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The 'Cancer Villages' in China: Toxicological Pathways And Susceptibility To Replication in Nigeria

[1]Anetor J.I., [1]Akinduko D. S., [2]Anetor G.O. [1]Igharo, G. O.

[1]*Toxicology & Micronutrient Metabolism Unit, Department of Chemical Pathology, College of Medicine, University of Ibadan & the University College Hospital, Ibadan, Nigeria.*

[2]*School of Health Science, National Open University of Nigeria, Ahmadu Bello Way, Victoria Island, Lagos.*

Abstract

The recent observation of the existence of 'cancer villages' in China appears a precise confirmation of the prediction of Rachel Carson over five decades ago; that 'one in every four' will develop cancer, a consequence of indiscriminate chemical application . The observation also appears an exquisite confirmation of recent reports that though the incidence of cancer is projected to increase globally, the developing nations will bear the brunt. The possible susceptibility to replication of the China 'cancer villages' in Nigeria despite obvious precursors has received little attention. China is perhaps the world's most polluted country currently owing to the fast pace of industrialization and has openly admitted that toxic chemicals have caused many environmental emergencies, including elevated cancer rates. The toxicological pathways though glaring have been ignored for years. China is one of the countries with the highest emission of cadmium (Cd); a prime and ubiquitous environmental pollutant which contributes to genome instability, precursor of the carcinogenic process through a number of pathways; direct damage to DNA and inhibition of DNA repair mechanisms as well as interference with signal transduction pathways among others. Additionally, Cd is a potent metabolic antagonist of zinc, an important component of p53 ('guardian of the genome'), regulator of the cell cycle and zinc fingers. Aside, from Cd, China currently uses enormous amount of other chemicals and physical agents; profusion of petrochemicals, existence of numerous steel and iron refineries, numerous power plants to drive her giant industries, a situation similar to that in Nigeria. Therefore, rather than be preoccupied with weight of evidence, Nigeria should thread the path of cautionary principle to avert the emergence of mega 'cancer villages'

Keywords: Cancer villages, Cadmium pollution, DNA damage repair, Chemoprevention, Nigeria.

1. Introduction

1.1 Cancer Statistics and the Developing Countries

Cancer is a group of dreaded diseases characterized by unregulated cell proliferation, the invasion and spread of cells from a site of origin to secondary sites in the body (metastasis) that defies many attempts to keep it in check. It is a very expensive disease to treat and manage. A sizeable part of the present incidence of cancer appears to be the result of chemical carcinogenesis. Varied estimates exist, ranging from 4 to 60% or more (True and Dreisbach, 2002). This places the rapidly industrializing nations where the applications of chemicals with very poor compliance with safety regulations at a greater risk (UNEP, 2012).

In 2008, about 12.7 million new cancer cases and 7.6 million deaths were documented (Jemal, et al., 2011). This is estimated to cost the global economy US$900 billion. Earlier, in 2003, the World Health Organization (WHO) predicted over 21 million new cancer cases and 13 million deaths with prohibitive costs to the society each year. These already gruesome statistics have been recently worsened by the release of newer ones showing that the incidence of cancer globally has risen from the 2008 figures to 14.1 million in 2012 with 8.2 million deaths (Boseley, 2014). Disturbingly, the resource poor countries of the world were predicted to be absolutely at greater risk in the couple of decades that follow by the diseases that are common in the developed countries now (Boyle and Levin, 2008; Boseley, 2014)). Cancer is the leading

Correspondence

one among these non- communicable diseases (O'Callaghan, 2011).

1.2. Cancer Statistics Old versus New

About five decades ago what may be described as the first shocking cancer statistics was released to the emerging industrializing nations, led by the United States at the time, by Rachel Carson, author of 'Silent Spring' (Carson, 1962). Rachel Carson put the estimate as 1 in 4. This is put as 1 in 3 people likely to suffer during life time currently making the situation more serious and calling for urgent and sustained efforts. Siegel et al (2011) estimated that 571,950 Americans would die from cancer in 2011. Cancer mortality rate for men in the UK was greater than 200 in men in 2008 (Cancer Research, UK). This probably reflects the number of cancer deaths per year per 100000 individuals. Worldwide, incidence; the number of new cases is estimated to be ~ 12.7 million cases in 2008 (Jemal et al., 2011). These figures have now been put at about 14.1 by new estimates from the WHO (Boseley, 2014)

