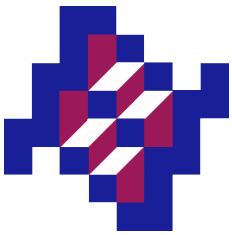

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Estilos de vida y riesgo de cáncer de próstata: Un estudio de casos y controles en la Ciudad de México

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Tesis para obtener el grado de doctora en ciencias en salud pública en epidemiología

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Resumen:

Antecedentes: Existen factores de riesgo bien establecidos para cáncer de próstata (CaP) como la edad, el antecedente familiar de CaP y la raza. Sin embargo, se han propuesto otros posibles factores de riesgo relacionados con el estilo de vida como la historia de vida sexual y la actividad física.

Métodos: Entre Noviembre del 2011 y Agosto del 2014 se realizó un estudio con 402 casos incidentes de CaP y 805 controles poblacionales pareados por edad (± 5 años). Ambos grupos debían tener un tiempo mínimo de residencia de 1 año en la Ciudad de México y no contar con antecedentes previos de ningún tipo de cáncer. Como potenciales controles se excluyeron aquellos que tenían sintomatología prostática, estaban en estudio por sospecha de enfermedad prostática o contar con un reporte de antígeno prostático ≥ 4 ng/ml. Mediante una entrevista directa se obtuvo información sobre la historia de vida sexual, antecedentes de infecciones de transmisión sexual (ITS), tipo de infección, así como de actividad física (AF) recreativa en tres diferentes etapas de la vida 15–18, 19–29, and ≥30 años. Para el análisis de la AF, estimamos el gasto energético en equivalentes metabólicos (METs) para cada etapa de la vida y usando el método k-means+ en el programa R reconstruimos las trayectorias o patrones históricos de AF recreativa a lo largo de la vida. La asociación entre ITS o trayectorias de AF recreativa con CaP se estimaron mediante modelos independientes de regresión logística no condicionada.

Resultados: El antecedente de al menos una ITS a lo largo de la vida se reportó en el 16.6% de los hombres. La más común, fue la infección por gonorrea (10.5%). El antecedente de ITS en general, se asoció con aproximadamente 2 veces más posibilidades de CaP ($OR_{si\ vs\ no}$2.67; IC 95% 1.91-3.73) y este se incrementó a 3 veces más cuando se analizó separadamente el antecedente de gonorrea ($OR_{si\ vs\ no}$3.04; IC 95% 1.99-4.64). Por su parte, el análisis de la AF recreativa a lo largo de la vida, mostró que 14.7% de los casos y 9.3% de los controles nunca realizaron ningún tipo de actividad y esta proporción incrementó conforme aumentó la edad. Entre los hombres que reportaron haber realizado algún tipo de AF recreativa en al menos una etapa de la vida identificamos 3 trayectorias: Trayectoria A, caracterizada por hombres que tenían alta frecuencia e intensidad de AF recreativa a los 15-18 años y en quienes la reducción de AF a lo largo de la vida fue más marcada. Las trayectorias B y C se caracterizaron por su regularidad a lo largo de la vida; sin embargo la intensidad en la Trayectoria B fue menor que la observada en la Trayectoria C. Comparados con los hombres inactivos, el CaP fue

significativamente menor en la trayectoria C ($OR_{Trayectoria\ C\ vs.\ ninguna}$ 0.38; 95% CI 0.19–0.76) o B ($OR_{Trayectoria\ B\ vs.\ ninguna}$ 0.54; 95% CI 0.35–0.82). En la trayectoria A también el CaP fue menos frecuente pero esta disminución no fue significativa ($OR_{Trayectoria\ A\ vs.\ ninguna}$ 0.81; 95% CI 0.50–1.32).

Conclusión: Nuestros resultados confirmar el role etiológico de las ITS en el CaP, en particular de la infección por gonococo. Así mismo sugieren que el efecto protector de la AF recreativa sobre el CaP puede ser consecuencia de un inicio temprano y la constancia en la práctica de la misma.

Introducción:

El cáncer de próstata (CaP) es una neoplasia de crecimiento lento, poco sintomático o con sintomatología inespecífica, que afecta a hombres mayores de 40 años, mostrando su mayor incidencia después de los 65 años de edad.[1-4] Desde el punto de vista histológico la mayoría de estos cánceres son adenocarcinomas, multifocales, principalmente localizados en la periferia de la glándula, que se extienden a órganos vecinos, siendo el tejido óseo el sitio principal de metástasis a distancia.[1-4]

A nivel mundial, es el segundo cáncer más común en hombres con una tasa de incidencia de 31.1 casos por 100,000. Australia y Nueva Zelanda reportan las mayores tasas a nivel mundial (111.6 casos por 100,000 hombres), mientras la menor incidencia es reportada en Bután (sur de Asia) con 1.1 casos por 100,000 hombres.[5] El incremento en la incidencia observada principalmente en los países desarrollados ha sido a expensas de los casos asintomáticos, de lento crecimiento y considerados como "indolentes". Probablemente esto es consecuencia de la introducción del antígeno prostático específico (APE) como prueba de tamizaje.[2-4,6]

Como causa de muerte por cáncer el CaP ocupa el quinto lugar con una tasa de 7.8 por 100,000 hombres y muestra amplias diferencias entre los países desarrollados y en desarrollo.[5] En países con altas tasas de incidencia como Australia (12.9 por 100,000 hombres) y Nueva Zelanda (12.8 por 100,000 hombres), la mortalidad es baja y probablemente esto es debido a la existencia de programas de detección temprana. En países menos desarrollados, donde el diagnóstico se hace en etapas avanzadas, la tasa de mortalidad se encuentra en promedio alrededor de 29 por 100,000 hombres.[5] Un patrón similar se observa en relación a la sobrevida a los 5 años después del diagnóstico, la cual, varía entre el 40% en países de África y Asia hasta prácticamente el 100% en Estados Unidos de América.[4,7]

Factores de riesgo:

Los factores de riesgo bien establecidos para cáncer de próstata son: la edad, el antecedente familiar de CaP y la raza.[2] En relación con la edad, la probabilidad de padecer este cáncer se incrementa conforme aumenta la edad, alcanzando un riesgo a lo largo de la vida de un 18%. El grupo de menor riesgo es el de 15 a 44 años con 0.2 por 100,000 hombres y a partir de allí aumenta a 10.6 entre los 45 a 54 años, 72.9 entre los 55 a 64 años y 259.6 a partir de los 65 años.[2, 4, 8]

El antecedente de familiares en primer grado (padre y/o hermanos) afectados por CaP, incrementa el riesgo y reduce la edad de aparición de este tipo de cáncer.[9-13] Los hombres con el antecedente de un hermano con CaP, tienen 4 veces más riesgo de presentar CaP antes de los 65 años y este riesgo se incrementa a 23 veces más si el CaP se presentó en al menos tres hermanos. En contraste, aquellos en quienes sólo el padre tuvo CaP, el riesgo de desarrollar esta neoplasia es 1.8 veces mayor y principalmente a partir de los 65 años. El riesgo total de CaP aumenta conforme disminuye la edad de diagnóstico de éste tumor en los familiares de primer grado.[9, 10] La historia familiar de otros tipos de cáncer como mama u ovario en familiares de primer grado, madre o hermanas, también se asocian con un riesgo de 4 a 6 veces más de cáncer de próstata.[11-13] El riesgo de morir por CaP entre aquellos con antecedentes familiares es similar a lo observado con la incidencia.[9, 10]

Los afroamericanos (342.8/100,000 hombres) tienen la incidencia más alta de CaP, seguidos de los europeos (156/100,000 hombres) con un riesgo intermedio, mientras que los asiáticos e hispanos (≤141/100,000 hombres) son los grupos con menor riesgo.[4, 14] La existencia de algunos factores biológicos como diferencias en las concentraciones hormonales y características genéticas; así como, algunas características socioculturales, pueden ser posibles explicaciones para estas diferencias interraciales en el riesgo de CaP.[8,15]

En relación a otros posibles factores de riesgo, se ha propuesto que algunas características relacionadas con el estilo de vida y exposiciones ambientales pueden afectar el riesgo de CaP; sin embargo, los resultados son poco consistentes. Como parte de este documento nos enfocaremos en características de historia de vida sexual y actividad física.

Historia de vida sexual:

La edad temprana de inicio de vida sexual,[16-17] una mayor frecuencia de relaciones sexuales,[17-21] un mayor número de parejas sexuales,[16,19-23] así como, una mayor frecuencia de infecciones de transmisión sexual (ITS),[19,21,23-27] se proponen como posibles factores de riesgo para CaP. El antecedente de infecciones de transmisión sexual depende en gran parte de las características de historia de vida sexual, antes descritas; por lo tanto, existen altas probabilidades de que las asociaciones observadas con estas variables pueden estar mediadas o ser debidas a la presencia de ITS.

Los estudios epidemiológicos que han evaluado la asociación entre ITS y CaP sugieren un incremento del riesgo de CaP y sus resultados varían en función de si se evaluaron ITS en general o algún tipo específico de ITS; así como, a la población en la cual se llevó a cabo el estudio. Los estudios que evalúan ITS en general, reportan un incremento de ~ 2 veces más en el riesgo de CaP,[21,24,27-28] siendo la infección por sífilis (OR=2.3; IC95%: 1.3- 3.9) y gonorrea (OR=1.4; IC95%: 1.05- 1.83) las más estudiadas y principalmente asociadas.[19,23,25-27] En relación al tipo de población estudiada, en una cohorte multiétnica realizada en California el análisis de la población completa no mostró asociación significativa entre ITS (RR=1.02; IC95% 0.91-1.15) o historia de gonorrea (RR=1.07; IC95% 0.94-1.15) y CaP.[27] No obstante, al estratificar por origen étnico, sólo los latinos nacidos en México o en Centro-Sudamérica mostraron un incremento en el riesgo de CaP asociado al antecedente de ITS (RR=1.43; IC95% 1.07-1.91) o historia de gonorrea (RR=1.39; IC95% 1.01-1.91).[27] En el mismo sentido una cohorte realizada en Taiwán reporta un aumento en el riesgo de casi dos veces en aquellos hombres con antecedente de alguna ITS (RR=1.95; IC95% 1.18-3.23).[28] En América Latina sólo existe un reporte de un estudio de casos y controles hospitalarios realizado en Cuba, el cual encontró un aumento de casi dos veces más posibilidad de CaP en aquellos hombres con antecedente de ITS.[21] Este estudio no evaluó el antecedente de cada tipo de ITS por separado.

Las ITS en general y algunas de ellas en particular, como es el caso de la infección por gonorrea, tienen un alto potencial inflamatorio crónico. El gonococo es un microorganismo que cuenta con una extraordinaria capacidad de alterar su material genético a lo largo de su ciclo de vida y de esta forma adaptarse a situaciones adversas que le permiten sobrevivir dentro del huésped.[29] Adicionalmente, el gonococo tiene una alta capacidad para desarrollar resistencia a los antibióticos y aunque en México no se cuenta con cifras específicas, la OMS reporta que la mayoría de los países de la región de las Américas presentan un 70% de resistencia a la penicilina y las cifras para otros antibióticos están entre el 31 y 70%.[30] Una estrategia para solucionar los problemas asociados a la resistencia a antibióticos, es el uso de antibióticos de nueva generación, los cuales, incrementan el costo del tratamiento y reducen las posibilidades de cumplimiento del mismo.

