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Platinum Priority – Prostate Cancer

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Physical Activity and Survival After Prostate Cancer

Christine M. Friedenreich[a,b,c,*], *Qinggang Wang*[a], *Heather K. Neilson*[a], *Karen A. Kopciuk*[a,b,d], *S. Elizabeth McGregor*[b,c,e], *Kerry S. Courneya*[f]

[a] *Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada;* [b] *Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada;* [c] *Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada;* [d] *Department of Mathematics and Statistics, Faculty of Science, University of Calgary, Calgary, Alberta, Canada;* [e] *Division of Population, Public and Aboriginal Health, Alberta Health Services, Calgary, Alberta, Canada;* [f] *Faculty of Physical Education and Recreation, University of Alberta, Edmonton, Alberta, Canada*

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Abstract

Background: Despite the high global prevalence of prostate cancer (PCa), few epidemiologic studies have assessed physical activity in relation to PCa survival.
Objective: To evaluate different types, intensities, and timing of physical activity relative to PCa survival.
Design, setting, and participants: A prospective study was conducted in Alberta, Canada, in a cohort of 830 stage II–IV incident PCa cases diagnosed between 1997 and 2000 with follow-up to 2014 (up to 17 yr). Prediagnosis lifetime activity was self-reported at diagnosis. Postdiagnosis activity was self-reported up to three times during follow-up.
Outcome measurements and statistical analysis: Cox proportional hazards models related physical activity to all-cause and PCa-specific deaths and to first recurrence/progression of PCa.
Results and limitations: A total of 458 deaths, 170 PCa-specific deaths, and, after first follow-up, 239 first recurrences/progressions occurred. Postdiagnosis total activity (>119 vs ≤42 metabolic equivalent [MET]-hours/week per year) was associated with a significantly lower all-cause mortality risk (hazard ratio [HR]: 0.58; 95% confidence interval [CI], 0.42–0.79; p value for trend <0.01). Postdiagnosis recreational activity (>26 vs ≤4 MET-hours/week per year) was associated with a significantly lower PCa-specific mortality risk (HR: 0.56; 95% CI, 0.35–0.90; p value for trend = 0.01). Sustained recreational activity before *and* after diagnosis (>18–20 vs <7–8 MET-hours/week per year) was associated with a lower risk of all-cause mortality (HR: 0.66; 95% CI, 0.49–0.88). Limitations included generalisability to healthier cases and an observational study design.
Conclusions: These findings support emerging recommendations to increase physical activity after the diagnosis of PCa and would inform a future exercise intervention trial examining PCa outcomes.
Patient summary: In a 17-yr prostate cancer (PCa) survival study, men who survived at least 2 yr who were more physically active postdiagnosis or performed more recreational physical activity before and after diagnosis survived longer. Recreational physical activity after diagnosis was associated with a lower risk of PCa death.

* Corresponding author. Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Holy Cross Centre, Box ACB, 2210 2nd Street SW, Calgary, Alberta T2S 3C3 Canada. Tel. +1 403 698 8009; Fax: +1 403 264 2654.
E-mail address: christine.friedenreich@albertahealthservices.ca (C.M. Friedenreich).

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1. Introduction

In Canada, 5-yr survival from prostate cancer (PCa) is high at 81%, yet 1 in 27 men will die from PCa [1]. Worldwide in 2012, an estimated 1.1 million new PCa cases were diagnosed [2]. Given the high disease burden, there is clear interest in identifying inexpensive, noninvasive strategies for improving PCa survival.

Three studies have assessed associations between postdiagnosis physical activity and PCa progression or survival [3–5]. Kenfield et al [3] evaluated postdiagnosis activity in 2705 PCa cases over 9.7 yr on average. Risk of PCa-specific death was significantly 61% lower for men reporting ≥3 versus <1 h per week vigorous activity. Furthermore, men who maintained the highest versus lowest level of vigorous activity pre- and postdiagnosis experienced a nonsignificant 60% lower PCa mortality risk. In the second study [4], 1455 men with localised PCa were followed 22 mo on average. Men who walked briskly ≥3 versus <3 h per week had a 57% significantly lower risk of progression. A third study [5] followed 4623 localised PCa survivors up to 15 yr. Postdiagnosis moderate walking/bicycling ≥20 versus <20 min per day and moderate-vigorous exercise ≥1 versus <1 h per week were associated with 39% and 32% significantly lower risks of PCa mortality, respectively.

Given limited epidemiologic evidence relating physical activity to survival, we conducted a prospective cohort study of PCa survivors in Alberta, Canada, to identify all deaths and first recurrences/progressions of PCa. We aimed to evaluate the type, intensity, and timing of activity associated with survival, the role of occupational sedentary behaviour, and associations with physical activity changes across the diagnostic period. We hypothesised that men who were more active before and after diagnosis would survive longer. Our goal was to inform a potential phase 3 trial on this question as well as clinical recommendations for survivors.

2. Patients and methods

2.1. Participants

Cases were participants in a case-control study [6], and subsequently our case-only survival analysis, who resided in Alberta with incident, histologically confirmed, clinically significant stage II–IV invasive PCa. Incident cases were identified through the Alberta Cancer Registry (ACR) from 1997 to 2000. Eligibility included no previous cancer except nonmelanoma skin cancer, English speaking, Alberta resident, not physician excluded, and age <80 yr. Permission to contact patients was sought through referring physicians. The case-control study received ethics approval from the former Alberta Cancer Board (ACB) and the University of Calgary. All cases provided written informed consent for the cohort study, beginning in 2000, and to recontact their physicians for missing medical data.

2.2. Data collection

2.2.1. Prediagnosis lifestyle

In-person interviews on lifetime physical activity were completed on average 4.3 mo (standard deviation: 1.3) after diagnosis. The Lifetime Total Physical Activity Questionnaire (LTPAQ) [7] was administered using cognitive interviewing methods and a recall calendar to assess the frequency, duration, and intensity of occupational, household, and recreational activities from childhood until diagnosis (Supplement 1). Each respondent reported demographic and personal health information, PCa screening history, prostate conditions/surgeries, family history of cancer, lifetime smoking, and alcohol consumption. Participants reported their usual diet for the year before diagnosis [8] and usual height and weight for each decade aged 20–60 yr. The interviewer took anthropometric measurements using standardised methods and calibrated scales.

