Research Article

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Jewish Ethnicity and Pancreatic Cancer Mortality in a Large U.S. Cohort

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Abstract

Background: An association between Jewish ethnicity and pancreatic cancer risk was suggested by analyses comparing pancreatic cancer mortality rates between Jews and non-Jews in New York in the 1950s. These analyses lacked information on potential confounding factors and the association between Jewish ethnicity and pancreatic cancer has not been examined in any contemporary U.S. population or in any cohort study.

Methods: We examined the association between Jewish ethnicity and pancreatic cancer mortality among approximately 1 million participants in the Cancer Prevention Study II cohort. Participants completed a questionnaire at enrollment in 1982 which included information on religion, smoking, obesity, and diabetes. During follow-up through 2006, there were 6,727 pancreatic cancer deaths, including 480 among Jewish participants. Proportional hazards modeling was used to calculate multivariable rate ratios (RR).

Results: After adjusting for age, sex, smoking, body mass index, and diabetes, pancreatic cancer mortality was higher among Jewish participants than among non-Jewish whites (RR = 1.43; 95% CI, 1.30–1.57). In analyses by birthplace, RRs were 1.59 (95% CI, 1.31–1.93) for North American–born Jews with North American–born parents, 1.43 (95% CI, 1.27–1.61) for North American–born Jews with 1 or more parents born outside North America, and 1.03 (0.73, 1.44) for Jews born outside North America ($P_{\text{heterogeneity}} = 0.07$).

Conclusions: These results support a higher risk of developing pancreatic cancer among U.S. Jews that is not explained by established risk factors.

Impact: Future studies may clarify the role of specific environmental or genetic factors responsible for higher risk among U.S. Jews. *Cancer Epidemiol Biomarkers Prev; 20(4); 691–8. ©2011 AACR.*

Introduction

Pancreatic cancer is highly fatal with a 5-year survival rate of less than 5% (1). In the United States, it is the fourth leading cause of cancer-related death (1). Risk factors positively associated with pancreatic cancer include smoking, obesity, and diabetes (2–5). In addition, in the United States, African Americans are at increased risk compared with whites (2).

Results from previous studies suggest that Jews in the United States may also be at higher risk of developing pancreatic cancer than non-Jewish U.S. whites (6–9). However, these studies have important methodologic limitations. The strongest evidence for higher risk among U.S. Jews is provided by 2 analyses of pancreatic cancer mortality rates based on data from New York City death certificates from the 1950s (6, 7). Both studies inferred ethnicity from the religious affiliation of the burial cemetery and estimated the Jewish and non-Jewish population at risk from a health insurance survey sample (10) whose validity is unclear. No previous study could examine the extent to which known risk factors, such as smoking or obesity, explained or confounded results. Furthermore, because most Jewish immigration to the United States occurred from 1880 to 1924 (11), the earlier U.S. studies likely included Jewish populations consisting predominantly of immigrants or children of immigrants. It is unclear whether results from these populations would generalize to contemporary, potentially more acculturated, Jewish populations.

Understanding whether U.S. Jews are truly at higher risk than non-Jewish whites may provide clues about the etiology of pancreatic cancer. In addition, although there is currently no widely used early detection test for pancreatic cancer (2), the finding of subgroups of the population at particularly high risk might have

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important implications for future screening. We, therefore, examined the association between Jewish ethnicity and pancreatic cancer mortality in the Cancer Prevention Study II (CPS-II) cohort—a well-defined contemporary U.S. study population with information on risk factors including smoking, obesity, and diabetes.

Materials and Methods

Study cohort and follow-up

The cohort consisted of 1,184,462 participants (508,256 men and 676,206 women) from the American Cancer Society (ACS) CPS-II. Participants were enrolled in 1982 in all 50 U.S. states, Washington, DC, and Puerto Rico as previously described (12, 13). CPS-II was approved by the Emory University (Atlanta, GA) Institutional Review Board.

At the time of enrollment, subjects completed a 4-page self-administered baseline questionnaire including information pertaining to demographics, medical history, family history of cancer, smoking habits, and diet. Jewish religion was assessed through a question about religious affiliation, wherein response options were Protestant, Catholic, Jewish, Latter Day Saints, other, or none. Self-reported Jewish religion was used as a surrogate for Jewish ethnicity. Place of birth of the participant and the parents of the participant were assessed along with the number of times the participant attended church or temple services in a month.

