Research Article

Cancer Prevention Research

Sedentary Behavior and Prostate Cancer: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

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Abstract

Prostate cancer is the second most common cancer in men worldwide, and sedentary behavior is widespread, yet reviews and meta-analyses summarizing the role of sedentary behavior as a potential risk factor for prostate cancer are scarce. We searched PubMed, Web of Science, and Cochrane databases for relevant articles up to January 2019. We pooled maximally adjusted risk estimates in a random effects model and performed meta-regression meta-analysis, assessed heterogeneity and publication bias using I^2, funnel plots, and Egger and Begg tests, and conducted sensitivity analyses and influence diagnostics. Data from 12 prospective cohort studies including a total of 30,810 prostate cancer cases were analyzed. We found no statistically significant association between high versus low sedentary behavior and prostate cancer incidence [RR = 1.07; 95% confidence interval (CI), 0.99–1.16; $P = 0.10$]. We noted that adjustment for body mass index (BMI) modified the relation of sedentary behavior to prostate cancer, particularly aggressive cancer. Sedentary behavior was related to a statistically significant increased risk of aggressive prostate cancer in analyses not adjusted for BMI (RR = 1.21; 95% CI, 1.03–1.43), whereas no association was apparent in BMI-adjusted analyses (RR = 0.98; 95% CI, 0.90–1.07), and the difference between those summary risk estimates was statistically significant ($P_{\text{difference}} = 0.02$). Sedentary behavior is not independently associated with prostate cancer. However, prolonged sedentary behavior may be related to increased risk of aggressive prostate cancer through a mechanism involving obesity. This finding represents a potentially important step toward considering sedentary behavior as a modifiable behavioral risk factor for aggressive prostate cancer.

Introduction

Sedentary behavior is widespread, with objectively assessed measures indicating that adults spend more than half their waking day in sedentary pursuits (1). Prolonged time spent sitting decreases energy expenditure and might displace time spent in light physical activities (2), which could subsequently contribute to weight gain over time (3).

Prostate cancer is the second most common cancer among men, accounting for 13.5% of all male cancer cases worldwide (4). Established risk factors include age, family history of prostate cancer, and African-American ethnicity (4, 5). There is increasing evidence that greater body fatness is related to risk of advanced prostate cancer, and research into additional modifiable risk factors such as diet and physical activity has gathered particular attention throughout the past years (5). Among these lifestyle factors, sedentary behavior has recently emerged as a potential determinant of prostate cancer risk. Although sedentary behavior has often been equated with physical inactivity, it actually represents a distinct risk factor independent of whether individuals meet physical activity recommendations (6). As such, sedentary behavior is defined as "any waking behavior characterized by an energy expenditure $\leq$ 1.5 metabolic equivalents, while in a sitting, reclining, or lying posture" (7).

Numerous observational studies have examined the association between sedentary behavior and prostate cancer. However, to the best of our knowledge, epidemiologic evidence regarding sedentary behavior and prostate cancer is limited to two subanalyses including only three studies each (8, 9). We therefore conducted a comprehensive systematic literature review and

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meta-analysis of published prospective cohort studies on sedentary behavior and total, advanced, and fatal prostate cancer. We paid particular attention to aggressive prostate cancer because obesity, a strong correlate of sedentary behavior, is linked to advanced prostate cancer only.

Materials and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; ref. 10). The PRISMA checklist (Supplementary Data S1) can be accessed online.

Eligibility criteria

We considered studies as potentially eligible if they: (i) represented a prospective cohort design; (ii) reported risk estimates (RR or HR) for prostate cancer incidence and/or mortality or provided sufficient data to calculate them; (iii) used total daily sitting time or sedentary behaviors during occupation, leisure time, or transportation as exposure variables; and (iv) were published in English language.

We excluded studies that defined sedentary behavior as being physically inactive. We further disregarded studies that failed to report incident or fatal prostate cancer as an outcome, assessed a different prostatic disease (e.g., benign prostatic hyperplasia), or focused on changes in serum PSA levels as the outcome of interest. We also excluded editorials, guidelines, comments, letters, conference abstracts, proceedings, and news articles.

Search strategy

Two authors (F.F. Berger and C. Jochem) developed the search terms (Supplementary Data S2), which comprised sedentary behavior and its synonyms, including terms used to describe sedentary behaviors (e.g., "time spent sitting," "screen time," and "TV watching") and to describe prostatic neoplasms or site-specific cancer, as well as keywords to screen for prostate cancer incidence or mortality.

We applied our search strategy to studies published in PubMed (from inception; 553 results), Web of Science (1,043 results), and the Cochrane Library databases [which encompassed Systematic Reviews (157 results), Controlled Trials (17 results), and Public Health databases (10 results)] and reiterated our search on a monthly basis up to January 2019.

F.F. Berger screened titles and abstracts. Following initial exclusions, F.F. Berger and C. Jochem independently read the eligible articles and excluded inadequate studies by consensus. In addition, both authors hand-searched the reference lists of retrieved full-text articles to find any relevant studies with similar designs or research questions.

F.F. Berger and C. Jochem independently extracted the data from the articles and differences were resolved by discussion with M.F. Leitzmann. We extracted the following data from each study: name of the first author, publication year, geographic study location, follow-up time (years), and size and age of the study population. For exposure data, we extracted the types of sedentary behaviors assessed (total/leisure/occupational sitting time, TV/video watching), the method of exposure ascertainment (self-report, interview, job title assignment, or a combination of those methods), and the mode of sedentary behavior assessment [quantitatively (i.e., hours per day spent sitting) or qualitatively (i.e., descriptive categories of sedentary behavior such as "mostly sitting" or "sitting half the time")]. For endpoint data, we extracted the type of outcome assessed (total incident/localized/advanced/fatal prostate cancer), the number of incident and fatal prostate cancer cases, the method of case ascertainment (self-report or linkage with cancer/death registries), and whether and to what extent risk estimates were adjusted for known or suspected risk factors of prostate cancer.

Quality assessment

The methodologic quality of each study was assessed using the Newcastle–Ottawa Scale (NOS), which uses a 9-point scale to evaluate observational studies in meta-analyses, including the quality of selection of study participants (maximum of four points), comparability of cohorts (maximum of two points), and adequate outcome assessment including the quality of follow-up (maximum of three points). We did not apply the quality score as weights in our analyses but performed predefined meta-regression analyses stratified by the NOS.

