The Role of Nutrition in Preventing and Treating Breast and Prostate Cancer

Clinical Trials of Breast and Prostate Cancer Prevention

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Decades of research have produced results suggesting that nutrition may have an important role in the etiology of many cancers, including cancers of the breast and prostate. Reducing the societal burden from breast and prostate cancer will have substantial benefits because these cancers, when combined, represent almost one of every three new cases and one in seven deaths attributable to cancer in the United States (Greenlee et al. 2000). The magnitude of this cancer burden is substantial; developing sound interventions, including sound nutrition-based cancer prevention strategies, offers promise for reducing this burden. A solid scientific foundation for developing nutritional strategies for the prevention of breast and prostate cancer is based on findings from animal and population studies. To some extent, determining the specific cancer-related effects of various nutritional factors is possible with well-designed randomized controlled trials (RCT); these aim to test hypotheses formulated by evaluating available experimental and epidemiologic evidence for a nutrition and cancer relationship. Examples of dietary constituents in clinical trials of breast cancer prevention include vitamins A and E, folic acid, fiber, indole-3-carbinol and selenium. In addition, diets low in fat and high in vegetables, fruits and fiber are being studied. Dietary constituents under study for the prevention of prostate cancer include vitamin E, selenium, soy, lycopene, green tea and (n-3) polyunsaturated fatty acids.

Rationale for nutrition and cancer prevention

Establishing a well-designed program of RCT to investigate scientific hypotheses must be based on a rationale supported by experimental and population studies. In nutrition and cancer research, the science base has been accumulated over many years from investigations with established animal models and data from numerous epidemiologic studies. Animal studies conducted more than 50 years ago first identified a relationship between dietary fat and breast cancer risk (Tannenbaum 1942). As our understanding of the process of carcinogenesis increased, animal models were developed to investigate specific mechanisms of action that might help define the diet and cancer relationship (World Cancer Research Fund 1997). For example, animal models for breast cancer were developed that indicated a relationship between H-ras mutations in rodent mammary tumors and exposure to heterocyclic amines; it was shown further that diet could modify the effect of this exposure (Roberts-Thomson and Snyderwine 1997). In addition, the identification of induced K-ras mutations as promoters of rodent prostate tumors was significant in developing animal and experimental models based on exogenous exposure to chemicals such as nitrosamines (Bosland 1992). When rodents were fed diets high in certain vegetables (e.g., cabbage, Brussels sprouts or broccoli), a lower incidence of experimentally induced mammary tumors was observed (Stoewsand et al. 1989). Wattenberg et al. 1989). More recently, TG.NK transgenic mice, mice with human genes inserted into their genome via recombinant DNA techniques, have been used in experimental models for evaluating dietary intervention strategies for the prevention of mammary tumors (Rao et al. 1997).

Population studies have added to the base of knowledge required to develop a scientific research framework for testing hypotheses about specific dietary constituents and increase the practicality of further investigation in RCT. Large-scale population studies support the hypotheses that breast cancer is positively associated with a high fat, high energy intake and prostate cancer with high fat intake. Both have been reported to be inversely associated (breast more so than prostate) with diets high in certain vegetables (e.g., cabbage, Brussels sprouts or broccoli), a lower incidence of experimentally induced mammary tumors occurs in Asian-Americans when they migrate to the United States and adopt a Western lifestyle, including dietary patterns. In a study of breast cancer incidence in Asian-American women, those who had lived in the West for 8 y or more had an ~80% higher risk than did more recent immigrants (Ziegler et al. 1993). In Japanese-American men who migrated to the United States, prostate cancer incidence rates generally increased over several generations, and total cancer prevalence almost doubled in Japanese Americans compared with native Japanese, suggesting a gradual influence of diet (Shibata et al. 1997).
Randomized controlled trials of nutrition and breast cancer

Current RCT investigating the role of nutrition in the prevention of breast cancer are focused on general dietary patterns and specific dietary constituents, based on rationales developed from findings in experimental and epidemiologic studies, as well as from results of previous RCT. The National Institutes of Health Women’s Health Initiative (WHI) is a large RCT investigating several nutritional strategies for lowering the risk of cancer, cardiovascular disease and osteoporotic fractures in postmenopausal women (Women’s Health Initiative Study Group 1998). The WHI anticipates an enrollment of 64,500 participants and is investigating the effects of the following: 1) a low fat (20% of energy from fat) eating pattern that includes at least five servings of vegetables and fruits and six or more servings of grain products per day; 2) calcium (1000 mg/d) and vitamin D-3 (400 IU/d) supplementation; and 3) hormone replacement therapy. An additional 100,000 women are being enrolled in a prospective surveillance study to identify new etiologic factors and biologic predictors of disease. The WHI has an average follow-up of 9 y.