2.2.2. Vital status

Vital status was checked periodically over 14 yr from 2000 to 2014 (Fig. 1). Death information was provided monthly by Vital Statistics Alberta (a legislated population-based registry) to the ACR with cause of death from Statistics Canada. The time between actual death and reporting to ACR was 3 mo on average. For men who left Alberta postdiagnosis but remained in Canada, vital status linkages were made with other provinces. For men not known to have died, annual linkage with the Alberta Health registration file allowed for vital status determination when last residing in Alberta. For men who left Alberta and vital status was unknown by end of study, censoring time was the date of leaving Alberta.

2.2.3. Postdiagnosis lifestyle

Postdiagnosis activity was measured up to three times per participant (Fig. 1) on average 2.5, 4.7, and 6.8 yr postdiagnosis. At first follow-up, in-person interviews assessed activity undertaken since the prediagnosis activity interview using the LTPAQ modified for a shorter time frame. Cases reported diet, smoking, alcohol, and comorbidities using the same questions as at diagnosis. Anthropometric measurements were taken. In the second follow-up, physical activity since first follow-up was assessed using a mailed version of the LTPAQ that we developed and validated [9] to capture the past 1–2 yr of activity. Similarly, a third follow-up was completed by mail, querying time since last follow-up.

2.2.4. Chart abstractions

In 2002 the first medical chart review was completed and data abstracted on staging, treatments, vital status, comorbidities, non-PCa diagnoses, and recurrences/progressions. Recurrence was defined as further disease, identified through prostate-specific antigen (PSA) changes and secondary treatments, following a significant disease-free period. Recurrence date was when second-line treatment began or a decision was made not to treat. Progression occurred if PSA did not drop to undetectable levels following radical prostatectomy, if a patient's condition became progressively worse, if treatment produced no positive results, or if distant metastases at diagnosis became clinically stable and then progressed. Progression date was when increased/abnormal PSA was recorded or other diagnostic testing indicated progression. Charts were sought from ACB treatment centres and, if necessary, attending physicians. Chart abstractions were performed by ACR health record technicians with no access to physical activity data; TNM staging followed American Joint Committee on Cancer guidelines [10], and interrater reliability of abstraction was assessed. Two additional abstractions were completed in 2008 and 2014. Personalised letters were mailed to physicians or a health record technician made office visits to obtain missing chart information.

2.3. Statistical analysis

The Compendium of Physical Activities [11] was used to assign metabolic equivalent (MET) values to each self-reported activity. Individual total physical activity was estimated as the sum of

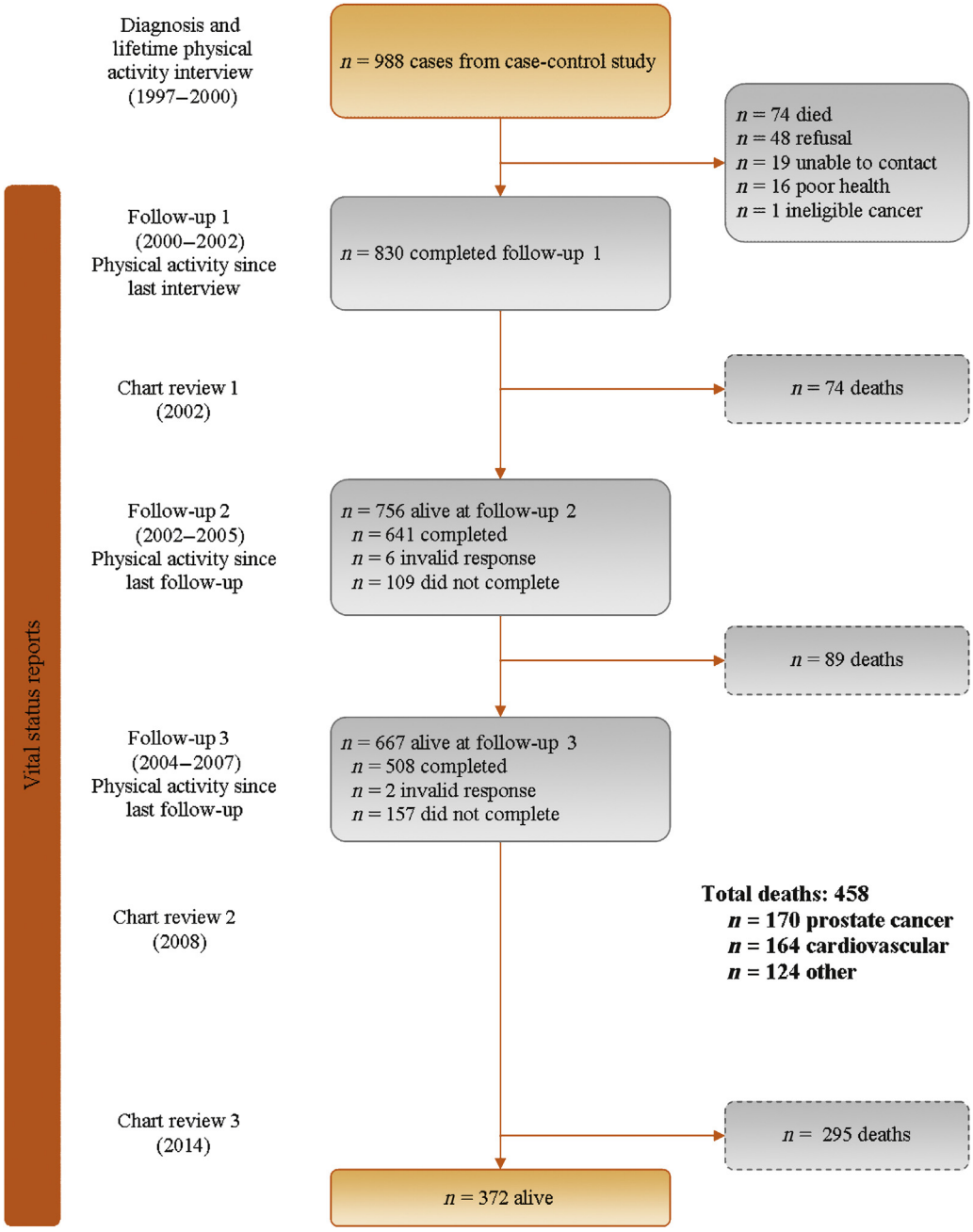

Fig. 1 – Study timeline for the Prostate Cohort Study, Alberta, Canada, 1997–2014. The number of deaths is indicated for 830 men with prostate cancer who completed the first physical activity follow-up interview.

nonsedentary occupational, household, and recreational activities. Vigorous activity was defined by a MET value ≥6 and occupational sedentary behaviour by a MET value ≤1.5. Sample size was predetermined from our case-control study [6].

