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Potential Correlation between Lactose Intolerance and Cancer Occurrence

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Lactase, the B-galactosidase enzyme, is responsible for splitting lactose molecule into glucose and galactose. Levels of lactase activity are a crucial determinant of lactose intolerance. Lactose intolerance causes diarrhea and subsequent chronically induced diarrhea results in colitis with chronic inflammation. Chronic inflammation often is linked to etiology of colon cancers. Two other hereditary disorders, uridyl transferase and galactokinase deficiency, such infants cannot utilize galactose, the sugar accumulates leading to cataracts, diarrhea, hepatomegaly, jaundice, and mental retardation as the child matures. Most soon die. A variant severe lactose intolerance is frequently linked to infant death. Prevalence of lactose maldigestion in adults based on the breath-hydrogen criteria in Korea, Japan, China, and South-East Asian countries ranges from 75~100%, while, the US and European countries range 0~75%. Thus, incidence of lactose intolerance in Asians is far greater than that of Caucasians. We have undertaken a retrospective studies to correlate between cancer incidence, death and dairy product consumption over the years in Korea, Japan, and the United States. The annual milk consumption per capita data from 1962 through 1995 in Korea was correlated to the total cancer incidence rates per 10,000 population from 1975 to 1996. The correlation coefficient was 0.953 and was highly significant. The average milk per capita consumption in Japan between 1930 and 1995 was significantly increased (4 fold increase). The correlation coefficient between the milk consumption per capita and the sum of cancer incidence in males and females was 0.943 and was highly significant. In the U.S., the milk consumption from 1909 to 1997 was relatively constant, but consumption of milk derived products such as whole dried milk, ice cream, cream, and cheese. The correlation coefficient of milk-derived product consumption per capita and cancers per 100,000 population was 0.922 and was highly significant. These retrospective correlation between cancer incidence and dairy milk consumption are significant, however, clearly dairy consumption is not the sole etiology factor for increase incidence of cancer(s). Other dietary factors, such as types of fatty acids, vitamins, antioxidants and other natural chemopreventive chemicals in a variety of vegetables and fruits including restricted diets also play a significant role in cancer prevention. Prevention of chronic colonic inflammation can be a major contributing factor for colonic carcinoma. Further mechanistic studies are needed to elucidate a precise reason why certain cancer types are being increased. Furthermore, potential link between lactose intolerance-induced chronic colitis and increase in colon

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cancer incidence should be further studied by determining PGE_2, $PGF2\propto$, leukotrien B_4, and cyclo-oxygenase 2 in flat colonic mucosal cells.

Key Words: Lactose, Lactase, Lactose intolerance, Dairy product consumption, Chronic colonic inflammation, Cancers

INTRODUCTION

1) Lactose intolerance and history of soy milk development in Korea

My topic of the presentation at Korean Association of Cancer Prevention is an epidemiological study of the relationship between lactose intolerance and cancer incidence. So-called lactose intolerant infants are unable to metabolize lactose in their gastrointestinal tract. Consequently, GI microorganisms metabolize lactose in colon to a variety of by-products, which may cause unfavorable side effects. I worked as pediatrician in a clinics since 1937. During the 1930s, our country was suffering from Japanese colonization, and the majority of pediatric patients visiting clinics and hospitals were suffering from diarrhea. Some of pediatric patients, who drank maternal or dairy milk continued to suffered from diarrhea despite the best ambulatory care available in those days. Eventually, these infants died from malnutrition along with other medical complications. I have studied and discussed with many colleagues for nearly 20 years to identify the etiology and a mode of treatment for infants with chronic diarrhea, but without success. In 1960, I decided to go abroad to study and research at the postmedical graduate school, University of London for 3.5 years, but no satisfactory discovery was made at that time. Subsequently, I went abroad again to study with Dr. Deamer, an allergy specialist at University of California Medical Center, San Francisco, CA for a year and a half. In 1964, for the first time, the presentation was on “Lactose Intolerance” in 8th edition of Nelson's Pediatric Text book. Normally, lactase containing mucosal cells are located in crypts and villi of the small intestine (ileum and jejunum), but a major etiology of lactose intolerant infants are congenitally lack such enzyme in mucosal cells in small intestine. Normal infants secrete sufficient lactase enzymes from mucosal cells in the small intestine to digest lactose to glucose and galactose, which are then absorbed into blood and each monosaccharide becomes a substrate for energy metabolism. In contrast, in lactose intolerant infants are congenitally lack lactase and unable to cleave disaccharides to monosaccharides and thus undigested lactose goes down into large intestine, wherein GI microflora will ferment lactose to generate excess H_2, and CO_2, and a short chain fatty acids as by-products. These by-products cause gaseous irritation, GI inflammation, and consequently induce chronic diarrhea. After one or two months later, infants become malnourished due to deficiency in protein(s) and essential nutrients due to malabsorption and dies. From this fact, formerly unknown etiology of lactose intolerance can be overcomed by finding the milk without lactose. During that time, I was working under Dr. Deamer convinced that soy, which contains 3 essential nutrients, protein, fats, and carbohydrates uniquely lacks the lactose and would be an ideal substitute for milk for lactose intolerant infants.

