

## Cancer and Diet Literatures

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**Abstract:** Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer and the Diet.

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### 1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

### Literatures

Adams, J. B. (1992). "Human breast cancer: concerted role of diet, prolactin and adrenal C19-delta 5-steroids in tumorigenesis." *Int J Cancer* **50**(6): 854-8.

The low incidence of breast cancer in Japan disappears within 2 generations in migrant Japanese in the USA. This is of fundamental importance if we are to understand, and perhaps reverse, the high rate seen in Western countries. Diet is the most likely factor involved, and a review of the topic of diet, body mass index, and gain in adult body mass, supports a relationship between these factors and breast-cancer risk in post-menopausal, but not pre-menopausal, women. A direct link between nutritional factors and secretion of the hormones prolactin and dehydroepiandrosterone sulfate is proposed. An estrogen 5-androstene-3 beta, 17 beta-diol is formed peripherally from the latter steroid, and in Western women attains a blood concentration at which it is biologically active. Thus diet/fat provides factors, viz., fatty acids, prolactin and estrogen, which in concerted fashion provide a milieu conducive to mammary tumorigenesis.

Ahmed, F. E. (2004). "Effect of diet, life style, and other environmental/chemopreventive factors on colorectal cancer development, and assessment of the

risks." *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **22**(2): 91-147.

This review presents a comprehensive, evenhanded evaluation of the evidence from experimental, in vitro and human studies associating environmental and therapeutic factors with risk of colorectal cancer. Life styles correlated with the greatest increase in colorectal cancer risk are the ones that typify a diet rich in fat and calories, alcohol drinking and tobacco smoking, and low intake of vegetable, fruits and fibers, referred to as a "western diet," as well as sedentary style (i.e., no- or low-exercise). This kind of life style has also been associated with other chronic diseases (other cancers, obesity, dyslipidemia, diabetes, hypertension cardiovascular, and hypertension). The evidence does not implicate red meat as a risk factor, and fiber has been shown to protect against colorectal adenomas and carcinomas. Calcium, vitamin D, folate, and some antioxidant vitamins and minerals (gamma-tocopherol and selenium) have protective effects, and daily exercise for > or =30 min results in a significant decrease in risk. Estrogen use (hormone replacement therapy) substantially reduces colorectal cancer risk in postmenopausal women. Nonsteroidal anti-inflammatory drugs (e.g., aspirin) in excessive doses is protective, especially in high risk populations, but the side effects of its use and cost incurred due to its continued intake over long periods must be carefully scrutinized before any recommendations are made for the general public.

Allinger, U. G., G. K. Johansson, et al. (1989). "Shift from a mixed to a lactovegetarian diet: influence on acidic lipids in fecal water--a potential risk factor for colon cancer." *Am J Clin Nutr* **50**(5): 992-6.

Although there have recently been reports in the literature indicating that vegetarian-type diets are protective against the development of human colon cancer, this is still far from clear. It was also recently

indicated that the concentration of acidic lipids in the aqueous phase of stool constitutes a risk factor for the development of colon cancer. Thus, we examined the effect of a change from a mixed to a lactovegetarian diet on this fecal variable. The dietary change caused a decrease in the total concentration of soluble fecal fatty acids (4310 +/- 3020 to 1080 +/- 1040 mumol/L, p less than 0.05) and deoxycholic acid (125 +/- 42 to 73 +/- 35 mumol/L, p less than 0.05). However, there was no change in either the total bile acid concentration in (164 +/- 54 to 107 +/- 41 mumol/L) or the cellular toxicity of (0.94 +/- 0.55 to 1.60 +/- 0.63 mumol/L, relative survival) the aqueous phase of stool. Thus, the consumption of a lactovegetarian diet may reduce certain risk factors of potential significance in colon carcinogenesis.

Bal, D. G. and S. B. Foerster (1991). "Changing the American diet. Impact on cancer prevention policy recommendations and program implications for the American Cancer Society." *Cancer* **67**(10): 2671-80.

In 1984, the American Cancer Society (ACS) determined that a substantial proportion of new cancer cases could be avoided if seven dietary guidelines were followed. Education programs were developed for the general public, young people, and the mass media. In 1989, a Working Group of the Society reviewed the guidelines and found them to be valid, the only change being to combine two of them. This paper summarizes recent dietary recommendations of other health authorities, describes progress in meeting ACS dietary recommendations, analyzes the barriers to and opportunities for dietary improvement, and proposes new leadership opportunities for the Society. Concern is expressed that the current guidelines lack the clarity and specificity needed for public education, and that they are inconsistent with recent dietary recommendations of other authorities such as the US Department of Health and Human Services and the National Academy of Sciences. Revisions to the ACS Dietary Recommendations and implications for ACS programs are proposed.

Ballard-Barbash, R., D. F. Birt, et al. (1997). "Perspectives on integrating experimental and epidemiologic research on diet, anthropometry and breast cancer." *J Nutr* **127**(5 Suppl): 936S-939S.

Three perspectives on the integration of experimental and epidemiologic research on diet, anthropometry and breast cancer are presented. 1) Although body weight and height have been linked to breast cancer risk by epidemiologic research, their roles have not been directly explored with animal models. However, basic, clinical and epidemiologic research on obesity and associated metabolic alterations may be pertinent. Individual differences in

the timing and magnitude of weight gain and loss during adult life need to be considered in epidemiologic studies of adiposity and breast cancer, along with individual differences in the pattern of body fat deposition, the hormonal and metabolic changes that accompany the adiposity, and family history of obesity-related chronic diseases. Animal models with genetic predispositions to obesity, diabetes and breast cancer merit further exploration, as well as models that can evaluate exposures occurring after puberty. 2) The synergy between experimental and epidemiologic studies on fat and energy intake and breast carcinogenesis has been productive because each discipline has had to incorporate recent findings of the other. Dietary studies utilizing animals with different genetic profiles are promising, but require identification of the critical genes in human carcinogenesis. 3) Controlled dietary intervention studies with human participants using intermediate endpoints can bridge the gap between animal and epidemiologic studies, but generally accepted intermediate endpoints for breast cancer need to be developed. Such studies would permit better control of diet than large clinical trials and the opportunity to explore mechanisms.

Bradlow, H. L. and D. W. Sepkovic (2002). "Diet and breast cancer." *Ann N Y Acad Sci* **963**: 247-67.

The preponderance of evidence suggests a role for fat and alcohol as risk factors for breast cancer. The role of milk is more controversial with some studies suggesting that milk is a risk factor and others that consumption of milk is protective against breast cancer. No other major nutrient appears to play a significant role in increasing breast cancer risk. On the other hand, there is increasing evidence that a variety of micronutrients and hormones appear to have significant anticancer activity. These range from steroids such as dehydroepiandrosterone (DHEA) and its analysis to indoles, isothiocyanates, and isoflavone derivatives. These compounds act directly by interfering with cyclins and promoting apoptosis as well as indirectly by altering estrogen metabolism in a favorable direction. These effects are not merely theoretical actions in cell culture and tissue explants; they have been demonstrated in human patients as a range of studies have demonstrated.

Brody, J. G., R. A. Rudel, et al. (2007). "Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention?" *Cancer* **109**(12 Suppl): 2627-34.

Breast cancer is the most common invasive cancer in women worldwide and the leading cause of death in US women in mid-life. Treatment has adverse

effects, adding to the importance of finding modifiable risk factors. At the invitation of Susan G. Komen for the Cure, we reviewed studies of breast cancer and environmental pollutants, diet (assessed prospectively), body size, and physical activity, and animal studies that identify chemicals as potential mammary carcinogens. Databases developed in the review include information on 216 chemicals that increased mammary gland tumors in animal studies and 450 epidemiologic studies (accessible at [www.silentspring.org/sciencereview](http://www.silentspring.org/sciencereview) and [www.komen.org/environment](http://www.komen.org/environment)). Exposure to potential mammary carcinogens is widespread from chemicals found in consumer products, air and drinking water pollution, food, and women's workplaces. Epidemiologic studies have included only a small number of chemicals identified as mammary carcinogens or as hormone disruptors, which may have implications for breast cancer; however, evidence is emerging for associations between breast cancer and polychlorinated biphenyls, polycyclic aromatic hydrocarbons, and organic solvents. Prospective diet studies have not revealed consistent associations with breast cancer. Improved exposure assessment methods will help advance future human studies of both diet and environmental pollutants. Studies of physical activity show that it is protective. In the same vein as evidence-based medicine, messages for patients, policymakers, and the public should support decision-making based on the strength of current evidence; such messages might address exposure reduction for some pollutants. Investments in research on environmental factors in breast cancer have potentially large public health benefits.

Bruce, W. R., A. Giacca, et al. (2000). "Possible mechanisms relating diet and risk of colon cancer." *Cancer Epidemiol Biomarkers Prev* **9**(12): 1271-9.

Two recent developments in cancer epidemiology and experimental carcinogenesis provide the basis for two possible mechanisms relating diet and colon cancer risk. The first development is the accumulating epidemiological evidence for an association between insulin resistance and colonic adenomas and cancers. This evidence suggests the following mechanism: the consumption of excess dietary energy results in the development of insulin resistance with increased circulating levels of insulin, triglycerides, and non-esterified fatty acids. These circulating factors subject colonic epithelial cells to a proliferative stimulus and also expose them to reactive oxygen intermediates. These long-term exposures result in the promotion of colon cancer. The second development is the continuing identification of agents that significantly inhibit experimental colon carcinogenesis. These observations suggest the

following mechanism: focal loss of epithelial barrier function resulting from a failure of terminal differentiation results in the "leak" of a presently undefined toxin and a focal inflammatory response characterized by evidence of the activation of the COX-2 enzyme and an oxidative stress with the release of reactive oxygen intermediates. The resulting focal proliferation and mutagenesis give rise to aberrant crypt foci and adenomas. The process is inhibited by: (a) demulcents confined to the colonic lumen that "repair" the surface; (b) anti-inflammatory agents; or (c) antioxidants. The two mechanisms, i.e., insulin resistance acting throughout the body and focal epithelial barrier failure acting locally, can describe most of the known relationships between diet and colon cancer risk.

Butrum, R. R., E. Lanza, et al. (1986). "The Diet and Cancer Branch, NCI: current projects and future research directions." *Prog Clin Biol Res* **222**: 773-88.

Diet, perhaps more than any other environmental factor, has a significant potential for reducing the incidence of cancer. It has been projected that as much as 35 percent of all human cancer can be prevented through effective dietary modification strategies. The comprehensive research program of the DCB significantly directs diet and cancer research toward the ultimate cancer prevention goal of modifying dietary habits of the general population for optimal health. The DCB is currently supporting projects along the entire continuum from laboratory research to human intervention trials: basic research projects in food composition, encompassing dietary fiber, vitamin A and carotenoids and development of INFOODS; physiologic studies establishing safe and effective levels of dietary fiber and carotenoids; modification of eating behavior; human intervention trials of low fat diets in prevention of breast cancer; and clinical nutrition research units.

Carreau, C., G. Flouriot, et al. (2008). "Enterodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERalpha transcriptional activation in human breast cancer cells." *J Steroid Biochem Mol Biol* **110**(1-2): 176-85.

Lignans are plant compounds metabolized in the mammalian gut to produce the estrogenic enterolignans, enterodiol (ED) and enterolactone (EL). Because estrogens have been linked to breast cancer etiology, enterolignans could affect breast cancer risk, but to our knowledge, the mechanisms by which they exert their estrogenic and/or anti-estrogenic effects in humans are still unclear. To better understand how estrogenic compounds from the food, such as the enterolignans, might influence breast cancer progression and their mechanisms to interfere with

human estrogen receptor (ER) signalling in hormone-dependant diseases, we examined and compared the ability of ED, EL and 17beta-estradiol (E2) to induce the transactivation of ERalpha and ERbeta, to modulate ERalpha target genes, to exert either growth stimulatory or anti-proliferative effects and finally to modulate MCF-7 cell migration by acting on matrix metalloproteases (MMP)-2 and -9, at concentrations that are achievable through a lignan-rich diet. This study indicates that enterolignans show distinct properties for transactivation of ERalpha and ERbeta. ED, as E2, induces ERalpha transcriptional activation through transactivation functions AF-1 and AF-2, while EL is less efficient in inducing AF-1, acting predominantly through AF-2. Furthermore, ED and EL modulate ERalpha mRNA and protein contents as well as MCF-7 cell proliferation and secreted MMP activities in a different way. Enterolignans are compounds of wide interest nowadays and our results help to unveil their mechanisms of action on ER, emphasizing the fact that the dietary load in lignans could be of importance in the balance between being risk or chemopreventive factors for breast cancer and women's health.

Clinton, S. K. (1997). "Diet, anthropometry and breast cancer: integration of experimental and epidemiologic approaches." *J Nutr* **127**(5 Suppl): 916S-920S.

