Obesity and Prostate Cancer Mortality

Subjects: Oncology

Contributor: Mario Rivera-Izquierdo

Obesity was associated with prostate cancer specific mortality and all-cause mortality. The temporal association was consistent with a dose-response relationship. Obesity, a potentially modifiable prognostic factor, was associated with higher prostate cancer mortality. Obesity had a moderate, consistent, temporal, and dose-response association with PC mortality. Weight control programs may have a role in improving PC survival.

Keywords: body mass index ; prostate cancer specific mortality ; all-cause mortality

1. Introduction

Prostate cancer (PC), the second most common cancer and the third leading cause of cancer death in men [1], is steadily increasing in incidence [2]. Worldwide, over 650 million adults are obese [3], and therefore exposed to the second most common cause of preventable death [4], while obesity has been proposed as a risk factor for aggressive PC [5]. Recent large studies, however, showed that this relationship is unclear [6][7]. The other known factors associated with PC mortality, older age, family history of any cancer and ethnicity [5], are not changeable. As a potentially modifiable factor, obesity merits evaluation as a prognostic factor.

Individual studies on the association between obesity and prostate cancer (PC) mortality show inconsistent results, including both positive [6] and negative [8] association. Evidence syntheses on the association between obesity and PC outcomes [9][10][11], when judged by AMSTAR 2 [12], demonstrate weaknesses in the description of the study population, investigation of the causes of heterogeneity, evaluation of the impact of risk of bias in stratified results, and reporting of funding or conflicts of interest. Since the last meta-analysis [9], 15 prognostic studies have been published [2][7][8][13][14][15][16][17][18][19][20][21][22][23][24] with data from 186,802 new PC patients added to the total. Consequently, the last review [9] could access only a third of the current body of evidence. Importantly, previous evidence syntheses have not formally evaluated causation [25]. Thus, there is need for a robust and reliable evaluation of the association between obesity and prostate cancer specific mortality (PCSM) and all-cause mortality (ACM) in patients diagnosed with PC.

2. Obesity as a Risk Factor for Prostate Cancer Mortality

Compiling all available data for precise quantitative estimation of the prognostic effect of obesity in PC mortality, we found that BMI ≥ 30 was associated with PCSM and ACM compared with normal weight. Both mortality outcomes showed dose-response relationship with every 5 kg/m^2 unit increase in BMI. In higher quality prospective studies evaluating temporal association, BMI ≥ 30 was associated with increased PCSM and showed dose-response association.

We performed a comprehensive literature search without language restrictions, increasing our potential to capture all relevant studies. Owing to the large sample size, we were able to undertake powerful analyses, including predefined subgroup analyses, to generate reliable results. There was considerable heterogeneity in the pooled analyses, and we used random effects models to obtain conservative precision estimates. The statistical significance of the observed heterogeneity could reflect the large number of studies we captured [26]. The exploration of reasons for heterogeneity showed that the main findings were not sensitive to variations in subgroups based on populations, settings, disease stage, and interventions. The measurement of exposure before or after the diagnosis provides a dichotomized assessment of a wide time range. The results in the postdiagnosis exposure measurement subgroup confirmed the prognostic association of continuous BMI with PCSM, which contributes to the specificity element of the causal criteria [27], and with ACM, consistent with the general adverse effects of obesity on overall survival. Conversely, obesity exposure throughout life captured in prediagnosis measurement showed an association with PCSM, although no association was found for ACM. The association between BMI and PC mortality might be different according to the treatment (e.g., better surgical success in patients with normal weight treated with radical prostatectomy). Subgroup analyses by ethnicity and other potentially important factors was not possible given that most of the selected studies did not report stratified results. However, adjusted hazard ratios were considered in the pooled analyses to reduce residual confusion. Our main findings were

backed by the high-quality subgroup of studies, highlighting that the observed association of obesity with PC prognosis merits consideration.

