Editorial on Nutrition

Green tea and the question of reduced liver cancer risk: the dawn of potential clinical relevance?

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Hepatocellular carcinoma (HCC) has a high incidence and prevalence in some Asian countries and is a major preventable disease. A meta-analysis published in this journal by Huang *et al.* (1) analyzed the chemopreventive potential of green tea in these Asian regions. Cumulative tea consumption, in the highest consumption range (>5 cups per day), the relative risk (RR) was reduced by 22%, with significance only for women, not in men. Results are confined to Asia, as studies from Western countries were not included. This limited effect in a subpopulation of Asian women does not allow a general recommendation for green tea as an HCC preventive. Other effective measures must be pursued including screening for, and vaccination against hepatitis, antiviral treatment, reducing alcohol and high caloric consumption, and avoiding smoking and food contaminated with aflatoxins.

HCC has a high incidence and prevalence in Asian countries and is a major health and economic burden in this region. This calls for new preventive measures in addition to already existing ones. Among the most promising approaches is the promotion of preventive food and beverages. A recent meta-analysis published in this journal focused on green tea and claimed a possible preventive effect of this popular beverage on HCC in Chinese women (1). The authors mentioned chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections as the major etiologic determinants of HCC, with other possible risk factors such as dietary aflatoxin B_1, excessive alcohol use, cigarette smoking, obesity, and diabetes. They also referenced and outlined some previous background information that ingredients of green tea may have protective effects directed to liver cancer, as evidenced by antimutagenic and anticarcinogenic activities of tea polyphenols (1,2). As an example, green tea was shown to inhibit aflatoxin B_1-induced initiation in experimental hepatocarcinogenesis (2).

Previous studies provided unequivocal results of green tea on possible HCC prevention, as referenced in detail (1). Various factors like low case numbers of cohort studies confound the interpretation of these studies, which may be overcome by combing several studies in a meta-analysis as done by Huang *et al.* (1). They included nine prospective cohort studies from China, Japan, and Singapore involving 465,274 participants and 3694 cases of liver cancer. They calculated a summative RR of 0.88, showing a significant reduction of liver cancer only in the group with the highest green tea consumption, i.e., >5 cups per day. Stratification by sex found a significant reduction by green tea consumption only for women (RR 0.78), with a nonsignificant decrease in men (RR 0.89). Most importantly, no reduction in HCC was observed with lower green tea consumption, i.e., one cup per day (RR 0.96). This meta-analysis clarifies that only high green tea consumption may lower the risk for HCC in female citizens of some Asian countries, whereas no protective

Table 1 Differences in HCC etiology in Asian countries as compared to Europe

HCC causes	China	Japan	Singapore	Europe
HBV	77%	11%	35%	13%
HCV	3%	79%	13%	21%
Obesity	1%	NA	NA	16%
Alcohol	3%	NA	NA	10%
Smoking	1%	NA	NA	31%
Aflatoxin B_1	NA	NA	NA	NA
Others	NA	NA	31%	NA

Data for China are derived from the study of Park *et al.* (3), for Japan and Singapore from the report of Zhu *et al.* (4), and for Europe from the analysis of Trichopoulos *et al.* (5). Alcohol refers to high alcohol consumption without clearly defined dose and duration of use; smoking combines previous and current smokers; Aflatoxin B_1 refers to contaminated food. NA, Not available.

effect was seen with low green tea consumption of one cup nor among males These limitations do not warranted a general recommendation for green tea in order to reduce the risk of HCC.

Overall, the results are neither encouraging nor do they hail the dawn of potent chemoprevention by green tea. In fact, a RR reduction of 22% as shown for women under observation (1) is far less than usually expected by clinicians and epidemiologists for effective preventive measures in a high prevalence disease like HCC in Asian countries (3,4). The results presented by the authors of the meta-analysis (1) are to be viewed along the substantial variability in incidence rates of HCC among countries and regions, likely due to variable etiology (3-5). Specific data are available for China, Japan, and Singapore (3,4), from which the meta-analysis studies originated (1), and for Europe (5), as summarized (*Table 1*).

