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WORLD DIGESTIVE HEALTH DAY 2013

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World Gastroenterology Organisation (WGO)
WGO Foundation (WGO-F)

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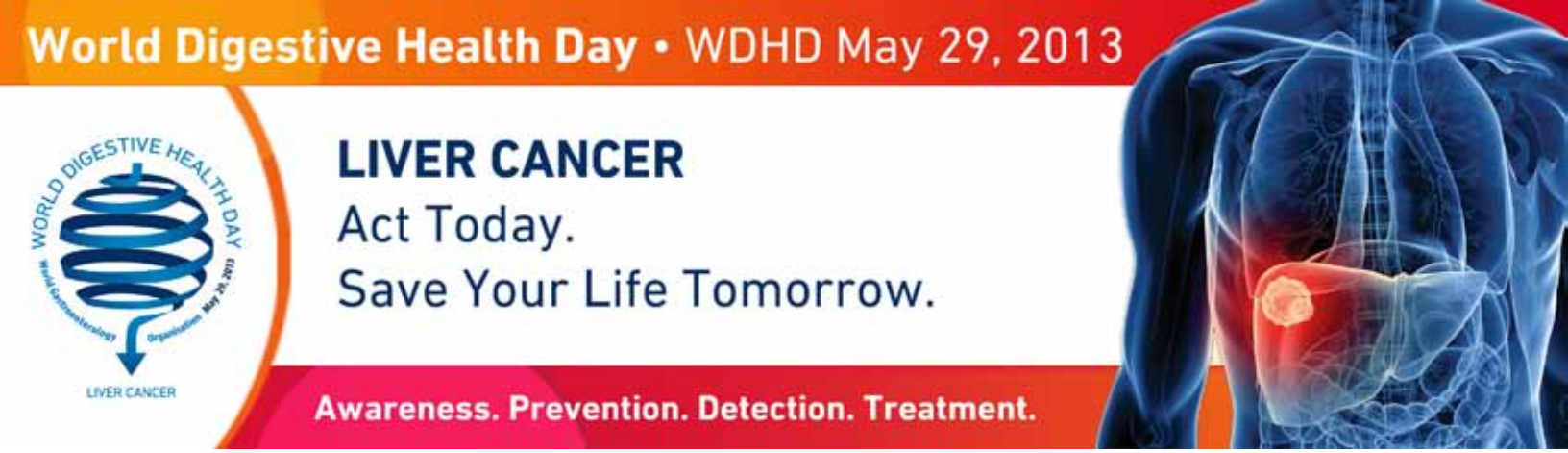

VIRAL HEPATITIS AND LIVER CANCER
A Global Crisis We Cannot Continue To Ignore

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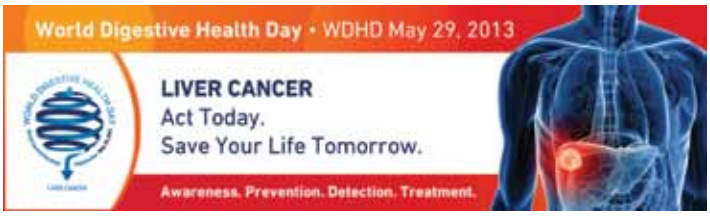
World Digestive Health Day 2013 (WDHD 2013) will attempt to focus the world's attention on the global health crisis caused by hepatocellular carcinoma (HCC).



Why did WGO choose liver cancer? HCC, is the fifth most common cancer in the world[1,2] and the third most common cause of death from cancer (second most common in men)[1,2]. In some countries, it is either the number one (Mongolia) or number 2 malignant neoplasm (China). In the United States of America, it is the fastest rising cancer by incidence and death rate[3]. **Every 30 seconds, one person in the world dies from liver cancer, which is almost entirely preventable.** The annual global death rate from HCC of just under 700,000 approximates the annual incidence, reflecting the limited therapeutic options as well as the late diagnosis in most cases[4].

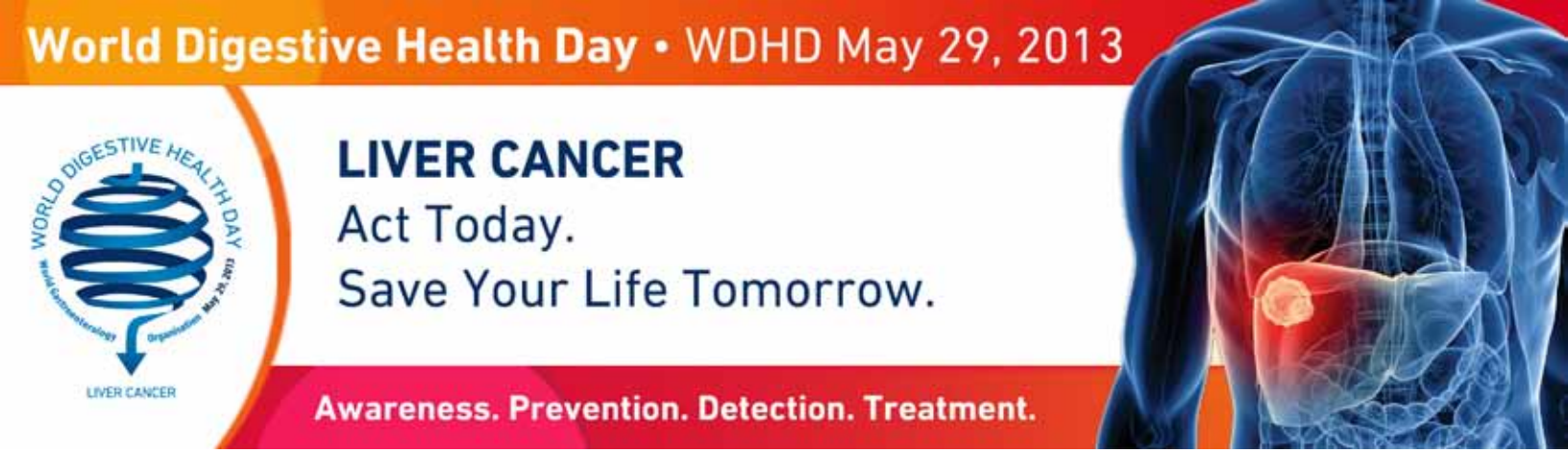
Significant advances in diagnosis and therapy now produce a 50-70% five year survival in those diagnosed with early, minimal disease who receive the best current therapies. But such therapies are almost exclusively available in high resource countries, and even there not to all of the affected patients. Low resource countries tend to lack the broad public awareness and medical infrastructure, as well as generally available state of the art technology (ultrasound, CT, MRI) for early diagnosis. The current best surgical and medical therapies are of very limited availability, if available at all, due to high costs and lack properly trained personnel and coverage by government health plans.

Unfortunately, low resource countries are disproportionately affected by HCC. Eighty-four percent of the almost 700,000 deaths reported by WHO in 2008 occurred in low resource countries. Over 80% of HCC occur in sub-Saharan Africa, southeast Asia and East Asia (including Mongolia)[5]. In a recent article, The African Middle Eastern Society for Digestive Oncology discussed its mission against viral hepatitis and Hepatocellular carcinoma[18]. At least 80% of all HCC are associated with chronic viral infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV)[6]. Additional risk factors, which may cause HCC or act as co-factors in producing cirrhosis and HCC, include consumption of foodstuffs contaminated by the fungal toxin aflatoxin B_1 (AFB_1), alcohol intake, diabetes/obesity/non-alcoholic steatohepatitis (NASH) and rare metabolic disorders, including tyrosinemia, hemochromatosis, alpha-1 anti-trypsin deficiency, and several prophyrias[6].

The above facts are well known. The two primary causes, HBV and HCV infection are both preventable and treatable and **1 in 12 of the world's population is currently living with chronic hepatitis B or C.**

HEPATITIS B

Hepatitis B is one of the most neglected epidemics in the world. 1 in 3 people worldwide have been infected with HBV and 400,000,000 have chronic hepatitis B. It is second only to tobacco in causing the most cancer deaths worldwide. The hepatitis B vaccine, the FIRST true anti-cancer vaccine, has been available since 1982 and is more than 95% effective. Global efforts at HBV vaccination of infants got underway in 1990, when the WHO estimated that only 1% of infants received the recommended three doses of hepatitis B vaccine. By 2011 that number had risen dramatically[7], but a full quarter of the world's infants remained uncovered. In SE Asia vaccination languishes at only 56%[8] and 7% of countries still have not introduced hepatitis B vaccine into their routine childhood vaccination schedules. Only 52% recommended that the initial dose be given within the first 24 hours to prevent perinatal transmission of the hepatitis B virus as per international standards[9]. 30-40% of those infected



with chronic hepatitis B can be expected to die from liver failure or HCC. And vaccination benefits are well documented. The last recorded case of small pox was in 1972. Only 222 cases of polio were reported in 3 countries in all of 2012 following a 20+ year international effort to eradicate this crippling disease. And the majority of the world's children now receive DPT vaccinations. Why has hepatitis B vaccination not been more universally incorporated into routine vaccine schedules?

While the benefits of true universal infant immunization against hepatitis B are obvious as a preventive measure, they will also not be realized for many decades. Meanwhile, over 400 million individuals with chronic hepatitis B remain at risk from the dire complications of this devastating infection. Excellent therapies are now available which significantly reduce the risk of progression to cirrhosis, liver failure and HCC. However, these drugs remain generally unavailable in major parts of the world where identical drugs are now routinely available for the treatment of HIV infection. This obvious inequity must be addressed and resolved quickly before additional large numbers of individuals in their prime years die unnecessarily. Programs to prevent aflatoxin contamination of foodstuffs have also been demonstrated to be highly successful, but remain difficult to implement broadly due to lack of education and cost.

HEPATITIS C

Prevention of hepatitis C infection presents a somewhat more difficult problem because there is no effective vaccine to prevent hepatitis C infection and there is unlikely to be one in the foreseeable future. Prevention must rely on education of patients concerning the risks of acquiring HCV infection from exposure to blood and bodily fluids and strict adherence to the principles of infection control. The WHO estimated in 2006 that 16 thousand million injections were administered annually in developing and transitional countries alone[10] and that the habitual reuse of needles and syringes accounted for 2 million new HCV infections each year (42% of new infections), 21 million new HBV infections per year (33% of new HBV infections) and 260,000 new HIV infections (2% of new infections)[11]. Fewer than 10% of injections were for vaccines and a large percentage of injections were actually unnecessary. Additionally, not all country's blood supplies are entirely safe due to irregular screening, especially for the hepatitis C virus. Finally, highly effective therapies for hepatitis C are now available which will cure 70% or more of patients and even better treatments are on the near horizon. However, as with earlier HIV therapies, they are extremely costly. A major campaign, similar to that carried out for treatment of HIV must be mounted to make such curative therapies generally available for those in low resource countries.

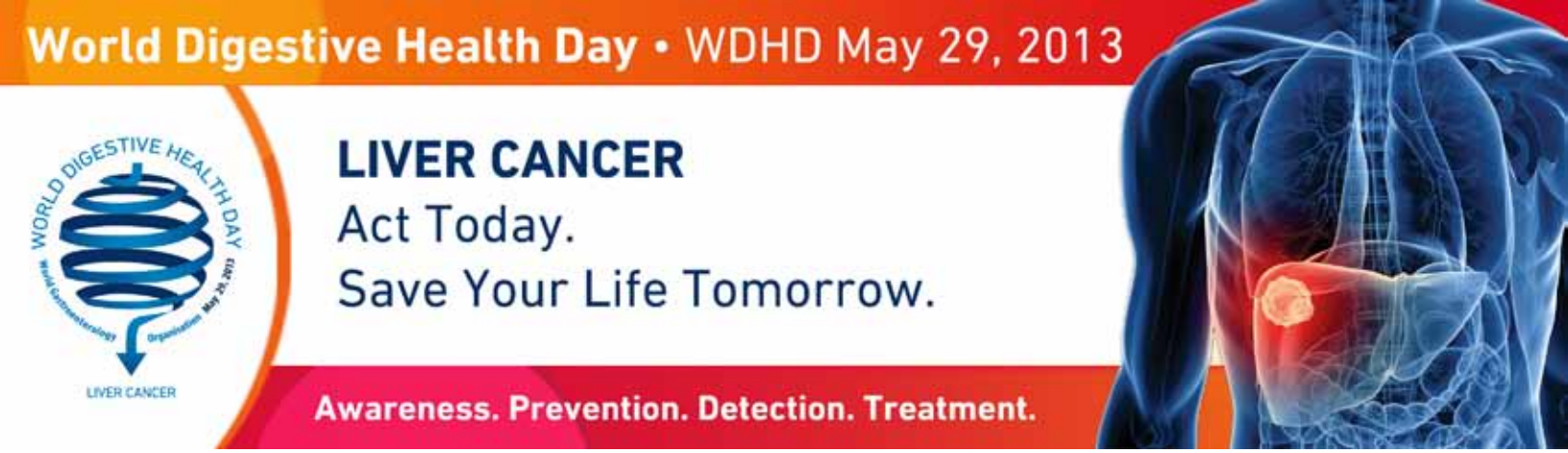
What To Do

A little over 20 years ago HIV/AIDS arrived and spread death far and wide, with most affected patients dying within one year of diagnosis. Scientists rose to the challenge and quickly identified the virus and developed a new class of anti-retroviral drugs which stopped the disease in its tracks. Still, it was predicted that low resource areas such as Africa would lose a whole generation to the disease due to the lack of infrastructure and the extremely high cost of the anti-retrovirals. Again, the world responded. Global Fund has contributed $23 billion dollars since 2002, the Bill and Melinda Gates Foundation has contributed tens of billions of dollars, and President Bush of the USA inaugurated the PEPFAR fund in 2003 to provide anti-retroviral drugs with a $45 billion fund over 5 years. In 2003 only 7,000 individuals in Africa were on treatment. Now over 7 million are on therapy. Mothers are surviving, rather than leaving orphans, and the infants are being born HIV free. This has been a remarkable global effort and there is talk of finally curing this disease. This is wonderful news for the 34 million chronic carriers of HIV, but where are the global programs to resolve the crisis presented by the 600 million chronic carriers of Hepatitis B and C? Polio is almost conquered thanks to the global efforts of the same groups above plus the American CDC, the Islamic Development Bank and Rotary International.

The effects of HCC, along with hepatitis B and hepatitis C, are global tragedies whose burden of disease has been neglected for far too long. A similar effort to eliminate HCC, with a full bore attack on hepatitis B and hepatitis C and their 600 million chronically infected patients (20 times more patients than those with HIV), is long overdue. The lessons learned and infrastructure developed in fighting HIV and polio must be applied to HCC, HBV, and HCV.

The WGO and its Foundation (WGOF) will attempt to put the spotlight on this long neglected epidemic in hopes galvanizing a response to the human tragedy caused by these inter-related diseases. In this battle it is critical to recognize that: **these diseases can be prevented and these diseases can be treated. But it will require a major global effort and investment by all affected parties.**

In the pages of this special WDHD publication you will find reports from around the world. There is a remarkable thread running through each of them, whether they be from Canada and Portugal, or Pakistan and South Africa. This is a major health problem with inadequate data, recognition and resources. Throughout this year, WGO will be co-sponsoring symposia in every region in the world to evaluate the problem locally and start to develop recommendations appropriate to the local situation. We will be collecting surveys to better define the problem in the many parts of the world where inadequate information is available to fully define the problem. In particular we will be collecting information concerning resources available for prevention, diagnosis and treatment. Our member national organizations will be joining us in holding events to publicize this issue. We invite you to consider organizing an event in your region to help raise awareness. On this website we will continue to publish reports similar to those in this first issue describing local condition around the world. We will also make available information sheets, talking points and posters which you are free to download for your own use. Over time they will be available



in multiple languages to further assist you. A final summary report will be presented at Gastro 2013 APDW/WCOG Shanghai in September.

This will truly take a global effort but it is too important to let these patients continue to die from preventable and treatable disease. We must make this issue clear to our government, NGO and philanthropic leaders and conquer it before we lose another large segment of our current population

NB A portion of this editorial previously appeared in e-WGN in the April issue.

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The World Gastroenterology Organisation and the WGO Foundation thank the following WDHD 2013 supporters for their generosity and support of the 2013 campaign.

WGO is particularly grateful to the following corporations for their support towards helping to better understand and recognize the global burden of liver disease:

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WGO Supporters are engaged in long-term, multi-faceted partnerships with the WGO in support of World Digestive Health Day.

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Hepatocellular Carcinoma in Sub-Saharan Africa: The Immediate Need is to Improve the Diagnosis and Treatment of the Tumor, and in the Longer Term to Prevent the Tumor

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One cannot fail to be aware of both the high incidence of hepatocellular carcinoma (HCC) in the Black African population of sub-Saharan Africa, accounting as it does for more than 90% of the 46,000 new cases of primary liver cancer occurring each year, and its grave prognosis (1). Incidences of HCC in this population range between 19.2 and 28.4 per 100,000 persons per year, and the tumor accounts for approximately 20% of all malignant diseases (Figure 1) (2). These patients often seek medical advice only when the tumor has reached an advanced stage (Figures 2-4). With the rapid growth rate of HCC in this population the patients survive, on average, for only approximately six months from the onset of symptoms, and have a 12 month fatality ratio of 0.96, the highest of any human tumor (3).

