Letters to the Editor


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Manetta et al. (1) provide interesting information on chemopreventive agents for CIN2 and suggest that a large percentage of patients with CIN I and II will respond to β-carotene supplementation at a dose of 30 mg daily. This study includes 18 and 12 patients with CIN I and II, respectively, and shows that response rate at 12 months was 43%. Nevertheless, the hypothesis that disease regression reflects a beneficial effect of β-carotene treatment is difficult to prove because of the high spontaneous regression rate of CIN, the small number of evaluated patients, and the short follow-up, all factors that may promote hazard influence.

Natural history studies on cervical precancer lesions, critically reviewed by Östör (2), indicate that the likelihood of spontaneous regression for CIN I and II (including 4155 patients corresponding to 16 studies) was 43%. Because this regression rate, coming from a much larger sample of patients without any treatment, is similar to that reported by Manetta et al., conclusions regarding β-carotene efficacy cannot be drawn.

Significant differences in response at 6 and 12 months in the study of Manetta et al. (21 of 30 versus 10 of 30) are probably a consequence of the biological behavior of dysplasia (given that this disease is an unstable multifocal condition) may often change over a period of time, and may recur after an apparent regression. These statements are especially true in low-grade lesions. Mikhail et al. (3), in 68 patients with histological diagnosis of CIN I who were serially monitored for a period of 1 year using computerized colposcopy and image analysis, show that 53% of patients had apparent spontaneous regression, whereas 27.9% had a complete change in the location of their original lesions with regression and subsequent appearance of a new lesion in a different location.

Other issues of the Manetta et al. study deserve consideration. Enrollment criteria included patients with a histological diagnosis of CIN. Although colposcopically directed biopsies are an appropriate diagnosis method, some authors accept that biopsy may itself be curative by either removing entirely or almost completely a small lesion or evoking an immune response and/or inflammatory reaction, which might be capable of erasing the disease (4).

Received 4/1/97; accepted 5/2/97.

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2 The abbreviation used is: CIN, cervical intraepithelial neoplasia.

Manetta et al. (1) found a difference in the response rate to β-carotene observed at 12 months, according to the number of involved cervical quadrants [10 of 22 (45%) with one to two quadrants versus 0 of 8 (0%) with three to four quadrants]. Although the authors do not discuss this finding, there are several possible explanations: (a) as stated, curative potential of diagnostic biopsy is more plausible in small lesions; (b) in general, the larger the lesion, the more severe the histological grade. In fact, we found that mean sizes of low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions measured by digital colposcopy were 77.7 mm² and 166.4 mm² (P = 0.016, respectively Ref. 5); (c) the size of the lesion is an independent prognostic factor for progression and has a significant effect on the natural history of preinvasive cervical disease; and (d) the most significant predictor of failure of treatment methods for CIN seems to be lesion size (6). Therefore, we agree with the authors that lesion size should be controlled for.

Assessing the therapeutic efficacy in cervical precancer disease is a hard task due to both the reported spontaneous regression rate, about 50%, and the recurrence rate of 5–10% even with the most effective treatments. Moreover, some other problems not related to the therapy should be taken into account, such as the difficulties in establishing the true diagnosis (e.g., false negatives and positives of cytology, low specificity of colposcopy, and lack of accuracy of directed biopsy versus complete excision of all transformation zone), the follow-up methodologies, and the effects of cofactors associated with progression and regression. Results from prospective randomized clinical trials are required before concluding that β-carotene treatment is effective for CIN.

References
Reply

Alberto Manetta, Toni Schubbert, Julia Chapman, Michael J. Schell, Yel-Mei Peng, Shu Yuan Liao, and Frank J. Meyskens, Jr.

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We would like to take this opportunity to thank Dr. Tome et al. for the comments expressed in their recent letter to the editor in reference to our article, "β-Carotene Treatment of Cervical Intraepithelial Neoplasia: A Phase II Study."

As we explained in the "Discussion" section, we agree that the effects of β-carotene are difficult to prove other than in a prospective randomized study due to the high spontaneous response rate of cervical intraepithelial neoplasia. We also agree, as stated clearly in the "Discussion," that the biopsy itself may alter the progression/regression of the lesion, and it is even possible that in some cases, it may be curative.

We are pleased to find that Tome et al. also agree with our conclusions that the size of the lesion is important, as we stated in the "Results" section.

The issue of spontaneous regression was also discussed in the "Discussion" section, as mentioned above. We are delighted that Tome et al. agree that our results indicate the need for a prospective, randomized study, as stated in the last paragraph of the "Discussion."

Overall, we are glad Dr. Tome et al. have taken the time to mention and underscore the points we made in our manuscript.
