RESEARCH ARTICLE

Serum Hepatitis a Antibody Positivity Correlates with Higher Pancreas Cancer Mortality in Adults: Implications for Hepatitis Vaccination in High Risk Areas

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Abstract

Background: This study used pre-hepatitis A vaccination era data in U.S. to study the relationship between serum hepatitis A antibody positivity with pancreas cancer mortality in adults. Patients and Methods: Public use National Health and Nutrition Examination Survey (NHANES III) data were employed. NHANES III uses complex probabilistic methods to sample nationally representative samples. Household adult laboratory and mortality data were merged. Sample persons who were available to be examined in the Mobile Examination Center (MEC) were included in this study. All results were obtained by using specialized survey software taking into account the primary sampling unit and stratification variables and the weights assigned to the sample persons examined in the MEC. Thus they are representative of the U.S. population. Results: The mean risk (95%CI) of death in the study population for pancreas cancer was 0.0014 (-0.000069 -.0029); their mean age (95%CI) at the mobile examination center (MXPAXTMR) was 473.43 (463.85-482.10); the follow up in months from their medical examination (permth_exm) was 170.12 (164.17-176.07). The odds ratios (S.E.) of the statistically significant univariables were: age, 1.007 (1.005-1.009); serum anti-hepatitis antibody status, 0.038 (0.004-0.376); and drinking hard liquor, 1.014 (1.004-1.023). The coefficients (S.E.) of the statistically significant variables after multivariate analysis were 0.006 (0.002-0.010) for age and -2.528 (-4.945--0.111) for serum anti-hepatitis A antibody negativity (using serum anti-hepatitis A antibody positivity as a reference). Conclusion: Serum hepatitis A antibody positivity correlates with higher pancreas cancer mortality in adults.

Keywords: NHANES III-serum hepatitis a antibody-pancreas cancer mortality-adults.

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Introduction

This study used pre-hepatitis A vaccination data from National Health and Nutrition Examination Survey (NHANES III) to examine the relationship between serum hepatitis a virus antibody positivity and pancreas cancer mortality in adults. This was a part of a more extensive study to screen the potential predictors of adult cancer mortality using that NHANES III data that were representative of U.S. population. Using NHANES III data, previous studies have found the serum hepatitis A antibody positivity was found to be correlated with racial, demographic and socio-economic factors (McQuillan et al., 2004). Age, ethnicity, poverty status and country of birth were the most important risk factors for serum hepatitis A virus antibodies positivity (Bell et al., 2005). Children with low height to age, belonging to certain ethnic groups, parental education, and with asthma were found to be related with serum positivity for hepatitis A virus using NHNAES III data (Dowd et al., 2009). In United States, hepatitis A virus vaccination was introduced in 1996, this study used the NHNAES III serum hepatitis A antibody positivity data collected before vaccination became available in U.S. The vital status of NHANES III participant was followed passively up to December 31, 2006. The data were contained in NHANES III linked mortality (Menke et al., 2010). This study used the extensive socio-demographic factors available in NHANES III data to adjust for the effects of serum hepatitis A antibody positivity on adult pancreas cancer mortality.

Materials and Methods

NHANES and NHANES III

NHANES is a major program of National Center of Health Statistics (a part of Center of Disease Control (CDC) of United States of America) started in 1971. NHANES III was a national study based on a complex, multi-stage probability sampling design. For details of NHANES III and NHANES III linked mortality data and statistical guidance as well as their analysis examples see NHANES website (http://www.cdc.gov/nchs/nhanes.htm). In brief, NHANES studies were approved by CDC internal institutional review boards. The public use data were made available to the public and researchers. The NHANES sample weights were calculated to represent non-institutionalized general U.S. population to account

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for non-coverage and non-response. Only participants who were interviewed at home and examined in mobile examination centers (MEC) were included in this study. This eliminated the cofounding effects of sample persons being too frail, too young or old to go to the MEC for examinations. In this study, NHANES III (conducted between1988 – 1994) household adult data file was merged with NHANES III laboratory data and the NHANES III linked cancer mortality data.

