Rethinking breast cancer screening strategies in resource-limited settings

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Abstract

The incidence of breast cancer in sub-Saharan nations is increasing. There is a worsening scarcity of Human Resource for Health in Uganda in particular and Sub Saharan Africa in general. Resources available for health care are predominantly spent on infectious disease care such as (HIV/AIDS, Tuberculosis and Malaria). These factors and more make the future of breast cancer care including screening in Sub Saharan African grim.

Although mass breast cancer screening by mammography has been proved to be efficacious in the developed nations of the world, this has not been replicated in the developing nations because mass screening is not yet possible for the reasons stated. This paper proposes an alternative to mammography mass screening.

Breast health programs for the most part are adhoc or non-existent in Uganda. The challenge of mass screening is not only limited to less readily available mammogram machines and trained human resources but also to the fact that the targeted population is of relatively young women in their 30s, implying that screening should commence earlier than it is practiced in nations where breast cancer peaks among women in their 50s. Mammography is not efficacious in young women with dense breast tissue. Ultra sound scans are not only up to 10 fold more available than mammography machines but are half the cost per examination.

Although using ultra sound Scan for screening for non-palpable lumps is not up to par with standard breast cancer care mammography. It may be better than nothing, may be beneficial in aiding early cancer diagnosis. This concept is akin to the ‘task shifting’ advocated by WHO. It is worth investigating use of ultra sound scan for mass screening for breast cancer in resource-limited environments. This is not in any way lowering standards of oncologic diagnosis but filling the otherwise unattended to gap, the unmet need.

Key words: breast, cancer, screening

Introduction

The use of mammogram in screening for breast cancer is a well established efficacious practice that is responsible for significant reduction of late presentation of breast cancers in women in the developed nations of the world¹, ². This practice of mass screening has been so effective that it is been strongly recommended for use in the developing nations and many work and look forwards to the day this will be possible. However it is difficult to predict when exactly this will be, yet there is an urgent need to screen as evidenced by increasing rates of up to 5% per year ³, ⁴.

This opinion piece advocates for mass use of cheaper, more widely available alternatives to mammography; Breast Self Examination and US Scan could be practical substitutes for mass screening in low resourced settings until such a time when we can afford mammograms and have more human resources for health. Currently the human resource for health ratios stand at 0.8 health workers per 1000 population at least 2.5/1000 is required to ease the human resource for health bottle neck⁵.
Table 1: Accuracy of Breast imaging modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>63-95% (&gt;95% palpable, 50% impalpable, 83-92% in women older than 50 y) (decreases to 35% in dense breasts)</td>
<td>14-90% (90% palpable)</td>
<td>10-50% (94% palpable)</td>
<td>Initial investigation for symptomatic breast in women older than 35 years and for screening; investigation of choice for micro calcification</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>68-97% (palpable)</td>
<td>74-94% (palpable)</td>
<td>92% (palpable)</td>
<td>Initial investigation for palpable lesions in women younger than 35 years</td>
</tr>
<tr>
<td>MRI</td>
<td>86-100%</td>
<td>21-97% (&lt;40%)</td>
<td>52%</td>
<td>Scarred breast, implants, multifocal lesions, and borderline lesions for breast conservation</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>76-95% (palpable)</td>
<td>62-94% (94% impalpable)</td>
<td>70-83% (83% palpable, 79% impalpable)</td>
<td>Lesions larger than 1 cm and axilla assessment; may help predict drug resistance</td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>96% (90% axillary metastases)</td>
<td>100%</td>
<td>Axilla assessment, scarred breast, and multifocal lesions</td>
<td></td>
</tr>
</tbody>
</table>

Adopted from e-medicine website

The emerging picture

Breast cancer in sub-Saharan Africa runs a very aggressive course and has higher fatality rates compared to those in the western world; breast cancer occurs 10-15 years earlier in black women compared to their white counterparts6, 7, 8; a similar story is found among UK’s Black women9. The resources available for Health Care in general are far less than the $15 per person per year recommended to governments by WHO as the minimum. Overall projections indicate a worsening picture of cancer epidemiology for the developing nations of the world, in terms of incidence and mortality10. In a recent Ugandan study11 the peak age for patients with breast cancer in Uganda is 30 -39 years, the majority of patients 77% presented late as stage III and IV. The incidence rate is going up in Uganda; it has tripled in the past three decades from 11 per 100,000 to 39.2 per 100,00012 while it has levelled out and now mortality is decreasing in North America and Europe.