1.3. The China 'Cancer Villages'

Existence of 'cancer villages' (cluster of cancer cases) has been accepted for the first time by China. The intensity of chemical application in china and attendant pollution is one of the highest in the world. Thus it is not surprising that China is experiencing the degree of incidence of cancer that is now described as the 'cancer villages'. Sixteen of the world most polluted cities are located in China, 760, 000 people die in China every year due to chemical pollution (Winston, 2010). Pollution is now described by some as public enemy and has led to strikes in some cities. Toxic chemicals are now recognized to cause many environmental problems in China; most dramatic being cancer. Cancer is the leading cause of death in urban China. Cancer accounts for 1: 4 (one in every four) deaths (Science, 2008; 2013). This is consistent with the earlier prediction of Carson (Carson, 2002)

China is generally accepted to be the world's most polluted country currently particularly with Cd (Nordberg et al., 2007) owing to the fast pace of industrialization and has openly admitted that toxic chemicals have caused many environmental emergencies, including elevated cancer rates. Cancer is thus the leading cause of death in urban China at the moment. The toxicological pathways though glaring have been ignored for years. China is one of the countries with the highest emission of cadmium (Cd) (Sun, 2006; Yan, 2007). Cadmium is a prime and ubiquitous environmental pollutant which contributes to genome instability, precursor of the carcinogenic process through a number of pathways; direct damage to DNA and inhibition of DNA repair mechanisms as well as interference with signal transduction pathways (Bertin and Averbeck, 2006; Thevenod, 2009). Additionally, Cd is a potent metabolic antagonist of zinc, an important component of p53 (guardian of the genome), regulator of the cell cycle and zinc fingers (Ho, 2003). Aside, from Cd, China currently uses enormous amount of other chemicals and physical agents; profusion of petrochemicals, existence of numerous steel and iron refineries, numerous power plants to drive her great number of giant industries. Though these cancer villages are little studied they have a lot of implications for Nigeria that is also rapidly industrializing with the added component of Nigeria being an oil producing country with associated intense chemical pollution (lot of hydrocarbons such as benzene) of the environment.

1.4. Toxicological Pathways

Toxicity may be regarded as an interaction between a xenobiotic (foreign chemical; toxicant) and a biological system that results in damage to the living organisms (Dear, 2014) including humans. Generally, the scientific community, including the medical community is often more concerned with acute episodes of toxicity and their clinical management, but it is often forgotten that the chronic effects of toxicants have much more serious effects and of greater importance globally (Dear, 2014). Though acute ingestion of the common social toxicant alcohol may lead to intoxication that may result in death from its characteristic depressant consequences as well as associated adverse outcomes of accidents, and violence may be pale in significance compared to long-term consequences. Some serious outcomes of chronic effects may include liver disease (particularly cirrhosis), and cancer. Some late effects of prolonged persistent excessive exposure to toxicants as is recognised in China ranges from teratogenicity, mutagenicity, and carcinogenicity. There is currently increasing concern about environmental pollution by chemicals particularly in toxicology and environmental science communities. The interaction between toxicants and biological systems pathway is exquisitely complex. The interaction may cause functional and metabolic disturbances of grave pathologic and epidemiological significance. An understanding of the nature of the interaction between toxicants and biological systems is essential for an intelligent intervention and management of toxicity generally and major consequences such as cancer.

Cadmium continues to cause concern as an environmental toxicant and epimutagen (Takiguchi, et al., 2003; ATSDR, 2005). The substantial demands globally for Cd by industries imply that the greatest impact will be in the rapidly industrializing countries. One of the characteristics of Cd that makes it particularly significant as a toxicant is that cadmium is not degraded in the environment, increasing the risk of human exposure constantly. Cadmium also as a result of its persistence in the environment easily enters the food chain raising the pathways through which Cd can reach humans (ATSDR, 2005).

The important toxicological pathways in addition to traditional ones like competition with the prime micronutrient zinc are that Cd disrupts physiological signalling processes, culminating in signalling dysfunction which is responsible partly at least for the pathological processes attributed to Cd toxicity (Thevenod, 2009). It is thought that these effects on signalling may potentiate and amplify the cell's response to other toxic effects of this environmental toxicant, including direct damage to enzymes, transport proteins, thiol oxidation which may all converge to raise reactive oxygen species and thus oxidative stress (Liu et al, 2009).