The interrelationships of dietary fat and energy, growth rates and anthropometry, and breast carcinogenesis have been examined by a diverse array of approaches throughout the last 50 y as new investigative tools have been developed by laboratory scientists and epidemiologists. A consensus among investigators has not emerged, however, and dietary recommendations for breast cancer prevention have not been clearly formulated or effectively communicated to the public. Indeed, the gap between those investigators utilizing laboratory-based approaches and those using epidemiologic models has expanded in recent years. Cancer epidemiologists have become increasingly skeptical that results derived from laboratory animal models of breast carcinogenesis and in vitro systems are directly applicable to human breast cancer risk. Concurrently, laboratory scientists have questioned the ability of epidemiological tools to accurately measure dietary intake and relevant biomarkers and to account for a diverse array of potentially confounding environmental and genetic factors characteristic of human populations under study. These polarized views are reinforced by a failure of investigators using diverse approaches to interact, integrate their skills and resources, develop novel hypotheses, and propose solutions using both laboratory and epidemiologic techniques. Therefore, the objectives of this

symposium are to summarize experimental and epidemiologic knowledge, foster communication and collaboration, and attempt to identify appropriate studies to bridge the gaps in our knowledge concerning dietary lipid and energy, anthropometrics, and breast cancer risk.

Coffey, D. S. (2001). "Similarities of prostate and breast cancer: Evolution, diet, and estrogens." *Urology* **57**(4 Suppl 1): 31-8.

Environment determines the risk of both prostate and breast cancer, and this risk can vary >10-fold. In contrast, no risk exists for human seminal vesicle cancer demonstrating tissue specificity. There is also species specificity, because there is no risk for prostate cancer in any other aging mammal except the dog. A study of evolution indicates that the prostate and breast appeared at the same time 65 million years ago with the development of mammals. All male mammals have a prostate; however, the seminal vesicles are variable and are determined by the diet so that species primarily eating meat do not have seminal vesicles. The exception is the human, who has seminal vesicles and consumes meat, although this is a recent dietary change. Human lineage departed from other higher primates 8 million years ago. The closest existing primate to humans is the bonobo (pigmy chimpanzee), which does not eat meat but exists primarily on a high fruit and fresh vegetable diet. Homo sapiens evolved only about 150,000 years ago, and only in the last 10% of that time (10 to 15 thousand years ago) did humans and dogs dramatically alter their diets. This is the time when humans domesticated the dog, bred animals, grew crops, and cooked, processed, and stored meats and vegetables. All current epidemiologic evidence and suggestions for preventing prostate and breast cancer in humans indicates that we should return to the original diets under which our ancestors evolved. The recent development of the Western-type diet is associated with breast and prostate cancer throughout the world. It is believed that the exposure to and metabolism of estrogens, and the dietary intake of phytoestrogens, combined with fat intake, obesity, and burned food processing may all be related to hormonal carcinogenesis and oxidative DNA damage. An explanatory model is proposed.

Colditz, G. A., M. J. Stampfer, et al. (1987). "Diet and lung cancer. A review of the epidemiologic evidence in humans." *Arch Intern Med* **147**(1): 157-60.

We reviewed the human epidemiologic studies of the possible protective effect against lung cancer of various dietary constituents, including preformed vitamin A, carotene, vitamin E, selenium, and vitamin C. Beta carotene has strong potential as a

protective agent, though constituents of green and yellow vegetables other than carotene may account for the reduced cancer incidence observed in many studies. Selenium also deserves attention as a potential chemopreventive nutrient, though data are limited. Data on vitamin E are sparse and inconclusive, and there is little evidence that vitamin C provides protection against human lung cancer. It is likely that cessation of cigarette smoking would have a far greater influence on reducing lung cancer incidence than any known dietary modification.

Colomer, R. and J. A. Menendez (2006). "Mediterranean diet, olive oil and cancer." Clin Transl Oncol **8**(1): 15-21.

Olive oil is an integral ingredient of the "Mediterranean diet" and accumulating evidence suggests that it may have a potential role in lowering the risk of several types of cancers. The mechanisms by which the cancer-preventing effects of olive oil can be performed, however, are not known. We recently hypothesized that a novel molecular explanation concerning the anti-cancer actions of olive oil may relate to the ability of its monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1n-9) to specifically regulate cancer-related oncogenes. Supporting our hypothesis, exogenous supplementation of cultured breast cancer cells with physiological concentrations of OA was found to suppress the overexpression of HER2 (Her-2/neu, erbB-2), a well-characterized oncogene playing a key role in the etiology, progression and response to chemotherapy and endocrine therapy in approximately 20% of breast carcinomas. OA treatment was also found to synergistically enhance the efficacy of trastuzumab, a humanized monoclonal antibody binding with high affinity to the ectodomain (ECD) of the Her2-coded p185(HER2) oncoprotein. Moreover, OA exposure significantly diminished the proteolytic cleavage of the ECD of HER2 and, consequently, its activation status, a crucial molecular event that determines both the aggressive behavior and the response to trastuzumab of Her2-overexpressing breast carcinomas. Our most recent findings further reveal that OA exposure may suppresses HER2 at the transcriptional level by up-regulating the expression of the Ets protein PEA3 -a DNA-binding protein that specifically blocks HER2 promoter activity- in breast, ovarian and stomach cancer cell lines. This anti-HER2 property of OA offers a previously unrecognized molecular mechanism by which olive oil may regulate the malignant behavior of cancer cells. From a clinical perspective, it could provide an effective means of influencing the outcome of Her-2/neu-overexpressing human carcinomas with poor prognosis. Indeed, OA-induced transcriptional repression of HER2 oncogene

may represent a novel genomic explanation linking "Mediterranean diet", olive oil and cancer as it seems to equally operate in various types of Her-2/neu-related carcinomas.

Escrich, E., R. Moral, et al. (2004). "Identification of novel differentially expressed genes by the effect of a high-fat n-6 diet in experimental breast cancer." Mol Carcinog **40**(2): 73-8.

In previous studies, we demonstrated that high corn oil diets promote the development of 7,12-dimethylbenz(alpha)anthracene (DMBA)-induced mammary tumors. In this study, we have investigated whether modulation of gene expression is one of the mechanisms by which this high-fat diet exerts such effects. Female Sprague-Dawley rats were induced with DMBA and fed normolipidic (3% corn oil) or high-fat (20% corn oil) diet. Screening of genes differentially expressed in adenocarcinomas from the high corn oil diet group compared to the control diet group was performed with cDNA microarrays. The resulting six upregulated and nine downregulated genes were validated by Northern blot and/or reverse transcription (RT)-polymerase chain reaction (PCR). Further investigation in a higher number of adenocarcinomas showed that in the high-fat n-6 diet group, where the tumor phenotype was verified to be more aggressive, the expression of submaxillary gland alpha-2u globulin, vitamin D(3)-upregulated protein 1 (VDUP1), H19, and the unknown function gene that codifies the expressed sequence tag (EST)-Rn.32385 was significantly decreased in comparison with the control group (C). These results, together with the fact that VDUP1, H19, and this globulin have been associated with cell proliferation and differentiation, open a new line of research about how the underexpression of these genes contributes to the stimulating effect of a high corn oil diet on experimental mammary carcinogenesis.

Ferguson, L. R. (1993). "Diet and the prevention of colorectal cancer." Mutat Res **290**(1): 139-43.

It is important for those working in the area of health-promotion that consensus be reached on the role of diet in colorectal cancer and its etiology. In developing health-promotion strategies, further research is needed into the beliefs, attitudes and behaviour of different groups. More qualitative data on the diet of different groups in the community is also needed. Further basic research on the role of diet in this cancer requires that biomarkers be related to human or animal dietary exposures. The development of new animal and human models may be appropriate.

Ferguson, L. R. (1994). "Antimutagens as cancer chemopreventive agents in the diet." Mutat Res **307**(1): 395-410.

It has been suggested that the use of antimutagens and anticarcinogens in everyday life will be the most effective procedure for preventing human cancer and genetic disease. There are several ways in which mutagenesis can be reduced or prevented. Chemicals which act to interfere with DNA repair or with mutagen metabolism can be effective antimutagens: however such compounds may also increase the probability of mutations by different chemicals or at different sites. In contrast, mutagen scavengers may be less prone to increase mutations by other chemicals. Selected examples illustrate that antimutagenic effects are often specific to certain classes of mutagen and/or certain test systems. Thus, if antimutagens are to have any impact on human disease, it is essential that they are specifically directed against the most common mutagens in daily life. On our current understanding, these are quite diverse in nature, so that combinations of antimutagens will probably be necessary. Two groups of mutagen scavengers (porphyrins and some types of dietary fibre) show some selectivity for large planar and hydrophobic types of carcinogen, which appear to be common in a normal Western diet. Increasing consumption of vitamins C and E, either through increased consumption of fruit and vegetables or through dietary supplementation might reduce formation of N-nitroso compounds, another common class of mutagens. Similarly, carotenoids and related compounds, already present at high quantities in some fruits and vegetables, have excellent antioxidant properties and should be able to counteract effects of endogenous metabolism and other events which generate oxidising species and free radicals. Still other types of antimutagen might be necessary to act against smaller non-planar carcinogens, but there is some question as to the importance of this type of carcinogen in a normal Western diet. It may be necessary to adjust the selection of antimutagens for different population groups, or as our understanding of mutagens in the diet develops further. Current assays for cancer chemoprevention in animals are unlikely to detect some important types of antimutagens, such as mutagen scavengers. A structured testing strategy is suggested, progressing from in vitro to in vivo antimutagenicity tests against a selected range of mutagens. Optimal use of antimutagens might be as a dietary supplement, additional to practical advice on increasing consumption of fruit and vegetables.

Fleshner, N. E. and L. H. Klotz (1998). "Diet, androgens, oxidative stress and prostate cancer susceptibility." Cancer Metastasis Rev **17**(4): 325-30.

Prostate cancer is the most common human malignancy and the second leading cause of cancer deaths among men in Western nations. Descriptive epidemiologic data suggest that androgens and/or environmental exposures, such as diet (in particular, dietary fat), play an important role in prostatic carcinogenesis. One plausible link between diet and prostate cancer is oxidative stress. This process refers to the generation of reactive oxygen species, which can then trigger a host of pro-carcinogenic processes. Recent studies also indicate that androgens increase oxidative stress within human prostate cancer cell lines. Recent data from our institution indicate that oxidative stress is higher within the benign epithelium of prostate cancer patients than men without the disease. This confirms our hypothesis and suggests that antioxidants such as lycopene, vitamin E, and selenium may play an important role in preventing disease progression. Large-scale clinical trials with some of these agents are currently in the design phase.

Gatof, D. and D. Ahnen (2002). "Primary prevention of colorectal cancer: diet and drugs." Gastroenterol Clin North Am **31**(2): 587-623, xi.

Primary prevention of colonic adenomas and cancer through dietary interventions or chemoprevention has great appeal. This article discusses primary prevention goals and promising nutritional or chemopreventive strategies. There is substantial observational evidence that diets high in total calories and fat and or low in fruits and vegetables or total fiber as well as low levels of physical activity are related to the risk of colonic neoplasia. Similar observational data indicate that diets high in specific nutrients such as antioxidant vitamins or calcium may be protective. The article describes some of the newer chemopreventive agents and reviews the data linking diet and lifestyle to colorectal cancer risk, focusing on interventions that have also been studied in prospective clinical trials. Finally the evidence supporting the role of non-steroidal anti-inflammatory drugs for the chemoprevention of CRC is reviewed and the status of several other promising newer agents that are entering human trials is summarized.

Gill, C. I. and I. R. Rowland (2002). "Diet and cancer: assessing the risk." Br J Nutr **88 Suppl 1**: S73-87.

Globally, colorectal cancer (CRC) is a leading cause of mortality from malignant disease. Case-control and cohort studies provide strong support for a role of diet in the aetiology of CRC. However to establish causal relationships and to identify more precisely the dietary components involved, intervention studies in human subjects are required. Cancer is an impractical endpoint in terms of

numbers, cost, study duration and ethical considerations. Consequently, intermediate biomarkers of the disease are required. This review aims to provide an overview of the intermediate endpoints available for the study of CRC, particularly non-invasive faecal biomarkers. Examples of their use in dietary intervention studies are given.

Glinghammar, B., M. Venturi, et al. (1997). "Shift from a dairy product-rich to a dairy product-free diet: influence on cytotoxicity and genotoxicity of fecal water--potential risk factors for colon cancer." *Am J Clin Nutr* **66**(5): 1277-82.

Several epidemiologic studies have suggested that dairy product intake is associated with a decreased incidence of colon cancer. To determine whether the cytotoxicity and genotoxicity of the aqueous portion of human stool (two potential risk markers for the disease) were affected by a change in dairy product intake, 18 healthy male and female volunteers were randomly divided into two groups. In a crossover design, the volunteers shifted from their normal dairy product-rich diet to a dairy product-free diet. Nutritional analysis of the food consumed during the study period showed a significant decrease in energy intake from 9000 to 7866 kJ/d because of a decreased intake of protein and fat. Carbohydrate and fiber intakes remained unchanged during the intervention. Calcium intake decreased significantly from 1488 to 372 mg/d, with similar significant decreases in phosphate and vitamin D intakes. Cytotoxicity of fecal water, analyzed by the HT-29 cytotoxicity assay, indicated a significant decrease in cell survival from 34% to 20% when dairy products were excluded from the participants' diets. Single-cell gel electrophoresis (COMET assay), used to analyze genotoxicity of fecal waters, indicated no differences brought about by the dietary intervention. In conclusion, our findings indicate that a shift from a dairy product-rich to a dairy product-free diet resulted in a significant effect on an accepted risk marker for colon cancer and may suggest that the mechanism by which dairy products are protective is at the level of tumor promotion rather than initiation.