Table 2: Early detection and access to care

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Detection method(s)</th>
<th>Evaluation goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Breast health awareness (education ± self-examination) Clinical breast examination (clinician education)</td>
<td>Baseline assessment and repeated survey</td>
</tr>
<tr>
<td>Limited</td>
<td>Targeted outreach/education encouraging CBE for at-risk groups Diagnostic ultrasound ± diagnostic mammography</td>
<td>Down staging of symptomatic disease</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Diagnostic mammography Opportunistic mammographic screening</td>
<td>Opportunistic screening of asymptomatic patients</td>
</tr>
<tr>
<td>Maximal</td>
<td>Population-based mammographic screening Other imaging technologies as appropriate: high-risk groups, unique imaging challenges</td>
<td>Population-based screening of asymptomatic patients</td>
</tr>
</tbody>
</table>
Constraints

Mammogram screening may not be wholly appropriate, since close to half of Ugandan women who need screening are 30 years and below (see figure 1). The average age for Ugandans is 15 years\(^\text{13}\). Mammography is generally not recommended for women below 35 years because women of this age and younger tend to have denser breasts making it more difficult to distinguish abnormal from normal tissue on the x-ray film\(^\text{8}\). For this reason mass screening is not entirely possible with mammogram use alone since nearly half of the eligible women would be left out because they are below 35 years. Only four mammogram machines exist for a population of 6 to 7 million eligible women (see table 3)\(^\text{11, 13}\). Three of which are privately owned and attract a fee of $25 per examination, a cost unaffordable by the average Ugandan woman or the government for that matter. The cost of a breast ultrasound scan is a little less than half the cost of a mammogram in the private sector. We may need to use the task-shifting concept\(^\text{5}\), can we then have USScan take on the task for screening, and can we take it away from the radiologist to the sonographer (non physician health worker)? Sonographers are less expensive, more likely to accept deployment out of the capital city, even though additional training for breast screening may be necessary. There are at least 30 radiologists in Uganda making a radiologist to patient ratio of \(1:300,000\) and at least 60 sonographists making a ratio of \(1:150,000\)\(^\text{14}\).

USScan may have a relatively low sensitivity and specificity (see table 1) but this would be better than no screening at all. Isn’t it prudent then to use it in the interim until such a time as when mammography will be widely available? But even if mammography were available to all women in Uganda, what about the half for which it may not be appropriate? (Until proven otherwise by research) Limited access to standard screening is a scenario not only unique to Uganda but common within the African sub continent.

Continuation of table 3

<table>
<thead>
<tr>
<th>Population of selected group</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women needing breast screening</td>
<td>6,483,082</td>
<td>26.5</td>
</tr>
<tr>
<td>Women 18 – 30 years</td>
<td>2,736,000</td>
<td>11.2</td>
</tr>
<tr>
<td>Secondary school age*</td>
<td>3,995,884</td>
<td>16.3</td>
</tr>
<tr>
<td>(13 – 19 years)</td>
<td></td>
<td></td>
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</table>

* On average 50.1% are female

Source: 2002 Uganda Population Census - UBOS

Global initiatives

The Breast Health Global Initiative (BHGI)\(^\text{15}\) (Anderson et al, 2006) strives to develop evidence based, economically feasible and culturally appropriate guidelines that can be used in nations with limited health care resources to improve breast cancer outcomes. Table 2 highlights the proposed framework to fit the level of resources available to the different nations.

Early breast cancer detection improves outcome in a cost effective fashion assuming treatment is available. The BHGI group recommends future research to better determine the best way to implement guidelines in limited resources settings.

Possible country specific initiatives

Uganda has close to 2,000,000 girls in the 13-19 age bracket who are in school. The figure shown in table 3 for secondary school age 13-19years is for both sexes. A little more than half of which are female (50.1%) if these two million girls were to be screened it would not be with mammography. Taking away the burden of imaging from the four available mammography machines to at least 60 US scans that exist in the country and mostly situated in or near district hospitals, is plausible and it is not meant to lower standards of oncological diagnosis but narrow the gap that exists.

