Hepatocellular Carcinoma in SSA – Some Info. to Guide the Guidelines

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Basic Demographics of SSA

- The 2nd Largest Continent and home to about 900 million peoples, less than 15% of the world population.
- Most Africans are blacks and live south of the Sahara desert.
- Perhaps up to 80% of African live in rural settings where medical facilities are sparse or non-existent altogether.
- The population is in a perpetual flux from famine, wars and economic pressures.
- Reliable population statistics are hard to come by.
Malignant Disease Burden in Africa – An Overview

• 10.1 million new cancer cases were recorded worldwide in the year 2000
• Expected to rise to 15 million by 2020, 27 million by 2030 and 20 million cancer-related deaths
• The brunt of this burden is expected to be borne by the poor countries, especially the countries of sub-Saharan Africa
• Obtaining accurate cancer statistics in Africa has been bedeviled by
  – Lack of population-based cancer registries
  – Non-uniform distribution of health centres and hospitals
  – Lack of diagnostic facilities and expertise
HCC Worldwide

• HCC constitutes 90 – 95% of all malignant tumours of the liver in the high-incidence settings
• It’s 70 – 85% in the low incidence areas
• 6th most common human malignancy and 9.25% of all new cancers in 2008
• M:F Ratio 2.3:1.0
• The Second most common cause of cancer deaths
• Annual fatality rate 0.93, the highest for any human tumour
• The vast majority of new cases are from low resource countries

HCC in Resource-poor Countries

- 626,700 were reported from resource-poor countries; 2/3rds were from men (No 3 Cancer) and 1/3rd from women (No 6 Cancer)
- 2nd leading cause of cancer deaths in men and the 5th in women
- These dismal figures are the tip of an iceberg: up to 85% of HCC may come from resource-poor countries.
- 55% is estimated to be from China alone
- High incidence HCC may be up to 100 times higher than the low-incidence HCC

Age-standardized rates

- High incidence = more than 15 cases per 100,000 population
- Low-incidence = Less than 5 per 100,000 person per year
- China has an estimated age-standardized rate of 52.1
- Melanesia 25 per 100,000
- Varies between 20 and 42/100,000 persons per year in SSA

Incidence in SSA

• West Africa 20.9 per 100,000 per year
• East Africa, 29.7 per 100,000 persons per year
• Middle Africa 42.1 per 100,000 persons per year
• Mozambique has a reported incidence of 101 per 100,000 male persons and 34 per 100,000 females
• Mozambique’s may be the world’s highest figures

Annual incidence/100,000 men

- Mozambique
- China
- Spain
- Norway

Age

10 20 30 40 50 60 70+


<table>
<thead>
<tr>
<th>Site</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>Total Number of cases</td>
<td>ASR (w) per 100000</td>
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<tr>
<td>-----------------------------------</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>17</td>
<td>0.55</td>
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<tr>
<td>Stomach</td>
<td>48</td>
<td>1.58</td>
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<tr>
<td>Colorectal, Anus</td>
<td>40</td>
<td>1.17</td>
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<tr>
<td>Liver</td>
<td>1215</td>
<td>32.84</td>
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<tr>
<td>Pancreas</td>
<td>22</td>
<td>0.73</td>
</tr>
<tr>
<td>Trachea, bronchus and lung</td>
<td>71</td>
<td>2.46</td>
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<tr>
<td>Kaposi sarcoma</td>
<td>21</td>
<td>0.51</td>
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<tr>
<td>Soft tissues</td>
<td>25</td>
<td>0.60</td>
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<tr>
<td>Breast</td>
<td>11</td>
<td>0.35</td>
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<tr>
<td>Cervix</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ovary</td>
<td>-</td>
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<td>Prostate</td>
<td>95</td>
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<td>Bladder</td>
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<td>0.91</td>
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<td>Thyroid</td>
<td>11</td>
<td>0.25</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>88</td>
<td>1.42</td>
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</table>
Age Distribution

• Mean age of Low-incidence HCC is 65 years
• HCC in SSA affects significantly your age groups
• This could be as low as 34.7 years in rural black men to 51 years in urban black women
• The mean age for urban southern African black men is 50.9 years
• In Mozambique, Prates et al reported that up to 50% of HCC patients were below the age of 30 years

Gender Distribution

- HCC affects more men than women worldwide
- In SSA, this is more so – M:F ratios vary from 1.8:1.0 to 28.0:1.0 (Mean ratio is 3.5:1.0)
- Male preponderance is particularly striking in young males in SSA – 8.1:1.0 in patients younger than 30 and 4.2:1.0 in patients older than 40 years
- The male preponderance reflects an equally high HBsAg seroprevalence among males

