

Re-introducing Tea to the West

-This Time to Fight Cancer

"Let food be your medicine"-Shennong (ca.2737 BC); Hippocrates (ca.400 BC)

Sin Hang Lee, MD, FRCP(C)*

Objective: To disseminate reliable information on the art and science of drinking tea, a conventional food, for health protection, especially for cancer prevention and management.

Data Source: Ancient Chinese writings and recent scientific research reports obtained through PubMed internet access of the National Library of Medicine.

Methods of Study Selection: The ancient Chinese references and current publications were reviewed and searched for science-based evidence relevant to the relationship between green tea and cancer.

Data Extraction and Synthesis: The data extracted from 63 relevant publications formed the scientific basis of using green tea as a non-toxic agent in the combat against cancer. The results presented in the 37 epidemiological and clinical studies offered the guidelines for designing a practical regimen in the application of green tea for health protection.

Conclusion: Green tea has been shown to be effective in suppressing cancer development at multiple steps in the laboratory and experimental animal studies, and may enhance the anticancer effects of some chemotherapeutic drugs. Daily consumption of high-antioxidant green tea in a sufficient quantity may reduce the risk of cancer of the esophagus, stomach, pancreas, colon, rectum, urinary bladder, prostate, lung, breast, liver, uterus and ovary. However, this benefit of tea consumption was apparently observed only in high-volume tea drinkers who had ready commercial access to high-quality green teas in the East. To illustrate the lack of understanding about tea in the West, the author relates his personal experience:

I asked the "Americans" about the meaning of the word "Orange Pekoe". Their answer was that it stands for top-grade black tea with a slight orange flavor. Worse, they even cited the Webster's New Collegiate Dictionary to back up their statement. The British has done better. At least the Oxford Dictionaries recognize that "Pekoe" means "white down" in Amoy dialect. It is used by Chinese tea traders to describe certain kinds of high-grade dried green tea leaves which retain the appearance of a down coat on them. Pekoe has never been associated with black teas in the Chinese language. – SHL

Green tea is now an acknowledged cancer-preventive beverage in Japan (1, 2). According to the Japanese experience, cancer risk may be reduced by daily consumption of a sufficient amount of quality green tea before clinical diagnosis of the tumor, or after its treatment. The scientific basis of using green tea, a conventional food, to control cancer growth and to boost the anticancer effects of certain chemotherapeutic agents is a subject of intense research worldwide (3-16).

In laboratory research at the cellular and molecular levels as well as in experimental animal studies, the anticancer effects of green tea or its ingredients have been consistently affirmed. In comparison, very little human study has been done by medical professionals to explore the potential benefits of using green tea for

human cancer prevention and management. One published study was designed to show that tea powder swallowed by patients did not cure advanced prostate cancer (17). Introduction of an inexpensive, readily available, non-toxic beverage or conventional food like green tea to help solve a complex medical problem like cancer is bound to encounter resistance from established trade professions. Even the physicians of traditional Chinese medicine have managed to exclude tea from their medical practice since the fall of the Ming dynasty. Historically, tea was considered as an important drug and a medicinal food in the early editions of *Shennong's Herbal Classic* (18), the world's first paperback *materia medica*, which has been edited by various authors since about 200 BC (19). However, it is not listed at all in the recent editions compiled by the contemporary

Presented in part at the Society for Integrative Oncology 1st International Conference, New York, NY November 17, 2004.

* 2nd edition, June 2005 Fleminger, Inc. 160 Hawley Lane, Suite 205, Trumbull, CT 06611 USA
Telephone: 203 385-3836 Fax 203 385-3832 www.teaforhealth.com

the special tea amino acid, theanine, is a biochemical modulator that has been shown to inhibit efflux of a DNA topoisomerase II inhibitor, doxorubicin, from the cancer cells, but not to reduce the outflow of the topoisomerase II inhibitor from the normal cells (14, 15, 33, 34). Therefore, green tea may potentiate the anticancer activities of these drugs and may reduce the drug dosage needed for effective cancer chemotherapy.

VIII. Green tea induces apoptosis via a mitochondrial pathway.

There are two distinct primary signaling pathways of apoptosis, one of which is the extrinsic or death receptor pathway controlled by caspase 8 and caspase 10 through a tumor necrosis factor receptor on surface of the cell membrane (TNF receptor).

The other is the intrinsic or mitochondrial pathway which occurs within the cell through release of cytochrome C from the mitochondria and activation of caspase 9. Normal Bcl-2 and Bcl-XL proteins in the mitochondrial membranes prevent pore formation and leakage of cytochrome C from the mitochondria to the cytoplasm. Cytochrome C activates caspase 9 which in turn activates other caspases, a series of proteases that digest the structural proteins in the cytoplasm, damage the DNA, and cause cell death. Bax protein is a Bcl-2 family member in the mitochondrial membranes, but is activated by this pathway to increase the permeability of the mitochondrial membrane, releasing cytochrome C to the cytoplasm.

EGCG decreases the Bcl-2 and Bcl-XL proteins, increases the Bax protein, and activates caspase 9 in the cancer cells. Therefore, its anticancer activity appears at least in part mediated by the mitochondrial pathway (7).

IX. Green tea exerts its effects on signal transduction - to inhibit activation of transcription factors, e.g. nuclear factor-kappaB (NF- κ B), Cyclin D1, tumor-associated protein kinases, epidermal growth factor (EGF) receptors, and the release of tumor necrosis factor-alpha (TNF- α), an endogenous promoter for cancer genes.

