Camellia sinensis Tea and Cancer Risk: A Systematic Review

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ABSTRACT

Background: This article aims to provide currently available data and insight science knowledge on association between teas, their polyphenols and the risk of cancers including prostate, liver, lung, gastric, breast, colon and colorectal, esophageal, oral cavity, non-hodgkin’s lymphoma, esdometri, and pancreatic based on published studies by searching Pub Med and database of Web of Science belonging Institute for Science Information and secondary referencing qualified for inclusion. In addition, the molecular mechanisms of tea in cancer prevention also briefly discussed. The authors hope that this work will be help for readers, researches, reviewers, and editors who are interested in the related field of the Camellia sinensis tea studies.

Keywords: Camellia sinensis, tea polyphenols, cancer risk, green tea, EGCG.

1. INTRODUCTION

Tea prepared from the leaves of Camellia sinensis species is one of the most world-wide favorite beverages and is consumed by over two-thirds of world’s population. Based on the processing methods and sensory qualities of products, the six types of tea were defined as green, yellow, dark, oolong, white, and black teas [12]. Of which, three types are widely available on the global markets and more often cited as green tea, black tea and oolong tea [13]. The consumption of tea has been believed to have association with cancer risk. Almost of in vitro and in vivo animal model experiments strongly evidenced that tea catechins have cancer inhibitory effects against carcinogenesis at different organ sites [13], while epidemiological studies in humans are not consistent in demonstrating association between tea intake and the risk of cancer [19]. Although there are many published review articles on tea consumption and cancer prevention, to our knowledge, this is the first review article that provides the most complete science knowledge about cancer cell and tumor growth inhibitory effect of tea extracts and their polyphenols in both in vitro and in vivo experiments, and the relation between tea consumption and cancer risk.

2. THE MOLECULAR MECHANISMS OF TEA IN CANCER PREVENTION AS BIOLOGICALLY PLAUSIBLE

2.1 Molecular targets of tea polyphenols in cancer prevention

Reactive oxygen species (ROS) are produced by various endogenous including cytokines, growth factors, and metabolic processes and exogenous substances such as cigarette smoke [5, 6]. Free radicals can be generated in biological systems in the form of ROS [7]. They, comprising various forms of activated oxygen including superoxide radicals, hydroxyl radicals, hydrogen peroxide, and nitric oxide, possess an unpaired electron, which makes them highly reactive and thereby dangerous to all macromolecules, including lipids, proteins and nucleic acids, and cell life [8, 9]. The ROS had been implicated in the etiology of various chronic diseases such as cancer [10]. Their signaling pathway in cancer cells is both ROS-induced tumor progression and ROS-induced tumor apoptosis [5]. Cancer cells produce free radicals and other ROS to help stimulate growth, cell survival, and inflammation, an established source of carcinogenesis [11]. However, the presence of macrophages and neutrophils in the inflammatory process can cause an increase in the production of superoxide and other ROS to toxic levels, eventually leading to tumor cell death and self-destruction [12]. Antioxidants provide an extra electron needed to stabilize or breakdown ROS [12]. Antioxidants scavenge and eliminate these ROS, and help to promote and stimulate apoptosis [5].

Polyphenols, the most investigated components of tea, act as antioxidants. Green tea contains the most plentiful catechin content, including epigallocatechin-3-gallate (EGCG),
epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC), and among them EGC is the highest. The catechin content of black tea is approximately a third compared to green tea because of the process of fermentation. Cell experiments indicated that catechins, especially EGCG could impede DNA damage and tumor promotion through its antioxidant activity, and due to their highly effective free radical scavenging capacity. From the large volume of previous researches on animal models, cancer preventive potential of tea EGCG and other catechins against carcinogenesis at different organ sites was demonstrated. In addition, caffeine in leaves and polysaccharides in flowers also contribute for evidence of antitumor activities. It was found that theaflavins, polyphenolic components of black tea, inhibited DNA cleavage caused by the combination of H$_2$O$_2$ and cytochrome c, and they were expected to act as antioxidants in the cells. Extract and fraction of green tea and black tea were demonstrated to have the scavenging and detoxifying capacity of hydrogen peroxide, superoxide radicals. Although tea polyphenols are considered as antioxidants, it was also recorded that they could produce hydrogen peroxide, and theaflavins also could produce hydrogen peroxide in cell lines. An insight further study on the antioxidant and anticancer molecule mechanisms of tea polyphenols is necessary.

