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ASSOCIATION BETWEEN HEPATITIS B AND C WITH HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

ASSOCIAÇÃO ENTRE A HEPATITE B E C COM O CARCINOMA HEPATOCELULAR: UMA REVISÃO DE LITERATURA

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed neoplasms. In addition, infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is associated with the development of HCC, although more genetic and pathophysiological studies are needed to consolidate the relationship. Thus, the aim of this study was to understand the association between HBV and HCV with HCC, and the association that can be established between antiviral therapy for HBV and HCV with this neoplasm. Therefore, a careful review of the literature published between 2016 and 2021 was developed in the databases of VHL and PubMed in Portuguese, English and Spanish. After applying filters and exclusion criteria, 21 articles were included in this review. In summary, the accumulation of mutations of the hepatitis B virus is inherently linked to the acceleration of the development of neoplasm. However, the association between PNPLA3 polymorphism rs738409 and HCC related to HCV is controversial in patients with cirrhosis. In addition, alpha-fetoprotein is the most used biomarker for HCC surveillance, but it has inadequate sensitivity and specificity, while prothrombin induced by vitamin K absence-II and Golgi protein 73 are more effective due to the reduction of false positive levels. Moreover, antiviral therapy with nucleotide analogues inhibits HBV replication, interfering with hepatocellular carcinogenesis. In relation to HCV, direct antiviral therapy reduces the risk of neoplasia because it presents high levels of sustained virological response.

Keywords: Adult. Chronic hepatitis B. Chronic hepatitis C. Liver neoplasm. Risk factors.

RESUMO

O carcinoma hepatocelular (CHC) é uma das neoplasias mais frequentemente diagnosticadas. Ademais, a infecção por vírus da hepatite B (VHB) e vírus da hepatite C (VHC) associa-se com o desenvolvimento do CHC, ainda que sejam necessários mais estudos genéticos e fisiopatológicos para consolidar a relação. Destarte, o objetivo deste estudo foi compreender a associação entre o VHB e o VHC com o CHC, e a associação que pode ser estabelecida entre a terapia antiviral para VHB e VHC com essa neoplasia. Portanto, uma revisão criteriosa da literatura publicada entre 2016 e 2021 foi desenvolvida nas bases de dados da BVS e da PubMed nos idiomas português, inglês e espanhol. Após a aplicação de filtros e critérios de exclusão, foram incluídos 21 artigos nesta revisão. Em síntese, o acúmulo de mutações do vírus da hepatite B está inerentemente ligado à aceleração do desenvolvimento da neoplasia. Contudo, a associação entre o polimorfismo PNPLA3 rs738409 e CHC relacionada ao VHC é controversa em pacientes com cirrose. Além disso, a alfa-fetoproteína é o biomarcador mais utilizado para vigilância do CHC, porém possui sensibilidade e especificidade inadequadas, enquanto a protrombina induzida pela vitamina K ausente-II e pela proteína Golgi-73 mostram-se mais eficazes devido à redução dos níveis de falsos positivos. Para mais, a terapia antiviral com análogos de nucleotídeos inibe a replicação do VHB, interferindo na carcinogênese hepatocelular. Em relação ao VHC, a terapia antiviral direta, por apresentar altos níveis de resposta virológica sustentada, reduz o risco de neoplasia.

Palavras-chave: Adulto. Fatores de risco. Hepatite B crônica. Hepatite C crônica. Neoplasia hepática.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most diagnosed neoplasms (GIRARDI, 2018). In 2018, 841 thousand confirmed cases and 781 thousand deaths of the disease were recorded, which corresponds to 8.2 % of all deaths from neoplasia in the world (BRAY *et al*., 2018). In Brazil, 10,902 deaths were recorded, 6,317 men and 4,584 women according to the *Instituto Nacional do Cancer* (INCA, 2019).

There are several risk factors already identified for the development of liver cancer; among them, chronic infection by hepatitis B virus (HBV) and hepatitis C virus (HCV), cirrhosis, excessive alcohol consumption, non-alcoholic fatty liver disease, family history symptoms of HCC, obesity, Type 2 diabetes mellitus and smoking (TANG *et al*., 2018). Since many of these factors are modifiable, it is important to understand the pathophysiology, genetic aspects, markers used in surveillance and the association of antiviral drugs with the development of hepatocarcinoma, in order to define prevention strategies and reduce the incidence of the disease.

