Mario Rivera Izquierdo

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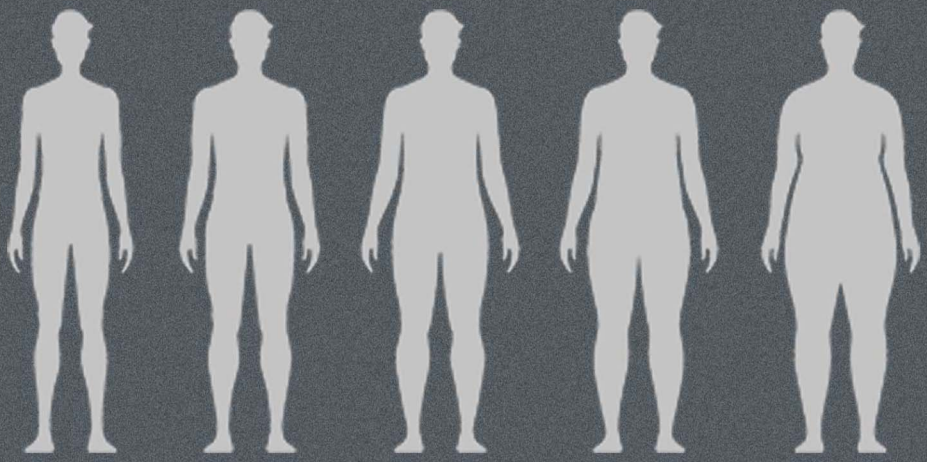
"Body mass index as a prognostic factor for prostate cancer outcomes"

DIRECTORES:
José Juan Jiménez Moleón
Virginia Ana Martínez Ruiz

UNIVERSIDAD DE GRANADA

TESIS DOCTORAL

Programa de Doctorado en Medicina Clínica y Salud Pública



GRANADA, MMXXII

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Memoria presentada por Mario Rivera Izquierdo para aspirar al grado de DOCTOR con Mención Internacional por la Universidad de Granada

Dirigido por:

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Trabajo 3. Rivera-Izquierdo M, Pérez de Rojas J, Martínez-Ruiz V, Arrabal-Polo MA, Pérez-Gómez B, Jiménez-Moleón JJ. Obesity and biochemical recurrence in clinically localized prostate cancer: a systematic review and meta-analysis of 86 490 patients. *Prostate Cancer Prostatic Dis*. 2021. doi: 10.1038/s41391-021-00481-7. FI: 5,554. Q1 (T1).

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"La epidemiología ha salvado más vidas que toda la terapéutica"

Héctor Abad Gómez

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A todos vosotros, GRACIAS.

ÍNDICE

RESUMEN / ABSTRACT

RESUMEN

Esta Tesis Doctoral está dedicada al estudio de la obesidad, un factor potencialmente modificable, como factor pronóstico para el desarrollo de desenlaces en pacientes con cáncer de próstata, asociación que hasta la fecha ha mostrado resultados inconsistentes en la literatura científica. Con el objetivo de analizar el papel de la obesidad en el pronóstico del cáncer de próstata, se han realizado diferentes aproximaciones metodológicas para dar respuesta a los siguientes puntos: 1) detectar la presencia de recomendaciones relativas a la obesidad y hábitos de vida saludables en las guías de práctica clínica disponibles para el cáncer de próstata mediante la realización de una revisión sistemática, 2) analizar si el índice de masa corporal y la obesidad, medida como índice de masa corporal $\geq$ 30 kg/m^2, se asocian con la mortalidad por cáncer de próstata mediante una revisión sistemática y metanálisis, 3) analizar si el índice de masa corporal y la obesidad, medida como índice de masa corporal $\geq$ 30 kg/m^2, se relacionan con el desarrollo de recurrencia bioquímica de la enfermedad después de una prostatectomía radical mediante una revisión sistemática y metanálisis, y 4) estimar la asociación de la obesidad con dichos desenlaces (mortalidad y recurrencia bioquímica) y con otros desenlaces pronósticos (metástasis y resistencia a la castración), a partir de la cohorte de casos con cáncer de próstata del estudio MultiCase-Control Spain (MCC-Spain), estudio realizado en población española, mediante la aplicación de técnicas de análisis de supervivencia. Para obtener los resultados, se utilizaron diversas estrategias de análisis (por ejemplo, técnicas metanalíticas utilizando modelos de efectos aleatorios, curvas de Kaplan-Meier, modelos de regresión multivariante mediante regresión de Cox, etc.), en función de los objetivos planteados y la aproximación elegida. Tras ello, se pueden concluir algunos hechos. Primero, que las recomendaciones sobre pérdida de peso y estilos de vida saludables en las

guías de práctica clínica de las sociedades profesionales y gobiernos se recogen de manera muy infrecuente. Segundo, que existe una elevada heterogeneidad entre los estudios que analizan la relación entre obesidad y pronóstico del cáncer de próstata. Las fuentes de heterogeneidad son diversas, incluyendo la variedad en las fuentes de recogida del índice de masa corporal y la definición de sobrepeso y obesidad, la diferente definición de algunos desenlaces, y los problemas de calidad y diseño de los estudios realizados hasta la fecha. Sin embargo, dicha heterogeneidad se redujo considerablemente en los análisis de subgrupos realizados a partir de las características anteriores. Tercero, que la obesidad se asoció con un mayor riesgo de mortalidad específica por cáncer de próstata y con un mayor riesgo de mortalidad por todas las causas en comparación con pacientes con normopeso. Además, el índice de masa corporal y la obesidad se asociaron a con mayor riesgo de recurrencia bioquímica después de recibir un tratamiento inicial basado en la prostatectomía radical. El conocimiento generado por esta Tesis Doctoral podría contribuir a la aplicación de diversas intervenciones para alcanzar y mantener un peso saludable con objeto de mejorar el pronóstico del cáncer de próstata.

ABSTRACT

This Doctoral Thesis is devoted to the study of obesity, a potentially modifiable factor, as a prognostic factor for prostate cancer outcomes, which has showed inconsistent results in the scientific literature to date. We used different methodological strategies aiming at analyzing the role of obesity in prostate cancer prognosis, to respond to the following points: 1) to detect the presence of recommendations regarding obesity and healthy lifestyles in clinical practice guidelines available for prostate cancer through a systematic review, 2) to analyze if body mass index (BMI) and obesity, measured as BMI $\geq$ 30 kg/m^2, were associated with prostate cancer mortality through a systematic review and meta-analysis, 3) to analyze if BMI and obesity, measured as BMI $\geq$ 30 kg/m^2, were associated with the development of biochemical recurrence after a radical prostatectomy through a systematic review and meta-analysis, and 4) to estimate the association of obesity with both outcomes (mortality and biochemical recurrence) and with other prognostic outcomes (metastases and castration resistance) from the cohort of prostate cancer cases provided by the MultiCase-Control Study (MCC-Spain), a study conducted on Spanish population, through the application of survival analysis techniques. To obtain the proper results, different analytical strategies were used (e.g., meta-analytic techniques using random-effect models, Kaplan-Meier estimations, multivariate Cox regression models, etc.), depending on the objectives and the approach selected. After that, several facts can be concluded. First, recommendations on weight loss and healthy lifestyle in prostate cancer's clinical practice guidelines of Societies and Governments were very infrequently covered. Second, high heterogeneity was found among the studies that analyzed the association between obesity and prostate cancer prognosis. The sources of heterogeneity were diverse, including the wide range of BMI sources of measurement and different

definitions of overweight and obesity, different outcome definitions and different quality and design of the individual studies. Nevertheless, the heterogeneity was considerably reduced in subgroup analyses performed according to these characteristics. Third, obesity (BMI ≥ 30) was associated with prostate cancer specific mortality and all-cause mortality compared with patients with normal weight (BMI < 25). Also, obesity was associated with higher risk of biochemical recurrence after receiving a radical prostatectomy. The knowledge generated by this Thesis may contribute to the application of different interventions to reach and maintain a healthy weight for improving prostate cancer outcomes.

I. INTRODUCCIÓN

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1. CONCEPTOS GENERALES

Esta Tesis Doctoral se enmarca en el estudio de la epidemiología y factores pronósticos asociados al cáncer de próstata, siendo un punto de encuentro entre la prevención, la oncología y la urología. Por ello, resulta ineludible iniciar esta introducción definiendo los conceptos que, en relación con estos ámbitos de estudio, irán surgiendo a lo largo de la lectura del texto.

1.1. OBESIDAD

Pese a que quizás pueda parecer innecesario, es conveniente comenzar por definir la exposición que nos ocupa: la *obesidad*. La obesidad se puede medir y definir de múltiples formas. Para la presente tesis doctoral, esta exposición se medirá de acuerdo con el índice de masa corporal (IMC), que se calcula como el peso (medido en kilogramos) partido por la altura elevada al cuadrado, medida en metros (IMC = kg / m^2). Así, de acuerdo con la Organización Mundial de la Salud (OMS), un IMC ≥ 18,5 kg/m^2 y < 25 kg/m^2 se considera normopeso, un IMC ≥ 25 kg/m^2 y < 30 kg/m^2 se considera sobrepeso, y un IMC ≥ 30 kg/m^2 se considera obesidad (OMS, 2021). No obstante, el IMC no se interpreta de manera homogénea lo largo de la vida, ni para todas las personas. Así, el IMC debería ajustarse por edad y sexo en los primeros y últimos años de la vida, especialmente a partir de los 65 años (Babiarczyk *et al*., 2012). En edades avanzadas, se considera sobrepeso a partir de cifras superiores a los puntos habituales utilizados para definir el exceso de peso, y el sexo también se debe considerar para su ajuste (Núñez Sánchez *et al*., 2017). Además, las diferencias biológicas entre etnias juegan un papel importante, puesto que la OMS describe otros puntos de corte para la población

asiática (OMS, 2021): un IMC ≥ 23,5 kg/m^2 ya es considerado como sobrepeso, aunque el límite para la obesidad se mantiene en los mismos valores que para el resto de las poblaciones (IMC ≥ 30 kg/m^2). No obstante, existen otros múltiples métodos para medir y evaluar la obesidad, como los parámetros antropométricos tales como la circunferencia abdominal, el índice cintura-cadera, o el porcentaje de grasa corporal, que es el método de referencia para medir la obesidad (Oviedo *et al*., 2006). También se han utilizado mediciones puramente genéticas para detectar el sobrepeso y la obesidad, como puede ser, por ejemplo, la identificación de polimorfismos de un solo nucleótido (Goodarzi, 2018), ampliamente descritos y estudiados por la literatura científica actual, pero rara vez asociados a la obesidad de forma aislada, sino en conjunción con hábitos de vida o en interacción con factores ambientales obesogénicos. Además, muchos autores abogan por considerar como factor de riesgo la evolución del IMC a lo largo de la vida, en lugar del IMC de manera aislada en momentos puntuales. Así, la obesidad durante la infancia (Weihrauch-Blüher *et al*., 2019), o el cambio de peso a lo largo de la vida (Chen *et al*., 2019), han sido relacionados con el posterior desarrollo de cáncer durante la edad adulta. En cualquier caso, la gran mayoría de los estudios publicados hasta la fecha han utilizado el IMC obtenido en momentos puntuales de la historia de la enfermedad (por ejemplo, en el momento del diagnóstico) como factor de exposición (Zhong *et al*., 2016), por lo que la elección de esta definición de obesidad facilita las comparaciones entre estudios con resultados previos.

1.2. CÁNCER DE PRÓSTATA

La Sociedad Europea de Urología, la Sociedad Europea de Medicina Nuclear, la Sociedad Europea de Radioterapia y Oncología, la Sociedad Europea de Radiología Urogenital y la

Sociedad Internacional de Geriatría Oncológica, desarrollan conjuntamente una guía de práctica clínica que sirve como referencia para el diagnóstico y tratamiento del cáncer de próstata en Europa (Mottet *et al*., 2021), en la que definen esta patología como una enfermedad neoplásica maligna que afecta al tejido glandular prostático y cuyo diagnóstico definitivo depende de la verificación histopatológica mediante biopsia. Esta será la definición que emplearemos en esta Tesis Doctoral, debido a que se apoya en sociedades ampliamente reconocidas, evitando hablar de cáncer de próstata ante una tumoración en la próstata sin confirmación histológica, o una elevación de parámetros analíticos sugestivos de esta enfermedad. Con respecto al *diagnóstico* de esta patología, la mayoría de los casos se sospechan tras solicitar el *antígeno prostático específico* (en adelante PSA, por sus siglas en inglés), dado que se trata de un test que se realiza en sangre y es cómodo, rápido y barato, o mediante *tacto rectal*, la prueba de exploración física por excelencia para su diagnóstico según el Instituto Nacional del Cáncer de los Estados Unidos de América (NIH, 2021). Cabe destacar que el PSA se puede elevar, en la mayoría de las ocasiones, por una hiperplasia benigna de próstata, tumoración benigna muy frecuente que requiere un diagnóstico diferencial con el cáncer de próstata (NIH, 2021).

1.3. PRONÓSTICO DEL CÁNCER DE PRÓSTATA

En cuanto al término *pronóstico*, el Instituto Nacional del Cáncer de los Estados Unidos de América (NIH, 2021) define este término como "resultado probable de la evolución de una enfermedad; la probabilidad de recuperación o de que la enfermedad reaparezca". Por tanto, aplicado al cáncer de próstata, podemos encontrar, eminentemente, los siguientes desenlaces pronósticos: 1) supervivencia, curación o mortalidad, 2) recurrencia o recidiva y 3) calidad de

vida. En cuanto a la mortalidad, se debe diferenciar entre mortalidad específica por cáncer de próstata y mortalidad por todas las causas. Respecto al primero de ellos, nos referiremos a *mortalidad específica por cáncer de próstata*, cuando no se puede atribuir la causa de muerte de un paciente a ninguna otra patología concomitante no relacionada con el cáncer de próstata. Por otra parte, nos referimos a *mortalidad por todas las causas* cuando un paciente fallece, independientemente de la causa del éxitus. Este segundo desenlace es mejor aceptado por la comunidad científica, dado que la mortalidad específica por cáncer de próstata requiere de la atribución de una causa de muerte, que en muchas ocasiones puede estar sesgada y posee un cierto componente evaluador-dependiente (Heijnsdijk *et al*., 2019).

Sin embargo, la supervivencia, que se suele evaluar a los 5 años tras el diagnóstico, no es sinónimo de curación, puesto que existe la posibilidad de recurrencia de la enfermedad. La recurrencia o recidiva de la enfermedad se puede evaluar de múltiples maneras en función de su presentación. La más frecuente, sin duda, es la *recurrencia bioquímica*, que se define, en la actualidad, como la presencia de PSA detectable o persistente tras la *prostatectomía radical*, habitualmente a partir de valores ≥ 0.2 ng/ml, aunque los valores ≥ 0.4 ng/ml son los que mejor predicen el futuro desarrollo de metástasis (Van de Broeck *et al*., 2020). La recurrencia bioquímica también se puede definir como la persistencia de valores de PSA superiores a un umbral predefinido, un incremento en el PSA o dos mediciones detectables tras el tratamiento *radioterápico*. Es importante destacar que este desenlace ha tenido históricamente formas muy variadas de ser medido, por lo que la falta de consistencia en sus mediciones supone habitualmente una fuente de heterogeneidad a la hora de reunir y sintetizar resultados de diversos estudios (Hu *et al*., 2014). La recurrencia bioquímica, no obstante, no siempre supone

una progresión real de la enfermedad o el desarrollo de metástasis, y la proporción de pacientes cuya enfermedad progresa es variable (Van de Broeck *et al*., 2020).

En la práctica clínica se pueden utilizar diversas escalas pronósticas para evaluar el riesgo *a priori* de los desenlaces definidos. Así, tras el diagnóstico histopatológico, se puede estratificar el grado de agresividad del cáncer de próstata a través de la *escala de Gleason*, basada en una observación microscópica de las características de las células obtenidas en la biopsia (Gleason, 1966). El procedimiento consiste en seleccionar dos zonas de la muestra y asignar a cada una de ellas un número entre 1 (tumor bien diferenciado, *a priori* poco agresivo) y 5 (tumor escasamente diferenciado, *a priori* de mayor agresividad). La sumatoria de ambos valores da lugar al valor total de la escala, cuya interpretación queda resumida en la Tabla 1. No obstante, la cifra absoluta de la escala de Gleason (sumatoria de las dos mediciones) no es el único valor que aporta información en esta escala. La medición más frecuente encontrada en el tejido glandular será más indicativa del pronóstico que aquella medición encontrada en zonas marginales o poco extensas de la próstata. Así, si la primera de las cifras que conforman la escala se refiriese al tejido glandular más frecuentemente encontrado en la biopsia, siendo el segundo número el referido a otras zonas menos frecuentes, una escala 4+3 indicaría un riesgo mayor que una escala 3+4, por ser el 4 (número que indica mayor gravedad que el 3) más frecuente en el tejido prostático en el primer ejemplo (Wright, 2009). Con el objetivo de tener en cuenta estas consideraciones y afinar más la escala de Gleason, la *International Society of Urologic Pathology (ISUP)* divide a los cánceres de próstata en 5 estadios de agresividad, con peor pronóstico a mayor número de la escala (Epstein *et al*., 2016) (Tabla 1).

Dicha escala ISUP, de acuerdo con las primeras series realizadas en el Johns Hopkins Hospital de Baltimore (Estados Unidos), supone una supervivencia libre de recidiva a los 5 años del

97%, 88%, 70%, 64% y 34%, respectivamente, para los grados 1 a 5 de la escala (Pierorazio *et al*., 2013).

Tabla 1: Interpretación del índice de Gleason y de la clasificación ISUP para el pronóstico del cáncer de próstata basado en datos histopatológicos.

Escala de Gleason	Interpretación
2 a 6	Cáncer muy diferenciado, de baja agresividad, crecimiento lento y mejor pronóstico
7	Cáncer de agresividad intermedia
8 a 10	Cáncer poco diferenciado, de elevada agresividad y peor pronóstico
Clasificación ISUP	**Interpretación**
1	Gleason ≤ 6, puntuación Gleason entre 1 y 3 para ambas mediciones. Únicamente glándulas individuales y bien diferenciadas.
2	Gleason 3 + 4. Predominio de glándulas bien formadas con un componente menor de glándulas pobremente formadas, fusionadas y/o cribiformes.
3	Gleason 4 + 3. Predominio de glándulas pobremente formadas, fusionadas y/o cribiformes con un componente menor de glándulas bien formadas.
4	Gleason = 8, puntuación de Gleason 4 + 4 (únicamente glándulas pobremente formadas, fusionadas y/o cribiformes), 3 + 5 (predominio de glándulas bien formadas con un componente menor no glandular) o 5 + 3 (predominio de componente no glandular con un predominio de glándulas bien formadas)
5	Gleason = 9-10, puntuación de Gleason entre 4 y 5 para ambas mediciones. Ausencia de formación glandular (o con necrosis) con o sin glándulas pobremente formadas, fusionadas y/o cribiformes.

Fuentes: Gleason, 1966; Epstein et al., 2016.

Otra escala de uso extendido, no solo para el cáncer de próstata sino para la mayoría de las neoplasias malignas, es la escala conocida como *TNM*, basada en el tamaño del tumor primario (*T*), la presencia de afectación linfática (*N*) y la presencia de metástasis a distancia (*M*), de

acuerdo con la octava edición de esta clasificación propuesta por la *AJCC (American Joint Comittee on Cancer)* (Buyyounouski *et al*., 2017) (Tabla 2).

Tabla 2: Interpretación del índice de Gleason y de la escala TNM.

TNM	Interpretación
Tx	El tumor primario no se puede evaluar
T0	No hay evidencia de tumor primario
T1	Tumor clínicamente inaparente, no palpable y no visible por técnicas de imagen
T1a	Hallazgo histológico incidental de tejido tumoral en menos del 5% del total de la muestra resecada
T1b	Hallazgo histológico incidental de tejido tumoral en más del 5% del total de la muestra resecada
T1c	Tumor identificado mediante punción biopsia con aguja tras PSA elevado
T2	Tumor confinado en la glándula prostática
T3	Tumor que se extiende más allá de la cápsula prostática
T3a	Extensión extracapsular (uni o bilateral), o invasión microscópica vesical
T3b	Tumor que invade una vesícula seminal
T4	Tumor que invade estructuras adyacentes (pared pélvica, recto, vejiga, esfínter externo, etc.)
Nx	No se pueden evaluar los ganglios linfáticos regionales
N0	No se demuestra invasión ganglionar regional
N1	Invasión ganglionar regional
Mx	No se pueden evaluar las metástasis a distancia
M0	No hay metástasis a distancia
M1	Metástasis a distancia
M1a	Afectación de ganglios linfáticos no regionales
M1b	Afectación de huesos
M1c	Afectación de otras localizaciones

Fuente: Buyyounouski et al., 2017.

De acuerdo con estos parámetros (escala de Gleason y TNM, entre muchos otros), se puede hacer una estimación *a priori* de la gravedad del cáncer, datos que ayudan a la toma de decisiones respecto a la mejor estrategia terapéutica a adoptar para cada paciente. Otra escala

de uso extendido para valorar el riesgo *a priori* de recidiva es la clasificación *D'Amico*, que determina tres categorías de riesgo de acuerdo con el estadio T clínico (basado en el tamaño del tumor primario), la escala de Gleason y el PSA (Tabla 3) (D'Amico *et al*., 1998). Asimismo, la Sociedad Española de Oncología Médica, en su guía clínica más reciente publicada en enero de 2021 (González del Alba *et al*., 2021), define numerosas características moleculares y biomarcadores asociados a la progresión y el desarrollo de cáncer de próstata avanzado.

Tabla 3: Interpretación de la escala D'Amico.

Riesgo	Características de la escala	Supervivencia libre de recurrencia a los 5 años
Bajo	T1 – T2a, Escala de Gleason ≤ 6, PSA < 10 ng/ml	85-90%
Intermedio	T2b, Escala de Gleason = 7, PSA = 10-20 ng/ml	70%
Alto	≥ T2c, Escala de Gleason ≥ 8, PSA > 20 ng/ml	40%

Fuente: D'Amico et al., 1998.

Por último, los factores asociados a la calidad de vida de los pacientes con cáncer de próstata también son relevantes, especialmente tras la realización de prostatectomía radical. Así, la *incontinencia urinaria* (Trofimenko *et al*., 2017), que se define como la incapacidad de controlar la micción, la *disfunción sexual* (Benson *et al*., 2012), referida al conjunto de síntomas y signos que impiden el correcto disfrute de la actividad sexual, especialmente la *disfunción eréctil* o incapacidad de conseguir y mantener la erección durante el acto sexual, así como los problemas de salud mental que estos síntomas generan (Ilie *et al*., 2020) (síntomas depresivos, ansiosos, etc.), son frecuentes tras el tratamiento.

2. IMPORTANCIA SANITARIA DE LA OBESIDAD

Según el último informe de la Organización Mundial de la Salud (OMS, 2016), aproximadamente 1.900 millones de adultos tenían sobrepeso, de los cuales más de 650 millones sufrían obesidad, datos que triplican al número de adultos obesos en todo el mundo informados en el año 1975. Estos datos implican que, en el año 2016, el 39% de las personas adultas tenían sobrepeso y el 13% obesidad. Además, estas cifras también se están incrementando en las edades más precoces, de manera que 340 millones de niños y adolescentes (de 5 a 19 años) presentan sobrepeso u obesidad. Para esta franja etaria, la frecuencia ha aumentado desde un 4% en 1975 hasta un 18% en 2016. Ello convierte a la obesidad infantil en uno de los principales problemas de salud pública en la actualidad. Teniendo en cuenta que el IMC elevado es un factor de riesgo prevenible, es fundamental actuar en las edades más precoces de la vida, puesto que el impacto que ello puede tener en la salud de los individuos sería más duradero y efectivo que intervenciones realizadas en etapas más tardías de la vida.

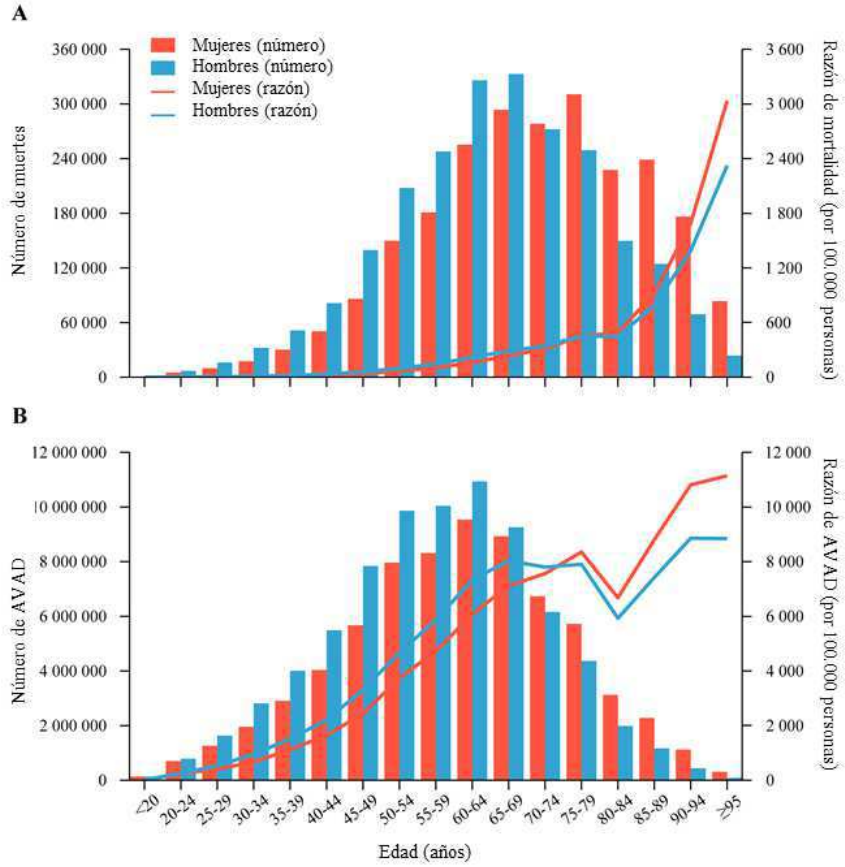
Dada la alarma producida por estos datos, la OMS creó el Plan de Acción Mundial para la Prevención y el Control de las Enfermedades No Transmisibles para el período 2013-2020, cuyo objetivo consistió en cumplir los compromisos de la Declaración Política de las Naciones Unidas sobre las Enfermedades No Transmisibles. Esta iniciativa recibió el respaldo de los Jefes de Estado y de Gobierno en septiembre del año 2011. El compromiso de los países con la reducción de las enfermedades no transmisibles, especialmente las enfermedades crónicas, muchas de las cuales están fuertemente asociadas a la obesidad, quedó acordado.

El Plan de Acción Mundial tiene como objetivo contribuir a realizar avances en nueve metas mundiales relativas a las enfermedades no transmisibles que deben alcanzarse no más tarde de 2025, incluidas una reducción relativa del 25% en la mortalidad prematura a causa de dichas enfermedades para el año 2025 y una detención del aumento de la obesidad mundial para coincidir con las tasas del año 2010. Asimismo, la Asamblea Mundial de la Salud apoyó el informe de la Comisión para acabar con la obesidad infantil en 2016 y sus seis recomendaciones, a fin de dar respuesta al entorno obesogénico y los periodos cruciales en el ciclo de vida, de manera que se combatiera la obesidad infantil desde sus inicios.

La Asamblea Mundial de la Salud convocada en el año 2017 desarrolló el plan de aplicación destinado a orientar a los países en la puesta en práctica de las recomendaciones de la Comisión. De acuerdo con las proyecciones estimadas (OMS, 2016), se calcula un 22% de población obesa en todo el mundo para el año 2045. Ello supone que casi una cuarta parte de los adultos en el mundo tendrán un IMC superior a 30. Ello es especialmente problemático puesto que el IMC elevado se asocia con una gran variedad de enfermedades. Así, un amplio estudio realizado en el año 2017 (Dai *et al*., 2020) mostró la elevada mortalidad y los años de vida perdidos ajustados por discapacidad atribuibles a la obesidad (Figura 1), que se acentúan en varones y a partir de los 60 años de edad.

Esta mortalidad y pérdida de calidad de vida asociadas a la obesidad están mediadas por el desarrollo de enfermedades crónicas, especialmente diabetes mellitus, hipertensión arterial, neoplasias y enfermedad cardiovasculares, entre otras.

Figura 1: Mortalidad y años de vida ajustados por discapacidad (AVAD) atribuibles a la obesidad, año 2017.



Fuente: Dai et al., 2020.

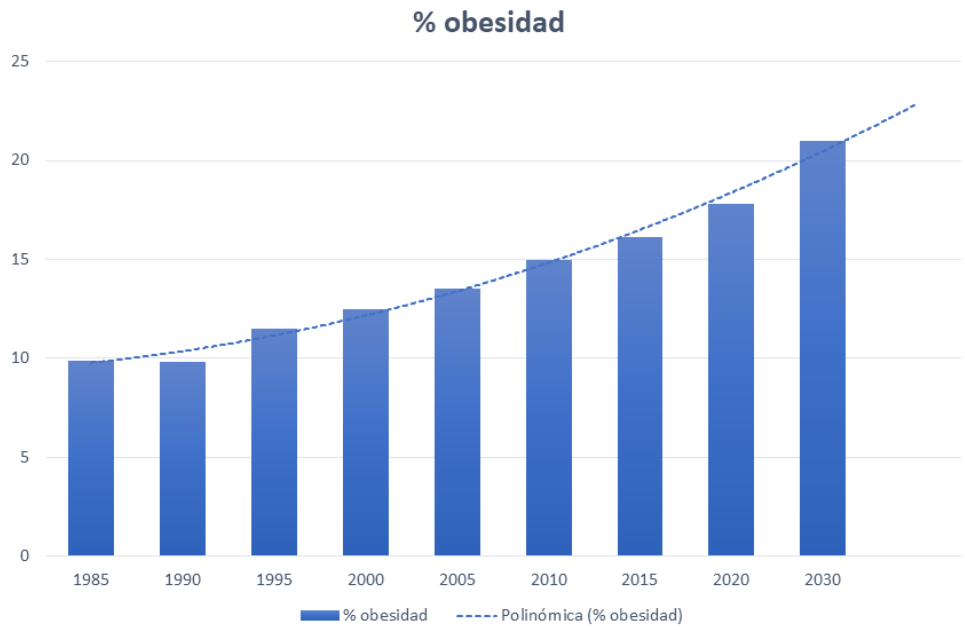
Estos datos sitúan a la obesidad como la segunda causa de muerte prevenible tras el hábito tabáquico, pues aumentan el riesgo de desarrollar diabetes mellitus, enfermedades cardiovasculares, hipertensión, hiperlipemia y numerosos tipos de cáncer (Panuganti *et al*., 2021). Por supuesto, la obesidad y los problemas de salud que generan también tienen su repercusión a nivel económico. Así, un estudio realizado en los Estados Unidos de América demostró que, solamente en este país, el gasto sanitario relacionado con la obesidad ascendía

a unos 100.000 millones de dólares anuales (Panuganti *et al*., 2021). Dada la magnitud y frecuencia del problema, así como su incremento gradual en los últimos años, la obesidad como factor de riesgo modificable, merece ser estudiada y abordada de manera preventiva desde los primeros años de la vida.

Con respecto a la situación de la obesidad en España, de acuerdo con la Organización para la Cooperación y Desarrollo Económico (OCDE, 2018), el 14,5% de los españoles padecía obesidad en 2017, y un 47,5% padecía sobrepeso (ambos valores por encima de las medias mundiales de 2017, que eran del 13% y 39%, respectivamente), datos que coinciden los datos más recientes de la Encuesta Europea de Salud en España (EESE, 2020). El informe, además, establece una proyección de obesidad en España del 21% para el año 2030, lo que supondría casi duplicar las cifras en algo más de una década.

La Figura 2 muestra la evolución de la prevalencia de obesidad en España desde el año 1985 hasta las proyecciones del año 2030. Aunque en los adultos no se ha incrementado de manera significativa desde el inicio del siglo, la prevalencia de obesidad infantil sí aumenta año tras año en nuestro país (OCDE, 2018). El Informe sobre el Estado de Salud en España (OCDE, 2019) sitúa a la obesidad como el tercer factor de riesgo más frecuente para la salud de los españoles, y la Encuesta Europea de Salud realizada en el año 2019-2020 sitúa la proporción de obesidad en España por encima de la media europea (EUROSTAT, 2020).

Figura 2: Evolución de la prevalencia de obesidad en adultos en España y proyecciones para el año 2030.

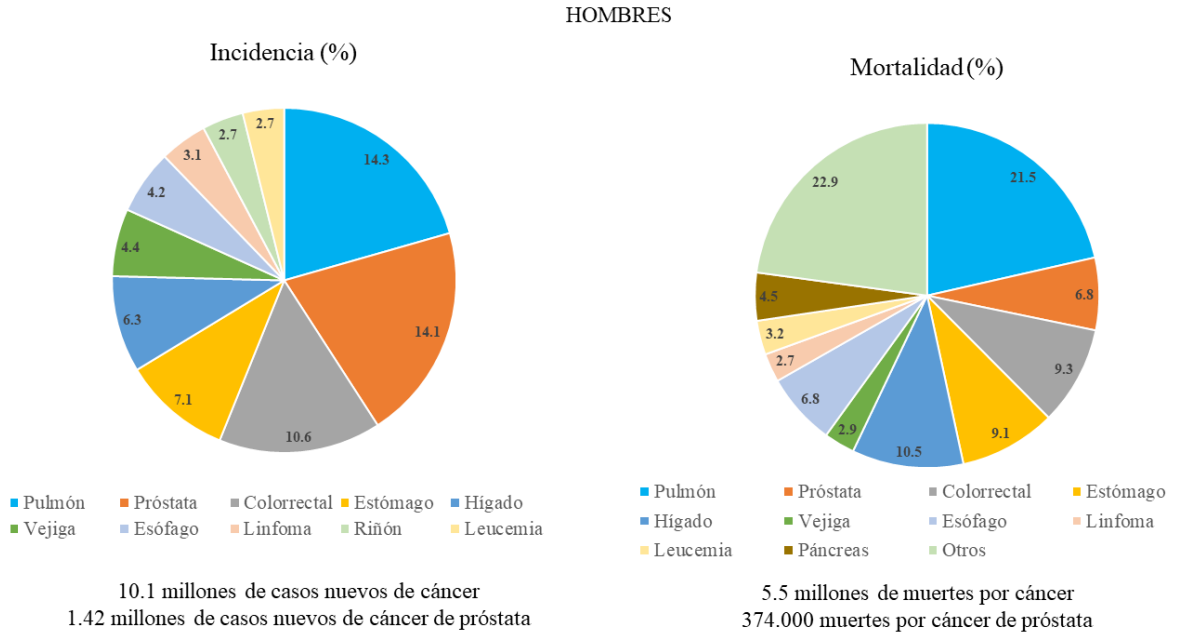


Fuente: OCDE, 2018.

3. IMPORTANCIA SANITARIA DEL CÁNCER DE PRÓSTATA

El cáncer de próstata supone la neoplasia maligna más frecuentemente diagnosticada en varones, con aproximadamente 1.280.000 casos nuevos cada año (Mattiuzzi *et al*., 2019). De acuerdo con las estadísticas ofrecidas por el *Global Cancer Observatory* (*GLOBOCAN)* de la Organización Mundial de la Salud en el año 2021, el cáncer de próstata se sitúa como la quinta causa de muerte por cáncer en los varones (6.8% de las muertes por cáncer), tras el cáncer de pulmón, hígado, colorrectal y estómago (Sung *et al*., 2021), y la segunda neoplasia en incidencia en varones tras el cáncer de pulmón (Figura 3).

Figura 3: Incidencia y causas de muerte en hombres por tipo de cáncer a nivel mundial.



Fuente: Sung et al., 2021.

Los síntomas característicos de esta enfermedad son relativos al tracto urinario inferior, tales como la nicturia o el flujo urinario deficiente, la disfunción eréctil o la hematuria (Merriel *et al*., 2018). Sin embargo, dichos síntomas se superponen a los de otras patologías prostáticas benignas, tales como la hiperplasia benigna de próstata o la prostatitis. De hecho, lo más habitual es que los pacientes con cáncer de próstata sean diagnosticados asintomáticos (NIH, 2021). Del total de cánceres de próstata diagnosticados, aproximadamente un 76,9% son clínicamente localizados (Fleshner *et al*., 2017) y, por tanto, requieren un tratamiento que, según cada caso, puede incluir la prostatectomía radical, la radioterapia de haz externo, la braquiterapia o, en un importante número de casos, la observación como actitud conservadora

(Wilt *et al*., 2020). Sin embargo, hasta un 27-53% de todos los casos desarrollan recurrencia bioquímica (Cornford *et al*., 2021), hasta un 30% desarrollará enfermedad avanzada que requerirá de tratamiento hormonal o quimioterápico (Sociedad Española de Oncología Médica, 2021) y hasta un 7,7% de los casos fallecen debido a la enfermedad (Sung *et al*., 2021). Por tanto, y aunque el cáncer de próstata presente una mayoría de casos asintomáticos, leves o que no generen mortalidad específica, existe un importante número de casos que se diagnostican en estadios avanzados y que generan desenlaces negativos en términos de calidad de vida o de mortalidad.

En España, según los datos facilitados por la *International Agency for Research on Cancer (IARC)*, el cáncer de próstata es el más prevalente en varones, con aproximadamente un total de 259.800 casos prevalentes en 2020 (IARC, 2020), y aproximadamente 35.700 casos nuevos cada año. Además, y a pesar de tener una tasa de supervivencia del 89,8% a los 5 años (la más alta de los tumores malignos), en España es la tercera causa de mortalidad por cáncer en varones (8,6%), tan solo por detrás del cáncer de pulmón y el cáncer colorrectal (IARC, 2020).

4. FACTORES PRONÓSTICOS DEL CÁNCER DE PRÓSTATA.

Dados los antecedentes previamente descritos, y puesto que existe un subgrupo de pacientes diagnosticados con cáncer de próstata que sí desarrollará enfermedad avanzada y, finalmente, fallecerán a causa de esta patología, conviene reconocer de manera precoz a este colectivo con finalidad preventiva. La cuestión que subyace a esta tesis doctoral es ¿qué es lo que hace diferentes a los pacientes que desarrollan cáncer de próstata avanzado del resto? O, lo que es

lo mismo, ¿hay factores que se puedan identificar para reconocer precozmente a este subgrupo? ¿Se puede mejorar el pronóstico de estos pacientes? Hasta la fecha, se conocen muy pocos factores pronósticos del cáncer de próstata, a pesar de la elevada frecuencia de esta enfermedad. Entre ellos, cabe destacar, como factores asociados a un peor pronóstico, las diferencias biológicas asociadas a las etnias negras, la edad avanzada y la historia familiar de cáncer de próstata (Schatten, 2018). Con respecto a la etnia, se ha demostrado que la mortalidad en pacientes afroamericanos diagnosticados de cáncer de próstata se duplica en comparación con pacientes de etnias caucásicas (Panigrahi *et al*., 2019). Además, la mortalidad varía de manera importante en función del país, de acuerdo con los datos ofrecidos por la *International Agency for Research on Cancer* (Ferlay *et al*., 2018). Así, las tasas de mortalidad ajustadas por edad más elevadas en el año 2018 a nivel mundial se encontraron en América Central (10,7 por 100.000 personas) seguido por Australia y Nueva Zelanda (10,2) y Europa Occidental (10,1), mientras que los datos más favorables se encontraron en Asia Central (3,3), Asia Oriental (4,7) y el Sudeste asiático (5,4) (Ferlay *et al*., 2018). Con respecto a la edad, las tasas de mortalidad aumentan conforme lo hace este factor, y más de la mitad de los fallecimientos por cáncer de próstata ocurren en personas mayores de 65 años (Rawla, 2019). Finalmente, la historia familiar de cáncer de próstata podría tener un elemento genético hereditario que aumenta la susceptibilidad a desarrollar cáncer de próstata más agresivo, pero parte de esta asociación también se podría explicar por patrones similares de exposición a carcinógenos ambientales y por hábitos de vida comunes (Gallagher *et al*., 1998).

No obstante, todos estos factores pronósticos identificados tienen algo en común: son factores no modificables y, por tanto, de escasa utilidad para el desarrollo de estrategias preventivas y de salud pública.

Así, al margen de factores no modificables o de marcadores pronósticos medidos en el momento del diagnóstico, tales como la escala de Gleason, la clasificación TNM o diversos marcadores moleculares (Pugliese *et al*., 2016) o genéticos (Yang *et al*., 2018), la literatura científica actual adolece de factores modificables relacionados con los estilos de vida sobre los que intervenir para mejorar el pronóstico de estos pacientes. La salud de los pacientes en el momento del diagnóstico (presencia de comorbilidades) también se ha asociado a los desenlaces pronósticos de esta enfermedad (Carwford *et al*., 2011) e, incluso, las creencias de los pacientes *a priori* con respecto a su enfermedad han sido postuladas como factores de riesgo de mortalidad (Soler-Vilá *et al*., 2011), puesto que éstas influyen en los estilos de vida y en la adherencia terapéutica.

En los últimos años, no obstante, se han propuesto algunos factores potencialmente modificables asociados al pronóstico del cáncer de próstata, entre ellos la dieta (Kaiser *et al*., 2019), el ejercicio físico (Bourke *et al*., 2016), la exposición a contaminantes ambientales (Sarafanov *et al*., 2011) y la obesidad (Schatten, 2018). De estos, el factor que se ha estudiado en mayor profundidad en revisiones realizadas en las últimas dos décadas es la dieta baja en grasas y con elevado contenido en fibra, que parece reducir la recurrencia y progresión de varios tipos de cáncer, incluido el cáncer de próstata (Davies *et al*., 2011). Otros investigadores han apostado por estudiar el efecto de programas globales de intervención en estilos de vida saludables, que incluyen dieta, ejercicio físico, manejo del estrés y apoyo social, demostrando que el grupo de no intervención presentaba una menor longitud en sus telómeros, dato directamente asociado con el envejecimiento, la mortalidad prematura y la progresión del cáncer de próstata (Ornish *et al*., 2013). Sin embargo, ninguno de estos factores

potencialmente modificables ha mostrado resultados consistentes suficientes como para ser considerados factores pronósticos del cáncer de próstata hasta la fecha.

5. OBESIDAD Y CÁNCER DE PRÓSTATA

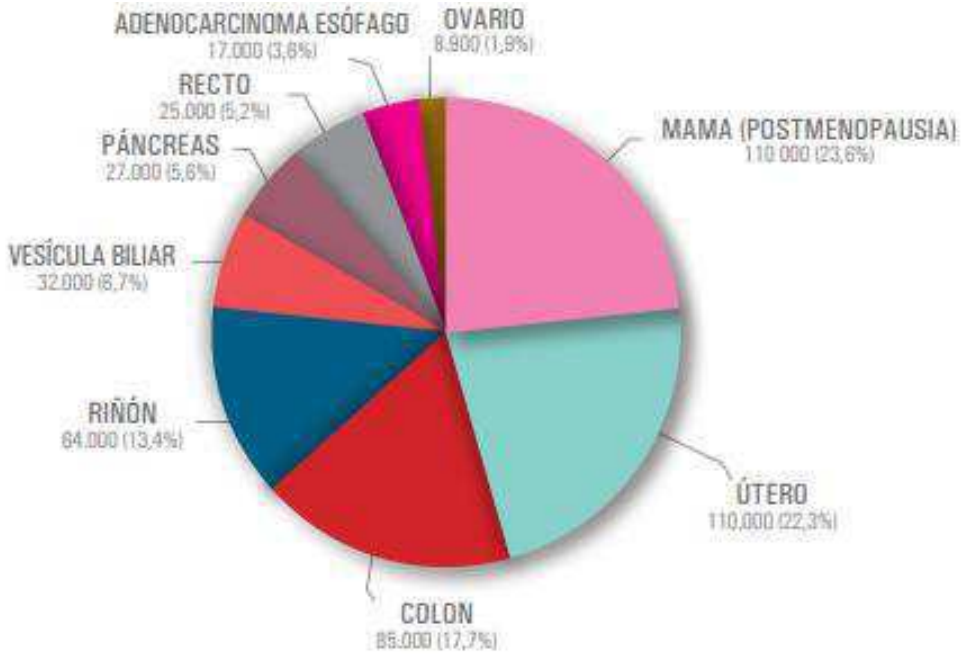
5.1. LA OBESIDAD COMO CAUSA DEL CÁNCER DE PRÓSTATA

En el siglo XIX, en pleno auge de los estudios microbiológicos, la epidemiología se dedicó a estudiar las enfermedades infecciosas (tuberculosis, cólera, etc.) y a desarrollar cadenas causales que explicaran por qué se producían. Es en el siglo XX cuando se añaden al estudio las enfermedades crónicas (cáncer, enfermedades cardiovasculares, diabetes, etc.). Numerosos estudios trataron de abordar, a lo largo de este siglo, la asociación causal entre factores de exposición y el desarrollo de cáncer. Naturalmente, el modelo determinista puro quedó obsoleto para investigar estas asociaciones, siendo reemplazado por un modelo determinista modificado (Rothman, 1986) o por un modelo probabilístico (Piédrola *et al*., 2001). A ello se añadió el hecho de que *el cáncer* no es una enfermedad homogénea y, por tanto, el estudio de factores de riesgo o pronósticos se debe realizar de manera separada para cada entidad neoplásica. Además, para cualquier cáncer, la conjunción e interacción de factores genéticos, ambientales, estilos de vida, etc., aumenta la complejidad para identificar factores independientes asociados al diagnóstico o desenlace de cualquier tipo de cáncer.

En los últimos tres años, la *International Agency for Research on Cancer* (mediante el *Global Observatory of Cancer*), dispone de datos relativos a la relación causal entre la obesidad y

diversos tipos de cáncer, concretamente nueve (mama, útero, colon, riñón, vesícula biliar, páncreas, recto, adenocarcinoma de esófago y ovario) (Plummer *et al*., 2018) (Figura 4).

Figura 4: Número de casos atribuibles a la obesidad a nivel mundial para el año 2012, por localización tumoral.



Fuente: Plummer et al., 2018.

Con respecto al cáncer de próstata, se ha discutido mucho la relación causal de la obesidad con su desarrollo y con su pronóstico, aunque con resultados inconsistentes hasta la fecha, hasta el punto de que el Fondo Mundial para la Investigación del Cáncer (*World Cancer Research Fund, 2020)*, consideró la obesidad como factor asociado al diagnóstico de cáncer de próstata

avanzado, pero posteriores estudios lo han puesto en entredicho (Genkinger *et al*., 2020; Jochems *et al*., 2020).

De acuerdo con datos del propio *World Cancer Research Fund* (2020), la dieta, la nutrición y la actividad física (factores relacionados de manera directa con la presencia de obesidad) afectan al riesgo de desarrollar cáncer de próstata. Así, en la última revisión realizada por esta organización, que incluyó 140 estudios reuniendo datos de 191.000 casos de cáncer de próstata (*Continuous Update Project, 2018)*, se concluyó la existencia de datos a favor de una probable asociación entre sobrepeso, obesidad y talla elevada con el incremento de riesgo de desarrollar cáncer de próstata. El elevado consumo de lácteos, las dietas con elevado consumo de calcio, las dietas pobres en vitamina E y la baja concentración de selenio en plasma mostraron una evidencia limitada de asociación con el desarrollo de cáncer de próstata. No se obtuvieron otras asociaciones de interés relacionadas con los estilos de vida. Dado que se trata de la mayor fuente mundial de investigación científica sobre la prevención y la supervivencia del cáncer a través de la dieta, la nutrición y la actividad física (*Continuous Update Project, 2018*), estos datos ayudan a reforzar la asociación entre obesidad (y determinados estilos de vida asociados a esta) y el riesgo de desarrollar cáncer de próstata.

Los posibles mecanismos implicados en esta asociación no están claramente establecidos. Sin embargo, se han postulado numerosas teorías, tales como la presencia de diversas alteraciones moleculares y metabólicas en pacientes obesos que incrementan el riesgo de desarrollo de cáncer de próstata.

Entre dichos mecanismos, destacan la alteración en la producción de insulina, las alteraciones en el factor de crecimiento insulínico tipo 1 (IGF-1), las alteraciones en la producción de esteroides sexuales y en la producción de adipoquinas, la inflamación crónica, el estrés oxidativo, la hipoxia inducida por la obesidad, los defectos inmunitarios y la susceptibilidad genética que afecta de manera conjunta al desarrollo de obesidad y de cáncer de próstata (De Pergola *et al*., 2013).

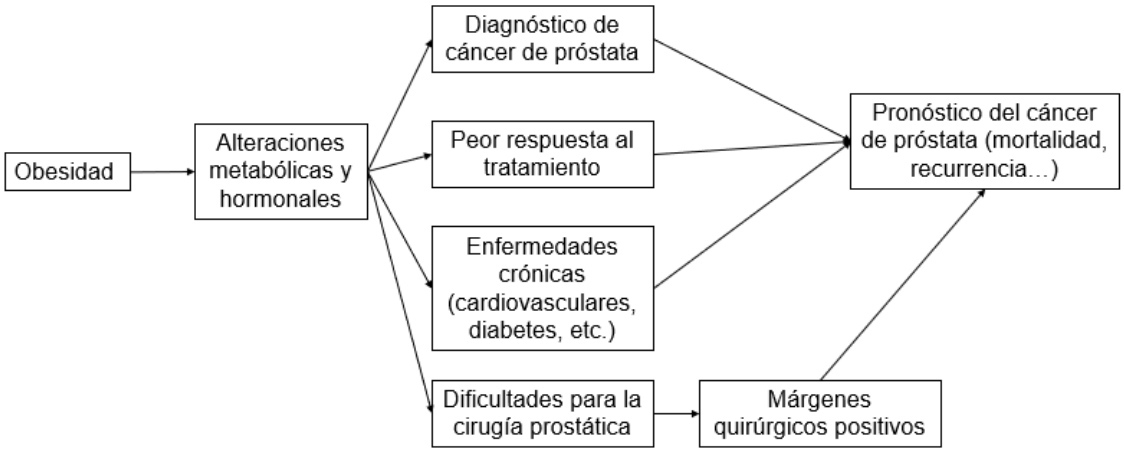
Finalmente, se ha establecido una relación entre la obesidad (o el incremento de peso) y los niveles de PSA que, recordemos, suponen la principal fuente de diagnóstico, tanto a través de estrategias de cribado como en el ámbito clínico ante pacientes con sintomatología sugerente de cáncer de próstata. El hecho de que la obesidad pueda afectar a los niveles de PSA tiene una implicación directa en el diagnóstico de esta entidad, pero también podría tener repercusiones en el grado en que dicha enfermedad se diagnostica. Así, si los niveles de PSA disminuyen en pacientes obesos, el cáncer de próstata se detectará de manera más tardía (Wilson *et al*., 2019).

Todos estos factores pueden jugar un rol importante en la cadena causal existente entre la obesidad y el riesgo de padecer cáncer de próstata, pero los mecanismos biológicos implicados se han de estudiar aun en mayor detalle.

5.2. LA OBESIDAD COMO FACTOR PRONÓSTICO DE CÁNCER DE PRÓSTATA

Al igual que lo referido en relación con la obesidad como causa del cáncer de próstata, su papel como factor pronóstico de esta entidad sigue siendo muy debatido. En la Figura 5 se puede observar la posible cadena epidemiológica implicada en la relación causal entre obesidad y desenlaces pronósticos del cáncer de próstata (elaboración propia).

Figura 5: Cadena epidemiológica de la relación causal posible entre obesidad y pronóstico del cáncer de próstata.



Fuente: elaboración propia.

En los siguientes epígrafes resumimos las evidencias disponibles hasta la fecha en relación con la asociación entre la obesidad y diversos desenlaces del cáncer de próstata.

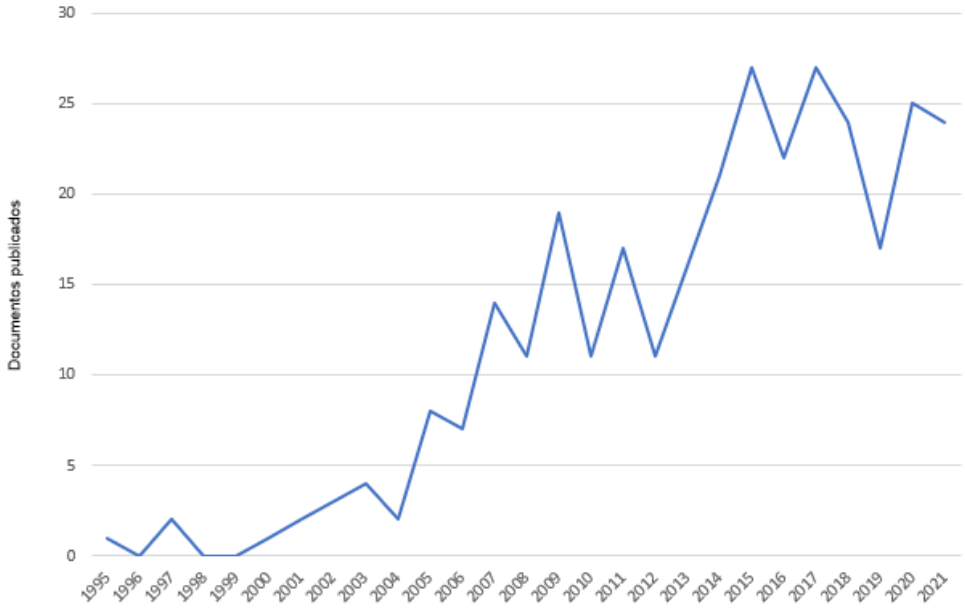
5.2.1. OBESIDAD Y MORTALIDAD POR CÁNCER DE PRÓSTATA

Los estudios realizados hasta la fecha que tratan de analizar la asociación entre la obesidad y la mortalidad por cáncer de próstata muestran resultados inconsistentes. En el año 1995 se publicó el primer estudio de cohortes sobre esta asociación (Gann, 1995), que incluyó a 22.280 pacientes en Chicago (Illinois, EEUU), pero los autores no hallaron una relación clara entre el índice de masa corporal y la mortalidad por cáncer de próstata, con un riesgo relativo (RR) = 1,03 y un intervalo de confianza al 95% (IC95%) = 0,74-1,42. Desde entonces, se han publicado una gran cantidad de estudios observacionales longitudinales que analizan esta asociación.

Introduciendo en la base de datos Scopus la ecuación de búsqueda *(obes* OR body mass index OR BMI) AND (prostate cancer) AND (cohort) AND (mortal* OR prognos* OR survival)* puede observarse cómo desde el citado año 1995 hasta la actualidad el número de trabajos publicados ha ido aumentando de forma sustancial, especialmente a partir del año 2014, (alcanzando picos de máximo número de artículos publicados en los años 2016 y 2018) tal y como puede comprobarse en la Figura 6.

La presencia de un número de estudios publicados muy elevado en los años más recientes (17 estudios en 2020 y 25 estudios en 2021) sugiere que esta asociación aún no está claramente establecida y que su análisis sigue siendo de interés para la comunidad científica en la actualidad.

Figura 6: Evolución anual del volumen de artículos publicados acerca de la asociación entre obesidad y mortalidad en el cáncer de próstata, 1995-2021.



Fuente: Scopus Database.

Ecuación de búsqueda: (obes OR body mass index OR BMI) AND (prostate cancer) AND (cohort) AND (mortal* OR prognos* OR survival).*

De todos los estudios de cohortes realizados, algunos identifican una asociación directa (Genkinger *et al*., 2020), y otros identifican una asociación inversa (Jackson *et al*., 2020). Las revisiones sistemáticas y metanálisis realizados hasta 2021 (Cao *et al*., 2011; Zhang *et al*., 2015, Zhong *et al*., 2016), al ser analizados mediante la herramienta de evaluación de la calidad AMSTAR-2 (Shea *et al*., 2017), muestran importantes debilidades metodológicas. Así, la descripción de la población del estudio, la investigación de causas de heterogeneidad, la evaluación del riesgo de sesgos en los resultados estratificados, o la consideración de los conflictos de interés de los estudios incluidos son pobremente recogidos en las revisiones

publicadas hasta la fecha (Tabla 4). Por lo tanto, y aunque numerosos estudios apunten hacia la relación entre un mayor IMC y el incremento en la mortalidad por cáncer de próstata, en la actualidad no se puede confirmar dicha asociación de forma consistente.

Tabla 4: Características de los metanálisis publicados hasta diciembre de 2020 sobre la asociación entre obesidad y mortalidad por cáncer de próstata.

