

# Hepatocellular Carcinoma: Implications for Asia-Pacific Oncology Nurses

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## ABSTRACT

Hepatocellular carcinoma (HCC) is a prominent malignancy in the Asia-Pacific region. Despite considerable knowledge about its scope and nature this malignancy remains incurable. This manuscript reviews the epidemiology of this cancer, its pathogenesis, risk factors, potential prevention, surveillance, treatment, and the oncology nurses' role relative to this malignancy. A literature search from the past decade was performed using the PubMed and CINAHL databases

using the search terms "hepatocellular carcinoma," "Asia," and "nursing issues". Themes such as etiology, prevention, treatment, and prognosis were included in this synthesis which has particular relevance to oncology nurses within the Asia-Pacific region.

**Key words:** Hepatocellular cancer, nursing interventions, oncology nurses' role

## Introduction

Worldwide, hepatocellular cancer (HCC) is the sixth most common cancer and the third leading cause of death.<sup>[1,2]</sup> More than a half million cases (i.e., 560,000) are diagnosed annually with global incidence tripling over the past three decades.<sup>[3,4]</sup> Unfortunately, HCC's general prognosis is poor with overall survival rates of 3%–5%.<sup>[5]</sup> Most patients succumb to their primary hepatic malignancies within a year of diagnosis, and if left untreated, survival is only 5 months.<sup>[3,4,6]</sup> HCC's dismal outcome is associated with the absence of early

observable symptoms and the common presentation of advanced disease at initial diagnosis.<sup>[2,7]</sup> Hence, HCC has the distinction of being a malignancy with one of the highest global mortality rates.<sup>[8]</sup>

HCC is a unique malignancy in that its cause is known in most cases.<sup>[9]</sup> The primary etiology of HCC is chronic infection with hepatitis B virus (HBV) which accounts for more than three quarters of all HCC cases worldwide.<sup>[10-12]</sup> Less frequently, hepatitis C virus (HCV)

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**Box 1: Risk factors for hepatocellular carcinoma**

Asia-Pacific region residence  
 Hepatitis B virus  
 Hepatitis C virus  
 Cirrhosis  
 Alcohol  
 Dietary aflatoxin exposure  
 Advanced age  
 Male gender  
 Obesity  
 Diabetes

is the etiology. Numerous other factors influence the development of HCC [Box 1]. These include chronic liver disease exacerbated by alcohol-related cirrhosis, obesity, type 2 diabetes, dietary aflatoxin exposure, and/or cigarette smoking. Older age and male gender are the other risk factors. The Asia-Pacific region, comprising many developing countries where this hepatitis infection is endemic, stands alone in its predominance of this fatal malignancy.<sup>[13]</sup> A less frequent origin of HCC is intrahepatic cholangiocarcinoma arising from parenchymal cells lining the bile duct.<sup>[14]</sup>

## Pathogenesis

The majority of HCC (70%–90%) is derived from hepatocytes in livers affected by cirrhosis. In HBV-related HCC, the virus causes genomic chromosomal alterations with resultant metaplasia in hepatocytes.<sup>[10]</sup> Upon pathological examination, HBV DNA is evident in the host genome of both infected and malignant hepatic cells.<sup>[3]</sup> It is postulated then that HBV exerts its carcinogenic potential by increasing its viral DNA in or near proto-oncogenes or tumor suppressor genes effecting cellular transformation over time. This repeated aberrant cellular regeneration typically results in a diagnosis of HCC after 25–30 years of HBV infection.<sup>[3,15]</sup>

Compared with HBV-related HCC, the HCV genome consists of RNA (vs. DNA integration) manifested by ongoing replication causing persistent infection. HCV-induced carcinogenesis is considered to evolve gradually and is dependent on a chronic inflammatory milieu that alters cell signaling and immune responses.<sup>[7,16]</sup> Ultimately, HCC results from decompensated liver function characterized by fibrotic/cirrhotic liver architecture from long-term HCV exposure.<sup>[17]</sup>

## Risk Factors

### Asia-Pacific region

Sixty percent of the world's population resides in Asia where 80% of all HCC occurs.<sup>[13,18,19]</sup> China alone accounts for 55% of the world's HCC incidence.<sup>[3,7]</sup> Other Asian

countries with high rates of HCC are Vietnam and Korea. In Hong Kong, HCC is the second most common cancer in men. However, due to vaccination programs that began there in the 1980s, HBV carrier rates have declined with a comparable reduction in HCC incidence. This similarly characterizes Singapore's HCC experience where decreased trends have been noted since the initiation of national vaccination programs.

