Minireview

Chemoprevention of Second Cancers

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Abstract

Background: “Second cancers” can be thought of in two general categories: (a) those occurring as a consequence of cancer treatment and (b) primary cancers that are thought to develop largely as a consequence of prior lifestyle habits (e.g., chronic smoking, drinking, sun exposures), genetic susceptibility, or interactions of the two. Because there has been limited work on chemoprevention of treatment-related secondary cancers, this minireview will focus on chemoprevention of secondary cancers with lifestyle/genetic origins. Methods/Results: Trials aimed at preventing second cancers in patients with tobacco-related cancers (head and neck, lung), skin cancers, breast cancer, and colorectal adenomatous polyps have been completed with some success. However, one finding that has emerged is that, across several cancer sites, subgroups are found with differential response to the chemopreventive agent. For example, smoking status, alcohol consumption, nutritional status, and host tumor characteristics seem to modify chemopreventive efficacy. Stratum-specific (subgroup) findings may occur by chance, requiring a need for supportive evidence from observational epidemiologic studies of the agent (where available), mechanistic studies, or results of other related trials. Conclusions: Although chemoprevention of second cancers has been realized, it has become increasingly apparent that not all benefit equally. The finding of subgroup effects in completed trials results in the need to consider such subgroup effects in the design of future trials, by either restricting enrollment to particular subgroups (e.g., never or former smokers), or by increasing sample size requirements to allow for variation in response in subgroups in a statistically powerful way. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2033–7)

Introduction

Cancer is increasingly becoming a survivable disease, and the number of cancer survivors is increasing each year. As noted in the accompanying minireview by Travis (1), second- or higher-order cancers now account for ~16% of incident cancers in the SEER (Surveillance, Epidemiology, and End Results) database. An important current research need is to better understand (a) the epidemiology of second cancers (including treatment-related, syndromic, and second cancers due to shared etiologic factors; ref. 2), (b) chemoprevention strategies for these second cancers, and (c) early detection strategies for second cancers. These three topics were each highlighted at a recent AACR Frontiers in Cancer Prevention Annual Meeting; the current minireview emphasizes chemoprevention of second cancers. The reader is directed to the accompanying minireviews by Travis (1) and Vogel (3) for coverage of the other two important areas of research in the field of second cancers.

Chemoprevention: Second Cancer versus Primary Cancer Prevention Trials

Chemoprevention describes the use of drugs, biologicals, or nutrients to inhibit, delay, or reverse the carcinogenic process (4). As comprehensively reviewed in a recent text (5), much progress has been made in discovering and performing preclinical evaluations on agents that hold promise for chemoprevention. Although many of these agents have yet to be formally evaluated for efficacy, several have been evaluated in phase II/III chemoprevention trials, including both primary prevention trials and trials aimed at preventing second cancers. In considering the latter category, it is readily apparent that little or no research has been conducted in the area of chemoprevention of treatment-related secondary cancers. Consequently, the emphasis of this minireview is on chemoprevention of second cancers with lifestyle/genetic origins (shared etiologic factors). Cancers that fall into this general category include nonmelanoma skin cancers, mouth and throat cancers, lung cancers, breast cancers, and also some precancerous conditions that have been widely studied in prevention trials (e.g., adenomatous polyps).

The search for effective chemoprevention agents generally requires evidence of efficacy from randomized cancer prevention trials. Such trials can be conducted in the setting of primary prevention; for example, targeting the general population or subjects at elevated risk of cancer due to prior lifestyle habits (e.g., cigarette smokers), and intervening with the goal of preventing incident cancer. An alternative design is to recruit participants who previously had cancer, and who are at risk for second cancers. The advantages of this trial design are many. First, persons who have had a previous cancer are at relatively high risk for developing a new cancer, such that sample size requirements are much more modest for second cancer prevention trials than for primary cancer prevention trials. As an example, the Lung Intergroup Trial was a second cancer prevention trial that will be discussed shortly; the
sample size for this trial was 1,200 randomized subjects with prior lung cancer (6). In contrast, primary prevention trials of lung cancer such as the ATBC (α-Tocopherol β-Carotene) Lung Cancer Prevention Trial randomized 29,133 subjects (7). The target sample size is obviously influenced by many design factors, but the baseline risk of cancer in the population under study is of prime importance. In addition to being a more "efficient" study design, it could be argued that second cancer prevention trials are more ethical in that exposing persons to agents with some risk may well be more justifiable in the second cancer prevention setting. That is, chemopreventive agents have risks, both known and unknown. Evaluation of efficacy in a statistically powerful second cancer prevention trial, while exposing fewer subjects to agents with risks, is reasonable. For the individual patient who is randomized, the risk-benefit ratio is also arguably more beneficial (greater expected incidence; if risk reduction occurs, more people benefit for a given incidence of adverse effects). A third obvious advantage to second cancer prevention trials is that results are directly relevant to the clinical management of patients with first primary cancers.