Go, V. L., R. R. Butrum, et al. (2003). "Diet, nutrition, and cancer prevention: the postgenomic era." *J Nutr* **133**(11 Suppl 1): 3830S-3836S.

The genomic era of human nutrition is upon us: the human genome and several plant genomes have been characterized, and genetically modified foods are now abundantly available in the marketplace. The link between diet and cancer is well established, and new genomic technologies have made possible the investigation of nutritional modulation of the carcinogenesis pathway with nutrients,

micronutrients, and phytochemicals. Current study of nutrient-modulated carcinogenesis involves exploring the effect of nutrients on DNA damage and repair mechanisms; DNA methylation, which influences gene expression and cellular phenotypes; antioxidant rearranging and oxidative stress; target receptors and signal transduction pathways; cell cycle controls and check points; apoptosis; and antiangiogenic processes. With nutritional genomics, proteomics, and metabolomics, scientists are able to simultaneously elucidate the biological effects of dietary constituents on cell function and global gene expression. This generation of new knowledge on nutrient-gene interactions provides the justification for a research framework for diet and cancer prevention that is focused on identifying and developing new biomarkers as well as a novel and contemporary paradigm for dietary intervention.

Go, V. L., D. A. Wong, et al. (2004). "Diet and cancer prevention: evidence-based medicine to genomic medicine." *J Nutr* **134**(12 Suppl): 3513S-3516S.

The practice of medicine, including health promotion and disease prevention, is on the verge of being revolutionized once again as the scientific and medical community transitions from evidence-based medicine to genomic medicine. Evidence-based medicine entails the systematic approach of formulating a question, developing literature search strategies, and evaluating and applying evidence to establish clinical practice guidelines. In 1982, when the National Research Council published the first comprehensive review of diet and cancer, the literature was primarily based on epidemiological studies, comparing dietary patterns between countries of low and high incidence for particular cancers. The American Institute for Cancer Research conducted an evidence-based review of the world literature and issued its first report in 1997, and the National Cancer Institute followed with evidence-based overviews of cancer prevention. The World Health Organization International Agency for Research on Cancer recently published a series of handbooks on cancer prevention in relation to dietary factors. The expert recommendations stemming from this extensive evidence subsequently influenced the clinical practice of medicine. In 2001, the complete sequencing of the human genome signified the beginning of the postgenomic era, in which new approaches and technologies are causing a shift in biomedical research. A widening understanding of the complex interactions among genotype, diet, lifestyle, and environment has evoked a change in clinical medical practice, where the evidence- and population-based protocol is evolving into a more personalized system that includes the analysis of individual genotype and

phenotype. The implications of this evolution are considerable, because genomic medicine has the potential to give rise to personalized nutrition recommendations and specialized medical treatment.

Gooderham, N. J., S. Murray, et al. (1996). "Heterocyclic amines: evaluation of their role in diet associated human cancer." *Br J Clin Pharmacol* **42**(1): 91-8.

1. Heterocyclic amines are formed in parts per billion levels when meat is cooked. 2. The heterocyclic amines MeIQx and PhIP are efficiently absorbed into the systemic circulation after ingestion of cooked food. 3. We have shown that MeIQx and PhIP, both in vitro and in vivo, are substrates for human hepatic CYP1A2, which exclusively and efficiently catalyses their conversion to genotoxic hydroxylamines. 4. MeIQx and PhIP are promutagens. MeIQx is a very powerful bacterial mutagen whereas PhIP is a more potent mammalian cell mutagen. Using a mammalian cell target gene, *hprt*, we have shown that PhIP induces a characteristic mutational 'fingerprint'. 5. MeIQx and PhIP are carcinogenic in bioassays. The PhIP mutational 'fingerprint' has been detected in the *Apc* gene of 5/8 colonic tumours induced by PhIP in rats.

Gordon, R. R., K. W. Hunter, et al. (2008). "Genotype X diet interactions in mice predisposed to mammary cancer: II. Tumors and metastasis." *Mamm Genome* **19**(3): 179-89.

High dietary fat intake and obesity may increase the risk of susceptibility to certain forms of cancer. To study the interactions of dietary fat, obesity, and metastatic mammary cancer, we created a population of F(2) mice cosegregating obesity QTL and the MMTV-PyMT transgene. We fed the F(2) mice either a very high-fat or a matched-control-fat diet, and we measured growth, body composition, age at mammary tumor onset, tumor number and severity, and formation of pulmonary metastases. SNP genotyping across the genome facilitated analyses of QTL and QTL x diet interaction effects. Here we describe effects of diet on mammary tumor and metastases phenotypes, mapping of tumor/metastasis modifier genes, and the interaction between dietary fat levels and effects of cancer modifiers. Results demonstrate that animals fed a high-fat diet are not only more likely to experience decreased mammary cancer latency but increased tumor growth and pulmonary metastases occurrence over an equivalent time. We identified 25 modifier loci for mammary cancer and pulmonary metastasis, likely representing 13 unique loci after accounting for pleiotropy, and novel QTL x diet interactions at a majority of these loci. These findings highlight the importance of

accurately modeling not only the human cancer characteristics in mice but also the environmental exposures of human populations.

Greenwald, P. (1989). "Strengths and limitations of methodologic approaches to the study of diet and cancer: summary and future perspectives with emphasis on dietary fat and breast cancer." *Prev Med* **18**(2): 163-6.

For many years, scientists have been studying the relationship between diet and certain cancers in animal and human population studies. With the exception of leukemia, nine of the leading cancers in humans may be associated positively or negatively with diet. Extensive literature reviewed by an expert group convened by the National Academy of Sciences concluded that the strongest evidence of an association between the incidence of certain cancers and dietary components is that for dietary fat, particularly for breast cancer (Committee on Diet, Nutrition and Cancer, National Research Council, National Academy of Sciences; Diet, Nutrition and Cancer; Washington, DC: National Academy Press, 1982). The conclusions reached by this group and the consensus of other advisory experts provided the rationale for the National Cancer Institute (NCI) to sponsor a multi-institutional breast cancer prevention trial. This trial was designed to test whether a diet containing 20% of calories from fat compared with the usual diet containing twice that amount would reduce breast cancer incidence in 45- to 69-year-old women. Ensuing controversies about the nature of the research evidence and methodologic issues related to the conduct of this trial led NCI, on advice of its counselors, to discontinue the full-scale implementation. It is clear from these debates that experts have looked at the same data and differed both in their interpretation and in their conception of what constitutes convincing evidence.

Halliwell, B. (2002). "Effect of diet on cancer development: is oxidative DNA damage a biomarker?" *Free Radic Biol Med* **32**(10): 968-74.

Free radicals and other reactive species are generated in vivo and many of them can cause oxidative damage to DNA. Although there are methodological uncertainties about accurate quantitation of oxidative DNA damage, the levels of such damage that escape immediate repair and persist in DNA appear to be in the range that could contribute significantly to mutation rates in vivo. The observation that diets rich in fruits and vegetables can decrease both oxidative DNA damage and cancer incidence is consistent with this. By contrast, agents increasing oxidative DNA damage usually increase risk of cancer development. Such agents include



cigarette smoke, several other carcinogens, and chronic inflammation. Rheumatoid arthritis and diabetes are accompanied by increased oxidative DNA damage but the pattern of increased cancer risk seems unusual. Other uncertainties are the location of oxidative DNA damage within the genome and the variation in rate and level of oxidative damage between different body tissues. In well-nourished human volunteers, fruits and vegetables have been shown to decrease oxidative DNA damage in several studies, but data from short-term human intervention studies suggest that the protective agents are not vitamin C, vitamin E, beta-carotene, or flavonoids.

Hebert, J. R. and D. R. Miller (1988). "Methodologic considerations for investigating the diet-cancer link." *Am J Clin Nutr* 47(6): 1068-77.

Evidence from human ecological studies and experimental animal studies suggest that a number of dietary factors may have a role in the etiology of cancers of various sites. When associations are examined within populations on the level of the individual, they often weaken or disappear. Although in some cases the suspect nutrient may have no real carcinogenic effect, it is proposed that there are at least three important methodologic problems that could prevent the observation of a true association between dietary factors and human cancer. First, diet assessment methods are inadequate to estimate true exposure with sufficient accuracy and precision especially over long periods. Second, use of retrospective diet assessment methods in case-control study designs can often introduce an important bias. Third, sufficient within-study-group contrasts are often lacking. These problems are discussed in interpreting recent cancer studies of diet, and recommendations are made for future research.

Hilakivi-Clarke, L., I. Onojafe, et al. (1996). "Breast cancer risk in rats fed a diet high in n-6 polyunsaturated fatty acids during pregnancy." *J Natl Cancer Inst* 88(24): 1821-7.

**BACKGROUND:** Women who took the synthetic estrogen diethylstilbestrol during pregnancy exhibit an elevated risk of breast cancer, whereas those who suffered from preeclampsia, which is associated with low circulating pregnancy estrogens, exhibit a reduced risk. Since a high-fat diet may increase circulating estrogen levels and possibly breast cancer risk, dietary factors during pregnancy could influence the risk of developing this disease. **PURPOSE:** We tested the hypothesis that consumption of a high-fat diet during pregnancy increases carcinogen-induced mammary tumor incidence in rats. **METHODS:** Pregnant or virgin female Sprague-Dawley rats that had been previously

treated with 10 mg 7, 12-dimethylbenz[a]anthracene (DMBA) by oral gavage when 55 days old were assigned to one of two isocaloric diets containing either 16% calories from fat (low-fat) or 43% calories from fat (high-fat) for the length of pregnancy or for the equivalent time of approximately 21 days. There were 20 pregnant and 10 nonpregnant DMBA-treated rats per group. Ten additional pregnant animals (not previously treated with DMBA) per group were used for hormone analysis. The fat source used was corn oil, which is high in n-6 polyunsaturated fatty acids, primarily linoleic acid. The animals were checked for tumors at least once per week by palpation. The tumor size, number, and latency to appearance after carcinogen exposure were recorded. The statistical significance of observed differences was tested by use of appropriate two-sided tests. **RESULTS:** Female rats on different diets had virtually identical food intakes and weight gains during pregnancy. On gestation day 19, serum estradiol levels were approximately twofold higher in rats fed a high-fat diet than in rats fed a low-fat diet ( $P < .02$ ). The serum insulin levels and insulin/glucose ratios (an index of insulin resistance) in rats fed the high-fat diet were approximately twofold lower than in rats fed the low-fat diet, but the differences did not reach statistical significance ( $P < .09$  and  $P < .09$ , respectively). On week 18 following DMBA administration, the number of rats developing mammary tumors was significantly higher in the group exposed to a high-fat diet (40% of animals) than in the group exposed to a low-fat diet (10% of animals) during pregnancy ( $P < .05$ ). Tumor multiplicity, latency to tumor appearance, and size of tumors upon first detection were similar among the dietary groups. No intergroup differences in the mammary tumor incidence were noted in virgin animals that were exposed to the high- or low-fat diets for an equivalent period of time. **CONCLUSIONS:** Our findings indicate that consumption of a diet high in fat (primarily in the form of n-6 polyunsaturated fatty acids) during pregnancy increases the risk of developing carcinogen-induced mammary tumors, possibly by increasing the pregnancy levels of circulating estrogens. **IMPLICATIONS:** If further studies find that the results from animal model studies are applicable to humans, some human breast cancers may be preventable by dietary manipulations during pregnancy.

Hursting, S. D., S. N. Perkins, et al. (2001). "Diet and cancer prevention studies in p53-deficient mice." *J Nutr* 131(11 Suppl): 3092S-4S.

Progress in mechanism-based cancer prevention research may be facilitated by the use of animal models displaying specific genetic susceptibilities for cancer such as mice deficient in the

p53 tumor suppressor gene, the most frequently altered gene in human cancer. We observed in p53-knockout (p53<sup>-/-</sup>) mice that calorie restriction (CR; 60% of the control group's intake of carbohydrate energy) increased the latency of spontaneous tumor development (mostly lymphomas) approximately 75%, decreased serum insulin-like growth factor (IGF)-1 and leptin levels, significantly slowed thymocyte cell cycle traverse and induced apoptosis in immature thymocytes. In heterozygous p53-deficient (p53<sup>+/-</sup>) mice, CR and 1 d/wk of food deprivation each significantly delayed spontaneous tumor development (a mix of lymphomas, sarcomas and epithelial tumors) and decreased serum IGF-1 and leptin levels even when begun late in life. We have also developed a rapid and relevant p53<sup>+/-</sup> mouse mammary tumor model by crossing p53-deficient mice with MMTV-Wnt-1 transgenic mice, and found that CR and 1 d/wk food deprivation significantly increased mammary tumor latency (greater than twofold) and reduced the mean serum IGF-1 and leptin levels to <50% of that of control mice (P < 0.0001). In addition, fluasterone, fenretinide and soy each delayed tumor development but had little effect on IGF-1 or leptin levels. We have capitalized on the susceptibility of p53<sup>+/-</sup> mice to chronic, low dose, aromatic amine-induced bladder carcinogenesis to develop a useful model for evaluating bladder cancer prevention approaches such as cyclooxygenase-2 inhibition. As demonstrated by these examples, mice with specific (and human-like) genetic susceptibilities for cancer provide powerful new tools for testing and characterizing interventions that may inhibit the process of carcinogenesis in humans.