The assessment of causation is integral to the evaluation of findings of observational meta-analyses [27]. We evaluated whether our observed association fulfilled the classical Bradford Hill principles of causation [25]. Our assessment showed evidence of moderate strength of association, consistency, temporality, specificity, dose-response gradient, biological plausibility and analogy. The association measured by pooled HR was statistically significant overall. The HR point estimate showed an increased strength of association in the higher-quality subgroup of studies. Consistency of individual studies, analyzed graphically, showed that point estimates of individual HRs on over three-quarters of the studies had an association. Although statistically I^2 measurements showed variation, this reflected differences in size of the association observed rather than differences in its direction. The association within subgroups showed lower level of heterogeneity. The association was consistently observed across the subgroups including different stages, treatments (e.g., prostatectomy or androgen deprivation therapy) and populations of PC patients. Studies that analyzed obesity with measurements different from BMI also showed consistent association with PC mortality [28][29][30]. Temporality was established by longitudinal (cohort) studies. The specificity of the association was reflected in the results concerning PCSM. Moreover, the studies synthetized in our meta-analysis were mostly adjusted by several potential confounders, as shown in Table S3. Regarding biological gradient, we showed dose-response relationship by using continuous BMI as exposure, which was associated with PCSM and ACM. The biological plausibility of the association is underpinned by several postulated mechanisms explaining the relationship between BMI and PC death [9]. For instance, obesity is the most common cause of insulin resistance, which has been associated with a greater inflammatory state, a risk factor for cancer progression [31]. Also, molecular mechanisms connecting obesity with PC and other urothelial cancers have been broadly established [32]. Finally, the relationship with PC outcomes met analogy criterion, as obesity has been linked for the last three decades to mortality from numerous types of cancer [11][33] and to other outcomes related to PC, for instance, the presence of metastases [34]. Therefore, objectively, several criteria for causation were met.

The World Cancer Research Fund [35] reported an increased risk of being diagnosed with advanced PC in obese patients, although large studies have recently questioned this point [6][7]. As it is potentially modifiable by lifestyle changes, future evaluations of the role of weight loss among obese patients with PC are required. For example, randomized interventions on diet and physical activity are needed to analyze PC outcomes [36][37]. Guidelines and patient information documents concerning PC would need to be updated to emphasize the role of obesity in prognosis.

3. Conclusions

Obesity currently poses an alarming burden on individuals, societies, and economies. Our study shows that in PC patients, obesity, a potentially modifiable risk factor, is moderately associated with temporality and a dose-response with PCSM and ACM. Therefore, obesity increases mortality in prostate cancer patients, according to the current observational evidence. This information should be useful in counselling PC patients and in planning future research concerning their lifestyle.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249.
2. Fillon, M. Rates of advanced prostate cancer continue to increase. CA Cancer J. Clin. 2020, 70, 427–429.
3. World Health Organization. Obesity and Overweight. Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 16 July 2021).
4. Panuganti, K.K.; Nguyen, M.; Kshirsagar, R.K. Obesity. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020.
5. Schatten, H. Brief Overview of Prostate Cancer Statistics, Grading, Diagnosis and Treatment Strategies. Adv. Exp. Med. Biol. 2018, 1095, 1–14.
6. Genkinger, J.M.; Wu, K.; Wang, M.; Albanes, D.; Black, A.; van den Brandt, P.A.; Burke, K.A.; Cook, M.B.; Gapstur, S.M.; Giles, G.G.; et al. Measures of body fatness and height in early and mid-to-late adulthood and prostate cancer: Risk and mortality in The Pooling Project of Prospective Studies of Diet and Cancer. Ann. Oncol. 2020, 31, 103–114.
7. Jochems, S.H.J.; Stattin, P.; Häggström, C.; Järvholm, B.; Orho-Melander, M.; Wood, A.M.; Stocks, T. Height, body mass index and prostate cancer risk and mortality by way of detection and cancer risk category. Int. J. Cancer. 2020,

147, 3328–3338.

