Is Hepatitis B Virus a Player in Pancreatic Cancer?

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Rezumat

Este virusul hepatitic B un jucător în cancerul de pancreas?

Cancerul de pancreas (carcinomul ductal, PDAC) reprezintă o problemă importantă de sănătate publică având letalitate ridicată. Astfel, aproximativ 80% dintre pacienții cu PDAC decedează în primul an de la momentul stabilirii diagnosticului. Factori de risc precum fumatul, obezitatea, vârsta înaintată, diabetul zaharat și pancreatita cronică au fost asociați cu apariția PDAC. Virusul hepatitic B (HBV) este de asemenea considerat un factor de risc pentru apariția PDAC în unele studii. Totuși, rolul HBV în PDAC este insuficient documentat. Lucrarea de față trece în revistă cercetările existente ce explorează impactul HBV în PDAC. Evaluarea impactului HBV în PDAC este dificilă deoarece efectele infecției virale pot fi ușor subestimate. Într-adevăr, rolul jucat de infecția ocultă HBV și dificultățile întâmpinate în detecția antigenului HBV sau a ADN-ului HBV în țesutul pancreatic reprezintă limitări importante în cercetarea acestor aspecte. La momentul actual, există suficiente date în literatură care să sugereze potențialul rol oncogenic al HBV în PDAC, dar datele din studiile experimentale sunt puține. În plus, se pare că HBV ar avea influență asupra unor factori clinici și patologici ai pacienților cu PDAC. Studii viitoare care să definească mai bine rolul HBV în apariția PDAC sunt imperios necesare.

Cuvinte cheie: virusul hepatitic B, infecție ocultă, cancer pancreatic, epidemiologie, factor de risc, rezultate

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Abstract

Pancreatic cancer (i.e., pancreatic ductal adenocarcinoma, PDAC) is an important healthcare issue and a highly lethal disease. Thus, almost 80% of patients with PDAC will die within one year after diagnosis. Several factors including smoking, obesity, advanced age, diabetes mellitus and chronic pancreatitis have been associated with increased risk of PDAC. Hepatitis B virus (HBV) infection is also considered as a risk factor for PDAC development in some studies. However, the role of HBV infection in PDAC is poorly explored. The present paper reviews the current relevant literature exploring the impact of HBV infection in PDAC. Assessment of HBV infection impact in PDAC is challenging because its effects could be easily underestimated. Indeed, the role played by occult B infection (OBI) and intrinsic difficulties to detect HBV antigens or DNA in pancreatic tissue remains major limitations to further progress. To date a significant proportion of available literature suggests the potential oncogenic role of HBV in PDAC but experimental evidences remain scarce. Remarkably, it appears that HBV infection might influence some clinical and pathological features of patients with PDAC. Future researches to better define the role of HBV infection in developing PDAC are urgently needed.

Key words: hepatitis B virus, occult B infection, pancreatic cancer, epidemiology, risk factor, outcomes

Introduction

Pancreatic cancer (i.e., pancreatic ductal adenocarcinoma, PDAC) is an important healthcare issue and a highly lethal disease (1-3). Thus, more than 50% of patients present distant metastases at diagnosis and the estimated 5-year survival rate for all stages is around 8% (4).

Overall, it appears that extremely modest improvements of survivals were observed for PDAC over the years (3,4), despite substantial treatment evolutions in the last 20 years (1,5-10). As a consequence, the short-term survival rate remains dismal with almost 80% of patients with PDAC who die within one year after diagnosis (2).

Pancreatic resection represents the single hope for long-term survival in PDAC but few patients are suitable for such intervention at the time of diagnosis (1,3,11). Interestingly, although more patients with PDAC undergo pancreatectomies (2,8), with improved median survivals (8), it appears that the 5-year survival rates after resection for PDAC did not improved significantly in the last period (8). Nevertheless, although long-term survival in patients with PDAC is widely considered as

extremely rare, the 5-year survival rate in resected patients is by far much better (i.e., 10.1%), compared with the 5-year survival rates of localized unresected or metastatic PDAC (i.e., 0.5% and 0.1%, respectively)(12).