In China, for instance, HBV infection contributes 77% to liver cancer cases and death, while for HCV, corresponding rates of 3% are much lower (*Table 1*) (3). Contribution of aflatoxin B_1 exposure is not separately listed (*Table 1*), as accurate data were not provided for these countries (3-5). In China, alcohol drinking as cause accounts for 3% of the HCC cases, and tobacco smoking for 1% (*Table 1*) (3). In Japan with its high HCC incidence rate, the causes of HCC differ greatly from other countries in the region (*Table 1*). HCV infection is more common than HBV in Japan, and hence HCV accounts for 79% of all HCC cases, as compared to HBV with 11% (4). In a Singaporean cohort of patients, who were 76% of Chinese ethnicity, HCC was caused by chronic HBV in 35%, chronic HCV in 13% (*Table 1*), and other causes in 31% (4).

HCC prevention in Asia should be directed toward effective hepatitis infection surveillance and early diagnosis of HBV and HCV infections. Individuals at risk for HBV infections should be vaccinated, chronic HBV infections treated with effective antiviral therapies including pegylated interferon (Peg-IFN) and/or nucleoside and nucleotide analogues (NAs) as inhibitors of HBV polymerase (i.e., lamivudine, telbivudine, entecavir, adefovir and tenofovir). For patients with chronic HCV infection also, the spectrum of therapeutic possibilities is variable and includes direct acting antivirals (DAAs) such as sofosbuvir, simeprevir and daclatasvir. At present, green tea alone or in combination with antiviral therapy certainly has no place for prevention of HCC by chronic HBV or HCV infections. Promoting green tea to treat such virus infections would be hazardous, especially if infected patients would abstain from effective antiviral treatment in the erroneous belief that green tea alone would be an effective preventive beverage.

The meta-analysis did not elucidate which etiology of HCC would benefit from green tea; the included cohort studies indicate that the preventive effect is higher in China and Japan as compared with Singapore (1). The reason for this difference among countries remains unclear.

As compared with the Asian region, conditions for HCC and its causative agents are different in Western areas such as Europe (*Table 1*) (5). Here, HCC is predominantly caused by smoking, contributing up to 31% of all HCC cases in either former or active smokers. Corresponding values for hepatitis infections were 21% for chronic HCV, 13% for chronic HBV, 16% for obesity, and 10%

for heavy alcohol consumption. To prevent HCC in Western countries, recommendations include changing life-style habits by reducing tobacco use, caloric intake, and alcohol consumption; if followed consequently, these measures could reduce the HCC incidence by almost two-third (5). However, green tea extracts that are marketed for weight reduction are not recommended due to their postulated dose-dependent hepatotoxicity (6,7); causality for green tea extracts was confirmed in some of these cases using the robust RUCAM (Roussel Uclaf Causality Assessment Method) algorithm or positive unintentional reexposure toxicities. As opposed to the extracted catechins, consumption of green tea beverages in normal amounts is not associated with a liver injury risk (7), while many other herbal TCMs (Traditional Chinese Medicines) show such an association (8).

On a molecular basis, green tea contains several catechins as major ingredients, which are seen as biologically active agents (1,2,6,7,9-13); one hypothesis assumes that the decreased carcinogen activation by catechins is the basis for the tumor prevention. However, most experimental studies have used laboratory animals, cell cultures, or *in vitro* systems, thus the results may not be transferable to humans. Substantial research tried to characterize the effect of catechins on human cytochrome P450 (CYP) (9-13). Catechins are not substrates for these hemoproteins, but they may modify the hepatic and intestinal CYP content and composition (*Table 2*) (6,7). CYP isoenzymes metabolize exogenous chemicals including drugs, alcohol, aflatoxin B_1, and various other carcinogens, e.g., from tobacco smoke; usually they activate pro-carcinogens to the ultimate reactive species. Cytochrome P450 induction and inhibition by green tea, green tea extracts, and their major catechins are summarized in *Table 2*.

