

Diet and Cancer: Future Etiologic Research

Arthur Schatzkin,¹ Joanne Dorgan,¹ Christine Swanson,² and Nancy Potischman²

¹Division of Cancer Prevention and Control; ²Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland

In light of several credible diet and cancer hypotheses, we suggest strategies for advancing our understanding in this area. Two conceptual approaches can be taken in defining dietary exposure: the decompositional approach focuses on specific nutrients and other chemical constituents of food, whereas the integrative approach emphasizes the action of whole foods or food patterns (cuisines). Diet-cancer hypotheses can be organized according to this conceptual framework. We review four types of scientific investigation available to us for advancing the diet and cancer field: metabolic (clinical nutrition) studies; animal studies; observational epidemiologic investigations; and clinical trials. Each of these designs has its strengths and limitations. Observational epidemiologic studies and trials have the particular advantage of examining explicit cancer end points in humans. Results from metabolic and animal research, however, can complement the findings from epidemiologic studies and trials. Finally, we briefly review strategies for evaluating promising hypotheses linking diet to cancers of the large bowel, lung, breast, and prostate. — *Environ Health Perspect* 103(Suppl 8):171–175 (1995)

Key words: antioxidants, breast cancer, cancer, colon cancer, diet, fat, lung cancer, nutrition, prevention, prostate cancer

Introduction

It is clear from Willett's review (1) that we have many credible hypotheses linking diet to several major cancers. In this paper we provide a brief critical overview of different research strategies in this area and suggest particular studies likely to advance our understanding of the connections between diet and cancer.

Conceptualizing Diet

Because what people eat is so complex and varied, we need some theoretical framework for defining diet. Two alternative conceptual approaches can be taken.

The first is the decompositional approach, which focuses on specific nutrients and other chemical constituents of food. The underlying premise of such an approach is that single nutrients or chemicals have a specific biologic effect on carcinogenesis and, further, that it is possible to isolate this biologic activity.

The alternative is the integrative approach, which considers the effects of whole foods or food patterns (cuisines). The underlying premise of this approach is that people eat whole foods containing hundreds of individual nutrients or chemicals that interact in highly complex ways—with one another and other, possibly unknown, substances—to influence carcinogenesis. It is therefore difficult on both theoretical and practical grounds to isolate the specific cancer-related biologic activities of single nutrients or chemicals.

We can group major diet and cancer hypotheses according to this framework, as the following examples show.

Nutrient- and Chemical-based Hypotheses

The Antioxidant Hypotheses. Antioxidants include such substances as carotenoids, vitamins C and E, and flavonoids (2). Specific examples of these hypotheses include β -carotene and lung cancer (3), and vitamin E in relation to prostate (4) and large bowel cancer (5).

Hypotheses Involving Other Nutrients. Examples include the possible protective effects of calcium (6) and folic acid (7) on large bowel carcinogenesis.

Hypotheses Implicating Various Macronutrients. Specific examples of macronutrient hypotheses include the often researched and still unresolved relation of dietary fat and breast cancer (8), the more recently proposed link between linolenic acid and prostate cancer (9), or

the (protective) association between dietary fiber intake and large bowel cancer (10).

The Food Mutagen Hypothesis. Heterocyclic amines, produced in high-temperature cooking of meats, have been suggested as factors in the genesis of large bowel malignancies (11).

Food- and Cuisine-based Hypotheses

Foods and Food Groups. Several hypotheses on the relations of various foods and food groups to cancer are under investigation. Red meat consumption, for example, has been linked to large bowel cancer (12). A protective effect of vegetable and fruit intake has been hypothesized for several cancers (13). Possible cancer-preventive roles for soy-based products (14) and garlic (15) have been proposed.

Dietary Patterns (Cuisines). It has been hypothesized that an overall low-fat, high-fiber, high-vegetable and -fruit eating plan reduces the risk of large bowel (16) and possibly other cancers, compared with the more typical Western high-fat, low-fiber, low-vegetable and -fruit fare. Some have argued that a vegetarian diet reduces cancer risk (17). In a similar vein, it has been proposed that Mediterranean and Asian cuisines, as opposed to U.S. or Western European eating patterns, protect against certain malignancies (18).