PDAC is subjected to geographical disparities regarding both its incidence and its mortality (13). Thus, the largest part of patients with PDAC is coming from Western Pacific, Europe and Americas (13). Unfortunately, the worldwide incidence rate of PDAC almost equals its mortality rate betraying its universal high lethality (13).

The predicted number of deaths from PDAC for 2018 is 44 500 in men and 44 400 in women in Europe (14) and 23 020 in men and 21 310 in women in the United States (4). Although PDAC is not in top 5 of the most frequent forms of cancers in both sexes (it ranks in 15th position), it represents, however, the 4th cause of deaths by cancer both in men and women (4). Furthermore, although PDAC shows stable rates in men, in women a steady rise is observed in Europe (14). Conversely, in the United States, PDAC shows stable rates in women and a rise in men (4). Moreover, the global burden of PDAC (incidence and mortality rates) is expected to rise significantly over the next few decades regardless

of age, gender or geographic location (13).

Hepatitis B virus (HBV) remains a topic of constant worries today although tremendous progresses have been made to overcome the burden of HBV infection(15).

A recent study has shown a mean global prevalence of hepatitis B surface antigen (HBsAg) carriage, that betrays persistent infection, of 4.9%, with considerable geographical disparities (16). Thus, the highest prevalence was observed in Africa and Western Pacific (7.1% - 9.5%)(16). Conversely, the lowest prevalence was observed in Americas and Europe (0.6% - 2%)(16).

Immunization dramatically reduced the burden of HBV infection in many countries and the role of the virus in hepatocellular carcinoma (HCC) epidemiology is predicted to decrease (17). Noticeably, the World Health Organization aims to eliminate HBV by 2030 (16).

It is worth to highlight the outstanding research on HBV of Pierre Tiollais and co-workers at Institut Pasteur in Paris(18-20), a place where the first cloning and sequencing of HBV genome was performed (21). The work of Pierre Tiollais and co-workers was a significant contribution to better understanding of HBV biology, its role in carcinogenesis and obtaining effective therapies, including vaccination. Thus, as an outcome of his research and that of others, millions of lives have been saved all over the world.

The role of HBV in pathogenesis of HCC has been highlighted for a long time(18;22;23). Moreover, not only patients with HBV are at high risk for developing HCC (24-26) but it appears that HBV infection modulates clinico-pathological features and long-term outcomes in HCC-treated patients (27,28).

HBV is a hepatotropic virus that is detected in several types of extra-hepatic tissues, including the pancreas (29-35). It is, therefore, considered to play a role in the development of extra-hepatic malignancies (25,26,36,37), including PDAC (25,29,33,37,38). However, detection of HBV in extra-hepatic tissues is challenging (29,31) and might explain the paucity of studies addressing this issue (38). It appears that detection of HBV DNA represents

the most accurate method to demonstrate the presence of HBV in extra-hepatic organs (29), and it is worth to mention the merit of Dejean and co-workers in Institut Pasteur to first extract HBV DNA from pancreas (30). Remarkably, HBV was shown to not only infect but also to replicate in the tumor and non-tumorous pancreatic tissue of patients with PDAC (33). As low levels of HBV replication are usually observed in pancreatic cancer cells, it is not surprising that molecular data about the potential role of HBV in PDAC remain scarce (31,33).

The present paper reviews the current relevant literature exploring the impact of HBV in PDAC

Is HBV infection a risk factor for PDAC? – Current evidence from epidemiological studies

Nowadays several factors have been associated with an increased risk of PDAC. Thus, smoking, obesity, alcohol abuse, male gender, advanced age, diabetes mellitus and chronic pancreatitis are widely considered the main risk factors for developing PDAC (3,39-43). In addition, infectious factors such as *Helicobacter pylori* have been associated with an increased risk of developing PDAC (39,43).

Several epidemiological studies, reaching conflicting conclusions, have explored the potential role of HBV as risk factor for PDAC (Table 1).

