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Review

Chemical carcinogenesis and chemoprevention: Scientific priority area in rapidly industrializing developing countries

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Occupational cancers are now a serious concern in industrializing developing countries where exposure levels to hazardous chemicals considerably exceed regulatory limits established in industrialized countries. The association between increasing use of chemicals and associated disorders and chemoprevention or anticarcinogenesis is insufficiently recognized in these countries. The eradication of chemicals would assist in cancer prevention. This is however, not pragmatic, thus the need to seek alternative means of cancer prevention. Cancer chemoprevention or anticarcinogenesis is the process of exposure of an animal including humans to a substance that will reduce the incidence of cancer that would otherwise develop. Lack of knowledge of the multiple pathways by which chemically induced cancer may arise has led to the erroneous view for a long time that the study of chemoprevention was academic. While this field is gaining an increasing and sustained attention in the developed countries it has received little attention in the industrializing developing countries where the incidence of cancers appears to parallel the pace of industrialization. Sub-optimal intake of specific micronutrients so common in developing countries may contribute to greater susceptibility to cancer. Micronutrient deficiency disorders (MDDs) is considered orders of magnitude more important than radiation because of constancy of exposure to a milieu promoting DNA damage. Zinc (Zn) for instance is an antioxidant, a component of p53 and a critical factor in gene expression. Poor Zn nutrition may be an important risk factor in oxidant release and development of DNA damage and cancer. A deficiency of Zn ranks among the top ten leading causes of death in developing countries. As chemo preventive agents are present in natural human foods abundant in developing countries, this should be one of the highest research priorities of the rapidly industrializing developing countries.

Key words: Chemical carcinogenesis, chemoprevention, DNA damage, oxidative stress, Industrialization, p53 protein, mutation.

INTRODUCTION

The rapid and desirable spate of industrialization in developing countries has brought in its wake a number of challenges. For generations the combination of malnutrition and infectious disease has sapped the vitality of these nations. Now additional challenges are being added. Industrialization often without the restraining laws and regulations of the advanced countries are causing serious environmental damage and occupational disease (Last, 1987). This arises from increasing use and traffic in chemicals.

There has been much discussion of chemicals in the work place and the general environment as causes of cancer. Pott (1775), a London surgeon was the first to relate occupation to cancer (association between occupa-

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tion and cancer). He reported that chimney cleaners (chimney sweepers) were prone to cancer of the scrotum, which he attributed, correctly to lodgment of soot in the ruggae of the scrotal skin. The responsible chemical carcinogen was identified nearly 200 years later by Kennaway as a polycyclic aromatic hydrocarbon (PAH) of the dibenzanthrene family. Many other chemicals in this group are carcinogenic and include several important substances beside coal tar.

Industrial chemicals of many varieties contain (or are themselves) chemical carcinogens. 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 (Bridbod et al., 1978) and more recent estimate put it at over 60% (Lichtenstein et al, 2000).

The number of chemicals to which humans are exposed has increased in the past 100 years, particularly in developing countries. Pimental et al. (1995) reported that some 80,000 chemicals are in use currently, that nearly 10% are recognized as carcinogens and that use of chemicals has increased 3-fold between 1941 and 1995. Many of these chemicals have not been adequately evaluated for human toxicity (particularly carcinogenicity) . Furthermore, while the number of occupational 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 developing countries (Tomatis and Huff, 2001). Occupational cancers are now a serious concern in developing countries where industrialization is a rather recent phenomenon and where exposure levels to hazardous chemicals considerably exceed regulatory levels established in industrialized countries (Parco, 1994).

The eradication of chemicals would assist in cancer prevention. This is however, not a pragmatic proposition, thus it is important to seek alternative means of cancer prevention. Additionally, the association between increasing use of chemicals and associated disorders arising from desirable progressive industrialization and the benefit of chemoprevention or anti carcinogenesis is insufficiently recognized in rapidly industrializing developing countries. This paper examines this unacceptable gap in knowledge and draws attention to mechanisms, benefits and progress in the field.

Chemical carcinogenesis and chemoprevention

Cancer chemoprevention also known as anti-carcinogenesis is the process of exposure of an animal to a substance that will reduce the incidence of cancer that would otherwise develop. Lack of knowledge of the multiple pathways by which chemically induced cancer may arise has led to the erroneous impression for a long time until recently that the study of cancer chemoprevention was only academic. In chemoprevention, it is desirable to be able to identify and test compounds or agents effective against a specific carcinogenic mechanism. While this field is gaining an increasing and sustained merited attention in the developed countries, it has received very little attention in the rapidly industrializing developing countries where the incidence of cancers appears to parallel the pace of industrialization.