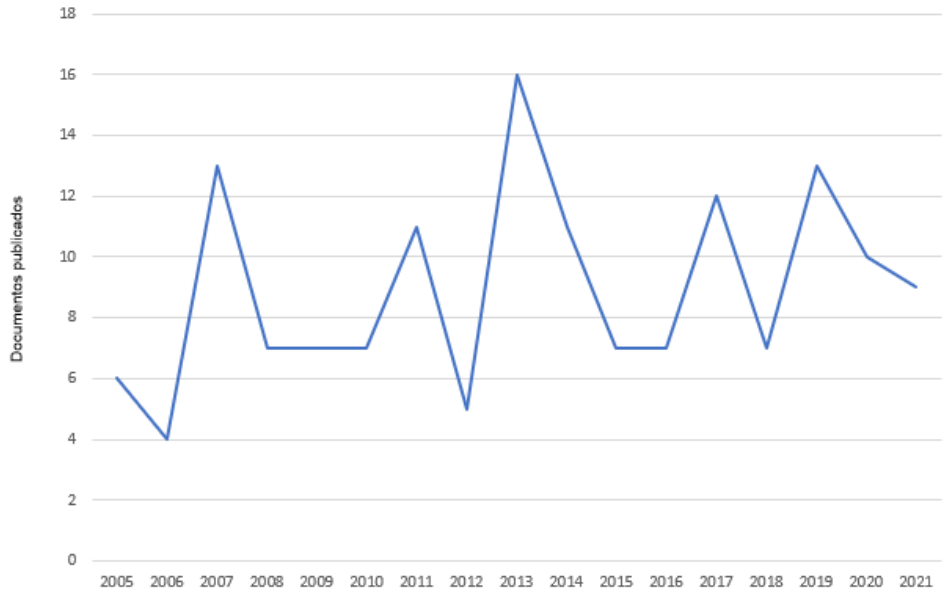
Autor, año	Número de estudios incluidos	Análisis del sesgo de publicación	Análisis de factores de heterogeneidad	Principales limitaciones
Cao, 2011	12	Sí	No	No análisis de conflictos de interés, no análisis detallado de fuentes de heterogeneidad
Zhang, 2015	17	No	No	Ecuación de búsqueda poco sensible, no análisis de sesgo de publicación, no análisis de conflictos de interés, no análisis detallado de fuentes de heterogeneidad
Zhong, 2016	38	Sí	No	No análisis detallado de fuentes de heterogeneidad, no análisis de conflictos de interés.

5.2.2. OBESIDAD Y OTROS DESENLACES PRONÓSTICOS DEL CÁNCER DE PRÓSTATA.

De forma similar a lo expuesto para la mortalidad, también existen numerosos estudios que analizan la relación entre la obesidad y otros desenlaces del cáncer de próstata. En particular, se ha estudiado de manera especial el desenlace *recurrencia bioquímica*. Así, en el año 2005 se publicaron los primeros trabajos observacionales longitudinales sobre esta asociación. Strom *et al*. (2005) mostraron una asociación positiva (RR = 1,40, IC95%: 1,10 – 1,84), datos

concordantes con los de Bassett *et al*. (2005) (RR = 2,49, IC95%: 1,10 – 5,57). Desde entonces se han publicado numerosos estudios de cohortes que analizan esta relación. Introduciendo en la base de datos Scopus la ecuación de búsqueda *(obes* OR body mass index OR BMI) AND (prostate cancer) AND (cohort) AND (recurrence OR relaps* OR progression)* puede observarse cómo desde el citado año 2005 hasta la actualidad el número de trabajos publicados ha sido dispar, manteniéndose un ritmo de entre 7 y 12 artículos anuales para casi todo el intervalo estudiado, tal y como puede comprobarse en la Figura 7. De nuevo, se pueden observar estudios que identifican una asociación directa (la gran mayoría), pero también otros que identifican una asociación inversa (Koo *et al*., 2014) o nula (Leal-García *et al*., 2020).

Figura 7: Evolución anual del volumen de artículos publicados acerca de la obesidad y la recurrencia del cáncer de próstata, 2005-2021.



Fuente: Scopus Database.

Ecuación de búsqueda: búsqueda *(obes* OR body mass index OR BMI) AND (prostate cancer) AND (cohort) AND (recurrence OR relaps* OR progression)*.

Nuevamente, la presencia de un número elevado de estudios en años recientes (13 estudios en 2020 y 9 estudios en 2021) sugiere que esta relación aún no está claramente establecida y que su análisis sigue siendo de interés en la actualidad para la comunidad científica.

Los metanálisis que evalúan la relación entre obesidad y recurrencia bioquímica publicados hasta 2021 se pueden consultar en la Tabla 5 (Cao *et al*., 2011; Hu *et al*., 2014; Bai *et al*., 2015; Luo *et al*., 2020). Aunque sus resultados muestran una asociación positiva consistente, presentan nuevamente debilidades metodológicas importantes de acuerdo con la escala AMSTAR-2 (Shea *et al*., 2017). Para empezar, la variabilidad en las ecuaciones de búsqueda da lugar a resultados sorprendentes, a pesar de tener criterios de selección similares. Por ejemplo, el metanálisis más reciente (Luo *et al*., 2020) únicamente identifica 8 estudios de cohortes sobre esta relación, mientras que el más antiguo (Cao *et al*., 2011) ya había identificado 16 estudios sobre este tema, datos que hablan de una desigualdad en la sensibilidad de las ecuaciones de búsqueda empleadas por diferentes autores. Además, la ausencia de un análisis de factores de heterogeneidad pormenorizado, capaz de identificar las principales fuentes de heterogeneidad, o de un análisis de potenciales sesgos de publicación en algunos de ellos también sugiere que la fiabilidad de los resultados obtenidos no es la óptima. Por tanto, y a pesar de que estos resultados de asociación entre obesidad y recurrencia bioquímica muestran una mayor consistencia que aquellos referidos a la mortalidad, no son lo suficientemente robustos como para identificar definitivamente a la obesidad como factor pronóstico del cáncer de próstata por parte de los organismos internacionales o las guías de práctica clínica. Es necesario, por tanto, disponer de nuevos y más válidos estudios que lo confirmen.

Tabla 5: Características de los metanálisis publicados hasta diciembre de 2020 sobre la asociación entre obesidad y recurrencia bioquímica en el cáncer de próstata.

Autor, año	Número de estudios incluidos	Análisis del sesgo de publicación	Análisis de factores de heterogeneidad	Principales limitaciones
Cao, 2011	16	Sí	No	No análisis de conflictos de interés, no análisis detallado de potenciales fuentes de heterogeneidad
Hu, 2014	26	Sí	Sí	No se consigue reducir la heterogeneidad a pesar del análisis de subgrupos, no análisis de conflictos de interés
Bai, 2015	8	No	No	Población muy específica (únicamente estudios realizados sobre pacientes en China), no análisis del sesgo de publicación, o análisis de conflictos de interés, no análisis detallado de potenciales fuentes de heterogeneidad
Luo, 2020	8	Sí	No	Ecuación de búsqueda poco sensible, no análisis de conflictos de interés, no análisis detallado de potenciales fuentes de heterogeneidad

Finalmente, también se ha estudiado la relación entre la obesidad y otros desenlaces del cáncer de próstata asociados a la calidad de vida, tales como la incontinencia urinaria, la disfunción sexual, o la salud mental, especialmente tras recibir prostatectomía radical. Sin embargo, el reducido número de cada uno de ellos (≤ 5) ha impedido que hasta la fecha se puedan realizar metanálisis sobre dichas asociaciones, salvo para la incontinencia urinaria (Wei *et al*., 2018), cuyos autores observaron una odds ratio (OR) de 2,00 (IC95%: 1,57 – 2,56) para pacientes que recibieron prostatectomía radical laparoscópica asistida por robot. No obstante, la asociación de la obesidad con otros parámetros de importancia relacionados, por ejemplo, con la calidad de vida, el bienestar y el nivel de dependencia del paciente, no han sido suficientemente explorados hasta la fecha.

II. JUSTIFICACIÓN / JUSTIFICATION

II. JUSTIFICACIÓN

Los factores que justifican iniciar una línea de investigación dedicada al estudio de la relación entre la obesidad y el pronóstico de cáncer de próstata quedan resumidos en los siguientes puntos:

1. Evolución del problema de salud. Como hemos comentado previamente, la obesidad es una pandemia que afecta cada año a un mayor número de personas, y que supone la segunda causa de mortalidad evitable en el mundo tras el tabaco. Además, el envejecimiento poblacional arrastra consigo un número creciente de pacientes con cáncer de próstata, una parte relevante de los cuales morirá o reducirá sustancialmente su calidad de vida por ello. Por tanto, tanto la exposición como los desenlaces bajo estudio de esta tesis doctoral suponen problemas de salud de gran magnitud, cuya prevención podría tener un impacto inestimable en la población.

2. Debilidades metodológicas y datos insuficientes de las síntesis de la evidencia científica publicados hasta la fecha. En la sección anterior analizamos las debilidades metodológicas de los metanálisis realizados hasta la fecha sobre la asociación entre obesidad y los tres desenlaces pronósticos más estudiados para el cáncer de próstata: mortalidad específica por el cáncer, mortalidad por todas las causas y recurrencia bioquímica. Respecto a los metanálisis sobre mortalidad (Cao *et al*., 2011; Zhang *et al*., 2015, Zhong *et al*., 2016), las debilidades metodológicas se unen a la inconsistencia de los resultados presentados por los estudios incluidos, que dan lugar a una heterogeneidad muy elevada, superior al 50% en todos los metanálisis. Además, desde la publicación del último metanálisis sobre esta relación (Zhong *et al*., 2016), se han publicado 15 estudios que recogen el papel pronóstico del peso corporal,

con datos de 186.802 pacientes añadidos a los ya existentes. Por lo tanto, la última revisión publicada (Zhong *et al*., 2016) solo pudo acceder aproximadamente a un tercio del total de la evidencia disponible en la actualidad. Además, las revisiones sistemáticas previas no evaluaron formalmente los criterios de causalidad de la asociación estudiada, de acuerdo con los criterios propuestos por Bradford Hill (Hill, 1965), y que deberían ser discutidos en los metanálisis que analizan relaciones causales (Khan *et al*., 2012). En definitiva, existe la necesidad de una evaluación robusta y fiable de la relación entre obesidad y mortalidad total y específica por cáncer de próstata en pacientes diagnosticados de esta enfermedad. Con respecto a la recurrencia bioquímica, desde el último metanálisis completo con criterios de selección amplios publicado hasta la fecha (Hu *et al*., 2014), se han publicado 15 estudios que evalúan el pronóstico acerca de esta relación, incluyendo un total de 47.422 casos nuevos de cáncer de próstata localizado. Por tanto, dicha revisión solo pudo acceder a un 55% del total de pacientes disponibles en la actualidad. Posteriormente, se publicó un metanálisis en 2015 (Bai *et al*., 2015), pero solo incluyó a población asiática, y otro en 2020 (Luo *et al*., 2020), que solo incluyó 8 estudios de cohortes relativos a la recurrencia bioquímica. Por tanto, hay una necesidad de una evaluación actualizada, robusta y fiable de la relación entre obesidad y pronóstico de cáncer de próstata.

3. Ausencia de datos nacionales. En nuestro país la epidemiología analítica de la relación entre la obesidad y el pronóstico del cáncer de próstata ha sido escasamente estudiada hasta el momento. Para confirmarlo, se realizó una búsqueda bibliográfica en diferentes bases de datos (Scopus, PubMed, Web of Science y el Índice Médico Español) introduciendo las ecuaciones anteriores y restringiendo los resultados a España. Tal y como se esperaba, los estudios realizados hasta 2021 fueron muy limitados. Entre ellos se encontraron dos trabajos, uno de

los cuales tomó como exposición la obesidad central en lugar del IMC (Morán Pascual *et al*., 2017), y otro de los cuales se adhirió a un estudio europeo bajo el amparo de la Sociedad Europea de Urología (Campi *et al*., 2019). Numerosos estudios realizados por el consorcio MultiCase-Control Spain (MCC-Spain), han analizado potenciales factores de riesgo asociados al cáncer de próstata, pero la obesidad aún no ha sido específicamente abordada en estudios originales de investigación en España ni como factor de riesgo ni como factor pronóstico.

Por tanto, parece quedar claro que existe un déficit de estudios de cohortes que analicen el efecto de la obesidad en los diversos desenlaces pronósticos de cáncer de próstata en nuestro medio. Dado que España se caracteriza por tener un sistema sanitario diferente de la mayoría de los países de su entorno, y dadas las características socioeconómicas y ambientales que podrían marcar la diferencia en términos de factores pronósticos con respecto a otros países, abordar este tema constituye una necesidad.

4. Posibilidad de mejorar el pronóstico del cáncer de próstata. La obesidad ha demostrado tener un impacto negativo en la salud de la población general, por lo que su abordaje como problema de salud en el cáncer de próstata, *a priori*, podría tener consecuencias positivas para estos pacientes. Además, uno de los objetivos fundamentales de la investigación en salud pública es el abordaje traslacional, esto es, que los resultados de los estudios tengan un impacto en la salud de los pacientes y sean trasladados a la práctica clínica. En este sentido, es importante investigar factores potencialmente modificables sobre los que diseñar estrategias preventivas. En esta Tesis Doctoral estudiamos un factor (la obesidad) que puede ser potencialmente modificable mediante estrategias adecuadas, tales como la implantación de programas dietéticos y/o de ejercicio físico y, por tanto, tienen el potencial de mejorar el

pronóstico de los pacientes con cáncer de próstata. La posibilidad de que nuestros datos sirvan para actualizar las guías de práctica clínica sobre el cáncer de próstata para alcanzar o mantener un peso saludable sugiere la necesidad de obtener datos fiables que puedan servir de referencia para las principales asociaciones profesionales de oncología y urología.

5. Factibilidad del estudio. En primer lugar, disponemos de los datos para realizar revisiones sistemáticas y metanálisis mediante el acceso a las principales bases de datos a través de nuestra institución, la Universidad de Granada, , y de la biblioteca virtual del Servicio Andaluz de Salud, lo que permite cubrir prácticamente el 100% de las revistas indexadas en el área *Urology & Nephrology* del *Journal Citation Reports*. Asimismo, disponemos de los datos necesarios para realizar un análisis de supervivencia en pacientes españoles gracias a la colaboración de nuestro grupo en el estudio MCC-Spain (Castaño-Vinyals *et al*., 2015). Con respecto a las estrategias de análisis, para la realización de la síntesis de la evidencia científica, se dispone de técnicas metanalíticas para estudios pronósticos que nos permiten reunir la información sobre estudios de cohortes que analizan una misma exposición (obesidad medida a través del IMC) y unos mismos desenlaces (pronóstico del cáncer de próstata) (Riley *et al*., 2019). Además, se dispone de las técnicas necesarias para realizar una síntesis de efectos aleatorios (Riley *et al*., 2011) un análisis detallado de las fuentes de heterogeneidad (Delgado-Rodríguez *et al*., 2018) y del sesgo de publicación (Egger *et al*., 1997; Palma Pérez *et al*., 2006) ayudando a superar las debilidades metodológicas de publicaciones previas. Finalmente, existe la metodología necesaria para poder realizar un análisis de supervivencia mediante la estimación de curvas de Kaplan-Meier y de regresión multivariante de riesgos proporcionales o regresión de Cox (Cox, 1972).

II. JUSTIFICATION

The factors that justify initiating a line of research dedicated to the study of the relationship between obesity and the prognosis of prostate cancer are summarized as follows:

1. Evolution of the health problem. As previously mentioned, obesity is a pandemic that affects an increasing number of people every year and is the second cause of avoidable mortality in the world after tobacco. In addition, the ageing population is causing a growing number of prostate cancer patients, and a significant proportion of them will die or substantially reduce their quality of life as a result. Therefore, both the exposure and the outcomes under study in this Doctoral Thesis represent major health issues, and their prevention could have an invaluable impact on the population.

2. Methodological weaknesses and insufficient data in the syntheses of scientific evidence published to date. In the previous section we discussed the methodological weaknesses of the meta-analyses conducted to date on the association between obesity and the three most studied prognostic outcomes for prostate cancer: cancer-specific mortality, all-cause mortality, and biochemical recurrence. Regarding meta-analyses on mortality (Cao *et al*., 2011; Zhang *et al*., 2015, Zhong *et al*., 2016), the methodological weaknesses are coupled with inconsistency in the results presented by the included studies, resulting in very high heterogeneity that exceeds 50% in all meta-analyses. Moreover, since the publication of the last meta-analysis on this relationship (Zhong *et al*., 2016), 15 studies have been published on the prognostic role of body weight, including data from 186,802 patients. Therefore, the latest published review (Zhong *et al*., 2016) was only able to access approximately one third of the total evidence currently available. Furthermore, previous systematic reviews did not formally assess the

causality criteria of the association studied, according to the criteria proposed by Bradford Hill (Hill, 1965), and which should be discussed in meta-analyses assessing causal relationships (Khan *et al*., 2012). Ultimately, there is a need for a robust and reliable assessment of the relationship between obesity and total and prostate cancer-specific mortality in patients diagnosed with prostate cancer. With respect to biochemical recurrence, since the last comprehensive meta-analysis with broad selection criteria published to date (Hu *et al*., 2014), 15 observational studies on this relationship have been published, including a total of 47,422 new cases of localized prostate cancer. Therefore, this review could only access 55% of the total number of patients currently available. Subsequently, a meta-analysis was published in 2015 (Bai *et al*., 2015), but only included Asian population, and another in 2020 (Luo *et al*., 2020), which only included 8 cohort studies regarding biochemical recurrence. Therefore, there is a need for an updated, robust, and reliable assessment of the relationship between obesity and prostate cancer prognosis.

3. Lack of national data. In our country, the analytical epidemiology of the relationship between obesity and prostate cancer prognosis has been scarcely studied to date. To confirm this, a bibliographic search was conducted in different databases (Scopus, PubMed, Web of Science and the Spanish Medical Index) introducing the above equations and restricting the results to Spain. As expected, the studies conducted up to 2021 were very limited. We found two papers, one of which considered central obesity instead of BMI as an exposure (Morán Pascual *et al*., 2017), and another of which adhered to a wider international study under the European Society of Urology (Campi *et al*., 2019). Numerous studies conducted by the MultiCase-Control Spain (MCC-Spain) consortium have analyzed potential risk factors

associated with prostate cancer, but obesity has not yet been specifically addressed in original research studies in Spain either as a risk factor or as a prognostic factor.

Therefore, it seems clear that there is a lack of cohort studies that analyze the effect of obesity on the various prognostic outcomes of prostate cancer in our setting. Given that Spain is characterized by a healthcare system that differs from most of the surrounding countries and given the socioeconomic and environmental characteristics that could make a difference in terms of prognostic factors with respect to other countries, there is a need to address this issue.

4. Possibility of improving the prognosis of prostate cancer. Obesity has been proven to have a negative impact on the health of the general population. Therefore, addressing obesity as a health problem in prostate cancer could have positive consequences for these patients. Furthermore, one of the fundamental objectives of public health research is the translational approach, i.e., that the results of the studies have an impact on the health of patients and are transferred to clinical practice. In this sense, it is important to investigate potentially modifiable factors to design preventive strategies. In this Doctoral Thesis we studied a factor (obesity) that may be potentially modifiable through appropriate strategies, such as the implementation of dietary and/or physical exercise programs, and therefore have the potential to improve the prognosis of prostate cancer patients. Our data might be useful for updating prostate cancer clinical practice guidelines including advice for achieving or maintaining a healthy weight. These data might enrich the knowledge of major oncology and urology professional associations.

5. Feasibility of the study. Firstly, we have the data to perform systematic reviews and meta-analyses by accessing the main databases through our institution, the University of Granada,

and the virtual library of the Andalusian Health Service, which allows us to cover practically 100% of the journals indexed in the Urology & Nephrology area of the *Journal Citation Reports*. We also have the necessary data to perform a survival analysis in Spanish patients thanks to the collaboration of our group in the MCC-Spain study (Castaño-Vinyals *et al*., 2015). Regarding strategies of analysis, for the synthesis of scientific evidence, meta-analytical techniques are available for prognostic studies that allow us to gather information on cohort studies that analyze the same exposure (obesity measured through BMI) and the same outcomes (prognosis of prostate cancer) (Riley *et al*., 2019). In addition, the necessary techniques are available to perform a random effects synthesis (Riley *et al*., 2011), a detailed analysis of the sources of heterogeneity (Delgado-Rodríguez *et al*., 2018) and publication bias (Egger *et al*., 1997; Palma Pérez *et al*., 2006), helping to overcome the methodological weaknesses of previous publications. Finally, there is specific methodology to perform survival analysis by estimating Kaplan-Meier curves and multivariate proportional hazards regression or Cox regression (Cox, 1972).

III. HIPÓTESIS / HYPOTHESIS

III. HIPÓTESIS

Nuestra hipótesis general es que la obesidad en pacientes diagnosticados de cáncer de próstata se asocia con un peor pronóstico de la enfermedad.

Las hipótesis que sustentan esta hipótesis general son:

1. La obesidad influye en una mayor mortalidad en la población general, por lo que afectaría negativamente a la mortalidad de pacientes diagnosticados de cáncer de próstata por las mismas causas que en la población general.
2. La obesidad influye específicamente en una mayor mortalidad atribuible al cáncer de próstata.
3. La obesidad influye en un mayor riesgo de recurrencia bioquímica (recidiva de la enfermedad).

Para testar dichas hipótesis, los objetivos descritos a continuación fueron escogidos como foco principal de esta investigación, que dio lugar a los cuatro trabajos desarrollados en esta Tesis Doctoral.

III. HYPOTHESIS

Our general hypothesis is that obesity in patients diagnosed with prostate cancer is associated with a worse prognosis of the disease.

The hypotheses underpinning this general hypothesis are:

1. Obesity influences a higher mortality in the general population, thus negatively affecting mortality in patients diagnosed with prostate cancer from the same causes as in the general population.
2. Obesity specifically influences higher mortality attributable to prostate cancer.
3. Obesity is associated with an increased risk of biochemical recurrence (disease recurrence).

To test these hypotheses, the objectives described in the next section were chosen as the main focus of this research, which resulted in the four papers developed in this Doctoral Thesis.

IV. OBJECTIVES

IV. OBJECTIVES

GENERAL OBJECTIVE

To quantify, in patients with prostate cancer, the magnitude of the association between BMI and obesity with the following outcomes: all-cause mortality, prostate cancer-specific mortality, and biochemical recurrence.

SPECIFIC OBJECTIVES

1. To describe the presence of recommendations on weight and healthy lifestyles in current clinical practice guidelines for prostate cancer.

2. To identify the association between obesity and BMI with prostate cancer outcomes by gathering all the information available in the scientific literature and obtaining quantitative estimators using meta-analytical techniques.

3. To identify potential heterogeneity sources that affect such associations:

   3.1. Study-related factors such as selection criteria and quality of the studies.

   3.2. Factors related to treatments and surgical techniques.

   3.3. Factors related to the collection of the exposure variable (BMI).

   3.4. Factors related to the collection of outcomes: all-cause mortality, prostate cancer specific mortality and biochemical recurrence.

4. To analyze the methodological quality of the studies included in the meta-analyses.

5. To analyze potential publication biases in the associations studied.

6. To identify the association between obesity and prostate cancer outcomes (i.e., prostate cancer specific mortality, all-cause mortality, biochemical recurrence, metastases and castration resistance) by means of a survival study conducted on a cohort of Spanish patients included in the MCC-Spain study.

7. To assess the convenience of including prognostic scales at diagnosis (e.g., Gleason score) in multivariate analyses of the association between obesity and prostate cancer outcomes.

V. MÉTODOS

V. METHODS

This section is presented in Spanish. The four studies developed in this Doctoral Thesis are fully presented in the Results section in English, where the methodology applied to each study is detailed.

V. MÉTODOS

Esta sección describirá la metodología general utilizada para esta Tesis Doctoral y los cuatro trabajos que de ella se desprenden:

Trabajo 1. *Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review*. Se trata de una revisión sistemática que cubre el objetivo 1 de esta Tesis Doctoral.

Trabajo 2. *Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients*. Se trata de una revisión sistemática y metanálisis que cubre los objetivos 2 a 5.

Trabajo 3. *Obesity and biochemical recurrence in clinically localized prostate cancer: a systematic review and meta-analysis of 86 490 patients*. Se trata de una revisión sistemática y metanálisis que cubre los objetivos 2 a 5.

Trabajo 4. *Evaluating the association between body mass index and prostate cancer outcomes. An observational longitudinal study from the Spanish multi-case control study (MCC-Spain)*. Se trata de un estudio observacional longitudinal que cubre los objetivos 6 y 7.

No obstante, en los apéndices se encuentra información más detallada, que será citada en la sección de Resultados de cada trabajo donde corresponda. La metodología descrita en esta sección tratará de responder a los objetivos específicos planteados, por lo que estos serán

ubicados donde corresponda a lo largo de la sección. Los métodos utilizados se pueden agrupar en tres grandes categorías: revisión sistemática de la literatura, técnicas metanalíticas y análisis de supervivencia. Todos los análisis estadísticos realizados durante la presente Tesis Doctoral han sido realizados con el programa estadístico Stata, versión 15.0 (StataCorp, 2017).

1. REVISIÓN SISTEMÁTICA DE LA LITERATURA.

1.1. METODOLOGÍA GENERAL

Esta metodología fue común a los tres primeros trabajos presentados en esta Tesis Doctoral. Para aplicarla, se siguieron las recomendaciones de la guía EQUATOR correspondiente, *the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* (Page *et al*., 2021), cuyo desarrollo se puede consultar como material suplementario correspondiente al Trabajo 1. Una vez realizada la búsqueda, la selección de documentos se realizó en dos fases. Los documentos fueron seleccionados por dos investigadores independientes en una primera fase (Mario Rivera Izquierdo y Virginia Martínez Ruiz o Javier Pérez de Rojas dependiendo del trabajo). Tras una primera selección de artículos basados en la lectura de títulos y resúmenes, se realizó una lectura a texto completo de los documentos en una segunda fase, seleccionando así aquellos que cumplieron con los criterios de elegibilidad. Un investigador sénior (José Juan Jiménez Moleón) resolvió los desacuerdos o inconsistencias en la selección de los documentos. Finalmente, los documentos duplicados se excluyeron.

La revisión sistemática del Trabajo 1, que aborda el *Objetivo 1) Describir la presencia de recomendaciones sobre peso y estilos de vida saludables en las guías de práctica clínica de cáncer de próstata actuales)*, cubrió el período comprendido entre enero de 2015 y agosto de 2021 y tuvo por objetivo recopilar todas las guías de práctica clínica y declaraciones de consenso actualizadas sobre diagnóstico y tratamiento del cáncer de próstata, desarrolladas por sociedades profesionales, organizaciones o agencias gubernamentales, sin restricciones por país o idioma. Los investigadores que, de forma independiente, realizaron la selección de trabajos fueron Mario Rivera Izquierdo y Virginia Martínez Ruiz. Se excluyeron todos los documentos que habían sido posteriormente actualizados, seleccionando únicamente los más recientes de cada organización o sociedad. Las variables descriptivas recogidas fueron: autor, año, tipo de documento (guía de práctica clínica o declaración de consenso), orientación del documento (diagnóstica o terapéutica), país, continente, año de su última actualización y publicación en una revista científica. La calidad de las guías de práctica clínica fue evaluada mediante la escala AGREE-II (Brouwers *et al*., 2016). Finalmente, para cumplir con el objetivo propuesto, se identificaron y recogieron las siguientes variables de interés: 1) reconocimiento de los estilos de vida como factores de riesgo del cáncer de próstata, 2)) mención de la obesidad, peso corporal o IMC como factores de riesgo del cáncer de próstata en el documento 3) reconocimiento de los estilos de vida como potenciales factores pronósticos del cáncer de próstata, 4) reconocimiento de la obesidad, peso corporal o IMC como potencial factor pronóstico del cáncer de próstata, 5) realización de recomendaciones sobre estilos de vida saludables para los pacientes diagnosticados de cáncer de próstata, y 6) presencia de recomendaciones sobre peso saludable para los pacientes diagnosticados de cáncer de próstata. Se procedió a realizar una descripción de las variables de interés, así como

análisis bivariantes con el objetivo de evaluar qué tipo de documentos recogían con mayor frecuencia recomendaciones relativas al peso y estilos de vida saludables.

Las revisiones sistemáticas de los Trabajos 2 y 3, realizadas para cumplir con el *Objetivo 2) Identificar la asociación entre obesidad y pronóstico del cáncer de próstata reuniendo toda la información disponible en la literatura científica y obteniendo estimadores cuantitativos mediante técnicas metanalíticas*), cubrieron el período comprendido desde el origen de las bases de datos consultadas (esto es, no se puso una fecha mínima) hasta el momento del envío de los trabajos (1 de abril de 2021 para el Trabajo 2 y 1 de junio de 2021 para el Trabajo 3), y tuvieron como objetivo recopilar todos los estudios observacionales longitudinales publicados que analizaron la relación entre obesidad y los desenlaces de interés, sin restricciones por país o idioma. Los investigadores que, de forma independiente, realizaron la selección de trabajos fueron Mario Rivera Izquierdo y Javier Pérez de Rojas. Cuando se detectaron trabajos que habían sido realizados sobre una misma cohorte de pacientes o que incluían subpoblaciones de pacientes ya consideradas en otros estudios, se seleccionó el trabajo más reciente con mayor tamaño de muestra para los objetivos de interés y se excluyeron el resto. Las variables descriptivas recogidas fueron: autor, año, diseño del estudio (estudios de cohortes o de casos y controles, y su carácter prospectivo o retrospectivo), país, continente, año de publicación, momento de obtención de la variable de exposición de interés (antes o después del diagnóstico de cáncer de próstata), fuente de la variable de exposición (peso corporal y talla medido por los investigadores, obtenido a través de las historias clínicas o referido por los pacientes), puntos de corte considerados para la variable de exposición (IMC) o para el desenlace recurrencia bioquímica, tiempo mediano de seguimiento de cada estudio, variables consideradas como variables de confusión en el análisis multivariante, valoración de cada ítem

considerado por la escala de calidad Newcastle-Ottawa (NOS), y puntuación total de la escala NOS (Wells *et al*., 2021). Las variables de interés recogidas para medir la fuerza de asociación fueron 1) Hazard ratio (HR) de asociación entre obesidad y el desenlace de interés, así como su intervalo de confianza al 95% (IC95%), 2) HR de asociación entre el incremento del IMC por cada 5 unidades y el desenlace de interés, así como su correspondiente IC95%. Los investigadores que, de forma independiente, obtuvieron estos datos de cada estudio fueron Mario Rivera Izquierdo y Javier Pérez de Rojas.

1.2. EVALUACIÓN DE LA CALIDAD METODOLÓGICA

El *Objetivo 4) Evaluar la calidad metodológica de los estudios incluidos en los metanálisis* (Trabajos 2 y 3) fue abordado mediante el uso de la escala de calidad NOS, específica para estudios observacionales longitudinales (estudios de cohortes y estudios de casos y controles), que fueron los únicos diseños incluidos en los metanálisis presentados en esta Tesis Doctoral. En primer lugar, se recogieron las variables relacionadas con los autores, año de publicación, ámbito del estudio, diseño del estudio, población del estudio, mediana de seguimiento, exposición, desenlaces, tipo de análisis y presencia de conflictos de interés declarados. Una vez recogida esta información, cada estudio fue analizado en detalle para cumplimentar los 9 ítems de la escala NOS, que sirven para analizar el riesgo de sesgos de acuerdo con tres indicadores: selección (hasta cuatro puntos), comparabilidad (hasta dos puntos) y medición del desenlace (para estudios de cohortes) o de la exposición (para estudios de casos y controles) (hasta tres puntos). Una puntuación igual o superior a 8 indica que el estudio presenta una alta calidad (bajo riesgo de sesgos), una puntuación de 6 a 7 indica calidad intermedia (riesgo intermedio de sesgos) y una puntuación de 5 o inferior indica una baja calidad (alto riesgo de sesgos) (Wells *et al*., 2021). La evaluación de la calidad de cada estudio para los metanálisis

de esta Tesis Doctoral fue realizada por dos investigadores independientes, Mario Rivera Izquierdo y Javier Pérez de Rojas. Las discrepancias entre ambas evaluaciones fueron consensuadas y resueltas con ayuda de un investigador sénior, José Juan Jiménez Moleón. La calidad de los estudios fue representada gráficamente y se utilizó como variable para el análisis estratificado de subgrupos en todos los metanálisis realizados.

2. TÉCNICAS METANALÍTICAS

Estas técnicas se aplicaron en los Trabajos 2 (cuantificar la asociación entre obesidad y mortalidad por cáncer de próstata) y 3 (cuantificar la asociación entre obesidad y recurrencia bioquímica) para dar respuesta al objetivo 2, a partir de las correspondientes revisiones sistemáticas descritas en el apartado anterior. Una vez seleccionados los documentos se procedió a aplicar las técnicas metanalíticas que se describen a continuación.

2.1. OBTENCIÓN DE ESTIMADORES RESUMEN

Para la obtención de estimadores resumen, y habiendo considerado los estudios que presentaron una misma exposición y un mismo desenlace, se procedió a realizar un metanálisis bajo un modelo de efectos aleatorios asumiendo que los estudios incluidos en el metanálisis no comprenden la totalidad de la evidencia existente, ayudando además a tener en consideración la heterogeneidad entre los estudios seleccionados (Riley *et al*., 2011; Martínez González *et al*., 2020). En resumen, dicho modelo asume que el efecto de la exposición varía entre estudios, y estima el promedio de la distribución entre dichos efectos. Como

consecuencia, los intervalos de confianza obtenidos como resultado del metanálisis serán más amplios que en el modelo de efectos fijos, que asume la homogeneidad entre estudios. En primer lugar, se obtuvieron las Hazard Ratios (HR) y sus correspondientes intervalos de confianza al 95% (IC95%) de los estudios seleccionados (estudios de cohortes con análisis de supervivencia). Se obtuvieron, siempre que fue posible, las HR ajustadas en los modelos multivariantes más completos referidos por los autores. Por lo tanto, ambos metanálisis se realizaron a partir de datos secundarios, esto es, a partir de las HR reportadas en dichos artículos, dado que los datos crudos (número de desenlaces en cada grupo de exposición) no estaban disponibles en la mayoría de los artículos seleccionados. Las HR de obesidad (IMC $\geq$ 30 kg/m^2) con respecto a normopeso (IMC < 25) y de sobrepeso (IMC $\geq$ 25 kg/m^2) con respecto a normopeso (IMC < 25) fueron obtenidas de cada artículo seleccionado. Posteriormente, dichas HR y sus IC95% fueron transformadas, mediante el método descrito por Greenland *et al*. (1992), en la HR por cada 5 unidades de incremento del IMC. Así, además de obtener comparaciones entre obesidad (o sobrepeso) y normopeso, se pudieron obtener estimaciones del efecto del IMC como variable cuantitativa continua, lo que permitió obtener conclusiones relativas a la relación dosis-respuesta entre el IMC y los desenlaces estudiados.

Cuando los autores reportaron las HR por cada unidad de incremento del IMC, estos fueron transformados a HR por incrementos de 5 unidades, de acuerdo con el método descrito por Zhong *et al*. (2016), basado en elevar a la quinta potencia tanto la estimación puntual como los extremos de los intervalos de confianza de cada HR.

Una vez obtenidas las HR, se procedió a la realización de los diagramas de bosque (*forest plot*). Dado que el eje de abscisas de dichos diagramas no permitía su adaptación a la escala logarítmica, puesto que para ello es preciso incluir datos crudos y no datos indirectos como

los presentados en esta Tesis Doctoral, la escala se adaptó a los puntos 0, 0,5, 1 y 4 para el metanálisis de mortalidad y 0, 0,5, 1 y 5 para el metanálisis de recurrencia bioquímica, al objeto de facilitar la correcta interpretación visual de los resultados. Mediante este proceso se obtuvieron los estimadores resumen para la consecución del objetivo 2, que se citan a continuación:

- HR de obesidad vs. normopeso para la mortalidad específica por cáncer de próstata.
- HR de sobrepeso vs. normopeso para la mortalidad específica por cáncer de próstata.
- HR por cada incremento en 5 unidades del IMC para la mortalidad específica por cáncer de próstata.
- HR de obesidad vs. normopeso para la mortalidad por todas las causas.
- HR de sobrepeso vs. normopeso para la mortalidad por todas las causas.
- HR por cada incremento en 5 unidades del IMC para la mortalidad por todas las causas.
- HR de obesidad vs. normopeso para la recurrencia bioquímica.
- HR de sobrepeso vs. normopeso para la recurrencia bioquímica.
- HR por cada incremento en 5 unidades del IMC para la recurrencia bioquímica.

2.2. ANÁLISIS DE HETEROGENEIDAD

A continuación, se describen los métodos empleados, en los Trabajos 2 y 3, para la consecución del *Objetivo 3) Identificar potenciales fuentes de heterogeneidad que afecten a las estimaciones de las asociaciones de interés*. La heterogeneidad de los resultados globales descritos en el anterior párrafo se evaluó mediante es test Q de heterogeneidad de Cochrane y mediante el estadístico I^2 de Higgins. Cuando el test arroja un valor $p < 0,05$ o, de acuerdo con

algunos autores, $p < 0,10$ (Higgins *et al*., 2011), se asume que existe heterogeneidad entre los estudios no debida exclusivamente al azar. Para cuantificar su magnitud, el índice I^2 arroja un valor porcentual mayor cuanto mayor es la heterogeneidad de los resultados existentes entre los estudios incluidos en el metanálisis. Así, el estadístico I^2 describe el porcentaje de variabilidad debida a la heterogeneidad y no al azar entre los estudios incluidos. Si bien no existe un punto de corte definitivo, puesto que la importancia de la inconsistencia depende de múltiples factores que se han de analizar e interpretar de manera específica para cada asociación, *The Cochrane Collaboration* sugiere que un I^2 de hasta el 40% sería lo esperable por el azar, siendo porcentajes superiores el resultado de otras causas de heterogeneidad que se han de explorar (Higgins *et al*., 2011). Existen otras pruebas estadísticas que arrojan información referente a la heterogeneidad, tales como el índice Tau^2, que estima la varianza entre los tamaños de efecto de los estudios. Sin embargo, aún no existe un consenso sobre qué puntos de corte utilizar para la interpretación de esta prueba (Higgins *et al*., 2011) y, por tanto, no ha sido utilizada ni interpretada en la presente Tesis Doctoral.

Una vez identificada la heterogeneidad entre estudios para los nueve diagramas de bosque explicitados en el punto anterior, se procedió a realizar un análisis de las potenciales fuentes de dicha heterogeneidad. Así, se realizó, en primer lugar, un análisis de subgrupos basado en variables consideradas *a priori* como potenciales factores de heterogeneidad. Dichas variables fueron agrupadas de acuerdo con el objetivo 3 en cuatro categorías:

- *Variables relacionadas con los estudios*: así, se consideró la calidad de cada estudio de acuerdo con las escala NOS, el nivel de evidencia de acuerdo con los Sistemas de Clasificación de la Calidad de los Estudios y otra Evidencia, modificado de la *Oxford Centre for Evidence-based Medicine for rating of individual studies* (Centre for

Evidence-based Medicine, 2021), el país de publicación, el desarrollo de dicho país de acuerdo con el *Fondo Internacional Monetario*, el tamaño muestral, el año de publicación y el diseño de cada estudio.

- *Variables relacionadas con los tratamientos y técnicas quirúrgicas:* se consideró el tratamiento primario recibido por los pacientes de cada estudio (prostatectomía radical, radioterapia, braquiterapia, o varios), la técnica quirúrgica realizada (laparoscopia asistida por robot, laparotomía, etc.,), el ajuste por estadio tumoral y por la presencia de márgenes quirúrgicos positivos.
- *Variables relacionadas con la recogida de la variable de exposición*: se recogió el momento en que se midió el peso corporal y/o la presencia obesidad (antes o después del diagnóstico de cáncer de próstata), la medición del peso corporal y los criterios utilizados para el diagnóstico de obesidad (de acuerdo con los estándares de la OMS para población general, de acuerdo con los estándares de la OMS para población asiática, el uso del IMC de manera únicamente cuantitativa, u otras mediciones) y la fuente de datos de donde provenía la medición de la obesidad para cada estudio (medida directamente por los investigadores, consultada en la historia clínica o en registros médicos, o referida por el propio paciente).
- *Variables relacionadas con la recogida de los desenlaces.* Con respecto a la mortalidad específica por cáncer de próstata o la mortalidad por todas las causas, no se encontraron diferencias en la medición de estos desenlaces. Sin embargo, para la variable de recurrencia bioquímica, se dividió a los estudios entre aquellos que consideraron este desenlace a partir de un PSA tras la prostatectomía > 0,1 ng/ml, aquellos que lo consideraron tras un PSA > 0,2 ng/ml, aquellos que lo consideraron

tras un PSA > 0,4 ng/ml y aquellos que definieron la recurrencia bioquímica mediante otros criterios.

Así, utilizando todas estas variables para estratificar los resultados, se obtuvieron los correspondientes análisis de subgrupos, que arrojaron valores de HR y sus IC 95% para cada subgrupo, así como índices I^2 muy reducidos en muchos subgrupos con respecto al análisis del total de estudios. Ello permitió, por tanto, identificar causas claras de heterogeneidad para cada metanálisis realizado y cumplir así con el objetivo 3.

2.3. EVALUACIÓN DEL SESGO DE PUBLICACIÓN

La consecución del *Objetivo 5) Analizar potenciales sesgos de publicación en las asociaciones estudiadas* se realizó para todos los metanálisis de esta Tesis Doctoral mediante varias estrategias metodológicas. En primer lugar, se analizó gráficamente el *efecto de los estudios pequeños (small-study effect)* mediante diagramas de embudo *(funnel plots)*. De acuerdo con este método, para asegurar la inexistencia de un sesgo de publicación, se debe encontrar una figura con forma similar a un embudo (esto es, con mayor número de estudios en la parte baja, y un número de estudios proporcional a cada lado de la línea vertical divisoria). Este gráfico representa en el eje de abscisas el estimador puntual de cada estudio (así, la línea vertical divisoria representa el valor nulo del HR, esto es, el valor 1 (o bien el valor 0 cuando se representa el logaritmo de la HR), y en el eje de ordenadas el tamaño de muestra de cada estudio medido como el inverso del error estándar de la HR, de tal manera que los estudios de mayor tamaño muestral se ubican en la parte superior de dicha gráfica.

Dado que esta es una forma visual de analizar el potencial sesgo de publicación, estos datos se complementaron con el test de Egger (Egger, 1997) que arroja un valor p significativo (inferior a 0,05) si existe efecto de estudios pequeños al detectar la asimetría del gráfico y, por tanto, es sugerente de un sesgo de publicación.

3. ANÁLISIS DE SUPERVIVENCIA

Finalmente, para el Trabajo 4, diseñado para dar respuesta al *Objetivo 6) Identificar la asociación del peso corporal y la obesidad con los desenlaces del cáncer de próstata (mortalidad, recurrencia bioquímica, desarrollo de metástasis y resistencia a la castración) mediante un estudio de supervivencia realizado sobre una cohorte de pacientes españoles en el seno del estudio MCC-Spain*, se obtuvieron los datos correspondientes a los pacientes con cáncer de próstata incidentes reclutados en 7 provincias españolas (Asturias, Barcelona, Cantabria, Granada, Huelva, Madrid y Valencia) dentro del estudio *MCC-Spain*, desde 2008 hasta 2013, y que fueron seguidos hasta el año 2018 (Alonso-Molero *et al*., 2019). El estudio MCC-Spain (Castaño-Vinyals *et al*., 2015), brevemente, es un estudio de casos y controles de base poblacional de 5 tumores frecuentes en España (cáncer de próstata, cáncer de mama, cáncer colorrectal, cáncer gastroesofágico y leucemia linfática crónica) con controles poblacionales comunes para los diferentes tipos de casos emparejados por frecuencia por edad, sexo y región de residencia. Los participantes respondieron a una entrevista personal informatizada sobre factores sociodemográficos, exposiciones ambientales, ocupación, medicación, estilos de vida e historia médica y personal. A estos datos se añaden la cumplimentación de un cuestionario alimentario, así como entrevistas telefónicas y acceso a

información clínica y relacionada con el tumor, su diagnóstico, estadiaje y tratamiento mediante las historias clínicas. Se trata de un estudio desarrollado en el Consorcio de Investigación Biomédica de Epidemiología y Salud Pública (CIBERESP) cuyo objetivo inicial fue evaluar factores etiológicos de tumores comunes para promover la prevención del cáncer en España (Castaño-Vinyals *et al*., 2015).

En los últimos años, y a partir de las cohortes de casos integrantes del estudio MCC-Spain, este estudio multicéntrico se ha centrado en la identificación de factores pronósticos del cáncer (Alonso-Molero *et al*., 2019). Con dichos pacientes diseñamos un estudio de cohortes cuyos resultados han sido presentados de acuerdo con la guía *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)* (von Elm *et al*., 2014). La información sobre variables sociodemográficas y clínicas se puede obtener del cuestionario utilizado, disponible en internet: https://mccspain.org/.

Al igual que en los metanálisis realizados en la presente Tesis Doctoral (Trabajos 2 y 3), la variable principal de exposición fue la obesidad (IMC ≥ 30), así como los incrementos del IMC en 5 unidades. Las variables de desenlace, además de la mortalidad específica por cáncer de próstata, mortalidad por todas las causas y recurrencia bioquímica, fueron la presencia de nuevas metástasis y el desarrollo de un cáncer de próstata resistente a la castración.

Tras la realización de un análisis descriptivo de las diferentes variables sociodemográficas y clínicas estratificado por los subgrupos del IMC, se procedió a realizar un análisis de supervivencia. En primer lugar, se obtuvieron los correspondientes gráficos de Kaplan-Meier (Kaplan *et al*., 1958) para estimar la probabilidad acumulada de supervivencia de cada desenlace para cada subgrupo definido por el IMC. En dichos gráficos, se sitúa en el eje de

abscisas el tiempo de seguimiento, y en el eje de ordenadas el porcentaje de personas supervivientes. Por tanto, al inicio de la gráfica (tiempo cero) hay un 100% de supervivientes, y este porcentaje va decayendo conforme avanza el tiempo. Se obtiene una curva de supervivencia de cada color por cada categoría del IMC estudiado, facilitando así la comparación visual de la supervivencia entre cada subgrupo de exposición. Una ventaja de este método es que tiene en cuenta las pérdidas durante el seguimiento, que se consideran como *datos censurados*. En nuestro estudio, se tomó como tiempo cero el momento del diagnóstico de cáncer de próstata. Se utilizó el test Log-Rank para detectar la existencia de diferencias estadísticamente significativas ($p < 0,05$) en las probabilidades de supervivencia de los subgrupos de exposición considerados. Esta prueba, también conocida como prueba de Mantel-Cox, es una prueba no paramétrica que contrasta las funciones de supervivencia de dos poblaciones y se puede usar en presencia de datos censurados (Mantel, 1966).

Finalmente, para estimar la fuerza de asociación potencialmente causal entre la obesidad y los desenlaces del cáncer de próstata, se aplicaron modelos de riesgos proporcionales o de regresión de Cox (Cox, 1972). Mediante estos modelos se obtuvieron las correspondientes HR ajustadas (y sus correspondientes IC95%) para cuantificar la asociación de la obesidad y de 5 unidades de incremento del IMC con cada desenlace. Para cada binomio exposición-desenlace se ajustaron dos modelos: el primero incluyó las principales variables sociodemográficas y clínicas, junto con la escala de Gleason. En el segundo se excluyó la escala de Gleason, pues sus valores podían considerase marcadores de posibles mediadores de la asociación causal entre la obesidad y los desenlaces, lo que conllevaría un sobreajuste de la estimación (sesgo hacia el nulo). Esto ocurriría si la obesidad influyera causalmente en el desarrollo de cáncer de próstata con escala de Gleason más avanzada y esta, a su vez, se asociase a un peor

pronóstico (mayor frecuencia de desenlaces). Siguiendo este razonamiento, la escala de Gleason sería un mediador de la asociación causal entre la obesidad y los desenlaces y, por tanto, su inclusión en los modelos multivariantes no sería adecuada. Este razonamiento se aplicó para responder al *Objetivo 7) Analizar la conveniencia de incluir las escalas pronósticas medidas al diagnóstico (por ejemplo, la escala de Gleason) en los análisis multivariantes de la asociación entre la obesidad y los desenlaces del cáncer de próstata*.

VI. RESULTS

VI. RESULTS

The presentation of the Results will be divided according to the 4 studies that have been developed during the present Doctoral Thesis. Each study has been designed, performed, and written independently of the others, because our aim was to publish each study as an independent article in a peer-review journal of high impact index. For the sake of clarity, we will show in this section the four complete studies with their own sections of introduction, methods, results, discussion, and references. Study 1 has been accepted but the definitive version was not published by the moment of presentation of this Thesis. Therefore, the accepted version is presented. Studies 2 and 3 have been published and are presented in their published versions after permission from the publishers. Study 4 has not been sent for publication and, therefore, the first draft of the study is presented.

STUDY 1. RECOMMENDATIONS ON WEIGHT LOSS AND HEALTHY LIFESTYLE IN PROSTATE CANCER CLINICAL GUIDELINES: A SYSTEMATIC REVIEW.

Rivera-Izquierdo M, Martínez-Ruiz V, Jiménez-Moleón JJ. Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review. Accepted in the *International Journal of Environmental Research and Public Health,* 2022; Impact Factor (2020): 3.390, position 42/176 in Public, Environmental & Occupational Health – SSCI; T1, Q1.

This study responds to the specific objective 1 of the Thesis.

Appendix 1 shows proof of acceptance of this study for publication.

Appendices 2, 3, 4, and 5 of this Doctoral Thesis correspond to Supplementary Tables S2, S3, S4 and S5 of the manuscript, respectively.

International Journal of Environmental Research and Public Health

MDPI

Review

Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review.

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Abstract: Obesity is associated with prostate cancer negative outcomes (e.g., specific mortality, all-cause mortality, biochemical recurrence, etc.), according to current scientific literature. Nevertheless, recommendations on weight loss and healthy lifestyle are poorly covered by clinicians. We aimed at identifying those recommendations from clinical practice guidelines (CPGs) of prostate cancer. We systematically searched on MEDLINE, EMBASE, Web of Science, Scopus, guideline databases and online sources, for CPGs updated from January 2015 to August 2021. The searches were independently conducted by two researchers without language restrictions. A total of 97 prostate cancer guidelines, including 84 (86.6%) CPGs and 13 (13.4%) consensus statements were included. Recommendations on reaching and maintaining healthy weight or healthy lifestyles were provided by 7 (7.2%) and 13 (13.4%) documents, respectively. No differences regarding recommendations were found by type of document, year of publication or country. Our results suggest that professional societies and governments should update prostate cancer guidelines to include these recommendations for improving prostate cancer prognosis.

Keywords: clinical guidelines; consensus statement; prostate cancer; obesity; mortality; body weight.

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1. Introduction

Prostate cancer (PC) is the most frequent cancer in men [1]. Nevertheless, few prognostic factors have been clearly associated with PC outcomes, mainly older age, ethnicity, and family history of PC [2], none of them modifiable. Since decades, obesity has been associated with negative PC outcomes, although results were not always consistent [3,4]. According to the PRACTICAL consortium [5] and the REDUCE study [6], among others, obesity may be considered as a modifiable risk factor for prostate cancer according to current data. Recently, new studies on molecular mechanisms linking obesity to prostate cancer have been developed [7], and several systematic reviews and meta-analyses have pointed obesity, measured as body mass index (BMI) ≥ 30 kg/m^2, as a prognostic factor associated with higher frequency of prostate cancer specific mortality [8], higher frequency of all-cause mortality [8], and higher frequency of biochemical recurrence after radical prostatectomy [9]. The World Cancer Research Fund [10] also reported an increased risk of being diagnosed with advanced PC in obese patients. Other authors have reported the increased difficulties in prostate cancer surgery in obese patients, which can lead to adverse events or disease recurrence [11], and higher association with the need for chemotherapy [12]. Other recent studies have pointed and association between higher BMI and multiple pelvic lymph nodes metastasis [13].

Given that obesity is associated with poorer health outcomes in the general population [14,15], and the wide range of works reporting its implications on PC negative outcomes, it seems logical to include recommendations on weight loss from clinicians to newly diagnosed PC patients. Therefore, several authors have pointed the need for including recommendations on reaching and maintaining healthy weight in clinical practice guidelines (CPGs), as weight loss programs have proved to be effective [16,17]. In fact, current research is focused on designing intervention healthy lifestyle and weight loss programs [18,19]. CPGs are documents that compile current evidence-based recommendations on how to diagnose and treat a medical condition, usually endorsed by medical organizations or governments. Consensus statements (CSs) are a comprehensive summary of the opinion of an expert panel to provide guidance on controversial or poorly understood aspects of health care. Therefore, both documents should include updated evidence-based information on modifiable prognostic factors such as weight loss of lifestyle habits.

The aim of this study was to compile all recent CPGs and CSs on prostate cancer diagnosis and treatment developed by professional societies or governments and to analyze the presence of recommendations regarding healthy weight and lifestyles.

2. Materials and Methods

The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] (Supplementary Table S1).

2.1. Search strategy and data source

We conducted a systematic search covering a period from January 2015 to August 2021 to avoid a selection bias as most of the guidelines before that date have been updated and replaced by more recent ones, combining MeSH terms "clinical practice guidelines", "guidelines", "consensus", "prostate cancer", "prostate cancer diagnosis", "prostate cancer treatment", and including word variants in TRIP database and MEDLINE, without language restrictions, to collect all updated CPGs and CSs. When the language of the document was not a mother tongue of the researchers (i.e., different from English or Spanish), we tried to contact with researchers of this language of our center. When this situation was not possible, we completely translated all the document using a free translator software, DeepL (https://www.deepl.com/translator).

Afterwards, we extended the search to other databases, such as EMBASE, Web of Science, Scopus, Cochrane Database of Systematic Reviews, and the ACP Journal Club. Eight guideline databases were searched, including the National Institute for Health and Care Excellence (NICE), the National Comprehensive Cancer Network (NCCN), the Scottish Intercollegiate Guidelines Network (SIGN), Fisterra, the Canadian Clinical Practice Guideline (CPG), the CMA Infobase, the National Health and Medical Research Council (NHMRC), the Health Services Technology Assessment Texts (HSTAT) and the Guidelines International Network (GIN). Finally, 77 professional society websites were visited to complete the search (Supplementary Table S2), and references from other relevant studies were manually searched.

2.2. Study selection and data extraction

We covered CPGs and CSs on diagnosis and therapeutic management of prostate cancer, developed by professional societies, organizations, or government agencies. We also included guidelines on management of cancer complications (e.g., castration-resistant prostate cancer). The documents were considered as CPGs and CSs as depicted by the authors after full-text reading, or when the search database considered it as so. The presence of keywords in the title, such as "guideline" for CPGs or "consensus" for CSs helped us in the classification of the documents. Obsolete documents updated in more recent years from the same organization or government, and CPGs or CSs for education or information purposes and documents designed only for patients were excluded. Two independent reviewers (MR-I and VM-R) identified titles and abstracts and performed full-

text assessment of the eligible studies. Disagreements or inconsistences were solved by consensus with a third senior reviewer (JJJ-M). Duplicate documents were identified and removed. Data extraction and identification of duplicates were conducted using the software Mendeley Reference Manager version 2.61.1.

2.3. Assessment

All CPGs and CSs were thoroughly assessed for the inclusion of recommendations concerning weight loss or lifestyles. The variables collected from each document were type of document (CPG or CS), focus of the document (diagnostic or treatment of PC); area (divided by continent and country), year of the last update and publication in a journal. The variables of interest were divided in the following groups: 1) acknowledgement of obesity, weight or body mass index (BMI) as a potential risk factor for PC; 2) acknowledgement of lifestyle as a risk factor for PC; 3) acknowledgement of obesity, weight or BMI as possible prognostic factors for PC; 4) acknowledgement of lifestyle as a prognostic factor for PC; 5) recommendations on healthy weight for PC patients; 6) recommendations on healthy lifestyle for PC patients; 7) recommendations on healthy diet for PC patients; and 8) recommendations on physical activity for PC patients. Finally, quality assessment of CPGs that included such recommendations was conducted using the AGRE-II tool. For points 1) to 5), we looked anywhere in the guideline text for an appropriate statement that included the presence of body weight or lifestyle as recognized risk or prognostic factor for PC, after full-text reading. For points 6) to 8) we looked for specific recommendations provided by the document. All the selected documents were assessed independently by two reviewers (MR-I and VM-R), and disagreements were resolved by the consensus of a third reviewer (JJJ-M).

2.4. Statistical analyses

We conducted descriptive analysis on the presence of obesity, weight, BMI or lifestyle in the guidelines. Country, year, type of document and focus of the document were considered for bivariate analyses. Differences in the presence of the variables of interest were analyzed using T-tests and chi-square tests for quantitative and qualitative variables, respectively. When chi-square conditions for applications were not met, Fisher exact test was applied.

3. Results

3.1. Study selection

Of the 2905 identified citations, 97 CPGs and CSs met inclusion criteria, 45 were (46.5%) published in a journal [21-65] and 52 (53.6%) were published in other sources (Supplementary Table S3). Figure 1 shows the flow chart of the study selection.

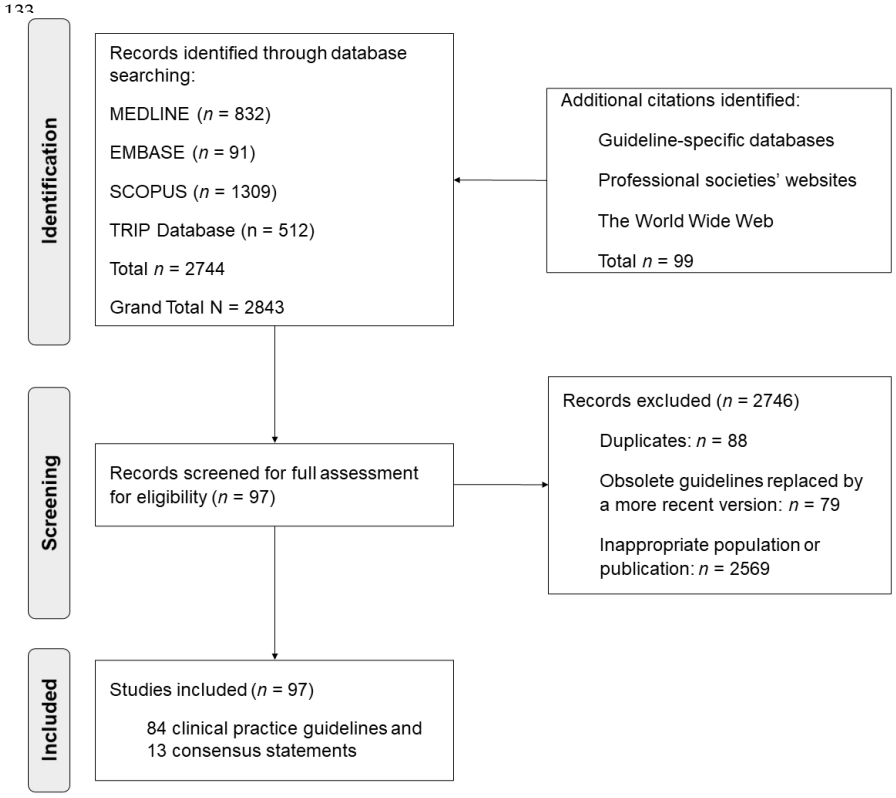

Figure 1. Flow chart of the study selection of the systematic review according to PRISMA guidelines.

