half of the entire population of cases.[16–22] These exclusions could have introduced selection bias if the association of AACs and cancer risk was different across those enrolled and not enrolled in the studies. This is further supported by the fact that the strongest associations were observed in studies that recruited the lowest number of cases.[16,17] Though prospective cohorts are susceptible to selection bias

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due to loss of follow-up, our cohort was able to monitor the outcomes of all of our participants by passive linkage to the statewide SEER registry and National Death Index.

Based on the existing literature, it appears that the influence of AACs on pancreatic risk may differ according to the type of allergy. Past case-control studies have showed fairly consistent inverse associations with hay fever and other nasal allergies,[4,16–19,21–23] but only a few studies have showed decreased risks for asthma[4,20,23] and skin allergies.[19,20,23] While most studies had null findings for skin allergies and asthma, one retrospective cohort from Sweden found an increased pancreatic cancer risk among hospitalized asthma patients,[8] suggesting that disease severity may also play a role in carcinogenesis. For several studies that used a composite assessment of allergies, the protective overall associations seemed to be driven by the individual effects of hay fever and other nasal allergies.[16–19,21,22] Since we do not know the breakdown and prevalence of each allergic condition in the Multiethnic Cohort, our null result could have been attributed to a condition that is not as strongly associated with pancreatic cancer. As hayfever represents a modest percentage of all atopic allergic conditions at roughly 30%,[24,25] it is plausible that we could have missed a strong association in this subset.

The mechanism in which allergies may impact cancer risk is still not well understood. AACs have been theorized to either decrease risk through heightened immunosurveillance or increase risk through chronic inflammation.[26] Although the protective associations from previous studies provide evidence for the immunosurveillance pathway, other studies have found no relationship between IgE levels, a biologic marker for allergic response, and pancreatic cancer risk.[27,28] Medical treatment of allergies may also modify the underlying mechanism, but there has been limited information regarding allergy medications and pancreatic cancer. Aside from our current analysis that detected no association of antihistamines, one other case-control study found protective associations among those who reported receiving medical treatment for allergies.[20] Another case-control study suggested that medication use may confound the association of allergies with pancreatic cancer, but did not conduct a formal analysis of this relationship.[18] In our study, we attempted to tease apart the interaction between allergies and medications with our allergy severity index, but did not observe any significant associations with this measurement.

Other important factors in determining pancreatic cancer risk could possibly include the timing and duration of allergic conditions. In the recent PanGenEU case-control study, researchers found that participants who had post-childhood onset or ≥17 years of asthma had a reduced risk for pancreatic cancer.[4] Likewise, the Pancreatic Cancer Case-Control Consortium observed a stronger protective effect among individuals with late onset of allergic conditions compared to those with early onset.[29] We addressed timing of AACs in our cohort by examining duration of antihistamine use and performing subgroup analyses by follow-up time, since those who had used medications for shorter lengths or completed the baseline questionnaire within five years may have had a more recent diagnosis of allergies. Hence, the borderline protective associations that we detected for the shorter periods of both antihistamine use and follow-up time may support the trend of a reduced risk among individuals with later onset allergies. In general, case-control studies would be more likely

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than prospective studies to catch more recent diagnoses of AACs since exposure assessment was done after identifying all cases and controls.

One of the major strengths of this study is the large and heterogeneous sample, which allowed us to evaluate the relationship between AACs and pancreatic cancer in many different subgroups. In comparison to the previous four prospective cohorts, the present results are based on the greatest number of pancreatic cancer cases and are more generalizable to a heterogeneous population. We were also able to examine both medication use and an allergy severity index, which was not done in the past prospective cohorts. Since we collected epidemiologic data prior to disease diagnosis and linked to cancer registries with virtually complete case-ascertainment, our study is less susceptible to the recall and selection bias that may exist in case-control studies. However, due to our single measure of AACs, we could not study individual conditions and may have missed associations for certain types of allergies. We also did not have any biological measurements (e.g. IgE) or information on the timing of AACs, limiting our ability to elucidate the detailed pathways in which allergies may impact risk.

