

scientific contact with (–)-epigallocatechin gallate, the main constituent of green tea, kindly provided by Dr. Takuo Okuda. In collaboration with him, previously Professor on the Faculty of Pharmacology at Okayama University, we studied the anticarcinogenic effects of polyphenols derived from medicinal plants and drugs. In 1987, we first reported, in the new British journal *Phytotherapy Research*, that repeated topical applications of EGCG to mouse skin treated with 7,12-dimethylbenz[*a*]anthracene (DMBA) as an initiator inhibited tumor promotion in a two-stage carcinogenesis experiment.¹ These results were the first suggestion that EGCG and tea polyphenols might be cancer preventives. Since then, numerous scientists in Japan and the USA have reported the anticarcinogenic effects of EGCG and tea polyphenols on various organs in rodent experiments.²

Results from a prospective cohort study with over 8,000 individuals in Saitama Prefecture demonstrated clearly that daily green tea consumption of 10 Japanese-size cups delayed cancer onset as well as death of cancer patients.³ This paper reviews the study of EGCG and green tea itself as possible cancer preventive prototypes in a practical sense.

3 Cancer Chemoprevention

Cancer chemoprevention is a new strategy of cancer prevention based on the modern understanding of cancer development in humans; it was defined as 'the prevention of the occurrence of cancer by administration of one or more compounds' by Michael Sporn in 1976.^{4,5} It is now generally known that cancer development in humans is a multi-stage process associated with numerous genetic changes occurring over an extended period of time, usually from 20 to 30 years.⁶ Thus, we have to realize that cancer prevention is essentially different from the prevention of infectious diseases, since cancer is a disease of the aging process, with multistages, while infectious disease is the reaction to a pathogen. My own definition of cancer chemoprevention is, administering cancer preventives to delay the carcinogenic processes in humans, no matter when the carcinogenesis starts, and thereby block the appearance of clinical symptoms.

If we accept my definition, it can now be shown that daily green tea consumption of over 10 cups per day results in delay of cancer onset for healthy persons and leads to more hopeful prognoses for cancer patients following cancer treatment. Since green tea is a common beverage, at least in Japan, we can bring the concept of cancer prevention into our daily life.

4 Anticarcinogenic Effects and Other Preventive Activities

Initially, repeated topical applications of EGCG resulted in inhibition of tumor promotion in a two-stage carcinogenesis experiment on mouse skin.¹ We proposed as a possible mechanism the sealing effect of EGCG; since topical

application of EGCG to mouse skin inhibited interaction of tumor promoters, hormones, and various growth factors with their receptors.⁷ Subsequently, green tea and EGCG in drinking water were found to inhibit carcinogenesis in a wide range of target organs in animal experiments, including esophagus, stomach, duodenum, colon, liver, lung, pancreas, skin, breast, bladder and prostate.^{2,7,8,9}

Furthermore, EGCG and tea polyphenols have antinitiation, antimutagenic, and antimicrobial activities; they inhibit various enzyme activities along with gene expression of inflammatory cytokines related to carcinogenesis; and they enhance activities of some biochemical reactions supporting anticarcinogenesis.^{8,10} Among the demonstrated effects, inhibition of urokinase,¹¹ telomerase,¹² p38 mitogen-activated protein kinase activation¹³ and angiogenesis¹⁴ have attracted attention recently. We also presented evidence that treatment with EGCG induced apoptosis and increased the percentages of cells with G2/M arrest in PC-9 cells.¹⁵

As can be seen above, tea polyphenols have multifunctions and are therefore quite distinct from enzyme inhibitors, which have specific functions. As for the essential activity of tea polyphenols for cancer prevention, we think their reduction of levels of TNF- α and similar cytokines is a common and key criterion.¹⁶

Recently we demonstrated the synergistic effects of EGCG with same standard cancer preventive agents:¹⁷ cotreatment with EGCG and sulindac, or EGCG and tamoxifen, synergistically or additively enhanced induction of apoptosis by EGCG in human lung cancer cell line, PC-9 cells. The results indicate the possibility of administering smaller doses of these chemical agents, with fewer adverse effects.

5 Bioavailability of Tea Polyphenols

Our study with ³H-EGCG (48.1 GBq mmol⁻¹), which was administered into mouse stomach, revealed wide distribution of radioactivity in mouse organs.¹⁸ Radioactivity was found in all reported target organs mentioned in Part 4 above, as well as in other organs (brain, kidney, uterus and ovary or testes) in mice (Table 1). We also found, by microautoradiography, that ³H-EGCG had incorporated into the cytosol as well as the nuclei.

6 Epidemiological Studies

The 10-year follow-up results of a prospective cohort study involving 8,552 individuals in Saitama Prefecture identified 164 female and 220 male cancer patients. Our colleagues who did the study found that cancer onset for patients who had consumed over 10 Japanese-size cups of green tea per day, was 8.7 years later among females, and 3.0 years later among males, than for patients who had consumed under three cups per day (Table 2).¹⁹

The cancer preventive effects of green tea were also found among breast cancer patients following cancer treatment. Our colleagues found that Stage I

Table 1 Incorporation of ³H-EGCG into target organs

Organs	% of total administered radioactivity (24 h after)	Reduction of tumor incidence
Stomach	3.93	62.0 → 31.0
Duodenum	0.35	63.0 → 20.0
Small intestine	5.69	n.d.
Colon	4.52	77.3 → 38.1 67.0 → 33.0*
Liver	0.89	83.3 → 52.2
Brain	0.32	n.d.
Kidney	0.28	n.d.
Lung	0.16	96.3 → 65.5
Pancreas	0.07	54.0 → 28.0
Skin	1.9 × 10 ⁴ /100 mg	65.0 → 28.0*

*: Green tea extract
n.d.: Not determined

Table 2 Average age at cancer onset and green tea consumption from prospective cohort study

	Green tea consumption (cups/day)		
	≤3	4-9	≥10
Males (220)	65.3 ± 1.5 (54)	67.6 ± 1.0 (102)	68.3 ± 1.2 (64)
Females (164)	65.7 ± 1.7 (49)	66.8 ± 1.2 (94)	74.4 ± 2.5 (21)

and II patients consuming over 5 cups per day showed a lower recurrence rate, 16.6%, and a longer disease-free period, 3.6 years, than those consuming less than 4 cups per day.²⁰ The results suggested that green tea is more effective in the early stage of second tumor development, even after the removal of the primary cancer, and that it will result in more hopeful prognoses for breast cancer patients.

7 Two Stages of Cancer Prevention with Green Tea

We have demonstrated the cancer preventive effects of green tea in two stages, cancer prevention before cancer onset and that following cancer treatment. In the former case, the cancer preventive dose of green tea is at least 10 Japanese-size cups per day. Since most Japanese use a medium-size (180 ml) cup for drinking green tea, the effective dose is, then, 360 to 540 mg of EGCG, and 0.8 g to 1.3 g green tea extract, per day.³ For those who, for whatever reason, are unable to drink 10 cups per day, green tea tablets will be a useful supplement to

20000219

以降のページは雑誌／図書等に掲載された論文となりますので
「研究成果の刊行に関する一覧表」をご参照ください。