

ORIGINAL ARTICLE

Sick leave and disability pension among Swedish testicular cancer survivors according to clinical stage and treatment

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ABSTRACT

Purpose. To investigate if testicular cancer survivors (TCSs) have a higher incidence of work loss compared with the population, accounting for stage, treatment and relapse.

Material and methods. A cohort of 2146 Swedish TCSs diagnosed 1995–2007 (seminoma $n = 926$, non-seminoma $n = 1220$) was identified in the SWENOTECA (Swedish-Norwegian Testicular Cancer Group) register, and matched 1:4 to population comparators. Prospectively recorded work loss data (both before and after diagnosis) were obtained from national registers through September 2013. Adjusted relative risks (RR) and 95% confidence intervals (CI) of sick leave and/or disability pension were calculated annually and overall with Poisson- and Cox regression, censoring at relapse. The mean number of annual work days lost was also estimated.

Results. TCSs were at a modestly increased annual risk of work loss up to the third year of follow-up (RR_{3rd year} 1.25, 95% CI 1.08, 1.43), attributed to a more pronounced risk among extensively treated patients (4 chemotherapy courses: RR_{3rd year} 1.60, 95% CI 1.19, 2.15; > 4 courses: RR_{3rd year} 3.70, 95% CI 2.25, 6.11). Patients on surveillance or limited treatment (radiotherapy, 1–3 chemotherapy courses) did not have an increased risk of work loss beyond the first year. TCSs receiving > 4 chemotherapy courses had higher mean number of annual days of work loss up to the 10th year post-diagnosis, and a five-fold risk of disability pension (RR 5.16, 95% CI 2.00, 10.3).

Conclusion. Extensively treated TCSs, but not those on surveillance or limited treatment, are at increased risk of work loss long-term, not explained by relapse. These patients may benefit from early rehabilitation initiatives.

In the US and most European countries, testicular cancer is the most common malignancy in young men aged 20–40 years, with a variation in incidence worldwide from 3 to 15 per 100 000 males and per year [1,2]. Since the introduction of cisplatin-based treatment in the 1980s, more than 95% of the patients are cured [3]. The increasing incidence of testicular cancer [4] and high survival rates, has led to a growing number of testicular cancer survivors (TCSs), underscoring the importance of monitoring long-term health in this group [5,6]. As the majority of the patients are in their working ages or just

entering the labor market when diagnosed, the ability to work following cancer treatment is an important aspect of rehabilitation, both individually, and for the society.

Cancer survivors in general are more likely to suffer from impaired health, leading to loss of work ability in comparison to healthy individuals, especially during the year of diagnosis and the year after [7,8]. In many previous investigations, however, researchers have had limited ability to consider potential variation in work loss by cancer site and especially by treatment [9–11]. Previous studies have mostly

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not reported any significantly increased risks of work loss among TCSs, but the studies have been limited in size ($n \leq 600$) [7,9,10,12]. Also, few previous studies have investigated the short- or long-term effects of work loss for testicular cancer survivors in relation to treatment modality [7,10], or in comparison to the general population [7,12] and none have considered the impact of cancer recurrence. Therefore, we aimed to investigate short- and long-term incidence of sick leave and disability pension among testicular cancer patients compared with the general population, separating the patients by stage and treatment intensity (no or limited treatment vs. extensive treatment). In this study, 2146 Swedish testicular cancer patients and 8448 matched population comparators, were investigated with up to 19 years of follow-up.

Material and methods

Setting

In Sweden, sick leave and disability pension, part- or full time, are tax-funded and open to everyone. The first day of sick leave is not compensated and Day 2 until Day 14 is paid by the employer. The Swedish social insurance system compensates and the Swedish Social Insurance Office (Försäkringskassan) administrates the compensation from the 14th day and onwards (except between January 1997 to March 1998 when 28 days was the limit). Disability pension is compensated from Day 1. The number of lost work days is registered in the Social Insurance Agency in the Micro Data Analysis of Social Insurance database (MiDAS). Sick leave episodes < 14 days are not registered, but sick leave episodes > 14 days as well as all disability pension episodes are registered from the first day and thus included in the database. Usually retirement takes place at 65 years of age but can be offered from the age of 61 or later up to the age of 67 years.