2.2 Inhibition of potential cancer risk factors and cancer cell proliferation

The antimutagenic activity of tea polyphenols was studied via microbial and mammalian in vitro and in vivo models, which was reported. ECG and EGCG showed significant preventing effect against the mutagenicity of Trp-P-2 and N-OH-Trp-2 by applying Salmonella typhimurium TA 98 and TA 100 with or without rat liver S9 mix, and against 6-thioguanine (6TG)-resistant mutations induced by 4-nitroquinoline 1-oxide (4NQO) in Chinese hamster V79 cells. In some animal model studies, oral administration of green tea and black tea can reduce and decrease the tumor initiating potency of the potent mutagen, and the extent of chromosome damage (micronuclei) in the peripheral blood of mice administrated with benzo[a]pyrene. However, it was found that there is no similar protective effect of these teas against the chromosome damaging action of γ-rays.

Inhibition of normal cell transformation factors of tea polyphenols was studied. EGCG can prevent x-ray inducing oncogenic transformation and reduced transformation frequency nearly to spontaneous levels at 15 μM concentration. Administration of 1.25 % green tea extract, with 708 μg/mL of EGCG, as the sole source of drinking water during skin-tumor promotion induced by UV inhibited formation and increased spleen size. Therefore, it can believe that prevention of oncogenic transformation by tea polyphenols is possibly associated with their antioxidant activities by inhibiting free radicals produced during promotion.

Inhibition of cancer cell proliferation of tea and its polyphenols was also reported in some studies. The activities of several key G1 regulatory proteins such as Cdk2 and Cdk4 were inhibited by EGCG. This component also could induce the protein expression of Cdk inhibitors including p21 and p27 in human breast carcinoma cells. EGCG exerts growth-inhibitory effects of mouse and human cancer cell types, such as prostate cancer cells, and induce apoptosis in human chondrosarcoma cells.

3. TEA AND CANCER RISK

3.1 Tea and prostate cancer risk

In relation to prostate cancer, it is found that tea polyphenols could prevent the growth of prostate cancer in animal model studies, the results from a comparative study on the chemopreventive effect of black tea and green tea provided evidence that green tea has the stronger chemopreventive effect. An exploratory meta-analysis of observational researches on green tea and black tea consumption and prostate cancer risk revealed that green tea drinking may have a protective effect on prostate cancer in Asian populations, especially in the Chinese population, while black tea drinking did not exhibit protective effects on prostate cancer. Some other studies, both control-case study and cohort study, also indicated that green tea drinkers have a highly significant inhibition result and reduction in the risk of advanced prostate cancer. However, Yuan and colleagues found that tea drinking could reduce the incidence of prostate cancer in two case studies, but other four cohort studies displayed no preventing effect.

3.2 Tea and liver cancer risk

There are many in vitro and in vivo studies as well as clinical studies on effects of tea polyphenolic constituents in liver cancer. EGCG have been a subject of intense in vitro investigation in hepatoma cell lines. The suppressive effect of EGCG on the growth with an accompanying decrease in the levels of α-fetoprotein was demonstrated on PLC/PFR/5 human hepatoma cells in vitro model. Inhibition of the growth, decrease of proliferation, and inducing apoptosis of EGCG and other catechins on HepG2 human hepatoma cells model were shown. The expression of apoptotic markers such as caspases -3, -8, and -9 as well as a decrease in Bcl-2 expression was exhibited. EGCG, EGC, and theaflavins (theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate B, theaflavin-3), independently, inhibited the proliferation of BEL cells group including BEL-7404/DDX resistant human hepatocellular carcinoma cells, BEL-7404/ADM and BEL-7402/5-FU human hepatocellular carcinoma cells, and BEL-7402 human liver cancer cells, respectively. EGCG decreased cell viability, induced apoptosis, and decreased PAR-mediated invasion and p42/p44 MAPK phosphorylation, and decreased the promoter activity and mRNA expression in HepG3 liver carcinoma cells. Inhibition of proliferation and inducing apoptosis of EGCG and tea polyphenols were also demonstrated in other liver cancer cell in vitro models such as HLF human hepatoma cells, SMMC-7721 liver cancer cells, LI90 human hepatic stellate cells, HuH7 human hepatocellular carcinoma cells, HLE hepatocellular carcinoma cells, and SK-Hep-1 liver carcinoma cells.

