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Chemoprevention: A Promising Prophylaxis to Risk of Leukemia in Polluted Environments and Indication for Creative Health Education

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Abstract

Though attention continues to be focused on the infectious and communicable diseases in the developing countries, recent data suggest that the combined effects of environmental chemical pollution were responsible for 268 million Disability-Adjusted Life Years (DALYs) and 9 million premature deaths yearly which exceed the total annual mortality from infectious and communicable diseases.

This high morbidity and mortality are disproportionately attributed to cancer from environmental pollution, a disease expensive to treat, particularly in the Low and Medium Income Countries (LMICs). Leukemia is a form of cancer that is rising and predominantly found in the younger population, thus has great impact on the future of these countries. Eradication of chemicals would aid cancer prevention, but it is not pragmatic, indicating alternative approach. Chemoprevention; the inhibition, delay or reversal of carcinogenesis at the premalignant phase based on molecular and cellular mechanisms, halting progression to invasive cancer, using mainly dietary factors, offers this approach. Numerous regulatory signals control cellular processes in health. In cancer these regulatory mechanisms are disrupted and cells grow and replicate unchecked. Signalling pathways restoration represents attractive targets for cancer prevention and therapy. Impaired signalling and DNA damage in carcinogenesis are repaired by chemopreventive agents especially zinc and retinoid derivatives. What has been neglected in chemoprevention is creative health education with great potential to unveil its untapped immense benefits in LMICs. Chemoprevention may indeed be linked with personalized nutrition, or personalized medicine, currently greatly advocated as the regimen of the future in health systems for a healthier world.

Keywords: Anticarcinogenesis; Antioxidants; Carcinogenesis; Chemoprevention; DNA repair; Environmental pollution; Personalized nutrition; p53; Signaling pathways; Zinc

Abbreviations

ALL: Acute Lymphocytic Leukemia; AML: Acute Myeloid Leukemia; APL: Acute Promyelocytic Leukemia; BHC: Benzene Hexachloride; CML: Chronic Myelogenous Leukemia; Cu-ZnSOD: Copper, Zinc Superoxide Dismutase; DALYs: Disability Adjusted Life Years; GBD: Global Burden of Disease; GBD-PHI: Global Burden of Disease Public Health Initiative; GPX: Glutathione Peroxidase; HSC: Hemopoietic Stem Cells; IARC: International Agency for Cancer Research; LMICs: Low and Medium Income Countries; MDS: Myelodysplastic Syndromes; PZ: Pyrithione zinc; SEM: Scanning Electron Microscope; Zf: Zinc Fingers

Introduction

There is current great international concern about the contribution of environmental pollution to the Global Burden of

Disease (GBD) [1]. This has translated into the formation of the Global Burden of Disease – Pollution and Health Initiative (GBD-PHI) [2]. The concern is greater in the Low and Medium-Income Countries (LMICs) or the developing world [3,4].

In these countries though attention continues to focus on the infectious and communicable diseases, recent data suggest that the combined effects of pollution by chemicals was responsible for 268 million Disability-Adjusted Life Years (DALYs) and 9 million premature deaths each year, which is 3 times greater than the total annual deaths attributed to the common communicable diseases, such as HIV/AIDS, tuberculosis and malaria with the greatest burden in the developing countries [5].

Environmental Pollution and Cancer Concern

Of the pollution associated diseases one of the most feared is cancer [6,7]. Cancer is a genetic disease because it can be traced to molecular alterations and in most cases is not inherited. The molecular alterations leading to most cancers arise in the DNA of a somatic cell during the individual's life span. Only 5-10% of all cancer cases may be attributed to genetic defects with the probability of inheritance, implying that 90-95 % may have their roots in the environment and life style [8]. This connotes that more serious attention should be paid to these root causes or factors contributing to cancer. Over two decades ago Zahm and Ward [9] drew the attention of the scientific community to childhood cancers associated with environmental pollution (external and domestic) largely to what was considered the most prevalent environmental pollutants, pesticides (many of which contain hydrocarbons like benzene). Today one of the most prevalent environmental pollutants is unarguably petrochemicals with hydrocarbons, particularly benzene, a known marrow toxicant implicated in myeloproliferative disorders especially, leukaemia [10] are among the most common. In the developed countries this may not be as well appreciated as in the developing countries where electricity generation is not very reliable like in Nigeria, and many individual families or organizations have to generate their own electricity using generators that run on petrol or diesel. Thus, aside from emissions from automobiles, there is continuous exposure to benzene in the home environment for a protracted period where children spend most of their time [6].

Nearly half a century now, the global community united to remove Pb from petrol (though it is still in paints), owing to its recognized adverse effects on neurological function particularly in children [11]. The same scientific community unwittingly is turning a blind eye to the prevalence of environmental pollution from petrochemicals and its chief constituent, benzene and its possible contribution to the known growing cases of leukaemia [12,13]. While this situation persists and not pragmatic to eliminate it; it is comforting that chemoprevention has been experimented with and is being practiced in several nations now to prevent or as prophylaxis in other environmental toxicants causing disease such as arsenic in Pakistan, using selenium fortified local lentils [14]. We believe this can also be extended to leukemia.

The incidence of cancer in children is increasing as revealed by data from 68 countries and more than 100 population-based registries by the International Agency for Research on Cancer (IARC) 1990-2017 showing an average of 215,000 incidence of cancer diagnosed in children per year [13]. The most prevalent type of cancer was leukemia and lymphoma in children [12,13]. This is not surprising as children are exposed to a wide range of cancer-causing pollutants in ambient air while playing outside for protracted periods. Diesel exhaust, other varieties of petrochemicals, diesel and gasoline exhaust increase increased risk of benzene exposure.

Chemoprevention to the Rescue

As part of the global concern for the continuing problem of cancer, the scientific community has been experimenting with vaccination for cancer with disappointments [15-17]. This disappointment comes understandably from the recognition that cancers mutate rapidly, creating variations unique to individual tumors. It is still incompletely elucidated how and when cancer is initiated but with the understanding of cancer biology so far and that of the molecular mechanisms of action of chemopreventive agents such as signal pathways restoration, DNA damage repair among others, chemoprevention offers a good deal of promise [18]. Damage to the genome is recognized as a fundamental cause of degenerative diseases including cancer of various types. A number of micronutrients play important roles in protecting against damage to DNA arising from endogenous and exogenous factors by acting as cofactors or substrate of enzymes that destroy genotoxicants in addition to DNA repair, restoration of altered cell signaling, methylation, and synthesis. Evidently, either micronutrient deficiency or their excess can modify genome stability [19,20]. These observations essentially underlie the concept of chemoprevention including the emerging science of genome health nutrigenomics, a science based on the principle that DNA damage is a fundamental cause of disease that may be diagnosed and prevented by nutritional factors on an individual or genetic subgroup or population basis [20]. This in turn is the driving force of personalized nutrition that is gaining recognition like personalized medicine or pharmacogenomics [21-23].

A number of compelling studies have shown that certain types of dietary agents may be protective against the adverse effects of benzene on the haemopoietic system leading to leukaemia in experimental and epidemiological cohorts [24,25].

We provide in this concise review the mechanistic evidence of the protection of these nutrients largely micronutrients and argue that they may serve as chemoprevention to the "Occult"

problem of leukaemia in occupational and the general population and examined the gap in knowledge as well as drawing attention to the progress in the field, the great potential benefits for the LMICs, and that this should be widely communicated by appropriate health education.