As disturbing as these statistics undoubtedly are, they under-estimate the true incidence and mortality rate of HCC in this population because in many Black African patients the tumor is not definitively diagnosed or, if so, is not entered into cancer registries. The main reasons for these shortcomings are the inadequate diagnostic facilities and the scarcity or incompleteness of cancer registries in rural areas, where the majority of the patients live. Moreover, the highly sophisticated (and very expensive) imaging equipment now used in the diagnosis of early HCC in resource-rich countries is not available in rural hospitals in sub-Saharan Africa, and is available in only a few urban hospitals. In addition, the treatment options now possible in resource-rich countries can seldom be offered in sub-Saharan African countries.

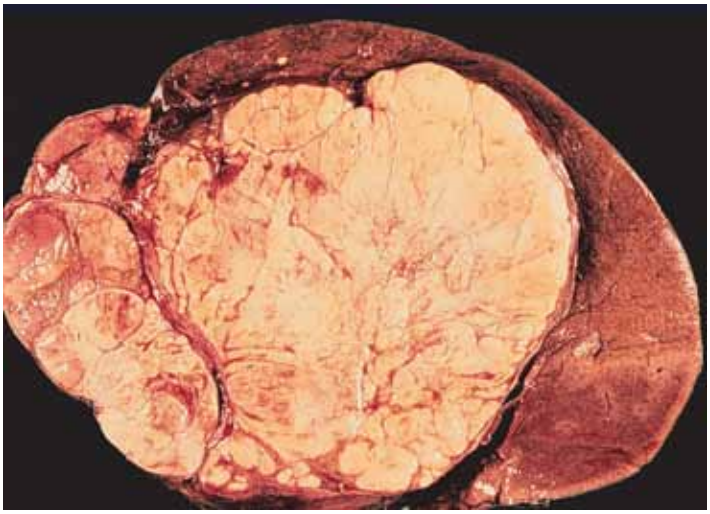


Figure 1: Massive enlargement of the liver in a Black African patient with hepatocellular carcinoma.

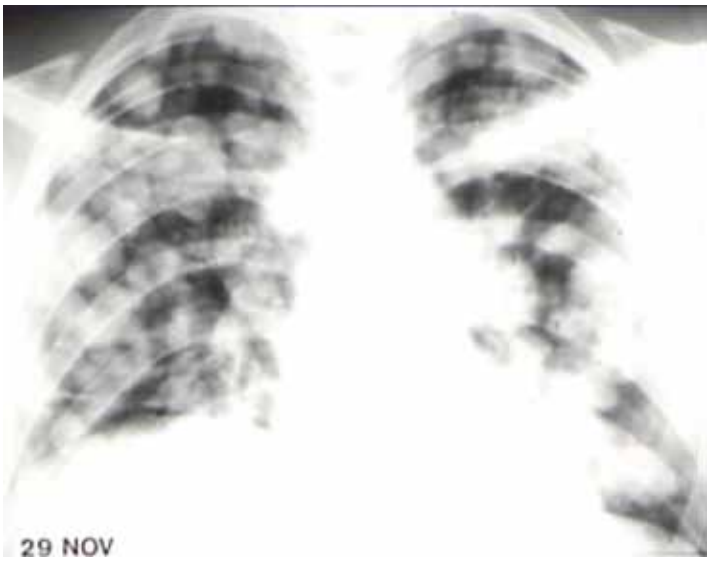
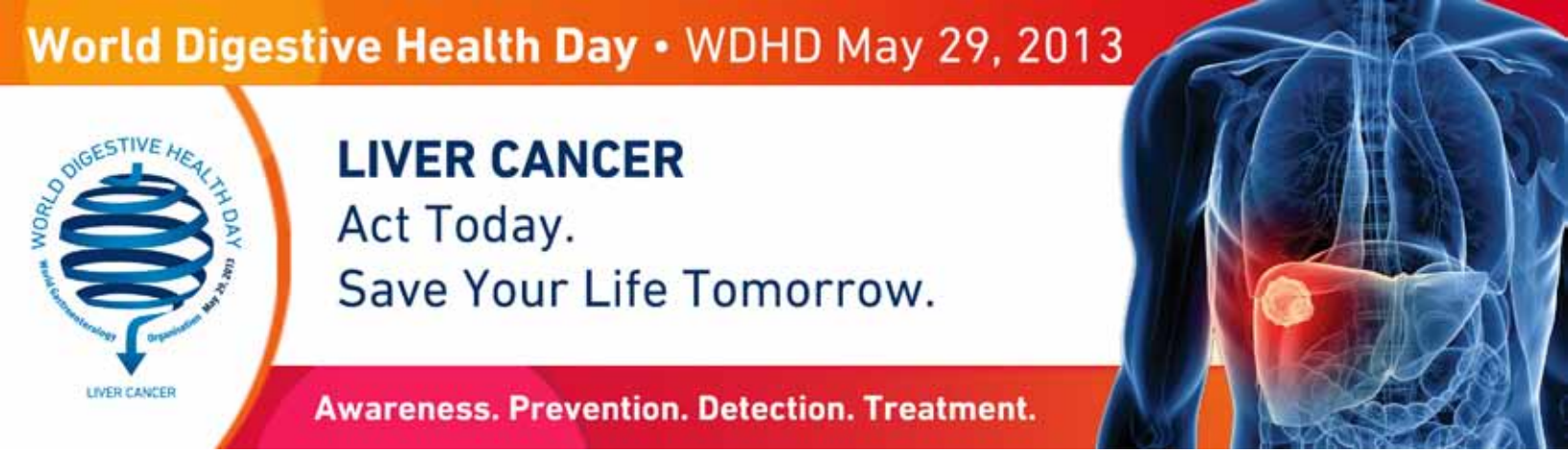


Figure 2: Liver tissue almost completely replaced by a massive hepatocellular carcinoma. Note that the tumour has arisen in a non-cirrhotic liver, a feature more frequently present in black African patients that in those in resource-rich regions. (Picture reproduced with permission from International Medical Press)

The tumor presents at a relatively young age in sub-Saharan Black Africans, especially in rural dwellers, who have a mean age of 34.7 years (4). Patients with hepatitis B virus-induced HCC, constituting the great majority of the patients, are on average 20 years younger than the relatively few patients with hepatitis C virus-induced tumors (5). Males are more often affected than are females (ratio 3.5:1.0) (6): Black African men and women with the tumor are of similar ages (7); HCC occurs in association with cirrhosis less frequently in sub-Saharan Black Africans than in patients in resource-rich regions. Patients with and without cirrhosis are of similar age (4).



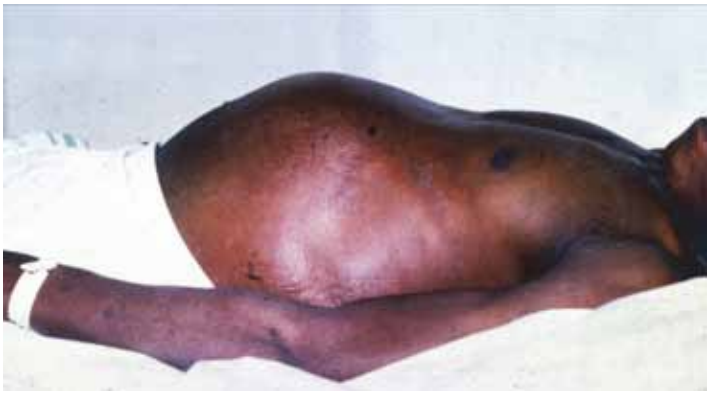


Figure 3: Typical chest radiograph in a Black African patient with hepatocellular carcinoma. Multiple pulmonary metastases are present in approximately 20% of the patients at the time of admission to hospital. The right hemidiaphragm may also be raised. (Picture published with the permission of the South African Medical Journal).

Although the serum α-fetoprotein (AFP) concentration is of limited value in the diagnosis of HCC in the patients in resource-rich countries (8, 9), it is a useful serum marker of the tumor in sub-Saharan Black Africans. As many as 90% of the patients have a serum value above the upper limit of normal (20 ng/ml) (4,10). Because slightly or even moderately raised serum levels may be present in patients with a variety of benign inflammatory hepatic diseases, a serum level above 400 ng/ml (or in some centers 500 ng/ml) is taken as a concentration diagnostic of HCC. Approximately 75% of Black African patients with HCC have a value greater than 500 ng/ml (4,10). The levels are age-related, the younger the patient the higher the concentration attained: a diagnostically-raised serum level is present in 83.1% of Black African patients under the age of 30 years, compared with 59.1% in those over the age of 50 years (6). A progressively rising serum AFP concentration, whatever its level, is highly suggestive of the presence of HCC. Production of the marker by the tumor is persistent, although the serum level may fall precipitously shortly before death.

Treatment of HCC in sub-Saharan Black Africans has long been, and remains, extremely unrewarding. This, despite the fact that the treatment available in resource-rich countries has improved considerably during recent years. In the latter countries more than 30% of patients with the tumor can now be treated with curative intent (11). More patients are undergoing successful resection of the tumor. Furthermore, 70% of the patients undergoing liver transplantation for HCC now have a five-year recurrence-free survival rate (12). Even if the HCC is initially deemed to be inoperable, it may be possible to 'down-stage' the tumor using radio-frequency ablation, ablation by injection of alcohol, or trans-arterial chemoembolization, thereby rendering the tumor amenable to surgical intervention (13). For those patients with surgically incurable tumors, sophisticated new radiotherapeutic techniques, in the form of three-dimensional high-dose photon beam radiotherapy or stereotactic radiotherapy, can accurately confine the rays to the tumor tissue, sparing the adjacent liver tissue, thereby achieving far superior results than were hitherto possible (14,15). Furthermore, the multikinase inhibitor, Sorafenib, has recently been shown to prolong survival in patients with inoperable HCC (16).

Because of the usually late presentation and hence the advanced stage of the tumor in Black African patients, especially those in rural areas, the diagnosis of HCC is generally made only at a time when the tumor is rarely amenable to resection or liver transplantation, and the results of chemotherapy and radiotherapy, when available, are very poor. No reports on the efficacy of Sorafenib in sub-Saharan Black Africans with HCC have yet been published.

So prevalent is HCC in sub-Saharan Black Africans, so inadequate are the diagnostic and treatment facilities available, and so grave is the present-day prognosis, that prevention of the tumor is an urgent priority. The etiological agents responsible for the tumor are largely known and are potentially preventable, opening the way to primary prevention.

Given that oncogenic hepatitis viruses cause approximately 90% of HCCs in sub-Saharan Black Africans, prevention of these viral infections alone would have an immense impact on the occurrence of the tumor in this population. A safe and effective vaccine against hepatitis B virus has been available for a number of years, and in those countries in which universal immunization has been in place for a sufficient length of time, the incidence of hepatitis B virus infection and the resulting HCC has been reduced to the extent expected. In order to obtain full protection

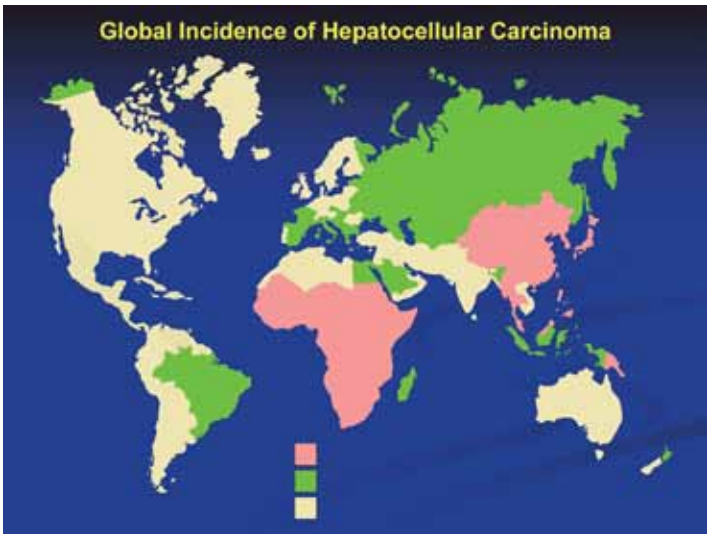
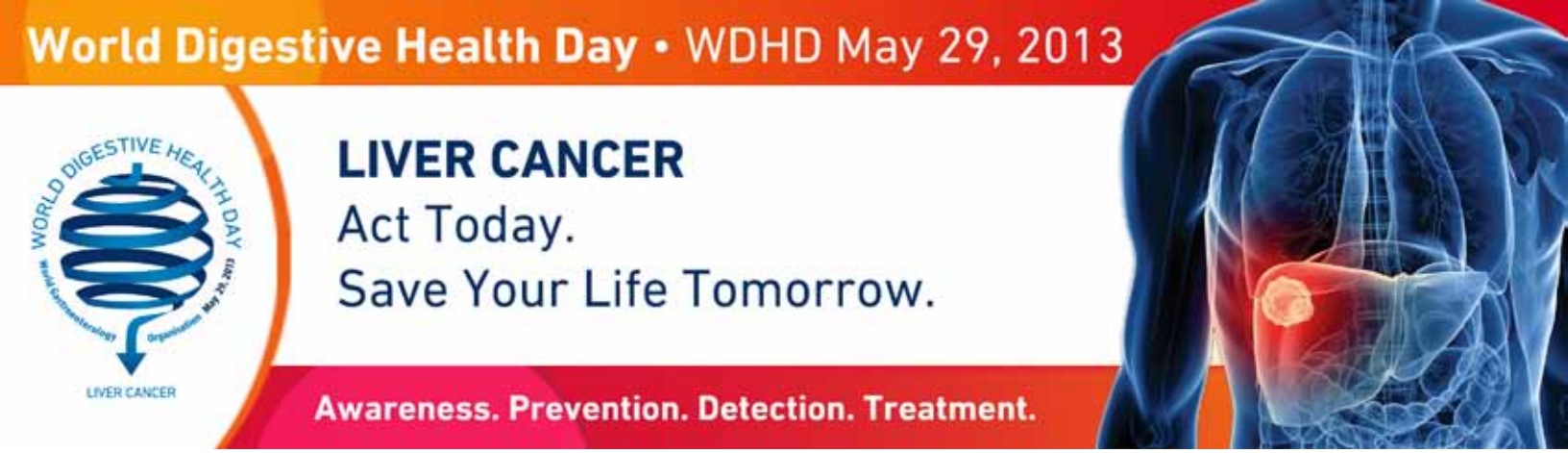


Figure 4: Markedly raised right hemidiaphragm in a Black African patient with hepatocellular carcinoma. (Picture reproduced with the permission of the South African Medical Journal).



against this viral infection, it is necessary to receive the full course of three injections of the vaccine. Regrettably, in sub-Saharan Africa as many as 50% of Black babies are still not receiving the full course of the vaccine (17). This short-coming urgently needs to be redressed. No vaccine against the hepatitis C virus is yet available. Safe injection practices will help to reduce the occurrence both hepatitis C and B virus infections (18). These include avoiding unnecessary injections, improving the safety of injection and infusion techniques, and the provision of needle and syringe exchange programs for drug addicts. Screening of donated blood for the presence of these viruses, as well as the use of viral inactivation steps in the manufacture of blood products, are also essential.

Dietary intake of the fungal toxin, aflatoxin, by rural sub-Saharan Black Africans act synergistically with hepatitis B virus and contribute significantly to the high incidence of HCC. Adequate irrigation of plants and pre-harvest prevention of contamination of foodstuffs by spraying the crops with fungicides are relatively simple prevention techniques. Other preventative policies include replacing crops susceptible to fungal contamination by others with a greater resistance to the fungi. The likelihood of stored crops being contaminated can also be lessened by sun-drying before storage and better storage facilities.

Another important cause of HCC in rural sub-Saharan Black Africans is iron overload resulting from the consumption of large volumes of home-made beer brewed in iron pots or drums (19). The acid pH of the fermenting beer leaches iron from the container into the contents. The low alcohol content of the beer means that large volumes must be consumed in order to achieve its desired affects. Prevention by replacing the iron containers with others is an obvious solution, although this has thus far proved to be an unpopular solution because the resulting beer is said not to have the desired taste obtained with fermentation in iron drums.

Secondary prevention of HCC in sub-Saharan Africa currently provides only a limited number of opportunities. No reports on the use of preventative agents such as chlorophyllin, oltipraz or polyprenoic acid in Black African patients have been published.

