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Nature versus nurture contribution to prostate cancer risk

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Abstract

Genetics has a role in predisposition towards prostate cancer, and an accurate prediction of prostate cancer risk can be made using polygenic risk scores. New evidence suggests that this risk is modifiable through lifestyle changes, but only in men at a high genetic risk of developing prostate cancer.

The three classic risk factors for prostate cancer are race, family history and old age. All these factors are considered non-modifiable, but family history is intriguing to dissect, as the extent to which family history involves genetics (nature) or shared environment and lifestyle factors (nurture) is unclear. Genetics is a well-established, strong risk factor for prostate cancer[1], although evidence suggests that lifestyle might also have a role in the onset of this disease[2,3]. Indeed, much effort has been put into finding modifiable risk factors with the idea to reduce prostate cancer risk and improve cancer outcomes, but the results to date have been inconclusive. Identifying modifiable risk factors would have a huge public health benefit, considering that prostate cancer is the second most common cancer among men worldwide and the most common cancer in male patients in 84 countries[4]. Thus, the question of how nature and nurture interact to influence prostate cancer risk needs to be addressed, with a special focus on understanding the role of lifestyle as a risk factor for prostate cancer and whether the benefits of a healthy lifestyle are equally shared among all men despite genetic differences.

Plym and colleagues[5] performed an approximately three-decade-long prospective cohort study to assess how genetics and lifestyle factors are associated with prostate cancer risk and progression. Two populations were included in this study: men from the Health Professionals Follow-Up Study (HPFS) and men from the Physicians' Health Study (PHS), which, together, included a total of 12,411 men. DNA from participants was collected at the baseline and genotyped for 269 single-nucleotide polymorphisms to generate a polygenic risk score (PRS), which was used to divide patients into quartiles based on the genetic risk of prostate cancer. Lifestyle factors including weight, amount of exercise, diet and smoking were also assessed. The authors used these factors to compute a healthy lifestyle

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Competing interests

The authors declare no competing interests.

score ranging from 0 to 6, on the basis of which patients were classified into unhealthy, moderate and healthy categories. The authors used inverse probability weighting to account for possible bias across the groups.

Intriguingly, among men within the highest quartile of prostate cancer risk according to the PRS model, men with a healthy lifestyle had a 45% decreased risk of lethal prostate cancer (pooled HR 0.55, 95% CI 0.36–0.86) compared with men in the same risk quartile who had an unhealthy lifestyle. However, healthy lifestyle was unrelated to overall prostate cancer risk in men within the same PRS group. Considering the individual lifestyle factors separately, the lifestyle components that were most strongly associated with a reduced rate of lethal disease in men in the top PRS quartile were healthy weight and vigorous exercise. Surprisingly, lifestyle factors were unrelated to the risk of overall or lethal prostate cancer among men in the other three PRS quartiles. Very similar results were observed in the HPFS and PHS cohorts when analysed separately, supporting the robustness of the results and providing strong credibility to the conclusions.

Genetics is known to have a strong role in prostate cancer and, therefore, understanding what men with a high genetic risk of developing prostate cancer can do to mitigate this risk is crucial.

Results from the study by Plym and colleagues[5] show that adhering to a healthy lifestyle, particularly performing vigorous exercise and maintaining a healthy weight, is associated with a decreased risk of lethal disease in men at very high genetic risk of prostate cancer. This evidence is interesting, but raises new questions about the definition of a healthy lifestyle, as many slightly different meanings of what can be considered a healthy lifestyle exist. For example, in the study by Plym and colleagues[5], the authors defined a healthy diet as one high in tomato, low in processed meat and high in fatty fish intake using dietary information collected from validated semiquantitative food frequency questionnaires. However, in other studies, other dietary schemes have been associated with prostate cancer. For example, high dairy product intake has been associated with an increased risk of aggressive prostate cancer, possibly owing to a high content of growth hormones, sex steroid hormones and/or calcium[6]. The effects of ultra-processed food and simple sugar intake on the risk of prostate cancer would be also interesting to consider. In summary, current evidence of the role of diet in prostate cancer is limited and non-conclusive, as also highlighted in the 2018 report by the American Institute for Cancer Research (AICR)[4]. Thus, the definition of a healthy diet is left to some extent to individual interpretation, which is perhaps one of the reasons why diet, among other lifestyle factors, was the factor least strongly associated with a reduced risk of prostate cancer in the study by Plym and colleagues[5].

Results from this study[5] suggest that men with low genetic risk scores might not benefit from a healthy lifestyle; however, in future clinical trials assessing lifestyle interventions, enrolling only men at a high genetic risk of

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prostate cancer does not seem reasonable. These men could certainly derive other benefits from a healthy lifestyle (such as weight loss or reduced cardiovascular risk), and denying these men the benefits of lifestyle interventions would be unethical. Alternatively, patients enrolled in clinical studies involving lifestyle interventions could be stratified by PRS. This solution would be applicable and would certainly be supported by the findings from the study by Plym and colleagues[5]. Moreover, these results should be confirmed in future validation studies also including men from minority groups. Specifically, one crucial direction for future clinical studies should be the inclusion of racial minorities. Indeed, genetic risk scores were mostly assessed in white men (99% and 93% in the HPFS and the PHS cohorts, respectively)[5], and no conclusions can be drawn regarding the possibility of reducing prostate cancer risk in patients from racial minority groups. African American men have the highest prostate cancer incidence and mortality[7]; thus, exploring the association of genetic risk and lifestyle with prostate cancer risk in these men is paramount.

In summary, results from the study by Plym and colleagues[5] are encouraging for men considered at highest risk of prostate cancer, who might be able to substantially reduce this risk by exercising vigorously and maintaining a healthy weight. The lack of benefit from lifestyle interventions for men in the low genetic risk categories (three-quarters of men included in the study) should not dissuade clinicians from encouraging these men to undertake lifestyle interventions for other health benefits. Lastly, further validation of these findings, especially in minority populations, is needed to draw solid conclusions.

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