Three survival outcomes—all-cause mortality, PCa-specific mortality (cause of death: "prostate gland"), and first recurrence/progression—were assessed over time by activity quartile using Kaplan-Meier survival curves and log-rank tests. Cox proportional hazards (PH) models were used to compute hazard ratios (HRs), treating pre- or postdiagnosis activity (in quartiles) as the exposure (linear tests for trend were confirmed by fitting restricted cubic splines in multivariable survival models [12] before categorising activity into quartiles [13]). The PH assumption was evaluated by including an interaction term between each activity variable and follow-up time. Fine and Gray competing risk Cox survival analyses were used [14] to assess PCa-specific mortality. Prediagnosis activity was derived from our lifetime questionnaire [7]. Postdiagnosis activity was a time-weighted average of up to three follow-up measures with missing follow-ups excluded (eg, if follow-ups 2 and 3 were missing, follow-up 1 was used). Participants with first recurrence/progression preceding follow-up 1 were excluded from recurrence/progression models. We also jointly modelled postdiagnosis activity and survival data using the JM R package (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) [15] where observed longitudinal activity at all follow-ups was explicitly modelled. Because results were similar between joint and Cox PH models, we provide only Cox PH model results.

Table 1 – Participant characteristics (1997–2000) and physical activity levels after prostate cancer diagnosis in the Prostate Cohort Study, Alberta, Canada, 1997–2014

Characteristics	All participants	All deaths	PCa deaths	First recurrence/progression[†]
No. of participants	830	458	170	239
Race (*n*, %)				
White	789 (95)	440 (96)	160 (94)	221 (92)
Other	41 (4.9)	18 (3.9)	10 (5.9)	18 (7.5)
Current married (*n*, %)	699 (84)	377 (82)	141 (83)	208 (87)
Educational level (*n*, %)				
Less than high school	258 (31)	170 (37)	62 (36)	69 (29)
High school diploma	87 (11)	40 (8.7)	12 (7.1)	26 (11)
Trade certificate	170 (20)	97 (21)	36 (21)	56 (23)
Other nonuniversity	172 (21)	81 (18)	33 (19)	52 (22)
University	143 (17)	70 (15)	27 (16)	36 (15)
Overall stage (*n*, %) [10]				
II (T1/T2, N0, M0)	642 (77)	327 (71)	98 (58)	168 (70)
III (T3, N0, M0)	57 (6.9)	24 (5.2)	9 (5.3)	16 (6.7)
III or IV (T3, NX, MX)	76 (9.2)	57 (12)	27 (16)	31 (13)
IV	55 (6.6)	50 (11)	36 (21)	24 (10)
T4, N0, M0	1 (1.7)	0 (0)	0 (0)	1 (4.0)
T4, N0/NX, M0/MX	5 (8.6)	4 (7.7)	1 (2.7)	2 (8.0)
Any T, N1, M0/MX	17 (31)	15 (30)	12 (33)	8 (32)
Any T, any N, M1	33 (60)	31 (62)	23 (64)	14 (56)
Any T, NX, MX	2 (3.4)	2 (3.8)	0 (0)	0 (0)
Gleason score (*n*, %)				
<7	317 (38)	152 (33)	29 (17)	68 (28)
7	356 (43)	190 (42)	68 (40)	110 (46)
>7	157 (19)	116 (25)	73 (43)	61 (26)
Primary treatment (*n*, %)[*]				
Prostatectomy	245 (30)	68 (15)	20 (12)	52 (22)
Radiation therapy	366 (44)	221 (48)	74 (44)	120 (50)
Hormone therapy[**]	527 (63)	335 (73)	145 (85)	172 (72)
First-degree relative history of PCa (*n*, %)	168 (20)	88 (19)	39 (23)	52 (22)
Heart disease (*n*, %)	161 (19)	105 (23)	27 (16)	42 (18)
High blood pressure (*n*, %)	271 (33)	169 (37)	59 (35)	79 (33)
Other chronic disease (*n*, %)	402 (48)	245 (53)	84 (49)	115 (48)
Smoking status (*n*, %)				
Never smoker	241 (29)	119 (26)	56 (33)	64 (27)
Occasional smoker	6 (0.7)	2 (0.4)	0 (0)	3 (1.3)
Former occasional smoker	29 (3.5)	14 (3.1)	6 (3.5)	13 (5.4)
Former smoker	444 (53)	245 (53)	84 (49)	128 (54)
Current smoker	110 (13)	78 (17)	24 (14)	31 (13)
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)
Age at diagnosis, yr	68 (62, 73)	71 (65, 75)	69 (63, 74)	68 (63, 73)
Body mass index, kg/m^2	27.7 (25.4, 30.3)	27.6 (25.4, 30.4)	28.0 (25.4, 30.8)	27.7 (25.4, 30.4)
Dietary caloric intake, kcal/d	2012 (1644, 2475)	1986 (1614, 2452)	2044 (1733, 2553)	2038 (1692, 2520)
Total lifetime alcohol intake, g/wk	37 (12, 85)	39 (12, 88)	44 (13, 105)	42 (14, 86)
Prediagnosis physical activity, MET-h/wk per year				
Total	144 (98, 198)	151 (104, 207)	147 (94, 210)	146 (94, 206)
Recreational	12.4 (6.6, 21.3)	10.8 (5.7, 19.4)	10.9 (6.5, 18.8)	12.1 (6.4, 21.6)
Nonsedentary occupational	107.3 (58.0, 159.5)	114.6 (66.7, 168.7)	102.9 (55.1, 176.3)	108.8 (52.3, 163.4)
Household	17.8 (9.0, 30.0)	17.9 (8.2, 30.6)	17.2 (8.6, 27.8)	18.6 (10.8, 30.2)
Prediagnosis vigorous physical activity, h/wk per year	5.3 (1.8, 11.5)	5.5 (1.8, 12.3)	4.8 (1.7, 13.2)	5.5 (2.2, 12.2)
Prediagnosis occupational sedentary behaviour, h/wk per year	4.5 (0.1, 12.8)	3.7 (0.0, 11.9)	3.6 (0.0, 12.1)	4.6 (0.0, 12.8)
Postdiagnosis physical activity, MET-h/wk per year				
Total	74 (42, 119)	61 (31, 98)	75 (36, 107)	80 (49, 125)
Recreational	12.8 (4.1, 26.5)	9.7 (2.5, 21.1)	9.6 (2.0, 21.8)	10.8 (3.6, 26.8)
Nonsedentary occupational	5.2 (0.0, 40.9)	0.0 (0.0, 24.0)	5.9 (0.0, 38.6)	6.4 (0.0, 46.2)
Household	29.6 (15.1, 52.2)	28.8 (13.5, 52.5)	31.1 (14.9, 56.0)	33.3 (17.5, 54.0)
Postdiagnosis vigorous activity, h/wk per year	0.0 (0.0, 1.6)	0.0 (0.0, 0.6)	0.0 (0.0, 0.7)	0.0 (0.0, 1.8)
Postdiagnosis occupational sedentary behaviour, h/wk per year	0.0 (0.0, 2.9)	0.0 (0.0, 1.5)	0.0 (0.0, 1.8)	0.0 (0.0, 2.4)