Two current multicenter RCT are investigating dietary modification strategies for the prevention of breast cancer recurrence. The Women’s Healthy Eating and Living Study (WHELS) has enrolled 3000 breast cancer survivors previously treated by mastectomy to investigate whether a diet rich in vegetables, fruits and fiber and low in fat is associated with a longer interval free of breast cancer events (Rock et al. 1997). An intervention group maintains a dietary pattern that is rich in vegetables, fruits and fiber and low in fat, whereas a control group has been advised to follow the dietary guidelines established by the National Cancer Institute and the USDA. In addition to recurrence of breast cancer, levels of circulating carotenoid and estrogen biomarkers will be used as outcomes measures in WHELS. The Women’s Intervention Nutrition Study (WINS) is an RCT investigating dietary fat reduction with conventional therapy in 2500 postmenopausal women previously treated surgically for primary invasive breast cancer (Chlebowski et al. 1993). Each of the two study groups will continue receiving adjuvant therapy and have been assigned randomly to either a diet with 15–20% of energy from fat plus dietary counseling or recommendations to follow the USDA Dietary Guidelines of no >30% of energy from fat, with minimal intervention. WINS will evaluate the differences in recurrence of breast cancer and mortality between the two study groups.

In addition to the large RCT, various dietary constituents, vitamins A and E, folic acid, fiber, indole-3-carbinol and selenium, are being investigated currently or are being considered for smaller phase II (biomarker endpoint) or phase III (incidence endpoint) clinical studies. Current phase I (pharmacologic and toxicologic profile) studies on breast cancer prevention include perillyl alcohol, indole-3-carbinol and isoflavones.

Randomized controlled trials of nutrition and prostate cancer

Evidence from experimental and epidemiologic studies is adequate to warrant an intensive research commitment for RCT investigating dietary constituents for the prevention of prostate cancer. The current rationale for such RCT is based in part on secondary endpoint results from the completed Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Analysis of follow-up data from the ATBC study found a 36% decrease in prostate cancer incidence and a 41% decrease in mortality from prostate cancer among smokers receiving vitamin E (Heinonen et al. 1998). In another RCT, Clark et al. (1998) reported a 63% reduction in the incidence of prostate cancer (as a secondary endpoint) in male skin cancer patients receiving selenium supplementation.

The proposed Southwest Oncology Group’s Selenium and Vitamin E Cancer Prevention Trial (SELECT), an intergroup phase III prevention trial, will investigate vitamin E, selenium and prostate cancer. SELECT will include 32,400 healthy men with no evidence of current or past prostate cancer or high grade intraepithelial prostatic neoplasia. Participants will be ≥55 y old (≥50 y old for African-Americans) and must have an entry prostate-specific antigen level ≤4.0 ng/mL. African-Americans will constitute 20% of study participants. Recruitment and randomization in a 2×2 factorial design will continue for 3 y at >200 study centers and sites, with results and follow-up anticipated by 2012.

The Physicians' Health Study II (PHS II) is an RCT that is currently investigating the primary prevention of total cancer and prostate cancer in 15,000 healthy physicians ≥55 y old (Christen et al. 2000). The study will test, alone and in combination, β-carotene, vitamins A and E and a multivitamin/min in a multifactorial design. PHS II was designed to test the findings from PHS I, which suggested that β-carotene supplementation reduced risk for total and prostate cancer in men with low baseline levels of β-carotene (Cook et al. 1999).

In addition to large-scale RCT, smaller phase III RCT are investigating green tea, vitamin E, lycopene, soy, low fat diets and diets high in vegetables and fruits. For example, a phase III RCT sponsored by the National Cancer Institute is investigating the effect of a diet low in fat and high in soy, fruits, vegetables, green tea, vitamin E and fiber on prostate-specific antigen levels in 154 patients with prostate cancer. Phase III trials are underway at present to investigate soy isoflavones and selenized yeast, and a phase I trial is investigating genistein.

Future directions

On the basis of our knowledge of a diet-cancer relationship, lowering risk of breast and prostate cancer has the potential for dramatic public health benefits. Progress in understanding this relationship, based on experimental and epidemiologic studies, has made it possible to design large-scale RCT of leading hypotheses; however, many unanswered questions remain. For example, gene-nutrient interactions play a key role in an individual’s ability to use anticarcinogenic dietary constituents and to withstand procarcinogens in the diet. A recent example was reported for the genetically controlled metabolic pathway of vitamin D. The pathway includes a vitamin D receptor in intron 8 (BsmI) with polymorphisms associated with changes in prostate cancer risk, a fourfold increase in risk among individuals with one polymorphism and a 60% reduction in risk among individuals with another (Singh and Caporaso 1999). Another promising area of research is the identification, validation and use of biomarkers, which are chemical or genetic markers used as surrogates to identify risk factors for disease (Srivastava and Rossi 1996). The use of validated biomarkers in RCT, as surrogate or intermediate endpoints, has the potential to reduce the time required to test the effects of dietary constituents in preventing initiation or progression of neoplasia.

While we await the results of current RCT in nutrition and cancer prevention for breast and prostate cancer, the goals for future research will include gaining a better understanding of the role of nutrition and gene-nutrient interactions in cancer risk as well as the identification and validation of biomarkers.
This information will facilitate the design of future large-scale RCT to test diet and cancer hypotheses.

LITERATURE CITED