A further aspect is that Cd in most cases bypasses cell surface receptors inducing near permanent changes in the position of second messenger that may be non-physiologically elevated or attenuated. This may affect a number of cellular functions such as gene transcription, and regulation that may lead to cell death, and or stress-induced adaptation and consequently survival (Thevenod, 2009). These events have far reaching effects in the carcinogenic process and may all play a part in the currently accepted 'cancer villages' in China.

Disruption of physiological and biochemical pathways of the body may occur in a remarkable number of ways. These toxicological pathways though obvious have been ignored for years. China as alluded to above is one of the countries with the highest emission of cadmium (Cd); which contributes to altered genome stability; precursor of the carcinogenic process through a number of pathways such as direct damage to DNA and inhibition of DNA repair mechanisms as well as interference with signal transduction pathways (Bertin and Averbeck, 2009; Tevenod, 2009). Additionally, Cd is a potent metabolic antagonist of zinc, an important component of p53 (guardian of the genome), regulator of the cell cycle and zinc fingers. Aside, from Cd, China currently uses enormous amount of other chemicals and physical agents; profusion of petrochemicals, existence of numerous steel and iron refineries, numerous power plants to drive her great number of giant industries. These may through a number of mechanisms including oxidative stress (Liu et al., 2009) and the other pathways indicated above contribute to the cancer clustering referred to as cancer villages in China. Though China is taking measures to ensure strict regulation of the use of chemicals, this has probably come too late, given the multiple stages of the carcinogenic process; initiation, promotion and progression. There are clearly parallels between Nigeria where pockets of the disease exist and China. One striking example is that every household in Nigeria is a mini power station, a coalescence of which may equal or even exceed the China situation. Additionally, the combination of the huge petrochemical burden and micronutrient deficiency disorders may be permissive. Singh et al (2005) have observed that the nutrient deficiencies in developing countries can be a significant factor in modifying the multistage process of carcinogenesis. This appears important in that cancer is considered as predominantly an environmental disease with over 65% contributed by the environmental component (Singh, 2005).