Thailand, Japan, Singapore, New Zealand, and Australia have unique HCC corollaries. In Thailand, the predominant type of primary liver cancer is cholangiocarcinoma (rather than HCC) thought to be associated with chronic exposure of liver fluke infestation.<sup>[14]</sup> HCC in Japan, Singapore, New Zealand, and Australia is associated with the HCV virus.<sup>[6,12]</sup> Both New Zealand and Australia are considered migrant countries and their rising HCC incidence has been correlated with mass immigration from the Asia-Pacific region. In Australia, for example, it has been noted that half to three quarters of all HCC cases are diagnosed in patients born in Asian countries.<sup>[20]</sup>

### Hepatitis B virus

HBV is a highly contagious virus most frequently transmitted from mother to newborn.<sup>[7,9,12,14]</sup> HBV carriers usually become infected at a young age; however, sexual transmission remains another mode of spread.<sup>[4]</sup> Five percent of the world's population is infected with HBV, considered responsible for 50%–80% of all HCC cases worldwide.<sup>[7,8]</sup> While HBV is endemic in the Asia-Pacific region, the incidence of HCC should decrease in the coming decades due to vaccination programs implemented in the late 1980s in Asia-Pacific countries.<sup>[6,12]</sup>

### Hepatitis C virus

HCV is one-third as prevalent as HBV. Unlike HBV, infection with HCV usually occurs as an adult resulting from exposure to contaminated needles and/or injected drugs.<sup>[4]</sup> Populations most at risk for HCV are those exposed to blood, hemodialysis, and tattooing.<sup>[7]</sup> This virus was first noted in mid-century (as the contemporary illicit drug culture evolved) and is thought to have migrated into blood supplies. It continued to circulate until a screening test became available in 1990. Other host, lifestyle, and environmental variables have been associated with HCV. These include the rising prevalence of obesity and diabetes, chronic alcohol use, and co-infection with HBV or HIV.<sup>[4,6]</sup>

### Cirrhosis and alcohol

Seventy to ninety percent of all HBV-related HCCs evolves in cirrhotic livers, making it the single largest risk factor.<sup>[1,8]</sup> The role of heavy alcohol intake (i.e., >50–70 g/day) in HCC has been studied with the resultant consensus being that alcohol is not carcinogenic in itself, but rather

leads to cirrhosis which in turn is a major risk factor for HCC.<sup>[7,10,21]</sup> Hence, alcohol is considered a co-carcinogen in the pathogenesis of HCC in that it induces cirrhosis which increases the risk of viral infections and the enhanced activation of carcinogens.<sup>[6]</sup>

### Aflatoxin B1 exposure

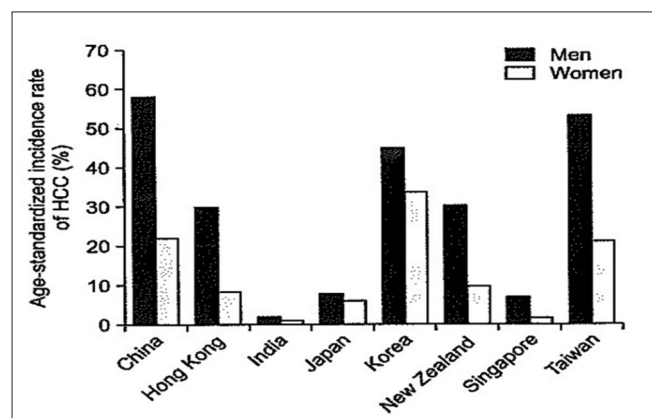
Aflatoxin, a secondary metabolite of *Aspergillus flavus* and *Aspergillus parasiticus*, is a potent hepatocarcinogenic mycotoxin.<sup>[8,10]</sup> It is a fungal contaminant of crops (i.e., grains, corn, peanuts, and soy beans) that appears as a weedy mold on products grown in humid areas of Southeast Asia.<sup>[7,8]</sup> Aflatoxins are thought to induce DNA mutations, particularly in the tumor suppressor gene p53, which are present in 30%–60% of all HCCs in Southeast Asia.<sup>[10]</sup> Aflatoxins and HBV are thought to have synergistic effects.