3.2. Characteristics of the studies

Table 1 shows the main characteristics of the selected documents, including the title, year, and country. There was a total of 40 (41.2%) North American guidelines, 35 (36.5%) European guidelines, 12 (12.4%) Asian guidelines, 6 (6.2%) South American guidelines, and 4 (4.1%) from other continents (African, Oceanian, or international guidelines that compiled countries from different continents). From the selected documents, 84 (86.6%) were CPGs and 13 (13.4%) were CSs. A total of 45 (46.4%) documents corresponded to diagnostic guidelines and 78 (80.4%) included information on therapeutic approaches and recommendations.

3.3. Factors associated with recommendations on obesity and healthy lifestyles

Only 11 (11.3%) documents acknowledged obesity, body mass index or weight as a risk factor for prostate cancer, and 5 (5.2%) as a prognostic factor. Similarly, 15 (15.5%) documents considered lifestyle factors as risk factors, and 7 (7.2%) as prognostic factors. Regarding recommendations, only 7 (7.2%) guidelines provided advice on reaching or maintaining healthy weight for PC patients, and 13 (13.4%) provided advice on healthy lifestyles. These 13 documents that presented recommendations showed reasonably high quality according to AGREE-II (Supplementary Table S4). Supplementary Table S5 shows examples of the specific recommendations provided by these 13 documents. Specifically, healthy diet and physical activity advice were provided in 9 (9.3%) and 10 (10.3%) documents, respectively (Table 2).

Table 3 shows the different characteristics of the guidelines when comparing the 13 documents that provided recommendations on healthy lifestyles with the 84 documents that did not. Although no significant differences were found between both subgroups, a tendency to provide more recommendations was observed in more recent documents, in CPGs compared with CSs and in therapeutic guidelines. Nevertheless, recommendations on healthy lifestyles were very infrequent for all subgroups.

Table 1. Clinical guidelines and consensus statements on diagnosis and treatment of prostate cancer (n=97), 2015-2021.

Name of the Clinical Practice Guideline	Entity	Country	Year	Recommendation [1]
PMB definition guideline: Prostate cancer	CMS	South Africa	2020	No
South African prostate cancer guidelines	SAUA	South Africa	2017	Yes
Chinese guidelines for diagnosis and treatment of prostate cancer 2018	NHC China	China	2018	No
Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition)	JUA	Japan	2016	No
2020 Korean guidelines for the management of metastatic prostate cancer.	KSMO	Korea	2020	No
Prostate cancer	MIMS	Malaysia	2021	Yes
Singapore Cancer Network (SCAN) Guidelines for the Management of Advanced Castrate-Resistant Prostate Cancer.	SCAN	Singapore	2015	No
Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for prostate cancer 2017	SOS-SUA	Saudi Arabia	2017	No
EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent	EAU-EANM-ESTRO-ESUR-SIOG	Europe	2020a	No
EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer	EAU-EANM-ESTRO-ESUR-SIOG	Europe	2020b	Yes
Biochemical recurrence in prostate cancer: The EAU Prostate Cancer Guidelines Panel's recommendations.	EAU-EANM-ESTRO-ESUR-SIOG	Europe	2020c	No
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of prostate cancer	ESMO	Europe	2020	Yes
Guidelines on Prostate Cancer	EAU-ESTRO-ESOR-SIOG	Europe	2018	No
EAU-ESTRO-SIOG Guidelines on prostate cancer: screening, diagnosis and local treatment with curative intent	EAU-ESTRO-SIOG	Europe	2017	No
DUCG's National Guidelines for Diagnosis and Treatment of Prostate Cancer	DUCG	Denmark	2015	No
French ccAFU guidelines - update 2020-2022: prostate cancer	CCAFU	France	2020	No
S3 - Prostate cancer guideline	AWMF-DKG-DKH	Germany	2021	Yes
PSMA ligand PET/CT in the diagnosis of prostate carcinoma.	AWMF	Germany	2019	No

National Prostate Cancer GP Referral Guideline	NCCP	Ireland	2018	No
Diagnosis, staging and treatment of patients with prostate cancer. National Clinical Guideline No. 8	NCCP	Ireland	2016	Yes
Prostate cancer, national guideline version 3.0	IKNL	Nether-lands	2017	Yes
Appropriate use of pharmaceutical products for patients with castration-refractory prostate cancer	Zorginstituut Nederland	Nether-lands	2016	No
Prostate cancer	NVU	Nether-lands	2016	No
SEOM clinical guidelines for the treatment of advanced prostate cancer (2020)	SEOM	Spain	2020	No
SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017)	SEOM	Spain	2017	No
Enzalutamide for treating hormone-sensitive metastatic prostate cancer (technology appraisal guidance TA712)	NICE	UK	2021	No
Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer (technology appraisal guidance TA660)	NICE	UK	2020	No
Prostate cancer: diagnosis and management. (NICE guideline NG131)	NICE	UK	2019a	No
Enzalutamide for hormone-relapsed non-metastatic prostate cancer (Technology appraisal guidance TA580)	NICE	UK	2019b	No
Padeliporfin for untreated localised prostate cancer (Technology appraisal guidance TA546)	NICE	UK	2018a	No
Memokath-051 stent for ureteric obstruction (Medical technologies guidance MTG35)	NICE	UK	2018b	No
Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline	MAGIC – BMJ	UK	2018	No
Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer (Interventional procedures guidance IPG590)	NICE	UK	2017	No
Irreversible electroporation for treating prostate cancer Interventional procedures guidance [IPG572]	NICE	UK	2016a	No
Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (Technology appraisal guidance TA412)	NICE	UK	2016b	No
Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (Technology appraisal guidance TA391)	NICE	UK	2016c	No
Degarelix for treating advanced hormone-dependent prostate cancer (Technology appraisal guidance TA404)	NICE	UK	2016d	No
Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (Technology appraisal guidance TA259)	NICE	UK	2016e	No
Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (Technology appraisal guidance TA387)	NICE	UK	2016f	No
Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (Technology appraisal guidance TA377)	NICE	UK	2016g	No

Suspected cancer: recognition and referral (NICE guideline NG12)	NICE	UK	2015	No
Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update	ASCO/CCOJ	USA/ Canada	2017	No
Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies	CUA	Canada	2021a	Yes
Canadian Urological Association best practice report: Prostate-specific membrane antigen positron emission tomography/ computed tomography (PSMA PET/CT) and PET/magnetic resonance (MR) in prostate cancer	CUA	Canada	2021b	No
2021 Canadian Urological Association (CUA)-Canadian Uro-Oncology Group (CUOG) guideline: Management of castration-resistant prostate cancer (CRPC)	CUA	Canada	2021c	No
Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer. Guideline 27-2 version 2	CCO	Canada	2021	No
A Canadian framework for managing prostate cancer during the COVID-19 pandemic: Recommendations from the Canadian Urologic Oncology Group and the Canadian Urological Association	CUA	Canada	2020a	No
Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer	CUA	Canada	2020b	Yes
Local prostate cancer. Clinical Practice Guideline GU-012 – Version 3	CCA	Canada	2020a	No
Advanced/Metastatic prostate cancer. Clinical Practice Guideline GU-010 – Version 2	CCA	Canada	2020b	No
Prostate Cancer Part 1: Diagnosis and Referral in Primary Care	BC	Canada	2020a	No
Prostate Cancer Part 2: Follow-up in Primary Care	BC	Canada	2020b	Yes
An Endorsement of the 2018 Guideline on Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline	CCO	Canada	2018	No
Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management. Evidence-Based Series 17-3 Version 2	CCO	Canada	2017a	No
Follow-up Care for Survivors of Prostate Cancer - Clinical Management: a Program in Evidence-Based Care Systematic Review and Clinical Practice Guideline	CCO	Canada	2017b	No
Canadian Urological Association recommendations on prostate cancer screening and early diagnosis	CUA	Canada	2017	No
Multiparametric magnetic resonance imaging for pre-treatment local staging of prostate cancer: A Cancer Care Ontario clinical practice guideline	CCO	Canada	2016a	No
Bone Health and Bone-Targeted Therapies for Prostate Cancer. Guideline 3-14 Version 2	CCO	Canada	2016b	Yes
Prostate cancer, 2015.	CCA	Canada	2015	No
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of urothelial cancer	SITC	USA	2021	No
Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update	ASCO	USA	2021	No

Advanced prostate cancer: AUA-ASTRO-SUO guideline	AUA-ASTRO-SUO	USA	2020	No
Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline	ASCO	USA	2020	No
Prostate cancer: NCCN Clinical Practice Guidelines in Oncology	NCCN	USA	2019a	No
Prostate cancer early detection. NCCN Clinical Practice Guidelines in Oncology	NCCN	USA	2019b	No
Incontinence after Prostate Treatment: AUA/SUFU Guideline (2019)	AUA-SUFU	USA	2019	No
Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline	ASTRO-AUA	USA	2019	No
Prostate cancer prevention and early detection.	ACS	USA	2019	No
Castration-resistant prostate cancer	AUA	USA	2018	No
Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement	USPSTF	USA	2018	No
Early detection of prostate cancer: AUA guideline	AUA	USA	2018	No
Clinically Localized Prostate Cancer: ASCO Clinical Practice Guideline Endorsement	ASCO	USA	2018	Yes
ASTRO/ASCO/AUA Guideline on Hypofractionation for Localized Prostate Cancer	ASTRO-ASCO-AUA	USA	2018	No
American Joint Committee on Cancer. Prostate	AJCC	USA	2017	No
Clinically Localized Prostate Cancer: AUA-ASTRO-SUO Guideline.	AUA-ASTRO-SUO	USA	2017	Yes
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 3.	NCCN	USA	2016	No
Radiotherapy for recurrent prostate cancer: 2018 Recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group	FROGG	Australia and New Zealand	2018	No
Clinical practice guidelines: PSA Testing and Early Management of Test-Detected Prostate Cancer	PCFA	Australia and New Zealand	2016	No
AUGE Clinical Guidelines. Prostate cancer in patients over 15 years old.	MSC	Chile	2015	No
Prostate cancer. Risk factors, early detection and PSA: screening, use and correct interpretation	AMUC	Costa Rica	2018	No
Prostate cancer diagnosis and treatment. Clinical practice guidelines.	IMSS	Mexico	2018	No
Clinical practice guideline: prostate cancer	AUNA	Peru	2019	No
Clinical practice guideline for the screening, diagnosis and treatment of localized and locally advanced prostate cancer	IETSI	Peru	2021	No
Clinical Practice Guideline for the early detection, diagnosis, staging, treatment, rehabilitation and follow-up of patients with prostate cancer.	INEN	Peru	2021	No

Name of the Consensus Statement	Entity	Country	Year	No
Update of Guidelines for Management of Prostate Cancer in West Africa 2019: Consensus Working Document.	WA	West Africa	2019	No
NCCN Asia Consensus Statement prostate cancer	NCCN	Asia	2018	No
Chinese Expert Consensus on the Diagnosis and Treatment of Castration-Resistant Prostate Cancer (2019 Update)	CEC	China	2019	No
Consensus statements on the management of clinically localized prostate cancer from the Hong Kong Urological Association and the Hong Kong Society of Uro-Oncology	HKUA-HKSUO	China	2019	No
Expert Group Consensus Opinion on Prostate Cancer Diagnosis and Management in India	Consensus	India	2020	No
Guidance for the assessment and management of prostate cancer treatment induced bone loss. A consensus position statement from an expert group	Expert group	UK	2020	Yes
Canadian consensus forum of key controversial areas in the management of advanced prostate cancer	GURC	Canada	2021	No
Current topics in radiotherapy for genitourinary cancers: Consensus statements of the Genitourinary Radiation Oncologists of Canada	GUROC	Canada	2020	No
Canadian consensus algorithm for erectile rehabilitation following prostate cancer treatment	CUA	Canada	2018	No
Cancer Care Ontario Position Statement on Prostate Cancer Screening using the Prostate-Specific Antigen (PSA) Test	CCO	Canada	2017	No
Second-Line Hormonal Therapy for Men With Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: ASCO Provisional Clinical Opinion	ASCO	USA	2017	No
Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017.	PPCCC	USA	2017	No
Management of patients with advanced prostate cancer: APCCC consensus conference	APCCC	International	2019	No

The guidelines are presented divided by type of document (CPGs or CSs), continent, country, and year. The complete names of the entities (abbreviations) are available in Supplementary Table S2. [1] Presence of any recommendation regarding body weight or lifestyle in the document.

Table 2. Characteristics of the clinical practice guidelines (CPGs) and consensus statements (CSs) on prostate cancer regarding assessment or recommendations on obesity and healthy lifestyles.

Characteristics	N	%
Total sample	97	100.0
Obesity, body mass index or weight are considered as risk factors for prostate cancer in the guideline	11	11.3
Lifestyle factors are considered as risk factors for prostate cancer in the guideline	15	15.5
Obesity, body mass index or weight are considered as prognostic factors for prostate cancer in the guideline	5	5.2
Lifestyle factors are considered as prognostic factors for prostate cancer in the guideline	7	7.2
Recommendations on reaching or maintaining a healthy weight are provided within the guideline	7	7.2
Recommendations on reaching or maintaining healthy lifestyle habits are provided within the guideline	13	13.4
Recommendations on healthy diet are provided within the guideline	9	9.3
Recommendations on physical activity are provided within the guideline	10	10.3

Table 3. Characteristics of the clinical practice guidelines (CPGs) and consensus statements (CSs) stratified by the presence of recommendations on obesity or healthy lifestyle.

Characteristics	Total (n = 97)	Presence of recommendations (n = 13)	Absence of recommendations (n = 84)	P-value [1]
	N (%)	N (%)	N (%)	
Year of publication				0.668
Published in 2018 or after	35 (36.1)	9 (14.5)	53 (85.5)	
Published before 2018	62 (63.9)	4 (11.4)	31 (88.6)	
Type of document				0.689
CPGs	84 (86.6)	12 (14.3)	72 (85.7)	
CSs	13 (13.4)	1 (7.7)	12 (92.3)	
Continent				
European guidelines	35 (36.1)	6 (17.1)	29 (82.9)	0.537
North American guidelines	40 (41.2)	5 (12.5)	35 (87.5)	0.827
South American guidelines	6 (6.2)	0 (0.0)	6 (100.0)	0.594
Asian guidelines	12 (12.4)	2 (16.7)	10 (83.3)	0.723
Publication in a journal				
Published in a journal	45 (46.4)	6 (13.3)	39 (86.7)	1.000
Not published in a journal	52 (53.6)	7 (13.5)	45 (86.5)	
Focus of the guideline[2]				
Diagnostic guidelines	45 (46.4)	6 (13.3)	39 (86.7)	0.985
Therapeutic guidelines	78 (80.4)	12 (15.4)	66 (84.6)	0.246

[1] P-value of chi-square test or Fisher exact test, when appropriate. [2] Diagnostic and treatment guidelines account for more than 100% as several documents were both diagnostic and treatment guidelines.

4. Discussion

We present a thorough systematic review including CPGs and CSs regarding prostate cancer diagnosis and treatment from 2015 to 2021 with no language restrictions. We found that acknowledgment and recommendations on healthy weight and lifestyle for PC patients were very infrequent, regardless of the type of document, year of publication and country. We surprisingly found a high quantity of guidelines (n = 97), most of them on the same topics, suggesting that it may exists a redundancy in prostate cancer guidelines.

Several studies have proved that obesity and other lifestyles such as healthy diet or physical exercise are both risk factors for being diagnosed of PC [66] and prognostic factors once the diagnosis is established [8,9]. Therefore, the World Cancer Research Fund [10] and the World Health Organization [67] have included obesity as an important factor to be controlled for improving PC risk or prognosis. Importantly, PC-specific mortality, all-cause mortality and biochemical recurrence have been reported to be increased in obese patients [8,9]; therefore, current studies are focused on testing programs for reaching and maintaining healthy weight after PC diagnosis [16-19]. There are also multiple agencies including the Prostate Cancer Foundation, Mayo Clinic and multiple patient advocacy groups that make recommendations on healthy lifestyle for PC patients. Nevertheless, as proved in this study, PC guidelines throughout the world poorly cover recommendations on this important aspect. As healthy lifestyles also improve different outcomes such as cardiovascular events [68], chronic diseases [69] and overall survival [8] it seems evident that recommendations on this topic should be reinforced from clinicians and official guidelines for all PC patients.

Specifically, guideline developers should include appropriate professionals (e.g., nutritional therapists or experts in adapted physical exercise) and patient representatives as proper members in guidelines panels, to ensure that nutritional and healthy lifestyle topics are included into the prioritized guideline questions. It is also advisable to perform scoping exercises at the beginning of guideline development to make sure that all aspects of health related to PC are properly covered. Also, clinicians and healthcare professionals that contact with PC patients should use our data to reinforce recommendations regarding weight loss and healthy lifestyles. As according to the recommendations summarized in Supplementary Table S5, PC patients should be counseled regarding the importance of modifiable health-related behaviors or risk factors, such as smoking and obesity, through healthy diet, toxic habits, and physical exercise assessment and counselling [32]. This is specially recommended, as according to evidence-based data, for patients under androgen-deprivation therapies [33] and for patients that receive surgical treatment (i.e., prostatectomy), where obesity has been more clearly associated with poorer prognosis [32].

It is important to note that different recommendations might be individualized according to the disease stage. For example, behavioral interventions regarding vegetable consumption have not proven to decrease cancer progression at early stages [70]. In this regard, several clinical trials are being developed to analyze the impact of weight loss interventions in patients with clinically localized PC [71]. A recent systematic review on the MARTINI-Lifestyle cohort also pointed that the adherence to lifestyle recommendations is very poor in PC patients [72]. However, this adherence has proven to reduce mortality in several types of cancer [73]. For PC, preclinical and observational studies have identified potential benefits for high vegetable, low fat, low meat diets, and increased exercise, but Level I evidence is still limited [74]. Therefore, randomized clinical trials are still needed to inform specific recommendations for PC patients, considering the stage of the disease and the most appropriate intervention.

Another important aspect for future research is to add information on the perspectives and values of patients through qualitative research, to optimize the design of healthy lifestyle interventions that better adhere to patients' possibilities and perspectives.

A key strength of our study was the global perspective, including guidelines from all the countries caught in our search, with almost a hundred documents included. No restriction to specific languages, data sources or type of documents were considered. For documents different from English or Spanish (mother tongue of the researchers), we tried

to contact with a pertinent researcher of our center but, when this situation was not possible, we used a free translator software. This could imply a limitation given that the translator software may present mistakes. A perceived limitation of the study was the difficulties in finding documents with languages different from English, French, Spanish, German or Chinese. We tried to minimize this issue by duplicating data extraction through two independent reviewers. An important limitation of this study is that no specific tool for evaluating the presence of recommendations in clinical guidelines was available; therefore, we analyzed its presence manually through extensive reading of the selected documents, and we used the tool AGREE-II for evaluating the quality of the guidelines that covered weigh loss or lifestyle recommendations. We did not prospectively register the protocol of this systematic review.

We found that only a seventh of all PC guidelines recommended to adopt healthy lifestyles and only a 7.2% provided advice on reaching or maintaining healthy weight, despite the current evidence regarding its usefulness. Our data suggest that professional societies and governments should update their guidelines and documents regarding PC and include recommendations on healthy lifestyles after diagnosis. Clinicians from Oncology, Urology and Primary Care should advice their PC patients to reach and maintain healthy weight through recommendations on diet and adapted physical activity, according to the patients' preferences. Future studies should provide reflections or data on how to systematically introduce weigh loss or healthy lifestyle programs for improving PC prognosis.

5. Conclusions

Recommendations on healthy weight or lifestyles are very infrequently provided in PC clinical guidelines from professional societies or governments, regardless of the date of publication, type of document or country. Nevertheless, current literature indicates that healthy weight and lifestyles improve PC risk and prognosis. Future clinical trials should be developed for informing the best lifestyle intervention to each PC patient, considering the disease stage. Therefore, there may not be a standard recommendation but different approaches depending on the patient's disease state, lipid profile, genetics, or other unknown variables. PC guidelines should be updated to cover this important issue. Future strategies or intervention programs to reach and maintain a healthy weight should be designed for improving PC care.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: PRISMA 2020 Checklist, Table S2: Data sources and search strategy, Table S3: Identified clinical guidelines and consensus statements not published in a journal.

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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. Schatten, H. Brief Overview of Prostate Cancer Statistics, Grading, Diagnosis and Treatment Strategies. *Adv. Exp. Med. Biol.* **2018**, *1095*, 1–14.
3. 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.
4. 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.
5. Davies, N.M.; Gaunt, T.R.; Lewis, S.J.; Holly, J.; Donovan, J.L.; Hamdy, F.C.; Kemp, J.P.; Eeles, R.; Easton, D.; Kote-Jarai, Z.; et al. The effects of height and BMI on prostate cancer incidence and mortality: a Mendelian randomization study in 20,848 cases and 20,214 controls from the PRACTICAL consortium. Cancer Causes Control. 2015, 26, 1603–1616.
6. Vidal, A.C.; Howard, L.E.; Moreira, D.M.; Castro-Santamaria, R.; Andriole, G.L. Jr.; Freedland, S.J. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. *Cancer Epidemiol Biomarkers Prev*. **2014**, 23, 2936–2942.
7. Chau, C.H.; Till, C.; Price, D.K.; Goodman, P.J.; Neuhouser, M.L.; Pollak, M.N.; Thompson, I.M.; Figg, W.D. Serum markers, obesity and prostate cancer risk: results from the prostate cancer prevention trial. *Endocr Relat Cancer*. **2022**, 20, 99–109.
8. Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Pérez-Gómez, B.; Sánchez, M.J.; Khan, K.S.; Jiménez-Moleón, J.J. Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients. *Cancers (Basel)*. **2021**, *13*, 4169.
9. Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Arrabal-Polo, M.Á.; Pérez-Gómez, B.; Jiménez-Moleón, J.J. Obesity and biochemical recurrence in clinically localised prostate cancer: a systematic review and meta-analysis of 86,490 patients. *Prostate Cancer Prostatic Dis*. **2022**.
10. 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 15 November 2021).
11. Han, H.; Cao, Z.; Qin, Y.; Wei, X.; Ruan, Y.; Cao, Y.; He, J. Morbid obesity is adversely associated with perioperative outcomes in patients undergoing robot-assisted laparoscopic radical prostatectomy. *Can. Urol. Assoc. J.* **2020**, *14*, E574–E581.
12. Bardhi, O.; Garcia-Zapirain, B.; Nuño-Solinis, R. Factors influencing care pathways for breast and prostate cancer in a hospital setting. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7913.
13. Porcaro, A.B.; Tafuri, A.; Sebben, M.; Processali, T.; Pirozzi, M.; Amigoni, N.; Rizzetto, R.; Shakir, A.; Cerruto, M.A.; Brunelli, M.; et al. High body mass index predicts multiple prostate cancer lymph node metastases after radical prostatectomy and extended pelvic lymph node dissection. *Asian J Androl*. **2020**, 22, 323–329.
14. Lean, M.E. Prognosis in obesity. *BMJ* **2005**, *330*, 1339–1340.
15. Ortega-Loubon, C.; Fernández-Molina, M.; Singh, G.; Correa, R. Obesity and its cardiovascular effects. *Diabetes Metab. Res. Rev.* **2019**, 35, e3135.
16. Wilson, R.L.; Shannon, T.; Calton, E.; Galvão, D.A.; Taaffe, D.R.; Hart, N.H.; Lyons-Wall, P.; Newton, R.U. Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Sur. Oncol.* **2020**, *35*, 182–188.
17. Hamilton-Reeves, J.M.; Johnson, C.N.; Hand, L.K., Bechtel, M.D.; Robertson, H.L.; Michel, C.; Metcalf, M.; Chalise, P.; Mahan, N.J.; Mirza, M.; et al. Feasibility of a weight management program tailored for overweight men with localized prostate cancer – a pilot study. *Nutr. Cancer* **2020**, 1–16.
18. Freedland, S.J.; Allen, J.; Jarman, A.; Oyekunle, T.; Armstrong, A.J.; Moul, J.W.; Sandler, H.M.; Posadas, E.; Levin, D.; Wiggins, E.; et al. A Randomized Controlled Trial of a 6-Month Low-Carbohydrate Intervention on Disease Progression in Men with Recurrent Prostate Cancer: Carbohydrate and Prostate Study 2 (CAPS2). *Clin. Cancer Res.* **2020**, *26*, 3035–3043. Erratum in: *Clin. Cancer Res.* **2021**, *27*, 1823.
19. van Rooijen, S.; Carli, F.; Dalton, S.; Thomas, G.; Bojesen, R.; Le Guen, M.; Barizien, N.; Awasthi, R.; Minnella, E.; Beijer, S.; et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer* **2019**, *19*, 98.
20. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 71.
21. Osaghae, S.O. Update of Guidelines for Management of Prostate Cancer in West Africa 2019: Consensus Working Document. *West Afr. J. Med.* **2020**, *37*, 159–172.
22. Hinotsu, S.; Namiki, M.; Ozono, S.; Akaza, H. NCCN Asia Consensus Statement prostate cancer. *Jpn. J. Clin. Oncol.* **2018**, *48*, 964–965.
23. Chinese guidelines for diagnosis and treatment of prostate cancer 2018 (English version). *Chin. J. Cancer Res.* **2019**, *31*, 67–83.
24. Zhu Y, Ye D; Expert Group. Chinese Expert Consensus on the Diagnosis and Treatment of Castration-Resistant Prostate Cancer (2019 Update). *Cancer Manag. Res.* **2020**, *12*, 2127–2140.
25. Ma, W.K.; Poon, D.M.; Chan, C.K.; Chan, T.W.; Cheung, F.Y.; Ho, L.Y.; Lee, E.K.; Leung, A.K.; Leung, S.Y.; So, H.S.; et al. Consensus statements on the management of clinically localized prostate cancer from the Hong Kong Urological Association and the Hong Kong Society of Uro-Oncology. *BJU Int.* **2019**, *124*, 221–241.

26. Ghose, A.; Khochikar, M.; Sabnis, R.; Parmar, N.M. Expert Group Consensus Opinion on Prostate Cancer Diagnosis and Management in India. *Korean J. Urol. Oncol*. **2020**, *18*, 170–182.
27. Kakehi Y, Sugimoto M, Taoka R; committee for establishment of the evidenced-based clinical practice guideline for prostate cancer of the Japanese Urological Association. Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition). *Int. J. Urol.* **2017**, *24*, 648–666.
28. Kim, I.H.; Shin, S.J.; Kang, B.W.; Kang, J.; Kim, D.; Kim, M.; Kim, J.Y.; Kim, C.K.; Kim, H.J.; Maeng, C.H.; et al. 2020 Korean guidelines for the management of metastatic prostate cancer. *Korean J. Intern. Med.* **2021**, *36*, 491–514.
29. Singapore Cancer Network. Genitourinary Cancer Workgroup. Singapore Cancer Network (SCAN) Guidelines for the Management of Advanced Castrate-Resistant Prostate Cancer. *Ann. Acad. Med. Singap.* **2015**, *44*, 397–405.
30. Aljubran, A; Abusamra, A.; Alkhateeb, S.; Alotaibi, M.; Rabah, D.; Bazarbashi, S.; Alkushi, H.; Al-Mansour, M.; Alharbi, H.; Eltijani, A.; et al. Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for prostate cancer 2017. *Urol. Ann.* **2018**, *10*, 138–145.
31. Mottet, N.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur. Urol.* **2021**, *79*, 243–262.
32. Cornford P, van den Bergh RCN, Briers E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur. Urol*. **2021**, *79*, 263–282.
33. Parker, C.; Castro, E.; Fizazi, K.; Heidenreich, A.; Ost, P.; Procopio, G.; Tombal, B.; Gillessen, S.; ESMO Guidelines Committee. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2020**, *31*, 1119–1134.
34. Mottet, N.; Bellmunt, J.; Bolla, M.; Briers, E.; Cumberbatch, M.G.; De Santis, M.; Fossati, N.; Gross, T.; Henry, A.M.; Joniau, S.; Lam, T.B.; et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur. Urol.* **2017**, *71*, 618–629.
35. Rozet, F.; Mongiat-Artus, P.; Hennequin, C.; Beuzeboc, P.; Cormier, L.; Fromont-Hankard, G.; Mongiat-Artus, P.; Ploussard, G.; Mathieu, R.; Brureau, L.; et al. Recommandations françaises du Comité de cancérologie de l'AFU – actualisation 2020–2022: cancer de la prostate [French ccAFU guidelines - update 2020-2022: prostate cancer] [published correction appears in *Prog. Urol.* **2021**, *31*, 381–382]. Prog Urol. **2020**, *30*, S136–S251.
36. González Del Alba, A.; Méndez-Vidal, M.J.; Vazquez, S.; Castro, E.; Climent, M.A.; Gallardo, E.; Gonzalez-Billalabeitia, E.; Lorente, D.; Maroto, J.P.; Arranz, J.A. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). *Clin. Transl. Oncol*. **2021**, *23*, 969–979.
37. Cassinello, J.; Arranz, J.Á.; Piulats, J.M.; Sánchez, A.; Pérez-Valderrama, B.; Mellado, B.; Climent, M.Á.; Olmos, D.; Carles, J.; Lázaro, M. SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017). *Clin. Transl. Oncol.* **2018**, *20*, 57–68.
38. Brown, J.E.; Handforth, C.; Compston, J.E.; Cross, W.; Parr, N.; Selby, P.; Wood, S.; Drudge-Coates, L.; Walsh, J.S.; Mitchell, C.; et al. Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group. *J. Bone Oncol.* **2020**, *25*, 100311.
39. Tikkinen, K.A.O.; Dahm, P.; Lytvyn, L.; Heen, A.F.; Vernooij, R.W.M.; Siemieniuk, R.A.C.; Wheeler, R.; Vaughan, B.; Fobuzi, A.C.; Blanker, M.H.; et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ*. **2018**, *362*, k3581.
40. Chin, J.; Rumble, R.B.; Kollmeier, M.; Heath, E.; Efstathiou, J.; Dorff, T.; Berman, B.; Feifer, A.; Jacques, A.; Loblaw, D.A. Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. *J. Clin. Oncol.* **2017**, *35*, 1737–1743.
41. Saad, F.; Hotte, S.J.; Finelli, A.; Malone, S.; Niazi, T.; Noonan, K.; Shayegan, B.; So, A.I.; Danielson, B.; et al. Results from a Canadian consensus forum of key controversial areas in the management of advanced prostate cancer: Recommendations for Canadian healthcare providers. *Can. Urol. Assoc. J.* **2021**, 10.5489/cuaj.7347.
42. Kokorovic, A.; So, A.I.; Serag, H.; French, C.; Hamilton, R.J.; Izard, J.P.; Nayak, J.G.; Pouliot, F.; Saad, F.; Shayegan, B.; et al. Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies [published correction appears in *Can. Urol. Assoc. J.* **2021**, *15*, E383]. *Can. Urol. Assoc. J.* **2021**, *15*, E307–E322.
43. Shaygan, B.; Zukotynski, K.; Bénard, F.; Ménard, C.; Kuk, J.; Sistani, G.; Bauman, G.; Veit-Haibach, P.; Metser, U. Canadian Urological Association best practice report: Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) and PET/magnetic resonance (MR) in prostate cancer. *Can. Urol. Assoc. J*. **2021**, *15*, 62–72.
44. Saad, F.; Aprikian, A.; Finelli, A.; Fleshner, N.E.; Gleave, M.; Kapoor, A.; Niazi, T.; North, S.A.; Pouliot, F.; Rendon, R.A.; et al. 2021 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) guideline: Management of castration-resistant prostate cancer (CRPC) [published correction appears in *Can. Urol. Assoc. J.* **2021**, *15*, E304]. *Can. Urol. Assoc. J*. **2021**, *15*, E81–E90.
45. Kokorovic, A.; So, A.I.; Hotte, S.J.; Black, P.C.; Danielson, B.; Emmenegger, U.; Finelli, A.; Niazi, T.; Pouliot, F.; Shayegan, B.; et al. A Canadian framework for managing prostate cancer during the COVID-19 pandemic: Recommendations from the Canadian Urologic Oncology Group and the Canadian Urological Association. *Can. Urol. Assoc. J.* **2020**, *14*, 163–168.
46. So, A.I.; Chi, K.N.; Danielson, B.; Fleshner, N.E.; Kapoor, A.; Niazi, T.; Pouliot, F.; Rendon, R.A.; Shayegan, B.; Sridhar, S.; et al. Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer. *Can. Urol. Assoc. J.* **2020**, *14*, 17–23.

47. Morgan, S.C.; Morton, G.C.; Berlin, A.; Cheung, P.; Chung, P.; Ménard, C.; Pickles, T.; Souhami, L.; Warde, P.R.; Lukka, H.R. Current topics in radiotherapy for genitourinary cancers: Consensus statements of the Genitourinary Radiation Oncologists of Canada. *Can. Urol. Assoc. J.* **2020**, *14*, E588–E593.
48. Elterman, D.S.; Petrella, A.R.; Walker, L.M.; Van Asseldonk, B.; Jamnicky, L.; Brock, G.B.; Elliott, S.; Finelli, A.; Gajewski, J.B.; Jarvi, K.A.; et al. Canadian consensus algorithm for erectile rehabilitation following prostate cancer treatment [published online ahead of print, 2018]. *Can. Urol. Assoc. J.* **2018**, *13*, 239–245.
49. Rendon, R.A.; Mason, R.J.; Marzouk, K.; Finelli, A.; Saad, F.; So, A.; Violette, P.D.; Breau, R.H. Canadian Urological Association recommendations on prostate cancer screening and early diagnosis. *Can. Urol. Assoc. J.* **2017**, *11*, 298–309.
50. Loblaw, A.; Souter, L.H.; Canil, C.; Breau, R.H.; Haider, M.; Jamnicky, L.; Morash, R.; Surchin, M.; Matthew, A. Follow-up Care for Survivors of Prostate Cancer - Clinical Management: a Program in Evidence-Based Care Systematic Review and Clinical Practice Guideline. *Clin. Oncol. (R. Coll. Radiol.)* **2017**, *29*, 711–717.
51. Salerno, J.; Finelli, A.; Morash, C.; Morgan, S.C.; Power, N.; Schieda, N.; Haider, M.A. Multiparametric magnetic resonance imaging for pre-treatment local staging of prostate cancer: A Cancer Care Ontario clinical practice guideline. *Can. Urol. Assoc. J.* **2016**, *10*, E332–E339.
52. Galsky, M.D.; Balar, A.V.; Black, P.C.; Campbell, M.T.; Dykstra, G.S.; Grivas, P.; Gupta, S.; Hoimes, C.J.; Lopez, L.P.; Meeks, J.J.; et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of urothelial cancer. *J. Immunother. Cancer* **2021**, *9*, e002552.
53. Virgo, K.S.; Rumble, R.B.; de Wit, R.; Mendelson, D.S.; Smith, T.J.; Taplin, M.E.; Wade, J.L. 3rd.; Bennett, C.L.; Scher, H.I.; Nguyen, P.L.; et al. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update. *J. Clin. Oncol.* **2021**, *39*, 1274–1305.
54. Saylor, P.J.; Rumble, R.B.; Tagawa, S.; Eastham, J.A.; Finelli, A.; Reddy, P.S.; Kungel, T.M.; Nissenberg, M.G.; Michalski, J.M. Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline. *J. Clin. Oncol*. **2020**, *38*, 1736–1743.
55. Mohler, J.L.; Antonarakis, E.S.; Armstrong, A.J.; D'Amico, A.V.; Davis, B.J.; Dorff, T.; Eastham, J.A.; Enke, C.A.; Farrington, T.A.; Higano, C.S.; et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Canc. Netw.* **2019**, *17*, 479–505.
56. Sandhu, J.S.; Breyer, B.; Comiter, C.; Eastham, J.A.; Gomez, C.; Kirages, D.J.; Kittle, C.; Lucioni, A.; Nitti, V.W.; Stoffel, J.T.; et al. Incontinence after Prostate Treatment: AUA/SUFU Guideline. J Urol 2019;202:369-78.
57. Pisansky, T.M.; Thompson, I.M.; Valicenti, R.K.; D'Amico, A.V.; Selvarajah, S. Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline Amendment 2018-2019. *J. Urol.* **2019**, *202*, 533–538.
58. US Preventive Services Task Force; Grossman, D.C.; Curry, S.J.; Owens, D.K.; Bibbins-Domingo, K.; Caughey, A.B.; Davidson, K.W.; Doubeni, C.A.; Ebell, M.; Epling, J.W. Jr.; et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement [published correction appears in JAMA **2018**, *319*, 2443]. JAMA. **2018**, *319*, 1901–1913.
59. Bekelman, J.E.; Rumble, R.B.; Chen, R.C.; Pisansky, T.M.; Finelli, A.; Feifer, A.; Nguyen, P.L.; Loblaw, D.A.; Tagawa, S.T.; Gillessen, S.; 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*, 3251–3258.
60. Morgan, S.C.; Hoffman, K.; Loblaw, D.A.; Buyyounouski, M.K.; Patton, C.; Barocas, D.; Bentzen, S.; Chang, M.; Efstathiou, J.; Greany, P.; et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline. *Pract. Radiat. Oncol.* **2018**, *8*, 354–360.
61. Amin, M.B.; Greene, F.L.; Edge, S.B.; Compton, C.C.; Gershenwald, J.E.; Brookland, R.K.; Meyer, L.; Gress, D.M.; Byrd, D.R.; Winchester, D.P. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J. Clin.* **2017**, *67*, 93–99.
62. Virgo, K.S.; Basch, E.; Loblaw, D.A.; Oliver, T.K.; Rumble, R.B.; Carducci, M.A.; Nordquist, L.; Taplin, M.E.; Winquist, E.; Singer, E.A. Second-Line Hormonal Therapy for Men With Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion [published correction appears in J. Clin. Oncol. **2017**, *35*, 2591] [published correction appears in *J. Clin. Oncol.* **2017**, *20*, 35, 4096]. *J. Clin. Oncol.* **2017**, *35*, 1952–1964.
63. Giri, V.N.; Knudsen, K.E.; Kelly, W.K.; Abida, W.; Andriole, G.L.; Bangma, C.H.; Bekelman, J.E.; Benson, M.C.; Blanco, A.; Burnett, A.; et al. Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. *J. Clin. Oncol.* **2018**, *36*, 414-–424.
64. Lieng, H.; Hayden, A.J.; Christie, D.R.H.; Davis, B.J.; Eade, T.N.; Emmett, L.; Holt, T.; Hruby, G.; Pryor, D.; Shakespeare, T.P.; et al. Radiotherapy for recurrent prostate cancer: 2018 Recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group. *Radiother. Oncol.* **2018**, *129*, 377–386.
65. Gillessen, S.; Attard, G.; Beer, T.M.; Beltran, H.; Bjartell, A.; Bossi, A.; Briganti, A.; Bristow, R.G.; Chi, K.N.; Clarke, N.; et al. Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur. Urol.* **2020**, *77*, 508–547.
66. Bandini, M.; Gandaglia, G.; Briganti, A. Obesity and prostate cancer. *Curr. Opin. Urol.* **2017**, *27*, 415–421.
67. World Health Organisation. Recommendations for preventing cancer. Available online: https://who.int/dietphysicalactivity/publications/trs916/en/gsfao_cancer.pdf (consulted on 15 November 2021).
68. Csige, I.; Ujvárosy, D.; Szabó, Z.; Lórincz, I.; Paragh, D.; Harangi, M.; Somodi, S. The impact of obesity on the cardiovascular system. *J Diabetes Res.* **2018**, *2018*, 3407306.

69. Lavie, C.J.; De Schutter, A.; Archer, E.; McAuley, P.A.; Blair, S.N. Obesity and prognosis in chronic diseases – impact of cardiorespiratory fitness in the obesity paradox [published correction appears in *Curr Sports Med Rep*. **2014**, *13*, 349]. *Curr Sports Med Rep*. **2014**, *13*, 240–245.
70. Parsons, J.K.; Zahrieh, D.; Mohler, J.L.; Paskett, E.; Hansel, D.E.; Kibel, A.S.; Liu, H.; Seisler, D.K.; Natarajan, L.; White, M.; et al. Effect of a Behavioral Intervention to Increase Vegetable Consumption on Cancer Progression Among Men With Early-Stage Prostate Cancer: The MEAL Randomized Clinical Trial. *JAMA*. **2020**, *323*, 140–148.
71. 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.
72. Thederan, I.; Chandrasekar, T.; Tennstedt, P.; Kuehl, L.; Sorbe C,: Tilki, D.; Augustin, M.; Heinzer, H.; Zyriax, B.C. Poor Adherence to International Cancer Prevention Recommendations Among Patients With Prostate Cancer: First Results From the MARTINI-Lifestyle Cohort. *Eur Urol Focus*. **2020**, *6*, 935–940.
73. Kohler, L.N.; Garcia, D.O.; Harris, R.B.; Oren, E.; Roe, D.J.; Jacobs, E.T. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*. **2016**, *25*, 1018–1028.
74. Ballon-Landa, E.; Parsons, J.K. Nutrition, physical activity, and lifestyle factors in prostate cancer prevention. *Curr Opin Urol*. **2018**, *28*, 55–61.

STUDY 2. OBESITY AS A RISK FACTOR FOR PROSTATE CANCER MORTALITY: A SYSTEMATIC REVIEW AND DOSE-RESPONSE META-ANALYSIS OF 280,199 PATIENTS.

Rivera-Izquierdo M, Pérez de Rojas J, Martínez-Ruiz V, Pérez-Gómez B, Sánchez MJ, Khan KS, Jiménez-Moleón JJ. Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients. *Cancers*. 2021;13(16):4169. doi: 10.3390/cancers13164169. Impact Factor (2020): 6.639, position 51/242 in Oncology; T1, Q1.

This study, aimed to address the objectives 2, 3, 4 and 5 for the association between obesity and mortality (both prostate cancer-specific mortality and all-cause mortality) in patients diagnosed with prostate cancer, has been published in *Cancers*.

Appendices 6, 7, 8, 9, 10 and 11 correspond to Supplementary Tables S2, S3, S4, S5, S6 and S7 of the manuscript, respectively.

cancers

MDPI

Systematic Review

Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients

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Simple Summary: Results from individual studies on the association between obesity and prostate cancer mortality remain inconclusive; additionally, several large cohort studies have recently been conducted. We aimed to systematically review all available evidence and synthetize it using meta-analytic techniques. The results of our study showed that obesity was associated with prostate cancer specific mortality and all-cause mortality. The temporal association was consistent with a dose-response relationship. Our results demonstrated that obesity, a potentially modifiable prognostic factor, was associated with higher prostate cancer mortality. This study improved the evidence regarding the potential impact of lifestyle on improving prostate cancer prognosis. Strategies aimed at maintaining normal, or reducing abnormal, body mass index in diagnosed prostate cancer patients might improve survival. These results should guide urologists, oncologists, patients, policy-makers and primary care providers with respect to evidence-based practice and counselling concerning lifestyle changes after prostate cancer diagnosis.

Abstract: The aim of this study was to systematically review all evidence evaluating obesity as a prognostic factor for PC mortality. Cohort and case-control studies reporting mortality among PC patients stratified by body mass index (BMI) were included. The risk of mortality among obese patients (BMI $\geq$ 30) was compared with the risk for normal weight (BMI < 25) patients, pooling individual hazard ratios (HR) in random-effects meta-analyses. Reasons for heterogeneity were assessed in subgroup analyses. Dose-response associations for BMI per 5 kg/m^2 change were assessed. Among 7278 citations, 59 studies (280,199 patients) met inclusion criteria. Obesity was associated with increased PC-specific mortality (HR: 1.19, 95% CI: 1.10–1.28, I^2: 44.4%) and all-cause mortality (HR: 1.09, 95% CI: 1.00–1.18, I^2: 43.9%). There was a 9% increase (95% CI: 5–12%, I^2: 39.4%) in PC-specific mortality and 3% increase (95% CI: 1–5%, I^2: 24.3%) in all-cause mortality per 5 kg/m^2 increase in BMI. In analyses restricted to the higher quality subgroup (NOS $\geq$ 8), obesity was associated with increased PC-specific mortality (HR: 1.24, 95% CI: 1.14–1.35, I^2: 0.0%) and maintained the dose-response relationship (HR: 1.11 per 5 kg/m^2 increase in BMI, 95% CI: 1.07–1.15, I^2: 26.6%). 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; outcomes; causation

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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 [9–11], 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 [2,7,8,13–24] 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.

We systematically reviewed all observational evidence that examined whether obesity influences mortality of PC patients and formally evaluated the dose-response relationship using meta-analytic techniques.

2. Materials and Methods

We used a prospective protocol registered in PROSPERO (CRD420202146000) [26]. The review team was composed of methodologists, investigators and researchers from public health, epidemiology, and urology specialties. For reporting, both Meta-analysis of Observational Studies in Epidemiology (MOOSE) [27] and the 2020 update of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [28] guidelines (Table S1) were followed.

2.1. Search Strategy and Study Selection Criteria

We searched Medline, Web of Science and Scopus from database inception prior to April 1, 2021, with no language restrictions. We used the following search terms: "prostat* cancer", "prostat* neoplasm" or "prostat* tumor" to search the population and combined it with relevant terms to the outcome "mortality", "death", "prognos*" or "survival" and exposure "obes*" or "body mass index" or "BMI" or "weight" (Table S2). We included studies with obesity (BMI $\geq$ 30) or BMI as continuous variable as exposure and mortality in PC patients as outcome (either PCSM, ACM or both) evaluated through observational analytical design (cohort and case-control). When the same cohort was reported more than once, we only considered the most recent study with the largest sample size for quantitative analyses. We excluded studies that assessed the risk of obesity on PC diagnosis with no prognostic evaluation or that did not provide sufficient data on mortality, as well as abstracts, case reports, reviews, and animal studies. When reported data were insufficient, we contacted the authors to include all available information. Studies reporting BMI only as a continuous variable were included in the synthesis. After electronic searches, we performed a manual search based on the reference lists from the selected studies and relevant reviews. Two independent reviewers (M.R.-I. and J.P.d.R.) conducted the search by screening titles and abstracts. Full text of potentially eligible studies was also assessed by two reviewers, and relevant information was retrieved. Potential disagreements were discussed and resolved with a third reviewer (J.J.J-M.).

2.2. Data Extraction and Quality Assessment

We used predesigned data extraction forms to collect information on authors, year of publication, study setting and design, population, median follow-up, exposures, outcomes, type of analysis and presence of conflicts of interests within all the selected studies. When a citation or article was written in a language different to English or Spanish, the evaluation involved the input of colleagues competent in that language. The methodological quality of the studies was evaluated independently by two researchers (MRI and JPD). Using the nine-star Newcastle-Ottawa Scale (NOS) [29], risk of bias regarding selection, comparability, and outcome (for cohort studies) or exposure (for case-control studies) were formally evaluated. Scores of 8 or more stars were considered as low risk of bias (high quality), and 6 to 7 stars were considered as having medium risk of bias. Discrepancies were solved by discussion with a senior reviewer (J.J.J.-M.) and consensus of all authors.

2.3. Exposure and Outcomes

Our main variable of exposure was obesity, either measured as body-mass-index equal or greater than 30 (BMI $\geq$ 30), compared with normal weight (BMI < 25) [30], or included as continuous BMI per 5 kg/m^2 for dose-response analysis. Timing of measurement of exposure was divided in two groups: studies that measured BMI before or after the diagnosis. Waist circumference, waist-to-hip ratio and weight change were also extracted, however, given the small number of studies (<5), these exposures were not synthesized. The outcomes explored were PCSM and ACM.

2.4. Data Synthesis

As the outcome was relatively rare, the odds ratios (OR) and relative risks (RR) were considered as approximations of hazard ratios (HR), as recommended in previous analyses [9]. Forest plots were generated using PC patient survival data (HR and 95% CI) from the selected studies, as commonly reported in prognostic meta-analyses [9,31]. If a study provided risk estimates for PCSM and other-cause deaths, a risk estimate for ACM was calculated. If a study did not provide a summary estimate for the cohort and only reported estimations of subgroups of populations, the study was not included in the analysis. Normal weight (BMI < 25) represented the reference category for all the comparisons except when BMI was analyzed as a continuous variable.

We reported pooled HR and 95% CIs using a random-effects model to allow for unexplained heterogeneity across studies [32]. Heterogeneity was assessed through Q heterogeneity tests and I^2 statistic. We compared the odds of prostate cancer specific mortality and all-cause mortality in the following groups: obesity (BMI $\geq$ 30) versus normal weight, as primary result, and abnormal weight (BMI $\geq$ 25) or overweight (BMI $\geq$ 25 and <30) versus normal weight as secondary outcomes. We also assessed association by an increase of 5 kg/m^2 in BMI as the quantitative variable for dose-response association. When the study did not provide this estimation, it was calculated using the method of Greenland and Longnecker [33].

We undertook subgroup analyses planned a priori to detect differences based on the following factors: study quality according to NOS, level of the evidence according to the Quality Rating Schemes for Studies and Other Evidence, modified from the Oxford Centre for Evidence-based Medicine for ratings of individual studies [34], country, country development according to the International Monetary Fund, sample size, year of publication, moment of BMI measurement (before or after diagnosis), population setting, stage and treatment. Temporality was established in cohort studies that properly measured BMI according to NOS (directly measured by the researchers or collected from clinical histories or databases), around the time of PC diagnosis and conducted a median or mean follow-up $\geq$ 5 years (high quality according to NOS evaluation). The association of overweight (BMI $\geq$ 25 and <30) and abnormal weight (BMI $\geq$ 25) compared with normal weight (BMI < 25) with PCSM, and ACM was assessed as secondary analyses. Sensitivity analysis was performed by excluding studies that presented high risk of bias in the sub-

group analyses. Funnel plots for potential publication bias and small-study effect were evaluated. Asymmetry was assessed using Egger's regression test [35]. All statistical tests were 2-sided using a significance level of $p < 0.05$. All analyses were performed using the Review Manager ® from Cochrane Library and Stata (StataCorp®), version 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX, USA).

3. Results

Of the 7278 citations identified, we selected 107 abstracts for detailed eligibility assessment (Figure 1). A total of 59 analyses reported in 57 published articles including 5146,333 participants and 280,199 PC patients met our inclusion criteria [2,7,8,13–24,36–77]. Sample sizes ranged from 55 to 90,694 PC patients, with a median of 1442. Among them, 48 studies (81.4%) provided data on PCSM, 28 studies (47.5%) provided data on ACM, and 17 studies (28.8%) studies provided data on both outcomes.

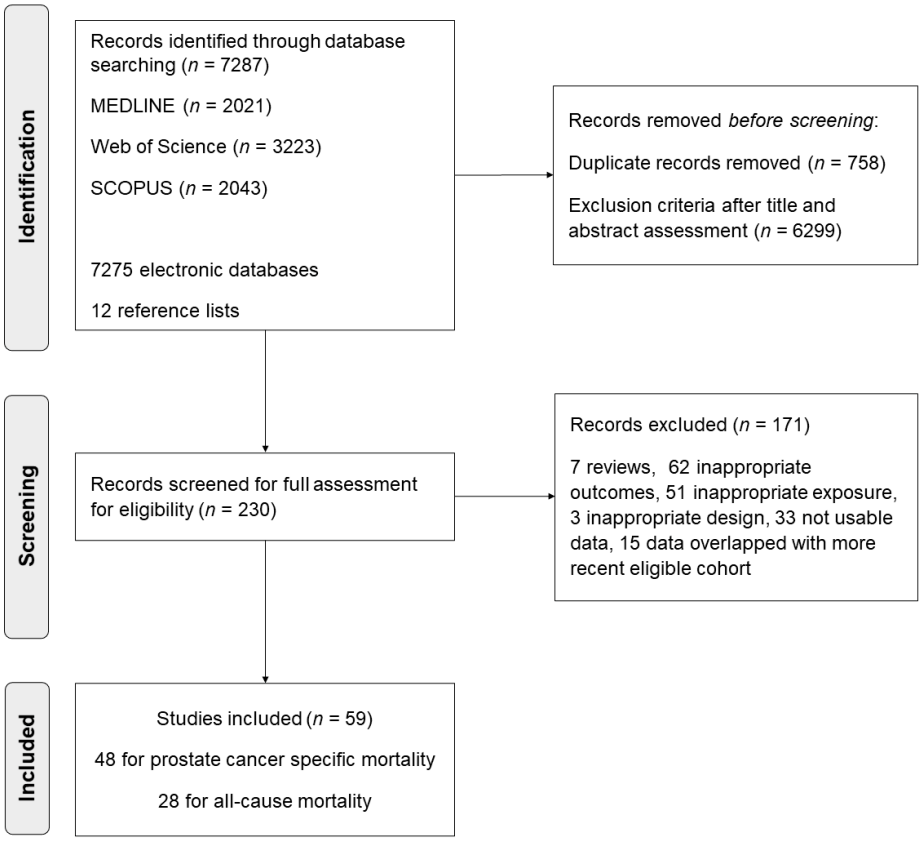

Figure 1. Study selection process in the systematic review and meta-analysis.

Of the 59 primary studies, 1 was a retrospective case-control study (1.7%) and 58 were cohort studies, of which 39 were prospective (67.2%) and 19 retrospective (32.8%). Data were obtained from population-based incident PC cohorts in 27 studies (45.8%), cohorts of incident PC among industry workers in 3 studies (5.1%), cohorts of patients after radical prostatectomy in 8 studies (13.6%), studies of patients with localized PC diagnosis in 9 cohorts (15.3%) and of patients with advanced PC diagnosis in 10 cohorts (17.0%). One study was conducted in African-Caribbean ancestry patients and 1 study was conducted in PC patients receiving androgen-deprivation therapy. Only 5 studies (8.5%) reported financial interests or potential conflicts of interest. Regarding the exposure of interest, its operational definition varied among the selected studies. Therefore, 38 studies (64.4%) used the World Health Organization categories, considering overweight as BMI $\geq$ 25 and

< 30; and obesity as BMI ≥ 30, 15 studies (25.4%) used different categories and 6 studies (10.2%) only considered BMI as continuous variable. Seventeen (28.8%) of the studies were published in 2016 or later. BMI before diagnosis was assessed in 28 studies (47.5%), while BMI after diagnosis was assessed in 32 studies (54.2%). Detailed information on the 59 primary studies is available in Table S3.

The study quality captured by NOS regarding risk of bias in study selection, comparability of the cohorts and outcome assessment is summarized in Figure 2 and detailed in Table S4. The mean NOS score was 6.8 (median 7, range 3–9), 15 (25.4%) studies presented low risk of bias (8–9 stars) according to NOS, 36 (61.0%) studies presented medium risk of bias and 8 studies (13.6%) presented high risk of bias. The pooled associations of obesity, compared with normal weight, and continuous BMI with PCSM and with ACM are presented in Figures 3 and 4, respectively.

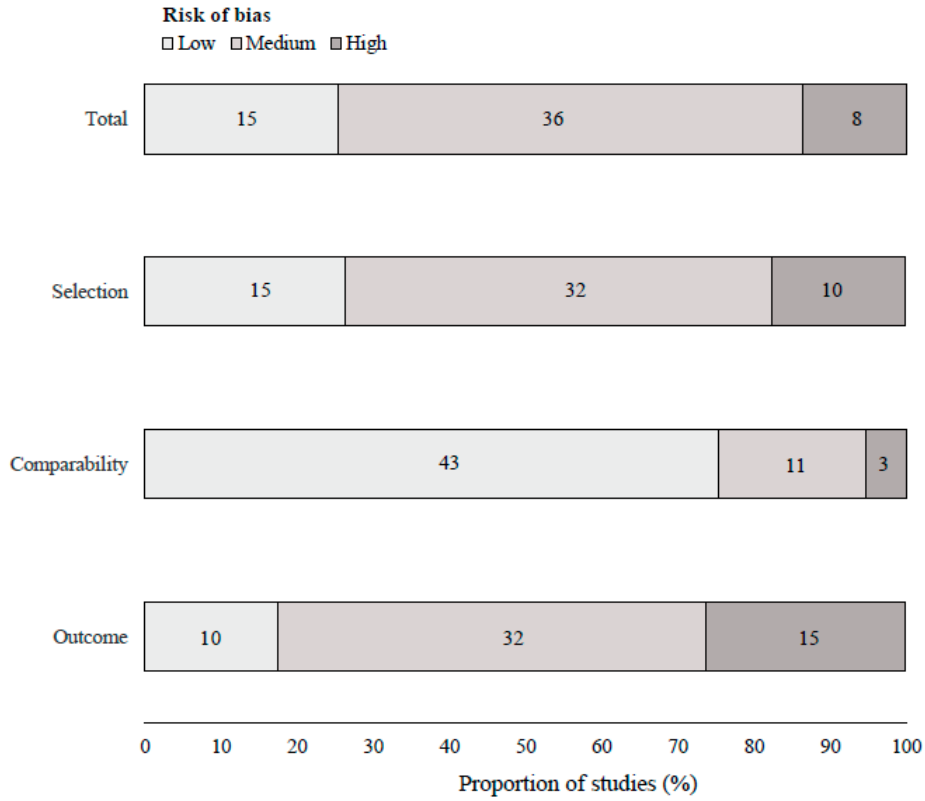

Figure 2. Newcastle-Ottawa Scale assessment of the cohort studies analyzing the association between obesity and mortality.

