RESEARCH ARTICLE

Does HBV Infection Increase Risk of Endometrial Carcinoma?

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Abstract

Objective: Connections between chronic inflammation and tumor development and progression are now generally accepted. Recent evidence indicates that hepatitis B is associated with several types of cancer, but whether endometrial carcinoma (EC) is included has not been reported. Methods: We analyzed HBV serum marker status in 398 patients with endometrial cancer, comparing them to 788 control women undergoing health examination. Results: The total prevalence of HBsAg tested positive in cancer group was significantly higher than the control group (12.8% vs 6.0%, P=0.001), while positive HBsAb was significantly lower (41.2% vs 68.5%, P=0.001). Hepatitis B carriers in endometrial cancer group were also more frequent than in the control group (9.3% vs 5.5%, P=0.013). Interestingly, in the endometrial cancer group, 147 cases were HBV serum marker negative, which was also higher than in the control group (36.9% vs 15.6%, P=0.001). Conclusion: There may be a correlation between HBV infection and endometrial carcinoma.

Keywords: Endometrial carcinoma - hepatitis B - serum markers

Introduction

The connection between inflammation and cancer is now generally accepted. In endometrial carcinoma (EC), several reports had demonstrated that tumor-associated macrophages (TAMs) in tumor microenvironment played an important role in the promotion of angiogenesis, progesterone receptor loss, and were also correlated with worse prognosis (Mantovani et al., 2005; Jiang et al., 2012; Jiang et al., 2013). Experimental and epidemiological studies also indicated a strong link between chronic inflammation and tumor progression. Recently it was reported that HBV infection was also associated with several type of cancers, such as hepatocellular carcinoma (Iavarone et al., 2013), non-Hodgkin lymphoma (Becker et al., 2012), pancreatic cancer (Jin et al., 2013), cervical cancer (Siu et al., 2007). Based on these studies, the status of HBV can not be ignored during the treatment of tumor diseases (King et al., 2010). In China, around 120 million people are carriers of HBV (almost a third of the people infected with HBV worldwide) (Liu et al., 2007) and endometrial carcinoma is the most common gynecologic malignancy. Whether there is an association between hepatitis B virus infection and endometrial carcinoma had not been reported. Thus, we analyzed HBV serum marker status in the 398 patients of endometrial cancer, compared to 788 women from health examination.

Materials and Methods

Patients

Two groups of southern Chinese subjects were recruited for this study. The cancer group consisted of 398 patients diagnosed with endometrial cancer were histologically confirmed from the First Affiliated Hospital of Jinan University and Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China, between January 2002 and January 2012. All patients received no hormone therapy and underwent modified radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy and para-aortic lymph nodes sampling. 788 women in the control group were recruited from the department of physical examination. Patients, who were non-Chinese, had history of cancer of any kind were excluded from the control group. The study was approved by the Ethical Committee of Human Experimentation of the First Affiliated Hospital of Jinan University in China. These patients were recruited during their subsequent follow-up visit; venous blood was collected, centrifuged and serum was stored at -80°C until analysis. ELISA assay

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Table 1. Demographic Characteristics of Endometrial Carcinoma

Cancer Group, n=398	
Age (mean±SD)	51.1±12.9
FIGO Stage I	248
Stage II	81
Stage III	45
Stage IV	24
Endometrioid grade 1	198
Endometrioid grade2	115
Endometrioid grade 3	85
Uuterine serous papillary	70
Clear cell type histology	28
Myometrial invasion<1/2	227
Myometrial invasion≥1/2	171
Lymphovascular invasion (+)	111
Lymphovascular invasion (-)	287
Lymph node metastsis (+)	104
Lymph node metastsis (-)	294
Control Group, n=788	
Age (mean±SD)	49.3±9.4

serum HBV surface antigen (HBsAg) was used to identify HBV carriers among HBcAb positive patients.

Detection of HBV serum markers

The presence of HBsAg, HBeAg and antibodies to HBsAg (anti-HBs), HBeAg (anti-HBe) and HBcAg (anti-HBc) in participants' serum was tested using the AXSYM HBV reagent pack (Abbott Laboratories, Abbott Park, IL). The laboratory technician who performed these assays was blind to the subjects' clinical status.

Statistical analyses

Statistical analyses were performed using Windows SPSS version 13.0 software. Chi-square test was used to test the difference between these two groups, $p<0.05$ is considered as statistically significant.