Jiang, Y., H. Z. Du, et al. (2008). "Effects of a regional Chinese diet and its vitamin supplementation on proliferation of human esophageal cancer cell lines." *Biomed Environ Sci* **21**(5): 442-8.

**OBJECTIVE:** To study the effects of a local diet popular in Yanting region (YT diet) on the proliferation of two human cell lines (Eca-109 esophageal squamous cell carcinoma line and HL7702 normal liver epithelial cell line) in rats by a sero-physiological approach. **METHODS:** Male SD rats were divided into six groups and fed respectively with a conventional diet and the YT diet (one of the five experimental diets) supplemented with two vitamin mixtures (Mix. 1: vitamins A, E, and folic acid; Mix.2: mix.1 plus riboflavin and vitamin C) at two different doses. On the 30th day, sera were collected from the rats and added into a medium for cell culture, with 10% FBS used as a serum control. The effects were assessed by MTT assay, DNA synthesis and flow cytometry assays. **RESULTS:** Compared with the control, the sera from rats fed with the YT diet

significantly promoted the proliferation of Eca-109 cells, which was, however, reversed by the supplementation with two vitamin mixtures at high doses. Surprisingly, the same treatment produced contrary effects on HL7702 cells as compared with Eca-109 cells. **CONCLUSION:** The sera from rats fed with the YT diet could promote the proliferation of human esophageal cancer cell line Eca-109, whereas the sera from those fed with the YT diet supplemented with vitamin mixtures might have inhibitory effects on the proliferation of Eca-109 cells.

Johansson, G. K., L. Ottova, et al. (1990). "Shift from a mixed diet to a lactovegetarian diet: influence on some cancer-associated intestinal bacterial enzyme activities." *Nutr Cancer* **14**(3-4): 239-46.

This investigation studied the effects of a shift from a mixed diet to a lactovegetarian diet on some cancer-associated bacterial enzymes in human feces (beta-glucuronidase, beta-glucosidase, and sulphatase). Three months after the shift to the lactovegetarian diet, there was a significant decrease in beta-glucuronidase, beta-glucosidase, and sulphatase activities per gram feces wet weight (p less than 0.05, less than 0.05, and less than 0.001, respectively). In contrast, glucuronide and glucoside hydrolysis remained unchanged per gram dry weight, although sulphatase activity was still significantly lowered when expressed this way (p less than 0.01). However, the fecal excretion increased significantly (p less than 0.05). Part of the explanation for the decreased enzyme activities is obviously a dilution effect, because much of the increased fecal weight after the shift in diet was associated with a higher water content. The higher water content was probably due to a higher fiber intake (p less than 0.001). Thus, the results in this paper indicate that a change from a mixed diet to a lactovegetarian diet leads to a decrease in certain enzyme activities proposed to be risk factors for colon cancer.

Jolly, C. A. (2005). "Diet manipulation and prevention of aging, cancer and autoimmune disease." *Curr Opin Clin Nutr Metab Care* **8**(4): 382-7.

**PURPOSE OF REVIEW:** Dietary supplementation and other dietary regimens have become increasingly popular in the US population. Information regarding how different dietary constituents interact when consumed simultaneously is needed. This review examines the recent literature on how different dietary constituents may interact physiologically when consumed in combination. Furthermore, the potential human relevance of calorie restriction and nonclassical function of vitamin E is discussed. **RECENT FINDINGS:** Long-term calorie restriction in monkeys has shown similar beneficial

effects as has been shown in rodents. Limited calorie restriction studies in humans have shown promise in reducing the incidence of heart disease and breast cancer. The combination of calorie restriction and omega-3 fatty acids may be a more potent antiinflammatory diet than either regimen alone. The type of fiber that is most protective against colon cancer may be dependent on the type of dietary fat consumed simultaneously. Vitamin E derivatives that possess no antioxidant activity may be potent inhibitors of cancer, but not normal, cell growth. SUMMARY: Dietary modification has shown its greatest beneficial effect when started prior to or immediately after the onset of disease. Also, understanding how the subtypes or isoforms of nutrients function is important since their physiological effects may be drastically different. It is important to understand the entire dietary profile of an individual when making dietary recommendations because one nutrient, or dietary ingredient, may enhance or cancel out the beneficial effects of another dietary ingredient.

Kobayashi, N., R. J. Barnard, et al. (2008). "Effect of low-fat diet on development of prostate cancer and Akt phosphorylation in the Hi-Myc transgenic mouse model." *Cancer Res* **68**(8): 3066-73.

This study evaluated the effect of dietary fat on prostate cancer development by using the Hi-Myc mouse transgenic prostate cancer model. Hi-Myc mice develop murine prostatic intraepithelial neoplasia (mPIN) as early as 2 to 4 weeks and invasive adenocarcinoma between 6 and 9 months due to the overexpression of human c-Myc in the mouse prostate. Three-week-old male Hi-Myc mice were placed on high-fat (HF; 42% Kcal) or low-fat (LF; 12% Kcal) diets, and equal caloric intake was maintained until euthanasia at 7 months. The number of mice that developed invasive adenocarcinoma at 7 months was 27% less in the LF diet group (12/28) compared with the HF diet group (23/33,  $P < 0.05$ ). Epithelial cells in mPIN lesions in the LF group had a significantly lower proliferative index compared with epithelial cells in the HF group (21.7% versus 28.9%,  $P < 0.05$ ). During the mPIN phase of carcinogenesis (4 months), the LF group had higher serum insulin-like growth factor (IGF) binding protein-1 levels (21.0  $\pm$  8.9 ng/mL versus 3.2  $\pm$  0.8 ng/mL,  $P < 0.05$ ) relative to the HF group. Akt (Ser(473)) phosphorylation, Akt kinase activity, and phosphorylation of downstream targets of Akt in prostates were significantly reduced in the LF diet group compared with the HF group. We conclude that dietary fat reduction delays transition from mPIN to invasive cancer in this Myc-driven transgenic mouse model, possibly through suppression of the IGF-Akt

pathway and decreased proliferation of mPIN epithelial cells.

Kritchevsky, D. (2003). "Diet and cancer: what's next?" *J Nutr* **133**(11 Suppl 1): 3827S-3829S.

Our advances in knowledge of the epidemiology of cancer and of the nutritional and genetic effects on this disease have not yet been translated into successful treatment. This is due in part to our tendency toward reductionist thinking, dating to the days when one drug killed one bug. We could learn something by trying to reconcile the differences. Cancer is a degenerative disease that develops over a long time and goes through many stages. Perhaps different nutritional approaches are needed at each stage. The same dietary treatment may not exert the same effects during all stages of tumor development. Obesity is one risk factor that is generally agreed upon. Energy (caloric) restriction has been shown to inhibit experimental carcinogenesis, and energy expenditure affects human carcinogenesis. It would be interesting to combine energy restriction with nutritional treatment. One neglected area of inquiry is that of interactions among nutrients. Substitution of nutrient A for nutrient B can precipitate a series of interactions between nutrient B and the rest of the diet. If more experimental work were done with spontaneous tumors, it would eliminate possible effects of carcinogen metabolism in carcinogenesis and might provide a more accurate reflection of human carcinogenesis. Focusing on one specific dietary component or class of components belies the complexity of the problem.

Lawson, J. S., D. Tran, et al. (2001). "From Bittner to Barr: a viral, diet and hormone breast cancer aetiology hypothesis." *Breast Cancer Res* **3**(2): 81-5.

It is hypothesized that the human homologue of the mouse mammary tumour virus (HHMMTV) and other viruses, such as human papillomavirus (HPV) and Epstein-Barr virus (EBV), act as cofactors with diet, oestrogens and other hormones in the initiation and promotion of some types of breast cancer in genetically susceptible women. It is further hypothesized that diet influences the risk of breast cancer, through its influence on oestrogen metabolism and that of other hormones, in combination with genetic and infectious agents.

Lee, H. P. (1993). "Diet and cancer: a short review." *Ann Acad Med Singapore* **22**(3): 355-9.

The idea that diet and nutrition have an important influence on health is an age-old one. Its link with cancer was mentioned in Chinese medical writings in the twelfth century. Recent interest in this subject started in the 1930s with animal studies.

Today, the notion that diet has an aetiological role in cancer is well accepted. Some of the methodological issues in human studies include the inherent difficulty in estimating dietary intakes, the effect of confounding and interaction, and the low risks associated with specific food items or nutrients. The paper will discuss the main factors implicated, with particular reference to studies in Singapore--on colorectal and breast cancers. The findings point to the profiling of a high-risk diet comprising high meat intake and a relative deficiency in fruits and vegetables (especially those of the cruciferae family). The active components of fruits and vegetables point to a number of micronutrients and substances which have cancer inhibitory properties. They are currently subjects of vigorous research all over the world.

Linseisen, J. and S. Rohrmann (2008). "Biomarkers of dietary intake of flavonoids and phenolic acids for studying diet-cancer relationship in humans." *Eur J Nutr* **47 Suppl 2**: 60-8.

**BACKGROUND:** For many polyphenolic compounds found in plant-derived food, biological effects possibly relevant for cancer prevention have been shown. Since dietary intake estimates suffer from imprecision, the measurement of these compounds (or metabolites of) in biological specimens collected in epidemiological studies is expected to improve accuracy of exposure estimation. **AIM OF THE STUDY:** The current use of biomarkers in etiologic studies on polyphenolics and cancer risk is evaluated. In addition, available analytical methods are discussed with respect to the requirements for their integration in epidemiological studies, putting specific emphasis on the epidemiological validation of such markers. **METHODS:** The scientific literature was screened for epidemiologic studies on the relationship of flavonoid and phenolic acid concentrations in human specimens (i.e. blood, urine) and cancer risk. In addition, original data on intra- and inter-subject variability of several flavonoids and phenolic acids are presented. **RESULTS:** Although several techniques are used in bioavailability or short-term intervention studies, their integration in epidemiological studies is very limited. An exception are phytoestrogens where validated immunoassays allow the rapid measurement of large sample numbers with small sample volume. For several polyphenols, the data on the epidemiologic validity encourages for their use in epidemiological studies. **CONCLUSIONS:** There are valid possibilities for additional biomarkers of flavonoid and phenolic acid intake that are best applied in prospective studies with more than one biological sample per subject. Currently, a combination of a single biomarker measurement with long-term dietary intake estimates

will probably be the most valuable choice to decrease measurement error in exposure data.

Longnecker, D. (1990). "Experimental pancreatic cancer: role of species, sex and diet." *Bull Cancer* **77(1)**: 27-37.

Pancreatic cancer has been experimentally induced in rodents by chemical carcinogens that have been used to establish "animal models" for pancreatic carcinogenesis. Recent work with transgenic mice provided a new model in which a dominantly expressed oncogene is transmitted in the germ cell line of homozygous strains. Carcinogens are not equally effective in all species and the histologic type of carcinoma that develops is strongly influenced by the species. Carcinomas that develop in rats and mice are predominantly acinar cell type. In contrast, hamsters characteristically develop duct-like carcinomas. The histologic type of carcinoma in hamsters resembles more closely the majority of carcinomas in the human pancreas than is the case in the rat or mouse. Studies in rats and guinea pigs have demonstrated that duct-like and undifferentiated carcinomas, as well as acinar cell carcinomas, can arise from acinar cells. Thus, the relative importance of ductal cells, centroacinar cells, acinar cells and putative stem cells in the origin of pancreatic carcinomas remains to be determined. In most rat models, males have developed a higher incidence rate of pancreatic cancers than females. Experimental evidence shows that testosterone promotes and estrogen inhibits the growth of preneoplastic lesions and cancers in the rat pancreas. Dietary composition and additives influence carcinogenesis in the pancreas. High fat diets promote carcinogenesis in rats and hamsters, and dietary trypsin inhibitors promote in rats. Other dietary additives such as retinoids and antioxidants have inhibited carcinogenesis in the animal models.

Mathers, J. C. (2004). "The biological revolution - towards a mechanistic understanding of the impact of diet on cancer risk." *Mutat Res* **551(1-2)**: 43-9.

There is strong epidemiological evidence to show that differences in diet explain a significant proportion of the variation in cancer incidence worldwide. However, because of the complex nature of eating behaviour and the chemical heterogeneity of foods, it remains very difficult to ascertain which aspects of diet, in what quantities and over what time-frames are responsible for modifying risk. In addition, there are few dietary intervention studies demonstrating reduction in cancer risk. Much faster progress has been made in understanding the biological basis of cancer. It is now clear that damage to the genome resulting in aberrant expression of genes (principally suppression of tumour suppressor

genes (TSGs) and inappropriate expression of oncogenes) is fundamental to tumorigenesis. It is also becoming clear that much of the inter-individual variation in cancer experience is due to differences in the amount of damage experienced and/or the capacity to repair that damage. Both of these processes are influenced strongly by dietary factors and by genetic predisposition (polymorphisms in the requisite genes). It is possible that understanding diet:gene interactions in DNA damage and in repair will not only explain much of the inter-individual variation in risk but also offer opportunities to design better dietary intervention studies aimed at chemoprevention. The Human Genome maps and the SNPs databases, together with the rapid development of tools suitable for investigating genetic and epigenetic changes in small tissue biopsies provide the means to begin to test hypotheses about the mechanisms by which diet influences cancer risk directly in human subjects. This is likely to form a significant component of the emerging science of nutrigenomics.

