REVIEW ARTICLE

PROSTATE CANCER WITH A PRESENTING SYMPTOM OF LOWER THORACIC BACK PAIN

Vasu Malhotra, OMS-II[1]; Chinar Singh, OMS-II[1]; Allison Weening, OMS-II[1]; Shreya Patel, OMS-II[1]; Bindu Mayi, MSc, PhD[1]; Joseph A. Migliozzi, MD[1]; Vikas Malhotra, MD[2]

[1]Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, FL
[2]Florida Cancer Specialists & Research Institute, Tampa, FL

KEYWORDS

Prostate cancer

Back pain

Aggressive pathology

Immune suppression

ABSTRACT

Back pain is a common complaint addressed by family physicians. This is an uncommon case of a patient presenting with back pain and subsequent workup revealing a new diagnosis of metastatic prostate cancer with bone metastasis. This case can be used to highlight an unusual presentation and to facilitate inclusion of prostate cancer in the differential diagnosis. A review of the literature calls attention to the clinical features that make such a scenario likely and guides the discussion of the current understanding of the mechanisms leading to such a presentation. Underlying risk factors of obesity, diabetes, and chronic kidney disease (CKD) may increase this risk. A high Gleason score with poorly differentiated features also increases the risk of de novo metastatic presentation.

INTRODUCTION

Prostate cancer generally presents with asymptomatic prostate-specific antigen (PSA) elevation or symptoms of prostatism, which include increasing frequency of urination, nocturia, increased urgency, urinary hesitancy, and incomplete bladder emptying.[1] This case highlights an uncommon presentation of prostate cancer. Back pain is not a common presenting symptom in early prostate cancer patients.[2] This highlights the need for primary care physicians to keep prostate cancer in the differential diagnosis for new and sudden onset of back pain without any previous history.

HISTORY

A 62-year-old white male, with a history of obesity, type 2 diabetes mellitus, hypertension, and chronic kidney disease (CKD), presented to his primary care physician with worsening lower thoracic back pain. The pain began worsening a week before the initial visit. The patient ranked the pain a 5 out of 10. The pain was aggravated by any activity and alleviated with oral acetaminophen. There were no other associated symptoms. There was no prior history of cancer, nor did the patient have any family history of cancer. He also did not have any autoimmune disorders or immune deficiencies. The patient had retired from his career as a physician before his initial complaint of back pain. A colonoscopy was performed a month before his initial visit and was normal. The patient had been monitoring his PSA annually and it was within normal limits a year prior to presentation. On physical examination, his temperature was 98.3°F, pulse 80 bpm, respirations 18 breaths/min, and blood pressure 145/85 mm Hg. On palpation, his lower thoracic spine was tender. His lungs were clear, his heart was regular, and the HEENT exam was normal. The patient declined a rectal prostate exam. Laboratory examination revealed a PSA of 9.9 ng/mL, creatinine of 5.3 mg/dL, and eGFR of 11 mL/min. A creatinine study done one month prior was at the same level. On the first visit, the patient was treated with acetaminophen and hydrocodone for symptomatic pain control. Follow-up plain radiographs did show a compression defect at the T12 vertebrae.

On a follow-up visit, one week later, he reported his back pain was 3 out of 10 with the prescribed pain medications. A CT scan with contrast was not performed because of the patient's history of CKD. Magnetic resonance imaging (MRI) of the thoracic spine revealed a compression fracture of the T12 vertebrae. The patient was referred for kyphoplasty, which showed metastatic prostate adenocarcinoma. A base-of-skull-to-upper-midthigh positron-emission tomography (PET)

CORRESPONDENCE:
Vikas Malhotra, MD | vmalhotra@flcancer.com

ISSN: 1877-573X doi:10.33181/13092

INTRODUCTION

Prostate cancer generally presents with asymptomatic prostate-specific antigen (PSA) elevation or symptoms of prostatism. Symptoms of prostatism include increasing frequency of urination, nocturia, increased urgency, urinary hesitancy, and incomplete bladder emptying.[1] We present this case to highlight an uncommon presentation of prostate cancer. Back pain is not a common presenting symptom in early prostate cancer patients.[2] This highlights the need for primary care physicians to keep prostate cancer in the differential diagnosis for new and sudden onset of back pain without any previous history.

