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# Dietary Modification to Prevent Hepatocellular Carcinoma Is Not Low-Hanging Fruit

**See "Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis," by Yang Y, Zhang D, Feng N, et al, on page 1031.**

Although overall cancer incidence slightly declined over the last decade, hepatocellular carcinoma (HCC) incidence rose in the United States.[1] Beyond established risk factors (alcohol, chronic viral hepatitis, tobacco, diabetes, obesity, aflatoxin exposure, and metabolic liver disease), accumulating evidence suggests an association between diet and HCC.[2] Establishing a causal relationship is difficult because healthy dietary habits are closely linked to other healthy behaviors and social determinants that influence cancer risk. Moreover, "diet" is an amorphous concept that incorporates both the composition and quantity of food and specific nutrients. Last, the reliability of long-term recall of dietary intake is imperfect. Despite these challenges, a complete understanding of the interplay between diet and cancer risk holds tremendous promise to improve population health because poor dietary habits are highly prevalent and modifiable. In this issue of *Gastroenterology*, Yang et al[3] pool the results of 19 observational studies to quantify the association of fruit and vegetable consumption with HCC risk.

The components of diet include micronutrients and macronutrients, whole foods, and combinations of foods (ie, dietary patterns). Understanding which whole foods predict disease may direct research hypotheses in both microscopic and macroscopic directions. For example, the protective effect of coffee consumption for HCC risk[4] motivated a cohort study that identified an inverse association between consumption of polyphenol compounds contained in coffee and HCC incidence.[5] Although the search for bioactive nutrients can lead to the development of preventive measures and potential treatments, proponents of whole food and dietary pattern analysis counter that this approach lacks context because these compounds are not consumed in isolation.[6] Instead, people tend to eat in dietary patterns, ranging from the healthy fat and plant-rich Mediterranean diet to the "meat-sweet" diet of developed countries heavy in processed foods, refined sugars, and red meat.[7] The current study,[3] and recent publications demonstrating reduced HCC risk in adherents to a Mediterranean food pattern or a diet low in red meat,[8–10] support this perspective.

Yang et al[3] present a meta-analysis including 10 cohort and 9 case-control studies conducted in Asia, Europe, and the United States that evaluated the association of 2 whole foods—fruits and vegetables—with HCC risk.[3] The authors rigorously conformed to reporting guidelines for the conduct of meta-analyses.[11] Although the combined number of HCC cases was 3,912 in >1.2 million participants, vegetable and fruit consumption were mostly evaluated separately in a subset of the 19 studies (17 evaluating vegetable intake, 14 fruit intake, and 2 both vegetable and fruit intake). Vegetable consumption had a significant although weak association with lower HCC risk, and fruit intake did not alter HCC risk. The pooled relative risk (RR) of HCC for high compared with low vegetable intake was 0.70 (95% CI, 0.56–0.87), and a dose-response gradient was observed, with RR 0.92 for each 100-g/d increase in vegetable intake (95% CI, 0.88–0.96). Supporting internal validity, the authors showed that the association persisted in subgroups (presence or absence of hepatitis, tobacco, or alcohol use, and high versus low body mass index). Although the meta-analysis of vegetable intake had high heterogeneity, analyses to diagnose the source revealed no differences among the studies in geographic location, study design and quality, food questionnaire type, or sample size. For fruit, the pooled RR for high compared with low intake was 0.93 (95% CI, 0.80–1.09), with RR 0.99 per 100-g/d increase (95% CI, 0.94–1.05). Although study heterogeneity was less (moderate) for the fruit meta-analysis, multiple discrepancies between the studies were identified. A subgroup analysis of fruit intake in non-Asian studies showed a significant but weak association with lower HCC risk, but the included studies were relatively old and of lower quality, suggesting this finding may be owing to bias.

Despite the methodological rigor of this well-conducted meta-analysis, the purported association of vegetable intake with lower HCC risk should be interpreted with caution. Crucially, higher vegetable intake may simply be a marker of healthy behavior, the true mediator of lower HCC

risk. Attempts to adjust for confounding are limited in several ways. First, some potentially important confounders do not lend themselves to binary categorization. For example, smoking is not a yes–no phenomenon, but rather has multiple dimensions including amount and duration (ie, pack-years), as well as timing (active or remote use). Second, some important factors known to be associated with both vegetable consumption and cancer risk, such as socioeconomic status and exercise, are unavailable in the majority of studies underpinning the meta-analysis. Third, multivariable adjustment was performed for different sets of variables in each primary study, making the pooled adjusted RR estimates in the meta-analysis unreliable (residual confounding may be present). For example, both obesity and alcohol intake are likely prevalent in persons with low vegetable intake, but only 5 of the primary studies simultaneously adjusted for both factors. Because obesity and alcohol intake synergistically contribute to HCC risk,[12] the consistent association of low vegetable intake and HCC risk with stratification by obesity or alcohol intake alone does not prove that the association is independent of both factors. Inability to adequately adjust for confounding is a greater limitation for meta-analyses of observational studies than meta-analyses of interventional trials owing to the lack of randomization in the primary studies. Given these limitations, it is difficult to definitively determine whether the current study's findings of a reduced HCC risk are related to vegetable intake or a dietary pattern, behavior, or health status linked to vegetable intake.

