Title:

Association of Tattooing and Hepatitis C Virus Infection: A Multicenter Case-Control Study.

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Abstract

Although injection drug use (IDU) and blood transfusions prior to 1992 are well-accepted risk factors for hepatitis C virus (HCV) infection, many prior studies that have evaluated tattooing as a risk factor for HCV infection did not control for a history of IDU or transfusion prior to 1992. In this large, multicenter case-control study we analyzed demographic and HCV risk factor exposure history data from 3,871 patients, including 1,930 with chronic HCV infection (HCV RNA positive) and 1,941 HCV negative (HCV antibody negative) controls. Crude and fully adjusted odds ratios of tattoo exposure by multivariate logistic regression in HCV infected versus controls were determined. As expected, injection drug use (65.9% vs. 17.8%, $p < 0.001$), blood transfusions prior to 1992 (22.3% vs. 11.1%, $p < 0.001$), and history of having one or more tattoos (OR = 3.81; 95% CI 3.23 – 4.49, $p<0.001$) were more common in HCV-infected patients than in control subjects. After excluding all patients with a history of ever injecting drugs and those who had a blood transfusion prior to 1992, a total of 1,886 subjects remained for analysis (465 HCV positive and 1,421 controls). Among these individuals without traditional risk factors, HCV positive patients remained significantly more likely to have a history of one or more tattoos after adjustment for age, sex, and race/ethnicity (OR = 5.17; 95% CI 3.75 – 7.11, $p<0.001$).

Conclusion: Tattooing is associated with HCV infection, even among those without traditional HCV risk factors such as injection drug use and blood transfusion prior to 1992.

Hepatitis C virus (HCV) infection is the most common blood born infection in the United States, affecting over 3 million people (1-4) of all ages, races, and genders (5, 6). By 2007, HCV had superseded HIV as a cause of death in the United States (4), yet approximately 50-75% of infected adults are unaware of their infection status. (7, 8) Injection drug use (IDU) is currently the leading cause of transmission, accounting for 60% of new cases each year (2,3) through both the sharing of needles (9, 10) and through drug preparation equipment (11); however, approximately 20% of incident cases have no history of IDU or other parenteral exposure (CDC Viral hepatitis surveillance 2009).

As new and better medications for the treatment of HCV become available (12-14), measures to increase detection rates and engagement in care are paramount. In the last decade an expanding body of research has emerged, evaluating both traditional and non-traditional risk factors for HCV infection in an effort to increase the yield from costly yet potentially life-saving screening efforts (7, 15-18). Most recently the US Department of Health and Human Services issued an action plan for the prevention, care and treatment of viral hepatitis, setting goals to increase the proportion of persons who are aware of their hepatitis C virus infection from 45% to 66%, and to reduce the number of new cases of HCV infection by 25% (19).

In contrast to the overwhelming evidence implicating IDU in HCV acquisition, the association between HCV transmission and other suspected risk factors such as tattooing is more controversial. While some studies have demonstrated an association between tattoos and HCV infection, others have not (20). Prior studies that examined tattooing behavior and HCV infection in the United States were limited by small sample sizes (<100 cases for case-control or < 2000 for cross-sectional studies) and failure to report adjusted odds ratios (20). Additionally, some studies that found an association between tattoos and HCV infection did not control for well-

established HCV risk factors such as IDU and transfusion before 1992 (20); thus limiting the interpretation of the results.

The prevalence of tattooing is on the rise in the United States. A recent Harris poll reflects a significant increase in tattooing among adults in the last decade, with 1 in every 5 reporting one or more tattoos in 2012 (21). Few states have effective public health and safety regulations relating to the application of body art, and little is known about the local or systemic consequences of body art application (22). Using a large, multi-center, case-controlled study, our aim was to assess the association between HCV infection and tattoos after excluding those who lack traditional risk factors such as prior IDU or pre-1992 blood transfusion, and number of sex partners.

