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Hepatitis C Virus Infection And Prostate Cancer Risk: A Population-Based Case-Control Study Using The Seer-Medicare Dataset

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ABSTRACT

Prostate cancer is the most common type of non-skin malignancy diagnosed among men, but the disease etiology and risk factors remain inconclusive. Hepatitis C virus (HCV) infection's prevalence is increasing in the US population. Studies have shown that the concentration of free serum testosterone, which may be directly associated with prostate cancer risk, was decreased among men with HCV infection. In order to evaluate the relationship between HCV infection and prostate cancer risk, we conducted a population-based case-control study using the SEER-Medicare dataset.

The study included 194,339 prostate cancer cases and 54,481 controls which were frequency-matched to the cases by age, race, and calendar period of selection. After adjusting for matching factors and potential confounders, including geographic region of SEER registry/area, HBV infection, HIV infection, hypertension, number of hospitalization, number of outpatient visits, number of physician visits, and PSA test 0-0.99 years prior to index date, history of HCV infection was significantly associated with decreased risk of prostate cancer (OR 0.76, 95% CI: 0.63-0.93). In addition, with the controls as the reference group, we observed HCV infection to be associated with reduced prostate cancer risk within each prostate cancer stage category at diagnosis: localized (OR 0.86, 95% CI: 0.59-1.24), regional (OR 0.90, 95% CI: 0.43-1.89), distant (OR 0.56, 95% CI: 0.26-1.17), and unstaged (OR 0.62, 95% CI: 0.38-1.00).

Our finding that HCV infection is associated with reduced prostate cancer risk may lead to a greater understanding of prostate cancer etiology. Future research will be needed to elucidate the underlying biological mechanism for this inverse association.

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INTRODUCTION

Prostate cancer is the most common type of non-skin malignancy diagnosed among men, and the American Cancer Society has projected that about 238,590 new cases of prostate cancer will be diagnosed in the United States during 2013. Despite the high disease burden and wide-scope of research on prostate cancer etiology, the established risk factors of prostate cancer only include older age, a positive family history, and African-American race (Hoffman, 2011; Dunn et al. 2011; Johns 2003). Interestingly, certain conditions, including diabetes mellitus (Kasper et al. 2006; Bonovas et al. 2004) and Human Immunodeficiency Virus (HIV) infection (Patel et al. 2008), seem to be associated with decreased risk of prostate cancer.

Prostate cancer is rarely diagnosed clinically among men less than 40 years of age. The serum prostate-specific antigen (PSA) test has been widely adopted as a screening test for prostate cancer since the late 1980s (Lin et al. 2008), but the efficacy of the test has been controversial, as it has not been demonstrated to decrease mortality but induce harms such as over-diagnosis and over-treatment (Chou et al. 2011). PSA test diagnosed prostate cancer is usually asymptomatic and localized, compared to clinically detected prostate cancer, which is more likely to be diagnosed with regional extension or metastases (Hoffman et al. 2005). In 2011, the U.S. Preventive Services Task Force (USPSTF) recommended against screening for prostate cancer among all American men, regardless of age, race/ethnicity, or family history, as the current evidence indicates that the benefits of the test do not outweigh the harms (Moyer, 2012).

It is estimated that approximately 2% (5.2 million) of the U.S. population is infected with hepatitis C virus (HCV) (Chak et al. 2011). HCV infection is an established strong risk factor for development of subsequent liver cirrhosis (Perz et al. 2006), hepatocellular carcinoma (HCC) (El-Serag 2000; Amin et al. 2006), and other liver complications (Hoofnagle 1997). Emerging evidence has also suggested a carcinogenic role of HCV infection in other types of cancer, including: non-Hodgkin lymphoma (NHL) (Matsuo et al. 2004; Giordano et al. 2007), thyroid cancer (Antonelli et al. 2007; Montella et al. 2003), pancreatic cancer (El-Serag et al. 2009), and intrahepatic cholangiocarcinoma (Yamamoto et al. 2004). HCV-induced chronic liver inflammation causes accumulation

of reactive oxygen intermediates, which creates a mutagenic environment that inhibits DNA repair and allows the mutated cells to proliferate (Colombo 2003). This has been suggested to increase the risk of HCC. The increased NHL risk seen after HCV infection may be due to HCV-induced immune disturbance and B-cell proliferation (Negri et al. 2004; Gasparotto et al. 2002). There is also evidence that HCV core protein promotes cell proliferation and inhibits apoptosis(Chen et al. 2005), as a possible mechanism of HCV carcinogenesis.

