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

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practitioners who apparently felt quite comfortable to include cockroach and lead tetroxide (a commonly recognized poison!) as drugs (20). This intentional omission may be another example of intellectual corruption in the practice of medicine.

The Zen in Dealing with Cancer

Death is not an option. If an aging human body is lucky enough to avoid heart attack and stroke, statistically cancer probably will be life's "*modus of exodus"*. The slogans "to cure cancer" and "to eradicate cancer" are only good for fund raising to do more research or to support the business of doing more research. Cancer is part of our life if we want to live long and to live the way we want to in an industrialized society. All we can do is to learn how to prevent it, to delay its occurrence or recurrence, and to deal with it.

At the cellular level, an original "cancerous" cell is nothing but an ordinary cell affected by genetic mutation, namely damage (alteration) to its DNA code by a carcinogen if the damage is not repaired. It is not possible to avoid carcinogens in life. Carcinogens, or pro-carcinogens, are being introduced into our bodies and formed in the body constantly. The genetically altered or mutated cells may remain dormant until a promoter comes along to encourage them to proliferate. During this latent period a number of mutated genes may accumulate in the damaged cell, causing it to become a biologically active cancer cell. To be fatal to the host like a human body, the cancer cells must be able to divide, to invade the surrounding normal tissues and to metastasize.

The clinical history of cancer development may be divided into three stages, namely *initiation, promotion and progression*. However, most genetically damaged cells which probably exist in every human body never become clinically cancerous to the day when the host dies of unrelated diseases. As soon as the cancerous cells become biologically active, most of them will be recognized and destroyed by the competent immune system of the host. The human body actually has many safeguards against fatal cancers. Cancer cells have their finite lifespan too. They divide and die as any actively proliferating cells do. As long as the number of the "newborn" cancer cells is equal to or below the number of dying cancer cells, the patient is generally safe or "in remission" clinically. Therefore, it is not necessary to use extreme measures to eradicate all cancer cells or cancer tissues at the expense of the host's immune system or to put the host's life in immediate danger. The purpose in dealing with cancer is to keep the patient alive, not to eradicate the cancer. It takes more consideration and care than placing the patient on a "protocol" of chemotherapy.

Green Tea in the Fight against Cancer

The US Food and Drug Administration (FDA) does not want the word "prevention" to be used in the health claims for food labeling, but would allow the words of "risk reduction" instead because the FDA does not want to mislead the public into believing that to take certain food or dietary supplements can prevent cancer as effectively as vaccination against small pox or polio virus infections can. However, in the medical literature the words "prevention" and "risk reduction" are often used interchangeably.

Prevention is the most effective way to practice medicine. The ancient Chinese physicians used food as medicine to prevent diseases about 5,000 years ago. The Greek physician Hippocrates also emphasized using food as medicine. However, the teaching of following a healthy diet program to prevent and to manage diseases is difficult in the modern society because it requires individual discipline, cultivated taste and personal responsibilities to put into practice. Both the health care professionals and the consumers want to see convincing evidence before even contemplating alteration of one's established convenient lifestyle and eating habit. Here is the science of green tea for the combat against cancer.

Mechanisms of anticancer activities of green tea

The exact mechanism of chemoprevention of green tea against cancer is still poorly understood. However, its anticancer activities at various steps of the cancer development have been extensively studied. A brief summary of some of these publications, which may be useful for the evidence-based counseling between doctor and patient to support an informed decision to use green tea as a functional food for reducing cancer risk is presented as follows.

I. Green tea inhibits formation of N-Nitroso-compounds (carcinogens) in stomach.

Some food products, for example, salt-preserved fish and preserved meats containing nitrite, are nitrosated in the stomach, resulting in release of potent clastogenic and mutagenic compounds which are carcinogenic. Green tea inhibits this chemical reaction. Simultaneous intake of green tea with these food products has been shown to reduce the formation of mutagenic nitrosamine products in the stomach (21).

II. Green tea modulates gene expression of enzymes responsible for carcinogen metabolism.

Certain environmental substances require an endogenous enzyme or enzymatic system in the body to convert them into active carcinogen. For example, when sodium nitrite and methylbenzylamine are administered in rats, *in vivo* nitrosation will take place to form N-

nitrosomethylbenzylamine, a carcinogen through enzymatic activities in the body. Green tea blocks the *in vivo* formation of the N-nitroso compounds and inhibits carcinogenesis (*22*).