Later, in 1965, I returned to my country and established a nutritional laboratory and experimental animal rooms in my pediatric clinic. In the beginning of 1966, I started a soy milk research in rats. During the course of two-year research, I have obtained a patent for soy milk invention as well as a permit for nutritional food. I have devoted myself to treat lactose intolerant infants and results were amazing. Previously dying lactose intolerant infants were no longer dying, but miraculously survived.

Epidemiological studies in Korea demonstrated that lactose intolerant populations were estimated

to be 0.5 ~ 1% and thus, it is estimated that lactose intolerant population is expected to be approximately 200,000. However, for the past 30 years, over one million bottles or packs were produced daily and supplied. At the present time, there is no report of death attributed to lactose intolerance. Prior to the August 15, 1945, a number of death due to lactose intolerance among nursing infants were very high, and average life span was under 50 years of age. At the present time, decreased infant death rate is associated with a significant increase of life span to over 70 years of age. An increase in average life span is not only attributed to decreased infant death rates, but also to advancement of medical science, improved medical care, nutrition, life style, and economic development, but one cannot denied the fact that soy product has significantly lowered the death rates of nursing infants.

So far, I have explained hereditary lactose intolerance, but also there is non-hereditary lactose intolerance in adults. In normal infants, lactase containing mucosal cells are very well developed and are able to digest lactose to galactose and glucose in small intestine to be absorbed to be utilized as energy substrates. However, after weaning, maternal milk is no longer consumed, but started to consume grains, vegetables and fruits, which do not contain lactose. Therefore, lactase secretion from lactase containing mucosal cells are no longer actively utilized and gradually decrease lactase in these mucosal cells. Consequently, lactose intolerance does develop in children and continue to be lactose intolerant thereafter. Of course, there are other theory that genetic polymorphism, racial difference, or recovering from GI inflammation are frequently accompanied by degeneration and sloughing of mucosal cells that often include lactase containing mucosal cells. A study of lactose intolerance among black population demonstrated that under 5 years of age, the incidence of lactose intolerance is approximately less than 10%, but in 8 ~ 9 years age group, lactose intolerant children are increased to 72%, and likewise lactose intolerance is increased to 90% after 20 years of age. Thus, lactose intolerant population increases with increasing age. A comprehensive MIT review paper on review of epidemiologicalstudies on lactose intolerance in the world population was used in our present study.[1)] This publication was the result of statistically-based epidemiological studies of 300 cases during 20 years between 1967 and 1987 with respect to national, ethnic race, age, and geographical difference. These studies showed that incidence of lactose intolerance among black and caucasian race in the United States were 60 ~ 90% and 15 ~ 30%, respectively. Through my life long clinical practice and the statistical data, it can be stated that cancer incidence among lactose intolerant population was higher than that of lactose tolerant population. I therefore became very curious as to the relationship between dairy product consumption and cancer incidence. Namely, that by-products of lactose intolerant adults are H_2, CO_2, a variety of peroxidated short chain fatty acids and both excess hydrogen and peroxidated fatty acids can be the causal agents for higher cancer incidence among lactose intolerant population. For example hydrogen, most of excess H_2 produced is exhaled via lung and therefore, measuring H_2 levels in exhaled breath is used to diagnose lactose intolerant population ($>$30 uL H_2/L of expired breath is considered to be lactose intolerant, while $<$20 uL H_2/L expired breath is considered to be normal). However, a part of the excess H_2 formed and in circulation and in the alveoli cells of the lung may interact with excess O_2 and generate H_2O_2 in the present of flavin adenine dinucleotide (Fig. 1). Subsequently, by Fenton reaction, free radicals can be formed, and these free radicals can readily interact with DNA, cell membrane and cause genetic instability, hyperproliferation, clonal selection, promotion and progression that ultimately lead to cancer. Especially, the products of peroxidated short chain conjugated enals are known to be a potent class of carcinogens.