Cancer Chemoprevention: Situation in the Resource Poor Countries

Cancer chemoprevention or anticarcinogenesis is the process of exposure of an animal to a substance that may reduce the incidence of cancer that would otherwise develop. Chemoprevention involves the intake of protective factors modulating the host defense mechanisms employing dietary and or pharmacological agents. Lack of adequate knowledge of the multiple pathways by which chemically induced cancer may arise and the mode of action of chemopreventive agents, has led to the erroneous impression for a long time that the study of chemoprevention is academic. While this field is gaining an increasing and sustained attention in the developed countries it has received no commensurate attention in the rapidly industrializing developing countries where the intensity of pollution is highest and incidence of cancers is growing, which appears to parallel the pace of industrialization and environmental pollution [26].

Leukemia may be regarded as a neoplastic disease that may in part be inducible by antioxidant and micronutrient alterations or imbalance [24,25]. This will be clearer when the biomolecular activities of chemopreventive agents are examined. Thus, the ability of the common chemopreventive agents to obliterate the imbalance and restore normal homeostasis is instructive. The increasing use of chemicals, particularly in the industrializing developing countries places new demands on these countries, as they have limited resources to adequately regulate exposure to chemicals and the associated disease, cancer is expensive to treat thus chemoprevention should be embraced by these countries. Very many factors including nutritional factors have been shown to delay the carcinogenic process [27].

Molecular Basis of Cancer Induction and Chemoprevention

Chemoprevention may also be considered the process of inhibiting, slowing or reversing carcinogenesis in the premalignant phase. It essentially aims to halt or reverse the development and progression of precancerous cells to invasive cancer through the use of nontoxic (dietary) nutrients, phytochemicals, and synthetic pharmacological agents [18]. Chemopreventive agents are considered to act through the various stages of carcinogenesis; initiation, promotion and progression. Bartsch and Gerhäuser [18] have argued that cancer chemoprevention had its precedence in the field of cardiology, in which lipid lowering, the use of antihypertensives, and antiplatelet agents are consumed as prophylaxis against coronary heart disease in at risk individuals. With this ahead, one is at times at a loss why there is still so much reluctance or resistance to chemoprevention. Yet the concept of chemoprevention is based on both sound experimental science and epidemiology as will be evident later, demonstrating that specific mostly, dietary agents can be employed to reduce the risk of carcinogenesis in various parts of the body including the lungs, colorectal, breast, prostate and skin but that of the haemopoietic system had not yet been explored.

Studies and reviews in the field of chemoprevention have been stimulated and sustained by epidemiologic evidence that have showed a relationship between consumption of large quantities of fruit and vegetables to lower the risk of cancer [20]. This appears to have been what set the stage for the subsequent identification of a growing list of naturally occurring compounds now known as chemopreventive agents. Surh [27] and Thomasset, et al. [28] have described the general categories of potential cancer chemopreventive agents with organosulfur compounds, polyphenols and terpenoids prominent on the list. As will be evident in the studies described in investigations showing great potentials for chemoprevention or implications for, chemopreventive agents suitable for the prevention of cancer in the general population should have the following qualities: high acceptance (still in dispute), low cost, oral route of intake, high efficacy, little or no toxicity (nontoxic) and a recognised mechanism of action [18].

Environmental Exposures and Chemoprevention: Benzene as a Case in Point

While great strides have been taken in our understanding of human genetics, the contribution of environmental exposures to disease remains fragmentary. This dearth of understanding impedes real progress in identifying genetically susceptible populations whose responses to environmental toxicants (chemicals) are severer or unique relative to the general population. This can be modulated for instance by micronutrients whose deficiency can accentuate genomic instability or altered cell signaling. Cell signaling refers to a complex interactive system of signals that act to regulate or modulate a cellular response. Environmental exposure assessment identifies targeted prevention and treatment strategies that might be applied to these at risk groups with potentially lifesaving or health promoting results. Without subject specific exposure data, researchers have a limited ability to identify population susceptibility genes that elevate disease risk.

This dysequilibrium between exposure and genetic studies shows the identification of environmental factors that if altered or removed could prevent some diseases from being established at all. It is often overlooked that certain micronutrients, key among which is zinc play a role in this. They can restore homeostasis or repair altered metabolic and signal pathways that lead to disease including leukemia induced by exposure to environmental chemicals key among which is benzene [29].

The understanding that certain chemicals and radiation can alter hematopoiesis, resulting in leukemogenesis is relatively recent. Though suggested by Hunter as early as 1939, following his observations on benzene exposure and Acute Myeloid Leukaemia (AML) [30], it was not until the introduction of radiation and chemotherapy as treatments for neoplasia that these agents became associated with blood dyscrasias including acute myeloid leukaemia [31].

Benzene is a volatile aromatic hydrocarbon and a component of crude oil and gasoline; it is also the starting point of many synthetic processes in the chemical industries [32-34]. Exposure to benzene occurs in a variety of occupations as an organic solvent and in engine exhaust arising from the 1% to 5% levels in gasoline [35]. It is noteworthy that the International Agency for Research on Cancer (IARC) classified benzene as carcinogenic to human (Group1 carcinogen) in adults [36]. In the developed countries, it was used on a large scale as an organic solvent, but its toxicity was such that it has been restricted from general use if present at a concentration greater than 1% in any solvent and it is used entirely in closed systems so that exposures are low in essential processes [37]. In contrast, developing countries such as Nigeria and other petroleum-exporting countries use benzene at an unregulated large scale, as a solvent in the manufacture of rubber or plastic shoes and in photogravure printing with little or no regulation. This is in addition to exposure from gasoline dispensers that are dotted all over these counties without vapor recovery systems [38]. Environmental exposures, mainly arising from locomotive emissions and cigarette smoke, in the general population are much lower than occupational exposures, ranging from 1 to 10 Part Per Billion (ppb) [39] also contribute. Smokers may be exposed to 10 times the level of non-smokers [40] and smoking is also less regulated in the LMICs than the developed countries. Exposure to benzene could also come from indoor environment, especially from building materials (paints, adhesives etc.) and it has been reported that air around buildings at close proximity to petrol filling stations also have increased levels of benzene [39]. Thus, there is increased benzene exposure in residential areas and probably substantially in buildings close to petrol filling stations [39]. Gasoline dispensing stations in Nigeria for instance are sited with little regulation and the sale of petroleum products is a very big business in the country as it is seen as very lucrative. Exposure to benzene through gasoline is therefore of great public health significance in both urban and rural areas in Nigeria [38]. It is thus evident that populations in the developing countries like Nigeria are at great risk for hematoproliferative disorders like leukemia and may benefit greatly from the promise of chemoprevention as prophylaxis.

A large number of studies and case reports have linked gasoline exposure, over the years, to lymphopoietic cancers such as multiple myeloma and leukaemia in refinery workers and other gasoline-exposed workers [41-46], many of these studies have at least in part mechanistically examined the pervasive problem of occupational and environmental gasoline exposure and approaches to mitigation but rarely explored the possibility of prophylaxis with chemopreventive agents. With the apparent daily exposure to various sources of benzene in highly polluted countries like Nigeria currently, there could be possible increase in the likelihood of developing leukaemia which might pose a grave risk to the health of the population and future of developing countries as leukemia largely affects the younger population (20 years and below). It is this great environmental, public health, potential economic implications and clinical importance of this subject that informed the examination of the possible role of chemopreventive agents as prophylaxis against the risk of leukaemia development in the general population in highly polluted environments especially those exposed to benzene through gasoline.

Epidemiological studies and case reports provide reasonable evidence of a causal relationship between occupational exposure to benzene and benzene-containing solvents and the occurrence of acute myelogenous leukemia [44,46]. Benzene, through its metabolites, particularly phenol, has been suggested to play central roles in the induction of leukemogenesis, frequently superimposed as a terminal event on aplastic anaemia. Phenol has been strongly implicated in leukemogenesis associated with benzene exposure because they are involved in the haematotoxicity of benzene; cause DNA and chromosomal damage leading to derangement of mechanisms of cell growth and differentiation found in leukaemia, inhibit topoisomerase II (via its activation by myeloperoxidase and H_2O_2) and alter hematopoiesis and clonal selection [47]. All these in addition to the substantial contribution of oxidative stress to the pathogenesis of leukaemia can be reversed by key components of chemopreventive agents like zinc [48] and selenium [25] along with other micronutrients [20,49].