Extrahepatic manifestations of chronic HCV infection have been reported to include altered seminal parameters and reduced spermatogenesis (Hofny et al. 2011). Compared to healthy controls, HCV infected men are observed to have reduced semen volume and sperm motility (Hofny et al. 2011), and significantly lower free serum testosterone concentration (Durazzo et al. 2006). The latter may be explained by increased excretion of sex hormone-binding globulin after HCV infection (Nguyen et al. 2005). Testosterone is an androgen essential for proper function of the prostate gland, and previous research has suggested that higher serum testosterone levels are associated with increased risk of developing prostate cancer (Parsons et al. 2005). Therefore, it is possible that HCV-infected men may have diminished risk of prostate cancer because of the decreased concentration of circulating testosterone.

To our knowledge, no published study has examined the relationship between HCV infection and prostate cancer risk. In order to fill this research gap, we have conducted a population-based case-control study using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database. Besides assessment of the exposure variable, this database also provides information about several other variables, including demographic features, medical history, healthcare utilization, and PSA testing history. The availability of these variables allowed us to adjust for potential confounders and obtain a more accurate estimate of prostate cancer risk among HCV-infected patients. Our research may lead to a greater understanding of prostate cancer etiology.

METHODS

SEER-Medicare dataset

The SEER program is funded by National Cancer Institute, and it collects data on cancer incidence and survival from US cancer registries. Presently, SEER includes 17 cancer registries, which covers approximately 26% of the US population. Medicare is a federally funded program which provides health insurance for approximately 97% of people aged 65 years or older in the US population, as well as individuals under age 65 who have end-stage renal disease or medical disability. Medicare is composed of four parts, including inpatient hospitalization program (Part A), physician visits and outpatient service program (Part B), Medicare Advantage plan (Part C) where benefits are provided by private companies that contract with Medicare, and outpatient prescription drug benefit (Part D).

The SEER-Medicare is a linked database that provides demographic and clinical information for all incident cancers in the SEER program, as well as claims data for the individuals that are covered under Medicare and living in SEER regions (Engels et al. 2011). Medicare data are available for both the cancer cases identified in the SEER program, and a 5% random sample of the Medicare population from the same geographic regions. Medicare data includes claims information for inpatient and hospitalization service (since 1986), and physician and outpatient services (since 1991). The claims are coded using International Classification of Diseases (ICD-9) codes, and Current Procedures Terminology (CPT-4) codes.

Study design and subject selection

In order to examine the risk of prostate cancer among HCV-infected individuals, we conducted a population-based case-control study using the SEER-Medicare dataset. Since almost all American people enter the Medicare program once their age reaches the eligibility criteria, Medicare can be considered as a cohort of the US general population 65 years of age or older.

This study was part of a larger project in which we systematically identified 1,084,247 first primary cancer cases of any type diagnosed during 1993-2005 and aged 66 or older

at the time of diagnosis. We excluded persons of age 65 to assure sufficient time for the ascertainment of exposure information. Individuals who were diagnosed with cancer before 1993 were also excluded, since the Medicare system does not have claims data for HCV infection prior to 1993. The cases were required to have at least 12 month non-health maintenance organization (HMO), Part A, and Part B Medicare claims data prior to the diagnosis of first cancer, in order to assure completeness of data and sufficient time to evaluate HCV infection status before cancer diagnosis. Cases diagnosed on autopsy or by death certificates only were excluded. The date of diagnosis was assigned as the index date for the cases.

A total of 100,000 controls were randomly selected from the 5% random sample of Medicare recipients. Controls were frequency matched to the all-cancer cases by calendar year of case diagnosis, age, sex, and race. We required that controls be alive, and with no SEER-reported cancer on or before July 1st in the calendar year of selection. The same control could be selected multiple times for cases in different calendar years, and could become a cancer case in the future. The index date of the controls was July 1st of the selection year. Like cases, we required controls to have at least 12 months of non-HMO, Part A, and Part B Medicare coverage prior to their index dates.

