Review

The Past and Future of Studies on Tea and Cancer Prevention

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Tea (Camellia sinensis, Theaceae) is the most popular beverage in the world. Tea preparations are classified into four types: green, black, oolong and pu-erh teas. The cancer-preventive effects of tea extracts and tea polyphenols have been demonstrated in various experimental systems of mutagenesis and carcinogenesis. Anticarcinogenic effects of tea polyphenols have been reported in the tissues/organs of skin, esophagus, stomach, colon, bladder, lung, liver, pancreas, prostate, and mammary glands of various animal models. These effects are believed to be based on green tea catechins and black tea theaflavins. Polyphenols play potential roles in reducing oxidative stress, modifying carcinogen metabolism, enhancing DNA damage repair, inhibiting tumor promotion and metastasis, and/or modulating cell-cycle arrest, apoptotic death of pre-cancerous/cancerous cells, and oncogenic signal transduction. Indeed, much evidence on the cancer preventive effects of tea polyphenols has been reported in vitro and animal experiments. However there is insufficient and inconsistent evidence for the association between tea consumption and cancer incidence or mortality in humans. This review includes perspective on: 1) antimutagenic and anticarcinogenic effects in vitro systems; 2) anticarcinogenic effects in animal models; 3) molecular mechanisms of anticarcinogenesis; 4) biotransformation and pharmacokinetics of tea catechin; 5) epidemiological studies; and 6) possibilities of human cancer prevention by tea polyphenols and future problems for clarification.

Key words: tea polyphenols/catechins, cancer prevention, antimutagenesis, anticarcinogenesis, target molecules of EGCG

Introduction

Tea (Camellia sinensis, Theaceae) is the most popular beverage in the world. Tea preparations are classified into four types, green, black, oolong and pu-erh teas, according to the manufacturing technique. The relative production is approximately 78, 20, and 2% in black, green, and other teas, respectively. Tea preparations contain varying amounts of polyphenols, including tea catechins in green tea, and red to brown pigments such as theaflavins and thearubigins in black tea. Green tea preparations consist of catechins (30–42%), flavonols (5–10%) and other flavonoids (2–4%), theogalin (2–3%), gallic acid (0.5%), quinic acid (2%), theanine (4–6%), and methylxanthines (7–9%), while black tea preparations consist of catechins (3–10%), flavonols (6–8%), theaflavins (3–6%), thearubigins (12–18%), and methylxanthines (8–11%). Caffeine, a representative methylxanthine, accounts for 2–5% of the water-soluble material in any type of tea leaves, and modulates the physiological effects of other tea ingredients (1,2,10). Green tea extract contains many polyphenols, known as catechins, including (-)-epigallocatechin-3-O-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-O-gallate (ECG), and (−)-epicatechin (EC). Among them, EGCG is the most abundant, well-studied, and potent cancer-preventive polyphenol in in vitro or experimental animal systems. However, the mechanisms for anti-carcinogenic activity of EGCG remain unclear.

The possible cancer-preventive activity by tea drinking has received much attention in the past three decades (3–14). Accumulating evidence on the anti-cancer activity of tea drinking has focused mainly on the tea catechins, especially EGCG, because the chemically defined EGCG and EGCG-enriched fractions such as Polyphenon E (PolyE) were provided by a tea manufacturer. Moreover, the cancer-preventive activity of tea extracts and tea polyphenols has been demonstrated in various experimental systems of mutagenesis and carcinogenesis (3–5). Anticarcinogenic effects of tea polyphenols have been reported in the tissues/organs of skin, esophagus, stomach, colon, bladder, lung, liver, pancreas, prostate, and mammary glands in various animal models (8,11,12). Polyphenols play potential roles in many mechanisms, including reduction of oxidative stress, modification of carcinogen metabolism, prevention/repair of DNA damage, cell cycle arrest, suppression of tumor promotion, apoptotic death in pre-cancerous/cancerous cells, inhibition of metastasis, and modulation of oncogenic signal transduction (6,8).