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Hepatocellular Carcinoma in Brazil

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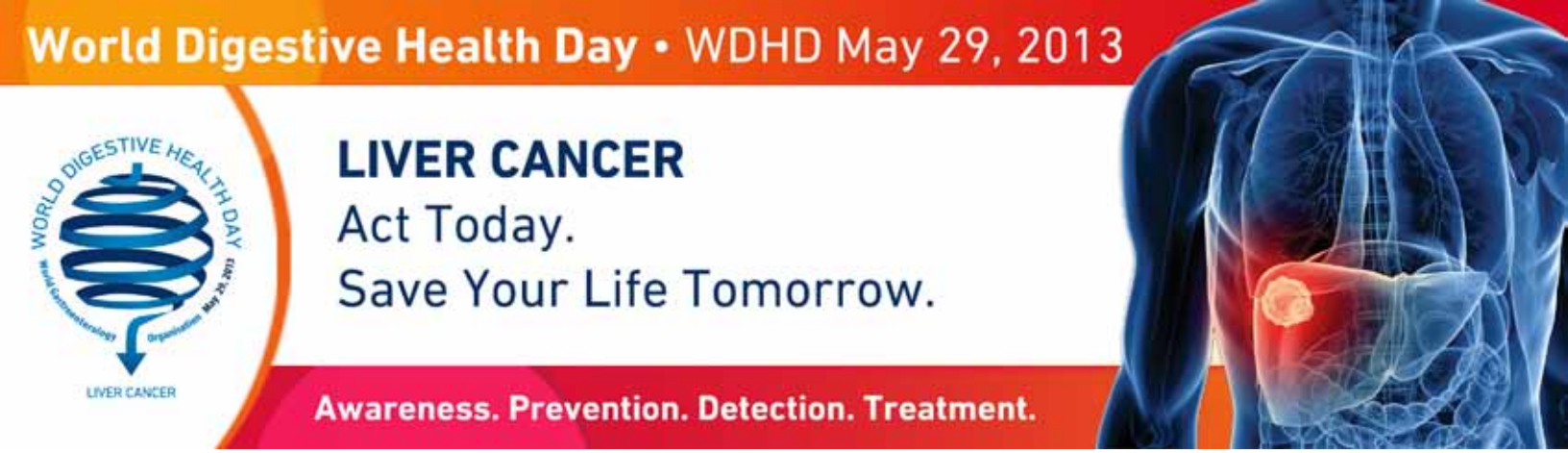
Hepatocellular carcinoma (HCC) is among the most frequent malignant tumors in adults, and its prevalence is noticeably increasing worldwide (1). It accounts for approximately 600,000 new cases per year in the whole world, affecting especially men. Associated to hepatitis B (HBV) and hepatitis C virus (HCV) chronic infection, HCC can indeed occur in cirrhosis of any etiology, including alcohol abuse, hemochromatosis and non-alcoholic steatohepatitis (NASH) (2, 3). Remarkably, almost 80% of the cases occur in developing countries (4). However, in Brazil, the Ministry of Health and Brazilian National Cancer Institute do not list HCC as the 10 more prevalent types of cancer (5). Likely, the Brazilian actual prevalence is underestimated, either due to underdiagnosis or underreport. In fact, there is no reliable data on HCC prevalence in the whole country. A few years ago, the Brazilian Hepatology Society (SBH, in Portuguese) made an attempt to retrospectively assess HCC diagnosis and treatment in real life (6). A total of 1,405 cases from 2004 to 2009 were reviewed, 2/3 of them from the Southeast region - which possibly does not represent the entire country experience. Ninety-eight percent of the reported cases were associated with cirrhosis, from which 39% was secondary to HCV infection, 15% to alcohol addiction, and 12% to HBV. Regarding HCC stage, accordingly to the Barcelona Clinic Liver Cancer criteria (BCLC), 43% were classified as early, 35% as intermediate, and 22% as advanced. Data on treatment was available in 1,290 patients. Unfortunately, only 19% of them were submitted to liver transplantation.

As viral hepatitis is among the most important risk factors, it must deserve special consideration. Concerning its epidemiology, were recently published the results of a nationwide population-based survey, conducted in the 26 State capitals and the Federal District. The data indicates that HBV and HCV prevalence's are low. The overall prevalence of hepatitis C antibodies was 1.38%, which indicates the existence of 1.3 million of anti-HCV-positive individuals in the country (7), while HBsAg was positive in less than 1% of non-vaccinated persons (8). There is no surveillance program to detect people infected with HBV or HCV, but in 2013 a national campaign will be launched, as the government has recently acquired 3 million rapid tests. Since 1998 Brazil has a mandatory (public and free) hepatitis B vaccination program, and currently more than 90% of newborn are being vaccinated (9). Any individual under 30 years old has access to the vaccine in the public health system as well as those from high-risk groups, like pregnant women, health workers, or drug users, despite the age. Moreover, since 1993 100% of blood units are screened in the blood banks for the presence of viral hepatitis. Patients with HBV (coinfected or not with delta virus) have access to antiviral treatment in the public health system, and interferon, entecavir and tenofovir are the therapeutic options available (10). There is a huge nationwide wire intended for HCV treatment. Government offers double therapy (interferon and ribavirin) and also triple therapy (interferon, ribavirin and a protease inhibitor) according to the patient's characteristics. For instance, in 2013 more than 5,000 HCV genotype 1 patients with advanced fibrosis (F3 and F4) will be treated with triple therapy in the whole country (11). This policy can help to decrease the burden of HCC in the next years.

Brazil has national guidelines on surveillance for HCC. State reimburses the costs of abdominal ultrasound (US) and determination of serum alpha-fetoprotein in patients with cirrhosis, HBV infection or NASH (12). However, the percentage of at risk patients that receives regular surveillance is unknown. There are also guidelines on diagnosis and treatment of HCC. Non-private patients have access to US-guided biopsy, as well as to triphasic computerized tomography, MRI and arteriography. The public health system covers the following therapeutic tools: percutaneous ethanol injection, transarterial chemoembolization, surgical resection, and liver transplantation. Private patients also have access to contrast-enhanced US for diagnosing the tumor, and for the treatment are still available radiofrequency ablation, DEB-eluting beads and sorafenib as well. The last one is often available for non-private patients by justice access.

The diagnosis and treatment of HCC in Brazil involves frequently a multidisciplinary team, including gastroenterologists, hepatologists, internists, radiologists, and surgeons. Considering that the number of gastroenterologists is around 5,000 – 10 times more than the number of hepatologists - GI doctors more frequently care for HCC patients in the country.



Brazil has the largest public liver transplant system in the world – in 2012, 1,492 patients had their liver transplanted, which means that only the United States transplanted more. Though we can estimate 30 to 40% of the transplants were performed in HCC patients, the real number is not available at the main Brazilian data bank (13). Since 2006, MELD score rules the waiting list in Brazil, and to patients with HCC are given 20 points in listing, 3 months later, 24, and 6 months later, 29. While on the waiting list, most of patients are submitted to locorregional therapy with percutaneous ethanol injection or transarterial chemoembolization. When fully documented, preoperative downstaging after locorregional therapy is accepted (14). Immunosuppressive regimen is regularly not tailored for HCC patients as in Brazil most of transplant recipients receive tacrolimus-based immunosuppression.

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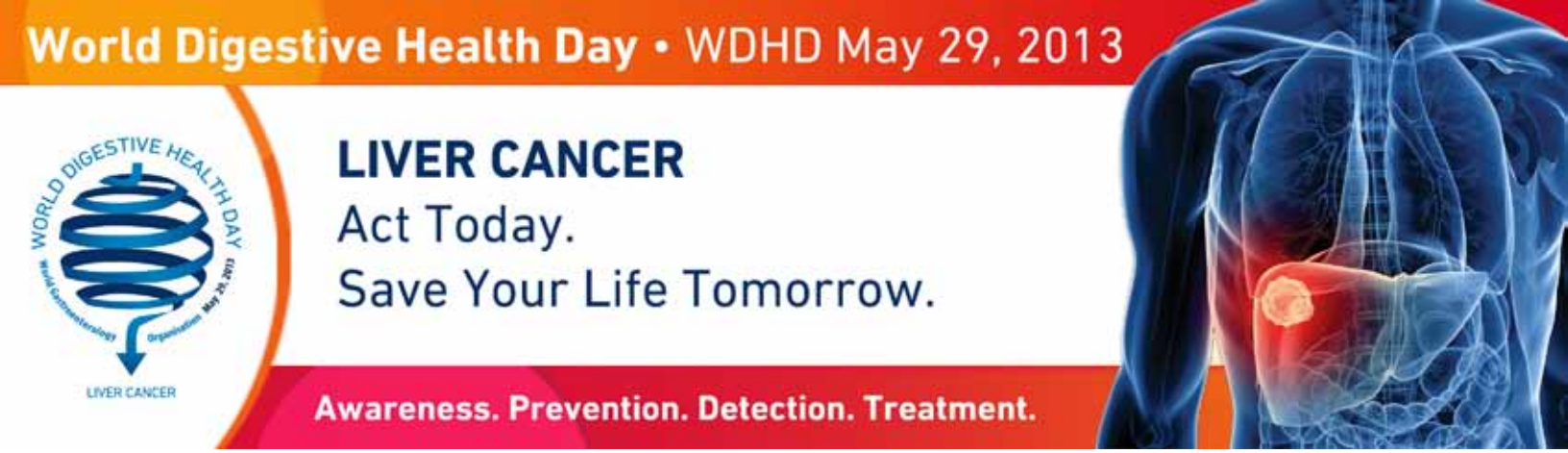

Hepatocellular Carcinoma in Egypt: An Updated Status

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Hepatocellular Carcinoma (HCC) accounts for most primary cancers of the liver (1). Worldwide, it is the fifth most common cancer and the third cause of cancer related mortalities (2-4). In Egypt and over the last decade, a remarkable growth, from 4.0% to 7.2%, was observed in the proportion of chronic liver disease patients diagnosed with HCC (5-7). Based on a recent worldwide systematic review from 90 studies concerned with viral hepatitis seroprevalence among HCC cases, a predominance of HBsAg was found in HCCs from most Asian, African and Latin American countries while anti-HCV predominated in Japan, Pakistan, Mongolia and Egypt (8).

While HCC is more prevalent in certain areas in Africa, like sub-Saharan Africa, nearly half of the data on HCC in Africa came from Egypt (9), being simultaneously plagued with the highest prevalence of HCV in the world (10, 11). While 30% of HCV infected individuals may clear the infection naturally, the remaining 70% will develop chronic disease that may result in liver cirrhosis and/or HCC (12). The two main risk factors for HCC in Egypt (Viral infection with HCV or HBV) took different patterns during the last decades. Two main factors are standing behind this; first, the high rates of HBV infection before the start of the national program for HBV vaccination of newborns in 1992 (13). Secondly, the wide use of Schistosomal parenteral therapy campaigns for more than 30 years ended in 1980 using non disposable glass syringes (14, 15). According to a recent meta-analysis, depending on a systemic search of most available electronic databases for relevant articles regarding viral hepatitis prevalence in Egypt, HBV and HCV were found among 6.7% and 13.9% healthy populations, and among 25.9% and 78.5% of HCC cases (16). Looking deeper, more recent studies evaluated the distribution of HCV genotypes in Egyptian individuals with HCC and liver cirrhosis (17). Phylogenetic analysis of sequence showed that 90.3% were genotype 4 and 9.7% were genotype 1. Among genotype 4, subtype 4a was predominant (79%), still without statistically significant difference between HCC cases, cirrhotic patients and non cirrhotic individuals. In another study, genotype 4 was similarly predominant (63%) but subtype 4a showed a statistically significant association with HCC (18).

Apart from hepatitis viruses and liver cirrhosis, there are different risk factors that can increase the hazards ratio of the previously mentioned main risk factors. During the last decade, a significant male predominance was observed in diagnosed HCC cases with a three times higher calculated risk in men than in women. The predominant age group (40-59 years) showed a slight increase compared with older groups (more than 60 years) (19). Environmental pollutants (such as aflatoxin B), chemical carcinogens (such as chlorination byproducts), insecticides and pesticides are all well reported to be classical promoters of HCC development (9, 20). Having ever worked in farming (21) or as an industrial worker and a lower level of education (22) were all significantly observed in HCC cases compared to different control groups. In addition, a positive correlation between a history of diabetes mellitus and HCC was observed (23).

HCC, as other cancers, is a multi-step process that involves many genetic alterations with an endpoint malignant transformation of hepatocytes (24). Recently, a study succeeded to provide a complete genetic profile for Egyptian HCC. Genome wide analyses were performed as a first step to identify the predictive signatures. Out of 25,000 studied cDNAs, 958 transcripts were differentially expressed between up and down regulation. Nineteen pathways were up regulated through 27 genes, and 13 pathways were down regulated through 19 genes. Real time PCR validation for the microarray was done. PPP3CA, ATG-5, BACE genes showed down regulation and ABCG2, RXRA, ELOVL2, CXR3 genes showed up regulation. Understanding HCC pathogenesis among Egyptian patients

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with identification and monitoring of gene expression profile changes will provide a chance to identify specific novel targets for disease detection and intervention (25).

The incidence and mortality rates for HCC used to be nearly identical with poor overall survival rates. However, recent focus on screening and surveillance for early detection as well as improving the different modalities of HCC management changed this gloomy picture. Regarding surveillance, a recent Egyptian study found that it improved HCC detection and treatment outcomes. More clearly, surveillance doubled the proportion of HCC cases detected at early BCLC stages as well as the patients' chance for getting ablative therapies and liver transplantation (26). The two main debates are the time interval for better screening and surveillance and the best method to do this. Depending on the fact that the doubling time of tumor size ranges from 1 to 19 months, with a median of 4-6 months (27), it has been suggested that the optimal interval is around 6 months. In this context, the Egyptian Society of Liver Cancer (ESLC) recently published the Egyptian HCC guidelines which recommend screening for high risk groups to be every 4 months with both abdominal ultrasonography combined with AFP. They further determined the high risk groups to be cirrhotic patients due to HBV, HCV, NASH, alcoholic and hemochromatosis and non cirrhotic patients in case of HBV infection (28). Research is still ongoing to increase early predictability of HCC development. A recent study found that the use of AFP combined with AFU and methylated p53-mRNA together could give a 100% early prediction in risky subjects (24). Moreover, another study considered SCCA and HSP70 as key biomarkers for HCC patients when the results for traditional biomarkers are negative (1).

In Egypt, all the known curative and palliative treatment options (surgical resection, liver transplantation, percutaneous ablation techniques and Trans-arterial chemo-embolization) are applied according to the international guidelines. However, for liver transplantation, living donor liver transplantation is the only option available in Egypt, which began in 2001, and HCC represents around 20% of the causes (26). The Egyptian National Committee for Control of Viral Hepatitis launched in the last 2 years a screening program for early detection of HCC that targets patients with established cirrhosis based on regular ultrasonographic examination and follow up of alpha feto protein test. Finally, HCC prevention should start from its very earlier steps such as prevention of HBV and HCV infection. In the absence of an HCV vaccine, HCV prevention is more challenging than the prevention of HBV. It requires an integrated strategy involving screening of blood donations, safe injection practices, and systematic avoidance of unnecessary injections (29).

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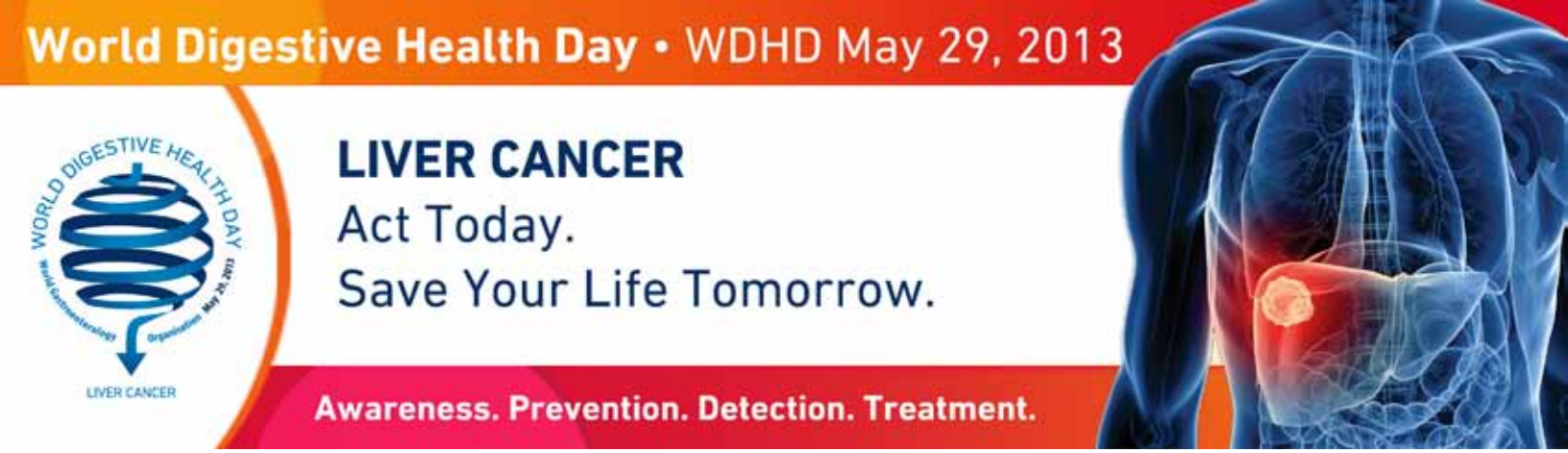

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Epidemic Proportions of HCC in Pakistan

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Pakistan is the sixth most populous country in the world, with an estimated population of over 180 million people. The Gross National Income per capita is suggested to be 770 USD. While 65% of people live in rural areas, 85% of the total health budget is spent on secondary and tertiary care facilities situated in larger urban centers where nearly 80% of the country's doctors practice, thus benefitting perhaps 15% of the population. Overall only 21% of the public accesses the public sector health facilities due to poor health care facilities, and the rest incur out of pocket expenses on health care. It is in this context that one has to understand the epidemic proportions of chronic viral hepatitis in Pakistan and the huge emerging threat of hepatocellular carcinoma (HCC).