Patient cohort

TCSs were identified from the Swedish part of the clinical SWENOTECA (Swedish Norwegian Testicular Cancer Group) database. The SWENOTECA register holds information on clinical stage [CS I-IV and tumor marker positive disease (Mk+)] [13], treatment modality and relapse for up to 10 years after diagnosis, for non-seminomas patients since 1995 and seminoma patients since 2000 [3]. All Swedish cancer centers report to the SWENOTECA database, which is then cross-checked with the Swedish Cancer Register [14] once a year through the personal national registration numbers assigned to each resident in Sweden at birth or permanent residency. The completeness of the registers is almost

100%. A total of 2292 TCSs with unilateral testicular cancer at ages 18–60 years were diagnosed from 1 July 1995 (seminomas from 1 July 2000) to 31 December 2007 (Supplementary Figure 1, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>). TCS that died ($n = 51$) (Causes of Death Register) [15] or emigrated ($n = 26$) (Statistics Sweden) [16] within two years from diagnosis, or those with a previous cancer diagnosis according to the Swedish Cancer Register [14] (except previous non-melanoma skin cancer) ($n = 28$), were excluded.

We classified the patients into two main groups and six subgroups based on treatment: 1) no or limited treatment including: 1a) surveillance, 1b) radiotherapy [for adjuvant (20 Gy/10 fractions or 25.2 Gy/14 fractions) or metastatic disease (27 Gy/15 fractions), 1c] chemotherapy one course (EP, BEP or carboplatin single), 1d) chemotherapy 2–3 courses (BEP, PEI or TIP) (SWENOTECA treatment Guidelines listed in Supplementary Table I and II available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>) extensive treatment: 2a) chemotherapy four courses and 2b) chemotherapy > 4 courses (with any of the above mentioned regimens and in some instances also high-dose chemotherapy with stem-cell support).

Comparison cohort

Four male cancer-free comparators for each TCS were randomly sampled from the National population register kept at Statistics Sweden [16], matched on birth year and calendar year of diagnosis of the patient. Comparators who died or emigrated within the first two years of follow-up were excluded (Supplementary Figure 1 available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>).

Sick leave and disability pension

For all study participants, we retrieved exact dates of all periods of sick leave (> 14 days) and disability pension from two years prior to diagnosis until end of follow-up 30 September 2013, as well as the number of days per year of sick leave and/or disability pension, from the Social Insurance Agency database [17]. “0” days thus represented individuals with no episodes longer than 14 days of sick leave absence per year (and no disability pension) since episodes shorter than 14 days are not registered in the Social Insurance Agency database. A new sick-leave episode occurring within five days of the previous episode was paid directly by the social security agent, and thus recorded. Disability pension is granted if work

capacity is reduced by at least 25%. There are three levels of disability pension, 25%, 50% or 100%. Periods of sick leave can occur during the time not covered by the disability pension. In case of recovery or decline of work capacity, the degree of disability pension could be changed. The terminology disability pension was used 1992–2002, but was changed to sickness compensation (30–64 years of age) or activity compensation (19–29 years of age) in 2003. We used the term disability pension to describe disability pension, sickness compensation or activity compensation.

Covariates

From the LISA-database (database for health insurance and labor market studies) held at Statistics Sweden [16], we gathered information for patients and comparators on educational level (≤ 9 , 10–12, > 12 years) and unemployment status (unemployed $> 50\%$ of the time: yes/no) within the year before diagnosis (data available on all Swedish residents 16 years or older).