Chemical carcinogenesis

Cancer is a family of diseases with a characteristic denominator of uncontrolled cell growth where regulatory signals instructing the cell cycle are disabled. Carcinogenesis or the sequence of events leading to cancer is a multiple step process involving both intrinsic and extrinsic factors. At the molecular level, cancer is caused by abnormal gene expression. This occurs through a number of mechanisms including direct damage to DNA and inappropriate transcription and translation of cellular genes. Consistent evidence shows carcinogenesis to be caused by certain chemicals, carcinogens. Over 67% of cancers are now attributed to environmental factors of which chemicals occupy a predominant proportion (Lichtenstein et al., 2000). Majority of chemical carcinogens cause mutation in DNA presumably in critical genes. Other chemicals alter cell growth and differentiation through epigenetic mechanisms. Some effects of these cancers appear to be mediated by cytotoxic insults and a compensatory regenerative response while others have been shown to act via receptor mediated events and transcription of critical genes.

Micronutrient deficiency and gene damage

Approximately 40 micronutrients are required in the human diet (Kaput and Rodriguez, 2004). Suboptimal intakes of specific micronutrients have been associated with cancer (folate, carotenoids etc) (Fairfield, 2002).

Deficiency of vitamins B12, Folic acid, B6, niacin, carotenoids or zinc appear to mimic radiation in damageing DNA by causing single and double strand breaks, oxidative lessons or both (Ames, 2001).

Micronutrient deficiency has been described as orders of magnitude more important than radiation because of constancy of exposure to milieu promoting DNA damage ((Ames and Gold, 2000; Ames and Wakimoto, 2002). Folate deficiency breaks chromosomes due to substantial incorporation of uracil in human DNA (Blount et. al, 1997). Single-strand breaks on opposite DNA strands leading to chromosome fragmentation have also been reported (Ames and Wakimoto, 2002). It is thought that micronutrient deficiency may explain why a quarter (25%) of the US population that consumes less than the recommended five portions a day of vegetables and fruits has approximately twice the rate for most types of cancer compared with the quarter with the highest intake (Ames and Gold, 2000).

Micronutrient deficiency, industrialization and risk of cancer

Chemoprevention is the use of synthetic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcino-genesis or by reversing the progression of premalignant cells in which such damage has already occurred. The marked micronutrient deficiency disorders (MDDs) in developing countries puts populations in these rapidly industrializing countries with attendant exposure to increased chemical burden at great risk for chemical carcinogenesis.

DNA repair in cancer risk assessment

DNA is constantly injured by external stress such as exposure to chemicals among others and free radicals which can also be derived from excessive exposure to chemicals. DNA lesions interfere with replication and with transcription and can trigger cell death, whereas mutations in critical regions can also trigger or promote carcinogenesis.

These events are usually prevented by DNA repair mechanisms, which remove or bypass the damaged site and restoring the original sequence (Paz-Elizur, 2005). Zinc plays a key role in this process, and it is a very essential micronutrient but unfortunately poorly recognized particularly in developing countries, which appear to need it most as an arsenal against genomic instability (Gibson, 1994; Sandstead, 1997).

Translating DNA repair biology to cancer prevention

DNA repair facilitates appreciation of the potential opportunities created by this complex but biologically elegant system. The importance of mutations in key genes coding for DNA repair enzymes in the carcinogenesis process is emphasized by the accelerated genomic instability associated with micronutrient deficiencies (Fenech, 2003).

Antioxidant host defense

Numerous studies have demonstrated consistently that oxidative processes participate in various stages of carcinogenesis and that micronutrients provide cancer prevention by virtue of their antioxidant properties. For instance increased consumption of fruit and vegetables rich in carotenoids and other antioxidant micronutrients lowered urinary indexes of oxidized lipids (malondialdehyde and 8-Isoprostane) and DNA (8-hydroxy deoxyguanosine, 8-OHd G) in healthy subjects (Thompson et al., 1999). 8-hydroxydeoxyguanosine is a marker of oxidative DNA damage. This view led to our recent observation that micronutrients, many of which are antioxidants may act as host defense against the health effects of some environmental contaminants implicated in carcinogenesis in developing countries (Anetor et al., 2007).

Zinc

Populations in developing countries are at a disadvantage in host defense against chemical carcinogens. Zinc for instance is a very important and an essential micronutrient, which is both an antioxidant and a critical factor in gene expression. A deficiency of this element ranks among the top ten leading causes of death in developing countries (WHO, 2002).