Mortality was ascertained by personal inquiry from ACS volunteers in September of 1984, 1986, and 1988. Reported death of a participant was recorded along with date and place and then verified using death certificates. At the completion of the 1988 follow-up, vital status was known for 98.2% of the cohort. Further follow-up of the cohort was completed on December 31, 2006, by automated linkage to the National Death Index, which also allowed for identification of 21,704 participants lost to follow-up between 1982 and 1988 (14). To date, death certificates or codes for cause of death have been obtained for 99.3% of all known deaths.

Pancreatic cancer mortality was defined as the underlying cause of death coded according to the 9th and 10th revisions of the World Health Organization International Classification of Disease (code numbers 157.0–157.9 for ICD-9 and C25.0–C25.9 for ICD-10; ref. 15). Known endocrine pancreatic cancers (codes 157.4 and C25.4; $n = 29$) were not included as outcomes because of their potentially different etiology.

The study excluded subjects missing religious information ($n = 17{,}282$; 1.5%), subjects who reported prevalent cancers at baseline, with the exception of nonmelanoma skin cancer ($n = 81{,}279$; 6.9%), and subjects who identified as nonwhite ($n = 71{,}276$; 6.0%). After exclusions, 1,014,625 study subjects remained, of whom 480 Jews and 6,247 non-Jews died of pancreatic cancer during follow-up.

Statistical analysis

A variable for ethnicity was dichotomized as Jewish or non-Jewish on the basis of self-reported religious affiliation. The participants were categorized according to their tobacco smoking habits into current cigarette smokers, current cigar/pipe smokers, former cigarette smokers, former cigar/pipe smokers, and never smokers. Cigarette smokers were then subcategorized on the basis of the number of pack-years (<20, 20 to <40, 40 to <60, 60+, and unknown). Subjects who recorded smoking pipes or cigars and cigarettes were assigned to the highest risk category (current smoking over former smoking, cigarette smoking over cigar/pipe smoking). Women were not asked about cigar or pipe smoking and were assumed to not smoke cigars or pipes. Among Jews, immigration status was categorized as North American–born subject with North American–born parents, North American–born subject with at least 1 parent born outside North America, or subject born outside of North America. Temple attendance was categorized as never or rarely attending, attending less than once per week, or attending at least once per week.

Age- and sex-standardized rates were obtained using the direct method of standardization, with the age and sex distribution of the cohort as the standardizing measure. Cox proportional hazards regression analysis was used to obtain rate ratio (RR) estimates for pancreatic cancer mortality associated with Jewish ethnicity (16). We adjusted for age, sex, body mass index (BMI), diabetes status, and smoking status. Age was adjusted by stratifying on exact year of age at enrollment (17), and smoking was modeled as a 14-level categorical variable, as described earlier. The remaining variables were modeled as categorized in Table 1. Further adjustment for education status, duodenal or gastric ulcers, family history of pancreatic cancer, vegetable consumption, red meat consumption, processed meat consumption, alcohol consumption, and geographic region of residence within the United States resulted in negligible changes in the risk estimates, and these factors were not included in final models.

The proportional hazards assumption for Jewish ethnicity was tested using linear time interaction in extended Cox modeling, as outlined by Kleinbaum and Klein (17). The test indicated that the proportional hazards assumption was met.

Multiplicative interaction was assessed between Jewish ethnicity and sex, attained age, BMI, family history, and smoking status. Age was dichotomized (<60 and $\geq$60 years) as was BMI (<25 and $\geq$25 kg/m^2), and smoking status was recategorized into never, former, and current smoker regardless of the type of tobacco product reported (cigarette, cigar/pipe). Models assessing multiplicative interaction by smoking status and stratified analyses among current and former smokers were adjusted for cigar/pipe smoking and cigarette pack-years. Significant interaction was assessed at the P value level of 0.05.

