Tree Nut and Peanut Consumption in Relation to Chronic and Metabolic Diseases Including Allergy\textsuperscript{1–3}

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Abstract

The New and Emerging Research session highlighted the emerging understanding of both the positive and negative effects of nuts consumption on health. The limited nature of both experimental and epidemiological evidence for positive relationships between nut intake and health were noted. Study inconsistency and limitations, particularly survey methodology, were explored. Recent results from epidemiologic studies indicating a potential negative association between nut and seed intake and cancer risk were reviewed. The ability of walnuts to reduce endothelin suggests an interesting biochemical mechanism of nut action that may affect other endothelin-associated diseases, which should be further explored. The effects of nuts and their constituents on a nuclear receptor screen (PPAR\textsubscript{\textalpha{}}, PPAR\textsubscript{\textbeta{}}/\gamma{}, LXR\textsubscript{\textalpha{}}, RXR\textsubscript{\textalpha{}}/\beta{}, PXR, and FXR) have been explored. Nut allergenicity and approaches necessary to minimize this effect were also described. In contrast to the positive effects, nut allergies present tree nut-allergic consumers with health challenges. The Food Allergy and Anaphylaxis Network stressed the importance of ensuring that consumers with food allergies have legible, accurate food labels. The Food Allergen Labeling and Consumer Protection Act has engendered precautionary, worst-case allergen scenario labeling statements with unknown benefits to consumer health. Issues of cross-contamination due to shared equipment and shared facilities highlighted the need to rely on allergen control programs that use ELISA technology and have increased understanding of nut allergens. Ultimately, to maximize the positive benefits of nuts, the consumer must be provided with all the information required to make an informed choice. J. Nutr. 138: 1757S–1762S, 2008.

Introduction

This session of the 2007 Nuts and Health Symposium focused on new and emerging research on nuts and the risk of cancer, cardiovascular disease (CVD),\textsuperscript{9} and glucose intolerance and on allergic reactions to nuts.

Cancer

Nuts and seeds are rich sources of PUFA, as well as a variety of different phytonutrients, and their intake may potentially affect the risk of several different cancers. However, experimental data on the role of this food group in carcinogenesis are limited and aside from some information on flaxseed (1–6) and almonds (7), there are little data available using animal carcinogenesis models. Thus, more experimental studies are needed to explore the potential effects of nut consumption and related biochemical mechanisms, such as oxidative stress and cell cycle kinetics, on cancer risk.

A few epidemiologic studies with different designs and methodologies have considered the association of nut intake with risk of several cancers (8–12). The results of these studies ranged from no association (8) to a beneficial one, but only in women (9). One reason for this inconsistency in findings is that any relationship...
may be obscured by the methodology of how nut and seed intake is assessed, because only a few studies utilized dietary questionnaires designed to specifically assess the intake of nuts and seeds alone rather than as part of larger food groups. For example, some of the dietary questionnaires used catchall categories that combined nuts and seeds with legumes, pulses, or dried fruits or considered them only as part of the main fruit and vegetable groups.

An association of nuts and seeds with colorectal cancer risk was studied in the European Prospective Investigation into Cancer and Nutrition, a large prospective cohort comprised of over 520,000 subjects from 23 centers in 10 European countries (13). The analysis utilized nut and seed intake determined from country-specific dietary questionnaires in which the amount of nuts and seeds consumed was derived from a wide array of questions ranging from general queries about the food group to specific questions about the intake of individual nuts and seeds, peanuts, peanut butter, or nut spreads. As part of the European Prospective Investigation into Cancer and Nutrition analysis, the dietary questionnaire estimates of nut and seed intake were calibrated against standardized 24-h recalls obtained from an 8%, 37,000-subject subset of the cohort. This procedure was used to allow comparability across centers on an absolute scale by correcting for systematic among-center over- or underestimations in assessments. The resulting data set included 478,000 subjects with a >2:1 ratio of women to men. These subjects had a total of 855 (327 men, 528 women) colon and 474 (215 men, 259 women) rectal cancer cases.

