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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