Hassan and co-workers in a study at M.D. Anderson Cancer Center have found that patients without HBsAg itself but positive for antibodies directed towards hepatitis B core protein (anti-HBc) with (OR=2.3) or without (OR=4.0) antibodies directed against hepatitis B surface antigen (anti-HBs) have an increased risk of developing PDAC(40). This observation suggests that past exposure to HBV or possible occult B infection (OBI) might represent risk factors for PDAC. In addition, in this series exposure to HBV was greatly increasing PDAC risk (OR=7.1) in diabetics.

The REVEAL-HBV study, in Taiwan, has shown that HBsAg(+) patients, in the settings either of a chronic active infection or inactive

Table 1. Epidemiological studies exploring in multivariate analyses the association of HBV infection biomarkers with the risk of pancreatic cancer development.

Author, year	HBsAg(+)	HBsAg(+)/ anti-HBc(+)	HBsAg(-)/ anti-HBc(+)	Anti-HBc(+) /anti-HBs(+)	Anti-HBc(+)/ anti-HBs(-)	HBsAg(+)/ HBeAg(-)	HBsAg(+)/ HBeAg(+)	HBsAg(+)/ HBV viral load undetectable	HBsAg(+)/ HBV viral load detectable
Hassan, 2008 (40)	-	-	2.5 (1.5 – 4.2)	2.3 (1.2 – 4.3)	4 (1.4 – 11.1)	-	-	-	-
Berrington de Gonzalez, 2008 (50)	1.1* (0.8 – 1.5)	-	-	-	-	-	-	-	-
Iloeje, 2009 (44)	1.9 (1.1 – 3.7)	-	-	-	-	1.6 (0.7 – 3.4)	5.7 (1.7 – 19)	0.6* (0.1 – 4.6)	2.4 (1.2 – 4.9)
Hong, 2010 (41)	0.9* (0.5 – 1.5)	-	-	-	-	-	-	-	-
Zhu, 2011 (47)	-	-	-	-	-	-	2.9 (1.1 – 7.9)	-	-
Ben, 2012 (45)	1.6 (1.1 – 2.2)	-	1.1* (0.8 – 1.3)	0.8* (0.6 – 1.1)	1.7 (1.2 – 2.4)	-	-	-	-
Wang, 2012 (46)	-	1.6 (1.1 – 2.3)	-	1.5 (1.1 – 2)	-	-	-	-	-
Liao, 2012 (42)	0.9* (0.3 – 2.4)	-	-	-	-	-	-	-	-
Huang, 2013 (49)	2* (0.7 – 5.3)	-	-	-	-	-	-	-	-
Woo, 2013 (53)	1.1* (0.6 – 1.5)	-	-	-	-	-	-	-	-
Sundquist, 2014 (26)	11.3 (2.1 – 33.4)	-	-	-	-	-	-	-	-
Chang, 2014 (48)	-	1.2* (0.8 – 1.6)	-	1.1* (0.8 – 1.2)	-	-	-	-	-
Tang, 2014 (51)	-	1.1* (0.1 – 7.7)	-	1.4* (0.8 – 2.2)	-	-	-	-	-
Andresen, 2015 (24)	0.8 (0.3 – 2.5)	-	-	-	-	-	-	-	-
Kamiza, 2016 (25)	2.7 (1.7 – 4.3)	-	-	-	-	-	-	-	-

Data are expressed as odd ratio (95% confidence intervals); 1 only for patients < 30 years; **P* values ≥ 0.05 , ns; HBsAg(+)/anti-HBc(+): chronic carrier; HBsAg(-)/anti-HBc(+): past exposure; anti-HBc(+)/anti-HBs(+): past exposure with natural immunity; HBsAg(+): chronic or inactive carrier; anti-HBc(+)/anti-HBs(-): possibly chronically infected and have undetectable levels of HBSAg present in the serum (OBI)

carriage, are at increased risk (OR=1.95) of developing PDAC(44). A higher viral DNA load was also correlated with a high risk of developing PDAC(44).