Using US Scan for screening in this scenario is the major stopgap measure this opinion paper emphasizes. School campaigns for BSE (Breast Self Examination), for all girls are the other possibility\(^\text{16}\). The feasibility and subsequent impact of this ought to be investigated and documented. Table 1 indicates how the different investigating modalities compare in terms of sensitivity and specifically in places where they are available for use (a western nation).

Gathering accurate data about breast cancer in Uganda is critical for problem characterization and subsequent evidence based solutions as indeed recommended by BHGI.
Conclusion
Breast Cancer screening, as we know is mostly by the use of mammograms; mammograms are few in Uganda as in many sub Saharan poor countries and wont be enough in the foreseeable future to cover the unmet screening need. In the meantime the next best options include use of USScan and Breast Self Examination (though little evidence to support efficaciousness for both is lacking). Other unexplored options in resource limited settings are, task shifting by the involvement of non-physician cadre in Breast Health Care. There is therefore a need to investigate efficacy of ultrasound in breast cancer screening in resource-limited environments as well as a lower cut off age for mammography screening.

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Hepatocellular carcinoma and the underlying mechanisms

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Abstract
The incidence of hepatocellular carcinoma is increasing worldwide as well as the associated risk factors, some of which include exposure to aflatoxin B1, Hepatitis B (HBV) virus and hepatitis C (HCV) virus. Mutation of tumour suppressor gene p53 at codon 249 at exon 7 has been found to contribute significantly to replication of damaged DNA and subsequent tumour progression. The x gene of HBV (HBx) is the most common open reading frame integrated into the host genome in hepatocellular carcinoma and the integrated HBx is frequently mutated in hepatocellular carcinoma. Mutant HBx proteins still retain their ability to bind to p53 thereby attenuating DNA repair and p53-mediated apoptosis.

Keywords: hepatocellular carcinoma, aflatoxin B1, HBV, HCV, p53

Introduction
Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. It is the fourth leading cause of cancer-related death in the world.¹ The major risk factors include chronic infections with the hepatitis B (HBV) or C (HCV) virus and exposure to dietary AFB1 or alcohol consumption. A link based on circumstantial evidence has been divulged between high exposure to AFB1 and mutation at the 3rd nucleotide base of codon 249, which is located on the 7th exon of p53 gene of cells of primary liver cancer from patients in tropical countries of the world and activation of the WNT signal transduction pathway.²³ AFB1 frequently induces G: C to T: A transversions at the third base in codon 249. Interestingly, mutant DNA in plasma is a biomarker of both AFB1 exposure and potential risk factor for HCC with subsequent p53 mutation.⁷ The tumour suppressor gene p53 is the most commonly mutated gene in human cancers.⁸ Chronic infections with HBV and HCV viruses and oxyradical disorders including hemochromatosis also generate reactive oxygen/nitrogen species that both damage DNA and mutate cancer-related genes such as tumour suppressor gene p53.⁹ The p53 biological network is a key responder to this oxidative and nitrosative stress. Depending on the extent of the DNA damage, p53 regulate transcription of protective antioxidant genes and the extent of DNA damage that ultimately trans-activates pro-oxidant genes which eventually contribute to apoptosis. The x gene of HBV (HBx) is the most common open reading frame integrated into the host genome in HCC and the integrated HBx is frequently mutated. Mutant HBx proteins still retain their ability to bind to p53 and attenuate DNA repair and p53-mediated apoptosis. Hence, both viruses and chemicals (especially vinyl chloride) are implicated in the etiology of p53 mutation during the molecular pathogenesis of HCC.