To conduct the current study, we extracted all first prostate cancer cases (194,339) and all male controls (54,481) into a sub-dataset, and used this sub-dataset to investigate the association between HCV infection and prostate cancer risk. This study can be conceptualized as a nested-case control study in the cohort of the US Medicare elderly population.

Ascertainment of HCV infection status and covariates

HCV infection status for the selected cases and controls was determined using the Medicare claims data. Subjects with one or more inpatient, hospital-based outpatient, or physician claims for HCV infection (ICD 9 codes: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, or V02.62) were classified as having HCV infection. It is possible that the cancer patients received more diagnostic tests, including laboratory tests for HCV, during the period preceding their diagnosis than did controls during the period preceding their index date. As a result, cases are more likely to detect their asymptomatic hepatitis

viral infection than controls. Therefore, we excluded the HCV infections diagnosed within the 12-month period before cancer diagnosis or index date for both cases and controls, so as to avoid information bias.

We collected information regarding other pertinent medical conditions for each selected individual, using the Medicare claims data for inpatient, hospital-based outpatient, or physician care. These conditions include diabetes mellitus (ICD 9 code: 250.0x), hepatitis B virus infection (HBV, 070.2, 070.3), hypertension (401.x-405.x), and HIV infection (042-044). We ascertained patients' numbers of hospitalizations, hospital-based outpatient visits, and physician visits between age 65 and their index date, since we believe the utilization pattern of healthcare service may be associated with the likelihood of being diagnosed with prostate cancer or HCV infection. We expect that patients with HCV infection or chronic medical conditions would receive more healthcare services, including PSA screening tests, which increases the likelihood of diagnosis of early-stage prostate cancer. For the patients who had screening-detected cancer, their PSA tests were most probably done within a short period prior to their cancer diagnosis. As a result, we also assessed whether each subject had received PSA test 0-0.99 years prior to the index date, in order to adjust for the potential confounding caused by PSA screening.

Statistical analysis

We computed descriptive statistics of demographic characteristics, medical conditions, and healthcare utilization, for both prostate cancer cases and controls. We assessed whether these covariates were significantly associated with the primary exposure variable and the cancer outcome.

We conducted stratified analyses by each covariate and examined whether the odds ratio (OR) for prostate cancer comparing HCV-infected to uninfected subjects was heterogeneous across levels of the covariates. For the continuous variables of healthcare utilization, we divided the variables at the median among the controls, and created new binary variables that represent the number of people who have more or less than or equal to the median numbers of visits to healthcare facilities. If no heterogeneity was found with assessment of the Breslow-Day test p-value, we used the Mantel-Haenzsel summary

OR to represent the risk of prostate cancer after HCV infection for each stratified analysis.

To compare prostate cancer risk between HCV-infected and non-infected subjects, we used an unconditional logistic regression model to compute ORs and 95% confidence intervals (95% CIs), with adjustment for the matching factors and other potential confounders. The covariates included in the model were age, race, calendar period of selection (1993-1995, 1996-2000, 2001-2005), geographic region of SEER registry/area, HBV infection, HIV infection, hypertension, number of hospitalizations, number of hospital-based outpatient visits, number of physician visits, and whether the individual had received a PSA test 0-0.99 years prior to the index date. A body of research has suggested that HCV infection leads to elevated risk of developing diabetes mellitus (Noto et al. 2006), and that the latter is associated with decreased the risk of prostate cancer, as mentioned previously. We therefore excluded diabetes from our model, since it may be in the causal pathway between HCV infection and prostate cancer risk.

We suspected that having a PSA test 0-0.99 years prior to the index date may also be an effect modifier of the association between HCV infection and prostate cancer risk, so we included an interaction term between our primary predictor, HCV infection, and our PSA test variable in the above unconditional logistic regression model. If this interaction term was found to be statistically significant, it would suggest that the effect of HCV infection on prostate cancer risk differs according to whether the patient has received a PSA test 0-0.99 years prior to their index date. As a result we would also report stratum-specific ORs according to PSA test status.