Ben and co-workers, in a Chinese study from Shanghai, have shown that HBsAg(+) patients (i.e., active infection or inactive carriers) have an increased risk (OR=1.6) of developing PDAC (45). By contrast, patients with isolated anti-HBc (i.e., potential OBI) and anti-HBs(+)/anti-HBc(+) patients (i.e. past exposure with natural immunity) were not found to be at risk of PDAC(45). In addition, in this survey, concomitant diabetes mellitus was further increasing the risk of PDAC.

Wang and co-workers, in another Chinese study from Guangzhou (South China), have shown that HBsAg(+)/anti-HBc(+) patients (i.e., chronic carriers) and anti-HBs(+)/anti-HBc(+) patients (i.e., previously exposed with natural immunity) are at significant risk (OR=1.6 and 1.5) to develop PDAC (46).

Jin and co-workers in a third Chinese study have shown that patients with isolated anti-HBc (i.e., past exposure and possible OBI) have increased risk of developing PDAC, while HBsAg(+) patients (i.e., chronic active infection or inactive carriers) were not at risk (33). Although a significantly higher proportion of HBV DNA(+) patients was observed in the

PDAC patients compared with “healthy” controls, however, no differences of viral load levels were observed (33). Interestingly, in more than 70% of patients with PDAC and positive for HBV DNA, the HBsAg in the serum was not detected suggesting the high prevalence of OBI (33).

Other studies with less convincing outcomes have been published. Kamiza and co-workers in a Taiwanese study have associated HBV infection to PDAC (25). However, the association did not reach statistical significance when patients with HBV and hepatitis C virus co-infection were excluded (25). An increased risk of PDAC among HBV patients who were infected at a younger age (i.e., < 30 years at diagnosis of HBV) was suggested in a study performed in Sweden (26). Positivity for HBeAg, a marker of HBV replication, was found to be a risk factor of developing PDAC in a Chinese study (47).

Finally, it is worth to mention that there are also studies such as two Taiwanese studies (42,48), a Swedish study (49), a Chinese study (47), the Japan Public Health Cancer study (50), the Danish Cancer Registry study (24), a US study (51) and three Korean studies

(41,52,53) that did not associate HBV with an increased risk of developing PDAC.

Nevertheless, several meta-analyses have shown that the PDAC risk positively correlates with HBV infection, particularly for chronic carriers and occult infection (54-61). However, it is worth to mention that most analyzed studies are coming from Asia and were case-control studies with a heterogeneous design of control group (*Table 2*). Anyhow, some researchers still question the association of HBV infection with PDAC considering it as a likely coincidence. In any case, the conclusions of meta-analyses and other studies as well should not be generalized and should be interpreted with caution.

What is known about the potential oncogenic mechanisms of HBV infection in PDAC?

The oncogenic potential of HBV in PDAC was presumed for a long time(62) but the mechanisms triggered by HBV in PDAC remain largely unknown. Several hypotheses have been proposed taking into consideration the fact that pancreas and liver share many features in their early embryological growth

Table 2. Meta-analyses exploring the association of HBV infection biomarkers with the risk of pancreatic cancer development

Author, year	HBsAg(+)	HBsAg(+)/ anti-HBc(+)	HBsAg(-)/ anti-HBc(+)	Anti-HBc(+)/ anti-HBs(+)	Anti-HBc(+)/ anti-HBs(-)	HBsAg(+)/ HBeAg(+)	Anti-HBs(+)	Anti-HBe(+)
Fiorino, 2013(54)	1.18 (1.04 – 1.33)	-	1.31* (0.93 – 1.84)	1.12* (0.78 – 1.59)	-	1.31* (0.85 – 2.02)	-	-
Li, 2013(55)	1.4 (1.13 – 1.72)	-	-	-	-	-	-	-
Luo, 2013(56)	-	1.36 (1.16 – 1.62)	-	1.41 (1.06 – 1.87)	-	3.83 (1.76 – 8.36)	-	-
Wang, 2013(58)	1.6 (1.26 – 2.05)	-	1.50* (0.92 – 2.43)	1.36* (0.79 – 2.32)	1.76 (1.05 – 2.93)	1.71* (0.76 – 3.82)	-	-
Xing, 2013(59)	-	-	1.54* (0.60 – 3.98)	1.62* (0.97 – 2.71)	2.16* (0.98 – 4.74)	1.7* (1.77 – 4.01)	0.40 (0.20 – 0.79)	0.62 (0.39 – 0.99)
Xu, 2013(60)	1.2 (1.01 – 1.39)	-	-	0.98* (0.80 – 1.16)	1.67 (1.13 – 2.22)	0.98* (0.27 – 1.68)	0.54 (0.46 – 0.62)	-
Majumder, 2014(57)	1.50 (1.21 – 1.87)	-	-	-	-	-	-	-
Zhuang, 2014(61)	1.24 (1.06 – 1.47)	-	-	-	-	-	-	-

