Toward a less reductionist approach to prostate cancer prevention

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Prostate cancer is typically framed as an aging-related disease with race/ancestry and family history often cited as the only confirmed risk factors and no known, universally accepted modifiable causes. Consequently, the typical focus is on early detection via PSA screening and treatment, resulting in reductions in mortality rates in recent decades but also considerable overdiagnosis and overtreatment.

Such a reductionist view of prostate cancer ignores that age-standardized prostate cancer mortality rates increased several-fold in the 20th century, preceding PSA screening. It also ignores that PSA screening is both a confounder and an effect modifier for the effects of typical cancer risk factors on prostate cancer. When these effects are taken into account, typical cancer risk factors such as smoking emerge as risk factors for aggressive prostate cancer. While prostate cancer is the cancer with the highest estimate of heritability and the best-performing polygenic risk scores, recent data demonstrate that typical modifiable cancer risk factors are strongly associated with prostate cancer mortality among men with high inherited polygenic risk. To help primary prevention of prostate cancer catch up with other cancer types, only well-designed prospective cohort studies with decades of follow-up can successfully address the challenges that have historically plagued epidemiologic research on this high-burden cancer.

Prostate cancer is molecularly and etiologically heterogeneous, similar to many other cancer types, with hormone receptor-positive and hormone receptor-negative breast cancer being a prime example. Tumor biorepositories integrated in well-designed prospective cohort studies are thus indispensable for etiologic and survivorship research on prostate cancer. For example, about half of all prostate tumors harbor a gene fusion between the androgen-regulated *TMPRSS2* gene and oncogenes of the ETS transcription factor gene family (e.g., *ERG*), while the other half does not. Risk factors related to hyperinsulinemia and insulin-like growth factor-1 signaling, such as height, adiposity, and germline polymorphisms, are associated with risk of prostate cancer carrying the *TMPRSS2:ERG* gene fusion but not with fusion-negative tumors.

Collectively, integrating molecular subtyping into well-designed prospective cohort studies with long-term follow-up has the potential to credential modifiable etiologic factors for common molecular subtypes of this high-burden cancer. Undertaking this work requires a team effort with multidisciplinary expertise and robust infrastructure. Ultimately, the goal remains a solid knowledge basis for primary prevention of the different subtypes of prostate cancer.