Controlling cancer by using one or more chemical compounds to prevent its occurrence has held tantalizing promise for decades (1). Nearly 30 years ago, when the research community was exploring the potential of ascorbic acid and α-tocopherol, proponents observed that chemoprevention had a solid theoretical base and examples of protection from neoplasia in experimental animals had been documented (2). Subsequently, chemoprevention trials have shown mixed results. Studies have disappointed for the effects of β-carotene, α-tocopherol, retinol, retinyl palmitate, N-acetylcysteine, and isotretinoin on lung cancer (3), one of the more intensely studied organ systems. On the other hand, use of selective estrogen receptor modulators, such as tamoxifen, has been shown to reduce the incidence of breast cancer in high-risk women (4), and dutasteride has been shown to decrease the incidence of prostate cancer (5). Funding for chemoprevention studies through the National Cancer Institute’s Research Portfolio has been robust for many years, with more than $200 million nominally allocated to this topic in 2011 (6).

Evidence has now accumulated that daily aspirin reduces the long-term risk of death due to cancer too (8,9). However, although aspirin has been shown to reduce incidence of colorectal cancer, the effects on incidence of other cancers are essentially unknown (9). Meanwhile, other nonsteroidal anti-inflammatory drugs (NSAIDs) have also shown promise in cancer chemoprevention. COX2 inhibitors, which slow the cyclooxygenase enzymes involved in the synthesis of prostaglandins, appear to prevent colon and breast cancer (10). In this issue of the Journal, Sahasrabuddhe et al. (11) examine the preventive benefits of NSAIDs for primary hepatocellular cancer (HCC) and the presumed intermediate surrogate of chronic inflammatory liver disease. The investigators make the promising observation that, in a large, prospective, cohort study, use of aspirin and other NSAIDs was associated with lower risk of death due to chronic inflammatory liver disease, and aspirin use was linked to reduced risk of developing HCC. Although the emerging research findings on cancer impacts have not yet translated into clinical recommendations such as those for prevention of vascular disease by the use of daily aspirin, the hype is building. A Google search of
“aspirin and cancer prevention” yielded, in September 2012, almost 2 million results, including personal interest articles in major print and television news media in the English-speaking world.

Yet enthusiasm among health professionals remains tempered. NSAIDs, including aspirin, are well known to increase the risk of bleeding, especially gastrointestinal bleeding (12), and it behooves those making individual clinical or population-level policy recommendations to carefully consider any potential benefit in light of the concomitant potential for inadvertent harm. For these reasons, even for cardiovascular disease prevention, use of aspirin continues to be questioned (13).

The work by Sahasrabuddhe et al. (11) adds important new information to this body of literature: the impacts of NSAIDs on HCC have not been widely studied, and the disease has a notoriously poor prognosis. Preventing it by using readily available, cheap medications is tempting. The investigators note with regret the absence of information with regard to gastrointestinal bleeding in their study, acknowledging that risks associated with gastrointestinal bleeding may negate the benefits possibly conferred by NSAIDs. But those benefits may be substantial: 37% lower risk of developing HCC in people aged 50–71 years who used aspirin, non-aspirin NSAIDs, or both in the 12 months preceding the study, and about a 50% reduction in risk of death due to chronic liver disease [Table 2, Sahasrabuddhe et al. (11)].

In practice, however, we know and understand the causes of most cases of chronic liver disease and primary liver cancer: viral infections, especially hepatitis B virus (HBV) and hepatitis C virus (HCV), and alcohol. And we already have cheap, readily available interventions to prevent a substantial majority of such diseases.

HCC is the sixth most common cancer worldwide, with about 85% of the burden borne by low-income countries (14). Chronic infection with HBV and HCV are the most important causes of HCC worldwide. However, in high-income countries, where the prevalence of HCV and HBV is lower, fewer than half of HCC cases are due to viral infections (15); instead, alcohol abuse is the major contributor. In the United States, an estimated 6% of adults abuse alcohol, which is five times greater than the prevalence of HCV (16). Obesity and diabetes have also emerged as independent risk factors for HCC, prompting discussion about their potential roles in explaining the steady increase in HCC that has been seen in North America and elsewhere in recent decades (16–18).

Universal infant HBV immunization produces long-lasting protection against chronic HBV infection, for both the recipients and, ultimately, their offspring; in Taiwan a decline of HCC has been seen in in adolescents and young adults born after the implementation of an HBV immunization program (19). Many countries now include HBV vaccine in their infant immunization programs, and global coverage is now about 75% (20). Screening of blood donors and testing of donated blood has dramatically reduced the risk of transfusion-associated HCV (21). Multicomponent harm reduction approaches have also reduced HCV incidence in injection drug users (22).

Alcohol abuse and obesity are complex and multifactorial challenges that require interventions at the individual and system levels. The use of alcohol above widely recommended levels [if alcoholic drinks are consumed, consumption should be limited to no more than two drinks a day for men and one drink a day for women (23)], the persistence of alcohol abuse in our society, and the dramatic rise in obesity rates in recent decades call for immediate actions by all sectors and offer immediately tangible and compelling health opportunities for all. Although the United States has achieved more than 90% coverage of HBV vaccine in children aged less than 3 years (24), effective strategies for reduction of HBV and HCV are not always available or fully applied, even in developed countries. The continuing occurrence of viral hepatitis outbreaks (25) as a result of deficiencies in infection control practices and the uneven access to clean needles for injection drug users in the US urban areas underscores this even locally. HBV vaccine coverage rates are appalling in some high-risk parts of the world: only about half of children in Southeast Asia have been immunized (20).

There is much we already know about how to prevent liver disease and cancer. While we study new possibilities, let’s also keep focused on what we already know.

References


**Note**
The authors have no conflicts of interest to disclose.

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