Prostate Cancer Foundation

ADVANCES

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Nutrition and Prostate Cancer Risk Reduction: Broccoli in a "Designer Diet"

OVERVIEW

The word nutrition traces its etymology to the Latin word *nutritionem*—meaning to suckle as a newborn. More molecular evidence now indicates that the newborn male prostate is both nourished—and made more cancer prone or cancer resistant—by dietary exposures that can occur decades earlier in life than when prostate cancer may be diagnosed. Thus, how your family feeds itself, and *where* your prostate is nourished on this globe both matter.

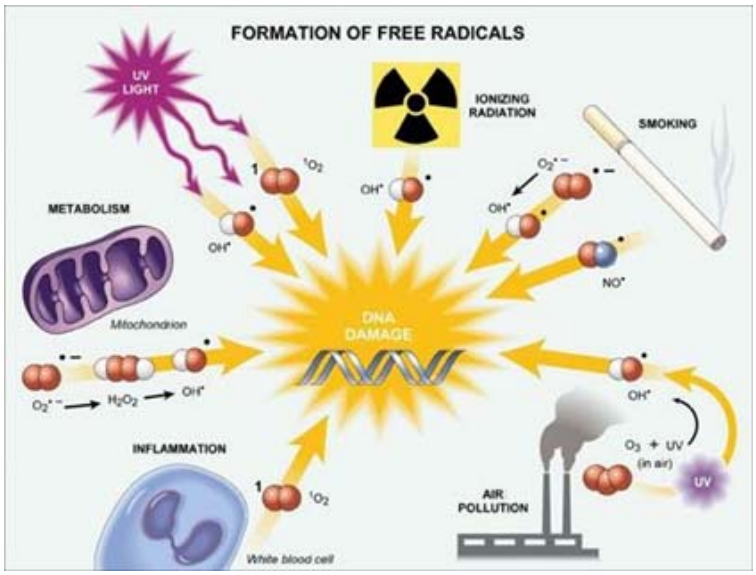
American black men have the highest rates of prostate cancer diagnosis in the world. In contrast, native Chinese and Japanese men, who customarily eat a low-fat, high-fiber diet with a high consumption of phytochemicals (including soy products and green tea), have the lowest prostate cancer rates. Chinese and Japanese immigration to North America and adoption of the local dietary habits increases prostate cancer risk.

The scientific principles guiding what to eat as "protective nutrition" against prostate cancer are just being developed. Because the prostate is such a unique organ, clues for nutritional scientists have had to be based on what actually causes cancer cells to arise from normal cells in the prostate. This has required a detailed genomic understanding of unique aspects of the initiation of human prostate cancer and fifteen years of molecular detective work. Nutritional epidemiology and biochemistry for colon, breast, and other cancers have only been partly relevant to prostate cancer. The genes involved in the initiation of prostate cancer that might be influenced by diet are different than those involved in other cancers. One diet may not reduce the risk of every cancer type given the differences in specific genes involved with the initiation of various cancers.

The PCF Has Driven Nutritional Cancer Research

PCF funding has stimulated some of the most rigorous nutrition and diet research of any cancer research funding agency during the past 15 years. That investment continues to bear fruit. In the last 24 months, there has been important research conducted in body mass index, insulin endocrinology, and phytochemicals in the diets of prostate cancer patients and men at risk of prostate cancer. We have learned that the most common and earliest molecular event in prostate cancer initiation involves loss of the Glutathione S Transferase Pi gene (GST pi). GST Pi research really turned nutritional speculations into focused hypotheses.

GST pi is a gene that has an interplay with nutrition—but not with every vitamin. While certain vitamins are crucial in human health (for example, Vitamin B and Vitamin E), their biochemistry is not directly involved with GST pi biochemistry. Foods that may affect GST Pi biochemistry are of great interest, and one of those foods is broccoli.



The sources of reactive oxygen molecules are varied.
Source: www.smokersrx.com

Studying the consequences of prostate cells losing the GST pi gene in cancer initiation created the concept that prostate cancer emerges from damage to the DNA by "reactive oxygen molecules" and that certain diets create far more reactive oxygen molecules than others within the prostate. The damage is done by electrons on the oxygen atoms. These electrons act like grenades at the atomic level, knocking out parts of the DNA code. When the DNA attempts to repair itself, mutations can occur if the code is not repaired correctly. We are all familiar with the biological effects of these electrons. One simple example is that of our skin wrinkling as we age. GST pi normally helps defend prostate cell DNA from mutation, but when it is lost in a premalignant prostate cell, mutations can accumulate towards prostate cancer.

A critical question now is how to get molecules from the stomach to the bloodstream and then into the prostate cells that have lost GST pi. These could "sponge up" the reactive oxygen species before they mutate prostate cell DNA. In a molecular sense, the ideal antiprostate cancer diet bathes the gland with molecular sponges that mop up any mutating reactive oxygen molecules.