Data are expressed as odd ratio (95% confidence intervals); *P values ≥ 0.05 , ns; HBsAg(+)/anti-HBc(+): chronic carrier; HBsAg(-)/anti-HBc(+): past exposure; anti-HBc(+)/anti-HBs(+): past exposure with natural immunity; HBsAg(+): chronic or inactive carrier; anti-HBc(+)/anti-HBs(-): possibly chronically infected and have undetectable levels of HBsAg present in the serum (OBI)

and that some altered cellular signaling/regulatory pathways are similar in PDAC and HCC (63).

Chronic pancreatitis and diabetes mellitus are well established conditions associated with high risk of developing PDAC (39,43). Hence, HBV infection has been linked to these affections both by epidemiological and pathological analyses. HBV DNA and HBsAg were detected in pancreatic tissue or juice and were associated with development of chronic pancreatitis (30,32-35,64). Chronic inflammation induced by HBV is known to participate eminently in liver tumorigenesis and might, therefore, contribute to development of PDAC as well (33). A significant synergistic effect between the presence of HBsAg and history of diabetes mellitus on PDAC risk was also highlighted in some studies (33,40,45). Epidemiological connections between HBV infection and diabetes mellitus are supported at the histological level by the occasional strong expression of HBsAg and HBcAg in islet cells (33).

Other mechanisms suggested to induce carcinogenesis include HBV DNA integration in infected cells and subsequent protracted immune reaction of the host to clear the HBV-containing cells, a situation observed in HCC patients (45).

Besides, Chen and co-workers have shown that HBV X protein promotes PDAC through modulation of the PI3K/ AKT signaling pathway (29).

Recently, Fiorino and co-workers have proposed a unified model that might explain the pancreatic carcinogenesis in patients with persistent HBV infection (65). This model hypothesizes that HBV-induced inflammation in the pancreas (and the liver as well) modifies the viscoelastic properties of the tissues. The increased stiffness generates a mechanical cellular stress that is translated by signaling pathways to produce an excess of radical oxygen species (ROS) leading on the long run to carcinogenesis.

Is there any influence of HBV infection on clinico-pathological features and long-term outcomes in patients with PDAC?

Previous studies have shown the impact of HBV in different malignancies (27,28,37,66). In HCC, our previous studies have shown significantly younger ages, male predominance and higher prevalence of liver cirrhosis, and less outside Milan criteria patients in the HBV-HCC group, compared with the non-viral HCC group of patients (27). However, no significant differences between groups were observed for postoperative mortality, disease-free and overall survival rates (27). A recent study has shown that HBsAg(+) patients with any cancer types and positive have significantly younger ages at time of diagnosis, compared with the non-viral patients with corresponding cancers (37).

A role of HBV in PDAC might, thus, come together with changes in the presentation of the disease. One might say that assessing the impact of HBV infection in PDAC is challenging and its effects could be easily underestimated (29). Indeed, OBI and difficulties to detect HBV in pancreatic tissue remains major limitations (29,33). Occult HBV infection is considered to play a role in promoting growth of tumors normally unrelated to the virus, and has been considered as a potential risk factor for development of several malignancies (67), including PDAC (58). Nevertheless, several studies have explored the potential impact of HBV in PDAC but have reached mixed conclusions.

