Diet and Cancer Biology Research Literatures

Mark Herbert, PhD

39-06 Main Street, Flushing, Queens, New York 11354, USA, ma8080@gmail.com

Abstract: 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. This article introduces recent research reports as references in the related studies.
[Mark H. **Diet and Cancer Biology Research Literatures.** *Rep Opinion* 2019;11(7):70-106]. ISSN 1553-9873 (print); ISSN 2375-7205 (online). http://www.sciencepub.net/report. 12. doi:10.7537/marsroj110719.12.

Key words: diet; cancer; life; research; literature; cell

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. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Andersen, V., et al. (2013). "Interactions between diet, lifestyle and IL10, IL1B, and PTGS2/COX-2 gene polymorphisms in relation to risk of colorectal cancer in a prospective Danish case-cohort study." PLoS One **8**(10): e78366.

BACKGROUND & AIMS: Diet contributes to colorectal cancer development and may be potentially modified. We wanted to identify the biological mechanisms underlying colorectal carcinogenesis by assessment of diet-gene interactions. METHODS: The polymorphisms IL10 C-592A (rs1800872), C-rs3024505-T, IL1b C-3737T (rs4848306), G-1464C (rs1143623), T-31C (rs1143627) and PTGS2 (encoding COX-2) A-1195G (rs689466), G-765C (rs20417), and T8473C (rs5275) were assessed in relation to risk of colorectal cancer (CRC) and interaction with diet (red meat, fish, fibre, cereals, fruit and vegetables) and lifestyle (non-steroid-anti-inflammatory drug use and smoking status) was assessed in a nested case-cohort study of nine hundred and seventy CRC cases and 1789 randomly selected participants from a prospective study of 57,053 persons. RESULTS: IL1b C-3737T, G-1464C and PTGS2 T8473C variant genotypes were associated with risk of CRC compared to the homozygous wildtype genotype (IRR=0.81, 95%CI: 0.68-0.97, p=0.02, and IRR=1.22, 95%CI: 1.04-1.44, p=0.02, IRR=0.75, 95%CI: 0.57-0.99, p=0.04, respectively). Interactions were found between diet and IL10 rs3024505 (P-value for interaction (P (int)); meat=0.04, fish=0.007, fibre=0.0008, vegetables=0.0005), C-592A (P (int); fibre=0.025), IL1b C-3737T (Pint; vegetables=0.030, NSAID use=0.040) and PTGS2 genotypes G-765C (P (int); meat=0.006, fibre=0.0003, fruit 0.004), and T8473C (P (int); meat 0.049, fruit=0.03) and A-1195G (P (int); meat 0.038, fibre 0.040, fruit=0.059, vegetables=0.025, and current smoking=0.046). CONCLUSIONS: Genetically determined low COX-2 and high IL-1beta activity were associated with increased risk of CRC in this northern Caucasian cohort. Furthermore, interactions were found between IL10, IL1b, and PTGS2 and diet and lifestyle factors in relation to CRC. The present study demonstrates that gene-environment interactions may identify genes and environmental factors involved in colorectal carcinogenesis.

Andersen, V., et al. (2013). "Systematic review: diet-gene interactions and the risk of colorectal cancer." Aliment Pharmacol Ther **37**(4): 383-391.

BACKGROUND: Diet contributes significantly to colorectal cancer (CRC) aetiology and may be potentially modifiable. AIM: To review diet-gene interactions, aiming to further the understanding of the underlying biological pathways in CRC development. METHODS: The PubMed and Medline were systematically searched for prospective studies in relation to diet, colorectal cancer and genetics. RESULTS: In a meta-analysis, no interaction between NAT1 phenotypes and meat intake in relation to risk of CRC was found (P-value for interaction 0.95). We found a trend towards interaction between NAT2

phenotypes and meat intake in relation to risk of CRC. High meat intake was not associated with risk of CRC among carriers of the slow NAT2 phenotype, whereas NAT2 fast acetylators with high meat intake were at increased risk of CRC (OR = 1.25; 95% confidence interval (CI): 0.92-2.01) compared with slow acetylators with low meat intake (reference), P-value for interaction = 0.07. Low meat intake in the studied populations may influence the result. Interactions between meat, cruciferous vegetables, fibres, calcium, vitamins, and alcohol and ABCB1, NFKB1, GSTM1, GSTT1, CCND1, VDR, MGTM, IL10 and PPARG are suggested. CONCLUSIONS: A number of interactions between genetic variation and diet are suggested, but the findings need replication in independent, prospective, and well-characterised cohorts before conclusions regarding the underlying biological mechanisms can be reached. When the above criteria are met, studies on diet-gene interactions may contribute valuable insight into the biological mechanisms underlying the role of various dietary items in colorectal carcinogenesis.

Andersen, V., et al. (2015). "No association between HMOX1 and risk of colorectal cancer and no interaction with diet and lifestyle factors in a prospective Danish case-cohort study." Int J Mol Sci **16**(1): 1375-1384.

Red meat is a risk factor for colorectal cancer (CRC). We wanted to evaluate whether a functional polymorphism in the HMOX1 gene encoding heme oxygenase modifies risk of CRC or interacts with diet or lifestyle factors because this would identify heme or heme iron as a risk factor of CRC. The HMOX1 A-413T (rs2071746) was assessed in relation to risk of colorectal cancer (CRC) and interactions with diet (red meat, fish, fiber, cereals, fruit and vegetables) and lifestyle (use of non-steroidal anti-inflammatory drug and smoking status) were assessed in a case-cohort study of 928 CRC cases and a comparison group of 1726 randomly selected participants from a prospective study of 57,053 persons. No association between HMOX1 A-413T and CRC risk was found (TT vs. AA + TA; IRR = 1.15, 95% CI: 0.98-1.36, p = 0.10 for the adjusted estimate). No interactions were found between diet or lifestyle and HMOX1 A-413T. HMOX1 A-413T was not associated with CRC risk and no interactions with diet or lifestyle were identified in this large, prospective cohort with high meat intake. The results reproduced the previous findings from the same cohort and did not support a link between heme or heme iron and colorectal cancer. These results should be sought and replicated in other well-characterized cohorts with high meat intake.

Andrade Fde, O., et al. (2015). "Lipidomic fatty acid profile and global gene expression pattern in mammary gland of rats that were exposed to lard-based high fat diet during fetal and lactation periods associated to breast cancer risk in adulthood." Chem Biol Interact **239**: 118-128.

The persistent effects of animal fat consumption during pregnancy and nursing on the programming of breast cancer risk among female offspring were studied here. We have previously found that female offspring of rat dams that consumed a lard-based high-fat (HF) diet (60% fat-derived energy) during pregnancy, or during pregnancy and lactation, were at a reduced risk of developing mammary cancer. To better understand the unexpected protective effects of early life lard exposure, we have applied lipidomics and nutrigenomics approaches to investigate the fatty acid profile and global gene expression patterns in the mammary tissue of the female offspring. Consumption of this HF diet during gestation had few effects on the mammary tissue fatty acids profile of young adult offspring, while exposure from gestation throughout nursing promoted significant alterations in the fatty acids profile. Major differences were related to decreases in saturated fatty acids (SFA) and increases in omega-6 polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs) and conjugated linolenic acid (CLA) concentrations. In addition several differences in gene expression patterns by microarray analysis between the control and in utero or in utero and during lactation HF exposed offspring were identified. Differential dependency network (DDN) analysis indicated that many of the genes exhibited unique connections to other genes only in the HF offspring. These unique connections included Hrh1-Ythdf1 and Repin1-Elavl2 in the in utero HF offspring, and Rnf213-Htr3b and Klf5-Chrna4 in the in utero and lactation HF offspring, compared with the control offspring. We conclude that an exposure to a lard-based HF diet during early life changes the fatty acid profile and transcriptional network in mammary gland in young adult rats, and these changes appear to be consistent with reduced mammary cancer risk observed in our previous study.

Arkan, M. C. (2017). "The intricate connection between diet, microbiota, and cancer: A jigsaw puzzle." Semin Immunol **32**: 35-42.

The microbial community has a decisive role in determining our health and disease susceptibility. Presumably, this is closely associated with the complex community network of bacteria, fungi, archaea and viruses that reside our guts. This dynamic ecosystem exists in a symbiotic relationship with its host and plays a fundamental role in the hosts' physiological functions. The microbial community is

highly personalized and therefore exhibits a high degree of inter-individual variability, which is dependent on host specifics such as genetic background, physiology and lifestyle. Although the gut microbiota is shaped early on during birth, there are several factors that affect the composition of microbiota during childhood and adulthood. Among them diet appears to be a consistent and prominent one. The metabolic activity of bacteria affects food digestion, absorption, energy production, and immunity. Thus, definition of the microbiota composition and functional profiles in response to a particular diet may lead to critical information on the direct and indirect role/use of the bacterial community during health and disease. In this review, I discuss gut microbiota and its potential link to cancer with specific emphasis on metabolism and diet.

Asgharpour, A., et al. (2016). "A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer." J Hepatol **65**(3): 579-588.

BACKGROUND & AIMS: The lack of a preclinical model of progressive non-alcoholic steatohepatitis (NASH) that recapitulates human disease is a barrier to therapeutic development. METHODS: A stable isogenic cross between C57BL/6J (B6) and 129S1/SvImJ (S129) mice were fed a high fat diet with ad libitum consumption of glucose and fructose in physiologically relevant concentrations and compared to mice fed a chow diet and also to both parent strains. RESULTS: Following initiation of the obesogenic diet, B6/129 mice developed obesity, insulin resistance, hypertriglyceridemia and increased LDL-cholesterol. They sequentially also developed steatosis (4-8weeks), steatohepatitis (16-24weeks), progressive fibrosis (16weeks onwards) and spontaneous hepatocellular cancer (HCC). There was a strong concordance between the pattern of pathway activation at a transcriptomic level between humans and mice with similar histological phenotypes (FDR 0.02 for early and 0.08 for late time points). Lipogenic, inflammatory and apoptotic signaling pathways activated in human NASH were also activated in these mice. The HCC gene signature resembled the S1 and S2 human subclasses of HCC (FDR 0.01 for both). Only the B6/129 mouse but not the parent strains recapitulated all of these aspects of human NAFLD. CONCLUSIONS: We here describe a diet-induced animal model of non-alcoholic fatty liver disease (DIAMOND) that recapitulates the key physiological, metabolic, histologic, transcriptomic and cell-signaling changes seen in humans with progressive NASH. LAY SUMMARY: We have developed a diet-induced mouse model of non-alcoholic steatohepatitis (NASH) and hepatic cancers in a cross between two mouse strains (129S1/SvImJ and C57Bl/6J). This model mimics all the physiological, metabolic, histological, transcriptomic gene signature and clinical endpoints of human NASH and can facilitate preclinical development of therapeutic targets for NASH.

Brandt, J., et al. (2018). "Thyroid-associated genetic polymorphisms in relation to breast cancer risk in the Malmo Diet and Cancer Study." Int J Cancer **142**(7): 1309-1321.

Previous studies have suggested that thyroid function is associated with breast cancer risk, which could have an important clinical impact, as one in eight women will develop a thyroid disorder during her lifetime. However, the underlying pathomechanism behind the association is still unknown. We used the Malmo Diet and Cancer Study (a population-based prospective study consisting of 17,035 women) to examine 17 single nucleotide polymorphisms (SNPs) previously related to levels of free thyroxine (free T4) and thyroid peroxidase antibodies (TPO-Ab) as potential genetic risk factors for breast cancer. A baseline examination including free T4 and TPO-Ab levels was conducted at the time of inclusion. Genotyping was performed on 901 breast cancer patients and 3335 controls. Odds ratios (95% confidence intervals) for high free T4, TPO-Ab positivity, and breast cancer were calculated by logistic regression and adjusted for confounders. We identified one free T4-related SNP (rs2235544, D101 gene) that was significantly associated with both free T4 level and breast cancer risk. There was a suggested association between rs11675434 (TPO gene) and TPO-Ab level, and TPO-Ab-related rs11675434 (TPO), rs3094228 (HCP5), rs1033662 (no registered gene), and rs301806 (RERE) were associated with breast cancer risk. There was an indicated interaction between rs6485050 (no registered gene) and free T4 level in regards to breast cancer risk. This is the first study to suggest an association between thyroid-related SNPs and breast cancer risk. All SNPs have a biological plausibility of being associated with breast cancer risk, and may contribute to the genetic predisposition to breast cancer.

Bultman, S. J. (2017). "Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer." Mol Nutr Food Res **61**(1).

Despite the success of colonoscopy screening, colorectal cancer (CRC) remains one of the most common and deadly cancers, and CRC incidence is rising in some countries where screening is not routine and populations have recently switched from traditional diets to western diets. Diet and energy balance influence CRC by multiple mechanisms. They modulate the composition and function of gut

microbiota, which have a prodigious metabolic capacity and can produce oncometabolites or tumor-suppressive metabolites depending, in part, on which dietary factors and digestive components are present in the GI tract. Gut microbiota also have a profound effect on immune cells in the lamina propria, which influences inflammation and subsequently CRC. Nutrient availability, which is an outcome of diet and energy balance, determines the abundance of certain energy metabolites that are essential co-factors for epigenetic enzymes and therefore impinges upon epigenetic regulation of gene expression. Aberrant epigenetic marks accumulate during CRC, and epimutations that are selected for drive tumorigenesis by causing transcriptome profiles to diverge from the cell of origin. In some instances, the above mechanisms are intertwined as exemplified by dietary fiber being metabolized by colonic bacteria into butyrate, which is both a short-chain fatty acid (SCFA) and a histone deacetylase (HDAC) inhibitor that epigenetically upregulates tumor-suppressor genes in CRC cells and anti-inflammatory genes in immune cells.

Carter, C. A. (2000). "Protein kinase C as a drug target: implications for drug or diet prevention and treatment of cancer." Curr Drug Targets **1**(2): 163-183.

Protein kinase C (PKC) isoforms are serine/threonine kinases involved in signal transduction pathways that govern a wide range of physiological processes including differentiation, proliferation, gene expression, brain function, membrane transport and the organization of cytoskeletal and extracellular matrix proteins. PKC isoforms are often overexpressed in disease states such as cancer. In this review, PKC in a variety of cancers is discussed along with some specific cell biological mechanisms by which PKC exerts its function (s). The PKC family consists of several isoforms comprising three groups: classical, novel and atypical. Although PKC has been investigated for around 2 decades, only recently has the specific function of each isoform started to be elucidated and the isoforms evaluated for use as targets of drug action. Phorbol esters such as the tumor-promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) or diacylglycerol (DAG) activate classical and novel PKC isoforms. Naturally occurring retinoids, antisense oligonucleotides against specific PKC isoforms and specific PKC inhibitors can block this activation. Beta carotene and retinoid derivatives act as anticarcinogenic agents and can antagonize some of the biological actions of phorbol esters and oxidants. Another important area of investigation is the use of antisense oligonucleotides to inhibit specific PKC isoforms. These compounds have proven effective in reducing specific types of cancer in rodents and humans and are currently used in clinical trials. This review examines PKC isoforms as a target of drug action with special emphasis on their use in cancer therapy.

Cartier, N., et al. (1994). "[Creation of diet-dependent cancer models in transgenic animals]." Bull Acad Natl Med **178**(1): 23-32; discussion 32-24.

We have created transgenic mice lines in which SV40 T and c-myc expression was controlled by the L-pyruvate kinase gene regulatory region which is responsible for hepatic and pancreatic expression specificity, and strong dependence of this expression upon the carbohydrate composition of the diet. Models of hepatoma and endocrine pancreatic tumors have been obtained. Both tumors were dependent upon the diet, since carbohydrates strongly increased frequency and precocity of both hepatic and pancreatic carcinomas.

Cartier, N., et al. (1994). "[The creation of diet-dependent cancer models using transgenesis in animals]." Ann Gastroenterol Hepatol (Paris) **30**(4): 175-179; discussion 180.

We have created transgenic mice lines in which SV40 T and c-myc expression was controlled by the L-pyruvate kinase gene regulatory region which is responsible for hepatic and pancreatic expression specificity, and strong dependence of this expression upon the carbohydrate composition of the diet. Models of hepatoma and endocrine pancreatic tumors have been obtained. Both tumors were dependent upon the diet, since carbohydrates strongly increased frequency and precocity of both hepatic and pancreatic carcinomas.

Chan, J. M., et al. (2005). "Role of diet in prostate cancer development and progression." J Clin Oncol **23**(32): 8152-8160.

Increasing evidence supports the important role of nutrition in cancer prevention, including prevention of prostate cancer. In this review, we summarize data for some of the most consistently observed dietary associations for prostate cancer incidence, briefly consider possible postdiagnostic effects of nutrition on prostate cancer progression/survival, discuss new but limited data on diet-gene interactions, and comment on current areas of controversy for future research focus. Potential protective dietary elements include tomatoes/lycopene, other carotenoids, cruciferous vegetables, vitamin E, selenium, fish/marine omega-3 fatty acids, soy, isoflavones and polyphenols; whereas milk, dairy, calcium, zinc at high doses, saturated fat, grilled meats, and heterocyclic amines may increase risk. It is important to note that randomized clinical trial data exist only for vitamin E, calcium, beta-

carotene, and selenium (all of which suggest inverse or no association). Several genes, such as MnSOD, XRCC1, and GST, may modify the association of specific nutrients and foods with prostate cancer risk; and further research is warranted to confirm these initial observed relationships. Until further clinical trial data are available on specific supplements and prostate cancer prevention, it would be prudent to emphasize a diet consisting of a wide variety of plant-based foods and fish; this is similar to what is recommended (and what is more well established) for the primary prevention of heart disease.

Chen, J. and X. Xu (2010). "Diet, epigenetic, and cancer prevention." Adv Genet **71**: 237-255.

Disruption of the epigenome has been a hallmark of human cancers and has been linked with tumor pathogenesis and progression. Since epigenetic changes can be reversed in principle, studies have been carried out to identify modifiable (such as diet and lifestyle) factors, which possess epigenetic property, in hope for developing epigenetically based prevention/intervention strategies. The goal is to achieve some degree of epigenetic reprogramming, which would maintain normal gene expression status and reverse tumorigenesis through chemoprevention or lifestyle intervention such as diet modification. The ability of dietary compounds to act epigenetically in cancer cells has been studied and evidence continues to surface for constituents in food and dietary supplements to influence the epigenome and ultimately individual's risk of developing cancer. In this chapter, we summarized the existing data, both from animal and human studies, on the capacity of natural food products to influence three key epigenetic processes: DNA methylation, histone modification, and microRNA expression. As discussed in the perspective, while diet-based intervention that targets epigenetic pathways is promising, significant challenges remain in translating these scientific findings into clinical or public health practices in the context of cancer prevention.

Chen, K., et al. (2006). "[A case-control study on the association between the genetic polymorphism of sulfotransferase 1A1, diet and susceptibility of colorectal cancer]." Zhonghua Zhong Liu Za Zhi **28**(9): 670-673.

OBJECTIVE: To investigate the relationship between sulfotransferase 1Al polymorphism, diet and colorectal cancer susceptibility. METHODS: A case-control study of 140 cancers and 343 health controls was conducted to investigate the role of sulfotransferase 1A1 polymorphism and meat consumption in colorectal carcinogenesis. Genotypes of sulfotransferase 1A1 polymorphism were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). RESULTS: There was no significant difference in allele frequency of SULT1A1 between the control and cancer patient populations. After adjustment for age, sex, smoking and history of diseases, red meat and well-done meat intake showed no significant association with colorectal cancer. Consumption of red meat more than 5 kg per year combined with SULT1Al slow sulfation (Arg/His and His/His) had a statistically significant association with the risk of rectal cancer (OR = 3.78; 95% CI: 1.08 - 13. 20) compared to that consumed red meat less than 5 kg per year with fast sulfation (Arg/Arg). CONCLUSION: This study suggests that SULT1A1 slow sulfation combined with higher intake of red meat may be associated with an elevated risk of rectal cancer.