We now briefly review four types of scientific investigation available to us for advancing the diet and cancer field: metabolic studies, animal studies, observational epidemiology, and randomized controlled trials.

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7–8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

Address correspondence to Dr. Arthur Schatzkin, Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, 9000 Rockville Pike, EPN 211, Bethesda, MD 20892. Telephone: (301) 496-8559. Fax: (301) 402-0553. E-mail: schatzka@dcpccepn.nci.nih.gov

Abbreviations used: AARP, American Association of Retired Persons; IU, international units; kcal, kilocalories; mg, milligram; NCI, National Cancer Institute; NIH, National Institutes of Health; PPT, Polyp Prevention Trial; WHI, Women's Health Initiative.

Metabolic Studies

Metabolic (or clinical nutrition) studies involve intensive, controlled supplement or dietary interventions with a relatively small number of people. Noncancer (biomarker) end points are used. Such studies can examine the effect of fat or meat intake on blood hormone levels (such as estrogens or androgens) (19); the intake of high-carotenoid-containing foods or carotenoid supplements in relation to blood or tissue carotenoid levels (20); the impact of a low-fat, high-fiber, high-fruit and -vegetable eating plan on fecal bile acids (21) or short-chain fatty acids (22); or the influence of alcohol consumption on endogenous estrogens and other hormones in women (23).

Metabolic studies have a number of advantages. They can aid in refining our dietary assessment questionnaires as well as the databases underlying these instruments. This is exemplified by recent studies of the types and amounts of mutagenic substances produced by high-temperature cooking of various meats (24). Metabolic studies can also demonstrate the relation of blood or tissue nutrient levels to intake (25) and thereby play a role in the development of biological markers of dietary intake. Still another advantage of these investigations is the possibility of intervening with well-defined diets. Finally, metabolic studies, which can involve multiple biomarker end points, may provide valuable insight into plausible mechanisms underlying carcinogenesis.

A major limitation of metabolic studies is the noncancer end points. The relation of such end points to cancer and neoplasia is not sufficiently clear to warrant conclusive inferences about diet and cancer from these studies (26). Studies, for example, demonstrating an effect of alcohol or dietary fat on endogenous estrogens suggest that these nutritional factors influence breast carcinogenesis. For two reasons, however, such studies are less than conclusive when it comes to establishing a causal connection between the nutritional factors and breast cancer: data establishing a direct relation between blood estrogen levels and breast cancer are, in fact, sparse at best (27); and even if the evidence were strong that a relatively high blood level of estradiol increased breast cancer risk, one could not rule out the possibility that the nutritional factors affected some other biologic intermediate that inhibited breast carcinogenesis.

Animal Studies

In a similar vein, animal studies can also enhance the biologic plausibility of diet

and cancer hypotheses. In particular, investigators conducting such studies can examine controlled diets, study cancer as an explicit end point, integrate biomarkers in animal models (creating a complete exposure-intermediate end point-cancer continuum) (28), and evaluate potential chemopreventive agents as well as some animal analogues of dietary patterns.

Given the often major differences in anatomy and physiology between laboratory animals and people, inferences from animal models to human malignancy are problematic. Animal studies, however, are not without inferential value. Consistency in diet-cancer relations across species and tumor models lends confidence that the relations hold in human populations. Moreover, delineation of mechanisms in many model systems can be useful in our approach to studying cancer in humans. For example, animal studies consistently indicating effects of dietary factors only on late-stage events suggest conducting human studies that focus on recent rather than remote diet.

Observational Studies

It is because of the limitations of metabolic and laboratory studies in making clear-cut inferences to cancer in people that observational epidemiologic studies and clinical trials are so important.

Observational investigations—the two major types are case-control and cohort studies—make several important contributions to the diet and cancer field. First, these studies do have cancer as an explicit end point. Second, they can look at exposures of long duration; i.e., dietary intake over many years. Third, large epidemiologic studies permit the evaluation of interactions between dietary and other risk factors. This is germane where another risk factor like obesity tends to overwhelm and obscure the weaker (but still important) dietary factor association. Analyses of diet and cancer in, for example, thin women may therefore be particularly revealing. Finally, observational epidemiologic studies are increasingly integrating intermediate biomarkers of carcinogenesis into their design. Observational studies also have their limitations, however, and some of these are discussed in the following sections.

