Integrative Molecular Medicine

Research Article ISSN: 2056-6360

Detection of serum hepatitis B Virus antigen and hepatitis C virus antibody from prostate cancer patients in Japan

Ishiguro H[1,2*†], Furuya K[2†], Izumi K[2†], Nagai T[1], Kawahara T[2,3], Kubota Y[1,2], Yao M[2] and Uemura H[2,3]

[1]Photocatalyst Group, Kanagawa Academy of Science and Technology, 3-25-13, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, Japan

[2]Department of Urology, Yokohama City University Graduate School of Medicine. 3-9, Fukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan

[3]Departments of Urology and Renal Transportation, Yokohama City University Medical Center, Yokohama, Japan

[†]These authors contributed equally

Abstract

Objective: Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection increases hepatocellular carcinogenesis. Some studies suggest that HBV and HCV can activate androgen signaling. We assessed the association between hepatitis virus infection and prostate cancer in the Japanese population.

Patients and methods: We retrospectively reviewed 212 patients who received needle biopsy of the prostate between 2013 and 2014. Hepatitis B surface antigen (HBsAg) and anti-HCV antibody in serum were evaluated by chemiluminescent immunoassay. Prostate cancer was detected in 182 (85.8%) patients.

Results: Serum HBsAg was positive in one (0.5%) prostate cancer patient and one (3.3%) control patient (p = 0.264). Serum anti-HCV antibody was positive in four (2.2%) prostate cancer patients and one (3.3%) control patient (p = 0.537).

Conclusions: Our results suggest that HBV and HCV infection is not associated with prostate cancer development and progression in Japanese patients.

Abbreviations: HBV: hepatitis B virus; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; AR: androgen receptor; CLIA: chemiluminescent immune assay; PSA: prostate-specific antigen; HBx: hepatitis B virus X

Introduction

Bacterial or viral infections may be involved in prostate cancer development and progression [1,2]. In particular, patients with hepatitis C virus (HCV) infection have a higher prevalence and mortality of prostate cancer [3-5]. Hepatitis B virus (HBV) and HCV are well-known carcinogenic viruses in human hepatocellular carcinoma (HCC), and chronic infection increases HCC risk. In addition to these viruses, androgenic steroids might be responsible for HCC [6,7]. Some studies have shown that HBV/HCV infections promote androgen receptor (AR) signaling in HCC [8-14]. Prevalence of HBV-associated HCC is higher in men than women [15], supporting the association between AR signaling and HBV infection. AR signaling is essential for prostate cancer development and progression, therefore, its association with HBV/HCV infection might play an important role in prostate cancer development or progression. Here, we evaluated the association between HBV/HCV infection and prostate cancer in Japanese patients.

Patients and methods

Patients

A total of 212 biopsy specimens were obtained from Yokohama City University Hospital and related hospitals. Thirty specimens were diagnosed as non-cancer tissues and 182 as prostate cancer. Each patient gave informed consent for the use of clinical information, and the study was approved by Yokohama City University Ethical Committee.

Hepatitis B Surface Antigen (HBsAg) and Anti-HCV Antibody Detection

To detect HBV and HCV infection, HBsAg and anti-HCV antibody were measured by chemiluminescent immune assay (CLIA), which is routinely used in our hospitals. The results of CLIA and related clinical information of each patient were used to detect HBV and HCV infection.

Statistical analysis

All statistical analysis was performed using PASW Statistics 18 (IBM Corp., Armonk, NY, USA). Age and prostate-specific antigen (PSA) level were tested for normality by Kolmogolov–Smirnov analysis. Then, the Mann–Whitney U test was used to test the association with cancer and normal samples. To test the association between each virus infection and clinical characteristics, we applied Fisher's exact test. A value of $p < 0.05$ indicated statistical significance.