Chen, Y. J., et al. (2016). "Dietary Broccoli Lessens Development of Fatty Liver and Liver Cancer in Mice Given Diethylnitrosamine and Fed a Western or Control Diet." J Nutr **146**(3): 542-550.

BACKGROUND: The high-fat and high-sugar Westernized diet that is popular worldwide is associated with increased body fat accumulation, which has been related to the development of nonalcoholic fatty liver disease (NAFLD). Without treatment, NAFLD may progress to hepatocellular carcinoma (HCC), a cancer with a high mortality rate. The consumption of broccoli in the United States has greatly increased in the last 2 decades. Epidemiologic studies show that incorporating brassica vegetables into the daily diet lowers the risk of several cancers, although, to our knowledge, this is the first study to evaluate HCC prevention through dietary broccoli. OBJECTIVE: We aimed to determine the impact of dietary broccoli on hepatic lipid metabolism and the progression of NAFLD to HCC. Our hypothesis was that broccoli decreases both hepatic lipidosis and the development of HCC in a mouse model of Western diet-enhanced liver cancer. METHODS: Adult 5-wk-old male B6C3F1 mice received a control diet (AIN-93M) or a Western diet (high in lard and sucrose, 19% and 31%, wt:wt, respectively), with or without freeze-dried broccoli (10%, wt:wt). Starting the following week, mice were treated once per week with diethylnitrosamine (DEN; 45 mg/kg body weight intraperitoneally at ages 6, 7, 8, 10, 11, and 12 wk). Hepatic gene expression, lipidosis, and tumor outcomes were analyzed 6 mo later, when mice were 9 mo old. RESULTS: Mice receiving broccoli exhibited lower hepatic triglycerides ($P < 0.001$) and NAFLD scores ($P < 0.0001$), decreased plasma alanine aminotransferase ($P < 0.0001$), suppressed activation of hepatic CD68(+) macrophages ($P < 0.0001$), and slowed initiation and progression of hepatic neoplasm.

Hepatic Cd36 was downregulated by broccoli feeding (P = 0.006), whereas microsomal triglyceride transfer protein was upregulated (P = 0.045), supporting the finding that dietary broccoli decreased hepatic triglycerides. CONCLUSION: Long-term consumption of whole broccoli countered both NAFLD development enhanced by a Western diet and hepatic tumorigenesis induced by DEN in male B6C3F1 mice.

Choi, Y., et al. (2013). "Induction of olfaction and cancer-related genes in mice fed a high-fat diet as assessed through the mode-of-action by network identification analysis." PLoS One **8**(3): e56610.

The pathophysiological mechanisms underlying the development of obesity and metabolic diseases are not well understood. To gain more insight into the genetic mediators associated with the onset and progression of diet-induced obesity and metabolic diseases, we studied the molecular changes in response to a high-fat diet (HFD) by using a mode-of-action by network identification (MNI) analysis. Oligo DNA microarray analysis was performed on visceral and subcutaneous adipose tissues and muscles of male C57BL/6N mice fed a normal diet or HFD for 2, 4, 8, and 12 weeks. Each of these data was queried against the MNI algorithm, and the lists of top 5 highly ranked genes and gene ontology (GO)-annotated pathways that were significantly overrepresented among the 100 highest ranked genes at each time point in the 3 different tissues of mice fed the HFD were considered in the present study. The 40 highest ranked genes identified by MNI analysis at each time point in the different tissues of mice with diet-induced obesity were subjected to clustering based on their temporal patterns. On the basis of the above-mentioned results, we investigated the sequential induction of distinct olfactory receptors and the stimulation of cancer-related genes during the development of obesity in both adipose tissues and muscles. The top 5 genes recognized using the MNI analysis at each time point and gene cluster identified based on their temporal patterns in the peripheral tissues of mice provided novel and often surprising insights into the potential genetic mediators for obesity progression.

Corella, D., et al. (2018). "Effects of the Ser326Cys Polymorphism in the DNA Repair OGG1 Gene on Cancer, Cardiovascular, and All-Cause Mortality in the PREDIMED Study: Modulation by Diet." J Acad Nutr Diet **118**(4): 589-605.

BACKGROUND: Oxidatively induced DNA damage, an important factor in cancer etiology, is repaired by oxyguanine glycosylase 1 (OGG1). The lower repair capacity genotype (homozygote Cys326Cys) in the OGG1-rs1052133 (Ser326Cys) polymorphism has been associated with cancer risk. However, no information is available in relation to cancer mortality, other causes of death, and modulation by diet. OBJECTIVE: Our aim was to evaluate the association of the OGG1-rs1052133 with total, cancer, and cardiovascular disease (CVD) mortality and to analyze its modulation by the Mediterranean diet, focusing especially on total vegetable intake as one of the main characteristics of this diet. DESIGN: Secondary analysis in the PREDIMED (Prevencion con Dieta Mediterranea) trial is a randomized, controlled trial conducted in Spain from 2003 to 2010. PARTICIPANTS/SETTING: Study participants (n=7,170) were at high risk for CVD and were aged 55 to 80 years. INTERVENTION: Participants were randomly allocated to two groups with a Mediterranean diet intervention or a control diet. Vegetable intake was measured at baseline. MAIN OUTCOME MEASURES: Main outcomes were all-cause, cancer, and CVD mortality after a median follow-up of 4.8 years. STATISTICAL ANALYSES: Multivariable-adjusted Cox regression models were fitted. RESULTS: Three hundred eighteen deaths were detected (cancer, n=127; CVD, n=81; and other, n=110). Cys326Cys individuals (prevalence 4.2%) presented higher total mortality rates than Ser326-carriers (P=0.009). The multivariable-adjusted hazard ratio for Cys326Cys vs Ser326-carriers was 1.69 (95% CI 1.09 to 2.62; P=0.018). This association was greater for CVD mortality (P=0.001). No relationship was detected for cancer mortality in the whole population (hazard ratio 1.07; 95% CI 0.47 to 2.45; P=0.867), but a significant age interaction (P=0.048) was observed, as Cys326Cys was associated with cancer mortality in participants <66.5 years (P=0.029). Recessive effects limited our ability to investigate Cys326Cysxdiet interactions for cancer mortality. No statistically significant interactions for total or CVD mortality were found for the Mediterranean diet intervention. However, significant protective interactions for CVD mortality were found for vegetable intake (hazard ratio interaction per standard deviation 0.42; 95% CI 0.18 to 0.98; P=0.046). CONCLUSIONS: In this population, the Cys326Cys-OGG1 genotype was associated with all-cause mortality, mainly CVD instead of cancer mortality. Additional studies are needed to provide further evidence on its dietary modulation.

Curtin, K., et al. (2004). "MTHFR C677T and A1298C polymorphisms: diet, estrogen, and risk of colon cancer." Cancer Epidemiol Biomarkers Prev **13**(2): 285-292.

5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism, diverting metabolites toward methylation reactions or nucleotide synthesis. Using data from an incident case-

control study (1608 cases and 1972 controls) we investigated two polymorphisms in the MTHFR gene, C677T and A1298C, and their associations with risk of colon cancer. All of the combined genotypes were evaluated separately, and the 1298AA/677CC (wild-type/wild-type) group was considered the reference group. Among both men and women, the 677TT/1298AA (variant/wild-type) genotype was associated with a small reduction in risk [men: odds ratio (OR), 0.7, 95% confidence interval (CI), 0.5-1.0; women: OR, 0.8, 95% CI, 0.5-1.2]. However, the 677CC/1298CC (wild-type/variant) genotype was associated with a statistically significant lower risk among women (OR, 0.6; 95% CI, 0.4-0.9) but not men. When the polymorphisms were considered individually, for A1298C a significant risk reduction associated with the homozygous variant CC genotype was seen among women only (OR, 0.6; 95% CI, 0.5-0.9), and nonstatistically significant reduced risks were observed for the variant 677 TT genotypes among both men and women. Stratification by nutrient intakes showed inverse associations with higher intakes of folate, vitamin B (2), B (6), B (12), and methionine among women with the MTHFR 677CC/1298AA genotypes, but not those with 677TT/1298AA. We observed opposite risk trends for both MTHFR variants, depending on whether women used hormone-replacement therapy or not (P for interaction = <.01). In summary, this study supports recent findings that the MTHFR A1298C polymorphism may be a predictor of colon cancer risk and have functional relevance. The possible interaction with hormone-replacement therapy warrants additional investigation.

Day, S. D., et al. (2013). "Linking inflammation to tumorigenesis in a mouse model of high-fat-diet-enhanced colon cancer." Cytokine **64**(1): 454-462.

Many observational epidemiologic studies suggest an association between high-fat-diet (HFD) and colon cancer risk. However, the lack of controlled experimental studies that examine this relationship and the mechanisms involved weaken the basis for inferring a causal relationship. Inflammation plays a role in colon cancer progression and HFDs have been reported to increase inflammation; however, the inflammatory effects of HFD in colon cancer have yet to be firmly established. We examined the effects of a novel HFD that closely mimics the standard American diet (12% and 40% of total caloric intake from saturated fat and total fat, respectively) on macrophage markers and inflammatory mediators in a mouse model of intestinal tumorigenesis and relate this to polyp characteristics as well as measures of adiposity. Male Apc (Min/+) mice (7-8/group) were fed a Control Diet (Con) or novel high-fat-diet (HFD) from 4 to 12weeks of age. Body weight and body composition were measured weekly and monthly, respectively. Intestinal tissue was analyzed for polyp burden (number and size). Gene expression of macrophage markers and inflammatory mediators were examined in the adipose tissue and polyps. The HFD increased the expression of macrophage markers and inflammatory mediators in the adipose tissue (F4/80, CD11c, TLR-4 and MCP-1) and tumor microenvironment (IL-12, MCP-1, IL-6 and TNF-alpha). As expected, the HFD increased body weight, body fat percent, fat mass and blood glucose (P<0.05), and was associated with an increase in the number of large polyps (P<0.05) but not total polyps. In summary, consumption of a HFD, similar in macronutrient composition to the standard American diet, altered the expression of macrophage phenotypic markers and inflammatory mediators in adipose tissue and intestinal polyps and this was associated with increased tumorigenesis.

de Oliveira Andrade, F., et al. (2014). "Exposure to lard-based high-fat diet during fetal and lactation periods modifies breast cancer susceptibility in adulthood in rats." J Nutr Biochem **25**(6): 613-622.

The present study investigated whether early life exposure to high levels of animal fat increases breast cancer risk in adulthood in rats. Dams consumed a lard-based high-fat (HF) diet (60% fat-derived energy) or an AIN93G control diet (16% fat-derived energy) during gestation or gestation and lactation. Their 7-week-old female offspring were exposed to 7,12-dimethyl-benzo [a]anthracene to induce mammary tumors. Pregnant dams consuming an HF diet had higher circulating leptin levels than pregnant control dams. However, compared to the control offspring, significantly lower susceptibility to mammary cancer development was observed in the offspring of dams fed an HF diet during pregnancy (lower tumor incidence, multiplicity and weight), or pregnancy and lactation (lower tumor multiplicity only). Mammary epithelial elongation, cell proliferation (Ki67) and expression of NFkappaB p65 were significantly lower and p21 expression and global H3K9me3 levels were higher in the mammary glands of rats exposed to an HF lard diet in utero. They also tended to have lower Rank/Rankl ratios (P=.09) and serum progesterone levels (P=.07) than control offspring. In the mammary glands of offspring of dams consuming an HF diet during both pregnancy and lactation, the number of terminal end buds, epithelial elongation and the BCL-2/BAX ratio were significantly lower and serum leptin levels were higher than in the controls. Our data confirm that the breast cancer risk of offspring can be programmed by maternal dietary intake. However, contrary to our expectation, exposure to high levels of

lard during early life decreased later susceptibility to breast cancer.

de Vogel, S., et al. (2011). "Dietary methyl donors, methyl metabolizing enzymes, and epigenetic regulators: diet-gene interactions and promoter CpG island hypermethylation in colorectal cancer." Cancer Causes Control **22**(1): 1-12.

Dietary methyl donors might influence DNA methylation during carcinogenesis of colorectal cancer (CRC). Among 609 CRC cases and 1,663 subcohort members of the Netherlands Cohort Study on diet and cancer (n = 120,852), we estimated CRC risk according to methyl donor intake across genotypes of folate metabolizing enzymes and methyltransferases.Although diet-gene interactions were not statistically significant, methionine intake was inversely associated with CRC among subjects having both common rs2424913 and rs406193 DNMT3B C > T genotypes (highest versus lowest tertile: RR = 0.44; p (trend) = 0.05). Likewise, vitamin B2 was modestly inversely associated among individuals with the MTHFR c.665CC (rs1801133) genotype (RR = 0.66; p (trend) = 0.08), but with a significant reduced risk when </= 1 rare allele occurred in the combination of folate metabolizing enzymes MTHFR, MTRR and MTR (RR = 0.30; p (trend) = 0.005). Folate or vitamin B6 were neither inversely associated with CRC nor was methyl donor intake associated with the CpG island methylator phenotype (CIMP).Despite the absence of heterogeneity across genotypes, might an effect of methyl donors on CRC be more pronounced among individuals carrying common variants of folate metabolizing enzymes or DNA methyltransferases. Combining genotypes may assist to reveal diet associations with CRC, possibly because rare variants of related genes may collectively affect specific metabolic pathways or enzymatic functions.

Del Corno, M., et al. (2017). "Linking Diet to Colorectal Cancer: The Emerging Role of MicroRNA in the Communication between Plant and Animal Kingdoms." Front Microbiol **8**: 597.

Environmental and lifestyle factors, including diet and nutritional habits have been strongly linked to colorectal cancer (CRC). Of note, unhealthy dietary habits leading to adiposity represent a main risk factor for CRC and are associated with a chronic low-grade inflammatory status. Inflammation is a hallmark of almost every type of cancer and can be modulated by several food compounds exhibiting either protective or promoting effects. However, in spite of an extensive research, the underlying mechanisms by which dietary patterns or bioactive food components may influence tumor onset and outcome have not been fully clarified yet. Growing evidence indicates that diet, combining beneficial substances and potentially harmful ingredients, has an impact on the expression of key regulators of gene expression such as the non-coding RNA (ncRNA). Since the expression of these molecules is deranged in chronic inflammation and cancer, modulating their expression may strongly influence the cancer phenotype and outcomes. In addition, the recently acquired knowledge on the existence of intricate inter-kingdom communication networks, is opening new avenues for a deeper understanding of the intimate relationships linking diet to CRC. In this novel scenario, diet-modulated ncRNA may represent key actors in the interaction between plant and animal kingdoms, capable of influencing disease onset and outcome. In this review, we will summarize the studies demonstrating a link between bioactive food components, including food-derived, microbiota-processed, secondary metabolites, and host ncRNA. We will focus on microRNA, highlighting how this plant/animal inter-kingdom cross-talk may have an impact on CRC establishment and progression.

Dizik, M., et al. (1991). "Alterations in expression and methylation of specific genes in livers of rats fed a cancer promoting methyl-deficient diet." Carcinogenesis **12**(7): 1307-1312.

We have reported earlier that hypomethylated DNA is rapidly induced in the livers of male Fischer rats fed an extremely methyl-deficient diet (MDD). The early effects of dietary methyl deficiency on the expression of several genes in the livers of such animals have now been investigated. Poly (A)+ RNA was isolated from the livers of rats fed MDD or a similar diet supplemented with adequate supplies of choline, methionine, folic acid and vitamin B12 (CSD) for periods ranging from 1 to 4 weeks. The levels of mRNAs for the c-myc and c-fos protooncogenes in livers of rats given either MDD or the liver carcinogen, 2-acetylaminofluorene (AAF), were compared by Northern blot analysis with those in livers of animals given control diets. Both AAF and MDD induced significant elevations in levels of mRNAs specific for these two genes. After 1 week of MDD intake, large increases in the levels of c-myc and c-fos mRNAs and a smaller increase in the levels of c-Ha-ras mRNAs were observed. In contrast, there were marked decreases in the levels of mRNAs for epidermal growth factor receptor and for epidermal growth factor. These effects on mRNA accumulation persisted and were further enhanced during a 4 week period of MDD feeding. The appearance of hypomethylated DNA in the livers of these MDD-fed rats coincided with the observed changes in levels of mRNA for these genes associated with the regulation of cell growth. Increases in levels of mRNA for c-fos, c-Ha-ras and c-myc were

correlated with loss of methylation at specific sites within these genes as early as 1 week after the start of MDD feeding. These combined observations are consistent with the hypothesis that methyl-deficient diets are cancer promoting and/or carcinogenic, at least in part, because they induce hypomethylation of DNA with concomitant alterations in the regulation of gene expression.

Dong, L., et al. (2017). "Diet-induced obesity links to ER positive breast cancer progression via LPA/PKD-1-CD36 signaling-mediated microvascular remodeling." Oncotarget **8**(14): 22550-22562.

Obesity increases cancer risk including breast cancer (BC). However, the direct regulatory mechanisms by which obesity promotes BC progression remain largely unknown. We show that lysophosphatidic acid/protein kinase D1 (LPA/PKD-1)-CD36 signaling is a bona fide breast cancer promoter via stimulating microvascular remodeling in chronic diet-induced obesity (DIO). We observed that the growth of an estrogen receptor (ER) positive breast cancer was markedly increased when compared to the lean control, and specifically accompanied by increased microvascular remodeling in a syngeneic BC model in female DIO mice. The tumor neovessels in DIO mice demonstrated elevated levels of alpha smooth muscle actin (alpha-SMA), vascular endothelial growth factor receptor 2 (VEGFR 2) and endothelial differentiation gene 2/LPA receptor1 (Edg2/LPA1), enhanced PKD-1 phosphorylation, and reduced CD36 expression. Tumor associated endothelial cells (TAECs) exposed to LPA demonstrated sustained nuclear PKD-1 phosphorylation, and elevated mRNA levels of ephrin B2, and reduced mRNA expression of CD36. TAEC proliferation also increased in response to LPA/PKD-1 signaling. These studies suggest that the LPA/PKD-1-CD36 signaling axis links DIO to malignant progression of BC via stimulation of de novo tumor arteriogenesis through arteriolar remodeling of microvasculature in the tumor microenvironment. Targeting this signaling axis could provide an additional novel therapeutic strategy.

Drew, J. (2011). "Janice Drew's work on diet and cancer." World J Gastrointest Pathophysiol **2**(4): 61-64.

Obesity and associated reduced consumption of plant derived foods are linked to increased risk of colon cancer as well as a number of other organ specific cancers. Inflammatory processes are a contributing factor but the precise mechanisms remain elusive. Obesity and cancer incidence are increasing worldwide, presenting bleak prospects for reducing, or preventing, obesity related cancers. The incidence of these preventable cancers can be achieved with greater understanding of the molecular mechanisms linking diet and carcinogenesis. Janice Drew has developed a research program over recent years to investigate molecular mechanisms related to consumption of anti-inflammatory metabolites generated from consumption of plant based diets, the impact of high fat diets and associated altered metabolism and obesity on regulation of colon inflammatory responses and processes regulating the colon epithelium. Comprehensive strategies have been developed incorporating transcriptomics, including the novel gene expression technology, the GenomeLab System and proteomics, together with biochemical analyses of plasma and tissue samples to assess correlated changes in oxidative stress, inflammation and pathology. The approaches developed have achieved success in establishing antioxidant and anti-inflammatory activity of dietary antioxidants and associated genes and pathways that interact to modulate redox status in the colon. Cellular processes and genes altered in response to obesity and high fat diets have provided evidence of molecular mechanisms that are implicated in obesity related cancer.

Eilati, E., et al. (2013). "Flaxseed enriched diet-mediated reduction in ovarian cancer severity is correlated to the reduction of prostaglandin E (2) in laying hen ovaries." Prostaglandins Leukot Essent Fatty Acids **89**(4): 179-187.