Repeated exposure to benzene may induce malignant changes in the bone marrow and eventual disruption of the hematopoietic system. This is because bone marrow cells, the main sites of hematopoiesis, are particularly vulnerable to oxidative DNA and chromosomal damage leading to derangement of cell growth mechanisms and differentiation that are precursors of leukaemia development [50]. Evidence from a number of animals, epidemiological and human studies as will be evident later show how common chemopreventive factors can mitigate these molecular and cellular lesions [51-54].

The possible roles of some key essential trace metals such as zinc, copper and iron in the haembiosynthetic pathway in the pathogenesis of leukaemia though suggested to be important [46] as several other studies [55,56] have been largely fragmentary and not synthesized. This paper attempts to bridge this gap and incorporate a vital missing link, the need for creative health

education for investigators, health professionals and policy makers, possibly including the FDA and similar agencies particularly in the developing countries, based on evidence which appears to have been lacking up till now.

There has long been much discussion of chemicals in the work place and the general environment as causes of cancer including hemopoietic cancers. Percivall Pott, a London surgeon was the first to relate occupation to cancer (association between occupation and cancer) which can be extrapolated to the general environment. He reported that chimney cleaners (chimney sweepers) were prone to cancer of the scrotum, which he attributed, correctly to lodgment of soot in the rugae of the scrotal skin [57]. The responsible chemical carcinogen was identified nearly 200 years later by Kennaway as a Polycyclic Aromatic Hydrocarbon (PAH) of the dibenzanthrene family [58]. Many other chemicals in this group are carcinogenic and include several important substances besides coal tar.

Industrial chemicals of many varieties contain (or are themselves) chemical carcinogens. The number of chemicals to which humans are exposed has increased in the past 100 years, particularly in the developing countries. Pimental, et al. [59] reported that some 80,000 chemicals were in use two and a half decades ago; that nearly 10% are recognized as carcinogens and that use of chemicals had increased 3-fold between 1941 and 1995. The estimate of Pimental, et al. [59] is most probably very conservative. There may indeed be about 6 million chemicals that exist in the world according to John Osterloh, (former Chief Medical Officer of the Centre of Disease Control and Prevention (CDC) Environmental Health Laboratory). According to him "Although estimates vary and no one really knows". "Many of these are not produced for commerce but rather exist as break down and incineration products of chemicals that are in commerce. The number of these substances that may reside for a long time in people is a mystery" [60]. This again is worse in the LMICs than the developed countries with well enforced regulations. Many of these chemicals have not been adequately evaluated for human toxicity (particularly carcinogenicity). Furthermore, while the number of occupational and environment associated cancers has decreased in most industrialized countries, in part due to transfer of hazardous industries to the developing countries, the reverse is the case in the developing [61] countries and may benefit more from embracing of chemoprevention. Occupational cancers are now a serious concern in the developing countries where industrialization is a rather recent phenomenon and where exposure levels to hazardous chemicals considerably exceed regulatory levels established in the industrialized countries [62]. The eradication of chemicals would assist in cancer prevention as a primary approach. This is however not a pragmatic proposition; thus, it is important to seek alternative means of cancer prevention or prophylaxis. The association between increasing use of chemicals and associated chronic disease arising from desirable progressive industrialization and chemoprevention or anticarcinogenesis is insufficiently recognized in these rapidly industrializing developing countries. One of the long-term objectives of this paper as earlier indicated is to narrow this unacceptable gap in knowledge and emphasize the mechanisms, benefits and progress in the field of chemoprevention or anti-carcinogenesis as a form of health education and arousing greater interest.

Estimates of the proportion of all cancers attributable to risk factors in the environment and specifically to occupation have been topic of some controversy. There are suggestions that 20 to 40% of all cancers were occupationally related [63], and more recent estimate put it at over 60% [64]. True and Dreisbach [65] have suggested this may be up to 60% or greater.

Historical Perspectives of Chemical Carcinogenesis

The history of chemical carcinogenesis is punctuated by key epidemiologic observations and animal experiments that identified cancer-causing chemicals that led to increasingly insightful experiments to establish molecular mechanisms and to reduction of human exposures [66]. In 1914, Boveri [67] made key observations of chromosomal changes, including aneuploidy. His analysis of mitosis in frog cells and his extrapolation to human cancer is an early example of a basic research finding generating an important hypothesis (the somatic mutation hypothesis). The first experimental induction of cancer in rabbits exposed to coal tar was performed in Japan by Yamagiwa and Ichikawa [68] and was a confirmation of Percival Pott's epidemiologic observation of scrotal cancer in chimney sweeps in the previous century [57] earlier alluded to above. Because coal tar is a complex mixture of chemicals, a search for specific chemical carcinogens was undertaken. British chemists, including Kennaway [69], took on this challenge and identified polycyclic aromatic hydrocarbons, for example, benzopryene, which was shown to be carcinogenic in mouse skin by Cook, Hewett, and Hieger in 1933 [70]. The fact that benzopyrene and many other carcinogens were polyaromatic hydrocarbons lead James and Elizabeth Miller [71] to postulate and verify that many chemical carcinogens required activation to electrophiles to form covalent adducts with cellular macromolecules. This in turn prompted Conney and the Millers [72] to identify microsomal enzymes (P450s, family of xenobiotic metabolising enzymes) that activated many drugs and chemical carcinogens. Though often ignored it should be remembered that some of these enzymes are dependent for their activities on the micronutrients that are key players in chemopreventive activities, making them useful targets for cancer prevention and or therapy.

Chemicals and Genome Instability: The Stabilizing Role of Chemopreventive Agents

The fact that chemicals cause random changes in our genome immediately implies that our efforts need to be directed

at quantifying these changes, reducing exposure, and developing approaches to prevention of which chemoprevention appears pragmatic and desirable.

Chemical carcinogens cause genetic and epigenetic alterations in susceptible cells imparting a selective growth advantage; these cells can undergo clonal expansion, become genomically unstable, and subsequently transformed into neoplastic cells [20]. This classic view of carcinogenesis has its origin in experimental animal studies conducted in the mid-20th century as evidenced by Boveri's studies [67] as earlier indicate above. The first stage of carcinogenesis, tumor initiation, involves exposure of normal cells to chemical or physical carcinogens. These carcinogens cause genetic damage to DNA and other cellular macromolecules that provide initiated cells with both an altered responsiveness to their microenvironment and a proliferative advantage relative to the surrounding normal cells. The initial steps of carcinogenesis of which the cell cycle is very central is amenable to factors regulating this cycle in which zinc plays a very crucial role [52,53] and thus a good candidate for chemoprevention which has been borne out by evidence from animal studies including some on the haemopoietic system [24,25].

Benzene and Leukemia: Chemoprevention as a Possible Prophylaxis

One of the commonest environmental pollutants as previously indicated above (low and high exposure) prevalent in our environment, particularly in the developing counties is benzene. The recognition that benzene was a leukemogen was established on the basis of research among occupationally exposed cohorts in Italy in 1976 [73]. Earlier reports also emanated from Turkey [74] with further observations by Aksoy and Erdem [75]. Additional reports also came from the United States [76] and ten years later from China [77).