Results

Patient characteristics are listed in Table 1. Thirty non-cancer and

Correspondence to: Hitoshi Ishiguro, Photocatalyst Group, Kanagawa Academy of Science and Technology, 3-25-13, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, Japan. Tel: +81-44-280-1181, Fax: +81-44-280-1182, E-mail: pg-ishiguro@newkast.or.jp

Key words: *hepatitis B virus, hepatitis C virus, infection, prostate cancer*

Received: January 22, 2017; **Accepted:** February 13, 2017; **Published:** February 15, 2017

Table 1. Clinical characteristics of analyzed patients.

	non cancer (n = 30)		cancer (n = 182)		
Characteristics	**n**	**(%)**	**n**	**(%)**	
Age (mean ± SD)	67.0 ± 9.3		68.3 ± 7.3		p = 0.624
PSA (mean ± SD) ng/ml	7.5 ± 5.4		42.1 ± 174.1		p = 0.112
≦4	5	-17	11	-6	
4<, <10	10	-33	85	-47	
10≦	4	-13	38	-21	
unknown	11	-37	48	-26	
Gleason score					
	≦6		64	-35	
	7		79	-43	
	≧8		21	-12	
	Unknown		18	-10	
Tumor stage					
	T1		77	-42	
	T2		77	-42	
	T3		6	-3	
	T4		2	-1	
	Unknown		20	-11	
Regional lymph nodes					
	N0		158	-87	
	N1		4	-2	
	Unknown		20	-11	
Distant metastasis					
	M0		157	-86	
	M1		5	-3	
	Unknown		20	-11	

Table 2. Association between prostate cancer and HBsAg.

	HBsAg (-)	HBsAg (+)	
Non Cancer (n = 30)	29	1	
Cancer (n = 182)	181	1	p = 0.264

Table 3. Association between prostate cancer and HCV.

	HCV (-)	HCV (+)	
Non Cancer (n = 30)	29	1	
Cancer (n = 182)	178	4	p = 0.537

182 cancer cases were analyzed to detect HBV and HCV infection. Mean age was 67.0 ± 9.3 years in non-cancer patients and 68.3 ± 7.3 years in cancer patients. There was no significant difference between non-cancer and cancer patients (p = 0.624). Mean PSA level was 7.5 ± 5.4 ng/ml in non-cancer patients and 42.1 ± 174.1 ng/ml in cancer patients. Thus, PSA level was marginally higher in the cancer group than normal group (p = 0.112). There were no cancer recurrences and cancer-related deaths in this study. Serum obtained from each patient was evaluated using CLIA by our hospital, regardless of whether prostate cancer patients had HBV or HCV infection. Results are summarized in Tables 2 and 3. HBV infection was detected only in one cancer case. This case had Gleason score 6 and clinical staging was T1cN0M0. There was no statistical significance between prostate cancer and HBV infection (p = 0.264). HCV infection was detected in four cancer cases and one non-cancer case. All four HCV-infected cancer cases had Gleason score 7. Clinical staging of three cases was T1cN0M0 and one was T2N0M0. There was also no statistical significant between prostate cancer and HCV infection (p = 0.537). As a result of the low infection rate in our samples, we could not perform further statistical analyses to confirm the association between infection and clinical characteristics.

Discussion

In this study, we did not find any association between HBV and HCV infections and prostate cancer. In support of our results, other studies have also failed to show infection of HBV in prostate tissues [2,16]. The association between HBV and AR activation in liver tissues or cells is reported. Hepatitis B virus X (HBx) protein regulates AR expression [9]. HBx protein also regulates AR activity and androgen-dependent gene expression [10-12]. Therefore, HBV might have a role in prostate cancer progression in some cases. Furthermore, some studies suggest the association between HCV infection and prostate cancer. Krystyna et al. [3] reported the association between HCV and prostate cancer in African and African–American individuals. HCV-positive patients have higher cancer prevalence and there is a correlation between HCV infection and prostate cancer progression [4,5]. Kanda et al. [13] showed that HCV regulates androgen signaling through activation of signal transducer and activator of transcription 3. Thus, HCV also might be involved in prostate cancer development and progression through androgen signaling.