A categorical (quintiles) multivariate Cox proportional hazards model that stratified by center was used in the analysis. Confounding factors adjusted for included age, sex, height, weight, intake of fruit (without nuts and seeds), dietary fiber, smoking, and physical activity as well as energy from fat, alcohol, and other sources. Higher intake of nuts and seeds was not associated with risk of colorectal, colon, and rectal cancers in men and women combined. However, upon subgroup analysis, there was a significant inverse association with colon cancer in women at the highest (>6.2 g/d intake of nuts and seeds) vs. the lowest (nonconsumer) category of intake (hazard ratio, 0.69; 95% CI, 0.50–0.95) and for the linear effect of log-transformed intake (hazard ratio, 0.89; 95% CI, 0.80–0.98). In contrast, no such associations were observed in men.

It is not clear to what extent the findings may be attributable to nuts and seeds themselves, or whether this food group is acting simply as a marker of a healthier diet pattern. Other issues of concern were: 1) the finding of an association in the colon (distal stronger than the proximal) but not in the rectum, which may reflect different etiologies for these sites or may be due to limited study power; and 2) the gender-specific observations. However, it was noted that 2 previous studies, Kune et al. (9) using nuts, seeds, legumes as a category and Yeh et al. (14) using peanut consumption, have both also reported an association in women, leading to speculation about the effects of phytoestrogens in nuts and seeds. Although the results of studies to date show some intriguing potential relationships between the consumption of nuts and the risk of some cancers, survey limitations prevent the isolation and identification of nut-specific effects. Methodological improvements in dietary questionnaires are necessary and more work is required on ways to better identify and quantify the intake of specific nuts and seeds. More research is also required to better determine whether the intake of this food group provides health benefits with respect to cancer and to identify some possible mechanisms of action.

**Mechanisms: CVD**

Cortes et al. (15) and Ros et al. (16) have published several studies showing an improvement in CVD risk markers in patients and, specifically, improved endothelial function due to walnut intake, although only some specific CVD-related systems were affected positively. Davis et al. (17) recently published a study that showed that walnut feeding reduces aortic endothelin messenger levels in an animal model of atherosclerosis. In addition to these studies, another unrelated study of feeding metabolic syndrome patients walnuts reported inhibitory effects on baroreflex sensitivity (18), which is linked to endothelin (19). Taken together, these studies suggest that walnut consumption affects endothelin. This effect then alters (inhibits) those CVD processes driven by endothelin that result in endothelial dysfunction, whereas CVD processes such as those that are interleukin (IL)-6 driven, e.g. intercellular adhesion molecule 1 induction (20), are only minimally affected.

**Cancer**

Several years ago, positive effects of almond feeding on colon cancer in rats were reported. This experimental chemical carcinogenesis-based approach prompted a follow-up experiment using a genetic cancer animal model, the Min mouse, which develops gastrointestinal tumors as a result of genetic mutations (21). The study apparently did not confirm a positive effect (22). However, this conclusion is now being reassessed as our understanding of the pathways of growth control in gastrointestinal cancers has increased. In the Min mice study, p27kip1 was induced by almond feeding. Subsequent studies have identified p27kip1, a cyclin-dependent kinase inhibitor, as a tumor suppressor and have shown it is induced by chemopreventive compounds (23,24). Critically, its signaling proceeds through the wnt/b-catenin pathway (25), which may explain the inability to confirm a positive almond effect, because the wnt/b-catenin pathway is specifically deranged in the Min mouse.

Another potential link between nuts and cancer was noted with HER2, an oncogene whose overexpression is linked to human cancer, especially breast cancer pathogenesis (26). Oleic acid, a major fat in almonds, and α-linolenic acid, a major fat in walnuts, induces transcriptional repression of Her-2/neu in cell culture, with oleate acting through PEA3 protein at the promoter level (27,28). Given the evidence for walnuts’ ability to reduce endothelin, effects on other systems where endothelin plays a major role should be elucidated. This then immediately suggests that cancer and walnuts should be explored, because the pharmaceutical industry has identified endothelin-1-based signaling systems as major targets for cancer treatment (29). In fact, Spinella et al. (30) have demonstrated that reducing endothelin is associated with less tumor growth in an ovarian cancer xenograft animal. Additionally, a recent study showed that green tea polyphenolics, which also reduce endothelin, accentuate the positive effects of a Cox-2 inhibitor in prostate cancer (31).