Among the seminal observations by these early investigators were, decreases in circulating blood cells, dysplastic marrow and Myelodysplastic Syndromes (MDS). The latter is considered a pre-leukemic phase (state) and is characterized by abnormal marrow architecture, impaired hematopoesis with many of the cells exhibiting chromosomal damage. Myelodysplastic syndrome itself is described as a clonal disorder [78] that may arise as a response to exposure to chemotherapy involving the use of alkylating agents [79] or to prolonged exposure to benzene [80-82]. The chromosomal and hematopoietic related damage associated with chronic benzene exposure progressing through acute myeloid leukaemia has been well described by Robert Snyder [83]. Though Snyder did not specifically mention chemoprevention he laid the foundation by indicating that altered differentiation was central to the process of leukemogenesis. Differentiation is a process that requires key members of the chemopreventive agents such as zinc and vitamin A [52,84].

In discussing leukaemia and chemoprevention it is particularly of interest that the process of differentiation and amplification mark the progression from pluripotential stem cells through the various intermediate stages of maturation is highly dependent on functional haematopoietic microenvironment. This is most likely a stage where adequate supply of micronutrients involved in chemoprevention like vitamin A [84] and other key micronutrients of the haem biosynthetic pathway; Cu, Fe and Zn [24] are very important and may mitigate the abnormal events at this stage. It is also important to recall that aside from the fundamental molecular roles of zinc; antioxidant, involvement in signalling, transcription [52], the adequate metabolism of vitamin A is dependent on optimum Zn level [85]. One of the strong hypotheses on the toxicity of benzene is that the damage to the stroma may be one of the central events culminating in the reduction of circulating erythrocytes that ultimately manifests as aplastic anaemia. As shall be clear subsequently because of the roles of the micronutrients involved in chemoprevention it is highly probable that through their inhibition of oxidative stress at play in this process [83], restoration of appropriate signalling, transduction and genomic stability for which they are known that they may reverse the process leading to carcinogenesis of the bone marrow presenting as leukaemia. Consequently, environmental toxicants like benzene that act progressively by impairing cellular functions; decreasing circulating blood cells, leading to pancytopenia, aplastic anemia, myelodysplastic syndrome ending up in one of the forms of leukaemia may be prevented with these biological factors or micronutrients. The observation by Schwartz, et al. [85a] that benzene inhibits DNA polymerase, which is a Zn-dependent enzyme and that by Rao [86] appears to strengthen the potentials of the micronutrients particularly zinc as chemopreventive agents that may mitigate, delay or reverse the process of carcinogenesis attributable to benzene or related environmental pollutants. The effects of benzene and its metabolites is essentially through DNA damage in the marrow and impaired differentiation of a pool of myeloid cells as a mechanism of leukaemia, particularly non-lymphocytic leukaemia [83]. This makes the involvement of micronutrients such as Zn and vitamin A very good candidates as chemopreventive agents. The observation of Cheng [19] about the role of these nutrients in preventing genome instability at play in this pathological state becomes also very relevant.

Benzene and Hematopoietic Proliferative Disorders: Risk to the General Population.

The most well-known hematoproliferative disorder is leukaemia. The historical association between benzene and leukaemia has earlier been described.

Benzene is used as components of many products used globally; as an ingredient in inks, in the printing industry, in organic solvents, it is also a starting material and intermediate

for the production of rubber, lubricants, dyes, cleaning agents, and pesticides in many chemical and in the pharmaceutical industries. It is as well an additive in unleaded petrol. A current major application of benzene is its use in the manufacture of organic chemicals [87]. In these current uses, benzene is chiefly employed for the production of styrene, phenol, cyclohexane, aniline, maleic anhydride, alkylbenzene and cyclobenzene mostly in Europe. Benzene is also used for the production of anthraquinone, hydroquinone, Benzene Hexachloride (BHC), benzenesulfonic acid and drugs, including dyes, pesticides and plastics [88]. Beside benzene being an intermediate of many other products, it is naturally occurring in petroleum products such as crude oil, gasoline and derivatives and added to unleaded gasoline to increase the octane number of unleaded gasoline to prevent the knocking of engine (as an antiknock) [88]. Clearly from the wide range of products in which it is either a constituent or an additive agent the exposure of the general population is considerable. This is much higher in the developing countries where measures to lower benzene constituents in products or in the environment are minimal or non-existent. Evidently, this therefore raises the risk of benzene associated lymphoproliferative disorders in the general population, thus an indication for chemoprevention to lower the risk to the general population and probably also a subject for health education.

Biological Mechanisms of Benzene in the Induction of Hematopoietic Cancer: Differentiation as a Biologic Target for Chemoprevention of Leukaemia.

Leukaemia as is now clear basically refers to the excessive proliferation of abnormal immature leukocytes caused by a number of stimuli affecting the blood or the bone marrow. Importantly, it is significant to recognize that the precursor cells of both lymphocytes and myeloid cells are derived from the same Haemopoietic Stem Cells (HSCs) by cell differentiation process [89]. During hemopoiesis in the bone marrow all blood cell types are produced and the HSCs are differentiated into the precursor or ancestral cells of each cell type. It is important to recognize that differentiation is a central process here. Thus, factors that are involved in differentiation and signalling such as vitamin A and zinc [18,52,48] that are chemopreventive agents promise to be significant here. This appears particularly important and relevant in that benzene metabolites including benzoquinone and mucoaldehyde (Figure 1) interfere with HSCs development and differentiation steps of progenitor cells of each blood cell type [88,90,91,91a]. Consequently, benzene may have global effect on the entire haemopoietic system [91a]. This in turn raises the [likelihood that key micronutrients involved in the hemopoietic pathway [24,25] may have biological ameliorative or corrective effects on benzene-altered hemopoietic activity.

Benzene and Its Metabolites

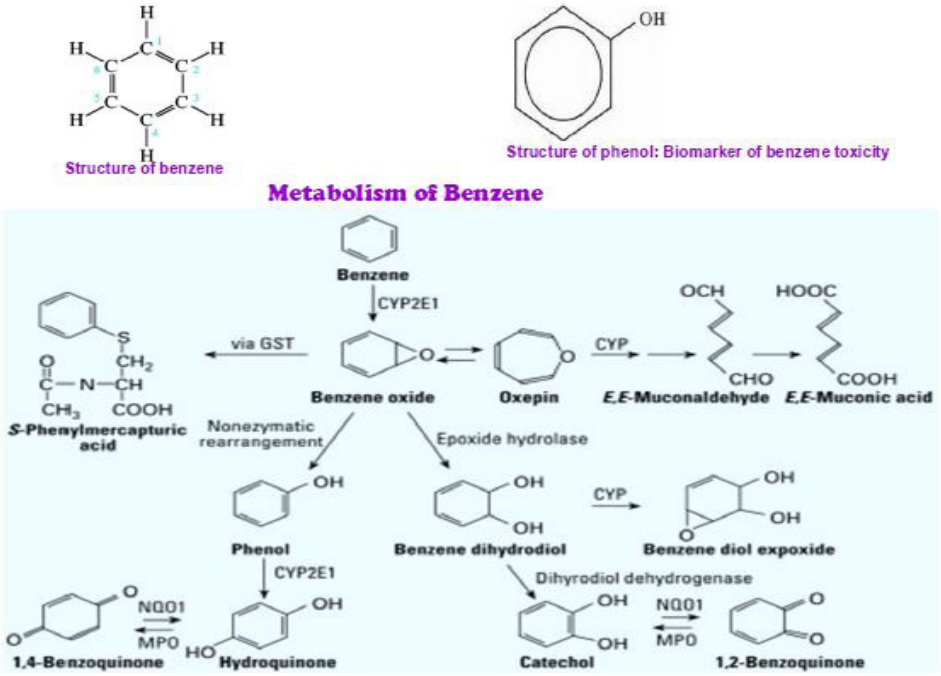

Figure 1: After Rappaport, et al. [92].

Biochemical pathway through which benzene may induce leukemia.