In order to explore the association between HCV infection and prostate cancer risk stratified by stage at diagnosis, cases were divided into four cancer-stage categories: localized (stage I and II by the TNM system), regional (stage III by the TNM system), distant (stage IV by the TNM system), and unstaged. Using polytomous logistic regression, we calculated ORs for HCV-infected versus HCV uninfected subjects for each cancer stage category compared to controls, and assessed whether the ORs were heterogeneous. The interaction term between HCV infection and the PSA test variable

was also included in the above polytomous logistic regression models, in order to detect effect modification from PSA screening.

To adjust for the multiple selection of a control across calendar years, and the possibility that a control can become a case in the future, the variance of the ORs from all logistic regression models were adjusted (Engels et al. 2011).

RESULTS

The study included 194,339 men with the diagnosis of first primary prostate cancer, and 54,481 male controls (Table 1). Because of the large sample size, even a slight numerical difference between cases and controls can be statistically significant, but not necessarily meaningful. The mean ages of cases and controls were similar, 74.73 ± 6.14 years and 75.17 ± 6.68 years, respectively. More than 80% of the subjects were white in both groups, but there were relatively more black subjects in the control group than in the case group (10.58% versus 6.43%, respectively). Among the cancer cases, 46% of the subjects were selected during 2001-2005, and approximately 25% were selected during 1993-1995 and 1996-2000, respectively. The distribution of calendar period of selection is slightly different in the control group. Overall, the cases and controls were fairly well-matched on age, race, and calendar period of selection from numerical comparison, despite the statistically significant difference.

Table 1. Characteristics of cancer cases and controls[a]

	Prostate cancer		
Characteristic	Yes (N = 194,339)[b]	No (N = 54,481)[b]	P
HCV			0.0015*
Yes	469 (0.2%)	174 (0.3%)	
no	193,870 (99.8%)	54,307 (99.7%)	
Age (years)	74.7 ± 6.1	75.2 ± 6.7	< 0.001**
Race			< 0.001*
White	45,747 (84.1%)	161,001 (83.0%)	
Black	3,497 (6.4%)	20,524 (10.6%)	
Others	5,124 (9.4%)	12,442 (6.4%)	
Calendar-period of selection			< 0.001*
1993-1995	49,918 (25.7%)	11,048 (20.3%)	
1996-2000	54,370 (28.0%)	16,277 (29.9%)	
2001-2005	90,051 (46.3%)	27,156 (49.8%)	

History of diabetes			< 0.001*
Yes	29,729 (15.3%)	9,780 (18.0%)	
No	164,612 (84.7%)	44,701 (82.1%)	
History of HBV			0.0018*
Yes	212 (0.1%)	88 (0.2%)	
No	194,127 (99.9%)	54,393 (99.8%)	
History of hypertension			< 0.001*
Yes	80,769 (41.6%)	23,719 (43.5%)	
No	113,570 (58.4%)	30,762 (56.5%)	
History of HIV			0.3751*
Yes	302 (0.2%)	94 (0.2%)	
no	194,037 (99.8%)	54,387 (99.8%)	
PSA test 0-0.99 years prior to the index date			< 0.001*
Yes	132,048 (68.0%)	19,341 (35.5%)	
no	62,291 (32.1%)	35,140 (64.5%)	
# of hospitalizations	1.5 ± 2.4	1.6 ± 2.8	< 0.001***
# of outpatient visit	11.7 ± 17.5	11.5 ± 19.7	< 0.001***
# of physician visit	98.2 ± 100.8	96.7 ± 112.2	< 0.001***

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Percentages may not sum to 100% due to rounding.
* P-value for χ^2 test. ** P-value for t-test. ***P-value for Non-parametric test.

In our dataset, 469 (0.24%) cases and 174 (0.32%) controls had a history of HCV infection. These proportions are substantially lower than the estimated prevalence of HCV infection (1.6%) in the US general population (Armstrong et al. 2006), but consistent with the percentage reported by Anderson et al. (2008) using analogous SEER-Medicare data. Approximately 18.0% of subjects in the control group had a history of diabetes, compared to 15.3% in the case group. Less than 0.2% of cases and controls, respectively, had a history of HBV infection; the proportion of subjects with HIV infection was equally small in both groups. Hypertension was diagnosed in 41.6% of cases, which was slightly lower than the percentage of controls with hypertension. In addition, 68.0% of cases received a PSA test 0-0.99 year prior to their index dates, compared to 35.5% of the controls. Among the cases, 83.0% of HCV-infected men received a PSA test 0-0.99 years prior to their index date, compared to 67.9% among the HCV un-infected men.