8. Jackson, M.D.; Tulloch-Reid, M.K.; McCaw-Binns, A.M.; Aiken, W.; Ferguson, T.S.; Bennett, N.R.; Harrison, L.; Badaloo, A.; McGrowder, D.; Grindley, A.; et al. Central adiposity at diagnosis may reduce prostate cancer-specific mortality in African-Caribbean men with prostate cancer: 10-year follow-up of participants in a case-control study. Cancer Causes Control. 2020, 31, 651–662.
9. Zhong, S.; Yan, X.; Wu, Y.; Zhang, X.; Chen, L.; Tang, J.; Zhao, J. Body mass index and mortality in prostate cancer patients: A dose-response meta-analysis. Prostate Cancer Prostatic Dis. 2016, 19, 122–131.
10. Zhang, X.; Zhou, G.; Sun, B.; Zhao, G.; Liu, D.; Sun, J.; Liu, C.; Guo, H. Impact of obesity upon prostate cancer-associated mortality: A meta-analysis of 17 cohort studies. Oncol. Lett. 2015, 9, 1307–1312.
11. Cao, Y.; Ma, J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: A systematic review and meta-analysis. Cancer Prev. Res. 2011, 4, 486–501.
12. Shea, B.J.; Reeves, B.C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017, 358, j4008.
13. Bluethmann, S.M.; Wang, M.; Wasserman, E.; Chen, C.; Zaorsky, N.G.; Hohl, R.J.; McDonald, A.C. Prostate cancer in Pennsylvania: The role of older age at diagnosis, aggressiveness, and environmental risk factors on treatment and mortality using data from the Pennsylvania Cancer Registry. Cancer Med. 2020, 9, 3623–3633.
14. Crump, C.; Stattin, P.; Brooks, J.D.; Stocks, T.; Sundquist, J.; Sieh, W.; Sundquist, K. Early-Life Cardiorespiratory Fitness and Long-term Risk of Prostate Cancer. Cancer Epidemiol. Biomarkers Prev. 2020, 29, 2187–2194.
15. Vidal, A.C.; Oyekunle, T.; Howard, L.E.; De Hoedt, A.M.; Kane, C.J.; Terris, M.K.; Cooperberg, M.R.; Amling, C.L.; Klaassen, Z.; Freedland, S.J.; et al. Obesity, race, and long-term prostate cancer outcomes. Cancer 2020, 126, 3733–3741.
16. Troeschel, A.N.; Hartman, T.J.; Jacobs, E.J.; Stevens, V.L.; Gansler, T.; Flanders, W.D.; McCullough, L.E.; Wang, Y. Postdiagnosis Body Mass Index, Weight Change, and Mortality From Prostate Cancer, Cardiovascular Disease, and All Causes Among Survivors of Nonmetastatic Prostate Cancer. J. Clin. Oncol. 2020, 38, 2018–2027.
17. Langlais, C.S.; Cowan, J.E.; Neuhaus, J.; Kenfield, S.A.; Van Blarigan, E.L.; Broering, J.M.; Cooperberg, M.R.; Carroll, P.; Chan, J.M. Obesity at Diagnosis and Prostate Cancer Prognosis and Recurrence Risk Following Primary Treatment by Radical Prostatectomy. Cancer Epidemiol. Biomarkers Prev. 2019, 28, 1917–1925.
18. Darcey, E.; Pereira, G.; Salter, A.; Fritschi, L.; Leavy, J.; Ambrosini, G.L.; Boyle, T. The Impact of Lifestyle-related Factors on Survival After a Prostate Cancer Diagnosis. Eur. Urol. 2019, 75, 884–885.
19. Wade, K.H.; Carslake, D.; Tynelius, P.; Davey Smith, G.; Martin, R.M. Variation of all-cause and cause-specific mortality with body mass index in one million Swedish parent-son pairs: An instrumental variable analysis. PLoS Med. 2019, 16, e1002868.
20. Farris, M.S.; Courneya, K.S.; Kopciuk, K.A.; McGregor, S.E.; Friedenreich, C.M. Anthropometric measurements and survival after a prostate cancer diagnosis. Br. J. Cancer 2018, 118, 607–610.
21. Hu, M.B.; Yang, T.; Hu, J.M.; Zhu, W.H.; Jiang, H.W.; Ding, Q. Prognostic factors in Chinese patients with prostate cancer receiving primary androgen deprivation therapy: Validation of Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score and impacts of pre-existing obesity and diabetes mellitus. Int. J. Clin. Oncol. 2018, 23, 591–598.
22. Perez-Cornago, A.; Appleby, P.N.; Pischon, T.; Tsilidis, K.K.; Tjønneland, A.; Olsen, A.; Overvad, K.; Kaaks, R.; Kühn, T.; Boeing, H.; et al. Tall height and obesity are associated with an increased risk of aggressive prostate cancer: Results from the EPIC cohort study. BMC Med. 2017, 15, 115.
23. Dickerman, B.A.; Ahearn, T.U.; Giovannucci, E.; Stampfer, M.J.; Nguyen, P.L.; Mucci, L.A.; Wilson, K.M. Weight change, obesity and risk of prostate cancer progression among men with clinically localized prostate cancer. Int. J. Cancer 2017, 141, 933–944.
24. Kelly, S.P.; Graubard, B.I.; Andreotti, G.; Younes, N.; Cleary, S.D.; Cook, M.B. Prediagnostic Body Mass Index Trajectories in Relation to Prostate Cancer Incidence and Mortality in the PLCO Cancer Screening Trial. J. Natl. Cancer Inst. 2016, 109, djw225.
25. Hill, A.B. The environment and disease: Association or causation? Proc. R. Soc. Med. 1965, 58, 295–300.
26. Huedo-Medina, T.B.; Sánchez-Meca, J.; Marín-Martínez, F.; Botella, J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol. Methods 2006, 11, 193–206.
27. Khan, K.S.; Ball, E.; Fox, C.E.; Meads, C. Systematic reviews to evaluate causation: An overview of methods and application. Evid. Based Med. 2012, 17, 137–141.