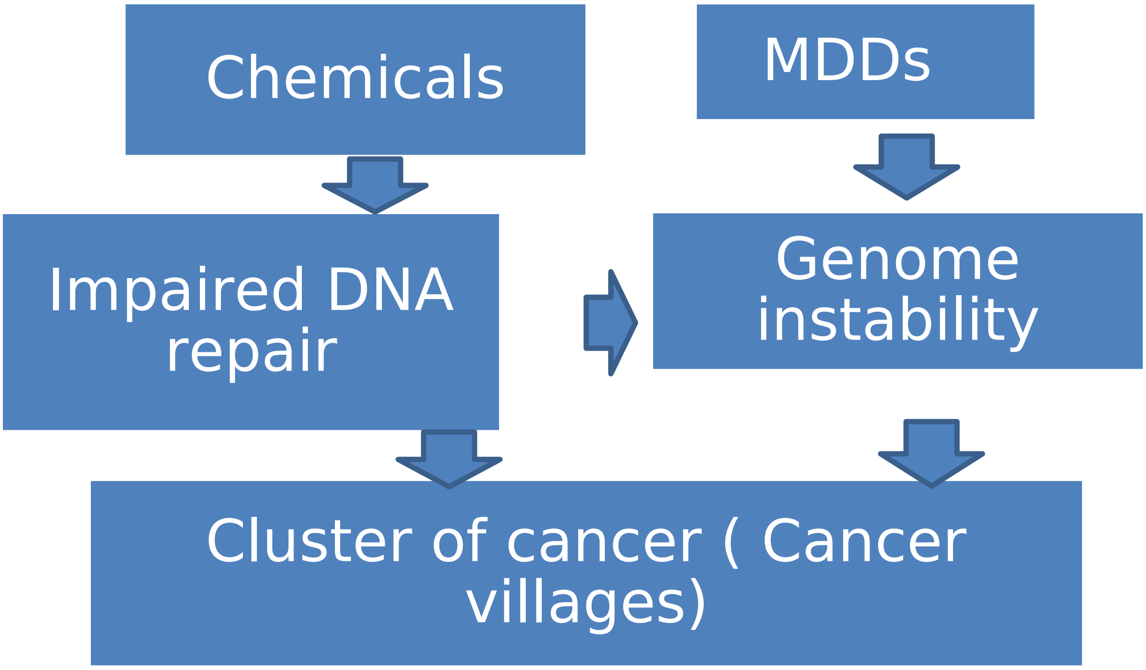

Figure 1: Key toxicological pathways operative in cancer clustering

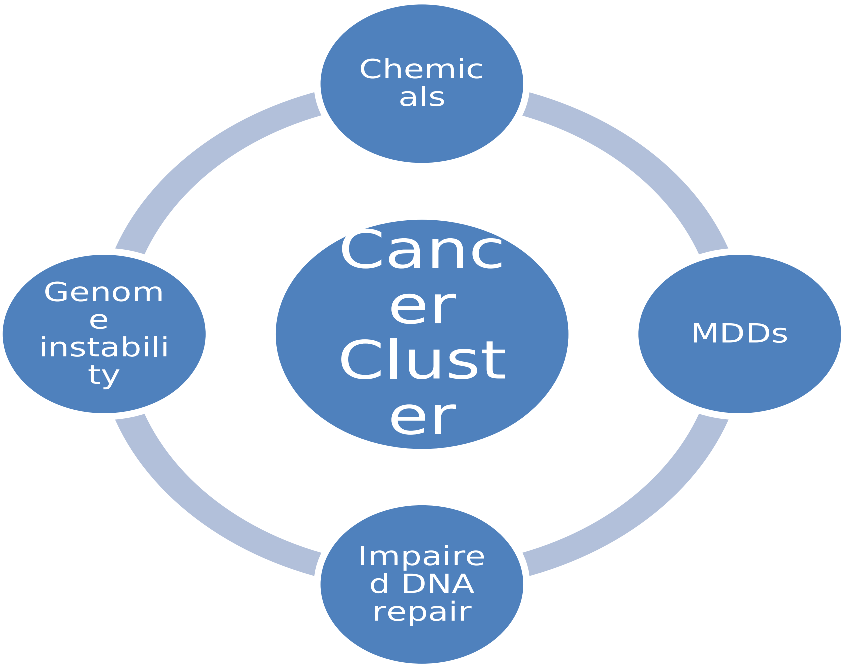

Figure 2: Relationship of chemicals, MDDs, impaired DNA repair, genome stability and cancer clusters

1.5. Cancer a Disease of the Genome

Ultimately cancer causing agents (carcinogens) cause alterations in the DNA sequence (mutation). Cancer is a culmination of alteration in DNA. An important observation is the ubiquitous chemical and potent environmental pollutant; cadmium which is rising in many developing countries especially in China and India (Bakshi, 2009, Sun, 2006). This may at least in part play a prominent role in the carcinogenic pathway. Though cancer arises largely from accumulation of mutations that could not be repaired, it is preceded by genome instability now high in developing countries including China (Cheng, 2009). Accumulation of mutations in cells over time represents a multi-step process underlying cancer; initiation→ promotion → progression.

Among the toxicological pathways of the China 'cancer villages' may be genome instability and tumor-promoting inflammation recently recognized as an important contributor to the carcinogenic process (Nordberg, 2009; Pecorino, 2012). Maintenance of genome stability is of fundamental importance for counteracting the carcinogenic process.

Micronutrient deficiency disorders (MDDs) may be another important but poorly recognized pathway to increased cancer incidence (Singh et al, 2005).This may also precipitate genome instability given the well-known roles micronutrients like Zn play in optimum genome function (Cheng, 2009) (Figure 3). It has been suggested that DNA damage induced by deficiency of micronutrients is responsible for over thirty per cent of preventable cancers (Ames, 2001; Ames and Wakimoto, 2002). Fenech has provided evidence confirming the vital contribution of micronutrient deficiency disorder as a precursor to the carcinogenic process (Fenech, 2002, 2004)

Requirement for an accumulation of mutations over time explains the increased risk of cancer with age and with increased life span accelerated with increased exposure to chemicals and radiation and continuous demand for micronutrients.

Accumulation of mutation occurs after a cell's defense mechanisms (such as DNA repair) have been compromised or evaded. This may arise through a number of pathways; competition between the rising level of Cd in the environment and essential micronutrients involved in the DNA repair process, a major example of which is zinc, a prime micronutrient and a metabolic antagonist of cadmium. This prime micronutrient is also a component of an important antioxidant, copper-zinc superoxide dismutase (Cu-ZnSOD). This implies that free radicals that are generated as a result of the increased chemical pollution cannot be effectively scavenged leading to the creation of a state of oxidative stress implicated in many pathologic state including cancer (Joseph, 2009).