Pakistan is also recognized as one of the countries of the world where hepatitis C virus (HCV) is endemic. Recent large national surveys suggest an overall HCV prevalence of 4.8% and that of HBV as 2.5%. There are however communities where the sero-prevalence of HCV can be as high as 23%. No wonder that chronic liver disease is the fifth most common reason for morbidity and mortality in the country and Pakistan has been perhaps accurately called a "cirrhotic state". Anis et al have tried to develop a best estimate model of the projected increase in HCV related cases and have shown an exponential rise in the infection.

It is therefore important to note that chronic HCV infection is the single largest cause of the development of HCC in Pakistan. HCV related HCC has also grown exponentially as shown by admission data from our university hospital, while HBV related HCC has remained stable or perhaps even declined a little (Figure 1). According to Globocan 2008 estimates, the age-standardized rate of HCC in Pakistan is 3.2 per 100,000 persons per year for males and 1.8 for females. The male to female ratio for HCC is 3:1, and most of the patients present in their 5th and 6th decade.

The large majority present late and therefore have limited treatment options available to them. The tumor burden is large and associated with other co-morbidities so that curative treatments are not possible. This is also because of the fact that there are hardly any liver transplant, or advanced liver surgery centers in the country. As a result most patients end up with palliative of comfort therapies. Therapies like RFA and TACE are available in few centers, mostly in the private sector, and therefore remain out of reach for most patients. Our center has now performed TACE in over

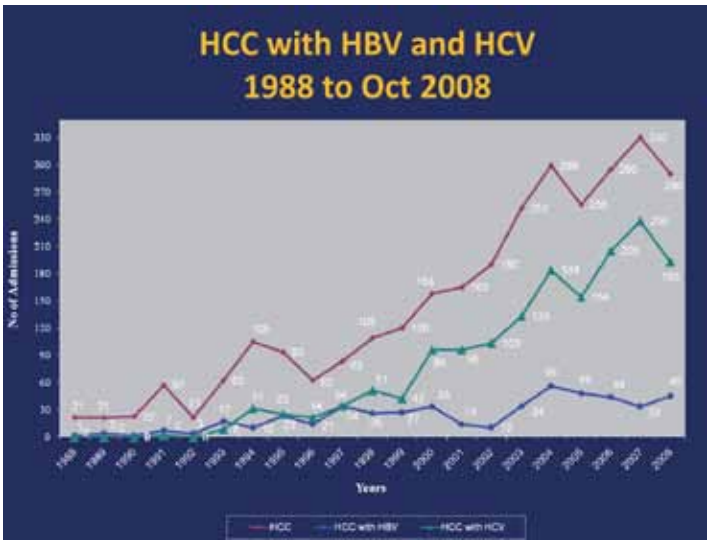
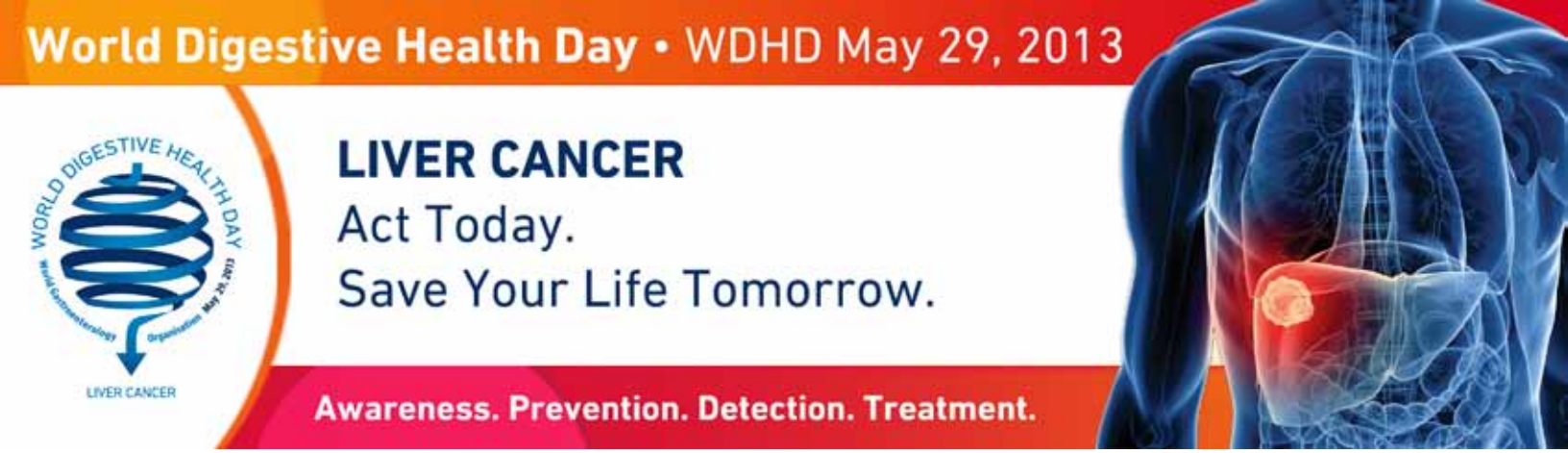


Figure 1. New cases of HCC seen per year at Aga Khan University Hospital, Karachi.

500 patients with good outcomes; however these are too few numbers considering the national disease burden.

The diagnosis of HCC in Pakistan, therefore, currently remains a death sentence, with poor overall survival. There is a dire need to treat this condition as a medical emergency in our country and to be able to institute the following measures for its control:

- There are no national programs for screening and early detection of HCC in patients with CLD. Centers need to be developed where basic facility of screening ultrasound and AFP testing is available freely.
- Aflatoxin exposure is considered to be high in Pakistan, mostly due to the way food spices are processed and stored. Regulatory inspections and testing of food items need to be instituted to control aflatoxin levels to international standards.
- Centers of Excellence in Liver Diseases need to be established where human and technical expertise is available for advanced diagnostics, treatment and research aspects of HCC.



- Needless to say, control of HCV and HBV infections will have the greatest impact on the control of HCC.

All above mentioned strategies need the support of national and international professional organizations like the WGO. The focus on HCC on the occasion of the World Digestive Health Day 2013 is therefore critical and timely.

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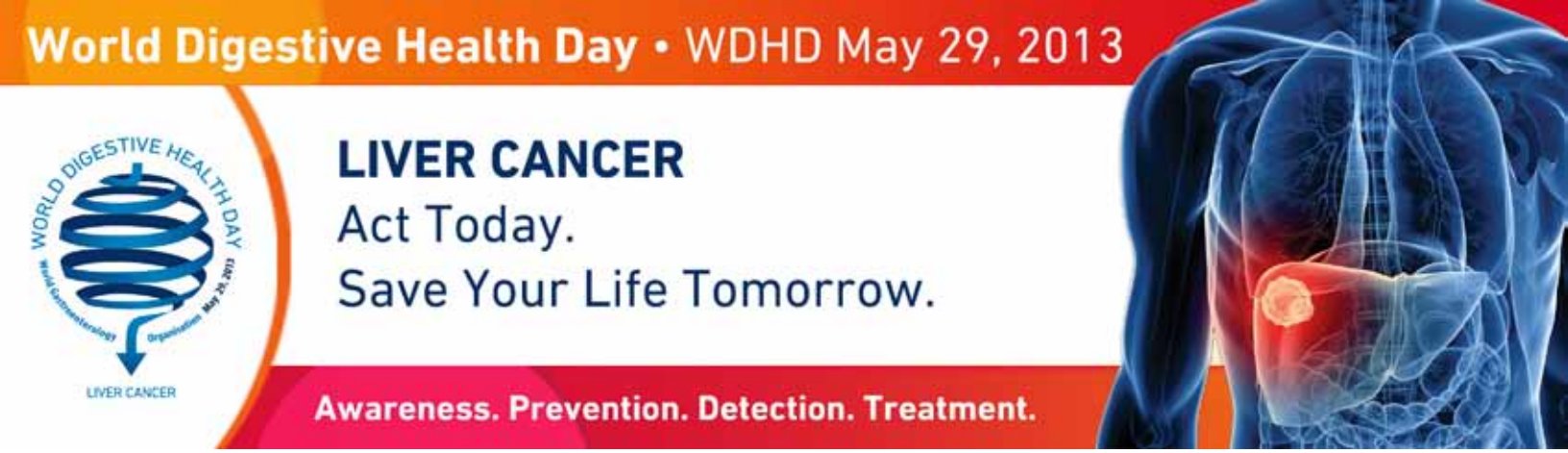

Hepatocellular Carcinoma in Argentina

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Argentina is considered to be an area of low risk for hepatocellular carcinoma (HCC) and epidemiologically similar to North America, other South American countries, Northern Europe and Oceania, where the annual incidence rates are <5 cases per 100,000 individuals (1). According to Globocan 2008 (International Agency for Research on Cancer, World Health Organization) the estimated crude annual incidence rate for HCC in Argentina is around 4.7/100,000. Unfortunately, and as it happens with many other diseases, there are no reliable local registries to assess the magnitude of the problem. According to the Ministry of Health of Argentina (www.deis.gov.ar, bulletin 31), primary liver cancer, including cholangiocarcinoma, accounted for 2.78% of all deaths (1673/60117) due to malignant solid tumors in 2009 (3.15% in males and 2.63% in females) and was the 9th cancer in frequency (8th in males). The highest incidence (0.93%) was observed in males aged 55-64 and 65-74 years. Most likely this data underestimate the true incidence of HCC. However, it is interesting that among the 278,357 individuals with a known cause of death, a similar number was ascribed to cirrhosis (n=1673, 0.6%) and to primary liver cancer (n=1692, 0.61%).

The low incidence of HCC in Argentina is not surprising because it is a region of low prevalence (<2%) for hepatitis B virus (HBV) infection (2-4). Similarly to North America and Western Europe, the prevalence of hepatitis C virus infection in Argentina is 0.6%-0.8% in blood donors and about 2% in the general population (5, 6), although higher rates have been observed in small communities with specific risk factors (7). As shown in Table 1, demographics and prevalence and etiology of cirrhosis have been reported in around 1,000 patients with HCC from Argentina, including publications (8, 9), abstracts (10) and personal communications to the author (Cejas N et al who analyzed data from the Argentina National Procurement Registry (https://cresi.incucai.gov.ar/public/documentos/ReporteOficial/EraMELD/SituacionesEspeciales/hepatocarcinoma.zip) and Allevato J on behalf of Hepatosur, a group of six gastroenterology centers from the Patagonia region). Despite the heterogeneity of the data sources (hepatology, liver transplant (LT) or gastroenterology units) results were quite homogeneous. The majority of patients with HCC in Argentina were males (71%-79.5%) aged between 58 and 64 years. Cirrhosis was present in >90% and was mostly due to either HCV infection or alcoholism (64%-82%). HCV infection was more frequent among patients with HCC referred for LT (Cejas et al) whereas alcoholic liver disease predominated in those managed in gastroenterology units as suggested by Allevato et al among patients from the Patagonia region (Table 1). In the largest multicenter study reported by Fassio et al, the prevalence of HCV infection was significantly higher among patients with HCC from LT centers compared to non-transplant centers (51% vs 26.5%, p<0.01) and the opposite occurred with alcoholic liver disease (14% vs. 40%, p<0.01). Interestingly, around 10% of patients with HCC had more than one etiology of cirrhosis with alcohol and HCV being the most frequent combination (Table 2).

Table 1. Demographics and etiology of cirrhosis in patients with hepatocellular carcinoma from Argentina.

						Etiology of Cirrhosis				
First Author	Year	N°	Median Age (yrs)	Gender (% Males)	Cirrhosis	HCV	Alcohol	HBV	Cryptogenic/NASH	Other
Findor J (10)	1998	216	63	77%	92%	41%	28%	20%	12%	6%
Fassio E (8)	2009	587	62	72%	92%	40.5%	42%	13.5%	9%	5%
Fassio E (9)*	2010	90	64	71%	92%	44%	35%	9%	14%	8%
Cejas N **	2012	209	58	77%	100%	46%	18%	6%	15%	15%
Allevato J***	2013	83	62	79.5%	98%	28%	51%	5%	8%	8%

**The publication included 240 cases from 9 countries. Data of the 90 patients from Argentina was kindly provided by Dr. Eduardo Fassio*

*** Analysis of the Argentina national liver transplantation database (INCUCAI)*

****Unpublished study performed in six centers from the Patagonia region*

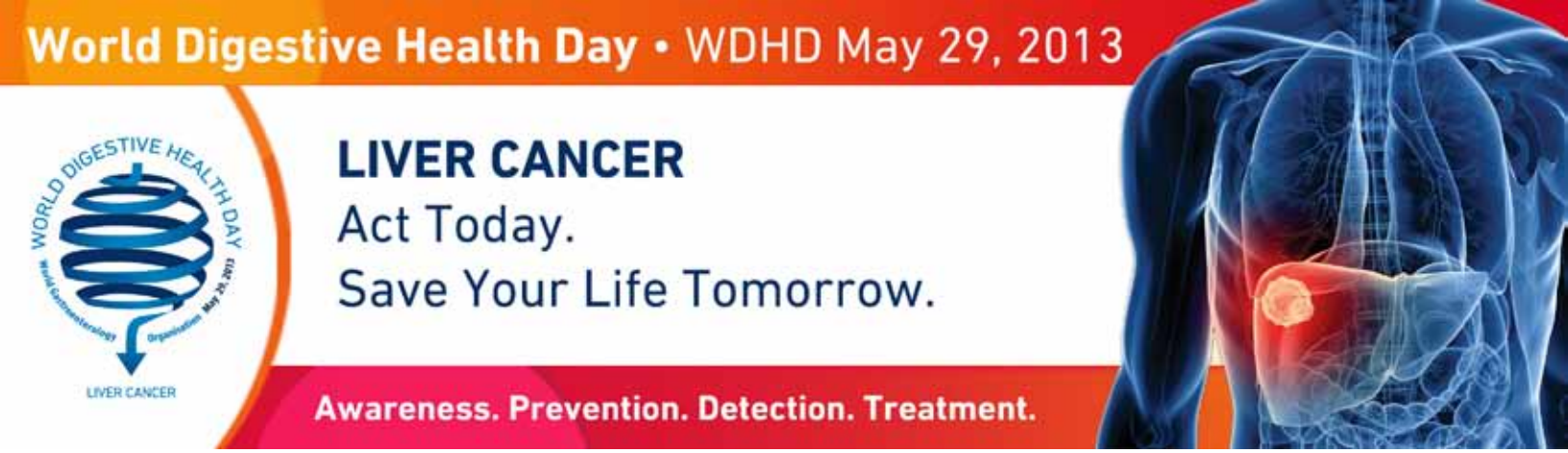

Table 2. Combined etiologies of cirrhosis in patients with hepatocellular carcinoma from Argentina.

First Author	N°	Alcohol + HCV	Alcohol + HBV	HCV + HBV	Total
Findor J (10)	216	17 (7.9%)	3 (1.4%)	5 (2.3%)	25 (11.6%)
Fassio E (8)	551	35 (6.3%)	12 (2.2%)	7 (1.3%)	54 (9.2%)
Fassio E (9)	90	8 (8.9%)	2 (2.2%)	2 (2.2%)	12 (13.3%)

All treatment options for patients with HCC are available in Argentina, both in the public and private health systems. However, it is difficult to assess treatment accessibility at a national level. Perhaps the most reliable data are those from the most complex treatment for HCC which is LT. In Argentina, LT is part of the so-called Mandatory Medical Program, a law establishing that all insurances should cover the procedure. In addition, patients without insurance have access to LT in four public programs, three for adults and one for children. Before 2005, when a Model for End Stage Liver Disease (MELD)-based system was adopted for organ allocation, HCC was the most frequent indication for adult-to-adult living donor liver transplantation in Argentina (11). Among 344 consecutive adults with chronic liver disease (2000-2004), the proportion of patients with HCC was significantly higher in those grafted with live donors than deceased donors (21% vs. 10%, p=0.008). After adopting the MELD system, patients with HCC fulfilling Milan Criteria (T2 stage) received 22 supplemental MELD points. From 2005 to 2012, 209 consecutive patients with HCC were listed of which 162 (77.5%) underwent LT with deceased donors and only 10% died or were withdrawn from the list (Cejas et al). Analysis of the explanted liver (n=158) showed absence of malignancy in 14 patients (9%), HCC T1 in 10 (5%), T2 in 99 (63%) and >T2 in 35 (23%). One and 5-year survival was 89.5% and 62.5% in 119 patients with HCC and 82% and 69% respectively in 805 non-HCC recipients (p=NS).