Prior to the end of World War II, the number of mortality attributed to cancer was less than 1,000 in Korea (North and South Korea). However, when

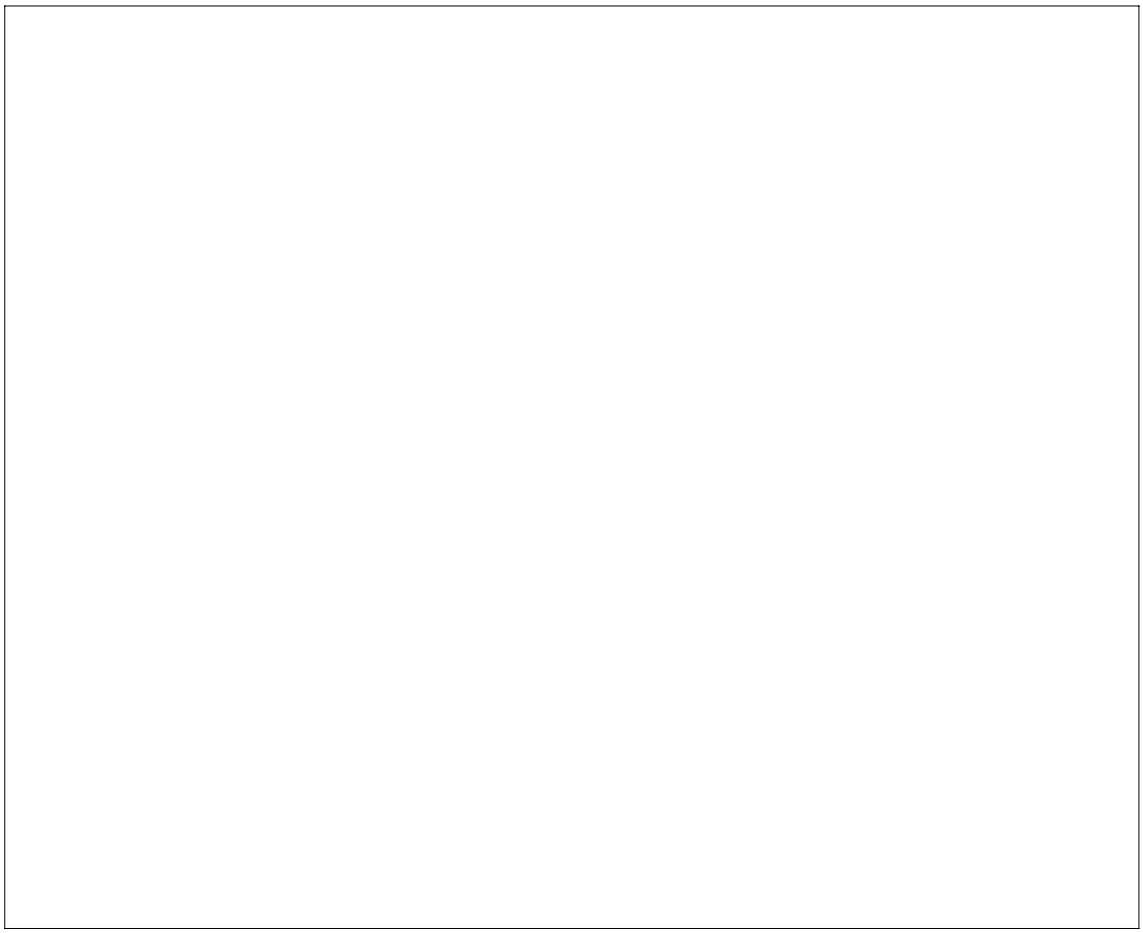

Fig. 1. A possible biochemical pathways for Excess H_2 Production By GI Flora in Lactose Intolerant Human Subject. The Excess H_2 is exhaled mostly, however, in the present of flavin adenine dinucleotide in the lung alveoli cell, wherein O_2 tension is high and can catalyze H_2 and O_2 to form H_2O_2·H_2O_2 in turn will generate a super oxide and hydroxy free radical via Fenton Reaction. These free radicals can cause age related disease including cancer, diabetes, cardiovascular disease and senile dementia.

the U.S. troops had established a military base and naturally brought with them a variety of dairy products to Korea. Since then (1945), consumption of a variety of dairy products in Korea had a significant increase and in 1996, the cancer registry's data shows 52,000 cancer death.[2] Furthermore, there was a unpleasant news that cancer deaths among age 40's was the highest in Korea.