Zinc functions as a catalyst in more than 300 enzymes and in more than 2000 zinc- dependent transcription factors involved in gene expression of varied proteins. Poor zinc nutrition may be an important risk factor in oxidant release and the development of DNA damage and cancer (Ho et al., 2003). A large proportion of the population in developing countries ingest less than 50% of the recommended daily allowance for Zn. Zinc is a co-factor in proteins involved in antioxidant defenses, DNA repair and p53 protein expression(Ho et al, 2003). The p53 protein, a DNA damage sensor that acts to prevent the accumulation of genetic lesions contributing to carcinogenesis may be dysfunctional in Zn deficiency. The p53 protein extends a diverse array of signaling pathways associated with cellular stress and DNA damage. Unfortunately this DNA damage sensor is among the most vulnerable to oxidative damage. Ubiquitous chemicals e.g. inorganic arsenic (iAs), a known human carcinogen induces a rapid burst of reactive oxygen species and attendant up regulation of cellular glutathione (GSH) a ubiquitous reducing sulphydryl tripeptide involved in ROS detoxification. Increased ROS implicated in various pathologies also mediates chemical induced cell signaling and transcriptional activation. Chronic alteration of signal transduction pathways due to changes in cellular redox levels may also play an important role in chemical induced oncogenesis. Alteration of cellular redox status by low chemical dose plays a critical role in the pathology of chemicals.

The potent ubiquitous environmental toxicant, cadmium has been shown to replace zinc in the tumour suppressor protein, p53 thereby impairing p53's DNA binding activity (Meplan et al., 1999). This impairment decreases the ability of cells to respond to DNA damage-impairing repair mechanisms and favouring chemical carcinogen-nesis.

Mechanism of chemoprevention

Inhibition of oxidative stress currently seems to be the most acceptable explanation. Oxidative stress appears to lead to multi damaging lesions in DNA and other cellular bio-molecules culminating in cell death and regeneration. Additionally evidence exists that oxidative stress leads to mutation and conversion of some normal cells to preneo-

plastic cells (Kuchino et al., 1987; Floyd, 1990).

Sources of chemopreventive agents

As Chemopreventive anti-oxidants are present in natural human foods abundant in developing countries, this is an ideal area for study in these countries. Most of the efforts towards the identification of cancer Chemopreventive agents are made largely in the United States and Japan (Clayson, 2001). This appears to be a response to the carcinogenic challenge and concern. The studies have focused on naturally occurring substances such as those normally present in food supply. Many investigators have concentrated on black and green tea and demonstrated their beneficial effects in animal models. Iwase (Clayson, 2001) studied extracts of rind and seeds of seventy-eight (78) varieties of citrus fruits (very abundant in our environment), which inhibited lymphopblastic activation of Epstein-Barr virus (EPV) in vitro. A lot of reports abound in the scientific literature adopting this approach. Ichihara et al. (2002) have recently demonstrated the Chinese herb ginseng and curcumin to have beneficial effects in rodents. Fukushima et al. ((2001) have recently reported on the suppressive effects of chemical carcinogenesis by water-soluble organosulfur compounds. It is important to note here that these investigators used substances very common in this part of the world; garlic and onion. It is well known that both oil soluble and water-soluble organo-sulfur compounds (OSC) are abundant in garlic and onions. Some of these particularly oil soluble OSC; have been demonstrated to be chemopreventive in the initiation stage of carcinogenesis. For instance Sparnins et al. (1988), Wargovich et al. (1987), Wattenberg et al. (1989), and Wargovich et al. (1998) have reported that dially sulfite (DAS), a flavor component of garlic (Allium Sativum) inhibits the development of colon carcinomas, eosophageal carcinomas, pulmonary adenomas and fore stomach tumors in rodents when administered before carcinogen exposure.

Ascorbic acid

A very common antioxidant is ascorbic acid (vitamin C), which has been described as one of the most interesting chemopreventive agents known. Its effect was discovered by Mirvish et al. (1972). These investigators failed to reproduce an observation by a colleague that co-feeding a pharmaceutical compound and sodium nitrite led to in vivo nitrosation in the acid conditions of the rodent stomach resulting in tumour formation.

Mirvish and his colleagues observed that the pharmaceutical which he collected from the hospital was compounded with ascorbic acid. This reacted as an antioxidant with the nitrite and effectively prevented nitrosation. This seminal observation has been repeated severally with a variety of nitro-stable amines and amides. Thus emphasizing the need to maintain adequate levels of this micronutrient, a point underscored in our earlier report (Anetor and Agbedana, 2001). Byer and Perry (1992) have also stressed that vitamin C is among the micronutrients protective against cancer.