When applied to the population, even relatively small associations may still have meaningful implications for public health. To better understand that impact, the authors determined that approximately 125,000 people would need to increase their vegetable intake by 100 g/d over 9.3 years to prevent 1 HCC death (a number needed to treat of 13,440 per year), a steep figure. The population-attributable fraction (PAF) better facilitates an understanding of the contribution of a risk factor to disease burden.[13] The PAF is the proportional reduction in population disease incidence that would occur if risk factor exposure were reduced to an alternative ideal exposure level. What proportion of HCC could be prevented if the entire population consumed a vegetable-rich diet? Calculation of the PAF often yields useful insights. For example, hepatitis C infection is much more strongly associated with HCC risk than diabetes/obesity (odds ratio, 39.89 vs 2.47), but because diabetes/obesity is more prevalent in the US population, the PAF for diabetes/obesity is higher than for hepatitis C (36.6% vs 22.4%).[14] In the Japanese Public Health Cohort study,[15] the PAF of HCC for low vegetable consumption can be calculated, with $p_d = 0.53$ (the proportion of HCC cases occurring in low vegetable intake participants) and RR = 1.10 (the RR of HCC for low compared with high intake), according to the equation:

$$\text{PAF} = p_d(\text{RR} - 1/\text{RR})$$

The PAF is 4.8%, the proportion of HCC that could be eliminated if a population similar to the cohort (Japanese persons aged 40–69 years) increased their vegetable consumption from the lowest to the highest level. In the present study, a pooled PAF cannot be calculated because many of the included studies do not report the $p_d$. However, because the Western diet includes fewer vegetables than in Japan, and the RR for HCC is similar, a slightly higher proportion of US HCC likely can be attributed to low vegetable consumption or linked risk factors. Compared with the PAF for other common HCC risk factors (6%–47%),[14,16] the low PAF for vegetable consumption suggests that this factor contributes in a small way to total HCC burden in the population.

After using measures like the PAF to estimate the relative contribution of a risk factor to HCC disease burden, the feasibility of eliminating the risk factor must be considered. Partially hydrogenated oils (artificial trans fats), which increase the risk of coronary artery disease, were successfully banned through governmental regulation in New York City and California in 2006 and 2008, and a national expansion has been proposed by the US Food and Drug Administration.[17] Unlike artificial trans fats, regulation of vegetable intake is unlikely to be efficient, because HCC disease burden is much lower than coronary artery disease, or enforceable (although this assessment could differ depending on the involved population and the disease burden).

Of the lifestyle factors implicated in HCC risk—diabetes/obesity, alcohol, and tobacco—we submit that tobacco control is the vital target for HCC prevention. The first priority, among 10, of the World Oncology Forum in the war against cancer is tobacco.[18] Strong epidemiologic evidence supports an association of tobacco use with HCC, independent of the effects of alcohol and hepatitis B or C.[19] Further, in a large European cohort, the PAF for tobacco use in HCC (47.6%) was more than twice the PAF of the second most attributed risk factor (hepatitis C, 20.9%).[16] Despite a reduction in the prevalence of smoking in the United States from 27.8% to 21.0% over the last 20 years, smoking prevalence remains nearly double the $\leq$12% objective endorsed by *Healthy People 2010*.[20] If the goal is to reduce HCC burden in the US population, tobacco control is likely to be the most effective public health intervention.

We commend Yang et al[3] for their thoughtful and rigorous analysis of fruit and vegetable intake and HCC risk. Processed food, alcohol, and tobacco are the agents of epidemic chronic disease in the modern era, industrial epidemics that far outscore the disease burden imposed by infectious agents or inherited disease. In the future, it may be possible to demonstrate an independent, causal association between vegetable consumption and HCC using individual participant data meta-analysis or other methods.[21] Even so, based on the current analysis, the magnitude of vegetable intake on HCC risk is likely to be modest and not readily amenable to public health interventions. We cannot ignore the epidemic of diabetes and obesity, both of which are closely linked to poor eating habits with lack of physical activity, and predispose to HCC. But in the near term, the available evidence suggests that the most sensible public health strategy for HCC prevention entails a redoubled effort on tobacco control. To stem the rising tide of HCC, we must dedicate the same assistance and support to smoking cessation that we currently dedicate to alcohol cessation.

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# A Little $O_2$ May Go a Long Way in Structuring the GI Microbiome

**See "Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota," by Albenberg L, Esipova TV, Judge CP, et al, on page 1055.**

The mammalian gastrointestinal (GI) tract houses hundreds of species of microbes from all domains of life—Archaea, Bacteria, and Eukarya. As in many environments, bacteria are the most abundant members of this complex microbial community. Hundreds of metabolites