Statistics

Three different methods were used to assess outcome. First, the relative risk (RR) and 95% confidence interval (CI) of having at least one period of sick leave (≥ 14 days) and/or disability pension (≥ 1 day) per year of follow-up were calculated in a Poisson regression analysis. In multivariable analyses, based on a priori knowledge of possible confounding, we adjusted for education level (< 9 , 10–12, > 12 years), sick leave 1–2 years prior to enrollment (yes/no), and unemployment ($> 50\%$ 0–1 year prior to enrollment, yes/no) and matching variables age (18–60) and calendar year of diagnosis (1995–2007). This model was also used to estimate RRs in patient subgroups stratified by tumor type, clinical stage and treatment. Here, we focused on risk in the third and fifth years of follow-up. Second, the mean number of days of sick leave and/or disability pension per year of follow-up was estimated and compared between groups [18]. The distribution of number of annual days of work loss were assessed as exact number of days and also in categories “0”, 15–120, 121–240, > 240 days per year and the 75th and 90th percentile days. Non-parametric bootstrapping was used to compute 95% CIs of mean annual days of work loss. Third, the hazard ratio (HR) and 95% CI of disability pension were calculated in a Cox regression analysis. Patients with a previous episode of disability pension were excluded from this analysis. Study participants were followed until death, emigration, age 65 years, testicular cancer relapse or 30 September

2013, whichever occurred first. Multivariable adjustment was performed with the same variables as in the Poisson regression model described above. χ^2 -test was used for comparison between groups. A p-value of 0.05 was considered statistically significant and all tests were two-sided. We used SAS (version 9.2, SAS institute Inc., Cary, NC, USA) and STATA (StataCorp, release 12.0. College Station, TX, USA) statistical software for analyses.

Ethics

The study was ethically approved by the Regional Ethics Review Board, Stockholm, Sweden.

Results

The patient cohort included 2146 TCSs and the comparator cohort 8448 men with a median follow-up of 10 years (range 2–19 years). The majority of the TCSs were diagnosed with non-seminoma (57% $N = 1220$), and most were diagnosed with stage I disease (seminoma 88% $N = 816$, non-seminoma 57% $N = 699$) (Table I). A total of 605 (29%) TCSs were followed with surveillance only. Treatment with radiotherapy only was restricted to patients with seminoma (32%). Patients with non-seminoma more often received > 4 courses of chemotherapy (5% vs. 0.3% in patients with seminoma). High-dose chemotherapy was given to 1% ($N = 22$) of the non-seminoma patients and to one of the seminoma patients. Relapse was diagnosed in 6% ($N = 124$) of all TCSs, and was more common among patients with non-seminoma (7%, $N = 88$) than seminoma (4%, $N = 35$).

In the year following diagnosis, 64% of the TCSs had registrations of at least one episode of sick leave or disability pension (38% with 1–120 days, 26% with > 120 days) in comparison to 12% among the population comparators (7% with 1–120 days, 5% with > 120 days) (Figure 1). During the second year after diagnosis and onwards, more than 80% of the TCSs no longer experienced work loss (Figure 1). In analyses of risk of work loss in patient subgroups, patients with non-seminoma, but not seminoma, were at an increased risk of work loss in the third year of follow-up [RR_{3rd year} 1.41, 95% (CI 1.18, 1.69)] (Table II). By stage, an increased risk was restricted to patients with CS II-IV and Mk+ in comparison to the comparators [RR_{3rd year} 1.76, 95% CI (1.40, 2.21)]. The risk of work loss was not increased in any subgroup based on tumor type or stage during the fifth year (Table II).

Stratified by treatment, TCSs with surveillance or limited treatment had no increased risk of work loss in the third or fifth year of follow-up compared with

Table I. Characteristics of testicular cancer survivors (TCSs) diagnosed in Sweden 2000–2007 (seminoma) or 1995–2007 (non-seminoma), and male population comparators matched to the patients by age and calendar year of diagnosis.