MET = metabolic equivalent; PCa = prostate cancer; Q = quartile.
Values are *n* (%) or median (quartile 1, quartile 3).
[†] First recurrence or progression; based on 723 cases (of 830) still at risk for first recurrence/progression at the time of the first postdiagnosis physical activity follow-up.
[*] Participants could have more than one treatment.
[**] Included bilateral orchiectomy, luteinising hormone-releasing hormone agonists, nonsteroidal antiandrogens, steroidal antiandrogens.

Known prognostic variables (age at diagnosis, stage, treatment) and prediagnosis activity (for postdiagnosis models) were forced into Cox PH models as covariates. Putative ones, namely, clinical Gleason score, diagnostic PSA, baseline comorbidity, first-degree relative PCa, body mass index (BMI), body weight, and variables with unknown prognostic value (marital status, education, ethnicity, residence (urban/rural), number of prediagnosis digital rectal examinations, and PSA measurements) and for all-cause mortality (prediagnosis alcohol and caloric intake) were removed sequentially based on statistical nonsignificance. For postdiagnosis activity analyses, we also assessed postdiagnosis smoking, body weight, caloric and alcohol intake, and comorbidities. We assessed interactions between physical activity and stage, hormone therapy, prostatectomy, radiation therapy, Gleason score, age, and BMI at diagnosis (continuous) by entering their cross products into multivariable Cox PH models.

All analyses were repeated to assess activity change (defined using pre- and postdiagnosis activity tertiles) over the diagnostic period. All tests for statistical significance were based on two-sided Wald tests. Analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC, USA) and R v.3.0 [16].

3. Results

Of 988 cases in the case-control study [6], one was an ineligible cancer and 830 participated in the first follow-up

Table 2 – All-cause and prostate cancer (PCa)–specific mortality in relation to physical activity postdiagnosis[§] of PCa in the Prostate Cohort Study, Alberta, Canada, 1997–2014

Quartiles of postdiagnosis physical activity	All-cause deaths/ cases	Multivariable adjusted HR (95% CI)[†]	PCa deaths/ cases	Multivariable adjusted HR (95% CI)[‡]
Total physical activity, MET-h/wk per year				
≤42	158/207	1.0	49/207	1.0
>42 to ≤73	116/208	0.72 (0.56–0.93)	34/208	0.66 (0.42–1.05)
>73 to ≤119	109/207	0.74 (0.57–0.97)	53/207	1.02 (0.64–1.61)
>119	75/208	0.58 (0.42–0.79)	34/208	0.65 (0.37–1.13)
p value for trend		<0.01		0.4
Recreational physical activity, MET-h/wk per year				
≤4	144/207	1.0	57/207	1.0
>4 to ≤13	123/208	0.79 (0.61–1.02)	45/208	0.74 (0.49–1.12)
>13 to ≤26	99/208	0.65 (0.50–0.85)	34/208	0.61 (0.39–0.95)
>26	92/207	0.64 (0.48–0.84)	34/207	0.56 (0.35–0.90)
p value for trend		<0.01		0.01
Nonsedentary occupational physical activity, MET-h/wk per year				
0	231/337	1.0	71/337	1.0
>0 to ≤16	84/162	0.84 (0.65–1.09)	28/162	0.91 (0.59–1.40)
>16 to ≤53	84/163	0.98 (0.75–1.28)	38/163	1.12 (0.71–1.77)
>53	59/168	0.65 (0.47–0.91)	33/168	0.90 (0.53–1.55)
p value for trend		0.04		0.9
Household physical activity, MET-h/wk per year				
≤15	132/208	1.0	43/208	1.0
>15 to ≤30	107/207	0.72 (0.55–0.93)	36/207	0.73 (0.46–1.17)
>30 to ≤52	101/207	0.72 (0.55–0.95)	40/207	0.90 (0.57–1.40)
>52	118/208	0.89 (0.69–1.16)	51/208	1.04 (0.67–1.63)
p value for trend		0.5		0.6
Vigorous physical activity, h/wk per year				
0	299/457	1.0	111/457	1.0
>0 to 1.0	59/123	0.68 (0.51–0.90)	19/123	0.68 (0.41–1.12)
1.0–3.5	59/124	0.86 (0.64–1.15)	19/124	0.70 (0.42–1.16)
>3.5	41/126	0.65 (0.46–0.92)	21/126	0.73 (0.45–1.20)
p value for trend		0.01		0.09
Occupational sedentary behaviour, h/wk per year				
0	308/482	1.0	111/482	1.0
>0 to 2.4	55/114	0.72 (0.54–0.98)	20/114	0.67 (0.40–1.11)
2.4–7.9	58/115	0.96 (0.72–1.29)	22/115	0.94 (0.59–1.52)
>7.9	37/119	0.72 (0.50–1.05)	17/119	0.66 (0.37–1.18)
p value for trend		0.11		0.19

CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent; PCa = prostate cancer; PSA = prostate-specific antigen.