It is perhaps relevant to note here that zinc deficiency in cereal consuming populations [93] prevalent in many developing countries that also suffer from high environmental pollution raises the risk or susceptibility to leukaemia in these populations.

Zinc as a member of the chemo preventive agents family can be exploited to reverse, delay or prevent the ensuing carcinogenesis. Maintenance of genome stability is of fundamental importance for counteracting carcinogenesis [19]. Many human genome instability syndromes exhibit a predisposition to cancer [20]. An increasing body of epidemiological evidence has suggested a link between nutrient status and risk of cancer. Many populations in the LMICs that are deficient of these protective micronutrients and are increasingly exposed to environmental chemicals from the unfolding industrialization are thus at increased risk [94].

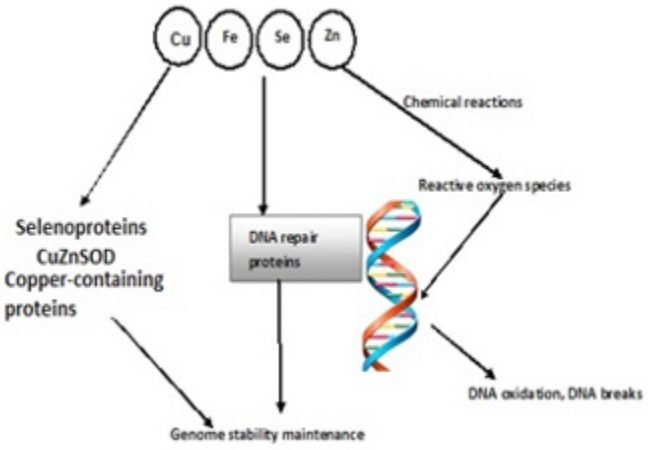

Figure 2: After Cheng [19].

Roles of micronutrients in maintenance of genome stability and possible prophylaxis to lymphoproliferative disorders key of which is leukemia.

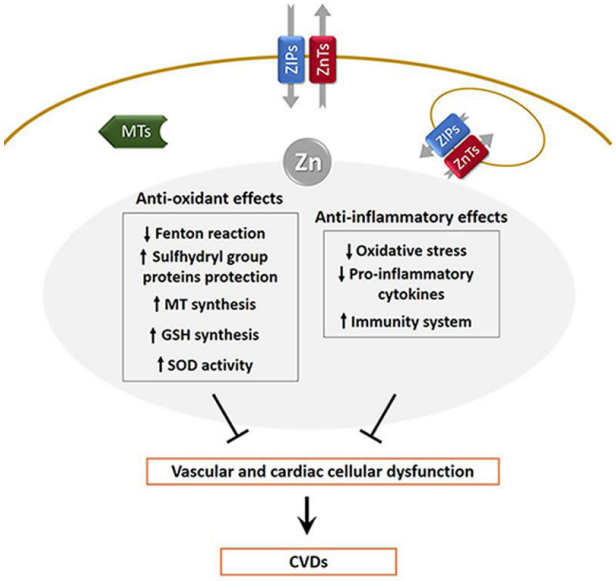

Figure 3: After Choi, et al. [95]. Some cellular and molecular roles of zinc that may mitigate fundamental processes in pathologic states including lymphoproliferative disorders.

Health Education

Health education defined by the WHO [96] as a means of consciously constructing opportunities for learning, involving some form of communication designed to improve health literacy, including improving knowledge and developing life skills conducive to individual and community has been largely absent in chemoprevention. This principle by which individuals and group of people learn to behave in a manner conducive to the promotion, maintenance or resolution of health need to be creatively applied to chemoprevention, particularly as it relates to leukemia. We have attempted do this in the past [97-101] to communicate this concept probably non-targeted. The current article attempts to synthesize our earlier efforts in a more creative manner to drive home the message and hopefully to a larger and more focused audience. That prolonged environmental chemical exposure may ultimately lead to the development of a number of serious diseases, one of

the most feared being cancer following a tortuous root needs to be communicated to the general population so that they can have an informed opinion and utilize same for their health maintenance and disease prevention.

It may also be important to educate the public on some key dietary factors that play crucial role in chemoprevention one of which is zinc. Plant–based foods very common in low income countries contain high phytic acid levels (myo-inositol hexaphosphate (InsP6) [102] that are associated with inorganic salts like, magnesium (Mg), potassium (K) and calcium (Ca). The salts of phytic acids referred to as phytates are potent inhibitors of the absorption of micronutrients like iron (Fe) and zinc (Zn) [102]. This qualifies as a candidate for health education. It appears consistent with the observation of Gibson, et al. [102] that the traditional processing of food can reduce InsP6 concentration through loss of water soluble phytates or through the use of phytase hydrolysis to reduce myo-inositol phosphate forms that can no longer inhibit vital micronutrients like zinc vitally important in chemoprevention needs to be made known to the people. It also appears currently very important as part of health education that some appropriate processing practices can reduce fortification of plant - based foods with attendant safety risks. This will contribute to the reduction of the prevalence of inadequate Zn intake by vulnerable populations particularly LMICs thus facilitating implementation of policies aimed at alleviating zinc deficiency and attendant disease risk.

It may in addition be important to teach to the public the good sources of key micronutrients like zinc (Table 1).

Oyster	From sea foods	Discretion and affordability –key
Crab		
Beef	Animal sources	“
Dark meat		
Pork		
Chick peas	Plant sources	“
Black beans		

Table 1: Good Sources of Zinc.

Dietary constituents such as phytates and fiber in whole grains and beans inhibit absorption.

Animal - based proteins enhance absorption of zinc among others. Recognition of this is important in low income countries.

After Linus Pauling Institute (LPI) modified [103].

As previously mentioned, the understanding that certain chemicals and radiation can lead to dysregulation of hematopoiesis, resulting in leukemogenesis is relatively recent. Though suggested by Hunter as early as 1939, from his observations on benzene exposure and Acute Myeloid Leukaemia (AML) [30], it was after the introduction of radiation and chemotherapy as therapy for neoplasia that these agents became associated with blood dyscrasias including acute myeloid leukaemia [31]. This may serve as a basis of a health education program for the general population in polluted environments along with the benefits of chemoprevention.

Biology of Leukemia and Chemoprevention: a Primer of General Public Health Education

Leukaemia is also widely considered a clonal disease resulting from genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell. The cause of leukaemia remains largely incompletely elucidated [104]. The large volume of research about the disease notwithstanding, clear understanding remains elusive. There are only mostly postulations about the probable origin of the disease, one of which is that there is a common form of lymphoblastic leukaemia which begins with a change in proliferating early B-cells in utero but requires subsequent genetic lesion to progress [105]. This immediately suggests a possible role for micronutrients and by extension chemoprevention, given the fundamental roles these micronutrients play in molecular events and genetics as illustrated by Figure 1 and Figure 2 above.

Experimental Studies in Chemoprevention: Role of Select Micronutrients

The maintenance of or ensuring of genome stability is fundamental for countering or prevention of carcinogenesis. Many genome instability syndromes exhibit a predisposition to cancer development [19]. A growing body of experimental and epidemiological evidence suggest an association between nutrient status and risk of cancer. Micronutrients such as copper (Cu), iron (Fe), selenium (Se), and Zn through redox regulation can mitigate genome instability syndromes and attendant cancer at optimum level [19,101]. This in part along with the antioxidant principle is the scientific basis and root operational mechanism of chemoprevention. Some studies that have applied this principle will help to drive this point home as shown in the sections that follow.