Statistical analysis

Primary random-effects meta-analysis. Risk estimates were interpreted as relative risks (RR_i), and natural logarithms of RRs with corresponding SEs ($s_i = d_i/1.96$) were computed, where d_i represented the maximum of [log(upper bound 95% confidence interval (CI) of RR_i) – log(RR_i)] and [(log(RR_i) – log(lower bound 95% CI of RR_i)]. Risk estimates were weighted by $\omega_i = 1/(s_i^2 + \tau_i^2)$, where s_i represented the SE of log(RR_i) and τ_i^2 represented the restricted maximum-likelihood estimate (REML) of the overall variance allowing for heterogeneity of the effect measure (11).

Because risk factors for prostate cancer may differ according to disease aggressiveness (12), we conducted separate random-effects meta-analyses for incident and fatal prostate cancers. We also considered a subgroup termed aggressive prostate cancer, which represented the combination of incident prostate cancers that were advanced at the time of diagnosis (defined as stages T3/T4, N1–N3, and/or M1) and fatal prostate cancers. Where possible, we selected maximally adjusted risk estimates, particularly those that were adjusted for measures of adiposity [body mass index (BMI)] and physical activity.

For seven studies (13–19) that used sedentary behavior as the unexposed category and light activity or standing as

the exposed category, we recalculated risk estimates using light activity or standing as the unexposed category and sedentary behavior as the exposed category (20). For publications that assessed sitting duration, we used the longest versus shortest time spent sitting, with the shortest time spent sitting as the reference group. For one study (21) that used the longest time period spent sitting (6–8 hours) as the reference group, we transformed the reference category to the shortest time spent sitting (<2 hours). Heterogeneity was assessed using the Q statistic and was further quantified by the I^2 statistic (22). Potential publication bias was analyzed by funnel plot (23), Egger regression test (23), and Begg rank correlation test (24). We further performed sensitivity analyses and outlier and influence diagnostics (25).

Meta-regression random-effects meta-analysis. We performed meta-regression random effects meta-analysis and REML estimation to assess potential heterogeneity by study geographic region, study time period, study quality score, domain of sedentary behavior, mode of assessment of sedentary behavior, and prostate cancer stage. Using the same computational models, we also conducted analyses stratified by adjustments for positive family history of prostate cancer, BMI, physical activity, and history of PSA testing. All statistical analyses were conducted using R, Version 3.4.2, and the metafor package (11), with $P < 0.05$ indicating statistical significance.

Results

Study selection

Our search of electronic databases and hand-searching of reference lists and other publications yielded 1,811 studies (Fig. 1). After removal of 23 duplicate publications, 1,788 studies remained for title and abstract

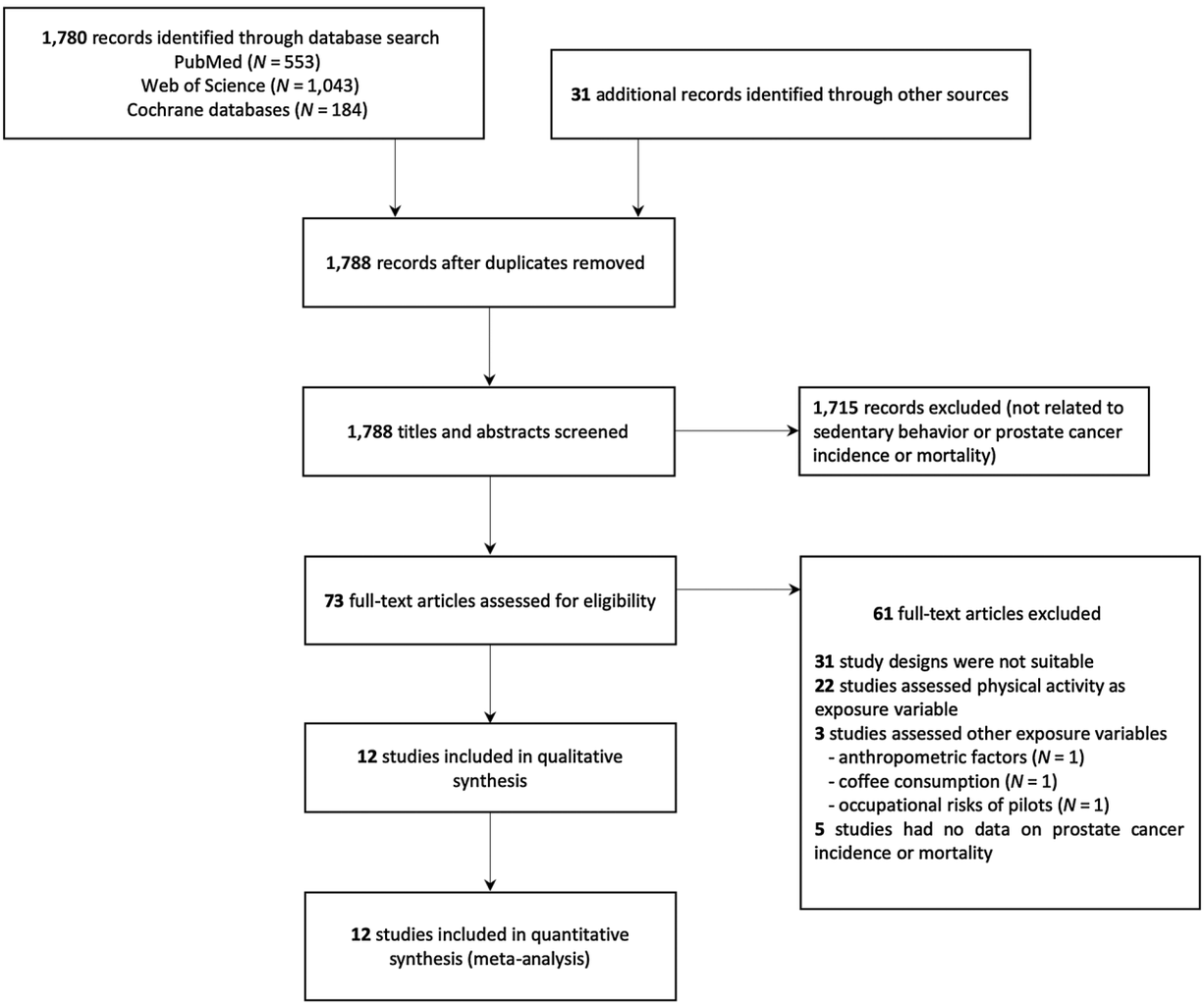

Figure 1.
PRISMA flow diagram depicting the process of study selection for meta-analysis.

