

## Perspective

Perspective on Chen et al., p. 41

## Strawberry Fields Forever?

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## Abstract

On the basis of copious preclinical data supporting the preventive efficacy of small fruits such as berries and grapes, Chen and colleagues conducted a randomized (noncomparative) phase II trial evaluating two doses of strawberry powder (60 g/d or 30 g/d for six months) to prevent esophageal cancer in China (reported in this issue of the journal, beginning on page 41); 60 g/d reduced the histologic grade of dysplastic lesions and reduced localized biomarkers, whereas 30 g/d was not effective. Fundamental questions remain such as the best formulation of strawberry powder, the active components associated with powder, and the actual mechanism of action, and standardized preparations will be required to permit the widespread use of strawberry powder with a predictable outcome. Clearly, however, this work is a good example of proof-of-principle and highlights the important role of diet, nutrition, and natural products in cancer prevention. *Cancer Prev Res*; 5(1); 30–33. ©2012 AACR.

Cancer is a complex and devastating disease that affects millions of people everyday. Even with recent advances with targeted therapies, it is challenging to treat this disease at late stages. Cancer prevention tries to reverse or prevent the development and progression of early-stage disease before it becomes aggressive and malignant. Because epidemiologic studies suggest the protective effects of small fruits and vegetables against cancer (1–3), consumption of a diet rich in fruit and vegetables, as well as natural product bioactive components, is one strategy to prevent cancer. In recent years, large-scale randomized prevention trials such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT) have shown some disappointing results (4, 5). On the other hand, some hope has been provided by clinical cancer prevention trials of broccoli sprout beverages in Qidong, China (6–8), and of tea catechins to prevent colorectal cancer in Shanghai, China (9, 10), and to prevent oral cancer in the United States (11). Small prevention trials focused on high-risk patients in early stages of carcinogenesis can be meaningful and feasible, as illustrated by the work reported by Chen and colleagues in this issue of the journal (12). This study provides new data on strawberry powder in a high-risk group with dysplastic esophageal lesions.

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In numerous preclinical studies of recent decades, berries have been shown to be protective against oral (13–16) and colon (17, 18) cancers, as well as against ulcerative colitis (19). Dietary black raspberries (5% and 10% of the diet) were chemopreventive in a hamster cheek pouch model of oral cancer (16). Further work showed that black raspberries inhibited azoxymethane-induced colon cancer in F344 rats (18). The role of berries in cancer prevention has been shown with lyophilized (freeze dried) black raspberries, blackberries, and strawberries in carcinogen-induced cancer of the rodent esophagus (20). In addition, lyophilized black raspberries have shown strong inhibitory effects against esophageal tumorigenesis in *N*-nitrosomethylbenzylamine (NMBA)-treated rats (21); the inhibitory effect correlated with inhibition of COX-2, inducible nitric oxide synthase (iNOS), c-Jun (22), and angiogenesis (23).

Dietary freeze-dried strawberries also have inhibited NMBA-induced esophageal tumorigenesis in rats (24, 25). Dietary administration of freeze-dried strawberries (10% of the diet) caused a significant reduction in tumor multiplicity and reduced *O*<sup>6</sup>-methylguanine levels in the esophageal DNA of animals (24). Strawberry polyphenols also attenuated ethanol-induced gastric lesions in rats (26). More recently, multiple berry types, including black raspberries, blueberries, strawberries, noni, acai, or wolfberries, have been tested in NMBA-induced rat esophageal cancer (27). Most of the berries at 5% of the diet provided protective effects against carcinogen-induced esophageal tumorigenesis and further decreased serum cytokines (27). Many small berries have been shown to have a similar chemopreventive potential, as might be expected on the basis of their similar compositions of key bioactive components.

