Title
Re: Cancer chemoprevention: Progress and promise [3] (multiple letters)

Journal
Journal of the National Cancer Institute, 91(6)

ISSN
0027-8874

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

Publication Date
1999-03-17

DOI
10.1093/jnci/91.6.563

Re: Cancer Chemoprevention: Progress and Promise

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 ($n \geqslant 1000$) 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.

NOTE

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.

RESPONSE

We appreciate Dr. Meyskens' thoughtful letter on our commentary *(1)*, which highlights the two definitive trial criteria with which we wrestled the most. After careful consideration, we chose cancer as the definitive end point because it is conservative, falling between the liberal end point—premalignancy—and the most conservative end point—cancer mortality. In harmony with Dr. Meyskens, we stated that the cardiovascular disease-related "surrogate end points of high blood pressure and cholesterol are accepted as valid surrogate end points (or diseases). Similar surrogate end points must be established in cancer." We caution readers that pharmacologic suppression or reversal of premalignant lesions, such as cervical intraepithelial neoplasia or others cited by Dr. Meyskens, has not yet been associated with longer term reduction in cancer incidence. Therefore, premalignant lesions are not yet generally accepted as surrogate end-point biomarkers (SEBs) for definitive trials designed to establish efficacy of an agent in reducing cancer risk.

We also deliberated at length on our choice of 1000 or more subjects as the definitive size, which we based largely on our choice of a cancer end point. This size generally is sufficient to meet the requirements of two of our other criteria—two-sided hypothesis testing and randomization with placebo control. We acknowledge that the size criterion is subject to debate, and future definitive trials (with cancer end points) may well require smaller sample sizes, especially if the anticipated treatment effect and/or event rate (e.g., achieved by targeting high-risk subjects) are sufficiently great.

We concur with Dr. Meyskens' view that developing new agents through molecular targeting approaches or modulating a biochemical event earlier in carcinogenesis (i.e., using an established SEB) should be a "major goal of chemoprevention research." Following the etiologic example of linkage between vitamin C and scurvy (cited by Dr. Meyskens) or between hepatitis B and hepatocellular cancer (cited in our commentary), we and other investigators *(1–3)* are searching for "surrogate end-point biomarkers [e.g., molecular targets] in preinvasive carcinogenesis that are tightly linked to cancer development" *(1)*. We further commented that "the surrogate end-point biomarker would have to be inextricably implicated in the causal pathway between an agent's effects and cancer development." For many years, M. D. Anderson's cancer chemoprevention programs have investigated potential SEBs and will continue along this critical path of discovery. Much of the second half of our commentary is devoted to this issue.

Dr. Meyskens' call for conducting "'definitive' large randomized trials . . . only after convincing experimental and clinical work has been done" echoes our statement that "basic science and translational studies continually re-examine criteria for initiating definitive cancer chemoprevention trials on the basis of strong scientific rationales and well-conceived hypotheses." Certainly, we believe that biologic advances will strengthen hypotheses, thus increasing the potential for positive results. This is not, however, to discount the value of past negative (harmful or neutral) definitive trials that have saved "lives . . . and resources by directing research efforts away from ineffective [or harmful] interventions" *(1)*. Another benefit of large-scale, long-term trials is in detecting infrequent or delayed and chronic side effects that would never be detected in relatively short-term definitive trials with surrogate, rather than cancer, end points. Nevertheless, we also believe that it would be highly desirable to develop trials with, as Dr. Meyskens described, "considerably less cost and effort than huge, expensive, and lengthy trials that use cancer as the end point." Repeating a theme we expressed 10 years ago in another commentary *(3)*, we stated that "valid surrogate end-point biomarkers . . . would . . . [allow] shorter, smaller, and less expensive definitive chemopreventive trials" *(1)*.

SCOTT M. LIPPMAN
J. JACK LEE
ANITA L. SABICHI

REFERENCES

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

(2) Greenwald P, Witkin KM, Malone WF, Byar DP, Freedman LS, Stern HR. The study of markers of biological effect in cancer prevention research trials. Int J Cancer 1992;52: 189–96.
(3) Lippman SM, Lee JS, Lotan R, Hittelman W, Wargovich MJ, Hong WK. Biomarkers as intermediate end points in chemoprevention trials. J Natl Cancer Inst 1990;82:555–60.

NOTES

Affiliations of authors: S. M. Lippman (Departments of Clinical Cancer Prevention and Thoracic/Head and Neck Medical Oncology), A. L. Sabichi (Department of Clinical Cancer Prevention), The University of Texas M. D. Anderson Cancer Center, Houston; J. J. Lee, Department of Biomathematics, The University of Texas M. D. Anderson Cancer Center, and Stanley S. Schor Visiting Scholar (1998–1999), Merck Research Laboratories, Rahway, NJ.

Correspondence to: Scott M. Lippman, M.D., Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Box 236, 1515 Holcombe Blvd., Houston, TX 77030-4096.