Commentary

Duration of Exposure, a Neglected Factor in Chemoprevention Trials

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Responding to the open invitation of the editors (1), we submit this commentary in the hope of contributing positively to the re-appraisal of chemoprevention trials. Well-deserved attention has been given to some limitations of trials especially as it relates to measurement errors, interaction of factors, and statistical power (2). Infection with *Helicobacter pylori* has been recognized by IARC are type I human carcinogen (3). Our recent experience with a chemoprevention trial of gastric dysplasia in Colombia led us to emphasize the somewhat underestimated role of time free of exposure to the carcinogenic agent(s) on the outcome of the intervention.

Our interpretation of the results of 12-year follow-up of our subjects is that the dynamics of cancer prevention parallels in reverse the dynamics of the prolonged carcinogenesis process itself (4). Figure 1A represents patients who cleared their initial infection. It is based on a histopathology score that was created, giving increasing weights to the type and extension of the precancerous lesions to the global diagnosis. It shows that the severity of the histopathology score of premalignant gastric lesions is a quadratic function of the time free of infection. No detectable healing effect is observed for the first 3 years of infection-free time. At 6 years, the healing effect is modest (the score is much less than the expected 50% in a linear relationship) and may not be significant if the power of the design is not strong. Doll and Peto (5) have shown that the duration of exposure to carcinogenic agents is a much more potent determinant of the outcome than other factors, such as the daily dose of the carcinogen. Their formula indicates that lung cancer incidence is determined by the dose (number of cigarettes per day) squared, times the duration of exposure (years) to the 4.5 exponent. Both curves (oncogenesis and antioncogenesis) are exponential in terms of duration of exposure. As such, they do not follow a straight line but rather an S-shaped curve. The first and last parts of the ''S'' have minimal inclinations, whereas the middle portion is considerably steeper. Our findings based on 6 and 12 years of follow-up (not shown) indicate that regression of the precancerous lesions is more complete in patients with less-advanced baseline diagnoses (absence of intestinal metaplasia) than in patients with more advanced lesions (intestinal metaplasia and dysplasia; refs. 4, 6).

Our trial provided dietary supplements of antioxidant micronutrients (ascorbic acid and β-carotene) for the first 6 years. At that time, we detected a protective effect (6). Such effect was not maintained after the supplements were no longer provided (4).

Interventions may also have less obvious beneficial effects on the carcinogenic process that may not be included as an outcome measure or insufficient in magnitude to meet the statistical power of the study design. Such may be the case, for example, when immunologic mechanisms are involved. They may be modulated to induce less damage even when some damage is inevitable. In our trial, some patients remained infected after 12 years of follow-up, including patients in the anti–*H. pylori* treatment arm and in the no-treatment arm. The former group was classified as a treatment failure in terms of harboring the bacterium in spite of anti-infection drugs. The two groups differed in their histopathology score outcome, as seen in Fig. 1B. Those subjects who never received antibiotic treatment continued to show an increase of their histopathology score: +0.18 at 12 years over the average histology score at baseline (3.77). Those who received anti–*H. pylori* treatment but remained infected showed a decrease in their 12-year histopathology score: −0.19 over the average histopathology score at baseline. One explanation of this unexpected result may be in the survival of less virulent strains of *H. pylori*. It is becoming increasingly clear that most infected patients harbor several genotypes of the bacteria. As is shown in Table 1, the bacteria that survived antibiotic treatment tended to be less virulent strains as indicated by the higher prevalence of less virulent genotypes, such as CagA negative and VacA s_2 m_2 (7).

Several lessons from this chemoprevention trial are as follows:

1. Any effect may be quadratic in terms of length of time after the chemoprevention intervention and may not be detectable in short-term studies lasting only a few years.

Table 1. Association between the efficacy of antibiotic treatment and the virulence-associated genotypes of *H. pylori* in Colombian patients

Genotype	Before therapy, *n* (%)	After unsuccessful therapy, *n* (%)	*P*
CagA			
Negative	10 (7.3)	7 (24.1)	0.01
Positive	126 (92.6)	22 (75.9)	
VacA			
s1	123 (93.9)	23 (82.1)	0.05
s2	8 (6.1)	5 (17.9)	
m1	119 (90.1)	20 (74.1)	0.04
m2	13 (9.8)	7 (25.9)	

NOTE: Adapted from ref. (7).

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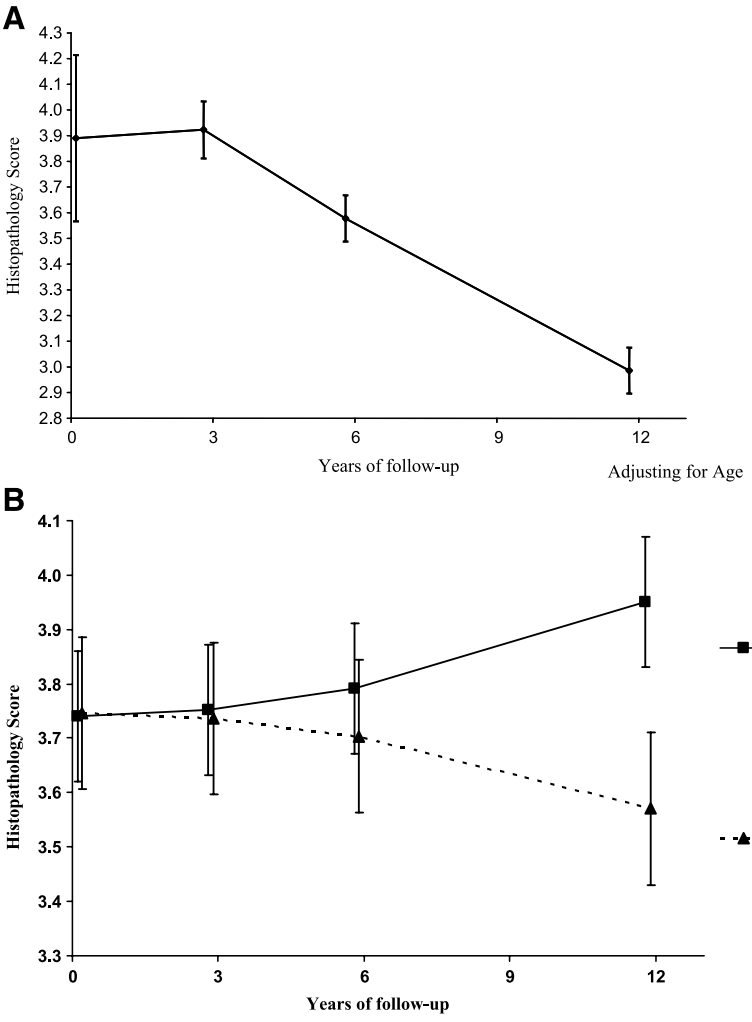

Figure 1. A. Histopathology score over time of patients who cleared the bacteria. **B.** Histopathology score over time of patients who remained infected, by treatment status.

2. Collateral beneficial effects may be subtler, especially if they involve the host response.
3. Any beneficial effect of dietary supplements of antioxidants may be detected only while they are provided.
4. Outcome may be dependent of the stage of the precancerous process at which the intervention is given.

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