Although our study showed no significant associations between HBV and HCV and prostate cancer, it was limited by surveillance of clinical history. We did not distinguish patients with active infection from virus carriers. Therefore, further investigation is needed to clarify the importance of HBV and HCV infection in prostate cancer.

Conclusion

We investigated whether HBV and HCV infection is linked to prostate cancer progression. Although HBV and HCV infection could accelerate androgen signaling in HCC, virus infection was not prevalent in prostate cancer patients. Future work is needed to understand the

biological mechanisms of prostate cancer progression in patients with HBV or HCV infection.

Acknowledgements

This study was supported by the Regional Innovation Strategy Support Program of MEXT (The Ministry of Education, Culture, Sports, Science and Technology) and Japan Society for the Promotion of Science (JSPS) KAKENHI for Grant-in-Aid for Exploratory Research (Grant Number 26670709).

Conflicts of interest

The authors declare that there is no conflicts of interest.

References

1. Caini S, Gandini S, Dudas M, Bremer V, Severi E, Gherasim A (2014) Sexually transmitted infections and prostate cancer risk: A systematic review and meta-analysis. *Cancer Epidemiol* 38: 329–338.
2. Chen Y, Wei J (2015) Identification of Pathogen Signatures in Prostate Cancer Using RNA-seq. *PLoS One* 10: e0128955. [Crossref]
3. Krystyna A, Safi T, Briggs WM, Schwalb MD (2011) Correlation of hepatitis C and prostate cancer, inverse correlation of basal cell hyperplasia or prostatitis and epidemic syphilis of unknown duration. *Int Braz J Urol* 37: 223-229. [Crossref]
4. Malaguarnera M1, Gargante MP, Risino C, Ranno S, Berretta M, et al. (2006) Hepatitis C virus in elderly cancer patients. *Eur J Intern Med* 17: 325-329. [Crossref]
5. Lee MH, Yang HI, Lu SN, Jen CL, You SL, et al. (2012) Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 206: 469–477.
6. Ao J, Meng J, Zhu L, Nie H, Yang C, et al. (2012) Activation of androgen receptor induces ID1 and promotes hepatocellular carcinoma cell migration and invasion. *Mol Oncol* 6: 507-515. [Crossref]
7. Agents classified by the IARC monographs, International Agency for Research on Cancer. Volume 1-112, http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf
8. Kanda T, Yokosuka O, Omata M (2013) Androgen receptor and hepatocellular carcinoma. *Journal of Gastroint Dig Syst* S12: 012.
9. Zhu R, Zhang JS, Zhu YZ, Fan J, Mao Y, et al. (2011) HBx-induced androgen receptor expression in HBV-associated hepatocarcinoma is independent of the methylation status of its promoter. *Histol Histopathol* 26: 23-35. [Crossref]
10. Chiu CM, Yeh SH, Chen PJ, Kuo TJ, Chang CJ, et al. (2007) Hepatitis B virus X protein enhances androgen receptor-responsive gene expression depending on androgen level. *Proc Natl Acad Sci* 104: 2571–2578.
11. Yang WJ, Chang CJ, Yeh SH, Lin WH, Wang SH, et al. (2009) Hepatitis B virus X protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3beta kinase pathways. *Hepatology* 49: 1515–1524.
12. Zheng Y, Chen WL, Ma WL, Chang C, Ou JH (2007) Enhancement of gene transactivation activity of androgen receptor by hepatitis B virus X protein. *Virology* 363: 454-461. [Crossref]
13. Kanda T, Steele R, Ray R, Ray RB. (2008) Hepatitis C virus core protein augments androgen receptor-mediated signaling. *J Virol* 82: 11066–11072.
14. Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, et al. (2009) Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. *Hepatology* 50: 1392-1402. [Crossref]
15. El-Serag HB, Rudolph KL. (2007) Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology* 132: 2557–2576.
16. Khoury JD, Tannir NM, Williams MD, Chen Y, Yao H, et al. (2013) Landscape of DNA virus associations across human malignant cancers: Analysis of 3,775 cases using RNA-seq. *J Virol* 87: 8916–8926.