NHNAES III linked mortality data

Detailed information about the data and analysis guidelines are available at their website (http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes3_linkage.htm). In brief, probability matching was used to link NHANES III with National Death Index for vital status and mortality. NHANES used multiple sources including the use of death certificates and with the National Death Index to ascertain vital status and cause of death. NHANES III codes of death (ucod_113) were used in this study.

Statistical analysis

NHANES III employed a complex sampling strategy and analysis (Ezzati-Rice and Murphy, 1995) (Lemeshow and Cook, 1999) (Chang et al., 2010) (Graubard and Korn, 1999). Matlab programs (posted on Matlab File Exchange) were developed to convert SAS files provided by NAHNES to STATA programs to download NHANES III data files for further analysis. Specialized survey software is needed for NHANES complex data analysis (Cohen, 1997). STATA 12 (College Station, TX) was among those recommended by CDC to analyze the complex NHANES data and was used in this study. The sampling weight used was WTPFEX6 because only the sample persons had examinations in the MEC were included in this study, SDPPSU6 was used for the probability sampling unit (PSU) and SDPSTRA6 was used to designate the strata for the STATA survey commands. STATA scripts were written for this analysis, and will be submitted for publication separately. Univariate and multivariate logistic regressions (Jewell, 2004) were used to study the relationship between predictors and pancreas cancer mortality (using ucod_113 codes) in adults. The symbols used were as follows: pancreasCancer (death from pancreas cancer): 0=alive, 1=dead from pancreas cancer, BMI (body mass index), MXPAXTMR (age at the MEC final examination), HSSEX (sex, _IHSSEX2=female, using male as the reference group), AHP (serum hepatitis A virus antibody status, _IAHP_2=negative, _IAHP_3=borderline status), DMPMETRO (urban rural residence status, _IDMPMETRO_2=rural residence, urban residence used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2=non-Hispanic black, _IDMARETHN_3=Mexican-American, _IDMARETHN_4=others, non-Hispanic white was used as the reference group), HAN6JS (alcohol consumption), and HAR4S (smoking), HFA6XCR (country of birth, _IHFA6XCR_2=born in Mexico, born in 50 states USA was used as reference and _IHFA6XCR_3=born in other countries), HFA8R (highest grade or year completed), newDMPPIR (poverty index ratio status, _InewDMPPIR_2=family income lower than the poverty level, family income higher than the poverty level was used as a reference). N=3373 samples were analyzed. Linearized Taylor Standard Error estimation was used.

For STATA analyses, only the patients without missing values for all of WTPFEX6, SDPPSU6, SDPSTRA6, BMI, MXPAXTMR, HSSEX, DMPMETRO, HAM5S, HAM6S, DMARETHN, DMPPIR, HAR4S, and HAN6JS, , MORTSTAT, AHP, HFA6XCR, HFA8R, newDMPPIR were included in this study. Further, these additional NHANES III codes considered not eligible: HAM6S (888), HAM6S (999), DMPPIR (888888), the numerator of DMPPIR was the midpoint of the observed family income category in the Family Questionnaire variable:HFF19R, and the denominator was the poverty threshold, the age of the family reference person, and the calender year in which the family was interviewed, HAR4S (666), HAR4S (777), HAR4S (888), HAR4S (999), HAN6JS (888), HAN6JS (999), not in BMI>15 and BMI<50, AHP(8), HAM5S (888), HAM5S(999), HAM6S(888), HAM6S(999), DMPPIR(888888), HFA6XCR(8), HFA6XCR(9), HFA8R(88), HFA8R(99), youth sample persons and incomplete mortality data. A total of 3373 sample persons were eligible for this study. 2599 participants with complete information in all subpopulations were used in univariate and multivariate analysis.

