Infection with hepatitis B and C viruses, social class and cancer

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The hepatitis B and C viruses (HBV and HCV) are major etiological factors in the occurrence of hepatocellular carcinoma (HCC) worldwide, but most especially in developing countries where the majority of liver cancer cases can be found. In parallel with the geographic distribution of HCC, high levels of HBV endemicity are concentrated in the developing world. The association between chronic infection with HBV and low social class is quite strong; socioeconomic factors such as low educational attainment, lower social stratum, and crowded urban residence have been reported to predict higher HBV chronic carrier prevalence in both developed and developing countries. More importantly, the effect of poverty on HBV endemicity is clearly evident among younger age groups, and earlier chronic HBV infection seems to increase the risk of development of HCC. As assays for detecting HCV antibodies have only recently become available, the data on the relationship between HCV infection and socioeconomic status are much fewer. However, the limited number of studies that have investigated the seroepidemiology of HCV report an association between higher prevalence of antibodies to HCV and indicators of low social class. It would appear that the striking correlation between HCC and low socioeconomic status is largely related to the impact of poverty on the spread of HBV and probably HCV.

The scope of the epidemiological and microbiological evidence that chronic infection with hepatitis B virus (HBV) causes hepatocellular carcinoma (HCC) is extensive. Based on the strength of the immense volume of collected data, the International Agency for Research on Cancer (IARC, 1994) recently concluded that HBV should be classified as a Group 1 human carcinogen. Hepatitis C virus (HCV), the newly identified virus responsible for most of non-A, non-B hepatitis, has also been etiologically linked with the development of HCC. Although much less is known about the natural history of HCV infection, the compelling nature of the existing data led the same IARC Working Group to categorize HCV similarly as carcinogenic to humans (IARC, 1994). Together, chronic infections with HBV and HCV are probably responsible for the majority of HCC cases occurring worldwide (Tomatis, 1990; Tanaka et al., 1991; Tabor & Kobayashi, 1992). Of additional importance is the possibility that HBV and HCV may act synergistically in the causation of this malignancy (Yu et al., 1990; Kaklamani et al., 1991).

Primary liver cancer (PLC), of which HCC is the dominant histological subtype, is the eighth most frequently occurring cancer in the world, and the sixth among males (Parkin et al., 1993). With respect to cancer mortality, PLC ranks even higher – the fourth most common cause of death worldwide and the third among males (Pisani et al., 1993) – due to its nearly uniform fatality. Moreover, 77% of all PLC cases and deaths occur in countries of the developing world (Parkin et al., 1993; Pisani et al., 1993). In such countries, liver cancer is the seventh most frequent malignancy, with the third highest number of deaths.

PLC’s variation worldwide is greater than that for any other major tumour site. The incidence of this cancer is relatively rare in some countries, such as the United States of America, Norway, and the United Kingdom (Stuver & Trichopoulos, 1994), but is very common in parts of Africa and Asia (Parkin et al., 1993). Intermediate risk areas include southern and eastern Europe, and Micronesia (Parkin et al., 1993). Socioeconomic differences have been implicated as an important causal component in the explanation of the wide geographic differences observed in HCC’s distribution, except in the case of Japan where PLC occurrence is relatively high (Pisani et al., 1993) and may be increasing (Stuver et al., 1994).
Within-country variation has been reported in provinces of China (Chen et al., 1990), in ethnic populations of South Africa (Muñoz & Linsell, 1982), and in Japan (Tanaka et al., 1994). In addition, incidence rates are higher among Blacks than Whites in the USA, the former group having a rate consistent with an intermediate risk pattern (Ries et al., 1994).

Studies in migrants, as discussed by Muñoz and Bosch (1987), show that population groups who migrate to other countries retain the PLC risks of their country of origin for at least one generation. A study of Chinese permanently residing in New York City (Szmuness et al., 1978) found that the age-standardized mortality rate from HCC in Chinese males was four times higher than that among Black males and 10 times higher than that among White males. This observation suggests that exposure during early life to the suspected risk factors is one of the main determinants of HCC risk in later life. Moreover, in populations with low and intermediate risk, HCC is rarely seen in people under 40 years of age, whereas in high-incidence areas a shift in the age curve towards the younger age groups can be observed (Muñoz & Bosch, 1987).

Hepatitis B virus

The etiological association of HBV, a double-stranded DNA virus, with HCC appears indisputable and is supported by the integration of HBV DNA sequences into the chromosomal DNA of hepatoma cells from HBV-positive HCC patients (Popper, 1988). In its causation of HCC, HBV probably acts as a ‘complete’ carcinogen (Pitot, 1982), both by initiation through HBV DNA integration and by promotion through cirrhosis-related liver regeneration (Trichopoulos et al., 1987). The proportion of HCC due to HBV infection is estimated to be between 60% and 90% in high-risk countries, but below 50% in low- or intermediate-risk countries (Bosch & Muñoz, 1989).