On average, the prostate cancer cases and controls were hospitalized 1.5 and 1.6 times, respectively, between age of 65 and the year of selection. The mean numbers of outpatient visits and physician visits were similar between cases and controls (about 12 outpatient visits and 97 physician visits).

Table 2. Characteristics of HCV infected and uninfected subjects[a]

Characteristic	HCV infection		
	Yes (N = 643)[b]	No (N = 248,177)[b]	p
Age (years)	74.0 ± 5.2	74.8 ± 6.3	< 0.001**
Race			< 0.001*
White	461 (71.8%)	206,287 (83.3%)	
Black	111 (17.3%)	23,910 (9.7%)	
Others	70 (10.9%)	17,496 (7.1%)	
Calendar-period of selection			< 0.001*
1993-1995	9 (1.4%)	60,957 (24.6%)	
1996-2000	110 (17.1%)	70,537 (28.4%)	
2001-2005	524 (81.5%)	116,683 (47.0%)	
Diabetes			< 0.001*
Yes	194 (30.2%)	39,313 (15.8%)	
No	449 (69.8%)	208,864 (84.2%)	
Hepatitis B			< 0.001*
Yes	55 (8.6%)	245 (0.1%)	
No	588 (91.5%)	247,932 (99.9%)	
Hypertension			< 0.001*
Yes	411 (63.9%)	104,077 (41.9%)	
No	232 (36.1%)	144,100 (58.1%)	
HIV			< 0.001*
Yes	19 (3.0%)	377 (0.2%)	
no	624 (97.1%)	247,800 (99.9%)	
PSA test 0-0.99 years prior to the index date			< 0.001*
Yes	472 (73.4%)	150,917 (60.8%)	
no	171 (26.6%)	97,260 (39.2%)	
Num of hospitalizations	2.9 ± 4.4	1.5 ± 2.5	< 0.001***
Num of outpatient visit	26.1 ± 34.0	11.6 ± 18.0	< 0.001***
Num of physician visit	205.6 ± 199.7	97.6 ± 102.9	< 0.001***

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b] Percentages may not sum to 100% due to rounding.
* P-value for χ^2 test. ** P-value for t-test. ***P-value for Non-parametric test.

Table 2 compares the characteristics of the HCV infected and uninfected subjects. Their mean ages were similar. Among the HCV-infected subjects, 71.8% were white and 17.3% were black, compared to 83.3% and 9.7%, respectively, for the uninfected subjects. More than 80% of the HCV-infected subjects, but only 47.0% of the HCV-uninfected subjects, were selected during 2001-2005. For every medical condition, including diabetes, hepatitis B infection, hypertension, and HIV infection, the proportion of subjects having the condition was significantly and substantially greater among HCV-infected subjects than among uninfected subjects. On average, the numbers of hospitalizations, outpatient visits and physician visits were approximately two times higher among HCV-infected subjects than among uninfected ones. Of note, 73.4% of

HCV-infected subjects received a PSA test 0-0.99 years prior to their index date, compared to approximately 60% among the uninfected subjects.