Figure 1. Liver cancer incidence rates per 100,000 Gambians by 5-years age groups. Data from the Gambia National Cancer Registry, 1998–2006.
A Non-Uniform Distribution is Strongly Suggestive of a Role for Environmental Factors

- In Mozambique, the incidence is highest in the Eastern region than the others
- There is a disparity in incidences between the low and highlands of Swaziland
- In Uganda, there is a significant differences between the tribes
- In South Africa, HCC incidence is strikingly higher in urban than rural black

Kew MC et al. Comparison between the polyclonal and 1st and 2nd generation monoclonal radioimmunoassays in the detection of HBsAg in patients HCC Hepatology 1986; 6: 636 - 9
Ethnicity and HCC

• Higher incidence in Fula and Wolof ethnicity
• Increase due to genetic polymorphism in enzymes in AFB1 metabolism
• Higher prevalence between Fula and Mandinka in Gly 399 Allele of XRCC1 responsible for genetic repair of DNA aflatoxin adducts

Kirk GD 2005 Cancer Epid Biomarkers Prev 14: 373-379
HCC With and Without Cirrhosis

• Low incidence HCC is associated with Cirrhosis in more than 90% of cases and this figure is higher in cohorts of older patients.

• In SSA HCC with cirrhosis is significantly less common and not related to age.

• 59.7% of patients less than 30 years have HCC with cirrhosis.

• Only 63.8% patients who are 50 or older have coexisting cirrhosis.


HCC In Black Children

• Unlike in low-incidence countries, HCC is common among African Black children but the incidence is lower than in adults
• Patients are usually between 5 and 15 years old
• M:F Ratio 2 – 3: 1.0
• HBV is strongly associated with childhood cases of the disease in SSA rather than the known metabolic causes of the disease in rich countries
• The fibrolamellar HCC is commoner in Black children than adults

Why the high incidence in Africa? - I

Three major environmental causes

• Chronic HBV infection
• Dietary exposure to fungal toxin aflatoxin B1
• Chronic HCV infection
Epidemiology of HBV infection in Africa

- ± 65 million chronically infected
- Responsible for ± 255,000 deaths each year
- Chronic carriage more common in males Vs Females (1.5-2.0 : 1.0)
- More common in rural than in urban dwellers
Hepatitis B Surface Antigenaemia among Adult Nigerians with Clinical Features of Liver Diseases

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>HBsAg Sero-positivity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Yes number (%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>17 (23.9)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>28 (39.5)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>26 (36.6)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (100.0)</td>
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</table>
PATHOGENESIS OF HEPATITIS B VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

HBV DNA does not contain an oncogene

• HBV DNA integration occurs in almost all patients with HBV-induced HCC

  *Cis*-activation of cellular genes
  1. Integration into or close to a gene disrupts the gene or interferes with its function
  2. Changes in flanking sequences
     - deletions, translocations, duplications

  *Trans*-activation of cellular genes

Mediated through signal transduction pathways

Two HBV proteins have *trans*-activating capability:
  - x protein
  - preS/S protein when 3’ truncated during integration
HEPATITIS B VIRUS INFECTION IN SOUTH AFRICAN BLACKS WITH HEPATOCELLULAR CARCINOMA

HBsAg: 69.5%
occult HBV 22.5%
Total HBV positivity ± 92%
Consequences of early hepatitis B virus infection

Infected in 1\textsuperscript{st} year of life: 90\% become chronic
Infected in 5\textsuperscript{th} year of life: 50\% become chronic
Infected in adulthood: < 10\% become chronic

27-40\% DEVELOP H.C.C
RELATIVE RISK OF H.C.C: > 100
PATHOGENESIS OF HEPATITIS B VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

Unrestrained proliferation of hepatocytes and
Series of genetic and epigenetic changes

- Dividing cells susceptible to viral integration
- Accelerated hepatocyte turnover rate allows less time for DNA repair before cell divides again, ‘fixing’ abnormal DNA in daughter cells
Why the high incidence of HCC in Africa? II

**Lesser risk factors**
- Alcohol
- Metabolic conditions associated with obesity and/or T2DM
- Dietary iron overload

Relative of importance of each risk factor vary widely as a function of geography and local prevalence of chronic viral hepatitis.
Dietary exposure to fungal toxin aflatoxin B1

- Difuranocoumarin derivatives of Aspergillus flavus and A. parasiticus
- Contaminate crops, particularly maize, ground nuts and fermented soy beans, in tropical and subtropical countries
- Associated with warm, humid climates
- Contamination occurs both during growth of the crops and as a result of their improper storage.
• Sub-Saharan Africa and the Asia-Pacific region have high levels of exposure to the fungal toxin.