Earlier chemopreventive experiments

Among the earlier substances used as potential chemopreventive agents were enzyme inducers, which were thought would reduce the proportion of electrophiles generator converted to their active form. Though some positive effects were found, the overall benefits were not adequately consistent to justify their application to humans, where the specific initiating carcinogen may not be known.

P53 and DNA damage repair

Beyond its role in tumour suppression, and having regard for the many complex signaling pathways with which p53 appears to be involved, Levine proposed that p53 may be ubiquitous sensor of stress and as such is involved in the prevention of other possibly aging related disorders. Thus rather that just acting to prevent genetic lesions accumulating in somatic tissues which can lead to cancer, p53 may act to dampen many physiological stresses that may, if unchecked, lead to others disorders.

The cumulative wear and tear in which p53 is involved is known as allostatic load (McEvens, 1998). The idea that p53 protein may be important in the control of allostatic load is very exciting as it may account for the large diversity of signals that appear to activate p53.

Selenium and chemoprevention

Before 1957, the only recognized biological effect of selenium was its toxicity. A landmark change in the concept of selenium metabolism occurred when it was shown to prevent hepatic necrosis in rats. Interestingly, selenium was also once considered to be carcinogenic, but now it is better known as an anti-carcinogen. In the late 1960s, epidemiological surveys suggested an inverse relationship between selenium and the incidence of certain cancers such as breast (Whanger, 2005). Between the 1970s and 1980s, the relationship between selenium and cancer in experimental animals was extensively investigated, resulting in discoveries that several seleno compounds inhibit or retard carcinogenesis. These studies in animal carcinogenesis indicated that mega doses (levels) (about 30 times nutritional requirement) of selenium gave the greatest protection. Over two hundred animal studies have been conducted to evaluate mega doses of selenium on experimental chemical carcinogenesis (also viral and transplantable tumour models). Over 66% of these studies demonstrated at least moderate reduction in tumorigenesis with high selenium level (15 - 30%) compared with controls but mostly very significantly (>

35%). Only a few cases reported no effect responses (Whanger, 2005). Most of these effects have been related to the antioxidant activities of selenium in such seleno enzymes as Glutathione peroxidase (GPx). In human, like animal models, selenium supplementation appears to offer some chemopreventive effects. To date, three human investigations have showed relationship between cancer and Se supplement. In one, selenium was added to salt and a significant reduction in hepato-cellular carcinoma (HCC) in a Chinese population was demonstrated (Clark et al., 1996) . Subsequent investigations have revealed that five years of combined supplementation with selenium, vitamin E and carotene significantly reduced the incidence of gastrointestinal and oesoph -ageal cancer in a Chinese population. In this latter study, the presence of other antioxidant micronutrients introduced some confounding effects.

A lesson from this experiment is that we can prevent or reduce the risk of chemical carcinogenesis by at least deliberately consuming adequate sources of selenium. The controversy about weight of evidence not withstanding, the precautionary principle appears desirable at the moment. It is note worthy that china with the lowest levels of selenium in soil and food has one of the highest prevalence of liver and GIT cancers in the world. Thus at least epidemiologically demonstrating a relationship between selenium deficiency and carcinogenesis. A third study by Clark et al. (1996) in humans in the United States demonstrated beneficial effects of selenium against carcinogenesis. Though this study was not directed at chemical carcinogenesis it can be extended as a prophylaxis in rapidly industrializing countries with increased risk of cancer from increased exposure to chemicals.

The study by Clark et al. (1996) is particularly signifycant in that Americans as a response to scientific evidence consume enough selenium in the diet to meet nutritional requirements. Averagely, American citizens consume about 100 ug of selenium daily from diet; this human trial of 200 – 400 ug revealed reduction of cancer incidence by about the same degree in individuals taking 200 or 400ug Se daily. This suggests that 200ug of additional Se was sufficient to inhibit certain carcinogenic processes.

An earlier case control study involving over 8,000 sujects in Finland (Salonen, 1984) supports the protective effect of selenium against cancer risk. In this report low selenium correlated with increased total cancer mortality. The relative risk in low selenium individuals was greatest if they also haboured low plasma levels of vitamins A and E. This suggests that other factors influence the anticarcinogenic effect of selenium, probably reflecting the synergistic effect of antioxidant micronutrients in enhancing antioxidant capacity.