To our knowledge, this is the first study to examine the relationship between AACs and antihistamines with pancreatic cancer in a diverse and well-powered prospective setting. Our results are consistent with that of past prospective studies and provide additional support of a null association for overall AACs. Future prospective studies should aim to conduct a more comprehensive assessment of specific AACs and allergy-treating medications on pancreatic cancer risk.

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Abbreviations

AAC	atopic allergic conditions
MEC	Multiethnic Cohort Study
RR	risk ratio
CI	confidence interval
BMI	body mass index
SEER	Surveillance, Epidemiology, and End Results

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Novelty and Impact

Atopic allergic conditions (AACs) have been associated with a reduced risk of pancreatic cancer in case-control studies, but have had mainly null associations in prospective cohorts. Here, in the largest and most diverse prospective study to date, the authors report no association between AACs or antihistamine use with overall pancreatic cancer incidence. These null relationships were also consistent across subgroups defined by ethnicity (African Americans, Japanese Americans, Latinos, Native Hawaiians, whites) and pancreatic cancer risk factors.

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Table 1

Baseline characteristics of Multiethnic Cohort Study participants from 1993–2012, stratified by atopic allergic conditions (AAC) status

	Total (N=187,226)		No AACs (N=137,530)		AACs (N=49,696)		
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**p[1]**
Pancreatic cancer cases	1,455	0.8	1,094	0.8	361	0.7	
Follow-up time (years)[2]	16.2	(4.7)	16.1	(4.8)	16.5	(4.5)	
Pancreatic cancer incidence rate[3]	49.0		50.2		44.8		
Age at baseline (years)[2]	59.9	(8.8)	60.2	(8.8)	58.8	(8.9)	<0.0001
Age group at baseline (years)							<0.0001
<50	31,454	16.8	21,439	15.6	10,015	20.2	
50–54	28,050	15.0	19,853	14.4	8,197	16.5	
55–59	29,875	16.0	21,830	15.9	8,045	16.2	
60–64	32,245	17.2	24,068	17.5	8,177	16.5	
65–69	32,885	17.6	25,093	18.2	7,792	15.7	
70+	32,717	17.5	25,247	18.4	7,470	15.0	
Sex							<0.0001
Male	85,381	45.6	67,962	49.4	17,419	35.1	
Female	101,845	54.4	69,568	50.6	32,277	64.9	
Ethnicity							<0.0001
White	46,858	25.0	32,245	23.4	14,613	29.4	
African American	31,500	16.8	23,252	16.9	8,248	16.6	
Latino	41,547	22.2	32,876	23.9	8,671	17.4	
Japanese American	53,746	28.7	39,484	28.7	14,262	28.7	
Native Hawaiian	13,575	7.3	9,673	7.0	3,902	7.9	
Family history of pancreatic cancer	3,193	1.7	2,197	1.6	996	2.0	<0.0001
Diabetes	21,997	11.7	16,773	12.2	5,224	10.5	<0.0001
Body mass index (kg/m^2)							<0.0001
<25	77,887	41.6	56,562	41.1	21,325	42.9	
25–30	71,887	38.4	54,141	39.4	17,746	35.7	
≥30	37,452	20.0	26,827	19.5	10,625	21.4	

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Characteristic	Total (N=187,226) N	%	No AACs (N=137,530) N	%	AACs (N=49,696) N	%	p[1]
Smoking status							<0.0001
Never	82,113	43.9	59,630	43.4	22,483	45.2	
Past	75,100	40.1	54,685	39.8	20,415	41.1	
Current	30,013	16.0	23,215	16.9	6,798	13.7	
Education							<0.0001
≤12 years	81,972	43.8	64,784	47.1	17,188	34.6	
Some college/vocational	55,406	29.6	39,211	28.5	16,195	32.6	
College graduate	49,848	26.6	33,535	24.4	16,313	32.8	
Alcohol intake (g/day)[4]							<0.0001
None	95,609	51.1	69,742	50.7	25,867	52.1	
<24 g	70,227	37.5	51,509	37.5	18,718	37.7	
24–48 g	13,351	7.1	10,069	7.3	3,282	6.6	
>48 g	8,039	4.3	6,210	4.5	1,829	3.7	
Ever use of antihistamines	28,413	15.2	8,381	6.1	20,032	40.3	<0.0001
Allergy severity							<0.0001
None	137,530	73.5	137,530	100.0	0	0.0	
AACs with no medication use	28,089	15.0	0	0.0	28,089	56.5	
AACs with medication use	20,032	10.7	0	0.0	20,032	40.3	