Table 3. Stratified analysis by categorical covariates

	HCV infection	Prostate cancer		Mantel-Haenzsel OR (95% CI)	Breslow-Day test p-value
		Yes	No		
Race				0.74 (0.62, 0.88)	0.7557
White	Yes	331	1300		
(N = 206,748)	No	160,67	45,617		
Black	Yes	93	18		
(N = 24,021)	No	20,431	3,479		
Others	Yes	44	26		
(N = 17,566)	no	12,398	5,098		
Calendar-period of selection				0.81 (0.68, 0.96)	0.7399
1993-1995	Yes	7	2		
(N = 60,966)	No	49,911	11,046		
1996-2000	Yes	77	33		
(N = 70,647)	No	54,293	16,244		
2001-2005	Yes	385	139		
(N = 117,207)	no	89,666	27,017		
Diabetes				0.78 (0.65, 0.92)	0.9530
Yes	Yes	136	58		
(N = 209,313)	No	29,591	9,722		
No	Yes	333	116		
(N = 39,507)	no	164,279	44,585		
Hepatitis B				0.78 (0.65, 0.93)	0.4010
Yes	Yes	39	16		
(N = 300)	No	173	72		
No	Yes	430	158		
(N = 248,520)	no	193,697	54,235		
Hypertension				0.77 (0.65, 0.91)	0.5084
Yes	Yes	301	110		
(N = 104,488)	No	80,468	23,609		
No	Yes	168	64		
(N = 144,332)	no	113,402	30,698		
HIV				0.76 (0.64, 0.90)	0.6453
Yes	Yes	12	7		
(N = 396)	No	290	87		
No	Yes	457	167		
(N = 248,424)	no	193,580	54,220		
PSA test 0-0.99 years prior to the index date				0.60 (0.50, 0.72)	0.0956
Yes	Yes	389	83		
(N = 151,389)	No	131,659	19,258		
No	Yes	80	91		
(N = 97,431)	no	62,211	35,049		
# of hospitalizations (median = 0)				0.73 (0.62, 0.87)	0.1256

> median	Yes	324	125		
(N = 130,359)	No	103,256	26,654		
<= median	Yes	145	49		
(N = 118,461)	no	90,614	27,653		
# of outpatient visits (median = 5)				0.71 (0.60, 0.85)	0.0147
> median	Yes	356	141		
(N = 127,598)	No	101,746	25,355		
<= median	Yes	113	33		
(N = 121,222)	no	92,124	28,952		
# of physician visits (median = 61)				0.72 (0.61, 0.86)	0.3000
> median	Yes	402	140		
(N = 130,678)	No	103,098	27,038		
<= median	Yes	67	34		
(N = 118,142)	no	90,772	27,269		

We conducted stratified analyses by each covariate and examined whether the OR for prostate cancer comparing HCV-infected to uninfected subjects was heterogeneous across levels of the covariates. Except for number of outpatient visits, the association between HCV infection and prostate cancer risk was not statistically different across categories of any covariates (Table 3). Thus, it is reasonable to use the Mantel-Haenzsel summary OR to represent the risk of prostate cancer after HCV infection for each stratified analysis except for number of outpatient visits. For all stratified analyses, the Mantel-Haenszel summary ORs were within the range of 0.60-0.81 and statistically significant, indicating that the risk of developing prostate cancer was lower among the HCV-infected compared to HCV-uninfected subjects after controlling for each covariate.

Table 4. Association between HCV infection and prostate cancer risk[a,b]

Prostate cancer	Number	Odds Ratio (95% CI)
Cancer	194,339	0.76 (0.63, 0.93)[b]
No cancer	54,481	1.00

[a.] The reference group is HCV-uninfected subjects.
[b.] Adjusted for age, race, calendar-period of selection, geographic region of SEER registry/selection, HBV infection, HIV infection, hypertension, number of hospitalization, number of outpatient visits, number of physician visits, and PSA test 0-0.99 year prior to index date.

With adjustment for matching factors and potential confounders, the interaction term between HCV infection and PSA test was not statistically significant (p=0.58), indicating that PSA test was not an effect modifier of this association, therefore our final model did not include interaction term. In the adjusted analysis, history of HCV infection was significantly associated with decreased risk of prostate cancer (OR 0.76, 95% CI: 0.63-

0.93) (Table 4). In other words, the risk of developing prostate cancer is suggested to decrease by approximately 25% after HCV infection. Including diabetes mellitus in the model did not alter the OR substantially, suggesting that minimal proportion of HCV infection's protective effect for prostate cancer is attributed to diabetes.

Table 5. Association between HCV infection and stage at diagnosis of prostate cancer[a,b]

Stage	Number	Odds Ratio (95% CI)
Controls	54,481	1.00
Localized	94,894	0.86 (0.59, 1.24)
Regional	14,406	0.90 (0.43, 1.89)
Distant	15,608	0.56 (0.26, 1.17)
Unstaged	69,431	0.62 (0.38, 1.00)
Localized	94,894	1.00
Regional	14,406	1.09 (0.71, 1.68)
Distant	15,608	0.64 (0.42, 0.99)
Unstaged	69,431	0.72 (0.58, 0.90)

[a.] The reference group is people without HCV infection.
[b.] Adjusted for age, race, calendar period of selection, geographic region of SEER registry/selection, HBV infection, HIV infection, hypertension, number of hospitalization, number of outpatient visits, number of physician visits, and history of PSA test 0-0.99 year prior to index date.