Mathers, J. C. (2007). "Overview of genes, diet and cancer." *Genes Nutr* **2**(1): 67-70.

Quantitative epidemiological analysis suggests that about one third of the variation in cancer risk can be attributed to variation in dietary exposure but it has proved difficult, using conventional epidemiological approaches, to identify which dietary components, in what amounts and over what time-scales are protective or potentially hazardous. Work in this area has been hampered by the lack of robust surrogate endpoints. However, the rapidly accumulating knowledge of the biological basis of cancer and the application of post-genomic technologies are helping the development of novel biomarkers of cancer risk. Genomic damage resulting in aberrant gene expression is the fundamental cause of all cancers. Such damage includes mutations, aberrant epigenetic marking, chromosomal damage and telomere shortening. Since both external agents and normal cell functions, such as mitosis, subject the genome to frequent and diverse insults, the human cell has evolved a battery of defence mechanisms which (a) attempt to minimize such damage (including inhibition of oxidative reactions by free radical scavenging and the detoxification of potential mutagens), (b) repair the damage or (c) remove severely damaged cells by shunting them into apoptosis. When such defences fail and a tumour becomes established, further genomic damage and further alterations in gene expression enable the tumour to grow, to cope with anoxia, to develop a novel blood supply (angiogenesis), to escape from the confines of its initiation site and to establish colonies elsewhere in the body (metastasis). All of these

processes are potentially modifiable by food components and by nutritional status. In addition, interactions between dietary (and other environmental and lifestyle) factors and genetic make-up [seen principally in the assembly of single nucleotide polymorphisms (SNPs) which is unique to each individual] contributes to interindividual differences in cancer risk.

McCullough, M. L. and E. L. Giovannucci (2004). "Diet and cancer prevention." *Oncogene* **23**(38): 6349-64.

Dietary effects are presumed to underlie many of the large international differences in incidence seen for most cancers. Apart from alcohol and a few micronutrients, however, the role of specific nutritional factors remains ill-defined. The evidence for a role of energy balance, physical inactivity, and obesity has strengthened, while for dietary fat it has weakened. Phytochemicals such as folate, lycopene and flavonoids are still the subject of active research. As the mechanisms underlying human carcinogenesis are better understood, dietary research will focus increasingly on intermediate markers such as the insulin-like growth factors and potentially carcinogenic metabolites.

McIntosh, G. H. (1993). "Colon cancer: dietary modifications required for a balanced protective diet." *Prev Med* **22**(5): 767-74.

**BACKGROUND:** There is increasing support of the view that our diet is too calorie dense, with its high animal fat, sugar, and alcohol content. Food processing has helped to create this situation as well as the desire to eat sugar- and fat-rich foods. By examining the influence of these dietary effects on colon cancer, experimental animal studies can help dissect the influences not readily assessable by epidemiological means. **METHODS:** The Sprague Dawley rat model of colon cancer induced by dimethylhydrazine provides a means of assessing dietary influences with the use of a semipurified diet and varying a single factor at a time. We have examined the influence of Ca vitamin E, protein type, and cereal dietary fiber sources on tumor burden and incidence in rats on a standardized experimental protocol. **RESULTS:** A significant interactive effect has been seen with high Ca and low vitamin E intake in protecting rats from tumors. When comparing differing protein sources, whey protein concentrate was found to be very protective relative to red meat and other protein sources. Spent barley grain was also shown to be very protective relative to wheat bran and commercial barley bran. **CONCLUSIONS:** There are several potentially useful strategies for protection from colon cancer by varying diet composition.

Protein sources such as whey protein concentrate, insoluble dietary fiber from barley grain, and high calcium intake seem to be very promising. These need further detailed examination as to whether they can combine to reduce risk further and to understand better the mechanisms responsible for protection. They may provide greater potential than attempts to lower the fat in the human diet.

Mendeloff, A. I. (1988). "Diet and colorectal cancer." *Am J Clin Nutr* **48**(3 Suppl): 780-1.

Data on the relationship of dietary intakes to the risk of colorectal cancer is controversial. The identification of any single causal feature in human diet for colorectal cancer is an improbable outcome because of the complexity of neoplasia, interaction of dietary factors and carcinogens, and the varied forms of colorectal cancer. The same general dietary program advocated for reduced cardiovascular risk is probably suitable for cancer reduction as well.

Menendez, J. A., A. Papadimitropoulou, et al. (2006). "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* **42**(15): 2425-32.

Olive oil is an integral ingredient of the "Mediterranean diet" and accumulating evidence suggests that it may have a potential role in lowering risk of several cancers. We recently hypothesized that the anti-cancer actions of olive oil may relate to its monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1n-9) content to specifically regulate oncogenes. In this study, transient transfection experiments with human Her-2/neu promoter-driven luciferase gene established the ability of OA to specifically repress the transcriptional activity of Her-2/neu gene. Gene repression was seen in tumour-derived cell lines with Her-2/neu gene amplification and overexpression, including SK-Br3 (56% reduction), SK-OV3 (75% reduction) and NCI-N87 (55% reduction) breast, ovarian and stomach cancer cell lines, respectively. Also marginal decreases in promoter activity were observed in cancer cells expressing physiological levels of Her-2/neu (20% reduction in MCF-7 breast cancer cells). Remarkably, OA treatment in Her-2/neu-overexpressing cancer cells was found to induce up-regulation of the Ets protein polyomavirus enhancer activator 3 (PEA3), a transcriptional repressor of Her-2/neu promoter. Also, an intact PEA3 DNA-binding-site at endogenous Her-2/neu gene promoter was essential for OA-induced repression of this gene. Moreover, OA treatment failed to decrease

Her-2/neu protein levels in MCF-7/Her2-18 transfectants, which stably express full-length human Her-2/neu cDNA controlled by a SV40 viral promoter. OA-induced transcriptional repression of Her-2/neu through the action of PEA3 protein at the promoter level may represent a novel mechanism linking "Mediterranean diet" and cancer.

Mucci, L. A. and K. M. Wilson (2008). "Acrylamide intake through diet and human cancer risk." *J Agric Food Chem* **56**(15): 6013-9.

More than one-third of the calories consumed by U.S. and European populations contain acrylamide, a substance classified as a "probable human carcinogen" based on laboratory data. Thus, it is a public health concern to evaluate whether intake of acrylamide at levels found in the food supply is an important cancer risk factor. Mean dietary intake of acrylamide in adults averages 0.5 microg/kg of body weight per day, whereas intake is higher among children. Several epidemiological studies examining the relationship between dietary intake of acrylamide and cancers of the colon, rectum, kidney, bladder, and breast have been undertaken. These studies found no association between intake of specific foods containing acrylamide and risk of these cancers. Moreover, there was no relationship between estimated acrylamide intake in the diet and cancer risk. Results of this research are compared with other epidemiological studies, and the findings are examined in the context of data from animal models. The importance of epidemiological studies to establish the public health risk associated with acrylamide in food is discussed, as are the limitations and future directions of such studies.

Nelson, W. G., T. L. DeWeese, et al. (2002). "The diet, prostate inflammation, and the development of prostate cancer." *Cancer Metastasis Rev* **21**(1): 3-16.

Evidence that somatic inactivation of GSTP1, encoding the human pi-class glutathione S-transferase, may initiate prostatic carcinogenesis is reviewed along with epidemiological evidence implicating several environment and lifestyle factors, including the diet and sexually transmitted diseases, as prostate cancer risk factors. An integrated model is presented featuring GSTP1 function as a 'caretaker' gene during the pathogenesis of prostate cancer, in which the early loss of GSTP1 activity renders prostate cells vulnerable to genome damage associated with chronic prostatic inflammation and repeated exposure to carcinogens. The model predicts that the critical prostate carcinogens will be those that are substrates for GSTP1 detoxification and are associated with high prostate cancer risk diet and lifestyle habits.

Ngo, T. H., R. J. Barnard, et al. (2003). "Effect of isocaloric low-fat diet on human LAPC-4 prostate cancer xenografts in severe combined immunodeficient mice and the insulin-like growth factor axis." *Clin Cancer Res* 9(7): 2734-43.

Over-consumption of dietary fat has been suggested to promote the development and progression of prostate cancer in men. The present study was conducted to answer the following questions: (a) Can dietary fat reduction decrease tumor growth rates of Los Angeles prostate cancer (LAPC)-4 xenografts in severe combined immunodeficient (SCID) mice independent of total caloric intake? and (b) Is the insulin-like growth factor (IGF) axis involved in the effects of dietary fat on LAPC-4 tumor growth in SCID mice? Twenty-eight male CB17 beige SCID mice (8 weeks old) were individually caged, randomized, and fed an isocaloric high-fat (HF, 42% kcal) or low-fat (LF, 12% kcal) diet. Each mouse was s.c. injected with  $1 \times 10^5$  LAPC-4 cells, and tumor volumes were measured weekly. At week 16, all animals were sacrificed, and serum and tumors were obtained for analysis. Although caloric intakes and mouse weights were equal between groups, the LF mice had significantly slower tumor growth rates and lower serum prostate-specific antigen levels compared with the HF mice. LF mice had significantly lower levels of serum insulin, tumor IGF-1 mRNA expression, and tumor IGFBP-2 immunostaining and higher levels of serum IGFBP-1 (by Western ligand blot) relative to the HF mice. There were no differences in the serum levels of IGFBP-3 and IGFBP-4 between the groups. LAPC-4 cells cultured in vitro with media containing serum from LF mice demonstrated slower growth than LAPC-4 cells cultured in media containing HF mice serum. These results demonstrate that intake of an LF diet was associated with slower LAPC-4 prostate tumor growth relative to mice fed an HF diet, independent of total caloric intake, and this effect may be mediated through modulation of the insulin/IGF axis.

Olesen, P. T., A. Olsen, et al. (2008). "Acrylamide exposure and incidence of breast cancer among postmenopausal women in the Danish Diet, Cancer and Health Study." *Int J Cancer* 122(9): 2094-100.

Acrylamide, a probable human carcinogen, is formed in several foods during high-temperature processing. So far, epidemiological studies have not shown any association between human cancer risk and dietary exposure to acrylamide. The purpose of this study was to conduct a nested case control study within a prospective cohort study on the association between breast cancer and exposure to acrylamide using biomarkers. N-terminal hemoglobin adduct

levels of acrylamide and its genotoxic metabolite, glycidamide in red blood cells were analyzed (by LC/MS/MS) as biomarkers of exposure on 374 breast cancer cases and 374 controls from a cohort of postmenopausal women. The adduct levels of acrylamide and glycidamide were similar in cases and controls, with smokers having much higher levels (approximately 3 times) than nonsmokers. No association was seen between acrylamide-hemoglobin levels and breast cancer risk neither unadjusted nor adjusted for the potential confounders HRT duration, parity, BMI, alcohol intake and education. After adjustment for smoking behavior, however, a positive association was seen between acrylamide-hemoglobin levels and estrogen receptor positive breast cancer with an estimated incidence rate ratio (95% CI) of 2.7 (1.1-6.6) per 10-fold increase in acrylamide-hemoglobin level. A weak association between glycidamide hemoglobin levels and incidence of estrogen receptor positive breast cancer was also found, this association, however, entirely disappeared when acrylamide and glycidamide hemoglobin levels were mutually adjusted.

O'Neill, I., S. Bingham, et al. (1993). "Magnetic microcapsule exploration in the gastrointestinal cavity of the origins of colorectal cancer-associated DNA-damaging agents in the human diet." *Environ Health Perspect* 99: 161-7.

Magnetically recoverable, semipermeable microcapsules have been devised for covalent entrapment of reactive substances in the intestinal cavity to biomonitor potentially DNA-damaging agents and the effects of etiologically important components of the human diet. These microcapsules have been shown to trap five types of agents in vivo, namely, carcinogen electrophiles, nitrosating agents, mutagens/carcinogens having a planar molecular structure, and as-yet unidentified endogenous cross-linking agents and precursors of reactive oxygen species. Substantial alterations in both total metabolites and types of metabolites trapped from [<sup>14</sup>C]benzo(a)pyrene were found to be caused by increasing (within the human intake range) the dietary levels of beef protein and dietary fiber. The system thus responds to a variety of potentially critical agents and in a manner consistent with epidemiologically important dietary modulators for colorectal carcinogenesis. Work toward recognizing entrapped endogenous agents has also begun.

Otto, C., U. Kaemmerer, et al. (2008). "Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides." *BMC Cancer* 8: 122.

