

# Green Tea Consumption: A Potential Chemopreventive Measure for Hepatocellular Carcinoma?

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**H**epatocellular carcinoma (HCC) is a major global health problem.<sup>(1)</sup> HCC is the sixth-most common incident cancer and the fourth-leading cause of cancer death in 2015.<sup>(2)</sup> HCC is more common in men; 1 in 45 men and 1 in 113 women develop liver cancer before age 79 years in the world.<sup>(2)</sup> HCC is a highly lethal cancer given that a majority of patients with HCC are diagnosed in noncurative stages.<sup>(3)</sup> Although patients with early-stage HCC are eligible for potentially curative treatment, up to 70% of patients who receive curative resection or local ablation eventually develop recurrent tumors within 5 years.<sup>(1)</sup> There are no effective chemopreventive strategies for these patients and those at risk for HCC development.

In order to decrease the burden of HCC mortality, it is crucial to identify high-risk groups of patients and provide interventions to decrease the risk of tumor development and recurrence after curative treatment.

*Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval;  $\gamma$ -OHPdG, gamma-hydroxy-1,N<sup>2</sup>-propanodeoxyguanosine; HCC, hepatocellular carcinoma.*

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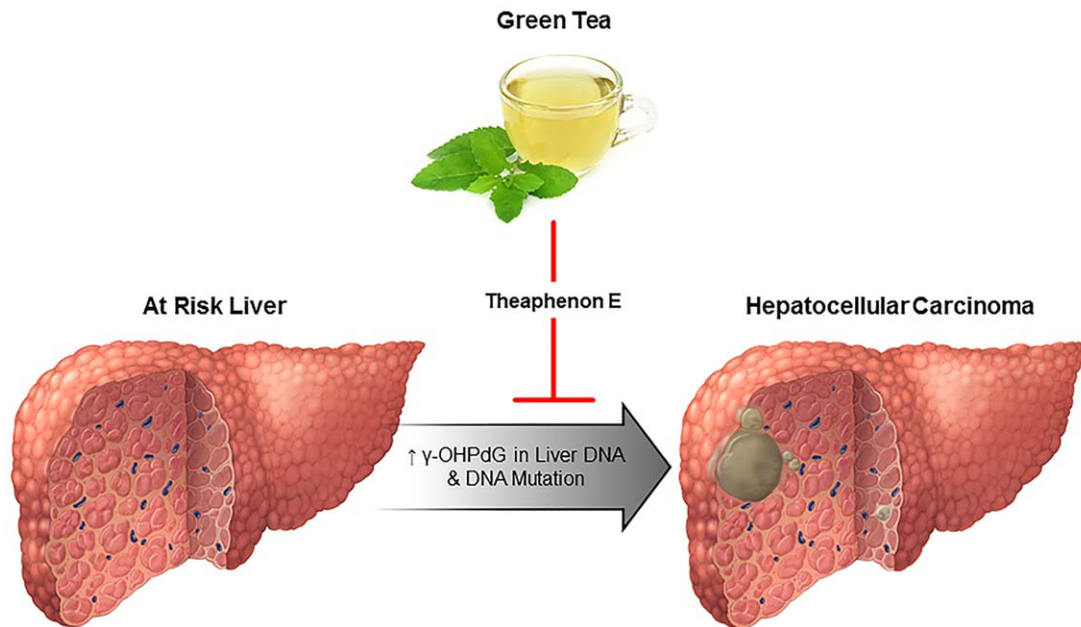
*Potential conflict of interest: Nothing to report.*

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Prognostic biomarkers should provide information to identify such high-risk patients. Serum alpha-fetoprotein (AFP) is a well-established diagnostic and prognostic biomarker for HCC.<sup>(4)</sup> Although highly elevated serum AFP predicts a poor clinical outcome, therapeutic implications of an elevated AFP in HCC patients remain unclear. Similarly, several other proteomic or genomic biomarkers aid in diagnosis and correlate with prognosis; however, they remain underutilized because of lack of wide availability. For example, with recent technical advances in genomics and transcriptomics, researchers used genome-wide expression profiling of liver cancer and adjacent benign tissues and showed that the gene expression pattern of tissue adjacent to the tumor predicts clinical outcome in HCC patients after surgical resection.<sup>(5)</sup> Although this gene expression signature provides prognostic information, it does not provide biological information amenable to interventions that may improve clinical outcomes. More recently, sorafenib was tested as an adjuvant treatment, but failed to prolong recurrent free survival following curative surgical resection or local ablation in a large, phase 3, double-blind, placebo-controlled trial.<sup>(6)</sup> Identification of mechanism-based prognostic biomarkers that can be intervened to improve the clinical outcomes is a critical unmet need in HCC research.