Displacement of zinc by cadmium has several implications. Zinc is a component of p53, the tumour suppressor protein which is susceptible to oxidation thus the roles played by this protein will be aborted and susceptibility to cancer by the affected population will be increased. Over- burdening of repair mechanisms (intense exposure) the raised level of pollution may overwhelm the defense again raising susceptibility.

1.6. Current rate of Cadmium release & Implications for the Genome

The current rate of release of Cd in to the environment increases cadmium content of the human body (Jarup, 2003; Satarug et al., 2003; Joseph, 2009). Cadmium emissions have increased dramatically during the 20th century due to the fact that cadmium containing products are rarely recycled, it has wide ranging consequences many of which may directly or indirectly contribute to the clustering of cancer in many communities in China.

Cadmium has genotoxic effects (Bertin and Averbeck, 2006, Thevenod, 2009; Joseph, 2009); modifies cellular, and biochemical activities and modulation of DNA repair mechanisms.

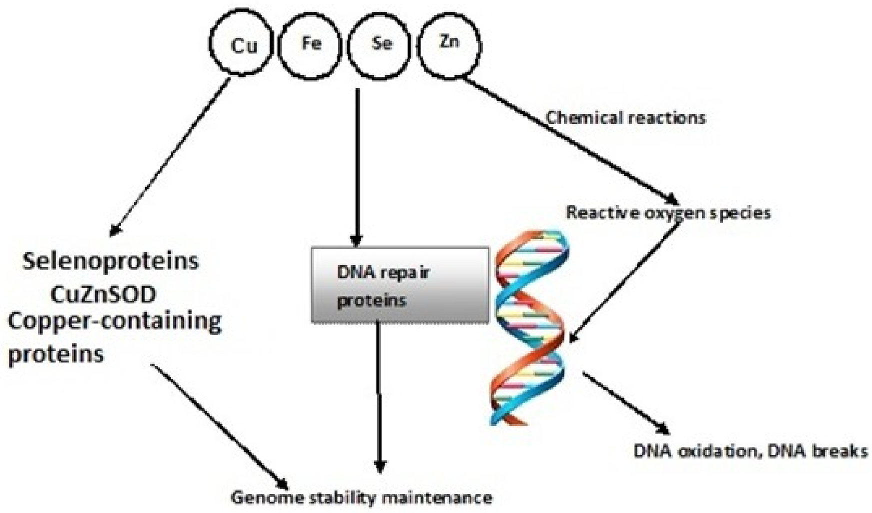

Figure 3. Some micronutrients in genome stability; after Cheng (2009)

1.7**. Inflammation: Pathway to Cancer**

One development which appears of particular relevance to Nigeria and other developing countries is the observation that long-term inflammation may promote the carcinogenic process (Aggarwal et al., 2006; Colotta et al., 2009; Mantovani et al, 2008; Pecorino, 2012) chronic inflammation plays multifaceted role in carcinogenesis. Mounting evidence from pre-clinical and clinical investigations suggests that persistent inflammation serves as a driving force in the events leading to cancer. Possible mechanisms include induction of genome instability, alteration in epigenetic events and attendant inappropriate gene expression (accentuated by MDDs), enhancing proliferation of initiated cells, resistance to apoptosis, aggressive tumour neovascularisation (angiogenesis by micronutrients such as Cu). Chronic inflammation is associated with an increased generation of ROS and nitric oxide species (NOS) increased risk of DNA damage, and therefore increased mutation rates all of which may promote the pathway to cancer (Pecorino, 2012). Kundu and Surh (2008) had earlier called chronic inflammation as a factor gearing the journey to cancer. These investigators implicated chronic inflammation in all stages of carcinogenesis, i.e. initiation, promotion, and progression. They like other investigators agree with the emerging view that in persistently inflamed tissue, excessive generation of reactive oxygen species can lead to genomic instability which may culminate in cancer.