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EGCG has recently been reported to bind to specific targets, i.e., the 67-kDa laminin receptor, vimentin and Fyn, which may alter the downstream signal transduction benefiting suppression of tumor formation (6,13). Indeed, much evidence on the cancer preventive effects of tea polyphenols has been reported in in vitro and animal experiments, but there is insufficient and inconsistent evidence on the associations between tea consumption and cancer incidence and mortality (7). To understand the relationship of tea drinking and cancer risk in humans, future translational studies need to reduce the discrepancies between non-human and human studies. This review discusses the following perspectives: 1) antimutagenic and anticarcinogenic effects in in vitro systems; 2) anticarcinogenic effects in animal models; 3) molecular mechanisms of anticarcinogenesis; 4) biotransformation and bioavailability of tea catechin; 5) epidemiological studies; and 6) possibilities of human cancer prevention by tea polyphenols and future problems for clarification.

Trend of Studies on Tea and Cancer Prevention

Based on a literature search for tea polyphenols and cancer using Medline (PubMed), 154 articles were reported during 1981–1990, 686 during 1991–2000, and 1887 during 2001–September 13, 2010 (Fig. 1). Initially, these kinds of scientific studies were initiated in the 1980s by Japanese investigators such as Kada et al. (15), who focused on the antimutagenic effects of tea polyphenols, and Oguni et al. (16), who connected tea drinking with human health benefits, especially the prevention of stomach cancer, in an epidemiological study in Shizuoka Prefecture, Japan. During the first decade, tea science-centered on the inhibition of mutagenic and carcinogenic events in in vitro and experimental animal systems. In the following decade, investigations on tea and cancer prevention spread throughout the world, and since then, over 200 articles related to tea polyphenols and cancer prevention have been published every 5 years. The focus of these studies has shifted from non-human to human subjects, in addition to an emphasis on elucidating the mechanism of EGCG actions.

Antimutagenic and Anticarcinogenic Effects in in Vitro Systems

In 1984, Okuda et al. (17) reported the inhibitory activities of tea catechins on the mutagenesis induced by chemical mutagen in Salmonella Typhimurium TA98 and TA100 for the first time, followed by Kada et al. (15) in 1985, who reported the suppressive activity of EGCG on spontaneous mutation in Bacillus subtilis NIG1125. After that, accumulating evidence has suggested that tea extracts and tea polyphenols inhibit or suppress mutagenic events in bacterial and mammalian cell culture systems. These antimutagenic events were summarized as deactivation of mutagens directly or indirectly (des-mutagenesis) and suppression of mutagenic process of cells, including induction of the excision repair system (bio-antimutagenesis) (3). Des-mutagenic actions include the reduction of mutagenic substances mediated by tea polyphenols via chemical and/or enzymatic processes, and bio-antimutagenic actions include the inhibitory or suppressive effects by polyphenols on the cellular mutagenic process such as DNA adduct formation and the repair system of DNA damage.

In the 1990s, the inhibition of the tumor promotion process by green or black tea preparations, tea catechins, and theaflavins was demonstrated using mammalian cells. Using JB6 epidermal cell lines which can
detect tumor promoting events in vitro, Nakamura et al. (18) reported the inhibitory effect of tea extracts, EGCG, and theaflavins on the neoplastic transformation induced by 12-O-tetradecanoylphorbol 13-acetate (TPA) in 1995, while Dong et al. (19) revealed that tea catechins inhibited tumor promotion-inducible events such as activator protein 1 (AP-1) activation, NFκB induction, and c-Jun phosphorylation induction in 1997.

Many articles have reported inhibition of carcinogenesis-related events by tea extracts or tea catechins, including modulation of signal transduction pathways that lead to the inhibition of cell transformation and proliferation, cell-cycle arrest, induction of apoptotic cell death in preneoplastic or neoplastic cells in in vitro mammalian cell systems and inhibition of tumor cell invasion, and inhibition of angiogenesis in tumor tissues in in vitro-in vivo systems (8).