Results

The mean risk (95%CI) of death in this study population for pancreas cancer was 0.0014 (-0.000069-0.0029) (Table

Table 1. Socio-demographic Factors of the Survey Participants

	Mean	Std. Err. Linearized	[95% Conf. Interval]	
pancreasCancer	0.0014385	0.0007501	-0.000068800	0.0029458
BMI	25.2292500	0.1451290	24.937600000	25.5209000
MXPAXTMR	473.4265000	4.7636550	463.853600000	482.9994000
HSSEX	1.4531050	0.0083385	1.436348000	1.4698620
AHP	1.6865990	0.0112467	1.663997000	1.7092000
DMPMETRO	1.5700510	0.0520759	1.465401000	1.6747020
DMARETHN	1.3536070	0.0328268	1.287639000	1.4195740
HAN6JS	2.7898260	0.2798906	2.227365000	3.3522870
HAR4S	19.8364400	0.4403406	18.951550000	20.7213400
permth_exm	170.1169000	2.9614320	164.165700000	176.0681000
HFA6XCR	1.1377900	0.0202389	1.097118000	1.1784610
HFA8R	11.8307600	0.0911532	11.647580000	12.0139400
newDMPPIR	1.1719940	0.0116172	1.148649000	1.1953400

*The symbols are as follows: pancreasCancer: 0=alive, 1=dead from pancreas cancer, BMI (body mass index), MXPAXTMR (age at the MEC final examination), HSSEX (_IHSSEX2=female, using male as the reference group), AHP (serum hepatitis A antibody status, _IAHP_2=negative, borderline status was omitted because of no subpopulation members), DMPMETRO (urban rural residence status, _IDMPMETRO_2=rural residence, urban residence used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2=non-Hispanic black, Mexican race was omitted because of no subpopulation members, other races category was omitted because of no subpopulation members, non-Hispanic white was used as the reference group), HAN6JS (alcohol consumption), and HAR4S (smoking), IHFA6XCR (country of birth, born in Mexico was omitted because of no subpopulation samples, born in 50 states USA was used as reference and _IHFA6XCR_3=born in other countries), HFA8R (highest grade or year completed), newDMPPIR (poverty index ratio status, _InewDMPPIR_2=family income lower than the poverty level, family income higher than the poverty level was used as a reference). N=3373 samples, 2599 samples with complete data were analyzed. Linearized Taylor Standard Error estimation was used

Table 2. Univariate Analysis of Variables Predicting Pancreas Cancer Mortality in Adults

Cancer	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Int]
BMI	1.077	0.092	0.87	0.388	0.907	1.279
MXPAXTMR	1.007	0.001	6.64	0.000	1.005	1.009
HSSEX	0.475	0.411	-0.86	0.394	0.084	2.702
AHP	0.038	0.043	-2.87	0.006	0.004	0.376
DMPMETRO	0.194	0.175	-1.81	0.076	0.031	1.193
DMARETHN	0.930	0.327	-0.21	0.837	0.459	1.884
HAN6JS	1.014	0.005	2.98	0.004	1.004	1.023
HAR4S	0.947	0.060	-0.86	0.392	0.833	1.075
HFA6XCR	1.402	0.837	0.57	0.574	0.422	4.655
HFA8R	1.048	0.105	0.46	0.644	0.857	1.281
newDMPPIR	0.396	0.366	-1.00	0.321	0.062	2.534

*The symbols are as follows: pancreasCancer: 0=alive, 1=dead from pancreas cancer, BMI (body mass index), MXPAXTMR (age at the MEC final examination), HSSEX (_IHSSEX2=female, using male as the reference group), AHP (serum hepatitis A antibody status, _IAHP_2=negative, borderline status was omitted because of no subpopulation members), DMPMETRO (urban rural residence status, _IDMPMETRO_2=rural residence, urban residence used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2=non-Hispanic black, Mexican race was omitted because of no subpopulation members, other races category was omitted because of no subpopulation members, non-Hispanic white was used as the reference group), HAN6JS (alcohol consumption), and HAR4S (smoking), IHFA6XCR (country of birth, born in Mexico was omitted because of no subpopulation samples, born in 50 states USA was used as reference and _IHFA6XCR_3=born in other countries), HFA8R (highest grade or year completed), newDMPPIR (poverty index ratio status, _InewDMPPIR_2=family income lower than the poverty level, family income higher than the poverty level was used as a reference). N=3373 samples, 2599 samples with complete data were analyzed. Linearized Taylor Standard Error estimation was used