Molecular signals, such as hormones or growth factors, are received by interaction between the signaling molecule (ligand) and a receptor specific for that signal on the surface of the cell. Through a series of steps, the message from that signal gets transmitted and amplified within the receiving cell, often leading to activation or deactivation of specific transcription factors in the nucleus, thus regulating the events in cell proliferation, differentiation and apoptosis, for example by controlling the gene expression of endogenous promoters like a tumor necrosis factor (35). This process is referred to as signal transduction pathways, involving the products of

several genes (for example, Ras) that are mutant in cancer cells.

One of the key pathways is the mitogenic signal transduction through the cascade of mitogen-activated protein (MAP) kinase that also includes other transducing molecules such as MAP kinase kinase (MEK) and Raf-1. The MAP kinase signaling, for instance, enhances cyclin D1 for cell proliferation, but also arrests cell growth by increasing expression of the cyclin kinase inhibitor p21 (Cip-1/MDA6/WAF1). The level and duration of MAP kinase expression appears to control this differential effect.

Overexpression of matrix metalloproteinases (MMPs) has been known to correlate closely with tumor cell invasion. EGCG may exert at least part of its anti-invasive effect by controlling MMP expression through the suppression of MAP kinase and AP-1 activation (36).

Green tea has been shown to inhibit activation of many transcription factors. For example, it inhibits the tumor necrosis factor- α (TNF- α) gene expression (37, 38) as well as the okadaic acid-induced AP-1 and NF-kappa B activation (38).

Green tea EGCG inhibits both the autocrine activation of epidermal growth factor receptor (EGFR) signaling and the activation of the signal transducer by exogenous transforming growth factor- α (TGF- α). As a consequence, EGCG also inhibits signaling to the extracellular regulated kinase (ERK) proteins and activation of transcription 3 (Stat 3) which lies downstream of the TGF- α /EGFR signaling pathway and apparently protects cancer cells from apoptosis (7).

X. Green tea regulates faulty apoptosis independent of the p53 suppressor genes.

Green tea and its components significantly restore cancer cell apoptosis (39). They also affect p53 gene mutations. However, the cancer chemopreventive efficacy of green tea may be independent of p53 status of the cancer cells (40, 41).

XI. Green tea inhibits angiogenesis necessary for rapid tumor growth.

The components of green tea inhibit the process of forming new blood vessels (42) which are needed to support the fast growing rate of a malignant tumor. The anticancer effect of EGCG is at least in part due to its inhibition of angiogenesis through blocking the induction of vascular endothelial growth factor (VEGF) in human colon cancer cells. EGCG, not other catechins, inhibits ErK-1 and ErK-2 activation in a dose dependent manner (43). Physiological concentrations (0.01-1 μ M) of EGCG induce a rapid and potent inhibition of VEGF-dependent tyrosine phosphorylation of VEGF receptor-2 (VEGFR-

2). The inhibition of VEGFR-2 by EGCG is similar to that induced by Semaxanib (SU5416), a specific VEGFR-2 inhibitor (44).

XII. Green tea inhibits proteolytic enzymes, urokinase and collagenase, needed to establish cancer metastasis.

Human cancers need proteolytic enzymes to invade other neighboring normal cells and form metastases. One of these enzymes is urokinase (uPA). Inhibition of uPA can decrease tumor size or even cause complete remission of cancers in mice. The known uPA inhibitors, for example, amiloride, are unlikely to be used in anticancer therapy because of their weak inhibitory activity or high toxicity. EGCG binds to uPA, blocking the amino acids His 57 and Ser 195 of the uPA catalytic triad and extending towards Arg 35 from a positively charged loop. Such localization of EGCG would interfere with the ability of uPA to recognize its substrates and inhibits its enzymatic activity. Based on laboratory studies, it has been recommended that drinking green tea containing 1,500 mg of EGCG per day may deliver more than adequate levels of EGCG to reduce the incidence of cancer in humans or the size of cancers already formed (45). A similar tea effect in suppressing cancer growth may be achieved by inhibition of type IV collagenase of the carcinoma cells by EGCG and some black tea components, such as theaflavin and theaflavin digallate (46).

XIII. Green tea boosting anticancer effects of chemotherapeutics

In experimental animal studies, green tea containing 708 µg/mL EGCG given orally was found to inhibit high-grade non-Hodgkin's lymphoma transplanted in mice and more effectively than cyclophosphamide (6). In *in vitro* studies, green tea EGCG at a low concentration of 0.1µg/mL enhances the anticancer effects of 5-fluorouracil by 45-fold (7). The tea amino acid, theanine, inhibits the efflux of doxorubicin from the cancer cells selectively, thus raising its intracellular concentration in the malignant cells by 2.9-fold compared to normal controls. Theanine as a biochemical modulator enhances the antitumor activity of doxorubicin by inhibition of a cell membrane transporter system which appears to be involved in glutamate uptake and export of topoisomerase inhibitors like doxorubicin. In the mice bearing P388 leukemia cells which were resistant to doxorubicin, administration of theanine rendered the leukemia cells sensitive to the cytotoxic effects of doxorubicin treatment again (14-16, 33, 34).

Based on the scientific publications summarized above, drinking green tea helps to fight cancer at numerous steps, ranging from suppression of the formation of carcinogens to hindering tumor metastases in the body after the cancer has been established, and

may even enhance the anticancer effects of the standard chemotherapeutic agents.