In another example, green tea inhibits the gene expression of the hepatic cytochrome P450-dependent mixed-function oxidase system, which is closely associated with bioactivation of chemical carcinogens. It is well known that aryl hydrocarbon induces cancers in animals and its action can be blocked by green tea. The aryl hydrocarbon receptor (AhR) mediates the transcriptional activation of CYP1A1 and CYP1A2. Green tea inhibits the transcription of a human CYP1A promoter-driven reporter gene induced by the AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in a concentration-dependent manner and inhibits the induced accumulation of both CYP1A1 and CYP1A2 mRNAs. Green tea extract and (-)-epigallocatechin gallate (EGCG), the most abundant active catechin antioxidant in tea leaves, were able to inhibit TCDD-induced binding of the AhR to DNA and subsequent CYP1A transcription (23). The effects of green tea polyphenols against skin-tumor-initiating activity induced by polycyclic aromatic hydrocarbons (PAHs), the "pro-carcinogens" present in smoke from cigarettes, automobile emissions and grilled foods have been known since 1989 (24).

On the other hand, green tea may activate numerous other detoxifying enzymes, such as quinone reductase, glutathione/glutathione-*S*-transferases, epoxide hydrolase, and UDP-glucuronosyltransferases, enhancing the activity of these so-called phase II enzymes, to metabolize the carcinogens (25, 26).

III. Green tea inhibits tumor promoters (e.g. TPA, enhancer of the effects of many carcinogens).

Topical application of a green tea polyphenol fraction on the mouse skin can inhibit the effects of the tumor promoter, 12-O-tetradecanoyphorbol-13-acetate (TPA), on the initiation of tumor induced by benzo[α]pyrene- and 7,12-dimethylbenz[α]-anthracene (DMBA). Topical application of the green tea polyphenol fraction also inhibits TPA-induced inflammation, ornithine decarboxylase activity, hyperplasia and hydrogen peroxide formation (27).

IV. Green tea inhibits inducible NO-synthase and cyclooxygenase-2

Chronic inflammation is associated with excessive release of nitric oxide (NO) and superoxide anion (oxygen with one extra electron) which can react together to yield peroxynitrite ($ONOO^-$). The latter compound can eventually cause damage to the DNA, inducing cancer formation. Green tea polyphenols are potent inhibitors of nitric oxide synthase gene expression, thus performing an important function of cancer prevention (28, 29)

Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are important enzymes that mediate inflammatory processes. Green tea suppresses improper up-regulation of COX-2 and/or iNOS, which is associated with pathophysiology of certain types of human cancers as well as inflammatory disorders. A green tea ingredient, (-)-epigallocatechin gallate (EGCG) may inhibit COX-2 and iNOS expression by blocking improper activation of a transcription factor, nuclear factor-kappa B [NF-kappa B] (10).

V. Green tea catechins are antioxidants to free radicals, thus reducing DNA damage by carcinogens, e.g. UV lights.

The most remarkable cancer chemopreventive effect of green tea (or its components) is due to its antioxidative activity. In the skin, oxidative stress induced by ultraviolet irradiation can be readily observed. The pathological changes may be in the form of erythema, edema, epithelial hyperplasia, dysplasia to skin cancer. Topical application of EGCG to human skin before UV irradiation decreases the UV-induced erythema, UV-induced production of hydrogen peroxide and nitric oxide in both epidermis and dermis. The degree of UV-induced infiltration of inflammatory leukocytes into the skin which are considered to be the major producers of reactive oxygen species is markedly reduced by EGCG pretreatment. The latter treatment also restores the UV-induced decrease in glutathione level and protects the antioxidant enzyme glutathione peroxidase (30). At high concentration, EGCG which is an antioxidant may have pro-oxidative activities causing generation of hydrogen peroxide, functioning as a mediator to apoptosis (31).

VI. Green tea inhibits telomerase that co-determines the division capacity of a cell.

More than 85% of all cancers express telomerase activity whereas most somatic cells appear to lack detectable levels of telomerase. Germ line cells also express telomerase activity, but they have longer telomeres than cancer cells. A group of researchers discovered that EGCG is a strong inhibitor of telomerase, and suggested that telomerase inhibition may be one of the major mechanisms underlying the anticancer effects of tea (32).

VII. Green tea inhibits DNA topoisomerases I and II which regulate DNA topology in cell division.

DNA topoisomerases I and II are essential for proper DNA rejoining and structural configuration during cell proliferation. DNA topoisomerases are the target of many anticancer drugs. Like doxorubicin, EGCG is a DNA topoisomerase inhibitor against cancer cells, but

without its toxicity to normal tissues (12, 13). In addition, 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-κB), 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 *p*53 suppressor genes.

