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Short communication

Association between hepatitis C and B viruses and head and neck squamous cell carcinoma

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ABSTRACT

Background: Hepatitis B and C viruses are known to be carcinogenic and have been associated with the development of non-Hodgkin's lymphoma as well as hepatocellular carcinoma. The incidence of head and neck cancer is increasing worldwide, and early diagnosis is vital in order to achieve good oncological outcomes.
Objectives: To investigate the association between chronic hepatitis B and C infection, and head and neck squamous cell carcinoma (HNSCC).
Study design: We performed a retrospective case control study with 774 head and neck squamous cell carcinoma (HNSCC) patients undergoing treatment, and 1518 cancer-free controls undergoing hernia surgery. Hepatitis B and C serologies were tested prior to treatment, and cases and controls were age- and sex-matched before analysing rates of infection.
Results: HNSCC patients were more likely than controls to have evidence of chronic hepatitis B (OR = 2.76; CI 95 %, 1.64–4.64) and hepatitis C (OR = 2.59; 95 % CI, 1.46–4.60) infection. No substantial association was found between hepatitis B and C infection and other known risk factors for head and neck cancer.
Conclusions: These findings suggest a positive association between both hepatitis B and hepatitis C chronic infection, and HNSCC. More work is needed to establish a causal role, however an awareness of the possibility of increased risk of HNSCC may lead to earlier diagnosis and better outcomes in patients with hepatitis B and C.

1. Background

In 2020, head and neck cancer (HNC) is expected to affect approximately 833,000 and 151,000 new patients worldwide and in Europe, respectively [1]. HNC includes a heterogeneous group of tumors; more than 90 % are squamous cell carcinoma (HNSCC) and about 70 % originate in the oral cavity, pharynx, and larynx [2]. Hepatitis B (HBV) and hepatitis C (HCV) viruses are carcinogenic pathogens associated with the development of hepatocellular carcinoma and non-Hodgkin's lymphoma [3]. Furthermore, HCV infection appears to increase mortality for other solid cancers [3–5]. HCV infection has previously been found to be associated with HNC, but the power to detect significant associations has generally been limited by sample size [6]. Evidence of HBV in HNC etiology is even scantier [7,8]. None of these studies were conducted in Italy.

2. Objectives

The aim of this case-control study is to investigate the association between HCV/HBV infection an HNSCC risk in Italy, using a cancer-free comparison group.

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3. Study design

After obtaining local ethics committee approval (n. 671/CE Marca), we enrolled 774 HIV-negative patients aged ≥18 years treated for HNSCC between 2000 and 2018. A control group of 1518 cancer-free patients aged ≥18 years undergoing hernioplasty (groin, hypogastric, umbilical, para-umbilical, anterior abdominal wall) was selected from hospital records. In both cases and controls, HBV and HCV serologies were tested before treatment. Previous cancer diagnoses resulted in exclusion from the control group. Controls were matched to cases according to age (± 5 years) and sex.

To improve the estimate precision of HBV/HCV prevalence in the younger population, the case:control ratio was set to 1:2 for patients aged < 55 years and to 1:1 for patients aged 55 years or older. HBV and HCV prevalence, and corresponding binomial confidence intervals, was calculated accounting for age-specific matching ratio. Different and comparisons between cases and controls were conducted through χ^2 test, controlling for age. The risk of HNSCC according to infection with HBV or HCV was reported as odds ratio (OR) and 95 % confidence intervals (CI), estimated through logistic regression modelling conditioned on gender and age group. Attributable fraction and corresponding 95 % CI were estimated according to the Mantel-Haenzeln method [9].

4. Results

The 774 HNSCC patients tested for HCV and HBV antibodies during the study period included 106 oral cavity (13.7 %), 202 oropharynx (26.1 %), 83 hypopharynx (10.7 %) and 383 larynx (49.5 %).

The prevalence of anti-HCV antibodies (aHCV) was much higher among cancer cases (3.49 %) than controls (1.34 %; p < 0.01), resulting in a 2.5-fold higher HNSCC risk (95 % CI 1.46–4.60) among HCV infected people (Table 1). Similarly, HBsAg prevalence was higher among cases than controls (4.52 % and 1.29 %; p < 0.01), with an OR of 2.76 (95 % CI: 1.64–4.64) for HBsAg-positive patients. Accordingly, 2.1 % (1.1 %–2.7 %) of HNSCC cases were attributable to HCV infection and 2.9 % (1.8 %–3.5 %) were attributable to chronic HBV infection.