### Advanced age

The incidence of HCC rises sharply after the age of 40.<sup>[6,8]</sup> For those > 75 years, there is a 14 times greater risk for developing HCC than those in younger age groups.<sup>[3,8]</sup> Figure 1 depicts age-related incidence rates of HCC in the Asia-Pacific region<sup>[8]</sup>. Chronic hepatitis virus exposure over time, along with the presence of concomitant risk factors, is thought to account for this advanced age prevalence in HCC. In the absence of prevention strategies, increasing global life expectancy rates will heighten HCC's prevalence in the coming years.<sup>[22,23]</sup>

### Male gender

Male gender is associated with nearly a 3-fold risk of developing HCC.<sup>[6-8]</sup> In Korea, Indonesia, and Vietnam, there is a 4-fold risk of prevalence in men versus women. Men's added exposure to other risk factors (i.e., alcohol, smoking, and obesity) is considered suspect in this gender-related incidence pattern. The exception is older Japanese women who have equivocal incidence rates of HCC to men.



**Figure 1:** Age-related hepatocellular cancer incidence rates in the Asia-Pacific region by gender

### Obesity and diabetes

Escalation of obesity worldwide and its association with diabetes has been implicated as a risk factor for HCC.<sup>[7]</sup> The synergism between these two conditions is thought to promote fatty liver disease which in turn may influence HCC's development.<sup>[14]</sup> A diagnosis of diabetes has been noted to increase HCC's risk 2–4 fold even after adjusting for other predisposing factors.<sup>[10]</sup>

### Co-existing risk factors

HCC is best characterized as a heterogeneous, complex malignancy with numerous co-existing risk factors and a grim prognosis.<sup>[4]</sup> While HBV is the primary etiology, other risk-enhancing conditions must be addressed in future efforts to reduce the incidence of this cancer throughout Asia. Yuen *et al.*<sup>[6]</sup> stated,

*“The impact of high rates of alcohol abuse in Asia, and the recent (10-15 years) obesity and type 2 diabetes epidemic in Asia may impact adversely on HCC incidence in the next 25 years (p. 352).”*

Due to the prominence of this aggressive malignancy in the Asia-Pacific region, both interdisciplinary and joint country ventures are needed to advance bench, clinical, and community-based research findings in HCC.

### Interventions

Unlike other malignancies, there are a multitude of interventions to manage HCC.<sup>[4]</sup> Despite this, however, HCC remains an incurable malignancy.

### Primary prevention

The most efficacious mean to reduce HCC globally is to prevent it.<sup>[13]</sup> HBV vaccines are 70%–95% effective at preventing mother–infant HBV transmissions when administered within 24 hours of birth.<sup>[12]</sup> This can reduce chronic HBV infection in endemic countries by 90% in a single generation.<sup>[13]</sup> Since 1982, there have been safe and effective HBV vaccines available, but due to their expense, it has taken decades to implement them worldwide. As of 2006, 164 countries have vaccinations available against HBV through national immunization programs (as compared to 31 countries having such in 1992). Taiwan, for example, has noted a significant decline in HCC incidence a decade following the start of its immunization initiative.

The Asia-Pacific Working Party On Prevention of Hepatocellular Cancers<sup>[13]</sup> recommends the following related to HCC prevention:

- A universal hepatitis B vaccination program should be in place
- All countries should prioritize efforts to adopt



extended infant immunization schedules that include hepatitis B vaccination and ensure coverage of these programs throughout all communities

- All blood products should be tested for HBV and HCV
- Adoption of universal precautions (which include using disposable needles, syringes and any device contaminated by blood or serum, adequate cleansing and sterilization of endoscopic equipment, gloving to handle wounds and blood products, avoiding multiple use vials for injectables, and avoiding transmission to patients from viremic health care workers.)<sup>[13]</sup> to avoid transmission of blood-borne viruses in health-care settings.