**Anticarcinogenic Effects in Animal Models**

Based on a two-stage carcinogenesis protocol, Yoshizawa et al. (20) showed for the first time in 1987 that EGCG significantly inhibits DMBA/teleocidin-induced skin tumorigenesis in mice. Thereafter, inhibitory activities of green and black tea polyphenols have been demonstrated in various animal models targeting various tissues/organs (i.e., skin, lung, oral cavity, esophagus, stomach, small intestine, duodenum, colon, liver, pancreas, bladder, prostate, and mammary glands), with few negative results, as summarized in Table 1 (8). There are several inconsistent data in rat colon tumorigenesis studies: Wargovich et al. (21) reported a marginal effect and Hirose et al. (22) and Weisburger et al. (23) reported a lack of inhibition, whereas Hirose et al. (24) reported enhancement. Although the possible reasons for the inconsistent results are stated in the review by Yang (13), they are still unclear, as introduced below.

**Molecular Mechanisms of Anticarcinogenesis**

It is commonly believed that the inhibitory effects against various experimental animal carcinogenesis studies are due to the antioxidative properties of tea polyphenols and their biological activities (13).

Tea polyphenols as natural compounds have strong activities against oxidative stress in the body through the trapping effects of metal ions and reactive oxygen/nitrogen species (i.e., ROS and NOS), although the reagent-grade tea catechins used in cell culture experiments act as prooxidants. Attention needs to be paid to the redox properties of antioxidative tea catechins, which may act as antioxidants or prooxidants in the human body; although still unclear, the inconsistent results of the effect of these compounds in animal carcinogenesis experiments might be attributed to their redox properties.

Tea polyphenols also modify various enzymes, especially those of the CYP family, to reduce the formation of mutagenic and carcinogenic compounds or to enhance their detoxification. Although these enzyme modifications occur at relatively high concentrations of tea polyphenols, EGCG can bind to some proteins on a much lower, micro- to nanomolar order to reduce the carcinogenic signal transduction. Such proteins include the plasma protein fibronectin; fibulogen; histidine-rich glycoprotein (25), which may act as a carrier protein of EGCG; Fas death receptor, which mediates the cascade for apoptotic cell death (26); the 67-kDa laminin receptor (67-LR), which acts as an EGCG receptor and possibly leads to the reduction of downstream carcinogenic signal transduction (27); vimentin, an intermediate filament protein (28); zeta chain-associated 70-kDa protein kinase (29); Fyn, a downstream kinase of EGF receptor resulting in inhibition EGF-induced cell transformation (30); and molecular chaperone glucose-regulated protein 78 (31). In 2004, 67-LR was identified as a cell surface receptor for the EGCG that may suppress tumorigenic cell growth (32). Tachibana et al. proposed the mechanism of that through both the cell surface receptor 67-LR and eukaryotic translation elongation factor 1 (eEF1A), EGCG induces reduction of the myosin phosphatase targeting subunit 1 phosphorylation at Thr-696, the activation of myosin phosphatase and inducing dephosphorylation of myosin regulatory light chain may result in growth inhibition in cancer cells.

All of these proteins, being directly bound to EGCG at their various concentrations, play important roles in carcinogenesis. EGCG was reported to bind the 67-kDa laminin receptor with a $K_d$ of 40 nM, and vimentin with a $K_d$ of 3.3 nM; such concentrations of EGCG are

### Table 1. Results of animal model studies on tea and cancer prevention

<table>
<thead>
<tr>
<th>Tissue/organ</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>24 (1)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>19 (1)</td>
<td>2</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Colon</td>
<td>7 (2)</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>8 (5)</td>
<td>4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>92 (15)</td>
<td>13</td>
</tr>
</tbody>
</table>

It is commonly believed that the inhibitory effects against various experimental animal carcinogenesis studies are due to the antioxidative properties of tea polyphenols and their biological activities (13).

