

Gene variations sway prostate cancer risk

When it comes to prostate cancer, all men may not be created equal. Likely to be diagnosed in more than 300,000 men in the United States this year, prostate cancer remains relatively rare in Asia, Africa, and South America. Furthermore, black U.S. men have the world's highest incidence of the cancer, nearly 40 percent higher than even that of white U.S. men.

Cancer investigators have long struggled to explain these disparities, citing differences in diet, particularly the amount of fat consumed, as one of many possible contributing factors.

More recently, however, scientists have begun to build a compelling case that genetic variation among populations may account for much, perhaps even most, of the difference in prostate cancer risk. A new study now offers evidence that differences in a gene that encodes an enzyme crucial to the growth of prostate cells make some groups more susceptible to prostate cancer than others.

Made primarily in the prostate, this enzyme, 5-alpha reductase type II, converts testosterone to dihydrotestosterone (DHT). Though both hormones, known as androgens, can induce prostate cells to divide, DHT is the more potent of the two. In fact, finasteride, a drug used to shrink enlarged prostates, blocks the creation of DHT by inhibiting 5-alpha reductase type II.

A few years ago, a group headed by Ronald K. Ross of the University of Southern California School of Medicine in Los Angeles proposed that elevated concentrations of testosterone in the blood—and therefore increased DHT concentrations in the prostate—might explain the higher prostate cancer risk in some populations.

Ross' group has now taken a close look at the gene encoding 5-alpha reductase type II. Other researchers had reported that inheriting a mutated form of the gene, which codes for a nonfunctioning enzyme, causes a rare disorder in which men appear female at birth but during puberty develop the muscles, hair growth, and other outward physical features of their sex.

Ross and his colleagues have found that the enzyme's gene comes in two functional versions, or alleles. The enzymes produced by these alleles differ by a single amino acid: A valine replaces a leucine at one site.

The researchers then examined whether the different prostate cancer risks of black and Asian American men might result from the alleles they possess. Almost 60 percent of blacks have two copies of the valine allele, while only 30 percent of Asian Americans do, Juergen K.V. Reichardt, a member of Ross' group, reported at last week's American Society of Human Genetics Meeting in San Francisco.

Furthermore, the investigators have preliminary evidence that the leucine-containing form of 5-alpha reductase type II is far less efficient at converting testosterone to DHT than the valine-containing enzyme made by the other allele.

One reason few Asian Americans get prostate cancer may be that their 5-alpha reductase type II genes tend to encode the enzyme that does a poor job of making DHT, suggests Reichardt. In contrast, black men generally have the enzyme most proficient at creating DHT, he adds.

Reichardt cautions that his group has to examine further the different DHT-making efficiency of the two forms of the enzyme. In addition, by surveying even more people, the researchers hope to confirm that racial or ethnic population differences exist in the distribution of the enzyme's alleles.

"It's an attractive hypothesis, but it certainly isn't ironclad yet," says William Isaacs of the Johns Hopkins University Medical Institutions in Baltimore.

Isaacs notes that prostate cancer researchers have also examined genetic variations in the androgen receptor, the cell surface protein that binds to testosterone or DHT and transmits commands into the cell. A few recent studies suggest that black men often have a shorter than normal form of the receptor gene, which may change how prostate cells with the receptors

respond to androgens.

This genetic variation also seems to increase the prostate cancer risk of black men and may even predispose them to more aggressive forms of the disease, says Issacs.

— *J. Travis*