Desde el punto de vista biológico, la atrofia focal prostática es una lesión inflamatoria característica de los procesos infecciosos, la cual puede disminuir la actividad de la enzima P1-Glutation-S transferesa (acrónimo en inglés GSTP1), la cual protege el

genoma de daño oxidativo. La atrofia focal se considera como una lesión precursora para el cáncer de próstata.[31]

Actividad física:

La actividad física (AF) se asocia consistentemente con una disminución en el riesgo de padecer algunos tipos de cáncer.[32] De acuerdo con Kruk et al. 2013, para cáncer de colon la evidencia de una reducción atribuida a la actividad física, es convincente; mientras que para cáncer de endometrio y cáncer de mama en mujeres postmenopáusicas se considera como probable.[32] En el caso del CaP, la evidencia sobre AF es limitada pero sugestiva y difiere de acuerdo con el tipo de actividad física.[32]

En general una mayor práctica de actividad física total (ocupacional y recreativa) tomando en cuenta la frecuencia de la AF o el gasto energético en equivalentes metabólicos (acrónimo en inglés METs), se asocia con una reducción del 10% en el riesgo de CaP (RR = 0.90; IC 95% 0.84–0.095).[33] Sin embargo, cuando se evalúan por separado, una mayor AF ocupacional (actividades realizadas en el trabajo)[34] es la que se asocia consistentemente con una disminución en el riesgo de CaP (RR: 0.81; 95% CI, 0.73–0.91; $p < 0.001$);[33] mientras que la asociación entre una mayor AF recreativa (actividades realizadas por diversión y/o placer)[34] y CaP es marginal (RR 0.95; IC 95% 0.90–1.0; $p = 0.07$) y se observa principalmente en estudios de cohorte.[33]

La AF ocupacional, generalmente es constate a lo largo de la vida y se ha evaluado principalmente a través de la historia detallada de las actividades física en el trabajo o a través de los registros laborales. En contraste, la AF recreativa se ha evaluado en diferentes formas. Algunas cohortes toman en cuenta la práctica de AF recreativa al momento del inicio del estudio,[35-43] mientras los estudios de casos y controles la evalúan al momento de la entrevista.[43,45] Otros estudios miden la práctica de AF recreativa en diferentes etapas de la vida[35,37,43] y/o como el acumulado de AF recreativa a lo largo de la vida, estimado mediante la suma de la AF recreativa en diferentes etapas.[42] Ninguna de éstas aproximaciones toma en cuenta la regularidad y la variabilidad individual de la AF recreativa a lo largo de la vida.

La información a nivel mundial sobre las prácticas de AF de acuerdo a edad y al tiempo, es escasa. Sin embargo, de acuerdo con estudios transversales realizados en diferentes países, se estima que alrededor del 31.1% de los sujetos ≥ 15 años son inactivos (<30

minutos de AF moderada/5 días/semana o <20 minutos de AF vigorosa/3 días/semana o <600 METs/minuto/semana) y esta proporción aumenta con la edad.[46] Adicionalmente, algunas características como el sexo, el estado de salud, la confianza en la habilidad de ser físicamente activo, y la motivación pueden afectar la práctica de AF a lo largo de la vida.[46]

Por lo anterior, el objetivo general de esta tesis fue evaluar la asociación entre cáncer de próstata y estilos de vida (infecciones de transmisión sexual y trayectorias de actividad física recreativa a lo largo de la vida), en hombres residentes de la Ciudad de México

Metodología:

Se usó la información correspondiente a un estudio de casos y controles que se llevó a cabo entre Noviembre del 2011 a Agosto del 2014 y cuyo objetivo fue determinar factores de riesgo genéticos y no genéticos para CaP, en hombres residentes de la Ciudad de México. Este estudio se conformó por 402 casos incidentes de CaP, histológicamente confirmados, identificados en los servicios de urología del Hospital General de México, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán e Instituto Nacional de Cancerología (SSA), así como en el Hospital de Oncología del Centro Médico Siglo XXI (IMSS), en el Hospital General Regional No.1 "Dr. Carlos McGregor Sánchez Navarro" (Segundo nivel del IMSS) y del Hospital Regional "Adolfo López Mateos" (ISSSTE). Todos los casos cumplieron con el criterio de por lo menos 1 año de residencia en la Ciudad y sin antecedentes de ningún otro tipo de cáncer.

Los controles fueron 805 hombres, pareados por edad (± 5 años), con un mínimo de residencia igual de los casos y sin antecedentes de algún tipo de cáncer. Como consideración adicional no se tomaron en cuenta como potenciales controles aquellos sujetos que manifestaron la presencia de sintomatología asociada con probable enfermedad benigna o maligna de próstata (ej. Disuria, hematuria, etc.), que estuvieran en estudio por sospecha de patología prostática o aquellos que reportaron un estudio previo de antígeno prostático específico > a 4 ng/ml. Los controles fueron seleccionados a través del marco muestral maestro de la Secretaría de Salud, una vez identificados los casos.

Las tasas de participación para casos y controles fueron 85.9% y 87.5%, respectivamente. Aquellos sujetos que no aceptaron participar en el estudio, nos proporcionaron información sobre algunas características sociodemográficas (edad, lugar de nacimiento,

estado civil y escolaridad). Además el estudio se realizó de acuerdo a la declaración de Helsinki y fue aprobado por el comité de ética del Instituto Nacional de Salud Pública (CI: 980), así como por los comités de ética de los hospitales participantes.

Entrevistas:

A los sujetos que sí aceptaron participar se les aplicó un cuestionario estructurado, mediante el cual, se obtuvo en forma directa información sobre características sociodemográficas, así como antecedentes familiares en primer y segundo grado de cáncer (cáncer de próstata, cáncer de mama, cáncer de ovario, cáncer de colon), antecedentes personales de diabetes, hipercolesterolemia, hipertrigliceridemia, historia de vida sexual (número y tipo de parejas sexuales, antecedente de ITS), historia de actividad física, hábitos dietéticos y tabáquicos. La duración promedio de la entrevista fue de 45 minutos.

Evaluación de historia de vida sexual:

La información recabada sobre la historia de vida sexual incluyó: edad de inicio de vida sexual, número de parejas sexuales antes de los 20 años y en toda la vida, sexo con trabajadoras sexuales y/o hombres, así como antecedente de ITS. En relación a las ITS, a cada participante se le preguntó sí alguna vez había sido diagnosticado con gonorrea, sífilis, verrugas genitales, herpes o chancro; el número de veces y la edad al momento del primer diagnóstico.

Evaluación de actividad física:

Mediante un cuestionario previamente validado en población hispanoparlante,[47] obtuvimos información sobre AF recreativa en 3 diferentes etapas de la vida: 15-18, 19-29 y >30 años. Para cada etapa consideramos las siguientes actividades: voleibol, pesas, bicicleta, caminar rápido por al menos 20 minutos, bailar, aerobics, box, básquetbol, jugar dobles de tenis, hacer bicicleta a moderada velocidad, nadar, fútbol, patinar, tenis, escalar y correr. De cada actividad contamos con información sobre el número de horas por día, días a la semana y número de meses por año invertidos en las actividades.

Evaluación dietética:

Se aplicó un cuestionario semicuantitativo de frecuencia de consumo de alimentos previamente validado que contiene 127 alimentos[48] y que tomó como referencia los tres

años previos al diagnóstico para los casos y los 3 años previos a la entrevista para los controles. Para cada alimento las opciones de respuesta variaron desde nunca hasta 6 veces al día. El consumo de energía se estimó usando las tablas de composición alimentaria del programa Food Processor, el cual incluye información sobre los alimentos incluidos en el cuestionario y comida tradicional mexicana.[49]

Tabaquismo:

La información sobre hábito tabáquico incluyó edad de inicio y edad de cesación del hábito tabáquico, además se evalúo el estatus de fumador y número promedio de cigarros fumados al día en diferentes etapas de la vida (≤ 20, 21-30, ≥ 30 años y 5 años antes de la entrevista) y al momento de la entrevista. Consideramos como fumador a aquellos hombres que fumaron al menos 100 cigarros en la vida.

Expediente clínico:

Se revisó el expediente clínico de cada uno de los casos, a través del cual se obtuvo información acerca del tipo histológico y de la escala de Gleason al momento del diagnóstico. Con la información previa, los casos se clasificaron como CaP de bajo (Gleason <7) y alto grado (Gleason ≥ 7).

Análisis estadístico:

Las características sociodemográficas, historia de vida sexual y AF recreativa se compararon entre casos y controles. Dependiendo del tipo de variable bajo estudio usamos Chi2 o la t-Student.

La asociación entre el CaP e ITS en general, así como para gonorrea, se estimó mediante modelos independientes de regresión logística no condicionada. Debido al tipo de pareamiento, los modelos bi y multivariados incluyeron a la edad al momento de la entrevista como variable de ajuste. Para evaluar la asociación entre el antecedente de ITS y la agresividad de CaP se usaron dos modelos independientes de regresión logística no condicionada en los que se compararon los cánceres clasificados como CaP de bajo (Gleason <7) y alto grado (Gleason ≥ 7) con todos los controles. Como potenciales variables confusoras se evaluaron aquellas que de acuerdo a la literatura son factores de riesgo para el cáncer de próstata y que no son variables intermedias en la asociación

entre CaP e ITS o gonorrea. En los modelos permanecieron sólo aquellas variables que modificaron en un 10% el estimador crudo entre ITS o gonorrea y CaP

El análisis de las trayectorias históricas de AF recreativa se hizo de manera semejante al mencionado para historia de vida sexual. Para evaluar la asociación entre CaP y AF recreativa (trayectorias históricas de AF recreativa, AF recreativa en cada etapa de la vida o la AF acumulada en la vida) usamos modelos independientes de regresión logística no condicionada ajustados por edad debido al pareamiento en rango de edad. Además estimamos la asociación entre las diferentes aproximaciones de AF y la agresividad de CaP (Gleason <7 o Gleason ≥ 7). En los modelos permanecieron sólo las variables que modificaron en un 10% el estimador crudo entre AF recreativa y CaP. Para todos los modelos, el grupo de referencia fueron los hombres inactivos.

Las especificaciones en extenso de los modelos así como las posibles variable confusoras se describen en la sección de análisis de cada uno de los artículos. Todos los análisis se realizaron mediante el uso del paquete estadístico STATA 13 y R estudio versión 3.0.2.

A continuación se encuentran en extenso los artículos “History of gonorrhea and prostate cancer in a population-based case–control study in Mexico” y “Lifespan leisure-time physical activity prevents prostate cancer”. El primero se publicó en The International Journal of Cancer Epidemiology, Detection and Prevention y el segundo será enviado a Lancet Oncology.