screening, of which 73 were potentially relevant for full text review. Among the 73 reviewed publications, we excluded 25 studies that did not assess sedentary behavior as an exposure, five studies that lacked appropriate data on the outcome, and 31 studies that lacked a prospective cohort design. Two main reasons for excluding case–control studies from our meta-analysis were considered. First, we aimed to produce a meta-analysis of studies that reflect strong evidence. In particular, prospective cohort studies are regarded as level 2, while case–control studies are considered level 3 studies (26). Second, the case–control studies identified were deemed low quality. One study used other cancer patients of a hospital population as controls (27), while another study (28) utilized interviews that were not blinded to case/control status. The third case–control study (29) classified sedentary behavior and light occupational physical activity as the same activity level, a likely source of exposure misclassification. After exclusions, 12 studies were included in our meta-analysis.

Characteristics of eligible studies

The relevant properties of the 12 cohort studies included are shown in Table 1. Those studies yielded a total of 671,852 study participants, 32,060 incident, and 1,253 fatal prostate cancer cases. A total of 30,810 prostate cancer cases and 1,120 deaths from prostate cancer with data on sedentary behavior were available for analysis. Among studies with information on prostate cancer stage, 3,310 cases were classified as localized cancers (stages T0–T2, N0, NX, and M0) and 5,376 cases were classified as advanced cancers (stages T3/T4, N1–N3, and/or M1). A total of 6,629 cases were classified as aggressive prostate cancers (combination of advanced and fatal cancers). Nine studies (13–19, 21, 30) originated from Europe and three (31–33) were from the United States. The majority of studies (13–15, 17–19, 30–33) assessed sedentary behavior through self-report, one study (16) used a combination of self-report and personal interviews, and one study (21) applied self-report and job title assignment. Five studies (21, 30–33) employed quantitative assessments of sedentary behavior levels, while seven investigations (13–19) categorized study subjects according to qualitative assessments. The number of adjustment factors ranged from two to 15 potential confounding factors. Study quality according to the NOS varied from a low of four to a high of eight points (Supplementary Table 1).

Sedentary behavior and total, incident, fatal, and aggressive prostate cancers

We pooled 14 risk estimates ($N = 11$ for incidence and $N = 3$ for mortality) from 12 studies and found a borderline statistically significant positive relation between high versus low sedentary behavior and risk of total prostate cancer (RR = 1.08; 95% CI, 1.00–1.16), with considerable heterogeneity among studies ($I^2 = 58.7\%$; $P_{\text{heterogeneity}} = 0.005$). We then performed stratified analyses to detect potential causes of heterogeneity. First, we summarized the data from 11 studies (13–19, 21, 30, 31, 33) on sedentary behavior and prostate cancer incidence and observed a statistically nonsignificant association between the two (RR = 1.07; 95% CI, 0.99–1.16), with slightly higher heterogeneity among studies ($I^2 = 66.3\%$; $P_{\text{heterogeneity}} = 0.002$; Fig. 2). Next, we summarized the data from three studies (15, 31, 32) on sedentary behavior and prostate cancer–related mortality and found a statistically nonsignificant association between the two (RR = 1.14; 95% CI, 0.94–1.38), with no heterogeneity between studies ($I^2 = 0.0\%$; $P_{\text{heterogeneity}} = 0.57$). The summary risk estimate for prostate cancer incidence did not differ significantly from that for prostate cancer–related mortality ($P_{\text{difference}} = 0.55$). We also considered a subgroup of aggressive prostate cancer (the combination of advanced and fatal prostate cancers) and found a null relation with sedentary behavior (RR = 1.05; 95% CI, 0.95–1.15), with low heterogeneity between studies ($I^2 = 21.7\%$; $P_{\text{heterogeneity}} = 0.39$; Fig. 3).

Analyses of potential sources of heterogeneity

We proceeded to explore potential sources of heterogeneity among studies of prostate cancer incidence (Table 2). Investigations that did not adjust for history of PSA testing ($N = 9$ studies) showed a statistically significant increased prostate cancer incidence with high versus low sedentary behavior levels (RR = 1.12; 95% CI, 1.02–1.23). However, between-study heterogeneity among those studies was still apparent ($I^2 = 43.6\%$; $P_{\text{heterogeneity}} = 0.06$). In contrast, studies that adjusted for history of PSA testing ($N = 2$ studies) showed no association between sedentary behavior and prostate cancer incidence (RR = 0.97; 95% CI, 0.93–1.02; $P_{\text{difference}} = 0.01$) and heterogeneity between the two studies involved was absent ($I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.83$). Coincidentally, the group of studies on prostate cancer incidence that did not adjust for history of PSA testing all originated from Europe, whereas the two studies that adjusted for history of PSA testing were both from the United States. Thus, we were unable to discern heterogeneity by adjustment for history of PSA testing from heterogeneity by study geographic region ($P_{\text{difference}} = 0.01$).