Tea polyphenols also modify various enzymes, especially those of the CYP family, to reduce the formation of mutagenic and carcinogenic compounds or to enhance their detoxification. Although these enzyme modifications occur at relatively high concentrations of tea polyphenols, EGCG can bind to some proteins on a much lower, micro- to nanomolar order to reduce the carcinogenic signal transduction. Such proteins include the plasma protein fibronectin; fibulogen; histidine-rich glycoprotein (25), which may act as a carrier protein of EGCG; Fas death receptor, which mediates the cascade for apoptotic cell death (26); the 67-kDa laminin receptor (67-LR), which acts as an EGCG receptor and possibly leads to the reduction of downstream carcinogenic signal transduction (27); vimentin, an intermediate filament protein (28); zeta chain-associated 70-kDa protein kinase (29); Fyn, a downstream kinase of EGF receptor resulting in inhibition EGF-induced cell transformation (30); and molecular chaperone glucose-regulated protein 78 (31). In 2004, 67-LR was identified as a cell surface receptor for the EGCG that may suppress tumorigenic cell growth (32). Tachibana et al. proposed the mechanism of that through both the cell surface receptor 67-LR and eukaryotic translation elongation factor 1 (eEF1A), EGCG induces reduction of the myosin phosphatase targeting subunit 1 phosphorylation at Thr-696, the activation of myosin phosphatase and inducing dephosphorylation of myosin regulatory light chain may result in growth inhibition in cancer cells.

All of these proteins, being directly bound to EGCG at their various concentrations, play important roles in carcinogenesis. EGCG was reported to bind the 67-kDa laminin receptor with a $K_d$ of 40 nM, and vimentin with a $K_d$ of 3.3 nM; such concentrations of EGCG are
sufficiently attractive for target molecules suppressing carcinogenesis, because the expected human blood concentration of EGCG is 0.1–0.6 μM after drinking an equivalent of 2–3 cups of green tea (33). Many target molecules for tea polyphenols have been identified; however, whether the mechanisms act in a similar nature in vivo has yet to be confirmed. As human cancer is complex and multiplex, target molecules of EGCG may differ depending on the cancer site and there may be multiple targets for each case of cancer.

Bioavailability and Pharmacokinetics of Tea Catechins

Extensive studies on the biotransformation of green tea polyphenols were conducted in the 2000s, as summarized by Yang et al. (13). Generally, when green tea is ingested, flavan-3-ols are absorbed, metabolized and then appear in the blood and urine. EGCG has been detected in the blood in its intact form and as metabolites, reaching the micromolar level in plasma. Its absorption appears to occur in the small intestine, while the remaining amount enters the colon, where it is degraded by microbes.

Tea catechins are basically metabolized by methylation, glucuronidation, sulfation, and ring-fission. Lu et al. (34,35) demonstrated that EGCG is enzymatically converted by catechol-O-methyltransferase to EGCG-4’-O-methylate and 4’,5’-O-di-methylates, and also by glucuronidase to EGCG-4’-O-glucuronide as a major metabolite in humans, mice and rats. As ring-fission metabolites of tea catechins in human urine and plasma after oral ingestion of decaffeinated green tea, three hydroxyphenyl-γ-valerolactone derivatives (e.g., 5-(3’,4’,5’-trihydroxyphenyl)-γ-valerolactone) have been identified (36). The valerolactone derivatives are assumed to be formed by colon microbial metabolism.

Modulation of bioavailability of EGCG and tea catechins by chemical agents and food components has been shown in several studies. Indomethacin increases the intracellular accumulation of EGCG and its 4’-O-methylate via multi drug resistance-associated protein (37). Co-administration of various ratios of EGCG and caffeine by human volunteers led to a 1.6-fold increase in the area under the plasma EGCG concentration-time curve (857 ng·h/mL for EGCG alone to 1370 ng·h/mL for EGCG 95 mg/caffeine 40 mg) (38). This finding supports the idea that consuming tea infusion is more beneficial to human health than the use of purified EGCG or the tea catechin fraction, as implied by Bode and Dong with the statement, “united they work, divided they fail” (39).