The key for success in patients with HCC is early diagnosis, at a stage where curative therapies can be instrumented. To achieve this goal it is imperative that all patients with cirrhosis or chronic HBV infection undergo screening for HCC with good quality ultrasound performed every six months. The Asociacion Argentina para el Estudio de las Enfermedades del Higado (Argentina Association for the Study of the Liver) has organized several consensus conferences and put together strong recommendations about screening for HCC (4, 6). However, lacking good quality or mandatory registries, it is difficult to assess whether there is an adequate access to screening and therapy of HCC at a national level in Argntina, especially in areas where the health system is less well developed. Having practiced hepatology since 1978, my personal feeling is that awareness of the importance of early diagnosis of HCC and also early referral to tertiary or LT centers has significantly increased over the last two decades.

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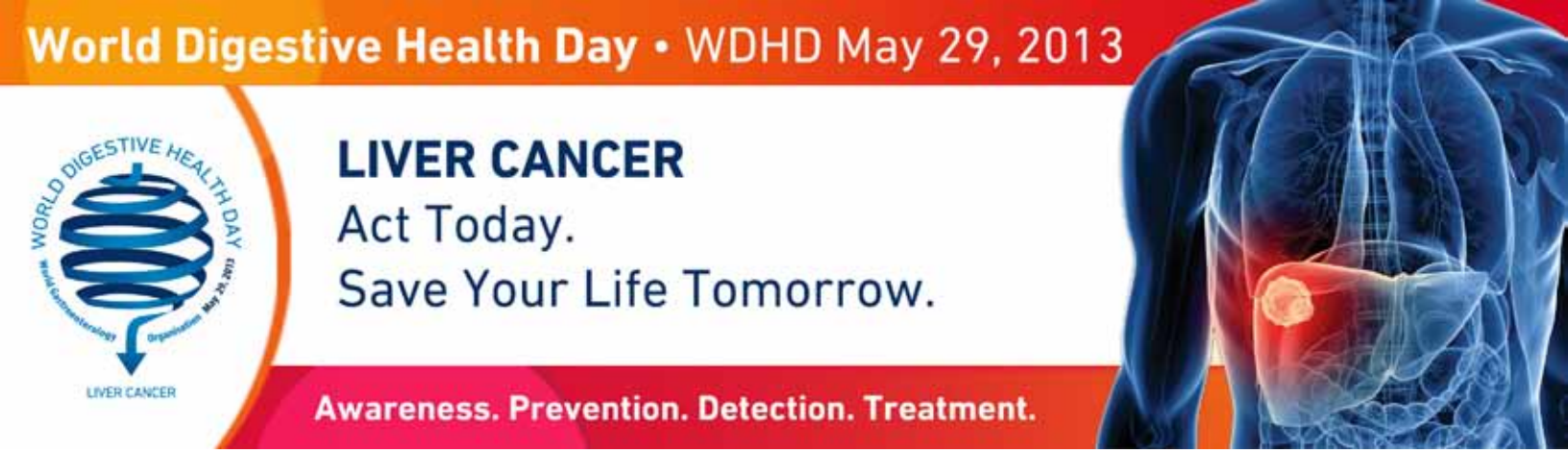

Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Hepatocellular Carcinoma

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The development of imaging criteria for response assessment in patients with hepatocellular carcinoma (HCC) has been a long process. In 2000, the European Association for Study of Liver (EASL) first proposed an amendment to the World Health Organization (WHO) criteria, the ones most commonly used at that time (1). The WHO criteria were designed for the evaluation of cytotoxic agents and recommended the use of the product of the two longest perpendicular diameters to monitor changes in tumor size. These criteria were unable to capture the anticancer activity of tumor-directed therapies used in the treatment of HCC, such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and transarterial chemoembolization (TACE). The EASL guideline recommended to take into account treatment-induced tumor necrosis and to measure the product of the longest diameters of the viable portion of the tumor – as recognized by contrast-enhanced radiological imaging – instead of the product of the longest diameters of the whole tumor mass. Assessment of tumor response according to the EASL amendment has been used in HCC patients receiving tumor-directed treatments for more than a decade.

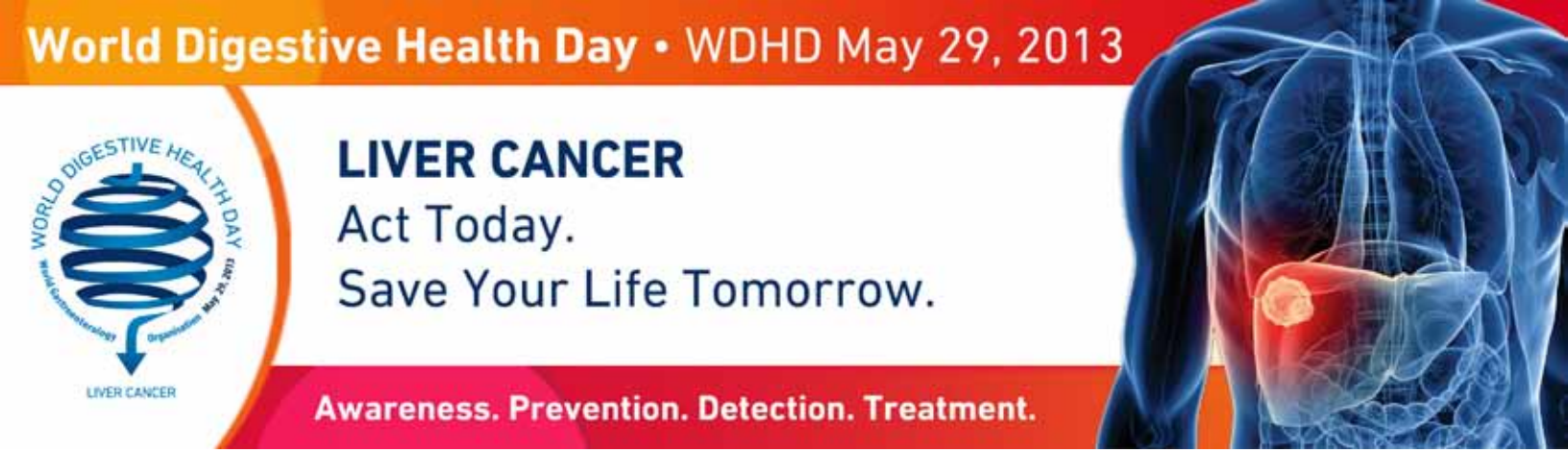
A limitation of the 2000 EASL guideline is that it only provides recommendations for the evaluation of target lesions. With the advent of systemic treatments for HCC, the need for a comprehensive model for response assessment has been widely acknowledged (2, 3). In the meantime, the WHO criteria were largely replaced by the Response Evaluation Criteria in Solid Tumors (RECIST) in oncology trials. The introduction of RECIST has been a major advancement in the standardization of response assessment. The RECIST model clearly defines the categories of target lesions, non-target lesions, and new lesions, and provides overall response classifications resulting from the different combinations of the responses observed in each of these categories. In addition, the RECIST criteria simplified the assessment of the target lesions by recommending the use of unidimensional measurements and the sum of the longest tumor diameters instead of the bidimensional approach of the WHO method including two measurements and the sum of the products.

The RECIST panel acknowledged that amendment to the guideline could be needed for specific tumors or anatomic sites presenting unique complexities. Specific refinements to standard RECIST criteria in the setting of HCC clinical research were introduced at the time of the SHARP trial comparing sorafenib versus placebo (4). The SHARP study identified a distinct overall survival benefit for sorafenib as compared to placebo. The assessment of the secondary endpoints, time-to-progression (TTP) and disease control rate (DCR), was conducted by an independent blinded radiological panel following specific recommendations for image interpretation aimed at preventing incorrect diagnoses of progression. In fact, in the SHARP trial, TTP and DCR data were consistent with overall survival. However, the objective response rate (ORR) in the sorafenib arm – calculated by standard RECIST metrics – was negligible.

A number of novel molecular targeted compounds that produce ORR of less than 10% by standard RECIST have shown significant improvement in survival in a variety of cancers in randomized controlled trials (2). The RECIST guideline, similar to the WHO criteria, is based on the concept of tumor shrinkage as the only measure of antitumor activity. These agents no longer induce tumor shrinkage and, thus, ORR is no longer a surrogate for overall survival (2).

In 2008, a group of experts was convened by the American Association for the Study of Liver Diseases (AASLD) to develop a set of guidelines aimed at providing a common framework for the design of clinical trials in HCC (2). This panel addressed the issue of the lack of correlation between response by conventional size-based criteria and survival observed in HCC trials with both tumor-directed therapies and molecular targeted agents, and produced formal amendments to standard RECIST. The resulting criteria were named mRECIST for HCC (4). Several changes were based on the recommendations produced at the time of the SHARP trial to prevent incorrect diagnoses of progression. In addition, the mRECIST criteria adapted the concept of viable tumor proposed by the 2000 EASL guideline to comply with the unidimensional approach of standard RECIST, by recommending to measure the longest diameter of the viable portion of the target lesions.

mRECIST appears to have broader applicability with respect to the EASL criteria. By keeping the accepted standard RECIST model as a reference,



mRECIST enables assessment of overall response by taking into account target lesions response, non-target lesions response, and presence or absence of new lesions. The mRECIST guidelines have been increasingly adopted in HCC clinical research. Several key recommendations, such as those concerning the classification of ascites, hepatic hilar lymph nodes, vascular invasion, and new lesions – all of which may have a major impact on the assessment of TTP and DCR – have been incorporated into the radiology charters of clinical trials, even when target lesions measurements were conducted according to standard metrics and, therefore, the criteria were formally named standard RECIST (5).

The main open question is whether the use of the mRECIST viable tumor concept for target lesions measurements can bring ORR back as a surrogate for survival. Several clinical trials from investigators around the globe have suggested that this is indeed the case in patients receiving tumor-directed therapies (6-12). However, data in patients treated with systemically-active, molecular targeted agents are still limited (13, 14), and further research is needed to understand the prognostic value of ORR as per mRECIST in this setting.

In conclusion, a growing body of scientific evidence suggests that mRECIST– designed for response assessment in clinical trials – may translate into a tool for clinical practice, a process that has already started with the recommendations issued in the recent clinical practice guidelines produced by the EASL and the European Organization for Research and Treatment of Cancer (15) and by the European Society of Medical Oncology and the European Society of Digestive Oncology (16).

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Incidence, Diagnostics and Treatment of HCC in Russia

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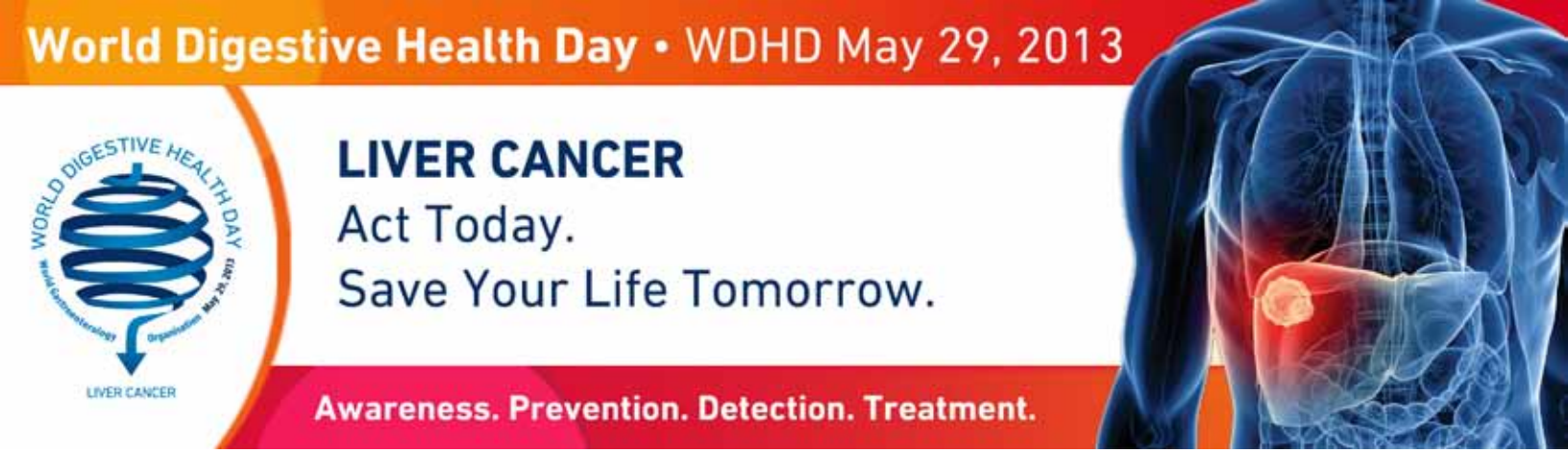
Although hepatocellular carcinoma (HCC) takes the 5th place in morbidity and the 3rd place in mortality from oncological diseases in the world, the incidence of it widely varies in different areas, depending mostly on the rate of the particular risk factors existing in these areas. The most common risk factor for HCC is cirrhosis, which occurs in chronic hepatitis B and C patients and in alcoholic liver disease patients. Never the less, it can also be caused by direct mutagenic affect on hepatocytes by aflatoxins, which are produced by *Aspergillus flavus.* Hepatitis B virus can also lead to a direct malignancy of liver, skipping the cirrhotic stage.

In Russia primary liver cancer is 14th in oncological morbidity and 10th in mortality (Aksel, Davydove 2010). In absolute numbers we had 6,298 new cases of HCC and 8,319 cases of death from HCC in 2009. This obviously shows that around 2,000 of cases are diagnosed in autopsies. Unfortunately, there are no statistical data about HCC itself, so considering it to be 85% from primary liver cancer, there should be around 5,350 new HCC cases and around 7,070 death cases per year.

The incidence of HCC etiology factors is not known exactly but probably not very different from Europe with alcoholic liver disease being the most important factor, followed by chronic viral hepatitis, and non-alcoholic fatty liver disease. For this reason, prevention of liver disease would be very important to reduce the number of HCC cases. Preventive programs exist for Hepatitis B with regard to vaccination but not for other causes of chronic liver disease.

Hepatitis B vaccination has been standard for all newborn babies for the last 10 years. Risk groups (doctors, HBV infected partners, etc.) also get vaccinated. In particular, chronic alcohol abuse is a big problem in Russia and has been recognized by the state authorities. Preventive program are being developed but have not been instituted yet.

Treatment for HCC depends on the stage of disease at presentation. Since HCC only becomes symptomatic at a late stage, early detection through screening of high risk groups (all patients with cirrhosis) would be mandatory. This would require two things: for one, patients with asymptomatic cirrhosis would have to be identified by their primary care physicians, which is not happening in many cases; and secondly, patients known to have cirrhosis should undergo a systematic screening program with regular ultrasound examinations. Even though such programs exist locally at highly specialized institutions, no such program exists on a nation-wide basis in Russia, just like in all of Europe or the United States. Russia, as a country with a strong centralized governmental structure, could be a model country for instituting such a screening program, but further efforts are required to put a screening and surveillance program into place.



All types of HCC treatment, including liver transplantation, liver resection, radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), and targeted therapy with Sorafenib, are available in Russia, albeit not for everyone.

The treatment is usually following the BCLC staging and treatment algorithms in big centers. In smaller cities, due to lack of opportunities and education of doctors, state-of-the-art treatment cannot be provided for all treatments stages. Demand for liver transplant exceeds the supply by far and needs to be thoroughly improved.

HCC-patients treated at the Russian Cancer Research Center n.a.N.N.Blokhin, RAMS:

We performed research investigating the incidence of different etiologic factors of HCC in our population of patients. Four-hundred and forty-eight patients with morphologically proven HCC from different centers of Russia had been analyzed (Table 1). The average age was 54.4 years; 65% of them were men, 92.2% had ECOG 0-1. In most cases HCC was diagnosed in an advanced stage when radical methods of treatment, such as resection and transplantation were not available any more: BCLC - B stage in 34.2% (n=153), BCLC - C stage in 51.1% (n=229) of patients. Only 6.7% (n=30) of patients were potentially curable with a 70% of 5-year survival. And 3.1% (n=14) had BCLC D stage at the time of HCC diagnosis and could only go for best supportive treatment. These data, unfortunately, greatly underestimate the real number of patients with terminal stage of HCC, because obviously most of them never were admitted to our clinic and therefore were not included in the analyses. When risk factor analyses was performed it came out that viral etiology was present in around a half patients (47.7%), with almost equal incidence of hepatitis B 24.1% (n=108) and hepatitis C 22.5% (n=101), and 1.1% (n=5) of B + C hepatitis co-infection. Non-viral etiology was diagnosed in 41.7% (n=187) of patients. Morphological proof of cirrhosis was not available in many case in our group. Therefore we could only analyze a presence of decompensated cirrhosis by portal hypertension signs. Only 60% (n=267) of patient were considered to be cirrhotics, in 40% (n=181) we didn't find any clinical signs of it. When Child-Pugh score was evaluated for cirrhotic patients (n=267), 73.0% (n=195) of them had class A (5-6 points). Child-Pugh B and C were present in 27% of patients: 22.8% (n=61) and 4.2% (n=11) respectively.

This results show us that HCC is mostly diagnosed in intermediate and advanced stages according to BCLC, which can only be treated with palliative methods such as TACE and sorafenib. Median of overall survival in these two groups is 20 months and 11 months respectively.

Table 1: Patient characteristics and risk factor incidence in HCC patients.