Lower than predicted weight gain from nut consumption, discussed in more detail in (32,33), may provide another mechanism whereby nuts can reduce cancer risk. Obesity is associated with inflammation and elevated endothelin (34). Potenza et al. (35) observed reduced weight in an animal model that altered endothelin by diet. This may be of importance, because Hursting et al. (36) reported that energy restriction reduces tumor burden and latency, and a recent article using an animal model reported that excess energy retention, rather than consumption, confers cancer risk (37). Together, these results make it likely that walnuts will affect those cancers that are driven by endothelin-related processes, e.g. ovarian and prostate.

**Glucose metabolism**

Endothelin concentrations are also increased in abnormal glucose tolerance (38) and are affected by serum insulin concentrations (39).
Glucose tolerance/insulin resistance is related to endothelial dysfunction, because insulin resistance is linked to derangements in both nitric oxide (NO) and endothelin (40). Altering endothelin increased insulin sensitivity but reduced blood pressure in spontaneously hypertensive rats in an NO-dependent manner (35), suggesting that endothelin and NO effects are linked. Increased NO is associated with increased insulin sensitivity in patients who have high NO due to genetic mutations (41) and a cGMP phosphodiesterase inhibitor (Sildenafil) to enhance NO-based signaling increased insulin sensitivity in mice fed high-fat diets (42). Quon et al. (39) have presented a model of the interrelationships between insulin, the reciprocal relationship between NO and endothelin, and the endothelium to explain the association noted between insulin sensitivity, glucose tolerance, and how derangements, particularly through inflammation, increase CVD.

**Inflammation**

Inflammation is common in a broad range of chronic diseases (39,43). The centrality of inflammation in those diseases, examined in the context of the ability of walnuts and perhaps other nuts to affect endothelin, a major messenger involved in inflammation, suggests that beneficial effects of walnuts and other nuts should be explored in a broad range of diseases, including metabolic syndrome, cancer, obesity, and Alzheimer's disease. The relationship between endothelin and insulin provides a link to inflammation, highlighted by reports that elevated insulin increases inflammatory markers in the cerebral-spinal fluid, perhaps explaining the relationship noted between high insulin and Alzheimer's disease (44) and suggesting that walnut feeding may affect this disease.

**Pharmacology-based search for nut-related effects and effectors**

The overlap between a nutritionally based and a pharmacology-based search for effectors is substantial, but these differ in 2 key aspects. The dietary approach is aimed at prevention and uses mixtures (diets) of bioactive molecules with typically low potency. The paradigm for diet-based treatment is to feed diets that affect multiple targets modestly and thereby provide an overall beneficial effect. In contrast, the pharmacological approach uses pure compounds with high potency as treatments. The restriction to pure compounds and high potency imposes limitations of the potential benefits by virtue of the use of a restricted set of known or well-characterized targets and/or markers and the potential for toxic side effects.

The pharmacological approach uses the concept of “druggable targets” to introduce several potentially overlapping metabolic disorders as endpoints, such as dyslipidemia and diabetes, and their links to nuclear receptors such as PPARα, β/δ, and γ; liver-X-receptor (LXRα, β), retinoid-X-receptor (RXRα, β, and γ); pregnane-X-receptor (PXR); and farnesoid-X-receptor (FXR). These receptors are important nutrient sensors and regulators of gene expression that maintain metabolic homeostasis. The specific, as well as overlapping, effects of nut components on PPARα, β/δ, γ, LXRα, β, RXRα, β, γ, PXR, and FXR as identifiable targets of nuts and their components was discussed. Extracts from walnut, pistachio, and peanut decreased inflammatory markers in cell culture and feeding a diet high in walnuts to humans lowered these markers in monocytes.

