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Prostate cancer: alcohol, cancer and 5α-reductase inhibitors-is there a link?

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Alcohol, Prostate Cancer and 5 Alpha Reductase Inhibitors: Is there a link?

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Commentary on: Alcohol Intake Increases High-grade Prostate Cancer Risk Among Men Taking Dutasteride in the REDUCE Trial. Fowke JH, Howard L, Andriole GL, Freedland SJ. Eur Urol. 2014 Feb 9 (E-pub on line)

Stand first
Two major trials, PCPT and REDUCE, used 5 alpha-reductase inhibitors to determine the impact on the subsequent diagnosis of prostate cancer. Both showed that high alcohol intake significantly increased prostate cancer risk among men randomized to the treatment arms. The recommendation that patients eliminate alcohol when taking 5 alpha-reductase inhibitors seems appropriate.

Fowke and associates have reviewed data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial relating to alcohol consumption patterns in the study (1). The REDUCE trial evaluated the effect of 5 alpha-reductase inhibitor (5-ARI) dutasteride on subsequent cancer diagnosis in a group of men with a prior negative biopsy (2). They found that alcohol intake was not associated with increased prostate cancer for men in the placebo arm of the study, adding support to the fact that alcohol intake is unrelated to prostate cancer risk. However, for men on dutasteride, the relationship of alcohol intake and prostate risk was far more complex. While alcohol intake was not associated with more low-grade prostate cancer for men on dutasteride, increased alcohol intake when combined with dutasteride increased the risk of high-grade prostate cancer. Among men randomized to dutasteride or placebo in the REDUCE trial, it appears that alcohol consumption negated the protective association between dutasteride and high-grade prostate cancer.

The use of alcohol has been associated with increased mortality risk for several cancers in men, but only for those with moderate and heavy drinkers based on a meta-analysis by Jin and associates (3). Heavy drinking in this meta-analysis was defined as > 50gm/day with light drinking at a level of ≤12.5 g/day being mildly protective of overall mortality. The risk of cancers of the oral cavity, larynx, and pharynx rise linearly with alcohol consumption. Heavy drinking is also known to be associated with pancreatic and hepatocellular cancers.

The authors note most cohort and case-control studies report no evidence of an association between alcohol use and prostate cancer. Other random studies that draw an association have been inconsistent. What is most provocative about this dutasteride based study is that the Prostate Cancer Prevention Trial (PCPT) found the highest category of alcohol intake was associated with increased risk of both low-grade (Gleason <7) and high-grade (Gleason >7) prostate cancer at follow-up biopsy but only among men taking the 5 alpha-reductase inhibitor finasteride (4). PCPT was also a prostate cancer prevention trial that used finasteride as the active agent (5). The findings from PCPT are consistent with the current Fowke study. Taken together, this suggests a possible class effect of 5 alpha-reductase inhibitors with alcohol interaction possibly increase the risk of prostate cancer.

A recent review notes that there are no long-term randomized trials of alcohol on overall clinical outcomes and alcohol consumption (6). There is strong evidence of causality based upon epidemiologic studies and short-term trials that have found beneficial effects of alcohol on cardiovascular risk factors with an increased risk of several cancers in men as noted. It remains possible that some of the health benefits and risks of alcohol consumption represent associations unrelated to the intake of alcohol itself but relate to the interaction between alcohol and other modifying factors. This study by Folke and associates adds validity to this observation concerning other modifying factors. In this case the 5-alpha reductase inhibitor seems to be modifying high grade prostate cancer risk. Other modifying factors on the diagnosis of high grade cancer such as statin use have been reviewed in the REDUCE data set. Statins were not associated with any prostate cancer including high-grade disease (7).

This effect of increased prostate cancer risk while on dutasteride is potentially explained by several concepts. One focuses on the fact that ethanol metabolism increases oxidative stress that may ultimately impact on prostate cancer initiation and progression. Other theories relate to hormonal changes such as increased estrogen with heavy alcohol consumption and other metabolic changes such as increased insulin levels or folate depletion that create a pro-carcinogenic effect. It should be noted that these are plausible theories that have not been proven.

The goal of the Fowke paper was to confirm an association between alcohol intake and cancer that was determined in the PCPT trial using data from the REDUCE trial. The interaction between alcohol, prostate cancer and 5 alpha reductase inhibitors in these retrospective analysis appears to be real. This raises the concern that men taking 5 alpha reductase inhibitors for symptomatic benign prostatic hypertrophy might potentially increase the risk of prostate cancer. The recommendation by the authors that patients consider elimination of alcohol when taking 5α-reductase inhibitors seems appropriate.

Competing interests

Past steering committee member on REDUCE Trial.

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