Epidemiological and clinical data on green tea and cancer risk in humans

Although many research institutes in the US have reported through the lay news media that green tea or one of its ingredients has been demonstrated to be effective in inhibiting cancer growth in their laboratories, they have made few attempts to conduct epidemiological or clinical research on the relationship between green tea consumption and cancer risk. A literature search through internet access to the US National Library of Medicine yielded 37 reports in which the relationship between green tea consumption and cancer risk in humans was studied. All of the reported studies were conducted in Japan and China except for one which was based on a survey of green tea consumption and risk of breast cancer in Asian Americans living in the state of California. In order to determine if tea consumption selectively affected the cancer risk of a specific organ, the data on each organ type were extracted from each article and presented under the heading of individual organ. Five studies reported the relationship between an overall cancer risk and green tea consumption in a population and were grouped separately following the organ-type presentation.

Esophagus		
Author, 1 st	Reference	Reduced Cancer Risk
Gao YT	47	yes
Inoue M	48	yes
Kinjo Y	49	no (hot tea)
Mu LN	50	yes
Wang M	51	yes
Stomach		
Author, 1 st	Reference	Reduced Cancer Risk
Hoshiyama Y	52	no
Inoue M	48	yes
Ji BT	53	yes
Koizumi Y	54	no
Kono S	55	yes
Kono S	56	yes
Mu LN	50	yes
Nakachi K	57	yes
Oguni I	58	yes
Setiawan VW	59	yes
Shibata K	60	yes
Tsubono Y	61	no
Wang M	51	yes
Ye WM	62	yes
Yu GP	63	yes
Yu GP	64	yes
Pancreas		
Author, 1 st	Reference	Reduced Cancer Risk
Goto R	65	yes
Ji BT	66	yes

The term "white tea" first appeared in a monograph entitled "A Grand Overview on Tea" which was written by emperor Hui Zhong of the Song Dynasty in 1107 AD. The emperor mistakenly thought a weakened mutant of tea plant with delicate light-colored leaves which had lost its ability to reproduce to be a rare species of tea trees. Nowadays, white tea is produced from the same tea leaves as those used for green tea, black tea and oolong tea, but without the process of heat inactivation. The manufacturing methods vary. One popular protocol of production is to let the newly harvested fresh young tea leaves air-dry at 28-30° C in 65-70% relative humidity for 34-38 hours to reduce the water contents to 14-16% in dry weight. Then the leaves with preserved white down are hand-picked for further drying in low heat or under the sun. Since the polyphenol oxidase of the tea leaves has not been inactivated, the tea catechins in the white tea undergo continuous oxidation at uncontrolled rates during production and storage. Its EGCG level cannot be standardized. There is no scientific evidence to substantiate the claim that white tea, usually sold at higher prices than those for green tea, contains more health-beneficial ingredients.

Tea For Health

The future of health care is to encourage the public to practice individual preventive medicine. The society cannot sustain the current disease-directed and procedure-oriented health care industry forever. Many economists predict that all health maintenance organizations (HMOs) in their present format and even the government-sponsored health care programs will go bankrupt if the US consumers and the health care industry continue their insatiable demands for health care services which may not necessarily translate into better health for the consumers. However, the medical profession has no incentive to guide the consumers, namely the potential patients, to practice preventive medicine to manage their own health. Unlike the ancient Chinese emperor, the HMOs do not pay the medical doctors to keep people healthy.

For at least 5,000 years, tea has been used as a medicinal beverage for prevention of various diseases. The earliest Chinese writing symbols for tea (*ku-tu* in phonics) had an adjective "bitter" preceding the noun "tea", indicating that tea was a bitter drug. Its intended use was for "detoxification" (18). Tea was used probably to counter metal poisoning (88, 89) due to excess intake of mercury, arsenic, lead, iron and cadmium, as a result of drinking the water boiled in primitive cookware made of clay, bronze and pig iron in ancient China, without knowing the scientific basis behind it. In the name of the emperor, a wise court physician had sent out an edict that all drinking water must be boiled in the Middle Kingdom to prevent waterborne diseases. In those days, most people died before reaching the age of 50 probably in significant percentage of arsenic and lead poisoning if

they had survived malnutrition and infectious diseases in their youth.

Boiling fresh tea leaves in water in contact with oxygen and in the presence of polyvalent metal oxidative catalysts converted the tea catechins into very bitter oxidized polyphenol polymers. Tea was an effective agent for chelating, binding and reducing the dissolved metal ions to protect health. Its bitterness was tolerated by the enlightened. In the classic Chinese literature and ancient pharmacology texts, the adjective "bitter" preceding the noun "tea" was dropped after the non-metallic utensils, now known as porcelain or china, were invented for tea preparation. Only then, from about 200 BC, tea gradually evolved into a beverage among the scholar elite in the next 800 years and other health benefits associated with tea consumption were recognized as the society became more prosperous and the average lifespan increased. The ancient Chinese pharmacology texts began to describe tea as a "sweetish" drink. In the book entitled "*The Pharmacology of Shennong's Herbal Classic*" edited by Mou Shi-Yong of the Ming dynasty (1624 AD), it stated that several grades of tea were recognized since Tang dynasty and that only the sweetish tea, but not the bitter tea, should be used for medicinal purpose (90). Due to lack of methods for preservation and storage, high-grade tea leaves were generally used within 6 months. Each spring, tens of thousands of tea peasant conscripts were forced to work in southern China to harvest and process "tribute teas" for the royal family and the government officials of all ranks. The tribute teas, in enormous quantities, must be delivered to the capital in the North before the Tomb-Sweeping Day in early April via non-stopped express horse relays since the Song dynasty, breeding bureaucracy and corruption along the way throughout the Chinese history.