		N=448 (100%)
Age (years)		54,4 ± 14,2
Sex	Mel Female	291 (65) 157 (35)
ECOG	0 1 2 3 4	73 (16,3) 340 (75,9) 26 (5,8) 8 (1,8) 1 (0,2)
TNM stage (AJCC, 2010)	I II III IV No data	34 (7,6) 89 (19,9) 194 (43,3) 107 (23,9) 22 (4,9)
BCLC stage (2007)	A B C D No data	30 (6,7) 153 (34,2) 229 (51,1) 14 (3,1) 22 (4,9)
Etiology	HCV RNA (+) HBV DNA (+) HCV (RNA) + HBV (DNA) Non-viral No data	101 (22,5) 108 (24,1) 5 (1,1) 187 (41,7) 47 (10,5)
Clinical signs of cirrhosis	No Yes	181 (40) 267 (60)
Child Pugh score (n=267)	A B C	195 (73,0) 61 (22,8) 11 (4,2)

Summary:

Although Russia has the opportunity to give a proper management of chronic liver diseases and treatment of hepatocellular carcinoma, still a lot could be done to improve the situation. First of all a proper register of patients with alcoholic liver disease, hepatitis B (including Delta superinfection) and hepatitis C should be organized on a national level. It will give us an idea of how many patients with risk of HCC we really have in Russia. It also will improve the ability of screening these patients for HCC properly using US (and maybe AFP) every half a year (for cirrhotics and chronic hepatitis B) which will improve the earlier stage HCC diagnostics and the possibility to cure those patients with early stage HCC using liver transplantation and resection/ablation for them. We also need a federal program for antiviral treatment for chronic hepatitis B including nucleoside analogs, and hepatitis C to reduce the number of patients with advanced liver disease, including cirrhosis and HCC.

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Hepatocarcinoma in Venezuela

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Liver cancer represents a *major* public *health concern but* has been underreported in Venezuela. Hepatocarcinoma (HCC) is a common final step for virus infection (HBV, HCV,+/- HIV), cirrhosis, and NAFLD/NASH. Venezuela has regional hepatitis programs (1) but lacks a national surveillance program for the entire population to detect virus infection. National guidelines for hepatocarcinoma are also required so there are no official incidence data in the general population. However, in the 2009 official mortality data, 3.2 and 3.1/100,000 males and females, respectively, died from HCC (2).

HBV is responsible for over 50% of the attributable risk of HCC. HBV exists as eight distinct genotypes that differ by their geographic distribution and their pathogenic properties, including their risk of persistence as chronic infection and their capacity to induce HCC (3). Genotype F is predominant in Venezuela in aborigine and urban populations (3, 4).

Since 1996, Venezuelan newborns, or during their first year of life, receive a mandatory hepatitis B vaccine: 14% of the population in 1999 and 78% in 2011 were vaccinated (Table 1) (5). Despite vaccination, the reported Hepatitis B virus (HBV) infection incidence is 5-15.3% in a series reported by personal communication; no official data are available (1, 6-9).

Transmission of HBV and HIV is predominantly sexual in Venezuela and HCV is nosocomially transmitted. Again, there are no official data. One hundred percent of blood units are screened for HBV, HCV, and HIV at blood banks across the country (10, 11). On the other hand, NAFLD/NASH incidence is between 14.7-40% (9, 10, 13-16).

Chronic hepatitis C virus infection is reported as 20-35.8% of HCC patients (6-17). However, 16-18% of deaths for liver diseases are undiagnosed (8) due to poor hepatological knowledge among the general practitioners, and mainly due to lack of availability of serologic diagnostic tests in the public practice.

However, in the regional reference centers, patients are managed by expert gastroenterologists and hepatologists with access to serological and molecular biology tests. Genotype and viral load tests, as well as HBV treatment (Peginterferon, α2a/α2b, lamivudine, entecavir, tenofovir) and HCV treatment (Peginterferon α2a/α2b, ribavirin) are covered by the social security system without charge for the patients. This issue helps with HCC prevention and avoids progression. Protease inhibitor (telaprevir) therapy, although approved, is not cost free.

Gastroenterologists, radiologists, oncologists, and multidisciplinary teams are primarily involved in the initial diagnosis and treatment of HCC in our country. According to the Venezuelan Gastroenterology Society data, there were 900 gastroenterologists and 12 hepatologists working in public and private practice in 2012. Seventy-four percent of at-risk patients receive regular surveillance in private practice. Policlinica Metropolitana Caracas and Hospital Universitario Maracaibo, are both regional referral centers for private and public patients respectively, with trained radiologist in HCC diagnosis. Diagnostic tools available are ultrasound, US guided biopsy, triphasic CT, Magnetic Resonance Imaging, and arteriography. Those tools are used in private practice in the most important cities (e.g CEUS are available only in Policlinica Metropolitana Caracas).

Hepatitis C is the more frequent etiology of HCC in Latin America followed by alcoholic cirrhosis (13). HCC treatment tools are available in Table 2.

Table 1. HBV Vaccination in Venezuela

Year	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998
% Hep B (Birth dose)	73	66	73	64	61	63	57	44	34	35	14		
% Hep B3 (third dose of hepatitis B vaccine)	78	84	53	62	71	88	82	72	60	53	5	1	1

Source: WHO. (data as 2-Oct-2012)

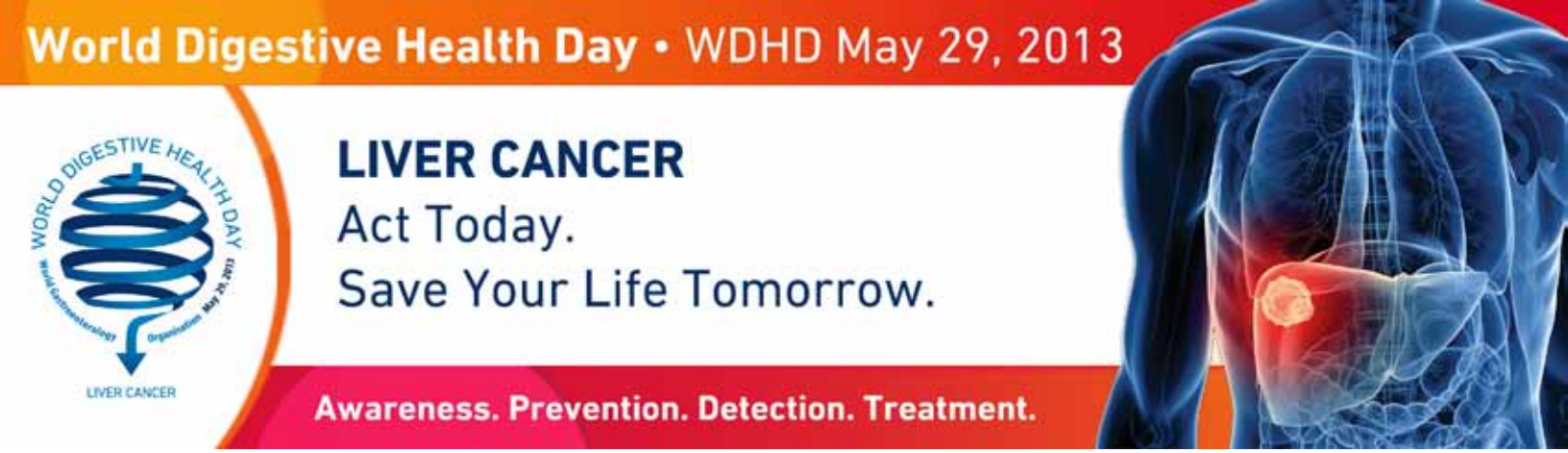

Table 2. HCC Available Treatment in Venezuela

	Available in Caracas Maracaibo	Approx. Cost ($) per Procedure	Covered by public health system
PEI	Yes	3.000 USD	No
RFA	Yes No	7.000 USD	No
TACE	Yes	20.000 USD	No
Radioembolisation	No		No
Surgical Resection	Yes	36.000 USD	Yes
Liver Transplantation	No	150.000 USD	Yes
Sorafenib (per month)	Yes	930 USD	Yes

Data source: Policlínica Metropolitana (private practice) Caracas; Hospital Universitario (public hospital) Maracaibo.

The Venezuelan social security system provides HCC treatment without charge (sorafenib). We hope and expect that the governmental agencies will keep on providing what it has so far and giving attention to this major health issue.

I want to thank Dr. Lucy Dagher for kindly contributing to this information.

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Hepatocellular Carcinoma in India

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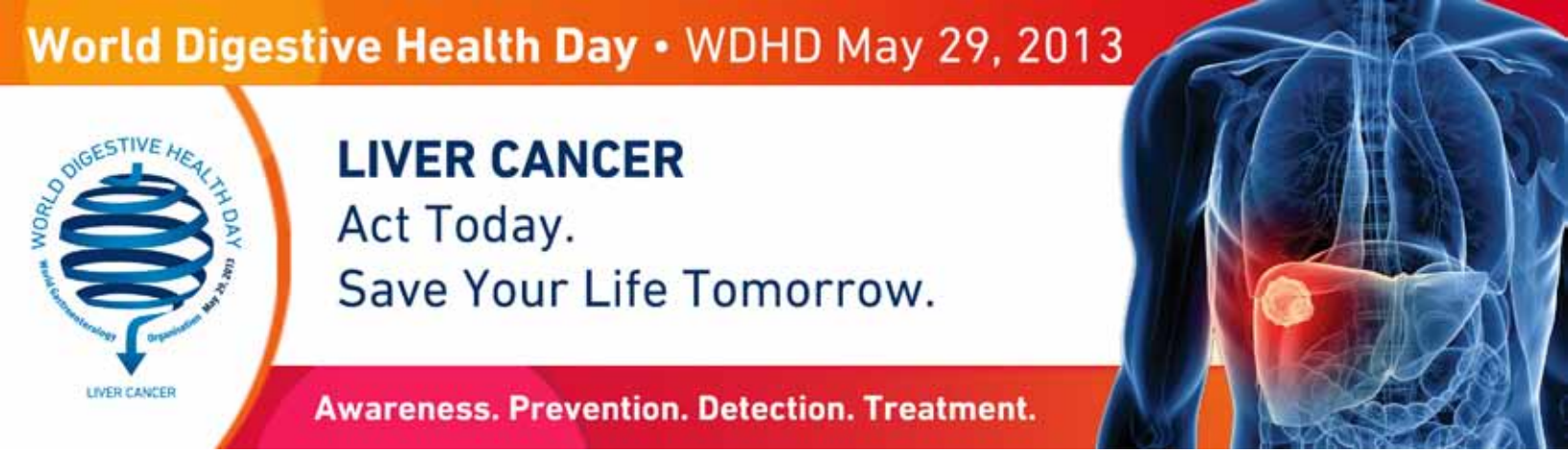
Hepatocellular carcinoma (HCC), besides being one of the common cancers in India, is also one of the major causes of mortality among patients of chronic liver disease. Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide with an estimated 500,000 to 1 million new cases per year (1). A rise in the incidence of mortality from HCC has been observed in different countries, and approximately 70-80% of deaths from HCC occur in developing countries (2).

The global distribution of HCC is very variable. According to the age adjusted HCC incidence per 100,000 population per annum, different geographic regions can be divided into three incidence zones: low (<5), intermediate (between 5 and 15), high (>15) (3). Most Asian countries are in intermediate or high incidence zones of HCC. The incidence of HCC varies widely with the geographic location as risk factors for the development are variably distributed across continents and within countries. Age-adjusted incidence rates for liver cancer in developing countries are 2- to 3- fold higher than in the developed countries (4). Approximately 80% of liver cancers occur in Asia and Africa (5). In India, information on epidemiology of HCC is inadequate. **Cancer is not a reportable disease in India and the cancer registries in India probably do not provide a very accurate estimate of HCC prevalence** in India. National cancer registry program was established by Indian Council of Medical Research (ICMR) in 1981. Initially, 3 hospital based cancer registry (HBCRs) and 3 population based cancer registries (PBCRs) were established. By now, 21 PBCRs and 6 HBCRs have been established. The last published registry data by ICMR, available at the cancer registry website (www.ncrpindia.org), was in 2008 which provides information on various cancers from 2006 to 2008 (6). The other source of information was the report published by International Agency for Research on Cancer (WHO) (7). According to these reports the age adjusted incidence rate of hepatocellular carcinoma (HCC) in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 populations per year. There is a male preponderance with a male: female ratio of 4:1. It was also found that the median age of presentation of HCC ranges between 40 and 70 years and with increasing age, the frequency of HCC increases. Dixit et al published an important population based survey to identify the cancer related mortality in India. The study was conducted by verbal autopsy study in 1.1 million homes representing the whole country. In 2010, at all ages, rates of cancer deaths were about 59/100,000 for men and about 52/100,000 for women. Among men, the first 4 causes of mortality included oral, stomach, lung and liver cancer. In 2010 approximately 14,000 deaths would have occurred due to liver cancer with an age standardized mortality rate (ASMR) of 6.8/100,000 population. In women liver cancer was the 8th most common cause of cancer related mortality accounting for 12,000 death in 2010 with an ASMR of 5.1/100,000 population (8).

The geographic model of HCC occurrence is frequently correlated with the etiologic factors. Hepatitis B virus (HBV) infection is the most common etiologic factor in high incidence areas, while hepatitis C (HCV) infection is more prevalent in the low incidence areas (9). Unlike other low incidence zones, in India HBV has been the main etiological factor associated with HCC in various published series (10,11,12). India lies in the intermediate endemic zone of HBV infection with hepatitis B surface antigen (HBsAg) carrier frequency of 2–4% in the community and HBV infection is the leading cause of chronic liver disease in India and is responsible for 35–60% of chronic liver disease and 60–80% of HCC (13,14,15). About 15 million people are infected by HCV and the population prevalence of anti-HCV antibodies is about 1% (16). Thus, there is a large pool of people who are at risk of developing chronic liver disease and, therefore, HCC. PCR-based studies have found HCV RNA positivity in 27–33% of patients with HCC (17,18). Serological evidence of HCV infection in patients with HCC in India is around 15-20% (15,10). Dual infection with or without alcohol was seen in 8-10% of patients (10, 15). India, despite being an intermediate endemic zone for HBV has low incidence of HCC unlike other Asian countries. This phenomenon is akin to low HCC incidence in Greenland Eskimos as compared to Alaskan Eskimos despite similar HBsAg positivity (20). In the only case control study for the risk factors of HCC in India. The ORs and 95% confidence intervals (CI) of HCC were 48.02 (25.06–91.98) for any HBV marker, 38.98 (19.55–77.71) for HBsAg positivity, 12.34 (2.84–53.61) for HBsAg negative and antibody positive (either of anti-HBe or total anti-HBc), 5.45 (2.02–14.71) for anti-HCV positive and HCV RNA positive, and 2.83 (1.51–5.28) for heavy alcohol use. No significant risk increase was evident for subjects who were anti-HCV positive and HCV RNA negative. Synergism between alcohol and

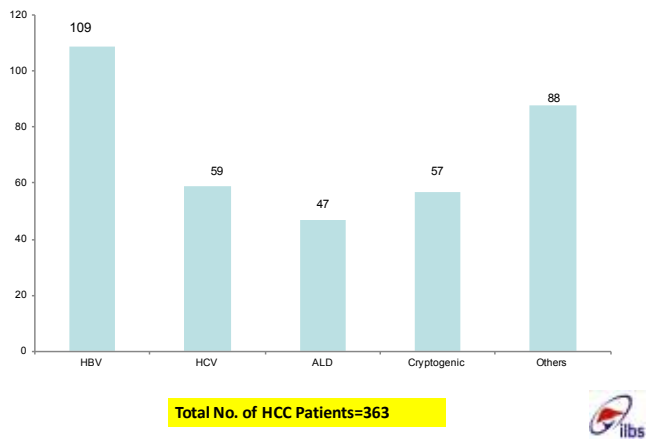


HCV infection in causing HCC was found, but not between alcohol and HBV. Overall, conclusive evidence of the presence or absence of cirrhosis was reached in 189 (88.73%) HCC patients; cirrhosis was present in 137 (72.48%) of them. ORs with 95% CI of HCC in the presence and absence of cirrhosis, respectively, for HBV were as follows: (i) 48.90 (24.61–97.19) and 35.03 (15.59–78.66) for any HBV marker; (ii) 39.88 (19.41–81.97) and 24.40 (10.60– 56.18) for HBsAg positivity; and (iii) 12.10 (2.67–54.88) and 19.60 (3.94–97.39) for HBsAg negativity and antibody positivity. Significantly increased risk was found among cirrhotic patients for anti-HCV positivity and HCV RNA positivity (OR = 7.53 (2.73–20.78)] and for heavy alcohol use [OR = 3.32 (1.70–6.47)]; however, in the absence of cirrhosis, no significant risk increase was evident for subjects who were anti-HCV positive and HCV RNA positive [OR = 0.97 (0.11–8.54)], or who had history of heavy alcohol use [OR = 1.58 (0.55–4.53)].(15).

Among the various etiological factors being implicated in the cause of HCC, the most important cause, is HBV infection. HBV genotype D was the predominant genotype associated with HCC cases seen in India (21). Occult HBV infection is also an important risk factor for HCC development, especially in patients with other causes of cirrhosis (22), although its epidemiological impact on HCC in the Indian population remains unexplored (23).