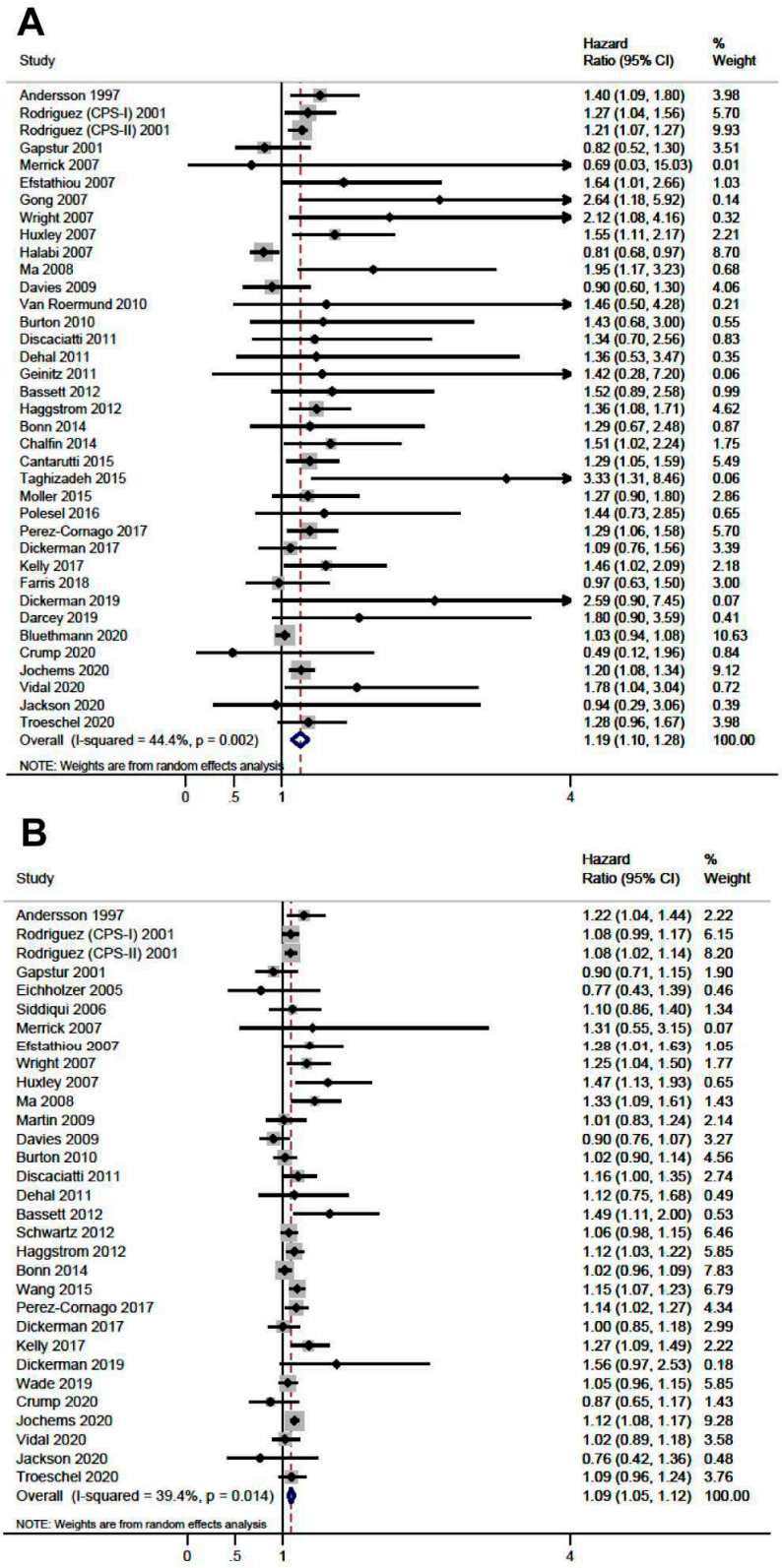

Figure 3. Forest plots of the association for prostate cancer specific mortality. (**A**) Obesity (body mass index $\geq$ 30 kg/m^2) compared to normal weight (body mass index < 25 kg/m^2). (**B**) Continuous body mass index per 5 kg/m^2 increment.

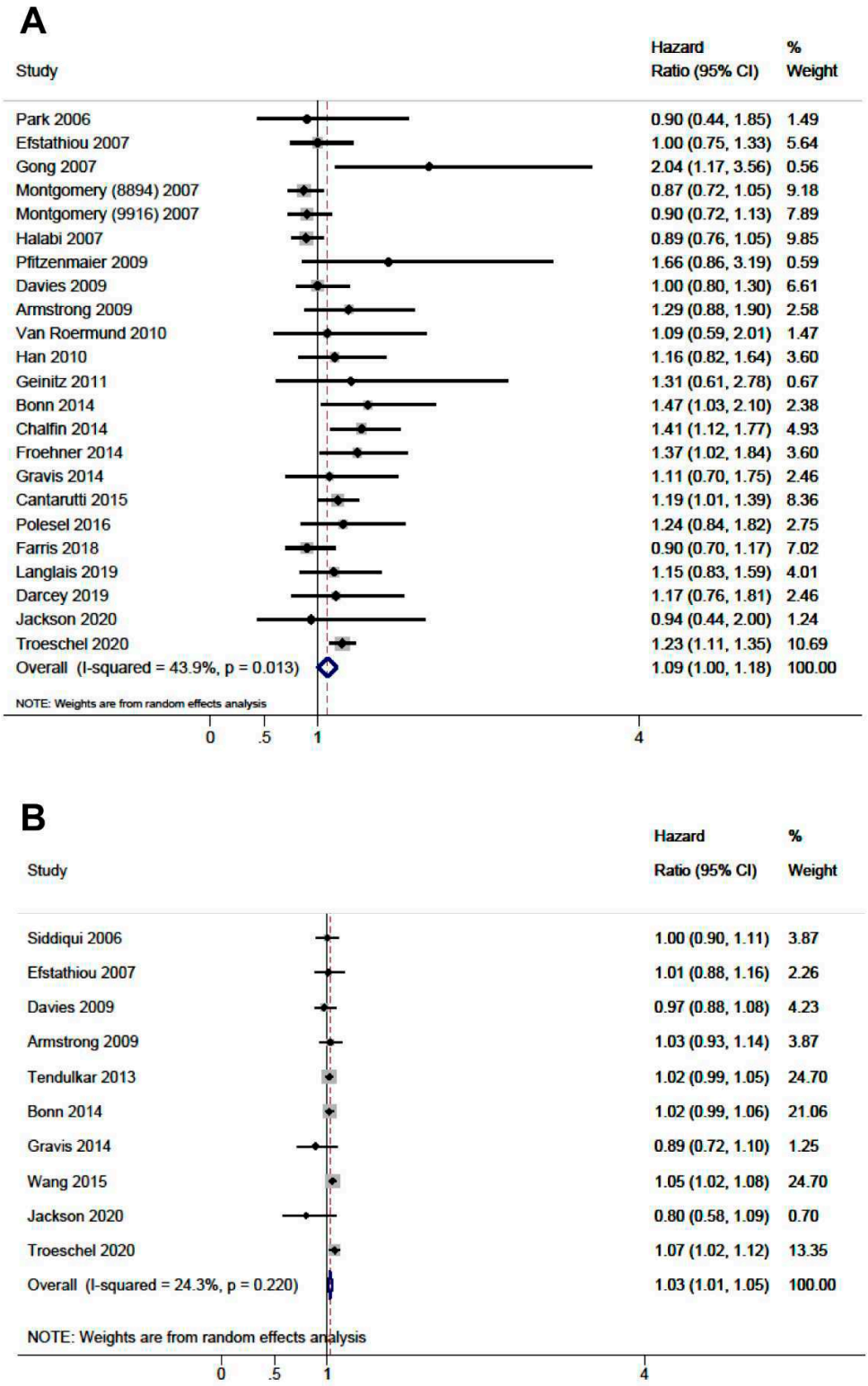

Figure 4. Forest plots of the association for all-cause mortality. (**A**) Obesity (body mass index $\geq$ 30 kg/m^2) compared to normal weight (body mass index < 25 kg/m^2). (**B**) Continuous body mass index per 5 kg/m^2 increment.

Obesity was associated with a greater hazard of PCSM (HR: 1.19, CI 95%: 1.10–1.28, I^2:44.4%) and ACM (HR: 1.09, CI 95%: 1.00–1.18, I^2:43.9%). A similar result was observed when we evaluated BMI as continuous variable, either with PCSM (HR per 5 kg/m^2: 1.09, CI 95%: 1.05–1.12, I^2: 39.4%) or with ACM (HR per 5 kg/m^2: 1.03, CI 95%: 1.01–1.05, I^2: 24.3%), suggesting a dose-response relationship. Table 1 presents the subgroup analyses based on population, stage, treatment, country, country status, quality of the evidence, risk of bias, causal criteria (detailed in Table S5), exposure measurement, and year of publication, and showed no significant differences between BMI strata. Heterogeneity was considerably reduced when stratified by population of origin and country, and when we restricted the analysis to high-quality studies according to NOS. Prospective cohort studies (HR: 1.19, 95% CI: 1.10–1.28, I^2:34.4%), high-quality studies according to NOS (HR: 1.24, 95% CI: 1.14–1.35, I^2:0.0%) and population-based cohorts (HR: 1.24, 95% CI: 1.18–1.31, I^2:0.0%) consistently showed a relationship between obesity and PCSM (Table 1). Regarding ACM, studies with higher quality according to NOS (8–9 stars) showed a positive association with obesity (HR: 1.46, 95% CI: 1.01–1.91, I^2:7.3%). The sensitivity analysis excluding lower quality studies did not show differences in the estimations of any comparison. The timing of measurements of BMI (prediagnosis or postdiagnosis) was a source of heterogeneity. Studies using prediagnosis BMI showed association between obesity and PCSM (HR: 1.23, 95% CI: 1.17–1.30, I^2:0.0%), but not with ACM (HR: 1.09, 95% CI: 0.98–1.18, I^2: 47.4%). In contrast, for postdiagnosis BMI, obesity was associated with ACM (HR: 1.20, 95% CI: 1.03–1.37, I^2:0.0%), but not with PCSM (HR. 1.07, 95% CI: 1.00–1.14, I^2: 48.5%). Studies that adjusted for cancer stage showed estimates of association similar to those that did not. The association of overweight and abnormal weight, assessed as secondary analyses, with PCSM and ACM is shown in Table S6. We did not observe evidence of small-studies effect for the analyzed outcomes in funnel plot analysis, except for obesity and PCSM where the funnel was truncated with small studies showing positive association missing (p-value of Egger test = 0.005; Table S7.

Table 1. Subgroup analysis of the pooled association of body mass index with prostate cancer specific mortality and all-cause mortality.

Subgroup	Prostate Cancer Specific Mortality						All-Cause Mortality					
	Obesity (BMI ≥ 30) Compared with Normal Weight (BMI < 25)			BMI Continuous Per 5 kg/m^2			Obesity (BMI > 30) Compared with Normal Weight (BMI < 25)			BMI Continuous Per 5 kg/m^2		
	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2
All Studies (Total)	37	1.19 (1.10–1.28)	44.3	31	1.09 (1.05–1.12)	44.3	23	1.09 (1.00–1.18)	43.9	10	1.03 (1.01–1.05)	24.3
Population												
Population-Based Incident PC	22	1.24 (1.18–1.31)	0.0	18	1.10 (1.07–1.14)	31.3	6	1.10 (0.92–1.28)	25.5	0	-	-
Industry Workers Incident PC	2	1.12 (0.55–1.68)	78.5	3	1.01 (0.74–1.27)	65.9	0	-	-	0	-	-
Radical Prostatectomy	2	1.58 (1.06–2.10)	0.0	2	1.04 (0.91–1.17)	0.0	5	1.29 (1.11–1.48)	0.0	1	1.00 (0.89–1.11)	-
Localized PC	8	1.04 (0.97–1.10)	0.0	6	1.05 (0.97–1.12)	55.3	5	1.20 (1.09–1.30)	0.0	4	1.04 (1.01–1.07)	39.3
Advanced PC	2	1.12 (0.33–1.91)	73.3	1	1.28 (0.97–1.59)	-	6	0.91 (0.83–1.00)	0.0	4	1.02 (0.99–1.05)	0.0
African-Caribbean Ancestry	1	0.94 (0.44–2.33)	-	1	0.76 (0.29–1.23)	-	1	0.94 (0.16–1.72)	-	1	0.80 (0.55–1.05)	-
Country												
USA	17	1.13 (1.00–1.28)	61.6	15	1.09 (1.04–1.14)	36.8	12	1.05 (0.93–1.17)	63.8	7	1.04 (1.02–1.05)	0.0
European Nordic Countries	9	1.22 (1.12–1.32)	0.0	9	1.08 (1.01–1.14)	45.5	2	1.22 (1.04–1.40)	0.0	1	1.02 (0.98–1.05)	-
European Central Countries	7	1.33 (1.14–1.53)	0.0	4	1.09 (1.01–1.17)	25.2	6	1.26 (1.02–1.50)	0.0	1	0.89 (0.70–1.08)	-
Other	4	1.51 (1.11–1.92)	0.0	3	1.25 (0.80–1.70)	68.9	3	1.04 (0.67–1.41)	0.0	1	0.80 (0.55–1.05)	-
Country status												
Developed Countries	35	1.18 (1.10–1.27)	45.2	29	1.09 (1.05–1.12)	36.6	22	1.09 (1.00–1.19)	46.3	9	1.03 (1.01–1.05)	8.4
Developing Countries	2	1.47 (0.98–1.97)	0.0	2	1.13 (0.43–1.82)	80.3	1	0.94 (0.44–2.00)	-	1	0.80 (0.55–1.05)	-
Exposure Measurement [1]												
Prediagnosis BMI	22	1.23 (1.17–1.30)	0.0	21	1.09 (1.06–1.13)	35.0	19	1.08 (0.98–1.18)	47.4	0	-	-
Postdiagnosis BMI	15	1.10 (0.96–1.23)	42.8	10	1.07 (1.00–1.14)	48.5	4	1.20 (1.03–1.37)	0.0	10	1.03 (1.01–1.05)	24.3
Quality of the Evidence [2]												
Level 2 (Prospective Cohort)	26	1.19 (1.10–1.28)	34.4	26	1.09 (1.05−1.13)	35.1	12	1.04 (0.92−1.16)	50.3	6	1.02 (0.98−1.07)	20.5
Level 3	11	1.27 (0.99−1.55)	57.5	5	1.08 (0.99−1.17)	61.5	11	1.17 (1.02−1.32)	40.0	4	1.03 (1.00−1.06)	46.2
Risk of Bias												
NOS: 8−9	9	1.24 (1.14−1.35)	0.0	12	1.11 (1.07−1.15)	26.6	2	1.46 (1.01−1.91)	7.3	1	1.05 (1.02−1.08)	-
NOS: 6−7	27	1.17 (1.07−1.27)	49.2	18	1.07 (1.02−1.12)	41.6	16	1.10 (1.01−1.20)	36.9	6	1.02 (0.98−1.06)	34.2
NOS <6	1	0.69 (0.03−15.03)	-	1	1.31 (0.55−3.15)	-	5	0.90 (0.80−1.07)	10.3	3	1.02 (0.99−1.05)	0.0
Design												
Cohort	36	1.19 (1.11–1.28)	45.9	30	1.09 (1.05–1.12)	39.1	22	1.09 (1.00–1.18)	43.9	9	1.03 (1.01–1.05)	8.4
Case-Control	1	0.94 (0.44–2.33)	-	1	0.79 (0.29–1.23)	-	1	0.94 (0.16–1.72)	-	1	0.80 (0.55–1.05)	-
Stage												
Adjustment for Stage	13	1.11 (0.95–1.27)	44.0	8	1.08 (1.01–1.16)	52.1	14	1.08 (0.95–1.21)	55.6	5	1.04 (1.01–1.07)	39.8
Not Adjustment for Stage	24	1.22 (1.16–1.29)	0.0	23	1.09 (1.05–1.13)	35.8	9	1.12 (1.00–1.23)	10.0	5	1.01 (0.99–1.04)	0.0
Year of Publication												
<2016	24	1.19 (1.10–1.28)	50.1	21	1.09 (1.05–1.12)	39.4	6	1.13 (0.99–1.27)	22.1	2	0.97 (0.71–1.22)	75.9
≥2016	13	1.15 (1.04–1.26)	28.9	10	1.08 (1.03–1.14)	35.4	17	1.08 (0.97–1.19)	42.4	8	1.03 (1.01–1.04)	0.0

BMI, body mass index; HR, hazard ratio; NOS, Newcastle-Ottawa scale; PC, prostate cancer. *p*-values of the table show the results from heterogeneity analyses of each subgroup. [1] Of the 28 studies evaluating prediagnosis BMI, 1 collected BMI one year before diagnosis [67], 1 measured BMI at 18 years old [14], and 26 collected BMI from retrospective sources or at recruitment and time from measurement to diagnosis was unreported. [2] Quality of the evidence according to the Quality Rating Schemes for Studies and Other Evidence, modified from the Oxford Centre for Evidence-based Medicine for ratings of individual studies [32].

4. Discussion

In this meta-analysis, compiling all available data for precise quantitative estimation of the prognostic effect of obesity in PC mortality, we found that BMI $\geq$ 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 $\geq$ 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 [78]. 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 [79], 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 (Table S3) 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 [79]. 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 (Table S5). 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 [80–82]. 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 [83]. Also, molecular mechanisms connecting obesity with PC and other urothelial cancers have been broadly established [84]. 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 [11,85] and to other outcomes related to PC, for instance, the presence of metastases [86]. Therefore, objectively, several criteria for causation were met.

The World Cancer Research Fund [87] reported an increased risk of being diagnosed with advanced PC in obese patients, although large studies have recently questioned this point [6,7]. Our findings provide strong evidence that obese men diagnosed with PC are more likely to have a worse prognosis. Not only does our review strengthen the prevailing hypothesis concerning the association between prediagnosis obesity and PCSM [9,11,80–82], it suggests an impact of postdiagnosis obesity on PC mortality outcomes. 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 [88,89]. Guidelines and patient information documents concerning PC would need to be updated to emphasize the role of obesity in prognosis.

5. 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.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cancers13164169/s1, Table S1: PRISMA checklist of the systematic review and meta-analysis, Table S2: Search strategy, Table S3: Main characteristics of the studies included in the systematic review of prognosis of prostate cancer with respect to obesity, Table S4: Methodological quality assessment of the selected studies according to Newcastle-Ottawa Scale, Table S5: Assessment of potential causation criteria for the association assessed in this systematic review, Table S6: Forest-plot of the associations between obesity (BMI $\geq$ 30), overweight (BMI < 30 and $\geq$25) and abnormal weight (BMI $\geq$ 25), compared to normal weight (BMI < 25), and continuous BMI per 5 units, on prostate cancer specific mortality and all-cause mortality, Table S7: Funnel plots of the pooled associations between obesity (BMI $\geq$ 30) and continuous BMI per 5 kg/m^2 with prostate cancer specific mortality and all-cause mortality.

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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. [CrossRef]
2. Fillon, M. Rates of advanced prostate cancer continue to increase. *CA Cancer J. Clin.* **2020**, *70*, 427–429. [CrossRef] [PubMed]
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. [PubMed]
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. [CrossRef]
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. [CrossRef] [PubMed]
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. [CrossRef] [PubMed]
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. [CrossRef]
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. [CrossRef] [PubMed]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef]
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. [CrossRef] [PubMed]
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. [CrossRef] [PubMed]
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. [CrossRef] [PubMed]
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. [CrossRef] [PubMed]
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. [CrossRef]

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. [CrossRef]
25. Hill, A.B. The environment and disease: Association or causation? *Proc. R. Soc. Med.* **1965**, *58*, 295–300. [CrossRef]
26. Rivera-Izquierdo, M.; Jiménez-Moleón, J.J. Is Obesity A Prognostic Factor for Prostate Cancer? A Systematic Review and Meta-Analysis of Analytic Studies. PROSPERO: International Prospective Register of Systematic Reviews 2020: CRD42020214600. Available online: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020214600 (accessed on 19 July 2021).
27. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **2000**, *283*, 2008–2012. [CrossRef] [PubMed]
28. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 71. [CrossRef] [PubMed]
29. Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 17 July 2021).
30. World Health Organization. Body Mass Index. Available online: https://www.who.int/data/gho/data/themes/theme-details/GHO/body-mass-index-(bmi) (accessed on 17 July 2021).
31. Riley, R.D.; Moons, K.G.M.; Snell, K.I.E.; Ensor, J.; Hooft, L.; Altman, D.G.; Hayden, J.; Collins, G.S.; Debray, T.P.A. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* **2019**, *364*, k4597. [CrossRef]
32. Riley, R.D.; Higgins, J.P.; Deeks, J.J. Interpretation of random effects metaanalyses. *BMJ* **2011**, *342*, d549. [CrossRef] [PubMed]
33. Greenland, S.; Longnecker, M.P. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am. J. Epidemiol.* **1992**, *135*, 1301–1309. [CrossRef]
34. Centre for Evidence-Based Medicine. Levels of Evidence. Available online: https://www.cebm.ox.ac.uk/resources/levels-of-evidence (accessed on 17 July 2021).
35. Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **1997**, *315*, 629–634. [CrossRef]
36. Polesel, J.; Gini, A.; Dal Maso, L.; Stocco, C.; Birri, S.; Taborelli, M.; Serraino, D.; Zucchetto, A. The impact of diabetes and other metabolic disorders on prostate cancer prognosis. *J. Diabetes Complicat.* **2016**, *30*, 591–596. [CrossRef]
37. Cushen, S.J.; Power, D.G.; Murphy, K.P.; McDermott, R.; Griffin, B.T.; Lim, M.; Daly, L.; MacEneaney, P.; O' Sullivan, K.; Prado, C.M.; et al. Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. *Clin. Nutr. ESPEN* **2016**, *13*, e39–e45. [CrossRef]
38. Fowke, J.H.; McLerran, D.F.; Gupta, P.C.; He, J.; Shu, X.O.; Ramadas, K.; Tsugane, S.; Inoue, M.; Tamakoshi, A.; Koh, W.P.; et al. Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium. *Am. J. Epidemiol.* **2015**, *182*, 381–389. [CrossRef]
39. Wang, L.S.; Murphy, C.T.; Ruth, K.; Zaorsky, N.G.; Smaldone, M.C.; Sobczak, M.L.; Kutikov, A.; Viterbo, R.; Horwitz, E.M. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. *Cancer* **2015**, *121*, 3010–3017. [CrossRef] [PubMed]
40. Cantarutti, A.; Bonn, S.E.; Adami, H.O.; Grönberg, H.; Bellocco, R.; Bälter, K. Body mass index and mortality in men with prostate cancer. *Prostate* **2015**, *75*, 1129–1136. [CrossRef] [PubMed]
41. Taghizadeh, N.; Boezen, H.M.; Schouten, J.P.; Schröder, C.P.; Elisabeth de Vries, E.G.; Vonk, J.M. BMI and lifetime changes in BMI and cancer mortality risk. *PLoS ONE* **2015**, *10*, e0125261. [CrossRef] [PubMed]
42. Mohammed, A.A.; El-Tanni, H.; Ghanem, H.M.; Farooq, M.U.; El Saify, A.M.; Al-Zahrani, A.S.; El-Shentenawy, A.; El-Khatib, H.M. Impact of body mass index on clinico-pathological parameters and outcome in patients with metastatic prostate cancer. *J. Egypt. Natl. Canc. Inst.* **2015**, *27*, 155–159. [CrossRef]
43. Møller, H.; Roswall, N.; Van Hemelrijck, M.; Larsen, S.B.; Cuzick, J.; Holmberg, L.; Overvad, K.; Tjønneland, A. Prostate cancer incidence, clinical stage and survival in relation to obesity: A prospective cohort study in Denmark. *Int. J. Cancer.* **2015**, *136*, 1940–1947. [CrossRef]
44. Bonn, S.E.; Wiklund, F.; Sjölander, A.; Szulkin, R.; Stattin, P.; Holmberg, E.; Grönberg, H.; Bälter, K. Body mass index and weight change in men with prostate cancer: Progression and mortality. *Cancer Causes Control* **2014**, *25*, 933–943. [CrossRef]
45. Chalfin, H.J.; Lee, S.B.; Jeong, B.C.; Freedland, S.J.; Alai, H.; Feng, Z.; Trock, B.J.; Partin, A.W.; Humphreys, E.; Walsh, P.C.; et al. Obesity and long-term survival after radical prostatectomy. *J. Urol.* **2014**, *192*, 1100–1104. [CrossRef]
46. Haque, R.; Van Den Eeden, S.K.; Wallner, L.P.; Richert-Boe, K.; Kallakury, B.; Wang, R.; Weinmann, S. Association of body mass index and prostate cancer mortality. *Obes. Res. Clin. Pract.* **2014**, *8*, e374–e381. [CrossRef]
47. Froehner, M.; Kellner, A.E.; Koch, R.; Baretton, G.B.; Hakenberg, O.W.; Wirth, M.P. A combined index to classify prognostic comorbidity in candidates for radical prostatectomy. *BMC Urol.* **2014**, *14*, 28. [CrossRef] [PubMed]
48. Gravis, G.; Boher, J.M.; Fizazi, K.; Joly, F.; Priou, F.; Marino, P.; Latorzeff, I.; Delva, R.; Krakowski, I.; Laguerre, B.; et al. Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. *Eur. Urol.* **2015**, *68*, 196–204. [CrossRef] [PubMed]

49. Tendulkar, R.D.; Hunter, G.K.; Reddy, C.A.; Stephans, K.L.; Ciezki, J.P.; Abdel-Wahab, M.; Stephenson, A.J.; Klein, E.A.; Mahadevan, A.; Kupelian, P.A.; et al. Causes of mortality after dose-escalated radiation therapy and androgen deprivation for high-risk prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2013**, *87*, 94–99. [CrossRef]
50. Bassett, J.K.; Severi, G.; Baglietto, L.; MacInnis, R.J.; Hoang, H.N.; Hopper, J.L.; English, D.R.; Giles, G.G. Weight change and prostate cancer incidence and mortality. *Int. J. Cancer* **2012**, *131*, 1711–1719. [CrossRef] [PubMed]
51. Schwartz, G.G.; Skinner, H.G. A prospective study of total and ionized serum calcium and time to fatal prostate cancer. *Cancer Epidemiol. Biomark. Prev.* **2012**, *21*, 1768–1773. [CrossRef]
52. Park, J.M.; Nam, J.S.; Na, W.; Oh, J.J.; Lee, S.; Hong, S.K.; Byun, S.S.; Lee, S.E. Prognostic value of body mass index in korean patients with castration-resistant prostate cancer. *Korean J. Urol.* **2012**, *53*, 761–765. [CrossRef]
53. Häggström, C.; Stocks, T.; Ulmert, D.; Bjørge, T.; Ulmer, H.; Hallmans, G.; Manjer, J.; Engeland, A.; Nagel, G.; Almqvist, M.; et al. Prospective study on metabolic factors and risk of prostate cancer. *Cancer* **2012**, *118*, 6199–6206. [CrossRef]
54. Discacciati, A.; Orsini, N.; Andersson, S.O.; Andrén, O.; Johansson, J.E.; Wolk, A. Body mass index in early and middle-late adulthood and risk of localised, advanced and fatal prostate cancer: A population-based prospective study. *Br. J. Cancer* **2011**, *105*, 1061–1068. [CrossRef]
55. Dehal, A.; Garrett, T.; Tedders, S.H.; Arroyo, C.; Afriyie-Gyawu, E.; Zhang, J. Body mass index and death rate of colorectal cancer among a national cohort of U.S. adults. *Nutr. Cancer* **2011**, *63*, 1218–1225.
56. Geinitz, H.; Thamm, R.; Mueller, T.; Jess, K.; Zimmermann, F.B.; Molls, M.; Nieder, C. Impact of body mass index on outcomes after conformal radiotherapy in patients with prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *81*, 16–22. [CrossRef]
57. Van Roermund, J.G.; Hinnen, K.A.; Battermann, J.J.; Witjes, J.A.; Bosch, J.L.; Kiemeney, L.A.; van Vulpen, M. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. *BJU Int.* **2010**, *105*, 42–48. [CrossRef]
58. Han, M.; Trock, B.J.; Partin, A.W.; Humphreys, E.B.; Bivalacqua, T.J.; Guzzo, T.J.; Walsh, P.C. The impact of preoperative erectile dysfunction on survival after radical prostatectomy. *BJU Int.* **2010**, *106*, 1612–1617. [CrossRef]
59. Burton, A.; Martin, R.; Galobardes, B.; Davey Smith, G.; Jeffreys, M. Young adulthood body mass index and risk of cancer in later adulthood: Historical cohort study. *Cancer Causes Control.* **2010**, *21*, 2069–2077. [CrossRef]
60. Martin, R.M.; Vatten, L.; Gunnell, D.; Romundstad, P.; Nilsen, T.I. Components of the metabolic syndrome and risk of prostate cancer: The HUNT 2 cohort, Norway. *Cancer Causes Control.* **2009**, *20*, 1181–1192. [CrossRef] [PubMed]
61. Pfitzenmaier, J.; Pritsch, M.; Haferkamp, A.; Jakobi, H.; Fritsch, F.; Gilfrich, C.; Djakovic, N.; Buse, S.; Pahernik, S.; Hohenfellner, M. Is the body mass index a predictor of adverse outcome in prostate cancer after radical prostatectomy in a mid-European study population? *BJU Int.* **2009**, *103*, 877–882. [CrossRef]
62. Davies, B.J.; Smaldone, M.C.; Sadetsky, N.; Dall'era, M.; Carroll, P.R. The impact of obesity on overall and cancer specific survival in men with prostate cancer. *J. Urol.* **2009**, *182*, 112–117. [CrossRef]
63. Armstrong, A.J.; Halabi, S.; de Wit, R.; Tannock, I.F.; Eisenberger, M. The relationship of body mass index and serum testosterone with disease outcomes in men with castration-resistant metastatic prostate cancer. *Prostate Cancer Prostatic Dis.* **2009**, *12*, 88–93. [CrossRef]
64. Ma, J.; Li, H.; Giovannucci, E.; Mucci, L.; Qiu, W.; Nguyen, P.L.; Gaziano, J.M.; Pollak, M.; Stampfer, M.J. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: A long-term survival analysis. *Lancet Oncol.* **2008**, *9*, 1039–1047. [CrossRef]
65. Merrick, G.S.; Galbreath, R.W.; Butler, W.M.; Wallner, K.E.; Allen, Z.A.; Adamovich, E. Obesity is not predictive of overall survival following permanent prostate brachytherapy. *Am. J. Clin. Oncol.* **2007**, *30*, 588–596. [CrossRef]
66. Efstathiou, J.A.; Bae, K.; Shipley, W.U.; Hanks, G.E.; Pilepich, M.V.; Sandler, H.M.; Smith, M.R. Obesity and mortality in men with locally advanced prostate cancer: Analysis of RTOG 85-31. *Cancer* **2007**, *110*, 2691–2699. [CrossRef] [PubMed]
67. Gong, Z.; Agalliu, I.; Lin, D.W.; Stanford, J.L.; Kristal, A.R. Obesity is associated with increased risks of prostate cancer metastasis and death after initial cancer diagnosis in middle-aged men. *Cancer* **2007**, *109*, 1192–1202. [CrossRef]
68. Montgomery, R.B.; Goldman, B.; Tangen, C.M.; Hussain, M.; Petrylak, D.P.; Page, S.; Klein, E.A.; Crawford, E.D.; Southwest Oncology Group. Association of body mass index with response and survival in men with metastatic prostate cancer: Southwest Oncology Group trials 8894 and 9916. *J. Urol.* **2007**, *178*, 1946–1951. [CrossRef] [PubMed]
69. Wright, M.E.; Chang, S.C.; Schatzkin, A.; Albanes, D.; Kipnis, V.; Mouw, T.; Hurwitz, P.; Hollenbeck, A.; Leitzmann, M.F. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer* **2007**, *109*, 675–684. [CrossRef] [PubMed]
70. Asia Pacific Cohort Studies Collaboration; Huxley, R.; Ansary-Mohaddam, A.; Huxley, R.; Barzi, F.; Lam, T.H.; Jamrozik, K.; Ohkubo, T.; Fang, X.; Sun, H.J. The impact of modifiable risk factors on mortality from prostate cancer in populations of the Asia-Pacific region. *Asian Pac. J. Cancer Prev.* **2007**, *8*, 199–205.
71. Halabi, S.; Ou, S.S.; Vogelzang, N.J.; Small, E.J. Inverse correlation between body mass index and clinical outcomes in men with advanced castration-recurrent prostate cancer. *Cancer* **2007**, *110*, 1478–1484. [CrossRef] [PubMed]
72. Siddiqui, S.A.; Inman, B.A.; Sengupta, S.; Slezak, J.M.; Bergstralh, E.J.; Leibovich, B.C.; Zincke, H.; Blute, M.L. Obesity and survival after radical prostatectomy: A 10-year prospective cohort study. *Cancer* **2006**, *107*, 521–529. [CrossRef]
73. Park, S.M.; Lim, M.K.; Shin, S.A.; Yun, Y.H. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. *J. Clin. Oncol.* **2006**, *24*, 5017–5024. [CrossRef]

74. Eichholzer, M.; Bernasconi, F.; Jordan, P.; Stähelin, H.B. Body mass index and the risk of male cancer mortality of various sites: 17-year follow-up of the Basel cohort study. *Swiss Med. Wkly.* **2005**, *135*, 27–33.
75. Rodriguez, C.; Patel, A.V.; Calle, E.E.; Jacobs, E.J.; Chao, A.; Thun, M.J. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. *Cancer Epidemiol. Biomark. Prev.* **2001**, *10*, 345–353.
76. Gapstur, S.M.; Gann, P.H.; Colangelo, L.A.; Barron-Simpson, R.; Kopp, P.; Dyer, A.; Liu, K. Postload plasma glucose concentration and 27-year prostate cancer mortality (United States). *Cancer Causes Control.* **2001**, *12*, 763–772. [CrossRef]
77. Andersson, S.O.; Wolk, A.; Bergström, R.; Adami, H.O.; Engholm, G.; Englund, A.; Nyrén, O. Body size and prostate cancer: A 20-year follow-up study among 135006 Swedish construction workers. *J. Natl. Cancer Inst.* **1997**, *89*, 385–389. [CrossRef]
78. 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. [CrossRef]
79. 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. [CrossRef] [PubMed]
80. 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. [CrossRef]
81. 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. [CrossRef] [PubMed]
82. 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. [CrossRef]
83. 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. [CrossRef] [PubMed]
84. 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. [CrossRef]
85. 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. [CrossRef] [PubMed]
86. Annett, S.; Moore, G.; Robson, T. Obesity and Cancer Metastasis: Molecular and Translational Perspectives. *Cancers* **2020**, *12*, 3798. [CrossRef]
87. 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).
88. 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. [CrossRef] [PubMed]
89. 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. [CrossRef] [PubMed]

STUDY 3. OBESITY AND BIOCHEMICAL RECURRENCE IN CLINICALLY LOCALIZED PROSTATE CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 86 490 PATIENTS.

Rivera-Izquierdo M, Pérez de Rojas J, Martínez-Ruiz V, Arrabal-Polo MA, Pérez-Gómez B, Jiménez-Moleón JJ. Obesity and biochemical recurrence in clinically localized prostate cancer: a systematic review and meta-analysis of 86 490 patients. *Prostate Cancer & Prostatic Diseases*. 2021. doi: 10.1038/s41391-021-00481-7. Impact Factor: 5.554, position 16/89 in Urology & Nephrology; T1, Q1.

This study, aimed to address objectives 2, 3, 4 and 5 for the association between obesity and biochemical recurrence in patients diagnosed with prostate cancer, has been published in *Prostate Cancer and Prostatic Diseases.*

Appendices 12, 13, 14, 15, and 16 of the Doctoral Thesis correspond to Supplementary Table 1, Supplementary Table 2, Supplementary Fig.1 and Supplementary Fig. 2 and Supplementary Table 3 of the manuscript.

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REVIEW ARTICLE

Obesity and biochemical recurrence in clinically localised prostate cancer: a systematic review and meta-analysis of 86,490 patients

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BACKGROUND: The association of obesity with biochemical recurrence (BCR) after treatment of clinically localised prostate cancer (PC) shows inconsistent results. Our aim was to systematically review all evidence evaluating obesity as a prognostic factor for BCR.
METHODS: We searched PubMed, Web of Science and Scopus, from inception to June 1, 2021. Cohort studies reporting BCR among PC patients stratified by body mass index (BMI) were included. To assess the quality of the selected studies, we used the Newcastle–Ottawa scale (NOS). Risk of BCR among obese patients (BMI ≥ 30 kg/m^2) was compared with normal weight (BMI < 25), pooling individual hazard ratios (HR) in random-effect meta-analysis. Associations for continuous BMI per 5 kg/m^2 were also calculated. Subgroup analyses were conducted to assess reasons for heterogeneity and causal criteria were formally evaluated.
RESULTS: We identified 46 cohort studies including 86,490 PC patients. A total of 14,719 (17.1%) patients developed BCR. There was no consistent definition of BCR. Obesity was associated with BCR (HR: 1.25, 95% CI: 1.11–1.39, I^2: 70.3%), and there was a 10% increase (95% CI: 4–15%, I^2: 66.3%) in BCR per 5 kg/m^2 increase in BMI. The heterogeneity was high but decreased in the subgroup of highest-quality NOS score and when the BMI was measured by the researchers (I^2: 0.0%). The association was consistent in patients receiving radical prostatectomy but not in patients receiving other therapies.
CONCLUSIONS: Obesity showed a moderate, consistent relationship with biochemical recurrence after radical prostatectomy. Measurement of BMI and BCR was variable, highlighting the need for standardised clinical guidelines. Preventive weight control programs may have a role in reducing BCR for clinically localised PC patients.

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INTRODUCTION

About 1,280,000 new cases of prostate cancer (PC) are diagnosed each year worldwide, representing the most diagnosed male malignancy [1]. From these cases, about 76.9% are clinically localised [2] and could require specific treatment such as radical prostatectomy (RP), external-beam radiation therapy or brachytherapy, among others, or even observational surveillance as a conservative strategy [3]. However, up to 27–53% of these cases progress to biochemical recurrence [4], a sign considered as treatment failure. To date, no clear modifiable prognostic factors are identified in the association between PC and BCR. Obesity, the second most common cause of preventable death [5], previously identified as a risk factor for prostate cancer mortality [6], merits evaluation as prognostic factor for biochemical recurrence.

Individual studies of the association between obesity and BCR show inconsistent results, including positive and negative findings. Several systematic reviews have been published about this topic [7–10]. Systematic synthesis of this association, when judged by AMSTAR 2 [11], show several weaknesses regarding adequate literature search, investigation of the potential sources of heterogeneity, evaluation of the risk of bias in stratified results, and reporting of financial relationship or conflicts of interest. Importantly, previous evidence syntheses did not formally evaluate causal criteria. Since the last complete meta-analysis with wide selection criteria [8], published in 2014, 15 prognostic studies have been published with data from 47,422 new clinically localised PC patients added to the total. So, the last review could access only 55% of the current body of evidence. After, a meta-analysis in 2015 [9] only included Asian PC patients. Finally, the last meta-analysis published in 2020 [10] only included eight studies regarding BCR. The authors analysed multiple outcomes with low specific search criteria. Therefore, there is a current need for a robust and reliable evaluation of the association of obesity on BCR in PC patients.

The aim of this study was to systematically review all observational available evidence to evaluate if obesity influences BCR in PC patients in longitudinal cohort studies, and to calculate summary estimates on this relationship using meta-analytic techniques.

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METHODS

We followed the recommendations for reporting systematic reviews and meta-analyses according to the 2020 update of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12] guidelines. The review team was composed by methodologists, researchers from public health, epidemiology, and urology specialties.

Search strategy and study selection

Medline, Web of Science, and Scopus were searched from inception to June 1, 2021, including studies in English, Spanish and French languages. We searched the terms "prostat* cancer" combined with relevant terms to the outcome "recurrence" or "failure" and the exposure "obesity" or "body max index" or "BMI" or "weight". We included cohort studies conducted on patients with clinically localised PC that provided original data on the relationship between body mass index (BMI) and BCR. When the same cohort or parts of it were reported more than once, we only included in the quantitative analyses the most recent data with the largest sample size. We included separately the information when data came from different populations (e.g., studies in patients treated with radical prostatectomy and studies in patients treated with radiation therapy). Data from studies that did not provide a summary estimate for the complete cohort and only reported estimations from subgroups of populations were discarded. Studies with other weight exposures different from BMI (e.g., weight change, waist circumference, etc.) or different design (e.g., case reports, reviews, animal studies…) were excluded. When the reported information was insufficient for analyses, we contacted the authors. After the electronic searches, a manual search was performed based on reference lists from the identified relevant reviews and the selected studies. Two reviewers (MR-I and JPD) conducted the search and screened titles and abstracts of each study. Assessment for eligibility by full-text review was independently done and relevant information was retrieved. Discrepancies were discussed and resolved by consensus with a third reviewer (JJJ-M).

Data extraction and quality assessment

Information on authors, year of publication, population, study design (prospective or retrospective cohort), setting, follow-up, treatment, exposure (BMI), outcome (BCR), adjustment covariates, quantitative results and presence of financial relationships or conflicts of interest of the selected studies were collected in predesigned data extraction forms. Articles written in a language different from English or Spanish were evaluated with the input of colleagues competent in those languages. The methodological quality of the studies was independently evaluated by two researchers (M-RI and JPD) using the Newcastle–Ottawa Scale (NOS) for cohort studies (range 1–9 stars) [13]. Therefore, the risk of bias regarding selection (four stars), comparability (two stars) and outcome assessment (three stars) was formally evaluated. High quality (low risk of bias) was considered in studies scoring ≥8 stars. Disagreements were solved by consensus of all authors after discussion with a senior reviewer (JJJ-M).

Exposure and outcome

The main exposure variable was obesity, measured as BMI ≥ 30 kg/m^2, compared with normal weight (BMI < 25 kg/m^2, reference category) according to the World Health Organisation boundaries [14]. When a study considered different boundaries (e.g., obesity as >27.5 kg/m^2), they were considered and separately approached in subgroup analyses. We also considered studies that provided quantitative measurement for BMI per 5 kg/m^2. The included studies collected BMI at any time. The outcome explored was BCR, either measured as prostatic specific antigen (PSA) levels after PSA nadir over a predefined threshold (PSA ≥ 0.1 ng/ml, PSA ≥ 0.2 ng/ml or PSA ≥ 0.4 ng/ml), two detectable consecutive PSA measures or specific increase in PSA, depending on each study. These operational definitions were dependent on the therapeutic procedure (e.g., radical prostatectomy or radiotherapy).

Data synthesis

We collected hazard ratios (HR) from the selected studies. Patient survival data (HR and 95% CI) from the selected cohort studies were represented in forest plots, as commonly performed in prognostic meta-analyses [15, 16]. In order to deal with unexplained heterogeneity across studies, we used a random-effects model for all the analyses [16]. Heterogeneity was assessed through Q tests and I^2 statistic. The odds of BCR were compared in the following groups of PC patients according to their BMI: obesity (BMI ≥ 30) vs. normal weight, as a primary result, and other BMI thresholds; abnormal weight (BMI ≥ 25) or overweight (BMI ≥ 25 and <30) vs. normal weight as secondary outcomes. We also analysed the association by an increase of 5 kg/m^2 of BMI; for studies that did not provide this data, we calculated the risk by 5 units increase when possible through the method of Greenland and Longnecker [17]. We performed a priori planned subgroup analyses in order to detect differences stratified by treatment received (radical prostatectomy, external-beam radiation therapy, brachytherapy or others); region (grouped in American, Asian, European and other countries); quality of the evidence according to the Quality Rating Schemes for Studies and Other Evidence modified from the Oxford Centre for Evidence-based Medicine for rating of individual studies [18] (prospective or retrospective cohort studies) as part of the causation assessment; [19] risk of bias according to NOS; BMI data source (measured by the researchers, collected from databases or clinical histories or self-reported); timing of BMI measurement, consideration of surgical margins in adjustments, and year of publication. Sensitivity analyses were performed by excluding individual studies with high risk of bias. Potential publication bias was assessed by evaluating the small-study effect [20]. Funnel plots were obtained, and asymmetry was assessed through Egger's regression test [21]. All statistical tests were two-sided using a significance level of $p < 0.05$. All analyses were performed using Stata (StataCorp®), version 15.0.

RESULTS

Figure 1 shows the flow chart of the study selection. Of the 5,490 citations identified, a total of 214 abstracts were selected for detailed eligibility. Inclusion criteria were met by 46 cohort studies [9, 22–66] including 86,490 PC patients and 14,719 (17.1%) of events (BCR, also referred to as treatment failure in some studies). Among them, 15 (32.6%) were prospective [24–26, 31, 36, 39, 46, 47, 54, 55, 57, 61, 62, 64, 66] and 31 (67.4%) were retrospective [9, 22, 23, 27–30, 32–35, 37, 38, 40–45, 48–53, 56, 58–60, 63, 65]. One study was conducted in African-Caribbean ancestry patients [32]. Only three (6.5%) studies reported financial relationships [39, 54, 61] and 10 (21.7%) did not include a conflict-of-interest disclosure statement [35, 40, 43, 48, 55, 62–66]. Detailed information on the 46 primary studies is shown in Table 1. Half of them were published after the last meta-analysis [8]. The included studies differed in the covariates used for multivariate analyses. Prognostic variables were included in most of them (e.g., Gleason score were considered in 84.8% of the studies).

Sample sizes of the included studies ranged from 90 to 13,218 PC patients, with a median of 927 patients. Regarding the treatment received by the participants, 34 studies (73.9%) analysed patients receiving radical prostatectomy; [9, 22–24, 26–30, 32–37, 39–50, 52, 57, 58, 60, 61, 64, 66] six studies (13.0%) followed patients receiving external beam radiation therapy; [38, 51, 56, 62, 63, 65] two studies (4.4%) evaluated patients treated with brachytherapy; [53, 59] one study (2.2%) assessed

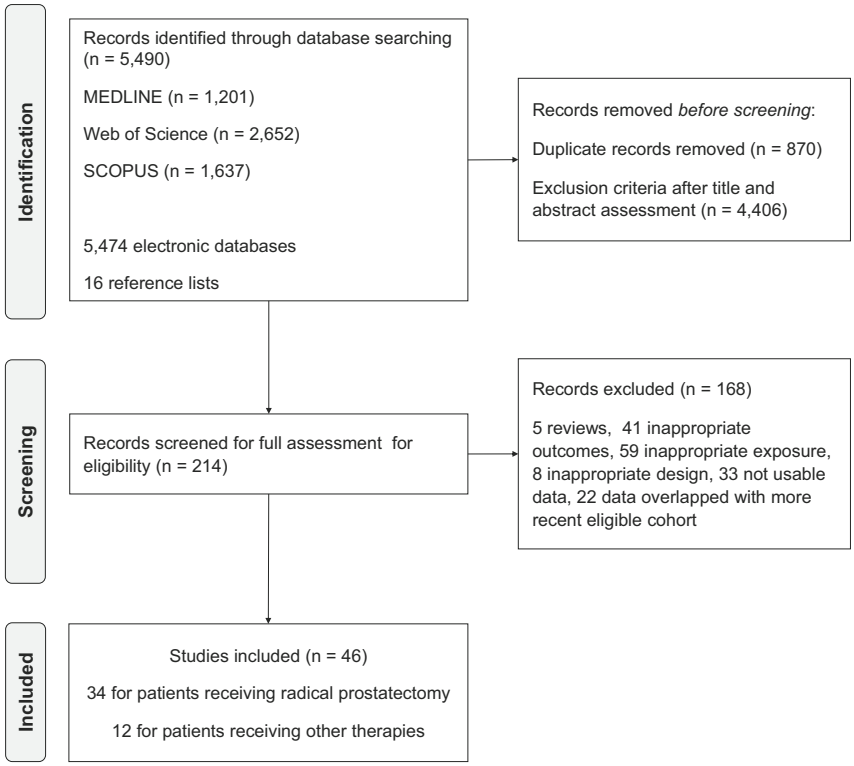

Fig. 1 Flow chart of the study selection of this systematic review and meta-analysis according to PRISMA guidelines (*n* = number of records).

patients receiving high intensity focused ultrasound; [55] and, finally, three studies (8.3%) included a mixture of patients receiving several of these treatments [25, 31, 54].

Regarding the exposure (BMI), its operational definition varied among the studies. Therefore, 33 (71.7%) studies used the WHO boundaries, considering obesity as BMI ≥ 30 and normal weight as BMI < 25, 8 (17.4%) studies used different categories [25, 27, 32, 38, 42, 48, 63, 65] (e.g., the cut-offs proposed by the International Association for the Study of Obesity and the International Obesity Task Force according to the disparity of BMI distribution in Asian-Pacific populations) [67] and five (10.9%) studies only reported BMI as continuous variable [9, 29, 41, 61, 62]. BMI was collected through clinical reports or databases in 29 (63.0%) studies, self-reported by the patients in seven (15.2%) studies [25, 31, 42, 49, 50, 61, 66] and directly measured by the researchers in 10 (21.7%) studies [9, 26, 30, 32, 37, 40, 47, 55, 60, 64]. All studies collected BMI at the time of diagnosis, except for three studies, which collected the exposure at age 21 [31], age 25 [66], and at age 50 years [25]. Regarding the outcome, 31 studies (67.4%) used PSA ≥ 0.2 ng/ml as cut-off for BCR, two studies (4.3%) used PSA ≥ 0.1 ng/ml, two studies (4.3%) used PSA ≥ 0.4 ng/ml, 10 studies (21.7%) used detectable PSA and need for salvage treatment and eight (17.4%) studies used increase in PSA after PSA nadir as measure for BCR, among others (specific measurements of each study can be consulted in Table 1).

The quality profile of the selected studies according to NOS regarding the risk of bias in the study selection, comparability of the cohorts, and outcome assessment is detailed in Supplementary Table 1. Globally, no study showed high risk of bias. The mean NOS score was 7.5 (median 7, range 6–9); 21 (45.7%) studies showed low risk of bias (8–9 stars) and 25 (54.3%) studies showed medium risk of bias. The most common problems identified were inadequacy of follow-up (69.6% of the studies) [9, 22–27, 29, 30, 32–39, 41–66] and lack of adjustment for age (34.8% of the studies) [28–30, 32, 33, 35, 41, 47, 48, 52, 54, 56, 57, 59, 63–66].

The forest plots of the pooled association of obesity vs. normal weight and continuous BMI with BCR, stratified by treatment, are presented in Fig. 2 and Fig. 3, respectively. Obesity (HR: 1.25, CI 95%: 1.11–1.39, I^2: 70.3%) and 5 kg/m^2 increase in BMI (HR: 1.10, 95% CI: 1.04–1.15, I^2: 66.3%) were associated with greater hazard of BCR. However, given the high heterogeneity showed through the I^2 statistic [68], subgroup analyses based on relevant stratification variables was performed, both for patients receiving radical prostatectomy (Table 2) and for all selected articles (Supplementary Table 2). Patients receiving radical prostatectomy showed a greater association between obesity and BCR (HR: 1.34, 95% CI: 1.18–1.49, I^2: 70.2%), while this association was not confirmed in patients receiving different treatments (external-beam radiation therapy, brachytherapy, or others). However, for these treatments, the number of studies was small. Regarding the source of BMI measurement, heterogeneity was low in the subgroup of studies in which BMI was directly measured by the researchers (HR: 1.65, 95% CI: 1.42–1.88, I^2: 0.0%). These corresponded to four studies conducted on patients receiving radical prostatectomy; three of them showed intermediate quality according to NOS (6-7 stars) [9, 30, 47] and 1 was assessed with nine stars (highest quality) [40]. This last study showed a hazard ratio of 1.48 (95% CI: 0.84–2.61) of BCR in obese patients. No important differences were shown regarding BMI boundaries, but studies using cut-offs different from the World Health Organisation showed a higher association between obesity and BCR (HR: 1.53, 95% CI: 1.22–1.83, I^2: 32.4%). The association was affected by the consideration of positive surgical margins in adjustments. Therefore, studies that did not include it in the models showed a higher association (HR: 1.70, 95% CI: 1.38–2.03, I^2: 70.2%) than studies adjusted for this variable (HR: 1.14, 95% CI: 1.02–1.26, I^2: 36.7%). Studies analysing obesity, conducted on patients receiving radical prostatectomy with high quality (NOS ≥ 8) showed low heterogeneity (HR: 1.08, 95% CI: 1.00–1.16, I^2: 6.1%) and so was observed for prospective cohort studies (HR: 1.31, 95% CI:

Table 1. Main characteristics of the cohort studies included in the systematic review of biochemical recurrence of clinically localised prostate cancer with respect to obesity.