HISTORY

A 62-year-old white male, with a history of obesity, type 2 diabetes mellitus, hypertension, and chronic kidney disease (CKD), presented to his primary care physician with worsening lower thoracic back pain. The pain began worsening a week before the initial visit. The patient ranked the pain a 5 out of 10. The pain was aggravated by any activity and alleviated with oral acetaminophen. There were no other associated symptoms. There was no prior history of cancer, nor did the patient have any family history of cancer. He also did not have any autoimmune disorders or immune deficiencies. The patient had retired from his career as a physician before his initial complaint of back pain. A colonoscopy was performed a month before his initial visit and was normal. The patient had been monitoring his PSA annually and it was within normal limits a year prior to presentation. On physical examination, his temperature was 98.3°F, pulse 80 bpm, respirations 18 breaths/min, and blood pressure 145/85 mm Hg. On palpation, his lower thoracic spine was tender. His lungs were clear, his heart was regular, and the HEENT exam was normal. The patient declined a rectal prostate exam. Laboratory examination revealed a PSA of 9.9 ng/mL, creatinine of 5.3 mg/dL, and eGFR of 11 mL/min. A creatinine study done one month prior was at the same level. On the first visit, the patient was treated with acetaminophen and hydrocodone for symptomatic pain control. Follow-up plain radiographs did show a compression defect at the T12 vertebrae.

On a follow-up visit, one week later, he reported his back pain was 3 out of 10 with the prescribed pain medications. A CT scan with contrast was not performed because of the patient's history of CKD. Magnetic resonance imaging (MRI) of the thoracic spine revealed a compression fracture of the T12 vertebrae. The patient was referred for kyphoplasty, which showed metastatic prostate adenocarcinoma. A base-of-skull-to-upper-midthigh positron-emission tomography (PET) scan showed hypermetabolic osseous metastases in the T12 vertebrae with kyphoplasty changes but with no other evidence of distant metastases. It also showed mild prostatomegaly with fluorodeoxyglucose (FDG) uptake along the right side of the prostate. The usage of both an MRI and PET scan allowed for the integration of the structural findings from an MRI into the functional findings of a PET scan. These findings, along with the immunohistochemistry profile detailed below, indicated metastatic adenocarcinoma suggestive of primary prostate cancer. Thoracic spine biopsies showed tumor cells positive for AE1/AE3 and CAM5[2], which are both epithelial markers, as well as NKX3[1], which is a prostate cancer marker.[3] The biopsies were negative for CK7 (a lung and upper GI marker), CK20 and CDX2 (lower GI markers), TTF1 (a lung marker), and GATA3 (a bladder marker).[3] Prostate biopsies showed adenocarcinoma with a Gleason score of 9 (4 + 5) in 8 out of 12 cores.

Most prostate cancers will present with a Gleason score of 6 to 7 consistent with low-risk cancer, however, his score indicated poorly differentiated and highly aggressive cancer with a predilection for metastasis.[4] He was first started on combined androgen blockade therapy with a combination of leuprolide acetate and bicalutamide, which is the standard of care for hormone-sensitive metastatic prostate cancer. Leuprolide acetate is a GnRH agonist that suppresses the production of testosterone through a feedback mechanism when given continuously. However, when first started, leuprolide acetate causes a temporary increase in testosterone levels that is blocked by concurrent use of bicalutamide, a direct testosterone antagonist.[5] The patient was referred to radiation oncology for definitive prostate radiation due to the limited metastasis of this patient's cancer to just one vertebral body. After completing this successfully, he received 40 fractions of 200 cGy each, for a total dose of 8000 cGy delivered to the prostate and seminal vesicles. The treatment began a few days after the initial visit and was completed 5 days a week for 8 weeks. His repeat PSA is undetectable (<0.64 ng/mL) and his back pain has resolved. The patient was on a renal transplant list due to end-stage renal disease. However, due to the finding of metastatic cancer, he no longer qualified for a transplant. The patient is currently in remission with no evidence of disease, with PSA levels monitored every 3 months. The patient's prognosis is guarded—although a cure is unlikely, a long-term durable remission is possible. The combination of immunosuppression from CKD and aggressive pathology likely contributed to his metastatic presentation.