Cirrhosis of the liver, a serious disease associated with alcoholism or chronic hepatitis, is present in about 50% of patients with HCC (INCA, 2021). In cases of chronic liver disease, the patient may present complications such as hepatocellular insufficiency, portal hypertension, hepatic encephalopathy, thrombocytopenia and HCC. These complications are usually the causative factors of the evolution to death (BRASIL, 2019).

Given the relevance of the association between hepatitis B and C and HCC, it is necessary to understand more about this relationship, due to the importance it represents for public health. Thus, this article is a literature review in order to understand the spare factors of the association between the aforementioned hepatitis and hepatocellular carcinoma and the association that can be established between antiviral therapy for HBV and HCV with related neoplasia.

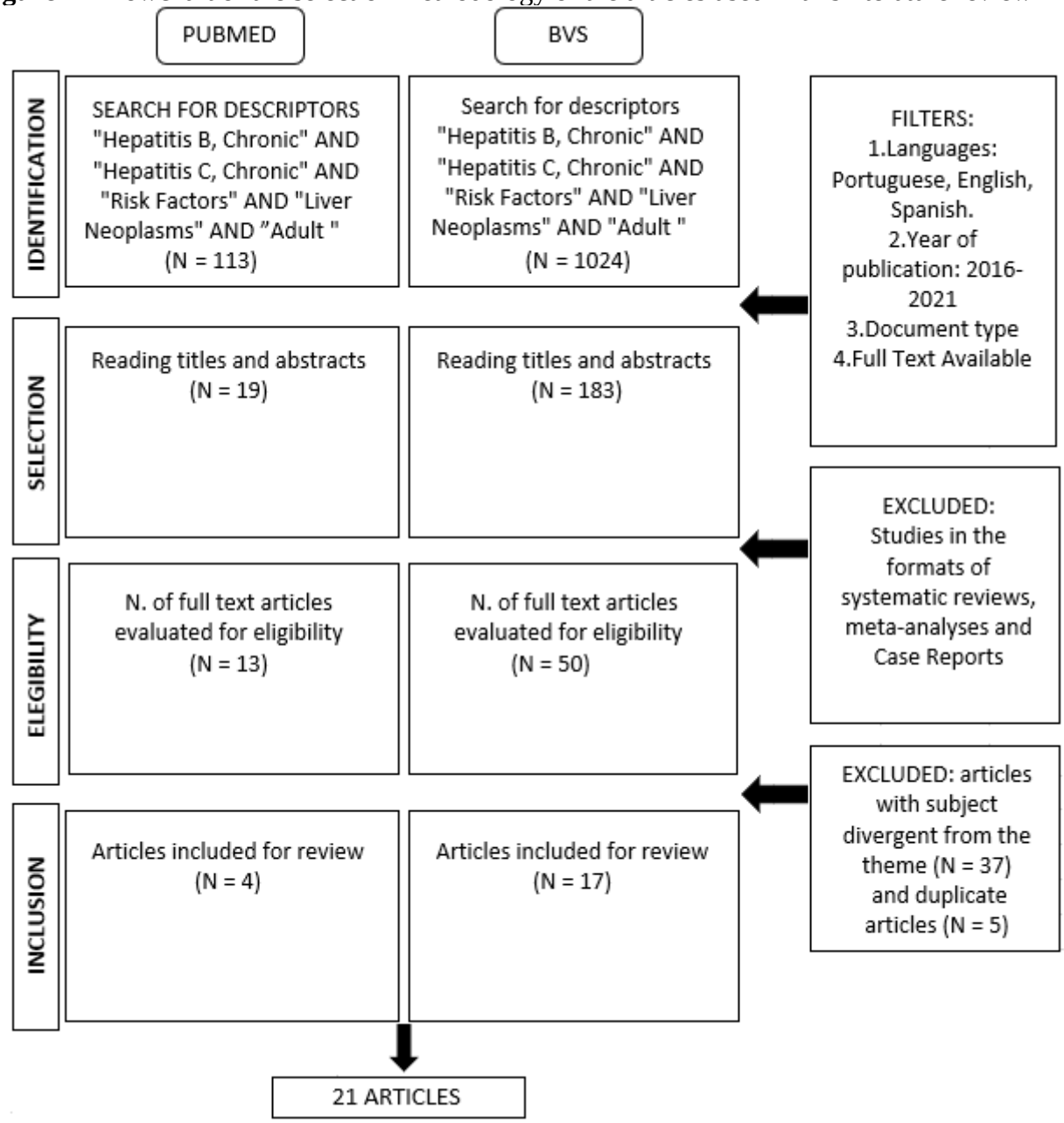
METHODOLOGY

This research is framed as a literature review, whose theme establishes an association between chronic hepatitis B and C with hepatocarcinoma in adults. In order to conduct the study, the keywords were extracted from the themes: “Hepatite B, Crônica”; “Hepatite C, Crônica”; “Fatores de Risco”; “Câncer de Fígado” and “Adulto”. Therefore, the keywords were inserted in the query by permuted index of the Health Sciences descriptors platform (DECS) of the Virtual Health Library and resulted in the five descriptors in English: “Hepatitis B, Chronic”; “Hepatitis C, Chronic”; “Risk Factors”; “Liver Neoplasms” and “Adult”.

Subsequently, the research of scientific articles was carried out in the health databases Virtual Health Library (VHL) and National Library of Medicine (PubMed), with the use of descriptors in English associated with the Boolean operator AND, during the period from January 06, 2021 until February 23, 2021.

We highlight the application of full text filters available, year of publication (between 2016 and 2021) and languages (English, Portuguese and Spanish) for the articles. In addition, there was the exclusion of systematic review articles, Case Reports, meta-analyses, editorials and those that were duplicated in the second research platform, in the case, PubMed. The other documents had previous reading of the titles and abstracts, being excluded in this review those whose thematic approach diverged from the proposed content. The details of the methodological steps for selecting the articles are described in Figure 01.

Figure 1 - Flowchart of the selection methodology of the articles used in this literature review



Source: authors.

DEVELOPMENT