Study Subjects and Methods

Patients were enrolled from the adult primary care and adult gastroenterology clinics at three main centers: the Manhattan and Brooklyn campuses of the Veterans Affairs New York Harbor Healthcare System along with the Bellevue Hospital Center in New York, NY. The latter site is a municipal hospital affiliated with New York University serving relatively poor and uninsured patients. Inclusion criteria for HCV-infected cases included labs showing a positive HCV antibody (HCV Ab) and the presence of HCV viremia by polymerase chain reaction (HCV PCR). The inclusion criteria for HCV-negative controls were those with negative HCV Ab. Patients presented to the outpatient care centers for either health screening or acute complaints. The reasons for presentation did not differ between cases and controls. Patients were excluded from this study if they had another cause of chronic liver disease, no prior HCV serological testing, a positive HCV Ab and negative PCR, were unable to read or understand the English language survey, or if they refused to complete the anonymous questionnaire. The dates of enrollment were from April 2004 to May 2006.

Questionnaire design and record of HCV serostatus

An anonymous questionnaire was designed by the study authors assessing patient demographics, knowledge of transmission of HCV infection and exposure history to proven and suspected risk factors for HCV infection. Separate surveys were designed with questions pertinent to HCV+ and HCV- participants. These surveys were tested for face and content validity by a group of adult gastroenterology and primary care physicians not directly involved in the study. The questionnaire was pre-tested in 10 HCV+ and 10 HCV- patients who provided feedback on the readability and clarity of the survey. After appropriate modifications, the questionnaire was again tested in 10 different HCV+ and HCV- before full implementation.

Each participant was asked to complete the survey at the time of his or her previously scheduled clinic visit. Patients submitted the survey anonymously and were not contacted after the survey was returned. No personal identifiers were recorded. Informed consent was obtained from prospective subjects and then their electronic medical record was accessed to ascertain HCV serostatus, and to determine which questionnaire to provide (HCV+, HCV -, or HCV untested). Individuals classified as “HCV untested” were not included in the present study. To minimize recall bias, subjects were informed that a study of HCV and hepatitis vaccination awareness was being conducted in the general adult population, and that there invitation was not to be interpreted as particular suspicion of HCV infection in their individual case. The HCV+ and HCV- surveys were marked in a discrete way such that the subjects were not informed of their serostatus by the questionnaire. Surveyors were trained to interact consistently with HCV+ and HCV- volunteers, as they were unmasked. Surveyors were forbidden to answer questions or assist in completion of the survey aside from providing a writing instrument as needed. The primary outcome was to compare the odds of having one or more tattoos in HCV positive cases compared to HCV negative controls. The exact question asked on the survey was “Have you

ever had a tattoo?" Information was entered into a database from which analyses were done. The institutional review boards of both the VA New York Harbor Healthcare System and the Langone Medical Center of New York University approved this study.

Statistical Analysis

Statistical analysis was performed using Stata version 11.2 (Stata, College Station, TX) and a two-tailed p-value of <0.05 was considered statistically significant. Colinearity of predictor variables were checked using the variance inflation factor test, using a cutoff of 2.5. Age was entered directly on the survey, while other variables considered were categorical and treated as ordinal or nominal where appropriate. The Student's *t* test was used to analyze continuous variables (i.e. age) and ordinal / nominal variables were compared using the chi-square test.

Univariate analyses were utilized to identify those variables that were significantly associated with case or control status, including the main exposure of interest and all potential confounders. Multivariate logistic regression was then performed using forced logistic regression for age, race, and gender. Finally, all statistically significant variables in the univariate analyses were considered in a model in through a forced logistic regression model. For each model, the adjusted odds ratio (AOR), p-value and 95% confidence interval (CI) of tattoo exposure were calculated.