Author, year	Country	Follow-up (years)	Design	PC patients (BCR)	Treatment	Definition of BCR (PSA measured as ng/ml)	Adjustment variables[a]	NOS
Vidal, [22]	USA	1990–2019 (7.4)[b]	Retrospective	5 929 (1 891)	RP	PSA > 0.2, 2 PSA = 0.2, or ST	1, 2, 4, 5, 6, 7, 9, 10, 16, 17	8
Leal-García, [23]	Mexico	Median (7.9)[b]	Retrospective	180 (75)	RP	2 consecutive PSA ≥ 0.4	7, 9, 10, 27	8
Langlais, [24]	USA	1995-2018 (4.5)[b]	Prospective	3 230 (685)	RP	2 consecutive PSA > 0.2 or ST	1, 2, 4, 5, 6, 19, 20, 28, 29	7
Khan, 2019	USA	2003–2010	Prospective	1 082 (131)	RP/EBRT	2 consecutive PSA > 0.2 (RP) or PSAn +≥2 (EBRT)	1, 19, 30	7
Wissing, [26]	Canada	2006–2013 (5.8)[b]	Prospective	1 714 (429)	RP	2 consecutive PSA > 0.2 or ST	1, 2, 4, 5, 6, 17, 31	7
Dong Yu, [27]	Korea	2006–2017 (3.3)[b]	Retrospective	2 997 (593)	RP	2 consecutive PSA ≥ 0.2	1, 4, 5, 9, 10, 18, 28	9
Cullen, [28]	USA	1994–2014 (5.1)[b]	Retrospective	930 (107)	RP	2 consecutive PSA ≥ 0.2 or ST after PSA ≥ 0.1	Univariate	7
Shiota, [29]	Japan	2008–2012 (2.2)[b]	Retrospective	283 (68)	RP	2 consecutive PSA ≥ 0.2	NA	7
Zhao, [30]	China	2004–2014 (7.1)[b]	Retrospective	100 (175)	RP	2 consecutive PSA > 0.2	Univariate	6
Dickerman, 2017	USA	1986–2012	Prospective	4 087 (804)	RP/EBRT/BT	2 consecutive PSA > 0.2 (RP), PSA increase ≥2 (EBRT) or ≥ 1 (BT)	1, 2, 4, 5, 18, 19, 20, 21, 29, 31, 32, 33	8
Roux, [32]	France	2000–2013 (5.4)[b]	Retrospective	393 (158)	RP	2 consecutive PSA > 0.2	1, 4, 5, 6, 10	6
Maj-Hes, [33]	International	2000–2011 (2.3)[b]	Retrospective	6 519 (590)	RP	2 consecutive PSA > 0.2	4, 5, 29	7
Schiffman, [34]	Germany	2004–2015 (3.0)[b]	Retrospective	13 218 (1 074)	RP	NA	1, 4, 5, 6, 9, 10, 16	8
Goto, [35]	Japan	2005–2014 (2.8)[b]	Retrospective	2 003 (396)	RP	2 consecutive PSA > 0.2	5, 6, 7, 10	7
Yamoah, [36]	USA	1990–2012 (2.0)[b]	Prospective	1 170 (171)	RP	PSA ≥ 0.2	1, 2, 4, 5, 6, 16	7
Ohwaki, [37]	Japan	2008–2012 (2.5)[b]	Retrospective	283 (41)	RP	2 consecutive PSA > 0.2	1, 4, 5, 10, 20	8
Bai, [9]	China	2006–2014 (2.0)[c]	Retrospective	213 (48)	RP	PSA > 0.2 or ST	1, 4, 5, 11, 29	7
Wang, [38]	USA	2001–2010 (4.0)[b]	Retrospective	1 442 (146)	EBRT	NA	1, 4, 5, 6, 22	8
Tanimoto, [39]	USA	2005–2013 (1.3)[b]	Prospective	439 (34)	RP	Two PSA > 0.2 or ST	1, 4, 5, 6, 10, 12, 28	7
Agalliu, [40]	USA	2005–2012 (2.6)[b]	Retrospective	610 (87)	RP	PSA elevation ≥ 0.2	1, 4, 5, 6, 10	9
Koo, [41]	Korea	2005–2011 (4.9)[c]	Retrospective	880 (157)	RP	PSA ≥ 0.2	4, 5, 6, 9, 10, 34	8
Hayashi, [42]	Japan	2002–2009 (3.2)[b]	Retrospective	703 (154)	RP	PSA ≥ 0.2	1, 4, 5, 6, 7, 8, 10, 18, 19, 23	7
Chalfin, [43]	USA	1982–2012 (5.0)[b]	Retrospective	11 152 (1 581)	RP	PSA ≥ 0.2	1, 2, 4, 5, 6, 10, 16	8
Narita, [44]	Japan	2000–2009 (4.1)[b]	Retrospective	1 257 (230)	RP	PSA > 0.2 or ST	1, 4, 5, 7, 8, 9, 10	8
Tomaszewski, [45]	USA	1999–2011 (4.6)[c]	Retrospective	2 500 (276)	RP	2 PSA ≥ 0.2 or PSA elevation > 0.1 with ST	1, 2, 4, 5, 6, 7, 8, 9, 10, 16, 18, 35, 36	8
Asmar, [46]	USA	1994–2007 (3.6)[b]	Prospective	1 428 (107)	RP	2 consecutive PSA > 0.2	1, 5, 6, 10, 18, 20	8
Campeggi, [47]	France	2003–2008 (3.2)[c]	Prospective	765 (87)	RP	2 consecutive PSA > 0.2	NA	7
Mucksavage, [48]	USA	1999–2005 (3.9)[c]	Retrospective	1 987 (278)	RP	PSA > 2 twice	4, 5, 7, 10	7
Kok, [49]	The Netherlands	2003–2006 (3.4)[b]	Retrospective	444 (NA)	RP	2 consecutive PSA > 0.2	1, 4, 5, 6, 9, 10	8
Joshu, [50]	USA	1993–2006 (7.3)[c]	Retrospective	1 337 (102)	RP	PSA ≥ 0.2 or CR	1, 2, 5, 6, 16, 19, 32	7
Geinitz, [51]	Germany	1994–2002 (4.3)[b]	Retrospective	564 (118)	EBRT	PSAn +≥2	1, 4, 5, 6, 21, 23	8
Komaru, [52]	Japan	1997–2007 (3.1)[c]	Retrospective	173 (50)	RP	2 consecutive PSA > 0.2	Univariate	7
Van Roermund, [53]	The Netherlands	1991–2008 (3.9)[b]	Retrospective	1 530 (249)	BT	PSAn +≥ 2	1, 2, 4, 5, 6, 9, 11, 16, 25	9
Ly, [54]	USA	1996–2005 (4.9)[b]	Prospective	2 687 (319)	RT/EBRT/BT		2, 4, 5, 13, 21	7

Table 1. continued

Author, year	Country	Follow-up (years)	Design	PC patients (BCR)	Treatment	Definition of BCR (PSA measured as ng/ml)	Adjustment variables[a]	NOS
						PSAn +≥ 2 (EBRT, BT) or PSA + ≥ 0.4 (RP)		
Sumitomo, [55]	Japan	1994–2003 (3.5)[b]	Prospective	115 (27)	HIFU	PSAn +≥ 2 or ST	1, 4, 5, 6, 11, 22, 26	9
King, [56]	USA	1984–2004 (3.7)[b]	Retrospective	90 (40)	EBRT	PSA ≥ 0.2	4, 5, 7, 8, 10, 23	7
Pfitzenmaier, [57]	Germany	NA (5.5)[b]	Prospective	620 (213)	RP	PSA recurrence-free	1, 4, 5, 7, 9, 10	9
Van Roermund, [58]	The Netherlands	1992–2005 and 1988–2007 (4.9)[b]	Retrospective	1 302 (297)	RP	PSA > 0.1 or ST	1, 4, 5, 6, 7, 8, 10, 16	9
Efstathiou, [59]	USA	1996–2001 (6.0)[b]	Retrospective	353 (73)	BT	PSAn +≥ 2	2, 4, 5, 6, 23	7
Hisasue, [60]	Japan	1998–2006	Retrospective	126 (30)	RP	PSA elevation > 0.2	1, 4, 5, 6, 10, 14, 16	7
Spangler, [61]	USA	1995–2004 (3.0)[b]	Prospective	924 (97)	RP	Two PSA ≥ 0.2	1, 2, 5, 6, 8	7
Efstathiou, [62]	USA	1995–2001 (6.9)[b]	Prospective	99 (25)	EBRT	PSA ≥ 0.1 and PSA elevation ≥ 0.2	1, 4, 5, 6	8
Stroup, [63]	USA	1989–2003 (3.6)[b]	Retrospective	1 320 (554)	EBRT	PSAn +≥ 2	2, 4, 5, 6, 15, 22, 23, 24	7
Siddiqui, [64]	USA	1990–1999 (10.1)[b]	Prospective	5 313 (1 678)	RP	PSA ≥ 0.4	4, 5, 8, 10, 23	8
Strom, [65]	USA	1988–2001 (8.0)[c]	Retrospective	873 (168)	EBRT	Three consecutive increase after PSAn	4, 5, 6, 15, 23	7
Strom, [66]	USA	1991–2001 (4.5)[c]	Prospective	526 (97)	RP	PSA ≥ 0.1	4, 5, 6, 7, 8, 9, 10	6

BCR biochemical recurrence, *BT* brachytherapy, *CR* clinical recurrence (local recurrence, metastasis, etc.), *EBRT* external-beam radiation therapy, *HIFU* high intensity focused ultrasound, *NA* no data available, *PSA* prostate specific antigen, *PSAn* PSA nadir, *PC* prostate cancer, *RP* radical prostatectomy, *ST* second or salvage treatment.

[a]Covariates considered for multivariate analyses in the results used for this meta-analysis. 1, age; 2, ethnicity; 3, risk group; 4, preoperative PSA; 5, biopsy grade group based on Gleason score; 6, pathologic stage; 7, extracapsular invasion or extra-prostatic extension; 8, seminal vesicle invasion; 9, lymph node involvement; 10, positive surgical margins; 11, prostate volume; 12, prostate weight; 13, PSA frequency before BCR; 14, testosterone; 15, year of diagnosis; 16, year of surgery or treatment; 17, centre of surgery; 18, diabetes mellitus; 19, smoking; 20, other comorbidities; 21, treatment method; 22, androgen-deprivation therapy; 23, adjuvant radiation therapy or dose; 24, PSA nadir after EBRT; 25, number of seeds; 26, HIFU procedure; 27, D'Amico classification; 28, surgical approach; 29, clinical stage; 30, education; 31, physical activity; 32, family history of PC; 33, dietary or nutritional intake; 34, perineural invasion; 35, percentage of tumour in the gland; 36, largest tumour nodule.

[b]Median.

[c]Mean.

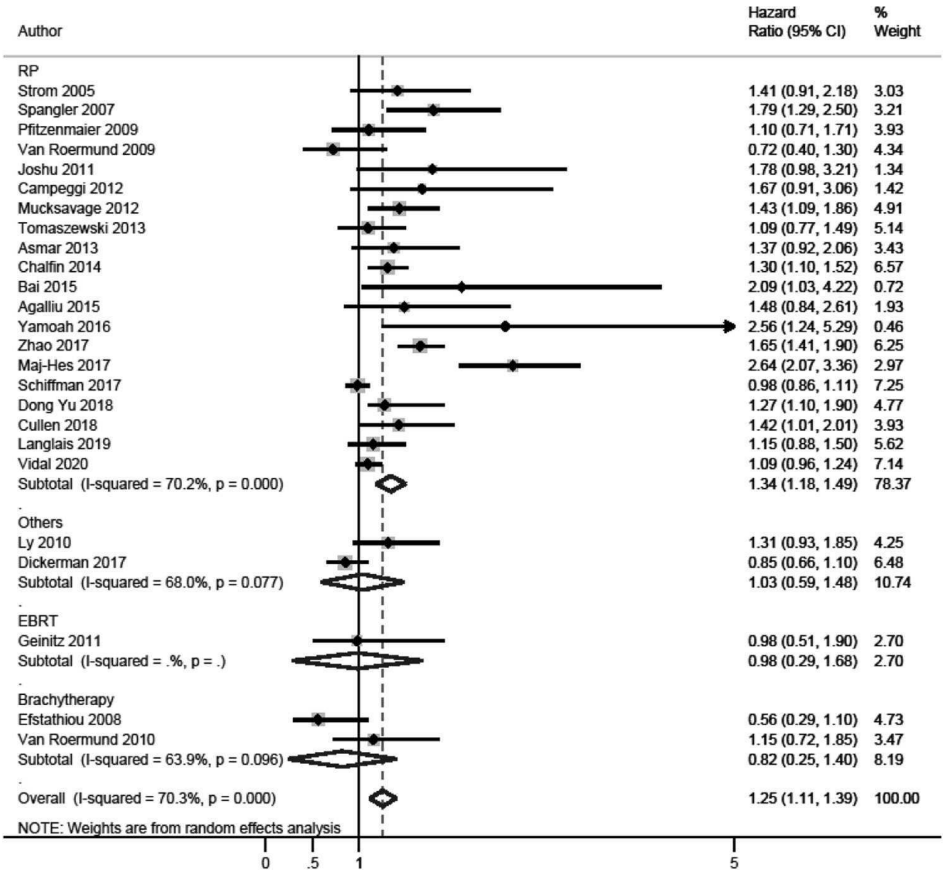

Fig. 2 Forest plot of the association between obesity (body mass index ≥30), compared with normal weight (body mass index <25) and biochemical recurrence. Data are stratified by treatment (RP radical prostatectomy, EBRT external-beam radiation therapy).

1.10–1.52, I^2: 2.4%). The association of continuous BMI per 5 units showed no heterogeneity in the subgroup of studies with lowest risk of bias (NOS = 9) (HR: 1.03, 95% CI: 0.89–1.17, I^2: 0.0%). The sensitivity analyses excluding individual lower-quality studies did not modify the estimations. The associations stratified by the definition of the outcome (BCR) did not show relevant differences, although a tendency to weaker associations with higher BCR cut-off points (i.e., PSA ≥ 0.4) were observed. The association of abnormal weight and overweight with BCR, assessed as secondary analyses, are provided in Supplementary Fig. 1. No association was found for any of these categories. Regarding publication bias, no evidence of small-studies effect was found in the funnel plot of the association of obesity and BCR (p value of the Egger test = 0.445). Regarding the association of continuous BMI per 5 kg/m^2 and BCR, evidence of missing small studies reporting positive association was detected (p value of the Egger test = 0.017; Supplementary Fig. 2).

DISCUSSION

In this systematic review and meta-analysis, pooling all available data to calculate a precise quantitative estimation of the prognostic effect of obesity (BMI ≥ 30) in patients diagnosed with clinically localised PC, we found a higher risk of BCR, compared with patients with normal weight, among patients treated with radical prostatectomy. Risk also increased per every five units increase in BMI. However, these associations should be considered cautiously as there was high heterogeneity in the crude results. Nevertheless, the main findings of our study were supported by the prospective and higher-quality subgroup analysis. The most consistent results for patients treated with radical prostatectomy were found among studies with high-quality NOS score (NOS ≥ 8), (HR: 1.08, 95% CI: 1.00–1.16; I^2: 6.1%), in prospective cohort studies (HR: 1.31, 95% CI: 1.10–1.52, I^2: 2.4%) and in those studies in which BMI was directly measured by the researchers (HR:1.65, 95% CI:1.42–1.88; I^2: 0.0%), but only 4 studies met this last criterion. However, heterogeneity was high for most of the other subgroups. Our results suggest that the association of obesity with BCR after radical prostatectomy merits consideration.

Causation assessment was performed according to the recommendations on evaluation of observational meta-analyses; [69] we evaluated the association of obesity with BCR considering the classical Bradford–Hill criteria [19]. Our evaluation showed evidence of moderate strength of association, temporality, biological plausibility and analogy (Supplementary Table 3), although we did not observe evidence of dose-response or specificity. Regarding the strength of association, the pooled HR was statistically significant overall and showed a moderate association (25% increase in BCR risk in obese patients, 95% CI: 11–39%). The consistency of the association could not be confirmed given the global heterogeneity and the observed changes in subgroup analysis. However, we detected that point estimates of the association between obesity and BCR showed significant association in half of the studies conducted in patients receiving radical prostatectomy, in the subgroup of prospective cohort studies and when the BMI was measured from researchers or from clinical histories or databases rather than self-reported. Although I^2 estimates showed variation, lower level of heterogeneity was detected among subgroups. The consistency of the association, in any case, might be met by patients receiving radical prostatectomy, whilst no association was confirmed in patients receiving different treatments. Inconsistencies in the association

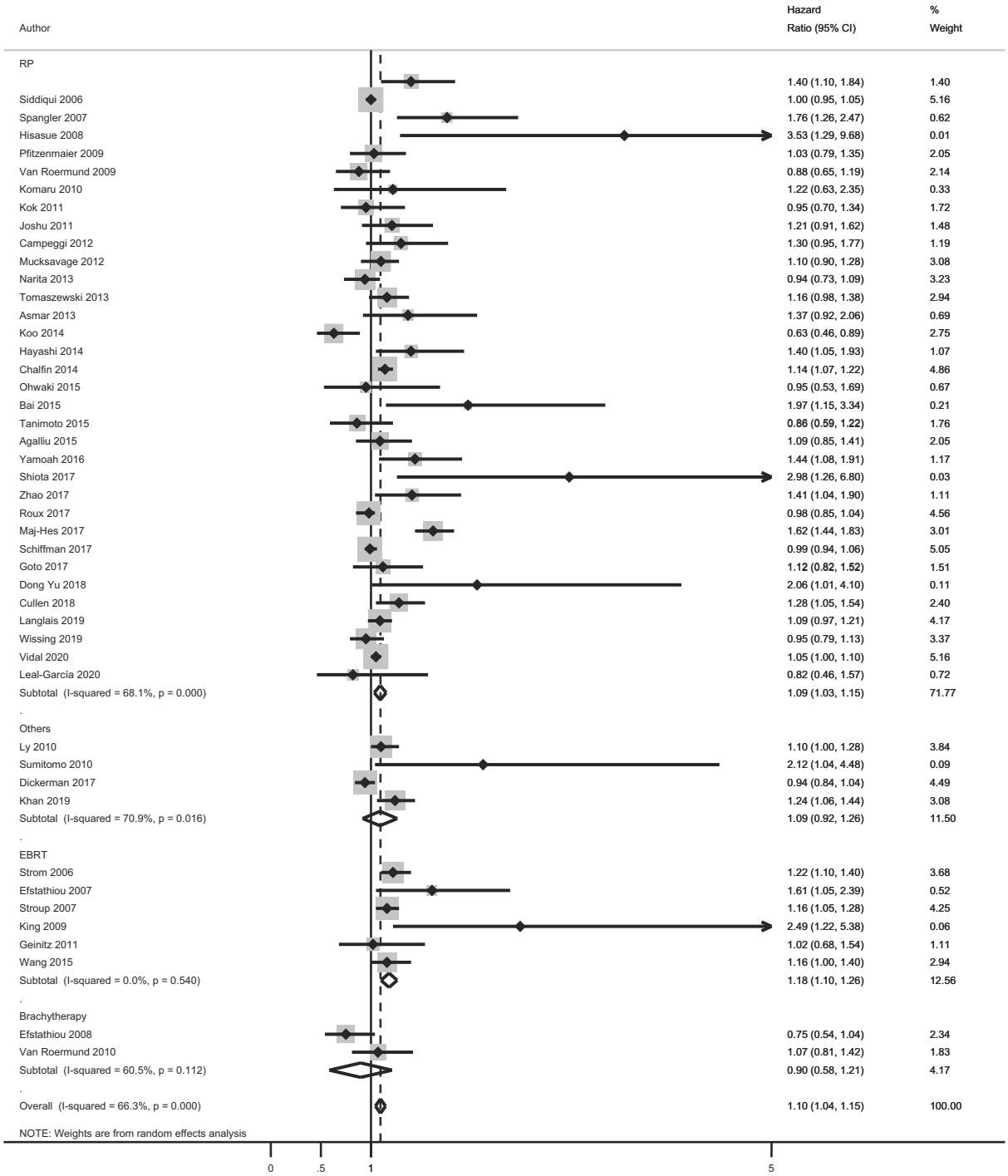

Fig. 3 Forest plot of the association between continuous body mass index per 5 kg/m^2 and biochemical recurrence. Data are stratified by treatment (RP radical prostatectomy, EBRT external-beam radiation therapy).

might be partially explained by the obesity paradox, as reported in some of the included studies [23]. This paradox has been previously suggested in PC, with reports that overweight or obese patients have a lower risk of metastasis after RP [25]. Studies that analysed obesity with measurement different from BMI (e.g., obesity-related genes or weight change) [25, 70–72], also showed consistent association with BCR, suggesting that the heterogeneity could be overestimated by the different sources and cut-offs of the BMI. Temporality was also established by the study design, as we restricted the search to longitudinal prospective cohort studies. Regarding biological gradient, we analysed the association between BMI change per 5 kg/m^2 and BCR, as shown in Table 2 and Fig. 3. Although a significant association was found, the relationship between BMI and BCR might not be linear, as no significant association was found in several subgroups of the continuous variable, suggesting that the association of obesity is more consistent than the association with continuous BMI per five units. The biological plausibility of the association is supported by

Table 2. Subgroup analysis of the pooled association of body mass index with biochemical recurrence in prostate cancer patients receiving radical prostatectomy.

Subgroup	Biochemical recurrence					
	Obesity (BMI ≥ 30) compared with normal weight (BMI < 25)			BMI continuous per 5 kg/m^2		
	N	HR (95% CI)	I^2	*N*	HR (95% CI)	I^2
All studies (total)	20	1.34 (1.18–1.49)	70.2	34	1.09 (1.03–1.15)	68.1
Country						
American countries	12	1.25 (1.13–1.37)	17.3	16	1.09 (1.03–1.15)	52.9
Asian countries	3	1.53 (1.22–1.83)	32.4	11	1.14 (0.89–1.39)	63.0
European countries	4	0.98 (0.85–1.11)	37.9	6	0.99 (0.94–1.04)	0.0
Other countries	1	2.64 (2.00–3.29)	–	1	1.62 (1.43–1.82)	–
Year of publication						
<2014	11	1.38 (1.16–1.59)	80.4	14	1.08 (0.99–1.17)	37.6
≥2014	9	1.27 (1.05–1.50)	70.2	20	1.10 (1.01–1.18)	76.6
Quality of the evidence[b]						
Level 2 (prospective cohort)	7	1.31 (1.10–1.52)	2.4	10	1.10 (0.99–1.21)	56.1
Level 3 (retrospective cohort)	13	1.33 (1.13–1.52)	78.6	24	1.09 (1.01–1.17)	71.8
Risk of bias						
NOS: 9	4	1.08 (0.79–1.38)	27.1	4	1.01 (0.85–1.17)	0.0
NOS: 8	5	1.11 (0.98–1.24)	48.0	11	1.01 (0.95–1.08)	66.7
NOS: 7	9	1.68 (1.33–2.03)	72.9	16	1.24 (1.10–1.39)	66.9
NOS: 6	2	1.62 (1.39–1.85)	0.0	3	1.22 (0.88–1.56)	74.6
Risk of bias (grouped)						
High quality (NOS = 8–9)	5	1.08 (1.00–1.16)	6.1	15	1.01 (0.96–1.07)	57.7
Intermediate quality (NOS < 8)	15	1.45 (1.24–1.66)	74.8	19	1.23 (1.11–1.35)	70.2
Conflicts of interest						
No	15	1.31 (1.11–1.50)	74.7	26	1.09 (1.02–1.17)	70.0
Not reported	4	1.34 (1.17–1.52)	0.0	6	1.10 (1.01–1.19)	62.4
Yes	1	1.79 (1.18–2.39)	–	2	1.27 (0.39–2.15)	85.0
Body mass index source						
Measured by the researchers	4	1.65 (1.42–1.88)	0.0	9	1.02 (0.94–1.09)	26.3
Clinical histories or databases	13	1.23 (1.07–1.40)	69.5	20	1.09 (1.01–1.17)	74.7
Self-reported	3	1.63 (1.22–2.04)	0.0	5	1.29 (1.04–1.53)	44.7
Body mass index boundaries						
World Health Organisation (obesity as BMI ≥ 30)	17	1.31 (1.14–1.48)	72.6	–	–	–
Other boundaries	3	1.53 (1.22–1.83)	32.4	–	–	–
PSM considered in adjustments						
No	9	1.70 (1.38–2.03)	70.2	13	1.32 (1.14–1.50)	70.1
Yes	11	1.14 (1.02–1.26)	36.7	21	1.03 (0.97–1.08)	53.0
Definition of the outcome (BCR)						
PSA ≥ 0.1	2	1.03 (0.36–1.70)	66.9	2	1.12 (0.62–1.63)	79.8
PSA ≥ 0.2	15	1.44 (1.25–1.63)	66.5	29	1.09 (1.03–1.15)	44.1
PSA ≥ 0.4	1	1.43 (1.04–1.81)	–	2	1.03 (0.94–1.12)	42.5
Other	2	0.99 (0.87–1.11)	0.0	1	1.03 (0.79–1.35)	–

BCR biochemical recurrence, *BMI* body mass index, *NOS* Newcastle-Ottawa scale, *PSM* positive surgical margins.
[a]Other treatments included one study of high-intensity focused ultrasound, and two studies that mixed patients receiving radical prostatectomy with patients receiving radiotherapy.
[b]According to the Centre for evidence-based medicine [17].

several postulated mechanisms. Dysregulation in the insulin/IGF-1 axis [23] and in adipokine signalling [73] are affected in obese patients, and this has been associated with BCR and severity of PC. Therefore, this potential mechanism may justify an increase of BCR frequency in obese patients. Finally, the analogy criterium (presence of reported associations with other similar outcomes in the literature) is underpinned by the relationship of obesity with local recurrence in other tumours [74, 75]. Although we did not study different outcomes, the fact that obesity has been linked to positive surgical margins or extra-prostatic invasion [27] supports

the credibility of the casual association. Therefore, several criteria for causation were objectively met. However, we could not confirm the causal association between obesity and BCR. Given that this association could only be adequately explored in patients receiving radical prostatectomy, it is possible that surgical procedure-related factors mediate the association described in this work. In other words, radical prostatectomy may present more difficulties in obese patients [76], which could influence the future occurrence of BCR. Several mechanisms have been postulated to explain this association, for example, the enlargement of prostate size associated with obesity [77], the association of obesity with positive surgical margins, the excessive fat tissue, limited working space, long distance from the skin to the operative field, and suboptimal visualisation [76]. Therefore, the causal association between obesity and BCR would be mediated by the quality of the prostatectomy. Concretely, the positive surgical margins could be an important mediator, as obesity may increase its presence, and it is also associated with BCR [76]. We detected in subgroup analyses that studies reporting results not adjusted for this variable showed a notably higher association than studies that did. In any case, an association between obesity and BCR was consistent in patients receiving radical prostatectomy, implying that weight loss after diagnosis could improve the prognosis for recurrence in these patients, both before surgery (given the increased surgical difficulties in obese patients) and after radical prostatectomy.

We performed a comprehensive literature search to increase our potential to capture all possible relevant studies. Given the large number of studies included, our analyses had enough statistical power to detect differences and obtain reliable results, even in predefined subgroup analysis. The large number of studies captured may partially explain the statistical significance of the observed heterogeneity [68]. The investigation of reasons of heterogeneity showed that variations on the country, quality of the evidence, study design and year of publication did not considerably variate the main findings. The treatment of clinically localised PC was an important factor of disparity in the results. Therefore, patients receiving radical prostatectomy showed an association between obesity and BCR, whilst other treatments did not show this relationship. Nevertheless, very few studies on other treatments were identified and, therefore, the associations were not conclusive. An association with continuous BMI was also detected in patients receiving external beam radiation therapy as primary treatment. We found that only three studies reported conflicting financial relationships, and ten did not include a conflict-of-interest disclosure statement. For the present research question, we believe that these omissions should not have a meaningful impact on their findings; however, the AMSTAR-2 scale recommends collecting this information in systematic reviews for quality assessment. Subgroup analyses showed no important differences according to this variable.

All the studies included in this meta-analysis measured post-diagnosis BMI, however, some recent studies have also proposed pre-diagnosis BMI or even BMI change throughout the life as a possible risk factor for BCR in PC patients. These different measurements of BMI in other studies could complement our approximation. Three studies conducted in Asia used different BMI boundaries (e.g., considering obesity as >27.5 kg/m^2) [9, 27, 41]. They were separately considered in subgroup analyses to control this potential bias. No substantial differences were found between these groups. We present the results of a meta-analysis collecting association measures instead of raw data as the rates of BCR among BMI subgroups were not reported for most of the studies. This prevented us from using meta-regression techniques to explore the effect of potential mediators or confounders such as the presence of positive surgical margins or the surgical approach (open vs. laparoscopic or robotic). Future studies should consider reporting these rates to elucidate their role in the association between obesity and BCR. Nevertheless, we conducted subgroup analyses to approximate the effect of each variable on the estimations. Finally, the outcome was not homogeneously measured. BCR was considered as PSA ≥ 0.2 ng/ml, PSA ≥ 0.1 ng/ml, PSA ≥ 0.4 ng/ml, detectable PSA and need for salvage treatment or increase in PSA after PSA nadir, among others. We also approached this limitation by performing a subgroup analysis according to the outcome definition. We observed clearer relationship between obesity and BCR in stricter definitions of the outcome, although most of the studies (75%) considered PSA ≥ 0.2 ng/ml as BCR. However, these limitations demonstrate the urgent need for future research to use a standardised definition of BCR, so that future studies can be comparable.

Our results provide evidence that obesity worsens the prognosis of PC patients, not only increases the risk of advance PC diagnosis as according to the World Cancer Research Fund [78]. Besides, although mortality and aggressiveness in PC have been associated with obesity, association with biochemical recurrence in clinically localised PC requiring radical prostatectomy has been widely discussed. Our review strengthens the hypothesis that obesity has a negative impact on clinically localised PC prognosis after radical prostatectomy. Given that obesity is a modifiable factor through lifestyle preventive programs or advice, future weight loss interventions among obese PC patients [79] that require radical prostatectomy should be implemented and evaluated. Programs like multimodal prehabilitation, tested in other cancers [80], might be useful for future clinical research in prostate cancer. As recently pointed, exercise and nutritional interventions will also help improving other outcomes (e.g., reducing androgen deprivation therapy-related problems) [81]. Guidelines and patient information need to be updated to highlight the role of obesity in prognosis.

CONCLUSIONS

We provide evidence that, in clinically localised PC patients receiving radical prostatectomy, obesity, a modifiable risk factor, is moderately associated with BCR. This information should be used in counselling PC patients receiving radical prostatectomy and in designing future research and preventive programs concerning lifestyle changes. Nevertheless, BCR definition was not always the same, indicating the need to homogenise its consideration and boundaries for future research.

CODE AVAILABILITY

Code will be made available for bona fide researchers on request.

REFERENCES

1. Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health. 2019;9:217–22.
2. Fleshner K, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol. 2017;14:26–37.
3. Wilt TJ, Vo TN, Langsetmo L, Dahm P, Wheeler T, Aronson WJ, et al. Radical prostatectomy or observation for clinically localized prostate cancer: extended follow-up of the prostate cancer intervention versus observation trial (PIVOT). Eur Urol. 2020;77:713–24.
4. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021;79:263–82.
5. Panuganti KK, Nguyen M, Kshirsagar RK Obesity. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
6. Rivera-Izquierdo M, Pérez de Rojas J, Martínez-Ruiz V, Pérez-Gómez B, Sánchez MJ, Khan KS, et al. Obesity as a risk factor for prostate cancer mortality: a systematic review and dose-response meta-analysis of 280,199 patients. Cancers (Basel). 2021;13:4169.

7. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Philos). 2011;4:486–501.
8. Hu MB, Xu H, Bai PD, Jiang HW, Ding Q. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Med Oncol. 2014;31:829.
9. Bai PD, Hu MB, Xu H, Zhu WH, Hu JM, Yang T, et al. Body mass index is associated with higher Gleason score and biochemical recurrence risk following radical prostatectomy in Chinese men: a retrospective cohort study and meta-analysis. World J Surg Oncol. 2015;13:311.
10. Luo R, Chen Y, Ran K, Jiang Q. Effect of obesity on the prognosis and recurrence of prostate cancer after radical prostatectomy: a meta-analysis. Transl Androl Urol. 2020;9:2713–22.
11. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, 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.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
14. World Health Organization. Body mass index. https://www.who.int/data/gho/data/themes/theme-details/GHO/body-mass-index-(bmi).
15. Riley RD, Moons KGM, Snell KIE, Ensor J, Hooft L, Altman DG, et al. A guide to systematic review and meta-analysis of prognostic factor studies. BMJ. 2019;364:k4597.
16. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects metaanalyses. BMJ 2011;342:d549.
17. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301–9.
18. Centre for Evidence-Based Medicine. Levels of Evidence. https://www.cebm.ox.ac.uk/resources/levels-of-evidence
19. Hill AB. The environment and disease: Association or causation? Proc R Soc Med. 1965;58:295–300.
20. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests. Res Synth Methods 2018;9:41–50.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
22. Vidal AC, Oyekunle T, Howard LE, De Hoedt AM, Kane CJ, Terris MK, et al. Obesity, race, and long-term prostate cancer outcomes. Cancer 2020;126:3733–41.
23. Leal-García M, Canto P, Cárdenas-Cárdenas E, Feria-Bernal G, García-García E, Méndez JP. Overweight and obesity in men with prostate cancer do not constitute risk factors for biochemical recurrence. Aging Male. 2020;23:1283–8.
24. Langlais CS, Cowan JE, Neuhaus J, Kenfield SA, Van Blarigan EL, Broering JM, et al. Obesity at diagnosis and prostate cancer prognosis and recurrence risk following primary treatment by radical prostatectomy. Cancer Epidemiol Biomark Prev. 2019;28:1917–25.
25. Khan S, Hicks V, Colditz GA, Kibel AS, Drake BF. The association of weight change in young adulthood and smoking status with risk of prostate cancer recurrence. Int J Cancer. 2018;142:2011–8.
26. Wissing M, Chevalier S, McKercher G, Laprise C, Aprikian S, O'Flaherty A, et al. The relationship between body-mass index, physical activity, and pathologic and clinical outcomes after radical prostatectomy for prostate cancer. World J Urol. 2019;37:789–98.
27. Yu YD, Byun SS, Lee SE, Hong SK. Impact of body mass index on oncological outcomes of prostate cancer patients after radical prostatectomy. Sci Rep. 2018;8:11962.
28. Cullen J, Young D, Chen Y, Degon M, Farrell J, Sedarsky J, et al. Predicting prostate cancer progression as a function of ets-related gene status, race, and obesity in a longitudinal patient cohort. Eur Urol Focus. 2018;4:818–24.
29. Shiota M, Takeuchi A, Sugimoto M, Kashiwagi E, Dejima T, Kiyoshima K, et al. The differential impact of body mass index and the feature of metabolic syndrome on oncological outcomes following different surgical procedures in japanese men with prostate cancer. Ann Surg Oncol. 2017;24:1443–50.
30. Zhao R, Cheng G, Wang B. BMI and serum lipid parameters predict increasing risk and aggressive prostate cancer in Chinese people. Oncotarget. 2017;8:66051–60.
31. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, Giovannucci E, Wilson KM, Aspelund T, et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. Cancer. 2019;125:2877–85.
32. Roux V, Eyraud R, Brureau L, Gourtaud G, Senechal C, Fofana M, et al. Impact du score de Gleason sur la survie sans récidive biologique après prostatectomie totale pour cancer avec marges chirurgicales positives [Impact of Gleason score on biochemical recurrence free survival after radical prostatectomy with positive surgical margins]. Prog Urol. 2017;27:467–73.
33. Maj-Hes AB, Mathieu R, Özsoy M, Soria F, Moschini M, Abufaraj M, et al. Obesity is associated with biochemical recurrence after radical prostatectomy: A multi-institutional extended validation study. Urol Oncol. 2017;35:460.
34. Schiffmann J, Salomon G, Tilki D, Budäus L, Karakiewicz PI, Leyh-Bannurah SR, et al. Radical prostatectomy neutralizes obesity-driven risk of prostate cancer progression. Urol Oncol. 2017;35:243–9.
35. Goto K, Nagamatsu H, Teishima J, Kohada Y, Fujii S, Kurimura Y, et al. Body mass index as a classifier to predict biochemical recurrence after radical prostatectomy in patients with lower prostate-specific antigen levels. Mol Clin Oncol. 2017;6:748–52.
36. Yamoah K, Zeigler-Johnson CM, Jeffers A, Malkowicz B, Spangler E, Park JY, et al. The impact of body mass index on treatment outcomes for patients with low-intermediate risk prostate cancer. BMC Cancer. 2016;16:557.
37. Ohwaki K, Endo F, Hattori K. Abdominal obesity, hypertension, antihypertensive medication use and biochemical recurrence of prostate cancer after radical prostatectomy. Eur J Cancer. 2015;51:604–9.
38. Wang LS, Murphy CT, Ruth K, Zaorsky NG, Smaldone MC, Sobczak ML, et al. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. Cancer. 2015;121:3010–7.
39. Tanimoto R, Fashola Y, Scotland KB, Calvaresi AE, Gomella LG, Trabulsi EJ, et al. Risk factors for biochemical recurrence after robotic assisted radical prostatectomy: a single surgeon experience. BMC Urol. 2015;15:27.
40. Agalliu I, Williams S, Adler B, Androga L, Siev M, Lin J, et al. The impact of obesity on prostate cancer recurrence observed after exclusion of diabetics. Cancer Causes Control. 2015;26:821–30.
41. Koo KC, Yoon YE, Rha KH, Chung BH, Yang SC, Hong SJ. Low body mass index is associated with adverse oncological outcomes following radical prostatectomy in Korean prostate cancer patients. Int Urol Nephrol. 2014;46:1935–40.
42. Hayashi N, Matsushima M, Kido M, Naruoka T, Furuta A, Furuta N, et al. BMI is associated with larger index tumors and worse outcome after radical prostatectomy. Prostate Cancer Prostatic Dis. 2014;17:233–7.
43. Chalfin HJ, Lee SB, Jeong BC, Freedland SJ, Alai H, Feng Z, et al. Obesity and long-term survival after radical prostatectomy. J Urol. 2014;192:1100–4.
44. Narita S, Mitsuzuka K, Yoneyama T, Tsuchiya N, Koie T, Kakoi N, et al. Impact of body mass index on clinicopathological outcome and biochemical recurrence after radical prostatectomy. Prostate Cancer Prostatic Dis. 2013;16:271–6.
45. Tomaszewski JJ, Chen YF, Bertolet M, Ristau BT, Woldemichael E, Nelson JB. Obesity is not associated with aggressive pathologic features or biochemical recurrence after radical prostatectomy. Urology. 2013;81:992–6.
46. Asmar R, Beebe-Dimmer JL, Korgavkar K, Keele GR, Cooney KA. Hypertension, obesity and prostate cancer biochemical recurrence after radical prostatectomy. Prostate Cancer Prostatic Dis. 2013;16:62–6.
47. Campeggi A, Xylinas E, Ploussard G, Ouzaid I, Fabre A, Allory Y, et al. Impact of body mass index on perioperative morbidity, oncological, and functional outcomes after extraperitoneal laparoscopic radical prostatectomy. Urology. 2012;80:576–84.
48. Mucksavage P, Mitchell C, Kutikov A, Wein AJ, Torigian D, Malkowicz SB. Anthropometric differences in obese men with biochemical failure after radical retropubic prostatectomy. Urol Oncol. 2012;30:590–5.
49. Kok DE, van Roermund JG, Aben KK, van de Luijtgaarden MW, Karthaus HF, van Vierssen Trip OB, et al. Body mass index is not a predictor of biochemical recurrence after radical prostatectomy in Dutch men diagnosed with prostate cancer. World J Urol. 2011;29:695–701.
50. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev Res (Philos). 2011;4:544–51.
51. Geinitz H, Thamm R, Mueller T, Jess K, Zimmermann FB, Molls M, et al. Impact of body mass index on outcomes after conformal radiotherapy in patients with prostate cancer. Int J Radiat Oncol Biol Phys. 2011;81:16–22.
52. Komaru A, Kamiya N, Suzuki H, Endo T, Takano M, Yano M, et al. Implications of body mass index in Japanese patients with prostate cancer who had undergone radical prostatectomy. Jpn J Clin Oncol. 2010;40:353–9.
53. van Roermund JG, Hinnen KA, Battermann JJ, Witjes JA, Bosch JL, Kiemeney LA, et al. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. BJU Int. 2010;105:42–8.
54. Ly D, Reddy CA, Klein EA, Ciezki JP. Association of body mass index with prostate cancer biochemical failure. J Urol. 2010;183:2193–9.
55. Sumitomo M, Asakuma J, Yoshii H, Sato A, Horiguchi A, Ito K, et al. Anterior perirectal fat tissue thickness is a strong predictor of recurrence after high-intensity focused ultrasound for prostate cancer. Int J Urol. 2010;17:776–82.

56. King CR, Spiotto MT, Kapp DS. Obesity and risk of biochemical failure for patients receiving salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys. 2009;73:1017–22.
57. Pfitzenmaier J, Pritsch M, Haferkamp A, Jakobi H, Fritsch F, Gilfrich C, et al. Is the body mass index a predictor of adverse outcome in prostate cancer after radical prostatectomy in a mid-European study population? BJU Int. 2009;103:877–82.
58. van Roermund JG, Kok DE, Wildhagen MF, Kiemeney LA, Struik F, Sloot S, et al. Body mass index as a prognostic marker for biochemical recurrence in Dutch men treated with radical prostatectomy. BJU Int. 2009;104:321–5.
59. Efstathiou JA, Skowronski RY, Coen JJ, Grocela JA, Hirsch AE, Zietman AL. Body mass index and prostate-specific antigen failure following brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;71:1302–8.
60. Hisasue S, Yanase M, Shindo T, Iwaki H, Fukuta F, Nishida S, et al. Influence of body mass index and total testosterone level on biochemical recurrence following radical prostatectomy. Jpn J Clin Oncol. 2008;38:129–33.
61. Spangler E, Zeigler-Johnson CM, Coomes M, Malkowicz SB, Wein A, Rebbeck TR. Association of obesity with tumor characteristics and treatment failure of prostate cancer in African-American and European American men. J Urol. 2007;178:1939–45.
62. Efstathiou JA, Chen MH, Renshaw AA, Loffredo MJ, D'Amico AV. Influence of body mass index on prostate-specific antigen failure after androgen suppression and radiation therapy for localized prostate cancer. Cancer. 2007;109:1493–8.
63. Stroup SP, Cullen J, Auge BK, L'Esperance JO, Kang SK. Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition. Cancer. 2007;110:1003–9.
64. Siddiqui SA, Inman BA, Sengupta S, Slezak JM, Bergstralh EJ, Leibovich BC, et al. Obesity and survival after radical prostatectomy: a 10-year prospective cohort study. Cancer. 2006;107:521–9.
65. Strom SS, Kamat AM, Gruschkus SK, Gu Y, Wen S, Cheung MR, et al. Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer. Cancer. 2006;107:631–9.
66. Strom SS, Wang X, Pettaway CA, Logothetis CJ, Yamamura Y, Do KA, et al. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. Clin Cancer Res. 2005;11:6889–94.
67. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157–63.
68. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11:193–206.
69. Khan KS, Ball E, Fox CE, Meads C. Systematic reviews to evaluate causation: an overview of methods and application. Evid Based Med. 2012;17:137–41.
70. Keith SW, Kwabi-Addo B, Zeigler-Johnson C. Interactions between obesity and one-carbon metabolism genes in predicting prostate cancer outcomes among white and black patients. J Racial Ethn Health Disparities. (2021). https://doi.org/10.1007/s40615-020-00958-6.
71. Whitley BM, Moreira DM, Thomas JA, Aronson WJ, Terris MK, Presti JC, et al. Preoperative weight change and risk of adverse outcome following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital database. Prostate Cancer Prostatic Dis. 2011;14:361–6.
72. Perez-Cornago A, Appleby PN, Pischon T, Tsilidis KK, Tjønneland A, Olsen A, 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.
73. Tan W, Wang L, Ma Q, Qi M, Lu N, Zhang L, et al. Adiponectin as a potential tumor suppressor inhibiting epithelial-to-mesenchymal transition but frequently silenced in prostate cancer by promoter methylation. Prostate. 2015;75:1197–205.
74. Kim SW, Chun M, Jung YS, Oh YT, Noh OK, Cho O. Impact of body mass index on local recurrence according to intrinsic subtype approximation in korean women with early stage invasive breast cancer receiving contemporary treatments. J Cancer. 2021;12:4648–54.
75. Scarpa M, Ruffolo C, Erroi F, Fiorot A, Basato S, Pozza A, et al. Obesity is a risk factor for multifocal disease and recurrence after colorectal cancer surgery: a case-control study. Anticancer Res. 2014;34:5735–41.
76. Han H, Cao Z, Qin Y, Wei X, Ruan Y, Cao Y, et al. Morbid obesity is adversely associated with perioperative outcomes in patients undergoing robot-assisted laparoscopic radical prostatectomy. Can Urol Assoc J. 2020;14:E574–E581.
77. Muller RL, Gerber L, Moreira DM, Andriole G Jr, Hamilton RJ, Fleshner N, et al. Obesity is associated with increased prostate growth and attenuated prostate volume reduction by dutasteride. Eur Urol. 2013;63:1115–21.
78. World Cancer Research Fund. American Institute for Cancer Research. Body fatness and weight gain. https://www.wcrf.org/dietandcancer/exposures/body-fatness
79. Freedland SJ, Allen J, Jarman A, Oyekunle T, Armstrong AJ, Moul JW, et al. A randomized controlled trial of a 6-month low-carbohydrate intervention on disease progression in men with recurrent prostate cancer: carbohydrate and prostate study 2 (CAPS2). Clin Cancer Res. 2020;26:3035–43.
80. van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer. 2019;19:98.
81. Galvão DA, Taaffe DR, Newton RU. Body weight, fat mass and metabolic complications during androgen deprivation therapy: should urologists recommend exercise and diet to help patients overcome toxicities? Prostate Cancer Prostatic Dis. 2021;24:591–3.

AUTHOR CONTRIBUTIONS

Conceptualisation: MR-I, JPdR, JJJ-M, Data curation: MR-I, JPdR, Formal analysis: MR-I, JPdR, VM-R, JJJ-M, Investigation: MR-I, JPdR, VM-R, MA-P, BP-G, JJJ-M, Methodology: MR-I, JPdR, JJJ-M, Supervision: VM-R, JJJ-M, Validation: MR-I, JPdR, VM-R, MA-P, BP-G, JJJ-M.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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STUDY 4. EVALUATING THE ASSOCIATION BETWEEN BODY MASS INDEX AND PROSTATE CANCER OUTCOMES. AN OBSERVATIONAL LONGITUDINAL STUDY FROM THE SPANISH MULTI-CASE CONTROL STUDY (MCC-SPAIN).

Rivera-Izquierdo M, Martínez-Ruiz V, Jiménez-Moleón JJ, and authors from MCC-Spain consortium. The study presented in this Thesis corresponds to the first draft of the manuscript sent for review to the authors from the MCC-Spain consortium as usually handled by the consortium. After their input, the manuscript will be sent to a referent journal indexed in the category *Urology & Nephrology* of the *Journal Citation Reports*. Therefore, this work has not been sent to a journal in the moment of the presentation of this Thesis.

This study responds to specific objectives 6 and 7 of the Thesis.

Authors

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Abstract

Objectives: To study the association between body mass index (BMI) and prostate cancer outcomes, and to analyse the effect of using the Gleason score in multivariate analyses of the association between BMI and prostate cancer prognosis.

Methods: Cohort study on prostate cancer patients from the multi-case-control study (MCC-Spain) conducted in 11 hospitals from 7 Spanish provinces. Participants were men diagnosed with prostate cancer. Body mass index was reported by the participants at the moment of diagnosis referring to a year before. The outcomes analysed were prostate cancer specific mortality, all-cause mortality, biochemical recurrence, castration resistance and incidence of new metastases. Kaplan-Meier survival estimates, and multivariant Cox regression models were applied.

Results: A total of 1093 patients were followed for a median of 7.3 years. The mean age was 66.1 years, 282 (25.8%) patients showed normal weight (BMI<25), 559 (51.1%) showed overweight (BMI≥25 and <30), and 252 (23.1%) showed obesity (BMI≥30). Continuous BMI per 5 kg/m^2 was associated with biochemical recurrence (HR: 1.16, 95%CI: 1.05-1.34) and castration resistance (HR: 2.01, 95%CI: 1.10-3.57). No clear associations were showed for the rest of the outcomes, although Gleason score was identified as a towards-the-null confounder for adjusted analyses.

Conclusions: BMI increased the risk of biochemical recurrence and castration resistance. Gleason score at diagnosis should not be used as covariates in studies analysing this association through multivariate models. Preventive programs aimed at controlling BMI could improve prostate cancer prognosis.

Keywords: Obesity; mortality; biochemical recurrence; castration resistance; metastases; survival analysis.

Introduction

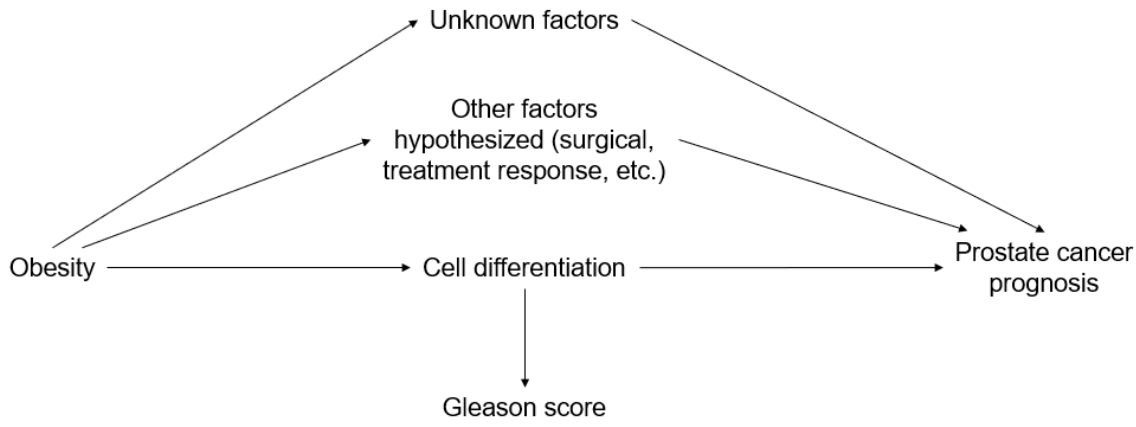
Prostate cancer (PC) is the second most frequent cancer and the third leading cause of cancer death in men [1]. However, little is known about modifiable prognostic factors for improving PC outcomes [2]. Obesity, measured as body mass index (BMI) > 30kg/m^2 has been suggested as a prognostic factor [2], although no consistent results are found in the literature, suggesting that this association is unclear to date [3,4].

Recent meta-analyses showed an association between obesity and prostate cancer specific mortality or all-cause mortality [5], but high heterogeneity was found among the studies. A relevant factor that might explain this heterogeneity is the different covariates used in the multivariate adjusted models [5]. For example, Gleason score or prognostic scores based on cancer grade were used for adjustments in around 40% of the articles, but they are mediators in the casual association between obesity and prostate cancer outcomes, as obesity increases the risk of presenting higher Gleason score [6]. Figure 16 shows an approximation of the directed acyclic graph that justifies this rationale. Briefly, there would be several causal paths between obesity and prostate cancer prognosis. One of these paths would involve unknown factors such as potential biochemical, endocrinological or metabolic consequences of obesity that may affect prostate cancer outcomes. Another path would involve other hypothesized factors that have been studied in previous works. For example, the association between obesity and technical complications in prostatectomy surgery [7], or worse response to treatment that may lead to biochemical recurrence [8]. Finally, the causal path relevant for our rationale would be explained by the association between obesity and less cell differentiation in prostate cancer, which is directly measured through Gleason score [9-11]. High BMI provides a favourable biological microenvironment for tumour onset and growth through some proposed

mechanisms which involve alterations in the endocrine system, notably, the levels of testosterone, estrogen, and insulin-like growth factor [11].

Mediators and colliders should not be used for adjustments and directed acyclic graphs should guide the election of covariates in multivariate models [12,13]. Therefore, as a mediator, Gleason score should not be used for adjustments, given that its inclusion as a covariate would close a causal path, therefore leading to a towards-the-null bias of the association between obesity and prostate cancer prognosis. This fact may partially explain the high heterogeneity found to date, along with the different results obtained after adjusting for either clinical prognostic assessment or pathological risk assessment at diagnosis or at surgery [14]. In any case, a complete directed acyclic graph of the association between obesity and prostate cancer outcomes, including all potential covariates is still needed for future research concerning this association.

Figure 16. **Directed acyclic graph of the association between obesity and prostate cancer prognosis**.



Similarly, meta-analyses on biochemical recurrence after radical prostatectomy have been conducted [10,15] and they also showed a positive association, but again with high heterogeneity between studies. Nevertheless, studies analysing other important outcomes, such as castration resistant prostate cancer or the development of metastases, are lacking.

The aim of this study was to analyse the impact of BMI on several prostate cancer outcomes (prostate cancer specific mortality, all-cause mortality, biochemical recurrence, castration resistance and development of new metastases) in a longitudinal multicentre study conducted on Spanish population (MCC-Spain study), and to identify the effect of not using clinical prognostic scores in the adjusted analyses.

Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for reporting the results of this cohort study [17].

Patients and data

The multicase-control study in Spain (MCC-Spain), started as a case-control study in 2008, on genetic and environmental exposures associated with colorectal, breast, gastric and prostate cancers [18]. Since 2016, this study has focused on the identification of prognostic factors associated with cancer prognosis [19]. Using the incident cases originally recruited from 2008 to 2013, inception cohort on prostate cancer was assembled, enrolling patients for a prospective follow-up conducted in 2017-2018. These patients were recruited from hospitals

of 7 provinces of Spain (Asturias, Barcelona, Cantabria, Granada, Huelva, Madrid, Santander and Valencia).

Inclusion criteria involved >18 years old, residence in the catchment area for 6 months before recruitment, capability of answering the epidemiological questionnaire, and presence of incident diagnosis of prostate cancer histologically confirmed. For recruitment, the study personnel contacted with newly diagnosed PC patients in the collaborating hospitals.

Information on sociodemographic and clinical data was gathered using a standardised questionnaire available at https://www.mccspain.org/. Trained researchers collected data in a face-by-face interview. Medical records were consulted to collect information on pathology characteristics, tumour extension, clinical data, treatments, and outcomes. Gleason score, D'Amico classification, TNM status, PSA levels at diagnosis, first-line treatment (surveillance, prostatectomy, hormonotherapy, radiotherapy or chemotherapy, as well as the therapy intention – neoadjuvant, adjuvant or palliative), and pathological extension of the tumour (extracapsular extension, vascular invasion, lymphatic invasion, perineural invasion and positive surgical margins) were collected. Vital status of the followed cohort was known by accessing to the clinical history of the participants, calling the participants, and consulting the National Death Index when it was not possible to know the vital status.

Exposure and outcomes

The main exposure was BMI. Body weight a year before diagnosis and height were referred by the participants. BMI was used either quantitatively per 1 and per 5 units, and categorical. BMI categories were based on the World Health Organisation boundaries [20]. Therefore,

normal weight was considered for BMI < 25 kg/m^2 and > 18.5 kg/m^2, overweight for BMI < 30 kg/m^2 and ≥ 25 kg/m^2, and obesity for BMI ≥ 30 kg/m^2.

The outcomes considered were prostate cancer specific mortality, all-cause mortality, biochemical recurrence, castration resistance, and the development of new metastases. We defined prostate cancer specific mortality as death with metastatic, progressive, or advanced PC with no other evident cause of death and/or when it was classified as that in the death certificate, whereas all-cause mortality included all patients that died during the follow-up. Biochemical recurrence was defined as a PSA measurement > 0.2 ng/ml or salvage treatment for an elevated PSA after surgery. Castration resistance was defined as a 25% increase in PSA from the PSA nadir after androgen deprivation therapy and a PSA increase > 2 ng/ml. Metastases were identified through bone scan or computed tomography imaging performed by indication of the physician.

Analysis

We measured differences in sociodemographic and clinical characteristics between BMI subgroups using ANOVA or Kruskal-Wallis tests for continuous variables and chi-square or Fisher exact test for categorical variables. Survival analyses were designed for identifying the effect of BMI categories on the time for developing each PC outcome. Kaplan-Meier graphs were used, and log-rank tests were conducted for identifying differences between BMI groups. Time of PC diagnosis was considered as time zero for all analyses. Cox proportional hazards models were used to assess the association between BMI and the different PC outcomes.

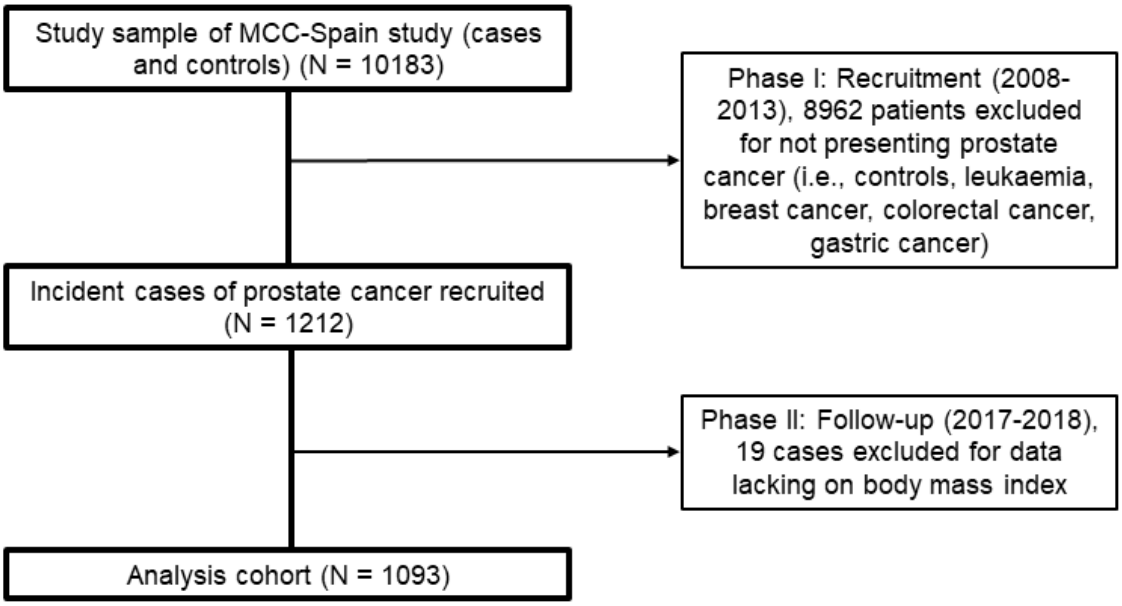
We conducted 2 adjusted models. One model (Model A) was adjusted for age, centre, PSA at diagnosis, Gleason score, extracapsular invasion, T score, lymph involvement, metastases, previous surgery and type of treatment. The second model (Model B) did not consider Gleason score at diagnosis and, therefore, was adjusted for age, centre, PSA at diagnosis, extracapsular invasion, T score, lymph involvement, metastases, previous surgery and type of treatment. All covariates were selected *a priori*. Stata statistical software version 15.0 (StataCorp®, TX, USA) was used and statistical significance was 2-sided and established at $p<0.05$.

Results

Characteristics of the sample

The sample included a total of 1112 patients diagnosed with prostate cancer in 11 hospitals from 7 provinces of Spain. For 19 (1.6%) patients there were no information on body mass index, therefore the total analysed sample were constituted by 1093 patients (Figure 17). The main characteristics of these 19 patients not included in the analyses, compared with the rest of the analysed cohort, can be consulted in Appendix 17.

Figure 17. Flow chart of the study selection process.



The median follow-up was 7.13 years (86 months). The mean age at diagnosis was 66.1 years (SD: 7.3; range 42 to 85). The mean BMI was 27.6 (SD: 3.8). Overall, 282 (25.8%) were of normal weight, 559 (51.1%) were overweight and 252 (23.1%) were obese. Table 12 shows the distribution of the clinical variables stratified by BMI groups. A higher BMI group was associated with diabetes ($p<0.001$), higher Gleason score group ($p=0.010$), and extracapsular extension ($p=0.012$). During the follow-up, 132 men (12.7%) died, 180 men (16.5%) developed biochemical recurrence, 22 men (4.3%) developed castration-resistant PC, 17 men (2.1%) developed metastasis, 132 (12.7%) died, and 35 (3.2%) died of PC specifically (Table 12).

Table 12. Demographic, clinical, and pathological features of the total sample and stratified by body mass index categories.

