Identifying cholesterol-dependent prostate cancers treatable with statins

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Background: Several observational studies have reported better prognosis for prostate cancer patients who use cholesterol-lowering statin medications. Assessing intratumoral cholesterol metabolism can inform whether these associations may be causal and help identify patients who are most likely to derive benefit from statin therapy.

Methods: We studied patients in prospective prostate cancer cohorts within in the Health Professionals Follow-up Study and the Physicians’ Health Study. Centralized histological review and whole-transcriptome mRNA expression profiling of tumor tissue from cancer diagnosis were performed. Patients were followed for >8 years for lethal cancer (prostate cancer mortality or metastases) in contrast to non-lethal disease without metastases. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between mRNA expression, Gleason grade, and lethal outcome, and adjustment for baseline characteristics was performed.

Results: 113 and 291 patients had lethal and non-lethal cancers, respectively. SQLE expression was higher while LDLR expression was lower in higher Gleason grade cancers. Cancers with higher intratumoral mRNA expression of cholesterol synthesis enzymes, as reflected by expression of the second rate-limiting enzyme squalene monooxygenase (SQLE), were more likely to become lethal despite prostatectomy (OR for fifth vs. first quintile, 6.0; 95% CI, 2.0 to 17.7). In contrast, lethal cancers had lower mRNA expression of the principal cholesterol uptake receptor, low-density lipoprotein receptor (LDLR; OR for fifth vs. first quintile, 0.37; 95% CI, 0.18 to 0.76). Adjustment for baseline characteristics including Gleason grade did not substantially change results, particularly for cholesterol synthesis.

Conclusions: High intratumoral cholesterol synthesis in prostate tumors, but not high cholesterol uptake, is associated with a higher risk of lethal disease. The results support a potential benefit of statin medications, which target the cholesterol synthesis pathway, for prostate cancer patients. We will test if cholesterol synthesis can serve as a predictive biomarker for statin therapy.

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