Dietary Measurement Error

Because eating habits are complex and human recall imperfect, the assessment of diet-related exposures is subject to considerable measurement error. This error generally tends to attenuate relative risks

and therefore makes it difficult to observe true associations (29).

Although statistical methods are available both to estimate and adjust for misclassification (30), these methods are not universally accepted (31) and the validation (calibration) studies required for the statistical corrections can be quite expensive. Furthermore, energy adjustment procedures continue to be controversial (32). It may not be possible, for example, to distinguish specific effects of fat from those of total caloric intake (33), although it may still be possible to derive practical overall dietary recommendations.

Work remains to be done in refining our dietary assessment instruments—particularly in rather understudied population subgroups—but it is unclear just how much better we can make these instruments. That is why there is so much interest in biomarkers of intake, but additional work is needed to develop accurate biomarkers of dietary intake at the individual level.

Dietary Homogeneity

The lack of dietary heterogeneity (the fact that in a given study carried out in a specific geographic region for a particular food or nutrient, people tend to eat somewhat alike) may make it difficult to make relevant comparisons between high and low levels of nutrients and foods. Investigators have recently adopted some innovative approaches to increase dietary heterogeneity. These include the investigation of multiple ethnic groups (34) and countries (35) and the implementation of a two-phase sampling design that explicitly captures the extremes of intake distribution (36).

Confounding

Confounding (37) is a serious potential problem in observational studies. People who eat differently may also differ in other ways related to carcinogenesis, and it may not always be possible to capture these other differences in our interviews and questionnaires.

Recall and Selection Bias

Case-control studies are subject to both recall and selection bias. Researchers have recently attempted to evaluate the extent of recall bias in case-control studies of diet and cancer by means of pre- and postdiagnosis assessments of persons developing malignancies within the setting of an ongoing cohort study (38,39). To reduce the likelihood of selection bias, epidemiologists have been developing a number of innovative approaches to increase participation

rates in case-control studies (40). The case-control design remains valuable for investigating emerging hypotheses (in a relatively short time) and examining the relatively rare malignancy lying beyond the statistical reach of most cohort studies. Because the cohort design largely circumvents recall and selection biases, several large prospective cohort studies of diet and cancer have been mounted around the world in recent years.

Uncertainty about Relevant Time of Exposure

Most epidemiologic studies of diet and cancer have assessed recent diet. Such assessments are appropriate if diet affects cancer risk by acting at a relatively late stage in the carcinogenic process or recent diet is a reasonable proxy for cumulative lifetime dietary exposure that is truly related to cancer development. Interest is growing in the possibility that early-life diet influences subsequent cancer. Methodologic studies are needed to determine whether early diet can be assessed with any useful degree of accuracy (41).

Intervention Studies

Another major research tool in this area is the randomized controlled trial (42). The interventions adopted in trials may be one of two types: supplements (vitamin pills or fiber wafers, for example), or a comprehensive eating plan (for example, one with specific targets for fat, red meat, fiber, or fruits and vegetables).

Trials have two distinct advantages. First, because of randomization, confounding is minimized. Second, because the trialist devises a specific intervention for comparison with the usual diet or nonsupplemented state, intake heterogeneity is built into the trial design. The National Cancer Institute (NCI)-sponsored Polyp Prevention Trial (PPT) is an example of this latter advantage (16). Whereas the usual intake among middle-aged and older persons in the United States (as reflected in the PPT control group) is about 35% calories from fat, 8 to 10 g of dietary fiber per 1000 kcal, and two to three daily servings of fruits and vegetables, the specific goals for the intervention group in the PPT are 20% calories from fat, 18 g of fiber per 1000 kcal/day, and five to eight servings of fruits and vegetables daily.

