

Tree Nut and Peanut Consumption in Relation to Chronic and Metabolic Diseases Including Allergy¹⁻³

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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 relationship(s) 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 α , β/δ , γ , LXR α , β , RXR α , β , γ , 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),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

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⁹ Abbreviations used: CVD, cardiovascular disease; FAAN, Food Allergy and Anaphylaxis Network; FXR, farnesoid-X-receptor; IL, interleukin; LXR, liver-X-receptor; PXR, pregnane-X-receptor; RXR, retinoid-X-receptor.

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, p27 kip1 was induced by almond feeding. Subsequent studies have identified p27 kip1, 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 "drugable targets" to introduce several potentially overlapping metabolic disorders as endpoints, such as dyslipidemia and diabetes, and their links to nuclear receptors such as PPAR α , β/δ , and γ ; liver-X-receptor (LXR α , β), retinoid-X-receptor (RXR α , 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 PPAR α , β/δ , γ , LXR α , β , RXR α , 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.

More data regarding the bioactive molecules in nuts, disease targets, and clinical endpoints (biomarkers) must be obtained. For example, to allow health claims for dietary recommendations as well as for personalized nutrition, all the nut-contained bioactive molecules, their targets, and the endpoints as well as the

connections among them must be known. Using this approach, it becomes obvious that for some diseases there are no data for any of these steps, whereas for other diseases, the endpoints and biomarkers are known, but the identity of bioactives and the nuts that might contain them remain unknown. In the case of inflammation, the effect of walnut feeding on a variety of adhesion molecules identified as markers for inflammation has been described (45). Different fatty acids common in nuts (linoleic acid, α -linolenic acid, docosahexaenoic acid, and palmitic acid) affect the production of IL-6, IL-1 β , and tumor necrosis factor- α in THP-1 cells stimulated by coinubation with LPS (1 mg/L) in the presence of fatty acids for 24 h (46).

PPAR, LXR, and RXR are important because of their possible role in the regulation of inflammation and immune responses. PPAR α and PPAR γ in particular have been implicated in the regulation of macrophage and endothelial cell inflammatory responses. For example, activation of PPAR γ decreases proinflammatory cytokines such as IL-1 α , IL-6, and tumor necrosis factor α . The antiinflammatory properties of PPAR, LXR, and RXR are important, because these receptors are the targets of nutritional components. (n-3) Fatty acids such as α -linolenic acid activate all 3 PPAR, whereas isoflavones, including genistein and daidzein, and polyphenols such as resveratrol are activators of both PPAR α and PPAR γ . The (n-3) PUFA, isoflavones, and polyphenols have been studied as preventative and treatment modalities for inflammatory diseases.

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 LXR β , it activated all PPAR tested but had little or no effect on LXR β . The hierarchical clustering of NR activation by fatty acids was determined from the relative activation of each receptor at 100 μ mol 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 PPAR β and RXR α . Using extracts from a variety of nuts, a complex pattern of inhibition and activation of LXR β , PPAR α , PPAR β , and PPAR γ 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 PPAR α with little if any effect on the other PPAR, RXR, or LXR. PPAR γ , 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 at issue will not cause a reaction and via notification 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 5149 self-reports with

substudies 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/sheanut 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