In the polytomous logistic regression model with the controls as the reference group, we observed HCV infection to be associated with reduced prostate cancer risk within each prostate cancer stage category at diagnosis: localized (OR 0.86, 95% CI: 0.59-1.24), regional (OR 0.90, 95% CI: 0.43-1.89), distant (OR 0.56, 95% CI: 0.26-1.17), and unstaged (OR 0.62, 95% CI: 0.38-1.00) (Table 5). The strongest association was observed for the most advanced stage of prostate cancer. However, none of these associations were statistically significant, possibly due to limited power. The ORs were not heterogeneous from each other (p=0.88). The interaction term between HCV infection and PSA test was found not statistically significant (p=0.26), suggesting no effect modification from screening.

When restricting our analysis to only cancer cases with localized cases as the reference group, we observed a weak, non-significant positive association between HCV infection and regional prostate cancer (OR 1.09, 95% CI: 0.71-1.68), but a negative and significant association between HCV infection and distant prostate cancer (OR 0.64, 95% CI: 0.42-0.99) (Table 5). Again, the ORs were not heterogeneous from each other (p=0.27), and the interaction terms between HCV infection and PSA test was not significant (p=0.31).

DISCUSSION

In this population-based case-control study, we have discovered that HCV infection was associated with reduced prostate cancer risk, after adjusting for demographic features, relevant medical conditions, numbers of visits to healthcare facilities, and PSA test history 0-0.99 years prior to the index date. In addition, our results suggested that this negative association was stronger for late stage prostate cancer than for earlier stage prostate cancer.

Acute HCV infection is rarely discovered in clinical practice, and patients usually carry the virus for several years until non-specific symptoms such as fatigue appear. Duzarro et al. (2006) and Hofny et al. (2011) both reported that HCV-infected patients showed significantly lower levels of free testosterone compared to healthy controls. Nguyen et al. (2006) found that free testosterone concentration was inversely correlated with the severity of liver disease, and the concentration of sex hormone-binding globulin (SHBG) was higher among patients with more severe liver conditions. Two possible biological mechanisms have been proposed to explain the observed low level of free testosterone after HCV infection. One theory is that HCV infection causes primary hypogonadism (Danoff et al. 2006), under which condition, the functionalities of testicles are compromised and thus less testosterone is produced. Secondly, the chronic inflammation at the liver after HCV infection elevates the level of estrogen production (Shimizu et al. 2001; Martino et al. 2004), and more SHBG are produced through the metabolism of estrogen. With increased the availability of testosterone-binding sites on SHBG, the concentration of free testosterone circulating in the system is decreased. High testosterone level has been linked with increased prostate cancer risk (Parsons et al. 2005). The resulting lower level of circulating testosterone level may provide a plausible biological explanation for the observed diminishing prostate cancer risk among HCV-infected subjects in our study.

In the meta-analysis published by Kasper et al. (2006), the authors observed a significant inverse association between diabetes mellitus and risk of prostate cancer (RR=0.84, 95% CI: 0.76-0.93). The underlying mechanism was suggested to involve decreased

concentration of two hormones: insulin and testosterone. Patel et al. (2008) reported that the incidence of prostate cancer was significantly lower among HIV-infected individuals than the general US population (SIR=0.6, 95% CI 0.4-0.8), and HIV infection is known to decreased androgen levels (Engels et al. 2008). These inverse associations suggest that decreased circulating testosterone level diminishes prostate cancer risk, as seen among the HCV-infected individuals.

In a study investigating cancer risks among elderly people with end-stage renal disease (ESRD, Shebl et al. 2012), the authors discovered that ESRD was associated with reduced risk for prostate cancer (OR=0.42, 95%CI: 0.35-0.50) using the same SEER-Medicare dataset. Shebl (2012) postulated that patients with ESRD in general have less life expectancy, and consequently are less likely to receive PSA screening. The authors attributed the observed lower risk to a low prevalence of PSA screening or decreased sensitivity of the PSA test among patients with ESRD, rather than biological modulation by ESDR.