1.8. Progress or Poison?

China can rightly be described as a powerhouse of industrial progress, it is estimated that every major town has air deemed unsuitable for breathing owing to intense industrial activities most of which involve the use large quantities of chemicals. Since 1985 the state has had the highest number of reported accidents; 80% of its 83, 000 industries pollute water and 15% pollute the air in China and other developing countries like India and possibly Nigeria [Winston, 2010]. One is therefore tempted to ask if the industrial activities in china and Nigeria as well as other developing nations constitute real progress or it amounts to chronic poisoning of the population. Often this is ignored as it is insidious because of the prolonged evolution of the carcinogenic process, usually decades. A similar picture emerges on manufacturing apart from China in other African countries and the former Soviet Union which a joint body of environmental groups recently issued as 'top ten' worst polluted places in the world (Winston, 2010). Top on the list is Sumgayit, in Azerbaijan, where cancer rates are estimated to be 20 % - 50% higher than the national average; the third placed is Tianying, one of the industrial cities in China. In ten sites in seven countries pollution greatly affected the health of over 12 million people. Damage is considered due to extensive mining, heavy industrial activities and commercial pressure (Winston, 2010). These activities are also on the increase in Nigeria thus susceptibility to replication of attendant disease especially cancer is not unlikely.

1.9. Strike in China for Industrial pollution

In 2005 in Zhejiang province some 30000 people clashed with the police in a pollution riot; grouse was increase in the number of factories. Emissions from these factories deleteriously affected agriculture (Winston, 2010). This may lead to a vicious cycle whereby apart from the direct damage of chemicals through which ever toxicological pathway, the repressed agricultural activities may lead to reduced production of micronutrients in turn leading to MDDs that may enhance susceptibility. This may bring one to the Niger Delta of Nigeria. What is the situation? Studies are clearly indicated.

1.10. Similarity of Pollution in China to that in Nigeria

There are clearly parallels between Nigeria where pockets of the disease exist and China. One striking example is that every household in Nigeria is a mini power station, a coalescence of which equals the China situation. Currently cadmium and its compounds are used globally in electroplating, batteries, pigments, and plastic production as stabilizers (Kwong et al, 2013). The latter may indeed be a significant source of cadmium in Nigeria as the production of plastics is a major industry in Nigeria for many social events. As they have a short life span they are discarded in waste bins and very often set on fire. This is not to mention used tyres which contain considerable amount of Cd and are often set on fire releasing huge fumes containing Cd. Again, like in China, in Nigeria major industrial releases of cadmium can also occur in wastewater and the numerous metal works in small scale industries. Additionally, the combination of the large petrochemical burden and micronutrient deficiency disorders is permissive. Rather than have a scientific approach and explanations we tend turn to blame nonexistent 'culprits'. It is perhaps in order to adopt the measures China is currently experimenting with to avoid a worse cancer catastrophe. This view point appears with what Tomatis and Huff (2001) have always believed about the evolution and primary prevention of cancer. There is need to remind ourselves of this concept as a veritable approach to reducing susceptibility to cancer clusters in Nigeria. If China with her level of compliance with the concept of chemoprevention and micronutrient therapy is affected to this degree, it may be unprecedented in Nigeria. Oxidative stress in mixed chemical workers that may through a tortuous pathway lead to altered genome stability has been reported in Nigerian mixed chemical workers who exhibited oxidative stress (Anetor et al, 2009). This has implications for genome instability. This suggests that simple tools for detecting oxidative stress and risk of genome instability (precursor of the carcinogenic state; future cancer) are desirable.

1.11. Optimum Micronutrients and Susceptibility to Cancer Clusters

Optimizing micronutrient intake optimizes metabolism resulting in decreased DNA damage and less cancer as well as other degenerative diseases of aging (Anetor et al, 2009; Anetor, 2009; Ames, 2010). Modest micronutrient deficiencies (common in Nigeria & other developing countries) may accelerate molecular aging including DNA damage and mitochondria decay, (Anetor, 2009; Ames, 2010). Optimizing micronutrient intake may be one of the pathways of preventing emergence of 'cancer villages' and other degenerative disease in Nigeria.

1.12. Genome Stability DNA Repair & Micronutrients

Through the action of micronutrients like Zn, P53 (guardian of the genome; lane 1992) may function optimally. The protein, p53, a tumour suppressor is a critical mediator in cell cycle arrest and apoptosis in response to genotoxic stress. Abrogation of p53 function is a major feature of tumour development → compromised DNA damage response. Vitamin A through its role in proper tissue differentiation may also reverse the carcinogenic process. Vitamin A may be dependent on adequate Zn status. Zinc deficiency common in many developing countries (WHO, 2002) may play a pivotal role in carcinogenesis.