Feature	Body mass index (kg/m^2)				
	Total sample	Normal weight (BMI < 25)	Overweight (25 to < 30)	Obese (≥ 30)	P-value
Number of patients, n (%)	1093 (100.0)	282 (25.8)	559 (51.1)	252 (23.1)	-
Age, x (s)	66.1 (7.3)	66.7 (7.7)	66.1 (7.0)	65.3 (7.4)	0.072[c]
Diabetes, x (s)	153 (14.0)	24 (8.5)	75 (13.4)	54 (21.4)	<0.001[a]
Hospital Centre, n (%)					0.401[b]
HUTiP, Barcelona	198 (18.1)	47 (16.7)	107 (19.1)	44 (17.4)	
HDM, Barcelona	152 (13.9)	40 (14.2)	66 (11.8)	46 (18.2)	
HC, Barcelona	52 (4.8)	15 (5.3)	21 (3.8)	16 (6.3)	
HUMV, Santander	173 (15.8)	42 (14.9)	98 (17.5)	33 (13.0)	
HURC, Madrid	157 (14.4)	47 (16.7)	77 (13.8)	33 (13.0)	
HULP, Madrid	153 (14.0)	41 (14.5)	84 (15.0)	28 (11.1)	
HUPF, Valencia	83 (7.6)	23 (8.2)	37 (6.6)	23 (9.1)	
HUSC, Granada	63 (5.8)	14 (5.0)	33 (5.9)	16 (6.3)	
HUJRJ, Huelva	33 (3.0)	6 (2.1)	17 (3.0)	10 (4.0)	
HUIE, Huelva	15 (1.4)	3 (1.1)	9 (1.6)	3 (1.2)	
HUC, Gijón	15 (1.4)	4 (1.4)	10 (1.8)	1 (0.4)	
PSA, ng/ml, median (IQR)	7.3 (5.6, 10.5)	7.5 (5.8, 11.6)	7.2 (5.6, 10.2)	7.5 (5.6, 9.7)	0.223[d]
T classification, n (%)					0.247[a]
T1	363 (33.2)	99 (35.1)	166 (29.7)	98 (38.9)	
T2-T4	611 (55.9)	155 (55.0)	330 (59.0)	126 (50.0)	
Unknown	119 (10.9)	28 (9.9)	63 (11.3)	28 (11.1)	
N: Lymph node involvement, n (%)					0.628 [b]
Yes	9 (1.1)	4 (1.9)	4 (0.9)	1 (0.6)	
No	268 (32.9)	69 (32.9)	137 (31.8)	62 (35.6)	
Not evaluated	538 (66.0)	137 (65.2)	290 (67.3)	111 (63.8)	
M: presence of metastasis, n (%)					0.280[a]
Yes	17 (2.1)	8 (3.8)	6 (1.4)	3 (1.7)	
No	523 (63.5)	131 (62.4)	274 (62.8)	118 (66.3)	
Not evaluated	284 (34.5)	71 (33.8)	156 (35.8)	57 (32.0)	
Gleason score biopsy grade group, n (%)					0.010[a]
<6	20 (1.8)	8 (2.9)	6 (1.1)	6 (2.4)	
6	477 (44.0)	128 (45.6)	253 (45.8)	96 (38.3)	
7	434 (40.0)	99 (35.2)	233 (42.1)	102 (40.6)	
>7	154 (14.2)	46 (16.4)	61 (11.0)	47 (18.7)	
D'Amico risk classification, n (%)					0.084[a]
Low risk	411 (37.7)	112 (39.7)	213 (38.2)	86 (34.1)	
Intermediate risk	448 (41.1)	112 (39.7)	239 (42.9)	97 (38.5)	
High risk	232 (21.3)	58 (20.6)	105 (18.9)	69 (27.4)	
Previous prostate surgery, n (%)	24 (2.3)	9 (3.4)	11 (2.1)	4 (1.7)	0.385 [b]
Extracapsular extension, n (%)	68 (13.6)	19 (14.7)	28 (10.1)	21 (22.1)	0.012[a]
Vascular invasion, n (%)	15 (3.0)	5 (3.8)	7 (2.6)	3 (3.1)	0.435[b]
Lymphatic invasion, n (%)	6 (1.2)	2 (1.5)	4 (1.4)	0 (0.0)	0.511[b]
Perineural invasion, n (%)	212 (41.7)	51 (38.9)	111 (39.8)	50 (51.0)	0.360[a]

Feature	Body mass index (kg/m^2)				
	Total sample	Normal weight (BMI < 25)	Overweight (25 to < 30)	Obese (≥ 30)	P-value
Positive surgical margins, n (%)	163 (14.9)	33 (11.7)	92 (16.5)	38 (15.1)	0.190[a]
Primary treatment, n (%)					
Active surveillance	36 (3.5)	12 (4.5)	21 (4.0)	3 (1.3)	0.095[a]
Surgery	633 (61.7)	164 (61.7)	333 (63.8)	136 (57.1)	0.395[a]
Radiotherapy	260 (25.1)	63 (23.6)	129 (24.4)	68 (28.1)	0.448[a]
Chemotherapy	9 (0.9)	4 (1.6)	4 (0.8)	1 (0.4)	0.386[b]
Hormone therapy	293 (30.2)	77 (31.1)	150 (30.1)	66 (29.7)	0.946[a]
Dead during follow-up, n (%)	132 (12.7)	42 (15.7)	57 (10.8)	33 (13.6)	0.127[a]
Dead of prostate cancer, n (%)	35 (3.2)	13 (4.6)	16 (2.9)	6 (2.5)	
Biochemical recurrence, n (%)	180 (16.5)	41 (14.5)	90 (16.1)	49 (19.4)	0.415[a]
Castration resistance (out of 162), n (%)	22 (13.6)	8 (22.2)	6 (7.6)	8 (17.0)	0.075[a]
Follow-up years, median (IQR)	7.1 (5.9-8.1)	7.1 (5.6-7.9)	7.2 (6.0-8.2)	7.0 (5.9-8.0)	0.911[d]

HUTiP, Hospital Germans Trias i Pujol; HUMV, Hospital Universitario Marqués de Valdecilla; HURC, Hospital Universitario Ramón y Cajal; HULP, Hospital Universitario La Paz; HDM, Hospital del Mar; HUPF, Hospital Universitario y Politécnico la Fe; HUSC, Hospital Universitario San Cecilio; HUJRJ, Hospital Universitario Juan Ramón Jiménez; HUIE, Hospital Universitario Infanta Elena; HUC, Hospital Universitario de Cabueñes. [a] Determined using the chi-square test. [b] Determined using the Fisher exact test. [c] Determined using the ANOVA test. [d] Determined using the Kruskal-Wallis test

Factors associated with prostate cancer outcomes

Kaplan-Meier survival estimates are graphically showed in Figure 17. No differences were detected among BMI strata in crude analyses according to log-rank tests. Crude and adjusted analyses of BMI for prostate cancer outcomes are detailed in Table 13 (overweight vs. normal weight, obesity vs. normal weight, and continuous BMI per 1 and 5 kg/m^2). BMI was not clearly associated with all-cause mortality. The only factor independently associated with this outcome was T stage (p=0.046).

Figure 17. Kaplan-Meier survival estimates for the association between body mass index groups and prostate cancer outcomes.

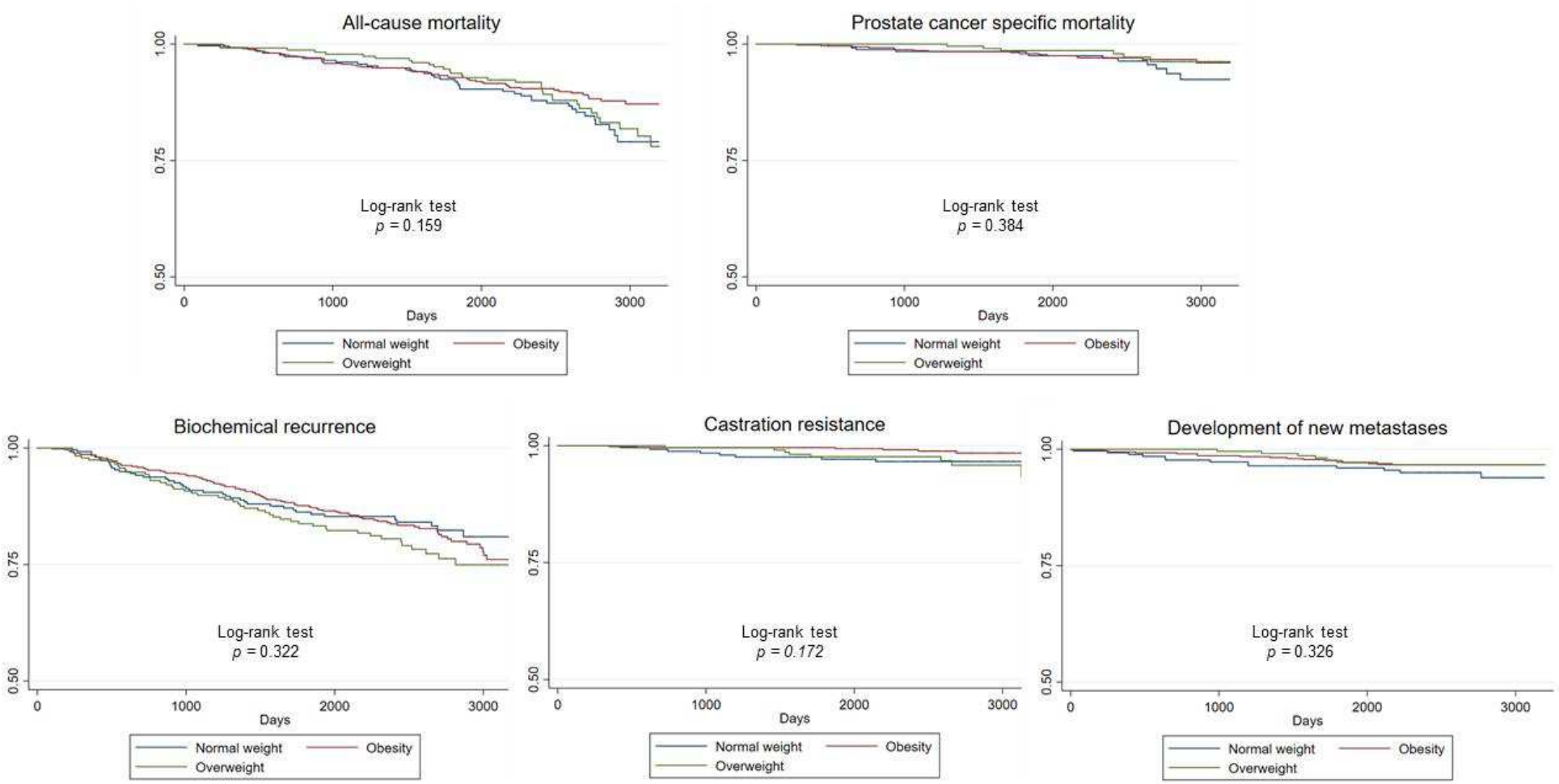


Table 13. Crude and adjusted HRs and 95% CI for the association between body mass index and prostate cancer outcomes.

	N	Unadjusted		Model A		Model B	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause mortality							
Normal weight	42/282	Ref	-	Ref	-	Ref	-
Overweight	57/559	0.69 (0.46-1.03)	0.076	1.39 (0.58-3.35)	0.457	1.41 (0.59-3.39)	0.437
Obese	33/252	0.90 (0.57-1.42)	0.644	0.95 (0.31-2.96)	0.934	1.43 (0.50-4.01)	0.506
BMI (continuous) per 1kg/m^2	132/1093	1.01 (0.96-1.05)	0.830	1.00 (0.90-1.11)	0.989	1.02 (0.93-1.12)	0.635
BMI (continuous) per 5kg/m^2	132/1093	1.03 (0.82-1.29)	0.830	1.00 (0.37-3.57)	0.989	1.13 (0.69-1.84)	0.635
Prostate cancer specific mortality							
Normal weight	13/282	Ref	-	Ref	-	Ref	-
Overweight	16/559	0.65 (0.31-1.38)	0.266	2.18 (0.24-19.71)	0.487	1.83 (0.22-15.31)	0.575
Obese	6/242	0.56 (0.21-1.50)	0.249	0.66 (0.22-1.99)	0.455	0.71 (0.23-2.17)	0.551
BMI (continuous) per 1kg/m^2	35/1093	0.99 (0.91-1.09)	0.886	1.04 (0.79-1.37)	0.777	1.04 (0.78-1.37)	0.831
BMI (continuous) per 5kg/m^2	35/1093	0.95 (0.62-1.54)	0.886	1.22 (0.31-4.83)	0.831	1.22 (0.29-4.83)	0.831
Biochemical recurrence							
Normal weight	41/164	Ref	-	Ref	-	Ref	-
Overweight	90/333	1.09 (0.75-1.57)	0.664	1.09 (0.71-1.65)	0.698	1.09 (0.71-1.64)	0.721
Obese	49/136	1.36 (0.90-2.06)	0.149	1.24 (0.77-2.11)	0.375	1.38 (0.86-2.22)	0.185
BMI (continuous) per 1kg/m^2	180/633	1.03 (0.99-1.07)	0.164	1.02 (0.98-1.06)	0.423	1.03 (1.01-1.06)	<0.001*
BMI (continuous) per 5kg/m^2	180/633	1.16 (0.95-1.40)	0.164	1.10 (0.90-1.34)	0.423	1.16 (1.05-1.34)	<0.001*
Castration resistance							
Normal weight	8/77	Ref	-	Ref	-	Ref	-
Overweight	6/150	0.37 (0.13-1.07)	0.067	0.81 (0.21-3.14)	0.760	0.53 (0.15-1.91)	0.335
Obese	8/66	1.11 (0.42-2.96)	0.835	1.63 (0.43-6.18)	0.470	1.65 (0.44-6.09)	0.450
BMI (continuous) per 1kg/m^2	22/293	1.04 (0.94-1.16)	0.435	1.08 (0.95-1.24)	0.248	1.15 (1.02-1.29)	0.008*
BMI (continuous) per 5kg/m^2	22/293	1.22 (0.73-2.10)	0.435	1.47 (0.77-2.93)	0.248	2.01 (1.10-3.57)	0.008*
Development of new metastases							
Normal weight	8/282	Ref	-	Ref	-	Ref	-
Overweight	6/559	0.61 (0.29-1.27)	0.189	0.76 (0.31-1.82)	0.531	0.65 (0.27-1.54)	0.329
Obese	3/252	0.59 (0.23-1.47)	0.255	0.62 (0.21-1.86)	0.396	0.69 (0.23-2.08)	0.511
BMI (continuous) per 1kg/m^2	17/1093	0.95 (0.87-1.04)	0.311	0.95 (0.85-1.07)	0.395	0.96 (0.86-1.08)	0.514
BMI (continuous) per 5kg/m^2	17/1093	0.77 (0.50-1.22)	0.311	0.77 (0.44-1.40)	0.395	0.82 (0.47-1.47)	0.514

Model A was adjusted for all the clinical and pathological variables of the study (age, diabetes, PSA at diagnosis, Gleason score, extracapsular invasion, T score, lymph involvement, metastases, previous surgery, and type of treatment) and model B was adjusted for the same variables except for Gleason score.

Regarding prostate cancer specific mortality, the BMI was not associated in the adjusted models. The only factors independently associated with prostate cancer specific mortality were Gleason score (p=0.003) and T stage (p=0.003). Biochemical recurrence (the most frequent outcome in our study) showed association with continuous BMI (p<0.001) in the adjusted models. T stage (p<0.001), Gleason score (p<0.001) and PSA at diagnosis (p<0.001) were also associated with higher rates of biochemical recurrence. Continuous BMI was also associated with the development of castration resistance (p=0.008), along with T stage (p=0.013), PSA at diagnosis (p=0.002), and older age (p=0.023). Finally, BMI showed no association with the development of metastases during the follow-up. PSA at diagnosis (p<0.001) and Gleason score (p<0.001) showed association with this outcome. Overweight was not associated with any of the analyzed outcomes.

The models showed that adjusting for Gleason score generated a toward-the-null bias, therefore most associations in Model B were stronger than in Model A (Table 13).

Discussion

We present the results of a cohort of prostate cancer patients during a median of 7.13 years of follow-up. The body mass index was associated with higher rates of biochemical recurrence and castration resistance, although no clear association was found for all-cause mortality, prostate cancer specific mortality, and the presence of metastases.

Obesity showed, for punctual crude estimations, protective associations regarding mortality (both all-cause mortality and prostate cancer specific mortality), as widely reported concerning the so-called *obesity paradox* in cancer mortality [21,22]. This non-significant association should be considered cautiously, as it became lower (or even opposite regarding all-cause mortality) when adjusting for confounders. The association of BMI with PC mortality, as

reported in a recent meta-analysis conducted by Rivera-Izquierdo *et al.* [5], is not strong and might be biased given the high heterogeneity showed between studies to date.

Our study extends the literature by including other less known outcomes, such as biochemical recurrence, castration resistance and metastases. We showed that BMI was associated with higher risk of biochemical recurrence and castration resistance ($p<0.001$). It is yet unclear whether the association of BMI with PC outcomes are explained by a biological effect of obesity on PC progression, or the result of less successful treatments for obese patients [23,24]. The difficulties on surgical treatments for obese patients with PC are widely reported [7], suggesting that there are technical challenges in operating on obese men [25], but this association has not been demonstrated for different non-surgical treatments. Hormonal therapy has also suggested to be affected by obesity and associated endocrine variation [26], thus influencing PC outcomes. These data are in accordance with our results, as the associations found between BMI and PC outcomes were mainly biochemical recurrence and castration resistance, outcomes that occur after surgical or hormonal treatment. Nevertheless, this association alone seems insufficient to explain the association of BMI with other PC outcomes (such as prostate cancer specific mortality or all-cause mortality), frequently reported in the literature [5,27]. This suggest that may be a biological link between obesity and worse PC outcomes [23,28], although more research is required in this field.

The prospective longitudinal design of the MCC-study minimizes the likelihood or a reverse causation bias, in case the recurrence (biochemical recurrence, castration resistance or development of new metastasis) influences body mass index. It is possible that the negative association between BMI and PC outcomes (especially regarding low-risk PC) by collider

stratification bias (selection bias due to the analysis of cases only), produces spurious associations in prognostic analyses, as recently suggested [23]. We tried to minimize this point by adjusting for important confounders that reduce the risk of collider bias, but residual confusion is expected due to unknown factors (e.g., genetics, lifestyle, etc.). The use of BMI only, rather than more markers of body composition, might also limit the results. This point has demonstrated to considerably reduce heterogeneity [5] and make the results more reliable. Also, as prostate cancer is mainly diagnosed in the elderly, BMI cut-offs for obesity should be adjusted according to age. Moreover, the best measurement for obesity (gold-standard) is the percentage of body fat. This measure should be considered for future studies instead of BMI. In this study, we collected BMI referred to one year before diagnosis, trying to minimize the obesity paradox (the negative effect of cachexia – low weight produced by advanced cancer – in prostate cancer outcomes) Finally, the covariates used in the adjusted models were mainly based on previous research, removing Gleason score at diagnosis as it acts as a mediator. Further research in the casual association between obesity and PC outcomes are required, and complete directed acyclic graphs guiding the right adjustment strategy will be of high value. Besides, mixed Cox regression models including the interviewer as a random effect term should be explored to eliminate the effect of the differences according to the collection of variables from different researchers. However, the number of interviewers was high, and the number of patients collected by each one was very varied, making it impossible to work with adequate models for the analysis. So, the center was considered as an approximation to eliminate this potential variability. PSA at diagnosis, Gleason score and T-stage were strong predictors of all the outcomes in our multivariate analyses, suggesting that these markers can be valuable for predicting PC prognosis. Finally, the inclusion of other obesity-related factors

regarding lifestyles, such as dietary habits or physical exercise, might add relevant information for future research in this field.

We found an association of obesity with biochemical recurrence and castration resistance, although we did not show association regarding mortality. Further research is warranted concerning the PC-specific benefits of weight loss among PC survivors. Nevertheless, given the relationship of obesity with many other chronic conditions (e.g., heart disease and other malignancies), men diagnosed with PC should be counseled to reach and maintain a healthy weight [29].

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. Schatten, H. Brief Overview of Prostate Cancer Statistics, Grading, Diagnosis and Treatment Strategies. Adv. Exp. Med. Biol. 2018, 1095, 1–14.

3. 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.

4. 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.

5. Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Pérez-Gómez, B.; Sánchez, M.-J.; Khan, K.S.; Jiménez-Moleón, J.J. Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients. Cancers 2021, 13, 4169.

6. Baillargeon, J.; Rose, D.P. Obesity, adipokines, and prostate cancer (review). Int J Oncol. 2006; 28, 737–745.

7. Abufaraj, M.; Mari, A.; Mansy, K.; Sievert, K.D. Obesity and its implications on oncological urological surgery. Curr Opin Urol. 2017, 27, 446–455.

8. Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Arrabal-Polo, M.Á.; Pérez-Gómez, B.; Jiménez-Moleón, J.J. Obesity and biochemical recurrence in clinically localised prostate cancer: a systematic review and meta-analysis of 86,490 patients. Prostate Cancer Prostatic Dis. 2022.

9. Di Sebastiano, K.M.; Pinthus, J.H.; Duivenvoorden, W.C.; Patterson, L.; Dubin, J.A.; Mourtzakis, M. Elevated C-Peptides, Abdominal Obesity, and Abnormal Adipokine Profile are Associated With Higher Gleason Scores in Prostate Cancer. Prostate. 2017, 77, 211–221.

10. Bai, P.D.; Hu, M.B.; Xu, H.; Zhu, W.H.; Hu, J.M.; Yang, T.; Jiang, H.W.; Ding, Q. Body mass index is associated with higher Gleason score and biochemical recurrence risk following radical prostatectomy in Chinese men: a retrospective cohort study and meta-analysis. World J Surg Oncol. 2015, 13, 311.

11. Nwadi, U.V.; Nwofor, A.M.E.; Oranusi, C.K.; Orakwe, J.C.; Obiesie, E.A.; Mbaeri, T.U.; Abiahu, J.A.; Mbonu, O.O. Correlation between Body Mass Index and Gleason Score in Men with Prostate Cancer in Southeastern Nigeria. Niger J Surg. 2021, 27, 22–27.

12. Inoue, K.; Goto, A.; Sugiyama, T.; Ramlau-Hansen, C.H.; Liew, Z. The Confounder-Mediator Dilemma: Should We Control for Obesity to Estimate the Effect of Perfluoroalkyl Substances on Health Outcomes? Toxics. 2020, 8, 125.

13. Yan, R.; Liu, T.; Peng, Y.; Peng, X. Can statistical adjustment guided by causal inference improve the accuracy of effect estimation? A simulation and empirical research based on meta-analyses of case-control studies. BMC Med Inform Decis Mak. 2020, 20, 333.

14. 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.

15. Hu, M.B.; Xu, H.; Bai, P.D.; Jiang, H.W.; Ding, Q. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Med Oncol. 2014, 31, 829.

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014, 12, 1495–1499.

18. Castaño-Vinyals, G.; Aragonés, N.; Pérez-Gómez, B.; Martín, V.; Llorca, J.; Moreno, V.; Altzibar, J.M.; Ardanaz, E.; de Sanjosé, S.; Jiménez-Moleón, J.J.; *et al*. PopulationBased multicase-control study in common tumors in Spain (MCCSpain): rationale and study design. Gaceta Sanitaria. 2015, 29, 308–315

19. Alonso-Molero, J.; Molina, A.J.; Jiménez-Moleón, J.J.; Pérez-Gómez, B.; Martin, V.; Moreno, V.; Amiano, P.; Ardanaz, E.; de Sanjose, S.; Salcedo, I.; *et al*. Cohort profile: the

MCC-Spain follow-up on colorectal, breast and prostate cancers: study design and initial results. BMJ Open. 2019, 9, e031904.

20. World Health Organization. Body Mass Index. Available online: https://www.who.int/data/gho/data/themes/theme-details/GHO/body-mass-index-(bmi) (accessed on 17 July 2021).

21. Lennon, H.; Sperrin, M.; Badrick, E.; Renehan, A.G. The Obesity Paradox in Cancer: a Review. Curr Oncol Rep. 2016, 18, 56.

22. Lee, D.H.; Giovannucci, E.L. The Obesity Paradox in Cancer: Epidemiologic Insights and Perspectives. Curr Nutr Rep. 2019, 8, 175–181.

23. 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.

24. Allott, E.H.; Masko, E.M.; Freedland, S.J. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013, 63, 800–809.

25. Freedland, S.J.; Grubb, K.A.; Yiu, S.K.; Nielsen, M.E.; Mangold, L.A.; Isaacs, W.B.; Epstein, J.I.; Partin, A.W.; *et al*. Obesity and capsular incision at the time of open retropubic radical prostatectomy. J Urol. 2005, 174, 1798–1801.

26. Sun, L.; Xu, T.; Yuan, X.; Liu, F.; Guan, F.; Ye, D.; Zhang, G. Obesity is a predictor in prostate cancer patients receiving prostatectomy after neoadjuvant hormonal therapy. Tumori. 2020, 106, 133–138.

27. 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.

28. 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.

29. Langlais, C.S.; Graff, R.E.; Van Blarigan, E.L.; Palmer, N.R.; Washington, S.L.3rd.; Chan, J.M.; Kenfield, SA. Post-Diagnostic Dietary and Lifestyle Factors and Prostate Cancer Recurrence, Progression, and Mortality. Curr Oncol Rep. 2021, 23, 37.

VII. DISCUSIÓN

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Esta Tesis Doctoral plantea un tema que hasta la fecha había generado resultados inconsistentes, cuya información no había sido aunada de manera robusta con los datos de los estudios recientes publicados, ni había sido abordado con datos de pacientes en nuestro país: el estudio de la relación entre la obesidad y el pronóstico del cáncer de próstata. Tal y como puede desprenderse de la lectura de los resultados presentados en cada uno de los trabajos que conforman la Tesis, la investigación desarrollada ha permitido:

1) Evaluar la escasa presencia de recomendaciones asociadas a un peso saludable (y, en general, a estilos de vida saludables) en las guías clínicas de cáncer de próstata actualizadas.

2) Comparar la magnitud de la asociación entre distintos grupos del IMC con el riesgo de desarrollar desenlaces pronósticos negativos tras el diagnóstico de cáncer de próstata, especialmente aquellos referidos a la mortalidad y a la recurrencia bioquímica.

3) Cuantificar la asociación entre la obesidad y el pronóstico de cáncer de próstata estratificada por diversos factores, considerados como potenciales fuentes de heterogeneidad, así como la presencia de potenciales sesgos de publicación.

4) Analizar la asociación entre la obesidad y el pronóstico del cáncer de próstata en una muestra amplia de pacientes diagnosticados en España, en el seno del estudio MCC-Spain.

En esta sección se procederá a discutir de forma conjunta los resultados obtenidos en los cuatro trabajos y su posible aplicación práctica. También se discutirá la metodología utilizada y se plantearán posibles líneas de trabajo futuras.

1. DISCUSIÓN DE LOS PRINCIPALES RESULTADOS

El primer trabajo (*Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review*) muestra que la presencia de recomendaciones relativas al peso saludable y, general, a hábitos de vida saludables, está pobremente recogida en las guías de práctica clínica actuales sobre cáncer de próstata realizadas por sociedades oficiales y gobiernos. Menos de uno de cada diez documentos oficiales registraron recomendaciones en este sentido, a pesar de la creciente evidencia de la relación entre peso y diagnóstico o pronóstico de cáncer de próstata. Al analizar los principales factores que podían estar asociados a esta baja frecuencia de recomendaciones, se observó que no existían diferencias por tipo de documento, país o año de publicación.

En el segundo trabajo, *"Obesity as a risk factor for prostate cancer mortality: A systematic review and dose-response meta-analysis of 280,199 patients"*, se confirma nuestra hipótesis de que, de acuerdo con los estudios observacionales analíticos publicados hasta la fecha, existe una asociación entre el IMC (tanto medido de forma cuantitativa por cada 5 unidades de incremento como categóricamente como obesidad = IMC ≥ 30) y la mortalidad en pacientes diagnosticados de cáncer de próstata. Esta asociación se observa para la mortalidad específica por cáncer de próstata y para la mortalidad por todas las causas. Sin embargo, observamos una heterogeneidad inasumible, por lo que los resultados sintetizados fueron estratificados por factores de heterogeneidad. Al realizar el análisis por subgrupos, comprobamos que los resultados se mantenían similares para casi todos los grupos analizados, aunque la heterogeneidad disminuyó notablemente, datos que se corroboraron en los estudios con mayor calidad de acuerdo con la escala NOS. No obstante, detectamos que los tratamientos, la

medición de la exposición (antes o después del diagnóstico) y la calidad de los estudios fueron fuentes de heterogeneidad considerable, si bien la heterogeneidad no se eliminó completamente en ninguno de los casos.

El tercer trabajo, "*Obesity and biochemical recurrence in clinically localized prostate cancer: A systematic review and meta-analysis of 86 490 patients",* pone de manifiesto la relación existente entre el IMC y el desarrollo de recurrencia bioquímica en pacientes diagnosticados de cáncer de próstata localizado, de acuerdo con la información disponible en estudios de cohortes publicados hasta la fecha. Este estudio indaga en la hipótesis de que la obesidad dificulta la cirugía prostática y ello, unido a las modificaciones biológicas y endocrinológicas de la obesidad, aumenta el riesgo de padecer recurrencia tras la prostatectomía. Nuevamente, la elevada heterogeneidad llevó a la realización de un análisis de subgrupos, en el que se observó que una forma poco estandarizada de recoger la variable de exposición (obesidad) y, sobre todo, de medir la variable de desenlace (recurrencia bioquímica) daba lugar a diferencias en la magnitud de la asociación. Nuestro análisis de subgrupos, en cualquier caso, nos permitió reforzar la asociación entre obesidad y recurrencia bioquímica, al valorar los estudios de mayor calidad de forma aislada.

En el cuarto trabajo, *"Evaluating the association between body mass index and prostate cancer outcomes. An observational longitudinal study from the Spanish multi-case control study (MCC-Spain)"*, evaluamos la relación entre obesidad y pronóstico de cáncer de próstata en una muestra amplia de pacientes diagnosticados en España. Este estudio atestigua la presencia de una asociación entre obesidad y dos desenlaces pronósticos negativos: la recurrencia bioquímica (tal como observamos en el tercer estudio) y la resistencia a la castración (que puede ser entendida como otra forma de recurrencia o fallo del tratamiento).

En este estudio, además, indagamos sobre la utilización de determinados factores dentro de los modelos multivariantes, de acuerdo con la búsqueda de una asociación causal. Así, las escalas pronósticas utilizadas al diagnóstico (tales como la escala de Gleason) demuestran ser mediadores de la asociación causal entre obesidad y pronóstico del cáncer de próstata.

A continuación, se revisarán los resultados comentados anteriormente, dividiéndolos en grandes bloques.

1.1. LA BAJA FRECUENCIA DE RECOMENDACIONES PRESENTES EN LAS GUÍAS DE PRÁCTICA CLÍNICA

Tal como se puede observar en el Trabajo 1 de esta Tesis Doctoral, existe una escasa presencia de recomendaciones relativas al peso o a estilos de vida saludables para pacientes diagnosticados de cáncer de próstata. Sin embargo, numerosos estudios hasta la fecha han mostrado que la obesidad y otros factores relacionados con los estilos de vida tienen implicación como factores de riesgo (Bandini *et al*., 2017) y como factores pronósticos (Hu *et al*., 2014) del cáncer de próstata. Ello ha dado lugar a que organismos internacionales tales como el *World Cancer Research Fund* (2021) y la Organización Mundial de la Salud (2021) hayan incluido la obesidad como un factor asociado al diagnóstico y pronóstico de esta enfermedad. Además, los estilos de vida saludables han probado mejorar el pronóstico de múltiples enfermedades en la población general, tales como enfermedades cardiovasculares (Csige *et al*., 2018), enfermedades crónicas (Lavie *et al*., 2014) y la supervivencia por todas las causas (Zhang *et al*., 2015). Por tanto, parece evidente que recomendar a los pacientes (diagnosticados de cáncer de próstata o de la población general) sobre estilos de vida

saludables es potencialmente beneficioso para la salud y genera pocos riesgos negativos para su pronóstico. Sin embargo, y a pesar de esta evidencia, las guías de práctica clínica de cáncer de próstata apenas abordan esta cuestión.

1.2. LA ASOCIACIÓN ENTRE OBESIDAD Y MORTALIDAD EN PACIENTES DIAGNOSTICADOS DE CÁNCER DE PRÓSTATA

Los resultados presentados en el Trabajo 2 de esta Tesis Doctoral muestran una asociación clara entre obesidad y mortalidad en pacientes diagnosticados de cáncer de próstata. Estos resultados, que ya habían sido sugeridos por otros autores utilizando como variable de exposición el IMC antes del diagnóstico, en diversos momentos de la vida (Nguyen *et al*., 2010; Cao *et al*., 2011; Chamberlain *et al*., 2011; Gerdtsson *et al*., 2015; Zhong *et al*., 2016), han sido confirmados también al utilizar como variable de exposición el IMC después del diagnóstico (Rivera-Izquierdo *et al*., 2021). Es importante recalcar que la asociación entre el IMC y la mortalidad por cáncer de próstata podría ser diferente de acuerdo con el tratamiento recibido por cada paciente (por ejemplo, en pacientes que reciben prostatectomía podría no ser igual que en los que reciben radioterapia, como atestiguan las diferencias observadas en el análisis de subgrupos, insuficiente por no contar con un número suficiente de artículos para cada tratamiento evaluado). Sin embargo, las HR ajustadas mostraron una asociación consistentemente positiva, aunque de magnitud variable, entre la mayoría de los subgrupos analizados. Nuestros resultados principales quedan respaldados por la presencia de una asociación positiva en el subgrupo de estudios de mayor calidad (NOS $\geq$ 8), lo que sugiere que la asociación entre estas variables (IMC y mortalidad) merece ser considerada.

Cuando se analiza la potencial asociación entre obesidad y mortalidad desde una perspectiva causal, es necesario considerar los criterios de causalidad de Bradford Hill (Hill, 1965). Estos criterios han de ser discutidos en toda revisión sistemática y metanálisis de estudios observacionales, con el objetivo de proponer (y nunca confirmar) posibles asociaciones causales (Khan *et al*., 2012). Nuestro análisis sugiere que existe una fuerza de asociación moderada, consistencia, temporalidad, especificidad, gradiente dosis-respuesta, plausibilidad biológica y analogía. Respecto a la fuerza de asociación, las HR ajustadas fueron todas significativamente superiores a 1. Además, dicha asociación se observó de manera consistente entre los subgrupos de análisis estratificado, incluidos aquellos en los que la heterogeneidad se redujo al máximo, lo que habla de una cierta consistencia entre los estudios. Aproximadamente tres cuartas partes de los estudios incluidos, como se observa gráficamente en los diagramas de bosque, mostró una asociación positiva entre el IMC y la mortalidad. Además, los estudios que analizaron la obesidad con mediciones diferentes a las aproximaciones realizadas en esta Tesis Doctoral (IMC), también mostraron una asociación consistente con la mortalidad por cáncer de próstata (Nguyen *et al*., 2010; Chamberlain *et al*., 2011; Gerdtsson *et al*., 2015). Respecto al criterio de temporalidad, este fue establecido al incluir únicamente estudios longitudinales (estudios de cohortes y de casos y controles) en el metanálisis. La especificidad, que es un criterio muy difícil de cumplir para cualquier estudio epidemiológico, se trató de abordar mediante el desenlace "mortalidad específica por cáncer de próstata", así como al incluir únicamente las HR ajustadas de los análisis multivariantes más completos de cada estudio. Respecto al gradiente biológico, mostramos una relación dosis-respuesta al utilizar el IMC como variable continua (por cada 5 unidades), y observar una asociación de esta con la mortalidad. La plausibilidad biológica de la asociación queda reforzada por numerosos mecanismos que han sido sugeridos para explicar por qué la obesidad

puede influir en la mortalidad por cáncer de próstata (Zhong *et al*., 2016). Por ejemplo, la obesidad es la causa más común de resistencia a la insulina, que ha sido asociada con un mayor estado inflamatorio sistémico, factor de riesgo para la progresión del cáncer (Arcidiacono *et al*., 2015). Otros mecanismos moleculares han sido también ampliamente descritos para explicar la conexión entre obesidad y mortalidad por cánceres uroteliales (Santoni *et al*., 2019). Finalmente, también creemos que el criterio de analogía está presente en esta asociación. Así, de acuerdo con la literatura científica actual, la obesidad ha sido asociada con la mortalidad por numerosos tipos de cáncer en las últimas décadas (Cao *et al*., 2011; Petrelli *et al*., 2021), y con otros desenlaces negativos del cáncer de próstata altamente relacionados con la mortalidad, como por ejemplo la presencia de metástasis en el momento del diagnóstico (Annett *et al*., 2020).

A pesar de todo ello, sin embargo, cuando analizamos esta relación en nuestro estudio original realizado sobre pacientes españoles, no pudimos observar una relación significativa en los análisis multivariantes.

En la actualidad, el *World Cancer Research Fund* (2021) asume que la obesidad está relacionada con el diagnóstico avanzado del cáncer de próstata, aunque estudios recientes de muy amplio tamaño muestral han cuestionado esta relación recientemente (Genkinger, 2020; Jochems, 2020). De acuerdo con lo anteriormente expuesto (esto es, la presencia de una asociación consistente en el metanálisis, el aparente cumplimiento de numerosos criterios de causalidad y, sobre todo, la relación establecida en la población general entre obesidad y peores desenlaces pronósticos) parece evidente la necesidad de incluir recomendaciones sobre peso saludable en las guías de práctica clínica, así como de enfatizar el rol de la obesidad en el pronóstico del cáncer de próstata desde el momento en que este se diagnostica.

1.3. LA ASOCIACIÓN ENTRE OBESIDAD Y RECURRENCIA BIOQUÍMICA

Con respecto a la asociación entre obesidad y recurrencia bioquímica, los resultados presentados en el Trabajo 3 de esta Tesis Doctoral muestran una asociación clara entre ambas variables, tanto al analizar el IMC de manera continua por cada 5 unidades como al analizar el IMC de manera categórica (obesidad = IMC ≥ 30, comparado con pacientes con normopeso, IMC < 25). Nuevamente, hemos de considerar esta asociación con cierta precaución, dado que la heterogeneidad hallada en los estudios incluidos fue excesivamente elevada. Sin embargo, los principales hallazgos de nuestro estudio fueron consistentes en el subgrupo de estudios de mayor calidad (NOS ≥ 8). Los resultados más consistentes presentados en esta Tesis Doctoral hacen referencia a los pacientes que recibieron prostatectomía, en los que la asociación se confirmó para los estudios de mayor calidad y para la mayoría de los subgrupos analizados, así como para el subgrupo de estudios en los que el IMC se midió directamente por los investigadores, en lugar de maneras indirectas como las historias clínicas, registros o referidos por los propios pacientes. En dichos subgrupos, la heterogeneidad alcanzó un valor I^2 del 0%, y la asociación se mantuvo positiva. Dados estos resultados, pensamos que la asociación entre obesidad y recurrencia bioquímica en el cáncer de próstata es aún más consistente que la hallada para la mortalidad y que merece ser considerada.

Los criterios de causalidad de Bradford Hill (Hill, 1965) fueron también aplicados al Trabajo 3 de acuerdo con las recomendaciones para metanálisis de estudios observacionales (Khan *et al*., 2012). En este caso, observamos una moderada fuerza de asociación, temporalidad, plausibilidad biológica y analogía, aunque no se pudieron observar evidencias de gradiente

dosis-respuesta o especificidad de la asociación. De acuerdo con la fuerza de asociación, la HR ajustada del metanálisis mostró una asociación significativa y moderada. La consistencia de la asociación no pudo ser confirmada dado que la heterogeneidad global del estudio fue muy elevada. Sin embargo, entre los subgrupos sobre los que se realizó el análisis estratificado, dicha asociación fue confirmada, especialmente para los estudios de mayor calidad. Podemos afirmar que la asociación fue consistente para pacientes con cáncer de próstata localizado que recibieron prostatectomía, pero no para aquellos que recibieron otros tratamientos (por ejemplo, radioterapia o braquiterapia).

Una parte de las inconsistencias observadas entre los estudios podría ser parcialmente explicada por la *paradoja de la obesidad* (Leal-García *et al*., 2020). Dicha paradoja ha sido ya sugerida en previos estudios realizados sobre el pronóstico de cáncer de próstata que reportan que los pacientes con sobrepeso u obesidad tienen mejor pronóstico (especialmente menor riesgo de desarrollo de metástasis) que aquellos obesos (Khan *et al*., 2018). Esta paradoja puede ser explicada, en parte, por la inclusión de pacientes con caquexia (dato que refleja un estado avanzado del proceso neoplásico) dentro de los grupos de comparación (IMC < 25). Al no ajustar por variables clínicamente relevantes, capaces de discernir entre personas con normopeso y personas con un estado avanzado del cáncer, la asociación se ve sesgada. Finalmente, con respecto a la consistencia, podemos observar que otros estudios que han analizado la obesidad con medidas diferentes al IMC (por ejemplo, mediante genes relacionados con la obesidad, cambios de peso a lo largo de la vida, etc.), muestran también una relación consistente con el desarrollo de recurrencia bioquímica (Whitley *et al*., 2011; Pérez-Cornago *et al*., 2017; Khan *et al*., 2018; Keith *et al*., 2021). Gran parte de la

heterogeneidad entre estudios, de acuerdo con estos datos y con nuestro análisis de subgrupos, se debió al uso de diferentes fuentes y puntos de corte para la medición de la exposición (IMC) y, sobre todo, del desenlace (recurrencia bioquímica), cuyos valores mínimos del PSA son considerados de manera diferente entre los estudios, aunque en los últimos años parece haberse establecido el límite de 0,2 ng/ml como el parámetro estándar para su diagnóstico. Con respecto a la temporalidad (evidencia de que la exposición ocurre antes que el desenlace), esta queda asegurada con la inclusión de estudios de cohortes exclusivamente en nuestro metanálisis. El gradiente biológico, por el contrario, no pudo ser confirmado, puesto que las asociaciones entre el IMC continuo por cada 5 unidades y la recurrencia bioquímica no fueron significativas en varios de los subgrupos analizados. En cualquier caso, ello solo indicaría la ausencia de una relación lineal, existiendo la posibilidad de que haya una relación dosis-respuesta de otro tipo entre ambas variables analizadas. La plausibilidad biológica de la asociación queda postulada por numerosos mecanismos. Por ejemplo, la desregulación del eje insulina – IGF-1 (Leal-Garcia *et al*., 2020) y de la señalización de las adipoquinas (Tan *et al*., 2015) están afectados en pacientes obesos, y ello ha sido asociación con la recurrencia bioquímica y la gravedad del cáncer de próstata. Por tanto, este potencial mecanismo bioquímico podría justificar el incremento en la frecuencia de recurrencia bioquímica en pacientes obesos. Además, el hecho de que la obesidad se relacione con este desenlace de forma consistente en los pacientes que reciben prostatectomía nos hace sospechar la presencia de dificultades quirúrgicas en pacientes con mayor IMC. De hecho, la obesidad se ha asociado con la presencia de márgenes quirúrgicos positivos o invasión extraprostática (Yu *et al*., 2018) en dicha operación. Los factores relacionados con la cirugía que pueden mediar en esta asociación han sido también descritos en previos trabajos. Así, la prostatectomía radical es más compleja en pacientes con mayor cantidad de grasa subcutánea y visceral (Han *et al*.,

2020), lo que dificulta la extracción completa y limpia de la víscera (próstata) y, por tanto, puede dar lugar a que pequeños restos de la glándula queden viables y den lugar a la recurrencia bioquímica de la enfermedad. Además, el aumento del tamaño de la glándula prostática asociada con la obesidad (Muller *et al*., 2013), el exceso de tejido adiposo, el limitado espacio quirúrgico de trabajo, la mayor distancia entre piel y zona quirúrgica y la visualización subóptima, también incrementados en pacientes obesos (Han *et al*., 2020), aumentan la probabilidad de futura recurrencia bioquímica. Respecto al criterio de analogía, la presencia de asociaciones detectadas entre la obesidad y la recurrencia local en otros tumores ha sido ampliamente descrita (Scarpa *et al*., 2014; Kim *et al*., 2021).

Además, en el Trabajo 4 de esta Tesis Doctoral encontramos una asociación clara entre obesidad y recurrencia bioquímica tras el análisis multivariante mediante regresión de Cox. Ello da fe de la consistencia de esta asociación en pacientes diagnosticados de cáncer de próstata en España.

De acuerdo con lo anteriormente expuesto (esto es, la presencia de una asociación consistente en el metanálisis, el aparente cumplimiento de numerosos criterios de causalidad, el hallazgo de esta asociación en nuestro estudio de supervivencia sobre pacientes en España y la relación establecida en la población general entre obesidad y peores desenlaces pronósticos) se refuerza la necesidad de incluir recomendaciones sobre peso saludable en las guías de práctica clínica sobre cáncer de próstata.

1.4. LA ASOCIACIÓN ENTRE OBESIDAD Y OTROS DESENLACES PRONÓSTICOS

Como podemos observar en el Trabajo 4, la obesidad se comparó con otros desenlaces pronósticos distintos de la mortalidad y la recurrencia bioquímica, tales como la aparición de nuevas metástasis y la resistencia a la castración. Para el primero de ellos no se observó asociación en los modelos multivariantes diseñados. Sin embargo, para la resistencia a la castración, la obesidad sí mostró una relación positiva.

Este estudio, por tanto, incrementa el conocimiento aportado por la literatura científica hasta la fecha respecto a la asociación de la obesidad con potenciales factores pronósticos del cáncer de próstata. No está claro si la asociación entre el IMC y la resistencia a la castración se debe a un efecto biológico de la obesidad o bien es resultado de un mayor fracaso terapéutico debido, quizás, a una menor efectividad de los tratamientos en pacientes obesos (Allott *et al*., 2012; Jochems *et al*., 2020). Se ha sugerido que la terapia hormonal utilizada en muchas ocasiones para el cáncer de próstata se ve afectada por la obesidad y se asocia a variaciones endocrinas que pueden influir en el pronóstico del cáncer de próstata (Freedland *et al*., 2005). Entre ellos, la obesidad podría contribuir a la resistencia a la castración debido a mayores niveles de testosterona total y libre (Armstrong *et al*., 2009).

Estos datos están de acuerdo con nuestros hallazgos, puesto que las principales asociaciones de la obesidad que encontramos en nuestro estudio original fueron con la recurrencia bioquímica y la resistencia a la castración, en ambos casos recidivas de la enfermedad tras el tratamiento de elección (quirúrgico u hormonal, respectivamente). Sin embargo, esta

asociación por sí misma parece insuficiente para explicar la asociación entre IMC y mortalidad, ampliamente descrita en la literatura científica y reforzada por nuestro metanálisis (Rivera-Izquierdo *et al*., 2021a). Ello sugiere la existencia de una asociación mediada por un mecanismo biológico aun no descrito, que requiere mayor investigación en el futuro.

Finalmente, la asociación entre la obesidad y los desenlaces pronósticos asociados a la calidad de vida, tales como la incontinencia urinaria o la disfunción sexual (especialmente tras recibir tratamiento quirúrgico) no ha sido estudiada en esta Tesis Doctoral, pero su análisis profundo sería de interés para complementar el efecto de la obesidad en el pronóstico del cáncer de próstata.

1.5. LA CONTRIBUCIÓN DE FUENTES DE HETEROGENEIDAD A LOS RESULTADOS OBSERVADOS

En los Trabajos 2 y 3 se han detectado importantes fuentes de heterogeneidad que, en el análisis de subgrupos, arrojaban valores del estadístico I^2 muy próximos al 0% (ausencia de heterogeneidad debida a causas diferentes al azar) al estratificar por dichas variables. La más importante de ellas es la medición de la exposición (IMC). Esta medida tuvo lugar, en función de los estudios, en tiempos diferentes (antes o después del diagnóstico), de fuentes diferentes (medida directamente por el investigador, mediante registros clínicos o referida por los pacientes) y de maneras diferentes (una amplia mayoría se ajustó a los criterios de la OMS para la población general, pero otros pocos se dividieron en función de los puntos de corte de

la OMS para población asiática, o el IMC únicamente de manera continua sin formar grupos de exposición).

Con respecto a las variables de desenlace, si bien la mortalidad es un fenómeno sencillo y homogéneo de medir, la recurrencia bioquímica no lo es tanto. Así, se definió como recurrencia bioquímica valores de entre 0,1 ng/ml hasta 0,4 ng/ml en distintos estudios, siendo la medición de 0,2 ng/ml la más utilizada, especialmente en los estudios más recientes. Nuestro metanálisis pone de manifiesto la necesidad de homogeneizar esta medida en distintos contextos y medios para facilitar las comparaciones entre estudios. Finalmente, la tercera fuente de heterogeneidad, también muy relevante, fue el tratamiento recibido por los pacientes. Así, la asociación entre obesidad y pronóstico no fue igual en pacientes tratados mediante prostatectomía que en aquellos que recibieron radioterapia o braquiterapia.

Hubo otras fuentes de heterogeneidad, tales como la región donde tuvo lugar el estudio (especialmente al considerar si se trataba de estudios en países desarrollados o en vías de desarrollo), el año de publicación, la calidad de los estudios y las variables por las que cada estudio ajustó en su análisis multivariante. En este sentido, no es de extrañar que la ausencia de un planteamiento causal postulado *a priori* entre la obesidad y los desenlaces en todos los estudios revisados (ninguno de los cuales presentó un gráfico acíclico dirigido con este propósito), dé como resultado la inclusión de covariables de ajuste muy dispares en cada estudio, lo que indudablemente contribuye a aumentar la heterogeneidad de los resultados observados. Todos estos factores fueron considerados en el análisis de subgrupos de ambos metanálisis.

2. DISCUSIÓN DE LA METODOLOGÍA Y FUENTES DE INFORMACIÓN UTILIZADAS

2.1. FORTALEZAS Y LIMITACIONES DERIVADAS DE LAS FUENTES DE INFORMACIÓN

Los Trabajos 1 a 3, al ser revisiones sistemáticas, se han basado en fuentes de información secundarias (esto es, en artículos y documentos publicados). Las principales fortalezas de estos trabajos se desprenden del diseño de los estudios incluidos y de la evaluación de la calidad metodológica realizada. Así, en el Trabajo 1 se consideraron únicamente las guías de práctica clínica y documentos de consenso diseñadas o respaldadas por sociedades profesionales o bien por organismos gubernamentales, y se excluyeron aquellos que aparecían en webs no respaldadas o aquellas dirigidas a los pacientes y a la población general. En los Trabajos 2 y 3 se incluyeron los estudios que por su diseño permitían analizar el papel de la obesidad como un factor pronóstico (obesidad), esto es, estudios observacionales longitudinales (analíticos), todos ellos (salvo uno) con sentido hacia delante (estudios de cohortes). Para tratar de reducir la posible heterogeneidad introducida por sesgos de confusión se obtuvo, además, información de los análisis multivariantes que tenían más variables de ajuste consideradas, y únicamente se consideraron asociaciones crudas (no ajustadas) cuando los autores no reportaron medidas de fuerza de asociación ajustadas. La principal limitación de estas fuentes de información, sin embargo, fue la ausencia de datos directos, esto es, del número de sujetos que desarrollaron el desenlace de interés (cada desenlace pronóstico analizado en esta Tesis Doctoral) estratificado por los grupos de exposición (en función del IMC). El hecho de no disponer de estos datos en

un amplio porcentaje de los estudios incluidos se unió al hecho de que realizamos técnicas metanalíticas para analizar un factor pronóstico y, por tanto, para trabajar con datos crudos habríamos necesitado de una tercera variable: el tiempo que tarda cada sujeto en desarrollar el desenlace de interés. Por desgracia, ningún estudio muestra estos datos, dado que cada paciente tarda un tiempo determinado en desarrollar (o no) el desenlace y, por tanto, se requeriría de las bases de datos de todos los estudios incluidos para poder hacer metanálisis de datos agrupados. Ello nos llevó a realizar metanálisis de datos indirectos, esto es, de las HR reportadas por cada estudio incluido. Naturalmente, esto introduce un potencial sesgo: en primer lugar, hemos de confiar en que las HR reportadas por los autores son correctas y reflejan el resultado de un adecuado análisis multivariante (si bien este difiere en cada estudio) y, en segundo lugar, obtenemos una estimación redondeada (habitualmente las HR reportadas no tienen más de uno o dos decimales). Finalmente, e igual de relevante, los estudios incluidos (que representan nuestra fuente de información para los Trabajos 2 y 3), no recogieron de igual manera la variable de exposición y la variable de desenlace. El hecho, por ejemplo, de obtener la obesidad de manera autorreferida por los pacientes ya introduce un sesgo de información importante en cada estudio individual. No obstante, la estratificación por fuentes de información en nuestros análisis de subgrupos trata de abordar este problema y obtener estimaciones menos sesgadas, que no resultaron en cambios significativos de la HR global. Con respecto al Trabajo 4, los datos analizados provienen del estudio MCC-Spain. A pesar de que este estudio trata de homogeneizar la recogida de datos entre los diferentes nodos, no sería de extrañar una recogida diferencial de algunas variables de interés entre los distintos investigadores y centros participantes. Otra forma de abordar este problema fue el análisis de los datos estratificados por centro, siempre y cuando el tamaño de muestra lo permitió, que no

mostraron diferencias importantes en los resultados para las principales variables de interés (datos no mostrados).

En relación con la variable de exposición, el peso corporal, el estudio MCC-Spain lo hace de forma autorreferida por el paciente para un año previo al diagnóstico. Esta forma de recoger la información puede dar lugar a sesgos de información por varios motivos: 1) Los pacientes tienden a infraestimar su peso y sobreestimar su altura, lo que daría lugar a un IMC menor que el real, lo que dificultaría la posibilidad de encontrar asociaciones (Basterra-Gotari *et al*., 2007); 2) Los puntos de corte utilizados para la definición de obesidad y sobrepeso a partir del IMC no son aplicables en poblaciones ancianas; 3) El peso un año antes del diagnóstico puede que no sea el real en el momento del diagnóstico y, sobre todo, durante el seguimiento, pudiendo infraestimar o sobreestimar la asociación encontrada. No obstante, el cáncer de próstata no suele asociarse con pérdidas importantes de peso antes del diagnóstico (Cornford *et al*., 2021), tratándose además de un peso bastante estable en estas edades de la vida (Babiarczyk *et al*., 2012).

Finalmente, en los dos metanálisis realizados se detectó un potencial sesgo de publicación en alguna de las asociaciones estudiadas (Trabajos 2 y 3). Así, se identificó el *efecto de estudios pequeños* mediante diagrama de embudo y el valor p del test de Egger para la asociación entre obesidad y mortalidad específica por cáncer de próstata, y para la asociación entre el incremento del IMC por cada 5 unidades y la recurrencia bioquímica. Estos datos indican que, a pesar de realizar una búsqueda sensible para tratar de incluir todos los estudios publicados, no se puede descartar un sesgo de publicación en el sentido en que estudios de pequeño tamaño muestral con asociaciones negativas (inversas) se publiquen con menor frecuencia que aquellos con asociaciones positivas y, por tanto, las HR obtenidas en los metanálisis podrían

tener un sesgo alejado hacia el nulo a favor de una magnitud de la asociación mayor a la realmente existente (salvo para la asociación entre IMC por cada 5 unidades y mortalidad por todas las causas, en la que se detectó un sesgo en sentido contrario).

2.2. FORTALEZAS Y LIMITACIONES DERIVADAS DE LA METODOLOGÍA

Parte de las fortalezas y limitaciones de la metodología ya han sido comentadas en el punto anterior en relación principalmente con las fuentes de información y medición de las variables de interés. No obstante, hay que destacar que los Trabajos 1 a 3 presentan como principal fortaleza la definición de una ecuación de búsqueda amplia y sensible, y la estrategia de búsqueda en numerosas bases de datos que dio lugar a una selección inicial de 2843, 7287 y 5490 documentos, respectivamente. Se siguieron las recomendaciones establecidas por la guía PRISMA (Page *et al*., 2021) para reportar y estructurar nuestros trabajos, siguiendo así con los estándares internacionalmente aceptados para revisiones sistemáticas y metanálisis.

Con respecto a las limitaciones, hay que destacar las propias de la naturaleza observacional de los estudios incluidos en las revisiones sistemáticas realizadas. No obstante, creemos que se trata del mejor diseño posible, dado que para un factor de riesgo no se pueden emplear estrategias experimentales, salvo que éstas se centren en la reducción del peso, estudios muy escasos hasta la fecha y que actualmente se encuentran en fase de diseño (Freedland *et al*., 2020). Con respecto al Trabajo 1, una limitación importante es que no se halló ninguna herramienta validada para el análisis de las recomendaciones sobre obesidad y estilos de vida y, por tanto, la presencia de dichas recomendaciones tuvo que ser recogida de manera manual y *ad hoc* por los investigadores, tras realizar una lectura detenida de cada documento

seleccionado. Respecto a los Trabajos 2 y 3, consideramos que la metodología aplicada en los metanálisis fue adecuada, como se ha comentado en apartados previos, al realizar un análisis detallado de las fuentes de heterogeneidad mediante análisis de subgrupos y al analizar el sesgo de publicación. No obstante, como principal limitación debemos destacar que la heterogeneidad no se eliminó completamente en el análisis de subgrupos, por lo que los resultados globales se han de interpretar con cautela. Finalmente, respecto al estudio 4, una fortaleza de nuestra metodología fue aplicar los criterios de la guía STROBE para redactar los resultados (von Elm *et al*., 2014) y realizar análisis multivariantes mediante regresión de Cox en los que se consideró la no inclusión de escalas pronósticas al diagnóstico. Como principal limitación de este estudio debemos destacar la ausencia de la realización de un diagrama acíclico dirigido completo que ilustre la asociación causal entre obesidad y pronóstico de cáncer de próstata incluyendo las potenciales variables asociadas, para optimizar el uso de las variables de ajuste en los modelos multivariantes de acuerdo con un modelo causal. En nuestro estudio, tratamos de abordar el papel de la escala de Gleason como mediador, pero la inclusión del resto de variables implicadas en esta asociación será sin duda necesaria para reducir la heterogeneidad y mejorar el diseño de los análisis multivariantes que se realicen en estudios futuros.