Trials, however, do have limitations. First, the intervention is generally of relatively short duration and the effects of much longer exposure to a given set of dietary factors cannot be easily established in

a trial. Second, the intervention generally is fixed for the duration of the trial and there often is considerable uncertainty in selecting the proper dosage or administration interval for a supplement study or the exact components of an eating plan in a dietary intervention. Third, dietary interventions, as opposed to supplements, cannot be double blind. If participants know they are changing their diet, they could also be changing other things related to cancer or neoplasia as a result of knowing about and being in the intervention group. Fourth, interventions are generally done only in adults because dietary effects resulting from earlier life exposure are difficult to test. Finally, trials are faced with difficulties in maintaining long-term adherence and are relatively expensive.

Future trials will continue as much as possible to make use of the factorial design, which gives, in essence, two or more studies for the price of one (43). Trials likely will increasingly use cancer precursors like adenomatous polyps as end points, although inferences from precursor studies are more limited than those from studies with cancer end points (44). Trials would also benefit from advances in biologic monitoring of intake as well as further development of behavioral techniques to improve dietary adherence. And, finally, there is increasing discussion of the need for longer follow-ups in nutritional chemoprevention and dietary trials (45).

In summary, trials can be extremely valuable in establishing causation and providing a rational, scientific basis for cancer prevention. However, they comprise only a part, albeit, an important one, of an overall research program. They are not a panacea.

Future Research for Major Diet and Cancer Hypotheses

Let us briefly illustrate the above points with reference to some key dietary hypotheses for cancers of the large bowel, lung, prostate, and breast.

Large Bowel Cancer

Data inconsistencies remain—with regard to animal fat and red meat consumption, for example—in observational epidemiologic studies of large bowel cancer. These inconsistencies need to be examined in other studies (46). Recent reports of an inverse relationship between dietary folate and colorectal cancer (47) are of considerable interest, but whether folate influences large bowel carcinogenesis independently or is merely a proxy for fruit and vegetable

intake remains to be determined. By integrating susceptibility markers into epidemiologic studies, it may be possible to increase observed relative risks among susceptible individuals (48). These susceptibility markers might include family history as well as genotypic and phenotypic characterizations of an individual's capacity to metabolize carcinogens (49).

A number of adenomatous polyp recurrence trials have been completed or are under way around the world. These include trials of vitamins (50), calcium (51), fiber supplements (51,52), folic acid (R Greenberg, personal communication), and a low-fat, high-fiber, high-fruit and -vegetable eating plan (16). Future polyp trials might include interventions involving reduced consumption of red meat or meat cooked at high temperatures. Because inferences from polyp trials to cancer are not absolute, there is need to consider polyp trial results together with the findings from well-designed observational studies with adequate intake range (44).

Two new large trials have large bowel cancer as an explicit end point. The Women's Health Study conducted by Buring and Hennekens will examine the effect of β -carotene (50 mg every other day), vitamin E (600 IU every other day), and aspirin among some 40,000 postmenopausal female health professionals 45 years of age and older. This study employs a 2³ factorial design and evaluates the three factors in relation to cardiovascular end points as well as total cancer and cancers of the breast, lung, and colon. The Women's Health Initiative (WHI), a very large, ambitious National Institutes of Health (NIH)-sponsored study of heart disease, cancer, and osteoporosis among women in the United States, will randomize 63,000 postmenopausal women aged 50 to 79 in its controlled clinical trial component. The trial has three interventions, although women can choose to be randomized into two or three of the overlapping studies. The interventions include a low-fat eating plan (with explicit emphasis on increasing consumption of fruits and vegetables), hormone replacement therapy, and calcium/vitamin D supplementation. Forty-eight thousand women will be randomized into the dietary component of the study (19,200 in the intervention arm, 28,800 in the control arm). The trial will require 4 years for protocol development and 9 years of follow-up. The trial has 90% power to detect a reduction of approximately 25% in the incidence of colorectal cancer.

