Title
Re: Cancer Chemoprevention: Progress and Promise

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Authors
Meyskens,, FL
Lippman, SM
Lee, JJ
et al.

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The commentary by Lippman et al. *(1)* provides a useful review of the topic by organizing a massive amount of information in an organized way. However, because this review will be widely read and referenced, there are two general points made by the authors that could be challenged. The authors define two of the four criteria for identifying a "definitive" chemoprevention trial as "primary end point of cancer incidence" and "large scale ($n \geq 1000$) with the definitive sample size and duration based on anticipated event rates in the intervention arm (treatment effect) and placebo arm."

One major goal of chemoprevention research is to determine the protective effect of an agent while placing as few participants as possible at risk. One straightforward way to accomplish this goal is to understand the process of the disease (carcinogenesis) sufficiently to conduct trials with markers that predispose to or predict the final end point of cancer. In general, most histologically identifiable precancers (e.g., cervical intraepithelial neoplasia, Barrett's esophagus, adenoma polyps, actinic kerotoses, and dysplastic nevi) evolve to cancer with a sufficiently predictable frequency to conclude that their reversal or suppression can be used to predict cancer development and to assess the value of a chemoprevention agent. There are, in fact, as the authors note, several studies *(2–6)* that have addressed the effectiveness of chemoprevention in this manner. The medical community accepts hypertension and cholesterol as surrogate "preneoplasias" of cardiovascular disease risk and their modulation as indicative of a favorable or unfavorable drug effect. Modulation of the pathobiology of precancers is as valid a marker of carcinogenesis as is the end point of cancer. Undoubtedly, advances in our understanding of carcinogenesis will allow us to identify and develop new agents by the modulation of a biochemical event earlier in the carcinogenic process and this should be a major goal of chemoprevention research.

Large numbers may provide comfort to the investigator that a definitive result has been obtained. However, there are many instances in medicine when large numbers were not required to make the point, i.e., where the underlying cause

was stumbled upon (e.g., scurvy), recognized (e.g., pellagra), or mechanistically defined (e.g., rickets). One would hope that, with the large number of molecular targets that have been identified for chemoprevention [e.g., Table 2 in *(1)*], at least one of them will be equivalent to the examples of nutrient deficiencies cited above. Intervention early in the disease process of carcinogenesis in a highly specific manner based on rational therapeutics will lead to sustainable advances at considerably less cost and effort than huge, expensive, and lengthy trials that use cancer as the end point. Although "definitive" large randomized trials will continue to be necessary to advance the field of chemoprevention, they should be uncommon and conducted only after convincing experimental and clinical work has been done *(7)*.

FRANK L. MEYSKENS, JR.

REFERENCES

(1) Lippman SM, Lee JJ, Sabichi AL. Cancer chemoprevention: progress and promise. J Natl Cancer Inst 1998:90:1514–28.

(2) Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323:795–801.

(3) Pastorino U, Infante M, Maioli M, Cheisa G, Buyse M, Firket P, et al. Adjuvant treatment of stage I lung cancer with high-dose vitamin A. J Clin Oncol 1993;11: 1216–22.

(4) Meyskens FL Jr, Surwit E, Moon TE, Childers JM, Davis JR, Dorr RT, et al. Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-*trans*-retinoic acid: a randomized trial. J Natl Cancer Inst 1994;86: 539–43.

(5) Levine N, Moon TE, Cartmel B, Bangert JL, Rodney S, Dong Q, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer Epidemiol Biomarkers Prev 1997;6: 957–61.

(6) Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 1999;340: 101–7.

(7) Meyskens FL Jr. Chemoprevention of human cancer: a reasonable strategy. Recent Results Cancer Res. In press. 1999.

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Correspondence to: Frank L. Meyskens, Jr., M.D., Chao Family Clinical Cancer Research Center, University of California, Irvine, 101 The City Dr., South, Rt. 81, Bldg. 23, Orange, CA 92868-3298.