Prevention of ovarian cancer is the best approach for reducing the impact of this deadly disease. The laying hen is a robust model of spontaneous ovarian cancer that recapitulates the human disease. Dietary intervention with flaxseed, the richest vegetable source of omega-3 fatty acids (OM-3FAs) and phytoestrogen lignans, demonstrate the potential for effective prevention and amelioration of ovarian cancer by targeting inflammatory prostaglandin pathways. Prostaglandin E2 (PGE2) is the most pro-inflammatory ecoisanoid and one of the downstream products of two isoforms of cyclooxygenase (COX) enzymes: COX-1 and COX-2. Our objective was to investigate the effect of flaxseed supplementation for one year on ovarian cancer and correlate its effects to expression of COX enzymes and concentrations of prostaglandins. White Leghorn hens were fed 10% flaxseed-enriched or standard diet for one year. The severity of ovarian cancer was determined by gross pathology and histology. COX-1 and COX-2 localization and protein and mRNA expression and PGE2 and PGE3 concentrations in ovaries were measured by IHC, western blot, quantitative real-time PCR and LC-MS-MS, respectively. The results demonstrated a significant reduction in late stage ovarian tumors in the flaxseed-fed hens compared with the control diet-fed hens. In correlation with decreased

ovarian cancer severity, concentrations of PGE2 and expression of COX-2 were diminished in ovaries of flaxseed-fed hens. PGE3 concentrations were below the level of detection. The results demonstrated that in normal ovaries, COX-1 was localized to the granulosa cell layer surrounding the follicles and ovarian surface epithelium (OSE) whereas COX-2 protein was localized to the granulosa cell layer in the follicle. Extensive COX-1 and COX-2 protein expression was found throughout the ovarian carcinoma. Our findings suggest that the flaxseed-mediated reduction in the severity of ovarian cancer in hens is correlated to the reduction in PGE2 in the ovaries of flaxseed-fed hens. These findings may provide the basis for clinical trials of dietary intervention targeting prostaglandin biosynthesis for the prevention and treatment of ovarian cancer.

Escrich, E., 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): 73-78.

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.

Escrich, E., et al. (2011). "Olive oil, an essential component of the Mediterranean diet, and breast cancer." Public Health Nutr **14**(12A): 2323-2332.

OBJECTIVE: The Mediterranean diet has been related to a lower risk of some chronic diseases, including cancer. We aim to gain insight into the effects of the main source of fat of this diet on breast cancer, the most common type of malignancy in women. DESIGN: Data from sixteen experimental series analysing the effects of dietary lipids on mammary carcinogenesis in an animal model, in the context of the international literature on the Mediterranean diet, olive oil and breast cancer risk. SETTING: Experimental and human data on the effects of olive oil and Mediterranean diet on breast cancer. SUBJECTS: An animal model of induced breast cancer and other human and experimental studies in the literature. RESULTS: Diets rich in extra virgin olive oil (EVOO) exert a negative modulatory effect on experimental breast cancer to a weak promoting effect, much lower than that obtained with a high-corn oil diet. EVOO confers to the mammary adenocarcinomas a clinical behaviour and morphological features compatible with low tumour aggressiveness. This differential effect, in relation to other dietary lipids, may be related to a lower effect on body weight and sexual maturation. In addition, EVOO induced different molecular changes in tumours, such as in the composition of cell membranes, activity of signalling proteins and gene expression. All these modifications could induce lower proliferation, higher apoptosis and lower DNA damage. These results, together with the favourable effect of olive oil reported in the literature when it is consumed in moderate quantities, suggest a beneficial influence of EVOO on breast cancer risk. CONCLUSIONS: Consumption of EVOO in moderate quantities and throughout the lifetime appears to be a healthy choice and may favourably influence breast cancer risk.

Fava, C., et al. (2012). "The Renalase Asp37Glu polymorphism is not associated with hypertension and cardiovascular events in an urban-based prospective cohort: the Malmo Diet and cancer study." BMC Med Genet **13**: 57.

BACKGROUND: Renalase (gene name RNLS), a recently discovered enzyme with monoamine oxidase activity, is implicated in the degradation of catecholamines. Recent studies delineate a possible role of this enzyme in blood pressure (BP) maintenance and cardiac protection and two single nucleotide polymorphisms, RNLS rs2576178 A > G and rs2296545 C > G have been associated with hypertension. The latter SNP leads to a non synonymous Asp to Glu substitution deleting a flavin adenine dinucleotide (FAD) binding site with possible impaired functionality. We tested the hypothesis that these polymorphisms could affect BP levels, hypertension prevalence, and risk of incident

cardiovascular events in middle-aged Swedes. METHODS: The polymorphisms were genotyped in 5696 participants of the population-based Cardiovascular Cohort of the "Malmo Diet and Cancer" (MDC-CC). The incidence of cardiovascular events (coronary events [n = 408], strokes [n = 330], heart failure [n = 190] and atrial fibrillation/flutter [n = 406]) was monitored for an average of approximately 15 years of follow-up. RESULTS: Both before and after adjustment for sex, age and BMI the polymorphisms did not show any effect on BP level and hypertension prevalence. Before and after adjustment for major cardiovascular risk factors, the hazard ratio for cardiac and cerebrovascular events was not significantly different in carriers of different genotypes. A significant interaction was found between the rs2296545 C > G and age with respect to BP/hypertension. CONCLUSIONS: Our data do not support a major role for these RNLS polymorphisms in determining BP level and incident events at population level. The positive interaction with age suggest that the effect of the rs2296545 C > G polymorphism, if any, could vary between different ages.

Ferguson, L. R. (2010). "Recent advances in understanding of interactions between genes and diet in the etiology of colorectal cancer." World J Gastrointest Oncol **2**(3): 125-129.

At an international level, colorectal cancer (CRC) is a major cause of morbidity and mortality. Diet plays a major etiologic role, and a range of putative dietary carcinogens have been identified. The probability with which these lead to mutations, and thereby cause cancer, is strongly impacted by variants in genes coding for xenobiotic metabolizing or DNA repair enzymes. Nutrient deficiencies also play a role, which will be exacerbated by variants in metabolic genes. However, many of the causal genes in sporadic CRC have hitherto proved elusive. The power of large international collaborations, coupled with genome-wide association studies, has implicated a major functional role of the tumour growth factor-beta pathway in CRC susceptibility. Nutrient regulation of gene expression may be especially important here. Future large collaborative studies must consider gene-gene and gene-diet interactions, coupled with high throughput genomic technologies, in order to uncover the relative roles of genetic variants, mutagenic xenobiotics, nutrient imbalance and gene expression in the etiology of CRC.

Figueiredo, J. C., et al. (2014). "Genome-wide diet-gene interaction analyses for risk of colorectal cancer." PLoS Genet **10**(4): e1004228.

Dietary factors, including meat, fruits, vegetables and fiber, are associated with colorectal cancer; however, there is limited information as to whether these dietary factors interact with genetic variants to modify risk of colorectal cancer. We tested interactions between these dietary factors and approximately 2.7 million genetic variants for colorectal cancer risk among 9,287 cases and 9,117 controls from ten studies. We used logistic regression to investigate multiplicative gene-diet interactions, as well as our recently developed Cocktail method that involves a screening step based on marginal associations and gene-diet correlations and a testing step for multiplicative interactions, while correcting for multiple testing using weighted hypothesis testing. Per quartile increment in the intake of red and processed meat were associated with statistically significant increased risks of colorectal cancer and vegetable, fruit and fiber intake with lower risks. From the case-control analysis, we detected a significant interaction between rs4143094 (10p14/near GATA3) and processed meat consumption (OR = 1.17; p = 8.7E-09), which was consistently observed across studies (p heterogeneity = 0.78). The risk of colorectal cancer associated with processed meat was increased among individuals with the rs4143094-TG and -TT genotypes (OR = 1.20 and OR = 1.39, respectively) and null among those with the GG genotype (OR = 1.03). Our results identify a novel gene-diet interaction with processed meat for colorectal cancer, highlighting that diet may modify the effect of genetic variants on disease risk, which may have important implications for prevention.

Fisher, M. L., et al. (2016). "The Ezh2 polycomb group protein drives an aggressive phenotype in melanoma cancer stem cells and is a target of diet derived sulforaphane." Mol Carcinog **55**(12): 2024-2036.

Melanoma is a metastatic cancer associated with poor survival. Here, we study a subpopulation of melanoma cancer cells displaying melanoma cancer stem cell (MCS cells) properties including elevated expression of stem cell markers, increased ability to survive as spheroids, and enhanced cell migration and invasion. We show that the Ezh2 stem cell survival protein is enriched in MCS cells and that Ezh2 knockdown or treatment with small molecule Ezh2 inhibitors, GSK126 or EPZ-6438, reduces Ezh2 activity. This reduction is associated with a reduced MCS cell spheroid formation, migration, and invasion. Moreover, the diet-derived cancer prevention agent, sulforaphane (SFN), suppresses MCS cell survival and this is associated with loss of Ezh2. Forced expression of Ezh2 partially reverses SFN suppression of MCS cell spheroid formation, migration, and invasion. A375

melanoma cell-derived MCS cells form rapidly growing tumors in immune-compromised mice and SFN treatment of these tumors reduces tumor growth and this is associated with reduced Ezh2 level and H3K27me3 formation, reduced matrix metalloproteinase expression, increased TIMP3 expression and increased apoptosis. These studies identify Ezh2 as a MCS cell marker and cancer stem cell prevention target, and suggest that SFN acts to reduce melanoma tumor formation via a mechanism that includes suppression of Ezh2 function. (c) 2015 Wiley Periodicals, Inc.

Gauger, K. J., et al. (2014). "The effects of diet induced obesity on breast cancer associated pathways in mice deficient in SFRP1." Mol Cancer **13**: 117.

BACKGROUND: Secreted frizzled-related proteins (SFRPs) are a family of proteins that block the Wnt signaling pathway and loss of Sfrp1 expression is observed in breast cancer. The molecular mechanisms by which obesity contributes to breast tumorigenesis are not well defined, but involve increased inflammation. Mice deficient in Sfrp1 show enhanced mammary gland inflammation in response to diet induced obesity (DIO). Furthermore, mammary glands from Sfrp1-/- mice exhibit increased Wnt signaling, decreased cell death responses, and excessive hyper branching. The work described here was initiated to investigate whether obesity exacerbates the aforementioned pathways, as they each play a key roles in the development of breast cancer. FINDINGS: Wnt signaling is significantly affected by DIO and Sfrp1-/- loss as revealed by analysis of Myc mRNA expression and active beta-catenin protein expression. Furthermore, Sfrp1-/- mice fed a high fat diet (HFD) exhibit an increase in mammary cell proliferation. The death response is also impaired in the mammary gland of Sfrp1-/- mice fed a normal diet (ND) as well as a HFD. In response to gamma-irradiation, mammary glands from Sfrp1-/- mice express significantly less Bax and Bbc3 mRNA, caspase-3 positive cells, and p53 protein. The expression of Wnt4 and Tnfs11 are critical for normal progesterone mediated mammary gland development and in response to obesity, Sfrp1-/- mice express significantly more Wnt4 and Tnfs11 mRNA expression. Evaluation of progesterone receptor (PR) expression showed that DIO increases the number of PR positive cells. CONCLUSIONS: Our data indicate that the expression of Sfrp1 is a critical factor required for maintaining appropriate cellular homeostasis in response to the onset of obesity.

Gay, L. J., et al. (2011). "MLH1 promoter methylation, diet, and lifestyle factors in mismatch repair deficient colorectal cancer patients from EPIC-Norfolk." Nutr Cancer **63**(7): 1000-1010.

There is conflicting evidence for the role diet and lifestyle play in the development of mismatch repair (MMR)-deficient colorectal cancers (CRC). In this study, associations between MMR deficiency, clinicopathological characteristics, and dietary and lifestyle factors in sporadic CRC were investigated. Tumor samples from 185 individuals in the EPIC-Norfolk study were analyzed for MLH1 gene promoter methylation and microsatellite instability (MSI). Dietary and lifestyle data were collected prospectively using 7-day food diaries (7dd) and questionnaires. MMR-deficient tumor cases (MLH1 promoter methylation positive, MSI-H) were more likely to be female, older at diagnosis, early Dukes' stage (A/B), and proximal in location (MSI-H P = 0.03, 0.03, 0.02, and 0.001, respectively). Tumors with positive MLH1 promoter methylation (>20%) were associated with poor differentiation (P = 0.03). Low physical activity was associated with cases without MSI (P = 0.05). MMR deficiency was not significantly associated with cigarette smoking or alcohol, folate, fruit, vegetable, or meat consumption. We conclude that MMR-deficient tumors represent a distinct subset of sporadic CRC that are proximal in location, early Dukes' stage, and poorly differentiated, in cases that are female and older at diagnosis. There is no overall role for diet and lifestyle in MMR status in CRC, consistent with age-related susceptibility to MLH1 promoter methylation.

Ghadirian, P., et al. (2009). "Breast cancer risk in relation to the joint effect of BRCA mutations and diet diversity." Breast Cancer Res Treat **117**(2): 417-422.

It has been suggested that gene-environment interaction is related to the risk of cancer. To evaluate departure from multiplicative effects between BRCA mutations and diet diversity in breast cancer (BC), a case-only study was carried out in a French-Canadian population including 738 patients with incident primary BC comprising 38 BRCA mutation carriers. Diet diversity was assessed using a validated food frequency questionnaire. Unconditional logistic regression analysis was performed to assess case-only odds ratio (COR) and 95% confidence interval (CI) while adjusting for age, body mass index, smoking, hormonal replacement therapy, and total energy intake. Ours results reveal a strong and significant interaction between BRCA mutations and vegetable and fruit diversity (COR = 0.27; 95%CI = 0.10-0.80; P = 0.03) when comparing the upper to the lower quartiles. The estimates for departure from multiplicative effects between BRCA mutations and total or other food groups' diversity were not supportive of the idea of a gene-environment interaction. The results of this study suggest that the combination of BRCA mutations and

vegetable and fruit diversity may be associated with a reduced risk of BC.

Gillman, A. S., et al. (2018). "Body mass index, diet, and exercise: testing possible linkages to breast cancer risk via DNA methylation." Breast Cancer Res Treat **168**(1): 241-248.

PURPOSE: To examine DNA methylation as a mechanism linking diet, physical activity, weight status, and breast cancer risk. METHODS: Insufficiently active women of varying weight status, without a history of cancer, completed a maximal exercise test, clinical measurement of height and weight, and a dietary intake measure. They also provided blood samples, which were analyzed to ascertain average methylation of candidate genes related to breast cancer (BRCA1, RUNX3, GALNT9, and PAX6) and inflammation (TLR4 and TLR6). RESULTS: Elevated weight status (r = -.18, p <.05) and poorer aerobic fitness (r =.24, p <.01) were each associated with decreased methylation of inflammation genes. Methylation of inflammation genes statistically mediated the relationship between weight status and cancer gene methylation (standardized indirect effect =.12, p <.05) as well as between cardiorespiratory fitness and cancer gene methylation (standardized indirect effect = -.172, p <.01). However, recent dietary behavior was not associated with methylation of either inflammation or cancer genes. CONCLUSIONS: Both weight status and cardiovascular fitness are associated with methylation of genes associated with both inflammation and cancer. Methylation of inflammatory genes might serve as a mechanistic link between lifestyle factors and methylation changes in genes that increase risk for breast cancer.

Hardy, T. M. and T. O. Tollefsbol (2011). "Epigenetic diet: impact on the epigenome and cancer." Epigenomics **3**(4): 503-518.

A number of bioactive dietary components are of particular interest in the field of epigenetics. Many of these compounds display anticancer properties and may play a role in cancer prevention. Numerous studies suggest that a number of nutritional compounds have epigenetic targets in cancer cells. Importantly, emerging evidence strongly suggests that consumption of dietary agents can alter normal epigenetic states as well as reverse abnormal gene activation or silencing. Epigenetic modifications induced by bioactive dietary compounds are thought to be beneficial. Substantial evidence is mounting proclaiming that commonly consumed bioactive dietary factors act to modify the epigenome and may be incorporated into an 'epigenetic diet'. Bioactive nutritional components of an epigenetic diet may be incorporated into one's regular dietary regimen and used therapeutically for medicinal or chemopreventive purposes. This article will primarily focus on dietary factors that have been demonstrated to influence the epigenome and that may be used in conjunction with other cancer prevention and chemotherapeutic therapies.

Hilakivi-Clarke, L., et al. (2005). "Mechanisms mediating the effects of prepubertal (n-3) polyunsaturated fatty acid diet on breast cancer risk in rats." J Nutr **135**(12 Suppl): 2946S-2952S.

Dietary exposures during childhood may influence later breast cancer risk. We tested in an animal model the hypothesis that prepubertal intake of (n-3) PUFAs, present mainly in fish, reduces susceptibility to breast cancer. Between postnatal days 5 to 25, rat pups were fed (n-3) PUFA-containing diets at a 2:1 ratio of (n-6): (n-3) PUFAs (typical of prehistoric societies) or a control (n-6) PUFA diet at a 17:1 ratio of (n-6): (n-3) PUFAs (comparable with current Western societies). These fatty acids were given in a low- or high-fat context (16 or 39% energy from fat). The low-(n-3) PUFA diet reduced while the high-(n-3) PUFA diet increased carcinogen-induced mammary tumorigenesis. The low-(n-3) PUFA diet reduced mammary cell proliferation and increased apoptosis, particularly in the terminal end buds (the mammary source of malignant breast tumors). The high-(n-3) PUFA diet had opposite effects on these 2 key biomarkers and increased phospho-Akt levels, a survival factor. Microarray analyses identified genes that were permanently upregulated in the low-(n-3) PUFA-exposed glands and function in oxidative damage repair. Serum levels of 8-hydroxy-2'deoxyguanosine, a marker of DNA damage, were significantly reduced in these low-(n-3) PUFA-fed rats, and increased in the high-(n-3) PUFA-exposed group. The latter group exhibited reduced expression of BRCA1, a DNA repair gene. Our results indicate that the opposing susceptibilities to mammary tumorigenesis between the low- versus high-fat (n-3) PUFA-exposed groups were associated with altered DNA damage repair and gene expression linked to proliferation, survival, and differentiation.

Hursting, S. D., et al. (2001). "Diet and cancer prevention studies in p53-deficient mice." J Nutr **131**(11 Suppl): 3092S-3094S.

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-/-) 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+/-) 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+/- 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+/- 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.

Kachroo, P., et al. (2011). "Classification of diet-modulated gene signatures at the colon cancer initiation and progression stages." Dig Dis Sci **56**(9): 2595-2604.

BACKGROUND: The effects of dietary polyunsaturated (PUFAs) and monounsaturated fatty acids (MUFAs) on intestinal cytokinetics within the context of colon cancer initiation and progression have been extensively studied. n-3 PUFAs have received the most attention due to their potential protective role. However, further investigation of the epigenetic perturbations caused by fatty acids in the context of colon cancer development is needed. METHODS: We used DNA microarrays to identify discriminative gene signatures (gene combinations) for the purpose of classifying n-3 PUFA-fed, carcinogen-injected, Sprague-Dawley rats at the initiation and progression stages. Animals were assigned to three dietary treatments differing only in the type of fat (corn oil/n-6 PUFA, fish oil/n-3 PUFA, or olive oil/n-9 monounsaturated fatty acid). RESULTS: The effects of diet on colonic mucosal gene expression signatures during tumor initiation and progression were subsequently compared (12 h and 10 weeks after azoxymethane injection). Microarray analysis revealed that the number of differentially expressed (DE) genes in each of the three diet comparisons increased with the progression of colon cancer. Each dietary lipid source exhibited its own unique transcriptional profile, as assessed by linear discriminant analysis. Applying this novel approach, we identified the single genes and the two- to three-gene combinations that best distinguished the dietary treatment groups. For the chemoprotective (fish oil) diet, mediators of stem cell homeostasis, e.g., ephrin B1 and bone morphogenic protein 4, were the top-performing gene classifiers. CONCLUSIONS: These results suggest that dietary chemoprotective n-3 PUFA impact genes that regulate the colon stem cell niche and tumor evolution.