Artículo 1

“History of gonorrhea and prostate cancer in a population-based case–control study in Mexico”

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History of gonorrhea and prostate cancer in a population-based case–control study in Mexico

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ABSTRACT

We evaluated the association between a history of sexually transmitted diseases (STDs) and the risk for prostate cancer (PC) among Mexican males.
Methods: PC incident cases ($n = 402$) that were identified at six public hospitals in Mexico City were matched by age (±5 years) with 805 population controls with no history of PC. By face-to-face interview, we obtained information about sexual history, previous STDs, sociodemographic characteristics, and familial history of PC. An unconditional logistic regression model was used to estimate the risk for PC.
Results: A total of 16.6% of men reported having had at least one previous STD, and the most frequently reported STD was gonorrhea (10.5%). After adjusting by PC familial history, the history of STD was associated with a two-fold greater risk of PC: odds ratio (OR) = 2.67; 95% confidence interval (95% CI = 1.91–3.73). When each STD was evaluated separately, only gonorrhea was associated with a significant increase in PC risk (OR = 3.04; 95% CI = 1.99–4.64). These associations were similar when we stratified by low-risk PC (Gleason <7) and high-risk PC (Gleason ≥7).
Conclusion: These results confirm that STDs, and particularly gonorrhea, may play an etiological role in PC among Mexican males, which is consistent with a previous report from a multiethnic cohort.

1. Introduction

Prostate cancer (PC) is the second most common cancer among men worldwide (31.1 cases per 100,000 inhabitants) and the fifth leading cause of death from cancer (7.8 per 100,000 inhabitants), with notable differences among different countries [1]. The well-established risk factors for PC include age, family history of cancer, and African–American ethnicity [2]. However, there is also evidence that some lifestyles might be associated with the risk of developing this disease; these include sexual habits, including a history of sexually transmitted diseases (STDs).

According to the hypothesis of the role of inflammation in the development of PC, STDs can cause bacterial prostatitis or chronic and asymptomatic inflammation of the prostate [3]. Focal atrophy is an inflammatory lesion that is characteristic of infectious processes and presents a reduction in the activity of glutathione-S-transferase P1 (GSTP1), an enzyme which protects the genome from oxidative damage; this lesion is thought to be a precursor of PC [4]. Higher concentrations of prostate-specific antigen (PSA) have been observed in men with prostatitis and a negative biopsy

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[5]. Men who presented a high PSA in early adulthood in regions with and without PC screening had a higher probability of being diagnosed with PC over the following 20–25 years [6].

Epidemiological reports on the relationship between a history of STD and PC risk are contradictory. In three reports from meta-analyses, a history of STD in general (OR = 1.48), as well as histories of gonorrhea (OR ∼ 1.30) and syphilis (OR ∼ 1.66) were associated with a nearly 1.5-fold higher risk for PC [7–9]. Other more frequent, but less symptomatic, STDs—such as those caused by *Trichomonas vaginalis* (OR = 1.43; 95% CI = 1.00–2.03) [10–12] and human papilloma virus (HPV) (OR = 1.52; 95% CI = 1.12–2.06) [8] have also been associated with PC. The majority of results derive from case–control studies, which could be susceptible to recall [13–17] and to selection bias because of the types of controls used. To our knowledge, only three cohort studies [18–20] have evaluated this association, and only two of these reported an association. One cohort study carried out in California, USA, found that STD and a history of gonorrhea were associated with a nearly two-fold increase of PC ($p = 0.014$) only among Hispanics born in Mexico, or Central or South America [18]. Another study conducted in Taiwan reported a nearly two-fold greater risk for PC among males diagnosed with an STD in an Asian population [19]. In Latin America, only one hospital case–control study performed in Cuba evaluated this association; this study reported that a history of STD in general is associated with a nearly two-fold risk for PC [14].

In Mexico, PC among males is the leading cause of cancer morbidity (27.3 per 100,000 inhabitants) and mortality (11.3 per 100,000 inhabitants) [1]. However, information regarding the prevalence of PC risk factors in this population is scarce. According to annual morbidity records [21] from the Mexican Ministry of Health, the incidence of the majority of STDs has remained constant over three decades, except for trichomoniasis (7.9 per 100,000 inhabitants) and HPV (2.1 per 100,000 inhabitants), which are the first and fourth leading causes of STD. Additionally, gonorrhea infection has exhibited a marked reduction from 1999 (18.6 per 100,000 inhabitants) to the present (∼1.1 per 100,000 inhabitants) and is the fifth leading cause of STD. Therefore, the objective of the present study was to evaluate the association between a history of STD and the risk of PC among male residents of Mexico City.

2. Materials and methods

A population-based case–control study was performed between November 2011 and August 2014 with men aged 42–94 years who were residents of Mexico City and had no previous history of any type of cancer. As cases, 468 men with newly diagnosed, histologically confirmed prostatic cancer at any clinical stage were identified in four tertiary and two secondary level hospitals, and only 402 (85.9%) of these persons agreed to participate in the study. From 920 eligible controls, 805 males with no diagnosis of PC agreed to participate (87.5%), and they were matched 2:1 by age (±5 years) with index cases. Men who were under evaluation due to symptoms likely to be related with PC (for example, dysuria, hematuria, etc.) or those with a previous report of PSA >4 ng/mL were not considered as potential controls.

Controls were selected after cases were identified following this procedure: first, 33 basic geostatistical areas (BGAs) were selected according to the proportional probability of the number of households recorded in the National Count of Households and Population of 2005. BGAs are defined by the National Institute of Geography and Statistics and usually comprised the first-stage unit of surveys on households. Next, ten blocks were selected from each BGA in the sample, and finally, starting from the northeast corner of the blocks, consecutive households were selected for participation in the study. Inquiries were made at each home as to whether a man resided there who met the eligibility criteria for this study and who would agree to participate. If two subjects with the required characteristics were identified, then one was randomly chosen. When a male with the required characteristics lived in a home but was not present at the time of the interview visit, three attempts to locate him were made before considering the option of looking for another participant. Construction of the control group was performed sequentially. After 12 cases, a new BGA was added to acquire controls. A brief questionnaire requesting information on age, educational level, civil status, and birth place was administered to all subjects who did not agree to participate.

The study was conducted in accordance with the principles established by the Declaration of Helsinki and was approved by the Ethics Committee of the Instituto Nacional de Salud Pública (INSP) (CI:980) and each of the participating hospitals. All of the study participants signed an informed consent letter after they had read it and after the interviewers had provided an explanation for any doubt.

2.1. Interviews

Men who agreed to participate in the study were interviewed in order to obtain information directly regarding social and demographic characteristics (age, highest educational level completed, usual occupation, marital status, birth place, and length of time residing in Mexico City). Information on sexual history included the following: age at first sexual intercourse, number of sexual partners, and sex with sex workers and/or with men. Regarding a history of STD, the subjects were asked whether they had ever been diagnosed with gonorrhea, syphilis, genital warts, herpes, or chancre; likewise, information was requested on number of episodes and age at first episode. We also asked about familial history of PC, breast cancer, ovarian cancer, and colon cancer in first-degree relatives, personal history of dyslipidemia and diabetes, as well as active smoking and the subjects' dietary habits for 3 years prior to the diagnosis for cases and 3 years prior to the interviews for controls.

2.1.1. Dietary information

A semi-qualitative, previously validated food frequency questionnaire (FFQ) was employed to assess the usual daily intake of 127 foods [22]; serving sizes were specified for each food item in the FFQ. The questionnaire had ten possible responses, ranging from 'never' to 'six per day', which were transformed into daily frequency consumption utilizing the following weights: 6 for reported frequencies of consumption of six per day; 4.5 for four or five per day; 2.5 for two or three per day; 1 for one per day; 0.7857 for five or six per week; 0.4286 for two to four per week; 0.1429 for once per week; 0.0658 for two or three per month; 0.0164 for one per month or less, and 0 for never. The foods included in the dairy group were freshly made cheese, Oaxaca, and Manchego cheeses, as well as yogurt. The dairy group was categorized as high, middle, and low consumption with regard to the tertile distribution of the control's consumption.

Cases were interviewed at the hospitals and controls were interviewed in their homes. Trained staff conducted both types of interview and were not aware of the study's hypothesis. The interviews lasted an average of 45 min. A pathologist with experience in PC reviewed the slides to verify the Gleason grade [23] and the histopathological diagnosis.

2.2. Statistical analysis

Social and demographic characteristics and the sexual lifestyles of cases and controls were compared. Depending on the type of

variable studied, *t*-Student, chi-square, or the Fisher exact test was used. History of STD and each type of infection was measured as "yes" or "no". Correlations between STD among controls were evaluated using the Spearman correlation coefficient. Gonorrhea was the STD with the highest number of episodes reported and was categorized as 0, 1, and ≥2.

Median age at first sexual encounter was categorized as ≥18 years old or <18 years old, according to the median age reported by controls. The number of sexual partners before the age of 20, and throughout their lifetime, was asked using an open question in which the interviewee had the opportunity of responding with the exact number of partners that he had had. Among controls who reported the beginning of sexual activity before the age of 20, the median number of partners was 1, and we categorized this as: 0, 1, and ≥2. Number of sexual partners over a lifetime was categorized according to the tertile distribution of the controls as ≤2, 3–6, and >6.

Birth place was divided into five regions according to the state in Mexico where the birth occurred: South (Campeche, Chiapas, Guerrero, Oaxaca, Quintana Roo, and Yucatán); West-Central (Aguascalientes, Colima, Guanajuato, Jalisco, and Michoacán); East-Central (Mexico City Federal District, Hidalgo, State of Mexico, Morelos, Puebla, Queretaro, and Tlaxcala); North (Chihuahua, Coahuila, Durango, San Luis Potosí, Zacatecas, Baja California, Baja California Sur, Sinaloa, Sonora, Nayarit, Nuevo León, and Tamaulipas), and East (Veracruz and Tabasco).

PC aggressiveness was classified according to the Gleason score reported at diagnosis. Cases with a Gleason <7 were categorized as well-differentiated cancers, or low-risk tumors, while those with a Gleason grade ≥7 were considered poorly differentiated or high-risk tumors [23].

The crude and adjusted associations between risk of PC and history of STD (overall and for each infection) were estimated using independent, unconditional logistic regression models, and age was included as an adjusting variable in the bi- and multi-variable models. To evaluate the association between history of STD and PC aggressiveness, two independent logistic regression models were employed to compare low-risk and high-risk cancer cases versus controls.

As potential confounders, we evaluated variables that, according to the literature, are PC risk factors, and they are not intermediate variables for association between PC and STD or gonorrhea. Besides age at interview, the STD final model included only those variables that changed the crude estimator of interest by more than 10%: educational level, family history of PC in first-degree relatives, history of dyslipidemia, smoking status 5 years before the interview, and dairy consumption. For the association between gonorrhea and PC, we also considered history of intercourse with sex workers. In order to estimate the risk associated with the age at which the first gonorrhea event occurred and the numbers of gonorrhea events over a lifetime, both of these variables were included in the model. To evaluate the effect of recall bias on the association between gonorrhea and PC, at the end of the interview we asked a sub-sample of 219 cases and 591 controls what they considered to be the cause of PC. With this question, we identified men who might relate their history of STD with PC. In this sub-sample, we performed the final logistic regression model and, after identifying cases who responded that STD caused PC, the final logistic regression model was run again without those cases and their respective controls. Coefficients from both models were compared with the model that included all of the study subjects.