The association between HBV and HCV infection and HNSCC risk was further investigated according to cancer site (Table 1). No heterogeneity across specific cancer sites was observed for either aHCV ($p_{Heterogeteity}$ = 0.95) and HBsAg ($p_{Heterogeteity}$ = 0.97). Nonetheless, the association between aHCV and cancer risk was weaker for oropharyngeal carcinoma than for the other cancer sites. Coinfection with HBV and HCV was reported in three cases (0.4 %) and no controls.

Finally, the association between HBV and HCV and known risk factors for HNSCC was evaluated among cancer cases. No substantial association emerged, although there was a slightly higher aHCV prevalence among women than men (5.8 % versus 3.0 %; p = 0.12). HBsAg prevalence was slightly higher among people aged < 65 years than among older ones (5.9 % versus 3.4 %; p = 0.12), and in current than in never smokers (5.7 % versus 2.0 %; p = 0.30).

5. Discussion

This study is the largest case-control study reporting a statistically significant association between HNSCC and infection with HCV and HBV. These findings are clinically relevant and add evidence that HBV and HCV infections are associated with HNSCC with a similar magnitude as the already well recognized association with B-cell non-Hodgkin's lymphoma [3,10].

Our results support the association between oral cavity SCC and HCV despite ongoing debate in the contemporary literature [11]. This remains a controversial topic, despite the convincing biological basis via oral lichen planus, a recognized premalignant condition and established sequela of HCV infection [12]. Other authors have analyzed the association between HCV and HNSCC, reporting HCV prevalence among HNC patients between 0.5 % and 24.0 % [6,7,11,13,14]. However, HCV prevalence may depend on baseline risk for HCV infection which varies across geographic areas and patient characteristics. Notably, despite heterogeneous HCV prevalence, HCV-infected patients were consistently reported to have a 2-to-3 times higher HNSCC risk [4,6].

The current evidence on HBV in HNSCC etiology is scanty but is in line with our results. A recent Chinese study [8] reported a 59 % higher incidence of oral cancer among HBsAg seropositive patients, similar to that reported in our study. A previous Turkish study [7] reported a HBsAg prevalence of 5.9 % among HNC patients compared to 3.3 % among controls.

Despite our study being the largest case-control study with cancer free controls associating HBV and HCV infection with HNSCC, it has some limitations. The retrospective design did not allow us to establish a causal relationship. In addition, the lack of complete serology for HCV and HBV (including, HCV RNA and IgM anti-HBc) may have produced some misclassification in defining patients with HCV infection or chronic HBV infection. Nonetheless, in epidemiological studies, aHCV and HBsAg are generally accepted as markers of hepatitis infection.

Table 1
Association between chronic infection with hepatitis C (aHCV) or hepatitis B (HBsAg) virus and the risk of HNSCC, according to specific cancer sites.

Hepatitis virus	All patients	Patients chronically infected		OR (95 % CI)[a]
	n	n	Prevalence (95 % CI)[a]	
aHCV				
Controls	1517	22	1.34 % (0.76 %–1.91 %)	Reference
Cases	774	27	3.49 % (2.20 %–4.78 %)	2.59 (1.46–4.60)
Specific cancer sites				
Oral cavity	106	4	3.77 % (1.48 %–9.30 %)	2.57 (0.82–8.10)
Oropharynx	202	4	1.98 % (0.77 %–4.98 %)	1.75 (0.59–5.18)
Hypopharynx	83	3	3.61 % (1.23 %–10.09 %)	2.73 (0.78–9.60)
Larynx	383	16	4.18 % (2.59 %–6.68 %)	3.01 (1.55–5.86)
HBsAg				
Controls	1518	26	1.29 % (0.72 %–1.86 %)	Reference
Cases	774	35	4.52 % (0.72 %–1.86 %)	2.76 (1.64–4.64)
Specific cancer sites				
Oral cavity	107	3	2.80 % (0.96 %–7.92 %)	1.94 (0.57–6.65)
Oropharynx	202	11	5.45 % (3.07 %–9.49 %)	3.25 (1.56–6.76)
Hypopharynx	83	4	4.82 % (1.89 %–11.75 %)	2.71 (0.91–8.10)
Larynx	382	17	4.45 % (2.80 %–7.01 %)	2.82 (1.50–5.31)

[a] Estimated from a logistic regression model conditioned on matching variables (gender and age).

Further, a higher prevalence of HNSCC risk factors (e.g., tobacco smoking and alcohol drinking) have been reported in HCV-infected people [15], so that the absence of information on these potential confounders in the control group did not allow for OR adjustment. Therefore, it is possible that unadjusted ORs were higher than the actual risk [15,16]. However, our ORs were similar to crude estimates reported in previous studies, which remained significant after adjustment for confounders, even if attenuated [15,16].