About 70%-90% of HCC have been reported globally in cirrhotic livers (24). The frequency of HCC in a cirrhotic may vary depending on underlying etiology of cirrhosis, such as HBV, HCV, alcohol and nonalcoholic fatty liver disease. The only Indian study that assessed the HCC incidence among patients with child's A and B cirrhosis without having any HCC at enrollment (n=194) followed patients for a median duration of 44 months. Each patient had ultrasonography and AFP at 6 month intervals and TPCT annually. Nine cases of HCC (all males) were detected with an annual incidence rate of 1.6% (95% CI 0.07-3.0) (25), during a cumulative 563 years follow up.

Figure 1: Etiologies of HCC at the Institute of Liver and Biliary Sciences (ILBS) at New Delhi (2011-12)



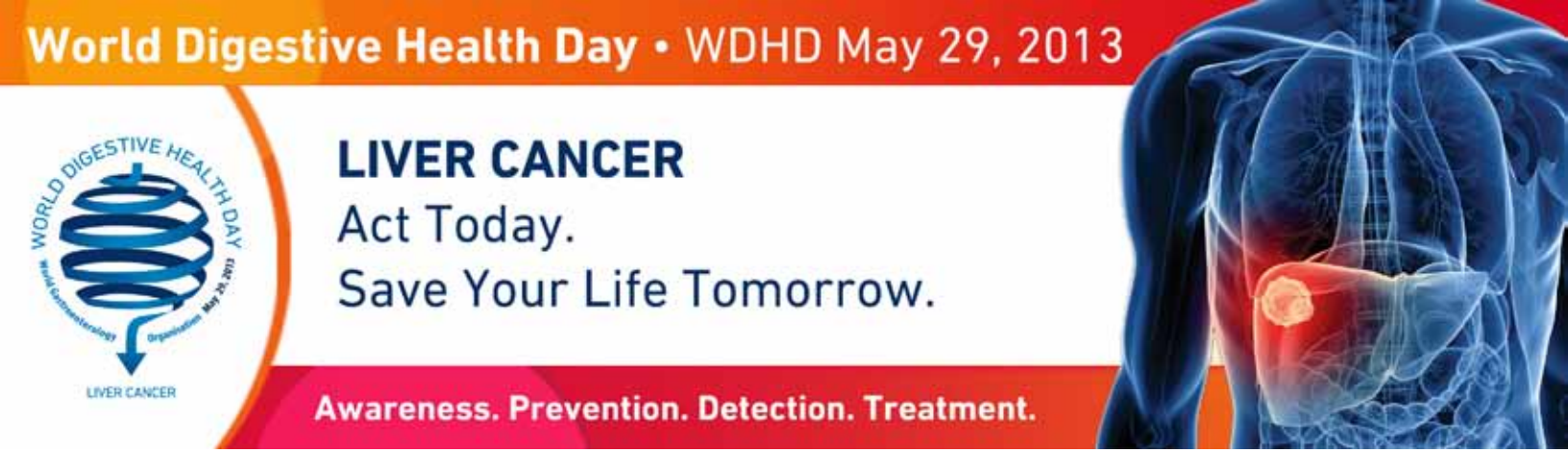
In India, although HBV infection, HCV infection, alcohol consumption, and aflatoxin exposure are important risk factors for HCC development, less common causes include nonalcoholic fatty liver disease, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, Wilson's disease, smoking and tobacco use (26, 27). At the institute where the authors work [Institute of Liver and Biliary Sciences, New Delhi, India], about 40% of patients were having etiologies other than HBV, HCV or alcohol abuse. These included patients with cryptogenic cirrhosis, diabetes or obesity developing HCC [unpublished data, Figure 1]. This could be due to referral bias as well, as increasing contribution of these etiologies to HCC development in the wake of rising epidemic of obesity and diabetes in India.

None of the case series published from India have provided year wise breakup to assess whether HCC burden is increasing. However personal experiences at tertiary care centers of India indicates that HCC burden is gradually increasing.

Early detection by surveillance is the only way to diagnose HCC when curative treatments are feasible (28). Detection because of symptoms (liver failure, jaundice, physical deterioration) reflects an advanced stage where cure is no longer an option. Surveillance aims to reduce disease-specific mortality by detecting HCC at a curable stage. The optimal profile for this endpoint is when the HCC is smaller than 2 cm. The decision to begin surveillance depends on the degree of risk of HCC for the individual and the extent to which he or she would be treated if diagnosed with the malignant disease. Level of awareness and attitude of physicians managing CLD patients is a major factor in surveillance of HCC. There is a need for greater health care provider awareness and education regarding HCC surveillance in India.

The mean age of the patients with HCC in Indian studies is 50-55 years (10, 13,14,15, 29). HBV-related HCC patients present about a decade earlier when compared to HCV-infected HCC patients (13, 14, 15). The younger age of HCC patients with HBV infection can be explained by 2 facts. First, the HBV people pool in India usually reaches a plateau by the age of 5 years. In the general population, it is estimated that about 75% people would have acquired infection up until early childhood (30). Second, HBV is a more potent oncogenic stimulus and can cause HCC without cirrhosis (31).

At presentation portal vein invasion is seen in 40-50% and distant metastases in 10-15% of HCC patients (13, 14). At presentation patients are generally having advanced stages [Child's class A (50-60%), B (30-40%), child C (15-20%); and BCLC -A (20-30%), B (30-40%), C (20-30%) and D (15-25%) respectively]. Thus, overall, only 40-50% could be offered treatment (10, 13, 14). In one study, therapy could be offered to



141 (43.5% of total HCC patients) patients with HCC. Treatment given and median survival time was as follows: surgical resection, 19 months (n = 14); transarterial chemoembolization, 11 months (n = 23); transarterial rhenium therapy, 26 months (n = 7); radiofrequency ablation, 24 months (n = 4); acetic acid ablation, 13 months (n = 17); oral chemotherapy, 26 months (n = 33), and combination therapy, 26 months (n = 32). Vascular invasion, Okuda staging and therapy were independent factors associated with survival. Treated patients had longer median survival compared to untreated ones (16 months vs. 7 months, p= 0.05) (13). Moreover, patients who underwent therapy at any stage had longer survival compared to untreated patients. On subgroup analysis, this was significant in early tumor stages (BCLC A and B) (13). Patients with portal vein thrombosis are generally offered no treatment, however one study from India found that treatment with high dose vitamin K produced objective response in 17% patients with improved survival in patients achieving objective response; however, it did not affect the overall survival (32).

Only 10% of patients are able to undergo hepatectomy and even fewer undergo liver transplantation. In India, living donor liver transplantation services are limited to a few centers in the country. Cadaveric liver transplantation is limited by shortage of donors, prolonged waiting periods, nonavailability and expense. **With health insurance facilities available to only a minority of the population and severe economic constraints, such care is virtually out of reach for the majority of the patients in India.**

Prevention of cancer seems to be the most cost-effective strategy in the war against cancer. In the context of HCC, primary prevention of HCC aims at prevention of individuals from exposure to various carcinogenic hepatotoxins. Secondary prevention of HCC aims at treating the chronic necroinflammatory state of liver produced by the carcinogenic hepatotoxin. Tertiary prevention aims at prevention of recurrence of HCC after successful treatment. Primary prevention strategies are better suited for India, because secondary preventive strategies using surveillance programs may be too expensive and not very cost-effective. Hepatocellular carcinoma related to HBV can be prevented by vaccination. In healthcare settings universal precautions to avoid transmission of blood borne viruses should be adopted. Testing of blood and blood products for HBV and HCV is mandatory and must be followed with utmost care. Since apart from hepatotropic viruses, obesity, NAFLD and alcohol use are important risk factors for HCC, healthy life-style should be encouraged including prevention of obesity and alcohol abuse. Metabolic conditions, such as diabetes and NAFLD should be appropriately treated. Among the secondary preventive strategies, suppression of viral hepatitis and surveillance for HCC are the most important strategies.

In India, a lot of exciting basic research work in HCC is already underway, ranging from chemoprevention, to genetic aspects, to development of newer drugs. Studies are on way on the molecular mechanisms involved in the pathogenesis (33, 34), chemoprevention of HCC (35), immunological mechanisms and immunotherapeutics in HCC (36,37) and anti-angiogenetic therapies in HCC (37), thus opening a newer therapeutic approach for HCC. These basic research endeavors in India need to be encouraged further. A registry or database of patients of HCC across the country is needed that will not only serve to characterize the clinical and etiological profile of HCC in India, it will also help in generating data on temporal trends of epidemiology of HCC in India. India also urgently needs clinical trials on various aspects of HCC which are specific to India.

CONCLUSIONS

In conclusion, HBV and HCV are the most common cause of HCC in India. Prevention of these etiologic agents is the only realistic means of reducing the morbidity and mortality of HCC. The survival of these patients can be improved by aggressively treating HCC, complications of cirrhosis and by controlling etiological factors. However, in India most HCC are diagnosed in fairly advanced stages, making treatment of HCC a great challenge. There is need to improve awareness among physicians regarding prevention and surveillance of HCC in India. Further impetus on basic science research and clinical studies is needed in the Indian context.

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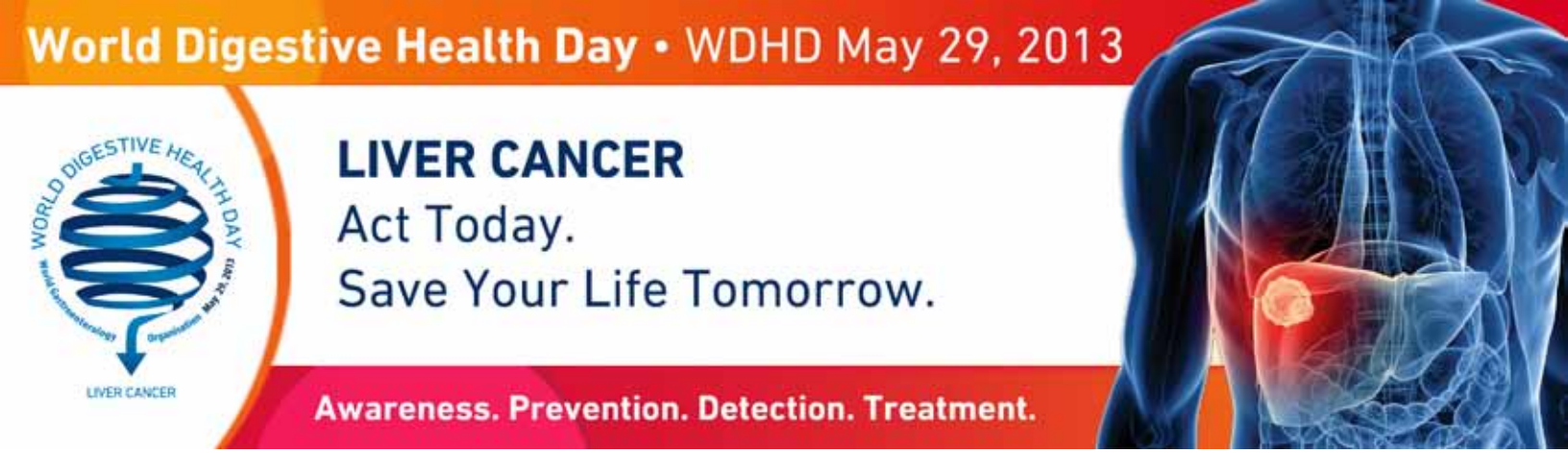

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Milestones in Prevention for Liver Cancer: Doctors Committment in Raising Public Awareness

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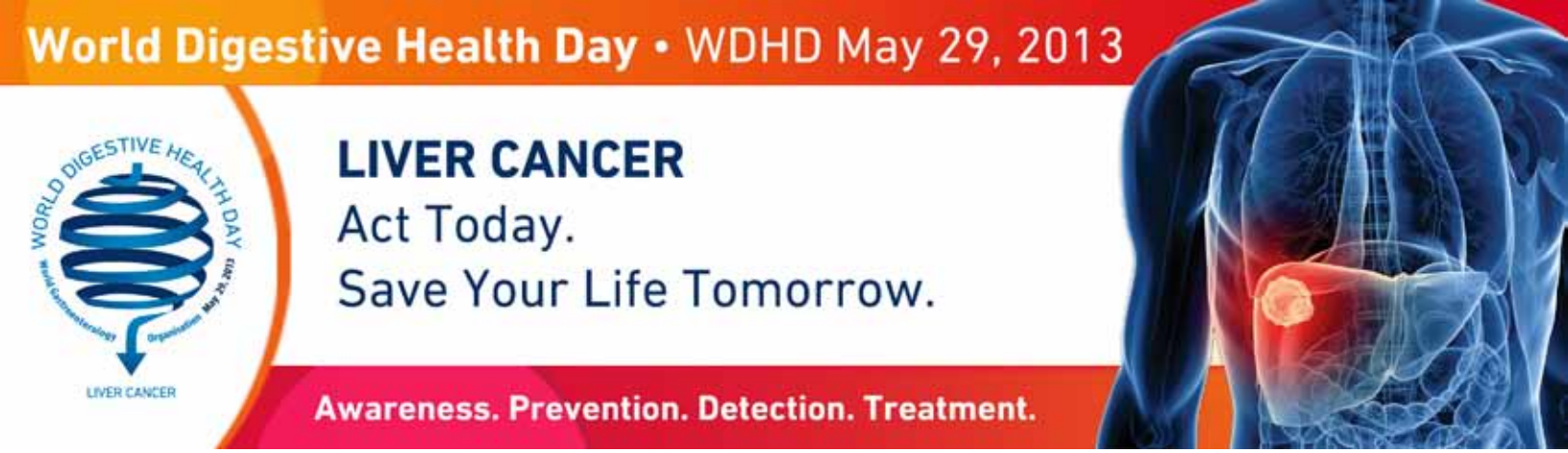
Liver cancer has proclaimed its deadliest prerogative all over the world, consistently the third most common cause of cancer death in recent years. Although every clinician is aware of the very heterogeneous distribution worldwide depending on the etiology of subjacent chronic liver disease, liver cancer is by no means an exotic illness, from distant latitudes: in Europe, it is the 5th most common cause of cancer, and is responsible for around 47,000 deaths per year. Reflecting the major role of chronic alcohol consumption and the prevalence of hepatitis B and hepatitis C infections, in Portugal, the incidence of hepatocellular carcinoma is rising, with a mortality rate affecting a quarter of HCC hospital admissions. Coming on board, also in Portugal, is the metabolic syndrome related to overweight and obesity. Clearly at this stage, many bells are ringing over gastroenterologists and hepatologists, urging them to promote intense discussion on the domains of awareness, prevention, diagnosis and treatment. The challenge is nowadays how to tackle chronic liver disease and turn the liver itself a barren soil for weed.

The facts are that the last 25 years have been a thrilling time for Portuguese Hepatologists. Our national meetings, either the Portuguese Association for the Study of liver Disease Annual Meeting or the Portuguese Digestive Disease Week, have been providing the forum for the exchange of scientific ideas and the presentation of clinical research in clinical Hepatology, a growing world of knowledge in medical care. Bridging the gaps between technology and clinical daily practice, the latest development and the almost humble bedside care, has been a challenge for the increasing numbers of doctors devoted to the diagnostic and treatment of liver disease.

We have been trying to be very persuasive among the portuguese medical community in demonstrating that cultural vectors which may influence the origin and pattern of liver disease among us. Viral hepatitis and alcoholic liver disease are paradigms of this assumption. Chronic liver disease is responsible for 3% of the deaths in Portugal, which accounts for the top 10 causes of death in our country. The recognition by Public Health authorities of this fact along with the national net of Hepatology outpatient consultation in Public Hospitals, has brought liver diseases under the lights of doctors concerns and an increased public awareness of its dimension. It is true that alcoholic liver disease is a dominant concern in this country and several reasons may contribute to this fact: Portugal, with temperate climate from Atlantic and Mediterranean origins, has a rich tradition in wine processing, and for years, many rural communities were actively involved in those processes. Alcohol consumption is thus a widespread habit, and in the traditional good-eating-and-drinking land (many times advertised abroad), it became a deep cultural characteristic lasting for decades. This creates a great challenge for us doctors, when trying to educate the population concerning the risks, the facts and the fancies about chronic alcohol consumption.

Hepatitis B changed recently among us. At the end of the millennium, HBs Ag prevalence was shown to be 1.25%, categorizing Portugal as a low prevalence area. Recently it has been claimed to be less than 1% (0.9%), in a national serological survey (2005), with an anti HBs prevalence of 47%, reflecting the vaccination policy adopted years ago. The overall prevalence of anti-HBc is now of 5%. Among us, HBV vaccine is included in the National Vaccination Program since 1993 for adolescents aged 10-13, and for all newborns since year 2000. The ongoing strategy is vaccination, of all newborns and adolescents, with additional recommendation of risk group vaccination as defined by regulatory ministerial documentation. Recent challenges however have been brought up by the intensive immigration from eastern european countries where HBsAg prevalence shifts between 4-10%, reproducing the same scenario as 40 years ago, when Angola and Mozambique citizens came back to mainland. The predominant form of chronic hepatitis B is the negative HBeAg chronic hepatitis, accounting for more than 80% of the cases, as a recent nation wide hospital survey showed.