RESULTS

A total of 3,871 patients were enrolled, including 1,930 with chronic HCV infection and 1,941 HCV negative controls (Table 1). There were no differences in the mean age (55.2 ± 9.0 vs. 55.6 ± 11.3 years, p = 0.34) or proportion male (80.3% vs. 81.4%, p = 0.39) between HCV-infected patients and controls; however, HCV positive patients were more likely to be racial/ethnic minorities (56.5% vs. 78.5%, p < 0.001). As expected, injection drug use (65.9% vs. 17.8%, p < 0.001), blood transfusions prior to 1992 (22.3% vs. 11.1%, p < 0.001), and history of having one or more tattoos (p < 0.001) were more common in HCV-infected patients than in control subjects.

Patients with HCV infection were significantly more likely to have a history of tattoo exposure (OR = 3.81; 95% CI 3.23 – 4.49; p<0.001) and this remained significant after adjustment for age, sex, and race/ethnicity (OR = 4.51; 95% CI 3.78 – 5.39, p<0.001), and all potential confounding variables identified in table 1 (OR = 3.74; 95% CI 2.95 – 4.73; p<0.001) (Table 2).

After excluding all patients with a history of ever injecting drugs and those who have had a blood transfusion prior to 1992, a total of 1,886 subjects remained for analysis, including 465 HCV positive and 1,421 controls (Table 3). Among this subset of individuals without traditional risk factors for HCV infection, we found that HCV positive patients were still significantly more likely to have a history of tattoo exposure (OR = 3.83; 95% CI 2.99 – 4.93, p<0.001) and this remained statistically significant after adjustment for age, sex, and race/ethnicity (OR = 4.48; 95% CI 3.42 – 5.87, p<0.001) and all potential confounding variables identified in table 3 at or below p=0.10 (OR = 5.17; 95% CI 3.75 – 7.11; p<0.001) (Tables 4, 5). In addition after excluding intranasal drug users from the analysis and adjusting for all potential confounding variables, HCV positive patients remained significantly more likely to have a history of tattoo exposure compared to HCV negative controls (OR = 8.22; 95% CI 5.45 – 12.40, p<0.001).

Discussion

In the present study of nearly 4,000 patients, we found that tattooing was significantly and independently associated with HCV infection. The association persisted after adjusting for age, sex, race/ethnicity as well as after excluding subjects with traditional risk factors such as injection drug use and blood transfusion prior to 1992. These findings have important implications for screening non-injection drug users in the United States, particularly since the prevalence of tattooing is on the rise and intravenous drug use is on the decline.

The prevalence of tattoos in the United States has been increasing during the past decade, particularly amongst youths (21-24). Although little is known about the prevalence of body art among minority adolescents; one study of African-American and Hispanic students from an inner city high school in Texas, found that 10% of the African-American students already had a tattoo by graduation, a rate that is comparable to prior studies which evaluated predominantly white college students (25). A 2004 study among persons aged 18-50 years in the United States found that 24% of respondents had at least 1 tattoo and an additional 21% of non-tattooed respondents had considered tattoo placement (22). Tattooing is more common among those of low socioeconomic status(22) despite its increased prevalence across all social groups and it is also highly prevalent among soldiers. In one study, almost 36% of soldiers in the US Army had at least 1 tattoo, and 76% experienced bleeding after the procedure, which might promote transmission of blood-borne infections (26).

The literature assessing the association between tattooing and HCV has heretofore been equivocal. Because of the wide variability of study populations with regards to baseline risk of HCV exposure, previous work has been risk-stratified by general population, blood donors, high-

risk groups (ie, drug users, homeless persons, sex-workers, and patients in sexually transmitted disease clinics), prisoners, and veterans. Although, studies that recruited >1000 veterans found almost 3 times higher risk of HCV infection among veterans with a tattoo, compared with those who did not have a tattoo (27-29); results from cross-sectional studies involving the general public, blood donors, and other high-risk groups have been inconsistent (20).

A recent review article of the best available data on the risk of HCV infection from tattoo exposure found that most studies relied on descriptive statistics alone and failed to report measures of association, such as odds ratios and relative risk. In fact, meta-analysis of the existing literature was deferred as several of the studies that found no association between HCV infection and tattooing in the univariate analysis either did not include those exposures in the multivariate analysis or did not report the AOR (20). Furthermore, few case-controlled studies completely excluded injection drug users and blood transfusion recipients (20).