• Aflatoxin B1 (AFB1) is the aflatoxin most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen

• **Strong statistical association between dietary ingestion of aflatoxin B₁ and the development of HCC**
Distribution of HCC cases attributable to aflatoxin in different regions of the world.

- Africa: 40%
- Southeast Asia: 27%
- Western Pacific: 20%
- Eastern Mediterranean: 10%
- Latin America: 3%
- North America: 0%
- Europe: 0%
Biotransformation of AFB1

Figure 2. Biotransformation of AFB1, which comprises CYP450-mediated reactions resulting in a highly nucleophilic genotoxic reactive intermediate (AFBO), hydroxylation (to AFM1 and AFQ1) or demethylation (to AFP1). When AFBO binds to liver cell DNA, it causes mutation of p53 that may lead to HCC. AFBO is also capable of causing aflatoxicosis when it binds to protein amino acids. AFB1, aflatoxin B1; AFBO, AFB1-8, 9 epoxide.
Detoxification pathway of AFBO

- AFBO
  - GST
    - AFB1-Glutathione conjugate
      - Excretion
  - mEH
    - AFB1-8,9-dihydrdriol
      - Physiological pH
        - Dialdehydic phenolate
          - AFB1 aldehyde
            - AFB1 dialcohol
              - Excretion
      - Schiff base reaction
        - Hepatotoxicity
Susceptibility to hepatocellular carcinoma is associated with genetic variation in the enzymatic detoxification of aflatoxin B₁


Individuals with mutant genotypes at epoxide hydroxylase and glutathione transferase M1 may be at greater risk of developing AFB1 adducts, p53 mutations, and HCC when exposed to AFB1.
Chronic hepatitis C

• Chronic hepatitis C virus (HCV) and HCV-induced HCC are significantly less common in developing than in developed countries
• Except Somalia where chronic HCV infection is as common as chronic HBV infection(3)

Hepatitis C prevalence

- <1
- 1 - 2.49
- 2.5 - 4.99
- 5 - 10
- > 10
- No Data
PATHOGENESIS OF HCV-INDUCED HEPATOCELLULAR CARCINOMA

Unrestrained proliferation of hepatocytes and
Series of genetic and epigenetic changes

HCV core and NS5a proteins:
- Generate reactive oxygen species
- Repress transcription of p21
- Induces mutations in p53
- Abolishes catalytic activity of PKR (antiviral, antiproliferative induced by IFN)
INTERACTION BETWEEN HEPATITIS B AND C VIRUSES IN HEPATOCARCINOCGENESIS IN SOUTHERN AFRICAN BLACKS

RELATIVE RISK FOR H.C.C:

HBV INFECTION ALONE: 23.3 (9.2 - 51.8)
HCV INFECTION ALONE: 6.6 (2.7 - 15.7)
HBV AND HCV CO-INFECTION: 82.5 (8.9 - 761.8)
Variation in prevalence of chronic infection with HBV and HCV in patients HCC

<table>
<thead>
<tr>
<th>Country</th>
<th>HBV (%)</th>
<th>HCV (%)</th>
</tr>
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<tbody>
<tr>
<td>China</td>
<td>99%</td>
<td>1%</td>
</tr>
<tr>
<td>Gambia</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Japan</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>USA</td>
<td>55%</td>
<td>45%</td>
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*Data from The oncologist 2010 15:5-13*
AFRICAN DIETARY IRON OVERLOAD AS A CAUSE OF HEPATOCELLULAR CARCINOMA

- Gordeuk et al (1996): R.R. 23.5 (95% C.L. 2.1-225) of HCC in those subjects with the highest levels of hepatic iron accumulation, after allowing for confounding effect of cirrhosis

- Moyo et al (1998): R.R. 3.1 (95% C.L. 1.05 - 9.4) of HCC after allowing for the confounding effects of cirrhosis

- Mandishona et al (1998): R.R. of 10.6 (95% C.L. 1.5 – 76.8), after allowing for confounding effects of chronic HBV and HCV infection and aflatoxin B₁ exposure, but not cirrhosis
Free hepatic iron

↓

ROS and oxidative damage

Chronic necroinflammatory hepatic disease (cirrhosis; portal fibrosis)

↓

HEPATOCELLULAR CARCINOMA
Thank you