Wang and co-workers have found that HBsAg(+) patients with PDAC are significantly younger and more predominantly males, compared with the PDAC patients never exposed to HBV infection (68). No differences were observed for tumor stage or grade of differentiation (68). The multivariate analysis did not find HBsAg positivity as risk factor modulating overall survival in PDAC patients (68).

Jin and co-workers observed that persistently HBV-infected patients with PDAC are significantly younger and increased rates of chronic

pancreatitis, compared with patients without HBV infection (33). No differences were observed for gender, tumor size and stage or perineural invasion (33). Interestingly, patients with HBV infection displayed more frequently well-differentiated tumors albeit the statistical significance was not reached (33).

According to Wei and co-workers, patients with PDAC and chronic HBV infection are significantly younger and more predominantly males, compared with the non-viral PDAC patients (69). No differences were observed for tumor size and stage (69). The issue of sex is somewhat expected though, as males are known to be more susceptible than females to HBV chronic infection.

Chen and co-workers did not find any significant differences of T stage, vascular, perineural and lymph nodes invasion between patients with PDAC with or without HBsAg (29). However, shorter overall survival times were observed in the HBsAg positive group albeit statistical significance was not reached (29).

In a study conducted in China, chronic active infection with HBV was associated with statistically significant decreased rates of synchronous and metachronous metastases in patients with advanced PDAC and improved survivals for patients with stage IV PDAC, compared with patients with no HBV infection (70,71). No differences were observed for inactive carriers (70). This observation is reminiscent of the fact that lower rates of liver metastases of colorectal cancer origin in patients with chronic liver diseases were previously highlighted in a meta-analysis (66). On the opposite, a previous study performed in China has shown significantly increased rates of synchronous liver metastases in patients with chronic HBV infection but no differences for general synchronous metastases, compared with the non-viral PDAC patients (69). In keeping with the work of Chen et al. significantly better overall survivals were observed for patients with chronic HBV infection (69).

Our previous studies have shown no significant differences between patients with pancreatectomies for PDAC, with or without

positive HBsAg, regarding age at diagnosis, gender, grade of differentiation, postoperative complications, completion of adjuvant therapy and overall survivals (72). However, tumor size and T stage tended to differ between the groups (72). Indeed, smaller tumors and earlier stages appear to be associated with HBV-PDAC patients albeit statistical significance was not reached (72). Nevertheless, this study had important limitations including overlooking of occult infection and past exposure to HBV infection and thus, its results should be regarded with caution (72).

Chemotherapy is frequently used for patients with PDAC in an adjuvant, neo-adjuvant or palliative setting (1). It is known that reactivation of HBV is not uncommon in patients receiving chemotherapy (73) and the prognosis of these patients has been reported to be poor (74). Thus, HBV infection might have a detrimental effect on patients with PDAC receiving chemotherapy because reactivation of HBV may lead to severe hepatitis and death from fulminant liver failure or may contribute to delay or premature interruption of chemotherapy (73). Fortunately, not all chemotherapy regimens are associated with the risk of HBV reactivation; gemcitabine/ carboplatin, oxaliplatin and irinotecan-based chemotherapy which are the most frequent regimens used to treat PDAC appears to have low risk for HBV reactivation (75). As a consequence, the risk of HBV reactivation in patients with PDAC appears to be very low (73). Hence, the first case of reactivation of HBV infection following chemotherapy in a patient with PDAC was described only in 2002 (76).

Conclusions

To date, and mostly based on epidemiological evidence, the available literature suggests the potential oncogenic role of HBV in PDAC even if the molecular evidence is scarce. Indeed, the putative instrumental role played by OBI in PDAC associated with difficulties inherent to HBV detection in pancreatic tissue remains major limitations to draw meaningful conclusions.

sions. In addition, HBV infection might influence some clinical and pathological features and it synergizes with selected comorbidities such as diabetes mellitus in patients with PDAC. Future researches to better define the role of HBV infection in developing PDAC are urgently needed.

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