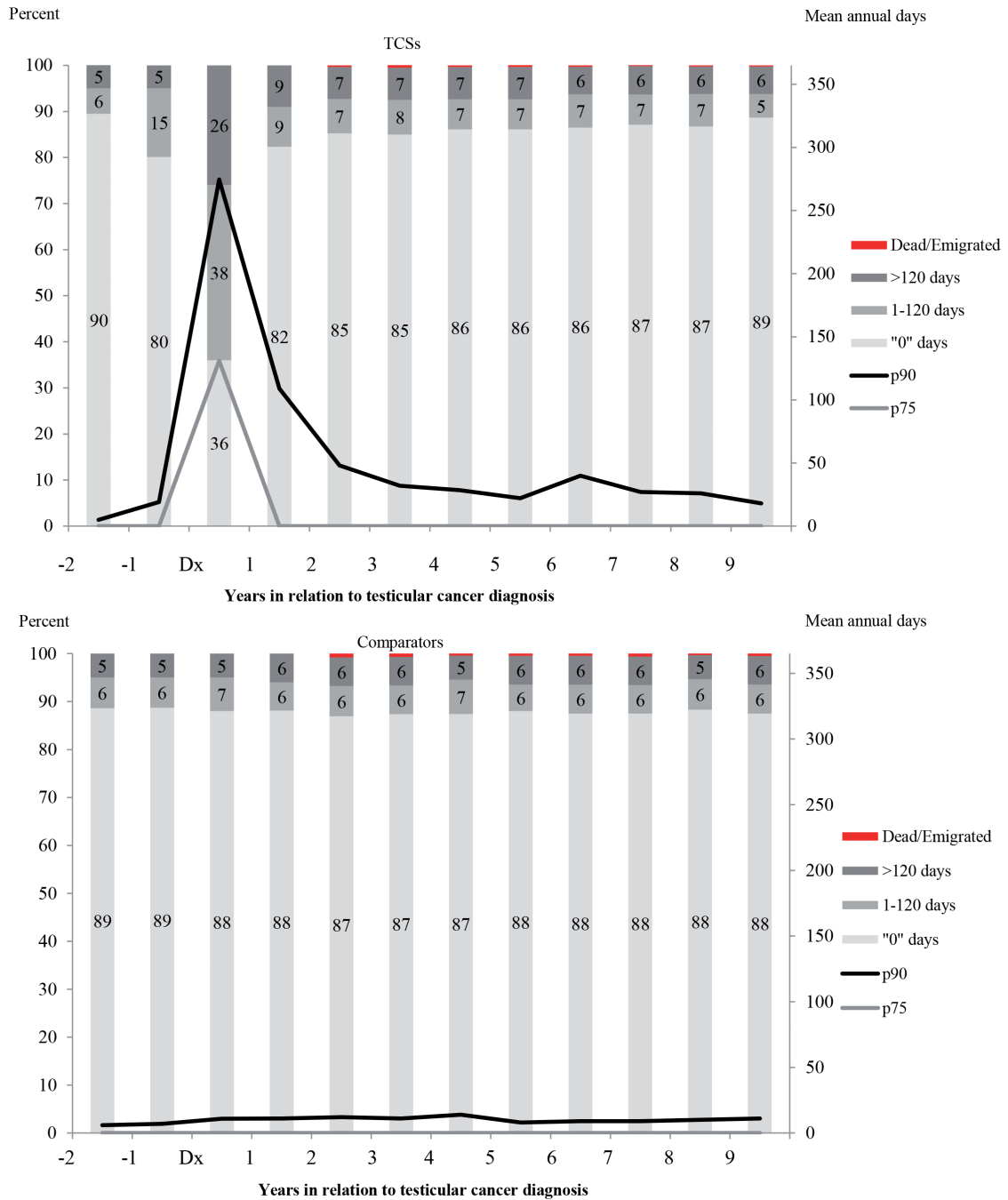
	Testicular cancer survivors	Population comparators	p-value	Testicular cancer survivors	
				Seminoma	Non-seminoma
N (%)	2146 (100)	8448 (100)		926 (43)	1220 (57)
Age (years), N (%)					
18–30	898 (42)	3541 (42)		203 (22)	695 (57)
31–40	802 (37)	3148 (37)		426 (46)	376 (31)
41–50	310 (14)	1224 (14)		200 (22)	110 (9)
51–60	136 (6)	535 (6)		97 (10)	39 (3)
Median (range)	32 (18–60)	32 (18–60)	1.00	36 (18–60)	29 (18–60)
Calendar period N (%)					A
1995–1998	314 (15)	1241 (15)		0	314 (26)
1999–2002	704 (33)	2778 (33)		304 (33)	400 (33)
2003–2006	896 (42)	3524 (42)		484 (52)	412 (34)
2007	232 (11)	905 (11)	1.00	138 (15)	94 (8)
Education N (%)					
≤ 9 years	324 (15)	1229 (15)		123 (13)	201 (16)
10–12 years	1150 (54)	4523 (53)		470 (51)	680 (56)
> 12 years	643 (30)	2591 (31)	0.85	322 (35)	321 (26)
Missing	29 (1)	105 (1)		11 (1)	18 (2)
Unemployment year –1 to 0 N (%) ^a	70 (4)	286 (4)	0.83	27 (3)	43 (4)
Sick-leave or disability pension year –2 to –1 N (%) ^b	221 (11)	900 (11)	0.63	111 (12)	110 (10)
Clinical stage N (%) ^c					
CS I	1515 (71)	–		816 (88)	699 (57)
CS II	361 (17)	–		89 (10)	272 (22)
CS III	37 (2)	–		13 (1)	24 (2)
CS IV	186 (9)	–		8 (1)	178 (14)
CS Mk+ ^d	47 (2)	–		NA	47 (4)
Primary treatment N (%)					
No or limited treatment					
Surveillance	605 (29)	–		309 (35)	296 (25)
Radiotherapy ^e	300 (14)	–		300 (32)	0
Chemotherapy					
1 course	621 (29)	–		219 (23)	402 (33)
2–3 courses	118 (6)	–		7 (1)	111 (9)
Extensive treatment					
4 courses	384 (18)	–		75 (8)	309 (25)
> 4 courses	102 (5)	–		3 (0.3)	99 (8)
Treatment missing	16 (0.6)	–		13 (1)	3 (0.2)
High dose chemotherapy ^f	22 (1)	–		1 (0.1)	21 (2)
Surgery ^g	313 (14)	–		6 (0.6)	307 (25)
Follow-up (years) median (range)	10 (2–19)	10 (2–19)		9 (2–14)	12 (2–19)
Relapse N (%)	124 (6)	–		35 (4)	88 (7)
Dead N (%)	33 (1.5)	137 (1.6)		12 (1)	21 (2)