Green tea and its components significantly restore cancer cell apoptosis (39). They also affect *p*53 gene mutations. However, the cancer chemopreventive efficacy of green tea may be independent of *p*53 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 μM) 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, 1st	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, 1st	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, 1st	Reference	Reduced Cancer Risk
Goto R	65	yes
Ji BT	66	yes

Colorectum

Author, 1st	Reference	Reduced Cancer Risk
Inoue M	48	yes
Ji BT	66	yes
Kato I	67	yes
Kono S	68	yes
Nakachi K	57	yes
Oguni I	58	yes

Urinary Bladder

Author, 1st	Reference	Reduced Cancer Risk
Nagano J	69	no
Ohno Y	70	yes
Wakai K	71	yes

Prostate

Author, 1st	Reference	Reduced Cancer Risk
Jian L	72	yes

Lung

Author, 1st	Reference	Reduced Cancer Risk
Ohno Y	73	yes
Zhong L	74	yes

Breast

Author, 1st	Reference	Reduced Cancer Risk
Inoue M	2	yes
Nakachi K	75	yes
Oguni I	58	yes
Wu AH	76	yes

Liver

Author, 1st	Reference	Reduced Cancer Risk
Mu LN	50	yes
Nakachi K	57	yes
Oguni I	58	yes

Uterus

Author, 1st	Reference	Reduced Cancer Risk
Oguni I	58	yes

Ovary

Author, 1st	Reference	Reduced Cancer Risk
Zhang M	77	yes
Binns CW	78	yes

Overall Cancer Rate

Author, 1st	Reference	Reduced Cancer Risk
Fujiki H	1	yes
Fujiki H	79	yes
Imai K	80	yes
Nakachi K	81	yes
Nagano J	69	no

Based on the data published in the literature, there is overwhelming evidence supporting the conclusion that regular consumption of green tea as practiced in the traditional Eastern culture is associated with reduced cancer risk in general and in many specific organs, including the esophagus, stomach, pancreas, colorectum, urinary bladder, prostate, lung, breast, liver, uterus and ovary. There are a few reports in which the data did not support such conclusion. A careful analysis of these latter reports revealed that several confounding factors in their research designs might have contributed to the lack of observed reduction in cancer risk associated with green tea consumption. For example, in one study, the purpose was to study thermal effects of the drinking fluid as a causative factor in carcinogenesis and green tea was used as a drink at high temperature for the testing (49). The conclusion was that drinking scorching "hot" green tea (or any other hot fluid) might be associated with a higher risk of developing esophageal cancer. In other series in which no benefits of tea consumption were observed in the tea drinkers living in rural northern Japan or in locations (54, 61) where the quality of green tea consumed was not comparable to that of the teas consumed in the traditional tea-producing prefectures in the South. The traditional or habitual methods of preparing tea drinks, especially the frequency of renewing tea leaves in the tea pot, might have influenced the daily intake of the bioactive substances ingested in different local populations and the observed cancer rates (69). Therefore, when data were pooled from different communities to perform large-scale statistical analyses (52, 54), the results might be difficult to interpret. The lack of a total agreement in the published human epidemiological data indicates the need for standardization of the quality of the green teas, the method of tea preparation and the dosage of the tea to be consumed if green tea is to be incorporated into our diets for cancer prevention.

Tea

All teas are manufactured from the leaves of the same plant species, *Camellia sinensis*, or *Thea sinensis* on the FDA "Generally Recognized As Safe" (GRAS) Substances list. However, the composition of the tea leaf varies with climate, season, horticultural practices, variety, and the age of leaf which is determined by its position on the harvested shoot. In the classic Chinese literature in which much of the information about the science and technology developed in ancient China is buried, tea always means non-fermented or non-oxidized tea leaves. The words "oolong tea" and "black tea (***red tea*** in Chinese)" were not in existence until after the collapse of the Ming dynasty in 1644 AD. Even to this date, the word "tea" means only "green tea" in the Japanese language, a tradition tracing back to the Tang dynasty.

Among several hundreds of chemicals which have been identified in the tea leaves, the polyphenols, especially the catechin group of the flavanols, and the unusual tea amino acid, theanine, are the most studied in connection with cancer research. For the standardization of methodology and for reproducibility of experimental results, most investigators involved in green tea research in the laboratory have chosen EGCG or theanine as the convenient materials for their protocol designs. However, the anticancer benefits of green tea cannot be attributed to the action of a single tea catechin or an

isolated amino acid, but rather the combined effects of a complex mixture in a natural tea drink. Other beneficial bioactive tea ingredients may have yet to be discovered. Below is a short summary of the essential information currently available which may be helpful for understanding the basic biology of the tea leaf as related to our daily practice.