Many pharmacokinetic studies of tea catechins were undertaken in mice, rat, and humans, as reviewed by Yang et al. (40). For instance, a rat model administered decaffeinated green tea (200 mg/kg) had plasma levels of EGCG, EGC, and EC (conjugated and non-conjugated forms) with elimination half lives of 165, 66, 67 min and absolute bioavailability of 0.1, 14, and 31%, respectively (41). Moreover, the bioavailability of EGCG administered orally was higher in mice than in rats, emphasizing the fact that differences in the absorption and elimination can be found even in the same rodent species. The plasma concentration of EGCG in rats given orally with green tea extract containing 50 mg/kg of EGCG exhibited elevated concentration between 1 and 3 h with a peak concentration of 65 ng/mL (147 nM) at 2 h and falling to low level of 7 ng/mL (16.5 nM) by 5 h (42).

Several human studies on the bioavailability of green tea or catechins have been conducted. In an experiment of human volunteers orally administered green tea 20 mg solids/kg body weight, the peak of plasma concentration (Cmax) for EGCG, EGC, and EC was 77.9, 223, and 124 ng/mL (176, 728, and 427 nM), respectively (43). Plasma EGCG was present in its free form at 77%, whereas EGC and EC were present mainly in conjugated forms of glucuronide or sulfate. Methylated EGC and EGCG were detected in plasma and urine, ring-fission metabolites of catechins were also identified in urine. On the other hand, Auger et al. recently reported the bioavailability of PolyE flavan-3-ols in humans with an ileostomy (44). PolyE is a tea catechin fraction provided by Mitsui Norin Co. Ltd. that contains EGCG, EGC, ECG, and EC at a molar ratio of 68:6:4:0:7:1:15:8%. Five individuals with an ileostomy ingested PolyE 200 mg in capsule form and the absorption of flavan-3-ols in the small intestine was investigated. Approximately 40% of tea catechins was recovered in the 24-h ileal fluid, and a substantial quantity was absorbed in the small intestine. Fourteen metabolites were identified, including glucuronides, sulfates, and methylated derivatives in the urine, and were classified into two metabolites, (epi)catechin and (epi)gallocatechin, representing 47±2 and 26±9% of the ingested parent compounds, respectively. The rather high recovery levels of urine metabolites indicated that the bioavailability of flavan-3-ols is much higher than that of most dietary flavonoids, which is supported by another green tea drinking study (45). Moreover, following intake of 500 mL Choladi green tea containing 648 μmol flavan-3-ols by 10 healthy individuals, the Cmax was 29–126 nM (EGCG: 55 nM, EGC: 25 nM) at 1.6–2.3 h after ingestion; urinary catechin metabolites corresponded to 11.4% of (epi)gallocatechin intake, while (epi)catechin metabolites detected amounts equivalent to 28.5% of (epi)catechin intake.

Epidemiological Studies

Starting from the epidemiological study by Oguni et al. (16) on the relationship between green tea consum-
Table 2. Number of studies on tea consumption and human cancer risk

<table>
<thead>
<tr>
<th>Tea</th>
<th>Tissue/organ</th>
<th>Cohort study</th>
<th></th>
<th>Case-control study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk reduced</td>
<td>No association</td>
<td>Risk increased</td>
<td>Total</td>
</tr>
<tr>
<td>Green tea</td>
<td>Lung</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Kidney and Bladder</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>9 (28.1)</td>
<td>20 (62.5)</td>
<td>3 (9.4)</td>
<td>32</td>
</tr>
<tr>
<td>Black tea</td>
<td>Lung</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Kidney and Bladder</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>7 (13.7)</td>
<td>39 (76.5)</td>
<td>5 (9.8)</td>
<td>51</td>
</tr>
</tbody>
</table>

Ju et al. in 2007(8) modified by the author in part. The percent is in parentheses.