^aUnavailable for subjects aged < 21 years at diagnosis/match date: TCSs n = 70 (Seminoma n = 4, Non-seminoma n = 66, Population comparators n = 280); ^b Unavailable for the years prior to 1994 or for subjects aged < 21 years at diagnosis/match date TCSs n = 105 (Seminoma n = 4, Non-seminoma n = 101), Population comparators n = 418; ^c According to Medical Research Council [13]; ^d Tumor marker positive without macroscopic metastasis; ^e Radiotherapy adjuvantly (n = 288, 20 Gy/10 fractions) or for metastatic disease (n = 12, 27 Gy/15 fractions); ^f High dose chemotherapy with stem cell support given as primary treatment. These patients were also included in the group chemotherapy: > 4 courses; ^g Post-chemotherapy retroperitoneal lymph node dissection and/or other surgery of metastases. These patients are also included in the chemotherapy groups.

the population comparators (Table II). This pattern of no association was consistent in all subgroups by age, educational level and calendar period as well as by the presence or absence of previous work loss or unemployment during the third and fifth year after diagnosis (Table III). In line with the results for the entire group of patients with limited treatment, further subdivision by specific adjuvant treatment modalities (adjuvant radiotherapy, 1 course of carboplatin,

1 course of BEP), did not reveal increased risks for work loss following the year of diagnosis in any group (Supplementary Figures 2 and 3, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>).

TCSs who had received extensive treatment were at increased risk of work loss during the third year in comparison to comparators [4 courses: RR_{3rd year} 1.60, 95% CI (1.19, 2.15); > 4 courses RR_{3rd year}



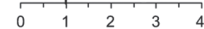
No at risk:												
TCSs (2146)	1939	1999	2021	2030	2028	2013	1988	1926	1680	1449	1248	1025
Comp (8467)	8030	8296	8400	8448	8447	8349	8251	7992	6975	6048	5199	4263
Risk Difference (%) (95% CI)												
Any Days	6 (4, 9)	18 (16, 21)	51 (49, 53)	15 (12, 17)	10 (8, 13)	11 (8, 13)	8 (6, 11)	11 (8, 14)	11 (9, 14)	12 (9, 15)	15 (11, 18)	14 (11, 18)