All of the analyses were performed using STATA version 13.0 statistical software.

3. Results

Of 402 subjects with histologically confirmed PC, 73.5% were classified as high-risk or poorly differentiated cancers (Gleason ≥7). By design, mean age at interview was similar among cases (67.7 ± 8.39 years) and controls (67.06 ± 9.03 years) (data not shown in tables). The association between family history of PC in first-degree relatives and the risk of this cancer was confirmed in this population. Personal history of dyslipidemia and high dairy consumption were associated with a two-fold higher possibility of

Table 1
Selected characteristics of the study population.

Characteristics	Cases (n = 402)	Controls (n = 805)	OR[a]	95% CI
Time living in Mexico City				
Mean ± SD	56.15 ± 16.53	60.03 ± 14.24	0.97	0.96–0.98
Min–max	2–94	2–91		
Birth place[b]				
South	32	55	1.0	–
West-Central	36	60	1.03	0.56–1.87
East-Central	296	649	0.80	0.50–1.26
North	16	19	1.44	0.65–3.20
East	19	20	1.67	0.78–3.59
Marital status				
United[c] versus not united	309	644	0.83	0.62–1.11
Educational level				
Elementary school or less	183	363	1.00	–
Junior high school	66	203	0.66	0.48–0.93
High school	70	146	0.99	0.70–1.39
University or more	83	93	**1.83**	**1.29–2.60**
Occupation[d]				
Others[e]	70	141	1.0	–
Sales	67	137	0.99	0.66–1.49
Services	79	198	0.81	0.55–1.19
Construction and mechanics	66	160	0.84	0.56–1.26
Professionals and technicians	119	168	**1.45**	**1.00–2.11**
Family history of PC[f]				
Yes versus no	41	21	**4.4**	**2.54–7.53**
History of diabetes				
Yes versus no	85	156	1.1	0.82–1.49
History of dyslipidemia				
Yes versus no	86	90	**2.2**	**1.59–3.05**
Smoking status[g]				
Never	129	264	1.0	–
Former smoker >15 years		174	1.09	0.79–1.52
Former smoker ≤15 years	95	112	1.50	1.05–2.14
Current smoker	96	255	0.78	0.57–1.07
Dairy consumption (portion/d)[h]				
Low	101	282	1.0	–
Middle	95	261	1.05	0.76–1.47
High	200	258	**2.25**	**1.67–3.02**

[a] Adjusted by age at time of interview.
[b] Birth place. South: Campeche, Chiapas, Guerrero, Oaxaca, Quintana Roo, and Yucatán; West-Central: Aguascalientes, Colima, Guanajuato, Jalisco, and Michoacán; East-Central: México, D.F. (Federal District); Hidalgo; State of Mexico, Morelos, Puebla, Querétaro, and Tlaxcala; North: Chihuahua, Coahuila, Durango, San Luis Potosí, Zacatecas, Baja California, Baja California Sur, Sinaloa, Sonora, Nayarit, Nuevo León, and Tamaulipas; East: Veracruz and Tabasco.
[c] United: married and common-law marriage.
[d] Habitual occupation during lifetime.
[e] Agricultural, crafts, and construction workers.
[f] Familial history of prostate cancer in first-degree relatives.
[g] Smoking condition 5 years prior to interview.
[h] Differences in n are because four cases and six controls were excluded due to out-of-range total energy values (>4500 calories).

PC. At 5 years before the interview, only former smokers who had a cessation time of <15 years presented a significant increased risk (50%) for PC (Table 1).

A total of 16.2% of the men reported having had at least one STD event, and the most frequently reported STDs were gonorrhea (10.5%), chancre (1.58%), acquired syphilis (1.33%), and genital warts (1.0%). The remaining STDs were less frequent. Among controls, a statistically significant correlation was observed between gonorrhea and syphilis (rho = 0.13; $p = 0.03$), but not with the remaining STDs. Maximal number of STDs reported over a lifetime was three events, while 2.98% of the men reported having had two or more STDs (data not shown in tables). Having had some type of STD was associated with a roughly three-fold higher risk of PC, and highest increase in risk for PC (OR = 4.14; 95% CI = 2.82–6.08) related to a history of gonorrhea. Other characteristics of sexual history significantly associated with PC risk included a larger number of sexual partners over a lifetime and, likewise, a history of sex with sex workers or with men (Table 2). All characteristics related with sexual history were significantly associated with a history of STD and gonorrhea, and likewise, dyslipidemia and a history of smoking (Table 3).

After adjusting for potential confounders, the association between history of STDs and PC (OR = 2.67; 95% CI = 1.91–3.73) remained significant, and similar results were obtained when we stratified by low-risk or well-differentiated cancers (Gleason <7) and the high-risk or poorly differentiated cancers (Gleason ≥ 7) (Table 4).

The association between history of gonorrhea and PC was analyzed separately. One or more previous gonorrhea episodes were associated with a three-fold increased risk of PC (OR = 3.04; 95% CI = 1.99–4.64), a history of one episode of gonorrhea was associated with a two-fold increase in risk for PC (OR = 2.08; 95% CI = 0.50–8.82), while two or more gonorrhea events were associated with a three-fold increase in the risk of PC (OR = 3.47; 95% CI = 0.65–18.48; p for trend = 0.15). In contrast, no association between age at first episode (OR = 1.02; 95% CI = 0.96–1.08) and PC risk was observed.

In order to evaluate the presence and impact of recall bias, we ran the same models with a subset of 219 cases and 591 of the controls, whom we asked what they considered to be the cause of PC. In this subset, the OR associated with a history of STD was 3.79 (95% CI = 2.45–5.86), and with a history of gonorrhea this was 4.23 (95% CI = 2.41–7.42). After excluding the four cases and nine controls that reported STD as the possible cause of the disease (data not show in tables), similar associations were observed for STD: 3.70 (95% CI = 2.38–5.77) and for gonorrhea, 4.24 (95% CI = 2.40–7.49), respectively.

Table 2
Sexual characteristics according to cases and controls.

Characteristics	Cases ($n = 402$)	Controls ($n = 805$)	OR[a]	95% CI
Age at first sexual encounter				
≤18 versus >18 years	274	517	1.25	0.96–1.61
Number of sexual partners over a lifetime				
≤2	88	267	1.0	–
3–6	118	276	1.31	0.95–1.81
>6	187	251	**2.27**	**1.67–3.09**
p for trend	<0.001			
Number of sexual partners before the age of 20 years				
None	93	197	1.0	–
1	135	298	0.97	0.70–1.34
≥2	161	300	1.15	0.84–1.58
History of sex with sexual workers				
Never	215	594	1.0	–
1–2	65	82	**2.21**	**1.54–3.17**
3–5	58	61	**2.63**	**1.77–3.88**
>5	54	62	**2.37**	**1.59–3.52**
p for trend	*<0.001*			
History of sex with men				
Yes versus no	16	9	**3.72**	**1.63–8.49**
History of STD				
Yes versus no	107	88	**2.95**	**2.16–4.03**
History of syphilis				
Yes versus no	7	9	1.59	0.59–4.32
History of gonorrhea				
Yes versus no	81	46	**4.14**	**2.82–6.08**
History of genital warts				
Yes versus no	7	4	3.47	1.01–11.95

[a] Adjusted by age at time of interview.

4. Discussion

This report identifies the history of STD, and particularly gonorrhea, as a potential modifiable risk factor for the development of PC in the Mexican population. Our results are consistent with previous findings from two meta-analyses [7,8], a case–control study performed in Cuba [14], and two recent cohort studies [18,19], which suggest an etiological association between PC and STD in general and gonorrhea in particular. In a multiethnic cohort study performed in the state of California, USA, an association between history of gonorrhea and PC was only evident among Hispanics born in Mexico, Central America, or South America-relative risk (RR) = 1.95; 95% CI = 1.20–3.16 and not among white males or those of Hispanic origin who were born in the US [18]. In contrast, our results are different from those reported in two other studies composed mainly of Caucasian males with a low STD prevalence [17,20].

According to the US Centers for Disease Control and Prevention, STD incidence is different among different ethnic groups. Highest incidences of gonorrhea (428.3 and 53.9 cases per 100,000 men), syphilis (27.0 and 8.5 cases per 100,000 men), and chlamydia (787.7 and 193.8 cases per 100,000 men) are observed among African-American males, followed by Hispanic males. Additionally, since 2010 the incidence of gonorrhea has increased 12.3%, while that of chlamydia and syphilis increased 14.4 and 4.5%, respectively, among Hispanic males [24]. However, there is evidences that the gonococcus is a microorganism with an extraordinary capacity to mutate during its life cycle [25], which contributes to antimicrobial resistance. The occurrence of bacterial resistance requires the use of latest-generation antibiotics, which significantly increases treatment costs and could reduce treatment adherence, contributing to the infection becoming chronic. According to the World Health Organization (WHO), the prevalence of penicillin resistance in the majority of countries in the Americas is 70%, and between 31 and 70% for other antibiotics. However, no information is available on the prevalence of antimicrobial resistance in Mexico [26].

To interpret these results adequately, it is necessary to take into account that the evaluation of previous history of STD and gonorrhea was based on self-reported physician diagnosis. As we do not have information about the reliability of exposure report, we do not reject the possibility that the observed association may be affected by a recall bias. However, to reduce the possibility of this bias, we took the precaution that study subjects and interviewers did not know *the specific hypothesis* of the study. Additionally, we analyzed the association between PC and a history of STD and gonorrhea in a sub-sample of males who answered what they considered to be the cause of PC. After those subjects

Table 3
History of sexually transmitted disease (STD) in general and gonorrhea in particular according to selected characteristics.