In the U.S. prior to 1915, there was neither statistical data regarding the dairy products nor demography regarding incidence of obesity or cancer deaths. However, since 1915, consumption of dairy products began to increase in volume, and in 1972, during the President Nixon era, cancer death rates had increased to 300,000, while total American soldiers killed in Vietnam war was only 28,000. President Nixon has declared a war against cancer and National Cancer Institute was placed directly under Presidential order. Since then, National Cancer Institute has spent 25 billion dollars for the past 20 years to understand cancer etiology and develop new anticancer drugs. However, cancer-death report in 1997 showed 43% increase

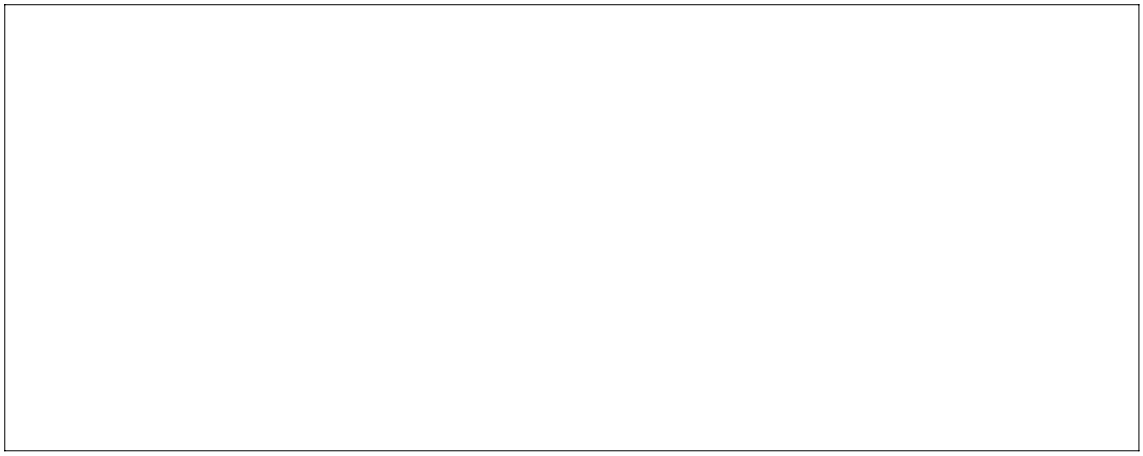

Fig. 2. Annual average milk per capita consumption and cancer incidence rates in Republic of Korea during 1975-1997. The left y-axis is annual milk consumption per capita in liters and the on the right y-axis represents cancer incidence rates per 100 thousand population.
Data Source: Journal of Korean Dairy Technology and Science Association Annual Report of the Central Cancer Registry in Korea

and the total cancer deaths reached over 500,000.[3] This phenomena, among many other etiological factors for cancer, may, partly have a causal attribution to increased consumption of steadily increased consumption of dairy products since 1915.