Kakkoura, M. G., et al. (2016). "MnSOD and CAT polymorphisms modulate the effect of the Mediterranean diet on breast cancer risk among Greek-Cypriot women." Eur J Nutr **55**(4): 1535-1544.

PURPOSE: Oxidative stress arises due to a cellular imbalance in oxidants and antioxidants and/or due to an altered activity of antioxidant enzymes, caused by SNPs. Oxidative stress increases susceptibility to breast cancer (BC) risk, and we previously showed that the Mediterranean diet (MD), which is rich in antioxidants, reduces BC risk in Greek-Cypriot women. Here, we investigated the effect of MnSOD (p.Val16Ala, rs4880) and CAT (-262C>T, rs1001179) SNPs on the association between the MD and BC risk in the case-control study of BC MASTOS in Cyprus. METHODS: Dietary intake data were obtained using a 32-item food frequency questionnaire, from which a dietary pattern was previously derived, using principal component analysis. This pattern included high loadings of vegetables, fruit, legumes and fish, a combination that closely resembles the MD and was used as our dietary variable. RESULTS: High vegetable intake lowered BC risk in women with at least one MnSOD Val allele (ORHigh vs. Low for Val/Val = 0.56, 95 % CI 0.35-0.88, for Val/Ala = 0.57, 95 % CI 0.39-0.82), or one CAT -262C allele (ORHigh vs. Low for -262CC = 0.66, 95 % CI 0.47-0.92, for -262CT = 0.53, 95 % CI 0.35-0.81). High fish intake conferred a decreased BC risk of CAT -262CC women (ORQ4 vs. Q1 0.66, 95 % CI 0.47-0.92) compared with the CAT -262TT women and low fish intake (ORQ2 vs. Q1 2.79, 95 % CI 1.08-7.17). Additionally, high fish intake reduced BC risk in MnSOD Val/Val women (ORQ4 vs. Q1 0.63, 95 % CI 0.40-0.98). p interaction values were, however, not statistically significant. CONCLUSION: Our results demonstrate that the antioxidative effects of the MD against BC risk may be enhanced by the wild-type alleles of the MnSOD or CAT SNPs among Greek-Cypriot women.

Kakkoura, M. G., et al. (2017). "The synergistic effect between the Mediterranean diet and GSTP1 or NAT2 SNPs decreases breast cancer risk in Greek-Cypriot women." Eur J Nutr **56**(2): 545-555.

PURPOSE: Xenobiotic metabolism is related to the interplay between diet and breast cancer (BC) risk. This involves detoxification enzymes, which are polymorphic and metabolise various dietary metabolites. An important characteristic of this pathway is that chemoprotective micronutrients can act not only as substrates but also as inducers for these enzymes. We investigated whether functional GSTP1 (p.Ile105Val-rs1695), NAT2 (590G>A-rs1799930) SNPs and GSTM1 and GSTT1 deletion polymorphisms could modulate the effect of the Mediterranean diet (MD) on BC risk, in Greek-Cypriot women. METHODS: Genotyping was performed on women from the MASTOS case-control study of BC in Cyprus. A 32-item food-frequency questionnaire was used to obtain dietary intake information. A dietary pattern, which closely resembles the MD (high loadings of vegetables, fruit, legumes and fish), was previously derived with principal component analysis and was used as our dietary variable. RESULTS: GSTT1 null genotype increased BC risk compared with the homozygous non-null GSTT1 genotype (OR 1.21, 95 % CI 1.01-1.45). Increasing adherence to the MD reduced BC risk in women with at least one GSTP1 Ile allele (OR for Ile/Ile = 0.84, 95 % CI 0.74-0.95, for Ile/Val = 0.73, 95 % CI 0.62-0.85) or one NAT2 590G allele (OR for 590 GG = 0.73, 95 % CI 0.63-0.83, for 590 GA = 0.81, 95 % CI 0.70-0.94). p interaction values were not, however, statistically significant. CONCLUSION: The homozygous null GSTT1 genotype could be a risk allele for BC among Greek-Cypriot women. The anticarcinogenic effects of the high adherence to MD against BC risk could also be further enhanced when combined with the wild-type alleles of the detoxification GSTP1 or NAT2 SNPs.

Kantor, E. D. and E. L. Giovannucci (2015). "Gene-diet interactions and their impact on colorectal cancer risk." Curr Nutr Rep **4**(1): 13-21.

A number of studies have evaluated the role of gene-diet interaction in the etiology of colorectal cancer (CRC). Historically, these studies focused on established dietary risk factors and genes involved in their metabolism. However, results from these candidate gene studies were inconsistent, possibly due to multiple testing and publication bias. In recent years, genome-wide association studies have identified a number of CRC susceptibility loci, and subsequent meta-analyses have observed limited evidence that diet may modify the risk associated with these susceptibility loci. Statistical techniques have been recently developed to evaluate the presence of interaction across the entire genome; results from these genome-wide studies have demonstrated limited evidence of interaction and have failed to replicate results from candidate gene studies and those using established susceptibility loci. However, larger sample sizes are likely needed to elucidate modest or weak interaction in genome-wide studies of gene-diet interaction.

Karunanithi, S., et al. (2017). "RBP4-STRA6 Pathway Drives Cancer Stem Cell Maintenance and Mediates High-Fat Diet-Induced Colon Carcinogenesis." Stem Cell Reports **9**(2): 438-450.

The transmembrane protein, STRA6, functions as a vitamin A transporter and a cytokine receptor when activated by vitamin A-bound serum retinol binding protein 4 (RBP4). STRA6 activation transduces a JAK2-STAT3 signaling cascade and promotes tumorigenesis in a xenograft mouse model of colon cancer. We show here that RBP4 and STRA6 expression is associated with poor oncologic prognosis. Downregulating STRA6 or RBP4 in colon cancer cells decreased the fraction of cancer stem cells and their sphere and tumor initiation frequency. Furthermore, we show that high-fat diet (HFD) increases LGR5 expression and promotes tumor growth in a xenograft model independent of obesity. HFD increased STRA6 levels, and downregulation of STRA6 delays and impairs tumor initiation, tumor growth, and expression of stemness markers. Together, these data demonstrate a key role of STRA6 and RBP4 in the maintenance of colon cancer self-renewal and that this pathway is an important link through which consumption of HFD contributes to colon carcinogenesis.

Kim, J., et al. (2014). "Gene-diet interactions in gastric cancer risk: a systematic review." World J Gastroenterol **20**(28): 9600-9610.

AIM: To conduct a systematic review of the published epidemiological studies investigating the association of the interactions between gene variants and dietary intake with gastric cancer risk. METHODS: A literature search was conducted in PubMed, EMBASE, and MEDLINE for articles published between January 2000 and July 2013, and 38 studies were identified. Previous studies included various dietary factors (e.g., fruits and vegetables, soybean products, salt, meat, and alcohol) and genetic variants that are involved in various metabolic pathways. RESULTS: Studies suggest that individuals who carry high-risk genetic variants and demonstrate particular dietary habits may have an increased risk of gastric cancer compared with those who do not carry high-risk genetic variants. Distinctive dietary patterns and variations in the frequency of genetic variants may

explain the higher incidence of gastric cancer in a particular region. However, most previous studies have limitations, such as a small sample size and a retrospective case-control design. In addition, past studies have been unable to elucidate the specific mechanism in gene-diet interaction associated with gastric carcinogenesis. CONCLUSION: Additional large prospective epidemiological and experimental studies are required to identify the gene-diet metabolic pathways related to gastric cancer susceptibility.

Kim, W. G., et al. (2013). "Diet-induced obesity increases tumor growth and promotes anaplastic change in thyroid cancer in a mouse model." Endocrinology **154**(8): 2936-2947.

Recent epidemiological studies provide strong evidence suggesting obesity is a risk factor in several cancers, including thyroid cancer. However, the molecular mechanisms by which obesity increases the risk of thyroid cancer are poorly understood. In this study, we evaluated the effect of diet-induced obesity on thyroid carcinogenesis in a mouse model that spontaneously develops thyroid cancer (Thrb (PV/PV)Pten (+/-) mice). These mice harbor a mutated thyroid hormone receptor-beta (denoted as PV) and haplodeficiency of the Pten gene. A high-fat diet (HFD) efficiently induced the obese phenotype in Thrb (PV/PV)Pten (+/-) mice after 15 weeks. Thyroid tumor growth was markedly greater and survival was significantly lower in Thrb (PV/PV)Pten (+/-) mice fed an HFD than in controls fed a low-fat diet (LFD). The HFD increased thyroid tumor cell proliferation by increasing the protein levels of cyclin D1 and phosphorylated retinoblastoma protein to propel cell cycle progression. Histopathological analysis showed that the frequency of anaplasia of thyroid cancer was significantly greater (2.6-fold) in the HFD group than the LFD group. The HFD treatment led to an increase in parametrial/epididymal fat pad and elevated serum leptin levels in Thrb (PV/PV)Pten (+/-) mice. Further molecular analyses indicated that the HFD induced more aggressive pathological changes that were mediated by increased activation of the Janus kinase 2-signaling transducer and activator of transcription 3 (STAT3) signaling pathway and induction of STAT3 target gene expression. Our findings demonstrate that diet-induced obesity exacerbates thyroid cancer progression in Thrb (PV/PV)Pten (+/-) mice and suggest that the STAT3 signaling pathway could be tested as a potential target for the treatment of thyroid cancer.

Knackstedt, R. W., et al. (2012). "Epigenetic mechanisms underlying diet-sourced compounds in the prevention and treatment of gastrointestinal cancer." Anticancer Agents Med Chem **12**(10): 1203-1210.

The development of colon cancer, the third most diagnosed cancer and third leading cause of cancer deaths in the United States, can be influenced by genetic predispositions and environmental exposures. As 80% of colon cancer cases are sporadic in nature, much interest lies in determining risk factors that may foster its development, as well as identifying compounds that could inhibit colon cancer development or halt progression. A major risk factor for sporadic colon cancer is a high fat, Western diet which has been linked to a cancer-prone, pro-inflammatory state. Cultures which place an emphasis on fresh fruits and vegetables demonstrate lower colon cancer incidences. Diet not only has the potential to encourage colon cancer development, but recent evidence demonstrates that certain dietary natural products can halt colon cancer development and progression via epigenetic regulation. Epigenetic dysregulation may contribute to inflammation-driven diseases, such as cancer, and can lead to the inappropriate silencing of genes necessary to inhibit cancer development. Natural compounds have shown the ability to reverse epigenetic dysregulation in in vitro and in vivo models. As current allopathic medicines aimed at reversing epigenetic silencing are accompanied with the risk of toxicity and side effects, much interest lies in being able to harness the disease preventing properties in natural products. Here, we discuss the epidemiology of colon cancer, describe the need for natural approaches to inhibit disease development and highlight natural products which have been shown to inhibit gastrointestinal cancer initiation and progression in vitro or in vivo through epigenetic modulation.

Kopp, T. I., et al. (2015). "Polymorphisms in ATP-binding cassette transporter genes and interaction with diet and life style factors in relation to colorectal cancer in a Danish prospective case-cohort study." Scand J Gastroenterol **50**(12): 1469-1481.

BACKGROUND AND AIMS: The ATP-binding cassette (ABC) transporter family transports various molecules across the enterocytes in the gut protecting the intestine against potentially harmful substances. Moreover, ABC transporters are involved in mucosal immune defence through interaction with cytokines. The study aimed to assess whether polymorphisms in ABCB1, ABCC2 and ABCG2 were associated with risk of colorectal cancer (CRC) and to investigate gene-environment (dietary factors, smoking and use of non-steroidal anti-inflammatory drugs) and gene-gene interactions between previously studied polymorphisms in IL1B and IL10 and ABC transporter genes in relation to CRC risk. MATERIALS AND METHODS: We used a Danish prospective case-cohort study of 1010 CRC cases and 1829 randomly

selected participants from the Danish Diet, Cancer and Health cohort. Incidence rate ratios were calculated based on Cox' proportional hazards model. RESULTS: None of the polymorphisms were associated with CRC, but ABCB1 and ABCG2 haplotypes were associated with risk of CRC. ABCB1/rs1045642 interacted with intake of cereals and fiber (p-Value for interaction (P (int)) = 0.001 and 0.01, respectively). In a three-way analysis, both ABCB1/rs1045642 and ABCG2/rs2231137 in combination with IL10/rs3024505 interacted with fiber intake in relation to risk of CRC (P (int) = 0.0007 and 0.009). CONCLUSIONS: Our results suggest that the ABC transporters P-glycoprotein/multidrug resistance 1 and BRCP, in cooperation with IL-10, are involved in the biological mechanism underlying the protective effect of fiber intake in relation to CRC. These results should be replicated in other cohorts to rule out chance findings.

La Merrill, M., et al. (2010). "Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence in mice." Environ Health Perspect **118**(5): 596-601.

BACKGROUND: RESULTS from previous studies have suggested that breast cancer risk correlates with total lifetime exposure to estrogens and that early-life 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure or diets high in fat can also increase cancer risk. OBJECTIVES: Because both TCDD and diet affect the estrogen pathway, we examined how TCDD and a high-fat diet (HFD) interact to alter breast cancer susceptibility. METHODS: We exposed pregnant female FVB/NJ mice (12.5 days postcoitus) to 1 microg/kg TCDD or vehicle; at parturition, the dams were randomly assigned to a low-fat diet (LFD) or a high-fat diet (HFD). Female offspring were maintained on the same diets after weaning and were exposed to 7,12-dimethylbenz [a]anthracene on postnatal days (PNDs) 35, 49, and 63 to initiate mammary tumors. A second cohort of females was treated identically until PND35 or PND49, when mammary gland morphology was examined, or PND50, when mammary gland mRNA was analyzed. RESULTS: We found that maternal TCDD exposure doubled mammary tumor incidence only in mice fed the HFD. Among HFD-fed mice, maternal TCDD exposure caused rapid mammary development with increased Cyp1b1 (cytochrome P450 1B1) expression and decreased Comt (catechol-O-methyltransferase) expression in mammary tissue. Maternal TCDD exposure also increased mammary tumor Cyp1b1 expression. CONCLUSIONS: Our data suggest that the HFD increases sensitivity to maternal TCDD exposure, resulting in increased breast cancer incidence, by changing metabolism capability. These results provide a mechanism to explain epidemiological data linking early-life TCDD exposure and diets high in fat to increased risk for breast cancer in humans.

Le Marchand, L., et al. (2004). "MTHFR polymorphisms, diet, HRT, and breast cancer risk: the multiethnic cohort study." Cancer Epidemiol Biomarkers Prev **13**(12): 2071-2077.

Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme in the metabolism of folate, a nutrient which has recently been found to be inversely related to breast cancer in women who drink alcohol. Two common variants in the MTHFR gene (C677T and A1298C) have been associated with a reduced activity of this enzyme, thereby increasing the availability of folate for thymidylate and purine synthesis. We investigated the relationship of these variants with invasive breast cancer in a case-control study of 1,189 cases and 2,414 controls nested within the Multiethnic Cohort Study. The Multiethnic Cohort Study is a large prospective study of men and predominantly postmenopausal women of Japanese, White, African American, Latino, and Native Hawaiian origin, residing in Hawaii and Los Angeles. We found an overall nonsignificant, weak inverse association between breast cancer risk and the 677TT genotype and no association with the 1298C variant. The odds ratio [OR and 95% confidence interval (95% CI)] for the 677CC, 677CT, and 677TT genotypes were 1.00, 0.98 (0.83-1.15), and 0.86 (0.67-1.09), respectively. Those for the 1298AA, 1298AC, and 1298CC genotypes were 1.00, 0.93 (0.79-1.08), and 1.20 (0.88-1.65), respectively. However, the inverse association with the 677TT genotype was stronger (OR, 0.62; 95% CI 0.39-0.98) among women who were on hormone replacement therapy (HRT) at baseline, and the increased breast cancer risk due to HRT was not observed in women with the 677TT genotype. An increased breast cancer risk was suggested for alcohol intake >10 g/d, when compared with nondrinkers, but only among HRT users with the 677CC genotype (OR, 1.51; 95% CI, 0.96-2.37). Folate intake exhibited no modifying effect on the genotype-breast cancer relationship. These findings suggest that the MTHFR 677TT genotype may confer a 40% decreased breast cancer risk in postmenopausal women using HRT. This is consistent with the role of MTHFR in facilitating the flow of folate for thymidylate and purine synthesis and with the increased nucleic acid need resulting from the hyperproliferative effect of HRT on mammary epithelial cells.

Logan, J. and M. W. Bourassa (2018). "The rationale for a role for diet and nutrition in the

prevention and treatment of cancer." Eur J Cancer Prev **27**(4): 406-410.

There is considerable evidence to support dietary recommendations for prevention of cancer as well as for patients undergoing or recovering from cancer treatment. We consider here implications from human, animal and in-vitro studies of the effects of dietary factors (macronutrients and micronutrients-phytochemicals) on cancer. An important epidemiology study, the China Project found a significant correlation between disease incidence and markers of animal product consumption. Evidence of the role of animal protein in the promotion of cancer also comes from animal studies. Food restriction has been shown in human and animal studies to slow cancer progression. Phytochemicals from whole plant foods are protective against oxidative stress, inhibit cell proliferation, induce cell-cycle arrest, and apoptosis, act as antiangiogenesis factors, and inhibit cyclooxygenase-2, which has been related to metastasis. Some mechanisms that mediate the effect of diet on cancer involve cell signaling through insulin factors and mammalian target of rapamycin, a nutrient sensing complex related to growth, altered gene expression through epigenetics, and the effects of microbial metabolites produced by the gut microbiota that is strongly influenced by dietary factors. The evidence accumulating for many years indicates that diet, what we eat every day, can affect disease. Besides preventing the development of cancer, this could also be harnessed to positively influence treatment outcomes as well as prevent recurrence. As research strategies developed for drug studies are not appropriate, it is important that new methodologies be developed to study these effects.

Low, Y. L., et al. (2005). "Phytoestrogen exposure correlation with plasma estradiol in postmenopausal women in European Prospective Investigation of Cancer and Nutrition-Norfolk may involve diet-gene interactions." Cancer Epidemiol Biomarkers Prev **14**(1): 213-220.

Cross-sectional studies investigating the relationship between phytoestrogens in diet, urine, or blood with plasma estradiol and sex hormone binding globulin (SHBG) have been inconclusive. We investigated the relationship among phytoestrogen exposure, polymorphisms in the ESR1, COMT, CYP19, and SHBG genes, and plasma estradiol and SHBG levels in 125 free-living postmenopausal women taking part in a cohort study (European Prospective Investigation of Cancer and Nutrition-Norfolk) using three different markers: dietary, urinary, and serum phytoestrogens. Phytoestrogen levels (daidzein, genistein, glycitein, O-desmethylangolensin, equol, enterodiol, and enterolactone) in spot urine and serum were analyzed by gas chromatography/mass spectrometry and liquid chromatography/tandem mass spectrometry, respectively. Plasma estradiol and SHBG were measured by immunoassays. Adjusting for age and body mass index, urinary daidzein, genistein, glycitein, and serum daidzein and glycitein were negatively correlated with plasma estradiol ($R = -0.199$ to -0.277, $P < 0.03$), with particularly strong associations found in the 18 women with CC genotype for ESR1 PvuII polymorphism ($R = -0.597$ to -0.834, $P < 0.03$). The negative correlations observed between isoflavones and estradiol in women as a whole became no longer significant when we excluded women with ESR1 PvuII CC genotype, indicating that the correlations observed were due mainly to this group of women. There was no relationship between dietary isoflavones and plasma estradiol and no association was found between any of the dietary, urinary, and serum phytoestrogen and plasma SHBG or between these factors and polymorphisms in CYP19, SHBG, and COMT. We conclude that higher isoflavone exposure is associated with lower plasma estradiol in postmenopausal women and that this preliminary study is suggestive of the involvement of diet-gene interactions.