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The next step is to understand the potential targets of the changes in the biomarkers. When walnut extract was tested for its ability to activate several different PPAR (α, β/δ, and γ) as well as LXRα, it activated all PPAR tested but had little or no effect on LXRα. The hierarchical clustering of NR activation by fatty acids was determined from the relative activation of each receptor at 100 μmol of different fatty acids using K-means clustering (47). This showed a complex pattern with stimulatory effects of the different natural fatty acids predominantly evident in the PPARβ and RXRα. Using extracts from a variety of nuts, a complex pattern of inhibition and activation of LXRα, PPARγ, RXRβ, and PPARγ was revealed. The difference between the 2 suggested that fatty acids were only 1 of the drivers in the responses. Using a specific nut, pistachios, the responses were examined in more depth. Both the whole oil as well as the lipid extract predominantly activated PPARα with little if any effect on the other PPAR, RXR, or LXR. PPARγ, as a target for the various nuts, links their consumption to possible effects on inflammation, diabetes, cancer, and aging. Thus, understanding which fractions (and subfractions) of the nuts have PPAR, LXR, or RXR activity can permit their antiinflammatory effects to be predicted accurately.

Finally, as an added complexity, the targets identified in these types of analyses are likely to be polymorphic and therefore make it all but certain that some groups will benefit from increasing their consumption of nuts high in certain bioactive molecules, whereas others may gain no benefit or even be affected adversely by increasing consumption of a particular nut.

**Food allergies**

One of the potential downsides to nut consumption has been a focus of the Food Allergy and Anaphylaxis Network (FAAN). FAAN was founded in 1991 and has over 30,000 members worldwide, which include families as well as representatives from government agencies and food and pharmaceutical industries, and physicians and other health professionals. FAAN understands its role as serving as a link between the patient and others, to raise public awareness, provide advocacy and education, and advance research on food allergies and anaphylaxis.
Approximately 12 million Americans or 4% of the U.S. population have food allergies, including 5–8% of children. The majority of reactions to food in the US are due to a limited set of allergens, with 90% due to 8 major allergens (milk, eggs, wheat, soy, fish, shellfish, peanuts, and tree nuts). Crustacean shellfish is the most common at 2%, followed by peanuts/tree nuts at 1.2% (48–50). The prevalence of food allergies appears to be increasing (49,51,52). Food allergies arise upon exposure to a novel entity to which the body reacts by initiating a process to repel the invader and creates IgE antibodies directed at the entity. Upon reexposure, the antibodies release large amounts of histamine and other signaling compounds and anaphylaxis can ensue with hives, wheezing, vomiting, diarrhea, throat swelling, hypotension, loss of consciousness, and death in some instances. Using 2000 U.S. Census data, these types of reactions were estimated to account for ~30,000 trips annually to emergency rooms and 200 fatalities (53). The causes of these reactions are unresolved. Food allergies appear to have a genetic component, because a high concordance rate of allergy among monozygotic twins has been reported (48). However, there appears to be an environmental aspect that may arise due to an overly sanitary environment wherein the immune system is not sufficiently challenged by environmental pathogens such as bacteria.

Approaching the issue of food allergies from a consumer perspective, several factors become prominent. Even trace amounts can cause a reaction and because there is currently no known cure or treatment, total avoidance is the only way to prevent a reaction. Consumers with food allergies are forced to rely on food labels and these must be read and accurate to save lives. Other issues involve cooking, childcare, school, and traveling with its associated dining away from familiar surroundings.

One regulatory response to these issues is the Food Allergen Labeling and Consumer Protection Act, which required as of January 1, 2006 that allergens be declared in plain language on labels of packaged foods. The Act provided no exemptions for labeling of allergens in spices and natural flavors but allows exemptions via petition that document that the food ingredient does not contain allergenic proteins. The Food Allergen Labeling and Consumer Protection Act has engendered precautionary labeling statements designed to convey warnings about the possible presence of unavoidable or inadvertent ingredients. The food-allergic consumer in general avoids these products that are labeled as “contain” or “may contain” his or her allergen. However, these labels are increasing in prevalence as legal pressure to prevent the worst case scenario is rising, although again at what cost to consumer choice or benefit to consumer health remains incompletely understood.