Results

398 patients diagnosed with endometrial cancer were histologically confirmed and 788 health women in the control group were recruited from physical examination. The demographic characteristics of theses patients including age, FIGO stage (Creasman et al., 2009), histopathological grade, myometrial invasion, lymphovascular invasion and lymph node metastsis were listed on Table 1. The mean age of the cancer group and control group was 51.1 and 49.3. There was no significant difference between the two groups age wise.

We therefore stratified patients into young age (less than 40 years old), middle age (40-59 years old) and old age

(greater than 60 years old) subgroups for further analysis. The prevalence of HBsAg tested positive in the young age group (less than 40 years old) was higher than the control group (28.6% vs 5.0%, $P=0.001$); the prevalences of HBsAg tested positive in the middle (40-59 years old) and old age (≥60) subgroups of endometrial cancer were also higher than those corresponding subgroups of the control group (13.2% vs 8.1%, $P=0.043$; 8.6% vs 2.3%, $P=0.027$, respectively). The total prevalence of of HBsAg tested positive in cancer group was also significantly elevated than the control group (12.8% vs 6.0%, $P=0.001$). (Tab. 2). The prevalences of hepatitis B carrier in the young age subgroup and total endometrial cancer group were higher than the control group (17.9% vs 3.6%, $P=0.001$; 9.3% vs 5.5%, $P=0.013$, respectively). HBsAb tested positive prevalence in endometrial cancer group were significantly lower than the control group (41.2% vs 68.5%, $P=0.001$). HBsAb tested positive prevalence was also significantly lower in each subgroup including young age, middle age and old age subgroups (28.6% vs 76.2%, $P=0.001$; 41.3% vs 61.6%, $P=0.001$; 43.8% vs 70.0%, $P=0.001$, respectively). Interestingly, in endometrial cancer group, 147 cases (36.9%) showed HBV serum marker negative, which was also higher than control group (36.9% vs 15.6%, $P=0.001$). Moreover, prevalence of HBV serum marker negative was also increase in each corresponding subgroup (32.1% vs 10.6%, $P=0.001$; 36.4% vs 19.0%, $P=0.001$; 39.1% vs 17.8%, $P=0.001$, respectively).

Discussion

Over the last two decades, viral infections have emerged to be one of the major causal factors for cancer. Besides hepatocellular carcinoma (HCC) that is linked to hepatitis B and C virus infection, human papillomavirus (HPV) and Epstein-Barr virus have been linked to uterine cervical carcinoma and nasopharyngeal carcinoma, respectively (Zur Hausen, 1999; Siu et al., 2007). More than 2 billion people worldwide have been infected with HBV, and, of these, approximately 350 million persons have chronic HBV infection, of which one-third reside in China, with 130 million carriers and 30 million chronically infected (Liu et al., 2007; King et al., 2010).

More and more studies showed that HBV infection was associated with cancer. In the present study, we first showed endometrial carcinoma (EC) was also associated with HBV infection. In endometrial cancer group, the prevalence of HBsAg and hepatitis B carrier were significantly elevated, and the prevalence of HBsAb test positive decreased. The total prevalence of HBsAg-positive was 12.8%, while control group was 6.0%, which was close to 7.2% in China (Liang et al., 2009). The prevalence of HBsAg tested positive in young age

Table 2. Prevalence of Serum Marker of Hepatitis B Virus in Endometrial Carcinoma

Age Group	HBsAg Tested Positive		P	HBsAb Tested Positive		P	Hepatitis B carrier		P	HBV Serum Marker Negative		P
	EC group	Control group		EC group	Control group		EC group	Control group		EC group	Control group	
<40	28.6% (8/28)	5.0% (15/302)	0.001	28.6% (8/28)	76.2% (230/302)	0.001	17.9% (5/28)	3.6% (11/302)	0.001	32.1% (9/28)	10.6% (32/302)	0.001
40-59	13.2% (32/242)	8.1% (29/357)	0.043	41.3% (100/242)	61.6% (220/357)	0.001	12.0% (29/242)	8.4% (30/357)	0.149	36.4% (88/242)	19.0% (68/357)	0.001
≥60	8.6% (11/128)	2.3% (3/129)	0.027	43.8% (56/128)	70.0% (90/129)	0.001	2.3% (3/128)	1.6% (2/129)	0.645	39.1% (50/128)	17.8% (23/129)	0.001
Total	12.8% (51/398)	6.0% (47/788)	0.001	41.2% (164/398)	68.5% (540/788)	0.001	9.3% (37/398)	5.5% (43/788)	0.013	36.9% (147/398)	15.6% (123/788)	0.001