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Table 1. Distribution of pancreatic cancer risk factors at enrollment by sex and Jewish ethnicity, CPS-II 1982–2006

	Men		Women	
	Jewish (n = 22,324)	Non-Jewish (n = 425,384)	Jewish (n = 25,614)	Non-Jewish (n = 541,303)
Age, y				
29–39	3.4	3.7	5.2	5.2
40–49	14.4	18.3	20.5	22.8
50–59	34.3	38.2	33.1	34.7
60–69	32.0	28.2	27.9	24.8
70–79	14.0	10.1	11.6	10.3
≥80	1.8	1.6	1.7	2.3
BMI, kg/m^2				
<20.0	1.1	1.8	9.8	8.6
20 to <22.5	10.4	10.1	30.8	25.9
22.5 to <25	31.2	26.4	26.8	25.6
25 to <27.5	34.0	33.3	15.7	17.6
27.5 to <30	13.2	15.7	6.4	8.3
≥30	7.7	9.5	6.7	9.2
Unknown	2.3	3.2	3.8	4.8
Diabetes				
Yes	6.4	5.4	3.9	4.1
No	93.6	94.6	96.1	95.8
Unknown	0.0	0.0	0.1	0.1
Education				
Some high school	5.8	15.3	5.2	12.9
High school graduate	11.0	20.6	23.6	31.6
Some college	22.5	27.4	31.2	30.3
College graduate	25.4	17.8	19.8	14.6
Graduate school	34.3	18.1	19.0	9.7
Unknown	0.9	0.7	1.1	0.9
Family history				
Yes	1.8	1.1	2.2	1.4
No	98.2	98.9	97.8	98.6
Smoking status[a]				
Never	25.8	25.1	37.5	53.7
Current cigarette[b]	14.4	23.6	19.0	20.0
Current cigar/pipe	9.1	5.5	–	–
Former cigarette[b]	39.9	36.6	37.0	20.1
Former cigar/pipe	6.4	3.7	–	–
Unknown	4.4	5.6	6.5	6.3

NOTE: Percentages adjusted to the age distribution of the entire study population. Numbers not adding up to 100% are due to rounding.
[a]Women were restricted to never, current cigarette, former cigarette, or unknown categories.
[b]Not shown are pack-year categories of <20, 20 to <40, 40 to <60, 60+, and unknown.

Results

As shown in Table 1, the analytic cohort consisted of approximately 56% female and at the time of enrollment the participants were predominantly older than 50 years. Jewish participants were more likely than non-Jewish participants to be highly educated and have a BMI less than 25 kg/m^2. Among men, Jewish participants were

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Table 2. Pancreatic cancer mortality by Jewish ethnicity, CPS-II 1982–2006

	Pancreatic cancer deaths	Person-years	Age- and sex-standardized rate[a]	RR (95% CI)[b]
Jewish ethnicity				
Non-Jewish	6,247	19,522,142	32.4	1.00
Jewish	480	972,639	45.1	1.43 (1.30–1.57)
Birthplace among Jews[c]				
Jewish, North American born with both parents born in North America	106	282,058	50.8	1.59 (1.31–1.93)
Jewish, North American born with ≥1 parent born outside North America	279	518,579	44.7	1.43 (1.27–1.61)
Jewish, born outside North America	34	74,869	28.3	1.03 (0.73–1.44)
Temple attendance among Jews[d]				
Never or rarely	111	274,779	38.4	1.21 (1.00–1.46)
<1 per week	169	312,318	53.1	1.71 (1.47–1.99)
≥1 per week	55	133,901	34.7	1.11 (0.85–1.45)

[a]Rate per 100,000; adjusted for age and sex.
[b]RR and 95% CI adjusted for age, sex, smoking, diabetes, and BMI.
[c]Referent category is non-Jewish; $P_{heterogeneity} = 0.07$.
[d]Referent category is non-Jewish; $P_{heterogeneity} = 0.003$.

less likely than non-Jewish participants to be current cigarette smokers. Among women, the proportion of current cigarette smokers was similar among Jews and non-Jews, but a greater proportion of Jewish women were former smokers (Table 1).

