Preventing Cancer by Disrupting Progression of Precancerous Lesions

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In this issue of the Journal, Correa et al. (1) provide results from the first reported randomized intervention trial of the effects of anti-*Helicobacter pylori* treatment and of vitamin supplementation on precancerous lesions of the stomach. The findings are encouraging, with evidence that therapy for *H. pylori* and supplementation with β-carotene or vitamin C may help limit progression and enhance regression of conditions believed to be in the pathway of gastric cancer.

Randomized clinical trials provide one of the most scientifically rigorous approaches to evaluate potential inhibitors of cancer. Trials directly evaluating cancer as an outcome require large numbers of persons to be followed, often for many years. In some circumstances, an effective alternative is a smaller, shorter term trial focusing on the carcinogenic process leading to the onset of clinically detectable cancer. Correa et al. followed this strategy in Colombia in an area where gastric cancer rates are high and precancerous lesions of the stomach are fairly common. By studying the effects of interventions on the progression/regression of these common lesions, information can be obtained on whether intervening may inhibit the early changes leading to cancer.

The inherent assumption in such a study is that the carcinogenic process does, in fact, involve a transition from normal epithelium through advancing precancerous lesions. Such a process may exist for a number of cancers, although evidence for most forms of cancer is scanty. For stomach cancer (especially the common intestinal type), however, epidemiologic and pathologic studies have documented that a series of transitions typically are involved (2). In most cases, particularly in high-risk areas, a sequence of events occurs whereby normal gastric mucosa...
cosa is affected by chronic atrophic gastritis, followed by intestinal metaplasia and then dysplasia prior to the onset of cancer. Direct evidence that these conditions are precursors is provided by observations of higher rates of gastric cancer among affected individuals, with the excess reaching as much as 100-fold for those with moderate or severe dysplasia (3).

With this background, the team in Colombia launched a randomized trial to see if either of three agents singly or in combination could halt the advance of chronic atrophic gastritis and intestinal metaplasia in a population in whom stomach cancer is the most common form of cancer. The interventions chosen were reasonable, since H. pylori is recognized as a cause of stomach cancer (4) and intake of diets high in fruit and vegetables (and thus β-carotene and vitamin C) has consistently been associated with reduced risk of this cancer (5). A total of 852 patients with chronic atrophic gastritis or intestinal metaplasia were administered combinations of therapy for H. pylori, daily supplementation with 30 mg of β-carotene, and/or daily supplementation with 2 g vitamin C. The supplements continued throughout the 6-year duration of the trial. A $2^3$ factorial design with the eight possible treatment arms (a pure placebo, the three single-agent interventions, the three pairs of double interventions, and the one three-agent intervention) was used to enable assessment of all three types of treatment and any interactions between them.

Repeat endoscopies were taken at 3 and 6 years after initiation of the interventions, and the systematically collected biopsy specimens were scored in a standardized manner for classification of each individual’s precursor lesion status. The key outcomes were whether, for each person, his/her mucosal status had advanced, stayed the same, or regressed. The analyses then evaluated whether the rates of change differed among the eight treatment groups.

The key finding was that the study subjects in the placebo group fared the worst, in the sense that they had the lowest percentage (7%) of lesion regression, whereas the seven other groups had regression percentages ranging from 19% to 29%. The percentage of lesions progressing to a more advanced stage did not differ greatly among the treatment groups, with the placebo percentage (26%) within the range of 19%–33% of the other groups. The authors calculated adjusted relative risks (RRs) of lesion regression for the seven treatments relative to the placebo, finding statistically significantly increased RRs of about 3–6 for each, consistent with the differences in regression percentages cited above. RRs of progression, however, were close to 1.0, although, among the subset with intestinal metaplasia at baseline, RRs of lesion progression tended to be statistically nonsignificantly below 1.0 for the seven groups. The authors conclude that all three treatments were successful, with no additional benefit from combinations of treatments.

One of the advantages of a factorial design is that the effects of each factor can be examined across levels of the others. Thus, consistency of effects can be evaluated, and the presence of interactions detected. If one examines the study data in this way, the conclusion is less clear that curative H. pylori treatment, β-carotene supplementation, and vitamin C supplementation have increased lesion regression. Consider therapy for H. pylori, for example. There are four comparisons available on the effectiveness of anti-H. pylori treatment, namely, comparing groups with 1) anti-H. pylori therapy alone versus placebo, 2) anti-H. pylori therapy plus vitamin C versus vitamin C alone, 3) anti-H. pylori therapy plus β-carotene versus β-carotene alone, and 4) anti-H. pylori therapy plus vitamin C plus β-carotene versus vitamin C plus β-carotene. All four provide an unbiased and independent assessment of the effect of anti-H. pylori therapy. The percentages of participants with treated versus untreated H. pylori undergoing lesion regression in these four comparisons, respectively, were 1) 19% versus 7%, 2) 24% versus 20%, 3) 19% versus 20%, and 4) 23% versus 29%. Hence, in only one (the first) of the four comparisons was there clear benefit of anti-H. pylori therapy. Why should H. pylori treatment be effective when given alone but convey no benefit (or even be detrimental) when given with β-carotene and/or ascorbic acid? No such interaction or antagonism of effects was predicted at the outset.

Similar situations apply when β-carotene and vitamin C are examined across strata of the other two factors. While it is possible that each of the three interventions may have been successful in enhancing regression and that regression occurs primarily in a susceptible subset so that combined intervention has no extra benefit, the lack of consistency of treatment effects in the majority of comparisons suggests caution in interpretation of the study findings. In effect, almost all of the apparent benefits for each of the three interventions hinge on the low rate of regression among the one-eighth of the participants who were in the straight placebo arm. Further caution is suggested by the finding that the rate of lesion progression in the placebo arm was not particularly high.

In summary, the study by Correa et al. (1) provides important leads to potential ways to reduce the toll of stomach cancer, still the second most common malignancy on a global scale. Ongoing studies in other locales are also assessing therapy for H. pylori infection and vitamin supplementation as inhibitors of the lesions that lead to this cancer, so that it will soon be possible to determine whether the results in Colombia can be validated. If confirmed, relatively inexpensive and minimally invasive procedures may be added to the arsenal of agents aimed at the prevention of cancer.

REFERENCES


