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Association of physical activity with overall mortality among long-term testicular cancer survivors: A longitudinal study

Lene Thorsen[1,2] | Kerry S. Courneya[3] | Jostein Steene-Johannessen[4] | Jon Michael Gran[5] | Hege S. Haugnes[6,7] | Helene F. S. Negaard[8] | Cecilie E. Kiserud[1] | Sophie D. Fosså[1,9]

[1]National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway

[2]Department of Clinical Service, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway

[3]Faculty of Kinesiology, Sport and Recreation, University of Alberta, Edmonton, Canada

[4]Department of Sports Medicine, Norwegian School of Sports Sciences, Oslo, Norway

[5]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

[6]Department of Oncology, University Hospital of North Norway, Tromsø, Norway

[7]Institute of Clinical Medicine, University of Tromsø – The Arctic University, Tromsø, Norway

[8]Department of Oncology, Oslo University Hospital, Oslo, Norway

[9]Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence
Lene Thorsen, National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Division of Cancer Medicine, Oslo University Hospital, Postbox 4953 Nydalen, 0424 Oslo, Norway.
Email: lka@ous-hf.no

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Abstract

Physical activity (PA) has been associated with reduced mortality among cancer survivors, but no study has focused on testicular cancer survivors (TCSs). We aimed to investigate the association of PA measured twice during survivorship with overall mortality in TCSs. TCSs treated during 1980 to 1994 participated in a nationwide longitudinal survey between 1998 to 2002 (S1: n = 1392) and 2007 to 2009 (S2: n = 1011). PA was self-reported by asking for the average hours per week of leisure-time PA in the past year. Responses were converted into metabolic equivalent task hours/week (MET-h/wk) and participants were categorized into: Inactives (0 MET-h/wk), Low-Actives (2-6 MET-h/wk), Actives (10-18 MET-h/wk) and High-Actives (20-48 MET-h/wk). Mortality from S1 and S2, respectively, was analyzed using the Kaplan-Meier estimator and Cox proportional hazards models until the End of Study (December 31, 2020). Mean age at S1 was 45 years (SD 10.2). Nineteen percent (n = 268) of TCSs died between S1 and EoS, with 138 dying after S2. Compared to Inactives at S1, the mortality risk among Actives was 51% lower (HR 0.49, 95% CI: 0.29-0.84) with no further mortality reduction among High-Actives. At S2, the mortality risk was at least 60% lower among the Actives, High-Actives and even the Low-Actives compared to the Inactives. Persistent Actives (≥10 MET-h/wk at S1 and S2) had a 51% lower mortality risk compared to Persistent Inactives (<10 MET-h/wk at S1 and S2; HR 0.49, 95% CI: 0.30-0.82). During long-term survivorship after TC treatment, regular and maintained PA were associated with an overall mortality risk reduction of at least 50%.

KEYWORDS
long-term testicular cancer survivors, overall mortality, physical activity

Abbreviations: CHEMO, chemotherapy; CRN, Cancer Registry of Norway; EoS, End of Study; MET, metabolic equivalent task; MET-h/wk, metabolic equivalent task hours per week; NTCP, Norwegian Testicular Cancer Project; PA, physical activity; RAD, radiotherapy; S1, Survey 1; S2, Survey 2; TC, testicular cancer; TCSs, testicular cancer survivors; WHO, World Health Organization.

What's new?

Testicular cancer survivors have increased risk of cardiovascular disease, second cancers and premature death. Regular physical activity has been shown to reduce overall mortality among cancer survivors. This longitudinal nationwide survey is the first study to investigate the association between physical activity and overall mortality among testicular cancer survivors. Compared to physically inactive testicular cancer survivors, physically active testicular cancer survivors treated between 1980 and 1994 had a reduced overall mortality risk of 50%. Clinicians and testicular cancer survivors should be aware of the association between physical activity and reduced risk of mortality during testicular cancer survivorship.