1.13. Cadmium, P53 and DNA Damage

Cadmium has been demonstrated to replace Zn in the tumour suppressor protein p53 (guardian of the genome; Lane 1992) which impairs DNA repair activity leading to decrease ability to respond to DNA damage. Cadmium alters the biotransformation of carcinogenic aromatic amines by aryl amine, N-acetyltransferase, xenobiotic metabolising enzymes (Ragnathan et al. 2010)

1.14. Micronutrient Deficiency Disorders and Societal Health

Little societal concern about micronutrients is expressed because no overt pathologies have been associated with marginal levels of deficiency of micronutrients; the pathology is insidious but real (Ames, 2010). Cancer appears to be one of the very severe and prolonged consequences of micronutrient deficiency and this may indeed be one of the coalescing events that have clustered in what is now known as the China cancer villages. In fairness to China, based on the extant RDI it may be assumed that they are compliant but the raised level of pollution requires a higher intake of micronutrients; an up - regulation to meet the degree of demand. This in contrast to what operates in Nigeria where current RDI may not have been met is probably critical. This view appears consistent with what was hypothesized by some investigators that among key consequences of MDDs are increased DNA damage (future cancer) immune dysfunction and mitochondrial decay (Ames and McCann, 2009).

2. Conclusion

Recent observations of the existence of 'cancer villages' in China appears a precise confirmation of the prediction of Rachel Carson over 5 decades ago, that 'one in every four' will develop cancer, a consequence of indiscriminate chemical application and pollution (Carson, 2002). China is one of the countries with the highest emission of cadmium (Cd); a prime and ubiquitous environmental pollutant contributing to genome instability, precursor of the carcinogenic process through a number of pathways; direct damage to DNA and inhibition of DNA repair mechanisms as well as interference with signal transduction pathways. Additionally, Cd is a potent metabolic antagonist of zinc; this may lead to abrogation of the molecular and cellular pathways in which Zn plays important biochemical roles particularly that of the tumour suppressor protein, p53. There are clearly parallels between Nigeria where pockets of the disease exist and China. One striking example is that every household in Nigeria is a mini power station, a coalescence of which equals the China's situation. The combination of the huge petrochemical burden and micronutrient deficiency disorders may accentuate susceptibility to cancer clusters in Nigeria. Rather than have a scientific approach and explanations we tend to blame non-existent 'culprits' (superstition). Strategies based on scientific basis employing health education should be embraced.

3. Recommendations

It is perhaps in order to adopt the preventive measures China is currently experimenting with to avoid a worse cancer catastrophe; environmental monitoring and control. If China with her level of compliance with the concept of chemoprevention and micronutrient therapy is affected to this degree, it may be unprecedented in Nigeria. Therefore, rather than be preoccupied with weight of evidence, Nigeria should thread the path of cautionary principle to avert the emergence of mega 'cancer villages' by embracing the combination of environmental regulation and chemoprevention.

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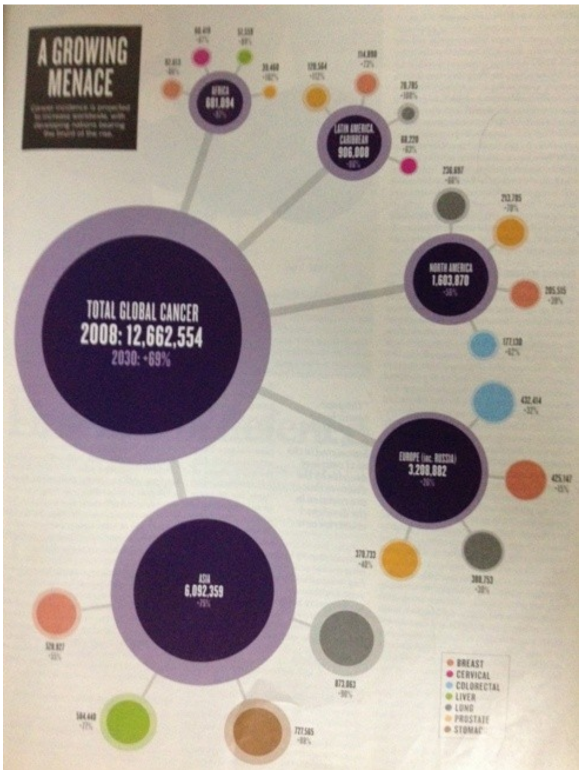

Figure 4. Projection of increase in cancer incidence worldwide, with the developing nations at greater risk after O' Callaghan (2011)