Green tea administration via oral resulted in reduce of the formation, both in terms of number and size, of gamma-glutamyl transeptidase positive (GGT⁺)-foci in male Wistar rats treated with the potent hepatocarcinogen aflatoxin B$_1$ (AFB$_1$). Dietary administration of green tea catechins suppressed the GST-P⁺ foci formation in male F344 rats with hepatocarcinoma induced by DENA and subsequently promoted by 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline, by DENA-initiated and promoted by 2,2'-dihydroxy-di-n-propyl nitrosamine, and by 2-amino-6-methylidipirido[1,2-a: 3', 2'-d]imidazole. The antihepatocarcinogenic effects of black tea polyphenols, as evidenced
by reduction of hepatic tumors in Sprague-Dawley rats treated with p-dimethylaminoazobenzene [65, 66].

Evaluating the chemopreventive and therapeutic effects of tea polyphenols in hepatocellular cancer was carried out in a series of clinical trials. However, studies showed major limitations such as improper comparison of control and treatment groups, lack of randomization, and selection bias. Moreover, significant protective effect of green tea consumption on both hepatocellular carcinoma incidence as well as hepatocellular carcinoma-related mortality did not reported in all clinical trials [67]. Although drinking green tea reduced levels of 8-hydroxydeoxyguanosine in patients expressing several risk factors for liver cancer, this result only is in very rudimentary stage [68]. Further studies should be carried out to firm evidence with clinical trials.

3.4 Tea and lung cancer risk

Lung cancer inhibitory activities of green tea and its ingredients have been reported in many animal experiment models. Administration of green tea and black tea, their polyphenols, or EGCG during the initiation, promotion, or progression stage inhibited 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone induced lung tumorigenesis in rats, mice, or hamsters [69-77]. The effects of tea consumption on risk of human lung cancer also have been investigated. One early population-based study demonstrated that green tea consumption was associated with decreased lung cancer risk [78]. Arts (2008) reported that high habitual drinking of green tea significantly lowered the incidence of lung cancer in only 4 out of 20 observational studies [79]. In addition, association between the habit of tea drinking and the risk of lung cancer was reported be no explicit in some studies [80, 81].

3.5 Tea and Breast cancer risk

Green tea and its individual catechin components were effective in inhibiting breast cancer and endothelial cell proliferation. In vivo experiments in rat model found that green tea extract suppressed xenograft size and decreased the tumor vessel density [82]. Regular green tea drinking significantly reduced breast cancer risk, which was reported in case-control studies [83-88], of which two studies showed that the amounts of green tea consumption and the numbers of years of drinking were inversely associated with the breast cancer risk [86, 87]. In addition, the relationship between green tea intake and four biomarkers (sex steroid hormones, mammographic density, insulin-like growth factor, adiponectin) was evaluated and discussed by reviewing human studies [89]. Five prospective cohort studies conducted in Japan, Singapore and Shanghai, China reported that green tea consumption appears to be unrelated to the breast cancer risk [90-95].

For black tea consumption, Sun and colleagues carried out a meta-analysis study based on 13 studies and their findings demonstrated that black tea consumption and breast cancer risk are no association [90]. Two other studies also reported that there is no association between black tea drinking and breast cancer risk [97, 98]. Three studies also failed to find an association between them [99-101]. It was reported that black tea consumption was positively associated with breast cancer risk, but there was unclear statistically significant [102]. Interestingly, Larsson and colleagues (2009) found that high black tea consumption could increase risk of breast cancer with a statistically significant [103]. In recent publication on meta-analysis study, Nei and colleagues (2014) also found that black tea drinking has no effects on breast cancer risk and the relation between black tea drinking and breast cancer incidence remains unclear [104].

3.6 Tea and esophageal cancer risk

In a population-based, case-control study, Gao and colleagues (1994) concluded that there is a positive association of green tea consumption with esophageal cancer risk [105]. A meta-analysis reported that there is a slightly inverse association between green tea drinking and esophageal cancer risk, and it was more evident in Chinese population; black tea consumption has no protective effect in esophageal cancer cases. Results revealed that pooled odds ratio (OR) of the esophageal cancer for highest versus non/lowest green tea drinking was 0.77 (95% confidence intervals (CI): 0.57, 1.04), while there was no significant association between the highest versus no/lowest black tea drinking and esophageal cancer risk (OR=1.35; 95% CI:0.86, 2.11) [108]. Further prospective cohort studies are warranted to evidence the relationships of tea with esophageal cancer risk. In another meta-analysis of published epidemiological studies, it was found that any association between green tea and esophageal cancer risk is unclear [107].

