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The association of family history of liver cancer with hepatocellular carcinoma: A case-control study in the United States^{*}

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Abstract

Background/Aims—The study aimed at addressing the connection between positive family history of liver cancer and hepatocellular carcinoma (HCC) development in the USA.

Methods—At The University of Texas M.D. Anderson Cancer Center, 347 patients with pathologically confirmed HCC and 1075 healthy controls were studied. All subjects were interviewed for their family history of cancer, including the number of relatives with cancer, the type of cancer, the individual's relationship with the relative, and the age at which the relative was diagnosed.

Results—Independently of hepatitis B virus (HBV) and hepatitis C virus (HCV), a history of liver cancer in first degree relatives was significantly associated with HCC development (AOR = 4.1 [95% CI, 1.3–12.9]). Multiple relatives with liver cancer were only observed among HCC patients with chronic HBV/ HCV infection. Affected siblings with liver cancer is significantly associated with HCC development with and without HBV/HCV infection; (AOR = 5.7 [95% CI, 1.2–27.3]) and (AOR = 4.3 [95% CI, 1.01–20.9]), respectively. Individuals with HBV/HCV and a family history of liver cancer were at higher risk for HCC (AOR = 61.9 [95% CI, 6.6–579.7]).

Conclusions—First degree family history of liver cancer is associated with HCC development in the USA. Further research exploring the genetic-environment interactions associated with risk of HCC is warranted.

Keywords

Family history; Liver cancer; Diabetes mellitus; Alcohol consumption; Cigarette smoking

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1. Background

Liver cancer is the sixth most common cancer and the third most common cause of cancer-related deaths worldwide [1]. Hepatocellular carcinoma (HCC), which comprises most primary liver cancer cases, is rarely detected early and is usually fatal within a few months of diagnosis [2]. HCC has a high incidence rate in sub-Saharan Africa and Southeast Asia, but a low incidence rate in the United States and Europe, with an age-standardized incidence rate of 5.3/100,000 in men and 1.9/100,000 in women in the United States [1].

Chronic infection with the hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most well-established environmental risk factors for HCC worldwide [3,4]. However, it has been estimated that 30–45% of HCC patients in the United States are related to HBV or HCV infection [5,6]. Other risk factors that have been associated with HCC development in the United States include diabetes mellitus, alcohol consumption, and cigarette smoking [7].

Familial aggregation of liver cancer has been reported. However, most of these studies were conducted among Asians, particularly in China [8–12]. Given the high prevalence of chronic infection with HBV and that vertical transmission of HBV is the major source for viral transmission among Asians, the reported association between a family history of liver cancer and HCC could be explained by clustering of HBV infection among members of the same family [13]. On the other hand, a family history of HCC in European populations is likely to be independent of chronic infection with HBV [14].

To our knowledge, it has yet to be determined if there is a correlation between a family history of HCC when the HCV/HBV infection is not present and the development of HCC in the United States. Therefore, in an ongoing case-control study we evaluated the effect of a family history of cancer in general and liver cancer in particular among patients with HCC who tested negative for HBV and HCV. After taking into consideration the possible confounding effects of HCC risk factors, we assessed for potential synergism between a positive family history of liver cancer and chronic HBV/HCV infection on the development of HCC.

2. Methods

2.1. Study design

The study design was a hospital-based case-control in which cases and controls were prospectively evaluated. The study was approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center. Written informed consent for an interview and for a biologic sample was obtained from each study participant.

2.2. Study population

A description of cases and controls was recently reported [15]. Briefly, case patients were prospectively recruited from gastrointestinal (GI) medical or surgical oncology outpatient clinics at M.D. Anderson Cancer Center. The inclusion criteria were as follows: pathologically confirmed diagnosis of HCC; U.S. residency; and ability to communicate in English. The exclusion criteria were presence of other types of primary liver cancer, such as cholangiocarcinoma and fibrolamellar hepatocellular carcinoma; concurrent or past history of cancer at another organ site. From January 2000 to February 2008, we enrolled 347 eligible patients with HCC and 1075 controls.

The control subjects were healthy individuals and genetically unrelated family members (spouses and in-laws) of patients at our institution who had cancers other than liver, GI, lung, or head and neck cancers (smoking-related cancers). The reason for excluding family members and spouses of patients with liver cancer, as controls, is to avoid induction of selection bias.