MacLennan, R. (1997). "Diet and colorectal cancer." Int J Cancer **Suppl 10**: 10-12.

Studies of migrants to Australia indicate that the risk of colorectal cancer (CRC) can be influenced by environment during adult life. Under a gene x environment interaction model for the risk of CRC, it is postulated that a high proportion of the variation in CRC incidence among populations is attributable to differences in diet, and that the average genetic susceptibility of populations to dietary carcinogenic components is similar. The possible relevance within populations of individual susceptibility to dietary components is supported by studies showing that the risk of CRC, compared with that of the general population, is not increased in the spouses of cases. It is postulated that, conditional upon a relevant dietary exposure, the level of susceptibility to diet is a major determinant of variation in individual risk. Despite high correlations of meat and fat with CRC among populations, the results of case-control studies have been inconsistent. Inability to stratify subjects by susceptibility may explain the lack of association of intake of fat and meat with CRC in many studies. A new generation of case-control and cohort studies of diet and CRC may extend the limits of epidemiology. Prevention trials with beta-carotene and other compounds have not protected against colorectal neoplasia, and may have exerted adverse effects. This possibility challenges the philosophy of chemoprevention trials in favor of trials of changes in

diet towards patterns that are associated with lower risk.

Martinez-Chacin, R. C., et al. (2014). "Analysis of high fat diet induced genes during mammary gland development: identifying role players in poor prognosis of breast cancer." BMC Res Notes **7**: 543.

BACKGROUND: Epidemiological studies have shown that consumption of a high-fat diet (HFD) increases the risk of developing breast cancer (BC). Studies in rodents have shown HFD causes changes in the genetic programming of the maturing mammary gland (MG) increasing the susceptibility of developing the disease. Less is known about how HFD induced genes impact BC development. HFD exposure two weeks before conception to six weeks of age was previously shown to dramatically change MG gene expression in 10 week old mice. Therefore, we investigated these differentially expressed HFD-induced genes for their expression in BC using the NKI 295 breast tumor dataset. RESULTS: To examine the potential role of HFD induced genes in BC, we first investigated whether these HFD-induced genes in mouse MGs were differentially expressed in different types of human BC. Of the 28 HFD induced genes that were differentially expressed between BC subtypes in the NKI set, 79% were significantly higher in basal-like BC. Next, we analyzed whether HFD induced genes were associated with BC prognosis utilizing gene expression and survival data for each HFD induced gene from the NKI data and constructed Kaplan Meier survival plots. Significantly, 93% of the prognosis associated genes (13/14) were associated with poor prognosis (P = 0.002). Kaplan Meier analysis with 249 non-basal-like BC found that all but one of the genes examined were still significantly associated with poor prognosis. Furthermore, gene set enrichment analysis (GSEA) with HFD microarray data revealed that invasive BC genes where enriched in HFD samples that also had lost expression of luminal genes. CONCLUSIONS: HFD exposed mouse MGs maintain differential expression of genes that are found highly expressed in basal-like breast cancer. These HFD-induced genes associate with poor survival in numerous BC subtypes, making them more likely to directly impact prognosis. Furthermore, HFD exposure leads to a loss in the expression of luminal genes and a gain in expression of mesenchymal and BC invasion genes in MGs. Collectively, our study suggests that HFD exposure during development induces genes associated with poor prognosis, thus identifying how HFD diet may regulate BC development.

Mathers, J. C. (2003). "Nutrition and cancer prevention: diet-gene interactions." Proc Nutr Soc **62**(3): 605-610.

Cancer is the major cause of death in the UK, and the Government has set a target to reduce death rate from cancer in individuals < 75 years by > or = 20% by 2010. Whilst earlier diagnosis and more effective treatments will contribute to meeting this target, there are considerable opportunities to prevent cancer by improving diet and other aspects of lifestyle. There is now a good understanding of the biological basis of carcinogenesis, which is providing the basis for mechanistic investigation of the chemo-preventive properties of certain foods and food components. It is becoming increasingly clear that there are important interactions between an individual's genotype (characterised by single nucleotide polymorphisms in particular genes) and habitual diet that modulate the risk of developing cancer. The technology to support this post-genomic revolution in nutrition research is now widely available, but brings with it considerable challenges in terms of study design and ethics. However, in the absence of a robust body of evidence on which dietary strategies will benefit which individuals, soundly based genetically-targeted nutrition advice to the public on cancer prevention is a little way in the future.

Mathers, J. C. (2004). "The biological revolution - towards a mechanistic understanding of the impact of diet on cancer risk." Mutat Res **551**(1-2): 43-49.

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.

Mathers, J. C. and J. E. Hesketh (2007). "The biological revolution: understanding the impact of SNPs on diet-cancer interrelationships." J Nutr **137**(1 Suppl): 253S-258S.

Evidence is accumulating that individual risk of neoplasia depends on complex interactions among genetic inheritance, a range of exposures both in utero and in postnatal life, and the play of chance. Knowledge of the portfolio of genetic variants that confer susceptibility or resistance to cancer is limited, and there is potential for genome-wide scans and hypothesis-driven studies to reveal novel polymorphisms and haplotypes that modify risk. There is only fragmentary evidence of the scale and nature of diet-gene interactions that modulate risk of neoplasia, but it seems probable that such interactions will play a significant role as they do in other complex diseases including cardiovascular disease and type 2 diabetes. All existing evidence about diet-gene interactions and cancer risk comes from observational studies, and it will be necessary to undertake intervention studies to test the hypotheses generated by epidemiologic investigations. Because it is very unlikely that primary cancer will be an endpoint in dietary intervention studies in the foreseeable future, development of robust surrogate endpoints is a high priority. Emerging biological science using epigenomics, proteomics, and other molecular technologies appears to offer novel approaches to the discovery and validation of surrogate endpoints.

McCullough, M. L., et al. (2007). "Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study." Breast Cancer Res **9**(1): R9.

INTRODUCTION: Vitamin D receptor (VDR) polymorphisms have been inconsistently associated with breast cancer risk. Whether risk is influenced by polymorphisms in other vitamin D metabolism genes and whether calcium or vitamin D intake modifies risk by genotype have not been evaluated. METHODS: We conducted a nested case-control study within the Cancer Prevention Study II Nutrition Cohort of associations between breast cancer and four VDR single-nucleotide polymorphisms (SNPs), Bsm1,Apa1,Taq1, and Fok1, a poly (A) microsatellite, and associated haplotypes (baTL and BAtS). We also examined one SNP in the 24-hydroxylase gene (CYP24A1) and two in the vitamin D-binding protein (group-specific component [GC]) gene. Participants completed a questionnaire on diet and medical history at baseline in 1992. This study includes 500 postmenopausal breast cancer cases and 500 controls matched by age, race/ethnicity, and date of blood collection. RESULTS: Incident breast cancer was not associated with any genotype examined. However, women with the Bsm1 bb SNP who consumed greater than the median intake of total calcium (> or = 902

mg/day) had lower odds of breast cancer compared to women with the Bb or BB genotype and less than the median calcium intake (odds ratio 0.61, 95% confidence interval 0.38 to 0.96; p (interaction) = 0.01). Similar interactions were observed for Taq1 (T allele) and the poly (A) (LL) repeat. CONCLUSION: We found no overall association between selected vitamin D pathway genes and postmenopausal breast cancer risk. However, certain VDR gene polymorphisms were associated with lower risk in women consuming high levels of calcium, suggesting that dietary factors may modify associations by VDR genotype.

Meadows, G. G. (2012). "Diet, nutrients, phytochemicals, and cancer metastasis suppressor genes." Cancer Metastasis Rev **31**(3-4): 441-454.

The major factor in the morbidity and mortality of cancer patients is metastasis. There exists a relative lack of specific therapeutic approaches to control metastasis, and this is a fruitful area for investigation. A healthy diet and lifestyle not only can inhibit tumorigenesis but also can have a major impact on cancer progression and survival. Many chemicals found in edible plants are known to inhibit metastatic progression of cancer. While the mechanisms underlying antimetastatic activity of some phytochemicals are being delineated, the impact of diet, dietary components, and various phytochemicals on metastasis suppressor genes is underexplored. Epigenetic regulation of metastasis suppressor genes promises to be a potentially important mechanism by which dietary components can impact cancer metastasis since many dietary constituents are known to modulate gene expression. The review addresses this area of research as well as the current state of knowledge regarding the impact of diet, dietary components, and phytochemicals on metastasis suppressor genes.

Menendez, J. A., 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): 2425-2432.

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.

Menendez, J. A., et al. (2006). "HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated fatty acid, alpha-linolenic acid (ALA; 18:3n-3), in breast cancer cells: the "fat features" of the "Mediterranean diet" as an "anti-HER2 cocktail"." Clin Transl Oncol **8**(11): 812-820.

BACKGROUND: Data derived from epidemiological and experimental studies suggest that alphalinolenic acid (ALA; 18:3n-3), the main omega-3 polyunsaturated fatty acid (PUFA) present in the Western diet, may have protective effects in breast cancer risk and metastatic progression. A recent pilot clinical trial assessing the effects of ALA-rich dietary flaxseed on tumor biological markers in postmenopausal patients with primary breast cancer demonstrated significant reductions in tumor growth and in HER2 (erbB-2) oncogene expression. HYPOTHESIS: The molecular mechanism by which ALA inhibits breast cancer cell growth and metastasis formation may involve a direct regulation of HER2, a well-characterized oncogene playing a key role in the etiology, progression and response to some chemo- and endocrine therapies in approximately 20% of breast carcinomas. METHODS: Using HER2-specific ELISA, flow cytometry, immunofluorescence microscopy, Western blotting, RT-PCR and HER2 promoter-reporter analyses, we characterized the effects of exogenous supplementation with ALA on the expression of HER2 oncogene, a master key player in the onset and metastasis formation of breast cancer

disease. Metabolic status (MTT) assays were performed to evaluate the nature of the cytotoxic interaction between ALA and the humanized anti-HER2 monoclonal antibody trastuzumab (Herceptin). To study these issues we used BT-474 and SKBr-3 breast cancer cells, which naturally exhibit amplification of the HER2 oncogene. RESULTS: ALA treatment dramatically suppressed the expression of HER2-coded p185Her-2/neu oncoprotein as determined by ELISA, flow cytometry, immunofluorescence microscopy and immunoblotting techniques. Interestingly, ALA-induced down-regulation of p185Her-2/neu correlated with a transcriptional response as no HER2 mRNA signal could be detected by RT-PCR upon treatment with optimal concentrations of ALA (up to 20 microM). Consistent with these findings, ALA exposure was found to dramatically repress the activity of a Luciferase reporter gene driven by the HER2 promoter. Moreover, the nature of the cytotoxic interaction between ALA and trastuzumab (Herceptin) revealed a significant synergism as assessed by MTT-based cell viability assays. CONCLUSIONS: i) These findings reveal that the omega-3 PUFA ALA suppresses overexpression of HER2 oncogene at the transcriptional level, which, in turn, interacts synergistically with anti-HER2 trastuzumab- based immunotherapy. ii) Our results molecularly support a recent randomized double-blind placebo-controlled clinical trial suggesting that ALA may be a potential dietary alternative or adjunct to currently used drugs in the management of HER2-positive breast carcinomas. iii) Considering our previous findings demonstrating the <<HER2 upregulatory actions>> of the omega-6 PUFA linolenic acid (LA; 18:2n-6) and the <<HER2 down-regulatory actions >> of the omega-3 PUFA docosahexaenoic acid (DHA; 22:6n-3) and of the omega-9 monounsaturated fatty acid oleic acid (OA; 18:1n-9), it is reasonable to suggest that a low omega-6/omega-3 PUFA ratio and elevated MUFA levels, the two prominent <<fat features>> of the <<Mediterranean diet>>, should be extremely efficient at blocking HER2 expression in breast cancer cells.

Michels, K. B., et al. (2007). "Diet and breast cancer: a review of the prospective observational studies." Cancer **109**(12 Suppl): 2712-2749.

The role of diet for the risk of breast cancer is of great interest as a potentially modifiable risk factor. The evidence from prospective observational studies was reviewed and summarized on selected dietary factors, gene-diet interactions, and breast cancer incidence. Dietary factors were considered that, based on their nutritional constituents, are of particular interest in the context of breast cancer: fat intake, biomarkers of fat intake, fruit and vegetable consumption, antioxidant vitamins (vitamins A, C, E, and beta-carotene), serum antioxidants, carbohydrate intake, glycemic index and glycemic load, dairy consumption (including vitamin D), consumption of soy products and isoflavones, green tea, heterocyclic amines, and adolescent diet. The PubMed database was searched for all prospective studies that relate these dietary items to the incidence of breast cancer or consider gene-diet interactions. Among the prospective epidemiologic studies conducted on diet and breast cancer incidence and gene-diet interactions and breast cancer incidence, to date there is no association that is consistent, strong, and statistically significant, with the exception of alcohol intake, overweight, and weight gain. The apparent lack of association between diet and breast cancer may reflect a true absence of association between diet and breast cancer incidence or may be due to measurement error exceeding the variation in the diet studied, lack of sufficient follow-up, and focus on an age range of low susceptibility. The risk of breast cancer can be reduced by avoidance of weight gain in adulthood and limiting the consumption of alcohol.

Milner, J. A. (2002). "Strategies for cancer prevention: the role of diet." Br J Nutr **87 Suppl 2**: S265-272.

Linkages between diet habits and cancer risk have surfaced from a multitude of epidemiological and preclinical studies. Collectively these studies provide rather compelling evidence that dietary components modify the incidence and biological behavior of tumors. While the risk of breast, prostate, colon, lung and liver cancers are frequently associated with dietary patterns, inconsistencies are not uncommon. These inconsistencies likely reflect the multi-factorial and complex nature of cancer and the specificity that individual dietary constituents have in modifying cancer related genetic pathways. The complexity of defining the role of diet is underscored by the numerous and diverse essential and non-essential components that may alter one or more phases of the cancer process. The explosive increase in the recognition of genes and pathways for regulating cell growth and development, and evaluating the response to hormones and other chemicals synthesized by the body, offers exciting opportunities for unraveling the molecular targets by which dietary components influence cancer prevention. It is recognized that all cells have unique 'signatures' that are characterized by active and inactive genes and cellular products. It is certainly plausible that bridging knowledge about these unique cellular characteristics with the molecular targets for nutrients can be used to assist in optimizing nutrition and minimizing cancer risk.

Milner, J. A. (2006). "Diet and cancer: facts and controversies." Nutr Cancer **56**(2): 216-224.

Evidence continues to mount that dietary components are important determinants of cancer risk and tumor behavior. Although these linkages are fascinating, numerous inconsistencies are also evident in the literature. Although multifactorial, these discrepancies likely reflect variation in the ability of food constituents to reach and/or modify critical molecular targets. Genetic polymorphisms can alter the response to dietary components (nutrigenetic effect) by influencing the absorption, metabolism, or site of action. Likewise, variation in DNA methylation patterns and other epigenomic events that influence overall gene expression can influence the biological response to food components and vice versa. Fluctuations in the ability of food components to increase or depress gene expression (nutritional transcriptomic effect) may also account for some of the inconsistencies in the response to foods. Functional proteomic studies that capture all of the proteins produced by a species and link them to physiological significance within the cell will be fundamental to understanding the relationship between dietary interventions, proteome changes, and cancer. Although a bioactive food component may influence a number of key molecular events that are involved with cancer prevention, to do so it must achieve an effective concentration within the target site, be in the correct metabolic form, and bring about a change in one or more small molecular weight signals in the cellular milleau (metabolomic effects). Fundamental to assessing and evaluating the significance of the interrelationships among bioactive food components with nutrigenetics, nutritional epigenomics, nutritional transcriptomics, proteomics, and metabolomics is knowledge about the appropriate tissue/cell or surrogate to evaluate and validated biomarkers that reflect changes in each. As the era of molecular nutrition grows, a greater understanding about the role of foods and their components on cancer risk and tumor behavior will surely unfold. Such information will be critical in the development of effective preemptive approaches to reduce the cancer burden.

Motti, M. L., et al. (2018). "MicroRNAs, Cancer and Diet: Facts and New Exciting Perspectives." Curr Mol Pharmacol **11**(2): 90-96.

BACKGROUND: MicroRNAs (miRNAs) are small non-coding RNAs able to regulate gene expression at multiple levels. They are detected in tissues, blood, and other body fluids with high stability and have a recognized role in maintaining of tissue homeostasis. Aberrant expression profile of miRNAs has been observed in several diseases, primarily cancer. As a consequence, the analysis of miRNA signature has recognized diagnostic and prognostic role in human diseases, and the development of miRNA-based therapies is currently under investigation. Recently, emerging but controversial data have revealed the possibility that diet-derived miRNAs might be transferred from food in living organisms to regulate gene expression. Thus, exogenous dietderived miRNAs might substantially contribute to the pool of circulating miRNAs to preserve tissue homeostasis and health status in recipient's organisms, opening new perspectives for diet in heath and disease. OBJECTIVE: This brief review aims at summarizing data concerning the recognized role of miRNAs as biomarkers, drugs and therapeutic targets in cancer and the detection and the activity of diet-derived miRNAs in both physiological and pathological conditions. CONCLUSION: MiRNAs have emerged as crucial molecules in anticancer therapies and diet-derived miRNAs might contribute to the pool of circulating miRNAs to preserve, maintain or restore health.

Nara, T., et al. (2016). "Altered miRNA expression in high-fat diet-induced prostate cancer progression." Carcinogenesis **37**(12): 1129-1137.

Recent evidence suggests that a high-fat diet (HFD) plays an important role in prostate carcinogenesis; however, underlying mechanisms largely remain unknown. Here, we investigated microRNA (miRNA) expression changes in murine prostate cancer (PCa) xenografts using two different diets: HFD and control diet. We then assessed the roles and targets of altered miRNAs in HFD-induced PCa progression. We identified 38 up- and 21 downregulated miRNAs in xenografts under HFD conditions using the miRCURY LNA microRNA array. The differences in 10 candidate miRNAs were validated using quantitative RT-PCR. We focused on miR-130a because the expression levels were significantly lower in the three PCa cell lines in comparison with benign prostate PINT1B cells. PCa cells cultured in a medium containing HFD mouse serum were associated with significantly higher cell proliferation rates and lower miR-130a expression levels. Further, miR-130a modulated MET expression in PCa cells, and MET was overexpressed in in vitro and in vivo HFD-induced PCa progression models. Moreover, ectopic miR-130a downregulated AR in LNCaP cells and DICER1 in PC-3 and DU145 cells, respectively. In human tissues, as elucidated using laser capture microdissection, the mean miR-130a expression level in cancer epithelium was significantly lower than that in normal epithelium. Furthermore, cytoplasmic MET in PCa tissues was overexpressed in patients with higher body mass index. In conclusion, a substantial number of miRNAs was altered in HFD-

induced PCa growth. Specifically, miR-130a was attenuated in HFD-induced PCa progression with MET overexpression. miRNAs thus have implications in the mechanism, prevention and treatment of HFD-induced PCa progression.

Nelson, W. G., et al. (2014). "The diet as a cause of human prostate cancer." Cancer Treat Res **159**: 51-68.