STATISTICAL CORRELATION BETWEEN MILK CONSUMPTION AND CANCER INCIDENCE OR MORTALITY

I have attempted to investigate whether increased milk consumption as well as lactose intolerance may be correlated to increase in cancer incidence or deaths. Statistical analyses were performed.

1) Republic of Korea

In 1960's, there was no reported case of milk consumption, however in 1990's, a dairy milk consumption has increase to 55 liter per capita/year, while cancer deaths increased from 20 per 100,000 in 1970 to 170 per 100,000 population/year in 1990.[2,4] This is approximately 8.5 fold increase in cancer deaths in 20 years (Fig. 2). Relationship between average milk per capita consumption and cancer incidence in Korea was analyzed and the data showed a significant correlation (Correlation coefficient of 0.953) (Fig. 3).

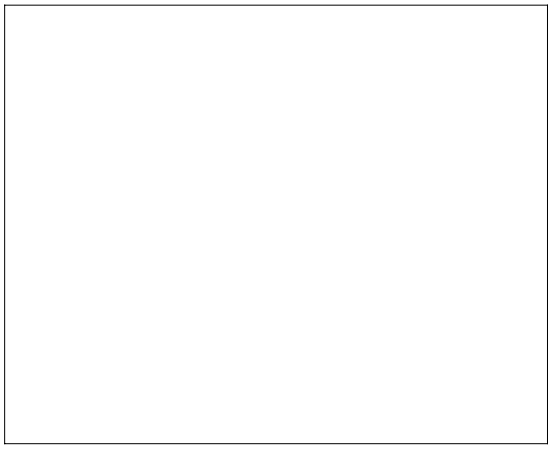

Fig. 3. Statistical analysis of two variables: annual milk consumption per capita and cancer incidence in Republic of Korea between 1975 ~ 1996. Linear regression analysis was performed with statistical software program. Correlation coefficient was 0.953 and was highly significant.

2) Japan

Consumption of milk and cancer death rates bet-

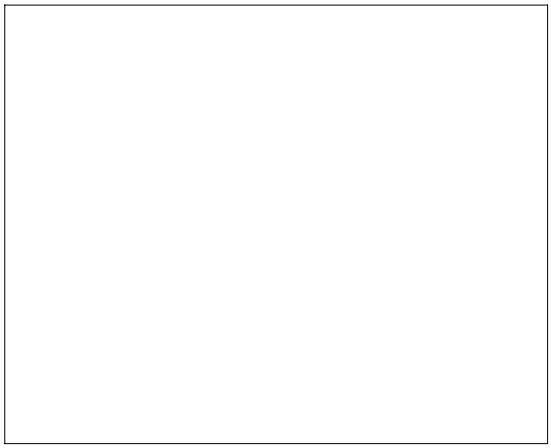

Fig. 4. Annual average milk consumption per capita and age-adjusted cancer deaths in Japan between 1960 ~ 1995. The left y-axis represents the annual average milk consumption per capita in liters and the right y-axis represents cancer deaths per 100 thousand population. Data Source: Japan Vital Statistics and Information Department. Ministry of Health and Welfare Male cancers in lung & bronchus, pancreas, colon and liver, and female cancers in breast, colon, lung & bronchus, pancreas and liver. 1999 March Ministry of Agriculture, Forestry, and Fishery. Food Production and Consumption.