Tea and Cancer Prevention

ption and stomach cancer risk in Shizuoka Prefecture, Japan, many review articles on this subject have been published since the 1990s. The International Agency for Research on Cancer (IARC) estimated the effects of tea on cancer and concluded that “there is inadequate evidence for the carcinogenicity in human and experimental animals of tea drinking” (46). The World Cancer Research Fund/American Institute for Cancer Research (47,48) changed the assessment on the cancer-preventive effect of tea from “green tea possibly protects against stomach cancer (1997)” to “that was not supported by the current review (2007)”, because the evidence was too limited to draw clear conclusions.

In the review by Ju et al. (8) of approximately 200 epidemiological studies on the association between tea consumption and human cancer risk in 2007, a lower cancer risk was more frequently observed in case-control studies (50%) than cohort studies (28%) in Asian countries where green tea is consumed, while it was less frequently observed in black tea-consuming countries in both case-control studies (30%) and cohort studies (14%) (Table 2). These results might be affected by the different parameters employed in each investigation. That is, assessing the quantity of tea consumption is difficult, as bioavailability could vary relative to the manner in which the tea is drunk, i.e., with/without milk, as well as to the target population, country, and kind of tea preparation. Therefore, Yang et al. (13) proposed the use of a biomarker, i.e., the amount of urinary metabolites of (epi)catechin or (epi)gallocatechin, for more accurate estimation of tea catechin intake. Indeed, studies have already implemented such urinary metabolites as indicators of tea consumption (49).

Although the results of epidemiological studies on tea consumption and cancer risk are not yet consistent, several studies that examined the relationship between green tea and prostate cancer deserve our attention (50). Bettuzzi et al. conducted a double blind randomized study by following 60 patients with high-grade prostate intraepithelial neoplasia (HG-PIN) who received green tea catechin extract (200 mg three times a day) or placebo for 12 months. After 1 year, only one tumor was diagnosed among the patients in the green tea group (incidence, approximately 3%) without significant side effects or adverse effects, compared to nine tumors among the patients in the placebo group (incidence, 30%) (51). This was the first study to show that green tea catechins are safe and effective for treating premalignant lesions before prostate cancer develops. The administration of green tea catechins also reduced lower urinary tract symptoms, suggesting that these compounds might also be helpful for treating the symptoms of benign prostate hyperplasia. In a prospective study of nearly 50,000 Japanese men, Kurahashi et al. also found a dose-dependent relationship between green tea con-
Possibilities of Human Cancer Prevention by Tea Polyphenols and Future Problems

In vitro and animal experimental studies have confirmed the antioxidative and anticarcinogenic activities of tea polyphenols over the last three decades. With the strong, yet still insufficient, evidence of cancer preventive activity in animal models, tea polyphenols are anticipated to play a role in human cancer prevention; however, such activity has yet to be consistently observed in human studies, most likely due to confounding factors in epidemiological studies involving differences in eating habits, life styles, genetic backgrounds, and target populations.

To achieve cancer prevention in humans, the following points need to be addressed:

1. What is the bioavailability of tea catechins ingested, as determined by an appropriate marker of 24-h urinary metabolite (e.g., EGC-conjugates) in human or animal efficacy studies investigating the relationship between tea polyphenol ingestion and cancer prevention?
2. What is the active component in tea polyphenols? Is it single or complex?
3. What is the target molecule for the active component? What kind of mechanism is involved in the action? Do they differ between cancer sites?
4. What is the amount of tea polyphenols needed for oral ingestion to achieve the estimated bioavailability in humans?
5. Is the availability of tea polyphenols affected by any factors? Which is the appropriate method to ingest tea polyphenols: with or without food? Which is the appropriate method to ingest tea infusion or the tea catechin fraction such as PolyE?
6. Finally, a well-conducted intervention study needs to be conducted in humans to confirm efficacy.

Acknowledgement: I am greatly indebted to Prof. Kayoko Shimo, University of Shizuoka for giving me the opportunity to deliver the plenary lecture on tea polyphenols and cancer prevention at the 38th Annual Meeting of JEMS (Nov. 2009) and write this review.

References

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