Approximately 0.6% of Americans suffer allergies to nuts, with 0.4% having only tree nut allergies and 0.2% having allergies to both tree nuts and peanuts. A large group of those with these allergies are sensitive to multiple nut types (48). Fatalities have occurred due to food allergies. Bock et al. (54) reported on 63 such fatalities. They documented that these happened to males (56%) more than females (44%) and 75% and 86% of the victims had known asthma or history of prior reactions, respectively (54). The predominant allergen was peanut (58.7%), tree nuts were the next highest (28.6%), and milk was next (7.9%) followed by seafood (4.8%). Teens accounted for almost one-half of the fatalities, whereas people aged 10–29 y accounted for three-quarters. Restaurant and packaged foods were responsible for >73% of the allergen sources. A peanut/tree nut allergy registry has been established and has collected over 3149 self-reports with subsudies on reactions in schools, restaurants, and airlines and in twins (55,56). Walnuts, almonds, and cashews cause a large proportion of all the nut-caused reactions.

There is hope for those with food allergies. Some fraction of children can outgrow their tree nut allergies (57) and there are some promising results among current research into treatments that include anti-IgE injections (58), Chinese herbal remedies (59), probiotics, the use of mutated epitopes to retrain the immune system, and oral immunotherapy (60).

For the food industry, the currently recognized list of allergenic tree nuts has created some controversy. Based on comparative prevalence, walnut, almond, hazelnut, pecan, cashew, pistachio, Brazil nut, macadamia nut, and pine nut are often acknowledged as commonly allergenic tree nuts. Some controversy has erupted recently, because the FDA has posted a much longer list of tree nuts, including some exotic nuts such as shea nut and non-nuts such as coconut (61). The list includes a variety of tree nuts that are only very rarely allergenic (beech nut, butternut, chestnut, chinquapin, coconut, ginkgo nut, hickory nut, lichee nut, pili nut, and shea nut) but excludes other rarely allergenic nuts (kola nut and nutmeg) with no real rationale why.

Because no cure exists for food allergies, individuals allergic to foods must use specific avoidance diets. However, this approach mandates that the consumer be informed. Labeling is the key to successful avoidance diets. Of concern to both the consumer and the producer is the potential for cross-contamination due to shared equipment and facilities in the food processing chain, or admixture, incorrect labeling, or contamination of raw materials. This suggests that food manufacturers must rely on allergen control programs to avoid the risks associated with exposure to allergens due to flaws in the systems in place to protect allergic consumers. A major risk is that of undeclared allergens; proper labeling along with good manufacturing processes are mandatory to eliminate the risks.

One food industry response to these issues has been through the Food Allergy Research and Resource Program at the University of Nebraska, Lincoln. Approaches to the issues arising from nut allergies include developing allergen control programs and monitoring incoming raw materials for allergens. In addition, manufacturers must label their foods so they declare allergens on ingredient statements. A very prevalent approach is to use precautionary/advisory language in labeling (e.g. “may contain tree nuts”) (62). Finally, to reduce risk, manufacturers need to validate elements of allergen control programs using allergen test method (63).

In recent years, allergen control has been improved by the development of ELISA to detect residues of allergenic foods in other foods or on shared processing equipment. Among the tree nuts, ELISA exist for almond, hazelnut, walnut, and pecan (64,65). The ELISA have a limit of detection in the low ppm range. The ELISA-based assays are being supplemented by PCR-based methods to screen for the presence of genetic material associated with several varieties of nuts of concern. Whereas these efforts represent responses aimed at detecting and minimizing allergens of concern, other issues have arisen, including how to handle the presence of tree nuts in food ingredient lists (tree nut oils, coconut oil, medium chain triglycerides, shea nut oil/shea nut butter, walnut hull extract, or black walnut hull extract).

Most nut species contain shared antigenic proteins as well as having some unique proteins. For example, Brazil nuts, English walnuts, cashews, and hazelnuts all contain 11S legumin, whereas hazelnuts and almonds share profilin (66), which is likely to account for the fact that many tree nut-allergic individuals have a high level of reactivity to a variety of nuts.
The push to identify and then utilize the beneficial effects of nut consumption with respect to health must be accompanied by efforts to ensure that those sensitive to the negative effects of nuts are protected by specific mechanisms for allowing that population to avoid nuts, which should include food manufacturing processes that detect, document, and mitigate hazards during this process. Our increased understanding of the nature of the various antigens holds the promise of being able to eliminate these hazards, although this will trigger concerns about genetically modified food. Ultimately, to maximize the positive benefits of nuts, the consumer must be provided with all the information required to make an informed choice.

Other articles in this supplement include references (67–71).

**Literature Cited**