While first degree family members may share the same genetic factors related to HCC, spouses may share similar lifestyle factors as the cancer patients, especially regarding factors that are highly associated with HCC, like HCV, HBV, cigarette smoking, and alcohol consumption. This may preclude us from determining the true relationship between HCC development and family history of liver cancer or some environmental risk factors. The inclusion criteria for controls were the same as those for patients, except for cancer diagnosis. Control subjects were recruited from M.D. Anderson central diagnostic radiology clinics, where cancer patients are sent for initial cancer diagnosis or post treatment follow-up examination. Eighty-four percent of the individuals who were accompanying cancer patients and who fulfilled the inclusion criteria for controls selection agreed to participate in the study. There were no significant differences in age, sex, race/ethnicity, educational level, or accompanied patient's type of cancer between those who agreed and those who refused to participate in this research. All control subjects reported that the underlying reason for their companionship with the cancer patients is care and altruism and they stated that they would select the same hospital if they had been diagnosed with cancer.

2.3. Participants' ascertainment

HCC patients and control subjects were simultaneously assessed and personally interviewed by well-trained interviewers. No proxy interviews were conducted. The interviewers used a structured and a validated questionnaire [16,17] to collect information on demographic features, family history of cancer, and risk factors of HCC (25–30 min interview). Cases and controls were blinded for the current study hypothesis.

We interviewed patients and controls for family history of cancer among first degree relatives (parents, siblings, and offspring), their age at the time of the study or at death, number of siblings (sisters and brothers) and offspring (daughters and sons), and history of cancer (yes or no). If a member had a positive history of cancer, we collected information about type of cancer, age at cancer diagnosis, and age at the time of death, if appropriate. The association between family history of cancer and HCC was adjusted for the confounding effects of other HCC risk factors including smoking, alcohol consumption, and diabetes which were previously described in a separate report [15].

2.4. Hepatitis virus testing

Blood samples were collected from patients and controls. At the M.D. Anderson GI laboratory facility, plasma samples were separated and tested for the presence of HCV antibodies (anti-HCV) using a third-generation enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, IL). The samples were also tested for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) using the enzyme-linked immunosorbent assay (ELISA). The laboratory researcher running these assays was blinded for the disease status (cases or controls) of the subjects' blood samples. Positive results prompted a repeated confirmatory ELISA testing at GI laboratory facility at M.D. Anderson. A second confirmatory ELISA test of the positive samples was performed at outside laboratories (University of Texas School of Public Health, Houston, Texas and at Quest diagnostic Laboratories).

2.5. Statistical analysis

We used Stata software version 9 (College Station, TX) for all statistical analyses. We performed multivariable unconditional logistic regression analyses to estimate the adjusted odds ratio (AOR) and 95% confidence interval (CI) for each risk factor using maximum likelihood estimation. All AORs (95% CIs) were adjusted for age, sex, race, education level, cigarette smoking, alcohol consumption, diabetes mellitus, family history of cancer, and HBV/HCV infection. The final model was chosen on the basis of biological plausibility and the

lowest -2 log likelihood function. We stratified patients and controls by HBV/HCV status to estimate the familial risk of HCC among subjects without evidence of chronic HBV/HCV infection. For less frequently reported variables (in ≤ 5 subjects), we performed multiple logistic regression analyses using LogXact for Windows (Cytel Software Corp., Cambridge, MA) for a precise estimation of the exact AORs.

3. Results

3.1. Participants' characteristics

Table 1 summarizes the demographic features of HCC patients and controls with and without HBV/HCV. There were 347 patients with HCC and 1075 healthy control subjects, with a patient: controls ratio of 1:3. A total of 157 (45.2%) HCC patients and 36 (3.3%) controls were positive for HCV and/or HBV markers. Most study subjects were non-Hispanic white males (HCC cases, 166 (47.8%); controls, 539 (50.1%). The mean age $\pm$ standard error (SE) was 61.8 ± 0.7 years for all HCC patients and 63.8 ± 0.9 for HCC patients without HBV/HCV. Patients were slightly older than controls, with a mean difference in age $\pm$ SE of 2.3 ± 0.7 years for the entire study population and 4.3 ± 0.9 years for those without HBV/HCV. There was no statistical difference in age between men with HCC (61.9 ± 0.8 years) and women with HCC (61.6 ± 1.3 years). Patients also had a lower educational level than controls ($P = 0.001$). Both patients and controls had similar USA geographic referral patterns.