Pathophysiological and genetic factors of the association between hepatitis B and C and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a primary, malignant and solid tumor that occupies, worldwide, the third and fourth place in the highest diagnostic frequency in women and men, respectively (GIRARDI, 2018; SUNG *et al*., 2021). Such a neoplasm may arise from infection by hepatitis B and C viruses, which offer risks for genetic mutation, or by chronic regeneration that generates excessive tissue multiplication and, consequently, assigns greater risks for errors in the DNA duplication process (SUNG *et al*., 2016; SINGER *et al*., 2018; TANG *et al*., 2018).

According to Tang *et al*. (2018), the neoplasm may come from viral necroinflammatory stimulation; thus, the progression and persistence of the infection may be related to the escape

capacity of the immune response. From this strand, it is possible to observe the imbalance of immunomediated mechanisms, since the asymmetry between Th1 and Th2 responses contributes to the installation of cancer (RAMZAN *et al*., 2016). In this sense, it is possible to observe that Interleukin-6 — responsible for regulating inflammatory processes — and interleukin-10 — inhibiting the synthesis of pro-inflammatory cytokines —, when they are in unregulated serum levels, stimulate the progression of neoplasia (SGHAIER *et al*., 2016).

The mechanism of inflammation of HBV and HCV, through inflammatory cytokines, in addition to producing reactive oxygen species, which can trigger malignant genetic changes, stimulates the cascade of liver fibrosis that acts in response to chronic injury and generates accumulation of connective tissue in the liver (TANG *et al*., 2018).

However, the progression of the infection is also influenced by several factors, such as sex, age, insulin resistance and alcohol consumption according to Sghaier *et al*. (2016). And is associated with the development of cirrhosis, a pre-malignant condition that increases the prevalence of hepatocellular carcinoma (ISMAIL *et al*., 2017; TANG *et al*., 2018). In cases of liver cirrhosis, the pathogenesis is observed with chronic inflammation and constant liver damage, in order to cause the differentiation of regenerative nodules to dysplastic nodules that will become hepatocellular carcinoma (ISMAIL *et al*., 2017).

The B virus also presents direct oncogenic potential, a fact that explains the development of HCC in patients chronically infected with HBV, even without progressing to the stage of liver cirrhosis. This phenomenon occurs by the repression of tumor suppressor genes and activation of oncogenes from the incorporation of viral genetic material (DNA) to the host genome (TANG *et al*., 2018). However, 70 % to 80 % of patients who presented HCC after infection with hepatitis B virus, first passed the stage of cirrhosis, obeying the indirect inflammatory pathway (TANG *et al*., 2018). This fact highlights the importance of fibrosis as the main risk factor for liver cancer.