Although comprehensive reviews of berries and cancer prevention summarize evidence that fruits and vegetables may reduce the risk for cancers of the oral cavity, esophagus, stomach, and colorectum (3, 28), a large-scale human

intervention study showed only a weak association between the intake of fruits and vegetables and the reduced risk of cancer (29, 30). The few randomized clinical cancer prevention studies of fruits, vegetables, and natural product bioactives conducted to date include trials of berry bioactives in Barrett's esophagus, colon polyps, and oral cancer (31). Earlier work assessed the clinical chemopreventive effects of lyophilized black raspberries, with interim results showing that berries modulate markers of oxidative stress in Barrett's esophagus patients (32). A small human trial (11 subjects) designed to determine safety and tolerability found that 45 g of freeze-dried black raspberries daily were well tolerated, but less than 1% of the berries' anthocyanins (such as cyanidin-3-glucoside, cyanidin-3-sambubioside, cyanidin-3-rutinoside, and cyanidin-3 xylosylrutinoside) were absorbed and excreted in the urine (33). In another phase I pilot study, 20 patients received black raspberries (60 g per day) for 1 to 9 weeks (34). This study evaluated biomarkers, including the Wnt pathway, proliferation, apoptosis, and angiogenesis (34). In sum, various studies have provided strong evidence for the chemopreventive effects of many types of berries such as strawberries, black raspberries, and blueberries.

In considering an approach to exploit the translational value of extensive preclinical work, it is important to note that China has the highest incidence of squamous esophageal cancer in the world. Specifically, as discussed by Chen and colleagues (12), a number of prospective studies have identified areas of a high risk for esophageal cancer in the Taihang mountain region of China, including Linxian and Anyang (Henan Province), Chaoshan (Guangdong province) and Cixian (Hebei province). Although it is challenging to conduct randomized trials in developing regions, there is an unmet medical need for preventing squamous esophageal cancer that could be of immediate benefit for high-risk populations in these regions, and a precedent could be established for broader or more widespread applications.

On the basis of these considerations, particularly the high risk of esophageal cancer, and solid preclinical data on berries in a rat esophageal cancer model (20, 24, 25), Chen and colleagues have now investigated the chemopreventive role of strawberries in a high-risk group of patients with mild or moderate dysplastic lesions of the esophagus (12). They conducted a randomized, 2-arm phase II trial of freeze-dried strawberry powder for 6 months in 75 patients in a poor rural farming region of China with the highest incidence of esophageal cancer. A major reason for choosing strawberries (vs. other berries) likely was that they are the major berry grown in China. They evaluated several endpoints of intermediate biomarkers in mild and moderate dysplasia. Patients were randomized to 30 g/d or 60 g/d of strawberry powder; there was no placebo group. Biomarker analyses took place in samples obtained before and after treatment. Strawberries at 60 g/d produced highly significant reductions in the histologic grade of dysplastic lesions (the primary endpoint;  $P < 0.0001$ ) and in study biomarkers (the inflam-

mation markers iNOS, COX-2, phospho-NF- $\kappa$ B-p65, and phospho-S6 and the proliferation marker Ki-67), whereas 30 g/d produced little change in histologic grade, notwithstanding modest effects on some biomarkers. Previous work suggested that the risk for cancers of the oral cavity, esophagus, stomach, and colorectum may be reduced by diets including at least 400 g/d of total fruits and vegetables (3), which roughly correlates with 60 g/d of freeze-dried strawberry powder, the approximate equivalent of 600 g/d of fresh strawberries.

Strawberry powder had no apparent toxicity, even at the high dose of 60 g/d. The strawberry powder administered in this trial was dissolved in water. Ethanol extract of freeze-dried black raspberries has been investigated as poly(DL-lactic-co-glycolic acid) and poly(DL-lactic acid) loaded injectable millicylindrical implants for sustained delivery of anthocyanins; this formulation was found to be optimal for 1 month continuous delivery of black raspberry anthocyanins (35). A non-water formulation of strawberry powder also perhaps would provide better bioavailability or allow a lower effective dose. The importance of working out optimal formulations in early-phase clinical trials is highlighted by 2 recent reports, one involving resveratrol (36) and one involving indole analogs (37). With regard to global prevention, the lyophilized powder formulation of strawberries is not inexpensive and, if established to be effective, likely would require special measures to become available in developing regions.