[§] For 830 men who lived at least 2 yr after diagnosis of PCa.

[†] Estimates for total physical activity were adjusted for age at diagnosis, overall stage (II, III, III/IV, IV), treatment (prostatectomy, radiation therapy, hormone therapy), Gleason score, PSA level, region (urban vs rural), number of times had PSA test done (never/once/twice or more), total pack-years of smoking at diagnosis, postdiagnosis total pack-years of smoking, prediagnosis total physical activity, postdiagnosis comorbidity (Charlson Comorbidity Score), and time to any first recurrence/progression of PCa. Models of each subtype of activity were further adjusted for the other types of activity; for vigorous activity or sedentary behaviour, the models were mutually adjusted for nonvigourous activity or nonsedentary behaviour, respectively. Variables were treated as continuous unless otherwise specified.

[‡] Estimates for total physical activity were adjusted for age at diagnosis, overall stage (II, III, III/IV, IV), treatment (prostatectomy, radiation therapy, and hormone therapy), Gleason score, region (urban vs rural), number of times had PSA test done (never/once/twice or more), prediagnosis total physical activity, postdiagnosis comorbidity (Charlson Comorbidity Score), and time to any first recurrence or progression of PCa. Models of each subtype of activity were further adjusted for the other types of activity; for vigorous activity or sedentary behaviour, the models were mutually adjusted for nonvigorous activity or nonsedentary behaviour, respectively. Variables were treated as continuous unless otherwise specified. For the outcome of PCa death, a competing risk survival analysis was used based on the Fine and Gray method [12]; deaths from other causes constituted the competing event.

(Fig. 1). Compared with 157 nonparticipants ($n = 74$ died, $n = 16$ poor health), participants on average had significantly lower stage cancer and Gleason scores. Of 830 cases, 458 deaths and 170 PCa-specific deaths were identified up to 2014. The leading cause of non-PCa death ($n = 288$) was cardiovascular disease (48%). Of 723 men with no recurrence/progression before first postdiagnosis follow-up, 239 first recurrences/progressions were identified. Follow-up was 100% for mortality and 96.5% for first recurrences/progressions. Median time from diagnosis to censoring/end of follow-up was 15.5 yr for survivors. Median survival time was 14.1 yr; 5-yr survival was 88%. The earliest death occurred 2.1 yr postdiagnosis. The median time between final activity follow-up and death was 3.0 yr (6 d to 12.7 yr) and for first recurrences/progressions was 1.1 yr (same day to 9 yr). At baseline, mean age was 67.3 yr, men were mainly overweight, 13% were current smokers, and most had stage II cancer (77%) (Table 1).

Multivariable-adjusted models revealed no consistent associations between lifetime prediagnosis activity and any outcome (Supplementary Tables 1–3). Postdiagnosis total activity >119 versus ≤42 MET-hours/week per year was associated with a 42% significantly lower risk of all-cause mortality (Table 2) (p value for trend <0.01). Kaplan-Meier curves were clearly differentiated between low versus high quartiles showing survival benefit in the higher activity group approximately 5 yr postdiagnosis for all-cause mortality ($p < 0.001$, log-rank test) and PCa-specific mortality ($p = 0.002$, log-rank test) (Fig. 2). All-cause mortality was significantly decreased in multivariable-adjusted models by approximately 35% with more postdiagnosis recreational activity (>13 vs ≤4 MET-hours/week per year; p value for trend <0.01), nonsedentary occupational activity (>53 vs 0 MET-hours/week per year; p value for trend = 0.04), or vigorous activity >3.5 versus 0 hours/week per year (p value for trend = 0.01) (Table 2). In a Fine and Gray competing risk analysis [12], risk of PCa-specific deaths was significantly decreased by approximately 40% comparing >13 versus ≤4 MET-hours/week per year recreational activity (p value for trend = 0.01) (Table 2). No convincing interactions were found. Excluding men diagnosed with distant metastasis or excluding men assessed within 12 mo of death somewhat attenuated linear trends that were statistically significant in primary analyses (Table 3), but inverse associations remained. No consistent associations were found between postdiagnosis activity and risk of first recurrence/progression (Supplementary Table 4).

Survival was assessed across four patterns of activity change. Crude/unadjusted relations with recreational activity are depicted in Figure 3. The consistently active subgroup (Supplementary Table 5), reporting >18–20 MET-hours/week per year recreational activity pre- and postdiagnosis, experienced the highest overall survival starting