C virus infection can also lead to HCC by several pathways, creating a mechanism that induces mutant and malignant cell rearrangements through the viral protein action (TANG *et al*., 2018). In this case, there is no incorporation into the host genome as in HBV, but there is direct liver damage from HCV-RNA. On the other hand, HCV activates an inflammatory and fibrotic process that stimulates cell death, carcinogenesis and necrosis in response to a persistent damaging stimulus (TANG *et al*., 2018).

As Yang *et al*. (2018) observed in a study conducted with European patients that analyzed seven single nucleotide polymorphisms previously associated with HCC risk, there is a significant association between STAT4-rs7574865 polymorphism and HCC risk in patients with chronic HBV infection; however, the association between PNPLA3-rs738409 polymorphism and HCC risk in patients with HCV-related cirrhosis remains controversial.

According to Sung *et al*. (2016), the accumulation of HBV viral mutations has significant importance in accelerating the neoplasia development. Song *et al*. (2018) found that viral mutation A1630G is a risk variation for HCC only in HBV genotype C infection, whereas mutation A1726T increased the risk for both the development of liver cirrhosis and HCC. However, Song *et al*. (2018) also speculates that host genetic factors may have a stronger influence than viral mutations on HBV infection outcomes.

Krupa *et al*. (2017) found that the polymorphisms rs1052133 and rs13181, present in DNA damage repair genes, have association with HCC. In addition, the authors suggest that the interruption of the expression of these genes is responsible for the development of neoplastic tissue in patients infected with HCV.

Useful markers in hepatocellular carcinoma surveillance

Alpha-fetoprotein is the most used biomarker for the diagnosis and monitoring of hepatocellular carcinoma, however, it has inadequate sensitivity and specificity, and there is a need for the development of more adequate markers that improve the accuracy of diagnosis and allow

better early diagnosis. Thus, other more sensitive markers, such as prothrombin induced by vitamin K II deficiency (PIVKA-II) and Golgi protein 73, were indicated as more effective, because they had higher detected levels, increasing the sensitivity and specificity of screening and diagnostic tests. However, it should be noted that there were no significant differences in the study with the biomarkers mentioned among patients with hepatocellular carcinoma, in relation to the type of chronic viral hepatitis (ISMAIL *et al*. 2017).

According to Qin *et al*. (2018), some polymorphisms of CXCL12 and CXCR4 may be markers of relevance for hepatocellular carcinoma, since they are expressed as risk factors when acting on angiogenesis, the described pathological mechanism for the development of HCC. While for Liu *et al*. (2019), the fibrosis-4 index (FIB-4), which is a biomarker of simple hepatic fibrosis stage, may assist in the clinical prediction of individuals doubly infected by hepatitis B and hepatitis C viruses, although other variables have assisted in the results for the prediction of hepatocellular carcinoma. Paik *et al*. (2017) also evaluated the use of FIB-4, together with the aspartate aminotransferase to platelet ratio index (APRI), to stratify the risk of hepatocellular carcinoma in chronic cases of hepatitis B infection with low viremia, and concluded that these tests could be used to stratify the risk of HCC in this patient profile.

Furthermore, certain cytokines, such as interleukin-6 and interleukin-10, can be studied as relevant biomarkers in the prevention and prognosis of hepatocellular carcinoma, since the signaling pathway of these elements, associated with certain polymorphisms, is inherent in the process of neoplasia development (SGHAIER *et al*., 2016).

According to Cheung *et al*. (2017), the binding protein WFA^+ - M2BP can be evaluated as a new risk marker for hepatocellular carcinoma, indicating that its higher levels are linked to the most significant risk of cancer in individuals with undetectable HBV DNA under therapy, with nucleotide analogues. In addition, the level of WFA^+ - M2BP is also more expressive in patients with hepatocellular carcinoma, regardless of the presence of cirrhosis.

Combination of antiviral therapy for hepatitis B and C with hepatocellular carcinoma

Currently, eight antiviral agents are globally approved for the treatment of chronic hepatitis B, including interferon-a (IFN-a), or pegylated interferon-A, along with six nucleotide analogues (NA), including lamivudine, telbivudine, entecavir, adefovir dipivoxil, tenofovir and tenofovir alafenamide (SARIN *et al*., 2018). In addition, Sarin *et al*. (2018), in a randomized study, showed that patients with chronic hepatitis B treated with interferon (IFN) had a lower incidence of HCC, when compared to untreated patients.