The chemical ability to "mop up" electrons is actually visible and you can see it in the green, red, orange colors in the visible range in fruits and vegetables. Phytochemicals (like the red polyphenol in pomegranate juice or the green in brocoli) are in fact potential dietary sponges for reactive oxygen species—if they can be transported intact from the stomach to the prostate tissue. This *Advances* letter describes the findings of research done recently in England, extending PCF-funded molecular sciences of nutrition to the study of broccoli as a true antioxidant therapy for the human prostate.

Richard Mithen, Ph.D. University of East Anglia/Institute of Food Research

The British study by Professor Richard Mithen and colleagues was based on epidemiological and molecular studies funded by the PCF and other agencies in the 1990s. These studies suggested that people who consume more than one portion of cruciferous vegetables per week are at lower risk of both the incidence of prostate cancer and of developing aggressive prostate cancer. Mithen's group built their study around the findings that GST enzymes at least in a test tube can be "supercharged" by the sulforophane in broccoli and become reactive oxygen sponges. While this is true in cancer cells in a laboratory dish or in rodents, it had not been proven in homo sapiens. There is still little understanding of the underlying mechanisms for this in humans.

Mithen's group designed a truly translational "first in man" research study to quantify and interpret changes in global gene expression patterns in human prostate glands and the human bloodstream before, during and after a 12-month, broccoli-rich diet. The clinical trial consisted of two dietary intervention groups: one group consuming 400 grams of broccoli per week and one "control group" consuming 400 grams of peas per week, in addition to their normal diet. The trial was conducted from April 2005–April 2007.

There was a high level of rigor in the study as food science. All volunteers received the same "lot" of broccoli to steam. Quoting directly from the paper: "Frozen peas (Birds Eye Garden Peas, http://www.birdseye.co.uk/) were purchased from a local retail outlet. To ensure consistency in glucosinolate content in frozen broccoli provided to the volunteers, the broccoli required for the intervention study was grown in one batch at an ADAS experimental farm at Terrington, near King's Lynn, UK (http://www.adas.co.uk/) and processed by Christian Salvesen (Bourne, Lincolnshire, UK, http://www.salvesen.co.uk/). It was blanched at 90.1°C for 74 s, frozen at −30°C and packaged into 100 g portions, then stored at −18°C until steamed by the volunteer."

To insure compliance, volunteers completed weekly "tick sheets" during the 12-month intervention period to identify when the portions of vegetables were eaten. Every two weeks, volunteers were contacted by telephone and asked about adherence to the diet. A seven-day estimated food intake diet diary was completed by volunteers at baseline, and after six months using household measures as an indication of portion size. As these studies go, this one was especially rigorous for ensuring the prostates that were biopsied were getting "dosed" correctly with either broccoli or peas as the nutritional intervention.

Twenty-two male volunteers aged 57–70 years were recruited, none having prostate cancer during the study or on biopsy. The study was evaluating the effects on clinically normal human prostate cells. Volunteers were excluded from participation if they were undergoing chemopreventive therapy, if they were receiving testosterone replacement or 5 alpha reductase inhibitor, if they had active infection requiring treatment, if they had a body mass index (BMI) <18.5 or >35, or were diabetic. Blood prostate specific antigen (PSA) levels were taken prior to the intervention study and after six and 12 months. The volunteers had transrectal ultrasound scan (TRUS)-guided needle biopsies of the prostate obtained immediately before the nutritional study commenced, and at six and twelve months post "treatment." Conducted using Affymetrix micro array technology, the biopsies were then used to evaluate thousands of human genes in a "global gene expression analysis." Multiple pathways of genes involved in cancer initiating could then be analyzed with bio-computing to assess the effects of "broccoli nutritional treatment" with either 400grams per day of broccoli or peas.

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After six months there were no differences in gene expression on the pea-rich diet. On the brococcoli diet significant differences were seen associated with transforming growth factor beta 1 (TGFβ1) gene pathway and epidermal growth factor (EGF) gene signaling pathways. Both of these pathways are involved in cancer initiation and growth. Altering the gene activity in these pathways by the 400 grams of broccoli per day was significant. This first in human prostate cell data suggested that the sulforophane or other components in broccoli were having a true biological effect—like a drug—within the prostate cells of the volunteers. Levels of testosterone and androgen signaling were not dramatically changed by either broccoli or peas. That data fits with the prediction that testosterone signaling would not be affected by phytochemicals or sulforphane either way.

This is the first recorded evidence in *homo sapien* prostates that dietary changes as simple as the weekly total "dose" of broccoli can impact signaling changes involved in tumor initiation in the prostate. The pilot data that the broccoli diet in humans altered their TGFβ1, EGF and insulin protein signaling in human prostate cells can also be further analyzed in mouse models of prostate cancer initiation where the entire prostate can be removed and studied. These are models where more biopsies can be taken, and more genetics can be done prior to doing another human volunteer study.