endometrial cancer subgroup (less than 40 years old) was the highest among three subgroups, reaching 28.6%. In addition, the prevalence of hepatitis B carrier in young age endometrial cancer subgroup was 17.9%, which was closed to the 12.9% in cervical cancer group in Hongkong (Siu et al., 2007). The results indicated that chronic inflammation induced by HBV infection might play a role in the development of endometrial cancer, especially in women less than 40 year old.

The cause of endometrial cancer remains unclear, however there are many known risk factors including long-term estrogen exposure, obesity, hypertension, and diabetes. In recent report (Hsu et al., 2012), HBV may also interact with host metabolism and the observed hyperinsulinemia in HBV-infected patients seems to be from altered insulin metabolism rather than HBV-specific effects (Park et al., 2009). Furthermore, chronic hyperinsulinemia can be linked to both obesity and metabolic syndrome which influences endometrial hyperplasia through direct and indirect actions, which are recognized risk factors for endometrial cancer (Campagnoli et al., 2013).

Another possible reason involved in HBV infection and endometrial cancer, approximately 20% of patients with HBV infection may have extrahepatic diseases, such as serum sickness-like syndrome, polyarteritis nodosa, glomerulonephritis, and various neurological and dermatologic diseases (Terrier et al., 2011). Although these extrahepatic disorders mainly result from an immunopathological reaction, viral replication in the extrahepatic tissues may also play a role in the development of these diseases since the suppression of viral replication with antiviral therapy or spontaneous viral clearance positively correlates with the resolution of extrahepatic diseases (Mason, 2006). Indeed, a number of extrahepatic sites have been found to support HBV infection and replication. These sites include peripheral blood mononuclear cells, bone marrow, the spleen, kidneys, bile ducts, the colon, the heart and lymph nodes (Mason et al., 1993). Whether endometrium was also an extrahepatic site in chronic HBV infection need to be verified histologically.

In the present study also showed that the patients with HBV serum marker negative were associated with endometrial cancer. The exact reason was unclear. One of possible reasons was occult HBV infection (OBI), which is defined for patients who are negative for HBsAg but positive for HBV DNA in sera or liver tissues. OBI had been reported to have clinical consequences, including acceleration of the progression toward cirrhosis and HCC (Jin et al., 2013) and also been considered to play a role in chronic hepatitis C virus (HCV) infection which was frequently coinfected with serum marker negative hepatitis B virus (silent HBV mutant) (Uchida et al., 1997). Therefore, some of patients with endometrial cancer and HBV serum marker negative may be involved in HCV infection or HBV mutant. Future study need to measure HCV-RNA and HBV-DNA in the patients with HBV serum marker negative.

To the best of our knowledge, this is the first report describing the relationship with endometrial cancer and HBV infection. Therefore, when we treat endometrial cancer, we should not ignore hepatitis B status and HBV reactivation. Yeo et al. (Yeo et al., 2003) demonstrated that reactivation of HBV occurred in 41% of those patients and resulted in a delay in chemotherapy or premature termination of therapy in the majority of the patients. Risk factors for HBV reactivation include chemotherapy regimens containing glucocorticoids and anthracyclines as well as elevated levels of HBV DNA prior to chemotherapy administration. Because of the risk for viral reactivation, the American Association for the Study of Liver Diseases (AASLD) recommends screening all persons at risk for HBV infection who require immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic and gastroenterological disorders, for chronic HBV infection. In light of these data, the AASLD issued practice guidelines recommending antiviral prophylaxis for HBV carriers who receive chemotherapy (Siu et al., 2007; King et al., 2010). Similarly, the National Institutes of Health Consensus Development Conference on the management of hepatitis B also issued recommendations for initiation of prophylactic antiviral therapy at the onset of chemotherapy (Sorrell et al., 2009).

In summary, we demonstrate that HBV infection was associated with endometrial cancer. Further studies are needed to confirm our finding in animal model and delineate the mechanism involved.

Acknowledgements

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