DISCUSSION

Prostate-specific antigen, also known as human kallikrein 3, belongs to a family of serine proteases. It is produced primarily in the prostate epithelium, which is why it gets this designation.[6] Prostate-specific antigen functions principally to allow for sperm motility and also may have some role in breaking down cervical mucus.[7] Prostate cancer is not the only pathology in which there will be elevated PSA levels; benign prostatic hyperplasia and prostatitis will also cause elevated levels. For this reason, PSA is used only as a screening tool for prostate cancer and requires additional testing for diagnosis. Contrary to what would be expected, in poorly differentiated prostate cancer, PSA levels will be significantly reduced due to the loss of prostate-specific phenotype, as demonstrated by negative PSA staining on immunohistochemistry.[6] Bonk et al demonstrated in a microarray study of 21,000 tissue samples that low PSA levels were correlated with TMPRSS2:ERG gene translocation and PTEN (phosphatase and tensin homolog) deletions.[6] Phosphatase and tensin homolog is a tumor suppressor gene that functions to turn off cell-signaling pathways. TMPRSS2:ERG is one of the most common genetic changes found in about half of all prostate cancers previously

example, 3 + 3 = 6, 4 + 3 = 7. The total scores or Gleason scores of 6 and 7 are reflective of low and intermediate risk; whereas, Gleason scores of 8 or higher are considered high risk.[16]

The primary and secondary histologic pattern of differentiation of cells noted after biopsies are each graded 1 through 5 and then summed together to achieve a Gleason score for the samples, for example, 3 + 3 = 6, 4 + 3 = 7. The total scores or Gleason scores of 6 and 7 are reflective of low and intermediate risk; whereas, Gleason scores of 8 or higher are considered high risk.[16]

B. Prostate cancer metastasis

Advanced cancers like breast and prostate primarily metastasize to bone causing compression and pathological fractures.[37] Metastasis of prostate cancer to bone occurs through hematogenous spread.[17] The release of exosomes from prostate cancer cells into the bloodstream show organotropism for bone, making bone the primary site for prostate cancer metastasis. The identification of organotropism is primarily determined by integrin components and proteins in epithelial-to-mesenchymal transition (EMT).[18] This tropism is determined by the noncollagen proteins found in the bone matrix.[19] Bone matrix is about 95% type I collagen, and the remaining 5% includes proteins like osteopontin, osteonectin, and bone sialoprotein.[19] These proteins are the targets of migratory prostate cancer cells, allowing for metastasis and growth at the bone.[19] In addition to tropism, EMT has been correlated with metastasis and later stages of cancer progression. Liu et al showed that fatty acid binding protein 12 (FABP12) expression was correlated with prostate cancer progression in PC3 cell lines. Fatty acid binding protein 12 acts through the peroxisome proliferator-activated receptor-gamma pathway, which will induce EMT as well as increase prostate cancer reliance on fatty acids for energy production.[20] Fatty acids are not only implicated in energy production but also in signal transduction (as second messengers).[21] Tumor growth factor-beta is also implicated in EMT progression and bone metastasis.[22] The metastasis to bone will result in altered bone density due to the altered activity of osteoblasts and osteoclasts.[22]