**BACKGROUND:** Among the most prominent metabolic alterations in cancer cells are the increase in glucose consumption and the conversion of glucose to lactic acid via the reduction of pyruvate even in the presence of oxygen. This phenomenon, known as aerobic glycolysis or the Warburg effect, may provide a rationale for therapeutic strategies that inhibit tumour growth by administration of a ketogenic diet with average protein but low in carbohydrates and high in fat enriched with omega-3 fatty acids and medium-chain triglycerides (MCT). **METHODS:** Twenty-four female NMRI nude mice were injected subcutaneously with tumour cells of the gastric adenocarcinoma cell line 23132/87. The animals were then randomly split into two feeding groups and fed either a ketogenic diet (KD group; n = 12) or a standard diet (SD group; n = 12) ad libitum. Experiments were ended upon attainment of the target tumour volume of 600 mm<sup>3</sup> to 700 mm<sup>3</sup>. The two diets were compared based on tumour growth and survival time (interval between tumour cell injection and attainment of target tumour volume). **RESULTS:** The ketogenic diet was well accepted by the KD mice. The tumour growth in the KD group was significantly delayed compared to that in the SD group. Tumours in the KD group reached the target tumour volume at 34.2 +/- 8.5 days versus only 23.3 +/- 3.9 days in the SD group. After day 20, tumours in the KD group grew faster although the differences in mean tumour growth continued significantly. Importantly, they revealed significantly larger necrotic areas than tumours of the SD group and the areas with vital tumour cells appear to have had fewer vessels than tumours of the SD group. Viable tumour cells in the border zone surrounding the necrotic areas of tumours of both groups exhibited a glycolytic phenotype with expression of glucose transporter-1 and transketolase-like 1 enzyme. **CONCLUSION:** Application of an unrestricted ketogenic diet enriched with omega-3 fatty acids and MCT delayed tumour growth in a mouse xenograft model. Further studies are needed to address the impact of this diet on other tumour-relevant functions such as invasive growth and metastasis.

Pendas, A. M., A. R. Folgueras, et al. (2004). "Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice." *Mol Cell Biol* **24**(12): 5304-13.

Matrix metalloproteinase 19 (MMP-19) is a member of the MMP family of endopeptidases that, in contrast to most MMPs, is widely expressed in human tissues under normal quiescent conditions. MMP-19 has been found to be associated with ovulation and angiogenic processes and is deregulated in diverse pathological conditions such as rheumatoid arthritis

and cancer. To gain further insights into the in vivo functions of this protease, we have generated mutant mice deficient in Mmp19. These mice are viable and fertile and do not display any obvious abnormalities. However, Mmp19-null mice develop a diet-induced obesity due to adipocyte hypertrophy and exhibit decreased susceptibility to skin tumors induced by chemical carcinogens. Based on these results, we suggest that this enzyme plays an in vivo role in some of the tissue remodeling events associated with adipogenesis, as well as in pathological processes such as tumor progression.

Pero, R. W., A. Olsson, et al. (1998). "Feasibility and quality of biological banking of human normal and tumor tissue specimens as sources of DNA for the Malmo Diet and Cancer Study." *Cancer Epidemiol Biomarkers Prev* **7**(9): 809-12.

Human tumor and normal tissue specimens, which were collected from autopsy material 1-6 days postmortem, were compared with similar tissue specimens collected within 2 h after surgical resection and transport to the pathology department. The end point criteria used to evaluate the quality of the specimens for biological banking purposes were the extractability and yield of high molecular weight DNA and UV absorption ratios at 260:280 after collection and immediate storage of the specimens at -80 degrees C. The data demonstrated that autopsy material was a quality source of DNA, although of not such high quality as surgical biopsy specimens <2 h after resection. The advantages of using autopsy material to supplement surgical specimen collection sent to pathology, as opposed to using specimen collection at surgery wards or formalin-fixed material, as sources of DNA are: (a) large amounts of tumor and normal tissues from a variety of organ sites can be obtained without regard to the patient's health status; (b) a higher percentage of retrieval of incident cases of cancer in prospective designed trials is more likely to be achieved; and (c) the extractable DNA is of sufficiently high enough quality to permit direct analyses by molecular hybridization and sequence methodologies.

Prasad, M. P., T. P. Krishna, et al. (1992). "Esophageal cancer and diet--a case-control study." *Nutr Cancer* **18**(1): 85-93.

It has been estimated that approximately 40% of human cancers may be associated with dietary factors. The relationship is more significant in esophageal cancers. Case-control studies involving 35 subjects of early-diagnosed esophageal cancers showed low mean blood levels of retinol, zinc (p less than 0.001), folic acid (p less than 0.01), and albumin (p less than 0.05). Relative risk was significantly



higher for low levels of retinol and zinc. Diet, in general, in both groups reflected poor intake of several nutrients.

Rafter, J., M. Govers, et al. (2004). "PASSCLAIM--diet-related cancer." *Eur J Nutr* **43 Suppl 2**: II47-II84.

**BACKGROUND:** The role of dietary factors in the aetiology of human cancer is an area, which has attracted intense interest in recent years. The suggestion that approximately one third of all cancers may be caused by an 'inappropriate' balance of food components has led to the attractive contention that we can significantly decrease cancer incidence through dietary recommendations and a change in dietary habits in populations. Thus, a key issue must be to establish clear criteria, which must be met in order to be able to make 'cancer risk reduction' claims for food components. In this area, the one true marker is the malignant human tumour, which for practical reasons is usually not accessible to claims. In its absence, we must rely on alternative markers--biomarkers/surrogate endpoints. This paper mainly deals with the link of these biomarkers to the endpoint tumour and their usefulness for making claims. Some claims have been made based on epidemiological studies. **AIM:** Can we identify targets/ biomarkers in the chain of events from initial 'exposure' to overt malignant tumour, whose modification can be used to make 'anticancer' claims for food components? **RESULTS:** We identified 18 targets/markers in the above chain of events whose modification 'have the potential' to be used for 'reduction of cancer risk' claims for food components. These targets/markers fall under 5 broad headings: tumours and preneoplastic changes; cellular targets/markers; gut luminal markers; angiogenesis and metastasis; carcinogen metabolising enzymes; genetic events. **CONCLUSIONS:** The strongest markers presently available are precancerous lesions (e. g. polyps or aberrant crypt foci) in humans and precancerous lesions and tumours in animal models. The only marker that presently can be used for a 'reduction of disease risk' claim (type B) for food components is 'polyp recurrence'. Type B claims cannot be made on the basis of results in animal models. All of the other biomarkers examined presently lack validation against the 'true endpoint', the tumour, and thus cannot be used for type B claims. 'Reduction of disease risk' claims in the area of 'diet-related cancer' should be based primarily on human intervention studies using relevant/acceptable endpoints. An important area for future research will be the validation of these surrogate endpoints.

Rao, G. N., E. Ney, et al. (1997). "Influence of diet on mammary cancer in transgenic mice bearing an

oncogene expressed in mammary tissue." *Breast Cancer Res Treat* **45(2)**: 149-58.

Breast cancer is one of the most common cancers in women. The laboratory rat treated with strong carcinogen is the most commonly used animal model for study of breast cancer. Transgenic mouse lines with homologues of human breast cancer oncogenes have been developed. The transgenic mouse line TG.NK with c-neu, the human breast cancer oncogene homologue of erbB2, was evaluated to determine its suitability for study of intervention strategies to delay/prevent the development of breast cancer. There were no palpable mammary tumor masses up to 22-weeks of age, and almost all mice fed a purified diet developed palpable mammary tumors by 28-weeks of age. Nonpurified diets decreased the incidence and multiplicity, and delayed the development of mammary tumors as compared to a purified diet. Increasing the fiber content of nonpurified diet decreased the tumor incidence further. There is approximately a 19-week interval between weaning and development of palpable mammary masses to evaluate intervention strategies to delay or prevent the development of mammary cancer in the TG.NK mouse model. Fiber from nonpurified cereal ingredients appears to be highly beneficial in delaying the development of mammary cancer in TG.NK mice, and this observation is in agreement with human epidemiological findings. Therefore, the TG.NK transgenic mouse with oncogene c-neu (erbB2), appears to be a useful animal model for evaluation of dietary intervention strategies.

Reszka, E., W. Wasowicz, et al. (2006). "Genetic polymorphism of xenobiotic metabolising enzymes, diet and cancer susceptibility." *Br J Nutr* **96(4)**: 609-19.

There is increasing evidence identifying the crucial role of numerous dietary components in modifying the process of carcinogenesis. The varied effects exerted by nutrient and non-nutrient dietary compounds on human health and cancer risk are one of the new challenges for nutritional sciences. In the present paper, an attempt is made to review the most recent epidemiological data on interactions between dietary factors and metabolic gene variants in terms of cancer risk. The majority of case-control studies indicate the significant relationship between cancer risk and polymorphic xenobiotic metabolising enzymes in relation to dietary components. The risk of colorectal cancer is associated not only with CYP2E1 high-activity alleles, but also GSTA1 low-activity alleles, among consumers of red or processed meat. Genetic polymorphisms of NAT1 and NAT2 may be also a breast-cancer susceptibility factor among postmenopausal women with a high intake of well-

done meat. On the other hand, phytochemicals, especially isothiocyanates, have a protective effect against colorectal and lung cancers in individuals lacking GST genes. Moreover, polymorphism of GSTM1 seems to be involved in the dietary regulation of DNA damage. The European Prospective Investigation into Cancer and Nutrition study shows a significant inverse association between the polycyclic aromatic hydrocarbon-DNA adduct level and dietary antioxidants only among GSTM1-null individuals. However, the absence of a modulatory effect of polymorphic xenobiotic metabolising enzymes and diet on the development of cancer has been indicated by some epidemiological investigations. Studies of interactions between nutrients and genes may have great potential for exploring mechanisms, identifying susceptible populations/individuals and making practical use of study results to develop preventive strategies beneficial to human health.

Sakai, R. (1989). "Epidemiologic survey on lung cancer with respect to cigarette smoking and plant diet." *Jpn J Cancer Res* **80**(6): 513-20.

This case-control study of lung cancer was based on a cross-sectional questionnaire survey of inpatients at 5 general hospitals in Okinawa, Japan, from 1982 to 1987. The purpose of the study was to clarify the relations of lung cancer to cigarette smoking and plant diet. Ingestion frequencies of 17 major dietary plants and/or herbs were obtained by means of a questionnaire interview. As eligible subjects for a case-control analysis, there were 673 respondents aged over 30 years with clear smoking history, age, sex and diagnosis. Psychiatric patients were excluded. Odds ratios of newly diagnosed lung cancer were calculated by the Mantel-Haenszel procedure. A pair consisted of a case and two controls which were selected randomly by using multivariate caliper matching. Sixty-four pairs matched for age (+/- 5) and sex showed a significantly high odds ratio of 2.9 (P less than 0.0005). However, three male groups who were categorized by the number of cigarettes smoked did not exhibit dose-dependency of lung cancer on smoking. Lung cancer was more prevalent in ex-smokers than in current smokers. Case-control analyses by male generations revealed that lung cancer incidence was age-dependent, and there was a clear dose-response relationship between smoking and lung cancer in males in their sixties. A case-control analysis of each of 17 edible plants based on 44 pairs who were matched for age (+/- 5), sex and smoking history demonstrated that the odds ratio of aloe (*Aloe arborescens* Mill var. *natalensis* Berger) was 0.5 (P less than 0.1), suggesting that the aloe may prevent human carcinogenesis at various sites.

Shigenaga, M. K. and B. N. Ames (1993). "Oxidants and mitogenesis as causes of mutation and cancer: the influence of diet." *Basic Life Sci* **61**: 419-36.

A very high level oxidative damage to DNA occurs during normal metabolism. In each rat cell, the steady-state level of this damage is estimated to be about 10(6) oxidative adducts, and about 10(5) new adducts are formed daily. This endogenous DNA damage appears to be a major contributor to cancer and aging. The oxidative damage rate in mammalian species with a high metabolic rate, short life span, and high age-specific cancer rate such as in rats is much higher than the rate in humans, long-lived mammals with a lower metabolic rate, and a lower age-specific cancer rate. It is argued that deficiency of micronutrients, that protect against oxidative DNA damage, is a major contributor to human cancer. Epidemiological studies, a large body of experimental evidence, and theoretical work on the mechanisms of carcinogenesis point to mitogenesis as a major contributor to cancer. Dividing cells, compared to nondividing cells, are at an increased risk for mutations due to: 1.) conversion of DNA adducts to mutations; 2.) chance of mitotic recombination, gene conversion, and nondisjunction; and, 3.) increased exposure of DNA to mutagens. Mitogenesis also increases the probability of gene amplification and loss of 5-methylcytosine. Dietary interventions that lower mitogenesis, such as calorie restriction, decrease cancer incidence.

Shrestha, R. D., S. Fujimoto, et al. (1992). "A novel anticancer treatment for xenoplated human gastric cancer using polyamine antimetabolites in a low polyamine diet." *Surg Today* **22**(2): 137-42.