Jewish ethnicity was significantly associated with a higher risk of pancreatic cancer mortality than non-Jews (multivariate adjusted RR = 1.43; 95% CI, 1.30–1.57; Table 2). RR estimates were slightly lower when only adjusted for age and sex (RR = 1.40; 95% CI, 1.28–1.54). Because some participants of Jewish ancestry might have reported "none" for religious affiliation, we also examined the association between Jewish ethnicity and pancreatic cancer mortality after excluding participants who reported "none" for religious affiliation, but results were unchanged (RR = 1.43; 95% CI, 1.30–1.57). A subanalysis did not reveal significant heterogeneity by place of birth among Jewish participants [$P = 0.07$, degrees of freedom (df) = 2]. Jewish participants born in North America were at higher risk regardless of whether both parents were born in North America or 1 or both parents were immigrants. No clear association was observed for foreign-born Jewish participants (RR = 1.03; 95% CI, 0.73–1.44). However, statistical precision was low and results do not preclude higher risk. Examination by frequency of temple attendance revealed no clear pattern of association despite a significant test of heterogeneity ($P = 0.003$, $df = 2$). Jewish participants who reported occasional temple attendance had the highest RR compared with non-Jews, whereas RRs seemed lower among Jews with rare or relatively frequent temple attendance.

RRs for Jewish ethnicity did not differ significantly by gender with RR = 1.49 (95% CI, 1.31–1.69) for men and RR = 1.35 (95% CI, 1.17–1.55) for women ($P_{interaction} = 0.44$). RRs also did not differ significantly by attained age with RR = 1.57 (95% CI, 1.03–2.39) among participants younger than 60 years, and RR = 1.42 (95% CI, 1.29–1.57) among participants 60 years or older ($P_{interaction} = 0.67$). RRs did not differ significantly by BMI with RR = 1.42 (95% CI, 1.25–1.62) among participants less than 25 kg/m^2, and RR = 1.46 (95% CI, 1.28–1.68) among participants 25 kg/m^2 or greater ($P = 0.99$). Finally, RRs did not differ significantly by family history of pancreatic cancer, with RR = 1.23 (95% CI, 0.70–2.14) among participants with a family history and RR = 1.43 (95% CI, 1.30–1.57) among participants without a family history of pancreatic cancer ($P_{interaction} = 0.55$).

In analyses stratified by smoking status, Jewish ethnicity was associated with significantly higher risk in all categories, with the RR highest among never smokers, intermediate among former smokers, and lowest among current smokers (Table 3). Statistically significant interaction was observed on a multiplicative scale for former versus never smokers ($P = 0.04$) and current versus never smokers ($P = 0.006$). However, examination of age- and sex-standardized rates suggested that the excess absolute risk associated with Jewish ethnicity did not differ substantially by smoking status. Analysis of interaction on an

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Table 3. Pancreatic cancer mortality by Jewish ethnicity and smoking status, CPS-II 1982–2006

	Non-Jewish	Jewish	$P_{interaction}$[a]
Never smoker			
Deaths/person-years	2,259/8,326,280	166/320,447	
Age- and sex-standardized rate[b]	27.4	47.1	
RR (95% CI)[c]	1.0	1.78 (1.52, 2.08)	
Former smoker			
Deaths/person-years	1,756/5,620,670	190/403,259	
Age- and sex-standardized rate[b]	29.5	43.1	
RR (95% CI)[c]	1.0	1.42 (1.22, 1.65)	0.04
Current smoker			
Deaths/person-years	1,814/4,502,512	113/197,726	
Age- and sex-standardized rate[b]	45.5	57.4	
RR (95% CI)[c]	1.0	1.29 (1.07–1.57)	0.006

[a]Multiplicative interaction with never smoker as comparison category.
[b]Per 100,000; adjusted for age and sex.
[c]RR and 95% CI adjusted for age, sex, diabetes, BMI, and pack-years.

additive scale (18) did not show statistically significant interaction for either former versus never smokers ($P = 0.08$) or current versus never smokers ($P = 0.10$).

Discussion

In this large contemporary U.S. study, Jewish ethnicity was associated with a higher risk of pancreatic cancer mortality that was not explained by established pancreatic cancer risk factors including smoking, obesity, and diabetes. To the best of our knowledge, this is the only cohort study of Jewish ethnicity and pancreatic cancer to date.

Four previous studies have examined the relationship between Jewish ethnicity and pancreatic cancer. Our results are generally consistent with 2 analyses examining pancreatic cancer mortality in New York City in the 1950s (6, 7). Using data from 1949 to 1951, an analysis by Seidman included 918 pancreatic cancer deaths and reported Jewish/non-Jewish RRs of 1.15 among men and 1.34 among women, with the latter estimate statistically significant at the 0.01 level (7). Using data from 1953 to 1958, an analysis by Newill included 4,029 pancreatic cancer deaths (6). In that study, the RR for pancreatic cancer mortality among men was 1.25 when comparing Jews with Catholics and 1.15 when comparing Jews with Protestants. Among women, the corresponding RRs were 1.28 and 1.27, respectively.