Our study confirms the association between tattoo exposure and hepatitis C infection in a very large ethnically diverse population of HCV cases and uninfected controls. To our knowledge, this is largest group of HCV cases and controls ever assembled to study this question after excluding all injection drug users and recipients of blood transfusions before 1992, along with verification of HCV seropositivity and viremia through the electronic medical record at each study location.

To date there is no definitive evidence that HCV infections occur through tattooing when sterile equipment is used. Although, no outbreaks of HCV infection have been detected in the United States that originate from professional tattoo parlors, case reports of acute HCV infection from tattooing in prison suggest that tattooing could be a mode of transmission (30-32). One case

report from a US prison documented HCV seroconversion in a prisoner, where tattooing in prison was the only known risk factor during the incubation period (32).

Underrepresentation due to self-reporting of intravenous drug use is a concern that could confound our result. Tattoos and drug use often co-exist, therefore the increased risk of HCV infection among tattooed individuals may in fact be a surrogate for unreported drug use (33-38). Although a case series of 301 patients by Flamm, et al. found that 8.5% of chronic HCV infected male patients younger than 45 who were initially referred with “no known risk factor” later endorsed a remote history of IV drug use (39), IV drug use self-reporting has been shown to be accurate when high methodological standards were applied (40). When our surveys were completed, there were no patient identifiers to subsequently associate patients with their answers, providing a confidentiality that was ensured to patients prior to receiving the survey during the consent process. Our questionnaires were completed anonymously, allowing subjects to report drug use and sexual behaviors without concern for personal identification.

Some may ascribe the risk of HCV infection from tattooing to another unrecognized high-risk behavior, for instance, increased intranasal drug use or sexual promiscuity among those having one or more tattoo; however, these concerns were not born out by our analysis. Sexual contact is responsible for a very low, but not negligible transmission of HCV (1, 41, 42). Our two cohorts without traditional risk factors had equal proportions reporting >25 lifetime sexual partners (27.5% for HCV+ and 26.6% for HCV-, p= 0.714), although their remained unequal proportions reporting prior sexual contact with a prostitute or same-sex partner (Table 3). Our study adjusted for these sexual contacts and other potential residual confounders in logistic regression and found that in those without prior IDU or pre-1992 blood transfusion, the odds of tattoo exposure were still higher in the HCV+ group than in the HCV negative controls.

Although commercial parlors have not been implicated in HCV transmission, such transmission could occur at different stages of tattooing; from the reuse of nondisposable needles, inappropriate sterilization of equipment, or reuse of ink contaminated with blood from an infected process. Although data on survival of hepatitis C in tattooing or piercing equipment are not available, survival of HCV ranges from a few days on inanimate surfaces to almost 1 month in propofol solutions (43-46). In fact, the US Occupational Safety and Health Administration (OSHA) recognizes tattooing as a potential mode of transmission of blood-borne pathogens, it is included in their blood-borne safety standards. Furthermore, more than 2/3 of state health jurisdictions in the United States have additional regulations for tattooing parlors (25). Tattooing in prison is of particular concern regarding the transmission of blood-borne infections, because tattooing in this setting is typically performed using non-sterile equipment, such as guitar strings, paper clips, or sewing needles, which are usually cleaned by heating or use of boiling water (47). A similar concern exists for other non-professional settings and non-professional tattoo-artists. Of particular concern are those parlors servicing adolescents without the informed consent of a parent. Many states require that minors obtain parental consent for tattoos and piercings; however, in one study from an urban Texas high school about 20% of those who obtained their art from a professional were not asked for proof of parental consent (48).