The aim of the present study was to evaluate a new anticancer treatment for gastrointestinal cancer, using a combination of polyamine antimetabolites, an anticancer agent and a low-polyamine state. Two polyamine antimetabolites, given as either 40 mg/kg of methylglyoxal-bis-guanylhydrazone (MGBG) or ethylglyoxal-bis-guanylhydrazone (EGBG) and a normal diet (ND), or 20 mg/kg of each drug and a low polyamine diet (LPD), together with 1,000 mg/kg of alphadifluoromethylornithine (DFMO) were administered ip to nude mice for six consecutive days. Mitomycin C (MMC) at 2 mg/kg was then given ip for 3 alternate days. The combination of MGBG or EGBG with DFMO plus MMC resulted in an enhanced antitumor efficacy on LPD. However, the combination which included EGBG was much more enhanced than that which included MGBG and there was no evidence of any tumor regrowth. Weight loss was minimal or nil in the mice given the combination with EGBG, but was evident in those given the combination with MGBG. These results led to the

conclusion that in mice, the combined therapy of EGBG with DFMO plus MMC and LPD is a safe and effective regimen for the treatment of gastric cancer.

Sian, M. S. (1987). "Diet and nutritional factors in the aetiology of colon cancer (review)." *Anticancer Res* 7(3 Pt A): 293-300.

Epidemiological studies suggest that diet may be a major risk factor in the aetiology of colon cancer. Total fat, meat, animal protein and dietary fibre have received most attention. A high-fat - high-protein diet leading to increased faecal steroids has been implicated, but no active carcinogen derived from these has been isolated from human faeces. Alternatively, a refined, low fibre diet with decreased faecal bulk leads to increased large bowel concentration of carcinogens of co-carcinogens which contribute to the development of a malignant tumour. The aetiology of colonic cancer is probably multifactorial but a diet low in animal fat and protein and abundant in vegetables containing vitamin A and lignans may protect against colon cancer.

Sinha, R. and N. Caporaso (1999). "Diet, genetic susceptibility and human cancer etiology." *J Nutr* 129(2S Suppl): 556S-559S.

There is evidence that high penetrance hereditary genes cause a number of relatively uncommon tumors in the familial setting, whereas common cancers are influenced by multiple loci that alter susceptibility to cancer and other conditions. The latter category of genes are involved in the metabolism of carcinogens (activation, detoxification) as well as those that interact with dietary exposure. This paper will consider some of the basic principles in studying susceptibility genes and provide a few examples in which they interact with dietary components.

Slattery, M. L., K. Curtin, et al. (2007). "Diet and lifestyle factor associations with CpG island methylator phenotype and BRAF mutations in colon cancer." *Int J Cancer* 120(3): 656-63.

It has been proposed that dietary factors such as folate, alcohol and methionine may be associated with colon cancer because of their involvement in DNA methylation processes. Data from a large population-based case-control study of incident colon cancer were used to evaluate whether intake of dietary, obesity, physical activity and nonsteroidal antiinflammatory drugs are associated with a CpG island methylator phenotype (CIMP). The BRAF V600E mutation and 5 CpG island markers (MINT1, MINT2, MINT31, p16 and hMLH1) were assessed in 1154 cases of colon cancer. We hypothesized that dietary factors involved in DNA methylation,

cruciferous vegetables and use of aspirin/NSAIDs would be associated with CIMP-high tumors. Dietary folate, vitamins B(6) and B(12), methionine and alcohol were not associated with increased likelihood of colon tumors with the CIMP-high (2 or more markers methylated) phenotype. Dietary fiber, physical activity and aspirin and other nonsteroidal antiinflammatory drugs were inversely associated with both CIMP-low and CIMP-high tumors. Our results also suggested non-CIMP pathways as well. Obese individuals were at 2-fold increased risk of having a CIMP-low tumor. Alcohol was associated with an increased risk of tumors that were MSI+ and CIMP-low. In the presence of smoking 20 or more cigarettes per day, use of NSAIDs did not protect against a BRAF mutation. Our data suggest multiple pathways to colon cancer. They do not support a unique role for dietary folate, alcohol, vitamins B(6) and B(12) and methionine in a CpG island methylator phenotype.

Smith, J. P., S. Kramer, et al. (1990). "Effects of a high-fat diet and L364,718 on growth of human pancreas cancer." *Dig Dis Sci* 35(6): 726-32.

The effects of a high-fat diet and the CCK-receptor antagonist, L364,718, were examined on growth of human pancreas cell line SW-1990 xenografted to nude mice. Sixty animals were fed either low-fat (4.3%) or high-fat (20.25%) diet. Fifteen mice in each diet group were treated with L364,718 (2 mg/kg) subcutaneously twice daily for 23 days. On day 24 the animals were sacrificed. Tumor and animal pancreases were dissected and evaluated for weight, protein, and DNA content. When comparing within each diet group, L364,718 significantly decreased tumor volume, weight, protein, and DNA content compared to untreated mice (P less than 0.005). Tumor volume and protein content were significantly larger in untreated animals on the high-fat diet (P less than 0.05) compared to the low-fat diet. Mouse pancreatic weight, protein, and DNA content per kilogram of animal weight were all significantly lower (P less than 0.005) in mice on the low-fat diet treated with L364,718. Pancreatic DNA content was also decreased in both groups of animals on the high-fat diet compared to untreated mice on the low-fat diet. These findings suggest that diets high in unsaturated fat promote the growth of human pancreatic cancer. Since both tumor and pancreas growth are inhibited by the specific CCK-antagonist, L364,718, it is possible that endogenous CCK promotes the growth.

Sonnenschein, E. G., L. T. Glickman, et al. (1991). "Body conformation, diet, and risk of breast cancer in pet dogs: a case-control study." *Am J Epidemiol* 133(7): 694-703.

Canine and human breast cancer share several important clinical and histologic features. A case-control study of nutritional factors and canine breast cancer was conducted at the Veterinary Hospital of the University of Pennsylvania in 1984-1987 by interviewing owners of 150 pet dogs diagnosed with breast cancer, owners of 147 cancer control dogs, and owners of 131 noncancer control dogs. The risk of breast cancer was significantly reduced in dogs spayed at or before 2.5 years of age. Neither a high-fat diet nor obesity 1 year before diagnosis increased the risk of breast cancer according to multiple logistic regression analysis. However, the risk of breast cancer among spayed dogs was significantly reduced in dogs that had been thin at 9-12 months of age (odds ratio (OR) = 0.04 (95% confidence interval (CI) 0.004-0.4) and OR = 0.04 (95% CI 0.004-0.5) for cases vs. cancer controls and cases vs. noncancer controls, respectively, after adjustment for age at spay). Among intact dogs, the risk associated with being thin at 9-12 months of age was reduced, but not significantly so (OR = 0.60 (95% CI 0.2-1.9) and OR = 0.51 (95% CI 0.2-1.4) for the two comparisons, respectively). Results of this study suggest that nutritional factors operating early in life may be of etiologic importance in canine breast cancer.

Spence, R. A. (2007). "Penman Lecture. Breast cancer--diet to genes: presented at the Department of Surgery, University of Cape Town, 20 July 2005." *S Afr J Surg* **45**(3): 76, 78, 80-5.

Frank Garfield Penman was a solicitor from England who died while on holiday in Cape Town in March 1963. Under a deed dated 9 November 1965, his widow Robina Douglas Penman established a Trust in his memory--the Penman Memorial Foundation. The object of the Foundation initially included scholarships to assist postgraduate medical students from South Africa, and in particular from Cape Town, to obtain teaching and further experience in the UK. Later, the Frank Penman Travelling Fellowship was established (the Visiting Professorship) to advance medical knowledge and practice in surgery by enabling a surgeon from the UK to give lectures and teach for a period of several weeks in South Africa. This paper is based on a lecture given on 20 July 2005 as part of the Penman Memorial Foundation Visiting Professorship to Cape Town.

Steineck, G., S. E. Norell, et al. (1988). "Diet, tobacco and urothelial cancer. A 14-year follow-up of 16,477 subjects." *Acta Oncol* **27**(4): 323-7.

Urothelial cancer has been linked with tobacco, phenacetin-containing analgesics and some

industrially-related carcinogens. Carotene has been suggested as reducing the risk of urothelial cancer but there is not much information on the relation between diet and the incidence of human urothelial cancer. Furthermore, the magnitude of the risk of urothelial cancer for pipe smokers remains unclear. In a 14-year follow-up of 16,477 Swedish twins the rate ratio of urothelial cancer (with 95% confidence interval) for subjects with a moderate/high intake of pork and beef respectively was 1.6 (1.0-2.7) and 1.6 (1.0-2.6). Meat consumption is widespread in Western populations. If the finding is supported by further data, a possible etiologic factor associated with the consumption of beef and pork would account for a substantial proportion of the cases of urothelial cancer. The rate ratio for men smoking a pipe/cigars, but not cigarettes, was 3.3 (95% confidence interval 1.5-7.4).

Stoll, B. A. (1998). "Breast cancer and the western diet: role of fatty acids and antioxidant vitamins." *Eur J Cancer* **34**(12): 1852-6.

Epidemiological reports are inconsistent on the association between breast cancer risk and the dietary intake of either individual fatty acids or of antioxidant vitamins. It is postulated here that the inconsistencies are in part due to interactions between the two classes of nutrients at the level of the cell membrane, affecting their potential role in mammary carcinogenesis. In this review, the effects of specific dietary fatty acids and antioxidant vitamins on experimental mammary cancer systems are compared with reported epidemiological associations of the same agents with breast cancer risk in humans. An increased ratio of n-3 to n-6 polyunsaturated fatty acids (PUFAs) in the diet inhibits the growth of the rat mammary cancer model. There is also evidence that members of the n-3 PUFA series can inhibit the growth of human breast cancer cells both in vitro and in explants. Clinical trials of supplementary n-3 PUFAs in conjunction with a reduced fat intake have been proposed for breast cancer prevention. It is postulated that further dietary supplementation with vitamin E and a retinoid is likely to increase the effectiveness of such a diet. A study of this type allows better control of specific dietary components than prospective trials of dietary fat reduction which are presently under evaluation. In particular, it is suggested that studies focusing on a single nutrient often fail to recognise interactions with other nutrients.

Stoll, B. A. (1998). "Western diet, early puberty, and breast cancer risk." *Breast Cancer Res Treat* **49**(3): 187-93.

The typical high fat, low fibre diet of the industrialised West, particularly when associated with

inadequate exercise, is likely to advance the onset of puberty. This will manifest in girls as an earlier menarche, earlier onset of breast development, and an earlier growth spurt. Both earlier menarche and adult tallness are markers of increased risk to breast cancer. Earlier menarche in the West is usually associated with earlier onset of hyperinsulinaemia, and multiple case-control studies report that hyperinsulinaemia too is a marker of increased breast cancer risk. Although the Western diet is linked both to earlier menarche and also to earlier hyperinsulinaemia, the mechanism involved is not necessarily the same. While menarche is likely to be triggered by a threshold level of fatness, manifestation of insulin resistance is genetically-determined and strongly influenced by the fatty acid profile of the diet. The putative mechanisms by which they influence mammary carcinogenesis also differ. Early menarche is reported to be associated with a raised oestradiol level persisting into early adult life. On the other hand, hyperinsulinaemia is commonly associated with abnormal aromatase activity in the ovaries. In addition, the concomitant increase in bioactive levels of insulin-like growth factor-I may synergise with oestrogen in stimulating proliferative activity in mammary epithelium. Dietary modification and exercise regimens are proposed in families at high risk to breast cancer. The measures have been shown to reduce insulin levels in both children and adults, and serial monitoring of insulin and sex steroid levels could be used to detect a metabolic-endocrine effect.

Sweeney, C., B. F. Coles, et al. (2002). "Novel markers of susceptibility to carcinogens in diet: associations with colorectal cancer." *Toxicology* **181-182**: 83-7.

Red meats cooked at high temperatures generate mutagenic heterocyclic amines, which undergo metabolic activation by hepatic cytochrome P450 1A2 and N-acetyltransferase-2. A primary detoxification pathway involves glutathione S-transferase A1 (GSTA1), which catalyzes the reduction of the carcinogenic N-acetoxy derivative back to the parent amine. Recently, we described a polymorphism in the GSTA1 proximal promoter; the variant (GSTA1\*B) allele significantly lowers enzyme expression. In a case-control study, GSTA1\*B/\*B genotype was associated with an increased risk of colorectal cancer, particularly among consumers of well-done meat. Dietary nitrosamines, which are bioactivated by CYP2A6, represent another potential etiologic factor for colorectal cancer. CYP2A6 converts the caffeine metabolite 1,7-dimethylxanthine (17X) to 1,7-dimethyluric acid (17U); we investigated CYP2A6 activity using the 17U/17X urinary metabolite ratio from case-control subjects who completed a caffeine phenotype assay. The

distribution of CYP2A6 activity was significantly different between CRCa cases and controls, with subjects in the medium and high activity groups having an increased risk (P for trend=0.001). GSTA1 genotype and CYP2A6 phenotype should be evaluated as markers of susceptibility to dietary carcinogens in future studies.

Takezaki, T., M. Inoue, et al. (2003). "Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption." *Nutr Cancer* **45**(2): 160-7.