The risk of HCC is a long-term threat to patients with HBV and HCV. Antiviral therapy using NA inhibits HBV replication, improves liver inflammation and reverses liver fibrosis, and may attenuate hepatocellular carcinogenesis (HSU *et al*., 2018). In a study evaluating the action of NA classes, Yip *et al*. (2020) showed that treatment with AN was generally associated with reduced risk of HCC in patients with chronic hepatitis B. Despite the good results, antiviral treatment does not completely eliminate the risk of HCC, requiring further clarification (HSU *et al*., 2018).

Evidence states that sustained virological response (SVR) followed by treatment with IFN-based therapy dramatically reduces, but does not completely eliminate, the risk of developing HCC (SINGER *et al*., 2018). Likewise, still according to Singer *et al*. (2018), there was an approximately 75% reduction in the risk of HCC with SVR among HCV patients at all stages of fibrosis. Based on the evidence of risk reduction of HCC associated with SVR with IFN-based therapy, it was postulated that uptake of direct Antiviral action therapy (DAA), with its high levels of SVR and ability to treat high-risk populations for HCV, will provide reductions in the incidence of HCV among HCV-infected populations (SINGER *et al*., 2018).

A recent study led by Wei *et al*. (2017), indicates that antiviral therapy increases overall survival in patients classified as B or C in the Barcelona criteria with respect to HCC-HBV.

The use of NA decreases the risk of HCC in patients with chronic hepatitis B (PAPATHEODORIDIS *et al*., 2017). For example, as Mak *et al*. (2018) described in a study, patients using entecavir, a first-line nucleoside analogue, were less likely to develop HCC when compared to the control group.

Recently, studies by Papatheodoridis *et al*. (2017) reported that patients with cirrhosis of the liver or aged over 50 years following five years post-treatment with entecavir and tenofovir had a substantial risk of developing HCC. In addition, Papatheodoridis *et al*. (2017) demonstrate that the factors age, abnormal platelet count and hepatic stiffness in the fifth year of *follow-up* were associated with the development of HCC at the end of the first decade of treatment.

Finally, Mak *et al*. (2018), corroborate the importance of appropriate tests and treatments, despite any cost barriers.

CONCLUSION

This literature review considered chronic hepatitis B and C as risk factors for the development of hepatocellular carcinoma in adults. Thus, the integration of viral DNA to the host influences cell proliferation by activating proteins related to the inhibition of tumor suppressor genes. Although the genetic mechanism of relationship of viruses with the development of this neoplasm has specificity, there are relevant associations of genetic polymorphisms with the risk of developing carcinoma in patients with chronic infection by overdosed viruses.

Currently, discrepant markers are being studied for a more effective alternative than alpha-fetoprotein in the surveillance of the development of hepatocellular carcinoma, due to the irregular sensitivity and specificity of this marker. Prothrombin induced by vitamin K absence-II and Golgi protein 73 have a density of false positives, that is, they have become targets of studies aimed at finding a more efficient alternative for surveillance of this neoplasm. On the other hand, the CXCL12 and CXCR4 polymorphisms are also under study for the category of appropriate markers because they play pathogenic action in the development of carcinoma.

Furthermore, the use of nucleotide analogues reduces the risk of hepatocarcinoma in patients with chronic hepatitis B; by inhibiting the virus replication, it corroborates for the improvement of liver inflammation and to reverse possible cases of fibrosis. While for patients infected with the hepatitis C virus, direct antiviral therapy, with high levels of sustained virological response, would have the ability to reduce the incidence of hepatocellular carcinoma. Nevertheless, multiple studies need to be developed to elucidate controversies and offer new information on this theme.

REFERENCES

BRASIL. MINISTÉRIO DA SAÚDE. **Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Coinfecções**. Brasília: Editora MS, 2019.

BRAY, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. **CA: A Cancer Journal for Clinicians**, v. 68, n. 6, p. 394-424, 2018.

CHEUNG, K. S. *et al.* Wisteria floribunda agglutinin-positive human Mac-2 binding protein predicts liver cancer development in chronic hepatitis B patients under antiviral treatment. **Oncotargt**, v. 8, n. 29, p. 47507-47517, 2017.

GIRARDI, D. M. Câncer de fígado. In: **Diretrizes Oncológicas**, 2018. p. 203-212.