3.7 Tea and gastric cancer risk

One hundred and ninety incident cases of gastric cancer occurring in members of the Shanghai cohort (18 244 Chinese men followed up for up to 12 years) were compared with 772 cohort control subjects. The results indicated that there is a statistically significant inverse association between tea catechins and gastric cancer [108]. By contrast, other studies reported that there is no association between tea consumption and gastric cancer risk [109-111]. In particular, a meta-analysis of 14 epidemiological studies found that the association between green tea consumption and incidence of gastric cancer is unclear [112]. Another meta-analysis of 13 epidemiological studies also found a similar result [113].

3.8 Tea and colon and colorectal cancer risk

A published population-based case-control study from Sweden reported that black tea consumption and colon cancer have no association and an inverse association with rectal cancer [114]. Another study from Japan found a positive association for black tea intake and colon cancer but no association for rectal cancer, while green tea intake was inversely associated with colon cancer risk but there is no association with rectal cancer risk [115]. Three former cohort studies found no association between tea consumption and colon cancer incidence [116-118]. Association between consumption of hot and iced teas and risk of colon and rectal cancers in a population-based, case-control study conducted in Iowa (United States). Results indicated that black tea consumption, either hot or iced, is not related to colon or rectal cancer risk [119].

A number of epidemiological studies have sought to establish a relation between tea consumption and colorectal cancer risk with various results. Green tea drinkers in case-control studies have lower risk of colorectal cancer [120-122] compared to in prospective cohort studies [123,124]. A meta-analysis study based on the findings of four case-control studies exhibited an odds ratio of 0.74 [95% confidence interval (CI): 0.63-0.86] for highest versus lowest green tea consumption, but the combination of four prospective cohort studies indicated no association [relative risk (RR) 0.97; 95% CI: 0.82-1.16] [125]. Wang and colleagues
(2012) reported that although there is limited evidence from studies in support of green tea as potential chemopreventive agents against colorectal cancer, available data from prospective cohort studies are insufficient to believe that green tea may protect against colorectal cancer [126].

3.9 Tea and the risk of other cancers

The relation between tea consumption and the risk of Non-Hodgkin’s Lymphoma (NHL) was concluded in a meta-analysis study. The results revealed that higher green tea intake was related with a 39% reduced risk of NHL in high- versus low-intake meta-analysis. No association was observed between black tea intake and risk of NHL in high- versus low-intake meta-analysis [127].

A meta-analysis of case-control researches demonstrated an inverse association for green tea consumption and endometrial cancer risk, while there was a positive association for black tea consumption [128]. A meta-analysis of prospective cohort researches reported no association between tea intake and endometrial cancer risk, in which it was driven mostly from studies with black tea. Authors believed that it still remains a possibility that green tea may be associated with lower risk of endometrial cancer [129].

A meta-analysis of published epidemiological studies on association between tea drinking and pancreatic cancer risk revealed that tea drinking and pancreatic cancer risk are no related, even at high doses [130].

The growth preventive activities of Pu-erh tea against oral cancer in vitro and in vivo have been studied. The results indicated that Pu-erh tea has inhibitory effect of human tongue carcinoma TCA8113 proliferation and induced apoptosis. In addition, Pu-erh tea administration reduced the levels of tumor necrosis factor-α, and interferon-γ to a greater extent compared with the control group, and also induced apoptosis in mice tissues by upregulating Bax and downregulating Bcl-2 [131].

4. CONCLUSION

In conclusion, studies have revealed anticancer effects of tea with consistently positive results in experiments of in vitro and in vivo animal models, but results on humans show with less consistent, and even conflicting. Whether teas and their polyphenols are able to induce cell death and prevent the migration of cancer cells and they might be useful in treating primary tumor and local migration to lymph nodes? which still demand insight studies and further scrutiny.

5. REFERENCES


HOW TO CITE THIS ARTICLE