1 | INTRODUCTION

Testicular cancer (TC) is the most common malignancy among men during adolescence and young adulthood. With a median age of 36 years at diagnosis and a current 15-year relative survival rate of more than 98%,[1] TC survivors (TCSs) have long life-expectancy. Studies, however, indicate that modern TC treatment increases the risk of cardiovascular disease, second cancer and premature mortality.[2-7]

While physical activity (PA) has been associated with reduced risk of recurrence and improved survival after breast, prostate and colorectal cancer,[8,9] no studies have focused on PA and mortality in TCSs.[10] Moreover, it is unknown whether increasing levels of PA during TC survivorship reduce the risk of death among TCSs, or how change in PA during TC survivorship is associated with mortality.

The *Norwegian Testicular Cancer Project* (*NTCP*)[11] is a nation-wide longitudinal study, which has collected data among long-term TCSs on adverse health outcomes, health-related quality of life and lifestyle. The *NTCP* provides the opportunity to explore the association between levels of PA and overall mortality in TCSs. The primary aim of our study was to investigate if rising levels of PA, measured at two different time-points during TC survivorship, predicts decreasing risk of overall mortality. The secondary aim was to explore the association between change in PA during survivorship and overall mortality.

2 | MATERIALS AND METHODS

2.1 | Study population and design

The Cancer Registry of Norway (CRN) identified TCSs treated for unilateral germ cell TC between 1980 and 1994. These TCSs were invited to complete a questionnaire at three surveys. The responses of the two first surveys, Survey 1 [S1]: 1998 to 2002 and Survey 2 [S2]: 2007 to 2009, provide data for the current study.[11] The study population is described in detail previously.[2,12] Dependent on histology and stage, postorchiectomy treatment consisted of no further therapy or retroperitoneal lymph node dissection (SURGERY-group), abdominal radiotherapy only (RAD-group), or platinum-based chemotherapy with or without major surgery or radiotherapy (CHEMO-group).

2.2 | Physical activity assessments

Regular PA was assessed by the Nord-Trondelag Health Study Physical Activity Questionnaire (HUNT 2 PA-Q) (HUNT – Trøndelag Health Study – NTNU) consisting of one question asking for the average hours per week during leisure time spent on two PA intensity levels during the last year (Figure S1). The descriptor "not sweaty/breathless" was considered to describe light to moderate PA, corresponding to a metabolic equivalent task (MET)-value of 4, whereas "sweaty/breathless" described vigorous PA, corresponding to a MET-value of 8. We assigned the time spent on PA for the <1 h/wk category to be 0.5 hours, for the 1 to 2 hours to be 1.5 hours and for the ≥3 hours to be 4 hours.

For each intensity level, the MET hours per week (MET-h/wk) were calculated by multiplying the corresponding MET-value with the assigned hours spent, resulting in 0, 2, 6 and 16 MET-h/wk for light to moderate PA, and 0, 4, 12 and 32 MET-h/wk for vigorous PA. The total weekly amount of PA per TCS was estimated by summing-up the two MET-h/wk values of each intensity level, thus providing 16 possible MET-h/wk values. TCSs with missing responses to both PA intensity levels were excluded from all analyses. When only one of the responses was missing, we assumed 0 hours at that intensity level when calculating total PA.

Based on the World Health Organization (WHO) PA guidelines for adults, that is, 150 to 300 min/week of moderate intensity PA or 75 to 150 min/wk of vigorous intensity PA or a combination (equivalent to ~10-20 MET-h/wk),[13] the TCSs were categorized into four PA groups;

- *Inactives*: 0 MET-h/wk
- *Low-Actives*: <10 MET-h/wk [2, 4 or 6 MET-h/wk]
- *Actives*: 10 to 20 MET-h/wk [10, 12, 14, 16 or 18 MET-h/wk]
- *High-Actives*: ≥20 MET-h/wk [20, 28, 32, 34, 38 or 48 MET-h/wk]

For each survey, TCSs were also grouped into *Overall Inactives* (Inactives and Low-actives [≤6 MET-h/wk]) and *Overall Actives* (Actives and High-Actives [≥10 MET-h/wk)].

For the analysis of PA change from S1 to S2, four categories were defined (Figure S2): *Persistent Actives* (Overall Actives at S1 and S2), *Improvers* (Overall Inactives at S1 but Overall Actives at S2), *Decliners* (Overall Actives at S1 but Overall Inactives at S2) and *Persistent Inactives* (Overall Inactives at S1 and S2).