In the past 10 years, numerous scientific studies have reported that regular consumption of green tea may be associated with multiple health benefits, for example, in weight control, reducing the risk of cardiovascular diseases, controlling diabetes, neuroprotection against Alzheimer's and Parkinson's disease, against degenerative arthritis through its anti-COX-2 activity (like Vioxx and Celebrex) and chemoprevention against cancer. A disproportionately large number of studies have been devoted to research on green tea against cancer because, unlike for other listed diseases, there are no known drugs for prevention or for the treatment of cancer without causing serious toxicity to the consumers or patients.

Cancer has become a major cause of death, second only to heart attack, as the average lifespan of the population increased in the past few decades. In the

United States, nearly 80% of cancer cases occur in people age 55 or older. Most of these adult cancers, take 20 to 30 years to become clinically detectable from the stage of cancer initiation. More than two thirds of the cancers are linked to environmental causes, including lifestyle choices and dietary habits and may be prevented by proper personal health management programs (91). Environmental factors contribute to 80-90% of the cancer risk (92). This review has summarized the most relevant laboratory and epidemiological studies available in the public domain to show that green tea can be used as a medicinal beverage to prevent the initiation of carcinogenesis and to interrupt cancer development after its initiation.

In addition to the publications about green tea and cancer which were presented above, the internet search of the web site of the National Library of Medicine yielded another 95 epidemiological studies on tea consumption and cancer risk in humans that had included black tea or oolong tea drinkers in the surveys. In 79 of these 95 studies, tea drinking was found to be not associated with a reduction in cancer risk while the other 16 found an association. The fact is that the majority of the investigators did not find consumption of black tea or oolong tea to be associated with a reduction in cancer risk. These references and a summary report were included in a petition submitted to the FDA for a food labeling health claim. Interested readers may view the entire document published on the FDA web site under docket No. 2004Q-0083.

The Art and Science of Drinking Tea

Tea was initially used as a drug and by the Taoists in association with their religious rituals. The Taoists and subsequently the Zen Buddhists, both heavy tea drinkers, are said to live longer than the average people in the history of China. The first edition of *Shennong's Herbal Classic* described the pharmacological properties of tea in the following words: "...Tea is bitter. Regular consumption of tea boosts mental function, reduces need for sleep, lightens body weight and improves eye sight" (18). It was probably written by a Taoist. These ancient observations have been confirmed by recent scientific research. The benefits of tea for preventing cardiovascular disease and cancer were not recognized in ancient China because these disorders were not major health concerns at the time when most people died before the age of 50.

The "art and science" of drinking tea perfected in the Song dynasty emphasized the importance of using fresh or well preserved dry tea leaves, porcelain or glass utensils and pure water collected from rain, melting snow or selected springs to brew tea drinks. The price of tea was not low enough for the populace to consume as their daily beverage until the Ming dynasty (1368-1644 AD) after the fall of the Mongolian Empire (1279-1368 AD).

While the methods of preparing tea may vary according to customs and traditions in different cultures, a few notes may be useful for the interested health care professionals and consumers to consider when they develop their own ways of tea preparation. These are summarized as follows.

The laboratory mice used for tea research, the Taoists and Zen Buddhists shared one thing in common that they all drink quality green tea and a lot of it. Carefully reading the scientific reports published recently by the serious cancer researchers using animals for their studies found that the tea leaves used as "Materials" for tea preparations in their research were usually procured as a special order, often from a colleague or a store having connection with a tea plantation directly or indirectly. The tea leaves were invariably extracted in hot water or other liquids in an Erlenmeyer flask, often under nitrogen (93). Then the EGCG concentration of the tea extracts would be measured and adjusted to about 710 μ g/mL before the tea was put into a feeding bottle for the mice to drink *ad libitum* which means tea is the only source of fluid intake other than dry foods for the mice (6). That is a huge dosage, amounting to 10 to 15% of the body weight per day.

It has taken 5,000 years for us to learn an important lesson that to maximize its health benefits, we must drink green tea like the laboratory mice or like the Taoists do. Some Japanese living around the traditional tea plantations have done just that though. They sip green tea practically all day long, consuming at least 10 Japanese cups (about 120-150 mL/cup) of green tea a day and enjoy significantly more cancer-free years in their lives on the average than their low-volume tea-consuming neighbors (37, 94). Thanks to a more stable society, the Japanese have preserved some of the treasures of the tea culture developed in the Tang-Song period better than the Chinese.

As mentioned above, a "typical" green tea drink contains 710 μ g/mL natural EGCG (82). Most people use a 1:100 w/v leaf-to-water ratio to brew tea. Therefore, the tea leaves must contain at least 7% EGCG in dry weight which is extractable with hot water to meet this requirement. The daily consumption of green tea should be at least 1,200 mL divided into three or more servings, to be sipped slowly with some food in the stomach or while eating. Unfortunately, the commercially available green teas in the Western world contain about one third (1/3) of that amount (95), if not lower. Besides, the traditional eating habits in the West would never contemplate drinking 1,200 mL of tea in the daily diet. This combination of low antioxidants in the tea drinks and low volume of daily intake might have accounted for the lack of epidemiological studies on the relationship between green tea and cancer risk in the West.

The lack of adverse effects even at high doses of green tea has been demonstrated in a phase I clinical trial conducted at M.D. Anderson Cancer Center in adult patients with solid tumors (96). Based on the trial data, a dose of green tea extract at 1.0 g/m² tid, equivalent to 840-960 mL of green tea three times daily, has been recommended for future therapeutic studies. This dose can be taken safely for at least 6 months in adults. The side effects, if any, were found to be caffeine-related.