HCC is a major cause of cancer morbidity and mortality in many parts of the world, including Asia and Sub Saharan Africa, where there are >500,000 new cases each year and >200,000 deaths annually in the People’s Republic of China (P.R.C) alone.¹⁰ The major etiological factors associated with development of HCC in these regions are infection with HBV and or HCV and long time exposure to high levels of AFB1 in the diet.¹¹⁻¹²

Mechanisms underlying Hepatocarcinogenesis
The biology, mode of transmission, and epidemiology of HBV continue to be actively investigated and have been recently reviewed.¹³ A mutation in the HBV genome can alter the expression of multiple proteins. In many cases of HCC in China and Africa, a double mutation in the HBV genome, an adenine-to-thymine transversion at nucleotide 1762 and a guanine-to-adenine transition at nucleotide 1764 (1762⁷/1764⁸) has been found in tumours.¹⁴⁻¹⁵
Heterogeneity in etiological factors of HCC

The frequency of HCC is particularly high in Asia and Africa due to the high frequency of viral hepatitis infections and to aflatoxin B1 exposure (AFB1). Over the last 10 years, the incidence of HCC has noticeably increased in United Kingdom, France and United States. This is probably linked to viral hepatitis C infections. Etiological factors that are associated with the development of hepatic tumours are well known in these regions. They include infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV), heavy alcohol intake, prolonged dietary exposure to AFB1 or vinyl chloride and primary hemochromatosis. In 90% of the HCC cases, at least one of these risk factors can be identified either alone or in combination with another factor. The presence of each risk factor among patients varies according to the geographical origin of the patients. Globally, exposure to HCV, HBV and AFB1 are responsible for about 80% of all HCC in humans' worldwide but the principal risk factor varies between countries. In Japan almost all HCC are linked to HCV infection, whereas in Africa HBV infections are predominant. In France, HBV and HCV infections and alcohol intake are identified with approximately equal frequency. Exposure to AFB1 is commonly found in sub-tropical countries where humid heat can lead to the development of Aspergillus flavus in improperly stored foods such as cereals and peanuts. This mycotoxin is strongly hepatocarcinogenic in experimental animal models and acts synergistically with HBV infection to increase the risk of HCC. Tobacco exposure is the leading carcinogen associated with multiple solid tumours. Several investigators have previously reported an association between tobacco and HCC with odds ratios ranging from 1.5 to 6.8. However, other studies found no association between tobacco and HCC.

Hepatocarcinogenesis

The different risk factors of HCC include chronic lesions in the liver with associated inflammation, necrosis of hepatocytes and fibrosis. Overall, HCC development is closely associated with cirrhosis and more than 80% of the tumours are found in a chronic hepatitis or a cirrhotic background. Dysplastic nodules and macrogeneitive nodules have long been considered to be the likely precursors of HCC because of their frequent association with the HCC occurrence. Chromosome aberrations occur in HCC and these may already contain genetic aberrations. However, in rare cases (less than 10% of the cases), HCC are observed in non-cirrhotic liver and even without inflammatory lesions. The HCC which develop in an otherwise normal liver are usually found in patients without well-established risk factors. Some of these cases may correspond to the malignant transformation of liver adenoma that are rare benign hepatocellular tumours sometimes found in young women taking oral contraceptives.
studies have found evidence for an HBV-aflatoxin interaction in hepatocarcinogenesis. 35-41 Several mechanisms underlying this principle have been proposed to explain the interaction between HBV and aflatoxin. The increase in cellular proliferation induced by HBV could increase the probability for clonal expansion of an existing aflatoxin induced-\(p53\) 249\(^{46}\) mutation\(^{42}\). An increase in levels of aflatoxin metabolism enzymes (e.g., P450 enzymes in which its activity is associated with increased hepatotoxicity of aflatoxin) has been described for HBV transgenic mice and has been postulated as a mechanism for interaction.\(^{43}\) The HBx protein, which is encoded by HBV interferes with the nucleotide excision repair pathway, a major repair pathway which cells use to repair damaged DNA.\(^{44}\) However, the presence of mutant HBx protein could increase the frequency of aflatoxin-induced mutations.\(^{44}\) Also, HBV infection was reported to increase oxidative stress, which could lead to an increase in \(p53\) mutations.\(^{45}\)