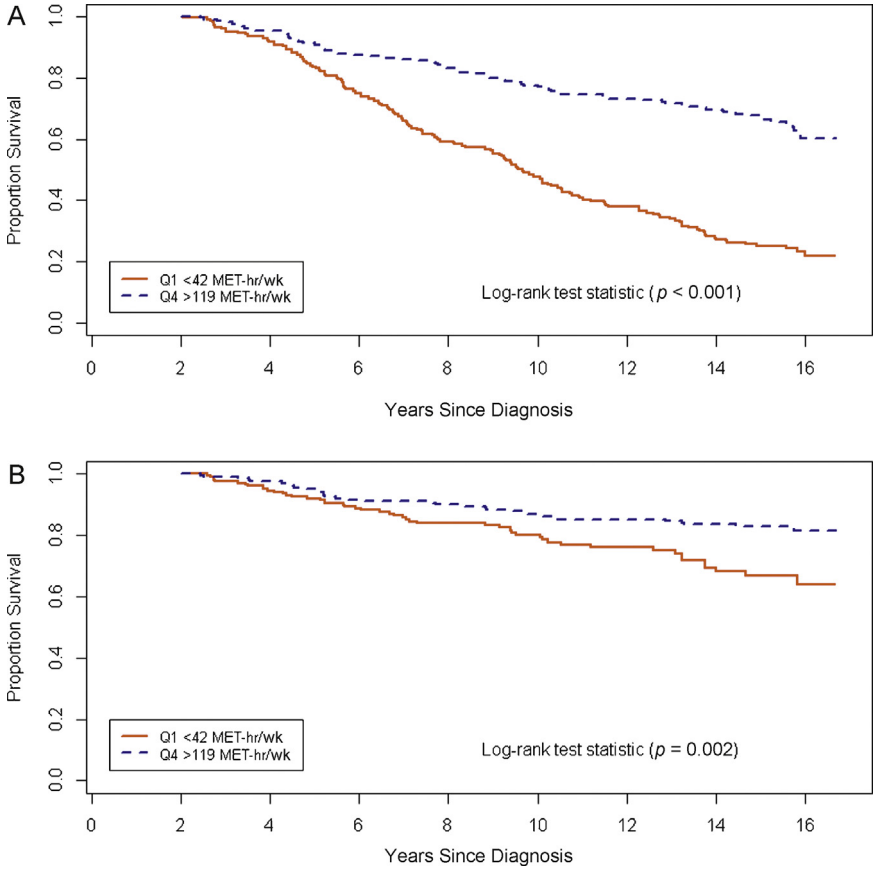

Fig. 2 – Kaplan-Meier curves for postdiagnosis total physical activity in relation to (A) all-cause mortality and (B) prostate cancer–specific death in the Prostate Cohort Study, Alberta, Canada, 1997–2014.
MET = metabolic equivalent; Q = quartile.

Table 3 – Sensitivity analyses of statistically significant physical activity variables in the primary analysis,[§] Prostate Cohort Study, Alberta, Canada, 1997–2014

Quartiles of postdiagnosis physical activity	All-cause deaths/ cases	Multivariable adjusted HR (95% CI)[†]	PCa deaths/ Cases	Multivariable adjusted HR (95% CI)[‡]
Exclude 33 men with distant metastasis at diagnosis: *n* = 797				
Total physical activity, MET-h/wk per year				
≤42	147/199	1.0	40/199	1.0
>42 to ≤74	111/200	0.80 (0.62–1.03)	31/200	0.73 (0.45–1.19)
>74 to ≤119	101/199	0.77 (0.59–1.01)	47/199	1.09 (0.67–1.76)
>119	68/199	0.59 (0.42–0.81)	29/199	0.72 (0.40–1.29)
p value for trend		<0.01		0.6
Recreational physical activity, MET-h/wk per year				
≤4	135/199	1.0	48/199	1.0
>4 to ≤13	113/199	0.82 (0.63–1.07)	39/199	0.78 (0.50–1.24)
>13 to ≤27	93/199	0.69 (0.52–0.90)	29/199	0.65 (0.40–1.05)
>27	86/200	0.68 (0.50–0.91)	31/200	0.67 (0.41–1.09)
p value for trend		<0.01		0.07
Nonsedentary occupational physical activity, MET-h/wk per year				
0	217/322	1.0	61/322	1.0
>0 to ≤17	79/157	0.86 (0.66–1.13)	25/157	1.02 (0.64–1.61)
>17 to ≤54	79/157	0.94 (0.71–1.23)	33/157	1.12 (0.70–1.79
>54	52/161	0.62 (0.43–0.88)	28/161	0.94 (0.53–1.69)
p value for trend		0.02		1
Vigorous physical activity, h/wk per year				
0	277/434	1.0	95/434	1.0
>0 to 1.0	57/120	0.68 (0.51–0.91)	17/120	0.67 (0.40–1.15)
1.0–3.5	53/118	0.82 (0.61–1.12)	14/118	0.62 (0.35–1.12)
>3.5	40/125	0.66 (0.47–0.94)	21/125	0.86 (0.52–1.42)
p value for trend		0.01		0.2
Exclude 68 physical activity assessments done within 12 mo of death: *n* = 804[*]				
Total physical activity, MET-h/wk per year				
≤42	148/201	1.0	42/201	1.0
>42 to ≤74	112/201	0.80 (0.62–1.04)	32/201	0.77 (0.48–1.23)
>74 to ≤118	105/201	0.81 (0.62–1.07)	51/201	1.23 (0.76–1.98)
>118	67/201	0.58 (0.42–0.81)	30/201	0.74 (0.41–1.32)
p value for trend		<0.01		0.7
Recreational physical activity, MET-h/wk per year				
≤4	137/201	1.0	54/201	1.0
>4 to ≤13	111/201	0.85 (0.66–1.10)	37/201	0.68 (0.44–1.07)
>13 to ≤27	97/201	0.72 (0.55–0.94)	31/201	0.59 (0.37–0.94)
>27	87/201	0.70 (0.52–0.94)	33/201	0.66 (0.42–1.06)
p value for trend		0.01		0.05
Nonsedentary occupational physical activity, MET-h/wk per year				
0	220/326	1.0	65/326	1.0
>0 to ≤16	80/158	0.83 (0.64–1.10)	26/158	0.90 (0.58–1.41)
>16 to ≤53	79/158	0.94 (0.71–1.24)	34/158	1.12 (0.69–1.80)
>53	53/162	0.63 (0.45–0.90)	30/162	0.94 (0.54–1.66)
p value for trend		0.03		1
Vigorous physical activity, h/wk per year				
0	249/385	1.0	87/385	1.0
>0 to 0.9	72/119	0.76 (0.58–1.00)	26/139	0.87 (0.56–1.36)
0.9–3.3	67/137	0.82 (0.62–1.09)	18/137	0.61 (0.35–1.06)
>3.3	44/143	0.70 (0.49–0.98)	24/143	0.83 (0.51–1.35)
p value for trend		0.02		0.18

CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent; PCa = prostate cancer; PSA = prostate-specific antigen.

[§] For men who lived at least 2 yr after diagnosis of PCa.

[†] Estimates for total physical activity were adjusted for age at diagnosis, overall stage (II, III, III/IV, IV), treatment (prostatectomy, radiation therapy, hormone therapy), Gleason score, PSA level, region (urban vs rural), number of times had PSA test done (never, once, twice or more), total pack-years of smoking at diagnosis, postdiagnosis total pack-years of smoking, prediagnosis total physical activity, postdiagnosis comorbidity (Charlson Comorbidity Score), and time to any first recurrence/progression of PCa. Models of each subtype of activity were further adjusted for the other types of activity (recreational, household, occupational); for vigorous activity the models were mutually adjusted for nonvigorous activity. Variables were treated as continuous unless otherwise specified.

