LETTER TO THE EDITOR

Cancer chemoprevention is not a failure

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Dear Sir:

We read with much interest the review by J.Potter on ‘The failure of cancer chemoprevention’ (1). We, as well as most researchers working in the area of cancer chemoprevention, are as frustrated as Dr J.Potter is, about the lack of unequivocal evidence of a high benefit/harm effect of cancer chemoprevention in clinical trials. However, we strongly feel that the failure of cancer chemoprevention is really analogous to the early days of adjuvant chemotherapy with similar issues: evidence of proof-of-concept but with appropriate concern for benefit/harm ratios; and our inability to test right agent(s), in right dose(s), in the right population(s). The review lays out in very unambiguous style the evidence suggesting failure of cancer chemoprevention without talking about its successes and discusses many reasons why it has evaded expected outcomes. We agree that many clinical trials have been conducted notwithstanding preclinical evidence and were generally based on ‘excited extrapolations’. However, we respectfully disagree with the author’s rather pessimistic contention that chemoprevention of cancer is an almost universal failure and argue that if modeled in the right way chemoprevention can offer an effective alternate strategy for the management of cancer at least for the high-risk individuals (2,3). A continued problem in cancer chemoprevention drug development is the difficulty in designing clinical trial interventions which actually mirror the animal modeling data from which they were derived. However, once an intervention is about to reach the clinical trial stage, it will be prudent to test it in a judiciously chosen animal model exactly in the fashion as is planned to be used in humans. Such an approach is likely to help discover potential adverse effects, the major reason for abandoning clinical trials.

The concept of disease prevention using chemicals is being successfully applied against cardiovascular, atherosclerosis, diabetes and other diseases. There is sufficient proof-of-concept from human studies that chemoprevention is a viable option for cancer management (4–22). A decrease with tamoxifen use was apparent in the incidence of invasive and non-invasive breast cancer in women at increased risk for the development of the disease (5,6). Non-steroidal anti-inflammatory drugs were reported as effective agents for the prevention of colorectal adenomas (7,8). Clinical studies of oral alpha-difluoromethylornithine use in patients with a history of prior non-melanoma skin cancer revealed a significant difference in new basal cell carcinomas (9). Meyskens et al. (10) observed that recurrent adenomatous polyps were markedly reduced by a combination of low oral doses of alpha-difluoromethylornithine and sulindac and with few side effects. Elmets et al. (15) observed significant prevention of squamous cell and basal cell carcinoma by celecoxib in individuals who had extensive actinic damage and were at high risk for development of non-melanoma skin cancers. Another successful trial worth mentioning here is the prostate cancer chemoprevention trial with green tea which for reasons unknown did not generate enough interest (12,13). This trial though small was geared toward the right population and was based on solid preclinical data (23,24). Two-year follow-up of the patients in the same trial suggested significant prevention of the disease (13). Recently Zu et al. (17) reported that dietary intake of lycopene was associated with reduced risk of lethal prostate cancer and with a lesser degree of angio genesis in the tumor. Wang et al. (16) tested the effect of black raspberries in familial adenomatous polyposis patients and observed significant regression in the burden of rectal polyps. To estimate the risk for ovarian cancer development with the use of oral contraceptive pills, Havrilesky et al. (18) conducted a systematic review and meta-analysis of 24 case–control and cohort studies and observed a significant reduction in ovarian cancer incidence in ever-users compared with never-users. A significant duration–response relationship was observed with reduc tion in incidence of >50% among women using oral contraceptive pills for 10 or more years (18,19). Diabetic patients have an increased risk for cancer development (20). A systematic review and meta-analyses of worldwide reports demonstrated that metformin is associated with a substantially lower risk of all-cancer mortality and incidence, compared with other treatments for diabetes (21). The studies also showed that metformin significantly reduced the risks of cancers of the colorectum, liver and lung. Evidence is emerging that aspirin may provide prophylaxis for cancer, primarily colorectal cancer, but also gastric cancer as well as breast, ovarian, prostate and lung cancer (22). It is reported that the benefits increase with use duration and an earlier effect was shown in trials using higher doses (22). The aforementioned discussion clearly suggests a potential for chemoprevention of cancer.

Many of the cancer chemoprevention studies have been guided by a vigorous knowledge of the mechanisms that drive carcinogenesis in different cancer types such as tamoxifen for breast, finasteride for prostate, non-steroidal anti-inflammatory drugs for colon cancer and others (25). The recent studies on epigenetics and its influence on cancer in subsequent generations needs to be considered for chemoprevention as well. Epidemiological studies suggest that dietary habits (consumption of higher levels of fruits and vegetables) are consistently associated with a reduced risk of cancer at most sites. This appears reasonable since cancer is a heterogeneous disease and uses multiple pathways to survive. Cancer chemoprevention may be a misnomer as the real disease to prevent is carcinogenesis, the process of cancer development, which by all means, as with any other process, can be slowed down. The issue is to what extent we have the armamentarium to slow the process.

We believe that the review missed out on the discussion of successful trials that would have helped lead the debate in assessing why cancer chemoprevention has been a failure. There are several issues which currently confound successful chemoprevention of cancer, in contrast to the trend in chemotherapy (2,3). Prominent among these issues are the absence of robust surrogate markers of efficacy which would help assessment of success or failure of early clinical trials, lack of interest of the pharmaceutical industry, lack of prevention awareness of members of the health care team, the public’s fatalistic attitude and finally unfounded scepticism toward the prevention approach among some basic scientists.

An important issue is our expectation of extent of preventive efficacy in any given trial. It seems crucial to recruit individuals into intervention trials for whom as many details as possible have been taken into account of their regular dietary habits and exposure to potentially preventive agents for example in the drinking water. Even if such details are considered, observing large effects in terms of trial outcome may be unrealistic. It may be prudent to optimize our ability to detect reliably subtle to moderate beneficial effects. Nevertheless chemoprevention could be an extremely viable option especially for high-risk individuals.

In summary, as with other accepted health care interventions (e.g. cardiovascular prevention, adjuvant chemotherapy, antihypertensives) it should not be expected that a sudden rush of unequivocal evidence supporting the societal benefit of cancer chemoprevention will occur; but persistence and careful assessment of proof of principles, measured improvements to further enhance the benefit/risk ratio, and a greater diversity of effort toward cancer chemoprevention...
are likely to lead to success. Current estimates suggest that one in two males and one in three females will be diagnosed with cancer sometime in their lifetime and many will die from the disease. Thus, some degree of risk in chemoprevention needs to be tolerated so that important issues related to the success of chemoprevention are recognized. Although biologically complex, the overall logic and simplicity of the concept of cancer chemoprevention are why it continues to be explored.

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References

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