Selenium, like Zn is an essential micronutrient that modulates a variety of cellular functions. Selenium compounds are effective antioxidants and inhibitors of experimental and clinical carcinogenesis. Elemental selenium compounds at comparatively low concentrations inhibit mutagenesis, chromosome break and cell proliferation from chemical carcinogens and provide anticarcinogenic activity. At higher doses Selenite is a potent inhibitor of cell growth and DNA synthesis. Selenodiglutathione is a more potent inhibitor of cell growth than is Selenite and exhibits both anticarcinogenic and cytotoxic effects.

Chemoprevention thus appears the best creative solution to protect human health in the face of inevitable chemical burden.

Environmental exposures and chemoprevention

While great strides have been achieved in our understanding of human genetics the contribution of environmental exposure is poorly recognized. 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. If identified, targeted prevention and treatment strategies might be applied to these risk groups with potentially life saving or health promoting results. Without subject specific exposure data researchers have a limited ability to identify population susceptibility genes that elevate disease risk.

This disequilibrum between exposure and genetic research shows the identification of environmental factors that if altered or removed could even prevent some diseases from being established at all. It is often forgotten that certain micronutrients key among which is zinc play a role in this.

Zinc in genetics and molecular biology

Zinc is an essential element in the nutrition of humans, animals and plants. It is required in the genetic make up of every cell and it is an absolute requirement for all biological reproduction. Zinc is needed in all DNA and RNA synthesis and is required at every step of the cell cycle. Poor zinc nutrition may be an important risk factor in oxidant release and the development of DNA damage and cancer. The pathway of signal transduction controls both cell cycle and apoptosis. This pathway is an orderly and specific transmission of growth regulatory messages from outside the cell to the processes (machinery) controlling replication inside the nucleus. Apoptosis, a programmed cell or physiological death is a natural self-destruct system present in all cells and it is indirectly Zn dependent. Failure of cells to undergo apoptotic cell death may result in cancer. Thus adequate zinc status, in excessive environmental exposure to chemicals may be protective as a chemopreventive agent.

Developing countries and zinc

Zinc is an essential nutrient that must be continually obtained in the diet. A deficiency of this element ranks among the top ten leading causes of death in developing countries (WHO, 2002) . An estimated 800,000 annual deaths worldwide could be prevented by correcting zinc deficiency. Certain populations in the developed countries are also at risk for poor health linked to inadequate zinc intake.

Chemical carcinogenesis and prophylaxis

The obvious question is should individuals at risk take supplements of chemopreventive agents? Though data available thus far appear encouraging it is premature to make a definitive recommendation. Rather, it will be generally advocated that this area should be given high scientific priority. There is the need for the health and agricultural sectors to collaborate closely in this respect. We have very recently suggested this in one of our reports (Anetor et. al, 2006). Welch and Graham (2005) had earlier also under scored the need for cognizance of the vital role of the agricultural sector in micronutrient bioavailability. Chemopreventive agents, many derived from agricultural produce are commercially available e.g. selenium-enriched yeast. Special supplement enriched vegetables are being developed. Animal investigations have reported for instance that selenium-enriched onions, broccoli, garlic; Brazil nuts are very effective in inhibiting tumourigenesis. The major seleno compound in these food substances has been shown to be one of the most effective seleno compounds tested thus far against experimental chemical carcinogenesis. Farombi (2004), one of the astute promoters of the use of anticarcinogens globally has suggested that each of the known anticarcinogens alone or in combination could provide a sustainable chemopreventive intervention that might be useful in retarding the progression of cancer in different populations of the world.

The only general recommendation while awaiting specifically targeted coordinated studies will be to recommend that copious consumption of natural sources of antioxidant micronutrients be seriously encouraged by health education. They are very abundant in numerous types of fruit and vegetables in most developing countries.

CONCLUSION

Chemical carcinogenesis is a current concern in rapidly industrializing developing countries. The success of several recent clinical trials in preventing cancer in high-risk populations like ours suggests that chemoprevention is a rational and appealing strategy for resource poor Industrializing countries. The disease cancer when fully established is very expensive to treat with conventional chemotherapy and radiotherapy. Developing Countries should institute research programmes aimed at identifying and addressing knowledge gaps and establishing internationally harmonized testing methods to take advantage of this field.

Though several aspects of carcinogenesis and chemoprevention are still unresolved based on weight of evidence, the precautionary principle is advocated to avoid late lessons from early warnings and should be one of the highest research priorities of developing countries.

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