With this background in mind, we will review and briefly comment on selected trials to illustrate an important theme that we believe is now emerging in the area of chemoprevention research, more specifically, the role of host and lifestyle factors in modifying the efficacy of chemopreventive agents.

Chemoprevention with β-Carotene/Retinoids

Some of the early work in chemoprevention was done in the setting of prevention of second skin cancers. One of the first large phase III trials in this setting to be completed was a trial that randomized 1,805 persons with prior nonmelanoma skin cancers to either β-carotene or placebo (8). After 5 years of follow-up, the relative rate of new nonmelanoma skin cancers was similar in the β-carotene arm compared with the placebo arm [risk ratio (RR), 1.05; 95% confidence interval (95% CI), 0.91-1.22]. Buried within this null measure of association, however, was the suggestion that smokers randomized to the intervention had a different intervention response compared with nonsmokers randomized to β-carotene (RR, 1.44; 95% CI, 0.99-2.09; RR, 0.97; 95% CI, 0.82-1.15, respectively; $P_{\text{interaction}} = 0.04$). At the time of publication of this article (1990), there was little or no evidence supporting the plausibility of such an interaction, leading the authors to do little more than present the stratum-specific risk estimates.

Over the ensuing 15 years, evidence has continued to mount from other β-carotene chemoprevention trials supporting the hypothesis that cigarette smoking affects the chemopreventive efficacy of β-carotene (effect modification). First, the ATBC primary prevention trial of lung cancer in Finnish smokers found that lung cancer was increased in men who received supplemental β-carotene (7), and that the risk was more pronounced as the amount smoked increased (9). Second, the Carotene and Retinol Efficacy Trial found that the combination of β-carotene plus retinyl palmitate increased lung cancer risk in a primary prevention trial of smokers and asbestos workers (10); the adverse effect was noted in current smokers (RR, 1.42; 95% CI, 1.07-1.87) but not former smokers (RR, 0.80; 95% CI, 0.48-1.31). One notable trial of supplemental β-carotene, the Physicians’ Health Study, did not reveal an apparent adverse effect of supplemental β-carotene in smokers (11), but this could relate to the lower plasma β-carotene concentrations achieved in this trial (12). Squamous metaplasia has been produced in the lungs of ferrets exposed to both cigarette smoke and high-dose β-carotene, supporting the plausibility of this subgroup effect (13). The implication is that trials are generally interpreted based on their summary relative risk estimate, but buried within that risk estimate may be subgroups with both qualitatively and quantitatively different risks.

The notion that chemopreventive efficacy may vary as a function of cigarette smoking status is not unique to β-carotene (14). As discussed elsewhere, the retinoids have been another widely studied class of chemopreventive agents, especially in the second cancer prevention setting (15). One such definitive trial of retinoids for secondary cancer chemoprevention was the Lung Intergroup Trial. This trial was designed to evaluate the efficacy of 13-cis-retinoic acid (30 mg/d) in reducing the incidence of second primary tumors, recurrences, and death in stage I non–small cell lung cancer patients. A total of 1,163 persons were randomized in this placebo-controlled prevention trial. At the planned conclusion of the trial, 13-cis-retinoic acid was found to have no benefit for any of the end points of interest (6). The hazard ratio for second primary tumors was 1.08 (95% CI, 0.78-1.49); the hazard ratio for recurrence was 0.99 (95% CI, 0.76-1.29), and the hazard ratio for overall mortality was 1.07 (95% CI, 0.84-1.35). Thus, at first glance, this trial produced a consistent null result. However, when the results were stratified by smoking status, a rather different picture emerged; 13-cis-retinoic acid seemed to be beneficial in nonsmokers but harmful in current smokers. As an example, the hazard ratio for recurrence was 0.44 in never smokers (95% CI, 0.15-1.27) versus a hazard ratio of 1.37 in smokers (95% CI, 0.9-2.1). A formal statistical evaluation of a treatment-by-smoking interaction was done; for example, current smokers randomized to the retinoid were 3.11 (95% CI, 1.00-9.71) times more likely to have a recurrence compared with never smokers randomized to the retinoid ($P_{\text{interaction}} = 0.07$). Similarly, current smokers randomized to the retinoid were 4.39 (95% CI, 1.11-17.29) times more likely to die compared with never smokers randomized to the retinoid ($P_{\text{interaction}} = 0.007$). Obviously, understanding the mechanistic basis for such a qualitative interaction, wherein one group of persons apparently benefited from an intervention whereas another group was apparently harmed, is an important priority for chemoprevention research.