HSU, Y. *et al.* Development of a scoring system to Predict Hepatocellular Carcinoma in Asians on Antivirals for Chronic Hepatitis B. **Journal of Hepatology**, v. 69, n. 2, p. 268-285, 2018.

INSTITUTO NACIONAL DO CÂNCER. **Atlas On-line de Mortalidade**, INCA, 2019.

INSTITUTO NACIONAL DO CÂNCER. **Câncer de Fígado**, INCA, 2021.

ISMAIL, M. M. *et al.* Evaluation of prothrombin induced by vitamin K absence, macrophage migration inhibitory factor and Golgi protein-73 versus alpha fetoprotein for hepatocellular carcinoma diagnosis and surveillance. **Scandinavian Journal of Clinical and Laboratory Investigation**, v. 77, n. 3, p. 175-183, 2017.

KRUPA, R. *et al.* The Relationship Between Single-Nucleotide Polymorphisms, the Expression of DNA Damage Response Genes, and Hepatocellular Carcinoma in a Polish Population. **DNA and Cell Biology**, v. 36, n. 8, p. 693-708. 2017.

LIU, C. J. *et al*. Profile and value of FIB-4 in patients with dual chronic hepatitis C and B. **Journal of Gastroenterology and Hepatology**, v. 34, n. 2, p. 410-417, 2019.

MAK, L. Y. *et al.* Global Epidemiology, Prevention, and Management of Hepatocellular Carcinoma. **American Society of Clinical Oncology Educational Book**, v. 38, p. 262-279, 2018.

PAIK, N. *et al.* Non-invasive tests for liver disease severity and the hepatocellular carcinoma risk in chronic hepatitis B patients with low-level viremia. **Wiley Online Library**, v. 38, n. 1, p. 68-75, 2017.

PAPATHEODORIDIS, G. *et al*. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. **Hepatology**, v. 66, n. 5, p.1444-1453, 2017.

QIN, L. F. *et al.* CXCL12 and CXCR4 polymorphisms and expressions in peripheral blood from patients of hepatocellular carcinoma. **Future Oncology**, v. 14, n. 13, p. 1261-1271, 2018.

RAMZAN, M. *et al.* Liver-infiltrating CD8+ lymphocytes as prognostic factor for tumour recurrence in hepatitis C virus-related hepatocellular carcinoma. **Liver International**, v. 36, n. 3, p. 434-444, 2016.

SARIN, S. *et al.* Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. **Hepatology International**, v. 10, n. 1, p. 1-98, 2018.

SGHAIER, I. *et al.* Genetic variants in IL-6 and IL-10 genes and susceptibility to hepatocellular carcinoma in HCV infected patients. **Elsevier**, v. 89, p. 62-67, 2017.

SINGER, A. W. *et al.* Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. **Alimentary Pharmacology & Therapeutics**, v. 47, n. 9, p. 1278-1287, 2018.

SONG, X. M. *et al.* The Effect of ICOS Polymorphism Interactions with HBV Mutations on HBV Subtype Infection Outcomes. **Annals of Hepatology**, v. 17, n. 6, p. 940-947, 2018.

SUNG, F. Y. *et al.* Progressive accumulation of mutations in the hepatitis B virus genome and its impact on time to diagnosis of hepatocellular carcinoma. **Hepatology**, v. 64, n. 3, p. 720-731, 2016.

SUNG, H. *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. **CA: A Cancer Journal for Clinicians**, v. 71, n. 3, p. 209-249, 2021.

TANG, A. *et al.* Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. **Abdominal Radiology**, v. 43, n. 1, p. 13-25, 2018.

WEI, H. Q. *et al*. Better prognosis of hepatic resection combined with antiviral therapy for HBV-related hepatocellular carcinoma with BCLC Stage B/C. **Asian Journal of Surgery**, v. 40, n. 6, 453-462, 2017.

YANG, J. *et al.* PNPLA3 and TM6SF2 variants as risk factors of hepatocellular carcinoma across various etiologies and severity of underlying liver diseases. **International Journal of Cancer**, v. 144, n. 3, p. 533-544, 2018.

YIP, T. C. *et al*. Secondary prevention for hepatocellular carcinoma in patients with chronic hepatitis B: are all the nucleos(t)ide analogues the same? **Journal of Gastroenterology**, v. 55, n. 11, p. 1023-1036, 2020.