Table 3. Multivariate Analysis of Variables Predicting Pancreas Cancer Mortality in Adults

Cancer	Linearized Coef.	Std. Err.	t	P>|t|	[95% Conf.	Int]
BMI	0.089	0.094	0.95	0.347	-0.099	0.277
MXPAXTMR	0.006	0.002	2.94	0.005	0.002	0.010
_IHSSEX_2	-0.716	0.823	-0.87	0.389	-2.371	0.939
_IAHP_2	-2.528	1.202	-2.10	0.041	-4.945	-0.111
_IDMPMETRO_2	-1.490	1.010	-1.48	0.147	-3.520	0.540
_IDMARETHN_2	0.669	1.511	0.44	0.660	-2.370	3.707
HAN6JS	0.012	0.010	1.22	0.229	-0.008	0.033
HAR4S	-0.048	0.070	-0.69	0.493	-0.189	0.092
_IHFA6XCR_3	0.756	1.427	0.53	0.599	-2.113	3.624
HFA8R	0.080	0.102	0.78	0.438	-0.125	0.284
_InewDMPPIR_2	-1.106	1.166	-0.95	0.347	-3.451	1.238
_cons	-10.932	3.372	-3.24	0.002	-17.712	-4.153

*The symbols are as follows: pancreas cancer: 0=alive, 1=dead from pancreas cancer, BMI (body mass index), MXPAXTMR (age at the MEC final examination), HSSEX (_IHSSEX2=female, using male as the reference group), AHP (serum hepatitis A antibody status, _IAHP_2=negative, borderline status was omitted because of no subpopulation members), DMPMETRO (urban rural residence status, _IDMPMETRO_2=rural residence, urban residence used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2=non-Hispanic black, Mexican race was omitted because of no subpopulation members, other races category was omitted because of no subpopulation members, non-Hispanic white was used as the reference group), HAN6JS (alcohol consumption), and HAR4S (smoking), IHFA6XCR (country of birth, born in Mexico was omitted because of no subpopulation samples, born in 50 states USA was used as reference and _IHFA6XCR_3=born in other countries), HFA8R (highest grade or year completed), newDMPPIR (poverty index ratio status, _InewDMPPIR_2=family income lower than the poverty level, family income higher than the poverty level was used as a reference). N=3373 samples, 2599 samples with complete data were analyzed. Linearized Taylor Standard Error estimation was used

1), the means (95%CI) of the other demographic variables were: body mass index (BMI), 25.22 (24.94-25.52); age at the mobile examination center (MXPAXTMR), 473.43 months (463.85-482.10); and follow up in months from the medical examination (permth_exm) was 170.12 (164.17-176.07).

Table 2 shows the univariate analysis of the covariates of pancreatic cancer death. The odds ratios (S.E.) of the statistically significant variables were: age, 1.007 (1.005-1.009); serum anti-hepatitis antibody status, 0.038 (0.004-0.376); and drinking hard liquor, 1.014 (1.004-1.023).

Table 3 shows the multivariate analysis of the covariates of pancreatic cancer death. The coefficients (S.E.) of the statistically significant variables were age 0.006 (0.002-0.010) and serum anti-hepatitis A antibody negativity (_IAHP_2) relative to positivity -2.528 (-4.945--0.111) with an odds ratio of 0.080 (0.0071 - 0.895).