3.2. Environmental risk factors

The results summarized in Table 2 show that HBV/HCV, cigarette smoking, heavy alcohol consumption, and diabetes mellitus were significantly related to HCC development. The association between cigarette smoking, alcohol consumption, and history of diabetes mellitus did not meaningfully change among subjects without evidence of hepatitis virus infection.

3.3. Family history of any cancer

Table 3 shows that the AOR of developing HCC given a positive family history of any cancer was 1.4 (95% CI, 1.1–1.6) for all subjects and 1.3 (95% CI, 0.9–1.9) for those without chronic HBV/HCV infection. Such null association among virus-negative subjects did not change when we looked at the number of affected family members (multiple members versus one member) and the type of relationship (parents, siblings, or off-spring) (Table 3). A history of other cancers at selected sites in first degree relatives (lung, prostate, kidney, colon, breast, uterine, ovarian, esophageal, stomach, pancreas, and melanoma cancers) was not associated with HCC development in the presence or absence of HBV/HCV infection.

3.4. Family history of liver cancer

Total of 21 HCC cases and 9 controls reported a positive family history of primary liver cancer among their parents, siblings, and/or offspring. Only primary liver cancer was considered in analyses. Liver cancer in conjunction with another cancer was considered as liver metastasis, and affected family members were excluded from analyses (HCC cases, $n = 2$; controls, $n = 5$). Of note, none of the patients with HCC were related to each other. After adjusting for possible confounding risk factors, such as age, sex, race, education level, cigarette smoking, diabetes mellitus, heavy alcohol consumption, and HBV/HCV infection, the estimated AOR was 3.9 (95% CI, 1.4–11.5) for all subjects and 4.1 (95% CI, 1.3–12.9) for those without HBV/HCV (Table 3). The association between family history of liver cancer and HCC development was significantly different for men (AOR = 9.2 [95% CI, 1.9–45.3]) and women (AOR = 1.6 [95% CI, 0.3–8.7]). Even among subjects without HBV/HCV the estimated AORs were 7.1 (95% CI, 1.4–26.2) and 1.9 (95% CI, 0.3–13.1) for men and women, respectively. No control subjects reported multiple family members with liver cancer. However, the estimated AOR for

those with a single family member with liver cancer; was 3.7 for all subjects and 4.1 for HBV/HCV negative population (Table 3). A history of liver cancer among parents (AOR = 3.8), $P = 0.09$ and siblings (AOR = 4.3), $P = 0.04$ was associated with HCC development in absence of HBV/HCV and after controlling for the confounding effect of other risk factors (Table 3).

3.5. Age at liver cancer diagnosis

The mean age of the patients' first degree relatives with liver cancer (64.8 ± 3.6 years) was not significantly different from the mean age of the controls' first degree relatives with liver cancer (71.3 ± 5.7 years) ($P = 0.3$). We did not find a significant difference between the mean age at HCC diagnosis in patients with relatives who had liver cancer ($n = 21$; 64.1 ± 2.7 years) and those who did not ($n = 156$; 59.9 ± 1.1 years) ($P = 0.1$).

3.6. Risk modification by environmental risk factors

HCC patients who had first degree relatives with liver cancer ($n = 21$) were classified into two groups: group 1 ($n = 13$) had prior hepatitis virus infection (HCV, $n = 7$; HBsAg, $n = 6$; anti-HBc, $n = 9$), and group 2 ($n = 8$) had no evidence of prior infection with HBV or HCV. Patients in group 1 developed HCC at an earlier age (58.7 ± 3.5 years) than those in group 2 (72.8 ± 1.4 years; $P = 0.006$). Patients' sex and race did not significantly vary between both groups ($P = 0.6$ and $P = 0.7$, respectively). We observed a significantly higher risk of developing HCC for subjects who had a history of HBV/HCV infection and a positive family history of liver cancer (AOR = 61.9 [95% CI, 6.6–579.7]) than for those with HBV/HCV infection alone (AOR = 24.9 [95% CI, 12.3–50.5]) or with a positive family history of liver cancer alone (AOR = 4.7 [95% CI, 1.6–14.1]).