Abbreviations: AAC, atopic allergic condition; SD, standard deviation

[1] From a t-test for age and chi-square test for all other variables

[2] Mean (SD)

[3] Incidence rate per 100,000 person-years, age-standardized to US Census 2000 standard population, left truncated at age 45

[4] Intake during the year prior to cohort entry

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Table 2

Associations between various allergy-related exposures and pancreatic cancer

Exposure	N	Cases	Minimally adjusted RR (CI)[1]	Fully adjusted RR (CI)[2]
Atopic allergic conditions (AACs)				
No	137,530	1,094	1 (ref)	1 (ref)
Yes	49,696	361	0.97 (0.86–1.10)	1.00 (0.88–1.12)
Ever use of antihistamines[3]				
No	149,760	1,191	1 (ref)	1 (ref)
Yes	28,413	190	0.90 (0.77–1.05)	0.92 (0.78–1.07)
Duration of antihistamine use[4]				
None	149,760	1,191	1 (ref)	1 (ref)
≤5 years of medication use	15,405	92	0.81 (0.65–1.00)	0.82 (0.66–1.01)
>5 years of medication use	9,538	76	1.09 (0.86–1.37)	1.12 (0.89–1.42)
p_{trend}[5]			0.71	0.94
Allergy severity				
None	137,530	1,094	1 (ref)	1 (ref)
AACs with no medication use	28,089	208	0.99 (0.85–1.15)	1.01 (0.87–1.17)
AACs with medication use	20,032	142	0.96 (0.81–1.15)	0.99 (0.83–1.19)
p_{trend}[5]			0.67	0.98

[1] Adjusted for age, sex, ethnicity

[2] Adjusted for age, sex, ethnicity, education, smoking status, family history of pancreatic cancer, education, BMI, diabetes, and alcohol intake.

[3] Information on antihistamine use missing for 9,053 participants (4.8% of cohort)

[4] Length of antihistamine use missing for 3,470 participants (12.2% of medication users)

[5] From a model treating exposure as a continuous variable

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Table 3

Association between atopic allergic conditions and pancreatic cancer among subgroups of cohort

Subgroup	Non-AAC Cases	AAC Cases	RR (CI)[1]	p
All	1,094	361	1.00 (0.88–1.12)	0.94
Age group at baseline				0.20[2]
<50	69	35	1.15 (0.76–1.74)	0.50
50–54	86	34	1.03 (0.69–1.54)	0.88
55–59	146	66	1.29 (0.96–1.74)	0.09
60–64	185	63	0.99 (0.74–1.32)	0.94
65–69	314	100	1.00 (0.80–1.26)	0.98
70+	294	63	**0.74 (0.56–0.98)**	**0.03**
Sex				0.91[2]
Male	555	133	1.01 (0.83–1.22)	0.95
Female	539	228	0.99 (0.84–1.15)	0.85
Ethnicity				0.52[2]
Whites	209	83	0.95 (0.73-1.23)	0.70
African Americans	216	68	0.92 (0.70-1.21)	0.54
Latinos	200	58	1.16 (0.86-1.56)	0.33
Japanese Americans	376	126	1.06 (0.86-1.30)	0.58
Native Hawaiians	93	26	0.78 (0.50-1.22)	0.28
Follow-up time (years)				0.27[2]
<5	211	54	0.76 (0.56-1.04)	0.08
≥5	883	307	1.04 (0.91-1.18)	0.59
Family history of pancreatic cancer				0.13[2]
No	1,055	351	1.01 (0.90-1.15)	0.85
Yes	39	10	0.61 (0.30-1.23)	0.17
Diabetes				0.74[2]
No	929	310	0.99 (0.87-1.13)	0.85
Yes	165	51	1.04 (0.75-1.43)	0.82
Body mass index (kg/m^2)				0.19[2]
<25	453	134	0.88 (0.72-1.07)	0.19
25-30	426	139	1.06 (0.87-1.28)	0.58
≥30	215	88	1.13 (0.88-1.46)	0.33
Smoking status				0.49[2]
Never	461	168	1.07 (0.89-1.28)	0.49
Past	424	133	0.89 (0.73-1.09)	0.25
Current	209	60	1.06 (0.79-1.42)	0.70
Alcohol intake (g/day)[3]				0.67[2]
None	579	202	1.03 (0.87-1.21)	0.75
<24 g	388	125	0.98 (0.80-1.20)	0.82