TABLE 1 Socio-demographic, cancer-related, comorbidity and lifestyle variables by four physical activity groups at Survey 1, and total physical activity at Survey 1 and Survey 2.

	Survey 1					Survey 2
	Overall Inactives (≤6 MET-h/wk; n = 428 [31%])		Overall Actives (≥10 MET-h/wk; n = 964 [69%])			
	Inactives (0 MET-h/wk) n = 85 (6%)	Low-Actives (2-6 MET-h/wk) n = 343 (25%)	Actives (10-18 MET-h/wk) n = 462 (33%)	High-Actives (≥20 MET-h/wk) n = 502 (36%)	Total n = 1392	Total n = 1011
Age, mean (SD), years*	45.2 (10.3)	46.0 (9.6)	44.7 (10.5)	43.4 (10.2)	44.6 (10.2)	53.5 (9.8)
Partnership[a], n (%)						
Paired	64 (75)	263 (77)	350 (76)	385 (77)	1062 (76)	805 (80)
Unpaired	21 (25)	78 (23)	112 (24)	115 (23)	326 (23)	205 (20)
Education level[b], n (%)**						
High	11 (13)	104 (31)	173 (38)	246 (49)	534 (38)	343 (34)
Low	73 (87)	237 (70)	287 (62)	254 (51)	851 (61)	640 (63)
Work force participation[c], n (%)**						
Yes	68 (80)	298 (87)	426 (93)	452 (90)	1244 (89)	880 (87)
No	17 (20)	44 (13)	33 (7)	49 (10)	143 (10)	120 (12)
Age at diagnosis, mean (SD), years	34.0 (9.7)	34.4 (9.2)	33.3 (9.8)	32.3 (9.6)	33.3 (9.6)	33.1 (9.4)
Time since orch., mean (SD), years	11.6 (4.2)	12.2 (4.1)	11.9 (4.4)	11.6 (4.2)	11.9 (4.2)	19.7 (4.2)
Histology, n (%)						
Seminoma	47 (55)	169 (49)	235 (51)	246 (49)	697 (50)	486 (48)
Non-seminoma	38 (45)	174 (51)	227 (49)	256 (51)	695 (50)	525 (52)
Initial extent of the disease, n (%)						
Metastatic (Stage IMk – IV)	22 (26)	113 (33)	128 (28)	147 (29)	410 (30)	300 (30)
No metastases (Stage I)	63 (74)	230 (67)	334 (72)	355 (71)	982 (71)	711 (70)
Treatment groups, n (%)						
SURGERY-group	16 (19)	68 (20)	83 (18)	98 (20)	265 (19)	204 (20)
RAD-group	44 (52)	130 (38)	209 (45)	213 (42)	596 (43)	416 (41)
CHEMO-group	25 (29)	145 (42)	170 (37)	191 (38)	531 (38)	391 (39)
≥1 major somatic co-morbidity[d], n (%)						
Yes	7 (8)	35 (10)	35 (8)	51 (10)	128 (9)	209 (21)
No	78 (92)	308 (90)	427 (92)	451 (90)	1264 (91)	802 (79)
	n = 85 (6%)	*n* = 343 (25%)	*n* = 462 (33%)	*n* = 502 (36%)	*n* = 1392	*n* = 1011
BMI, mean (SD), kg/m^2	27.4 (4.7)	26.7 (4.0)	26.4 (3.8)	26.3 (3.7)	26.5 (3.9)	26.7 (3.7)
Daily smoker[e], n (%)**						
Yes	51 (62)	142 (42)	157 (34)	138 (28)	488 (35)	198 (20)
No	31 (38)	197 (58)	303 (66)	358 (72)	889 (64)	812 (80)
Hazardous alcohol use, n (%)						
Yes	21 (28)	53 (17)	82 (19)	86 (19)	242 (17)	152 (15)
No	53 (72)	264 (83)	341 (81)	377 (81)	1035 (74)	778 (77)

Note: Numbers may not add up to 1392 because of missing data and percentages may not add up to 100 because of rounding.