The previous examples emphasized the increasing evidence supporting an interaction between carotenoids/retinoids and tobacco in cancer chemoprevention, but the apparent interactions are not limited to tobacco. Alcohol consumption is another lifestyle factor that not only interacts with tobacco to modify cancer risk (16), but may also jointly interact with tobacco and chemopreventive agents to affect risk. An example of this is suggested in the results of the Antioxidant Polyp Prevention Trial (17). This trial randomized 860 persons with prior colorectal adenoma to β-carotene and/or vitamins C/E (2 × 2 factorial design). The primary end point for this trial was adenoma recurrence. Overall, neither of the antioxidant interventions was found to affect the primary end point (e.g., for the β-carotene intervention group, the RR for adenoma recurrence was 1.01; 95% CI, 0.85-1.20). However, when the population was stratified by tobacco use and alcohol intake (18), a different picture emerged. In persons who were nonsmokers/nondrinkers, supplemental β-carotene reduced the risk of adenoma recurrence (RR, 0.56; 95% CI, 0.35-0.89). In contrast, among persons who smoked cigarettes and drank more than one alcoholic drink per day, supplemental β-carotene increased the risk of adenoma recurrence (RR, 2.07; 95% CI, 1.39-3.08; $P$ for difference from nonsmoker/nondrinker RR < 0.001). Again, this trial revealed both quantitative and qualitative interactions, with the relative risk estimates for...
Clinical trialists appropriately caution against overinterpretation of subgroup effects within trials (19). This is because subgroup differences can arise simply due to chance, or subgroups may differ from each other in ways other than just the stratification variable of interest. Confirmation of subgroup leads may be warranted in follow-up trials, if the totality of the evidence supports a particular subgroup benefit. To accomplish this, publication of subgroup findings must be encouraged in the primary efficacy publications to see if certain subgroups are consistently helped or harmed by chemopreventive agents of interest.

Chemoprevention in Smokers

Smokers are at elevated risk for malignancies, especially smokers with a previous cancer diagnosis, so are a priority group for chemoprevention research. To date, however, chemopreventive approaches for lung and head and neck cancers in smokers have been disappointing, emphasizing the need for novel approaches.

In contrast to the carotenoids and retinoids, vitamin E is an agent that may hold potential for chemoprevention of certain cancers in smokers. More specifically, the ATBC lung cancer primary prevention trial enrolled only smokers at entry. Although vitamin E was not found to reduce the incidence of the primary end point in this trial (lung cancer), a notable decrease in prostate cancer was observed in men randomized to receive vitamin E (20). The suggestion that vitamin E might reduce the incidence of prostate cancer in smokers also has some basis in the observational epidemiology literature. Chan et al. (21) examined the association between supplemental vitamin E use and risk of prostate cancer in the Health Professionals’ Follow-up Study. Overall, supplemental vitamin E (≥100 IU/d) was not associated with prostate cancer risk in this study (RR, 1.07; 95% CI, 0.95-1.20). However, among current smokers/recent quitters, an inverse association was suggested for metastatic/fatal prostate cancer (RR, 0.44; 95% CI, 0.18-1.07). Kirsh et al. (22) also conducted a prospective cohort analysis of supplemental vitamin E and prostate cancer risk, but in this case using men from the screening-only arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Supplemental vitamin E was not related to prostate cancer risk overall; however, use of >400 IU of supplemental vitamin E per day was associated with a substantial risk reduction for advanced prostate cancer in current/recent smokers (RR for >400 IU/d versus none, 0.29; 95% CI, 0.12-0.68; P \text{ trend } = 0.01) but not in never smokers (RR, 1.29; 95% CI, 0.84-1.98) or former smokers (RR, 0.95; 95% CI, 0.65-1.40).