3. UTILIDAD PRÁCTICA DE LOS RESULTADOS OBTENIDOS

El Trabajo 1 muestra que, a pesar de la asociación establecida entre obesidad y peor pronóstico del cáncer, estas recomendaciones no se incluyen en las guías de práctica clínica de cáncer de próstata actuales. Numerosas organizaciones tales como la *Prostate Cancer Foundation*, la

Clínica Mayo o la Organización Mundial de la Salud (OMS, 2021) recomiendan el mantenimiento de un peso adecuado para evitar la aparición y peor pronóstico de numerosos tipos de cáncer. Aún en el caso de que la asociación entre obesidad y pronóstico específico del cáncer fuese incierta, múltiples estudios han demostrado que el peso adecuado y los estilos de vida saludables mejoran el pronóstico de enfermedades cardiovasculares (Csige *et al*., 2018) y de enfermedades crónicas (Lavie *et al*., 2014), y se asocian a una reducción de la mortalidad global por todas las causas (Cao *et al*., 2011). Por tanto, recomendaciones que son útiles y válidas para la población general podrían ser también aplicables a los pacientes de cáncer de próstata, por lo que realizar recomendaciones en este sentido parece tener un riesgo bajo para la salud de estos pacientes.

Los Trabajos 2 a 4 muestran que la asociación entre el peso corporal y los desenlaces pronósticos del cáncer de próstata puede ser una realidad y, por tanto, sugieren que la actuación sobre este factor podría tener beneficios en términos de prevención. Los resultados de esta Tesis Doctoral avalan, por tanto, que las guías de práctica clínica sobre cáncer de próstata incluyan recomendaciones sobre peso y estilos de vida saludables. Además, nuestros trabajos tienen implicaciones interesantes de cara al diseño y realización de estudios futuros: mostramos recomendaciones sobre cómo recoger las variables de exposición y desenlace de forma homogénea, así como las principales limitaciones de los estudios observacionales publicados hasta la fecha, la mayoría de las cuales son relativamente fáciles de subsanar. Finalmente, proponemos líneas de investigación futuras que sirvan para seguir avanzando en el conocimiento de esta asociación y en su correcto abordaje preventivo, como mostramos en el siguiente punto.

4. ESTRATEGIAS FUTURAS DE INVESTIGACIÓN

En primer lugar, los estudios observacionales realizados hasta el año 2021 no han incluido algunas variables de interés en sus ajustes, tales como los estilos de vida que pueden estar directamente relacionados con la obesidad (factores dietéticos, ejercicio físico, etc.). Además, la medición del peso se realiza en un momento puntual (generalmente en el momento del diagnóstico), si bien se trata de una variable dinámica que se modifica con el tiempo y cuyos efectos en la salud pueden estar relacionados con dichas variaciones. Por tanto, futuros estudios deberán tener en cuenta estas consideraciones para aproximarnos a la relación entre obesidad y pronóstico de cáncer de próstata de manera diferente a la que se ha publicado hasta el momento de la presentación de esta Tesis Doctoral.

En segundo lugar, sería necesario evaluar la efectividad de los diferentes tratamientos del cáncer de próstata en función del peso corporal. Estos datos, junto con la demostración de una relación entre obesidad y márgenes quirúrgicos positivos durante la prostatectomía u otras complicaciones, ayudarían a optimizar y actualizar las guías de práctica clínica referidas al tratamiento del cáncer de próstata. Asimismo, se requieren estudios que evalúen si, en la actualidad, se está cumpliendo con el tratamiento de elección en cada paciente de acuerdo con las recomendaciones de las guías de práctica clínica actuales.

En tercer lugar, sería de interés estudiar la adopción de estilos de vida saludables por parte de los pacientes después del diagnóstico de cáncer de próstata en comparación con los hábitos previos.

Finalmente, la naturaleza observacional de los estudios realizados hasta la fecha nos lleva a plantear estudios experimentales que se basen en programas de intervención relacionados con

la pérdida de peso, mantenimiento de un peso saludable o mejora en los estilos de vida. En este sentido, numerosos estudios se están enfocando en diseñar y analizar programas de intervención en pacientes diagnosticados de cáncer de próstata (Van Rooijen *et al*., 2019; Wilson *et al*., 2020; Hamilton-Reeves *et al*., 2020; Freedland *et al*., 2021). No obstante, conviene matizar que las recomendaciones podrían ser individualizadas de acuerdo con el estado de la enfermedad. Por ejemplo, es posible que no se deban realizar las mismas intervenciones en pacientes con cáncer localizado o avanzado, en pacientes que están en vigilancia activa, previo a prostatectomía, en tratamiento quimioterápico, etc. A modo de ejemplo, algunos ensayos clínicos están analizando el impacto de la pérdida de peso en pacientes con cáncer de próstata clínicamente localizado (Schenk *et al*., 2019). Una revisión sistemática reciente realizada sobre la cohorte MARTINI-Lifestyle mostró que la adherencia a las recomendaciones sobre estilos de vida era muy pobre en pacientes con cáncer de próstata (Thederan *et al*., 2020). Sin embargo, esta adherencia ha probado reducir la mortalidad por varios tipos de cáncer (Kohler *et al*., 2016). Es, por tanto, fundamental que los estudios futuros aporten evidencias experimentales de la mejoría pronóstica, abordando potenciales estrategias para perder peso (dieta, ejercicio físico, etc.), dado que hasta la fecha las evidencias en este sentido han sido muy escasas (Ballon-Landa *et al*., 2018).

Si dichos estudios consiguen diseñar intervenciones útiles, que se puedan incluir en las guías de práctica clínica, y que se puedan individualizar para cada paciente en función del estado de su enfermedad, los datos observacionales hallados en esta Tesis Doctoral podrán tener su eco en intervenciones clínicas, llegando así a los pacientes y mejorando el pronóstico del cáncer de próstata en el futuro.

VIII. CONCLUSIONS

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According to the objectives proposed in this Doctoral Thesis, the results obtained in the four studies performed allowed us to draw the following conclusions:

1. The presence of recommendations regarding healthy weight or lifestyles is very poor in current prostate cancer clinical guidelines. Only a seventh of all guidelines recommended to adopt healthy lifestyles and only a 7.2% provided advice on reaching or maintaining healthy weight.

2. Considering all analytical observational studies published to date and after obtaining quantitative estimators through meta-analytical techniques, obesity (BMI $\geq$ 30) and continuous BMI of patients diagnosed with prostate cancer were associated with higher risk of prostate cancer specific mortality, all-cause mortality, and biochemical recurrence after radical prostatectomy. Nevertheless, high heterogeneity was found regarding mortality, therefore, no specific relationship between obesity and mortality in prostate cancer patients can be concluded. The association of obesity with biochemical recurrence was stronger and more consistent.

3. The main sources of heterogeneity found in our meta-analyses were the differences in the collection of the exposure variable (BMI) and the collection of the outcome biochemical recurrence. Our results suggest that BMI should be ideally measured by the researchers at the time of diagnosis and collected both quantitatively and according to the WHO boundaries. Biochemical recurrence should be considered homogeneously in future

research (ideally ≥ 0.2 ng/ml after radical prostatectomy). Therefore, it is necessary to obtain a consensus about how to measure corporal weight or biochemical recurrence rightly for this type of studies.

4. The methodological quality of the observational longitudinal studies analyzing the association between obesity and prostate cancer outcomes was intermediate-high according to Newcastle-Ottawa scale. Therefore, 34.3% of the studies presented low risk of bias, 58.1% showed medium risk of bias and 7.6% showed high risk of bias.

5. Small-study effect was identified in several associations suggesting potential publication biases. Specifically, for the association between obesity and prostate cancer specific mortality (p-value of Egger test = 0.005), and for the association between five-unit increment of BMI and biochemical recurrence (p-value of the Egger test = 0.017), evidence of missing small studies reporting positive association was detected.

6. Obesity and continuous BMI of patients diagnosed with prostate cancer in the MCC-Spain study were associated with higher risk of biochemical recurrence and castration resistance. No relationship was observed for all-cause mortality or for prostate cancer specific mortality.

7. Prognostic scales at diagnosis (e.g., Gleason score) should not be included in multivariate analyses of the association between obesity and prostate cancer outcomes. A deep analysis of the casual association through directed acyclic graphs is required for optimizing the selection of covariates in multivariate analyses and reduce heterogeneity.

IX. BIBLIOGRAFÍA

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Allott, E.H.; Masko, E.M.; Freedland, S.J. Obesity and prostate cancer: weighing the evidence. Eur Urol. 2013, 63, 800–809. doi: 10.1016/j.eururo.2012.11.013

Alonso-Molero, J.; Molina, A.J.; Jiménez-Moleón, J.J; Pérez-Gómez, B.; Martin, V.; Moreno, V.; Amiano, P.; Ardanaz, E.; de Sanjose, S.; Salcedo, I.; *et al*. Cohort profile: the MCC-Spain follow-up on colorectal, breast and prostate cancers: study design and initial results. BMJ Open. 2019, 9, e031904. doi: 10.1136/bmjopen-2019-031904

Annett S., Moore G., Robson T. Obesity and Cancer Metastasis: Molecular and Translational Perspectives. Cancers. 2020, 12, 3798. doi: 10.3390/cancers12123798

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. doi: 10.1155/2012/789174

Armstrong, A.J.; Halabi, S.; de Wit, R.; Tannock, I.F.; Eisenberger, M. The relationship of body mass index and serum testosterone with disease outcomes in men with castration-resistant metastatic prostate cancer. Prostate Cancer Prostatic Dis. 2009, 12, 88–93. doi: 10.1038/pcan.2008.36

Babiarczyk, B.; Turbiarz, A. Body mass index in elderly people - Do the reference ranges matter? Prog Health Sci. 2012, 1, 58–65

Bai, P.D.; Hu, M.B.; Xu, H.; Zhu, W.H.; Hu, J.M.; Yang, T.; Jiang HW, Ding Q. Body mass index is associated with higher Gleason score and biochemical recurrence risk following radical prostatectomy in Chinese men: a retrospective cohort study and meta-analysis. World J Surg Oncol. 2015;13:311. doi: 10.1186/s12957-015-0725-0

Ballon-Landa, E.; Parsons, J.K. Nutrition, physical activity, and lifestyle factors in prostate cancer prevention. Curr Opin Urol. 2018, 28, 55–61. doi: 10.1097/MOU.0000000000000460

Bandini, M.; Gandaglia, G.; Briganti, A. Obesity and prostate cancer. Curr. Opin. Urol. 2017, 27, 415–421. doi: 10.1097/MOU.0000000000000424

Bassett, W.W.; Cooperberg, M.R.; Sadetsky, N.; Silva, S.; DuChane, J.; Pasta, D.J.; Chan, J.M.; Anast, J.W.; Carroll, P.R.; Kane, C.J. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. Urology. 2005, 66, 1060–1065. doi: 10.1016/j.urology.2005.05.040

Basterra-Gortari, F.J.; Bes-Rastrollo, M.; Forga, L.; Martínez, J.A.; Martínez-González, M.A. Validación del índice de masa corporal auto-referido en la Encuesta Nacional de Salud. Anales del sistema sanitario de Navarra. 2007, 30, 397–381. doi: 10.4321/S1137-66272007000500006

Benson, C.R.; Serefoglu, E.C.; Hellstrom, W.J. Sexual dysfunction following radical prostatectomy. J Androl. 2012, 33, 1143–1154. doi: 10.2164/jandrol.112.016790

Bourke, L.; Smith, D.; Steed, L.; Hooper, R.; Carter, A.; Catto, J.; Albertsen, P.C.; Tombal, B.; Payne, H.A.; Rosario, D.J.; *et al*. Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016, 69, 693–703. doi:10.1016/j.eururo.2015.10.047

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. doi: 10.1158/1940-6207.CAPR-10-0229

Castaño-Vinyals, G.; Aragonés, N.; Pérez-Gómez, B.; Martín, V.; Llorca, J.; Moreno, V.; Altzibar, J.M.; Ardanaz, E.; de Sanjosé, S.; Jiménez-Moleón, J.J.; *et al*. Population-

based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac Sanit. 2015, 29, 308-315. doi: 10.1016/j.gaceta.2014.12.003

Centre for Evidence-Based Medicine. Levels of Evidence [accedido el 27 de diciembre de 2021]. Disponible en: https://www.cebm.ox.ac.uk/resources/levels-of-evidence

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. doi: 10.1002/ijc.25739

Chen, C.; Ye, Y.; Zhang, Y.; Pan, X.F.; Pan, A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. BMJ. 2019, 367, l5584. doi: 10.1136/bmj.l5584

Continuous Update Project. World Cancer Research Fund. [Accedido el 3 de enero de 2022]. Disponible en: https://www.wcrf.org/diet-and-cancer/continuous-update-project/

Cornford, P.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; *et al*. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021, 79, 263–282. doi: 10.1016/j.eururo.2020.09.046

Cox, D.R. Regression models and life tables (with discussion). Journal of the Royal Statistical Society: Series B. 1972, 34, 187–220.

Crawford, E.D.; Grubb, R. 3rd.; Black, A.; Andriole, G.L. Jr.; Chen, M.H.; Izmirlian, G.; Berg, C.D.; D'Amico, A.V. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol. 2011, 29, 355–361.

Csige, I.; Ujvárosy, D.; Szabó, Z.; Lórincz, I.; Paragh, D.; Harangi, M.; Somodi, S. The impact of obesity on the cardiovascular system. J Diabetes Res. 2018, 2018, 3407306. doi: 10.1155/2018/3407306

D'Amico, A.; Whittington, R.; Malkowicz, S.; Schultz, D.; Blank, K.; Broderick, G.; Tomaszewski, J.E.; Renshaw, A.A.; Kaplan, I.; Beard, C.J.; *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998, 280, 969–974. doi: 10.1001/jama.280.11.969

Dai, H.; Alsalhe, T.A.; Chalghaf, N.; Riccò, M.; Bragazzi, N.L.; Wu, J. The global burden of disease attributable to high body mass index in 195 countries and territories, 1990-2017: An analysis of the Global Burden of Disease Study. PLoS Med. 2020, 17, e1003198. doi:10.1371/journal.pmed.1003198.

Davies, N.J.; Batehup, L.; Thomas, R. The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. Br J Cancer. 2011, 105, S52–S73. doi: 10.1038/bjc.2011.423.

De Pergola, G.; Silvestris, F. Obesity as a major risk factor for cancer. J Obes. 2013, 2013, 291546. doi: 10.1155/2013/291546

Delgado-Rodríguez, M.; Sillero-Arenas, M. Systematic review and meta-analysis. Med Intensiva (Engl Ed). 2018, 42, 444–453. doi: 10.1016/j.medin.2017.10.003

EESE. Encuesta Europea de Salud en España. Ministerio de Sanidad. 2020 [accedido el 12 de enero de 2022]. Disponible en: https://www.mscbs.gob.es/estadEstudios/estadisticas/EncuestaEuropea/Enc_Eur_Salud_en_Esp_2020.htm

Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629–634. doi: 10.1136/bmj.315.7109.629

Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A.; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016 Feb;40(2):244-52. Am J Surg Pathol. 2016, 40, 244-252. doi: 10.1097/PAS.0000000000000530

EUROSTAT. Obesity rate by body mass index (BMI). 2020 [accedido el 27 de diciembre de 2021]. Disponible en: https://ec.europa.eu/eurostat/databrowser/view/sdg_02_10/default/table?lang=en

Ferlay, J.E.M.; Lam, F.; Colombet, M.; Mery, L.; Pineros, M.; Znaor, A.; Soerjomataram, I. *et al*. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer [Accedido el 3 de enero de 2021]. Disponible en: https://gco.iarc.fr/today

Fleshner, K.; Carlsson, S.V.; Roobol, M.J. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol. 2017, 14, 26–37. doi: 10.1038/nrurol.2016.251

Freedland, S.J.; Allen, J.; Jarman, A.; Oyekunle, T.; Armstrong, A.J.; Moul, J.W.; Sandler, H.M.; Posadas, E.; Levin, D.; Wiggins, E.; *et al*. A Randomized Controlled Trial of a 6-Month Low-Carbohydrate Intervention on Disease Progression in Men with Recurrent Prostate Cancer: Carbohydrate and Prostate Study 2 (CAPS2). Clin. Cancer Res. 2020, 26, 3035–3043. Erratum in: Clin. Cancer Res. 2021, 27, 1823. doi: 10.1158/1078-0432.CCR-19-3873

Freedland, S.J.; Grubb, K.A.; Yiu, S.K.; Nielsen, M.E.; Mangold, L.A.; Isaacs, W.B.; Epstein, J.I.; Partin, A.W.; *et al*. Obesity and capsular incision at the time of open retropubic radical prostatectomy. J Urol. 2005, 174, 1798–1801. doi: 10.1097/01.ju.0000177077.53037.72

Gallagher, R.P.; Fleshner, N. Prostate cancer: 3. Individual risk factors. CMAJ. 1998, 159, 807–813.

Gann, P.H.; Daviglus, M.L.; Dyer, A.R.; Stamler, J. Heart rate and prostate cancer mortality: results of a prospective analysis. Cancer Epidemiol Biomarkers Prev 1995, 4, 611–616.

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. doi: 10.1016/j.annonc.2019.09.007

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. doi: 10.1016/j.eururo.2015.03.017

Gleason, D.F. Classification of prostatic carcinomas. Cancer Chemother Rep. 1966, 50, 125-128.

González Del Alba, A.; Méndez-Vidal, M.J.; Vazquez, S.; Castro, E.; Climent, M.A.; Gallardo, E.; Gonzalez-Billalabeitia, E.; Lorente, D.; Maroto, J.P.; Arranz, J.A. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). Clin. Transl. Oncol. 2021, 23, 969–979. doi: 10.1007/s12094-021-02561-5

Goodarzi MO. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. Lancet Diabetes Endocrinol. 2018, 6, 223–236. doi: 10.1016/S2213-8587(17)30200-0

Greenland, S.; Longnecker, M.P. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am. J. Epidemiol. 1992, 135, 1301–1309. doi: 10.1093/oxfordjournals.aje.a116237

Hamilton-Reeves, J.M.; Johnson, C.N.; Hand, L.K., Bechtel, M.D.; Robertson, H.L.; Michel, C.; Metcalf, M.; Chalise, P.; Mahan, N.J.; Mirza, M.; *et al*. Feasibility of a weight management program tailored for overweight men with localized prostate cancer – a pilot study. Nutr. Cancer. 2020, 1–16. doi: 10.1080/01635581.2020.1856890

Han, H.; Cao, Z.; Qin, Y.; Wei, X.; Ruan, Y.; Cao, Y.; He, J. Morbid obesity is adversely associated with perioperative outcomes in patients undergoing robot-assisted laparoscopic radical prostatectomy. Can Urol Assoc J. 2020, 14, E574–E581. doi: 10.5489/cuaj.6389

Heijnsdijk, E.A.M.; Csanádi, M.; Gini, A.; Ten Haaf, K.; Bendes, R.; Anttila, A.; Senore, C.; de Koning, H.J. All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: A review and modeling study. Cancer Med. 2019, 8, 6127–6138. doi: 10.1002/cam4.2476

Higgins, J.P.T.; Green, S. Cochrane Handbook for Systematic Revies of Interventions Version 5.1.0. The Cochrane Collaboration, 2011 [accedido el 27 de diciembre de 2021]. Disponible en: www.handbook.cochrane.org

Hill, A.B. The environment and disease: Association or causation? Proc. R. Soc. Med. 1965, 58, 295–300.

Hu, M.B.; Xu, H.; Bai, P.D.; Jiang, H.W.; Ding, Q. Obesity has multifaceted impact on biochemical recurrence of prostate cancer: a dose-response meta-analysis of 36,927 patients. Med Oncol. 2014, 31, 829. doi: 10.1007/s12032-013-0829-8

Ilie, G.; White, J.; Mason, R.; Rendon, R.; Bailly, G.; Lawen, J.; Bowes, D.; Patil, N.; Wilke, D.; MacDonald, C.; *et al*. Current Mental Distress Among Men With a History of Radical Prostatectomy and Related Adverse Correlates. Am J Mens Health. 2020, 14, 1557988320957535. doi: 10.1177/1557988320957535.

International Agency for Research on Cancer (IARC). 2020 [accedido el 27 de diciembre de 2021]. Disponible en: http://gco.iarc.fr/

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. doi: 10.1007/s10552-020-01306-z

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. doi: 10.1002/ijc.33150

Kaiser, A.; Haskins, C.; Siddiqui, M.M.; Hussain, A.; D'Adamo, C. The evolving role of diet in prostate cancer risk and progression. Curr Opin Oncol. 2019, 31, 222–229. doi:10.1097/CCO.0000000000000519

Kaplan, E. L.; Meier, P.: Nonparametric estimation from incomplete observations. J. Amer. Statist. Assn. 53:457–481, 1958.

Keith, S.W.; Kwabi-Addo, B.; Zeigler-Johnson, C. Interactions Between Obesity and One-Carbon Metabolism Genes in Predicting Prostate Cancer Outcomes Among White and Black Patients. J Racial Ethn Health Disparities. 2021. doi: 10.1007/s40615-020-00958-6

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. doi: 10.1136/ebmed-2011-100287

Khan, S.; Hicks, V.; Colditz, G.A.; Kibel, A.S.; Drake, B.F. The association of weight change in young adulthood and smoking status with risk of prostate cancer recurrence. Int J Cancer. 2018, 142, 2011–2018. doi: 10.1002/ijc.31229

Kim, S.W.; Chun, M.; Jung, Y.S.; Oh, Y..T; Noh, O.K.; Cho, O. Impact of Body Mass Index on Local Recurrence according to Intrinsic Subtype Approximation in Korean Women with Early Stage Invasive Breast Cancer Receiving Contemporary Treatments. J Cancer. 2021, 12, 4648–4654. doi: 10.7150/jca.59064

Kohler, L.N.; Garcia, D.O.; Harris, R.B.; Oren, E.; Roe, D.J.; Jacobs, E.T. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer Epidemiol Biomarkers Prev. 2016, 25, 1018–1028. doi: 10.1158/1055-9965.EPI-16-0121

Koo, K.C.; Yoon, Y.E.; Rha, K.H.; Chung, B.H.; Yang, S.C.; Hong, S.J. Low body mass index is associated with adverse oncological outcomes following radical prostatectomy in Korean prostate cancer patients. Int Urol Nephrol. 2014, 46, 1935–1940. doi: 10.1007/s11255-014-0729-7

Lavie, C.J.; De Schutter, A.; Archer, E.; McAuley, P.A.; Blair, S.N. Obesity and prognosis in chronic diseases – impact of cardiorespiratory fitness in the obesity paradox

[published correction appears in Curr Sports Med Rep. 2014, 13, 349]. Curr Sports Med Rep. 2014, 13, 240–245. doi: 10.1249/JSR.0000000000000067

Leal-García, M.; Canto, P.; Cárdenas-Cárdenas, E.; Feria-Bernal, G.; García-García, E.; Méndez, J.P. Overweight and obesity in men with prostate cancer do not constitute risk factors for biochemical recurrence. Aging Male. 2020, 23, 1283–1288. doi: 10.1080/13685538.2020.1764523

Luo, R.; Chen, Y.; Ran, K.; Jiang, Q. Effect of obesity on the prognosis and recurrence of prostate cancer after radical prostatectomy: a meta-analysis. Transl Androl Urol. 2020, 9, 2713–2722. doi: 10.21037/tau-20-1352

Mantel, N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Reports. 1966, 50, 163–170.

Martínez González, M.A.; Sánchez Villegas, A.; Toledo Atucha, E.; Faulin Fajardo, J. Bioestadística amigable. 4ª edición. 2020. Elsevier, ISBN: 9788491136019.

Mattiuzzi, C.; Lippi, G. Current Cancer Epidemiology. J Epidemiol Glob Health. 2019, 9, 217–222. doi: 10.2991/jegh.k.191008.001

Merriel, S.W.D.; Funston, G.; Hamilton, W. Prostate Cancer in Primary Care. Adv Ther. 2018, 35, 1285–1294. doi:10.1007/s12325-018-0766-1

Morán Pascual, E.; Martínez Sarmiento, M.; Budía Alba, A.; Broseta Rico, E.; Cámara Gómez, R.; Boronat Tormo, F. Central Body Fat Mass Measured by Bioelectrical Impedanciometry But Not Body Mass Index Is a High-Grade Prostate Cancer Risk Factor. Urol Int. 2017, 98, 28–31. doi: 10.1159/000447249

Mottet, N.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; *et al*. EAU-EANM-

ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur. Urol. 2021, 79, 243–262. doi: 10.1016/j.eururo.2020.09.042

Muller, R.L.; Gerber, L.; Moreira, D.M.; Andriole, G.Jr.; Hamilton, R.J.; Fleshner, N.; Parsons, J.K.; Freedland, S.J.; *et al*. Obesity is associated with increased prostate growth and attenuated prostate volume reduction by dutasteride. Eur Urol. 2013, 63, 1115–1121. doi: 10.1016/j.eururo.2013.02.038

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. doi: 10.1200/JCO.2009.27.0793

NIH, Instituto Nacional del Cáncer [accedido el 27 de diciembre de 2021]. Disponible en: https://www.cancer.gov/espanol/publicaciones/diccionarios/diccionario-cancer/def/pronostico

Núñez Sánchez, M.C.; Reyes Huarcaya, R.M.E. Importancia de diferenciar puntos de corte del IMC de acuerdo a la edad. Nutr Hosp. 2017, 34, 1263. doi: 10.20960/nh.1416

Organización Mundial de la Salud, 2021. Obesity and overweight [accedido el 27 de diciembre de 2021]. Disponible en: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

Organización Mundial de la Salud, 2016. Obesity [accedido el 27 de diciembre de 2021]. Disponible en: https://www.who.int/health-topics/obesity#tab=tab_1

Organización para la Cooperación y Desarrollo (OCDE), 2018. Obesity update 2017 [accedido el 27 de diciembre de 2021]. Disponible en: https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf

Organización para la Cooperación y Desarrollo (OCDE), 2019. State of Health of the EU. España. Perfil sanitario nacional [accedido el 27 de diciembre de 2021]. Disponible en: https://ec.europa.eu/health/sites/default/files/state/docs/2019_chp_es_spanish.pdf

Ornish, D.; Lin, J.; Chan, J.M.; Epel, E.; Kemp, C.; Weidner, G.; Marlin, R.; Frenda, S.J.; Magbanua, M.J.M.; Daubenmier, J.; *et al*. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. Lancet Oncol. 2013, 14, 1112–1120. doi: 10.1016/S1470-2045(13)70366-8

Oviedo, G.; Morón de Salim, M.; Solano, L. Indicadores antropométricos de obesidad y su relación con la enfermedad isquémica coronaria. Nutr Hosp. 2006, 21, 694–698.

Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021, 372, 71. doi: 10.1136/bmj.n71

Palma Pérez, S.; Delgado Rodríguez, M. Consideraciones prácticas acerca de la detección del sesgo de publicación. Gac Sanit. 2006, 20, 10–16. doi: 10.1157/13101085

Panigrahi, G.K.; Praharaj, P.P.; Kittaka, H.; Mridha, A.R.; Black, O.M.; Singh, R.; Mercer, R.; van Bokhoven, A.; Torkko, K.C.; Agarwal, C.; *et al*. Exosome proteomic analyses identify inflammatory phenotype and novel biomarkers in African American prostate cancer patients. Cancer Med. 2019, 8, 1110–1123.

Panuganti, K.K.; Nguyen, M.; Kshirsagar, R.K. Obesity. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 11, 2021. Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK459357/

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. doi: 10.1186/s12916-017-0876-7

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. doi: 10.1001/jamanetworkopen.2021.3520

Piédrola G. Medicina Preventiva y Salud Pública. 10ª Edición. Barcelona: Masson, 2001.

Pierorazio, P.M.; Walsh, P.C.; Partin, A.W.; Epstein, J.L. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013, 111, 753–760. doi: 10.1111/j.1464-410X.2012.11743.x

Pugliese, D.; Palermo, G.; Totaro, A.; Bassi, P.F.; Pinto, F. Clinical, pathological and molecular prognostic factors in prostate cancer decision-making process. Urologia. 2016, 83, 14–20. doi: 10.5301/uro.5000166

Rawla, P. Epidemiology of Prostate Cancer. World J Oncol. 2019, 10, 63–89. doi: 10.14740/wjon1191.

Riley, R.D.; Higgins, J.P.; Deeks, J.J. Interpretation of random effects metaanalyses. BMJ 2011, 342, d549. doi: 10.1136/bmj.d549

Riley, R.D.; Moons, K.G.M.; Snell, K.I.E.; Ensor, J.; Hooft, L.; Altman, D.G.; Hayden, J.; Collins, G.S.; Debray, T.P.A. A guide to systematic review and meta-analysis of prognostic factor studies. BMJ. 2019, 364, k4597. doi: 10.1136/bmj.k4597

Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Pérez-Gómez, B.; Sánchez, M.J.; Khan, K.S.; Jiménez-Moleón, J.J. Obesity as a Risk Factor for Prostate Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis of 280,199 Patients. Cancers (Basel). 2021, 13, 4169. doi: 10.3390/cancers13164169.

Rivera-Izquierdo, M.; Pérez de Rojas, J.; Martínez-Ruiz, V.; Arrabal-Polo, M.Á.; Pérez-Gómez, B.; Jiménez-Moleón, J.J. Obesity and biochemical recurrence in clinically localised prostate cancer: a systematic review and meta-analysis of 86,490 patients. Prostate Cancer Prostatic Dis. 2022. doi: 10.1038/s41391-021-00481-7.

Rothman, KJ. Epidemiología moderna. 1ª Edición. , Boston, Little Brown & Co, 1986.

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. doi: 10.3390/cancers11091225

Sarafanov, A.G.; Todorov, T.I.; Centeno, J.A.; Macias, V.; Gao, W.; Liang, W.M.; Beam, C.; Gray, M.A.; Kajdacsy-Balla, A.A. Prostate cancer outcome and tissue levels of metal ions. Prostate. 2011;71(11):1231-1238. doi:10.1002/pros.21339

Scarpa, M.; Ruffolo, C.; Erroi, F.; Fiorot, A.; Basato, S.; Pozza, A.; Canal, F.; Massani, M.; Cavallin, F.; Antoniutti, M.; *et al*. Obesity is a risk factor for multifocal disease and recurrence after colorectal cancer surgery: a case-control study. Anticancer Res. 2014, 34, 5735–5741.

Schatten, H. Brief Overview of Prostate Cancer Statistics, Grading, Diagnosis and Treatment Strategies. Adv. Exp. Med. Biol. 2018, 1095, 1–14. doi: 10.1007/978-3-319-95693-0_1

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. doi: 10.1016/j.cct.2019.04.004

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. doi: 10.1136/bmj.j4008

Sociedad Española de Oncología Médica (SEOM). Cáncer de próstata. 2021. Disponible en: https://seom.org/info-sobre-el-cancer/prostata

Soler-Vilá, H.; Dubrow, R.; Franco, V.I.; Kasl, S.V.; Jones, B.A. The prognostic role of cancer-specific beliefs among prostate cancer survivors. Cancer Causes Control. 2011, 22, 251–260. doi: 10.1007/s10552-010-9693-4.

StataCorp, 2017. Stata Statistical Software: Release 15. College Stataion, TX: StataCorp LP.

Strom, S.S.; Wang, X.; Pettaway, C.A.; Logothetis, C.J.; Yamamura, Y.; Do, K.A.; Babaian, R.J.; Troncoso, P. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. Clin Cancer Res. 2005, 11, 6889–6894. doi: 10.1158/1078-0432.CCR-04-1977

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. doi: 10.3322/caac.21660

Tan W, Wang L, Ma Q, Qi M, Lu N, Zhang L, Han B. Adiponectin as a potential tumor suppressor inhibiting epithelial-to-mesenchymal transition but frequently silenced in prostate cancer by promoter methylation. Prostate. 2015; 75:1197–205. doi: 10.1002/pros.23002

Thederan, I.; Chandrasekar, T.; Tennstedt, P.; Kuehl, L.; Sorbe C.: Tilki, D.; Augustin, M.; Heinzer, H.; Zyriax, B.C. Poor Adherence to International Cancer Prevention Recommendations Among Patients With Prostate Cancer: First Results From the MARTINI-Lifestyle Cohort. Eur Urol Focus. 2020, 6, 935–940. doi: 10.1016/j.cct.2019.04.004

Trofimenko, V.; Myers, J.B.; Brant, W.O. Post-Prostatectomy Incontinence: How Common and Bothersome Is It Really? Sex Med Rev. 2017, 5, 536–543. doi: 10.1016/j.sxmr.2017.05.001

Vallejos, J.; Villaronga, A.; Álvarez, C.; Mariluis, C.; Paganini, L.; González, C.; De Luca, S.; Dieguez. A. Actualización de la estadificación del cáncer de próstata. Staging of prostate cancer: An update. Revista Argentina de Radiología. 2013, 77, 301–305.

Van den Broeck, T.; van den Bergh, R.C.N.; Briers, E.; Cornford, P.; Cumberbatch, M.; Tilki, D.; De Santis, M.; Fanti, S.; Fossati, N.; Gillessen, S.; *et al*. Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations. Eur Urol Focus. 2020, 6, 231–234. doi: 10.1016/j.euf.2019.06.004

van Rooijen, S.; Carli, F.; Dalton, S.; Thomas, G.; Bojesen, R.; Le Guen, M.; Barizien, N.; Awasthi, R.; Minnella, E.; Beijer, S.; *et al*. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer 2019, 19, 98. doi: 10.1186/s12885-018-5232-6

von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P.; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014, 12, 1495–1499. doi: 10.1016/j.ijsu.2014.07.013

Wei, Y.; Wu, Y.P.; Lin, M.Y.; Chen, S.H.; Lin, Y.Z.; Li, X.D.; Zheng, Q.S.; Xue, X.Y.; Xu, N. Impact of Obesity on Long-Term Urinary Incontinence after Radical Prostatectomy: A Meta-Analysis. Biomed Res Int. 2018, 8279523. doi: 10.1155/2018/8279523

Weihrauch-Blüher, S.; Schwarz, P.; Klusmann, J.H. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. Metabolism. 2019, 92, 147–152. doi: 10.1016/j.metabol.2018.12.001

Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [accedido el 27 de diciembre de 2021]. Disponible online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Whitley, B.M.; Moreira, D.M.; Thomas, J.A.; Aronson, W.J.; Terris, M.K.; Presti, J.C.; Kane CJ, Amling CL, Freedland SJ; SEARCH Database Study Group. Preoperative weight change and risk of adverse outcome following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital database. Prostate Cancer Prostatic Dis. 2011, 14, 361–366. doi: 10.1038/pcan.2011.42

Wilson, K.M.; Mucci, L.A. Diet and Lifestyle in Prostate Cancer. Adv Exp Med Biol. 2019, 1210, 1–27. doi: 10.1007/978-3-030-32656-2_1

Wilson, R.L.; Shannon, T.; Calton, E.; Galvão, D.A.; Taaffe, D.R.; Hart, N.H.; Lyons-Wall, P.; Newton, R.U. Efficacy of a weight loss program prior to robot assisted radical

prostatectomy in overweight and obese men with prostate cancer. Sur. Oncol. 2020, 35, 182–188. doi: 10.1016/j.suronc.2020.08.006

Wilt, T.J.; Vo, T.N.; Langsetmo, L.; Dahm, P.; Wheeler, T.; Aronson, W.J.; Cooperberg, M.R.; Taylor, B.C.; Brawer, M.K. Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the Prostate Cancer Intervention Versus Observation Trial (PIVOT). Eur Urol. 2020, 77, 713–724. doi: 10.1016/j.eururo.2020.02.009

World Cancer Research Fund. American Institute for Cancer Research. Body fatness and weight gain. 2020 [accedido el 27 de diciembre de 2021]. Disponible en: https://www.wcrf.org/dietandcancer/exposures/body-fatness

Wright, J.L.; Salinas, C.A.; Lin, D.W.; Kolb, S.; Koopmeiners, J.; Feng, Z.; Stanford, J.L. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4+3 and Gleason 3+4 tumours in a population based cohort. J Urol. 2009;182(6):2702-7. doi: 10.1016/j.juro.2009.08.026

Yang, L.; Roberts, D.; Takhar, M.; Erho, N.; Bibby, B.A.S.; Thiruthaneeswaran, N.; Bhandari, V.; Cheng, W.C., Haider, S.; McCorry, A.M.B.; *et al*. Development and Validation of a 28-gene Hypoxia-related Prognostic Signature for Localized Prostate Cancer. EBioMedicine. 2018, 31, 182–189. doi: 10.1016/j.ebiom.2018.04.019.

Yu, Y.D.; Byun, S.S.; Lee, S.E.; Hong, S.K. Impact of Body Mass Index on Oncological Outcomes of Prostate Cancer Patients after Radical Prostatectomy. Sci Rep. 2018, 8, 11962. doi: 10.1038/s41598-018-30473-y

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. doi: 10.3892/ol.2014.2841

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. doi: 10.1038/pcan.2015.64

X. APPENDICES

Appendix 1. Proof of acceptance for publication of Study 1 (Rivera-Izquierdo M, Martínez-Ruiz V, Jiménez-Moleón JJ. Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review. *International Journal of Environmental Research and Public Health*, 2022; Impact Factor (2020): 3.390, position 42/176 in Public, Environmental & Occupational Health – SSCI; T1, Q1.

International Journal of
Environmental Research and Public Health

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CERTIFICATE OF ACCEPTANCE

Certificate of acceptance for the manuscript (**ijerph-1549382**) titled:

Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review.

Authored by:

Mario Rivera-Izquierdo; Virginia Martínez-Ruiz; José Juan Jiménez-Moleón

has been accepted in *Int. J. Environ. Res. Public Health* (ISSN 1660-4601) on 26 January 2022

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[IOAP] [IJERPH] MDPI Institutional Open Access Program - for Manuscript ID:ijerph-1549382 [Non-central: Invoiced to author] Accepted

From noreply@mdpi.com on 2022-01-26 03:18

Detalles

Dear all,

The following article has now been accepted for publication:

Manuscript ID: ijerph-1549382
Type of manuscript: Review
Title: Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review.
Authors: Mario Rivera-Izquierdo *, Virginia Martínez-Ruiz, José Juan Jiménez-Moleón
Received: 25 December 2021
Institute: University of Granada
E-mails: mariorivera@ugr.es, virmruiz@ugr.es, jjmoleon@ugre.es

Kind regards,
Ms. Pepper Cao
E-Mail: pepper.cao@mdpi.com

[IJERPH] Manuscript ID: ijerph-1549382 - Accepted for Publication

From IJERPH Editorial Office on 2022-01-26 03:18

Detalles

Dear Dr. Rivera-Izquierdo,

Congratulations on the acceptance of your manuscript, and thank you for your interest in submitting your work to IJERPH:

Manuscript ID: ijerph-1549382
Type of manuscript: Review
Title: Recommendations on weight loss and healthy lifestyle in prostate cancer clinical guidelines: A systematic review.
Authors: Mario Rivera-Izquierdo *, Virginia Martínez-Ruiz, José Juan Jiménez-Moleón
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Editor Decision

Decision	Accept in current form
Comments	Dear Authors, Thanks for a nice paper I think it will prove useful in advancing thinking about lifestyle related guidelines in prostate cancer care
Decision Date	25 January 2022

Appendix 2. Detailed data sources and search strategy of the Study 1 (Supplementary Table S2 of the manuscript).

Sample search strategy for Medline
#1 Practice guideline [pt] #2 Practice guidelines as topic [mesh] #3 Guideline [pt] #4 guidelines as topic [mesh] #5 consensus [mesh] #6 OR #1-#5 #7 prostate neoplasms [mesh] #8 prostate neoplasms [all] #9 prostate cancer [mesh] #10 prostate cancer [all] #10 OR #7-9 #11 2015 [pdta] : 3000[pdta] # #6 AND # 10 AND #11
Online databases
1. MEDLINE 2. EMBASE 3. Web of Science 4. Scopus 5. The Cochrane Database of Systematic Reviews 6. Cochrane Methodology Register 7. ACP Journal Club 8. Database of Abstracts of Reviews of Effects 9. Cochrane Central Register of Controlled Trials (CENTRAL) 10. The Health Technology Assessment
Guideline-specific databases

1. National Health and Medical Research Council (NHMRC), Australia
2. Canadian Medical Association (CMA) Infobase, Canada
3. Clinical Practice Guidelines (CPG) Infobase, Canada
4. New Zealand Guidelines Group (NZGG), New Zealand
5. National Institute for Health and Care Excellence (NICE), UK
6. Trip Database, UK
7. Scottish Intercollegiate Guidelines Network (SIGN), UK
8. Fisterra, Spain
9. Heath Services and Technology Assessment Texts (HSTAT), USA
10. National Comprehensive Cancer Network (NCCN), USA

Professional societies' websites

1. Academia Nacional de Medicina (ANM), Argentina
2. Australian Government, Australia
3. Faculty of Radiation Oncology Genito-urinary group (FROGG), Australia & New Zealand
4. Prostate Cancer Foundation of Australia (PCFA), Australia & New Zealand
5. Belgian Healthcare Knowledge Centre (KCE), Belgium
6. Brazilian Society of Surgical Oncology (BSSO), Brazil
7. Alberta Health Services, Canada
8. CancerCare Manitoba, Canada
9. Cancer Care Ontario (CCO) Canada
10. Ontario Ministry of Health, Canada
11. Genito-urinary radiation oncologists of Canada (GUROC), Canada
12. Ministerio de Salud de Chile, Chile
13. Chinese expert consensus meeting, China
14. Chinese Ministry of Health, China
15. National Health Commission (NHC), China
16. Hong Kong Urological Association (HKUA), China
17. Hong Kong Society of Uro-Oncology (HKSUO), China
18. Instituto Nacional de Cancerología, Colombia
19. Dirección de desarrollo de Servicio de Salud, Costa Rica
20. Asociación de Médicos Urólogos Costarricenses (AMUC), Costa Rica
21. Danish Prostate Cancer Database (DUCG), Denmark
22. European Association of Urology (EAU), Europe
23. European Association of Nuclear Medicine (EANM), Europe
24. European Society of Medical Oncology (ESMO), Europe
25. European School of Oncology (ESO), Europe
26. European School of Radiology (ESOR), Europe
27. European Society of Pathology (ESP), Europe
28. European Society of Radiation Oncology (ESTRO), Europe
29. European Society of Urogenital Radiology (ESUR), Europe
30. International Society of Geriatric Oncology (SIOG), Europe
31. St. Gallen/Vienna, Europe
32. Cancer Committee of the French Urological Association (CCAFU), France
33. Association of the Scientific Medical Societies in Germany (AWMF), Germany

34. German Cancer Aid (DKH), Germany
35. German Cancer Society (DKG), Germany
36. Urological Society of India (USI), India
37. Indian Cooperative Oncology Network (ICON), India
38. Expert group consensus opinion, India
39. Advanced Prostate Cancer Consensus Conference (APCCC), International
40. Enhanced Recovery After Surgery (ERAS), International
41. International expert panel, International
42. International Society of Urological Pathology (ISUP)
43. National Cancer Control Programme (NCCP), Ireland
44. Japanese Urological Association (JUA), Japan
45. Korean Society of Medical Oncology (KSMO), Korea
46. Lithuanian oncologist, endocrinologist and General practitioners, Lithuania
47. Medical Malaysian Multi-channel (MIMS), Malaysia
48. Instituto Mexicano del Seguro Social (IMSS), Mexico
49. Netherlands Comprehensive Cancer Organisation (IKNL)
50. Dutch Urological Association (NVU), Netherlands
51. Richtlijnendatabase, Netherlands
52. Ministry of Health from New Zealand, New Zealand
53. Instituto de Evaluación de Tecnologías en Salud e Investigación (IETSI), Peru
54. Instituto Nacional de Enfermedades Neoplásicas (INEN), Peru
55. Saudi Oncology Society (SOS), Saudi Arabia
56. Saudi Urology Society (SUA), Saudi Arabia
57. Compliance Association & Network (SCAN), Singapore
58. South African Urological Association (SAUA), South Africa
59. Federación de Sociedades Españolas de Oncología (FESEO), Spain
60. Sociedad Española de Oncología Médica (SEOM), Spain
61. British Association of Urological Surgeons (BAUS), UK
62. Joint Guidelines from British Surgical Associations, UK
63. National Health Service, UK
64. The Royal College of Pathologists, UK
65. The Royal College of Radiologists, UK
66. Royal College of Radiologists (RCR), UK
67. Scottish Cancer Taskforce, UK
68. American Board of Internal Medicine's, USA
69. American Brachytherapy Society, USA
70. American Society of Plastic Surgeons, USA
71. American Society for Radiation Oncology, USA
72. American Cancer Society (ACS), USA
73. American Medical Society (AMS), USA
74. American Society of Clinical Oncology (ASCO), USA
75. American Society for Radiation Oncology (ASTRO), USA
76. American Urological Association (AUA), USA
77. Society of Surgical Oncology (SSO), USA

The professional societies are presented divided by alphabetical order of their country.

Appendix 3. Appraisal of Guidelines for Research & Evaluation (AGREE-II) assessment of clinical practice guidelines on prostate cancer that complied with recommendations for healthy weight (Supplementary Table S3 of the Study 1). The complete version of the tool is available from https://agreetrust.org. The tool is composed by 23 items. Each item is assessed in a 7-point scale (from 1: strongly disagree to 7: strongly agree). The percentage according to the maximum possible punctuation for each domain in presented in the cells. Correspondence between each guideline (Entity, year) and their complete name can be consulted in Table 6 of the Doctoral Thesis (Results, Study 1). The guidelines are presented divided by year of the last update.

Entity, year	**Domain 1: Scope and purpose (items 1-3)**	**Domain 2: Stakeholder involvement (items 4-6)**	**Domain 3: Rigour of development (items 7-14)**	**Domain 4: Clarity of presentation (items 15-17)**	**Domain 5: Applicability (items 18-21) (MPP: 28)**	**Domain 6: Editorial Independence (items 22-23)**	**Total score (Global Quality)**
AWMF-DKG-DKH, 2021	85.7%	76.2%	75.0%	85.7%	71.4%	42.9%	5 / 7
CUA, 2021a	80.1%	47.6%	46.4%	90.5%	85.7%	28.6%	4 / 7
MIMS, 2021	47.6%	57.1%	44.6%	76.2%	71.4%	35.7%	3.5 / 7
BC, 2020b	80.1%	57.1%	42.8%	81.0%	67.9%	71.4%	4 / 7
CUA, 2020b	85.7%	85.7%	83.9%	81.0%	67.9%	50.0%	5.5 / 7
EAU-EANM-ESTRO-ESUR-SIOG, 2020b	80.1%	81.0%	87.5%	85.7%	71.4%	85.7%	6 / 7
ESMO, 2020	71.4%	81.0%	87.5%	85.7%	78.6%	85.7%	6 / 7
ASCO, 2018	80.1%	76.2%	83.9%	100%	67.9%	71.4%	6 / 7
IKNL, 2017	42.8%	28.6%	35.7%	47.6%	60.7%	28.6%	3 / 7
SAUA, 2017	52.4%	52.4%	35.7%	28.6%	50.0%	28.6%	3 / 7
CCO, 2016b	52.4%	76.2%	92.9%	85.7%	85.7%	35.7%	5.5 / 7
NCCP, 2016	90.5%	85.7%	92.9%	90.5%	89.3%	35.7%	6.5 / 7
Mean	70.4%	67.1%	67.4%	78.2%	72.3%	50.0%	4.5 / 7

Appendix 4. Examples of recommendations regarding healthy weight or lifestyles in clinical practice guidelines of prostate cancer (Supplementary Table S4 of the Study 1).

Entity, year	Examples of recommendations
AWMF-DKG-DKH, 2021	Recommendations. "The four main recommendations of the guideline are: a. Aim for a healthy weight. b. Be physically active. c. Be sure to eat a healthy diet with an emphasis on plant-based products. d. Reduce your alcohol consumption"
CUA, 2021a	Recommendations. "Providers should obtain a comprehensive baseline physical examination prior to ADT initiation that includes blood pressure, weight, waist circumference, and calculation of body mass index (BMI)" "Management of the complications of androgen-deprivation therapy: • Lifestyle changes to promote healthy diet and weight • Smoking cessation • Exercise therapy"
MIMS, 2021	"Advise patients on ADT to have a healthy weight and diet, stop smoking, lessen alcohol intake, meet recommended levels of calcium and vitamin D, and have an annual screening for diabetes and dyslipidemia" "While further studies are needed, the results suggest that modifiable factors can mitigate the consequences of having a genetic susceptibility to prostate cancer"
BC, 2020b	*Patients with primary treatment of surgery, radiation therapy, or androgen deprivation therapy. Management options.* General quality of life and psychosocial sequelae. "Men should be encouraged to participate in an exercise program. • Advise patients on strategies for achieving and maintaining a healthy weight using diet and exercise. • During scheduled follow-up clinical visits, assess men's psychosocial status; if distress is evident, refer to specialized care to address social and emotional quality of life, as well as support groups for coping training for couples when applicable.

	• Use of standardized assessment tools is recommended (e.g., EPIC or PHQ9)"
CUA, 2020b	"Men with mCNPC/mCSPC treated with ADT should be encouraged to take vitamin D (1000 IU daily) and total calcium intake of at 800–1000 mg daily, and to make specific lifestyle changes, including smoking cessation, reduction in alcohol and caffeine intake, and increase in weight-bearing exercises"
EAU-EANM-ESTRO-ESUR-SIOG, 2020b	"Prostate cancer patients should be counseled regarding the importance of modifiable health-related behaviors or risk factors, such as smoking and obesity (Expert Opinion)" "While age is a well-established risk factor for prostate cancer, there are now clear data showing that other patient-related factors such as smoking and excess body weight, typically assessed as a high body mass index (BMI), are correlated with prostate cancer death. Moreover, these factors are also risk factors for death from any cause. As such, clinicians are strongly encouraged to use the time of prostate cancer diagnosis as a "teachable moment" to counsel patients about weight loss and smoking cessation. In regards to surgically treated patients, in general, smoking, older age, and obesity increase the risk of perioperative complications, including bleeding, infections, and deep venous thromboses in non-prostate surgeries. As similar results have been seen elsewhere in the urological literature, there is no reason to believe these factors do not contribute to perioperative morbidity from prostate cancer" "In summary, there is strong circumstantial evidence that smoking and obesity may adversely impact treatment outcomes in men undergoing treatment for prostate cancer. Given these concerns, the Panel felt that patients should be informed of the risks. Moreover, the Panel agreed that most patients should be offered the opportunity to delay therapy for a few months to allow them time to lose weight or stop smoking to reduce these perioperative risks as long as doing so does not significantly impair cancer control"
ESMO, 2020	"Lifestyle measures to maintain bone health are recommended for men on ADT: weight-bearing exercise, stopping smoking, two or fewer units alcohol daily, adequate calcium intake and vitamin D status (reach and maintain reference vitamin D levels) [IV, B]"
ASCO, 2018	"For guideline statement 2: Prostate cancer patients should be counseled regarding the importance of modifiable health-related behaviors or risk factors, such as smoking and obesity (Expert Opinion), the panel also suggests that patients in need of counseling for smoking cessation and/or weight loss be referred to appropriate evidence-based intervention programs as warranted"
ASCO-ASTRO-SUO, 2017	"While age is a well-established risk factor for prostate cancer, there are now clear data showing that other patient-related factors such as smoking and excess body weight, typically assessed as a high body mass index (BMI), are correlated with prostate cancer death. Moreover, these factors are also risk factors for death from any cause. As such, clinicians are strongly encouraged to use the time of prostate cancer diagnosis as a "teachable moment" to counsel patients about weight loss and smoking cessation. In regards to surgically treated patients, in general, smoking, older age, and obesity increase the risk of perioperative complications, including bleeding, infections, and deep venous thromboses in non-prostate

	surgeries. As similar results have been seen elsewhere in the urological literature, there is no reason to believe these factors do not contribute to perioperative morbidity from prostate cancer"
IKNL, 2017	Measures. • Determine the goal of nutritional treatment. • Encourage the patient to exercise, preferably under the direction of an (oncology) physiotherapist. In complex situations, advice from an oncological physiotherapist, rehabilitation physician or sports physician is advisable. • Check whether the advised nutrition can be used and adjust the advice if necessary. • Check the weight progression and if possible the body composition. • Evaluate whether the goal of the nutritional treatment is being achieved"
SAUA, 2017	Prevention. "A healthy lifestyle is the backbone of prevention of the vast majority of cancers and must be given as generic advice" Prevention and treatment of adverse events due to prostate cancer treatments. • Lifestyle/Exercise/Diet"
CCO, 2016b	"[…] counselling about lifestyle management and risk factor modification to reduce the risk of bone loss and falls (e.g., moderating alcohol intake, stopping smoking, optimizing calcium intake, and vitamin D supplementation)", "At the same time, multiple studies have demonstrated important gaps in the quality of bone health care for men with prostate cancer, including low rates of BMD testing either before or while on ADT, low rates of diet and lifestyle counselling". Research questions. "Intervention: Drugs, supplements, lifestyle modifications, exercise"
NCCP, 2016	"The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and their families and healthcare professionals in relation to healthy lifestyle, disease prevention and control"

Appendix 5. Identified clinical practice guidelines and consensus statements not published in a journal (Supplementary Table S5 of the Study 1). The abbreviations can be consulted in Appendix 2.

(ACS). ACS. Prostate cancer prevention and early detection. 2019.
(AMUC). AMUC. Prostate cancer. Risk factors, early detection and PSA: screening, use and correct interpretation. 2018.
AUA-ASTRO-SUO. Advanced prostate cancer: AUA-ASTRO-SUO guideline. 2020.
(AUA). AUA. Castration-resistant prostate cancer Cookson. 2019.
(AUA). AUA. Early detection of prostate cancer: AUA guideline. 2018
(AUA-ASTRO-SUO). Clinically Localized Prostate Cancer: AUA-ASTRO-SUO Guideline. 2017.
(AUNA). AUNA. Clinical practice guideline: prostate cancer. 2019.
(AWMF-DKG-DKH). AWMF-DKG-DKH. S3 prostate cancer guideline. 2021.
(AWMF). AWMF. PSMA ligand PET/CT in the diagnosis of prostate carcinoma. 2019.
(BC). British Columbia. Prostate Cancer Part 1: Diagnosis and Referral in Primary Care. 2020.
(BC). British Columbia. Prostate Cancer Part 2: Follow-up in Primary Care. 2020.
(CCA). Cancer Care Alberta. Local prostate cancer. Clinical Practice Guideline GU-012 – Version 3. 2020.
(CCA). Cancer Care Alberta. Advanced/Metastatic prostate cancer. Clinical Practice Guideline GU-010 – Version 2. 2020.
(CCA). Cancer Care Alberta. Prostate cancer. 2015.
(CCO). CCO. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer. Guideline 27-2 version 2. 2021.

(CCO). Cancer Care Ontario. An Endorsement of the 2018 Guideline on Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. 2018.
(CCO). Cancer Care Ontario. Guideline for Optimization of Surgical and Pathological Quality Performance for Radical Prostatectomy in Prostate Cancer Management. Evidence-Based Series 17-3 Version 2. 2017.
(CCO). Cancer Care Ontario. Cancer Care Ontario Position Statement on Prostate Cancer Screening using the Prostate-Specific Antigen (PSA) Test. 2017.
(CCO). Cancer Care Ontario. Bone Health and Bone-Targeted Therapies for Prostate Cancer. Guideline 3-14 Version 2. 2016.
(CMS). Council for Medical Schemes. PMB definition guideline: Prostate cancer. 2020.
(DUCG). DUCG's National Guidelines for Diagnosis and Treatment of Prostate Cancer, 2015.
(EAU-EANM-ESTRO-ESUR-SIOG). EAU-EANM-ESTRO-ESUR-SIOG. Biochemical recurrence in prostate cancer: The EAU Prostate Cancer Guidelines Panel's recommendations. 2020.
(EAU-ESTRO-ESOR-SIOG). EAU-ESTRO-ESOR-SIOG Guidelines on prostate cancer. 2018.
(IETSI). IETSI. Clinical practice guideline for the screening, diagnosis and treatment of localized and locally advanced prostate cancer. 2021.
(IKNL). IKNL. Prostate cancer, national guideline version 3.0. 2017.
(IMSS). IMSS. Prostate cancer diagnosis and treatment. Clinical practice guidelines. 2018.
(INEN). INEN. Clinical Practice Guideline for the early detection, diagnosis, staging, treatment, rehabilitation and follow-up of patients with prostate cancer. 2021.
(MIMS). Malaysian multi-channel provider of drug information, medical education and services. Prostate Cancer. 2021.
(MSC). MSC. AUGE Clinical Guidelines. Prostate cancer in patients over 15 years old. 2015.
(NCCN). Prostate cancer early detection. NCCN Clinical Practice Guidelines in Oncology. 2019.

(NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 3. 2016.
(NCCP). NCCP. National Prostate Cancer GP Referral Guideline. 2018.
(NCCP). NCCP. Diagnosis, staging and treatment of patients with prostate cancer. National Clinical Guideline No. 8. 2016.
(NICE). The National Institute for Health and Care Excellence. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (technology appraisal guidance TA712). 2021.
(NICE). The National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer (technology appraisal guidance TA660). 2020.
(NICE). The National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. (NICE guideline NG131). 2019.
(NICE). The National Institute for Health and Care Excellence. Enzalutamide for hormone-relapsed non-metastatic prostate cancer (Technology appraisal guidance TA580). 2019.
(NICE). The National Institute for Health and Care Excellence. Padeliporfin for untreated localised prostate cancer (Technology appraisal guidance TA546). 2018.
(NICE). The National Institute for Health and Care Excellence. Memokath-051 stent for ureteric obstruction (Medical technologies guidance MTG35). 2018.
(NICE). The National Institute for Health and Care Excellence. Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer (Interventional procedures guidance IPG590). 2017
(NICE). The National Institute for Health and Care Excellence. Irreversible electroporation for treating prostate cancer. Interventional procedures guidance [IPG572]. 2016.
(NICE). The National Institute for Health and Care Excellence. Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (Technology appraisal guidance TA412. 2016.
(NICE). The National Institute for Health and Care Excellence. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (Technology appraisal guidance TA391). 2016.