Abbreviations: BMI, body mass index; CHEMO, chemotherapy; MET h/wk, metabolic equivalent task hours per week; RAD, radiotherapy; S1, Survey 1.

[a]Never married, widower, separated or divorced.

[b]High-school or less.

[c]Unemployed, temporarily laid off, rehabilitation or on disability benefits.

[d]Myocardial infarction, angina pectoris, stroke, diabetes or history of none-testicular cancer.

[e]Smoking cigarettes, cigars/cigarillos and/or pipe on a daily basis.

*$P = 0.003$;

**$P < 0.001$.

TABLE 2 Association between physical activity at Survey 1 and Survey 2 and overall mortality in long term testicular cancer survivors.

	Model 1: S1			Model 2: S2		
	No. deaths/ no. total (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)	No. deaths/ no. total (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
	268/1392 (19%)			138/1011 (14%)		
Age		1.09 (1.08-1.11)	1.10 (1.08-1.11)		1.10 (1.08-1.12)	1.10 (1.08-1.12)
PA groups						
Inactives (0 MET-h/wk) (Reference)	26/85 (30.6)	1	1	11/28 (39.3)	1	1
Low-Actives (2-6 MET-h/wk)	90/343 (26.2)	0.75 (0.48-1.15)	0.94 (0.57-1.56)	26/178 (14.6)	0.39 (0.19-0.79)	0.37 (0.17-0.80)
Actives (10-18 MET-h/wk)	69/462 (14.9)	0.38 (0.24-0.60)	0.49 (0.29-0.84)	46/351 (13.1)	0.31 (0.16-0.60)	0.29 (0.14-0.60)
High-Actives (≥20 MET-h/wk)	83/502 (16.5)	0.48 (0.31-0.75)	0.71 (0.42-1.19)	55/454 (12.1)	0.31 (0.16-0.59)	0.27 (0.13-0.55)
Education level						
High (Reference)	85/534 (15.9)	1	1	44/381 (11.5)	1	1
Low	180/851 (21.2)	1.34 (1.04-1.74)	1.12 (0.85-1.47)	93/627 (14.8)	1.39 (0.97-1.99)	1.24 (0.85-1.82)
Treatment groups						
SURGERY-group (Reference)	28/265 (10.6)	1	1	17/204 (8.3)	1	1
RAD-group	142/596 (23.8)	1.62 (1.08-2.44)	1.59 (1.03-2.46)	69/416 (16.6)	1.32 (0.77-2.26)	1.29 (0.74-2.26)
CHEMO-group	98/531 (18.5)	1.90 (1.25-2.89)	1.71 (1.09-2.67)	52/391 (13.3)	1.53 (0.89-2.65)	1.37 (0.77-2.44)
≥ 1 Major somatic co-morbidity						
No (Reference)	213/1264 (16.9)	1	1	78/802 (9.7)	1	1
Yes	55/128 (43.0)	1.73 (1.27-2.35)	1.85 (1.33-2.56)	60/209 (28.7)	1.95 (1.37-2.78)	1.95 (1.35-2.83)
Daily smoker						
No (Reference)	129/889 (14.5)	1	1	101/812 (12.4)	1	1
Yes	135/488 (27.7)	2.58 (2.02-3.29)	2.22 (1.69-2.90)	37/198 (18.7)	2.16 (1.47-3.17)	2.31 (1.53-3.48)
Hazardous alcohol use						
No (Reference)	182/1035 (17.6)	1	1	100/778 (12.9)	1	1
Yes	56/242 (23.1)	1.92 (1.42-2.61)	1.61 (1.18-2.19)	27/152 (17.8)	1.88 (1.23-2.89)	1.81 (1.17-2.80)

Abbreviations: CHEMO, chemotherapy; CI, confidence interval; HR, hazard ratio; MET-h/wk, MET-hours/week; No, number; PA, physical activity; RAD, radiotherapy.

[a]Overall mortality model is adjusted for age at S1, education, treatment, major somatic co-morbidity, smoking and hazardous alcohol use.

[b]Overall mortality model is adjusted for education, treatment and hazardous alcohol use at S1; and age, major somatic co-morbidity and smoking at S2.