Ibrahim, et al. [106] examined the protective role of Zn and Se in attenuating benzene–induced haematotoxicity in male Sprague- Dawley rats. They injected 0.5ml/kg body weight of benzene intra peritoneally and administered dietary a supplement containing Se and Zn. Biochemical and histopathological findings were quite revealing. Ancillary data showed that food intake and weight gain of the benzene exposed group were significantly lower than in corresponding control rats. Importantly, the exposed group demonstrated increased plasma level of malondialdehyde (MDA) (reflective of oxidative stress) and reduced activity of glutathione

peroxidase (GPx), an important antioxidant enzyme dependent on Se. Additionally, catalase, dependent on Fe, superoxide dismutase (Cu,Zn-SOD), another potent antioxidant enzyme dependent on both Cu and Zn, including the intracellular tripeptide, glutathione (GSH) also revealed reduced activities in the exposed group compared to the unexposed group. Histopathological studies of the liver of these rats showed structural abnormalities in the benzene treated group. Remarkably, the group given supplement of Se and Zn demonstrated significant reduction in MDA level and showed raised levels of GSH, GPx, SOD and catalase.

Additionally, these investigators observed a reversal of all the depressed haematological indices in the supplement group compared to the benzene exposed group. These results at least in part show that selenium and zinc can ameliorate the pathologic abnormalities caused by oxidative stress in turn arising from benzene exposure through their antioxidant activities in Sprague-Dawley rats with a promise (extrapolation) of similar effects in human populations.

In study involving arsenic (As), another environmental pollutant like benzene implicated in a number of cancers, micronutrients demonstrated hematopoietic system protection. Though arsenic has not been overtly implicated in leukaemia, through its depressive effects on the immune [107] system it may indirectly be contributory or act synergistically with benzene. Bhardwaj and Dhawan [25] in their recent study have shown how zinc treatment modulated hematological and morphological abnormalities in rat erythrocyte after chronic arsenic exposure. In brief, these investigators set up four experimental groups: a control group, an arsenic treated group, a zinc supplement group and zinc combined with arsenic group (zinc+ arsenic group). The arsenic treated group was administered arsenic orally in drinking water in the form of sodium arsenite at a dose of 100mg/ L. While zinc was administered to the zinc group as zinc sulfate also orally in drinking water at a dose of 227mg/L. All treatments went on for 12 weeks. Aside from the biochemical studies, Scanning Electron Microscopic (SEM) studies were conducted to demonstrate erythrocyte morphology. The arsenic treated group exhibited significantly reduced serum Zn levels that were restored to near-normal level with Zn supplementation. Similarly, the altered antioxidant status that was evident in the arsenic treated group was significantly improved in the Zn supplement group. Haematological indices that were all reduced in the arsenic exposed group also all reverted to near normal levels in the Zn supplemented group. A protective effect was also discernible with SEM in the morphology of erythrocytes of the Zn supplement group. This study also appears to provide experimental evidence of the protective effect of zinc on the hematopoietic system that is so vulnerable to benzene and other hematopoietic toxicants that may predispose it to hematopoietic proliferative disorders such as leukemia. Anetor, et al. [98] had earlier provided evidence of the protective role of zinc on the haembiosynthetic pathway in lead workers.

A human study by Zuo, et al. [24] an investigation of a cohort of leukemia patients examined the levels and alterations of select key micronutrients on the hemopoitic system, copper (Cu), selenium (Se) and zinc (Zn), two potent antioxidant enzymes that we earlier examined above whose activities are dependent on these micronutrients relating them to the different types (phenotypes) of leukemia. The investigators determined the serum levels of Cu, Se, Zn, and red blood cell Glutathione Peroxidase (GPx) activity, plasma activity of copper – Zinc Superoxide Dismutase (Cu-ZnSOD), and Lipid Peroxidation (LPO) levels in 49 patients suffering from different types of leukemia before initial therapy (pre-treatment). The results revealed lower serum levels of Se and Zn in the leukemia patients than in control ($p<0.01$). Expectedly, Cu was elevated ($p<0.01$) owing to acute phase response (ceruloplasmin the Cu-transporter protein rises as an acute phase response). The activities of GPx, Cu-ZnSOD, were also significantly raised in leukemia patients (probably Upregulation), particularly in Acute Leukemia (AL), Acute Lymphocytic Leukemia (ALL), and Acute Nonlymphoid Leukemia (ANLL) ($P<0.05$). No difference was observed between Chronic Myelogenous Leukemia (CML) and controls. The investigators found similar LPO levels in controls and leukemia patients. Some remarkable findings were unlike in normal individuals [52] observed. Serum levels of Se were not correlated with GPx, neither was the Zn level also correlated with Cu-ZnSOD. Noteworthy in these leukemic patients also is that serum Zn level exhibited an inverse correlation with absolute peripheral blast count, probably suggesting increased consumption of and insufficient Zn to effect differentiation. Thus, probably need to provide more to arrest blast cells formation or promote their differentiation to normal leukocytes. In contrast, Cu exhibited a positive correlation with absolute peripheral blast cell, this is probably a reflection of the level of inflammation or acute phase response and probably also reflecting relative zinc deficiency (Zn is an anti-inflammatory, Prasad [53,54]. Though Zuo, et al. [24] interpreted the raised GPX and Cu-ZnSOD activities and the normal levels of LPO as protective mechanisms (responses) against oxidative stress (and severity of the pathology) operative in this disease; oxidative stress is implicated in the pathogenesis of leukemia [108], it also implies that the micronutrients, Cu, Se, and Zn may also serve as chemopreventive agents in this condition. Again though the conclusion of Zuo, et al. [24] that the demonstrated low levels of Se, Zn and high Cu levels are some of the pathological changes associated with leukemia and referred to imbalance between Reactive Oxygen Species (ROS) and the scavenging antioxidant enzymes, they appeared to have overlooked the other possible interpretation of their data - a role for mitigation or prophylaxis of the disease. The observation of Cheng [19] regarding the roles of these nutrients in maintaining genomic stability appears instructive here. The recent report of

Orlov and his colleagues as detailed below [48] may corroborate this hypothesis. Additional to this is the very recent study of Bhardwaj and Dhawan, [25] which demonstrated the protective role of Cu and Zn on the hemopoitic system against toxic insult, a key factor in lymphoproliferative disorders.

In our very recent study Akiibinu et al. [108a] in 25 freshly diagnosed patients with acute lymphoblastic leukemia (ALL) aged 10-14 years and 25 non-leukemic, non-septicaemia patients aged 4-14 years apparently healthy children as control, we examined cobalt (Co) level, C-reactive protein (CRP), total plasma peroxide (TPP), malondialdehyde (MDA), total antioxidant potential (TAP) and computed oxidative stress index (OSI). The ALL patients exhibited unequivocal oxidative stress and inflammatory response compared to control. Very importantly, Co, a micronutrient and cofactor for Cyanocobalamin (B12), involved in genome stability through its involvement in one- carbon metabolism [20] was reduced. We concluded that the demonstrated oxidative stress and reduced cobalt level appear to elegantly argue for micronutrient supplementation as adjunct therapy in the treatment of ALL which may be extrapolated to prophylaxis for populations in polluted environments at risk of leukemia as a form of proactive oncology. It should be remarked that Zn may also be helpful here as an anti-inflammatory factor [95].

Orlov, et al. [48] in their very comprehensive review on the mechanisms of Zn action presented compelling evidence of the specific mechanistic, including the kinetics and molecular roles of zinc and it's compounds in leukemia. The role of zinc in apoptosis a process disrupted in carcinogenesis was clearly delineated by Orlova and Orlov [109]. Maret [110] had earlier outlined the contribution of zinc to molecular aspects of cellular homeostasis especially the redox control of Zn and its participation in signalling. This corroborates the role of Zn in fundamental molecular events that are disrupted in carcinogenesis that may be reversed or repaired by optimal Zn levels and providing a basis for its chemopreventive property.

