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Researchers Identify Possible Explanation for Link Between Exercise and Improved Prostate Cancer Outcomes

SAN DIEGO — Men who walked at a fast pace prior to a prostate cancer diagnosis had more regularly shaped blood vessels in their prostate tumors compared with men who walked slowly, providing a potential explanation for why exercise is linked to improved outcomes for men with prostate cancer, according to results presented here at the AACR-Prostate Cancer Foundation Conference on Advances in Prostate Cancer Research, held Jan. 18–21.

Men who engage in higher levels of physical activity have been reported to have a lower risk of prostate cancer recurrence and mortality compared with men who participate in little or no physical activity. The biological mechanisms underlying this association are not known.

"Prior research has shown that men with prostate tumors containing more regularly shaped blood vessels have a more favorable prognosis compared with men with prostate tumors containing mostly irregularly shaped blood vessels," said Erin Van Blarigan, Sc.D., assistant professor in the Department of Epidemiology and Biostatistics at the University of California, San Francisco. "In this study, we found that men who reported walking at a brisk pace had more regularly shaped blood vessels in their prostate tumors compared with men who reported walking at a less brisk pace.

"Our findings suggest a possible mechanism by which exercise may improve outcomes in men with prostate cancer," continued Van Blarigan. "Although data from randomized, controlled trials are needed before we can conclude that exercise causes a change in vessel regularity or clinical outcomes in men with prostate cancer, our study supports the growing evidence of the benefits of exercise, such as brisk walking, for men with prostate cancer."

The Health Professionals Follow-up Study, which was initiated in 1986, enables researchers to examine how nutritional and lifestyle factors affect the incidence of serious illnesses, such as cancer and heart disease. Every two years, participants receive questionnaires that ask about diseases and health-related topics like smoking, physical activity, and medications taken. Questionnaires that ask detailed dietary information are administered every four years.

Van Blarigan and colleagues investigated whether prediagnostic physical activity was associated with prostate tumor blood vessel regularity among 572 men enrolled in the Health Professionals Follow-up Study. Prediagnostic physical activity was determined through analysis of questionnaire answers. Blood vessel regularity was established by semiautomated image analysis

of the tumor samples. Blood vessels that are perfect circles are considered the ideal shape and given a score of 1. Higher values indicate less regular blood vessels.

The researchers found that men with the fastest walking pace (3.3–4.5 miles per hour) prior to diagnosis had 8 percent more regularly shaped blood vessels compared with men with the slowest walking pace (1.5–2.5 miles per hour).

"Our study, which provides a potential explanation by which exercise may improve outcomes in men with prostate cancer, highlights the value of multidisciplinary collaborations between laboratory, clinical, and population scientists to explore new pathways by which lifestyle factors or other exposures may affect disease," said Van Blarigan. "It is reasonable to hypothesize that the same explanation could exist for the beneficial effects of exercise in other cancers, and it would be interesting to examine this in future studies."

This study was supported by funding from the National Institutes of Health and the Prostate Cancer Foundation. Van Blarigan declares no conflicts of interest.

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Abstract: 275791_1

Presenter: Erin Van Blarigan, Sc.D.

Title: Physical activity and tumor vessel morphology among men with prostate cancer

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Background: Brisk walking and vigorous activity have been associated with lower risk of prostate cancer recurrence and mortality. Exercise has been reported to normalize tumor vasculature in a murine prostate cancer model, and we previously showed that the extent of small, irregularly shaped vessels in human prostate tumors is associated with increased risk of lethal disease. We hypothesized that brisk walking and vigorous activity would be associated with larger, more regularly shaped vessels in human prostate tumors.

Methods: We examined whether pre-diagnostic physical activity was associated with prostate tumor vessel morphology among 572 men in the Health Professionals Follow-up Study who underwent radical prostatectomy or transurethral resection of the prostate. Total, vigorous, and non-vigorous activity and walking pace were assessed via a validated questionnaire administered every two years starting in 1986; participants completed 4.8 questionnaires on average prior to diagnosis. Vessel morphology, including vessel size (μm^2), regularity of the vessel lumen ($perimeter^2 / 4 \cdot \pi \cdot area$), and microvessel density (number of vessels per high powered field), were ascertained via semi-automated image analysis of tumor sections stained for protein expression of endothelial cell marker CD34. We examined the association between activity (quartiles for non-vigorous and total activity; tertiles for vigorous activity and walking pace) and vessel morphology markers (log-transformed, continuous) using linear regression adjusting for age, body mass index (<25, 25-29.9, 30+ kg/m^2), smoking (never, former, current), radical prostatectomy (yes/no), lycopene intake (quartiles), vitamin E intake (quartiles), regular aspirin use (yes/no), activity other than the exposure of interest (e.g. walking pace was adjusted for vigorous and non-vigorous activity), clinical stage (T1/T2 vs. T3/T4), and Gleason score ($\leq$6, 7, $\geq$8).

Results: Brisk walking prior to diagnosis was associated with more regularly shaped vessels in prostate tumors. Men with the fastest walking pace (range: 3.3-4.5 mph) prior to diagnosis had 8% more regularly shaped vessels compared to men with the slowest walking pace (range: 1.5-2.5 mph; β = -0.08; standard error = 0.03; p-value: 0.01). This association was slightly attenuated, but remained statistically significant, after adjusting for clinical stage and Gleason score (Δ = -7%; β = -0.07; standard error = 0.03; p-value: 0.04). Brisk walking pace was also suggestively associated with larger vessel size (Δ = -10%; β = -0.10; standard error = 0.05; p-value: 0.06); there was no association between walking pace and microvessel density. Time spent engaging in vigorous and non-vigorous activities was not associated with tumor vessel

morphology.

Conclusion: Brisk walking may be associated with more regularly shaped vessels in prostate tumors. Normalization of tumor vasculature may in turn inhibit tumor aggressiveness and improve response to anticancer therapies. Future studies should investigate whether increasing brisk walking after diagnosis is associated with favorable changes in tumor vasculature.