2.3 | Outcome

The outcome of the study was overall mortality from S1 and S2, respectively, to End of Study (EoS: December 31, 2020). For each TCS, the CRN provided the date of last observation, that is, death, emigration or EoS, whichever occurred first. The postsurvey observation times ranged from the date of S1 or S2 until date of last observation.

2.4 | Other covariates

The multivariable models were adjusted for confounding factors including age at S1 or S2, level of education (high [college or university] vs low [high-school or less]); self-reported major somatic co-morbidity (≥1 of the following myocardial infarction, angina pectoris, stroke, diabetes, history of non-TC cancer; yes vs no); current daily smoking (yes vs no); hazardous alcohol use (yes vs no)[14]; and treatment groups (SURGERY-group vs RAD-group vs CHEMO-group). Due to the well-known correlation between treatment and histology and initial stage, treatment was the only independent variable included in the multivariable models.

2.5 | Statistics

Descriptive statistics were presented by means and SDs for continuous variables, and by absolute numbers and percentages for categorical variables. Using the Kaplan-Meier estimator, crude overall mortality rates were studied for the four PA groups after S1 and S2 respectively, and after S2 the mortality rates were studied for PA change. The log-rank test was used for assessment of differences between groups. Three multivariable Cox proportional hazards regression models were applied to estimate the association between overall mortality and levels of PA at S1, levels of PA at S2 and PA changes

from S1 to S2, adjusted for other covariates. For the multivariable adjusted analyses only HR's for PA groups should be interpreted. Other HR's are only included for comparison with unadjusted HR's. The proportional hazard assumptions were not violated as tested by the estat phtest command in Stata version 17.0. The other statistical analyses were performed using SPSS for Windows, version 26.

3 | RESULTS

TCSs: At S1, 1437 TCSs completed the questionnaire (response rate 79%), of whom 45 were excluded from all analyses due to missing responses to both PA intensity categories (Figure S3). Age and cancer-related variables were similar among the 1392 S1 evaluable participants and the 376 nonresponders (Table S1).

S1: On average 12 years had elapsed since orchiectomy (Table S2), and S1 participants were aged mean 45 years (SD 10.2) (Table 1). Overall 50% had non-seminoma histology, and 19% had only had surgery. High-Actives (≥20 MET-h/wk) were younger than those in the other PA groups. Compared to the other PA groups, more Inactives (0 MET-h/wk) had a low education level, were out of the work, and were daily smokers. In total, 31% and 69% were considered as Overall Inactives (≤ 6 MET-h/wk) and Overall Actives (≥ 10 MET-h/wk), respectively (Figure S2).

S2: At S2, on average 20 years had elapsed since orchiectomy (Table S2), and the mean age of the S2-participants was mean 54 years (SD 9.8). Twenty-one percent reported ≥1 major somatic co-morbidity, and 20% were daily smokers (Table 1). In total 20% were Overall Inactives (≤6 MET-h/wk) (Figure S2). Further, 62% of the S2-participants were categorized as Persistent Actives, with 17% Improvers, 9% Decliners and 12% Persistent Inactives (Figure S2).

PA at S1 and overall mortality: After a median post-S1 observation time of 20 years (range 0-22) (Table S2), 268 of the 1392 S1-participants (19%) had died (Table 2) (information about percentage of deaths caused by TC, secondary cancer, cardiovascular diseases and other diseases are presented in Table S3). The Kaplan-Meier plot revealed no significant difference of crude mortality rates between the Inactives and the Low-Actives, but documented a significant lower mortality rate for the Actives and for the High-Actives compared to the Inactives (Figure 1A), though without difference between the Actives and High-Actives. Results from multivariable Cox regression analysis (Table 2) confirmed the Kaplan-Meier plots: Actives (10-18 MET-h/wk) had a 51% reduced overall mortality risk compared to the Inactives (0 MET-h/wk) (HR 0.49, 95% CI: 0.29-0.84). No further mortality risk reduction emerged among the High-Actives (≥20 MET-h/wk). Increasing age, treatment with radiotherapy or chemotherapy, ≥1 co-morbidity, daily smoking, or hazardous alcohol use were also associated with increased overall mortality. Compared to the Overall Inactives (≤6 MET-h/wk), the risk of overall mortality was reduced by almost 40% among the Overall Actives (≥10 MET-h/wk) (HR 0.63, 95% CI: 0.48-0.82) (data not shown).