Characteristics	STD				Gonorrhea			
	Yes (n = 195)	No (n = 1010)	OR[a]	95% CI	Yes (n = 127)	No (n = 1078)	OR[a]	95% CI
Time living in Mexico City								
Mean ± SD	57.51 ± 15.36	58.90 ± 15.13	0.99	0.98–1.00	57.83 ± 15.67	58.90 ± 15.05	0.99	0.98–1.00
Min–max	8–86	2–94			8–86	2–94		
Educational level								
Elementary school or less	83	462	1.0	–	61	484	1.00	–
Junior high school	46	222	1.19	0.80;1.76	27	241	0.93	0.57–1.51
High school	37	179	1.21	0.78;1.85	20	196	0.86	0.50–1.48
University or more	29	146	1.41	0.72;1.82	19	157	1.00	0.58–1.75
Family history of PC[b]								
Yes versus no	15	47	1.75	0.96;3.20	8	54	1.33	0.61–2.86
History of dyslipidemia								
Yes versus No	41	135	**1.76**	**1.19;2.60**	29	147	**1.94**	**1.23–3.04**
Smoking[c]								
Never	56	337	1.0	–	37	356	1.0	–
Former smoker >15 years	46	223	1.21	0.79–1.86	31	238	1.20	0.72–1.99
Former smoker ≤15 years	43	151	**1.71**	**1.10–2.67**	30	164	**1.76**	**1.05–2.95**
Current smoker	50	299	1.02	0.68–1.55	29	320	0.90	0.54–1.49
Dairy consumption[d]								
Low	50	333	1.0	_	39	344	1.0	–
Middle	56	299	1.30	0.86;1.96	30	325	0.86	0.52–1.42
High	87	370	1.63	1.11;2.39	56	401	1.30	0.84–2.01
Age at first sexual encounter								
≤18 versus >18	153	637	**2.11**	**1.46;3.05**	104	686	**2.60**	**1.62–4.16**
Number of sexual partners over a lifetime								
≤2	14	341	**1.0**	–	4	351	**1.0**	–
3–6	46	348	**3.26**	**1.76;6.04**	29	365	**7.14**	**2.48–20.54**
>6	132	304	**10.67**	**6.02;18.92**	92	344	**23.90**	**8.68–65.80**
Number of sexual partners before the age of 20 years								
None	27	262	1.0	–	15	274	1.0	–
1	56	377	1.47	0.90;2.39	31	402	1.45	0.77–2.75
≥2	107	353	**3.02**	**1.92;4.76**	78	382	**3.90**	**2.19–6.94**
History of sex with sexual workers								
Never	62	746	**1.0**	–	36	772	**1.0**	–
1–2	32	114	**3.39**	**2.12;5.43**	18	128	**3.06**	**1.68–5.56**
3–5	44	75	**7.06**	**4.48;11.10**	33	866	**8.23**	**4.88–13.88**
>5	50	66	**9.03**	**5.74;14.19**	35	81	**9.02**	**5.36–15.19**
History of sex with men								
Yes versus no	11	14	**4.30**	**1.92;9.62**	7	18	**3.52**	**1.44–8.61**

[a] Adjusted by age at the moment of the interview.
[b] Familial history of prostate cancer in first-degree relatives.
[c] Smoking condition 5 years before the interview.
[d] Differences in n are because four cases and six controls were excluded due to out-of-range total energy values (>4500 calories).

that identified a history of STD as the cause of their disease were excluded, the association remained in the same direction but, due to the smaller sample size, estimator precision was lower. It is probable that the potential bias in the recall of STDs should be limited in this population because the STD/PC issue has not received widespread interest. To reject the possibility that the interviewers' knowledge about the disease could have affected the results, the proportion of those who reported a history of STD and gonorrhea was determined for each of the interviewers, and we did not find any differences.

The rates of participation between cases and controls were similar (85.9 versus 87.5%). We did not find significant differences in relation to age, birth place, marital status, and educational levels among men who agreed or did not agree to participate in the study (cases and controls) (Supplementary material, Table 5). The use of population controls reduces the possibility of selection bias, which can occur in clinical case–control studies. Although no sensitive and specific serological tests exist to determine the actual prevalence of the history of gonorrhea, the frequency of gonorrhea events reported by controls (5%) was consistent with the prevalence of IgG serology (∼4%) reported by Cravioto et al. [27] with subjects in Mexico City . Thus, we consider that selection bias may not be a possible explanation for these results.

In contrast, we do not reject the presence of detection bias, because subjects with a history of STD or gonorrhea could have had more opportunities to be diagnosed with PC. To evaluate this possibility, we employed the number of PSA determinations as a proxy of contact with health services. Although cases reported having had a significantly higher number of previous PSA tests than controls (4.5 versus 1.0; p = 0.000), when adjusting the final model

Table 4
Risk and aggressiveness of prostate cancer in relation to the history of sexual transmitted diseases and gonorrhea in Mexican population.

Characteristics	All				Gleason <7			Gleason ≥7		
	Cases (402)	Controls (805)	OR	95% CI	Cases (103)	OR	95% CI	Cases (288)	OR	95% CI
Sexually transmitted diseases[a]										
Yes versus no	105	88	**2.67**	**1.91;3.73**	**24**	**2.19**	**1.29;3.72**	**77**	**2.66**	**1.84;3.83**
History of gonorrhea[b]										
Yes versus no	79	46	**3.04**	**1.99;4.64**	**18**	**2.48**	**1.28;4.83**	**62**	**3.32**	**2.11;5.23**
Number of gonorrhea episodes[c]										
None	320	758	1.0	–	–	–	–	–	–	–
1	63	40	2.08	0.49; 8.82						
≥2	17	6	3.47	0.65;18.48						
p for trend				0.15						
Age at first episode of gonorrhea[c]										
Median ± SD	24.4 ± 7.5	24.0 ± 9.3	1.02	0.96; 1.08	–	–	–	–	–	–

[a] Adjusted by age, educational level, history of prostate cancer in first-degree relatives, dyslipidemia, smoking status 5 years before the interview, dairy consumption, and energy.
[b] Adjusted by age, educational level, history of prostate cancer in first-degree relatives, dyslipidemia, history of sex with sexual workers, smoking status 5 years before the interview, dairy consumption, and energy.
[c] Adjusted by age, educational level, history of prostate cancer in first-degree relatives, dyslipidemia, history of sex with sex workers, age at first episode of gonorrhea, smoking status 5 years before the interview, dairy consumption, and energy.

by the reported number of PSA tests, the directions of the association between PC and history of STD (OR = 2.49; 95% CI = 1.54–4.01) and gonorrhea (OR = 2.86; 95% CI = 1.57–5.22; $p = 0.001$) remained significant, although smaller in magnitude. Another possible indicator of additional detection opportunities may be the proportion of cases with Gleason <7 at time of diagnosis. If detection bias exists, we would expect a larger proportion of cases to be detected at earlier and less aggressive stages of the disease. However, regardless of the hospital, the majority of cases at time of diagnosis had Gleason score >7 (73.4%). In Mexico, there is no national cancer registry; however, a small population-based PC-screening trial carried out in Monterrey City identified a high proportion of PCs with Gleason score ≥7 (93%) at diagnosis [28].

The possibility that our results could be the consequences of a lack of confounding control is low, because the main risk factors reported in the literature – such as age, dairy consumption, educational level, smoking status, and PC family history – were considered in our analysis. Because information about STD history was obtained by interview, we are unable to rule out that other microorganisms such as *Trichomonas vaginalis* or *Chlamydia trachomatis* could be associated with PC or that they could coexist, thus overestimating the association observed with gonorrhea. These infections could be asymptomatic, underdiagnosed, and unknown to the subject. In this study, no subject reported a history of *trichomoniasis* and only 0.51% reported having had a chlamydia infection. Recent studies suggest that *trichomonas* infection could increase the risk of PC (OR = 1.23; 95% CI = 0.94–1.61), mainly the extra-prostatic PC risk (OR = 2.17; 95% CI = 1.08–4.37) [10].

5. Conclusion

Notwithstanding the limitations of case–control studies, we believe that the positive association observed between the history of STD or/and gonorrhea with PC is plausible and is according to the inflammatory hypothesis. Risky sexual behavior and the possibility of acquiring STD are potentially modifiable conditions. Although this study did not assess the frequency of condom use, it is probably necessary to improve the promotion of STD prevention and control programs as a means to reduce the incidence of PC in this population. Additionally, in Mexico, there is a need to enhance the STD surveillance system, mainly to document the presence, magnitude, and type of gonococcal antimicrobial resistance in order to control the use of antibiotics and improve the likelihood of successful treatment, as well as to drive the performance of studies that permit remedy for the problems associated with evaluation of the STD antecedent and type, with the purpose of establishing its role in the etiology of prostate cancer.

Conflict of interest

The authors declare there is no conflict of interest

Authors contribution

Ruth Argelia Vázquez Salas: Performed the statistical analysis of the data and wrote the first draft of the manuscript. Luisa Torres-Sanchez: conceptualized the study, participated in the interpretation of data and redaction of the manuscript. Lizbeth Lopez-Carrillo: made a critical revision of the manuscript. Martín Romero- Martínez selected the Basic Geostatistical Areas (BGA) according to the proportional probability of the household number, also he made a critical review of the manuscript. The remain authors (Hugo A Manzanilla-García, Carlos Humberto Cruz-Ortíz, Fernando Mendoza-Peña, Miguel Ángel Jiménez-Ríos, Francisco Rodríguez-Covarrubias, Narciso Hernández-Toríz, Othón Moreno-Alcázar) identified the possible participants and collaborate in the initial draft of the manuscript. All authors approved the final version and participated sufficiently in the final document.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.12.001.

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Artículo 2

"Lifespan leisure-time physical activity prevents prostate cancer"

Lifespan leisure-time physical activity prevents prostate cancer

Running Title: Physical activity and prostate cancer

Keywords: Mets, Physical activity**,** prostate cancer, Mexico, trajectory analysis.

Abstract

Background: Inconsistent associations between leisure-time Physical Activity (PA) and low Prostate Cancer (PC) risk could be a consequence of differences in leisure-time PA evaluation, or failure to measure the individual variation in PA behavior throughout life. Our aim was to evaluate the association between PC and leisure-time PA among Mexican males using information at different life stages and historical PA patterns or trajectories throughout life.

Methods: From November 2011 to August 2014, we conducted a population-based case-control study. The study sample consisted of 402 incident PC cases and 805 controls matched by age (± 5 years) without a history of cancer. Based on leisure-time PA information from three life stages: 15–18, 19–29, and ≥30 years we estimated Metabolic equivalents (METs) for each stage. Using k-means+ method in R software for longitudinal data, we reconstructed historical PA patterns or trajectories throughout life. The association between PC and leisure-time PA was estimated by unconditional logistic regression model.

Findings: Among males who reported any leisure-time PA, we identified three trajectories: Trajectory A, males who had high PA intensity and frequency at 15-18 years and showed a higher reduction throughout life; Trajectory B, males who maintained constantly low PA; and Trajectory C, males who constantly performed more PA. Compared with inactivate males, those males categorized in Trajectory C ($OR_{\text{Trajectory C vs. none}}$ 0·38; 95% CI 0·19–0·76) or B ($OR_{\text{Trajectory } B \text{ vs. none}}$ 0·54; 95% CI 0·35–0·82) had a lower PC. Males in Trajectory A had a non-significant reduction in PC possibilities ($OR_{\text{Trajectory A vs. none}}$ 0·81; 95% CI 0·50–1·32).

Interpretation: Our results suggest that the protective effect of PA on PC could

be a consequence of age-onset, intensity, and regularity in PA practice throughout life. However, this type of PA classification requires further evaluation in prospective longitudinal studies.

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Introduction:

Physical Activity (PA) is associated with a lower risk of some types of cancer. Convincing evidence indicates that PA reduces colon cancer risk; meanwhile, probable evidence suggests that PA protects against endometrium and post-menopause breast cancer.[1] Evidence regarding PA and prostate cancer (PC) association is limited but suggestive.[1]

Total PA is associated with 10% PC risk reduction (Odds Ratio [OR] = 0·90; 95% Confidence Interval [95% CI] = 0·84–0·095); however this association differs according to PA type.[2] Occupational PA, or activity performed at work,[3] is consistently significantly associated with a reduced PC risk (RR: 0·81; 95% CI, 0·73–0·91; p < 0·001).[2] Meanwhile, the association between leisure-time PA and PC (activities done for enjoyment and/or pleasure),[3] is marginal (OR = 0·95; 95% CI = 0·90–1·0; *p* = 0·07) and mainly observed in cohorts studies.[2]

Occupational PA is generally constant throughout life and has been primarily evaluated by historical register or self-report. In contrast, leisure-time PA has been evaluated in different ways. Some cohort studies take into account the leisure-time PA practice at baseline,[4-12] while case control studies evaluate leisure time PA at the moment of the interview.[13,14] Other studies have evaluated leisure-time PA practice at different life stages;[4,6,12] and/or the PA accumulated by the sum of the leisure-time PA at each life stage.[11] None of these measurements consider the regularity and variability of leisure-time PA throughout life.