4. Discussion

In this large case-control study, we evaluated whether the risk of HCC is related to a family history of liver cancer in the United States. We observed that 6.1% of the 347 patients with HCC reported having first degree family members with liver cancer compared with 0.8% of the 1075 healthy controls, yielding an approximately 4-fold increase in HCC risk. The significant association between positive family history of liver cancer and HCC development was observed in absence of HBV/HCV infection and after adjusting for the confounding effects of demographic and environmental risk factors.

Our results are similar to those from previous epidemiologic studies among Asian and European populations with HCC [12,14]. In a case-control study in Italy [14], 37 of 284 HCC patients and 28 of 464 controls reported having first degree relatives with liver cancer, yielding a 2-fold increase in HCC development independently of chronic hepatitis virus infection. In China, Yu et al. [12] studied 553 patients with HCC and 4684 controls and reported an OR of 2.4 (95% CI, 1.5–3.9) for HCC development in subjects with HBV and a family history of HCC as compared to subjects with HBV but no family history of HCC. A later study by the same investigators showed that familial segregation of HCC in HBsAg carriers is associated with familial clustering of liver cirrhosis [18]. A segregation analysis of Chinese HCC patients suggested that a Mendelian autosomal recessive major gene might also play role in HCC etiology [9].

We also observed a relationship between subjects' family history of liver cancer and chronic HBV/HCV infection, which were independent of each other's effects, implying that individuals with these dual risk factors are at the highest risk of developing HCC, especially at a young age. This synergism between HBV/HCV and a family history of liver cancer was also noted by Donato et al. [14], who reported ORs of 67.8 and 70.1 among Italian individuals with family histories of liver cancer who had HCV and HBV infections, respectively.

The observed significant association of positive family history of liver cancer and HCC among men is not surprising since HCC is predominant in males in all human populations; the male-to-female ratio varies from a low of 2 to 1 in low-risk populations (such as US whites) to a high of 5–6 to 1 in high-risk populations (such as the southern Chinese) [19]. It is unlikely that sex hormones play a role, since both androgens and estrogens can affect the replication rate of hepatocytes and promote the growth of liver tumors [20]. There could be a gene-environment interaction given that some environmental risk factors, such as cigarette smoking, occur more frequently in men. In fact Evans et al. [21] reported a significant relationship between HCC-associated mortality and a family history of HCC in men, with an estimated relative risk of 2.3 (95% CI, 1.9–2.7). A 10-year follow-up study of 145 men with chronic HBV infection reported a 6-fold increase in HCC risk for men with a family history of HCC [11].

The observed risk of HCC for subjects with siblings with liver cancer in this and other studies suggests that a recessive model of inheritance may play a role in familial HCC [9]. However, the lack of significant association between HCC and affected parents or offspring in the current study can be related to the small numbers of the exposed cases and controls. Thus, potential association between affected parents and offspring with liver cancer and HCC development can not be entirely excluded and might be further evaluated in a multi-center study to ensure larger sample size of such rare cancer.

Despite the observed familial tendency for HCC development, we found no association between a family history of cancer at specific sites other than the liver and risk of HCC development. HCC has rarely been reported to occur in association with a definite clinical syndrome. For instance, classic HCC and fibrolamellar hepatocellular carcinoma were observed in association with Gardner syndrome, a variant of familial adenomatous polyposis syndrome [22], and familial polyposis coli was associated with childhood hepatoblastoma [23–25]. We found no association between familial HCC development and a family history of colon cancer.

The current hospital-based study has some limitations due to the source of HCC patients. However, because of the high fatality of HCC, a hospital-based design is more appropriate to catch newly diagnosed patients with pathologically confirmed HCC. Moreover, we believe that the control group was appropriate and representative of the study base from which HCC patients were assessed. Moreover, cases and controls have similar geographic distribution (US state of residency). Another limitation was that family history of liver cancer was self-reported by patients and controls during personal interviews. Thus, both cases and controls are equally vulnerable for exposure misclassification (non-differential misclassification of family history of liver cancer) which implicates bias toward the null and underestimation of the true association [26,27] and which may not explain the risk elevation we observed in subjects with a family history of liver cancer. Meanwhile, we restricted our analysis to first degree relatives; other studies have shown that patient-reported family histories for first degree relatives are accurate and valuable for other cancers such as breast and colon cancer [28,29]. Chang et al. [30] reported that patients and control subjects demonstrated similar reliability of self-reported family histories of cancers affecting most individual anatomic sites, with no significant differences between cancer patients and controls. Similar studies have reported that 88% of subjects were able to correctly identify primary sites of cancer among their first degree relatives [17]. Moreover, cases and controls were personally interviewed, using a structured-validated questionnaire, where the questions of family history of cancers were part of a long list of questions and study subjects were blinded for the study hypothesis and its specific aims. We found that the proportions and rankings of cancers among first degree relatives were similar in patients and controls. For example, breast, colon, lung, and prostate cancer were the most common types of cancer reported by patients and controls. HCC patients reported breast, colon, lung, and prostate cancer in 24.1%, 16.2%, 15.7%, and 13.6%, respectively, of their first degree