This study had a few limitations in addition to the question of optimal formulation. For example, it examined only the few markers iNOS, COX-2, phospho-NF- $\kappa$ B-p65, phospho-S6, and Ki-67. Although the results are encouraging, berry bioactives and berry powders have been shown to regulate multiple pathways including NF- $\kappa$ B (I $\kappa$ B $\alpha$ , I $\kappa$ B kinase, iNOS, and COX-2), proliferating cell nuclear antigen, cell adhesion proteins (inter-cellular adhesion molecule 1), phosphoinositide 3-kinase/Akt, mitogen-activated protein kinase (extracellular signal-regulated kinase, c-Jun N-terminal kinase, and p38), angiogenesis (VEGF-1), and apoptosis (Bcl-2, p21, Bax, Bak, cytochrome c, and caspase-3; ref. 31). Multiple mechanisms could be responsible for strawberry activity because multiple bioactive components are present in berries. Therefore, investigation of more diverse biomarkers should be considered to more fully characterize the molecular mechanisms of the chemopreventive effects of strawberry powder.

Although Chen and colleagues conducted some analysis of the components from freeze-dried strawberries, another study limitation is not investigating the levels of key components in the serum, urine, or target tissues from patients who received the 2 different doses of freeze-dried strawberries. More important, it is not clear which components of strawberries contributed to the changes in biomarkers associated with the dysplastic lesions. Therefore, no specific correlation can be drawn from the strawberry intake and chemopreventive effects in this study. It would be of interest to investigate any association of patients who had histologic and biomarker responses with higher levels of

key components of strawberries. Several bioactive phytochemicals commonly present in berries are possibly important, which helps in predicting that most berries, to a certain degree, may have a similar benefit in cancer prevention. These bioactive phytochemicals include anthocyanidins, proanthocyanidins, flavonoids and flavonols, hydroxybenzoic acid, hydroxycinnamic acid, stilbenoids, catechins, and ellagitannins (31, 38). Earlier work with black raspberries indicated that anthocyanins are key bioactive components responsible for preventing esophageal tumors in rats (39). Other studies found that berry ellagitannins did not effectively prevent rat esophagus tumors (40). Clearly, it will be important to identify which active components and molecular targets/mechanisms may be responsible for the efficacy of strawberries. Such work has recently been reported in regard to the epigallocatechin gallate component of green tea (41).

Chen and colleagues indicate that bioactivity guided fractionation is underway. On the basis of known responses, it is not especially clear which assay or assays will be utilized to identify active components. In addition, it is possible that multiple active principle components may be necessary to show efficacy (i.e., combination chemoprevention may be a more attractive option). Thus far, freeze-dried powder, extracts, or active components such as anthocyanins have been used for berry studies. In the future, it will be important to consider factors such as stability, toxicity,

bioavailability, synthesis, and costs for human trials. Furthermore, it is essential that each berry preparation is standardized so that activity can be correlated with a specific content profile associated with the overall batch administered in a given study. Otherwise, interstudy, or even intrastudy, results could be confounded by different preparations going under the same name.

Thus, we pose the question, Is the best approach "Strawberry Fields Forever," or would a novel formulation comprising one or more active principle components achieve greater efficacy with a more predictable outcome? Only time will tell, but Chen and colleagues are to be commended for showing an important "proof-of-principle" in clinical cancer prevention study. This randomized phase II trial in a high-risk group with dysplastic esophageal lesions has provided useful data on intermediate endpoints and biomarkers in regard to the chemopreventive effects of strawberries. The work signifies the overall importance of cancer prevention with dietary, nutritional, and natural products and lays the groundwork for future investigations.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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