For prostate cancer incidence, the only other variable for which the heterogeneity analyses generated a $P < 0.1$ was adjustment for BMI. Specifically, we found a statistically significant positive relation (RR = 1.18; 95% CI, 1.01–1.39) of sedentary behavior to prostate cancer incidence in analyses that did not adjust for BMI ($N = 4$ studies), whereas the association was null (RR = 1.02; 95% CI, 0.94–1.11; $P_{\text{difference}} = 0.09$) in analyses that adjusted for BMI ($N = 7$ studies). In comparison, the

Table 1. Study characteristics of the 12 included studies

First author, year, country/region	Study design details, sample population, and follow-up time	Number of cases and method of assessment	Assessment and categorization of sedentary behavior	Exposure, prostate cancer endpoint, and risk estimate included in main analysis	Confounding variables	NOS
Rangul et al., 2018 (30), Norway	Prospective cohort study, 18,771 men from the HUNT2 survey, mean age 47 years at baseline. Follow-up of 16 years.	889 PCa cases identified by linkage to the Cancer Registry of Norway.	Self-reported total sitting time, categorized as <8 h/day and ≥8 h/day	Sitting ≥ 8 h/day, total PCa: HR = 1.22 (1.05–1.42)	Age, education, smoking, alcohol, BMI	7
Patel et al., 2015 (33), USA	Prospective cohort study, 69,260 men from the ACS CPS-II Nutrition Cohort, ages 50–74 at enrollment. Mean follow-up 13.2 years.	8,276 (1,705 advanced) PCa cases identified by self-report, verified by medical records, cancer registries, or National Death Index (NDI).	Self-reported leisure-time sitting, categorized as 0–≤ 3, 3–5, or ≥6 h/day	Sitting ≥ 6 h/day, total PCa: RR = 0.97 (0.91–1.03); advanced PCa: RR = 0.96 (0.85–1.09)	Age, physical activity (exercise, daily-life, housekeeping), race, smoking status, duration and frequency of smoking among current smokers, years since quitting among former smokers, education, alcohol intake, total energy intake, red/processed meat intake, family history of cancer, prevalent chronic disease, diabetes, PSA-testing, and BMI	8
Hrafnkelsdóttir et al., 2015 (13), Iceland	Prospective cohort study, 8,221 men from the population-based Reykjavik Study, mean age 51.7 years at enrollment. Average follow-up time of 24.8 years.	1,052 (349 advanced) PCa cases identified by linkage to the Icelandic Cancer Registry. Information on PCa as the underlying cause of death retrieved from Statistics Iceland.	Self-reported occupational activity: mostly sitting, mostly standing, mostly on the move during their current work	Mostly sitting; total PCa: RR = 1.03 (0.85–1.25); localized PCa: RR = 0.99 (0.79–1.24); advanced PCa: RR = 1.14 (0.80–1.62)	Age, birth-year, height, BMI, type 2 diabetes, smoking, family history of prostate cancer, education, residency in early life, and regular health check-ups	8
Grotta et al., 2015 (14), Sweden	Prospective cohort study, 13,109 men from the Swedish National March Cohort, mean age 55.1 years at baseline, followed for 13 years.	904 (407 advanced and 68 unclassified) PCa cases, 133 deaths from PCa, identified through linkage with the Swedish National Cancer Register and National Prostate Cancer Register (NPCR) of Sweden for clinical data.	Self-reported occupational activity: light, mostly sedentary; light, but moved a little; rather strenuous; very strenuous during the past 12 months	Light, mostly sedentary, total PCa: RR = 1.04 (0.83–1.30); localized PCa: RR = 1.03 (0.76–1.39); advanced PCa: RR = 1.11 (0.78–1.58)	Age, BMI, education, smoking, alcohol consumption, diabetes, and leisure-time physical activity	6
Lynch et al., 2014 (31), USA	Prospective cohort study, 170,481 men from the NIH-AARP Diet and Health Study, ages 51–72 at risk factor questionnaire. Mean follow-up 8.5 years.	13,751 (1,365 advanced) PCa cases, 669 deaths from PCa, identified through 11 state cancer registries or NDI.	Self-reported total daily sitting time and TV/video viewing time; predefined categories for time spent watching TV or videos, and sitting during a typical 24-hour period in past 12 months; total PCa: <1, 1–2, 3–4, 5–6, ≥7 h/day; advanced PCa: <3, 3–4, ≥5 h/day; PCa-related mortality: <3, 3–4, ≥5 h/day	Sitting ≥ 9 h/day, total PCa: RR = 0.98 (0.91–1.05); sitting ≥ 7 h/day, advanced PCa: RR = 0.91 (0.77–1.08); sitting ≥ 7 h/day, PCa-related mortality: RR = 1.07 (0.85–1.35) TV/video viewing ≥ 7 h/day, total PCa: RR = 1.03 (0.92–1.15); TV/video viewing ≥ 5 h/day, advanced PCa: RR = 0.93 (0.79–1.09); TV/video viewing ≥ 5 h/day, PCa-related mortality: RR = 1.07 (0.85–1.33)	Age, age squared, race, marital status, education, family history of PCa, digital rectal examination in past 3 years, PSA-testing in past 3 years, history of diabetes, smoking, caloric intake, alcohol intake, recreational physical activity, and BMI	8

(Continued on the following page)

Table 1. Study characteristics of the 12 included studies (Cont'd)