The limitations of our study include a patient population from two veteran administration hospitals that are predominantly male and one urban municipal hospital slanted towards the lower end of the socioeconomic scale, limiting how these findings could be generalized to other segments of the population, particularly women or more affluent populations. Compared to the control group, the hepatitis C cohort had a higher proportion of self-identified racial or ethnic minorities (56.5% vs. 78.5%, $p < 0.001$). Furthermore, our study did not recruit patients with incident cases of HCV infection and ask about tattoo exposure or specify the venue of tattoo

placement, which hinders drawing temporal causal relationships between HCV infection and tattooing as well as limiting our ability to comment on how sterile infection control practices can mitigate the risk of transmission. Future analysis will help determine how these distinctions would further qualify the overall result.

In summary, tattoo exposure is associated with HCV infection, even among those without traditional risk factors. All patients who have tattoos should be considered at higher risk for HCV infection and should be offered HCV counseling and testing. Expanding screening recommendations to cover individuals with one or more tattoos, offers a potential compliment to current risk-based screening recommendations. Because of the increasing prevalence of tattooing, particularly among youths, awareness campaigns should highlight the danger of transmitting blood-borne infections such as HCV, regardless of the venue of placement.

Author Contributions:

Study concept and design: Bini

Acquisition of data: All

Analysis and interpretation of data: Bini, Dhalla

Critical revision of the manuscript for important intellectual content: Dhalla, Bini, Tenner, Francois

Statistical analysis: Bini, Dhalla

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Table 1. Baseline Characteristics of the 1,930 HCV Positive and 1,941 Control Subjects

	HCV Positive N=1930	Control Subjects N=1,941	P-value
Age [a]	55.2 ± 9.0	55.6 ± 11.3	0.33
Male	80.3%	81.4%	0.39
Race/Ethnicity[b]			<0.001
White	21.5%	43.5%	
Black	41.0%	30.1%	
Hispanic	19.8%	17.8%	
Other	17.7%	8.6%	
Born in the U.S.	69.7%	73.6%	0.003
Married	26.7%	32.5%	<0.001
>12 years education	35.9%	22.7%	<0.001
Income > $15,000	46.7%	55.5%	<0.001
Currently employed	31.5%	40.1%	<0.001
Injection drug use[c]	65.9%	17.8%	<0.001
Transfusion before 1992	22.3%	11.1%	<0.001
Intranasal drug use[c]	61.8%	22.6%	<0.001
Number of lifetime sexual partners			<0.001
0 – 2	13.6%	17.4%	
3 – 9	20.9%	29.8%	
10 – 25	38.2%	24.9%	
26+	27.3%	27.9%	

Sex with a prostitute[c]	59.5%	37.7%	<0.001
Sex with same-sex partner[c]	13.1%	12.4%	0.49
Incarcerated for >48 hours[c]	48.8%	13.9%	<0.001
Body piercing[c]	35.2%	21.3%	<0.001
Acupuncture[c]	21.7%	14.7%	<0.001
Drinks of alcohol per week			<0.001
None	69.3%	55.8%	
1 – 6	35.8%	35.8%	
7 or more	6.4%	8.4%	

[a] Mean +/- standard deviation (SD) reported, [b] Self-reported, [c] Any prior history

Table 2: Crude and Adjusted Odds ratios for tattoo exposure in 1,930 HCV+ compared with 1,941 HCV- controls

Model	Odds Ratio	95% Confidence Interval	p-value
Crude	**3.81**	**3.23-4.49**	**<0.001**
Adjusted[a]	**4.51**	**3.78-5.39**	**<0.001**
Fully Adjusted[b]	**3.74**	**2.95-4.73**	**<0.001**

[a] Adjusted for Age, Race, Gender

[b] Adjusted for Age, Race, Gender, clinic site and all significant differences listed in Table 1 with p-value < 0.10

Table 3: Self-reported patient Demographics for all HCV+ cases and HCV negative controls, excluding traditional risk factors[d]