N-cadherin and E-cadherin expression are also implicated in prostate cancer progression and metastasis. Patients with higher-grade lesions, ie, a Gleason score ≥8, show lower concentrations of E-cadherin and higher concentrations of N-cadherin.[19] The elevated levels of N-cadherin are also implemented in promoting castration resistance, which could potentially be a target to protect against malignancy.[23] MicroRNAs (miRs) are another option for novel therapy for prostate cancers. For instance, miR15/16 are tumor suppressors shown to be downregulated in prostate cancer[24]; miR15/16 are involved in cell-cycle control mechanisms by binding and inactivating cyclin D1, cyclin E, Bcl-2, c-Myc, and EF2.[25] The downregulation of these miRs result in increased cell cycling. Reintroduction of these miRs has been shown to stimulate apoptotic pathways (through Bcl-2), decreased growth, and proliferation.[25] Also, miR-145 is implicated in prostate cancer; however, this miR upregulates metastasis of prostate cancer cells by increasing motility through inactivation of the N-cadherin.[25] Zaman et al showed that upregulating miR-145 decreases proliferation of prostate cancer cells and increases apoptotic cells, indicating its use as a therapeutic target.[27] Other options are BRCA and poly(ADP-ribose) polymerase, which are both involved in DNA repair mechanisms and are current therapeutic targets of prostate cancer according to the American Cancer Society.

C. Reasons for unusual presentation

The development of Type 1 and Type 2 diabetes may be related to our body's immune function.[28] In Type 1 diabetes, the immune cells, such as the T cells and macrophages, proliferate abnormally and produce numerous proinflammatory markers that may also be defective in diabetic patients with increased glucose levels in blood.[29] Certain receptors on the immune cells that recognize pathogens are defective in patients with sustained high glucose levels, leading to an overall immunosuppression and increased susceptibility to various diseases.[30] There are also studies that show that blood from patients who do not have diabetes, when subjected to increased glucose levels, had reduced cytokines. Cytokines are biomarkers produced to recruit more immune cells when pathogens invade our body.[31]

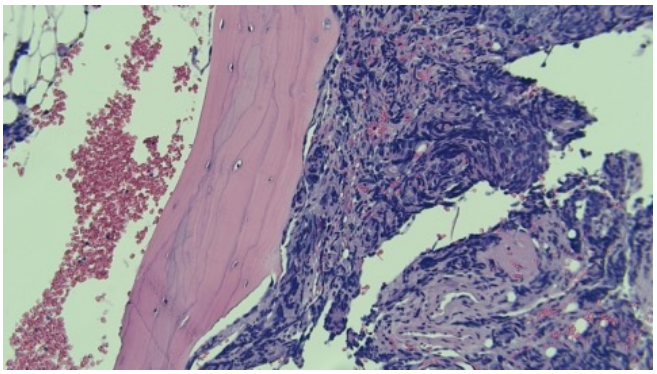
The human body has two types of immunity, namely innate and adaptive. When a patient has end-stage renal disease, the increased activation of the innate immune cells leads to increased inflammation and oxidative stress on the kidney cells. This, in turn, activates the adaptive immunity, persistently leading to more inflammation.[32] Dysregulation of immunity in CKD may contribute to increased risk of malignancy.[33]

Excess body weight and obesity happen when the total body energy expenditure is less than the consumption, making elevated amounts of adipose tissue deposit in various areas of the body. Therefore, adiposity plays a major role in development of diseases affecting the heart and body metabolism.[34] There is also increased evidence that obesity may lead to higher risk for different kinds of cancer, such as breast, thyroid, gastric, colorectal, gallbladder, and multiple myeloma.[35] Obesity and excess body weight are determined by measuring the body mass index. According to the World Cancer Research Fund Report, obesity's role in prostate cancer is probable but not investigated. There were restrictions such that imaging without contrast had to be performed due to CKD and renal insufficiency, but PET and MRI helped with identification of bone metastases.[36]

CONCLUSION

There is a need for inclusion of back pain as risk scoring for prostate cancer. As a standard of care, worsening low thoracic pain is usually not tested for prostate cancer. There is also a need for active surveillance as standard of care, not only for patients with a high PSA level, but also for patients who may not have a high PSA level but do have other indications such as aggressive Gleason score patterns and MRI imaging results.[38] There is literature available that points toward hereditary factors leading to an increased risk of prostate cancer as an outcome; therefore, a genetic risk evaluation via a polygenic risk score may help with early identification of such cases.[39]

FIGURE 1:
Low- and high-power view of decalcified bone show extensive involvement by solid sheets of carcinoma cells with prominent nucleoli.