Worldwide information about PA trends according to age and calendar time are scarce. However, evidence from cross-sectional studies in different countries show that around 31·1% of subjects aged 15 years old or older are physically

inactive (<30 minutes of moderate-intensity PA/5 days/week or <20 min of vigorous-intensity PA/3 days/week or <600 MET/min/week), and this proportion increases with age.[15] Additionally, there are some characteristics like sex, health status, confidence in the ability to be physically active, and motivation that could affect the PA practice throughout life.[16]

Therefore, we hypothesized that the marginal association observed between leisure-time PA and PC could be the consequence of inadequate evaluation of historical PA variability throughout life. We propose to evaluate this association in males living in Mexico City, taking into account their leisure-time PA information in three different life stages and the reconstruction of historical leisure-time PA patterns or trajectories throughout life using statistical techniques for longitudinal analysis.

Methods

From November 2011 to August 2014, we conducted a population-based case-control study of males between 42 and 94 years old living in Mexico City. This study was conducted according to the Helsinki Declaration and was approved by the National Institute of Public Health Ethics Committee (CI: 980) and all participating hospitals' committees.

Study details were reported previously.[17] Briefly, cases were 402 men with incident and histological confirmed PC diagnosis, without history of any other type of cancer, who were identified and interviewed in two secondary- and four tertiary-level hospitals in Mexico City. In accordance with Gleason score[18] at diagnosis, cases were categorized as low- (Gleason <7) or high-risk (Gleason ≥7) PC. Regarding age at diagnosis, cases diagnosed before age 60 were

classified as early-onset PC and cases diagnosed at 60 years old or older were classified as late-onset PC.

Controls comprised 805 males age-matched (± 5 years) with the index case, without a history of previous cancer or prostate diseases. Subjects reporting urological symptoms such as dysuria, hematuria, or those under clinical prostate evaluation or reported a prostate specific antigen (PSA) ≥4 ng/mL, were not considered as potential controls. For control selection, we choose 33 basic geostatistical areas according to the proportional probability of the number of households recorded in the National Count of Households and Population from 2005 (INEGI). In each selected home, we verified the presence of a male meeting eligibility criteria. If we found more than one male meeting study requirements, then we randomly selected one male and the interview was conducted at their home. If the potential control was not present, we performed up to three attempts to localize him before searching for another possible control.

Participation rates among cases and controls were 85·9% and 87·5%, respectively. Subjects declining participation in the study provided information regarding age, birthplace, marital status, and educational level.

Interview

Trained staff unaware of the specific study hypothesis conducted face to face interviews. Through these questionnaires we obtained information regarding sociodemographic characteristics, familial history in first-degree relatives of prostate, breast, ovarian, and colon cancer, as well as, personal history of chronic diseases (diabetes, arterial hypertension, dyslipidemia, etc.). We also inquired about sexual history, physical activity, dietary and smoking habits.

Anthropometric characteristics, such as waist (cm) and hip (cm) circumferences, height (cm), and weight (kg) were measured at interviews. Waist-to-hip ratios and Body Mass Indexes (BMI) were calculated. Using self-reported weight (kg), we also calculated BMI two years prior to the diagnosis or interview. Both BMIs were categorized according to the World Health Organization recommendation (<25, 25–<30, and ≥30).

Leisure-time physical activity

Through a PA questionnaire previously validated in Spanish-speaking population,[19] we obtained information about moderate (≥ 3 Mets) and vigorous intensity (≥ 6 Mets) leisure-time activities (Annex 1 and Figure 1) in three different life stages: 15–18, 19–29, and >30 years old. For each stage we considered the following activities: volleyball, lifting, bicycling, faster walking for at least 20 minutes, dancing, aerobics, boxing, basketball, doubles tennis, bicycling at moderate velocity, swimming, football soccer, skating, tennis, climbing, and running. For each activity, we requested the number of hours per day, days per week, and the number of months per year in which the activity was performed.

We estimated separately time invested in each activity (minute/day/year) during each life stage and according to the energy expenditure stated for each activity in the PA compendium,[20] we estimated METs minute/day/year for each activity (Annex 1). Afterward, total energetic expenditure in each life stage was calculated by the sum of all METs minute/day/year from reported activities in each stage. Accumulated leisure-time PA during life was estimated by the sum of total METs minute/day/year of each life stage. Then, leisure-time PA at each

stage and accumulated during life for subjects performing any PA were categorized in tertiles based on METs/ minute/day/year controls distributions. Additionally, we took the total METs minute/day/year from each life stage (Figure 1) and using KmL packages (k-means+ method)[21] for longitudinal data in R software, we reconstructed the individual leisure-time historical PA patterns or trajectories throughout life. Among males who reported any leisure-time PA in at least one life stage, we identified three PA trajectories: Trajectory A, characterized by males who had high PA intensity and frequency at 15-18 years old and showed a reduction throughout life; Trajectory B, males who maintained constantly low PA; and Trajectory C, males who constantly performed more PA (Figure 2). These trajectories were verified using the quality criteria of Calinski & Harabasz.[21] Further, we reconstructed historical PA trajectories by k-means++[21] (Annex 2) and we obtained the same historical PA patterns or trajectories.

Dietary Information.

Dietary information was obtained by a validated, semi-quantitative Food Frequency Questionnaire (FFQ) that contains 127 food-items;[22] with a reference time of 3 years before diagnosis for cases and 3 years before the interview for controls. For each food reported frequency consumption ranked between never and up to six times per day. According to reported daily intake of cheese (freshly made, Oaxaca and Manchego) and yogurt, we constructed the dairy intake group. Energy intake was estimated using the food composition database from Food Processor Software, which includes data on traditional Mexican food.[23] Nineteen subjects were excluded from final analysis due to

extremely low (*n* = 9, <800 calories) or high (*n* = 9, >4,500 calories) dietary energy intake, and one subject who did not answered the FFQ.

Statistical analysis

PA and other selected characteristics were compared between cases and controls; depending on the variable type, we employed Student *t* or chi-squared test.

To estimate the association between PC and leisure-time historical PA patterns or trajectories throughout life, as well as with PA at each life stage or accumulated during life we employed independent, unconditional logistic regression models that included age at interview. Further, we estimated the association between leisure-time PA (trajectories, life stages and accumulated during life) and PC aggressiveness, as well as, PC-onset by independent unconditional logistic regression models. For all models, the reference group comprised of males not performing any PA.

As potential confounders, we evaluated variables that, according to the literature, are known risk factors for the association between PA and PC. Final models included only variables changing the crude estimator between PA and PC by >10%. Besides age at interview, we included the following variables: educational level; PC first-degree family history; history of chronic diseases; smoking status 5 years before the interview; BMI 2 years before the interview; dairy and energy intake.

All analyses were performed in STATA ver. 13·0 and R Studio ver. 3·0·2.

Results

Mean age was similar among cases and controls (67·74±8·39 vs. 67·06±9·03). A higher proportion of cases than controls had higher educational level (20·7 vs. 11·6%), were former smokers (44·0 vs. 35·5%), had history of chronic diseases (58·4 vs. 41·2%), and familial history of PC (10·2 vs. 2·6%). Similarly, cases reported greater dairy consumption (41·8 vs. 32·2%) and energy intake (2172·13 ± 717·81 vs. 1959·28 ± 681·88) than controls (Table 1). No differences were observed in relation to BMI two years before or at diagnosis.

The majority of males (71·1%) reported constantly low leisure-time PA throughout life and only 7·0% reported relatively higher PA. For all trajectories, higher activity occurred at 15-18 years old, with a reduction later in life. Highest reduction was identified in Trajectory A (46·6%), while reductions in Trajectories B and C were ~33% (Table 2).

A higher proportion of cases than controls reported not having performed any PA or having substantially reduced their PA trajectory throughout life. The majority of controls reported having engaged in constantly low or high PA. At age 15–18 years, a higher proportion of cases than controls (19·9 vs. 11·3%) were inactive; in contrast, when we evaluated the two later life stages and accumulated PA during life, a higher proportion of cases reported being more active than controls (Table 3).

After adjusting for potential confounders, PA trajectories throughout life were consistently associated with a lower probability of PC. However, this association was significant only among males who always performed regular PA throughout their life. The main reduction in PC probability was observed among males who constantly performed more PA (Trajectory C*)* ($OR_{Trajectory\ C\ vs.\ none}$ = 0·38; 95% CI

= 0·19–0·76). This result was similar for males with aggressive ($OR_{Trajectory\ C\ vs.\ none}$ = 0·49; 95% CI = 0·24–1·0) and late-onset PC ($OR_{Trajectory\ C\ vs.\ none}$ = 0·29; 95% CI = 0·13–0·65). In contrast, when we evaluated the accumulated leisure-time PA during life, the PC reduction associated to a higher PA, ($OR_{\geq 994{\cdot}20\ vs.\ none}$ = 0·76; 95% CI = 0·49–1·20; *p* for trend 0·43) was not significant. Meanwhile, when we evaluated life stages, those more physically active males at ages 15–18 years had a significant decrease in PC probability ($OR_{\geq 538{\cdot}02\ vs.\ none}$ = 0·62; 95% CI = 0·41–0·95) and this result remained for more aggressive and late-onset PC (Table 4).

Discussion:

These results suggest that PC decrease risk could be consequences of consistency and intensity of PA performance throughout life. Among males who maintained constantly low PA throughout their lives we observed a significant reduction of PC; however this reduction was higher for those males who constantly performed more PA.