**Mechanisms of HBV-mediated hepatocarcinogenesis**

HBV infection can promote carcinogenesis by at least 3 different mechanisms. First, integration of the viral DNA in the host genome can induce chromosome instability. Second, insertional mutations of HBV are known to activate endogenous genes of retinoic acid \(\alpha\)-receptor, cyclin A and mevalonate kinase which are involved in cell cycle control, cellular proliferation and differentiation. The second mechanism is associated with specific intracellular receptors. Recently, 15 new genes were found to be altered by HBV integration in tumors suggesting that viral integration in the vicinity of genes controlling cell proliferation, viability and differentiation is a mechanism frequently involved in HBV hepatocarcinogenesis. The third mechanism of carcinogenesis linked to HBV infection is based on the expression of viral protein, in particular HBxs, to modulate cell proliferation and viability. Moreover, HBxs bind to \(p53\) and inactivates \(p53\)-dependent activities, including \(p53\)-mediated apoptosis. Recently, the association between hepatitis B virus and Hepatocellular carcinoma and the molecular mechanism of action that is involved in the hepatocarcinogenesis has been extensively described.\(^{46,47}\)

**Interaction of AFBl with DNA and chromatin proteins (histone)**

After an exposure to AFBl, accumulations of damaged DNA are found in the liver, as a result of conversion of the AFBl to its active metabolites. AFBl is a very potent mutagen and the AFBl epoxides (active metabolites of aflatoxin) react with guanine in DNA, leading to genetic changes. The most frequent mutation induced is the (guanine-cytosine to thymine-adenine) \(GC\) to \(TA\) transversion. However, quantitative determination of AFBl in human aflatoxin albumin adducts has been elucidated.\(^{46}\) The mutational pattern of \(p53\) gene in HCC from regions where AFBl exposure level is high, revealed (guanine to thymine) \(G\) to T transversion at codon 249 in more than 50% of the cases. A more detail study revealed that AFBl binds preferentially to lysyl amino acid residues in histone proteins.\(^{10}\) The binding of AFBl to histone proteins has significant functional implications because histone has been reported to be the packaging material for DNA and histone H1 is the most external of the histone proteins wrapped around DNA.\(^{10,45}\) Because of the high content of basic amino acids in histones, it is conjectured that there is a strong electrostatic interaction between them and DNA and that (addition of acetyl group) acetylation of the lysyl sites which is involved in this type of interaction, reduces the net positive charge of the histone and loosens the bonds between histone and DNA. Acetylation is reported to occur at the amino group of lysyl amino acid residues which is the same binding site of AFBl.\(^{50,10}\)

The effect of AFBl binding to histone is therefore likely to be similar to reaction elicited by Acetylation (a post transcriptional modification), which is the partial loosening of the histone-DNA bond and the consequent degradation of the histone by specific proteases.\(^{30}\) It is generally accepted that such a partial loosening of the histone DNA bonds always precedes gene expression. This means that it is most likely that it is the binding of AFBl to lysyl amino acid residues in histone with the consequent loosening of the histone-DNA bond that makes \(p53\) accessible for damage. It is also likely that the binding of AFBl to histones with the consequent loosening of histone is primary to its binding to the DNA of \(p53\) genes even though the binding to DNA subsequently exceeds its binding to histone. Taken together, the binding of AFBl to DNA is responsible for the inhibition of RNA Synthesis, which is involved in gene expression.
The implication of the above is that it is the binding to chromatin proteins (histone) may be involved in the expression of the mutated p53 gene resulting from the interaction of AFBI with DNA and chromatin proteins. The p53 gene is reported to be mutated in HCC after exposure to aflatoxin. Recently, some authors have extensively discussed the association between AFBI and the associated risk factors involved in HCC.

**Conclusion**

The nexus between hepatocellular carcinoma and the associated risk factors cannot be overemphasized. The interaction between aflatoxin and HBV or HCV in hepatocarcinogenesis and multi-stage carcinogenesis is grossly elucidated. Characterization of the genetic alterations associated with HCC tumors is an essential step to increase our knowledge of hepatocarcinogenesis. Systematic search for these alterations in series of tumors including tumour grades, stages, etiologies and the associated pre-neoplastic lesions is therefore necessary to find and identify the pattern of accumulation of the genetic alterations during tumour progression. Microarray analysis and metagenomics may also contribute significantly to identifying new carcinogenic pathways altered in these tumors. New insight should therefore be geared towards getting a better clinical application, to identify tumour markers that are useful for early detection of tumors, to predict prognosis, or to find new therapeutic targets with their underlying molecular mechanism of action.

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