REFERENCES

1. Lepor H. Pathophysiology, epidemiology, and natural history of benign prostatic hyperplasia. *Rev Urol*. 2004;6(suppl 9):S3–S10.
2. Bekelman JE, Rumble RB, Chen RC, et al. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. *J Clin Oncol*. 2018;36(32):3251–3258. doi:10.1200/JCO.18.00606
3. Bakhshwin A, Berry RS, Cox RM, et al. Malignant solitary fibrous tumour of the prostate: four cases emphasising significant histological and immunophenotypical overlap with sarcomatoid carcinoma. *Pathology*. 2020;52(6):643–648. doi:10.1016/j.pathol.2020.06.004
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7–30. doi:10.3322/caac.21442
5. Mazhar D, Waxman J. Prostate cancer. *Postgrad Med J*. 2002;78(924): 590–595. doi:10.1136/pmj.78.924.590
6. Bonk S, Kluth M, Hube-Magg C, et al. Prognostic and diagnostic role of PSA immunohistochemistry: a tissue microarray study on 21,000 normal and cancerous tissues. *Oncotarget*. 2019;10(52):5439–5453. doi:10.18632/oncotarget.27145
7. Arneth BM. Clinical significance of measuring prostate-specific antigen. *Lab Med*. 2009;40(8):487–491. doi:10.1309/LMEGGGLZ2EDWRXUK
8. Tomlins SA, Laxman B, Varambally S, et al. Role of the TMPRSS2-ERG gene fusion in prostate cancer. *Neoplasia*. 2008;10(2):177–188. doi:10.1593/neo.07822
9. Adamo P, Ladomery MR. The oncogene ERG: a key factor in prostate cancer. *Oncogene*. 2016;35(4):403–414. doi:10.1038/onc.2015.109
10. US Preventive Services Task Force; Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–1913. doi:10.1001/jama.2018.3710
11. Naji L, Randhawa H, Sohani Z, et al. Digital rectal examination for prostate cancer screening in primary care: a systematic review and meta-analysis. *Ann Family Med*. 2018;16(2):149–154. doi:10.1370/afm.2205
12. Borkenhagen JF, Eastwood D, Kilari D, See WA, Van Wickle JD, Lawton CA, Hall WA. Digital rectal examination remains a key prognostic tool for prostate cancer: a National Cancer Database review. *J Natl Compr Canc Netw*. 2019;17(7):829–837. doi:10.6004/jnccn.2018.7278
13. Herrera-Caceres JO, Wettstein MS, Goldberg H, et al. Utility of digital rectal examination in a population with prostate cancer treated with active surveillance. *Can Urol Assoc J*. 2020;14(9):E453–E457. doi:10.5489/cuaj.6341
14. Punnen S, Pavan N, Parekh DJ. Finding the wolf in sheep's clothing: the 4Kscore is a novel blood test that can accurately identify the risk of aggressive prostate cancer. *Rev Urol*. 2015;17(1):3–13. Accessed December 23, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444768/
15. Voigt JD, Dong Y, Linder V, Zappala S. Use of the 4Kscore test to predict the risk of aggressive prostate cancer prior to prostate biopsy: overall cost savings and improved quality of care to the US healthcare system. *Rev Urol*. 2017;19(1):1–10. doi:10.3909/riu0753
16. Tagai EK, Miller SM, Kutikov A, et al. Prostate cancer patients' understanding of the Gleason scoring system: implications for shared decision-making. J Cancer Edu. 2019;34(3):441–445. doi:10.1007/s13187-018-1320-1
17. Yang JC, Bai L, Yap S, Gao AC, Kung H-J, Evans CP. Effect of the specific Src family kinase inhibitor saracatinib on osteolytic lesions using the PC-3 bone model. *Mol Cancer Ther*. 2010;9(6):1629–1637. doi:10.1158/1535-7163.MCT-09-1058
18. Lorenc T, Klimczyk K, Michalczewska I, Słomka M, Kubiak-Tomaszewska G, Olejarz W. Exosomes in prostate cancer diagnosis, prognosis and therapy. *Int J Mol Sci*. 2020;21(6):2118. doi:10.3390/ijms21062118
19. Jin JK, Dayyani F, Gallick GE. Steps in prostate cancer progression that lead to bone metastasis. *Int J Cancer*. 2011;128(11):2545–2561. doi:10.1002/ijc.26024
20. Liu RZ, Choi WS, Jain S, et al. The FABP12/PPAR pathway promotes metastatic transformation by inducing epithelial-to-mesenchymal transition and lipid-derived energy production in prostate cancer cells. *Mol Oncol*. 2020;14(12):3100–3120. doi:10.1002/1878-0261.12818
21. Koundouros N, Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. *Br J Cancer*. 2019;122(1):4–22. doi:10.1038/s41416-019-0650-z
22. Bonci D, Coppola V, Patrizii M, et al. A microRNA code for prostate cancer metastasis. *Oncogene*. 2016;35(9):1180–1192. doi:10.1038/onc.2015.176
23. Warde N. Prostate cancer: Cadherin 2: an important new player in castration resistance. *Nat Rev Urol*. 2011;8(1):3. doi:10.1038/nrurol.2010.222
24. Bonci D, Coppola V, Musumeci M, et al. The miR-15a–miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities. *Nat Med*. 2008;14(11):1271–1277. doi:10.1038/nm.1880
25. Ramaiah MJ. Functions and epigenetic aspects of mir-15/16: possible future cancer therapeutics. *Gene Reports*. 2018;12:149–164. doi:10.1016/j.genrep.2018.06.012
26. Zeng H, Huang Y, Liu Q, et al. MiR-145 suppresses the motility of prostate cancer cells by targeting cadherin-2. *Mol Cell Biochem*. 2021;476(10):3635–3646. doi:10.1007/s11010-021-04188-0
27. Zaman MS, Chen Y, Deng G, et al. The functional significance of microrna-145 in prostate cancer. *Br J Cancer*. 2010;103(2):256–264. doi:10.1038/sj.bjc.6605742
28. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab*. 2009;94(9): 3171–3182. doi:10.1210/jc.2008-2534
29. Zhou T, Hu Z, Yang S, Sun L, Yu Z, Wang G. Role of adaptive and innate immunity in type 2 diabetes mellitus. *J Diabetes Res*. 2018;2018:7457269. doi:10.1155/2018/7457269