Lung Cancer

There is much evidence from observational epidemiologic studies as well as metabolic and laboratory investigations suggesting that β -carotene intake is inversely associated with lung cancer risk. The Alpha-Tocopherol-Beta Carotene Trial carried out among 29,133 male Finnish smokers, however, showed no protective effect for β -carotene (4). This is an instance in which results from one large, well-designed intervention study raise questions about a whole body of epidemiologic evidence. One explanation for the disparity between the epidemiologic and trial findings that warrants further study is that it is not β -carotene per se that protects against lung cancer but rather other nutrients or foods that are highly correlated with β -carotene intake (or blood levels).

Breast Cancer

The observational epidemiology of diet and breast cancer has not been particularly revealing. Further insight might emerge if we are able in such studies to increase dietary heterogeneity, either through greater study population diversity or the two-stage cohort construction strategy being employed in the NCI-American Association of Retired Persons (AARP) Health Study (36). A successful implementation of the large-scale dietary trial in the NIH-sponsored Women's Health Initiative certainly would be informative. Because of the large body of evidence

implicating reproductive hormones in breast carcinogenesis (53), further metabolic studies of diet and hormones will be useful in conjunction with additional (and larger) observational studies of the precise relation of hormones to breast cancer. There is the very interesting hypothesis that pesticides enhance breast carcinogenesis (54)—this is not a hypothesis about foods or nutrients per se, but about potentially carcinogenic substances carried in foods.

Prostate Cancer

Some interesting findings have emerged, largely from observational studies, suggesting that red meat, and particularly linolenic acid, may increase prostate cancer risk (9) and that vitamin E (4) or vitamin A (55) may protect against this risk. More observational epidemiology is needed to confirm these findings. Metabolic studies of, for example, meat or linolenic acid in relation to androgens may provide additional biologic support for this hypothesis. And the time may be at hand to conduct trials to test these hypotheses further.

Additional Considerations in Diet and Cancer Research

Dietary factors may well be important in the etiology of other cancers, but the evidence to date is even more limited than that for the four sites we emphasized. Valuable information on diet in relation to cancers of, for example, the ovary and pancreas may come from some of the

ongoing large prospective cohort studies that will eventually yield substantial numbers of these malignancies.

Both the decompositional and integrative approaches to diet and cancer are spawning new avenues of research. Considerable attention recently has been focused on the possible anticancer effects of various nonnutritive constituents of foods, including flavonoids and other phytochemicals. Methodologic work is currently under way to develop the assessment instruments and databases necessary for further investigations of these compounds. From the integrative perspective, innovative approaches for the analysis of dietary data, especially ones taking into account multiple nutrients and foods, are greatly needed. There are, for example, no standardized, readily interpretable methods for identifying dietary patterns. This methodologic work on dietary patterns will not only enhance epidemiologic analyses and dietary intervention study planning but may even be of value in future animal studies.

Conclusions

In conclusion, diet and cancer hypotheses are promising. But they remain just that—hypotheses. As yet, nothing is proven. Given the enormous public health importance of putative diet and cancer relations, researchers in this area have a responsibility to seek that proof as vigorously and rapidly as possible.

REFERENCES

1. Willett WC. Diet, nutrition, and avoidable cancer. *Environ Health Perspect* 103(Suppl 8):165-170 (1995).
2. Dorgan JF, Schatzkin A. Antioxidant micronutrients in cancer prevention. *Hematol Oncol Clin North Am* 5:43-68 (1991).
3. Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the risk of cancer. *J Nutr* 119:116-122 (1989).
4. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029-1035 (1994).
5. Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, Folsom AR. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res* 53:4230-4237 (1993).
6. Garland CF, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19 year prospective study in men. *Lancet* 1:307-309 (1985).
7. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE, Willett WC. Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J Natl Cancer Inst* 85:875-883 (1993).
8. Schatzkin A, Greenwald P, Byar DP, Clifford CK. The dietary fat-breast cancer hypothesis is alive. *JAMA* 261(22):3284-3287 (1989).
9. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85:1571-1579 (1993).
10. Trock B, Lanza E, Greenwald P. Dietary fiber, vegetables, and colon cancer: critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* 82(8):650-661 (1990).
11. Weisburger JH. Heterocyclic amines in cooked foods: possible human carcinogens. *Cancer Res* 53:2422-2424 (1993).
12. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54:2390-2397 (1994).
13. Steinmetz KA, Potter JD. A review of vegetables, fruit, and cancer. 1: Epidemiology. *Cancer Causes Control* 2:325-357 (1991).
14. Messina MJ, Persky V, Setchell KDR, Barnes S. Soy intake and cancer risk: a review of the *in vitro* and *in vivo* data. *Nutr Cancer* 21:113-131 (1994).
15. Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 139:1-15 (1994).
16. Schatzkin A, Lanza E, Kruse L. The Polyp Prevention Trial: rationale and design. In: *Dietary Fiber in Health and Disease* (Kritchevsky D, Bonfield C, eds). St. Paul, MN: Eagan Press, 1995:219-225.
17. Willett WC. Micronutrients and cancer risk. *Am J Clin Nutr* 59(Suppl):1162S-1165S (1994).