The suggestion that smokers might uniquely benefit from supplemental vitamin E for prevention of advanced prostate cancer could theoretically be formally evaluated in the ongoing Selenium and Vitamin E Chemoprevention Trial (SELECT; ref. 23); this would require adequate representation of smokers in the trial population. Randomization is now complete with >35,000 men randomized; unfortunately, a large majority of the participants are not current smokers. If vitamin E exerts its primary chemopreventive effect in smokers only, with regard to advanced prostate cancer, SELECT will likely lack the statistical power to detect such a stratum-specific effect.

The notion that different groups in a population may respond differentially with regard to a chemopreventive agent raises some interesting considerations with regard to sample sizes. That is, both primary prevention trials and trials aimed at preventing second cancers would benefit from more generous sample sizes to allow examination of effects in subgroups of the population. Because primary prevention trials are already very large and extraordinarily expensive to conduct, increasing sample sizes to accommodate subgroup analyses in primary prevention trials is not likely to occur. This highlights the importance of trials aimed at preventing second cancers, where increased sample sizes are not as cost-prohibitive as in the primary prevention setting.

Effect Modification by Baseline Nutrient Status

The previous sections highlighted the potential role that smoking and drinking can have in modifying the efficacy of potential chemopreventive agents; another factor that may play a similar role in effect modification is baseline nutritional status. This is obviously most relevant in the setting of nutrient-based chemoprevention trials, wherein the baseline status of the target intervention nutrient/nutrients, or the baseline status of the population with regard to related nutrients, might modify efficacy. As an example of this, selenium is a trace mineral of considerable interest for a possible role in cancer prevention (24). A landmark prevention trial, the Nutritional Prevention of Cancer (NPC) Study, was done to evaluate the efficacy of supplementation with selenium-enriched yeast (200 μg/d) versus placebo yeast in 1,312 persons with prior skin cancers recruited from low-selenium regions around the United States (25). The trial was designed to evaluate the efficacy in the prevention of second skin cancers. Selenium was not found to reduce the risk of second skin cancers in this trial; however, fewer cancers of the prostate, lung, and colon-rectum, and fewer total cancers, were observed in the selenium-supplemented group. In secondary analyses, the authors stratified the population by baseline selenium status as assessed by plasma selenium at entry and reexamined the effect of selenium on total cancer mortality (26). In these subgroup analyses, the protective effect of selenium was only observed in those who were in the lowest two tertiles of plasma selenium at entry. More specifically, the hazard ratios were 0.50 (95% CI, 0.30-0.80) for the lowest tertile, 0.70 (95% CI, 0.44-1.12) for the second tertile, and 1.19 (95% CI, 0.75-1.90) for the highest tertile. That is, selenium was only effective as a chemopreventive agent in those people (selected from lower selenium regions) who had lower plasma selenium levels at entry. Additional support for the theory that baseline selenium status modifies the chemopreventive efficacy of selenium comes from another analysis of NPC data, which showed that selenium supplementation was associated with a significantly reduced risk of colorectal adenomas, but only among subjects with low baseline selenium status, or among current smokers (27). The NPC finding that baseline selenium status modifies chemopreventive efficacy for selenium is biologically plausible, but being based on subgroup findings from one intervention trial, replication in the ongoing SELECT trial or other trials is needed.

Another example where baseline nutrient status seemed to modify the efficacy of a nutrient-based chemopreventive intervention comes from the trial of Baron et al. (28). This trial randomized 930 subjects with previous colorectal adenomatous polyps to calcium (3 g/d) or placebo. The primary end point of this prevention trial was recurrent adenomas. Calcium supplementation was found to significantly reduce the risk of the recurrent adenomas in this study (RR, 0.85; 95% CI, 0.74-0.98). When the authors subsequently stratified the population by vitamin D status at baseline as assessed by 25-hydroxy vitamin D concentrations in blood (29), they observed that supplemental calcium had no effect in persons with

β-carotene varying ~4-fold, depending on lifestyle factors of the subjects in the trial.