PA at S2 and overall mortality: After a median post-S2 observation time of 13 years (range 0 to 14) (Table S2), 138 of 1011 S2-participants (14%) had died (Table 2) (information about the percentage of deaths caused by TC, secondary cancer, cardiovascular disease and other disease are presented in Table S3). The Kaplan-Meier plot showed that each of the three active groups had lower overall mortality rates than the Inactives ($P = .001$), but without significant differences between the three active groups (Figure 1B). The

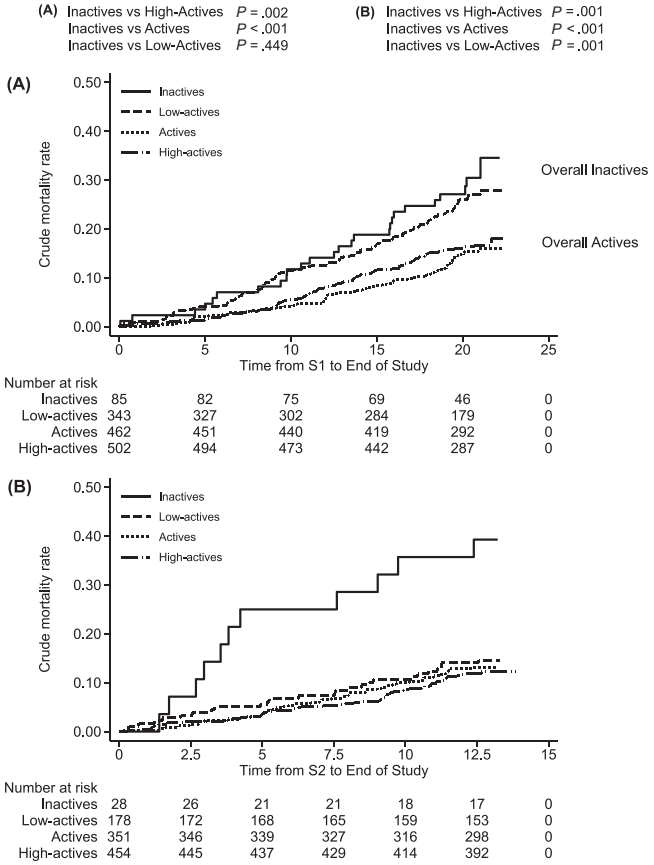

FIGURE 1 Overall mortality and physical activity at Survey 1 (A) and Survey 2 (B).

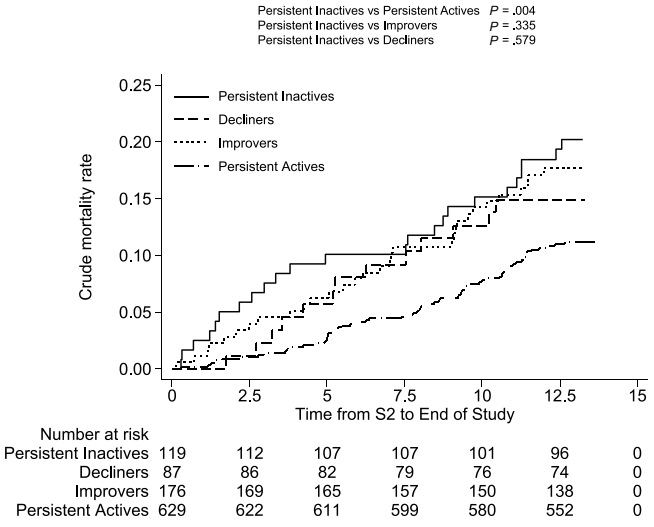

FIGURE 2 Overall mortality and change in physical activity from Survey 1 to Survey 2.

TABLE 3 Association between change in physical activity and overall mortality in long term testicular cancer survivors (Model 3) (n = 1011).