N-3 polyunsaturated fatty acids in fish oil exhibit a variety of health benefits, and there is evidence that they can inhibit the development of human lung mucoepidermoid and other carcinomas. To examine the hypothesis that fish consumption reduces the risk of lung cancer, we conducted a population-based prospective study, following 5,885 residents for 14 yr. Person-years were used to calculate the relative risk (RR) by the Cox proportional hazards model, with adjustment for potential confounding factors. A total of 51 incident lung cancer cases were observed, and we found linearly decreasing RRs for lung cancer with increased frequency of consumption of fish and shellfish (RRs = 1.00, 0.99, and 0.32, P for trend = 0.003) but not with intake of dried/salted fish. Decreased RRs were apparent with both broiling and boiling cooking methods, but reduction with raw and deep-fried fish consumption was not statistically significant. We conclude that frequent fresh fish consumption, irrespective of the cooking method, may reduce the risk of lung cancer.

Trichopoulos, D., A. Tzonou, et al. (1990). "Diet and cancer: methodological complexities and case-control studies in Greece." *Prog Clin Biol Res* **346**: 45-53.

Some methodological difficulties of epidemiological studies exploring the role of diet in the etiology of human cancer are considered and suggested corrective approaches are discussed. The advantages and disadvantages of case-control studies in this field are critically examined. The results and implications of several such studies undertaken in Greece are reviewed.

Tseng, M., T. A. Sellers, et al. (2008). "Mediterranean diet and breast density in the Minnesota Breast Cancer Family Study." *Nutr Cancer* **60**(6): 703-9.

Mediterranean populations' lower breast cancer incidence has been attributed to a traditional Mediterranean diet, but few studies have quantified Mediterranean dietary pattern intake in relation to breast cancer. We examined the association of a Mediterranean diet scale (MDS) with mammographic

breast density as a surrogate marker for breast cancer risk. Participants completed a dietary questionnaire and provided screening mammograms for breast density assessment using a computer-assisted method. Among 1,286 women, MDS was not clearly associated with percent density in multivariate linear regression analyses. Because of previous work suggesting dietary effects limited to smokers, we conducted stratified analyses and found MDS and percent density to be significantly, inversely associated among current smokers ( $\beta = -1.68$ ,  $P = 0.002$ ) but not among nonsmokers ( $\beta = -0.08$ ,  $P = 0.72$ ;  $P$  for interaction = 0.008). Our results confirm a previous suggestion that selected dietary patterns may be protective primarily in the presence of procarcinogenic compounds such as those found in tobacco smoke.

Valdes-Ramos, R., N. W. Solomons, et al. (2001). "Can the degree of concordance with recommendations for a cancer prevention diet and lifestyle be assessed from existing survey information data?" *Am J Clin Nutr* 74(6): 848-51.

**BACKGROUND:** The World Cancer Research Fund convened an expert committee who analyzed the literature related to the causation of human cancers. Recommendations for preventing cancer through behavioral practices were formatted into a 14-point guideline. **OBJECTIVE:** We parsed the cancer prevention guidelines to determine to what extent relevant information on individual behavior could be assessed from conventional food-frequency questionnaires, which are being used in surveys conducted in developing countries. **DESIGN:** We examined a convenience sample of archival forms completed during 2 independent studies (a case-control and a field study) that used an adapted Willett food-frequency questionnaire that was translated into Spanish for use in Guatemala. **RESULTS:** All dietary related guidelines, except for salt, were evaluated by both questionnaires. Physical activity, food handling, and food preparation were not addressed by either of the questionnaires, although body mass index and dietary supplements were addressed in the case-control study and field-study questionnaires, respectively. **CONCLUSIONS:** Although concordance with some of the cancer prevention goals and guidelines can be evaluated from the existing questionnaires, adjustments and additions must be made with respect to salt and supplement use, physical activity, and food handling. Actual weight and height measurements are also needed, particularly in low-income populations.

Venkateswaran, V., A. Q. Haddad, et al. (2007). "Association of diet-induced hyperinsulinemia with

accelerated growth of prostate cancer (LNCaP) xenografts." *J Natl Cancer Inst* 99(23): 1793-800.

**BACKGROUND:** Prior research suggested that energy balance and fat intake influence prostate cancer progression, but the influence of dietary carbohydrate on prostate cancer progression has not been well characterized. We hypothesized that hyperinsulinemia resulting from high intake of refined carbohydrates would lead to more rapid growth of tumors in the murine LNCaP xenograft model of prostate cancer. **METHODS:** Athymic mice were injected subcutaneously with LNCaP human prostate cancer cells and, when tumors were palpable, were randomly assigned ( $n = 20$  per group) to high carbohydrate-high fat or low carbohydrate-high fat diets. Body weight and tumor volume were measured weekly. After 9 weeks, serum levels of insulin and insulin-like growth factor 1 (IGF-1) were measured by enzyme immunoassay. AKT activation and the levels of the insulin receptor in tumor cells were determined by immunoblotting. The in vitro growth response of LNCaP cells to serum from mice in the two treatment groups was measured based on tetrazolium compound reduction. All statistical tests were two-sided. **RESULTS:** After 9 weeks on the experimental diets, mice on the high carbohydrate-high fat diet were heavier (mean body weight of mice on the high carbohydrate-high fat diet = 34 g versus 29.1 g on the low carbohydrate-high fat diet, difference = 4.9 g, 95% CI = 3.8 to 6.0 g;  $P = .003$ ), experienced increased tumor growth (mean tumor volume in mice on high carbohydrate-high fat diet = 1695 versus 980 mm<sup>3</sup> on low carbohydrate-high fat diet, difference = 715 mm<sup>3</sup>, 95% CI = 608 to 822 mm<sup>3</sup>;  $P < .001$ ), and experienced a statistically significant increase in serum insulin and IGF-1 levels. Tumors from mice on the high carbohydrate-high fat diet had higher levels of activated AKT and modestly higher insulin receptor levels than tumors from mice on the low carbohydrate-high fat diet. Serum from mice on the high carbohydrate-high fat diet was more mitogenic for LNCaP cells in vitro than serum from mice fed the low carbohydrate-high fat diet. **CONCLUSION:** A diet high in refined carbohydrates is associated with increased tumor growth and with activation of signaling pathways distal to the insulin receptor in a murine model of prostate cancer.

Yeh, C. C., L. L. Hsieh, et al. (2005). "MS-920: DNA repair gene polymorphisms, diet and colorectal cancer risk in Taiwan." *Cancer Lett* 224(2): 279-88.

This hospital-based case-control study examined whether polymorphic DNA repair genes: XRCC1 Arg399Gln, XRCC3 Thr241Met and XPD Lys751Gln, play a role in the susceptibility to colorectal cancer. We genotyped these polymorphisms

for 727 newly diagnosed colorectal adenocarcinoma cases and 736 age and sex matched healthy controls in Taiwan. Although the colorectal cancer risk was not significantly associated with these genes, the risk was significantly elevated in younger subjects (< or =60 years) with the XRCC1 399Arg/Arg genotype compared to those with XRCC1 399Gln allele (OR=1.46, 95% CI=1.06-2.99, P=0.02). The stratified analysis showed that XRCC3 interacted with meat consumption (P for interaction=0.02), but was limited to the low meat consumption (OR=2.34, 95% CI=1.28-4.29). Our results suggest that the XRCC1 Arg399Gln polymorphism may contribute to the risk of early-onset colorectal cancer and the XRCC3 Thr241Met polymorphism may modify the risk for meat-associated colorectal cancer.

Yeung, K. S., G. E. McKeown-Eyssen, et al. (1991). "Comparisons of diet and biochemical characteristics of stool and urine between Chinese populations with low and high colorectal cancer rates." *J Natl Cancer Inst* **83**(1): 46-50.

In an investigation of the roles of diet and stool biochemistry in human colorectal carcinogenesis, 24-hour food, urine, and stool samples were collected from randomly selected participants from two populations with a fourfold difference in colorectal cancer risk: Chinese in Sha Giao, People's Republic of China (low risk), and Chinese-Americans of similar ages in San Francisco County, Calif, in the United States (high risk). The findings supported the hypotheses that colorectal cancer risk is increased by the consumption of high-fat, high-protein, and low-carbohydrate diets and is associated with high levels of cholesterol in stool as well as increased daily outputs of 3-methyl-histidine and malonaldehyde in urine. However, risk does not increase with low stool bulk and low total stool fibers.

Z'Graggen, K., A. L. Warshaw, et al. (2001). "Promoting effect of a high-fat/high-protein diet in DMBA-induced ductal pancreatic cancer in rats." *Ann Surg* **233**(5): 688-95.

**OBJECTIVE:** To investigate whether a high-fat/high-protein diet (HFPD) acts as a promoter of the natural course of cancer growth in the 7,12-dimethylbenzanthracene (DMBA)-induced ductal pancreatic cancer model in rats. **SUMMARY BACKGROUND DATA:** DMBA implantation to the rat pancreas induces ductal adenocarcinoma. Information regarding the effects of diet and the presence of K-ras mutation in this model is not available. **METHODS:** Rats were randomly assigned to regular rat chow or a diet with a 30% content in fat and protein (HFPD). The presentation of cancer, the histologic spectrum of neoplasia at 1 and 9 months,

and the prevalence of cancer in relation to diet were assessed. Histologic specimens comprising normal ducts, hyperplasia, dysplasia/carcinoma in situ, or carcinoma were designated by a pathologist and microdissected. Genomic DNA was extracted, and K-ras and H-ras gene mutations were determined by a mutant-enriched polymerase chain reaction assay and direct sequencing. **RESULTS:** Rats fed HFPD increased their weight significantly compared with controls. DMBA induced characteristic stages of neoplasia at the implant site but not elsewhere. Macroscopic cancers of the pancreatic head presented regularly with common bile duct and gastric outlet obstruction. The prevalence of K-ras mutations was proportional to the degree of epithelial abnormality. K-ras mutations were significantly more frequent in cancer than in normal and hyperplastic ducts. H-ras mutations were not found. At 1 month in the HFPD-fed rats, the prevalence of cancer (16%) and dysplasia (16%) was not significantly different from the prevalence of cancer (29%) and dysplasia (8%) in the chow-fed rats. At 9 months the prevalence of cancer in the HFPD-fed rats increased to 29%, whereas that in the chow-fed rats decreased to 17%. The combined prevalence of cancer and dysplasia at 9 months in the HFPD-fed rats (34%) significantly exceeded that in the chow-fed rats. **CONCLUSIONS:** DMBA induces characteristic stages of neoplasia in the evolution of ductal pancreatic cancer in rats. K-ras mutations occur progressively in the ladder of oncogenesis, as in human pancreatic neoplasms. The addition of a diet with a high fat and protein content acts as a promoter of carcinogenesis, possibly by interfering with repair mechanisms and natural regression of early lesions.

Zhou, W., P. Mukherjee, et al. (2007). "The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer." *Nutr Metab (Lond)* **4**: 5.

**BACKGROUND:** Malignant brain cancer persists as a major disease of morbidity and mortality in adults and is the second leading cause of cancer death in children. Many current therapies for malignant brain tumors fail to provide long-term management because they ineffectively target tumor cells while negatively impacting the health and vitality of normal brain cells. In contrast to brain tumor cells, which lack metabolic flexibility and are largely dependent on glucose for growth and survival, normal brain cells can metabolize both glucose and ketone bodies for energy. This study evaluated the efficacy of KetoCal, a new nutritionally balanced high fat/low carbohydrate ketogenic diet for children with epilepsy, on the growth and vascularity of a malignant mouse astrocytoma (CT-2A) and a human malignant glioma (U87-MG). **METHODS:** Adult mice were implanted

orthotopically with the malignant brain tumors and KetoCal was administered to the mice in either unrestricted amounts or in restricted amounts to reduce total caloric intake according to the manufacturers recommendation for children with refractory epilepsy. The effects KetoCal on tumor growth, vascularity, and mouse survival were compared with that of an unrestricted high carbohydrate standard diet. RESULTS: KetoCal administered in restricted amounts significantly decreased the intracerebral growth of the CT-2A and U87-MG tumors by about 65% and 35%, respectively, and significantly enhanced health and survival relative to that of the control groups receiving the standard low fat/high carbohydrate diet. The restricted KetoCal diet reduced plasma glucose levels while elevating plasma ketone body (beta-hydroxybutyrate) levels. Tumor microvessel density was less in the calorically restricted KetoCal groups than in the calorically unrestricted control groups. Moreover, gene expression for the mitochondrial enzymes, beta-hydroxybutyrate dehydrogenase and succinyl-CoA: 3-ketoacid CoA transferase, was lower in the tumors than in the contralateral normal brain suggesting that these brain tumors have reduced ability to metabolize ketone bodies for energy. CONCLUSION: The results indicate that KetoCal has anti-tumor and anti-angiogenic effects in experimental mouse and human brain tumors when administered in restricted amounts. The therapeutic effect of KetoCal for brain cancer management was due largely to the reduction of total caloric content, which reduces circulating glucose required for rapid tumor growth. A dependency on glucose for energy together with defects in ketone body metabolism largely account for why the brain tumors grow minimally on either a ketogenic-restricted diet or on a standard-restricted diet. Genes for ketone body metabolism should be useful for screening brain tumors that could be targeted with calorically restricted high fat/low carbohydrate ketogenic diets. This preclinical study indicates that restricted KetoCal is a safe and effective diet therapy and should be considered as an alternative therapeutic option for malignant brain cancer.

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