First author, year, country/region	Study design details, sample population, and follow-up time	Number of cases and method of assessment	Assessment and categorization of sedentary behavior	Exposure, prostate cancer endpoint, and risk estimate included in main analysis	Confounding variables	NOS
Kim et al., 2013 (32), USA	Prospective cohort study, 61,395 men from the Multiethnic Cohort Study, ages 45–75 years, five ethnic groups (African-American, Latino, Japanese American, Native Hawaiian, and White), median follow-up: 13.7 years.	324 deaths from PCa, identified through linkage with death certificate files in Hawaii and California and periodic linkages with the NDI.	Self-reported total daily sitting time assessed for five types of sitting on a 24-hour basis; PCa-related mortality and sitting stratified for daily sitting watching TV (hours): <1, 1–4, ≥5 h/day	Daily time sitting watching TV ≥ 5 h/day and PCa-related mortality: HR = 1.39 (0.90–2.14)	5-year age groups at cohort entry, education, ethnicity, history of hypertension or diabetes at enrollment, alcohol consumption, energy intake, physical activity (METs per week for moderate activity, vigorous work, and strenuous sports), trend of hours for other sitting behaviors, and smoking history	7
Orsini et al., 2009 (15), Sweden	Prospective cohort study, population-based sample of 45,887 Swedish men, ages 45–79 at baseline, followed for 8 years.	2,735 PCa cases identified through national and regional cancer registries, and 190 deaths identified through the Swedish Register of Death Causes. Subjects with missing variables; number of PCa cases with occupational sitting behavior assessed: 1,948 total; data on stage available for 1,541 cases: 686 advanced, 728 localized, and 127 fatal.	Self-reported occupational activity; predefined categories for occupational activity levels: mostly sitting, sitting half the time, mostly standing, and heavy manual labor	Mostly sitting, total PCa: RR = 1.27 (1.11–1.46); localized PCa: RR = 1.39 (1.12–1.73); advanced PCa: RR = 1.14 (0.90–1.45); PCa mortality: RR = 1.14 (0.64–2.04)	Age, lifetime walking and bicycling levels, waist–hip ratio, height, diabetes, alcohol consumption, smoking status, education, total energy intake, consumption of dairy products, red meat consumption, and parental history of PCa	7
Johnsen et al., 2009 (16), Europe	Prospective cohort study, 127,923 men from 8 European countries from the EPIC cohort, ages 20–97 years. Median follow-up of 8.5 years.	2,458 PCa cases, identified through population cancer registries (Denmark, Italy, the Netherlands, Spain, Sweden, and United Kingdom) or self-report questionnaires, health insurance records, contact with study participants or their next of kin and verified through medical records (Germany and Greece). Data on stage available for 1,402 PCa cases: 914 localized, 488 advanced. Data on grade for 1,414 PCa cases: 832 low-grade and 582 high-grade.	Self-report or interview, occupational activity: employment status and intensity of occupational activity in four categories: nonworking, sedentary, standing, and manual work	Sedentary, total PCa: RR = 1.06 (0.93–1.20); localized PCa: RR = 0.93 (0.76–1.14); advanced PCa: RR = 1.27 (0.94–1.72)	Leisure-time activity, height, weight, marital status, and education	5
Zeegers et al., 2005 (21), the Netherlands	Prospective cohort study, 58,279 men ages 55–69 years. Case–cohort approach: 2,335 subcohort men and 1,386 cases. Mean follow-up of 9.3 years.	1,386 PCa cases identified through record linkage with all nine cancer registries in the Netherlands and with the Dutch National Data Base of Pathology reports (PALGA). Data on stage available for 979 cases; 526 localized, 453 advanced.	Self-report of job title and subsequent assignment of occupational activity of longest held job and last held job: sitting time (hours per day); low activity: 6–8 h/day, moderate activity: 2–6 h/day, and high activity: <2 h/day	Sitting 6–8 h/day (longest held job), total PCa: RR = 0.86 (0.68–1.09)	Age, alcohol intake from wine (g ethanol/d), BMI, energy intake (kcal/day), family history of PCa (yes/no), and level of education (low, medium, and high)	7

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Table 1. Study characteristics of the 12 included studies (Cont'd)

First author, year, country/region	Study design details, sample population, and follow-up time	Number of cases and method of assessment	Assessment and categorization of sedentary behavior	Exposure, prostate cancer endpoint, and risk estimate included in main analysis	Confounding variables	NOS
Hartman et al., 1998 (17), Finland	Prospective cohort study, 29,133 male smokers ages 50–69 years from the ATBC Cancer Prevention Study, median follow-up of 7.0 years.	317 PCa cases identified through linkage to the Finnish Cancer Registry and the Register of Causes of Death; medical records were reviewed centrally by study physicians (including oncologists) to confirm diagnoses. Cases with histology or cytology available (98%) were reviewed by pathologists.	Self-reported occupational activity: work within the past year as mainly sitting, walking quite a lot, walking and lifting, and heavy physical work	Mainly sitting, total PCa: RR = 1.67 (1.02–2.73)	Age, living in an urban area, smoking, history of benign prostatic disease, intervention (alpha-tocopherol, β-carotene, both; placebo group as reference)	4
Veierød et al., 1997 (18), Norway	Prospective cohort study, 25,708 men ages 16–56 years attending a Norwegian Health screening from 1977 to 1983; mean follow-up of 12.4 years.	72 (26 advanced) PCa cases identified through linkage to the Cancer Registry of Norway, deaths ascertained through linkage to the Central Bureau of Statistics of Norway.	Self-reported occupational activity: categorized as sedentary, walking, lifting and walking, and heavy manual work	Sedentary, total PCa: RR = 1.00 (0.58–1.72)	Age at inclusion and attained age	6
Thune and Lund, 1994 (19), Norway	Prospective cohort study, 43,685 men from a health screening program by the National Health screening service from 1972 to 1978, ages 19–50 years at study entry, mean follow-up of 16.3 years.	220 PCa cases identified through linkage to the Cancer Registry of Norway; deaths ascertained through linkage to the Norwegian Central Bureau of Statistics.	Self-reported occupational activity: mostly sedentary work, work with much walking, work with much lifting and walking, and heavy manual work	Mostly sedentary work, total PCa: RR = 1.30 (0.92–1.84)	Age at entry to the study, geographic region, and BMI	5

NOTE: Values in brackets indicate the corresponding 95% CI.

Abbreviations: ACS CPS-II, American Cancer Society Cancer Prevention Study-II; ATBC, alpha-tocopherol, beta-carotene Cancer Prevention Study; EPIC, European Investigation into Cancer and Nutrition; h/day, hours per day; HUNT2, Nord-Trøndelag Health Study 2; PCa, prostate cancer; NIH-AARP, NIH-American Association of Retired Persons; TV, television.