	No. deaths/no. total (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted[a] HR (95% CI)
Age		1.10 (1.08-1.12)	1.10 (1.10-1.12)
Change in PA			
Persistent inactives (Reference)	24/119 (20.2)	1	1
Decliners	13/87 (14.9)	0.77 (0.39-1.52)	0.76 (0.38-1.56)
Improvers	31/176 (17.6)	0.85 (0.50-1.45)	0.74 (0.42-1.30)
Persistent actives	70/629 (11.1)	0.52 (0.33-0-83)	0.49 (0.30-0.82)
Level of education			
High (Reference)	44/381 (11.5)	1	1
Low	93/627 (14.8)	1.39 (0.97-1.99)	1.20 (0.82-1.77)
Treatment groups			
SURGERY-group (reference)	17/204 (8.3)	1	1
RAD-group	69/416 (16.6)	1.32 (0.77-2.26)	1.40 (0.80-2.45)
CHEMO-group	52/391 (13.3)	1.53 (0.89-2.65)	1.41 (0.80-2.51)
≥1 major somatic co-morbidity			
No (Reference)	78/802 (9.7)	1	1
Yes	60/209 (28.7)	1.95 (1.37-2.78)	1.99 (1.37-2.87)
Daily smoker			
No (Reference)	101/812 (12.4)	1	1
Yes	37/198 (18.7)	2.16 (1.47-3.17)	2.21 (1.47-3.32)
Hazardous alcohol use			
No (Reference)	100/778 (12.9)	1	1
Yes	27/152 (17.8)	1.88 (1.23-2.89)	1.79 (1.16-2.76)

Abbreviations: CHEMO, chemotherapy; CI, confidence interval; HR, hazard ratio; No, number; PA, physical activity; RAD, radiotherapy.
[a]Overall mortality models are adjusted for education, treatment and hazardous alcohol use at S1; and age, major somatic co-morbidity and smoking at S2.

Cox regression analysis showed a reduction of overall mortality by at least 60% in the Low-Actives, Actives or High-Actives compared to the Inactives (Table 2). Previous treatment with radiotherapy or chemotherapy did no longer predict overall mortality at S2.

PA change: The Kaplan-Meier plot showed a lower crude mortality of the Persistent Actives than the Persistent Inactives ($P = .004$), without significant differences comparing the Persistent Inactives with Improvers or Decliners (Figure 2). In the multivariable Cox analysis, compared to the Persisting Inactives, a significant mortality risk reduction by 51% was observed only for the Persistent Actives (HR 0.49, 95% CI: 0.30-0.82) (Table 3).

4 | DISCUSSION

This longitudinal nation-wide survey shows that in long-term TCSs, regular and maintained PA according to the WHO recommendation (10-20 MET-h/wk) halved the risk of overall mortality 20-year post-survey compared to physically inactive. PA beyond the WHO recommendation did not further reduce the risk of death. In the subsequent survey, about 20 years after treatment, even the low active TCSs significantly reduced the mortality risk by more than 60%.

Our results confirm previous studies on PA and mortality among survivors of other cancers. In a recent meta-analysis of 51 studies, Friedenreich et al examined the association between postdiagnosis PA and overall mortality among cancer survivors.[10] Comparing high- vs low-level PA, the hazards for overall mortality varied between 0.58 and 0.79. Moreover, comparing the highest vs lowest level of post-diagnosis PA, a meta-analysis in 2014 by Schmid and Leitzmann demonstrated 48% and 42% risk reductions on mortality among breast and colorectal cancer survivors, respectively.[9] Neither review included any study on TCSs. The above findings correspond well to our study, with almost 40% risk reduction when comparing Overall Actives with Overall Inactives at S1.

Contrary to our expectation, the mortality risk was not further reduced in the High-Actives compared to the Actives. This is in line with the studies among breast cancer survivors by Holmes et al (median 38 months after diagnosis) and Sternfeld et al (within 39 months after diagnosis), demonstrating that an intermediate PA level was followed by larger reduction of mortality than the highest PA level.[15,16] Also, an upper threshold of 15 to 18 MET-h/wk seemed to be the optimal exercise level among adult survivors after childhood cancer 8 to 31 years (median 18 years) after diagnosis in the study of Scott et al.[17] Among breast cancer survivors postdiagnosis,