Exposure of hot teas to oxygen may lead to loss of antioxidants (97), especially in the presence of ferrous or ferric ions (98). Deionized water is recommended for making tea, as commonly practiced in the research laboratories. Metal ions, oxidizing agents, like chlorine and its derivatives, and some detergent residues may cause degradation of antioxidants and turn the green tea into bitter brownish drinks. This phenomenon can be readily observed right in the cup provided a high grade green tea is being brewed. Brewing hot tea in deionized water in a steeper without free air contact may preserve 15-20% more antioxidants.

Tea antioxidants are readily destroyed at the temperature above 100°C (97). Therefore, it is not recommended to put partially dry tea leaves in water into the microwave oven for heating.

Infusion tea bags are made of thin tissue paper treated with urea formaldehyde and melamine-formaldehyde resins to prevent their disintegration in hot water. About 40 known organic chemicals, including formaldehyde, can be extracted from these infusion tea bags by hot water (99). These chemicals are not in sufficient amounts to be harmful to the human body. However, their effects on tea antioxidants have not been studied.

All known health-beneficial ingredients in green tea leaves are extracted out after 15-20 minutes steeping in hot water cooling down from the peak temperature of 90-92°C which is the starting temperature of the tea brew after the boiling hot water is poured into a tea steeper at room temperature. Prolonged steeping only dissolves more bitter substances like caffeine and polyphenols of large molecular sizes from the tea leaves. The second infusion by adding more hot water into the tea pot without new tea leaves added, a common practice in the Chinese restaurants, yields dilute tea-tasting water without expected health benefits.

Drinking scorching hot tea, or any fluids, may increase risk of developing esophageal cancer. Therefore, hot tea should be cooled down to below 60°C before use as a beverage.

Expensive green teas may taste better, more sweetish and less bitter, due to a variety of factors. But the price may not correlate with the antioxidant contents

in the tea leaves. One may not have to buy the most expensive green tea to get the best health benefits of tea drinking.

Since tea catechins are strong reducing molecules, they may interact with microorganisms in the lumen of the bowel and with the cells in the bowel wall before they reach the blood. They may preferentially bind to certain cellular or tissue structures. In other words, they are short-lived functional molecules in the human body after ingestion. For them to be effective, the bioactive ingredients must be supplied continuously. To swallow one or two pills of green tea products a day cannot be considered substitute for drinking natural green tea in the traditional manner. Measuring the levels of EGCG in the blood as in assays for antibacterial antibiotics may not be a useful tool to determine the potential anticancer function of green tea. The anticancer activities of green tea take place in the cell or even in the nucleus and the mitochondria of a cell, which may have little to do with its blood concentration.

The difficulty in human clinical studies with a conventional food like green tea is that the established protocol in the pharmaceutical industry cannot be easily applied, let alone the lack of incentives for any tea traders to do so. The customarily accepted protocol of "double-blind, randomized, placebo-control, multi-center safety and efficacy clinical studies" in new drug development is difficult to design with green tea as the pharmacologically active ingredients because pure water would have to be used as the placebo. The patients assigned to the placebo group would know immediately that they are not drinking the potentially effective liquid, and may have the tendency to drink some green tea on the side without informing the investigator, or to refuse participation in the first place. This unblinding of active product and placebo in clinical trials will invalidate any critical data analyses. Therefore, the industry is more interested in supporting the development of synthetic chemical analogs of EGCG as cancer preventive drugs (100) which may have a better financial return than making high quality natural green tea available to the public.

In conclusion, the consumers who by definition include all living individuals, namely future patients, current patients and health care professionals, must be self-educated to obtain reliable science-based information for managing their own health. We are all on our own. Green tea just happens to be one of the conventional foods that may be helpful in realigning our lifestyle and diet habits for a better health. The Zen Buddhist teaching invariably ends with the wisdom from the master's mouth: "*Go to drink tea*". It means to enjoy it which is tea, but also encompasses everything in life, seeking gratification in mind, not in the taste buds—a profound Eastern philosophy for the enlightened to comprehend.