Asymptomatic prostate inflammation and prostate cancer have reached epidemic proportions among men in the developed world. Animal model studies implicate dietary carcinogens, such as the heterocyclic amines from over-cooked meats and sex steroid hormones, particularly estrogens, as candidate etiologies for prostate cancer. Each acts by causing epithelial cell damage, triggering an inflammatory response that can evolve into a chronic or recurrent condition. This milieu appears to spawn proliferative inflammatory atrophy (PIA) lesions, a type of focal atrophy that represents the earliest of prostate cancer precursor lesions. Rare PIA lesions contain cells which exhibit high c-Myc expression, shortened telomere segments, and epigenetic silencing of genes such as GSTP1, encoding the pi-class glutathione S-transferase, all characteristic of prostatic intraepithelial neoplasia (PIN) and prostate cancer. Subsequent genetic changes, such as the gene translocations/deletions that generate fusion transcripts between androgen-regulated genes (such as TMPRSS2) and genes encoding ETS family transcription factors (such as ERG1), arise in PIN lesions and may promote invasiveness characteristic of prostatic adenocarcinoma cells. Lethal prostate cancers contain markedly corrupted genomes and epigenomes. Epigenetic silencing, which seems to arise in response to the inflamed microenvironment generated by dietary carcinogens and/or estrogens as part of an epigenetic "catastrophe" affecting hundreds of genes, persists to drive clonal evolution through metastatic dissemination. The cause of the initial epigenetic "catastrophe" has not been determined but likely involves defective chromatin structure maintenance by over-exuberant DNA methylation or histone modification. With dietary carcinogens and estrogens driving pro-carcinogenic inflammation in the developed world, it is tempting to speculate that dietary components associated with decreased prostate cancer risk, such as intake of fruits and vegetables, especially tomatoes and crucifers, might act to attenuate the ravages of the chronic or recurrent inflammatory processes. Specifically, nutritional agents might prevent PIA lesions or reduce the propensity of PIA lesions to suffer "catastrophic" epigenome corruption.

Nelson, W. G., 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 GSTPI function as a 'caretaker' gene during the pathogenesis of prostate cancer, in which the early loss of GSTPI 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.

Newmark, H. L., et al. (2009). "Western-style diet-induced colonic tumors and their modulation by calcium and vitamin D in C57Bl/6 mice: a preclinical model for human sporadic colon cancer." Carcinogenesis **30**(1): 88-92.

We reported previously that a new Western-style diet (NWD) for 18 months, consisting of elevated lipids and decreased calcium, vitamin D and methyl-donor nutrients, induced colonic tumors in normal C57Bl/6 mice [Newmark, H.L. et al. (2001) A Western-style diet induces benign and malignant neoplasms in the colon of normal C57Bl/6 mice. Carcinogenesis, 22, 1871-1875], suggesting a new mouse model for human sporadic colon cancer. Here, we have extended this study during a longer feeding period of 2 years wherein tumor formation, tumor inhibition by addition of dietary calcium and vitamin D and their effects on gene expression were determined. We also similarly tested individual supplements of methyl donor (transfer) nutrients (folic acid, choline, methionine and dietary fiber), but these had no significant effect on colonic tumor incidence or multiplicity, whereas supplementation with combined calcium and vitamin D produced significant decrease in both colon tumor incidence and multiplicity, during 2 years of feeding. No visible colonic tumors were found at 6 months, very few at 12 months, more at 18 months and significantly at 24 months. In a related study of gene changes of the mouse colonic mucosa at 6 months of feeding taken from this study, long before any tumors were visibly detectable, indicated altered profiles of gene expression linked to later risk of dietary initiation of colon tumor formation. This type of early genetic altered profile, an indication of increased risk of later colonic tumor development, may become a useful tool for prediction of colon

tumor risk while the colon grossly still appears histologically and physiologically normal.

Nguyen, N. M., et al. (2017). "Maternal intake of high n-6 polyunsaturated fatty acid diet during pregnancy causes transgenerational increase in mammary cancer risk in mice." Breast Cancer Res **19**(1): 77.

BACKGROUND: Maternal and paternal high-fat (HF) diet intake before and/or during pregnancy increases mammary cancer risk in several preclinical models. We studied if maternal consumption of a HF diet that began at a time when the fetal primordial germ cells travel to the genital ridge and start differentiating into germ cells would result in a transgenerational inheritance of increased mammary cancer risk. METHODS: Pregnant C57BL/6NTac mouse dams were fed either a control AIN93G or isocaloric HF diet composed of corn oil high in n-6 polyunsaturated fatty acids between gestational days 10 and 20. Offspring in subsequent F1-F3 generations were fed only the control diet. RESULTS: Mammary tumor incidence induced by 7,12-dimethylbenz [a]anthracene was significantly higher in F1 ($p < 0.016$) and F3 generation offspring of HF diet-fed dams ($p < 0.040$) than in the control offspring. Further, tumor latency was significantly shorter ($p < 0.028$) and burden higher ($p < 0.027$) in F1 generation HF offspring, and similar trends were seen in F3 generation HF offspring. RNA sequencing was done on normal mammary glands to identify signaling differences that may predispose to increased breast cancer risk by maternal HF intake. Analysis revealed 1587 and 4423 differentially expressed genes between HF and control offspring in F1 and F3 generations, respectively, of which 48 genes were similarly altered in both generations. Quantitative real-time polymerase chain reaction analysis validated 13 chosen up- and downregulated genes in F3 HF offspring, but only downregulated genes in F1 HF offspring. Ingenuity Pathway Analysis identified upregulation of Notch signaling as a key alteration in HF offspring. Further, knowledge-fused differential dependency network analysis identified ten node genes that in the HF offspring were uniquely connected to genes linked to increased cancer risk (ANKEF1, IGFBP6, SEMA5B), increased resistance to cancer treatments (SLC26A3), poor prognosis (ID4, JAM3, TBX2), and impaired anticancer immunity (EGR3, ZBP1). CONCLUSIONS: We conclude that maternal HF diet intake during pregnancy induces a transgenerational increase in offspring mammary cancer risk in mice. The mechanisms of inheritance in the F3 generation may be different from the F1 generation because significantly more changes were seen in the transcriptome.

Nkondjock, A., et al. (2006). "Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians." Breast Cancer Res Treat **98**(3): 285-294.

BACKGROUND: Although the connection between diet, lifestyle and hormones suggests that nutritional and lifestyle factors may exert an influence in the etiology of breast cancer (BC), it is not clear whether these factors operate in the same way in women with BRCA1 and BRCA2 (BRCA) gene mutations who already have an elevated BC risk. METHODS: A case-control study was conducted within a cohort of 80 French-Canadian families with 250 members involving 89 carriers of mutated BRCA gene affected with BC and 48 non-affected carriers. A validated semi-quantitative food frequency questionnaire was used to ascertain dietary intake, and a lifestyle core questionnaire, to gather information on physical activity and other lifestyle risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in unconditional logistic regression models. RESULTS: After adjustment for age, maximum lifetime body mass index (BMI) and physical activity, a positive association was found between total energy intake and BRCA-related BC risk. OR was 2.76 (95%CI: 1.10-7.02; p=0.026 for trend), when comparing the highest tertile of intake with the lowest. The intake of other nutrients and dietary components was not significantly associated with the risk of BC. Age at the time the subjects reached maximum BMI was significantly related to an elevated BC risk (OR=2.90; 95%CI: 1.01-8.36; p=0.046 for trend). In addition, a direct and significant relationship was noted between maximum weight gain since both age 18 and 30 years and BC risk. The ORs were 4.64 (95%CI: 1.52-14.12; p=0.011 for trend) for weight gain since age 18 years and 4.11 (95%CI: 1.46-11.56; p=0.013 for trend) for weight gain since age 30 years, respectively. No overall association was apparent between BRCA-related BC risk and BMI, smoking, and physical activity. CONCLUSION: The results of this preliminary study suggest that weight control in adulthood through dietary energy intake restriction is an important factor for the prevention of BRCA-related BC risk.

O'Keefe, S. J. (2016). "Diet, microorganisms and their metabolites, and colon cancer." Nat Rev Gastroenterol Hepatol **13**(12): 691-706.

Colorectal cancer is one of the so-called westernized diseases and the second leading cause of cancer death worldwide. On the basis of global epidemiological and scientific studies, evidence suggests that the risk of colorectal cancer is increased by processed and unprocessed meat consumption but suppressed by fibre, and that food composition affects

colonic health and cancer risk via its effects on colonic microbial metabolism. The gut microbiota can ferment complex dietary residues that are resistant to digestion by enteric enzymes. This process provides energy for the microbiota but culminates in the release of short-chain fatty acids including butyrate, which are utilized for the metabolic needs of the colon and the body. Butyrate has a remarkable array of colonic health-promoting and antineoplastic properties: it is the preferred energy source for colonocytes, it maintains mucosal integrity and it suppresses inflammation and carcinogenesis through effects on immunity, gene expression and epigenetic modulation. Protein residues and fat-stimulated bile acids are also metabolized by the microbiota to inflammatory and/or carcinogenic metabolites, which increase the risk of neoplastic progression. This Review will discuss the mechanisms behind these microbial metabolite effects, which could be modified by diet to achieve the objective of preventing colorectal cancer in Western societies.

Ou, J., et al. (2013). "Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans." Am J Clin Nutr **98**(1): 111-120.

BACKGROUND: Epidemiologic studies have suggested that most cases of sporadic colon cancer can be attributed to diet. The recognition that colonic microbiota have a major influence on colonic health suggests that they might mediate colonic carcinogenesis. OBJECTIVE: To examine the hypothesis that the influence of diet on colon cancer risk is mediated by the microbiota through their metabolites, we measured differences in colonic microbes and their metabolites in African Americans with a high risk and in rural native Africans with a low risk of colon cancer. DESIGN: Fresh fecal samples were collected from 12 healthy African Americans aged 50-65 y and from 12 age- and sex-matched native Africans. Microbiomes were analyzed with 16S ribosomal RNA gene pyrosequencing together with quantitative polymerase chain reaction of the major fermentative, butyrate-producing, and bile acid-deconjugating bacteria. Fecal short-chain fatty acids were measured by gas chromatography and bile acids by liquid chromatography-mass spectrometry. RESULTS: Microbial composition was fundamentally different, with a predominance of Prevotella in native Africans (enterotype 2) and of Bacteroides in African Americans (enterotype 1). Total bacteria and major butyrate-producing groups were significantly more abundant in fecal samples from native Africans. Microbial genes encoding for secondary bile acid production were more abundant in African Americans, whereas those encoding for methanogenesis and hydrogen sulfide production were higher in native Africans. Fecal secondary bile acid concentrations were higher in African Americans, whereas short-chain fatty acids were higher in native Africans. CONCLUSION: Our results support the hypothesis that colon cancer risk is influenced by the balance between microbial production of health-promoting metabolites such as butyrate and potentially carcinogenic metabolites such as secondary bile acids.

Parasramka, M. A., et al. (2012). "MicroRNAs, diet, and cancer: new mechanistic insights on the epigenetic actions of phytochemicals." Mol Carcinog **51**(3): 213-230.

There is growing interest in the epigenetic mechanisms that impact human health and disease, including the role of microRNAs (miRNAs). These small (18-25 nucleotide), evolutionarily conserved, non-coding RNA molecules regulate gene expression in a post-transcriptional manner. Several well-orchestered regulatory mechanisms involving miRNAs have been identified, with the potential to target multiple signaling pathways dysregulated in cancer. Since the initial discovery of miRNAs, there has been progress towards therapeutic applications, and several natural and synthetic chemopreventive agents also have been evaluated as modulators of miRNA expression in different cancer types. This review summarizes the most up-to-date information related to miRNA biogenesis, and critically evaluates proposed miRNA regulatory mechanisms in relation to cancer signaling pathways, as well as other epigenetic modifications (DNA methylation patterns, histone marks) and their involvement in drug resistance. We also discuss the mechanisms by which dietary factors regulate miRNA expression, in the context of chemoprevention versus therapy.

Paul, B., et al. (2015). "Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases." Clin Epigenetics **7**: 112.

Epigenetic modulation of gene activity occurs in response to non-genetic factors such as body weight status, physical activity, dietary factors, and environmental toxins. In addition, each of these factors is thought to affect and be affected by the gut microbiome. A primary mechanism that links these various factors together in mediating control of gene expression is the production of metabolites that serve as critical cofactors and allosteric regulators of epigenetic processes. Here, we review the involvement of the gut microbiota and its interactions with dietary factors, many of which have known cellular bioactivity, focusing on particular epigenetic processes affected and the influence they have on human health and disease, particularly cancer and response to treatment. Advances in DNA sequencing have

expanded the capacity for studying the microbiome. Combining this with rapidly improving techniques to measure the metabolome provides opportunities to understand complex relationships that may underlie the development and progression of cancer as well as treatment-related sequelae. Given broad reaching and fundamental biology, both at the cellular and organismal levels, we propose that interactive research programs, which utilize a wide range of mutually informative experimental model systems-each one optimally suited for answering particular questions-provide the best path forward for breaking ground on new knowledge and ultimately understanding the epigenetic significance of the gut microbiome and its response to dietary factors in cancer prevention and therapy.

Pendas, A. M., et al. (2004). "Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice." Mol Cell Biol **24**(12): 5304-5313.

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.

Perloy, A., et al. (2018). "The Role of Genetic Variants in the Association between Dietary Acrylamide and Advanced Prostate Cancer in the Netherlands Cohort Study on Diet and Cancer." Nutr Cancer **70**(4): 620-631.

To investigate the association between dietary acrylanide and advanced prostate cancer, we examined acrylamide-gene interactions for advanced prostate cancer risk by using data from the Netherlands Cohort Study. Participants (n = 58,279 men) completed a baseline food frequency questionnaire (FFQ), from which daily acrylamide intake was calculated. At baseline, 2,411 men were randomly selected from the full cohort for case-cohort analysis. Fifty eight selected single nucleotide polymorphisms (SNPs) and two gene deletions in genes in acrylamide metabolism, DNA repair, sex steroid systems, and oxidative stress were analyzed. After 20.3 years of follow-up, 1,608 male subcohort members and 948 advanced prostate cancer cases were available for Cox analysis. Three SNPs showed a main association with advanced prostate cancer risk after multiple testing correction: catalase (CAT) rs511895, prostaglandin-endoperoxide synthase 2 (PTGS2) rs5275, and xeroderma pigmentosum group C (XPC) rs2228001. With respect to acrylamide-gene interactions, only rs1800566 in NAD (P)H quinone dehydrogenase 1 (NQO1) and rs2301241 in thioredoxin (TXN) showed a nominally statistically significant multiplicative interaction with acrylamide intake for advanced prostate cancer risk. After multiple testing corrections, none were statistically significant. In conclusion, no clear evidence was found for interaction between acrylamide intake and selected genetic variants for advanced prostate cancer risk.

Poomphakwaen, K., et al. (2014). "XRCC1 gene polymorphism, diet and risk of colorectal cancer in Thailand." Asian Pac J Cancer Prev **15**(17): 7479-7486.

BACKGROUND: Colorectal cancer (CRC) is one of the most common cancers worldwide. This study aimed to investigate the interaction between the presence of a polymorphism of the XRCC1 gene and known risk factors for colorectal cancer in Thailand. MATERIALS AND METHODS: A hospital-based case-control study was conducted in Thailand. The participants were 230 histologically confirmed new cases and 230 controls matched by sex and age and recruited from the same hospital. Information about demographic characteristics, life style, and dietary habits was collected using structured interviews, and blood samples were taken which were used for the detection of a homozygous and heterozygous polymorphisms of XRCC1. Associations were assessed using multiple conditional logistic regression. RESULTS: In the univariate analysis, factors found to be significantly associated with an increased risk for CRC were the presence of the XRCC1 AA homozygote (OR= 4.95; 95% CI: 1.99-12.3), a first degree family history of cancer (OR= 1.74; 95% CI: 1.18-2.58), and a high frequency of pork consumption (OR= 1.49; 95% CI: 1.00-2.21). Intakes of fish fruit and vegetables appeared to be protective factors, but the associations were not statistically significant. In the multivariate analysis only the XRCC1 AA homozygote polymorphism and a family history of cancer emerged as risk factors (OR= 4.96; 95% CI: 1.90- 12.95 and OR=1.80; 95% CI: 1.18-2.72, respectively). CONCLUSIONS: While the XRCC1 AA homozygote and a family history of cancer were found to be associated with an increased risk of CRC,

none of the dietary intake variables were clearly identified as risk or protective factors. There is a need for further research to determine the reasons for this.

Pussila, M., et al. (2013). "Cancer-predicting gene expression changes in colonic mucosa of Western diet fed Mlh1+/- mice." PLoS One **8**(10): e76865.

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the Western world and interactions between genetic and environmental factors, including diet, are suggested to play a critical role in its etiology. We conducted a long-term feeding experiment in the mouse to address gene expression and methylation changes arising in histologically normal colonic mucosa as putative cancer-predisposing events available for early detection. The expression of 94 growth-regulatory genes previously linked to human CRC was studied at two time points (5 weeks and 12 months of age) in the heterozygote Mlh1(+/-) mice, an animal model for human Lynch syndrome (LS), and wild type Mlh1(+/+) littermates, fed by either Western-style (WD) or AIN-93G control diet. In mice fed with WD, proximal colon mucosa, the predominant site of cancer formation in LS, exhibited a significant expression decrease in tumor suppressor genes, Dkk1, Hoxd1, Slc5a8, and Socs1, the latter two only in the Mlh1(+/-) mice. Reduced mRNA expression was accompanied by increased promoter methylation of the respective genes. The strongest expression decrease (7.3 fold) together with a significant increase in its promoter methylation was seen in Dkk1, an antagonist of the canonical Wnt signaling pathway. Furthermore, the inactivation of Dkk1 seems to predispose to neoplasias in the proximal colon. This and the fact that Mlh1 which showed only modest methylation was still expressed in both Mlh1(+/-) and Mlh1(+/+) mice indicate that the expression decreases and the inactivation of Dkk1 in particular is a prominent early marker for colon oncogenesis.

Reszka, E., et al. (2006). "Genetic polymorphism of xenobiotic metabolising enzymes, diet and cancer susceptibility." Br J Nutr **96**(4): 609-619.

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.

Ritenbaugh, C. (2000). "Diet and prevention of colorectal cancer." Curr Oncol Rep **2**(3): 225-233.

There is a 20-fold difference in incidence rates of colorectal cancer between the areas of highest incidence (North America and Australia) and lowest incidence (India). Animal studies, epidemiologic research, and clinical trials continue to focus on diet in the search for responsible environmental factors. Between 1997 and 1999, a number of research areas have had considerable activity, and they provide the focus for this review. Among foods, vegetables, cereals, and soy have been topics of recent research. Nutrients from foods and supplements have also gained attention, including n-3 fatty acids, calcium, and B vitamins. Gene-environment interactions are beginning to be studied in populations. Studies of the interaction between polymorphisms in the gene for methylenetetrahydrofolate reductase (MTHFR) and dietary components for risk of both colorectal cancer and adenomatous polyps provide a glimpse into the future of diet and cancer research.

Ross, S. A. (2003). "Diet and DNA methylation interactions in cancer prevention." Ann N Y Acad Sci **983**: 197-207.

Epigenetic events constitute an important mechanism by which gene function is selectively activated or inactivated. Since epigenetic events are susceptible to change they offer potential explanations

of how environmental factors, including diet, may modify cancer risk and tumor behavior. Abnormal methylation patterns are a nearly universal finding in cancer, as changes in DNA methylation have been observed in many cancer tissues (e.g., colon, stomach, uterine cervix, prostate, thyroid, and breast). Site-specific alterations in DNA methylation have also been observed in cancer and may play a significant role in gene regulation and cancer development. This review presents intriguing evidence that part of the anticancer properties attributed to several bioactive food components, encompassing both essential nutrients and non-essential components, may relate to DNA methylation patterns. Four sites where dietary factors may be interrelated with DNA methylation are discussed. First, dietary factors may influence the supply of methyl groups available for the formation of S-adenosylmethionine (SAM). Second, dietary factors may modify the utilization of methyl groups by processes including shifts in DNA methyltransferase (Dnmt) activity. A third plausible mechanism may relate to DNA demethylation activity. Finally, the DNA methylation patterns may influence the response to a bioactive food component.

Ross, S. A. (2010). "Evidence for the relationship between diet and cancer." Exp Oncol **32**(3): 137-142.