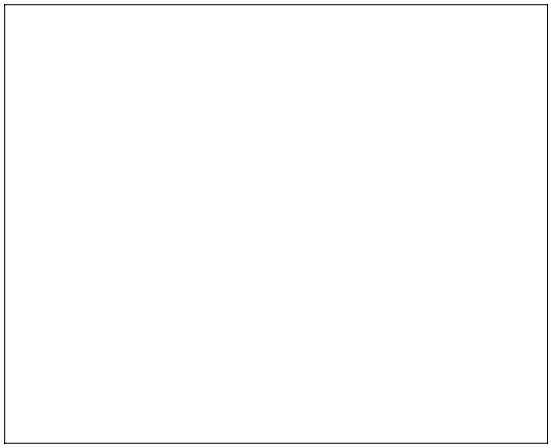

Fig. 5. Statistical analysis of two variables: annual milk consumption per capita and cancer incidence in Japan between 1960 ~ 1995. Linear regression analysis was performed with statistical software program. Correlation coefficient was 0.943 and was highly significant.

ween 1960s and 1990s demonstrated that milk consumption per capita/year in 1960 and 1990 were 10 and 40 liters, respectively, and demonstrated 4 fold increase in milk consumption in 30 years.[5,6] For the same period, cancer death rates increased from 20 per 100,000 in 1960s to 150 per 100,000 population/year in 1990s and increase of 7.5 times (Fig. 4). Statistical analysis of correlation between increase in milk consumption rates versus increase in cancer death rates demonstrated to be very high (r=0.943) (Fig. 5).

3) The United States

There was no significant increase of milk consumption over the period between 1970s and 1990s. However, consumption of dairy products over the period between 1970s and 1990s was significantly increased with concomitant increase of cancer death rates from 20 per 100,000 in 1930s (Data not shown) to 130 per 100,000 population/year in 1990s and demonstrating 7 ~ 8 fold increase (Fig. 6)[3,7] Statistical analysis of correlation between the dairy consumption rates and the cancer death rates among both males and females shows a significantly high correlation (r=0.922) (Fig. 7).

It is clear that a biological significance of the high correlation between the increased milk or dairy product consumption and the increased cancer death rates in Korea, Japan and the United States are uncertain since etiology of cancer is a very complex process and in addition causal agents are too numerous to list. To list a few from already known cancer causal agents are attributed to ever increasing environmental contaminants with countless chemical carcinogens, PCBs, dioxins, smoking cigarettes, alcohol consumption, mental stress due to living in a highly busy industrial society, radiation, and ultraviolet radiation, most of all, imbalanced dietary habits, and sedentary life style. Consumption of milk or dairy products may be one of the contributing factor in over-all direct or indirect carcinogens or a potential carcinogen generating chemicals in other foods as well. The assumption that higher cancer risk among lactose intolerant population was based on the fact that

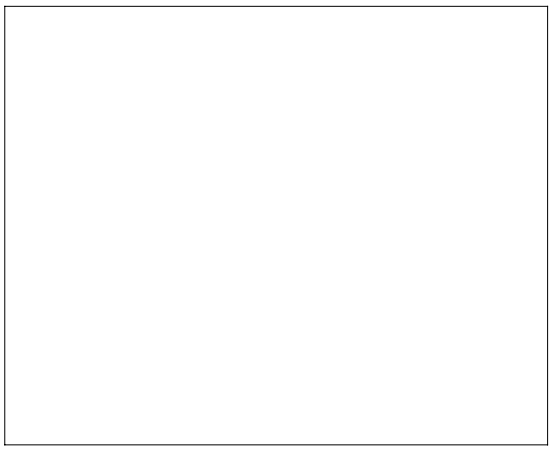

Fig. 6. Annual average dairy product consumption per capita and age-adjusted cancer deaths in the U.S. between 1930~1995. The left y-axis represents the annual average dairy products per capital consumption in kilograms and the right y-axis represents cancer deaths per 100 thousand population.
Data Source: USDA/Economic Research Service Vital Statistics of the United States, 1998. Male cancers in lung & bronchus, pancreas, leukemia and female cancers in lung & bronchus, pancreas