Further research is required in order to clarify the molecular mechanisms underlying HCV-related oncogenesis in HNSCC and the prognostic implications of HCV associated HNSCC, however we may conclude that clinicians should be aware that patients with HCV or chronic HBV infection are at increased risk of developing HNSCC. Additionally, oncologists treating patients with HNSCC should consider testing patients for HCV to enable early identification and linkage of care for this infection and to prevent progression of underlying liver disease.

It remains unknown whether early HCV treatment may prevent development of HCV-associated HNSCC or improve oncologic outcomes as reported in patients with HCV-associated non-Hodgkin's lymphoma [10].

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Ethical approval

Not required.

Author contributions

PBR, DB, JP, SD have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

VB, EV have made substantial contributions to acquisition of data and analysis

DB, JF, AM, MCDM, GS have been involved in drafting the manuscript or revising it critically for important intellectual content; PBR, RR, SD, DB, JP Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors should agreed on the order in which their names will be listed in the manuscript.

Each Author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Declaration of Competing Interest

None declared.

References

[1] J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent, et al., Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012, Eur. J. Cancer 49 (6) (2013) 1374–1403.
[2] A.-D. Heroiu Cataloiu, C.E. Danciu, C.R. Popescu, Multiple cancers of the head and neck, Maedica 8 (1) (2013) 80–85.
[3] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Biological agents. Volume 100 B. A review of human carcinogens, IARC Monogr. Eval. Carcinog. Risks Hum. 100 (Pt B) (2012) 1–441.
[4] R.D. Allison, X. Tong, A.C. Moorman, et al., Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010, J. Hepatol. 63 (4) (2015) 822–828.
[5] H.A. Torres, T.L. Shigle, N. Hammoudi, et al., The oncologic burden of hepatitis C virus infection: a clinical perspective, CA Cancer J Clin. 67 (5) (2017) 411–431.
[6] P. Mahale, E.M. Sturgis, D.J. Tweardy, E.J. Ariza-Heredia, H.A. Torres, Association between hepatitis C virus and head and neck cancers, J. Natl. Cancer Inst. 108 (8) (2016).
[7] H. Kocoglu, M. Karaca, D. Tural, et al., Hepatitis B and C rates are significantly increased in certain solid tumors: a large retrospective study, J. Cancer Res. Ther. 14 (2018) S774–S778.
[8] C. Song, J. Lv, Y. Liu, et al., Associations between hepatitis B virus infection and risk of all cancer types, JAMA Netw. Open 2 (6) (2019) e195718.
[9] J. Benichou, A review of adjusted estimators of attributable risk, Stat. Methods Med. Res. 10 (3) (2001) 195–216.
[10] T. Iqbal, P. Mahale, F. Turturro, A. Kyvernitakis, H.A. Torres, Prevalence and association of hepatitis C virus infection with different types of lymphoma, Int. J. Cancer 138 (4) (2016) 1035–1037.
[11] S. Fiorino, L. Bacchi-Reggiani, D. de Biase, et al., Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: a systematic review, World J. Gastroenterol. 21 (45) (2015) 12896–12953.
[12] M. Balakrishnan, M.T. Glover, F. Kanwal, Hepatitis C and risk of nonhepatic malignancies, Clin. Liver Dis. 21 (3) (2017) 543–554.
[13] J.B. Rangel, L.C.S. Thuler, J.F.D.C. Pinto, Prevalence of hepatitis C virus infection and its impact on the prognosis of head and neck cancer patients, Oral Oncol. 87 (2018) 138–143.
[14] G. Angelidakis, E.M. Sturgis, M.P. Economides, Y. Jiang, H.A. Torres, Chronic hepatitis C virus infection in patients with nonoropharyngeal head and neck cancers, Oral Oncol. 85 (2018) 103–105.
[15] H. Innes, A. McAuley, M. Alavi, H. Valerio, D. Goldberg, S.J. Htchinson, The contribution of health risk behavious to excess mortality in American adults with chronic hepatitis C: a population cohort-study, Hepatology 67 (1) (2018) 97–107.
[16] F.H. Su, S.N. Chang, Chen, F.C. Sung, S.F. Huang, H.Y. Chiou, C.T. Su, C.C. Lin, C.C. Yeh, Positive association between hepatitis C infection and oral cavity cancer: a nationwide population-based cohort study in Taiwan, PLoS One 7 (10) (2012) e48109.