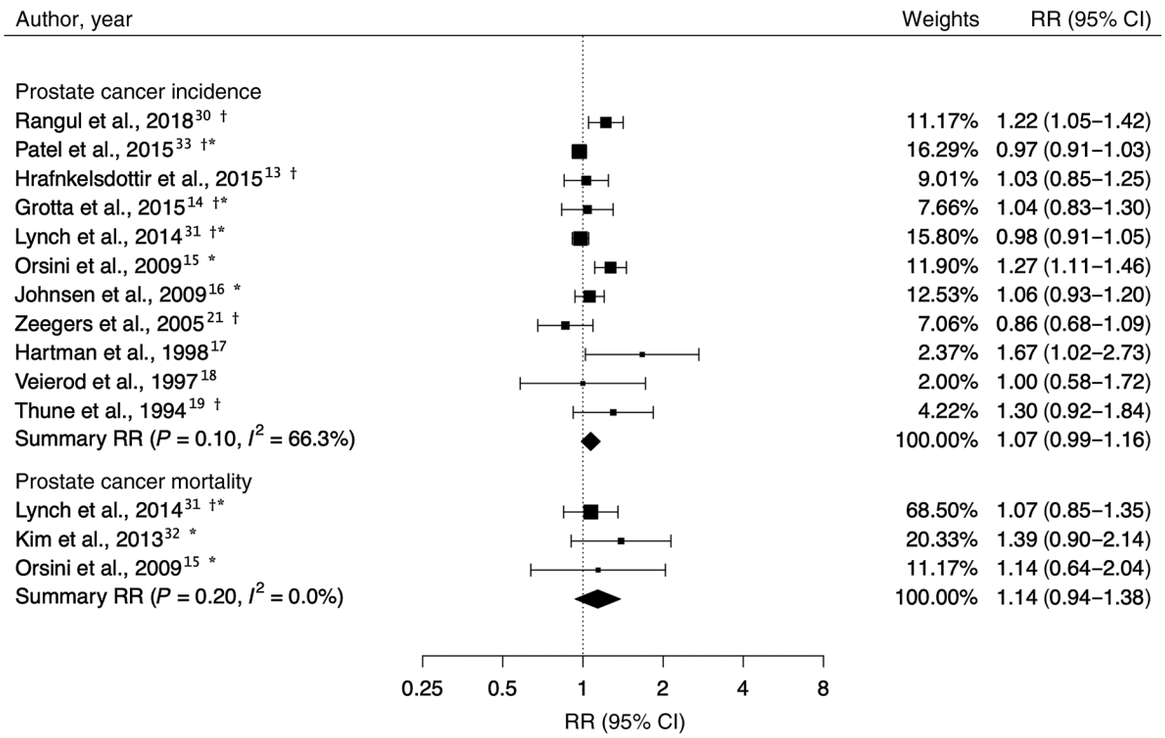

Figure 2.

Random-effects meta-analysis of adjusted RRs of sedentary behavior and total prostate cancer incidence and prostate cancer–related mortality. The black square and the respective line represent the risk estimate and the corresponding 95% CI for each study. The diamond represents the summary relative risk with the corresponding CI for prostate cancer incidence and prostate cancer–related mortality studies, respectively. *P*, *P* value (significance); I^2, heterogeneity among studies; †, risk estimate adjusted for BMI; *, risk estimate adjusted for physical activity.

relation of sedentary behavior to prostate cancer incidence was not modified (all $P_{\text{difference}} > 0.05$) by study time period [*N* (before 2000) = 3 studies and *N* (2000 or after) = 8 studies], study quality score [*N* (NOS $\geq$ 6) = 8 studies, *N* (NOS < 6) = 3 studies], domain of sedentary behavior [*N* (occupational) = 8 studies, *N* (recreational) = 2 studies], mode of assessment of sedentary behavior [*N* (quantitative) = 4 studies and *N* (qualitative) = 7 studies], incident prostate cancer stage [*N* (localized) = 4 studies and *N* (advanced) = 6 studies], adjustment for positive family history of prostate cancer [*N* (adjusted for family history) = 4 studies and *N* (not adjusted for family history) = 7 studies], or adjustment for physical activity [*N* (adjusted for physical activity) = 5 studies and *N* (not adjusted for physical activity) = 6 studies; Table 2].

We next performed stratified analyses of studies of aggressive prostate cancer (Supplementary Table 2). The suggestive divergence between studies with and without BMI adjustment previously observed for prostate cancer incidence was more pronounced for aggressive prostate cancer (Fig. 3). Specifically, we noted that high versus low sedentary behavior was related to an increased risk of aggressive prostate cancer (RR = 1.21; 95% CI, 1.03–1.43) in analyses that did not adjust for BMI (*N* = 3 studies), whereas the association was null (RR = 0.98; 95% CI, 0.90–1.07) in analyses that adjusted for BMI (*N* = 4 studies), and the difference between summary risk estimates was statistically significant ($P_{\text{difference}} = 0.02$).

In addition, studies that used qualitative assessments of sedentary behavior (*N* = 4 studies) yielded a statistically significant positive relation to aggressive prostate cancer (RR = 1.16; 95% CI, 1.01–1.35), whereas those employing quantitative assessments of sedentary behavior (*N* = 3 studies) were null (RR = 0.98; 95% CI, 0.89–1.07), and that difference was statistically significant ($P_{\text{difference}} = 0.04$). Studies of aggressive prostate cancer stratified according to geographic region showed complete overlap with studies stratified by mode of sedentary behavior assessment; thus, we were unable to discern heterogeneity by mode of sedentary behavior assessment from heterogeneity by study geographic region ($P_{\text{difference}} = 0.04$). The relation of sedentary behavior to aggressive prostate cancer was not modified (all $P_{\text{difference}} > 0.05$) by study quality [*N* (NOS $\geq$ 6) = 5 studies and *N* (NOS < 6) = 2 studies], domain of sedentary behavior [*N* (occupational) = 4 studies and *N* (recreational) = 2 studies], type of prostate cancer endpoint [*N* (advanced) = 6 studies and *N* (fatal) = 3 studies], adjustment for positive family history of