[‡] Estimates for total physical activity were adjusted for age at diagnosis, overall stage (II, III, III/IV, IV), treatment (prostatectomy, radiation therapy and hormone therapy), Gleason score, region (urban vs rural), number of times had PSA test done (never, once, twice or more), prediagnosis total physical activity, postdiagnosis comorbidity (Charlson Comorbidity Score), and time to any first recurrence or progression of PCa. Models of each subtype of activity were further adjusted for the other types of activity (recreational, household, occupational); for vigorous activity, the models were mutually adjusted for nonvigorous activity. Variables were treated as continuous unless otherwise specified. For the outcome of PCa death, a competing risk survival analysis was used based on the Fine and Gray method [12]; deaths from other causes constituted the competing event.

[*] *n* = 26 men had only one assessment.

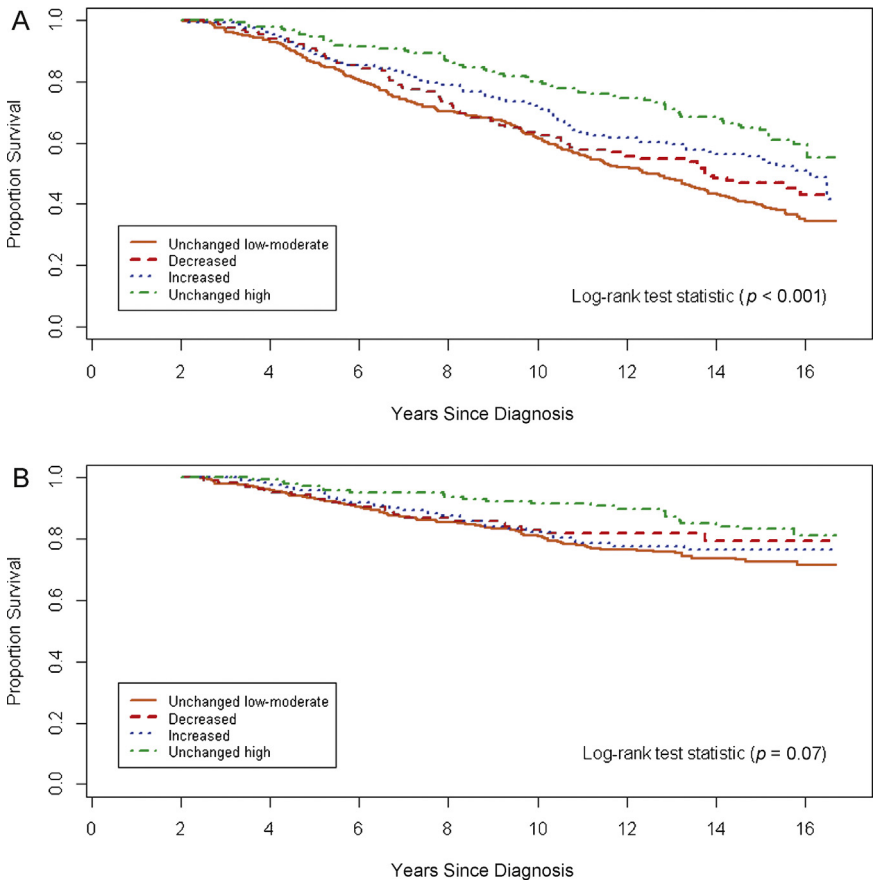

Fig. 3 – Kaplan-Meier survival curves for change in recreational physical activity from prediagnosis to postdiagnosis of prostate cancer (PCa) in relation to (A) all-cause mortality and (B) PCa-specific mortality in the Prostate Cohort Study, Alberta, Canada, 1997–2014. Subgroups were defined based on tertiles of average physical activity before and after diagnosis; high represents the highest tertile, and low-moderate represents the lowest and middle tertiles (defined in Supplementary Table 5). Postdiagnosis activity represents average activity across follow-up questionnaires 1, 2, and 3 (for participants who did not complete three assessments, the average was derived from one or two assessments).

4–5 yr postdiagnosis, which was significantly higher than for men remaining less active (HR: 0.66; 95% confidence interval, 0.49–0.88) (Supplementary Table 6). Although the consistently active subgroup also experienced the lowest risk of PCa-specific mortality, risk was not statistically significantly different from the consistently inactive subgroup (Supplementary Table 6).

4. Discussion

Men diagnosed with stage II–IV PCa who survived at least 2 yr and reported higher total activity, occupational activity, or vigorous activity experienced statistically significant lower risks of all-cause mortality over 15.5 yr. Postdiagnosis recreational activity was associated with significantly lower risks of all-cause and PCa-specific mortality. Men who were the most recreationally active before *and* after diagnosis experienced the lowest risk of all-cause mortality (and PCa mortality, although not statistically significant).

The inverse association between total activity and all-cause mortality may have been influenced by cardiovascular deaths, which were prevalent in our study and others [17,18] and are preventable with exercise [19]. We also showed that men maintaining high recreational activity levels pre- and postdiagnosis experienced the lowest all-cause mortality rates. This finding, consistent with earlier results [3], could inform prevention counselling of family members, analogous to body weight [20,21] and smoking [22] advice. We found no statistically significant association with first recurrence/progression, unlike Richman et al who assessed a similar outcome in T1–T2 cases [4]. The reasons for discrepancy are unclear but may include different definitions of cancer progression or different disease profiles or treatments. The association with postdiagnosis recreational activity was inverse, as with PCa-specific mortality, but nonsignificant possibly because recurrence/progression models were based on a subgroup of men (n = 723).

Only recreational activity was associated with PCa-specific deaths. Studies in humans and animals have shown exercise to decrease risk of progression [4,23], and biologic mechanisms are proposed [24–26]. Bonn et al [5] found that PCa mortality was reduced with walking/bicycling or exercise but not with housework or overall recreational activity. Indirectly our findings implicate higher intensity activity in PCa survival because high volumes of occupational and household (>52–53 MET-hours/week) activity were not associated with risk of PCa death, whereas lower

volumes of recreational activity >13 MET-hours/week were associated with decreased risk. Yet the inverse association we observed between PCa survival and vigorous activity did not reach statistical significance, perhaps because few men reported vigorous activity. In previous studies, significant inverse trends were found between risk of progression and walking pace [4], and risk of PCa death and vigorous recreational activity [3]. In the latter study [3], a significant 58% risk reduction for PCa deaths was observed with ≥48 versus <3 MET-hours/week leisure-time activity (37% of MET-hours were vigorous). A comparable analysis of our data (Table 3) showed a nonsignificant 33–34% risk reduction with >27 versus ≤4 MET-hours/week recreational activity (28% of MET-hours were vigorous). To our knowledge, our study is the first to assess pre- and postdiagnosis sedentary behaviour relative to PCa survival and to show no statistically significant trend.