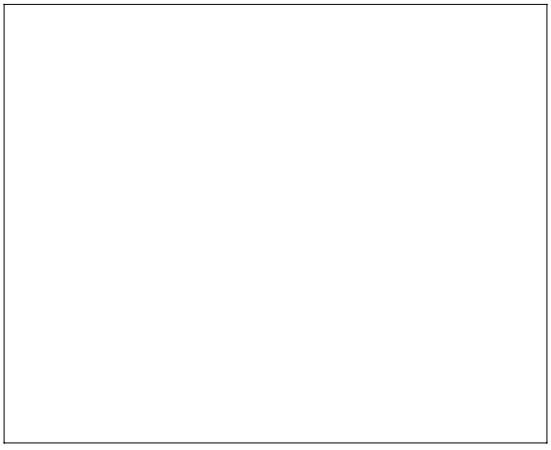

Fig. 7. Statistical analysis of two variables: annual dairy product consumption per capita and age-adujusted cancer deaths in the U.S. between 1930~1995. Linear regression analysis was performed with statistical software program. Correlation coefficient was 0.922 and was highly significant.

lactose intolerant population, they are unable to metabolize normally of lactose in milk or dairy products and thus, excess H_2 is produced by microorganisms of gastrointestinal tract.[8] Excess hydrogen gas is mostly exhaled via lung, however, the excess H_2 may react with O_2 in the presence of carbohydrate oxidase(s) coupled with the oxidized coenzyme, flavin-adenine dinucleotide (FAD), which accept H_2 to reduced form, $FADH_2$, which in turn reacts with O_2 to form H_2O_2. H_2 can also react with $O_2^{-\bullet}$ superoxide anion to form H_2O_2.[9] For the past decade, from numerous research studies in the field of medical science, genetics, nutrition, biochemistry and toxicology were related to toxicity of free radicals and antioxidants. One of the reason for a greater impetus on free radial research is that 90% of age-related disease are thought to be attributable to free radicals, while 60% of age-related disease are attributable to food factors.

REACTIVE OXYGEN SPECIES

1) The superoxide anion

The superoxide anion is formed when molecular oxygen acquires an additional electron. O_2+electron$^- \rightarrow O_2^{-\bullet}$.[9] It is formed during mitochondrial oxidation of acetate, a final metabolic product of Emden-Myerhof anaerobic pathway, that undergoes further oxidation to CO_2+H_2O to generate ATP. Superoxide is also formed at the endoplasmic reticulum, where xenobiotic activation and detoxication reaction takes place. In addition, superoxide anion is formed from a variety of biochemical metabolic pathways such as xanthine oxidase, flavoprotein oxidases, autooxidation of hydroquinone, catecholamine, thiols, reaction of oxygen with hemoglobin and myoglobin in a variety of cells. Furthermore a major microbicide, H_2O_2 is also secreted by leukocytes during phagocytosis at infected sites. Therefore, superoxide anion formation during a variety of normal cellular metabolism, which essentially require oxygen for maintenance of life. It has been calculated that every 100 tons of oxygen we breath, 2 tons form

reactive oxygen species. For every 10^{12} oxygen molecules entering a cell each day 1/100 damages protein and 1/200 damages DNA.[9] It is this damage to DNA, protein and lipids that makes the reactive oxygen that makes the reactive species so dangerous, especially if the body's natural defenses are compromised. Even under normal conditions, these reactive species are produced by the body as a part of normal metabolism as previously mentioned, but their rate of production does not exceed the capacity of the tissue enzymes such as superoxide dismutase (SOD), peroxidases, and catalase to catabolize them. When their superoxide anion production exceeds the body's natural defenses a variety of diseases can occur, such as cancer, stroke and neuro-degeneration. Normally the superoxide anion is short-lived and is converted to hydrogen peroxide by the enzyme superoxide dismutase (SOD) which maintains the steady-state levels of superoxide at $<10^{-11}$ M. Altered SOD function has been linked to both Down's syndrome (the over expression of SOD) and to amyotrophic lateral sclerosis or Lou Gehrig's disease (a dysfunctional SOD activity).