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Subgroup	Non-AAC Cases	AAC Cases	RR (CI)[1]	p
24-48 g	78	25	1.11 (0.70-1.75)	0.67
>48 g	49	9	0.62 (0.30-1.28)	0.19

[1] Adjusted for age, sex, ethnicity, education, smoking status, family history of pancreatic cancer, education, BMI, diabetes, and alcohol intake. Among subgroups, models are not adjusted for the subgroup variable

[2] P-value for heterogeneity

[3] Intake during the year prior to cohort entry

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Table 4

Association between antihistamine medication use and pancreatic cancer among subgroups of cohort

Subgroup	Cases with no antihistamine use	Cases with antihistamine use	RR (CI)[1]	p
All	1,191	190	0.92 (0.78-1.07)	0.26
Age group at baseline				0.36[2]
<50	80	18	1.11 (0.66-1.87)	0.69
50-54	103	16	0.82 (0.48-1.40)	0.47
55-59	167	34	1.04 (0.72-1.51)	0.84
60-64	206	34	0.91 (0.63-1.32)	0.62
65-69	334	58	1.03 (0.78-1.37)	0.84
70+	301	30	**0.66 (0.45-0.96)**	**0.03**
Sex				0.09[2]
Male	578	76	1.08 (0.85-1.38)	0.52
Female	613	114	0.82 (0.67-1.00)	0.05
Ethnicity				0.28[2]
Whites	244	42	0.78 (0.56-1.09)	0.15
African Americans	221	37	0.76 (0.54-1.08)	0.13
Latinos	206	33	0.89 (0.62-1.29)	0.54
Japanese Americans	421	66	1.15 (0.89-1.50)	0.29
Native Hawaiians	99	12	0.95 (0.52-1.75)	0.88
Follow-up time (years)				0.73[2]
<5	220	28	0.83 (0.55-1.23)	0.35
≥5	971	162	0.94 (0.79-1.11)	0.46
Family history of pancreatic cancer				0.30[2]
No	1,149	185	0.93 (0.79-1.09)	0.35
Yes	42	5	0.62 (0.24-1.58)	0.32
Diabetes				0.11[2]
No	1,019	158	0.87 (0.73-1.03)	0.10
Yes	172	32	1.24 (0.84-1.81)	0.23
Body mass index (kg/m^2)				0.72[2]
<25	488	79	0.97 (0.76-1.23)	0.79
25-30	466	73	0.91 (0.71-1.17)	0.46
≥30	237	38	0.83 (0.59-1.18)	0.30
Smoking status				0.81[2]
Never	503	89	0.97 (0.77-1.22)	0.79
Past	464	71	0.86 (0.67-1.11)	0.24
Current	224	30	0.90 (0.61-1.22)	0.60
Alcohol intake (g/day)[3]				0.79[2]
None	634	97	0.88 (0.71-1.09)	0.23
<24 g	421	76	1.00 (0.78-1.27)	0.97

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Subgroup	Cases with no antihistamine use	Cases with antihistamine use	RR (CI)[1]	p
24-48 g	87	10	0.77 (0.40-1.49)	0.44
>48 g	49	7	0.93 (0.42-2.07)	0.86

[1] Adjusted for age, sex, ethnicity, education, smoking status, family history of pancreatic cancer, education, BMI, diabetes, and alcohol intake. Among subgroups, models are not adjusted for the subgroup variable

[2] P-value for heterogeneity

[3] Intake during the year prior to cohort entry