Our findings are in accord with mechanistic anti-carcinogenic metabolic evidence about the role of PA. A single bout of PA has been shown to increase insulin sensitivity for about 60 hours.[3] Meanwhile a constant PA practice of moderate intensity may also reduce insulin-like growth factor I (IGF-I) serum levels,[3] which may increase liver production of Sex Hormone Binding Globulin (SHBG) and decrease testosterone and estradiol serum levels.[24] Low IGF-I serum concentration also stimulates the action of p53, which could regulate cell growth (↑p21) and facilitate apoptosis (↓Bcl-2) at the nuclear level.[24] Another anti-proliferative effect appears to be mediated by activin, inhibin, and myostatin, which are secreted by skeletal muscles. Activin could arrest PC cell

growth by blocking cell cycle (cells in G_0/G_1 or G_2/M) and this arrest is enhanced by inhibin. Myostatin facilitates apoptosis of tumor cells through a metabolic change from oxidative phosphorylation to glycolysis.[25] Additionally, other anti-inflammatory mechanisms could contribute to this anti-carcinogenic PA role.[25]

It is difficult to compare our results because this is the first study that uses historical leisure-time PA patterns or trajectories throughout life to evaluate its association with PC. Most of the cohort studies suggest a protective effect of leisure-time PA on PC.[6-12] Notwithstanding, just two cohorts that evaluated leisure-time PA through energy expenditure (METs), reported a significant PC risk reduction associated with average PA from three different life stages or baseline leisure-time PA.[8,11] In case-controls studies,[13,14] the reduction on PC associated with leisure-time PA was no significant. Friedenreich *et al.* evaluated leisure-time PA at different life stages and total accumulated PA by the sum of all stages; being that result similar to ours when we used the accumulated leisure-time PA during life.[13]

For an adequate interpretation of these results, some considerations need to be taken into account. One of the main limitations of case-control studies is the possibility that results could be consequences of recall bias. However, we consider it unlikely; our questionnaire evaluated multiple potential PC risk factors (not solely PA) and participants were unaware of the specific study hypothesis. The differential PA report should have occurred in all life stages for affecting the historical leisure-time PA trajectories and probably we would not have found congruent results in relation with the observed associations between each identified trajectories and PC. Additionally, for supporting this

statement, the knowledge about PA effect or its potential exposure windows on PC is not well-established and the information about PA and PC is not widespread among the general population. In contrast, even though PA questionnaire section has not been validated in Mexican population, a previous study among Spanish-speaking population reported a Spearman correlation of 0·51; for this reason we do not rule out the presence of no differential measurement error and the possibility that our results could be underestimate.

Unlike when we evaluated separately leisure-time PA at each stage and accumulated during life, the historical PA patterns or trajectories has the advantage of taking into account the within-subject variability and cluster the PA pattern or trajectories into different groups according to homogeneous characteristics.[21] Leisure-time PA accumulated during life and mainly PA closer to age-at- diagnosis could be affected by other health conditions; this situation could mask the within-subject PA variability and its potential association with PC. PA practice is a medical recommendation for the control of chronic diseases, and a higher proportion of cases had a history of chronic diseases with a median evolution time around 8 years. These could be the explanation of a higher PA prevalence among cases at life stage >30 years, as well as it association with higher PC possibility.

We also consider unlikely the existence of a selection bias. Participation rates between cases and controls were similar (85·9 vs. 87·5%), and we did not find differences regarding sociodemographic characteristics between males who agreed or did not agree to participate in the study.[17] However, as we did not include cases from private hospitals our results could only be extrapolated to those males who attend public hospitals.

The lack of information about PA trends in time (individual PA trajectories), limited the evaluation whether the PA trajectories among controls represents the exposure prevalence in the population. However, the reported leisure-time physical inactivity prevalence observed during the three life stages varied according to expectations. Further, considering the three life stages, our accumulated prevalence of physical inactivity was similar to that reported for Mexican males aged ≥ 15 years (31·0 vs. 37·1 %).[15]

In relation to confounding control, all of the final models were adjusted by main known risk factors for PC, such as educational level; PC history in first-degree relatives; smoking status 5 years before the interview; history of chronic diseases; BMI 2 years before the interview; age; dairy and energy intake. However, we cannot reject the possibility of residual confounding because we were unable to adjust by alcohol intake due to the small frequency reported.

Conclusion:

PA is a modifiable lifestyle and the association observed between historical PA trajectories throughout life and PC is biologically plausible. Our results contribute to evidence concerning the PA protective effect on PC and suggest that this effect is determined by early-age adoption of PA and consistency throughout life. From a research standpoint, we recommend that this approach be used and validated in prospective studies.

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Table 1. Selected characteristics of the study population.

Characteristics	Cases (n=402)	Controls (n=805)	p value[a]
Age			
Mean ± SD	67·74 ±8·39	67·06 ±9·03	0·21
Marital status (%)			
United vs. Not united [b]	309 (76·9%)	644 (80·0%)	0·21
Educational level (%)			
Elementary school or less	183 (45·5%)	363 (45·1%)	<0·001
Junior high school	66 (16·4%)	203 (25·2%)	
High school	70 (17·4)%	146 (18·1%)	
University or more	83 (20·7%)	93 (11·6%)	
Smoking (%) [c]			
Never	129 (32·1%)	264 (32·8%)	0·004
Former smoker >15 years	95 (23·6%)	174 (21·6%)	
Former smoker ≤ 15 years	82 (20·4%)	112 (13·9%)	
Current smoker	96 (23·9%)	255 (31·7%)	
History of chronic diseases (%) [d]			
Yes vs. No	234 (58·4%)	332 (41·2%)	<0·001
Family history of PC (%) [e]			
Yes vs. No	41 (10·2%)	21 (2·6%)	<0·001
Body mass index (%) [f]			
<25	103 (26·8%)	219 (28·2%)	0·76
25-29	188 (48·8%)	383 (49·2%)	
≥30	94 (24·4%)	176 (22·6%)	
Body mass index (%) [g]			
<25	129 (32·9%)	216 (27·2%)	0·11
25-29	188 (48·0%)	402 (50·7%)	
≥30	75 (19·1%)	175 (22·1%)	
Dairy consumption (portion/d) (%)			
Low	129(32·1%)	295(36·7%)	0·004
Middle	105(26·1%)	251(31·1%)	
High	168(41·8%)	259(32·2%)	
Energy [h]			
Mean ± SD	2172·13 ± 717:81	1959·28 ± 681·88	<0·001

a t test and x^2
b United: Married and common law
c Smoking condition 5 years before the interview
d Hypertension, diabetes or dyslipidemia
e Familiar history of prostate cancer in first degree relatives
f Two years before the interview
g At the moment of the interview
h Differences in n are because seven cases and eleven controls had out of range total energy values (<800 or >4500 calories) and one case without FFQ responses

Table 2. Average Physical activity at life stages according to historical leisure-time PA pattern or trajectory

PA trajectories throughout life [a]	Mets/minute/day/year			% of change[b]
	15-18 years old	19-29 years old	>30 years old	
	Mean ± SD	Mean ± SD	Mean ± SD	
Trajectory A (71·1%)	855·22 ± 342·77	652·78 ± 320·30	399·0 ± 406·23	46·6
Trajectory B (21·9%)	292·53 ± 195·27	191·91 ± 173·07	96·45 ± 153·59	32·9
Trajectory C (7·0%)	1863·01 ± 551·83	1254·20 ± 645·66	622·38 ± 639·22	33·4
Total	467·83 ± 509·32	326·34 ± 402·47	177·33 ± 318·62	37·9

a Trajectory A, characterized by males who had high PA intensity and frequency at 15-18 years old and showed a higher reduction throughout life; Trajectory B, males who maintained constantly low PA, and Trajectory C, males who constantly performed more PA.
b PA at >30 years old vs. at 15- 18 years old

Table 3. Leisure-time physical activity in different stages and throughout life

Physical activity	Cases (n=402)	Controls (n=805)	p value[a]
Trajectories throughout life [b]			
None	59 (14·7%)	75 (9·3%)	
A	99 (24·6%)	136 (16·9%)	<0·001
B	222 (55·2%)	541 (67·2%)	
C	22 (5·5%)	53 (6·6%)	
At 15-18 years old [c]			
None	80 (19·9%)	91 (11·3%)	
≤220·93	78 (19·4%)	266 (33·0%)	<0·001
220·94-538·01	107 (26·6%)	210 (26·1%)	
≥538·02	137 (34·1%)	238 (29·6%)	
At 19-29 years old [c]			
None	101 (25·1%)	227 (28·2%)	
≤220·93	106 (26·4%)	249 (30·9%)	0·04
220·94-441·86	73 (18·2%)	142 (17·6%)	
≥441·87	122 (30·3%)	187 (23·2%)	
> 30 years old [c]			
None	170 (42·3%)	451 (56.0%)	
≤118·75	62 (15·4%)	119 (14·8%)	<0·001
118·76-331·40	69 (17·2%)	115 (14·3%)	
≥331·41	101 (25·1%)	120 (14·9%)	
Accumulated during life [d]			
None	59 (14·7%)	75 (9·3%)	
≤473·42	79 (19·7%)	244 (30·3%)	<0·001
473·43-994·19	103 (25·6%)	245 (30·4%)	
≥994·20	161 (40·0%)	241 (29·9%)	

a x^2 test
b Trajectory A, characterized by males who had high PA intensity and frequency at 15-18 years old and showed a higher reduction throughout life; Trajectory B, males who maintained constantly low PA, and Trajectory C, males who constantly performed more PA.
c Physical activity measured in MET/minute/day/year
d Accumulated MET/minute/day/year of the life stages 15-18, 19-29 and >30 years old

Table 4. Association between leisure-time physical activity and prostate cancer risk, aggressiveness and onset

Physical activity	All	Gleason <7		Gleason≥7		Early onset		Late onset	
	OR[a](95% CI)	Cases[b] (n=103)	OR[a](95% CI)	Cases[b] (n=288)	OR[a](95% CI)	Cases[b] (n=67)	OR[a](95% CI)	Cases[b] (n=335)	OR[a](95% CI)
Trajectories throughout life [c]									
None	1·0	15		41	1·0	4	1·0	54	1·0
A	0·81(0·50-1·32)	26	---	70	0·80(0·47-1·37)	16	0·48(0·13-1·80)	82	0·85(0·51-1·43)
B	0·54(0·35-0·82)	59		153	0·53(0·33-0·85)	38	0·63(0·19-2·05)	180	0·52(0·33-0·81)
C	0·38(0·19-0·76)	1		18	0·49(0·24-1·0)	8	0·34(0·07-1·60)	12	0·29(0·13-0·65)
At 15-18 years old									
None	1·0	18	1·0	56	1·0	5	1·0	73	1·0
≤220·93	0·36(0·23-0·55)	21	0·40(0·1890·84)	54	0·34(0·21-0·56)	15	0.80(0·25-2·55)	62	0·32(0·20-0·51)
220·94-538·01	0·55(0·36-0·85)	34	0·76(0·38-1·52)	69	0·49(0·30-0·79)	19	0·56(0·18-1·80)	86	0·54(0·34-0·85)
≥538·02	0·62(0·41-0·95)	28	0·51(0·25-1·05)	103	0·64(0·40-1·0)	27	0·57(0·18-1·81)	107	0·62(0·40-0·97)
	p for trend 0·77		*p for trend* 0·45		*p for trend* 0·87		*p for trend* 0·30		*p for trend* 0·80
At 19-29 years old									
None	1·0	23	1·0	73	1·0	11	1·0	89	1·0
≤220·93	0·94(0·65-1·35)	29	0·99(0·54-1·85)	75	0·92(0·62-1·38)	20	0·96(0·40-2·34)	85	0·93(0·63-1·38)
220·94-441·86	1·17(0·77-1·75)	21	1·32(0·67-2·59)	47	1·04(0·65-1·65)	11	0·68(0·25-1·85)	60	1·23(0·79-1·92)
≥441·87	1·30(0·90-1·88)	28	1·15(0·61-2·17)	87	1·31(0·87-1·96)	24	0·83(0·34-2·03)	94	1·32(0·88-1·96)
	p for trend 0·09		*p for trend* 0·51		*p for trend* 0·15		*p for trend* 0·56		*p for trend* 0·09
> 30 years old									
None	1·0	42	1·0	121	1·0	23	1·0	145	1·0
≤118·75	1·30(0·88-1·91)	15	1·12(0·58-2·20)	43	1·30(0·84-2·0)	13	1·68(0·73-3·88)	48	1·21(0·79-1·85)
118·76-331·40	1·62(1·11-2·37)	18	1·49(0·79-2·80)	50	1·62(1·06-2·47)	11	1·33(0·53-3·33)	58	1·71(1·13-2·57)
≥331·41	1·82(1·27-2·61)	26	1·87(1·05-3·37)	68	1·71(1·15-2·56)	19	1·62(0·75-3·49)	77	1·81(1·22-2·70)
	p for trend <0·001		*p for trend* 0·03		*p for trend* 0·003		*p for trend* 0·25		*p for trend* 0·001
Accumulated during life [d]									
None	1·0	15	1·0	41	1·0	4	1·0	54	1·0
≤473·42	0·43(0·27-0·68)	20	0·35(0·16-0·77)	56	0·44(0·26-0·74)	13	0·70(0·20-2·50)	66	0·40(0·24-0·66)
473·43-994·19	0·57(0·36-0·91)	28	0·56(0·27-1·16)	72	0·55(0·32-0·91)	15	0·43(0·12-1·53)	87	0·58(0·36-0·95)
≥994·20	0·76(0·49-1·20)	38	0·59(0·29-1·23)	113	0·77(0·47-1·26)	34	0·66(0·19-2·24)	121	0·73(0·45-1·19)
	p for trend 0·43		*p for trend* 0·95		*p for trend* 0·51		*p for trend* 0·69		*p for trend* 0·55

a Adjusted by educational level, history of prostate cancer in first degree relatives, smoking status 5 years before the interview, history of chronic diseases, body mass index two years before interview, dairy intake energy and age.