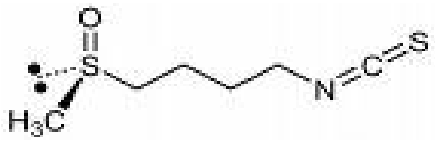
Mithen and his colleagues were also able to look at the genetics in the normal volunteers of breakdown (metabolism) of the broccoli molecules after ingestion (a genetic profile called GSTM1). They found pilot evidence for making dietary recommendations based on the genetic profile of the normal human male prior to getting prostate cancer. Previous research studies have indicated that people who have a GSTM1 "genotype"

might gain more benefit for preventing cancers from eating broccoli and cruciferous vegetables than those who lack this gene.

More studies are needed however, as this British study had less than thirty normal volunteer men in it despite its use of ultra-sophisticated clinical and molecular research methods. But the GSTM1 genetic profile is now added to the increasing list of human genes that may be involved in understanding how to create a "designer diet" for all men, starting as newborns, to prevent prostate cancer. It may be particularly relevant as a dietary intervention in families that carry increased genetic risk for prostate cancer. Intentional weekly dietary intake of cruciferous vegetables—like monitoring cholesterol and blood pressure—are now on a list of health maintenance activities that men can incorporate in their daily routines.

I am quoting directly from the Mithen paper: "These findings suggest that consuming broccoli interacts with *GSTM1* genotype to result in complex changes to signalling pathways associated with inflammation and carcinogenesis in the prostate. We propose that these changes may be mediated through the chemical interaction of isothiocyanates with signalling peptides in the plasma. This study provides, for the first time, experimental evidence obtained in humans to support observational studies that diets rich in cruciferous vegetables may reduce the risk of prostate cancer and other chronic diseases."

The University of East Anglia research team at the Institute of Food Research is currently planning a larger study with men with early stage prostate cancer. They plan to compare the activity of "standard broccoli" with the special varieties of broccoli that should be better cancer pathway inhibitors. For more information see *www.ifr.ac.uk.*



The sulphorophane structure. Its sulfer base accounts for the odor typically associated with cooking broccoli, cabbage and cauliflower.

There are many other cruciferous vegetable varieties that conceivably could be tested head to head against "A+" broccoli to assess the greatest overall suppression of cancer pathways in the normal prostate. Much like drug development, where there is a "foothold molecular signature" on human biopsies of a positive treatment effect, this molecular research in prostate nutritional prevention will require teams of researchers in food biochemistry, human metabolism, and cancer biology. This development will require continuous clinical trials.

In the meantime, given the safety "profile" of broccoli, Professor Mithen has recommended eating three portions of cruciferous vegetables per week. The dose of 400 grams is 15 ounces of broccoli per week. For men with high grade prostate intraepithelial neoplasia (PIN), but not prostate cancer, 400 grams of broccoli/week is an informed and rational, but not proven lifestyle change. For men with prostate cancer on "active surveillance" with "watchful waiting" of early, low grade prostate cancers, there is no data yet on broccoli affecting clinical outcomes. There are legitimate scientific

arguments that the sulphorophanes in broccoli prevent initiation of prostate cancers, and the emergence of second prostate cancers, and will have lesser effects on prostate cancer cell growth once it has initiated.

Critical constituents in broccoli may have their biggest impact in the nutritional programs of sons and grandsons of prostate cancer survivors and in modifying the western diet. Mithen's paper did show, however, that plasma PSA levels were not affected by either broccoli or peas in normal volunteers who were "treated" for a year, making it unlikely that 400 grams of broccoli per week will change PSA levels directly. Therefore, PSA monitoring in "watchful waiting" patients will not be affected. Prostate cancer survivors should discuss broccoli and all other nutritional decisions with their urologists and oncologists: specific recommendations always have to be made around the specific clinical circumstances of each patient.

"Critical constituents in broccoli may have their biggest impact in the nutritional programs of sons and grandsons of prostate cancer survivors."

Nutrition is as complex and as rigorous a science in medical research as genetics or endocrinology. Real nutritional science in cancer prevention is not as simple as going into a nutrition store or supermarket aisle and filling up a cart. The field is much closer now to the efforts of two decades ago in atherosclerosis research in trying to understand the role of cholesterol in heart attacks and strokes in order to then block that pathway. In prostate cancer we have seen the global impact of PCF-funded ideas in the 1990s, now manifested in elegant translational science in one of the leading European centers for nutritional science and agriculture. That work now spans beyond animal testing into global gene analysis in volunteer prostate biopsies to test the hypothesis that GST genes are critical in human prostate biology. Mithen's model argues for far more human volunteer studies to replace rodent studies where appropriate. We expect to see similar studies from China that begin to dissect the favorable elements of Chinese foods and their preparation. Continue to visit our website (pcf.org) for new delicious recipes that build directly upon inhibiting the TGF-beta pathway and EGF and other pathways in the normal human prostate with 400g of broccoli per week.

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