There are six principal catechins, namely (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate, (-)-epigallocatechin, (-)-epicatechin, (+)-gallocatechin and (+) catechin in a fresh tea leaf. EGCG is the most abundant and constitutes 7-13% of the dry weight of the fresh tea leaf. It is one of the most active antioxidants if not the most active found in teas, and is often used as a surrogate yardstick to measure the antioxidant level of a natural tea drink. For example, the US National Cancer Institute defines that a "typical" green tea drink contains 710μg/mL EGCG (82). In experimental animal cancer studies, the tea drink was adjusted to a concentration containing 708μg/mL EGCG before it was administered orally to the laboratory mice (6).

Catechins are small polyphenol molecules in the tea leaf. They undergo oxidation, polymerization and epimerization readily and lose their antioxidant activities as a result. In the intact tea leaf the catechins are compartmentalized in vacuoles of various sizes confined by delicate membranes and anatomically located in the spongy mesophyll between the two layers of epithelial cells. The catechins are shielded from contact with an endogenous enzyme, polyphenol oxidase. As soon as a tea leaf is plucked from the live shoot, "postmortem" changes set in immediately. The process is accelerated by mechanical damages done to the leaf. Breakdown of the internal structure of the tea leaf puts the polyphenol oxidase (the enzyme) in contact with the catechins (the enzymatic substrate). Since the tea catechins are very strong reducing molecules, they are almost oxidized instantaneously upon contact with polyphenol oxidase in the presence of molecular oxygen. By controlling the degrees of oxidation, a process mistakenly thought to be fermentation in the past, oolong tea and black tea are produced with some newly added aromas as a result of oxidation and polymerization of the tea catechins. The tea catechin molecules carry loosely attached electrons, and are ready to give them away as electron donors. However**,** after they lose their electrons upon oxidation, the former tea catechins, now just called polyphenols, can no longer function as antioxidants. They may polymerize to form large polyphenol molecules, for example, the theaflavins, thearubigens, and many others, which account for the brownish and blackish colors of the oolong tea and black tea, and for some of their bitter tastes. It is very important to inactivate the polyphenol oxidase as soon as the tea leaves are harvested if high-antioxidant green teas are to be manufactured.

The polyphenol oxidase in tea leaf is most active at 40-45ºC and is inactivated at 70ºC. The art for green tea production is to inactivate this enzyme quickly, but not to overheat the tea leaves. Heating applied too slowly will induce violent oxidation at the temperature range around 40-45ºC, turning the tea into "black" leaves. Overheating will denature the antioxidants and introduce a burnt smell into the tea leaves. The principle of preserving the high-antioxidant properties of fresh tea leaves by heat was perfected in the Song dynasty (960-1279 AD) with only minor technical variations in the ensuing centuries. The top-grade tea harvested in the early spring of each year, properly preserved in tightly pressed small cakes and sealed in bees-wax wraps for oxygen exclusion packaging, considered good enough as "tribute tea" for the emperors and for those with power and means was priced at two ounces of pure gold per one pound of tea net weight (83). Based on a recent market survey conducted in China, Taiwan and Japan, this pricing ratio between gold and the top-grade tea has been found to be remarkably stable over the past 1,000 years.

While tea catechins exist only in a negligible amount in black tea, theanine can generally survive the oxidation process during manufacturing of black teas. Theanine is an N-methylated derivative of glutamine. It constitutes about 2% of the dry weight which is about one half of the total amino acid content in tea leaves and accounts for most of the sweet taste in quality green tea drinks. In addition to its effects on modulating the intracellular concentration ratio of doxorubicin between cancer cells and normal cells, theanine may prime certain human T lymphocytes for memory and nonmemory cytokine responses, thus may boost the immune system against cancer cells (84).

There is 2.5-4.5% caffeine in dry green tea leaves. The amount of caffeine in the tea drinks also depends on the methods of extraction. In general, the amount of caffeine in the green tea drink is about one third (1/3) of that in black tea and is about 1/10 to 1/5 of that in brewed coffee. Caffeine is known to be anti-initiative against carcinogenesis by inhibition of intracellular accumulation of certain carcinogens (85). Even the oxidized products of EGCG, such as theaflavins in black tea, still have significant growth-inhibitory activities against human cancer cells although not as potent as EGCG (86). Therefore, it is not certain if any processed products of green tea, including the de-caffeinated green tea, will deliver the same health benefits of the natural green tea. An ethanolic extract product of green tea marketed in several European Union member states has been found to cause hepatotoxicity in women (87), indicating that deviation from the traditional methods of tea preparation with hot water extraction may be associated with unexpected adverse side-effects or lack of potential health benefits.

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 28-30º 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 710μg/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 710μg/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/m^2 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 100ºC (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 90-92ºC 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.

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