Of note also are consideration of other potentially modifiable risk factors related to HCC. The Asia-Pacific working party recommended efforts to ensure that a clean water supply is available to the public and that prevention of fungal contamination of grains and ground crops through refrigeration and food safety measures is addressed. These measures can reduce aflatoxin's hepatic carcinogenic effects and ultimately reduce HCC risk.<sup>[10]</sup>

### Surveillance/screening

There are multiple approaches to ideal early detection surveillance initiatives. Consider for example, a composite of a high-risk patient for HCC based on known risk factors. This patient would be an older, overweight man with diabetes, has known HBV and cirrhosis, has a heavy alcohol intake, and lives in rural Korea or Vietnam. Any early screening for this high-risk patient would then require a known blood assay, radiologic sensitivity to small hepatic abnormalities, a mechanism to inform him of his heightened risk, and compliance with screening recommendations.

Currently, hepatic ultrasonography and serum alpha-fetoprotein testing are used to screen for HCC (i.e., patients with known cirrhosis).<sup>[13,24]</sup> This is generally recommended for every 6 months.<sup>[4,12]</sup> Japan recently reported the results of their HCC experience and noted improvements in overall survival in part due to their nationwide surveillance program.<sup>[19]</sup> Further intensive efforts at screening by other countries could potentially replicate these findings.

### Management

The complexity of HCC requires a highly individualized treatment approach. Numerous guidelines for staging and treatment are available worldwide. Yu,<sup>[25]</sup> Fong, and Tanabe<sup>[4]</sup> reviewed and compared existing guidelines in an effort to delineate best practices relevant to the management of HCC in the Asia-Pacific region. They identified that the existing guidelines may not be translatable to all regions

based on resource and technology availability and personnel expertise.

The assessment of tumor extension is crucial to treatment decision-making.<sup>[26]</sup> In general, there are four options for treating HCC, all of which are stage dependent. Treatments include surgical resection, loco-regional approaches, systemic therapy, and liver transplantation. Table 1 outlines these options and patient eligibility criteria for each. Factors considered in treatment choice include the size and number of hepatic tumors, degree of vascular invasion, and status of regional lymph nodes and distant metastases.<sup>[4,12,25]</sup>

Surgery is generally appropriate for noncirrhotic patients with local lesions who have adequate liver function to prevent liver failure, a major cause of postoperative mortality.<sup>[4,12]</sup> Factors that preclude resection are related to the complications of cirrhosis (i.e., bleeding, ascites, portal hypertension, and evidence of insufficient hepatic reserve to withstand a partial hepatectomy).<sup>[12]</sup> A very low percentage of HCC patients in Asia (10%–15%) have resectable disease at initial diagnosis. Hence, other measures are frequently used to treat HCC.

The intent of loco-regional treatment of HCC is to interfere with tumor growth and microvascular invasion that leads to metastases. It is indicated in patients with good hepatic function, having solitary tumors or up to three small tumors.<sup>[25]</sup> Examples of loco-regional therapy include radiofrequency ablation, percutaneous ethanol injection, transarterial chemoembolization, and intrahepatic arterial infusion of yttrium-90. Isolation of the arterial blood supply to the tumor bed is required to deliver these therapies. Ultimately, tumor necrosis results from the creation of a hypoxic, ischemic microenvironment.<sup>[4,23]</sup> The benefit that is commonly associated with systemic anti-neoplastic therapy.<sup>[2]</sup>

Systemic treatment is prescribed to patients with unresectable, advanced HCC. Sorafenib, a multikinase inhibitor with antiangiogenic and antiproliferative effects, is the only systemic chemotherapy that has demonstrated a survival benefit in a prospective clinical trial.<sup>[4]</sup> It disrupts

**Table 1: Treatment options for hepatocellular cancer and patient eligibility considerations**

Treatment type	Eligibility considerations
Surgical resection	Absence of cirrhosis and portal hypertension; solitary, isolated lesion or <3 small intrahepatic tumors without macrovascular invasion
Loco-regional	Ineligible for hepatic resection; good hepatic function; presence of up to 3 tumors ≤3 cm each; absence of macrovascular invasion or extrahepatic spread
Systemic	Unresectable, advanced HCC; survival benefit (in months) with sorafenib use
Transplantation	Early HCC (single 5 cm lesion) or up to 3 small separate lesions; not candidates for surgical resection (i.e., presence of moderate-to-severe cirrhosis)