(NICE). The National Institute for Health and Care Excellence. Degarelix for treating advanced hormone-dependent prostate cancer (Technology appraisal guidance TA404). 2016.
(NICE). The National Institute for Health and Care Excellence. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (Technology appraisal guidance TA259). 2016.
(NICE). The National Institute for Health and Care Excellence. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (Technology appraisal guidance TA387). 2016.
(NICE). The National Institute for Health and Care Excellence. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (Technology appraisal guidance TA377). 2016.
(NICE). The National Institute for Health and Care Excellence. Suspected cancer: recognition and referral (NICE guideline NG12). 2015.
(NVU). NVU. Prostate cancer. 2016.
(PCFA). PCFA. Clinical practice guidelines: PSA Testing and Early Management of Test-Detected Prostate Cancer. 2016.
(SAUA). South African Urological Association. South African prostate cancer guidelines. 2017.
(Zoginstituut Netherlands). Zorginstituut Netherlands. Appropriate use of pharmaceutical products for patients with castration-refractory prostate cancer. 2016.

The documents are presented divided by alphabetical order of the organization and by year.

Appendix 6. Search terms used in the Study 2 (Supplementary Table S2 of the Study 2).

1. prostat* cancer.ti,ab
2. prostat* neoplasm.ti,ab
3. prostat* tumor.ti,ab
4. mortality.ti,ab
5. death.ti,ab
6. prognos*.ti,ab
7. survival.ti,ab
8. outcome*.ti,ab
9. obes*.ti,ab
10. body mass index.ti,ab
11. BMI.ti,ab
12. weight.ti,ab
13. cohort.ti.ab
14. case-control.ti.ab
15. follow-up.ti.ab
16. 1 OR 2 OR 3
17. 4 OR 5 OR 6 OR 7 OR 8
18. 9 OR 10 OR 11 OR 12
19. 13 OR 14 OR 15
20. 16 AND 17 AND 18 AND 19

Appendix 7. Main characteristics of the studies included in the systematic review of prognosis of prostate cancer with respect to obesity (Supplementary Table S3 of the Study 2).

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Bluethmann	2020	USA	2004-2014	cohort, prospective	90,694 PC survivors of >40 years	BMI postdiagnosis	PCSM	age, race/ethnicity, insurance status, rurality, lymph node status, PC aggressiveness, serum PSA, smoking, physical inactivity, chronic drinking, and fruit/vegetable intake	6
Crump	2020	Sweden	1972-2017, mean 39.5 years	cohort, prospective	699,125 participants. 10,782 incident PC	BMI prediagnosis	PCSM	age, year of military conscription examination, CRF, muscle strength, country of birth, education, neighbourhood SES, FHPC	9
Jochems	2020	Sweden	1971-2016, mean 28 years	cohort, prospective	431,902 participants. 38,871 incident PC	BMI prediagnosis	PCSM	age at study entry, smoking status, healthcare region, country of birth and education, income closest to diagnosis, source of income closest to diagnosis, civil status closest to diagnosis, Charlson comorbidity index, primary treatment for PC, PC risk category	8
Vidal	2020	USA	1990-2019, median 7.4 years	cohort, retrospective	5,929 PC patients who underwent RP	BMI postdiagnosis	PCSM	age, race, surgical center, year of surgery, PSA, biopsy grade group, pathologic grade group (not biopsy), positive surgical margins, seminal vesicle invasion,	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
								extracapsular invasion, and lymph node involvement	
Jackson	2020	Jamaica	2005-2017, median 11.3 years	cohort, retrospective	242 incident PC in African-Caribbean ancestry	BMI postdiagnosis	PCSM, A-CM	age, smoking, diabetes, Gleason score, primary treatment modality, FHPC and androgen deprivation therapy	6
Troeschel	2020	USA	1992-2016, median 5.7 years	cohort, prospective	11,788 participants. 8,330 non-metastatic PC	BMI postdiagnosis	PCSM, A-CM	age, education, smoking, PSA, T, Gleason, initial treatment, year of diagnosis	6
Dickerman	2019	Iceland	2002-2015, median 10.1 years	cohort, prospective	5,764 participants. 172 incident PC	BMI postdiagnosis	PCSM	age, family FHPC, smoking status, education, frequency of moderate/ vigorous physical activity during youth and midlife, presence of a physician visit over the past year	8
Langlais	2019	USA	1995-2018, median 4.5 years	cohort, prospective	3,230 PC patients who underwent RP	BMI postdiagnosis	A-CM	age, race, smoking status, comorbidities, surgical approach, PSA, pathologic Gleason score, pathologic T-stage pathologic N-stage, and clinical stage	6
Darcey	2019	Australia	2001-2017, median 15 years	cohort, retrospective	572 incident PC	BMI postdiagnosis	PCSM, A-CM	age, Gleason score	7
Wade	2019	Sweden	1961-2004	cohort, prospective	996,898 participants,	BMI prediagnosis	PCSM	educational and occupation socioeconomical index	8

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
					12,712 incident PC				
Farris	2018	Canada	1997-2017	cohort, prospective	829 incident PC	BMI postdiagnosis	PCSM, A-CM	age at diagnosis, stage, prostatectomy, initial hormone therapy treatment, initial radiation therapy treatment, PSA levels at diagnosis, and post-diagnosis Charlson comorbidity index score	7
Hu	2018	China	2003-2015, median 49 months	cohort, retrospective	435 PC patients receiving androgen deprivation therapy	BMI postdiagnosis	A-CM	age, diabetes, Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score	6
Pérez-Cornago	2017	Europe	1992-2013, average 13.9 years	cohort, prospective	141,896 participants, 7,024 incident PC	BMI postdiagnosis	PCSM	age, center, education level, smoking status, marital status, Diabetes, physical activity	9
Dickerman	2017	USA	1986-2012,	cohort, prospective	5,158 patients with clinically localized PC	BMI postdiagnosis	PCSM	age at diagnosis, race, FHPC, smoking status at diagnosis, diabetes at diagnosis, heart/lung disease by time of diagnosis, physical activity, energy intake, tomato sauce intake, coffee intake, alpha-linolenic acid and calcium intake, clinical stage, grade, PSA at diagnosis, primary treatment	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Kelly	2017	USA	1993-2009, median 11.5 years	cohort, prospective	7,822 incident PC	BMI prediagnosis	PCSM	screening arm, family history of prostate cancer, race, study center, education, marital status, cigarette smoking status, diabetes, myocardial infarction, PSA history during the three years prior to enrolment	8
Polesel	2016	Italy	1995-2002, median 11.6 years	cohort, retrospective	715 incident PC	BMI prediagnosis	PCSM, A-CM	age, area of residence, calendar period, years of education, Gleason score, smoking habits	7
Cushen	2016	Ireland	2008-2014	cohort, retrospective	63 patients with metastatic castrate-resistant PC treated with docetaxel	BMI postdiagnosis	A-CM	age, bone metastases and non-osseous metastases, anaemia, muscle density, sarcopenia, visceral fat (VAT) index and subcutaneous fat (SAT) index	5
Fowke	2015	Asian countries	1963-2006, mean 9 years	18 cohort, prospective studies	522,736 participants, 634 PC deaths	BMI prediagnosis	PCSM	age, education, population density, marital status, history of severe cancer, heart disease, or stroke at baseline	7
Wang	2015	USA	2001-2010, median 47.6 months	cohort, retrospective	1,442 localized PC after receiving intensity-modulated RT	BMI postdiagnosis	PCSM, A-CM	age, androgen deprivation therapy (ADT), pretreatment PSA as a log-transformed variable (iPSA), Gleason score and T classification	8
Cantarutti	2015	Sweden	2001-2012	cohort, retrospective	3,161 incident PC	BMI prediagnosis	PCSM,	age at inclusion to study, PSA, treatment	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
							A-CM		
Taghizadeh	2015	The Netherlands	1965-2008, median 34.5 years	cohort, prospective	3,718 incident PC	BMI prediagnosis	PCSM	age, smoking and place of residence	7
Mohammed	2015	Saudi Arabia	2011-2015, median 14.4 months	cohort, retrospective	71 metastatic PC	BMI postdiagnosis	PCSM	age, PSA, alkaline phosphatase, visceral metastasis, bone, lactate dehydrogenase, albumin and poorly differentiated pathology	7
Moller	2015	Denmark	1993-2011, median 15.5 years	cohort, prospective	26,877 participants, 1,813 incident PC	BMI prediagnosis	PCSM	stage (TNM)	7
Bonn	2014	Sweden	1997-2007, median 4 years	cohort, retrospective	4,367 clinically localized PC	BMI postdiagnosis	PCSM, A-CM	age at diagnosis, primary treatment, Gleason score at diagnosis, PSA level, T-, N- and M-stages at diagnosis, smoking habits, and total metabolic equivalent time (MET-h) at age 50	6
Chalfin	2014	USA	1982-2012, median 5 years	cohort, retrospective	11,152 PC patients who underwent RP	BMI postdiagnosis	PCSM, A-CM	age, year of surgery, race, preoperative PSA, pathology stage, pathologic Gleason sum, and positive surgical margin	6
Haque	2014	USA	1971-2001	case-control, retrospective	751 PC patients who underwent RP	BMI postdiagnosis	PCSM	age at diagnosis, health plan site, race, year of diagnosis, stage at diagnosis, duration of health plan membership, PSA at diagnosis,	8

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
								surgical margins status, and lymph node status	
Froehner	2014	Germany	1992-2005, median 8.6 years	cohort, retrospective	2,131 PC patients who underwent RP	BMI postdiagnosis	A-CM	age, Gleason score, tumor stage, Charlson score and American Society of Anesthesiologists physical status class	8
Gravis	2014	France, Belgium	2004-2008, median 58.4 months	cohort, prospective	385 non-castrate metastatic PC	BMI postdiagnosis	A-CM	univariate	4
Tendulkar	2013	USA	1996-2009, median 74 months	cohort, retrospective	660 high-risk PC treated with RT and AD	BMI postdiagnosis	PCSM	univariate	3
Bassett	2012	Australia	1990-2009, mean 15 years	cohort, prospective	16,514 participants, 1,374 incident PC	BMI prediagnosis	PCSM	country of birth and education	8
Schwartz	2012	USA	1988-2006	cohort, prospective	6,707 participants, 49 PC deaths	BMI prediagnosis	PCSM	age, ionized calcium, serum albumin and 25-OH vitaminD	8
Park	2012	Korea	2003-2009, median 24.6 months	cohort, retrospective	55 castration-resistant PC	BMI postdiagnosis	PCSM	age, Gleason score, log PSA, hemoglobin, Eastern Cooperative Oncology Group Performance Status, alkaline phosphatase, visceral metastasis,prior retropublicradical prostatectomy and prior radiation therapy	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Haggstrom	2012	Norway, Sweden, Austria	1972-2006, mean 12 years	cohort, prospective (7 cohorts)	289,866 participant, 6,673 incident PC	BMI prediagnosis	PCSM	smoking, five birth cohorts and five categories of age at measurement	8
Discaciatti	2011	Sweden	1998-2007	cohort, prospective	36,959 participants, 2,084 incident PC	BMI prediagnosis	PCSM	age at baseline, BMI at age 30 years, total energy intake, total physical activity, years of education, smoking status, family history of prostate cancer and, personal history of diabetes	7
Dehal	2011	USA	1971-1992, average 17 years	cohort, prospective	7,016 participant, 3,127 incident PC	BMI prediagnosis	PCSM	age, socio-economic status variables, cigarette smoking, alcohol drinking and dietary pattern	9
Geinitz	2011	Germany	1994-2002, median 51 months	cohort, retrospective	564 localized PC after conformal RT	BMI postdiagnosis	PCSM, A-CM	age, PSA, and radiation dose, endocrine treatment, T stage, and histological grade	7
Van Roermund	2010	The Netherlands	1991-2008, median 47 months	cohort, retrospective	1,530 localized PC who underwent brachytherapy	BMI postdiagnosis	PCSM, A-CM	age, preoperative PSA, pathological stage, pathological grade, risk group, prostate volume, preoperative pelvic lymph node dissection, treatment period and number of seeds	7
Han	2010	USA	1983-2000, median 13 years	cohort, retrospective	2,718 PC patients who underwent RP	BMI postdiagnosis	A-CM	univariate	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Burton	2010	UK	1948-2009, median 49 years	cohort, prospective	9,549 participants, 211 incident PC	BMI prediagnosis	PCSM	smoking, father's social class and height	7
Martin	2009	Norway	1995-2005, median 9.3 years	cohort, prospective	29,364 participants, 687 incident PC	BMI prediagnosis	PCSM	age, height, smoking, marital status, education, physical activity, International Prostate Symptom Score	8
Pfitzenmaier	2009	Germany	median 5.5 years	cohort, prospective	620 PC patients who underwent RP	BMI postdiagnosis	A-CM	tumor extension, lymph node, tumor grading, PSA and resection margin	4
Davies	2009	USA	1995-2007, mean 51.3 months	cohort, prospective	7,274 clinically localized PC	BMI postdiagnosis	PCSM, A-CM	age, clinical risk, presence of diabetes and type of therapy	6
Armstrong	2009	USA	2000-2006	cohort, prospective	1,001 castration-resistant metastatic PC	BMI postdiagnosis	A-CM	baseline pain, presence of liver metastases, performance status, hemoglobin, alkaline phosphatase, PSA, PSA doubling time, number of sites of metastatic disease, type of progression, high-grade disease and treatment group	5
Ma	2008	USA	1982-2007, median 7 years	cohort, prospective	2,546 incident PC	BMI prediagnosis	A-CM	age at diagnosis, baseline smoking status, time interval from BMI measurement to PC diagnosis, clinical stage and Gleason grade	7
Merrick	2007	USA	1995-2003, mean 5.9 years	cohort, prospective	1,093 localized PC who	BMI prediagnosis	PCSM, A-CM	univariate	5

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
					underwent brachytherapy				
Efstathiou	2007	USA	1987-2005, median 8.1 years	cohort, prospective	945 locally advanced PC	BMI postdiagnosis	PCSM, A-CM	age, race, treatment arm, history of prostatectomy, nodal involvement, Gleason score and clinical stage	6
Gong	2007	USA	1993-2004, average 9.5 years	cohort, prospective	752 incident PC	BMI prediagnosis	PCSM, A-CM	age at diagnosis, race, smoking status, Gleason score, stage at diagnosis and primary treatment	8
Montgomery (8894)	2007	USA	1989-1994	cohort, prospective	1,006 metastatic PC treated with AD	BMI postdiagnosis	A-CM	treatment arm, race, pre-study Gleason sum, pre-study bone pain, disease extent, performance status and pre-study PSA	5
Montgomery (9916)	2007	USA	1999-2003	cohort, prospective	671 metastatic PC treated with chemotherapy	BMI postdiagnosis	A-CM	treatment arm, race, pre-study Gleason sum, pre-study bone pain, disease extent, performance status and pre-study PSA	5
Wright	2007	USA	1995-2001	cohort, prospective	287,760 participants, 9,986 incident PC	BMI prediagnosis	PCSM	age, race, smoking status, education, personal history of diabetes, FHPC	6
Huxley	2007	Asia-Pacific region	median 6.8 years	cohort prospective, 24 cohorts	320,852 participants, 308 PC deaths	BMI prediagnosis	PCSM	smoking and diabetes	6

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Halabi	2007	USA	1991-2004, median 33.8 months	cohort, retrospective	1,226 castration-recurrent PC	BMI posdiagnosis	PCSM, A-CM	age race, ECOG performance status, Gleason score, hemoglobin, testosterone, PSA, alkaline phosphatase, LDH, presence of visceral disease, prior treatment with radiotherapy, years since diagnosis	6
Siddiqui	2006	USA	1990-1999, median 10.1 years	cohort, prospective	5,313 PC patients who underwent RP	BMI posdiagnosis	PCSM, A-CM	Gleason score, preoperative serum PSA, surgical margin status, seminal vesicle invasion and adjuvant treatment	6
Park	2006	Korea	1996-2004, median 3.86 years	cohort, prospective	14,578 participants, 256 incident PC	BMI prediagnosis	A-CM	age, alcohol consumption, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities	7
Eichholzer	2005	Switzerland	1971-1990	cohort, prospective	2,974 participants, 30 PC deaths	BMI prediagnosis	PCSM	age and smoking	6
Rodriguez (CPS-I)	2001	USA	1959-1972	cohort, prospective	456,490 participants, 2,277 PC deaths	BMI prediagnosis	PCSM	age at interview, race, height, education, exercise, smoking status and FHPC	7
Rodriguez (CPS-II)	2001	USA	1982-1996	cohort, prospective	508,351 participants, 5,414 PC deaths	BMI prediagnosis	PCSM	age at interview, race, height, education, exercise, smoking status and FHPC	7
Gapstur	2001	USA	1967-1997, mean 27 years	cohort, prospective	20,433 participant, 176 PC deaths	BMI prediagnosis	PCSM	age, postload plasma glucose level, heart rate, education and race	7

Author	Year	Country	Follow-up	Design	Participants and population	Exposure	Outcome	Adjustment variables	NOS
Andersson	1997	Sweden	1971-1991, average 18 years	cohort, retrospective	135,006 participants, 2,368 incident PC	BMI prediagnosis	PCSM	age	7

Appendix 8. Methodological quality assessment of the selected studies (Supplementary Table S4 of the Study 2) according to NOS.

A. Cohort studies (n=58)

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	**Total score**
Bluethmann	2020	0	1	0	1	1	1	1	1	0	**6**
Crump	2020	1	1	1	1	1	1	1	1	1	**9**
Jackson	2020	0	1	0	1	1	1	1	1	0	**6**
Jochems	2020	1	1	1	1	1	1	1	1	0	**8**
Vidal	2020	0	1	1	1	1	1	1	1	0	**7**
Troeschel	2020	0	1	0	1	1	1	1	1	0	**6**
Dickerman	2019	1	1	1	1	1	1	1	1	0	**8**
Langlais	2019	0	1	0	1	1	1	1	1	0	**7**
Darcey	2019	1	1	0	1	1	1	1	1	0	**7**
Wade	2019	1	1	1	1	1	1	1	1	0	**8**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	**Total score**
Farris	2018	1	1	1	1	1	1	1	0	0	**7**
Hu	2018	0	1	1	1	1	1	1	0	0	**6**
Pérez-Cornago	2017	1	1	1	1	1	1	1	1	1	**9**
Dickerman	2017	0	1	0	1	1	1	1	1	1	**7**
Kelly	2017	1	1	0	1	1	1	1	1	1	**8**
Polesel	2016	1	1	0	1	1	1	1	1	0	**7**
Cushen	2016	0	1	0	1	1	1	1	0	0	**5**
Fowke	2015	1	1	0	1	1	1	1	1	0	**7**
Wang	2015	0	1	1	1	1	1	1	1	1	**8**
Cantarutti	2015	1	1	0	1	1	1	1	1	0	**7**
Taghizadeh	2015	1	1	0	1	1	1	0	1	1	**7**
Mohammed	2015	0	1	1	1	1	1	1	0	1	**7**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	**Total score**
Moller	2015	1	1	1	1	0	1	1	1	0	**7**
Bonn	2014	0	1	0	1	1	1	1	1	0	**6**
Chalfin	2014	0	1	0	1	1	1	1	1	0	**6**
Froehner	2014	0	1	1	1	1	1	1	1	1	**8**
Gravis	2014	0	1	1	1	0	0	0	1	0	**4**
Tendulkar	2013	0	1	0	1	0	0	0	1	0	**3**
Bassett	2012	1	1	1	1	0	1	1	1	1	**8**
Schwartz	2012	1	1	1	1	1	1	1	1	0	**8**
Park	2012	0	1	1	1	1	1	0	1	1	**7**
Haggstrom	2012	1	1	1	1	1	1	1	1	0	**8**
Discaciatti	2011	1	1	0	1	1	1	1	1	0	**7**
Dehal	2011	1	1	1	1	1	1	1	1	1	**9**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	**Total score**
Geinitz	2011	0	1	1	1	1	1	1	1	0	**7**
Van Roermund	2010	0	1	1	1	1	1	1	0	1	**7**
Han	2010	0	1	1	1	1	1	1	1	0	**7**
Burton	2010	1	1	1	1	0	1	1	1	0	**7**
Martin	2009	1	1	1	1	1	1	1	1	0	**8**
Pfitzenmaier	2009	0	1	0	1	0	1	0	1	0	**4**
Davies	2009	0	1	1	1	1	1	1	0	0	**6**
Armstrong	2009	0	1	1	1	0	1	1	0	0	**5**
Ma	2008	1	1	0	1	0	1	1	1	1	**7**
Merrick	2007	0	1	1	1	0	0	1	1	0	**5**
Efstathiou	2007	0	1	1	1	1	1	0	1	0	**6**
Gong	2007	1	1	0	1	1	1	1	1	1	**8**

Study	Year	**Selection**				**Comparability**		**Outcome**			**Total score**
		Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	
Montgomery (8894)	2007	0	1	1	1	0	1	0	0	1	**5**
Montgomery (9916)	2007	0	1	1	1	0	1	0	0	1	**5**
Wright	2007	1	1	0	1	1	1	1	0	0	**6**
Huxley	2007	1	1	1	1	0	1	0	1	0	**6**
Halabi	2007	0	1	0	1	1	1	0	1	1	**6**
Siddiqui	2006	0	1	1	1	0	1	0	1	1	**6**
Park	2006	1	1	1	1	1	1	1	0	0	**7**
Eichholzer	2005	0	1	1	1	1	1	0	1	0	**6**
Rodriguez (CPS-I)	2001	1	1	0	1	1	1	0	1	1	**6**
Rodriguez (CPS-II)	2001	1	1	0	1	1	1	0	1	1	**6**

		Selection				**Comparability**		**Outcome**			**Total score**
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur	Adequacy of follow-up[4]	
Gapstur	2001	0	1	1	1	1	1	1	1	0	**7**
Andersson	1997	0	1	1	1	1	0	1	1	1	**7**

[1] The point was assigned for objectively measured body mass index. [2] If adjusted for age, the point was assigned. [3] If adjusted for any other additional factor, the point was assigned. [4] If the completeness of follow-up was 90% or more, or characteristics of lost cohort were similar to the rest of the cohort, the point was assigned.

B. Case-control studies (n = 1)

		Selection				**Comparability**		**Exposure**			**Total score**
Study	Year	Definition of cases	Representative-ness of cases	Selection of controls	Definition of controls	Important factor[1]	Additional factor[2]	Ascertainment[3]	Same method for subjects	Non-response rate	
Haque	2014	1	1	1	1	1	1	0	1	1	**8**

[1] If adjusted for age, the point was assigned. [2] If adjusted for any other additional factor, the point was assigned. [3] The point was assigned for objectively measured body mass index.

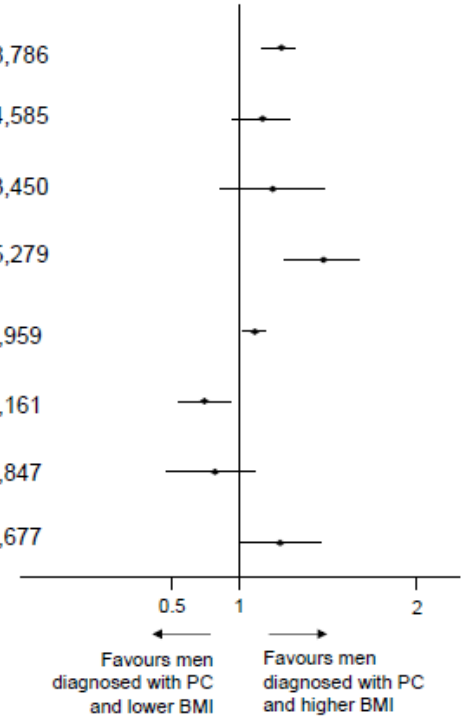
NOS, Newcastle-Ottawa Scale.

Appendix 9. Assessment of potential causation criteria for the association assessed in the systematic review of the Study 2 (Supplementary Table S5 of the Study 2).

Causal criteria	Evaluative systematic review methods applied
Strength of association	The measures of strength of association in this systematic review were hazard ratios (HR) for quantifying the association between obesity and mortality of each individual study. Pooled analysis showed HR = 1.19 (95% CI: 1.10-1.28) for the association between obesity and prostate cancer specific mortality and HR = 1.09 (95% CI: 1.00-1.18) for the association between obesity and all-cause mortality. The strength of association between obesity and prostate cancer specific mortality was especially high when analysing the subgroup of higher quality (HR = 1.24, 95% CI: 1.14-1.25).
Consistency	Consistency of individual studies was analysed graphically using forest plots and statistically by χ^2 test and I^2 statistic. We performed heterogeneity analysis to evaluate sources of heterogeneity and obtained pooled results with acceptable heterogeneity (several subgroups showed I^2=0.0%). When analysing the pooled estimators stratified by potential heterogeneity factors, the associations between obesity and prostate cancer specific or all-cause mortality remained.
Temporality	We only included follow-up (cohort or case-control) studies. Cross-sectional studies were excluded from the search. We also evaluated if the outcome was proven to be absent at the beginning of the study to ensure temporality. This item was evaluated in the Newcastle-Ottawa Scale (NOS). The pooled results according to NOS (high quality) and according to design (prospective cohort studies) showed the same associations.
Specificity	Attempts to study the specifical effect of obesity on mortality were made through heterogeneity analyses.
Biological gradient	We analysed the gradient of BMI on mortality and showed greater association according to higher BMI strata. Continuous BMI per 5 kg/m^2 were analysed in the dose-response meta-analysis association were found regarding prostate cancer specific and all-cause mortality.
Plausibility, coherence and analogy	Obesity is presumed aetiological factor biologically plausible. There are also analogous causal relationships between the aetiological factor and mortality from other cancers. These conditions have been analysed throughout the discussion section of the manuscript.
Experimental evidence	Not applicable to risk factors.

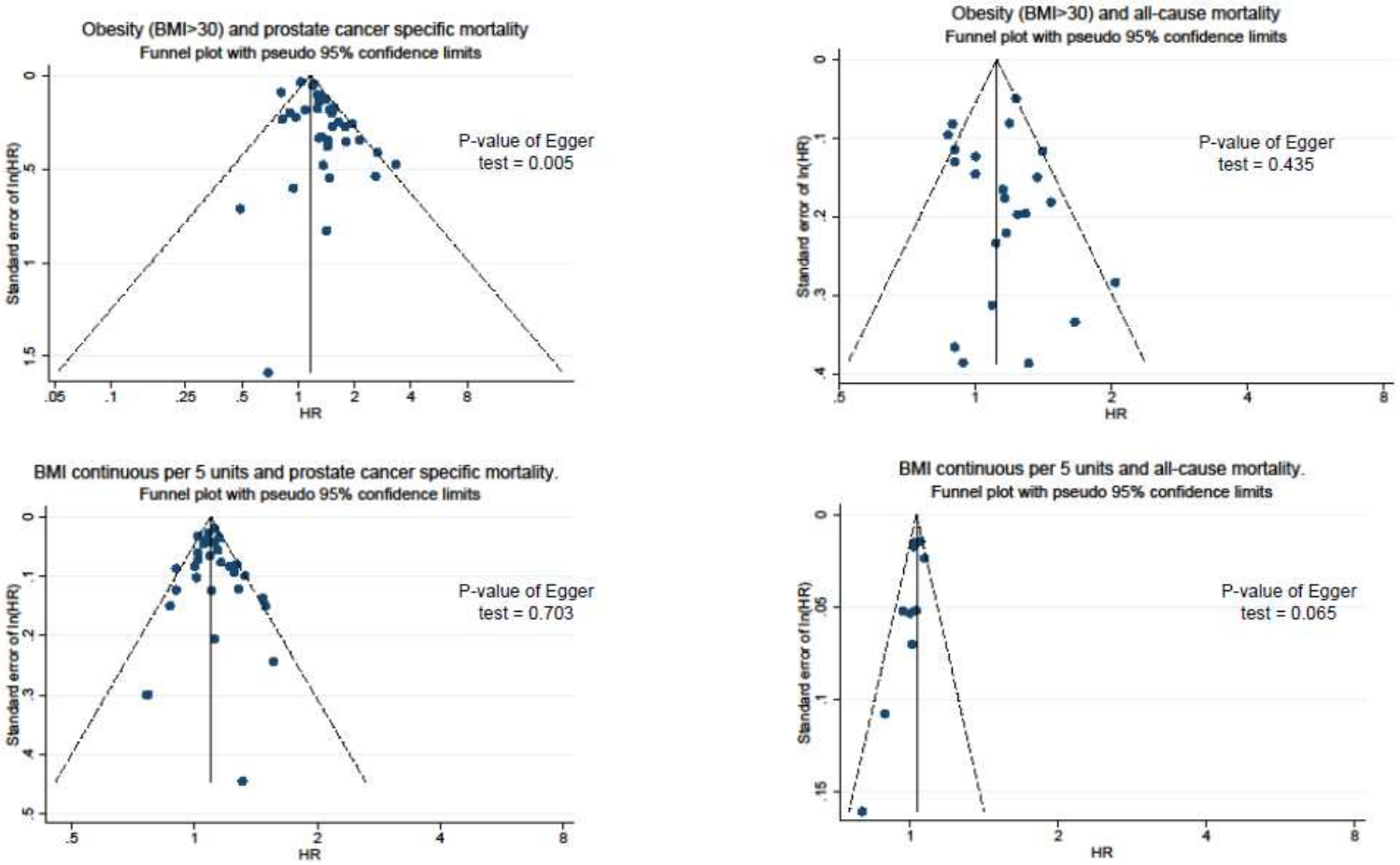
Appendix 10. Forest-plot of the associations between obesity (BMI ≥ 30), overweight (BMI < 30 and ≥ 25) and abnormal weight (BMI ≥ 25), compared to normal weight (BMI < 25), and continuous BMI per 5 units, on prostate cancer specific mortality and all-cause mortality (Supplementary Table S6 of the Study 2).

	Studies (n)	Events (n)	Participants (n)	Hazard ratio (95% CI)	p value	I^2 (%)
Prostate Cancer specific mortality					*	
BMI continuous, per 5 kg/m²	31	30,891	148,786	1.09 (1.05–1.12)	0.003	44,3
Overweight (BMI ≥ 25 & < 30)	36	13,621	154,585	1.05 (0.99–1.11)	0.003	44,3
Abnormal weight (BMI ≥ 25)	33	19,637	133,450	1.07 (0.96–1.19)	<0.001	83,6
Obesity (BMI ≥ 30)	37	20,721	245,279	1.19 (1.10–1.28)	0.002	44,4
All-cause mortality						
BMI continuous, per 5 kg/m²	10	5,795	29,959	1.03 (1.01–1.05)	0.220	24,3
Overweight (BMI ≥ 25 & < 30)	21	10,849	51,161	0.93 (0.88–0.98)	0.146	24,9
Abnormal weight (BMI ≥ 25)	23	10,818	50,847	0.95 (0.86–1.03)	<0.001	74,2
Obesity (BMI ≥ 30)	23	11,302	53,677	1.09 (1.00–1.18)	0.013	43,9



** P-values of the heterogeneity test.*

Appendix 11. Funnel plots of the pooled associations between obesity (BMI ≥ 30) and continuous BMI per 5 kg/m2 with prostate cancer specific mortality and all-cause mortality (Supplementary Table S7 of the Study 2).



Appendix 12. Methodological quality assessment of the selected studies according to NOS (Supplementary Table 1 of the Study 3).

Cohort studies (n=46)

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur[4]	Adequacy of follow-up[5]	**Total score**
Vidal	2020	1	1	1	1	1	1	1	1	0	**8**
Leal-García	2020	1	1	1	1	1	1	1	1	0	**8**
Langlais	2019	1	1	0	1	1	1	1	1	0	**7**
Khan	2019	1	1	0	1	1	1	1	0	1	**7**
Wissing	2019	1	1	0	1	1	1	1	1	0	**7**
Dong Yu	2018	1	1	1	1	1	1	1	1	1	**9**
Cullen	2018	1	1	1	1	0	0	1	1	1	**7**
Shiota	2017	1	1	1	1	0	1	1	1	0	**7**
Zhao	2017	1	1	1	1	0	0	1	1	0	**6**
Dickerman	2017	1	1	0	1	1	1	1	1	1	**8**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur[4]	Adequacy of follow-up[5]	**Total score**
Roux	2017	0	1	0	1	1	1	1	1	0	**6**
Maj-Hes	2017	1	1	1	1	0	1	1	1	0	**7**
Schiffman	2017	1	1	1	1	1	1	1	1	0	**8**
Goto	2017	1	1	1	1	0	1	1	1	0	**7**
Yamoah	2016	1	1	1	1	1	1	1	0	0	**7**
Ohwaki	2015	1	1	1	1	1	1	1	1	0	**8**
Bai	2015	1	1	1	1	1	1	1	0	0	**7**
Wang	2015	1	1	1	1	1	1	1	1	0	**8**
Tanimoto	2015	1	1	1	1	1	1	1	0	0	**7**
Agalliu	2015	1	1	1	1	1	1	1	1	1	**9**
Koo	2014	1	1	1	1	0	1	1	1	1	**8**
Hayashi	2014	1	1	0	1	1	1	1	1	0	**7**
Chalfin	2014	1	1	1	1	1	1	1	1	0	**8**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur[4]	Adequacy of follow-up[5]	**Total score**
Narita	2013	1	1	1	1	1	1	1	1	0	**8**
Tomaszewski	2013	1	1	1	1	1	1	1	1	0	**8**
Asmar	2013	1	1	1	1	1	1	1	1	0	**8**
Campeggi	2012	1	1	1	1	0	0	1	1	1	**7**
Mucksavage	2012	1	1	1	1	0	1	1	1	0	**7**
Kok	2011	1	1	0	1	1	1	1	1	1	**7**
Joshu	2011	1	1	0	1	1	1	1	1	0	**7**
Geinitz	2011	1	1	1	1	1	1	1	1	0	**8**
Komaru	2010	1	1	1	1	0	0	1	1	1	**6**
Van Roermund	2010	1	1	1	1	1	1	1	1	1	**9**
Ly	2010	1	1	1	1	0	1	1	1	0	**7**
Sumitomo	2010	1	1	1	1	1	1	1	1	1	**9**

		Selection				**Comparability**		**Outcome**			
Study	Year	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start	Important factor[2]	Additional factor[3]	Assessment	Exposure follow-up long enough for outcomes to occur[4]	Adequacy of follow-up[5]	**Total score**
King	2009	1	1	1	1	0	1	1	1	0	**7**
Pfitzenmaier	2009	1	1	1	1	1	1	1	1	1	**9**
VanRoermund	2009	1	1	1	1	1	1	1	1	1	**9**
Efstathiou	2008	1	1	1	1	0	1	1	1	0	**7**
Hisasue	2008	1	1	1	1	1	1	1	0	0	**7**
Spangler	2007	1	1	0	1	1	1	1	1	0	**7**
Efstathiou	2007	1	1	1	1	1	1	1	1	0	**8**
Stroup	2007	1	1	1	1	0	1	1	1	0	**7**
Siddiqui	2006	1	1	1	1	0	1	1	1	1	**8**
Strom	2006	1	1	1	1	0	1	1	1	0	**7**
Strom	2005	1	1	0	1	0	1	1	1	0	**6**

[1] The point was assigned for objectively measured body mass index (measured by the researchers or obtained from clinical histories or databases) [2] If adjusted for age, the point was assigned. [3] If adjusted for any other additional factor, the point was assigned. [4] If median (or mean) follow-up was reported and over 2 years, the point was assigned. [5] If the completeness of follow-up was 90% or more, or characteristics of the lost cohort were reported and similar to the rest of the cohort, the point was assigned.

Appendix 13. Subgroup analysis of the pooled association of body mass index with biochemical recurrence in prostate cancer patients (Supplementary Table 2 of the Study 3).

Subgroup	Biochemical recurrence					
	Obesity (BMI ≥ 30) compared with normal weight (BMI < 25)			BMI continuous per 5 kg/m²		
	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2
All studies (total)	25	1.25 (1.11-1.39)	70.3	46	1.10 (1.04-1.15)	66.3
Treatment received						
Radical prostatectomy	20	1.34 (1.18-1.49)	70.2	34	1.09 (1.03-1.15)	68.1
EBRT	1	0.98 (0.29-1.68)	-	6	1.18 (1.10-1.26)	0.0
Brachytherapy	2	0.82 (0.25-1.40)	63.9	2	0.90 (0.58-1.21)	60.5
Other treatments [a]	2	1.03 (0.59-1.48)	68.0	4	1.09 (0.92-1.26)	70.9
Country						
American countries	15	1.20 (1.05-1.35)	54.4	25	1.10 (1.05-1.15)	59.7
Asian countries	3	1.53 (1.22-1.83)	32.4	12	1.16 (0.91-1.41)	61.7
European countries	6	0.98 (0.87-1.10)	0.0	8	0.99 (0.94-1.04)	0.0
Other countries	1	2.64 (2.00-3.29)	-	1	1.62 (1.43-1.82)	-
Year of publication						
<2014	13	1.18 (0.98-1.38)	45.9	23	1.10 (1.02-1.17)	48.8
≥2014	12	1.32 (1.11-1.52)	81.2	23	1.10 (1.02-1.17)	75.8
Quality of the evidence [b]						
Level 2 (prospective cohort)	9	1.25 (1.01-1.48)	49.0	15	1.10 (1.01-1.18)	58.5
Level 3 (retrospective cohort)	16	1.25 (1.07-1.43)	76.9	31	1.09 (1.03-1.16)	69.3

Subgroup	Biochemical recurrence					
	Obesity (BMI ≥ 30) compared with normal weight (BMI < 25)			BMI continuous per 5 kg/m^2		
	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2
Risk of bias						
NOS: 9	5	1.09 (0.86-1.32)	4.0	6	1.03 (0.89-1.17)	0.0
NOS: 8	7	1.07 (0.94-1.19)	47.5	15	1.02 (0.96-1.08)	62.7
NOS: 7	11	1.51 (1.16-1.86)	72.9	22	1.19 (1.09-1.28)	64.7
NOS: 6	2	1.62 (1.39-1.85)	0.0	3	1.22 (0.88-1.56)	74.6
Conflicts of interest						
No	19	1.20 (1.03-1.37)	73.8	33	1.08 (1.01-1.15)	67.9
Not reported	4	1.34 (1.17-1.52)	0.0	10	1.14 (1.05-1.22)	62.8
Yes	2	1.51 (1.04-1.97)	34.7	3	1.14 (0.81-1.48)	70.5
BMI source						
Measured by the researchers	4	1.65 (1.42-1.68)	0.0	9	1.02 (0.94-1.10)	0.0
Clinical histories or databases	17	1.18 (1.04-1.33)	66.3	30	1.09 (1.03-1.16)	70.0
Self-reported	4	1.37 (0.81-1.93)	74.5	7	1.20 (1.01-1.40)	71.1
BMI boundaries						
World Health Organization (obesity as BMI ≥ 30)	22	1.22 (1.08-1.37)	71.8	-	-	-
Other boundaries	3	1.53 (1.22-1.83)	32.4	-	-	-
BMI moment of measurement						
At diagnosis	23	1.28 (1.13-1.43)	69.8	43	1.09 (1.04-1.15)	65.5
Other moments	2	1.05 (0.52-1.57)	62.5	3	1.16 (0.88-1.43)	62.6

Subgroup	Biochemical recurrence					
	Obesity (BMI ≥ 30) compared with normal weight (BMI < 25)			BMI continuous per 5 kg/m^2		
	N	HR (95% CI)	I^2	N	HR (95% CI)	I^2
Definition of the outcome (BCR)						
PSA ≥ 0.1	2	1.03 (0.36-1.70)	66.9	2	1.34 (0.79-1.68)	72.5
PSA ≥ 0.2	16	1.79 (1.29-2.50)	72.7	31	1.09 (1.01-1.16)	62.5
PSA ≥ 0.4	1	1.31 (0.85-1.77)	-	2	1.03 (0.94-1.12)	42.5
PSA nadir + elevation ≥ 2	3	0.84 (0.45-1.23)	35.1	8	1.05 (0.80-1.29)	65.3
Other	3	1.13 (0.84-1.42)	58.6	10	1.11 (1.00-1.22)	25.7

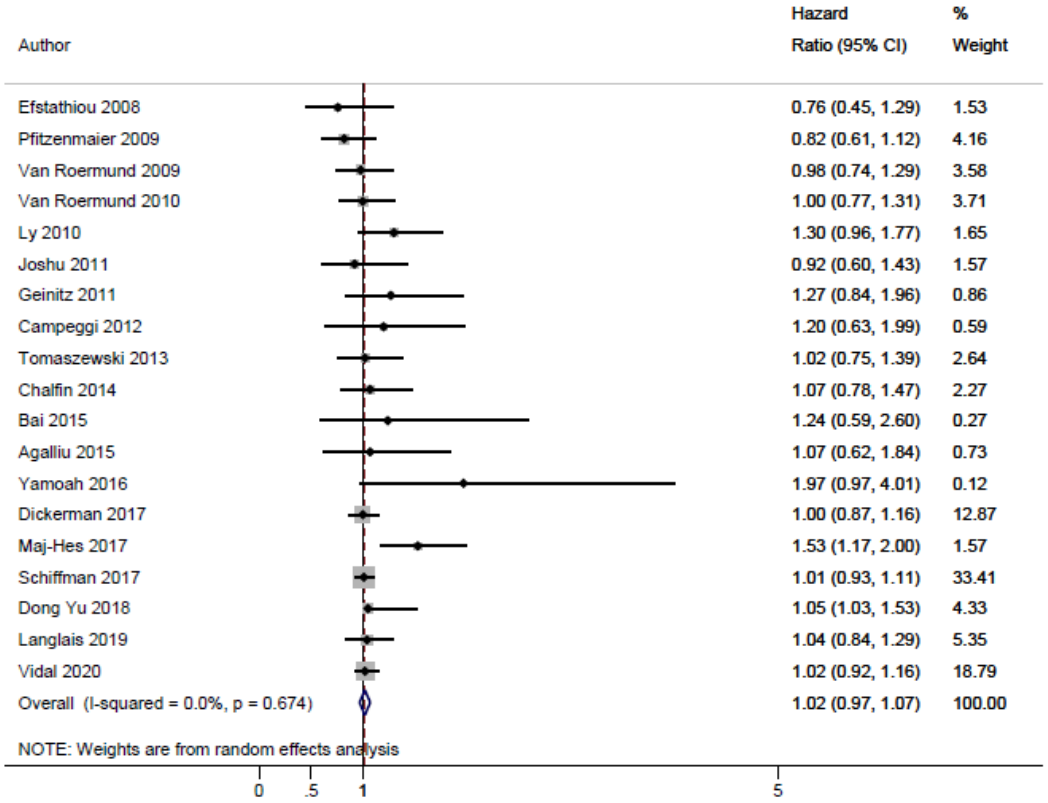
BCR, biochemical recurrence; BMI, body mass index; NOS, Newcastle-Ottawa scale. [a]

Other treatments included one study of high-intensity focused ultrasound, and two studies that mixed patients receiving radical prostatectomy with patients receiving radiotherapy. [b]

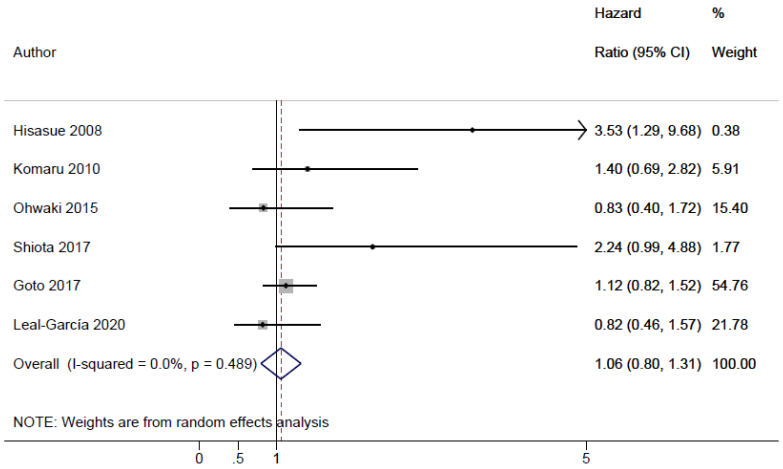
According to the Centre for evidence-based medicine.

Appendix 14. Forest-plot of the associations between A) overweight (BMI < 30 and ≥ 25) and B) abnormal weight (BMI ≥ 25), compared to normal weight (BMI < 25), on biochemical recurrence in clinically localized prostate cancer patients (Supplementary Fig. 1 of the Study 3).

A

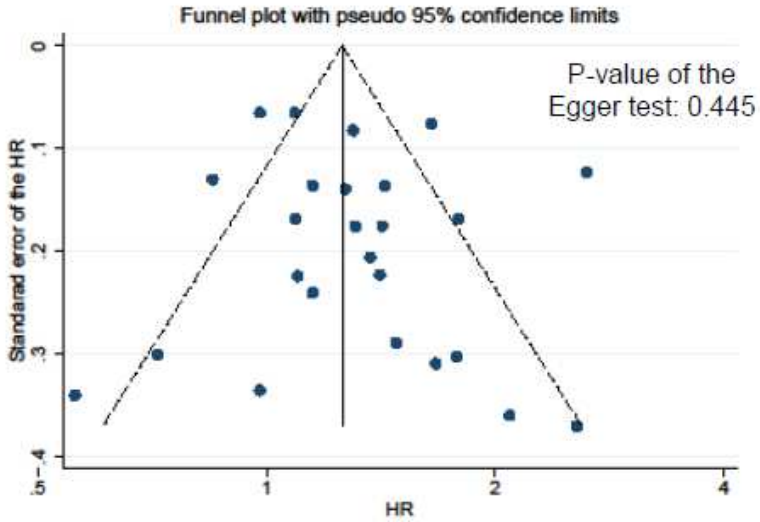


B

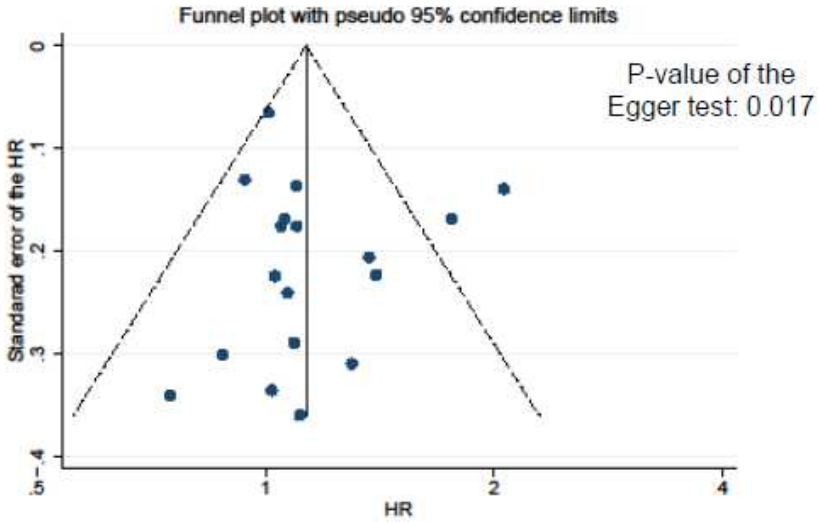


Appendix 15. Funnel plots of the pooled associations between obesity (BMI ≥ 30) and continuous BMI per 5 kg/m^2 with prostate cancer specific mortality and all-cause mortality (Supplementary Fig. 2 of the Study 3).

Funnel plot of the association between obesity (BMI ≥ 30) and biochemical recurrence



Funnel plot of the association between BMI per 5 kg/m^2 and biochemical recurrence



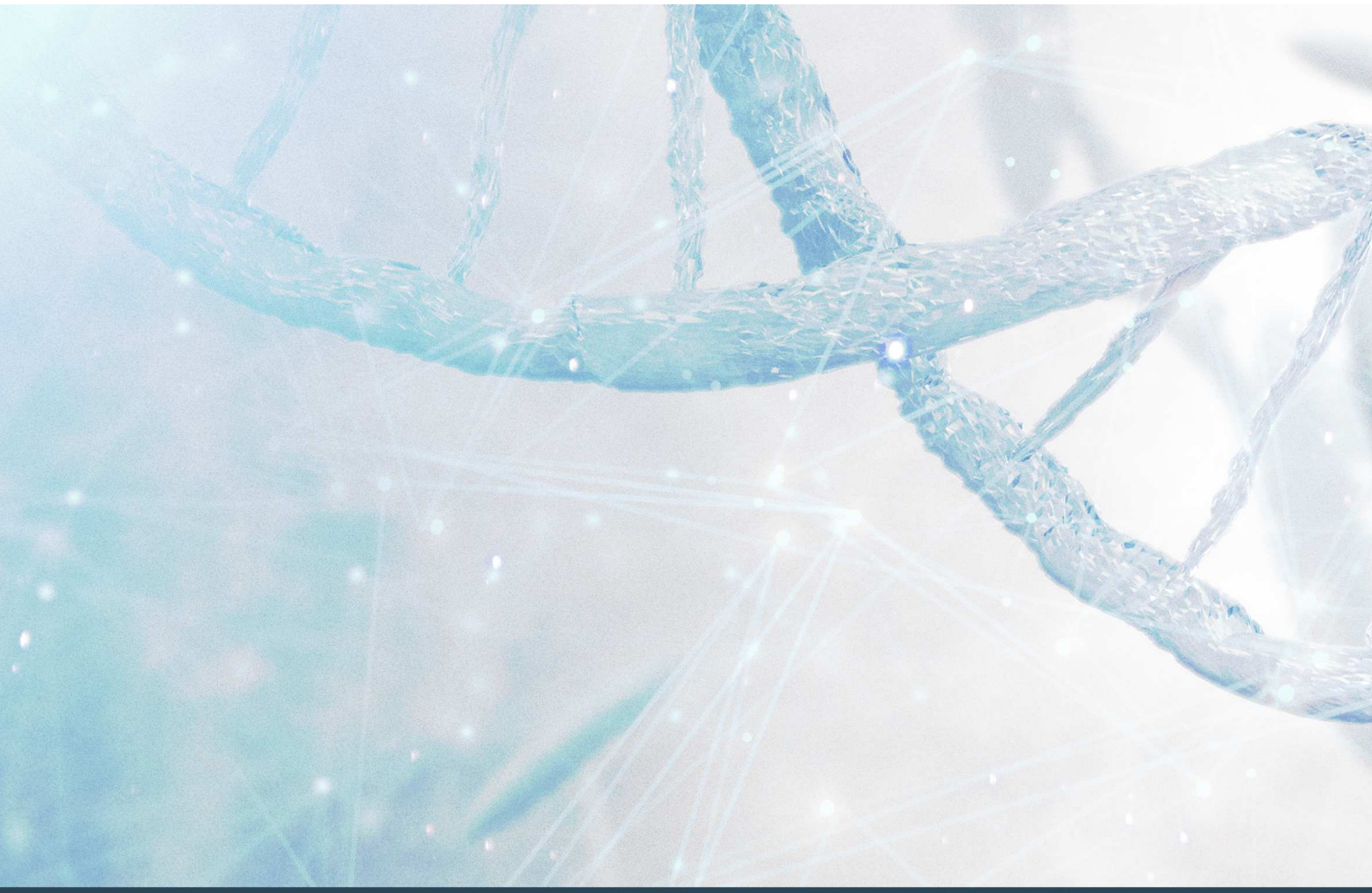
Appendix 16. Assessment of causation criteria (Supplementary Table 3 of the Study 3).

Causal criteria	Evaluative systematic review methods applied
Strength of association	The measures of strength of association in this systematic review were hazard ratios (HR) for quantifying the association between obesity and biochemical recurrence of each individual study, adjusted for several potential confounders (see Table 1 of the manuscript). Pooled analysis showed (HR: 1.25, 95% CI: 1.11-1.39) for the association between obesity and biochemical recurrence. The strength of association between obesity and biochemical recurrence was especially high for the subgroup of patients that received radical prostatectomy (HR: 1.34; 95% CI: 1.18-1.49).
Consistency	Consistency of the included individual studies was analysed graphically using forest plots and statistically by χ^2 test and I^2 statistic. We performed heterogeneity analyses to evaluate sources of heterogeneity and obtained pooled results with acceptable heterogeneity (several subgroups showed I^2=0.0%). When analysing the pooled estimators stratified by potential heterogeneity factors, the associations between obesity and biochemical recurrence remained. Specifically, consistent association was found in the subgroup of studies in which BMI was directly measured by researchers (HR: 1.64, 95% CI: 1.42-1.68) or collected from clinical histories or databases (HR: 1.18, 95% CI: 1.04-1.16), in prospective cohort studies (HR: 1.25, 95% CI: 1.01-1.48) and in different areas of the world except for European studies.
Temporality	We only included follow-up (cohort) studies. Cross-sectional studies and other designs were excluded from the search. We also evaluated if the outcome was proven to be absent at the beginning of the study to ensure temporality. This item was evaluated in the Newcastle-Ottawa Scale (NOS). The pooled results design (prospective cohort studies) showed the same associations.
Specificity	Attempts to study the specifical effect of obesity on mortality were made through heterogeneity analyses. Several subgroups showed non-significant association. Therefore, this criterium was not confirmed.
Biological gradient	We showed greater association according to higher BMI strata (overweight, obesity). Continuous BMI per 5 kg/m^2 were analysed and showed association. Although association was found in the total pooled analysis, results of subgroup analyses showed variation. Besides, no clear linear relationship is established according to previous literature; therefore, this criterium was not confirmed.
Plausibility, coherence and analogy	Biological plausibility of obesity as prognostic factor for prostate cancer is theorised and provided in the discussion. There are also analogous causal relationships between the aetiological factor and other negative outcomes (e.g., mortality) from prostate cancer and from other types of cancer. These conditions have been analysed throughout the discussion section of the manuscript.
Experimental evidence	Not applicable to risk factors.

Appendix 17. Characteristics of the 19 patients that were not included in the analyses for unknown data on body mass index, compared with the rest of the cohort (Study 4).

Feature	Total sample (n=1093)	Patients not included (n=19)
Age, x (s)	66.1 (7.3)	66.8 (8.7)
Diabetes, x (s)	153 (14.0)	2 (10.5)
Hospital Centre, n (%)		
HUTiP, Barcelona	198 (18.1)	1 (5.3)
HDM, Barcelona	152 (13.9)	1 (5.3)
HC, Barcelona	52 (4.8)	1 (5.3)
HUMV, Cantabria	173 (15.8)	2 (10.5)
HURC, Madrid	157 (14.4)	4 (21.1)
HULP, Madrid	153 (14.0)	1 (5.3)
HUPF, Valencia	83 (7.6)	3 (15.8)
HUSC, Granada	63 (5.8)	1 (5.3)
HUJRJ, Huelva	33 (3.0)	3 (15.8)
HUIE, Huelva	15 (1.4)	1 (5.3)
HUC, Asturias	15 (1.4)	1 (5.3)
PSA, ng/ml, median (IQR)	7.3 (5.6, 10.5)	10.2 (8.9)
T classification, n (%)		
T1	363 (33.2)	5 (26.3)
T2-T4	611 (55.9)	13 (73.7)
Unknown	119 (10.9)	0 (0.0)
N: Lymph node involvement, n (%)		
Yes	9 (1.1)	0 (0.0)
No	268 (32.9)	3 (18.8)
Not evaluated	538 (66.0)	13 (81.4)
M: presence of metastasis, n (%)		
Yes	17 (2.1)	0 (0.0)
No	523 (63.5)	9 (56.3)
Not evaluated	284 (34.5)	7 (43.8)
Gleason score biopsy grade group, n (%)		
<6	20 (1.8)	0 (0.0)
6	477 (44.0)	8 (42.1)
7	434 (40.0)	8 (42.1)
>7	154 (14.2)	3 (15.8)
D'Amico risk classification, n (%)		
Low risk	411 (37.7)	8 (42.1)
Intermediate risk	448 (41.1)	7 (36.8)
High risk	232 (21.3)	4 (21.1)
Previous prostate surgery, n (%)	24 (2.3)	0 (0.0)
Extracapsular extension, n (%)	68 (13.6)	1 (5.3)
Vascular invasion, n (%)	15 (3.0)	1 (5.3)
Lymphatic invasion, n (%)	6 (1.2)	0 (0.0)
Perineural invasion, n (%)	212 (41.7)	4 (30.8)
Positive surgical margins, n (%)	163 (14.9)	9 (69.2)
Primary treatment, n (%)		
Active surveillance	36 (3.5)	2 (11.1)

Feature	Total sample (n=1093)	Patients not included (n=19)
Surgery	633 (61.7)	14 (77.8)
Radiotherapy	260 (25.1)	2 (10.5)
Chemotherapy	9 (0.9)	0 (0.0)
Hormone therapy	293 (30.2)	7 (38.9)
Dead during follow-up, n (%)	132 (12.7)	3 (15.8)
Dead of prostate cancer, n (%)	35 (3.2)	2 (10.5)
Biochemical recurrence, n (%)	180 (16.5)	3 (15.8)
Castration resistance (out of 162), n (%)	22 (13.6)	3 (15.8)
Follow-up years, median (IQR)	7.1 (5.9-8.1)	6.9 (5.9-7.9)



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