References

1. Fujiki H, Suganuma M, Imai K, et al. Green tea: cancer preventive beverage and/or drug. *Cancer Lett* 2002;188:9-13.
2. Inoue M, Tajima K, Mizutani M, et al. Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. *Cancer Lett* 2001;167:175-182.
3. Mukhtar H, Ahmad N. Green tea in chemoprevention of cancer. *Toxicol Sci* 1999; 52 (2 Suppl):111-117.
4. Katiyar SK, Ahmad N, Mukhtar H. Green tea and skin. *Arch Dermatol* 2000;136:989-994.
5. Bickers DR, Athar M. Novel approaches to chemoprevention of skin cancer. *J Dermatol* 2000;27:691-695.
6. Bertolini F, Fusetti L, Rabascio C, et al. Inhibition of angiogenesis and induction of endothelial and tumor cell apoptosis by green tea in animal models of human high-grade non-Hodgkin's lymphoma. *Leukemia* 2000;14:1477-1482.
7. Masuda H, Suzui M, Weinstein IB. Effects of Epigallocatechin-3-gallate on Growth, Epidermal Growth Factor Receptor Signaling Pathways, Gene Expression, and Chemosensitivity in Human Head and Neck Squamous Cell Carcinoma Cell Lines. *Clin Cancer Res* 2001;7:4220-4229.
8. Jung YD, Ellis LM. Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. *Int J Exp Pathol* 2001;82:309-316.
9. Sueoka N, Suganuma M, Sueoka E, et al. A new function of green tea: prevention of lifestyle-related diseases. *Ann N Y Acad Sci* 2001;928:274-280.
10. Surh YJ, Chun KS, Cha HH, et al. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. *Mutat Res* 2001;480-481:243-268.
11. Lee YK, Bone ND, Strege AK, et al. VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. *Blood* 2004;104:788-794.
12. Berger SJ, Gupta S, Belfi CA, et al. Green tea constituent (-)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells. *Biochem Biophys Res Commun* 2001;288:101-105.
13. Suzuki K, Yahara S, Hashimoto F, et al. Inhibitory activities of (-)-epi-gallocatechin-3-O-gallate against topoisomerase I and II. *Biol Pharm Bull* 2001;24:1088-1090.
14. Sadzuka Y, Sugiyama T, Miyagishima A, et al. The effects of theanine, as a novel biochemical modulator, on the antitumor activity of adriamycin. *Cancer Lett* 1996;105:203-209.
15. Sadzuka Y, Sugiyama T, Sonobe T. Effects of tea components on doxorubicin induced antitumor activity and reversal of multidrug resistance. *Toxicol Lett* 2000;114:155-162.
16. Sugiyama T, Sadzuka Y. Theanine and glutamate transporter inhibitors enhance the antitumor efficacy of chemotherapeutic agents. *Biochim Biophys Acta* 2003;1653:47-59.
17. Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer* 2003;97:1442-1446.
18. Wu Su-liang. Quotation of "Shennong's Herbal Classic" of the Warring States-Han dynasty period. In "Tea as Drug and Medicinal Food". China Medical and Drug Science Technology Publisher, Beijing 1999. ISBN 7-5067-2119-8
19. Shang Z. Discussion on the date of appearance of the title Shen nong ben caojing (*Shennong's Herbal Classic*). *Zhonghua Yi Shi Za Zhi*. 1999;29:135-138. [Article in Chinese]
20. Shen Lien-sheng (Editor in Chief). "Shenong's Herbal Classic Chinese Medicine Color Atlas". China Traditional Chinese Medicine Drug Publisher. Beijing 1996. ISBN 7-80089-542-4/R.542
21. Stich HF. Teas and tea components as inhibitors of carcinogen formation in model system and man. *Prev Med* 1992;21:377-384.
22. Chen J. The effects of Chinese tea on the occurrence of esophageal tumors induced by N-Nitrosomethylbenzylamine in rats. *Prev Med* 1992;21:385-391.
23. Williams SN, Shih H, Guenette DK, et al. Comparative studies on the effects of green tea extracts and individual tea catechins on human CYP1A gene expression. *Chem Biol Interact* 2000;128:211-229.
24. Wang ZY, Khan WA, Bickers DR, et al. Protection against polycyclic aromatic hydrocarbon-induced skin tumor initiation in mice by green tea polyphenols. *Carcinogenesis* 1989;10:411-415.
25. Bu-Abbas A, Clifford MN, Walker R, et al. Selective induction of rat hepatic CYP1 and CYP4 proteins and of peroxisomal proliferation by green tea. *Carcinogenesis* 1994;15:2575-2579.
26. Khan SG, Katiyar SK, Agarwal R, et al. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer

- chemoprevention. *Cancer Res* 1992;52:4050-4052.
27. Huang M-U, Ho C-T, Wang ZY, et al. Inhibitory effect of topical application of a green tea polyphenol fraction on tumor initiation and promotion in mouse skin. *Carcinogenesis* 1992;13:947-954.
 28. Chan MM-Y, Fong D, Ho C-T, et al. Inhibition of inducible nitric oxide synthase gene expression and enzyme activity by epigallocatechin gallate, a natural product from green tea. *Biochem Pharmacol* 1997;54:1281-1286.
 29. Srivastava RC, Husain MM, Hasan SK, et al. Green tea polyphenols and tannic acid act as potent inhibitors of phorbol ester-induced nitric oxide generation in rat hepatocytes independent of their antioxidant properties. *Cancer Lett* 2000;153:1-5.
 30. Katiyar SK, Afaq F, Perez A, et al. Green tea polyphenol (-)-epigallo-catechin-3-gallate treatment of human skin inhibits ultraviolet radiation-induced oxidative stress. *Carcinogenesis* 2001;22:287-294.
 31. Yang G-Y, Liao J, Li C, et al. Effects of black and green tea polyphenols on c-jun phosphorylation and H₂O₂ production in transformed and non-transformed human bronchial cell lines: possible mechanisms of cell growth inhibition and apoptosis induction. *Carcinogenesis* 2000;21:2035-2039.
 32. Naasani I, Seimiya H, Tsuruo T. Telomerase inhibition, telomere shortening, and senescence of cancer cells by tea catechins. *Biochem Biophys Res Commun* 1998;249:391-396.
 33. Sugiyama T, Sadzuka Y. Combination of theanine with doxorubicin inhibits hepatic metastasis of M5076 ovarian sarcoma. *Clin Cancer Res* 1999;5:413-416.
 34. Sadzuka Y, Yamashita Y, Sugiyama T, et al. Effect of dihydrokainate on the antitumor activity of doxorubicin. *Cancer Lett* 2002;179:157-163.
 35. Komori A, Yatsunami J, Suganuma M, et al. Tumor necrosis factor acts as a tumor promoter in BALB/3T3 cell transformation. *Cancer Res* 1993;53:1982-1985.
 36. Kim HS, Kim MH, Jeong M, et al. EGCG blocks tumor promoter-induced MMP-9 expression via suppression of MAPK and AP-1 activation in human gastric AGS cells. *Anticancer Res* 2004;24(2B):747-753.
 37. Fujiki H, Suganuma M, Okabe S, et al. A new concept of tumor promotion by tumor necrosis factor-alpha, and cancer preventive agents (-)-epigallocatechin gallate and green tea—a review. *Cancer Detection and Prevention* 2000;24:91-99.
 38. Okabe S, Ochiai Y, Aida M, et al. Mechanistic aspects of green tea as a cancer preventive: effect of components on human stomach cancer cell lines. *Jpn J Cancer Res* 1999;90:733-739.
 39. Yang GY, Liao J, Kim K, et al. Inhibition of growth and induction of apoptosis in human cancer cell lines by tea polyphenols. *Carcinogenesis* 1998;19:611-616.
 40. Liu Q, Wang Y, Crist KA, et al. Effect of green tea on p53 mutation distribution in ultraviolet B radiation-induced mouse skin tumors. *Carcinogenesis* 1998;19:1257-1262.
 41. Zhang Z, Liu Q, Lantry LE, et al. A germ-line p53 mutation accelerates pulmonary tumorigenesis: p53-independent efficacy of chemopreventive agents green tea or dexamethasone/myo-inositol and chemotherapeutic agents Taxol or Adriamycin. *Cancer Res* 2000;60:901-907.
 42. Cao YH, Cao RH. Angiogenesis inhibited by drinking tea. *Nature* 1999;398:381.
 43. Jung YD, Kim MS, Shin BA, et al. EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. *Br J Cancer* 2001;84:844-850.
 44. Lamy S, Gingras D, Beliveau R. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation. *Cancer Res* 2002;62:381-385.
 45. Jankun J, Selman SH, Swiercz R, et al. Why drinking green tea could prevent cancer. *Nature* 1997;387:561.
 46. Sazuka M, Imazawa H, Shoji Y, et al. Inhibition of collagenases from mouse lung carcinoma cells by green tea catechins and black tea theaflavins. *Biosci Biotechnol Biochem* 1997;61:1504-1506.
 47. Gao YT, McLaughlin JK, Blot WJ, et al. Reduced risk of esophageal cancer associated with green tea consumption. *J Natl Cancer Inst* 1994;86:855-858.
 48. Inoue M, Tajima K, Hirose K, et al. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control* 1998;9:209-216.
 49. Kinjo Y, Cui Y, Akiba S, et al. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol* 1998;8:235-243.
 50. Mu LN, Zhou XF, Ding BG, et al. A case-control study on drinking green tea and decreasing risk of cancers in the alimentary canal among cigarette smokers and alcohol drinkers. *Zhonghua Liu Xing Bing Xue Za Zhi* 2003;24:192-195.
 51. Wang M, Guo C, Li M. A case-control study on the dietary risk factors of upper digestive tract

- cancer. *Zhonghua Liu Xing Bing Xue Za Zhi*. 1999;20:95-97.
52. Hoshiyama Y, Kawaguchi T, Miura Y, et al. Japan Collaborative Cohort Study Group. A prospective study of stomach cancer death in relation to green tea consumption in Japan. *Br J Cancer* 2002;87:309-313.
 53. Ji BT, Chow WH, Yang G, et al. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer* 1996;77:2449-2457.
 54. Koizumi Y, Tsubono Y, Nakaya N, et al. No association between green tea and the risk of gastric cancer: pooled analysis of two prospective studies in Japan. *Cancer Epidemiol Biomarkers Prev* 2003;12:472-473.
 55. Kono S, Ikeda M, Tokudome S, et al. A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res* 1988;79:1067-1074.
 56. Kono S. Green tea and gastric cancer in Japan. *N Engl J Med* 2001;344:1867-1868.
 57. Nakachi K, Matsuyama S, Miyake S, et al. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. *BioFactors* 2000;13:49-54.
 58. Oguni I, Cheng SJ, Lin PZ, et al. Protection against cancer risk by Japanese green tea (abstract) *Prev Med* 1992;21: 332.
 59. Setiawan VW, Zhang ZF, Yu GP, et al. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. *Int J Cancer* 2001;92:600-604.
 60. Shibata K, Moriyama M, Fukushima T, et al. Green tea consumption and chronic atrophic gastritis: a cross-sectional study in a green tea production village. *J Epidemiol* 2000;10:310-316.
 61. Tsubono Y, Nishino Y, Komatsu S, et al. Green tea and the risk of gastric cancer in Japan. *N Engl J Med* 2001;344:632-636.
 62. Ye WM, Yi YN, Luo RX, et al. Diet and gastric cancer: a case control study in Fujian Province, China. *World J Gastroenterol*. 1998;4:516-518.
 63. Yu GP, Hsieh CC. Risk factors for stomach cancer: a population-based case-control study in Shanghai. *Cancer Causes Control*. 1991;2:169-174.
 64. Yu GP, Hsieh CC, Wang LY, et al. Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China. *Cancer Causes Control*. 1995;6:532-538.
 65. Goto R, Masuoka H, Yoshida K, et al. A case control study of cancer of the pancreas. *Gan No Rinsho*. 1990 Feb; Spec No:344-50 [Article in Japanese]
 66. Ji BT, Chow WH, Hsing AW, et al. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer* 1997;70:255-258.
 67. Kato I, Tominaga S, Matsuura A, et al. A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res* 1990;81:1101-1108.
 68. Kono S, Shinchi K, Ikeda N, et al. Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan. *J Clin Epidemiol* 1991;44:1255-1261.
 69. Nagano J, Kono S, Preston DL, et al. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). *Cancer Causes Control* 2001;12:501-508.
 70. Ohno Y, Aoki K, Obata K, et al. Case-control study of urinary bladder cancer in metropolitan Nagoya. *Natl Cancer Inst Monogr* 1985;69:229-234.
 71. Wakai K, Ohno Y, Obata K, et al. Prognostic significance of selected lifestyle factors in urinary bladder cancer. *Jpn J Cancer Res* 1993;84:1223-1229.
 72. Jian L, Xie LP, Lee AH, et al. Protective effect of green tea against prostate cancer: a case-control study in southeast China. *Int J Cancer* 2004; 108: 130-135.
 73. Ohno Y, Wakai K, Genka K, et al. Tea consumption and lung cancer risk: a case-control study in Okinawa, Japan. *Jpn J Cancer Res* 1995;86:1027-1034.
 74. Zhong L, Goldberg MS, Gao YT, et al. A population-based case-control study of lung cancer and green tea consumption among women living in Shanghai, China. *Epidemiology* 2001;12:695-700.
 75. Nakachi K, Suemasu K, Suga K, et al. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res* 1998;89:254-261.
 76. Wu AH, Yu MC, Tseng CC, et al. Green tea and risk of breast cancer in Asian Americans. *Int J Cancer* 2003;106:574-579.
 77. Zhang M, Binns CW, Lee AH. Tea consumption and ovarian cancer risk: a case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2002;11:713-718.
 78. Binns CW, Zhang M, Lee AH, et al. Green tea consumption enhances survival of epithelial ovarian cancer patients. *Asia Pac J Clin Nutr* 2004;13(Suppl):S116.
 79. Fujiki H, Suganuma M, Okabe S, et al. Cancer prevention with green tea and monitoring by a new biomarker, hnRNP B1. *Mutat Res* 2001;480-481:299-304.