18. Willett WC. Diet and health: What should we eat? *Science* 264:532-537 (1994).
19. Prentice R, Thompson D, Clifford C, Gorbach S, Goldin B, Byar D. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. *J Natl Cancer Inst* 82:129-134 (1990).
20. Brown ED, Micozzi MS, Craft NE, Bieri JG, Beecher G, Edwards BK, Rose A, Taylor PR, Smith JC Jr. Changes in plasma carotenoids in normal men after a single ingestion of vegetables or purified beta-carotene. *Am J Clin Nutr* 49:1258-1265 (1989).
21. Reddy BS. Diet and excretion of bile acids. *Cancer Res* 41:3766-3768 (1981).
22. Fleming SE, Fitch MD, Chansler MW. High-fiber diets: influence on characteristics of cecal digesta including short-chain fatty acid concentrations and pH. *Am J Nutr* 50:93-99 (1989).
23. Reichman ME, Judd JT, Longcope C, Schatzkin A, Nair PP, Campbell WS, Clevidence BA, Taylor PR. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst* 85(9):722-727 (1993).
24. Sinha R, Rothman N, Brown ED, Levander OA, Hoover RN, Lang NP, Kadlubar FF. Pan fried meat containing high levels of heterocyclic amines but low levels of polycyclic aromatic hydrocarbons induces cytochrome P4501A2 activity in humans. *Cancer Res* 54:6154-6159 (1994).
25. Micozzi MS, Brown ED, Edwards BK, Bieri JG, Taylor PR, Khachik F, Beecher GR, Smith JC Jr. Plasma carotenoid response in men to chronic intake of selected foods and beta-carotene supplements. *Am J Clin Nutr* 55:1120-1125 (1992).
26. Schatzkin A, Freedman LS, Schiffman MH, Dawsey SM. The validation of intermediate end points in cancer research. *J Natl Cancer Inst* 82(22):1746-1752 (1990).
27. Zumoff B. Hormone profiles in women with breast cancer. *Anticancer Res* 8:627-636 (1988).
28. Magnuson BA, Carr I, Bird RP. Ability of aberrant crypt foci characteristics to predict colonic tumor incidence in rats fed cholic acid. *Cancer Res* 53:4499-4504 (1993).
29. Freudenheim JL, Marshall JR. The problem of profound mis-measurement and the power of epidemiological studies of diet and cancer. *Nutr Cancer* 11:243-250 (1988).
30. Rosner B, Spiegelman D, Willett WC. Correction of logistic regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error. *Am J Epidemiol* 132:734-745 (1990).
31. Wacholder S, Armstrong B, Hartge P. Validity studies using an alloyed gold standard. *Am J Epidemiol* 139:853-854 (1994).
32. Kipnis V, Freedman LS, Brown CC, Hartman A, Schatzkin A, Wacholder S. Interpretation of calorie adjustment models for nutritional epidemiology. *Am J Epidemiol* 137(12):1376-1380 (1993).
33. Wacholder S, Schatzkin A, Freedman LS, Kipnis V, Hartman A, Brown CC. Can pure effects of macronutrients and energy be separated? *Am J Epidemiol* 140:848-855 (1994).
34. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AMY, West DW, Wu-Williams AH, Kolonel LN, Horn-Ross PL, Rosenthal JF, Hyer MB. Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst* 85:1819-1827 (1993).
35. Riboli E. Nutrition and cancer: background and a rationale of the European Prospective Investigation into Cancer Nutrition (EPIC). *Ann Oncol* 3:783-791 (1992).
36. Freedman LS, Schatzkin A, Wax Y. The impact of dietary measurement error on the sample size required in a cohort study. *Am J Epidemiol* 132(6):1185-1195 (1990).