Abbreviations: TCS, Testicular Cancer Survivors; Comp, Comparators

Figure 1. Total number of days of sick leave or disability pension from 2 years before, up to maximum 10 years after diagnosis (Dx) among TCSs and comparators (Comp). The numbers at risk and differences in mean annual days between TCSs and comparators, with 95% CI, are displayed below the graphs. Numbers within the bars represent percentages. The 75th percentile (p75) and 90th percentile (p90) are indicated by the lines and refers to the mean annual days of sick-leave or disability pension indicated on the secondary y-axis.

Table II. Relative risk (RR) and 95% confidence intervals (CI) of annual sick-leave or disability pension among TCSs compared with matched population comparators in the 3rd and 5th year after diagnosis. First, patients are grouped by tumor subtype and clinical stage (CS) and second by treatment modality. Follow-up is censored at relapse.

	On sick-leave or disability pension N/Total (%)	Crude RR (95% CI)	Adjusted RR* (95% CI)	Forest plot*
Tumor subtype/clinical stage				
3 years after diagnosis				
Comparator cohort	1034/8380 (12)	Ref.	Ref.	
TCSs	310/2026 (16)	1.18 (1.04, 1.34)[†]	1.25 (1.08, 1.43)[†]	
Seminomas	118/889 (13)	0.94 (0.77, 1.15)	1.04 (0.84, 1.31)	
Non-seminomas	192/1136 (17)	1.41 (1.19, 1.66)[‡]	1.41 (1.18, 1.69)[‡]	
CS I	183/1463 (13)	1.00 (0.85, 1.17)	1.03 (0.86, 1.23)	
CS II-IV, Mk+	127/590 (22)	1.63 (1.32, 2.00)[‡]	1.76 (1.40, 2.21)[‡]	
5 years after diagnosis				
Comparator cohort	1046/8216 (13)	Ref.	Ref.	
TCSs	280/1981 (14)	1.06 (0.93, 1.21)	1.05 (0.91, 1.21)	
Seminomas	116/863 (13)	0.96 (0.78, 1.18)	0.97 (0.78, 1.21)	
Non-seminomas	164/1118 (15)	1.15 (0.96, 1.36)	1.11 (0.92, 1.34)	
CS I	190/1404 (14)	1.03 (0.87, 1.20)	1.02 (0.86, 1.21)	
CS II-IV, Mk+	90/577 (16)	1.15 (0.91, 1.45)	1.13 (0.88, 1.46)	
Treatment modality				
3 years after diagnosis				
Comparator cohort	1034/8380 (12)	Ref.	Ref.	
Surveillance	72/551 (13)	0.97 (0.75, 1.26)	0.99 (0.74, 1.32)	
Radiotherapy	40/298 (13)	0.85 (0.61, 1.20)	1.10 (0.76, 1.60)	
Chemotherapy				
1 course	70/599 (12)	1.06 (0.81, 1.38)	0.98 (0.74, 1.31)	
2-3 courses	20/114 (18)	1.32 (0.80, 2.20)	1.19 (0.68, 2.08)	
4 courses	72/358 (20)	1.51 (1.15, 1.98)[†]	1.60 (1.19, 2.15)[†]	
> 4 courses	33/191 (36)	3.17 (2.00, 5.01)[‡]	3.70 (2.25, 6.11)[‡]	
5 years after diagnosis				
Comparator cohort	1046/8216 (13)	Ref.	Ref.	
Surveillance	76/538 (14)	1.02 (0.79, 1.31)	1.04 (0.79, 1.38)	
Radiotherapy	44/288 (15)	0.99 (0.71, 1.38)	1.11 (0.78, 1.58)	
Chemotherapy				
1 course	69/590 (12)	1.01 (0.77, 1.31)	0.91 (0.69, 1.21)	
2-3 courses	12/112 (11)	0.98 (0.52, 1.84)	0.71 (0.36, 1.40)	
4 courses	52/350 (15)	1.02 (0.75, 1.38)	0.96 (0.69, 1.33)	
> 4 courses	25/89 (28)	2.18 (1.33, 3.55)[†]	2.71 (1.61, 4.54)[‡]	



RR, relative risk; CS, clinical stage.