80. Imai K, Suga K, Nakachi K. Cancer-preventive effects of drinking green tea among a Japanese population. *Prev Med* 1997;26:769-775.
81. Nakachi K, Eguchi H, Imai K. Can teatime increase one's lifetime? *Ageing Res Rev* 2003;2:1-10.
82. NCI, DCPC, Chemoprevention Branch and Agent Development Committee, Clinical development plan: tea extracts green tea polyphenols epigallocatechin gallate. *J Cell Biochemistry* 1996;26S:236-257.
83. Ouyang Xiu (1007-1072 AD). Song dynasty scholar. "Memoirs chronicled after retirement".
84. Kamath AB, Wang L, Das H, et al. Antigens in tea-beverage prime human Vgamma 2Vdelta 2 T cells *in vitro* and *in vivo* for memory and nonmemory antibacterial cytokine responses. *Proc Natl Acad Sci U S A* 2003;100:6009-6014.
85. Kim SH, Lee CS. The effect of caffeine on diethylnitrosamine-initiated hepatic altered foci in a mid-term induction system. *In Vivo* 1992;6:223-226.
86. Yang GY, Liao J, Kim K, et al. Inhibition of growth and induction of apoptosis in human cancer cell lines by tea polyphenols. *Carcinogenesis* 1998;19:611-616.
87. WHO Pharmaceuticals Newsletter No. 3, 2003.
88. Harper M. Possible toxic metal exposure of prehistoric bronze workers. *Br J Ind Med* 1987;44:652-656.
89. Linduff KM. The incidence of lead in late Shang and early Chou ritual vessels. *Expedition* 1977;19:7-16.
90. Mou Shi-yong. The Pharmacological interpretations of *Shennong's Herbal Classic*. Original published in Ming dynasty. 1624 AD. Edited by Zheng Jin-Seng. Page 502. Traditional Chinese Medicine Ancient Classics Publisher. Beijing 2002. ISBN 7-80013-969-7/R.965
91. Cancer and the Environment. NIH Publication 03-2039. National Cancer Institute and National Institute of Environmental Health Sciences. August 2003.
92. Blair, Aaron. Chief of Occupational Epidemiology Branch in NCI's Division of Cancer Epidemiology and Genetic. The Majority of Cancers Are Linked to the Environment. Reported by Nancy Nelson in: *BenchMarks Issue No.3, Volume 4, June 17, 2004.*
93. Mukhtar H, Wang ZY, Katiyar SK, et al. Tea Components: Antimutagenic and Anticarcinogenic Effects. *Prev Med* 1992; 21:351-360.
94. Fujiki H, Suganuma M, Okabe S, et al. Cancer inhibition by green tea. *Mutat Res* 1998;402:307-310.
95. Khokhar S, Magnúsdóttir SGM. Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom. *J Agric Food Chem* 2002;50:565-570.
96. Pisters KM, Newman RA, Coldman B, et al. Phase I trial of oral green tea extract in adult patients with solid tumors. *J Clin Oncol* 2001;19:1830-1838.
97. Chen Z, Zhu QY, Tsang D, et al. Degradation of green tea catechins in tea drinks. *J Agric Food Chem* 2001;49:477-482.
98. Kumamoto M, Sonda T, Nagayama K, et al. Effects of pH and metal ions on antioxidative activities of catechins. *Biosci Biotechnol Biochem* 2001;65:126-132.
99. Mongelard P. Formaldehyde in Tea-bag Tissue. Food Surveillance Information Sheet. No. 26, May 1994. Joint Food Safety and Standards Group. Additives and Novel Foods Division. MAFF UK
100. Kazi A, Wang Z, Kumar N, et al. Structure-activity relationships of synthetic analogs of (-)-epigallocatechin-3-gallate as proteasome inhibitors. *Anticancer Res* 2004;24(2B):943-954.