It should be noted that both of these New York City analyses had methodologic limitations. First, numerators for rates were obtained by identifying pancreatic cancer deaths from the New York City death record and inferring religion from the religious affiliation of the burial cemetery. An earlier study by Koller and MacMahon estimated that while New York City graves in Jewish cemeteries were nearly exclusively Jewish, approximately 8% of burials in Protestant and nonsectarian cemeteries were Jewish (19). Second, denominators for rates (the Jewish and non-Jewish population at risk) were calculated using a 1952 area probability sample survey of 4,190 households by the Health Insurance Plan of Greater New York to estimate proportions of the Jewish and non-Jewish population (6, 7, 10). The validity of this survey sample is unclear (10). Moreover, neither analysis could adjust for potential confounders such as smoking, obesity, or diabetes, and both adjusted for age by using very broad categories (<15, 15–44, 45–65, and >65 years) potentially resulting in residual confounding by age.

In an analysis of Los Angeles cancer registry data conducted in the 1970s, Mack and colleagues found that pancreatic cancer accounted for a higher proportion of all incident cancers among Jews than among non-Jewish whites (8). However, after adjustment for social class and nativity, the proportional incidence ratios were no longer statistically significant (8), leading the authors to attribute the association with Jewish ethnicity to these factors. A small hospital-based case–control study conducted in the 1970s reported an association between Jewish ethnicity and a higher risk of developing pancreatic cancer among men but not among women (9).

The estimated 43% excess risk of developing pancreatic cancer observed in our study is somewhat larger than that found in previous studies (6–8). This difference could be due, in part, to the inability of previous studies to adjust for confounding factors such as smoking and obesity. In our study, adjustment for these factors produced a slightly larger RR than the age- and sex-adjusted RR. In addition, results from prior studies on pancreatic

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cancer mortality (6, 7) could have been biased because of errors in estimating rates from cemetery of burial and sampled residential data. It should be noted that the excess risk of mortality among Jews compared with whites observed in our study (RR = 1.43) is slightly higher than the excess risk of mortality among African Americans compared with whites (RR = 1.32) observed by the SEER (Surveillance and Epidemiology End Results) cancer registries (20).

Data on the risk of pancreatic cancer among Israeli Jews are available from Israel National Cancer Registry. Age-standardized rates of pancreatic cancer are considerably higher among Israeli Jews than among Israeli Arabs (21). However, the relevance of this finding to U.S. populations is unclear, as there may be marked differences in cancer-related health and lifestyle factors between Jews and Arabs in Israel. Such differences are suggested by the fact that the risk of breast cancer is substantially higher among Israeli Jews than among Israeli Arabs (22), whereas Jewish ethnicity does not seem to be associated with the increased risk of breast cancer in the United States (23).

We observed a statistically significant interaction between Jewish ethnicity and smoking status on a multiplicative scale, although not on an additive scale. RRs for Jewish ethnicity were highest among never smokers and lowest among current smokers. It is unlikely that smoking biologically attenuates the excess risk associated with Jewish ethnicity. A more likely explanation is that because of the substantially higher rates of pancreatic cancer among current smokers, an equal increase in absolute risk due to Jewish ethnicity results in a less pronounced increase in relative risk among current smokers than among former and never smokers. It is also possible that residual confounding by smoking might have contributed to the lower RRs for Jewish ethnicity observed among former and current smokers. This could have occurred if Jewish current smokers were more likely than non-Jewish current smokers to quit smoking during follow-up. This possibility is supported by data from a subset of approximately 184,000 CPS-II participants who completed a second questionnaire in 1992 (24), of whom 30,595 had been smokers in 1982. Among these participants, Jewish smokers in 1982 were slightly more likely to have quit smoking by 1992 than non-Jewish smokers (68.5% vs. 56.6%).