HCC: Hepatocellular cancer

the integrity of multiple cell surfaces and interferes with downstream kinases that promote tumor progression.<sup>[26]</sup> Common side effects of sorafenib are diarrhea, fatigue, hand-foot skin reactions, and rashes, which are the most frequent causes of dose reduction or treatment interruption.<sup>[2]</sup>

As HCC is increasingly recognized as a lethal malignancy with limited therapeutic options, it has been considered as a focus for novel immunotherapy interventions. The immune system's inability to recognize and eradicate hepatic cancer cells has been the focus of increasing attention in the study of novel antineoplastic agent development. In particular, targeted therapies (i.e., immune checkpoint inhibitors) in combination with other established treatment modalities (i.e., surgery, loco-regional interventions) characterize the next phase of therapeutic interventions to be studied in this patient cohort.<sup>[27]</sup>

Of note is that despite old age being a key risk factor, the elderly have been underrepresented in clinical trials for HCC.<sup>[22]</sup> Their exclusion influences recommendations on the management of HCC as a gap exists between clinical practice realities and interventional guidelines.<sup>[16]</sup> Elder-specific clinical trials must be created and incorporate the presence of comorbidity into their design as safety concerns are integral to trial development.<sup>[16,22,23]</sup>

The exorbitant cost of sorafenib (\$5400 USD/month) makes it unavailable to patients in developing countries, particularly as it is offered with palliative intent.<sup>[4]</sup> Future promise portends the availability of direct-acting antiviral agents to manage HCV prior to its evolution to HCC. These compounds could not only eradicate the virus, but also improve liver function, stop or reverse fibrosis and cirrhosis, and lower or even eradicate the risk for HCC.<sup>[17]</sup>

Liver transplantation is appropriate for a small percentage of patients with a good performance status, who have minimal tumor burden, and their condition remains stable during the wait time for a donor. Acute decompensated cirrhosis may also be an indication for transplantation.<sup>[25]</sup>

Until universal efforts to promote screening are operational and the identification of patients with early HCC can be optimized, oncology nurses' expertise during treatment primarily focuses on caring for patients with advanced HCC. Therefore, the promotion of survival quality and comfort should be the areas of expertise employed with this patient cohort.

## The Oncology Nurses' Role

Oncology nurses in Asia-Pacific countries have two important opportunities to impact the occurrence and management of HCC. Both opportunities would be best served by formal sponsorship from national oncology nursing societies promoting these interventions by a position paper, consensus panel, and/or collaboration with health

ministries. These interventions by specialty oncology nurses involve education and advocacy.

First, is the provision of widespread public education. This should target the importance of vaccinations in the prevention of HCC, the dangers of intravenous drug use, and the importance of universal precautions. Oncology nurses can either provide themselves or partner with health-care colleagues and educators to inform the public about the HBV vaccination prevention strategy for potential HCC. An Asia-Pacific countrywide education initiative by oncology nurses could be an effective intervention to solicit public attention and prompt prevention behaviors related to this potentially preventable cancer. Oncology nurses may also offer education to nursing students and generalist nurses providing community health. Education may also be required for elected or appointed officials to lobby for additional resources (both financial and people) to implement outreach vaccination efforts in remote areas.

Second, oncology nurses practicing in treatment settings have a significant advocacy role as it relates to HCC. In planning for, and providing care to, patients diagnosed with HCC, it is important to lobby for the introduction of palliative care early in the patient's experience. Expertise in symptom management (i.e., pain, fatigue, anorexia and gastrointestinal distress) and the enhancement of quality of life is paramount for HCC patients and their caregivers. Families also need instructions specific to home care when increased debility impairs the patient's functional status and symptom distress prevails. The provision of emotional support for family caregivers is also needed as they assume responsibility for the majority of their loved one's care at a distance from the oncology team.

## Conclusion

Due to the prominence of HCC in the Asia-Pacific region, oncology nurses practicing in these countries need to be apprised of trends and care practices specific to this cancer. From a research perspective, the nursing care requirements of caring for patients with HCC also merit description and quantification.

Asia-Pacific oncology nurses have the potential to provide the rest of the world's oncology nurses with "Best Practices" for this prominent subset of patients. The enhancement of professional awareness, public education, symptom management expertise, and research efforts, are critical vehicles to reach this goal.

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### Conflicts of interest

There are no conflicts of interest.

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