Discussion

This study used pre-hepatitis A vaccination era data in U.S. to study the relationship between serum hepatitis A positivity with pancreas cancer mortality in adults. NHANES III data (1988 – 1994) was linked to the NHNAES III linked mortality data that have mortality data available up to December 31, 2006. Age, ethnicity, poverty and country of birth were found to be important risk factors for serum hepatitis A serum positivity (Bell et al., 2005). 1n 1995, hepatitis A vaccines were licensed in U.S., shortly after Advisory Committee on Immunization Practices (ACID) recommended vaccinations for children older than 2 years old (Klevens et al., 2011) for the high risk groups. By 1999, the vaccines were introduced to 11 Western states in U.S. with high hepatitis A virus infection rate. By 2003, the infection rate was decreased by 76% (Klevens et al., 2011). In 2006, the vaccination was recommended for all 12-23 month old children (Velasco-Mondragon et al., 2012). Additional at risk people were also recommended to be vaccinated. For example, adults with chronic liver diseases and diabetes were recommended to receive hepatitis A vaccination (Younossi and Stepanova, 2011). There was a small percentage of sample participants reported a history of vaccination for CDC designated high risk persons (Bell et al., 2005). Given that these pre-dated US approval of hepatitis vaccination, and no data available on which other NHANES III survey participants received hepatitis vaccination, the results of this study did not take these potential cofounders for hepatitis A antibody positivity into account. Hepatitis A viral infection has been associated with decreased psychomotor speed of community dwelling elders (Hsieh et al., 2009). Hepatitis A infection was related to central obesity in females (Schooling et al., 2011). However, hepatitis A is not known to be correlated with pancreas cancer mortality. Thus, NHANES III data provided a valuable source of information to correlate hepatitis A serum positivity with pancreas cancer adult mortality.

All of the results were obtained by using specialized survey software taking into account the primary sampling unit and stratification variables and the weights assigned to the sample persons examined in the MEC. Thus these results are representative of the US population. The mean risk of death in the study population for pancreas cancer was 0 .0014 (Table 1), the mean age was 473.43 and a 170.12 months of follow up from their medical examination.

The odds ratios (S.E.) of the statistically significant

univariables were (Table 2): age, 1.007 (1.005-1.009); serum anti-hepatitis antibody status, 0.038 (0.004-0.376); and drinking hard liquor, 1.014 (1.004-1.023). Alcohol consumption has been associated with increased pancreas cancer mortality (Gapstur et al., 2011) and this was confirmed here. This study found the relationship between poverty and pancreas cancer death was more complex.

Many studies have found a poverty level to be related to serum hepatitis A antibody positivity (Bell et al., 2005) (Verma and Khanna, 2012). Other studies have not found statistically significant association between hepatitis A serum antibody positivity and poverty level (Klevens et al., 2011). The association between hepatitis A serum positivity and poverty has been found to be U-shaped. This U-shape was still evident even after adjusting for factors that predispose participants to hepatitis A infections (Velasco-Mondragon et al., 2012). This study found no statistically significant association between hepatitis A serum antibody positivity and pancreas cancer death in adults. Different from previous studies using serum hepatitis A antibody positivity as an end point, this study used pancreas cancer mortality as an end point. However, the relationship between poverty level and pancreas cancer death needs be further studied. All of the univariables were used in the final multivariate analysis so as not to miss potentially important predictors.

The coefficients (S.E.) of the statistically significant variables after multivariate analysis were age 0.006 (0.002-0 .010) and serum anti-hepatitis A antibody negativity -2.528 (-4.945--0.111) (Table 3). This study found a statistically significant protective effect of serum anti-hepatitis A antibody negativity for pancreas cancer death. In other words, this study found a statistically significant association between serum anti-hepatitis A antibody positivity and pancreas cancer death. There is a high prevalence of antibody positivity of hepatitis A in developing countries (Halicioglu et al., 2012). The data here suggest that hepatitis A vaccination may decrease pancreas cancer mortality rate in addition to preventing hepatitis A infections.

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