No previous studies have examined whether the risk associated with Jewish ethnicity varied by place of birth and religious practice. Jewish immigrants, the children of Jewish immigrants, and Jews who attend temple more frequently might be expected to differ more from non-Jewish whites than other, potentially more acculturated, Jews with respect to lifestyle or behavioral factors. We, therefore, hypothesized that the association between Jewish ethnicity and pancreatic cancer mortality would be strongest for Jewish immigrants, the children of Jewish immigrants, and Jews who attended temple frequently. However, neither of these hypotheses was supported by the data. The absence of a clear increase in risk among Jews born outside North America may be due to chance ($P_{heterogeneity} = 0.07$) but could also be due, at least in part, to unknown environmental or genetic differences between North American–born and immigrant Jewish populations. Our results provide evidence that if there are unmeasured environmental factors responsible for the elevated risk among Jews, they are unlikely to be positively associated with immigrant status or frequent temple attendance.

The underlying reason for the higher risk of pancreatic cancer mortality among Jews could be genetic, nongenetic, or both. In our study, the risk among Jews was not explained by the measured nongenetic factors, including smoking, obesity, and diabetes. Furthermore, the higher risk among Jews seems unlikely to be explained by any factor positively associated with immigrant status or temple attendance. In the absence of evidence for a nongenetic explanation, the higher risk of pancreatic cancer associated with Jewish ethnicity could conceivably be predominantly due to genetic factors.

Genetic mutations or variants in *BRCA2*, and *BRCA1*, and *ABO* (the gene that determines ABO blood type) may contribute to the higher pancreatic cancer risk among Jews but are unlikely to account for more than a small proportion of the approximately 40% observed higher risk associated with Jewish ethnicity. Deleterious *BRCA2* mutations are estimated to be associated with an RR of approximately 3.5 for pancreatic cancer (25), but the prevalence of the mutation in the Ashkenazi Jewish population is only about 1% (26–28). On the basis of this prevalence and relative risk, the 6174delT *BRCA2* mutation would be expected to account for only an estimated 2.5% increase in risk among Jews. Deleterious *BRCA1* mutations have a pancreatic cancer relative risk of approximately 2.25 (29), and these mutations are present in approximately 1% of the Jewish population (27). Therefore, they would be expected to account for an estimated 1.3% increase in risk among Jews. Finally, compared to blood type O, the non-O blood types (A, B, AB) are estimated to be associated with a relative risk of 1.42 for pancreatic cancer (30). The prevalence of non-O blood types seem to be approximately 65% among U.S. Jews (31) and 55% among U.S. whites (32), which would account for an additional 3% expected increase in pancreatic cancer among Jews. There may be additional as yet unidentified genetic variants that contribute to the higher pancreatic cancer risk observed among U.S. Jews. If any such variants were rare in non-Jewish populations, genetic analyses specifically in Jewish populations would be required to identify them. To the best of our knowledge, there are no published studies examining genetic risk factors for pancreatic cancer specifically among Jews, although a genome-wide association study of breast cancer among Jews has been conducted (33).

A limitation of our study is that DNA from participants was not available and therefore we could not examine whether genetic variants associated with Jewish ethnicity explained the higher pancreatic cancer risk among Jews.

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In addition, we defined Jewish ethnicity on the basis of self-identified Jewish religion. Undoubtedly, some participants of Jewish ancestry did not identify as being of Jewish religion and were misclassified as non-Jewish, potentially resulting in an underestimate of the RR. However, these participants could have constituted only a very small proportion of the nearly 1 million subjects classified as non-Jewish in our analysis and therefore are likely to have had negligible effect on our results. In addition, participants who were converts to Judaism are likely to have been misclassified as being of Jewish ancestry. However, it is estimated that only 3% of the U.S. Jewish population in this time period were converts (34) and therefore converts would have had negligible effect on our results. Another limitation is that we did not have information pertaining to Ashkenazi or non-Ashkenazi Jewish origin. It is likely that our population is predominantly Ashkenazi (11) and therefore the results of this study may not generalize to non-Ashkenazi Jews in the United States.

In summary, results from this large cohort study indicate that risk of pancreatic cancer mortality is likely to be significantly higher among contemporary U.S. Jews than among non-Jewish U.S. whites. This association is not explained by known environmental risk factors, and only a small part can be attributed to mutations in *BRCA2* and *BRCA1*, or the ABO blood type, suggesting that there are unknown environmental or genetic factors associated with Jewish ethnicity that increase risk of developing pancreatic cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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