In the current issue of HEPATOLOGY, Fu et al. have published their research examining the utility of an exocyclic deoxyguanosine DNA adduct, gamma-hydroxy-1,N<sup>2</sup>-propanodeoxyguanosine ( $\gamma$ -OHPdG), in three mouse models of hepatocarcinogenesis and its utility as a prognostic biomarker with further validation in human HCC samples.<sup>(7)</sup>  $\gamma$ -OHPdG is one of the most common lipid peroxidation-derived DNA adducts that can modify DNA bases, including p53 genes, and it frequently causes G to T and G to A mutations. It is a well-established mutagen in smoking-induced lung cancer. However, the role of  $\gamma$ -OHPdG in HCC has not been investigated in the past. The investigators showed that  $\gamma$ -OHPdG levels increase with age in nucleotide excision repair-deficient mice (*Xpa*<sup>-/-</sup>) and the whole-liver levels correlated with



**FIG. 1.** Green tea for the chemoprevention of HCC.  $\gamma$ -OHPdG, a mutagenic lipid peroxidation-induced DNA adduct, correlates with HCC incidence in experimental murine models of HCC. Theaphenon E administration reduced the HCC tumor burden and  $\gamma$ -OHPdG levels, suggesting that the chemopreventive effect of green tea might be mediated by Theaphenon E by decreasing  $\gamma$ -OHPdG in liver DNA and consequent DNA mutations.

HCC development. With whole-exome sequencing of tumors and adjacent benign tissues, they determined that GC>TA mutation is the dominant alteration in *Xpa*<sup>-/-</sup> mice, implying that  $\gamma$ -OHPdG may play a role in HCC-specific mutagenesis. Next, investigators showed that suppression of  $\gamma$ -OHPdG formation in the mouse liver led to inhibition of hepatocarcinogenesis. Three antioxidants (Theaphenon E,  $\alpha$ -lipoic acid, and  $\alpha$ -tocopherol) were tested. Theaphenon E, which is a potent antioxidative green tea extract, was shown to lower the level of  $\gamma$ -OHPdG the most. Furthermore, Theaphenon E prevented tumor formation and decreased tumor number and size in diethylnitrosamine-injected mice (Fig. 1). Last, the investigators examined the levels of  $\gamma$ -OHPdG in HCC patients who had undergone a liver resection and stratified them by  $\gamma$ -OHPdG expression level. Higher levels of  $\gamma$ -OHPdG were strongly associated with shorter overall survival and recurrence-free survival, confirming the role of  $\gamma$ -OHPdG as a prognostic biomarker in human HCC.

The current study findings provide biological evidence of the chemopreventive effect of Theaphenon E for HCC. A population-based case-control study from China on 204 HCC cases and 415 healthy controls showed that green tea consumption was inversely

associated with the risk of HCC. Individuals who drank green tea longer than 30 years were at lowest risk compared with nondrinkers (adjusted odds ratio, 0.44; 95% confidence interval [CI], 0.19-0.96).<sup>(8)</sup> A recent meta-analysis of nine prospective cohort studies (465,274 subjects and 3,694 cases) again confirmed the association between green tea consumption and reduced risk for liver cancer (relative risk, 0.88; 95% CI, 0.19-0.96).<sup>(9)</sup> Whereas the vast majority of epidemiological evidence supporting the protective effect of green tea is from Asia, a recent European study confirmed a preventative effect of tea on HCC: Tea intake was associated with a 59% reduction in the risk of HCC development among 486,799 subjects after a median follow-up of 11 years.<sup>(10)</sup> However type of tea was not available in that European study.

An important limitation of the current study is the small number of human HCC tissues analyzed. It remains unclear whether  $\gamma$ -OHPdG levels are independently associated with clinical outcomes after adjusting for known prognostic factors, such as tumor size, number of lesions, AFP, vascular invasion, and metastasis. For the same reason, it has not been investigated whether  $\gamma$ -OHPdG is implicated in hepatocarcinogenesis in an etiology-specific manner. Nonetheless, the

investigators reported a mechanistically relevant prognostic biomarker that can help select a subgroup of HCC patients who may benefit from Theaphenon E/green tea consumption.

Should we recommend green tea consumption in patients who are at increased risk for HCC development or recurrence? The current study provides a biological mechanism for the protective effect of green tea on HCC, which has been demonstrated in previous epidemiological studies. Therefore, we may encourage high-risk patients to drink green tea. In order to clearly measure the biological impact of Theaphenon E/green tea, the associations between green tea consumption, the level of  $\gamma$ -OHPdG in tumor and adjacent benign tissues DNA, and HCC development and recurrence should be externally validated, especially in Western countries where it has been under studied. Last, it is worth mentioning that green tea catechins exert chemopreventive properties by modulating signal transduction and metabolic pathways, hence inhibiting metabolic syndrome-related carcinogenesis in addition to antioxidant and anti-inflammatory activities.<sup>(11)</sup> This might provide a different level of preventive effect in nonalcoholic steatohepatitis, which is emerging as a major etiology of HCC. The etiology-specific mutagenic role of  $\gamma$ -OHPdG in hepatocarcinogenesis should be further investigated in the future, and this will help toward identifying patients who may get the most benefit from an antioxidant effect of green tea in the era of precision and individualized medicine.

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