28. Gerdtsson, A.; Poon, J.B.; Thorek, D.L.; Mucci, L.A.; Evans, M.J.; Scardino, P.; Abrahamsson, P.A.; Nilsson, P.; Manjer, J.; Bjartell, A.; et al. Anthropometric Measures at Multiple Times Throughout Life and Prostate Cancer Diagnosis, Metastasis, and Death. Eur. Urol. 2015, 68, 1076–1082.
29. Chamberlain, C.; Romundstad, P.; Vatten, L.; Gunnell, D.; Martin, R.M. The association of weight gain during adulthood with prostate cancer incidence and survival: A population-based cohort. Int. J. Cancer 2011, 129, 1199–1206.
30. Nguyen, P.L.; Ma, J.; Chavarro, J.E.; Freedman, M.L.; Lis, R.; Fedele, G.; Fiore, C.; Qiu, W.; Fiorentino, M.; Finn, S.; et al. Fatty acid synthase polymorphisms, tumor expression, body mass index, prostate cancer risk, and survival. J. Clin. Oncol. 2010, 28, 3958–3964.
31. Arcidiacono, B.; Iiritano, S.; Nocera, A.; Possidente, K.; Nevolo, M.T.; Ventura, V.; Foti, D.; Chiefari, E.; Brunetti, A. Insulin resistance and cancer risk: An overview of the pathogenetic mechanisms. Exp. Diabetes Res. 2012, 2012, 789174.
32. Santoni, M.; Cimadamore, A.; Massari, F.; Piva, F.; Aurilio, G.; Martignetti, A.; Scarpelli, M.; Di Nunno, V.; Gatto, L.; Battelli, N.; et al. Key Role of Obesity in Genitourinary Tumors with Emphasis on Urothelial and Prostate Cancers. Cancers 2019, 11, 1225.
33. Petrelli, F.; Cortellini, A.; Indini, A.; Tomasello, G.; Ghidini, M.; Nigro, O.; Salati, M.; Dottorini, L.; Iaculli, A.; Varricchio, A.; et al. Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis. JAMA Netw. Open 2021, 4, e213520.
34. Annett, S.; Moore, G.; Robson, T. Obesity and Cancer Metastasis: Molecular and Translational Perspectives. Cancers 2020, 12, 3798.
35. World Cancer Research Fund. American Institute for Cancer Research. Body Fatness and Weight Gain. Available online: https://www.wcrf.org/dietandcancer/exposures/body-fatness (accessed on 17 August 2021).
36. Freedland, S.J.; Howard, L.; Allen, J.; Smith, J.; Stout, J.; Aronson, W.; Inman, B.A.; Armstrong, A.J.; George, D.; Westman, E.; et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: Carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. Prostate Cancer Prostatic Dis. 2019, 22, 28–37.
37. Schenk, J.M.; Neuhouser, M.L.; Beatty, S.J.; VanDoren, M.; Lin, D.W.; Porter, M.; Gore, J.L.; Gulati, R.; Plymate, S.R.; Wright, J.L. Randomized trial evaluating the role of weight loss in overweight and obese men with early stage prostate Cancer on active surveillance: Rationale and design of the Prostate Cancer Active Lifestyle Study (PALS). Contemp. Clin. Trials 2019, 81, 34–39.