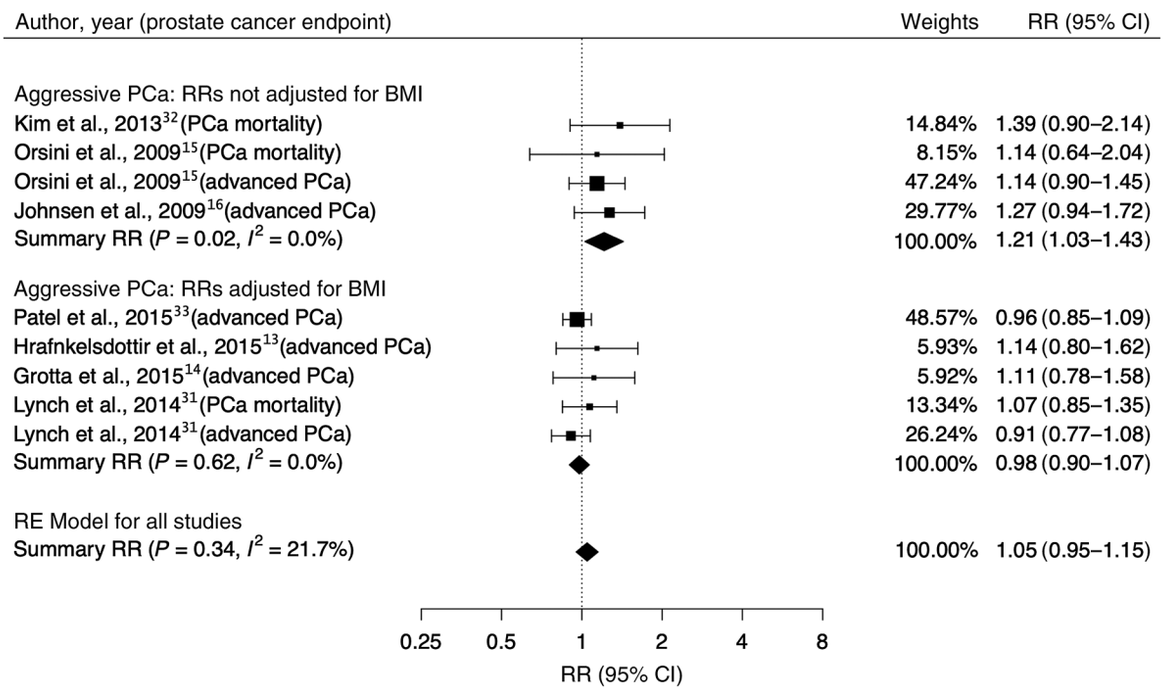

Figure 3.

Random-effects meta-analysis of studies which did and did not adjust risk estimates of sedentary behavior and aggressive prostate cancer for BMI. The black square and the respective line represent the risk estimate and the corresponding 95% CI for each study. The diamond represents the summary RR with the corresponding CI of aggressive prostate cancer studies not adjusted/adjusted for BMI, respectively. I^2, heterogeneity among studies; *P*, *P* value (significance); PCa, prostate cancer.

prostate cancer [*N* (adjusted for family history) = 3 studies and *N* (not adjusted for family history) = 4 studies], or adjustment for physical activity [*N* (adjusted for physical activity) = 6 studies and *N* (not adjusted for physical activity) = 1 study]. There were too few studies to perform meaningful stratified analyses of fatal prostate cancer.

Sensitivity analyses, influence diagnostics, and publication bias

Sensitivity analyses and influence diagnostics (25) of all 12 included studies did not yield statistically significant divergent results. When omitting one study at a time to explore whether an individual study influenced results strongly, summary risk estimates were not altered significantly, yielding summary risk estimates ranging from a minimum RR of 1.05 (95% CI, 0.97–1.22) to a maximum RR of 1.10 (95% CI, 1.01–1.20). When the single study (21) that utilized job title assignment was excluded, the summary risk estimate was RR = 1.09 (95% CI, 1.00–1.19). When four studies (14, 17–19) that utilized light activity or walking instead of standing in comparison with sedentary behavior were excluded, the summary RR was in the range of summary risk estimates of previously conducted sensitivity analyses (RR = 1.06; 95% CI, 0.97–1.16). The funnel plot was symmetrical (Supplementary Figure 1) and results of Egger regression test ($P = 0.09$) and Begg rank correlation test ($P = 0.38$) indicated no evidence of publication bias.

Discussion

This is the first comprehensive systematic review and meta-analysis to examine sedentary behavior in relation to prostate cancer. Our primary finding is that sedentary behavior shows no statistically significant association with prostate cancer. However, in *a priori* determined subanalysis, we found that adjustment for BMI modified the relation of sedentary behavior to prostate cancer, particularly aggressive prostate cancer. Specifically, high versus low sedentary behavior was associated with a statistically significant 21% increased risk of aggressive prostate cancer in studies that were unadjusted for BMI, whereas no such relation was apparent in BMI-adjusted analyses. In comparison, the relation of sedentary behavior to aggressive prostate cancer was not modified by study quality, domain of sedentary behavior, type of prostate cancer endpoint, or adjustment for positive family history of prostate cancer. Six of the included studies adjusted risk estimates for physical activity; meta-regression analysis (Table 2; Supplementary Table 2) showed that neither results for prostate cancer incidence ($P_{interaction} = 0.52$) nor aggressive

Table 2. Stratification criteria, RR, difference between included prostate cancer incidence studies and results of random-effects meta-regression meta-analysis for each subgroup

Stratification criteria	Number of included RRs	RR (high vs. low SB)	95% CI	I^2 (%)	P_{diff}
Total incident prostate cancer risk	11	1.07	0.99–1.16	66.3	NA
Study geographic region					
Europe	9	1.12	1.02–1.23	43.6	
USA	2	0.97	0.93–1.02	0	0.01
Study time period					
Before year 2000	3	1.31	1.02–1.69	0	
Year 2000 or after	8	1.05	0.97–1.14	71.3	0.12
Study quality score					
NOS $\geq$ 6	8	1.05	0.95–1.16	72.5	
NOS < 6	3	1.22	0.95–1.55	50.0	0.28
SB domain					
Occupational	8	1.10	0.99–1.23	45.1	
Recreational	2	0.98	0.93–1.04	0	0.18
Mode of SB assessment					
Quantitative	4	1.01	0.90–1.13	79.9	
Qualitative	7	1.14	1.03–1.25	29.2	0.10
Prostate cancer stage					
Localized	4	1.07	0.89–1.29	61.4	
Advanced	6	1.02	0.92–1.14	24.8	0.77
Adjustment for positive family history of prostate cancer					
Adjusted for positive family history of PCa	4	1.04	0.89–1.21	77.6	
Not adjusted for positive family history of PCa	7	1.09	0.98–1.21	55.0	0.52
Adjustment for BMI					
Adjusted for BMI	7	1.02	0.94–1.11	56.4	
Not adjusted for BMI	4	1.18	1.01–1.39	49.2	0.09
Adjustment for physical activity					
Adjusted for physical activity	5	1.05	0.95–1.15	76.8	
Not adjusted for physical activity	6	1.11	0.95–1.31	51.2	0.52
Adjustment for history of PSA testing					
Adjusted for history of PSA testing	2	0.97	0.93–1.02	0.0	
Not adjusted for history of PSA testing	9	1.12	1.02–1.23	43.6	0.01

Abbreviations: I^2, heterogeneity among studies; PCa, prostate cancer; P_{diff}, P value for difference in the result of moderator analysis; SB, sedentary behavior.

prostate cancer ($P_{interaction} = 0.65$) were influenced by adjustment for leisure-time physical activity.