As in many types of cancer, initiation phase or the progression phase is related to perturbation of and mutations of transcription factors dependent on zinc; zinc fingers (Zfs) or zinc binding enzymes. Leukemia is no exception to this general situation and zinc may indeed have a special role in this hematopoietic or lymphoproliferative disorder. Recent studies have focused on the initiation and development of cancer and other proliferative diseases due to disruption of post-translational regulation and mutations. Zinc plays a vital role in signalling and post-translational events. Zinc is responsible for post-translational modification; is a critical transcriptional regulator of genes required for proper development [52-54,93].

The p53 Gene and Protein: Role in Chemoprevention

The p53 tumor suppressor gene controls cellular growth after DNA damage through mechanisms involving cell cycle arrest and apoptosis [49]. The p53 phosphoprotein is zinc dependent and may be dysfunctional in conditions of zinc deficiency or unavailability [49,111]. An alteration of p53 tumor suppressor gene results in defective cellular responses after DNA damage and predisposes cells to deregulated growth, initiation of carcinogenesis and progression [18,112]. Of particular importance here is that p53 is often highly expressed in chemical carcinogenesis [112].

It is perhaps of particular relevance here that resveratrol (3, 4' ,5-trihydroxy-trans-stilbene), a naturally occurring polyphenol found in over seventy plant types, especially grapes, cranberries and peanuts as well other herbs can induce p53 [4,113]. This may be synergistic with the retinoids [114]. Polidori and Stahl [114] have observed the inducing of differentiation of Acute Promyelocytic Leukemia (APL) cells instead of killing them by employing all-trans-retinoic acid (derivative from retinoids) in therapy for APL resulted in in appropriate differentiation (terminal differentiation) of APL cells with 90-95% complete remission rate in patients, consequently suggesting that differentiation which can be employed in therapy may have greater promise in prophylaxis. Polidori and Stahl [114] also observed that the combination of all-trans-retinoic acid with chemotherapy further improved the 5-year overall survival especially after incorporating arsenic trioxide. Importantly, they also observed that the combination of all-trans-retinoic acid and arsenic trioxide triggered catabolism of the PML-RAR-α fusion protein, a critical factor in APL leukemogenesis.

Since the discovery over two decades ago by Jang and his colleagues [115] that resveratrol has in vivo antitumor activities, growing scientific evidence has demonstrated the ability of this polyphenol to modulate certain intracellular mediators in the process of carcinogenesis; initiation, promotion and progression [115-117]. Consequently, many chemopreventive and chemotherapeutic mechanisms to prevent, arrest or delay the carcinogenic process by resveratrol from which leukemia may also benefit have been suggested [112,116-118]. Resveratrol is involved in a number of fundamental biological processes such as regulation of signalling pathways involving procarcinogen bioactivation, carcinogen detoxification [119,120], reduction of oxidative stress [121], inflammation [122] and apoptosis via the intrinsic and extrinsic pathways [4]. Growing consistent evidence also suggest that resveratrol can induce p53-dependent cell death in various types of cell line [123-128]. It is particularly significant that Bernhard et al. [129] showed that resveratrol causes arrest in the S-phase prior to Fas-independent apoptosis in CEM-C7H2 acute leukemia cells. This suggests the particular promise of resveratrol in preventing leukemia at the fundamental level. Harikumar and Aggarwal [128a] have demonstrated the multitarget activity of resveratrol; they examined the antitumor and immunomodulatory effects of the chemopreventive agent on mouse lymphocytic leukemia cells L1210 in in vivo studies. Resveratrol exerted dose-dependent

regulatory effects on both innate and adaptive immune functions in L1210 mice. They showed normalization (restoration) of CD4/CD8 ratios in these tumors post- treatment with resveratrol including improvement of lymphocyte proliferation NK cell among others. This appears to further underscore the potential of chemopreventive agents like resveratrol in protection against leukemia.

Early reports revealed that resveratrol promotes the activation and stabilization of biological levels of p53 in cancer cell culture through the process of posttranslational modifications, including phosphorylation and acetylation (epigenetics) [4]. These modifications are important for the transcriptional activation of genes that are responsive to this 'guardian of the genome' (p53) [130,131]. Thus, the role of p53 in guarding the genome of the population in polluted environments in LIMCs available in chemopreventive agents such as resveratrol is significant. It is perhaps also noteworthy that p53 is a zinc dependent protein.

Another protein that is highly dependent on zinc is the zinc finger (Zf) (Figure 4) [131a], a transcription factor. Many of its isoforms are involved in numerous molecular events. Accurate regulation of nuclear factor-kB (NF-kB) is crucial to the prevention of a variety of disorders including proliferative disorders. Zinc through its Zf proteins is mediated by NF-kB and enables the process of apoptosis. Zinc finger protein is also important in differentiation of hematopoietic progenitor cells [48].

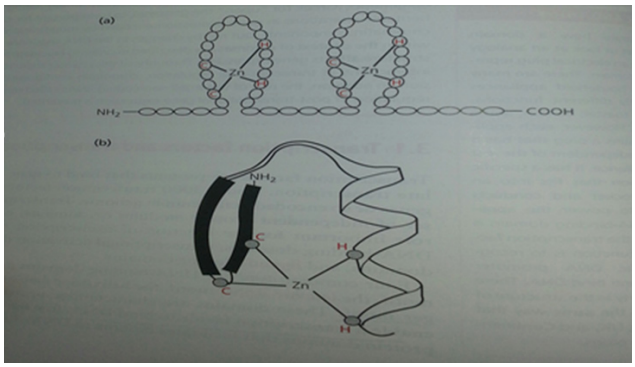

Figure 4: Structure of zinc finger protein showing incorporation of zinc atoms (After Pecorino [131a]).

Zinc and the IKAROs & KRAB -Zinc Finger Protein Families

The Ikaros family of Zf transcription factors is crucial for leukemogenesis [132]. Members of the IKAROs regulate functions of hematopoietic stem cells, processes of cell survival and self-renewal, appropriate to lymphogenesis, cell cycle [133] and are tumor suppressor in B-ALL [134]. The IKAROS-C2H2Zf Motifs [135] are among the most important antileukemic transcription factors [136-138].

It appears pertinent to stress here that a change in in the concentration of zinc in blood, which is usually observed in different types (phenotypes) of leukemia as corroborated by the study of Zuo, et al. [24] is largely related to a change in zinc finger production (i.e. with gene expression) [48]. This appears to underscore the importance of zinc and its pivotal role in carcinogenesis, particularly in chemical carcinogenesis that is more common in polluted in environments. This has indeed been exploited therapeutically in antileukemic drugs largely based on the molecular regulatory roles of Zn [48]. This seems to represent a paradigm shift for molecular targeted therapy.

Pyrithione Zinc (PZ) III

Pyrithione Zinc (PZ) III is yet another Zn-dependent protein that has been identified as a potential anti-leukemic agent in AML [139,140]. The PZ III complex is one of the heterocyclic zinc complexes (Figure 5) that are antitumor (anti-carcinogen) agents participating in different signalling pathways e.g. PZ III. Frequently, the genesis of leukemia is insidious at the level of transcription disruption, Zf proteins; highly dependent on Zn status may mitigate this process at the primordial level by restoring normal signalling pathways and in the process aborting cancer cell proliferation [141].

(III)

Figure 5: Pyrithione zinc (PZ) III. An antileukemic protein incorporating zinc in its structure important for its function. (After Orlov, et al., [48].