Relative to other studies [3,5], our longitudinal assessment of all types and intensities of activity done pre- and postdiagnosis, a long follow-up, high study power, and measurement of sedentary behaviour are study strengths. Limitations include possible misreporting of activity that might have attenuated associations (particularly prediagnosis), a possible healthy worker effect in analysing occupational activity, measuring sedentary behaviour only in the occupational domain, and possible uncontrolled (or imprecise control for) confounding, although numerous lifestyle factors were assessed for model inclusion and were not statistically significant. Preexisting diabetes mellitus and statin use, however, were not assessed. The generalisability of our findings is limited to mainly stage II cases, patients aged <80 yr at diagnosis, and healthier patients who survived at least 2 yr (because we excluded patients unable to complete follow-up 1). Finally, reverse causation may have occurred if questionnaires assessed the same 2-yr period (approximately) when men experienced mortality-related symptoms and therefore lowered their activity. However, sensitivity analyses to assess this possibility (Table 3) supported our primary results.

5. Conclusions

Physical activity is advised for PCa patients to alleviate treatment-related side effects [27] and improve quality of life [28], especially for patients receiving androgen-deprivation therapy [29]. Some authors have advised daily physical activity and minimising sedentary behaviour [30]. It is important to note, however, that very limited epidemiologic evidence to date has investigated survival outcomes in relation to these behaviours. Consequently, findings from our study provide support for these emerging recommendations and can inform a future exercise intervention trial examining PCa outcomes.

Author contributions: Christine M. Friedenreich had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Friedenreich, McGregor, Kopciuk, Courneya.
Acquisition of data: Friedenreich, McGregor.
Analysis and interpretation of data: Wang, Kopciuk, Neilson, Friedenreich, McGregor, Courneya.
Drafting of the manuscript: Neilson, Friedenreich, Kopciuk, Wang.
Critical revision of the manuscript for important intellectual content: Neilson, Friedenreich, Kopciuk, Courneya, McGregor.
Statistical analysis: Wang, Kopciuk.
Obtaining funding: Friedenreich, Courneya, McGregor, Kopciuk.
Administrative, technical, or material support: Friedenreich, McGregor, Kopciuk.
Supervision: Friedenreich, McGregor, Kopciuk.
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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.eururo.2015.12.032.

References

[1] Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015. Canadian Cancer Society Web site. https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf

[2] International Agency for Research on Cancer and Cancer Research UK. World cancer factsheet. Cancer Research UK Web site. http://publications.cancerresearchuk.org/downloads/Product/CS_REPORT_WORLD.pdf

[3] Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol 2011;29:726–32.

[4] Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res 2011;71:3889–95.

[5] Bonn SE, Sjolander A, Lagerros YT, et al. Physical activity and survival among men diagnosed with prostate cancer. Cancer Epidemiol Biomarkers Prev 2015;24:57–64.

[6] Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-control study of lifetime total physical activity and prostate cancer risk. Am J Epidemiol 2004;159:740–9.
[7] Friedenreich CM, Courneya KS, Bryant HE. The lifetime total physical activity questionnaire: development and reliability. Med Sci Sports Exerc 1998;30:266–74.
[8] Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
[9] Friedenreich CM, Courneya KS, Neilson HK, et al. Reliability and validity of the Past Year Total Physical Activity Questionnaire. Am J Epidemiol 2006;163:959–70.
[10] American Joint Committee on Cancer. AJCC cancer staging manual. ed. 5 Philadelphia, PA: Lippincott-Raven; 1997.
[11] Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–81.
[12] Li R, Hertzman E, Louie M, Chen L, Spiegelman D. SAS LGTPHCURV9 macro. Harvard School of Public Health Web site. http://www.hsph.harvard.edu/donna-spiegelman/software/lgtphcurv9/
[13] Harrell Jr FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst 1988;80:1198–202.
[14] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Statist Assoc 1999;94:496–509.
[15] Rizopoulos D. JM: An R package for the joint modelling of longitudinal and time-to-event data. J Stat Softw 2010;35:1–33.
[16] R Core Team. R: A language and environment for statistical computing. 3.0 ed. Vienna, Austria: R Foundation for Statistical Computing; 2014.
[17] Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104:1335–42.
[18] Shikanov S, Kocherginsky M, Shalhav AL, Eggener SE. Cause-specific mortality following radical prostatectomy. Prostate Cancer Prostatic Dis 2012;15:106–10.
[19] Scott JM, Koelwyn GJ, Hornsby WE, et al. Exercise therapy as treatment for cardiovascular and oncologic disease after a diagnosis of early-stage cancer. Semin Oncol 2013;40:218–28.
[20] Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2011;4:486–501.
[21] Chalfin HJ, Lee SB, Jeong BC, et al. Obesity and long-term survival after radical prostatectomy. J Urol 2014;192:1100–4.
[22] Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA 2011;305:2548–55.
[23] Esser KA, Harpole CE, Prins GS, Diamond AM. Physical activity reduces prostate carcinogenesis in a transgenic model. Prostate 2009;69:1372–7.
[24] Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun 2013;30(Suppl):S75–87.
[25] Wekesa A, Harrison M, Watson RW. Physical activity and its mechanistic effects on prostate cancer. Prostate Cancer Prostatic Dis 2015;18:197–207.
[26] Jones LW, Antonelli J, Masko EM, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. J Appl Physiol (1985) 2012;113:263–72.
[27] Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol 2014;32:335–46.
[28] Baumann FT, Zopf EM, Bloch W. Clinical exercise interventions in prostate cancer patients–a systematic review of randomized controlled trials. Support Care Cancer 2012;20:221–33.
[29] Winters-Stone KM, Beer TM. Review of exercise studies in prostate cancer survivors receiving androgen deprivation therapy calls for an aggressive research agenda to generate high-quality evidence and guidance for exercise as standard of care. J Clin Oncol 2014;32:2518–9.
[30] Chan JM, Van Blarigan EL, Kenfield SA. What should we tell prostate cancer patients about (secondary) prevention? Curr Opin Urol 2014;24:318–23.