Editorial on Nutrition

Green tea and liver cancer

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Tea is second only to water among the most widely consumed beverages in the world. Several animal and *in vitro* studies indicated a protective role of polyphenolic antioxidants of tea on carcinogenesis. Green tea, which accounts for 20% of total tea production worldwide, is produced by steaming or heating (or pan-frying) fresh tea leaves at high temperature. These processes, as compared to black tea preparation, result in minimal oxidation, and hence better preservation, of the main tea polyphenols, i.e. catechins. The major catechins in green tea are epigallocatechin-3-gallate (EGCG, 50–75% of the catechins), epigallocatechin (EGC), epicatechin-3-gallate, and epicatechin. Several *in vitro* studies and *in vivo* animal models reported that EGCG has strong antioxidant proprieties and inhibits the initiation and development of cancer at different sites, including the liver (1). However, EGCG serves also as pro-oxidant and may induce hepatic toxicity at high intakes (1). In addition, liver damage (mainly hepatitis) due to green tea product (e.g., herbal drugs, dietary supplements, plant extracts) consumption has been reported in humans (2), and an increased risk of liver cancer was observed in a Chinese cohort for a high urinary EGC among chronic carriers of hepatitis B virus (HBV) (3).

Thus, the effects of green tea on liver cancer deserve further investigation, in particular in populations with high intake of green tea, namely Japan and China. In addition, rates of liver cancer among South-Eastern Asian countries are particularly high (although declining in recent years), reflecting the peculiar patterns of the main risk factors—HBV and hepatitis C virus (HCV) infections, and aflatoxin in China—in these regions (4,5).

In this context, Huang and colleagues published in 2016 a meta-analysis based on prospective studies from Asian populations, considering the role of green tea consumption on either liver cancer incidence or mortality (6). A total of 11 Asian cohort studies were selected from a comprehensive search of the most relevant databases including PubMed, EMBASE, ISI Web of Sciences, and Chinese Biomedicine Database up to April 2015. There was no evidence of publication bias.

Overall these studies accounted for 465,274 participants and 3,694 liver cancer cases. All the included studies except one reported a relative risk (RR) below unity for the highest versus the lowest category of consumption, while Inoue *et al.* from the well-recognized Japan Public Health-Center Based Prospective Study Cohort II found a non-significant increase in risk [RR =1.44, 95% confidence interval (CI): 0.84–2.45] (7). The overall estimate was 0.88 (95% CI: 0.81–0.97), in the absence of heterogeneity among studies (P=0.199). The inverse association was somewhat stronger among women (overall RR =0.78) than men (overall RR =0.89), although estimates were based on a selection of studies and were not significantly different.

Huang and colleagues also carried out subgroup analyses for other covariates, including geographic area, outcome (incidence or mortality), adjustment for alcohol, and number of liver cancer cases in the cohort, and did not report materially different results across strata. In a dose-response analysis, they also estimated a summary RR of 0.97 (95% CI: 0.95–1.00) for an increase of 1 cup in daily green

tea consumption.

These results are in line with those of a previous meta-analysis, including both cohort and case-controls studies, which provided an estimate for the highest versus the lowest category of consumption of 0.79 (95% CI: 0.68–0.93, based on 8 studies) for green tea, and of 0.77 (95% CI: 0.57–1.03, based on 11 studies) for any tea (8).

Results from studies assessing particularly high green tea intakes were reassuring against an unfavourable effect of green tea on liver cancer. In particular, the RR were 0.58, 1.44, and 0.90 in three studies considering ≥5 cups per day, and 0.53 in one study considering ≥10 cups per day. Moreover, studies investigating the duration of green tea consumption suggested a reduction in liver cancer risk for a longer duration (9,10).

A few studies have assessed the role of green tea consumption on liver cancer by HBV and/or HCV infection status, with controversial results. A Chinese population-based case-control study found a double-fold risk for non-green tea drinkers only among individuals affected by HBV/HCV (9), whereas in a Japanese cohort no association with green tea consumption was observed overall nor in those with HCV and/or HBV infection, or those with HCV alone (7).

Outside Asia, three studies investigated the role of tea on liver cancer (11-13). They were conducted among European populations, where the tea-drinking culture is less frequent and black rather than green tea is usually consumed. No association was found in two Italian case-control studies [odds ratio (OR) for ≥1 cup/day *vs.* abstainers, 1.3 and 1.4] (12,13), whereas the European Prospective Investigation into Cancer and nutrition (EPIC) indicated an inverse, dose-dependent association, with a hazard ratio of 0.41 (95% CI: 0.22–0.78) for the highest compared to the lowest quintile of intake, and no evidence of effect modification by HBV/HCV status (11).

The inverse association between (green) tea and liver cancer is small, and any inference on RR of the order of 0.9–0.8 from observational studies remains an open issue. In addition, this relation is less consistent and less strong as compared to that between coffee consumption and liver cancer. A 50% reduction (RR =0.50, 95% CI: 0.43–0.58) in the risk of hepatocellular carcinoma was indeed observed for the highest versus the lowest coffee intake in a meta-analysis including 11 prospective studies (14). Thus, whereas it is now clear that coffee is inversely and strongly related to hepatocellular carcinoma risk, the issue of (green) tea and liver cancer is open to discussion.

Besides liver cancer, several other cancer sites have been investigated in relation to (green) tea consumption. Inverse association were reported for oral, esophageal, stomach, colon, lung (confined to non-smokers), and breast cancer, but, despite the accumulating evidence on the chemopreventive potential of green tea constituents from *in vitro* and animal studies, findings from epidemiological studies are not conclusive, and causality remains controversial (15,16). Still, there is suggestion that, even for the same cancer type, the role of tea may differ across geographic areas—possibly due to different types of tea—or in selected subgroups of population.

In conclusion, unfavorable effects of (green) tea drinking on cancer risk appear unlikely. Future large and well controlled studies—i.e., including information on HBV, HCV, smoking, alcohol, overweight, aflatoxin and other lifestyle risk factors for liver cancer—would provide more definitive information on the role of green tea as liver cancer preventive agent for humans and on specific populations who may benefit from tea drinking.

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Footnote

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

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