- Jenab M, Thompson LU. The influence of flaxseed and lignans on colon carcinogenesis and beta-glucuronidase activity. *Carcinogenesis*. 1996; 17:1343–8.
- van Kranen HJ, Mortensen A, Sorensen IK, van den Berg-Wijnands J, Beems R, Nurmi T, Adlercreutz H, van Kreijl CF. Lignan precursors from flaxseed or rye bran do not protect against the development of intestinal neoplasia in ApcMin mice. *Nutr Cancer*. 2003;45:203–10.
- Oikarinen S, Heinonen SM, Nurmi T, Adlercreutz H, Mutanen M. No effect on adenoma formation in Min mice after moderate amount of flaxseed. *Eur J Nutr*. 2005;44:273–80.
- Oikarinen S, Pajari AM, Salminen I, Heinonen SM, Adlercreutz H, Mutanen M. Effects of a flaxseed mixture and plant oils rich in alpha-linolenic acid on the adenoma formation in multiple intestinal neoplasia (Min) mice. *Br J Nutr*. 2005;94:510–8.
- Bommareddy A, Arasada BL, Mathees DP, Dwivedi C. Chemopreventive effects of dietary flaxseed on colon tumor development. *Nutr Cancer*. 2006;54:216–22.
- Williams D, Verghese M, Walker LT, Boateng J, Shackelford L, Chawan CB. Flax seed oil and flax seed meal reduce the formation of aberrant crypt foci (ACF) in azoxymethane-induced colon cancer in Fisher 344 male rats. *Food Chem Toxicol*. 2007;45:153–9.
- Davis PA, Iwahashi CK. Whole almonds and almond fractions reduce aberrant crypt foci in a rat model of colon carcinogenesis. *Cancer Lett*. 2001;165:27–33.
- Pickle LW, Greene MH, Ziegler RG, Toledo A, Hoover R, Lynch HT, Fraumeni JF Jr. Colorectal cancer in rural Nebraska. *Cancer Res*. 1984;44:363–9.
- Kune S, Kune GA, Watson LF. Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer Study. *Nutr Cancer*. 1987; 9:21–42.
- Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol*. 1998;148:761–74.
- Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. *Nutr Cancer*. 1999;34:173–84.
- Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D. Diet in relation to endometrial cancer risk: a case-control study in Greece. *Nutr Cancer*. 2002;44:16–22.
- Jenab M, Ferrari P, Slimani N, Norat T, Casagrande C, Overad K, Olsen A, Stripp C, Tjonneland A, et al. Association of nut and seed intake with colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1595–603.
- Yeh CC, You SL, Chen CJ, Sung FC. Peanut consumption and reduced risk of colorectal cancer in women: a prospective study in Taiwan. *World J Gastroenterol*. 2006;12:222–7.
- Cortes B, Nunez I, Cofan M, Gilabert R, Perez-Heras A, Casals E, Deulofeu R, Ros E. Acute effects of high-fat meals enriched with walnuts or olive oil on postprandial endothelial function. *J Am Coll Cardiol*. 2006;48:1666–71.
- Ros E, Nunez I, Perez-Heras A, Serra M, Gilabert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation*. 2004;109:1609–14.
- Davis P, Valacchi G, Pagnin E, Shao Q, Gross HB, Calo L, Yokoyama W. Walnuts reduce aortic ET-1 mRNA levels in hamsters fed a high-fat, atherogenic diet. *J Nutr*. 2006;136:428–32.
- Schutte AE, Van Rooyen JM, Huisman HW, Mukuddem-Petersen J, Oosthuizen W, Hanekom SM, Jerling JC. Modulation of baroreflex sensitivity by walnuts versus cashew nuts in subjects with metabolic syndrome. *Am J Hypertens*. 2006;19:629–36.
- Ormezzano O, Poirier O, Mallion JM, Nicaud V, Amar J, Chamontin B, Mounier-Vehier C, Francois P, Cambien F, et al. A polymorphism in the endothelin-A receptor gene is linked to baroreflex sensitivity. *J Hypertens*. 2005;23:2019–26.
- Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, Dhillon B, Mickle DA. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation*. 2002; 105:1890–6.
- Yamada Y, Mori H. Multistep carcinogenesis of the colon in Apc(Min/+) mouse. *Cancer Sci*. 2007;98:6–10.
- Davis P, Iwahashi CK, Yokoyama W. Whole almonds activate gastrointestinal (GI) tract anti-proliferative signaling in APC(min) (multiple intestinal neoplasia) mice. *FASEB J*. 2003;17:A1153.
- Aggarwal BB, Banerjee S, Bharadwaj U, Sung B, Shishodia S, Sethi G. Curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines. *Biochem Pharmacol*. 2007;73:1024–32.
- Eto I. Nutritional and chemopreventive anti-cancer agents up-regulate expression of p27Kip1, a cyclin-dependent kinase inhibitor, in mouse JB6 epidermal and human MCF7, MDA-MB-321 and AU565 breast cancer cells. *Cancer Cell Int*. 2006;6:20.
- Hulit J, Lee RJ, Li Z, Wang C, Katiyar S, Yang J, Quong AA, Wu K, Albanese C, et al. p27Kip1 repression of ErbB2-induced mammary tumor growth in transgenic mice involves Skp2 and Wnt/β-catenin signaling. *Cancer Res*. 2006;66:8529–41.
- Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene*. 2007; 26:6469–87.
- Menendez JA, Papadimitropoulou A, Vellon L, Lupu R. A genomic explanation connecting “Mediterranean diet”, olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory “PEA3 transcription factor-PEA3 DNA binding site” complexes at the Her-2/neu (erbB-2) oncogene promoter in breast, ovarian and stomach cancer cells. *Eur J Cancer*. 2006;42:2425–32.
- Menendez JA, Vazquez-Martin A, Ropero S, Colomer R, Lupu R. HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated fatty acid, alpha-linolenic acid (ALA; 18:3n-3), in breast cancer cells: the “fat features” of the “Mediterranean diet” as an “anti-HER2 cocktail”. *Clin Transl Oncol*. 2006;8:812–20.
- Nelson J, Bagnato A, Battistini B, Nisen P. The endothelin axis: emerging role in cancer. *Nat Rev Cancer*. 2003;3:110–6.
- Spinella F, Rosano L, Di Castro V, Decandia S, Albini A, Nicotra MR, Natali PG, Bagnato A. Green tea polyphenol epigallocatechin-3-gallate inhibits the endothelin axis and downstream signaling pathways in ovarian carcinoma. *Mol Cancer Ther*. 2006;5:1483–92.
- Adhami VM, Malik A, Zaman N, Sarfaraz S, Siddiqui IA, Syed DN, Afaq F, Pasha FS, Saleem M, et al. Combined inhibitory effects of green tea polyphenols and selective cyclooxygenase-2 inhibitors on the growth of human prostate cancer cells both in vitro and in vivo. *Clin Cancer Res*. 2007;13:1611–9.
- Sabate J, Cordero-Macintyre Z, Siapco G, Torabian S, Haddad E. Does regular walnut consumption lead to weight gain? *Br J Nutr*. 2005;94:859–64.
- Mattes RD, Kris-Etherton PM, Foster GD. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J Nutr*. 2008; 138:1741S–5S.
- Silver AE, Beske SD, Christou DD, Donato AJ, Moreau KL, Eskurza I, Gates PE, Seals DR. Overweight and obese humans demonstrate increased vascular endothelial NAD(P)H oxidase-p47(phox) expression and evidence of endothelial oxidative stress. *Circulation*. 2007; 115:627–37.
- Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, Kim JA, Quon MJ, Montagnani M. EGCG, a green tea polyphenol, improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. *Am J Physiol Endocrinol Metab*. 2007;292:E1378–87.

