Risk of Gene-Fusion Positive Prostate Cancer is Lower Among Obese

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Approximately 50% of prostate cancers harbor a T2E gene fusion. As an early driver of prostate carcinogenesis, this gene fusion may characterize distinct molecular subtypes of prostate cancer with different etiologies. It is not known, however, whether lifestyle factors such as obesity have different associations with prostate cancer risk depending on this molecular characterization. In a recent study in the*American Journal of Epidemiology*, Ms. Lieke Egbers and Dr. Janet Stanford and colleagues in the Public Health Sciences Division provide evidence that obesity is associated with a reduced risk of androgen-regulated *T2E* fusion-positive tumors, but not with *T2E* fusion-negative tumors.

The *T2E* gene fusion consists of the fusion of the transmembrane protease, serine 2 (*TMPRSS2*) and erythroblast transformation-specific-related (*ERG*) genes. *TMPRSS2* harbors androgen-responsive elements in the promoter region, while ERG encodes a nuclear protein that acts as a transcription factor. Androgens have been implicated in the induction of these fusion events, which once fused leads to overexpression of *ERG* and disruption of androgen receptor signaling. As obesity alters the circulating levels of sex hormones compared to normal-weight men, including lowering androgen levels, the authors hypothesized that obesity may decrease the risk of *T2E* gene fusion-positive prostate tumors.

The authors measured *T2E* gene fusion status in 563 prostate cancer tumors, using tumor tissue from two population-based case-control studies conducted in the King County, Washington area. "The ability to obtain formalin-fixed paraffin embedded (FFPE) tumor tissue blocks and utilize the latest technologies for molecular profiling of such tissues is key for this type of molecular epidemiologic research," said lead author Ms. Egbers. The association between quartiles of body mass index (BMI) and prostate cancer risk was then evaluated according to fusion status. "This ability to stratify prostate cancer cases according to tumor molecular subtype (such as *T2E* fusion status) now allows us to study etiologic heterogeneity, with different molecular subtypes having distinct risk factor profiles," said Ms. Egbers.

Comparing the highest BMI quartile with the lowest, the authors found an inverse association with the risk of *T2E*-positive prostate cancer, but no association was seen with risk of *T2E*-negative prostate cancer (see figure). Other characterizations of obesity were consistent with this finding, such as evaluating standard WHO BMI categories (obese vs. normal) or BMI as a continuous variable (in 5-unit increments). "These data provide new evidence that these different molecular subtypes of prostate cancer may have different etiologies," said Ms. Egbers.

"At present the biological mechanism by which obesity decreases risk for *T2E* positive prostate cancer, but not for *T2E* negative tumors, is not known," said Ms. Egbers. "Since the *T2E* fusion is responsive to androgens, we hypothesize that the altered steroid hormone profile in obese men (e.g., lower circulating levels of androgens) may contribute to the reduction in risk for *T2E*positive prostate cancer. Further research will be needed to explore the biological mechanism behind this finding." Understanding these etiological differences may lead to better understanding of risk factors for particular subtypes of prostate cancer, which should eventually lead to improvements in prevention, screening, and treatment.

Other PHS researchers contributing to this project were Drs. Jonathan Wright and Marian Neuhouser, as well as Ms. Suzanne Kolb.

Citation:

Egbers L, Luedeke M, Rinckleb A, Kolb S, Wright JL, Maier C, Neuhouser ML, Stanford JL. 2015. Obesity and Prostate Cancer Risk According to Tumor TMPRSS2:ERG Gene Fusion Status. *Am J Epidemiol*. 181(9):706-13. doi: 10.1093/aje/kwu344.

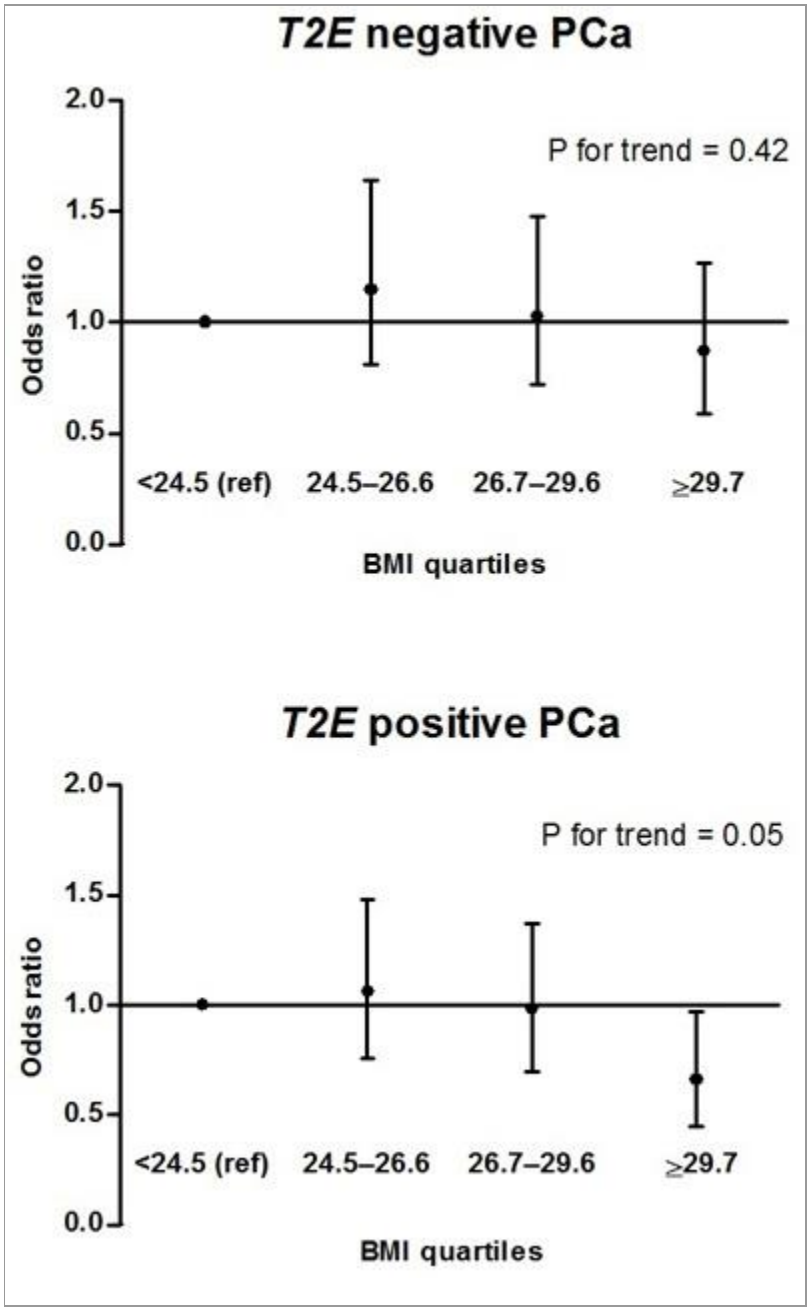

Image provided by Ms. Lieke Egbers

Association of quartiles of body mass index (compared to the lowest quartile) with risk of T2E negative (top) or positive (bottom) prostate cancer.