2) Hydrogen peroxide

Hydrogen peroxide is formed by several metabolic reactions including those catalyzed by SOD and by oxidase(s) of D-amino acid, amines, glucose, galactose coupled with coenzyme FAD. In addition, superoxide anion $O_2^{-\bullet}+H^+ \rightarrow HO_2^{\bullet}$ with hydrogen forms hydroperoxyl radical, which is very short lived and spontaneously generates hydrogen peroxide and oxygen. The H_2O_2 can transverse the plasma and nuclear membranes, there by contributing to DNA adduct formation as it enters the nuclear compartment. Similar to FAD and galactose oxidase reaction, which generates H_2O_2 from H_2+O_2. Likewise, SOD catalyzes the formation of H_2O_2 as follows, $2O_2^{-\bullet}+2H^+ \rightarrow H_2O_2+O_2$, Hydrogen peroxide is catabolized by catalase and by several peroxidases (e.g. glutathione peroxidases): $2H_2O_2 \rightarrow 2H_2O+O_2$ catalase.

3) Hydroxyl free radicals

Hydroxyl free radicals can be formed from either the superoxide anion (Harber-Weiss reaction) or from hydrogen peroxide (Fenton reaction).[10] Both reaction require a transitional metal such as iron or copper: $O_2^{-\bullet}+H_2O_2 \rightarrow O_2+OH^-+HO^{\bullet}$ (Harber- Weiss reaction) (1 and $Fe^{2+}+H_2O_2 \rightarrow Fe^{3+}+HO^-+HO^{\bullet}$ (Fenton Reaction). Hydroxy free radical is a very energetic, short-lived and toxic oxygen species. Some scientists suggest that the toxicity of hydrogen peroxide and superoxide anion radicals may be due to their conversion to the hydroxyl free radicals.

Other known diseases associated with free radicals are adult respiratory distress syndrome, aging, alcoholism, atherosclerosis, cancer, cardiovascular disease, cataract, Crohn's disease, cystic fibrosis, diabetes, hepatitis, inflammation, motor neuron disease brain disease, oxygen toxicity, renal failure, ischemia, rheumatoid arthritis, septic shock syndrome, Down's syndrome, Duchenne's muscular dystrophy, andhemoglobin-related disease.[11-32]

I have spent nearly 60 years of my life since 1937 concerned with lactose intolerance problems among infants and children. Since 1967, I personally experienced in treating a severe case of lactose intolerant infants with simply soy milk with great success. It is speculated that by-products among lactose Intolerant population, may have partly contributed to increased incidence of cancers, while soy milk can certainly prevent sufferings of both hereditary and acquired lactose Intolerant infants, children or adult with soy milk.

A comparison of chemical composition between dairy milk and soy milk showed that in soy milk, neither lactose nor cholesterol is found while methionine and lysine levels are relatively lower than that of dairy milk, but these essential amino acids are fortified along with vitamins, minerals and functional nutrients to soy milk. Considering fatty acid composition, the ratio of n-6, linoleic acid to n-3, α-linolenic acid is 7.5 in soy milk as compared to that of 16 in dairy milk, soy milk contains much healthier nutrients and presents as foods that possess potential chemopreventive properties.

Here at this cancer prevention meeting, I presented to you a case history of dairy milk versus soy

milk to expand scientific evaluation of two products with respect to prevention of cancer or age-related diseases through your research to elucidate why soy milk offers a better health than that of dairy milk. Furthermore, why lactose intolerance may be associated with higher incidence of cancers.

CONCLUSION

This presentation hypothesized that excess byproducts such as H_2, or peroxidated fatty acids (e.g. conjugated enals, products of oxidized fatty acids) may be a factor in causing cancers. Now many systematic research is required to prove this hypothesis. I ask you to join in research together to elucidate many scientific questions that are unresolved for the sake of promoting public health.

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