Hepatitis C also has clearly gained full media and patient attention in recent years. Our estimated antiHCV prevalence (based on blood donors statistics, and many clinical observations) is 1.5%. Interesting cultural and historical facts made a significant contribution for this, namely our prolonged sojourn in Africa and ancient folk medical practices, very common until the late eighties, allowing in those times widespread contacts with contaminated instruments or equipments.

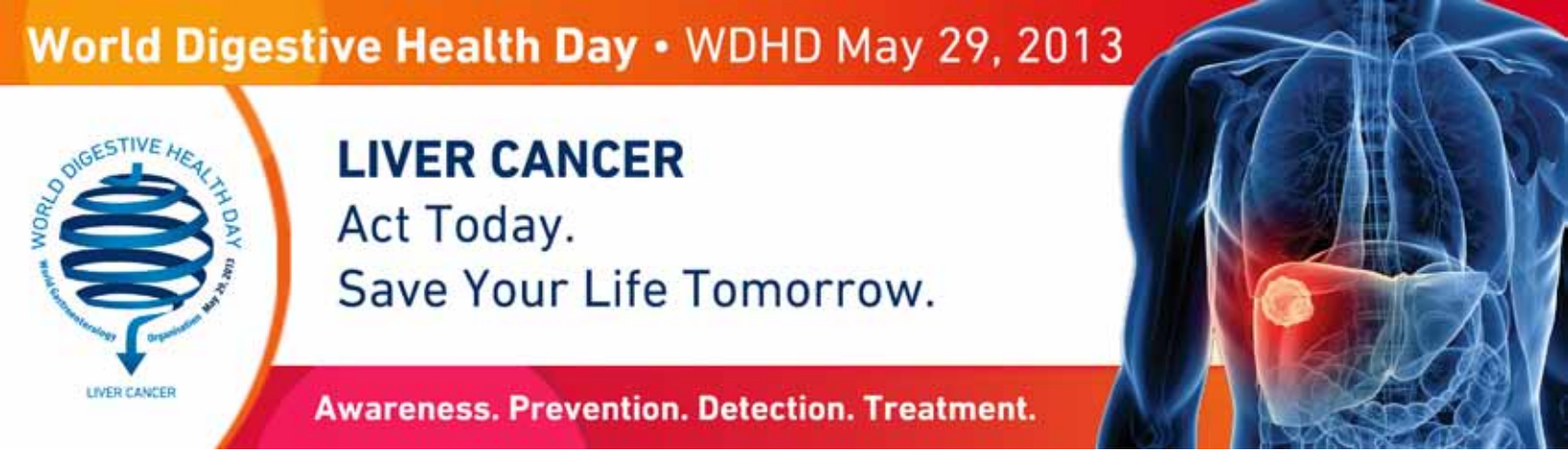


Portuguese Hepatologists have been trying to discuss the viability of creating a National Strategy Plan for Prevention and Control of Hepatitis C. This ambitious plan stands on the tripod base of quality information, reinforced prevention and cost-effective modalities, and intend to gather many society vectors like Health related Authorities, Scientific Societies beyond the conventional Gastro/Hepatology Association, Pharmaceutical Companies, Patients Organizations, and of course, Politicians and the Media.

In spring time 2010, we also promoted the "Liver on Tour", a special Project devoted to increase public awareness of Liver health and Liver disease. All counties in Portugal were visited on a road show, with lots of simple, reliable and practical information on liver problems. Members of the Portuguese Association for the Study of Liver Diseases Board of Directors were literally on the road, claiming for attention and protection for the liver. In 2011 another two "out of the box" meetings addressed this anthropological insight of liver health: Sports and the Liver (along with major conferences from well known Portuguese sportsmen) and The Liver and Social Exclusion, showing how liver diseases promote exclusion and how exclusion itself is a vector for liver diseases.

Creativity is the hallmark of every successful campaign. Committed to care for liver health, we know that we can not avoid the public stage, and to be under the spot light in the appropriate moments may be decisive to bring new worlds to the known world.

Liver on Tour Project, in 2010



World Hepatitis Day

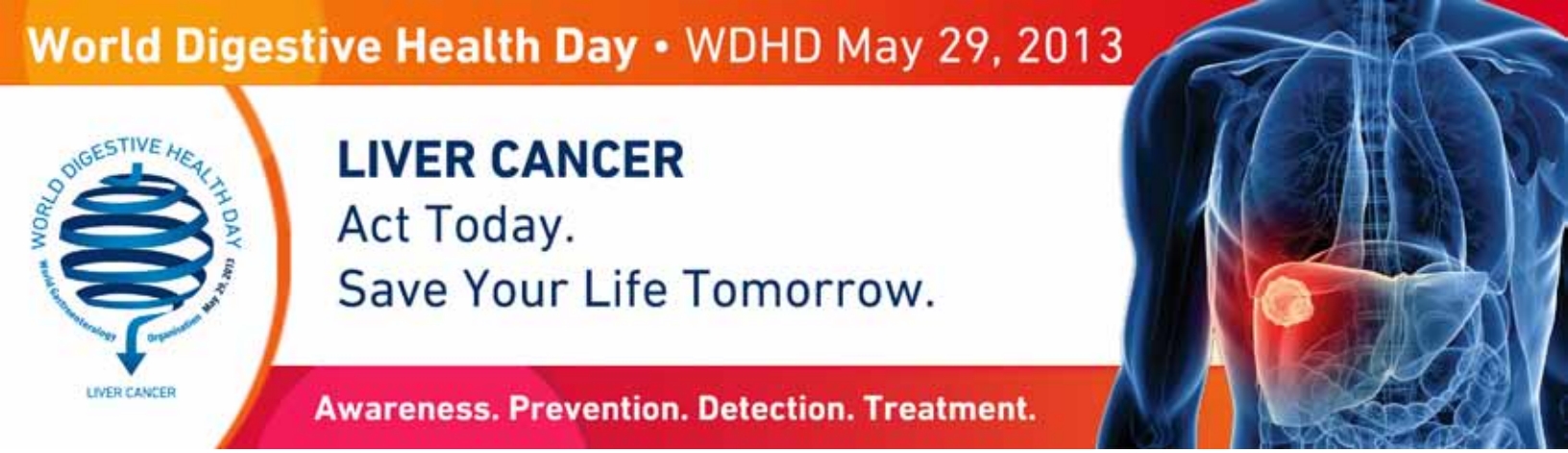
On 28th July 2013, thousands of people from around the world will join together to celebrate World Hepatitis Day, a chance to raise awareness, promote testing and vaccination, and advocate for better treatment for viral hepatitis patients.

To tackle the devastating lack of awareness about viral hepatitis, our 2013 campaign focuses on the theme 'This is hepatitis… Know it. Confront it.' World Hepatitis Day is a chance to speak out with this message, to demand that people stop ignoring hepatitis and to give it the priority it deserves.

Previous years have seen some fantastic events including concerts, seminars, testing and information drives, and this year we're hoping for even more! Anyone can take part in World Hepatitis Day; events happen all across the world and there are lots of resources available to help you set up your own. You could even be part of the global events, such as our online picture campaign or the global effort to beat our Guinness World Record that we set last year! For more information on World Hepatitis Day, visit the World Hepatitis Alliance website. Alternatively, email contact@worldhepatitisalliance.org to find out what's going on near you.

http://www.worldhepatitisalliance.org/WorldHepatitisDay/WHD2013.aspx

World Hepatitis Alliance



Liver Diseases Are Killing More Canadians Every Year But No One Seems to Notice

As the largest internal organ, the liver is tied into virtually every critical process of the body. Despite its vital role in maintaining overall health, the liver is routinely ignored by the majority of Canadians. Unfortunately dismissing the liver has dangerous consequences to quality of life and life expectancy but few understand just how high the stakes are.

Over a period of only eight years, the death rate from liver disease has risen by nearly 30%. Those directly involved in the care of liver disease patients have seen this tragedy play out again and again in hospitals across the country. And yet there is no sense of urgency to collect or evaluate data to measure the true scope of the disease burden nor is there a sense of urgency to deal with it. Alcohol abuse does cause liver disease however a lack of data and a persistent assumption and stigma linking liver disease with only alcohol have made it difficult to overcome both public and government apathy.

It is estimated that one in 10 Canadians, or more than three million people, has some form of liver disease. The most common forms of liver disease – viral hepatitis, fatty liver disease and liver cancer – are all on the rise which means that the increase in death rates from these diseases and their complications will continue to climb if there is no effective intervention.

Liver disease does not need to be a death sentence. Effective screening, diagnostic and treatment options exist for many patients but without coordinated strategies, supportive government policies and financial investments in patient care and research, liver disease will continue to strike from the shadows taking lives and exacting a high toll on the nation's health care systems. The key findings from this report highlight missed opportunities for prevention, gaps in care and the human impact of liver disease.

All major forms of liver disease are increasing in Canada.

- Liver disease can be difficult to diagnose because the symptoms can be vague or even non-existent until the disease is advanced.
- It's estimated that one in ten Canadians, or more than three million people, has some form of liver disease.
- 95% of deaths from liver disease are due to chronic hepatitis B and C, non-alcoholic fatty liver disease, liver cancer and alcoholic liver disease.
- Viral hepatitis (specifically chronic hepatitis B and C) is far more common and more infectious than many other infectious diseases, including HIV, and affects more than 500 million worldwide and an estimated 600,000 in Canada.
- Liver failure related to hepatitis C is the leading cause of liver transplants.

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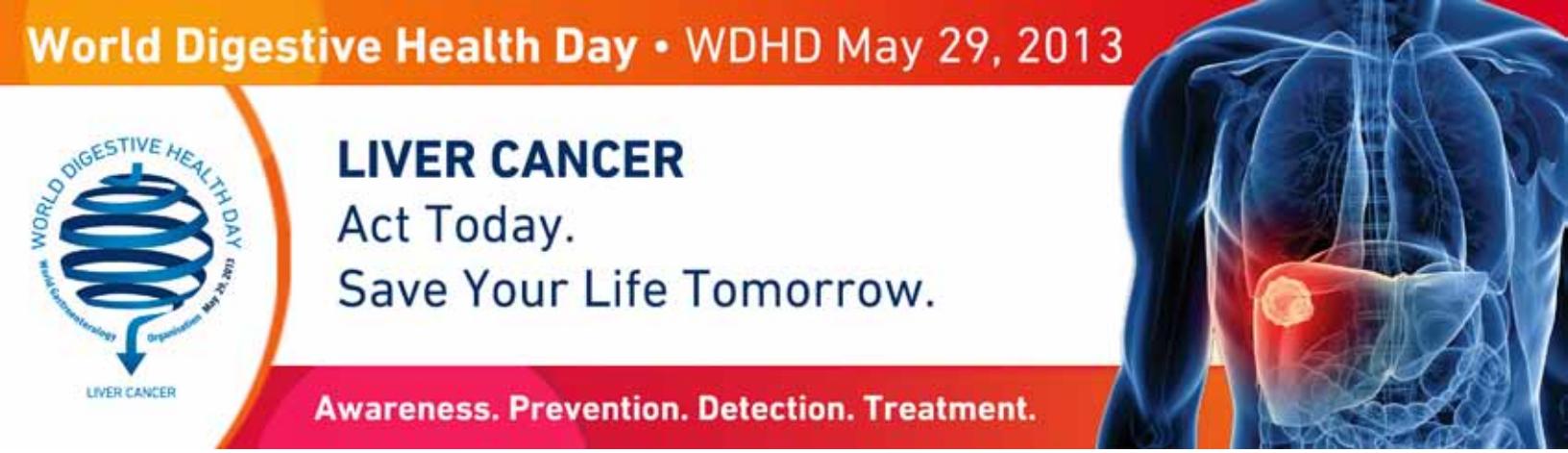
- Liver cancer is one of the few forms of cancer on the rise and liver cancer death rates related to hepatitis B are predicted to rise by 50%. The relative contribution of chronic hepatitis B and C, alcoholic liver disease and non-alcoholic fatty liver disease to the rising death rate from liver disease is unknown.
- An estimated 25% of Canadians, or 8.5 million people, are obese. Fatty liver disease linked to obesity is the most common form of liver disease in Canada.
- In Canada, each 1 litre increase in alcohol consumption per capita is associated with a 16% increase in cirrhosis deaths in men and 12% in women.

The most severe consequences of liver disease can be avoided through prevention or through early detection but we are missing opportunities to intervene.

- Hepatitis B and C often have no symptoms until complicated by liver cancer, cirrhosis and liver failure. Despite the risk and the high prevalence, there are no widespread screening programs for either disease.
- 90% of infants who contract hepatitis B will develop life-long infection and yet only three provinces offer universal neonatal immunization.
- Less than 10% of hepatitis B patients and less than 25% of hepatitis C patients have been treated due to high cost, restrictive reimbursement policies, lack of health care resources and poor understanding amongst patients and primary health care providers.
- In Canada, the most potent drug therapies for hepatitis B are not available for reimbursement in many provinces. In 2009, 58% of patients requiring government assistance for drug costs received a low-cost but less-potent drug that is no longer recommended by liver specialists in this country or around the world.
- The only treatment for end-stage liver disease is a liver transplant. In Canada, there are an estimated 5,000 deaths per year due to liver disease and approximately 400 liver transplants. Approximately one third of patients on the waiting list for transplants will die due to a shortage of donor organs.



- Liver cancer is the leading cause of death of hepatitis B patients and a major cause of death for patients with other chronic liver diseases. Although liver cancer can be successfully detected and treated if caught early, there are no government screening recommendations for at-risk patients.
- Government agencies spend 5 to 10 times more on research into diseases that affect significantly fewer people than hepatitis B or C.
- Only four provinces have multidisciplinary groups to provide specialized care for liver cancer patients.

Treating liver disease is costly but ignoring it will cost even more in lives and resources.

- In Canada, there are 400 physicians and specialists who treat viral hepatitis but of these, fewer than 50 treat more than 50 patients per year.
- From 2006-2009, in-hospital procedures for liver disease patients (including transplants) cost in excess of $157 million and this estimate does not include all procedures, nor hospital stays and physician costs.
- Liver transplants cost more than $100,000 per person including hospital costs and immunosuppressive drugs. Treating hepatitis B may cost $7,000-$9,000 per year for 10-20 years while a course of treatment for hepatitis C may be $20,000-$70,000.

We need to do more to fight liver disease... and we need to do it now.

Unlike other major diseases, there has been no national strategy put in place for a public health response to liver disease. Without a coordinated effort involving investment and resources for prevention, screening, treatment, patient care and research, thousands of Canadians will die needlessly. The Canadian Liver Foundation, in partnership with liver experts from across the country, is sounding the alarm and recommending short-term and long-term solutions to help defuse this ticking time bomb. We urge federal and provincial/territorial governments and health agencies to make liver disease a priority and to act to protect the health and well-being of Canadians of all ages.

To download the **full "Liver Disease in Canada: A Crisis in the Making" Report, visit:** http://www.liver.ca/support-liver-foundation/advocate/Liver_Disease_in_Canada_Report.aspx

Key recommendations:

1. Health Canada, in conjunction with the provinces and territories, must establish a national liver disease strategy.
2. Establish provincial agencies to manage liver disease beginning in Ontario, Quebec, Alberta and British Columbia where liver disease is most prevalent. Using the cancer agency model, these agencies would be responsible for determining priorities, ensuring efficient use of public funds, and establishing control programs. The agency should be governed by an external board of directors comprised of members of the public and physicians with expertise in liver disease and epidemiology who are independent of the provincial health ministry.
3. Encourage family physicians to incorporate liver enzyme (ALT) screening into all annual physicals.
4. Conduct a national seroprevalence survey with oversampling in high-risk communities to determine the prevalence of hepatitis B and C in Canada and identify the communities with the greatest need for resources.
5. Increase treatment capacity by:
   a. Establishing in-patient units and out-patient clinics staffed with trained physicians and nurses to care for liver disease patients in major urban and regional hospitals in each province.
   b. Setting up provincial funding resources for nurse practitioners specializing in liver disease.
   c. Recruiting family physicians to treat patients as part of hepatitis treatment groups.
6. Mandate standardized provincial/territorial reporting procedures for acute and chronic hepatitis B and C with information being collected and collated by the Public Health Agency of Canada.
7. Implement universal screening for hepatitis C for all adults born between 1945-1975 and widespread screening of new immigrants for hepatitis B.
8. Implement universal neonatal hepatitis B immunization with a catch-up program for provinces switching from an adolescent vaccination program. Harmonize hepatitis B immunization programs between provinces for high-risk adults.
9. Simplify and improve coding for liver disease procedures and deaths.
10. Establish liver cancer (HCC) screening programs for all at-risk patients with outcome tracking and quality assurance protocols.
11. Enhance resources (equipment and personnel) at existing regional cancer centres to facilitate multidisciplinary care of liver cancer.
12. Improve access to treatment for hepatitis B and C patients by establishing less restrictive reimbursement policies based on the most up-to-date approaches to the management of these diseases and not strictly on cost of treatment. Eliminate reimbursement restrictions based on ALT level and presence of cirrhosis.
13. Establish research programs for hepatitis B and C that examine innovative ways to deliver care.