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Genetic Reasons to Walk the Extra Mile to Prevent Prostate Cancer

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As human society has developed over the centuries, we have made our lives easier by constructing machines that do much of what used to require hard manual labour and vehicles that take us from A to B. Over the past few decades we have become increasingly aware that our modern "comfortable life" has considerable side effects in the form of metabolic disorders, cardiovascular disease, and cancer. The worldwide geographic and temporal variations in prostate cancer incidence and mortality clearly show that the "developed" Western lifestyle is a fertile soil for this cancer [1]. The "metabolic syndrome", which is often the consequence of too much energy-rich food and too little physical activity, is associated with worse oncological outcomes among men with prostate cancer [2]. Epidemiological studies on the correlation between physical activity and prostate cancer are, however, conflicting. A recent systematic review concluded that the relationship remains elusive [3].

In this issue of *European Urology*, a multinational research group report on their investigation of the association between physical activity and advanced prostate cancer at diagnosis (defined as stage T3b, T4, N1, or M1) and lethal prostate cancer (defined as distant metastases or death from prostate cancer during follow-up) using the American Health Professionals Follow-up Study [4]. Data, including physical activity, were collected every second year between 1986 and 2012 from almost 50 000 men aged 40–75 yr.

There was no evidence of an association between total physical activity and risk of prostate cancer in the overall cohort, but men in the highest quintile of vigorous activity had a 30% lower risk of advanced prostate cancer and a 25% lower risk of lethal prostate cancer than men in the lowest quintile. The association was independent of screening history. The study is large with high-quality long-term follow-up, so these results add substantial weight to the accumulating evidence of a clinically important inverse relation between physical exercise and clinically significant prostate cancer [3]. However, the really interesting finding in this study is that men with higher vigorous activity had a lower probability of having a cancer that expressed the *TMPRSS2:ERG* gene fusion.

TMPRSS2 expression is regulated by the androgen receptor (AR) in prostate cells. In 2005, Attard and colleagues [5] discovered that when the *TMPRSS2* binding site for the AR is fused with the ETS factor oncogene *ERG*, AR stimulation of the *TMPRSS2* pathway also stimulates the oncogenic *ERG* pathway, driving carcinogenesis and cancer progression. The *TMPRSS2:ERG* gene fusion is present in approximately half of primary prostate cancers and is the most common of the known prostate cancer molecular subtypes (ref. [12] in the paper [4]). It is noteworthy that the group chose to measure *TMPRSS2:ERG* expression via an immunohistochemistry assay for ERG expression. We attempted a similar assay for ERG transcript expression using a number of probes and found very poor consistency with definitive break-apart fluorescence in situ hybridisation assays [6]. It would be interesting to see their validation controls for this element of the study. While we do have some concerns about this, on the assumption that these hold up, then we find this element of the paper compelling. Unlike with breast cancer, we have struggled to identify discrete genetic descriptors to stratify localized prostate cancer except in advanced disease [7]. Despite this, *TMPRSS2:ETS* fusions are probably the most established [8].

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The nature versus nurture debate continues in many areas of health, not least prostate cancer. Hereditary genetic susceptibility is more important in prostate cancer than in most other common cancers [9,10]. Nonetheless, environmental factors such as smoking, diet, occupation, and weight are now being associated with risk of prostate cancer alongside the heritable genetic factors and acquired genetic alterations associated with prostate cancer progression [6]. To the best of our knowledge, the study by Pernar et al. [4] is the first to investigate a possible association between exercise and a specific genetic mutation. Therefore, this is an exciting piece of work, merging as it does the nature versus nurture debate, or, more precisely, "environment" and "acquired genetics". Of course, the study is purely associative with no effort to interrogate the mechanism.

Although these results are important and it is likely that physical exercise reduces men's risk of advanced prostate cancer, we must put reducing prostate cancer mortality in a wider perspective: more men die from cardiovascular disease than from prostate cancer and we know that physical activity reduces cardiovascular and overall mortality [11]. Therefore, regardless of the underlying genetic mechanisms, it does make sense for men to walk that extra mile.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Lichtensztajn DY, Gomez SL, Sieh W, et al. Prostate cancer risk profiles of Asian-American men: disentangling the effects of immigration status and race/ethnicity. J Urol 2014;191:952–6. http://dx.doi.org/10.1016/j.juro.2013.10.075.

[2] Gacci M, Russo GI, De Nunzio C, et al. Meta-analysis of metabolic syndrome and prostate cancer. Prostate Cancer Prostatic Dis 2017;20:146–55. http://dx.doi.org/10.1038/pcan.2017.1.

[3] Benke IN, Leitzmann MF, Behrens G, et al. Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis. Ann Oncol 2018;29:1154–79. http://dx.doi.org/10.1093/annonc/mdy073.

[4] Pernar CH, Ebot EM, Pettersson A, et al. A prospective study of the association between physical activity and risk of prostate cancer defined by clinical features and TMPRSS2:ERG. Eur Urol 2019;76:33–40. http://dx.doi.org/10.1016/j.eururo.2018.09.041.

[5] Attard G, Clark J, Ambroisine L, et al. Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer. Oncogene 2008;27:253–63. http://dx.doi.org/10.1038/sj.onc.1210640.

[6] Ross-Adams H, Lamb AD, Dunning MJ, et al. Integration of copy number and transcriptomics provides risk stratification in prostate cancer: a discovery and validation cohort study. EBioMedicine 2015;2:1133–44. http://dx.doi.org/10.1016/j.ebiom.2015.07.017.

[7] Lamb AD, Massie CE, Neal DE. The transcriptional programme of the androgen receptor (AR) in prostate cancer. BJU Int 2014;113:358–66. http://dx.doi.org/10.1111/bju.12415.

[8] Clark JP, Cooper CS. ETS gene fusions in prostate cancer. Nat Rev Urol 2009;6:429–39. http://dx.doi.org/10.1038/nrurol.2009.127.

[9] Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. Nat Rev Urol 2014;11:18–31. http://dx.doi.org/10.1038/nrurol.2013.266.

[10] Bratt O, Drevin L, Akre O, et al. Family history and probability of prostate cancer, differentiated by risk category: a nationwide population-based study. J Natl Cancer Inst 2016;108:djw110. http://dx.doi.org/10.1093/jnci/djw110.

[11] Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet 2017;390:2643–54. http://dx.doi.org/10.1016/S0140-6736(17)31634-3.