b Differences in n are because seven cases and eleven controls had out of range total energy values (<800 or >4500 calories) and one case without FFQ responses

c Trajectory A, characterized by males who had high PA intensity and frequency at 15-18 years old and showed a higher reduction throughout life; Trajectory B, males who maintained constantly low PA, and Trajectory C, males who constantly performed more PA

d Accumulated MET/minute/day/year of the life stages 15-18, 19-29 and >30 years old

Figure 1
Lifespan leisure-time PA evaluation

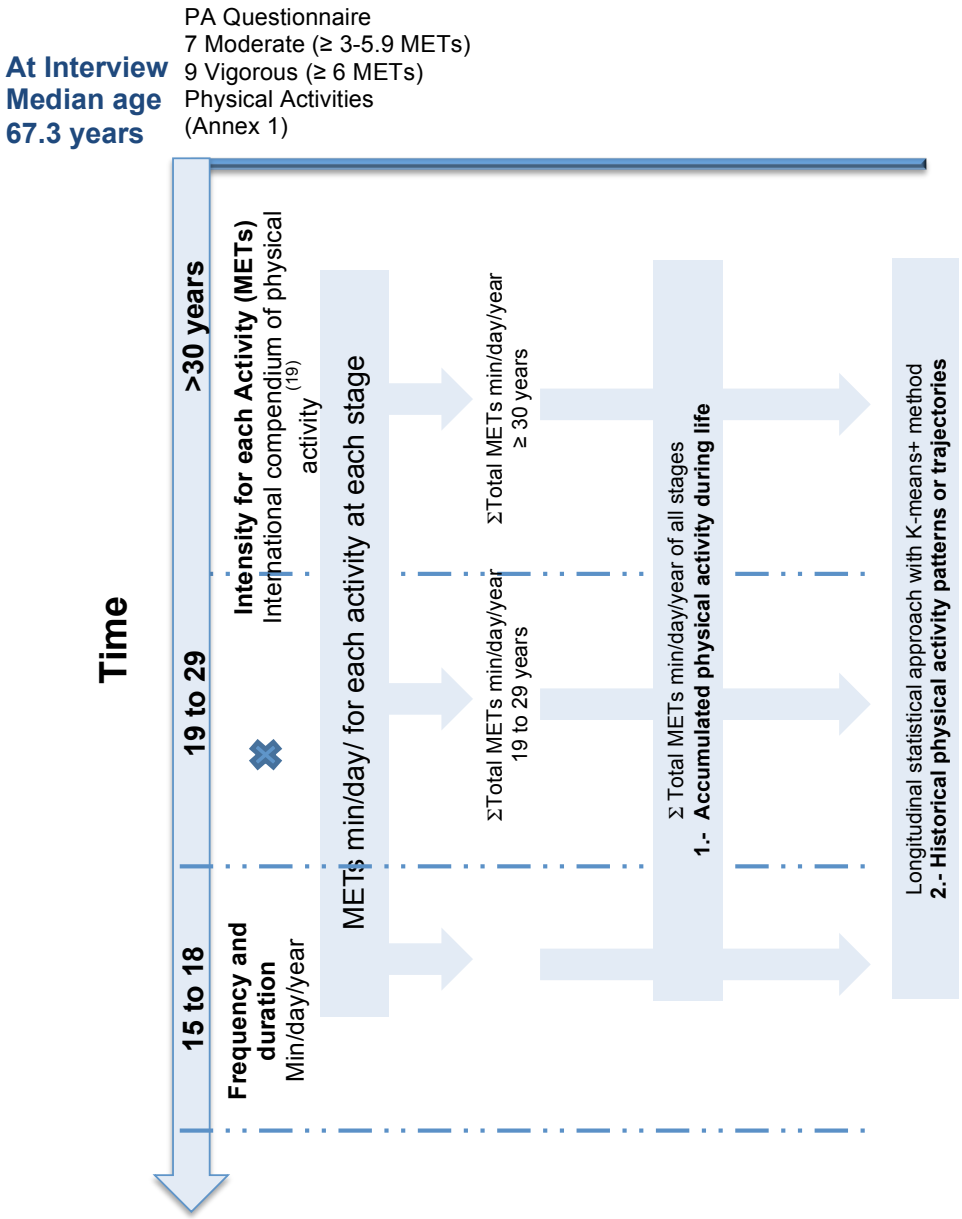
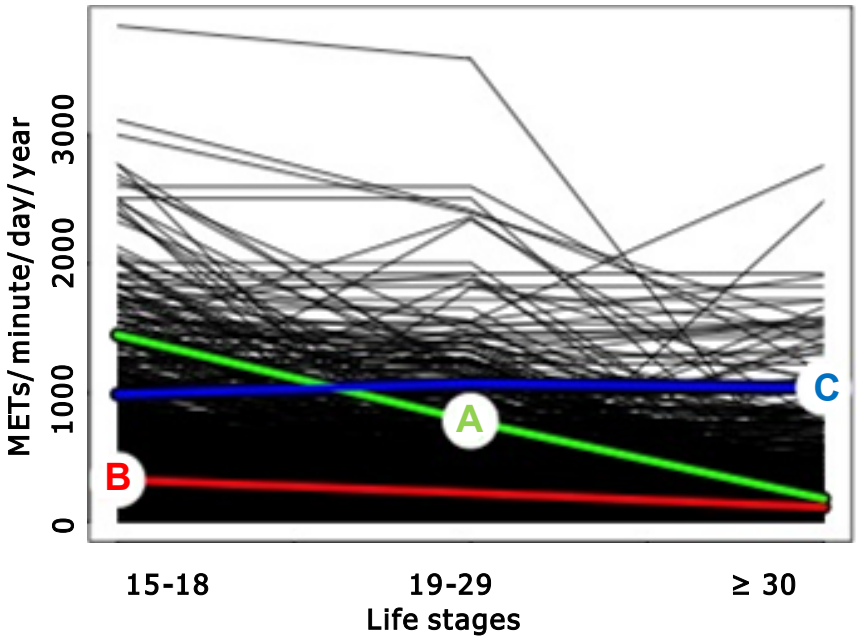


Figure 2. Historical leisure-time physical activity patterns or trajectories



Trajectory A, characterized by males who had high PA intensity and frequency at 15-18 years old and showed a higher reduction throughout life (21·9%); Trajectory B, males who maintained constantly low PA (71·1%), and Trajectory C, males who constantly performed more PA (7·0%).

Annex 1. Energy expenditure (Mets) of activities according with PA compendium[13]

Mets	Activity
3.0	Volleyball
3.0	Lifting
4.0	Bicycling
4.3	Faster walking for at least 20 minutes
5.0	Dancing
5.5	Aerobics
5.5	Boxing
6.0	Basketball
6.0	Doubles tennis
6.8	Bicycling at moderate velocity
7.0	Swimming
7.0	Football soccer
7.0	Skating
7.3	Tennis
8.0	Climbing
8.0	Running

Conclusiones:

Desde el punto de vista de salud pública la relevancia de esta tesis radica en que se trata del primer estudio sobre factores de riesgo que se realiza en población Mexicana. Los dos factores de riesgo evaluados son condiciones susceptibles de modificación y sobre las cuales se puede incidir mediante programas de prevención primaria. En el caso de la historia de infecciones de transmisión sexual (ITS), especialmente gonorrea, nuestros hallazgos refuerzan la necesidad de difundir información en población joven y adulta acerca de las consecuencias de las ITS y reforzar el uso de condón. Así mismo, evidencia la necesidad de llevar a cabo un adecuado sistema de vigilancia que identifique la magnitud real de los problemas de resistencia antimicrobiana.

Desde el punto de vista clínico es necesario evaluar e identificar los factores relacionados con la falta de cumplimiento en el tratamiento; así como, reforzar entre los médicos (generales y especialistas) la importancia de la historia clínica, especialmente el interrogatorio enfocado a historia de vida sexual, antecedentes de infecciones de transmisión sexual, tipo de tratamiento usado, etc. Desde el punto de vista de investigación, esto nos deja claro que no es eficiente evaluar el antecedente de infecciones de transmisión sexual de forma global. Además de hacerlo de esta forma es necesario hacerlo separadamente. El potencial de generar inflamación crónica a nivel de la próstata varía dependiendo del agente infeccioso involucrado. Manejar de manera global el antecedente de ITS, puede generar un sesgo de mala-clasificación, cuya magnitud dependerá del tipo de infección prevalente o prevalentes dentro de la población bajo estudio.

En relación a la práctica de actividad física (AF) nuestros resultados contribuyen a la evidencia científica previa y sustenta el efecto que ésta tiene sobre el CaP. Desde el punto de vista de salud pública, es importante resaltar que se deben reforzar los programas y recomendaciones de salud para un inicio temprano en la práctica de actividad física, así como, la constancia o regularidad en la práctica de la misma.

En el campo de la investigación la recomendación va en el sentido de mejorar las mediciones de la misma. La realización de estudios prospectivos con mediciones regulares de los diferentes dominios de AF, en particular de la AF recreativa con estimación del gasto energético y la reconstrucción de la historia de AF (trayectorias o patrones) puede ser una buena aproximación para mejorar la medición de este factor de

riesgo modificable.

En ambos casos, pero principalmente en relación con el antecedente de ITS o gonorrea, esta información junto con la presencia de otros factores ya claramente establecidos (por ejemplo: edad, historia familiar de CaP), serviría para identificar a grupos de alto riesgo de desarrollar cáncer de próstata y así diseñar estrategias dirigidas y efectivas para la prevención de esta enfermedad.

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