An important observation relevant to the role of chemopreventive agents is that for the growth of malignant cells or tumors is that a decrease in the concentration of zinc in blood can be used for early cancer diagnosis [48]. This had indirectly been stressed in many of the recent reports of Ananda Prasad, the discoverer of zinc deficiency and its great biological and clinical significance [52,53,93]. This probably suggests Zn as an emerging biomarker in the prediction of risk of cancer that may aid chemoprevention by monitoring Zn levels in at risk populations. This may be considered a secondary prevention by early detection and intervention before the condition becomes clinically apparent, contributing to the goal of chemoprevention. Along with the role of Zn for inhibition of altering of conformation or of signalling pathway, Zn plays a role in pharmacokinetics (PK) and Pharmacodynamics (PD) of antitumor agents [142,143].

In summarizing the pivotal roles of Zn, it is perhaps appropriate to state that current comprehensive studies herald zinc as a cofactor for many important biomolecular processes such as participation in:

- Antioxidant system
- Signalling
- Apoptosis
- Anti-inflammatory events
- Hemopoiesis
- p53 activity

From the foregoing very many factors including nutritional factors have been shown to modulate the carcinogenic process. Thus, this can be exploited to reverse, delay or prevent carcinogenesis in many sites including that of the hemopoietic system that has received insufficient attention. Maintenance of genome stability is of fundamental importance for counteracting carcinogenesis. Many human genome instability syndromes exhibit a predisposition to cancer. The growing body of epidemiological evidence has suggested a link between nutrient status and risk of cancer. Populations in developing countries that are deficient in these protective micronutrients [4] and are increasingly exposed to environmental chemicals owing to progressive or rapid industrialization are thus at increased risk of chemical carcinogenesis and may benefit immensely from chemoprevention as a prophylaxis against leukemia.

Based on public health data from the Healthy People 2010 Project, it is estimated that up to 80% of colon and prostate cancers, the more popular (better known) cancers but in adults may be influenced by diet, nutrition, and life styles. From the evidence presented it can be deduced that this may be extrapolated to leukemia, commoner in the younger generation. It has also been proposed that DNA damage induced by dietary micronutrient deficiency accounts for one-third of preventable cancers. Because micronutrient deficiencies can induce DNA damage in forms similar to those induced by ionizing radiation and Reactive Oxygen Species (ROS), it has been suggested that oxidative stress and associated DNA breaks are critical targets for nutritional control of carcinogenesis. It is also evident from the evidence presented that this also applies to leukemia. If left unrepaired, DNA lesions can promote accumulation of mutations that facilitate the process of carcinogenesis. Micronutrients may act directly on the genome to prevent mutations, or indirectly as enzyme cofactors in cellular processes that modulate transformation [20]. Thus, micronutrient status may serve as biomarkers of risk of carcinogenesis [144]. For instance, low selenium status is a biomarker of risk of many cancers including cancer of the prostate and leukemia [24] just as for Zn [48].

Mechanism of Oxidative Stress and DNA Damage due to Micronutrient Deficiency

Based on the same public health data emanating from the above study (Healthy People 2010 Project), it has been estimated that a disproportionate form of cancers particularly the better-known ones; colon and prostate cancers, may be influenced by diet, nutrition, and life style [8]. This can be extended to the lesser known ones like leukemia, hence indication for health education. The seminal observation that DNA damage induced by dietary micronutrient deficiency accounts for about 33% of preventable cancers [49,145,146] argues for the important role of chemoprevention. Building on the knowledge that micronutrient deficiencies can induce DNA damage in a manner similar to those induced by ionizing radiation and Reactive Oxygen Species (ROS), it has also been inferred that oxidative stress and the associated DNA breaks are critical targets for nutritional factors in carcinogenesis [18,19] and perhaps a marker for early detection [48]. When DNA lesions are disregarded, left uncorrected or unrepaired they can promote accumulation of mutations that may favour the carcinogenic process including chemical carcinogenesis. Micronutrients as components of the chemopreventive class may act directly on the genome to prevent mutations, or indirectly as enzyme cofactors in cellular processes that modulate transformation or ensure genome stability [19,147,148] or molecular targeted therapy. By yet incompletely defined mechanisms, micronutrients at levels higher than nutritional requirements may also activate DNA damage response or senescence, which are processes that are recognised to eliminate cancer cells or limit the progression of precancerous cells [149-151]. The recommendation of De Flora, et al. [153] that just as combined chemotherapy is optimal in the treatment of cancer and CVD, as well as other leading pathologies, combined chemoprevention based on mechanistic attributes is a promise for the future in chemoprevention, may improve the situation. Additional to this is the admonition by Gerhäuser [153] about methods employed in studying alterations in cell signalling and the use of preoneoplastic markers [154]. This has to be understood and incorporated in the proposed creative health education. There is probably also the need to creatively search for enduring chemopreventive agents, single or combined just like the Ames test in carcinogenicity testing [155]. The micronutrients including copper, iron, selenium and zinc as well as many vitamins and micronutrients play important roles in genome stability. In particular, these micronutrients including microminerals have significant impact on oxidative DNA damage and the corresponding repair pathways [19,20].

Micronutrient intakes below recommended levels are known to be unusually widespread in poor countries, though also reported from some advanced countries especially among the poor, children, adolescents [49,101] who are at greater risk of leukemia. It has been hypothesised that among some of the many insidious but measurable consequences of moderate micronutrient deficiency are increased DNA damage (a precursor of cancer) and mitochondria dysfunction which can cause mutagenic oxidant release also play a role in the process of carcinogenesis. Several

investigations indicate that sensitive assays targeted at these end points have a high probability of detecting changes in individuals with micronutrient deficiencies and exposed to environmental chemicals [8,24,49,52] which if combined with chemoprevention is of great public health significance, particularly in LMICs.

From the exhaustive review embracing the kinetics and highly mechanistic activities of Zn earlier described above it is not surprising that Orlov and his colleagues came to the conclusion that zinc is a cell protector and defender of the body against oxidative stress [48]. This is similar to a conclusion we earlier came to in one of our reports regarding risk of leukemia in gasoline dispensers [100]. This is probably also similar to the observation of Bruce Ames [49] about a decade ago that optimizing micronutrient as preventive (prophylactic) agents or chemoprevention of cancer which includes leukemia will optimize metabolism resulting from DNA damage and thus risk of this cancer. Bruce Ames observed that the triage theory which posits at least in part that moderate micronutrient deficiencies (common in much of the population, particularly, LMICs, [49,52] may accelerate molecular deterioration including DNA damage [19,49]. This presupposes that the converse would hold, that is it may be protective or prophylactic. The important observation of Ames [49] that optimizing micronutrient intake could have a major effect on the prevention of degenerative diseases including cancer appears appropriate and argues for a place for chemoprevention even if not specifically targeted at leukemia it can be reasonably extrapolated to it.

Conclusion

Just like happened when Prasad and his colleagues were trying to convince the scientific community about the essentiality of zinc to human health and it took the National Academy of Sciences (NAS) of the United States' intervention in 1974 when it threw its weight behind Prasad's seminal findings [52,54], it may be approaching the same situation as regards chemoprevention. At the moment on the basis of sound scientific evidence, one is compelled to agree with Orlov and his colleagues [48] that the use of zinc complexes among others can significantly extend the capabilities of anticancer therapy (by extrapolation, prophylaxis) due to their numerous biological protective and repair actions and mechanisms. What appears to have been missing or neglected for a long time in the field of chemoprevention is creative health education. This has the great potential to raise awareness of the benefits of chemoprevention and how it may be applied to reduce the risk of haemopoietic proliferative disorders including leukaemia that parallel environmental pollution. The benefits of the promise of Chemoprevention can only be truly realized if creative health education is embraced by both investigators and health professionals alike. Chemoprevention may indeed be linked with personalized nutrition, similar to personalized medicine which is currently greatly advocated as the regimen of the future in health systems for a healthier world. While awaiting the resolution of the vestigial scientific gaps that still exist in chemoprevention regarding weight of evidence and the precautionary principle, it is perhaps more rational to err on the side of the precautionary principle.

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