Particular attention was given to examine whether obesity represents an intermediate step in the causal pathway potentially linking prolonged sedentary behavior to aggressive prostate cancer, because there is ongoing debate about the directionality of the sedentary behavior and obesity relation. The vast majority of investigations show a positive relation between sedentary behavior and obesity (34), particularly in older adults (35), and obesity represents an important risk factor for advanced (36) and fatal prostate cancer (37). In contrast, one study showed that markers of obesity at baseline predicted adults' sedentary time at follow-up but not vice versa (38), but studies investigating children's and adolescent's sedentary behavior largely show that weight gain and adiposity are a consequence of prolonged sedentary behavior (39), likely persisting into adulthood. That prolonged sedentary behavior affects prostate cancer risk through a mechanism involving weight control is supported by a large prospective analysis (31) showing a suggestive positive relation of sedentary behavior to prostate cancer (RR = 1.28; 95% CI, 0.98–1.69) that was restricted to obese men ($P_{interaction} = 0.02$). That previous observation coupled with current findings from our meta-analysis indicates that the association between sedentary behavior and prostate cancer may be at least partly mediated by obesity and its metabolic sequelae. To formally test this mediation hypothesis, analysis of studies with repeated measurements of sedentary behavior and obesity is needed.

Underlying biologic mechanisms are speculative but may involve metabolic and hormonal perturbations resulting from the combined effects of sedentary behavior, obesity, and adiposity-associated insulin resistance (40). TV viewing is associated with increased serum concentrations of insulin (41), and replacing sedentary behaviors with standing or stepping is related to decreased insulin concentrations (42), even after adjustment for BMI. Chronic hyperinsulinemia is linked to higher bioavailability of insulin-like growth factor-1 (IGF-1; ref. 43), and IGF-1 has neoplastic effects involving increased antiapoptosis and cell migration (44). Circulating levels of IGF-1 are positively associated with prostate cancer risk in epidemiologic studies (45).

In our meta-analysis, adjustment for history of PSA testing modified the relation of sedentary behavior to prostate cancer incidence. High compared with low sedentary behavior was associated with a statistically significant 12% increase in prostate cancer incidence in studies that were not adjusted for history of PSA testing, whereas the relation was null in studies with adjustment for history of PSA testing. A likely explanation for this

observation is more frequent prostate cancer diagnoses among sedentary men coinciding with greater probability of prostate cancer detection. Possibly, men with high levels of socioeconomic status, high education levels (46), and white-collar jobs (47) spend more time in occupational sitting than their blue-collar counterparts and also more frequently engage in screening practices such as PSA testing, which tracks with greater prostate cancer detection rates (48).

Our meta-analysis has some limitations. First, all underlying studies used self-administered questionnaires or interviews to assess sedentary behavior rather than objective measures such as accelerometers. In one study (21), sedentary behavior assessment was based on job titles attained by its questionnaire, which may not have accurately reflected the actual activities performed or may not have accounted for within-job variation, seasonal changes, or changes in job requirements over time. While such shortcomings may have introduced some degree of measurement error (49), nondifferential misclassification of sedentary behavior levels would have tended to underestimate but not overstate risk estimates. Second, there was a certain amount of variability in the definitions of high and low levels of sedentary behavior in the underlying studies we were unable to account for due to a lack of a sufficient number of studies with comparable doses of sedentary behavior. To account for differences in assessments of sedentary behavior across studies, we differentiated between studies that assessed sedentary time quantitatively versus those that used qualitative data (Table 2; Supplementary Table 2). In addition, we conducted extensive stratified analyses to rule out other potential sources of heterogeneity. Third, the modest number of studies on TV/video viewing, leisure-time sitting, and total daily sitting time did not permit us to conduct pooled analyses of those particular aspects of sedentary behavior. Fourth, our results are based on studies that originated from Europe and the United States and may therefore not apply globally.

Our meta-analysis also has several notable strengths. To our knowledge, it is the first comprehensive systematic review and meta-analysis with a specific focus on the link between sedentary behavior and prostate cancer, making a novel contribution to the literature. Its large sample size provided substantial statistical power and permitted us to conduct numerous informative subanalyses, including an assessment of effect modification of the relation of sedentary behavior to the clinically relevant subgroup of aggressive prostate cancer. Also, we employed a study quality score that addressed potential selection bias, misclassification, and confounding, and we examined the potential for publication bias. We excluded studies that assessed the absence of physical activity rather than the presence of sedentary behavior as the exposure of interest. We paid attention to using light activity or standing and not moderate to vigorous activity as the referent category, which avoided attributing part of the increase in risk associated with sedentary behavior to the inverse of the risk reduction related to physical activity (20). All studies included in our meta-analysis used cancer registries to confirm prostate cancer diagnoses, and mortality ascertainment was achieved by linkage to national death registries, rendering diagnostic certainty high.

Additional well-designed prospective cohort studies using objective assessments of sedentary behavior are needed to more fully understand the potential risk of prostate cancer posed by prolonged sedentary behavior. Such investigations need to take into consideration possible causal intermediates such as adiposity, potential confounding by physical activity, and detection bias operating through differences in PSA testing and digital rectal examination across levels of sedentary behavior. Such knowledge would help inform future intervention studies on interruptions in sitting time and provide evidence needed for policy makers to update and reemphasize sedentary behavior guidelines similar to what has been achieved for physical activity recommendations. Future epidemiologic research will largely rely on the results of large-scale cohort studies or harmonized analyses conducted within consortia to build reliable, sustainable evidence. In addition, further mechanistic research is warranted to examine whether sedentary behavior is related to probable epigenetic changes in high-risk molecular pathways of prostate carcinogenesis (50).

To conclude, sedentary behavior is unlikely to represent a strong independent risk factor for incident and aggressive prostate cancer. However, our results raise the possibility that prolonged sedentary behavior is related to increased risk of aggressive prostate cancer through a mechanism involving obesity, an observation that requires replication in future studies. While precise biologic mechanisms through which sedentary behavior may influence adiposity and therefore aggressive prostate carcinogenesis remain elusive, our finding represents a step toward considering sedentary behavior as a contributing risk factor to a higher risk of aggressive prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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