However, the current analysis of the association between HCV infection and prostate cancer risk yielded a different explanation. In the current study, 73.4% HCV-infected subjects received PSA test 0-0.99 year prior to their index date, compared to approximately 60% among the uninfected subjects. Since the prevalence of PSA screening among HCV-infected subjects was substantially higher than the prevalence in HCV-uninfected subjects, HCV-infected subjects should be more likely to be diagnosed with prostate cancer. However, we actually observed a significantly reduced risk of prostate cancer for patients with prior HCV infection (OR 0.76, 95%CI: 0.63-0.93), indicating that this association would be even stronger without the attenuation effect from screening. Thus, it is very likely that the decreased prostate cancer risk after HCV infection is mediated by a biological substance-mediated mechanism and is not an artifact caused by screening.

Interestingly, HCV infection was found to be associated with reduced prostate cancer risk within each cancer stage category (localized, regional, distant, and unstaged) comparing to the controls, and the strongest protective effect was observed for the most advanced stage of prostate cancer. In addition, among prostate cancer cases, a history of HCV

infection was associated with significantly decreased risk of distant cancer compared with localized cancer (OR 0.64, 95% CI: 0.42-0.99), suggesting that prostate cancer patients with HCV infection were more likely to have non-advanced cancer than advanced cancer. However, such findings may have been due to residual confounding by PSA screening. First, 68.0% of cases received a PSA test 0-0.99 years prior to their index dates, compared to 35.5% of the controls; secondly, among the cases, 83.0% of HCV-infected subjects received a PSA test versus 67.9% of the HCV un-infected subjects. Since PSA testing tends to diagnose asymptomatic cancers at an early stage, it is possible that more non-advanced cancers were diagnosed due to the higher prevalence of PSA screening among cases, and particularly, among HCV-infected cases. Thus, the HCV-infected cases may have been more likely to be diagnosed with non-advanced cancers, but they may not truly enjoy a biological protective effect against advanced cancer.

The credibility of these findings is supported by various features of our study. The large sample size of the study provided substantial statistical power to detect the association between HCV infection and prostate cancer risk, and it enabled us to obtain a precise OR estimate. We included all prostate cancers cases aged 66 and older in the SEER program diagnosed during 1993-2005 and controls of the same age and from the same geographic areas. Thus, our study subjects were highly representative of the US elderly population. In addition, for patients who had screening-detected cancer, they were most likely to have received their PSA test within a short period prior to their cancer diagnosis. Thus, adjustment for PSA test 0-0.99 years prior to the index dates in the multivariate model addressed the potential confounding caused by screening, and ensured the validity of the observed association between HCV infection and decreased prostate cancer risk.

Some limitations of our study are worth noting. First, we used Medicare claims data to ascertain HCV infection status, which is likely to underestimate the prevalence of HCV infection, considering that people often live asymptomatically for decades after their initial acute infection with HCV; in addition, it is possible that some of the identified subjects with ICD-9 code for HCV infection are actually false positives, which would decrease the specificity of our method of identifying exposure status. These situations would jeopardize the validity of our point estimate if the prostate cancer cases and

controls exhibited systematically different likelihoods of detection of their HCV infection. Secondly, controls were frequency matched to the age, race and calendar year of selection distribution of cancer cases of all type; selection of prostate cancer cases and all male controls for the current study broke this matching. However, the prostate cancer cases and controls were very balanced on age and race, and reasonably balanced on calendar-period of selection (Table 1); furthermore we adjusted for these variables in the multivariate model to adjust for any residual confounding. Thirdly, some of the identified PSA test may be performed after prostate cancer was suspected due to signs or symptoms, in which case, the PSA tests were not used as screening tests but diagnostic tests.

CONCLUSIONS

In conclusion, we conducted the first population-based case-control study to investigate the association between HCV infection and prostate cancer risk with a large sample size. We found that HCV infection was significantly associated with decreased risk of developing prostate cancer. This association is grounded by a plausible biological mechanism involving decreased concentration of circulating testosterone. More in-depth research is needed to verify the underlying mechanism for the inverse association between HCV infection and prostate cancer. Further exploration of the association between HCV infection and stage at diagnosis of prostate cancer, as well as the role of PSA screening in this association, will also help elucidate the biological basis for our novel finding.

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