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Cause or Effect: Which Genetic Changes Are Associated With Cancer?

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Dear Editor,

Almost every day, there are reports in the media that a particular gene "causes cancer". Typically, deeper reading shows that the discovery is actually a specific mutation or polymorphism which is associated with a particular type of cancer. A critical issue in such cases is determining whether the genetic change is a cause of the cancerous state, or a consequence of it. Cancer cells are generally radically different to normal cells; in particular, they tend to divide more rapidly and they may be more motile. Thus increases in the expression of genes that are involved in mechanisms such as DNA replication, energy production or cellular motility might cause cancer (since they would dispose the cell towards cancer-like behavior) or they might be an effect of cancer (since the cell adapts to its new phenotype). Prostate cancer is a particularly difficult disease to treat: there are only a limited number of drugs and prospects for patients are generally poor (1, 2). Therefore, identifying genetic changes associated with this disease is a particularly important task. Seidabadi et al. studied an alteration in the RNASEL gene, which encodes the endonuclease RNAaseL (Uniprot Q05823) (3). This alteration of arginine 462 to glutamine (p.R462Q; rs486907) has previously been shown to reduce the activity of the enzyme (4). Both Seidabadi et al.'s work and other studies demonstrate that there is no statistically significant association between this mutation and prostate cancer occurrence or severity (3, 4). However, other studies disagree and demonstrate a positive correlation between the mutation and prostate cancer (5). Contradictory findings such as these are common in studies attempting to assign links between polymorphisms and diseases. The p.R462Q variant of RNAseL has lower activity than the wild-type protein (5). One function of the protein is to degrade "foreign" RNA molecules, for example those produced by viruses. It is also linked to induction of apoptosis in infected cells. Therefore, it is plausible to link a loss of activity with an increased likelihood of infection by cancer-causing viruses (6). Further biochemical studies would be desirable to understand the causes of this loss of activity more deeply. It may be that there is a direct effect on residues involved in catalysis. However, in many cases, cancer-associated variants have reduced activity resulting from failure to fold properly: the delicate equilibrium between the fully folded and partially unfolded states is disturbed (for examples, see (7-9)). Biochemical and cell biological experiments to better understand the links between RNAseL and apoptosis would also be beneficial. Both sets of basic science experiments could potentially inform whether, or not, this variant is associated with prostate cancer. If an association is established, then they may also point towards potential therapies: the apoptosis pathways could be stimulated or the protein may be stabilized by "pharmacological chaperones". The latter approach would involve identifying molecules which stabilize the native, folded state of the protein over partly unfolded forms (10). Potential drugs identified by this method could be given to individuals in population groups at high risk who are homozygous for the unstable form. However, to justify the risk and expenses of such large scale and long-term medications, it would need to be established that there is a highly increased chance of prostate cancer associated with this polymorphism. To date, this has not been demonstrated. Different conclusions from various studies on this polymorphism have most likely resulted from different environmental and genetic backgrounds of the patient groups studied. Meta-analyses, which aggregate the data into larger, more statistically sound groups, need to also take into account such differences. One plausible hypothesis to explain the differences is that some populations may have a higher prevalence of viral infections of the prostate. Investigating the relationship between

viral disease burden in the prostate and RNAseL polymorphisms may address this issue.

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