The strong and specific association between HBV and HCC is restricted to the chronic carrier form of infection, which can be distinguished by the presence of hepatitis B surface antigen (HBsAg) (Muñoz & Bosch, 1987; IARC, 1994). The likelihood of becoming a chronic carrier of HBV is very high for neonatal exposure (~90% for babies born to HBsAg-positive mothers), but appears to decrease with increasing age at first infection (Tabor, 1988; Thomas, 1990). Interestingly, in the study of Chinese immigrants described above (Szmuness et al., 1978), the few subjects tested who were born in the USA had a lower prevalence of markers of HBV infection than those born in Asia, which implied that most of the migrants positive for HBsAg were infected before they came to the USA. A number of epidemiological studies also strongly support the importance of chronic HBV infection early in life for the subsequent development of HCC (Chang et al., 1989; Muñoz et al., 1989; Hsieh et al., 1992).

The World Health Organization classifies HBV endemcity according to the proportion of the adult population who are chronic HBV carriers (that is, positive for HBsAg). Populations with 0–2% carriers are considered as having low endemcity for HBV; those with 2–7%, intermediate endemcity; and those with 8% or more, high endemcity (IARC, 1994). In general, low prevalences of HBV carriers are found in North America, western Europe, Australia, and South America with the exception of the Amazon region. Intermediate levels occur in eastern and southern Europe, the Middle East, Japan, and South Asia. Finally, high prevalences are found in China, South-East Asia, and sub-Saharan Africa (IARC, 1994). The striking graphical correlation in the geographic distribution of the prevalence of chronic carriers of HBV and the occurrence of liver cancer has been pointed out by Maupas and Melnick (1981). Their mapping also effectively characterized the concentration in the developing world of both elevated HCC incidence and HBsAg endemcity. Thus, South-East Asia and sub-Saharan Africa, which have very high HBsAg prevalence, also have the highest rates of HCC, and most populations in the USA and Europe that have low rates of HCC have a low prevalence of HBsAg carriers (Muñoz & Bosch, 1987).

HBV infection is strongly associated with low socioeconomic status in both developed and developing countries (IARC, 1994). As reported by Szmuness (1975), a nationwide survey carried out in the USA in 1971 showed an important variation in the prevalence of HBsAg between geographic regions, with 0.5/1000 in north-central USA versus 3.4/1000 in Puerto Rico. Moreover, the differences in HBsAg detection between ethnic groups found among volunteer blood donors in the USA probably reflected socioeconomic factors. Szmuness also noted that both Whites and non-
Whites with a lower socioeconomic status showed significantly higher prevalences of HBsAg than individuals of a higher educational level (Szmuness, 1975). In the Middle East, a study of seroprevalence of HBV infection carried out in 1985 revealed that HBV carrier status was inversely associated with socioeconomic status, being sixfold greater in the lower socioeconomic stratum compared with the upper stratum (Toukan et al., 1990). Moreover, Phoon et al. (1987) reported a slightly higher risk of HBsAg positivity among male agricultural and factory workers and unskilled labourers than among men in professional, technical and administrative occupations; the investigators felt that the difference was due to socioeconomic factors.

In addition, volunteer blood donors in Jordan who lived in high-class, uncrowded urban areas were shown to have an HBsAg prevalence of 0.7%; those living in intermediate socioeconomic level urban areas had a prevalence of 1.7%; and those from poor, crowded urban areas, refugee camps, or rural areas had a prevalence of 6.9% (Awidi et al., 1984). A relationship between HBsAg prevalence and low socioeconomic status was also reported among blood donors in Thailand (Nuchprayoon & Chumnijarakij, 1992).

The association between poverty and HBsAg positivity seems to hold among younger age groups for whom the risk of developing HBV-related HCC is likely to be greatest. Several studies have reported associations between the prevalence of HBsAg among pregnant women, who represent an important reservoir for HBV transmission to their offspring, and indicators of socioeconomic status. In France, 1.5% of women attending the Centre d'Hématobiologie Péritonale in Paris were chronic carriers, a level sixfold higher than that for the general female population of France; 78% of these women with HBsAg were from outside the metropolitan area (many from Africa), and 80% were of a low socioeconomic level (Soulié, 1984). In Venezuela, as well, none of the pregnant women tested in a private clinic used by a medium to high social class population was found to be positive for HBsAg, whereas 3.8% of women tested in the maternity unit serving a low-income population were HBV carriers (Pujol et al., 1994). In addition, a study of the coverage rate for a neonatal vaccination programme in New York City involving 830 HBsAg-positive mothers reported that infants of mothers covered by Medicaid (government-sponsored) insurance or of uninsured Black and Hispanic women were significantly less likely to have completed the HBV vaccine series (Henning et al., 1992).

