Cancer, Epigenetics, and Nutrigenomics - **How Food Affects Your Cancer Genes**

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One of the causes of cancer is abnormal genes. Cancer causing genes are called oncogenes and genes that prevent cancer are called tumor suppressor genes. Cancers can occur when the normal genes are not functioning normally. Genes, as you know, are the blueprints to the body. They tell a cell what it will be and what it will do. We could not function if the process did not run well. There is a system in place that is designed to keep good genes running and suppress bad genes. This process is called epigenetics.

Epigenetic changes are modifications to the genome that are heritable during cell division but do not involve a change in DNA sequence. Expression of genes is not regulated by the DNA sequence, which is the same in every cell, but by epigenetic marking and packaging. This process regulates chromatin structure through DNA methylation, histone variants, post-translational modifications, nucleosome positioning factors or chromatin loop and domain organization.

How can this cause cancer? Well, if a tumor suppressor gene is abnormally turned off, or an oncogene is turned on, then cancer (carcinogenesis) can occur. One key is a chemical change to the DNA called methylation. First, we need to define the process to make it clearer.

DNA contains four bases: adenine, guanine, cytosine, thymidine, but there is a fifth base methylated cytosine. DNA methyl-transferase (DNMT) produces methyl-cytosine where cytosines precede guanine (CpG). The CpG areas are not symmetric but clustered in CpG islands located at promoter regions. The promoter region is the region at the beginning of a gene and it controls the start of gene transcription. If the promoter is off, then the gene never is expressed.

Abnormal methylation in cancer has been known for 20 years. Hypo-methylated areas turn on normally silent areas such as virally inserted genes or inactive X-linked genes. Hyper-methylated areas silence tumor suppresser genes.
We know that cancers have abnormal levels of methylation and we know foods can help prevent cancers. Is there a link between foods and epigenetics? Yes!

The study of food nutrients and their effect on disease through epigenetics is known as nutrigenomics. This is a growing field, in fact, it is exploding. A Google search for the term nutrigenomics produces 127,000 entries.
Epidemiologic studies suggest there are bad foods and good foods. BAD: red meat, processed meat, grilled meat, dairy, animal fat, partially hydrogenated fats. Good: Fish, fruits, vegetables, tree nuts, omega-3 fatty acids, whole grains.

You can study the epigenetic effects of bad or good foods. I'm going to talk about some of the cancer preventing foods and how their mechanisms include epigenetic effects.

Foods with epigenetic effects include green tea, cruciferous vegetables, and grapes. Usually we hear about antioxidants and foods. Antioxidants are important but there are beneficial substances in foods called polyphenols which can affect genes. Of the polyphenols, different forms exist but flavonoids are the most highly cited for health benefits and are found in a variety of vegetables and fruits. Types of flavonoids include flavanols in tea, isothiocyanate in cruciferous vegetables, anthocyanidins in grapes and berries, flavonone in citrus fruits, flavonols in onions, isoflavones (genistein) in soy.

All tea contains polyphenols, but the highest levels are in green and white tea. Green tea has been well studied and appears to have anti-cancer benefits. In China, green tea drinkers are 50% less likely to develop gastric or esophageal cancer (Carcin 2002; 23 (9): 1497), and 2 cups daily added to topical tea extract reversed oral leukoplakia (J. Nutri Biochem 2001; 12 (7): 404).Green tea has powerful antioxidant effects but it also helps to balance normal methylation in DNA. In fact, one study in esophageal cancer cells demonstrated that EGCG from green tea is able to turn on tumor suppressor genes that had been chemically silenced by methylation (Cancer Research 2003;63:7563).

Cruciferous vegetables include broccoli, cauliflower, kale, Bok choi and their anti-cancer effects have been demonstrated in epidemiologic studies. These powerful vegetables not only induce enzymes that break down carcinogens but they also inhibit DNA methylation allowing tumor suppressor genes to thrive. Inhibiting abnormal methylation also helps cruciferous vegetables to inhibit the cancer causing action of tobacco smoke by preventing the formation of nitrosamine-DNA adducts.
Grapes, which contain reserveratrol, are excellent for heart health and they have anti-cancer activity. Grapes work by preventing the formation or initiation and promotion of cancers. They don't have methylating actions as discussed above but they work by modulation histones.

Histones are the chief protein component of the DNA chain (chromatin). They act as spools for the DNA to wind around which then shortens the length of the DNA to 30,000 times shorter than an unwrapped strand. This process not only allows the long DNA chain to fit into a cell but also plays a role in gene expression because how the genes are wound affects which are exposed and available for turning on or off. Rolling the spool a different way would expose other genes and change their expression.

Histones are modified after translation by acetylation, methylation, phosphorylation, ubiquitination. The changes occur at lysine residues (except for phosphorylation of serine or threonine). When the histone is acetylated the charge is changed and the histone loosens its grip on the DNA strand and the DNA unwinds, exposing the genes to be transcribed, or repaired. When histone tails (H3,H4) are acetylated, genes are transcribed, when they are deacetylated, genes are turned off. Histone deacetylases work to maintain deacetylated sites.

Resveratrol, found in grapes, activates Sirtuins; SirT1 (Sir2 proteins). There are at least 7 Sir2-like proteins and they are histone deacetylators. Sirtuins are induced in animals during starvation states. They seem to have a life preservation effect. Interestingly, when an animal is starved, it can live longer. When the calorie intake of rodents was decreased by 40% in rodents, they actually lived 50% longer and appear to have fewer chronic diseases. The same benefit occurs when rodents when they are given resveratrol in their diet.

Resveratrol deacetylates histones causing tighter packing of the chromatin and a lower level of transcription of DNA. This silencing of the DNA is thought to be the mechanism of life prolongation, heart health, and its beneficial actions to prevent cancers. This is why grapes or red wine is beneficial to your health. How much red wine should you drink? No one knows for sure, but any beneficial effects might be negated after two glasses a day because of the alcohol. I wouldn't advise drinking more than this until more is known. The data is very promising, but more research is needed.

Our knowledge of disease expanded in the genomic era due to the human genome project but the study of genes is not enough. Epigenetics is a very important and complicated concept that helps explain how genes are turned on or off. As more studies are completed we will be able to unlock the mechanisms to diseases and produce new therapies that could turn off bad genes and turn on good genes. More importantly, these studies will demonstrate how foods affect your genes and can prevent or reverse diseases or cancers. Nutrigenomics, the study of how food chemicals (nutrients) affect genes, is a growing field and promises to change the way we look at and eat our meals. Some of the most beneficial foods include green tea, cruciferous vegetables and grapes, but don't stop there. The more fruits and vegetables the better when it comes to your health.

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