family members; controls reported breast, colon, lung, and prostate cancer in 21.6%, 16%, 15.7%, and 11.2%, respectively, of their first degree relatives.

It is possible that the significant association between family history of liver cancer and HCC development is a function of some environmental or medical risk factors, such as diabetes mellitus and heavy alcohol consumption that tend to be clustered among first degree relatives. However, we found no significant difference in the proportions of diabetes mellitus and heavy alcohol consumption in HCC patients with a family history of liver cancer as compared to those with no family history of liver cancer.

Although the observed association between positive family history of liver cancer and HCC development was independent of HBV or HCV, we cannot exclude the possibility of hereditary diseases that are related to HCC development, such as hemochromatosis [31] and α -antitrypsin deficiency [32]. Nevertheless, we found no evidence in the patients' medical records indicating the presence of these genetic disorders in patients with a positive family history of liver cancer.

In conclusion, our results indicated that family history of liver cancer among first degree relatives augments the risk of HCC development. This implicates that genetic factors or a shared environment may increase the familial tendency to HCC. To better assess HCC susceptibility in a population where hepatitis virus infection is not prevalent, future studies exploring new environmental risk factors such as metabolic disorders, occupational, and dietary exposures with the potential for genetic and environmental interactions are warranted.

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Abbreviations

AOR	adjusted odds ratios
CI	confidence intervals
ELISA	enzyme-linked immunosorbent assay
FDR	first degree relatives

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Table 1

Characteristics of study participants.

Characteristic	Total	P value	
		HCC N = 347 (%)	Controls N = 1075 (%)
Sex			
Male	245 (70.6)		615 (57.2)
Female	102 (29.4)		460 (42.8)
Age (years)			
<40	15 (4.3)		47 (4.4)
41–50	44 (12.7)		174 (16.2)
51–60	101 (29.1)		332 (30.9)
61–70	96 (27.7)		347 (32.3)
>70	91 (26.2)		175 (16.3)
Race/ethnicity			
White	238 (68.6)		948 (88.2)
African-American	33 (9.5)		38 (3.5)
Hispanic	50 (14.4)		82 (7.6)
Asian	26 (7.5)		7 (0.7)
Education level			
≤High school	166 (47.8)		307 (28.6)
Some college	75 (21.6)		285 (26.5)
≥College degree	106 (30.5)		483 (44.9)
State of residency			
Texas or surrounding states ^a	257 (74.1)		791 (73.6)
Other states	90 (25.9)		284 (26.4)

^a Louisiana, Arkansas, Oklahoma, New Mexico.

Table 2
Environmental risk factors of HCC.

Factor	Total		Absence of hepatitis virus	
	Cases/controls 347/1075	AOR (95% CI) ^a	Cases/controls 190/1039	AOR (95% CI) ^b
<i>Cigarette smoking^c</i>				
No	111/566	1	72/545	1
Yes	236/509	1.7 (1.2–2.4)	118/494	1.5 (1.1–2.1)
≤20 pack-year	97/250	1.5 (0.9–2.2)	44/244	1.2 (0.8–1.8)
>20 pack-year	137/259	2 (1.4–2.9)	72/250	1.8 (1.2–2.7)
<i>Alcohol consumption^d</i>				
Never	119/475	1	74/457	1
Mild/moderate drinking	153/533	1.1 (0.8–1.6)	81/521	1.1 (0.7–1.6)
Heavy drinking ^d	73/64	3.1 (1.8–5.2)	34/59	3.5 (2–6.3)
<i>Diabetes mellitus^e</i>				
No	227/963	1	111/932	1
Yes	120/112	4.4 (3–6.3)	79/107	4.9 (3.3–7.1)
≤1 years	15/29	3.1 (1.5–6.4)	12/29	3.2 (1.5–6.7)
>1 years	103/83	4.6 (3.1–6.8)	65/78	5.2 (3.5–7.9)
<i>Hepatitis virus status</i>				
No virus infection	190/1039	1		
Anti-HCV+	79/6	79.2 (30.6–204.8)		
HBsAg+/anti-HBc+	27/3	75.9 (20.5–281.1)		
HBsAg–/anti-HBc+	18/24	4.1 (2–8.2)		
Both HBV&HCV	33/3	49.5 (14.3–171.5)		