	HCV Positive N = 466	Control Subjects N = 1,421	P-value
Age [a]	52.0 ± 7.6	53.1 ± 10.6	0.04
Male	78.5%	80.4%	0.32
Race/Ethnicity[b]			<0.001
White	26.4%	43.0%	
Black	41.2%	29.5%	
Hispanic	18.9%	18.7%	
Other	13.5%	8.9%	
Born in the U.S.	71.0%	71.6%	0.8
Married	30.7%	33.6%	0.251
Education > 12 years	65.7%	79.17%	<0.001
Income > $15,000	53.0%	56.3%	0.214
Currently Employed	36.1%	45.7%	<0.001
Intranasal Drug Use[c]	34.6%	21.7%	<0.001
Number of lifetime sexual partners			0.08
0 – 2	22.3%	18.4%	
3 – 9	24.9%	30.5%	
10 – 25	25.3%	24.4%	
26+	27.5%	26.6%	

Sex with a prostitute[c]	47.4%	36.7%	<0.001
Sex with same-sex partner[c]	5.8%	12.0%	<0.001
Incarcerated for >48 hours[c]	41.4%	13.9%	<0.001
Body piercing[c]	28.8%	22.5%	0.006
Acupuncture[c]	12.0%	13.1%	0.548
Drinks of alcohol per week			<0.001
None	67.0%	55.4%	
1 – 6	24.2%	35.2%	
7 or more	8.8%	9.4%	

[a] Mean +/- standard deviation (SD) reported, [b] Self-reported, [c] Any prior history [d] traditional risk factors is defined as any prior Injection drug use or blood transfusion prior to 1992 (when HCV screening of the blood supply began)

Table 4: Crude and Adjusted Odds ratios for tattoo exposure in 466 HCV+ compared to1421 HCV- controls without traditional risk factors

Model	Odds Ratio	95% Confidence Interval	p-value
Crude	3.83	2.99-4.93	<0.001
Adjusted[a]	4.48	3.42 – 5.87	<0.001
Fully Adjusted[b]	5.17	3.75 – 7.11	<0.001
Fully Adjusted[b] and INDU excluded	8.22	5.45 – 12.40	<0.001

[a] Adjusted for Age, Race, Gender

[b] Adjusted for Age, Race, Gender, clinic site and all significant differences listed in Table 1 with p-value < 0.10

Table 5: Crude and Adjusted Odds ratios for all variables included in model assessing tattoo exposure in 466 HCV+ compared to1421 HCV- controls after excluding IDU and blood transfusion recipients

	Odds Ratio		
Risk Factor	Crude (95% CI)	Adjusted[a] (95% CI)	p-value for adjusted OR
Born in the U.S.	0.97 (0.77-1.22)	1.06(.81-1.39)	0.44
Married	0.94 (0.88 – 1.00)	0.96(0.90-1.03)	0.23
< or = 12 years education	1.98 (1.57-2.50)	2.13 (1.67-2.71)	<0.001
Income < $15,000	1.14 (0.92-1.41)	1.12 (0.90-1.40)	0.31
Currently employed	0.67 (0.54-0.83)	0.61 (0.49-0.77)	<0.001
Intranasal drug use[c]	1.91 (1.52-2.40)	1.82 (1.43-2.31)	<0.001
>25 sexual partners	1.04 (0.82-1.32)	1.18 (0.92-1.51)	0.18
Sex with a prostitute[c]	1.59 (1.29-1.97)	1.65 (1.31-2.08)	<0.001
Sex with same-sex partner	0.44 (0.29-0.68)	0.56 (0.37-0.87)	0.009
Incarcerated for >48 hours	5.20 (4.08-6.64)	4.84 (3.76 – 6.25)	<0.001
Body piercing	1.39 (1.10-1.70)	1.18 (0.92 – 1.51)	0.19
Acupuncture	0.91 (0.66-1.25)	0.88 (0.64-1.23)	0.48
Drinks of alcohol per week	0.66 (0.56-0.79)	0.73 (0.61 – 0.88)	<0.001

[a] Adjusted for Age, Race, Gender