Apart from HCC (1), many studies analyzed the effect of green tea, green tea extracts, or their catechins on the

Table 2 Modification of human cytochrome P450 isoforms by green tea, green tea extracts, and their individual catechin constituents

Green tea/green tea extracts/catechins	Clinical/experimental conditions	Parameter
Green tea	NR	NR
Decaffeinated green tea	Clinical study: oral intake of capsules for 4 weeks	Human CYP activity
		CYP1A2 → (9)
		CYP2C9 → (9)
		CYP2D6 → (9)
		CYP3A4 (↓) (9)
	Clinical study: oral intake of capsules for 2 weeks	Human CYP activity
		CYP2D6 → (10)
		CYP3A4 → (10)
Green tea extracts	*In vitro* study: human hepatic microsomes	Human CYP activity
		CYP2C8 ↓ (11)
		CYP2B6 ↓ (11)
		CYP2C9 ↓ (12)
		CYP2C19 ↓ (11)
		CYP2D6 ↓ (11,12)
		CYP3A ↓ (11)
		CYP3A4 ↓ (12)
	In vitro study: human intestinal microsomes	Human CYP activity
		CYP3A4 ↓ (11)

Table 2 *(continued)*

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Green tea/green tea extracts/catechins	Clinical/experimental conditions	Parameter
Epigallocatechin-3-gallate (EGCG)	*In vitro* study human hepatic microsomes	Human CYP activity
		CYP2B6 ↓ (11)
		CYP2C8 ↓ (11)
		CYP2C19 (↓) (11)
		CYP2D6 (↓) (11)
		CYP3A ↓ (11)
	In vitro study: human intestinal microsomes	Human CYP activity
		CYP3A4 ↓ (11)
	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1,538 cells expressing human liver CYP	Human CYP activity
		CYP1A1 ↓ (13)
		CYP1A2 ↓ (13)
		CYP3A4 ↓ (13)
		CYP2A6 ↓ (13)
		CYP2C19↓ (13)
		CYP2E1↓ (13)
Epicatechin (EC)	*In vitro* study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity
		CYP1A1 ↓ (13)
		CYP1A2 ↓ (13)
		CYP3A4 ↓ (13)
Epicatechin-3-gallate (ECG)	*In vitro* study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity
		CYP1A1 ↓ (13)
		CYP1A2 ↓ (13)
		CYP3A4 ↓ (13)
Epigallocatechin(EGC)	*In vitro* study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity
		CYP1A1 ↓ (13)
		CYP1A2 ↓ (13)
		CYP3A4 ↓ (13)

CYP, cytochrome P450; NR, not reported. Symbols show →: unchanged activity; ↓: decreased activity; (↓): marginally decreased activity. Modification from a previous report (6,7) with results based on various publications (9-13).

prevention of human cancer at organs other than the liver, usually with disappointing results; for a limited number of tumors, a marginal preventive effect by catechins was observed in subgroups of patients (14). Study publications often were of low quality and difficult to interpret; this has also been discussed by Huang *et al.* (1) for their meta-analysis, which is heavily influenced by one study contributing half of all cases. Valid efficacy data can only be obtained by randomized clinical trials comparing against conventional, well-established therapies of modern medicine (15), or prospective cohort studies rather than retrospective case control studies.

In essence, green tea at best has only a limited value to prevent HCC. In areas of high rates of HBV and HCV

infections, prevention should emphasize established approaches such as screening for chronic hepatitis infection, HBV vaccination, antiviral therapy, reduced consumption of alcohol and calories, cessation of smoking, and avoiding food contaminated with aflatoxin B_1.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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