The relationship between diet and cancer has advanced in recent years, but much remains to be understood with respect to diet and dietary components in cancer risk and prevention. Evidence from clinical trial outcomes, epidemiological observations, preclinical models and cell culture systems have all provided clues about the biology of cancer prevention. Sequencing of the human genome has opened the door to an exciting new phase for nutritional science. There are also many advances in our understanding of the control of gene expression in eukaryotic cells that might impact cancer development, including mechanisms regulating chromatin structure and dynamics, epigenetic processes (DNA methylation, histone posttranslational modification), transcription factors, and noncoding RNA and evidence suggests that environmental factors such as diet influence these processes. Unraveling the effects of bioactive food components on genes and their encoded proteins as well as identifying genetic influences on dietary factors is essential for identifying those who will and will not benefit from intervention strategies for cancer prevention. Additional research needs concerning diet and cancer prevention include: identification and validation of cancer biomarkers and markers of dietary exposure; investigation of the exposure/temporal relationship between food component intakes and cancer prevention; examination of possible tissue specificity in response to dietary factors; and examination of interactions among bioactive food components as determinants of response. Other emerging areas that require greater attention include understanding the link between obesity, diet and cancer, the interaction between diet and the microbiome, as well as how bioactive food components modulate inflammatory processes. Importantly, for the future of nutrigenomics, the "omics" (e.g., genomics, epigenomics, transcriptomics, proteomics, metabolomics) approach may provide useful biomarkers of cancer prevention, early disease, or nutritional status, as well as identify potential molecular targets in cancer processes that are modulated by dietary constituents and/or dietary patterns.

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**: 419-436.

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.

Simopoulos, A. P. (2004). "The traditional diet of Greece and cancer." Eur J Cancer Prev **13**(3): 219-230.

The term 'Mediterranean diet', implying that all Mediterranean people have the same diet, is a misnomer. The countries around the Mediterranean basin have different diets, religions and cultures. Their diets differ in the amount of total fat, olive oil, type of meat, wine, milk, cheese, fruits and vegetables; and

the rates of coronary heart disease and cancer, with the lower death rates and longer life expectancy occurring in Greece. The diet of Crete represents the traditional diet of Greece prior to 1960. Analyses of the dietary pattern of the diet of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of n-6/n-3 essential fatty acids (EFA), high amounts of fibre, antioxidants (especially resveratrol from wine and polyphenols from olive oil), vitamins E and C, some of which have been shown to be associated with lower risk of cancer, including cancer of the breast. Epidemiological studies and animal experiments indicate that n-3 fatty acids exert protective effects against some common cancers, especially cancers of the breast, colon and prostate. Many mechanisms are involved, including suppression of neoplastic transformation, cell growth inhibition, and enhanced apoptosis and anti-angiogenicity, through the inhibition of eicosanoid production from n-6 fatty acids; and suppression of cyclooxygenase 2 (COX-2), interleukin 1 (IL-1) and IL-6 gene expression by n-3 fatty acids. Recent intervention studies in breast cancer patients indicate that n-3 fatty acids, and docosahexaenoic acid (DHA) in particular, increase the response to chemopreventive agents. In patients with colorectal cancer, eicosapentaenoic acid (EPA) and DHA decrease cell proliferation, and modulate favourably the balance between colonic cell proliferation and apoptosis. These findings should serve as a strong incentive for the initiation of intervention trials that will test the effect of specific dietary patterns in the prevention and management of patients with cancer.

Singh, S. M., et al. (2003). "Involvement of gene-diet/drug interaction in DNA methylation and its contribution to complex diseases: from cancer to schizophrenia." Clin Genet **64**(6): 451-460.

Most biological processes, including diseases, involve genetic and non-genetic factors. Also, the realization of a genetic potential may depend on environmental factors by directly affecting the expression of gene (s). Exactly how different environmental factors affect gene expression is not well understood. One of the mechanisms may involve DNA methylation and thereby gene expression. Diet, chemicals, and metals are known to affect DNA methylation and other epigenetic processes but are just beginning to be elucidated. For example, methylation of cytosine (s) in the promoter region could prevent the binding of transcription factors or create binding sites for complexes that deacetylate neighboring histones that in turn compact the chromatin, encouraging a gene to become silent. This article will discuss DNA methylation as an epigenetic mechanism of gene regulation and examine how factors like diet, chemicals, and metals may affect DNA methylation. The effect of alterations in DNA methylation may include aberrant expression of genes or genomes and chromosomal instability, which in turn may contribute to the etiology of complex multifactorial diseases. A similar mechanism is now recognized in a number of cancers. There is also indirect evidence to suggest that methylation could apply to a number of complex diseases, including schizophrenia.

Slattery, M. L., et al. (2014). "Diet and lifestyle factors interact with MAPK genes to influence survival: the Breast Cancer Health Disparities Study." Cancer Causes Control **25**(9): 1211-1225.

INTRODUCTION: MAPK genes are activated by a variety of factors related to growth factors, hormones, and environmental stress. METHODS: We evaluated associations between 13 MAPK genes and survival among 1,187 nonHispanic White and 1,155 Hispanic/Native American (NA) women diagnosed with breast cancer. We assessed the influence of diet, lifestyle, and genetic ancestry on these associations. Percent NA ancestry was determined from 104 Ancestry Informative Markers. Adaptive rank truncation product (ARTP) was used to determine gene and pathway significance. RESULTS: Associations were predominantly observed among women with lower NA ancestry. Specifically, the mitogen-activated protein kinases (MAPK) pathway was associated with all-cause mortality (P ARTP = 0.02), but not with breast cancer-specific mortality (P ARTP = 0.10). However, MAP2K1 and MAP3K9 were associated with both breast cancer-specific and all-cause mortality. MAPK12 (P ARTP = 0.05) was only associated with breast cancer-specific mortality, and MAP3K1 (P ARTP = 0.02) and MAPK1 (P ARTP = 0.05) were only associated with all-cause mortality. Among women with higher NA ancestry, MAP3K2 was significantly associated with all-cause mortality (P ARTP = 0.04). Several diet and lifestyle factors, including alcohol consumption, caloric intake, dietary folate, and cigarette smoking, significantly modified the associations with MAPK genes and all-cause mortality. CONCLUSIONS: Our study supports an association between MAPK genes and survival after diagnosis with breast cancer, especially among women with low NA ancestry. The interaction between genetic variation in the MAPK pathway with diet and lifestyle factors for all women supports the important role of these factors for breast cancer survivorship.

Slattery, M. L., et al. (2011). "Diet and colorectal cancer: analysis of a candidate pathway using SNPS, haplotypes, and multi-gene assessment." Nutr Cancer **63**(8): 1226-1234.

There is considerable biologic plausibility to the hypothesis that genetic variability in pathways involved in insulin signaling and energy homeostasis may modulate dietary risk associated with colorectal cancer. We utilized data from 2 population-based case-control studies of colon (n = 1,574 cases, 1,970 controls) and rectal (n = 791 cases, 999 controls) cancer to evaluate genetic variation in candidate SNPs identified from 9 genes in a candidate pathway: PDK1, RP6KA1, RPS6KA2, RPS6KB1, RPS6KB2, PTEN, FRAP1 (mTOR), TSC1, TSC2, Akt1, PIK3CA, and PRKAG2 with dietary intake of total energy, carbohydrates, fat, and fiber. We employed SNP, haplotype, and multiple-gene analysis to evaluate associations. PDK1 interacted with dietary fat for both colon and rectal cancer and with dietary carbohydrates for colon cancer. Statistically significant interaction with dietary carbohydrates and rectal cancer was detected by haplotype analysis of PDK1. Evaluation of dietary interactions with multiple genes in this candidate pathway showed several interactions with pairs of genes: Akt1 and PDK1, PDK1 and PTEN, PDK1 and TSC1, and PRKAG2 and PTEN. Analyses show that genetic variation influences risk of colorectal cancer associated with diet and illustrate the importance of evaluating dietary interactions beyond the level of single SNPs or haplotypes when a biologically relevant candidate pathway is examined.

Slattery, M. L., et al. (2015). "MAPK genes interact with diet and lifestyle factors to alter risk of breast cancer: the Breast Cancer Health Disparities Study." Nutr Cancer **67**(2): 292-304.

Mitogen-activated protein kinases (MAPK) are integration points for multiple biochemical signals. We evaluated 13 MAPK genes with breast cancer risk and determined if diet and lifestyle factors mediated risk. Data from 3 population-based case-control studies conducted in Southwestern United States, California, and Mexico included 4183 controls and 3592 cases. Percent Indigenous American (IA) ancestry was determined from 104 ancestry informative markers. The adaptive rank truncated product (ARTP) was used to determine the significance of each gene and the pathway with breast cancer risk, by menopausal status, genetic ancestry level, and estrogen receptor (ER)/progesterone receptor (PR) strata. MAP3K9 was associated with breast cancer overall (P (ARTP) = 0.02) with strongest association among women with the highest IA ancestry (P (ARTP) = 0.04). Several SNPs in MAP3K9 were associated with ER+/PR+ tumors and interacted with dietary oxidative balance score (DOBS), dietary folate, body mass index (BMI), alcohol consumption, cigarette smoking, and a history of diabetes. DUSP4 and MAPK8 interacted with calories to alter breast cancer risk; MAPK1 interacted with DOBS, dietary fiber, folate, and BMI; MAP3K2 interacted with dietary fat; and MAPK14 interacted with dietary folate and BMI. The patterns of association across diet and lifestyle factors with similar biological properties for the same SNPs within genes provide support for associations.

Slattery, M. L., et al. (2014). "Diet and lifestyle factors modify immune/inflammation response genes to alter breast cancer risk and prognosis: the Breast Cancer Health Disparities Study." Mutat Res **770**: 19-28.

Tumor necrosis factor-alpha (TNF) and toll-like receptors (TLR) are important mediators of inflammation. We examined 10 of these genes with respect to breast cancer risk and mortality in a genetically admixed population of Hispanic/Native American (NA) (2111 cases, 2597 controls) and non-Hispanic white (NHW) (1481 cases, 1585 controls) women. Additionally, we explored if diet and lifestyle factors modified associations with these genes. Overall, these genes (collectively) were associated with breast cancer risk among women with >70% NA ancestry (P (ARTP) = 0.0008), with TLR1 rs7696175 being the primary risk contributor (OR 1.77, 95% CI 1.25, 2.51). Overall, TLR1 rs7696175 (HR 1.40, 95% CI 1.03, 1.91; P (adj) = 0.032), TLR4 rs5030728 (HR 1.96, 95% CI 1.30, 2.95; P (adj) = 0.014), and TNFRSF1A rs4149578 (HR 2.71, 95% CI 1.28, 5.76; P (adj) = 0.029) were associated with increased breast cancer mortality. We observed several statistically significant interactions after adjustment for multiple comparisons, including interactions between our dietary oxidative balance score and CD40LG and TNFSF1A; between cigarette smoking and TLR1, TLR4, and TNF; between body mass index (BMI) among pre-menopausal women and TRAF2; and between regular use of aspirin/non-steroidal anti-inflammatory drugs and TLR3 and TRA2. In conclusion, our findings support a contributing role of certain TNF-alpha and TLR genes in both breast cancer risk and survival, particularly among women with higher NA ancestry. Diet and lifestyle factors appear to be important mediators of the breast cancer risk associated with these genes.

Slattery, M. L., et al. (1999). "Methylenetetrahydrofolate reductase, diet, and risk of colon cancer." Cancer Epidemiol Biomarkers Prev **8**(6): 513-518.

Individuals with different forms of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, carriers of the C677T mutation versus wild type, show differences in enzyme levels; these differences have been hypothesized to be related to DNA methylation and, perhaps, to the nucleotide pool size. Using data

from an incident case-control study, we evaluated the combined effect of dietary intake of folate, methionine, vitamin B6, vitamin B12, and alcohol and various forms of the MTHFR gene on risk of colon cancer. Individuals homozygous for the variant form of the MTHFR gene (TT) had a slightly lower risk of colon cancer than did individuals who were wild type [CC, odds ratio (OR) = 0.8, 95% confidence interval (CI) = 0.6-1.1 for men; and OR = 0.9, 95% CI = 0.6-1.2 for women]. High levels of intake of folate, vitamin B6, and vitamin B12 were associated with a 30-40% reduction in risk of colon cancer among those with the TT relative to those with low levels of intake who were CC genotype. Associations were stronger for proximal tumors, in which high levels of intake of these nutrients were associated with a halving of risk among those with the TT genotype. The inverse association with high levels of these nutrients in those with the TT genotype was stronger among those diagnosed at an older age. Although imprecise, the inverse association with the low-risk diet that was high in folate and methionine and without alcohol was observed for both the TT genotype (OR = 0.4 95% CI = 0.1-0.9) and the CC/CT genotype (OR = 0.6, 95% CI = 0.4-1.0), but this association was not seen with the high-risk diet for either the TT or CC/CT genotype. Although associations were generally weak, these findings suggest that those with differing MTHFR genotypes may have different susceptibilities to colon cancer, based on dietary consumption of folate, vitamin B6, and vitamin B12.

Slattery, M. L., et al. (2001). "A molecular variant of the APC gene at codon 1822: its association with diet, lifestyle, and risk of colon cancer." Cancer Res **61**(3): 1000-1004.

The adenomatous polyposis coli (APC) gene is important in the etiology of colon cancer. Although germ-line mutations of this gene rarely occur in the population, less penetrant variants of the gene have been reported. One variant, producing an aspartate to valine change at codon 1822 (D1822V) [corrected] has been previously reported as having an allele frequency of 10%. The purpose of this study was to determine whether this D1822V [corrected] variant of the APC gene is associated with colon cancer and whether its association is influenced by other genetic or environmental factors. We used data collected as part of a multicenter study of 1,585 incident cases of colon cancer and 1,945 age- and sex-matched population-based controls to evaluate genetic, dietary, and environmental associations with the D1822V [corrected] variant of the APC gene. The frequency of the valine/valine allele at codon 1,822 was 22.8% in this population. In the control population, 61.5% were homozygote wild type, 33.3% were heterozygotes, and 5.2% were homozygote variant. Cases were slightly less likely to have the homozygous variant APC genotype than were controls [odds ratio (OR), 0.8; 95% confidence interval (CI), 0.6-1.1]; for those diagnosed after age 65, the homozygous APC variant was associated with reduced risk of colon cancer (OR, 0.6; 95% CI, 0.4-1.0). Assessment of the homozygous APC variant with dietary, genetic, and environmental factors showed that individuals with this genotype were at lower risk if they consumed a low-fat diet (OR, 0.2; 95% CI, 0.1-0.5) relative to those who were homozygous wild type and ate a high-fat diet. This finding was specific to a low-fat diet and was unrelated to other dietary variables. These results suggest that the codon 1,822 variant of the APC gene may have functional significance. Individuals who have the valine/valine variant of this gene may be at reduced risk of colon cancer if they eat a low-fat diet.

Smits, K. M., et al. (2010). "Body mass index and von Hippel-Lindau gene mutations in clear-cell renal cancer: Results of the Netherlands Cohort Study on diet and cancer." Ann Epidemiol **20**(5): 401-404.

PURPOSE: Body mass index (BMI) is an important risk factor for clear-cell renal cancer (cc-RCC). A common molecular alteration in cc-RCC is loss-of-function of the von Hippel-Lindau (VHL) gene. We evaluated the association between BMI and VHL mutations in cc-RCC by using data from the Netherlands Cohort Study (NLCS), a prospective study, which comprises 120,852 persons. METHODS: After 11.3 years of follow-up, 337 incident RCC cases were identified; 185 cc-RCC cases were included for analyses. RESULTS: A high BMI at baseline was associated with an increased risk of cc-RCC with or without VHL mutations (per 1 kg/m (2): hazard ratio [HR] = 1.09, 95% confidence interval [CI]: 1.02-1.16 and HR = 1.08, 95%CI: 1.01-1.15, respectively). BMI at age 20 was only associated with an increased risk of cc-RCC with VHL mutations (per 1 kg/m (2): HR =1.09, 95% CI: 1.03-1.16). In contrast, BMI gain since age 20 was only associated with an increased risk in VHL wild-type cases (per 1 kg/m (2): HR = 1.10, 95% CI: 1.03-1.19). CONCLUSION: Our findings indicate that BMI may be differently associated with subtypes of RCC based on VHL mutations.

Smits, K. M., et al. (2008). "Polymorphisms in genes related to activation or detoxification of carcinogens might interact with smoking to increase renal cancer risk: results from The Netherlands Cohort Study on diet and cancer." World J Urol **26**(1): 103-110.

Metabolic gene polymorphisms have previously been suggested as risk factors for renal cell carcinoma (RCC). These polymorphisms are involved in

activation or detoxification of carcinogens in cigarette smoke which is another RCC risk factor. We evaluated gene-environment interactions between CYP1A1, GSTmicro1 and smoking in a large population-based RCC case group. The Netherlands Cohort Study on diet and cancer (NLCS) comprises 120,852 persons who completed a questionnaire on smoking and other risk factors at baseline. After 11.3 years of follow-up, 337 incident RCC cases were identified. DNA was collected for 245 cases. In a case-only analysis, interaction-odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using logistic regression. We observed a moderate, not statistically significant, interaction between current smoking and CYP1A1*2C (OR 1.42; 95% CI 0.70-2.89) and GSTmicro1 null (OR 1.35; 95% CI 0.65-2.79). For current smokers with both a variant (heterozygous or homozygous) in CYP1A1 and GSTmicro1 null, risk was also increased (OR 1.63; 95% CI 0.63-4.24). No interaction was observed between ever smokers, smoking duration (increments of 10 smoking years) or amount (increments of 5 cigarettes/day) and CYP1A or GSTmicro1. Our results show a modest trend towards a statistically significant gene-environment interaction between CYP1A1, GSTmicro1 and smoking in RCC. This could indicate that RCC risk among smokers might be more increased with the CYP1A1*2C genotype, GSTmicro1 null, or both a CYP1A1 variant and GSTmicro1 null.

Sonestedt, E., et al. (2012). "Genetic variation in the glucose-dependent insulinotropic polypeptide receptor modifies the association between carbohydrate and fat intake and risk of type 2 diabetes in the Malmo Diet and Cancer cohort." J Clin Endocrinol Metab **97**(5): E810-818.

CONTEXT: A common genetic variant (rs10423928, A-allele) in the glucose-dependent insulinotropic polypeptide receptor gene (GIPR) is associated with decreased insulin secretion. Glucose-dependent insulinotropic polypeptide is secreted after food consumption and gipr knockout mice fed a high-fat diet are protected against obesity and disturbances in glucose homeostasis. OBJECTIVE: Our objective was to examine the interactions between rs10423928 and macronutrients and fiber intakes on body mass index and type 2 diabetes risk. DESIGN, SETTING, AND PARTICIPANTS: Among nondiabetic subjects in the Swedish population-based Malmo Diet and Cancer cohort (n = 24,840; 45-74 yr), 1541 diabetes cases were identified during 12 yr of follow-up. Dietary intakes were assessed using a diet history method. MAIN OUTCOME MEASURE: Incident type 2 diabetes was identified through registers. RESULTS: There was no indication that dietary intakes significantly modify the association between GIPR genotype and body mass index (P interaction >0.08). We observed significant interactions between GIPR genotype and quintiles of carbohydrate (P = 0.0005) and fat intake (P = 0.0006) on incident type 2 diabetes. The TT-genotype carriers within the highest compared with the lowest carbohydrate quintile were at 23% (95% confidence interval = 5-39%) decreased type 2 diabetes risk. In contrast, AA-genotype carriers in the highest compared with the lowest fat quintile were at 69% (95% confidence interval = 29-86%) decreased risk. CONCLUSIONS: Our prospective, observational study indicates that the type 2 diabetes risk by dietary intake of carbohydrate and fat may be dependent on GIPR genotype. In line with results in gipr knockout mice, AA-genotype carriers consuming high-fat low-carbohydrate diets had reduced type 2 diabetes risk, whereas high-carbohydrate low-fat diets benefitted the two thirds of population homozygous for the T-allele.