36. Patel AC, Nunez NP, Perkins SN, Barrett JC, Hursting SD. Effects of energy balance on cancer in genetically altered mice. *J Nutr*. 2004;134:S3394-8.
37. Huffman DM, Johnson MS, Watts A, Elgavish A, Eltoum IA, Nagy TR. Cancer progression in the transgenic adenocarcinoma of mouse prostate mouse is related to energy balance, body mass, and body composition, but not food intake. *Cancer Res*. 2007;67:417-24.
38. Kida T, Sugiyama T, Oku H, Harino S, Ikeda T. Plasma endothelin-1 levels depress optic nerve head circulation detected during the glucose tolerance test. *Graefes Arch Clin Exp Ophthalmol*. 2007;245:1289-93.
39. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation*. 2006;113:1888-904.
40. Potenza MA, Marasciulo FL, Chieppa DM, Brigiani GS, Formoso G, Quon MJ, Montagnani M. Insulin resistance in spontaneously hypertensive rats is associated with endothelial dysfunction characterized by imbalance between NO and ET-1 production. *Am J Physiol Heart Circ Physiol*. 2005;289:H813-22.
41. Davis PA, Pagnin E, Semplicini A, Avogaro A, Calo LA. Insulin signaling, glucose metabolism, and the angiotensin II signaling system: studies in Bartter's/Gitelman's syndromes. *Diabetes Care*. 2006;29:469-71.
42. Ayala JE, Bracy DP, Julien BM, Rottman JN, Fueger PT, Wasserman DH. Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. *Diabetes*. 2007;56:1025-33.
43. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860-7.
44. Craft S. Insulin resistance syndrome and Alzheimer disease: pathophysiological mechanisms and therapeutic implications. *Alzheimer Dis Assoc Disord*. 2006;20:298-301.
45. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr*. 2004;134:2991-7.
46. Zhao G, Etherton TD, Martin KR, Vanden Heuvel JP, Gillies PJ, West SG, Kris-Etherton PM. Anti-inflammatory effects of polyunsaturated fatty acids in THP-1 cells. *Biochem Biophys Res Commun*. 2005;336:909-17.
47. Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver X receptor-beta, and retinoid X receptor-alpha. *Toxicol Sci*. 2006;92:476-89.
48. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol*. 1999;10:226-34.
49. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol*. 2003;112:1203-7.
50. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol*. 2004;114:159-65.
51. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol*. 2002;110:784-9.
52. Weiss C, Munoz-Furlong A, Furlong TJ, Arbit J. Impact of food allergies on school nursing practice. *J Sch Nurs*. 2004;20:268-78.
53. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol*. 1999;104:452-6.
54. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191-3.
55. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. The US Peanut and Tree Nut Allergy Registry: characteristics of reactions in schools and day care. *J Pediatr*. 2001;138:560-5.
56. Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol*. 2001;108:128-32.
57. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol*. 2005;116:1087-93.
58. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med*. 2003;348:986-93.
59. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, Goldfarb J, Sampson HA, Li XM. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol*. 2005;115:171-8.
60. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, Steele PH, Pons L, Helm RM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol*. 2007;119:199-205.
61. Office of Nutritional Products, and Dietary Supplements, Center for Food Safety and Applied Nutrition, FDA. Questions and answers regarding food allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004 (Edition 4). 2006 [cited 2008 Apr 3]. Available from: <http://www.cfsan.fda.gov/~dms/alrguid4.html>
62. Taylor SL, Hefle SL, Farnum K, Rizk SW, Yeung J, Barnett ME, Busta F, Davis S, Newsome R, et al. Survey and evaluation of pre-FALCPA labeling practices used by food manufacturers to address allergen concerns. *Comprehensive Reviews in Food Science and Food Safety*. 2007;6:36-46.
63. Taylor SL, Hefle SL, Farnum K, Rizk SW, Yeung J, Barnett ME, Busta F, Shank FR, Newsome R, et al. Analysis and evaluation of food manufacturing practices used to address allergen concerns. *Comprehensive Reviews in Food Science and Food Safety*. 2006;5:138-57.
64. Hlywka JJ, Hefle SL, Taylor SL. A sandwich enzyme-linked immunosorbent assay for the detection of almonds in foods. *J Food Prot*. 2000;63:252-7.
65. Holzhauser T, Vieths S. Quantitative sandwich ELISA for determination of traces of hazelnut (*Corylus avellana*) protein in complex food matrixes. *J Agric Food Chem*. 1999;47:4209-18.
66. Roux KH, Teuber SS, Sathe SK. Tree nut allergens. *Int Arch Allergy Immunol*. 2003;131:234-44.
67. King JC, Rechkemmer G, Geiger CJ. Second international nuts and health symposium, 2007: introduction. *J Nutr*. 2008;138:1734S-5S.
68. King JC, Blumberg J, Ingwersen L, Jenab M, Tucker KL. Tree nuts and peanuts as components of a healthy diet. *J Nutr*. 2008;138:1736S-40S.
69. Kris-Etherton PM, Hu F, Ros E, Sabate J. The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. *J Nutr*. 2008;138:1746S-51S.
70. Jenkins DJA, Hu FB, Tapsell LC, Josse AR, Kendall CWC. Possible benefit of nuts in type 2 diabetes. *J Nutr*. 2008;138:1752S-6S.
71. Allen LH. Priority areas for research on the intake, composition and health effects of tree nuts and peanuts. *J Nutr*. 2008;138:1763S-5S.