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Breast Cancer: Second Cancer Prevention Trials

Breast cancer is one site where prevention of second breast cancer (as well as primary breast cancer) has been realized. Considering prevention of second cancers, adjuvant use of tamoxifen has been shown to reduce contralateral breast cancer by 13% (SD 13), 26% (SD 9), and 47% (SD 9) in trials of 1, 2, or ~5 years of therapy (31). However, tamoxifen therapy is not effective in women with estrogen receptor–negative tumors, and also has been shown to significantly increase the risk of endometrial cancers.Raloxifene is another selective estrogen receptor modulator that shows promise in breast cancer chemoprevention (see ref. 32 for review), and seems to lack the increased endometrial cancer risk. These two compounds are being compared in the ongoing Study of Tamoxifen and Raloxifene trial.1

Aromatase inhibitors, such as anastrozole and letrozole, also show promise for breast cancer chemoprevention (33). The Anastrozole, Tamoxifen, Alone or in Combination trial showed that anastrozole was more effective than tamoxifen in reducing contralateral breast cancer (34). As is the case with tamoxifen, these agents target hormone-sensitive breast cancers.

Basic science research has revealed promising molecular targets for cancer prevention and therapy, such as the epidermal growth factor receptor signaling pathway (35). Epidermal growth factor receptor–targeted agents hold promise in the prevention of cancer and its recurrence. For example, the monoclonal antibody trastuzumab (Herceptin) is an example of a molecularly targeted drug that has been proven effective in reducing the risk of recurrent breast cancer (36, 37).

This body of research shows that effective prevention of second cancers is possible. However, these approaches are not appropriate for all women with breast cancer; for example, trastuzumab is only appropriate for women with HER2-positive tumors, and selective estrogen receptor modulators target hormone-responsive tumors. Thus, other strategies are needed that can be more broadly applied.

Two prevention trials involving diet modification in breast cancer survivors are worthy of mention here. The first is the Women’s Intervention Nutrition study, which was a randomized trial of dietary fat reduction in women surgically treated for primary invasive breast cancer. A total of 2,437 postmenopausal women with early stage breast cancer were randomized to a standard diet or a low-fat diet (20% of total kilocalories from fat). Preliminary results of the trial have been released; after 5 years of follow-up, there was an overall 24% reduction in risk of recurrent breast cancer in the low-fat intervention group (38). This consisted of a 42% reduction in risk for women with estrogen receptor–negative tumors, versus a 15% reduction in risk for women with estrogen receptor–positive tumors. Another trial, the Women’s Healthy Eating and Living Study, is a randomized trial of increased consumption of fruits and vegetables in women with breast cancer. Results of this trial are anticipated in the next year or so.

Conclusions and Recommendations

This minireview has provided research examples that show that chemoprevention of secondary primary cancers has been realized. However, what we have also learned through these trials is that not all populations seem to benefit equally from chemopreventive approaches. Examples were provided demonstrating that both qualitative and quantitative differences in the efficacy of various chemopreventive agents seem to exist as a function of various lifestyle factors such as smoking, drinking, nutritional status, and also host tumor characteristics. A pressing need is to characterize and fully understand these subgroup differences. Trials aimed at preventing second cancers are arguably the best design to evaluate and understand subgroup-specific findings to contribute to knowledge and efficacy for more ”personalized” chemoprevention.

In the interim, although research continues to seek targeted, evidence-based chemoprevention for second cancers, the recommendations for prevention in cancer survivors parallel recommendations for cancer prevention in the general population. That is, strategies that continue to make sense for cancer survivors include tobacco cessation, promoting physical activity/avoidance of weight gain, ingesting a prudent diet consisting of more plant-based foods, drinking in moderation for those who choose to drink, and avoidance of excessive solar radiation.

References


Note added in proof: Results of the Study of Tamoxifen and Raloxifene have been released and indicate that raloxifene was just as effective as tamoxifen in reducing the risk of invasive breast cancer, and lessened some of the side effects known to occur with tamoxifen; however, noninvasive breast cancer was nonsignificantly higher in the raloxifene group. Vogel V, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006;296:2727–41.


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