Friedenreich et al found a significant reduction in all-cause mortality up to 10 to 15 MET-h/wk, with less reduction associated with PA above 20 MET-h/wk.[10] In contrast, Holick et al observed a dose-response association between multiple levels of postdiagnosis PA and overall mortality in breast cancer survivors.[18] We cannot rule out that lack of a dose-response association in our study is caused by methodological weaknesses such as an imprecise self-report of PA intensity and duration, problems recalling the actual PA level over the past year and/or a small sample. On the other hand, our observation is in line with the nonlinear association observed in a recent meta-analysis among adults in the general population, demonstrating that mortality risk decreased with increasing objectively assessed PA up to a level corresponding to the WHO recommendations, and thereafter plateaued.[19]

At S2, in contrast to the results at S1, PA at the level of 2 to 6 MET-h/wk also predicted reduced mortality risk of more than 60%. At this time of assessment, the participating TCSs were almost 10 years older than at S1. Treatment no longer represented a significant covariate associated with the mortality risk, suggesting that the participants were more similar to men in the general population than earlier during survivorship. This observation should be regarded in the context of recent studies which have demonstrated reduced mortality even after light-intensity PA among elderly individuals from the general population.[20,21] In cancer survivors, one should not ignore the impact of treatment-induced premature aging, which may contribute to the effects of chronological aging.[22] These limited findings indicate a need to further study the effects of light-intensity PA on mortality in advanced age, especially in cancer survivors.

As expected, maintaining activity during TC survivorship was associated with reduced mortality compared to persistently being inactive over time. In contrast to the study of Scott et al and our expectations, we did not observe significantly decreased mortality among the Improvers,[17] though nonsignificant favorable Hazard ratios in Improvers and Decliners indicated an association.

The strengths of our nation-wide study are its longitudinal design, a post-treatment observation time of three decades and high response rates (>70%) at both surveys. Furthermore, it is the first study to show the association between different levels and change of PA and mortality among long-term TCSs.

Self-reported PA represents the principal independent variable of our study. Similar to other large surveys, PA was measured by self-report due to practical and economic reasons. The validity of self-reported PA can be influenced by recall bias and misinterpretation of questions. However, Kurtze et al validated the HUNT 2 PA-Q, and found that METs values above 6 measured by Actireg correlated with vigorous PA in HUNT 2 PA-Q ($r = .31$).[23] On the other hand, over-reporting of PA and misclassifications by questionnaires have been demonstrated in accelerator based validation studies, and cannot be excluded in our study.[24] Moreover, HUNT 2 PA-Q used in our study only assessed leisure time PA. Therefore, it is unknown whether occupational and household PA may have influenced the results. Furthermore, it is also unknown if sedentary behavior may have influenced the results, since sedentary time is not assessed in HUNT 2 PA-Q. Positive selection bias should not be ignored in our longitudinal study covering three decades since cancer treatment.[11] Moreover other potential confounders (eg, drug use, poor diet, stress) not measured in our study may explain some of the association. Finally, the design of our study documents associations and does not assess causal effects of physical activity on overall mortality.

In summary, regular and maintained PA are associated with a reduced risk of overall mortality in long-term TCSs. Although prospective studies on the causal effect of PA are needed, TCSs and their healthcare professional should be aware of the prognostic value of PA on overall long-term mortality.

AUTHOR CONTRIBUTIONS

Lene Thorsen: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Visualization, Funding acquisition. **Kerry S. Courneya:** Methodology, Writing – Review & Editing. **Jostein Steene-Johannessen:** Methodology, Writing – Review & Editing. **Jon Michael Gran:** Methodology, Formal analysis, Writing – Review & Editing. **Hege S. Haugnes:** Investigation, Resources, Writing – Review & Editing. **Helene F. S. Negaard:** Investigation, Resources, Writing – Review & Editing. **Cecilie E. Kiserud:** Writing – Review & Editing, Project administration. **Sophie D. Fosså:** Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author, and with permission from Regional Committee for Medical and Health Research Ethics.

ETHICS STATEMENT

Our study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (2015/1264; S-98094; S-07305b). All participants provided written informed consent.

ORCID

Lene Thorsen https://orcid.org/0000-0002-7857-5475

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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