Finally, seroepidemiological studies in Greece (Papaevangelou & Roumeliotou-Karayannis, 1988) and Italy (D'Amelio et al., 1992) both observed recent reductions in the prevalence of HBsAg among military recruits, which were attributed by the authors to improvements in societal and economic conditions over the past 10 to 20 years. Moreover, the incidence of HBV seroconversion was reported to be shifting from childhood to older age groups where the probability of becoming a chronic carrier is lower (Papaevangelou & Roumeliotou-Karayannis, 1988; D'Amelio et al., 1992). Decreases in HBsAg positivity have also been reported among children in Japan, again ascribed to better environmental, hygienic and nutritional conditions (Matsuto et al., 1990). It seems likely that decreasing trends in the occurrence of PLC in some countries may be a direct result of such socioeconomic changes (Stuver & Trichopoulos, 1994).

Hepatitis C virus

HCV is a single-stranded RNA virus that has no reverse transcriptase and is non-integrating (Tabor, 1992). Its role in hepatocarcinogenesis is believed to lie in the realm of progression and growth enhancement through the pathogenesis of cirrhosis (Kaklamani et al., 1991; Tabor, 1992; Tabor & Kobayashi, 1992). Because specific tests for HCV infection became available only in 1989, studies investigating the seroepidemiology of this infection are scarce. However, in most populations of the world, 0.5–2% of individuals have serological evidence of past or current HCV infection (IARC, 1994). Ngatchu et al. (1992) carried out a study in Cameroon on children 4–14 years old to evaluate the seroprevalence of HCV and its relationship with sociodemographic factors. The overall prevalence was found to be 14.5%, and a significant elevation of anti-HCV seroprevalence was observed in the lowest social class.

A number of studies of volunteer blood donors also have noted an association between positivity for anti-HCV and indicators of low socioeconomic status. As for HBsAg prevalence in blood donors in the USA (Szmuness, 1975), anti-HCV was detected
more frequently in Black and Hispanic donors than in White donors (Stevens et al., 1990). In a study of Finnish blood donors, the investigators reported an inverse relationship between increasing level of education and positivity for HCV antibodies as confirmed by recombinant immunoblot assay (RIBA) (Kolho & Krusius, 1992). A similar trend was found for RIBA-confirmed, anti-HCV-positive blood donors seen at a Cairo hospital in 1992 (Darwish et al., 1993). Furthermore, Patiño-Sarcinelli et al. (1994) reported a decreased anti-HCV prevalence in Brazil among those with an education beyond the college level compared with those with a lower educational attainment. In that study, non-White race was a significant risk factor for a positive anti-HCV test, which the authors felt reflected a relationship between lower socioeconomic conditions and exposure to HCV infection (Patiño-Sarcinelli et al., 1994).

**HCC and socioeconomic status**

Evidence linking HCC with lower socioeconomic status is primarily based on the studies of the geographic variation of liver cancer (Maupas & Melnick, 1981; Muñoz & Linsell, 1982), with higher rates observed in developing countries, for the most part (Parkin et al., 1993). In addition, the United Kingdom Registrar General's Decennial Supplement (Office of Population Census and Surveys, 1978) on occupational mortality for England and Wales reported that the standardized mortality ratio for HCC was highest for the lowest social classes. Further support of the association between HCC and socioeconomic status is provided by a small number of analytical studies. A case-control study in Taiwan (Pan et al., 1993) showed that poor education and occupation as a farmer or labourer, in addition to heavy alcohol consumption and smoking, were risk factors for HBV-related HCC. In northern Italy, an inverse association was reported between lower social class and fewer years of education on the one hand and the risk of HCC on the other (La Vecchia et al., 1988); in that study, information on HBV and HCV seromarkers was not available. Furthermore, in a Greek case-control study, cases of HCC, particularly those linked to HBV infection, were more likely to be of lower socioeconomic status than were controls (Trichopoulos, 1981). Finally, a study by Ross et al. (1992) found an inverse association between higher level of education and HCC incidence in China.

Although the relation of low socioeconomic class and cancer cuts across a wide spectrum of malignancies, the association of poverty with HCC is both more striking than most and better understood. Low socioeconomic level facilitates transmission of many infectious agents, including HBV, thereby shifting the age of first exposure towards younger groups and increasing the likelihood of the development of the chronic carrier state. Moreover, HBV is frequently transmitted perinatally. Thus, to the extent that early establishment of the carrier state increases the risk of subsequent liver cancer occurrence, the existing socioeconomic class gradient of chronic HBV infection among young people indicates that HCC will continue to be a malignancy disproportionately concentrated among poor populations and individuals. Other important and common factors in the etiology of HCC, such as HCV infection, tobacco smoking, and heavy alcohol drinking, tend also to be more prevalent among the poor. Lastly, efforts to vaccinate against HBV have been less successful in lower socioeconomic status groups and have not even been systematically attempted in several poor countries at high risk of HCC.

It would appear that HCC is at present, and is likely to remain, a paradigm of a poverty-related cancer, both among countries on an international scale and among individuals within most countries.

**References**


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