Sotos-Prieto, M., et al. (2014). "The association between Mediterranean Diet Score and glucokinase regulatory protein gene variation on the markers of cardiometabolic risk: an analysis in the European Prospective Investigation into Cancer (EPIC)-Norfolk study." Br J Nutr **112**(1): 122-131.

Consumption of a Mediterranean diet (MD) and genetic variation in the glucokinase regulatory protein (GCKR) gene have been reported to be associated with TAG and glucose metabolism. It is uncertain whether there is any interaction between these factors. Therefore, the aims of the present study were to test the association of adherence to a MD and rs780094 (G>A) SNP in the GCKR gene with the markers of cardiometabolic risk, and to investigate the interaction between genetic variation and MD adherence. We studied 20 986 individuals from the European Prospective Investigation into Cancer (EPIC)-Norfolk study. The relative Mediterranean Diet Score (rMED: range 0-18) was used to assess MD adherence. Linear regression was used to estimate the association between the rMED, genotype and cardiometabolic continuous traits, adjusting for potential confounders. In adjusted analyses, we observed independent associations of MD adherence and genotype with cardiometabolic risk, with the highest risk group (AA genotype; lowest rMED) having higher concentrations of TAG, total cholesterol and apoB (12.5, 2.3 and 3.1%, respectively) v. those at the lowest risk (GG genotype; highest rMED). However, the associations of MD adherence with metabolic markers did not differ by genotype, with no significant gene-diet interactions for lipids or for glycated Hb. In conclusion, we found independent associations of the rMED and of the GCKR genotype with cardiometabolic profile, but found no evidence of interaction between them.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Andersen, V., et al. (2013). "Interactions between diet, lifestyle and IL10, IL1B, and PTGS2/COX-2 gene polymorphisms in relation to risk of colorectal cancer in a prospective Danish case-cohort study." PLoS One 8(10): e78366.
2. Andersen, V., et al. (2013). "Systematic review: diet-gene interactions and the risk of colorectal cancer." Aliment Pharmacol Ther 37(4): 383-391.
3. Andersen, V., et al. (2015). "No association between HMOX1 and risk of colorectal cancer and no interaction with diet and lifestyle factors in a prospective Danish case-cohort study." Int J Mol Sci 16(1): 1375-1384.
4. Andrade Fde, O., et al. (2015). "Lipidomic fatty acid profile and global gene expression pattern in mammary gland of rats that were exposed to lard-based high fat diet during fetal and lactation periods associated to breast cancer risk in adulthood." Chem Biol Interact 239: 118-128.
5. Arkan, M. C. (2017). "The intricate connection between diet, microbiota, and cancer: A jigsaw puzzle." Semin Immunol 32: 35-42.
6. Asgharpour, A., et al. (2016). "A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer." J Hepatol 65(3): 579-588.
7. Baidu. http://www.baidu.com. 2018.
8. Brandt, J., et al. (2018). "Thyroid-associated genetic polymorphisms in relation to breast cancer risk in the Malmo Diet and Cancer Study." Int J Cancer 142(7): 1309-1321.
9. Bultman, S. J. (2017). "Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer." Mol Nutr Food Res 61(1).
10. Carter, C. A. (2000). "Protein kinase C as a drug target: implications for drug or diet prevention and treatment of cancer." Curr Drug Targets 1(2): 163-183.
11. Cartier, N., et al. (1994). "[Creation of diet-dependent cancer models in transgenic animals]." Bull Acad Natl Med 178(1): 23-32; discussion 32-24.
12. Cartier, N., et al. (1994). "[The creation of diet-dependent cancer models using transgenesis in animals]." Ann Gastroenterol Hepatol (Paris) 30(4): 175-179; discussion 180.
13. Chan, J. M., et al. (2005). "Role of diet in prostate cancer development and progression." J Clin Oncol 23(32): 8152-8160.
14. Chen, J. and X. Xu (2010). "Diet, epigenetic, and cancer prevention." Adv Genet 71: 237-255.
15. Chen, K., et al. (2006). "[A case-control study on the association between the genetic polymorphism of sulfotransferase 1A1, diet and susceptibility of colorectal cancer]." Zhonghua Zhong Liu Za Zhi 28(9): 670-673.
16. Chen, Y. J., et al. (2016). "Dietary Broccoli Lessens Development of Fatty Liver and Liver Cancer in Mice Given Diethylnitrosamine and Fed a Western or Control Diet." J Nutr 146(3): 542-550.
17. Choi, Y., et al. (2013). "Induction of olfaction and cancer-related genes in mice fed a high-fat diet as assessed through the mode-of-action by network identification analysis." PLoS One 8(3): e56610.
18. Corella, D., et al. (2018). "Effects of the Ser326Cys Polymorphism in the DNA Repair OGG1 Gene on Cancer, Cardiovascular, and All-Cause Mortality in the PREDIMED Study: Modulation by Diet." J Acad Nutr Diet 118(4): 589-605.
19. Curtin, K., et al. (2004). "MTHFR C677T and A1298C polymorphisms: diet, estrogen, and risk of colon cancer." Cancer Epidemiol Biomarkers Prev 13(2): 285-292.
20. Day, S. D., et al. (2013). "Linking inflammation to tumorigenesis in a mouse model of high-fat-diet-enhanced colon cancer." Cytokine 64(1): 454-462.
21. de Oliveira Andrade, F., et al. (2014). "Exposure to lard-based high-fat diet during fetal and lactation periods modifies breast cancer susceptibility in adulthood in rats." J Nutr Biochem 25(6): 613-622.
22. de Vogel, S., et al. (2011). "Dietary methyl donors, methyl metabolizing enzymes, and epigenetic regulators: diet-gene interactions and promoter CpG island hypermethylation in colorectal cancer." Cancer Causes Control 22(1): 1-12.
23. Del Corno, M., et al. (2017). "Linking Diet to Colorectal Cancer: The Emerging Role of MicroRNA in the Communication between Plant and Animal Kingdoms." Front Microbiol 8: 597.
24. Dizik, M., et al. (1991). "Alterations in expression and methylation of specific genes in livers of rats fed a cancer promoting methyl-deficient diet." Carcinogenesis 12(7): 1307-1312.
25. Dong, L., et al. (2017). "Diet-induced obesity links to ER positive breast cancer progression via LPA/PKD-1-CD36 signaling-mediated microvascular remodeling." Oncotarget 8(14): 22550-22562.

26. Drew, J. (2011). "Janice Drew's work on diet and cancer." World J Gastrointest Pathophysiol 2(4): 61-64.
27. Eilati, E., et al. (2013). "Flaxseed enriched diet-mediated reduction in ovarian cancer severity is correlated to the reduction of prostaglandin E (2) in laying hen ovaries." Prostaglandins Leukot Essent Fatty Acids 89(4): 179-187.
28. Escrich, E., 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): 73-78.
29. Escrich, E., et al. (2011). "Olive oil, an essential component of the Mediterranean diet, and breast cancer." Public Health Nutr 14(12A): 2323-2332.
30. Fava, C., et al. (2012). "The Renalase Asp37Glu polymorphism is not associated with hypertension and cardiovascular events in an urban-based prospective cohort: the Malmo Diet and cancer study." BMC Med Genet 13: 57.
31. Ferguson, L. R. (2010). "Recent advances in understanding of interactions between genes and diet in the etiology of colorectal cancer." World J Gastrointest Oncol 2(3): 125-129.
32. Figueiredo, J. C., et al. (2014). "Genome-wide diet-gene interaction analyses for risk of colorectal cancer." PLoS Genet 10(4): e1004228.
33. Fisher, M. L., et al. (2016). "The Ezh2 polycomb group protein drives an aggressive phenotype in melanoma cancer stem cells and is a target of diet derived sulforaphane." Mol Carcinog 55(12): 2024-2036.
34. Gauger, K. J., et al. (2014). "The effects of diet induced obesity on breast cancer associated pathways in mice deficient in SFRP1." Mol Cancer 13: 117.
35. Gay, L. J., et al. (2011). "MLH1 promoter methylation, diet, and lifestyle factors in mismatch repair deficient colorectal cancer patients from EPIC-Norfolk." Nutr Cancer 63(7): 1000-1010.
36. Ghadirian, P., et al. (2009). "Breast cancer risk in relation to the joint effect of BRCA mutations and diet diversity." Breast Cancer Res Treat 117(2): 417-422.
37. Gillman, A. S., et al. (2018). "Body mass index, diet, and exercise: testing possible linkages to breast cancer risk via DNA methylation." Breast Cancer Res Treat 168(1): 241-248.
38. Google. http://www.google.com. 2018.
39. Hardy, T. M. and T. O. Tollefsbol (2011). "Epigenetic diet: impact on the epigenome and cancer." Epigenomics 3(4): 503-518.
40. Hilakivi-Clarke, L., et al. (2005). "Mechanisms mediating the effects of prepubertal (n-3) polyunsaturated fatty acid diet on breast cancer risk in rats." J Nutr 135(12 Suppl): 2946S-2952S.
41. Hursting, S. D., et al. (2001). "Diet and cancer prevention studies in p53-deficient mice." J Nutr 131(11 Suppl): 3092S-3094S.
42. Kachroo, P., et al. (2011). "Classification of diet-modulated gene signatures at the colon cancer initiation and progression stages." Dig Dis Sci 56(9): 2595-2604.
43. Kakkoura, M. G., et al. (2016). "MnSOD and CAT polymorphisms modulate the effect of the Mediterranean diet on breast cancer risk among Greek-Cypriot women." Eur J Nutr 55(4): 1535-1544.
44. Kakkoura, M. G., et al. (2017). "The synergistic effect between the Mediterranean diet and GSTP1 or NAT2 SNPs decreases breast cancer risk in Greek-Cypriot women." Eur J Nutr 56(2): 545-555.
45. Kantor, E. D. and E. L. Giovannucci (2015). "Gene-diet interactions and their impact on colorectal cancer risk." Curr Nutr Rep 4(1): 13-21.
46. Karunanithi, S., et al. (2017). "RBP4-STRA6 Pathway Drives Cancer Stem Cell Maintenance and Mediates High-Fat Diet-Induced Colon Carcinogenesis." Stem Cell Reports 9(2): 438-450.
47. Kim, J., et al. (2014). "Gene-diet interactions in gastric cancer risk: a systematic review." World J Gastroenterol 20(28): 9600-9610.
48. Kim, W. G., et al. (2013). "Diet-induced obesity increases tumor growth and promotes anaplastic change in thyroid cancer in a mouse model." Endocrinology 154(8): 2936-2947.
49. Knackstedt, R. W., et al. (2012). "Epigenetic mechanisms underlying diet-sourced compounds in the prevention and treatment of gastrointestinal cancer." Anticancer Agents Med Chem 12(10): 1203-1210.
50. Kopp, T. I., et al. (2015). "Polymorphisms in ATP-binding cassette transporter genes and interaction with diet and life style factors in relation to colorectal cancer in a Danish prospective case-cohort study." Scand J Gastroenterol 50(12): 1469-1481.
51. La Merrill, M., et al. (2010). "Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence in mice." Environ Health Perspect 118(5): 596-601.
52. Le Marchand, L., et al. (2004). "MTHFR polymorphisms, diet, HRT, and breast cancer risk: the multiethnic cohort study." Cancer Epidemiol Biomarkers Prev 13(12): 2071-2077.
53. Logan, J. and M. W. Bourassa (2018). "The rationale for a role for diet and nutrition in the

prevention and treatment of cancer." Eur J Cancer Prev 27(4): 406-410.
54. Low, Y. L., et al. (2005). "Phytoestrogen exposure correlation with plasma estradiol in postmenopausal women in European Prospective Investigation of Cancer and Nutrition-Norfolk may involve diet-gene interactions." Cancer Epidemiol Biomarkers Prev 14(1): 213-220.
55. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
56. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
57. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.
58. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
59. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.
60. MacLennan, R. (1997). "Diet and colorectal cancer." Int J Cancer Suppl 10: 10-12.
61. Marsland Press. http://www.sciencepub.net. 2018.
62. Martinez-Chacin, R. C., et al. (2014). "Analysis of high fat diet induced genes during mammary gland development: identifying role players in poor prognosis of breast cancer." BMC Res Notes 7: 543.
63. Mathers, J. C. (2003). "Nutrition and cancer prevention: diet-gene interactions." Proc Nutr Soc 62(3): 605-610.
64. Mathers, J. C. (2004). "The biological revolution - towards a mechanistic understanding of the impact of diet on cancer risk." Mutat Res 551(1-2): 43-49.
65. Mathers, J. C. (2007). "Overview of genes, diet and cancer." Genes Nutr 2(1): 67-70.
66. Mathers, J. C. and J. E. Hesketh (2007). "The biological revolution: understanding the impact of SNPs on diet-cancer interrelationships." J Nutr 137(1 Suppl): 253S-258S.
67. McCullough, M. L., et al. (2007). "Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study." Breast Cancer Res 9(1): R9.
68. Meadows, G. G. (2012). "Diet, nutrients, phytochemicals, and cancer metastasis suppressor genes." Cancer Metastasis Rev 31(3-4): 441-454.
69. Menendez, J. A., 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): 2425-2432.
70. Menendez, J. A., et al. (2006). "HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated fatty acid, alpha-linolenic acid (ALA; 18:3n-3), in breast cancer cells: the "fat features" of the "Mediterranean diet" as an "anti-HER2 cocktail"." Clin Transl Oncol 8(11): 812-820.
71. Michels, K. B., et al. (2007). "Diet and breast cancer: a review of the prospective observational studies." Cancer 109(12 Suppl): 2712-2749.
72. Milner, J. A. (2002). "Strategies for cancer prevention: the role of diet." Br J Nutr 87 Suppl 2: S265-272.
73. Milner, J. A. (2006). "Diet and cancer: facts and controversies." Nutr Cancer 56(2): 216-224.
74. Motti, M. L., et al. (2018). "MicroRNAs, Cancer and Diet: Facts and New Exciting Perspectives." Curr Mol Pharmacol 11(2): 90-96.
75. Nara, T., et al. (2016). "Altered miRNA expression in high-fat diet-induced prostate cancer progression." Carcinogenesis 37(12): 1129-1137.
76. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2018.
77. Nelson, W. G., et al. (2002). "The diet, prostate inflammation, and the development of prostate cancer." Cancer Metastasis Rev 21(1): 3-16.
78. Nelson, W. G., et al. (2014). "The diet as a cause of human prostate cancer." Cancer Treat Res 159: 51-68.
79. Newmark, H. L., et al. (2009). "Western-style diet-induced colonic tumors and their modulation by calcium and vitamin D in C57Bl/6 mice: a preclinical model for human sporadic colon cancer." Carcinogenesis 30(1): 88-92.
80. Nguyen, N. M., et al. (2017). "Maternal intake of high n-6 polyunsaturated fatty acid diet during pregnancy causes transgenerational increase in mammary cancer risk in mice." Breast Cancer Res 19(1): 77.
81. Nkondjock, A., et al. (2006). "Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians." Breast Cancer Res Treat 98(3): 285-294.
82. O'Keefe, S. J. (2016). "Diet, microorganisms and their metabolites, and colon cancer." Nat Rev Gastroenterol Hepatol 13(12): 691-706.
83. Ou, J., et al. (2013). "Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans." Am J Clin Nutr 98(1): 111-120.
84. Parasramka, M. A., et al. (2012). "MicroRNAs, diet, and cancer: new mechanistic insights on the

epigenetic actions of phytochemicals." Mol Carcinog 51(3): 213-230.
85. Paul, B., et al. (2015). "Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases." Clin Epigenetics 7: 112.
86. Pendas, A. M., et al. (2004). "Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice." Mol Cell Biol 24(12): 5304-5313.
87. Perloy, A., et al. (2018). "The Role of Genetic Variants in the Association between Dietary Acrylamide and Advanced Prostate Cancer in the Netherlands Cohort Study on Diet and Cancer." Nutr Cancer 70(4): 620-631.
88. Poomphakwaen, K., et al. (2014). "XRCC1 gene polymorphism, diet and risk of colorectal cancer in Thailand." Asian Pac J Cancer Prev 15(17): 7479-7486.
89. Pussila, M., et al. (2013). "Cancer-predicting gene expression changes in colonic mucosa of Western diet fed Mlh1+/- mice." PLoS One 8(10): e76865.
90. Reszka, E., et al. (2006). "Genetic polymorphism of xenobiotic metabolising enzymes, diet and cancer susceptibility." Br J Nutr 96(4): 609-619.
91. Ritenbaugh, C. (2000). "Diet and prevention of colorectal cancer." Curr Oncol Rep 2(3): 225-233.
92. Ross, S. A. (2003). "Diet and DNA methylation interactions in cancer prevention." Ann N Y Acad Sci 983: 197-207.
93. Ross, S. A. (2010). "Evidence for the relationship between diet and cancer." Exp Oncol 32(3): 137-142.
94. 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: 419-436.
95. Simopoulos, A. P. (2004). "The traditional diet of Greece and cancer." Eur J Cancer Prev 13(3): 219-230.
96. Singh, S. M., et al. (2003). "Involvement of gene-diet/drug interaction in DNA methylation and its contribution to complex diseases: from cancer to schizophrenia." Clin Genet 64(6): 451-460.
97. Slattery, M. L., et al. (1999). "Methylenetetrahydrofolate reductase, diet, and risk of colon cancer." Cancer Epidemiol Biomarkers Prev 8(6): 513-518.
98. Slattery, M. L., et al. (2001). "A molecular variant of the APC gene at codon 1822: its association with diet, lifestyle, and risk of colon cancer." Cancer Res 61(3): 1000-1004.
99. Slattery, M. L., et al. (2011). "Diet and colorectal cancer: analysis of a candidate pathway using SNPS, haplotypes, and multi-gene assessment." Nutr Cancer 63(8): 1226-1234.
100. Slattery, M. L., et al. (2014). "Diet and lifestyle factors interact with MAPK genes to influence survival: the Breast Cancer Health Disparities Study." Cancer Causes Control 25(9): 1211-1225.
101. Slattery, M. L., et al. (2014). "Diet and lifestyle factors modify immune/inflammation response genes to alter breast cancer risk and prognosis: the Breast Cancer Health Disparities Study." Mutat Res 770: 19-28.
102. Slattery, M. L., et al. (2015). "MAPK genes interact with diet and lifestyle factors to alter risk of breast cancer: the Breast Cancer Health Disparities Study." Nutr Cancer 67(2): 292-304.
103. Smits, K. M., et al. (2008). "Polymorphisms in genes related to activation or detoxification of carcinogens might interact with smoking to increase renal cancer risk: results from The Netherlands Cohort Study on diet and cancer." World J Urol 26(1): 103-110.
104. Smits, K. M., et al. (2010). "Body mass index and von Hippel-Lindau gene mutations in clear-cell renal cancer: Results of the Netherlands Cohort Study on diet and cancer." Ann Epidemiol 20(5): 401-404.
105. Sonestedt, E., et al. (2012). "Genetic variation in the glucose-dependent insulinotropic polypeptide receptor modifies the association between carbohydrate and fat intake and risk of type 2 diabetes in the Malmo Diet and Cancer cohort." J Clin Endocrinol Metab 97(5): E810-818.
106. Sotos-Prieto, M., et al. (2014). "The association between Mediterranean Diet Score and glucokinase regulatory protein gene variation on the markers of cardiometabolic risk: an analysis in the European Prospective Investigation into Cancer (EPIC)-Norfolk study." Br J Nutr 112(1): 122-131.
107. Wikipedia. The free encyclopedia. Cancer. https://en.wikipedia.org/wiki/Cancer. 2018.
108. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2018.
109. Wikipedia. The free encyclopedia. Stem cell. https://en.wikipedia.org/wiki/Stem_cell. 2018.

7/22/2019