37. Rothman KJ. *Modern Epidemiology*. Boston:Little, Brown and Company, 1986.
38. Friedenreich CM, Howe GR, Miller AB. The effect of recall bias on the association of calorie-providing nutrients and breast cancer. *Epidemiology* 2:424-429 (1991).
39. Giovannucci E, Stampfer MJ, Colditz GA, Manson JE, Rosner BA, Longnecker M, Speizer FE, Willett WC. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. *Am J Epidemiol* 137:502-511 (1993).
40. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. III: Design options. *Am J Epidemiol* 135:1042-1050 (1992).
41. Friedenreich CM, Slimani N, Riboli E. Measurement of past diet: review of previous and proposed methods. *Epidemiol Rev* 14:177-196 (1992).
42. Byar DP. Some statistical considerations for design of cancer prevention trials. *Prev Med* 18:688-699 (1989).
43. Freedman LS, Green SB. Statistical designs for investigating several interventions in the same study: methods for cancer prevention trials. *J Natl Cancer Inst* 82:910-914 (1990).
44. Schatzkin A, Freedman LS, Dawsey SM, Lanza E. Interpreting precursor studies: what polyp trials tell us about large bowel cancer. *J Natl Cancer Inst* 86:1053-1057 (1994).
45. Hennekens CH, Buring JE, Peto R. Anti-oxidant vitamins—benefits not yet proved. *N Engl J Med* 330:1080-1081 (1994).
46. Schatzkin A, Schiffman M, Lanza E. Research priorities in large bowel cancer prevention. *Semin Oncol* 17(4):425-437 (1990).
47. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Alcohol low-methionine-low-folate diets, and risk of colon cancer in men. *J Natl Cancer Inst* 87:265-273 (1995).
48. Khoury MJ, Beaty TH, Cohen BH. *Fundamentals of Genetic Epidemiology*. New York:Oxford University Press, 1993.
49. Kadlubar FF. Biochemical individuality and its implications for drug and carcinogen metabolism: recent insights from acetyltransferase and cytochrome P4501A2 phenotyping and genotyping in humans. *Drug Metab Rev* 26:37-46 (1994).
50. Greenberg ER, Baron JA, Tosteson TD, Freeman DH Jr, Beck GJ, Bond JH, Colacchio JA, Collier JA, Frankl HD, Haile RW, Mandel JS, Nierenberg DW, Rothstein R, Snover DC, Stevens MM, Summers RW, vanStolk RU. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 331:141-147 (1994).
51. Hill MJ. ECP trial of fibre in precancerous lesion of the large bowel. In: *Dietary Fiber in Health and Disease* (Kritchevsky D, Bonfield C, eds). St. Paul, MN:Eagan Press, 1995:219-225.
52. Alberts DS, Einspahr J, Rees-McGee S, Ramanujam P, Buller MK, Clark L, Ritenbaugh C, Atwood J, Pethigal P, Earnest D, Villar H, Phelps J, Lipkin M, Wargovich M, Meyskens FL. Effects of dietary wheat bran fiber on rectal epithelial cell proliferation in patients with resection for colorectal cancers. *J Natl Cancer Inst* 82:1280-1285 (1990).
53. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. *Epidemiol Rev* 15:48-65 (1993).
54. MacMahon B. Pesticide residues and breast cancer. *J Natl Cancer Inst* 86:572-573 (1994).
55. Reichman ME, Hayes RB, Ziegler RG, Schatzkin A, Taylor R, Kahle LL, Fraumeni JF. Serum vitamin A and subsequent development of prostate cancer in the first NHANES I Follow-Up Study. *Cancer Res* 50(8):2311-2315 (1990).