30. Berrou J, Fougeray S, Venot M, et al. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. *PLoS ONE*. 2013;8(4):e62418. doi:10.1371/journal.pone.0062418

31. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev*. 2020;16(5):442–449. doi:10.2174/1573399815666191024085838

32. Diaz-Ricart M, Torramade-Moix S, Pascual G, et al. Endothelial damage, inflammation and immunity in chronic kidney disease. *Toxins*. 2020;12(6):361. doi:10.3390/toxins12060361

33. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. *Clin Exp Immunol*. 2018;192(2):142–150. doi:10.1111/cei.13119

34. Avgerinos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism*. 2019;92:121–135. doi:10.1016/j.metabol.2018.11.001

35. Dalamaga M, Christodoulatos GS, Mantzoros CS. The role of extracellular and intracellular nicotinamide phosphoribosyl-transferase in cancer: diagnostic and therapeutic perspectives and challenges. *Metabolism*. 2018;82:72–87. doi:10.1016/j.metabol.2018.01.001

36. Sartor O, de Bono JS. Metastatic prostate cancer. *N Engl J Med*. 2018;378(7):645–657. doi:10.1056/NEJMra1701695

37. Hiraga T. Bone metastasis: interaction between cancer cells and bone microenvironment. *J Oral Biosci*. 2019;61(2):95–98. doi:10.1016/j.job.2019.02.002

38. Klotz L. Active surveillance in intermediate-risk prostate cancer. *BJU Int*. 2020;125(3):346–354. doi:10.1111/bju.14935

39. Sipeky C, Talala KM, Tammela TLJ, Taari K, Auvinen A, Schleutker J. Prostate cancer risk prediction using a polygenic risk score. *Scientific Reports*. 2020;10(1):17075. doi:10.1038/s41598-020-74172-z