^a Logistic model included subjects' age, sex, race, educational level, cigarette smoking, alcohol consumption, diabetes mellitus, family history of cancer, anti-HCV, HBsAg, and anti-HBc.

^b Logistic model included subjects' age, sex, race, educational level, cigarette smoking, alcohol consumption, diabetes mellitus, and family history of cancer.

^c Ever smokers were defined as subjects who had smoked ≥100 cigarettes during their lifetime; duration of smoking was missing from 2 HCC patients.

^d Ever-alcohol drinkers were defined as subjects who had consumed at least four alcoholic drinks of beer, wine, or hard liquor each month for 6 months in their lifetime. Heavy drinking = ≥60 mL ethanol/day; duration of drinking was missing from two HCC patients and three controls.

^e Duration of diabetes mellitus was missing from two HCC patients.

Table 3
First degree family history of cancer and liver cancer and risk for HCC development.

Factor	Total		Absence of hepatitis virus	
	Cases/controls 347/1075	AOR (95% CI) ^a	Cases/controls 190/1039	AOR (95% CI) ^b
<i>First degree history of any cancer</i>				
No	156/488	1	79/475	1
Yes	191/587	1.4 (1.1–1.6)	111/564	1.3 (0.9–1.9)
<i>Number of FDR^c with any cancer</i>				
Single member	126/381	1.4 (0.9–1.9)	78/368	1.6 (1.1–2.3)
Multiple members	65/206	0.9 (0.6–1.4)	33/196	0.9 (0.6–1.5)
<i>Type of relationship</i>				
Parents	133/443	1.1 (0.8–1.6)	77/427	1.2 (0.9–1.8)
Fathers	78/267	1.2 (0.8–1.8)	44/257	1.3 (0.8–2)
Mothers	71/261	1 (0.6–1.4)	42/251	1.1 (0.7–1.7)
Siblings	82/217	1 (0.7–1.6)	44/207	1.1 (0.7–1.8)
Brothers	41/105	1.1 (0.7–1.8)	24/99	1.3 (0.7–2.3)
Sisters	51/133	1.1 (0.7–1.8)	27/128	1.1 (0.7–1.8)
Offspring	16/42	1.3 (0.6–2.9)	10/39	1.6 (0.7–3.6)
Sons	7/17	1.5 (0.5–4.5)	3/17	1.2 (0.3–4.3)
Daughters	9/25	1.2 (0.4–3.5)	7/22	1.9 (0.7–5.5)
<i>First degree history of liver cancer</i>				
Yes	21/9	3.9 (1.4–11.5)	8/8	4.1 (1.3–12.9)
<i>Number of FDR^c with liver cancer</i>				
Single member	16/9	3.7 (1.3–11.1)	8/8	4.1 (1.3–12.9)
Multiple members	5/0		0/0	
<i>Type of relationship</i>				
Parents	13/5	2.8 (0.7–11.6)	4/4	3.8 (0.8–19.7)
Fathers	7/3	2.4 (0.3–20.1)	1/3	1.7 (0.1–23.2)
Mothers	6/2	3.2 (0.5–22.3)	3/1	8.3 (0.7–96.6)
Siblings	9/4	5.7 (1.2–27.3)	4/4	4.3 (1.01–20.9)
Brothers	6/2	7.7 (0.8–70.1)	2/2	5.2 (0.5–48.9)
Sisters	4/2	4.7 (0.6–38.3)	2/2	3.5 (0.4–32.7)
Offspring	1/0		0/0	
Sons	0/0		0/0	
Daughters	1/0		0/0	

^a Logistic model included subjects' age, sex, race, educational level, cigarette smoking, alcohol consumption, diabetes mellitus, anti-HCV, HBsAg, and anti-HBc.

^b Logistic model included subjects' age, sex, race, educational level, cigarette smoking, alcohol consumption, and diabetes mellitus.

^c FDR = first degree relatives.