*RRs adjusted for education level, sick-leave 1–2 years prior to diagnosis, unemployment > 50% 0–1 years prior to diagnosis and region of residence in Sweden. Patients with relapse were censored 3 months before the event.

[†]p-value > 0.01.

[‡]p-value > 0.001.

3.70, 95% CI (2.25, 6.11)] (Table II). This risk was still detectable the fifth year after diagnosis among those TCSs who had received > 4 courses of chemotherapy [RR_{5th year} 2.71, 95% CI (1.61, 4.54)] (Table II). After excluding TCSs, who had received high-dose chemotherapy (N = 22), the risk was similarly increased [> 4 courses excl. high-dose treatment: RR_{5th year} 2.85, 95% CI (1.78, 5.36)]. The risk also remained increased after excluding patients who underwent metastatic surgery [> 4 courses excl. surgery: RR_{5th year} 3.04, 95% CI (1.22, 7.55)]. Further analyses of risks in the eighth and 10th years of follow-up did not reveal any increased risk of work loss in any of the treatment subgroups but the numbers were low (data not shown).

In analyses of mean lost work days the third and fifth year after diagnosis (Table III) among extensively treated TCSs compared to comparators, significant differences were observed in all age groups, but did not reach statistical significance during the period 2000–2007 (Table III). Notably, significant differences compared to comparators were also observed among TCSs with no previous sick leave and/or disability pension (Table III). During the first 10 years of follow-up (Figure 2), TCSs who received > 4 courses of chemotherapy had significantly more mean days of sick leave and/or disability pension than comparators almost every year up to the 10th year [difference 30 days the 10th year (95% CI 2, 59)] and those TCSs receiving four courses

Table III. Mean days of sick-leave or disability pension among TCSs and population comparators (Comp) in the 3rd and 5th years after diagnosis. Patients are stratified by no or limited treatment versus extensive treatment, and then further by age, calendar period, educational level and previous sick-leave or disability pension. Follow-up is censored at relapse.

	3rd year					5th year				
	TCSs/ Comp N	Mean days of sick-leave and disability pension			TCSs/ Comp N	Mean days of sick-leave and disability pension				
		TCSs	Comp	Difference (95% CI)		TCSs	Comp	Difference (95% CI)		
No or limited treatment ^a	1545/8293	22	21	1 (-3, 6)	1476/7956	21	19	2 (-2, 6)		
Age										
18–35	933/5158	16	14	2 (-2, 7)	897/4996	15	12	3 (-2, 7)		
36–60	612/3135	32	32	-1 (-8, 7)	579/2960	31	30	1 (-8, 9)		
Calendar period										
1995–1999	252/1597	20	17	3 (-7, 13)	248/1566	28	19	9 (-3, 20)		
2000–2007	1293/6696	22	22	1 (-4, 6)	1228/6390	20	19	1 (-4, 6)		
Education										
≤ 9 years	206/1198	48	50	-2 (-19, 15)	195/1140	50	45	5 (-13, 23)		
10–12 years	831/4477	20	19	1 (-5, 6)	804/4314	18	17	1 (-4, 6)		
> 12 years	490/2520	10	6	4 (-1, 9)	460/2411	9	7	2 (-3, 6)		
Sick-leave/disability pension year -2 to -1										
No	930/5423	8	8	0 (-2, 3)	646/3859	9	9	0 (-3, 3)		
Yes	128/675	128	128	0 (-27, 228)	88/457	116	103	13 (-13, 39)		
Extensive treatment ^b	440/8293	34	21	14 (5, 22)[‡]	429/7956	32	19	13 (4, 22)[‡]		
Age										
18–35	306/5158	26	14	12 (3, 22)[†]	302/4996	23	12	11 (2, 21)[†]		
36–60	134/3135	53	32	21 (2, 40)[†]	127/2960	51	30	21 (2, 40)[†]		
Calendar period										
1995–1999	166/1597	41	17	24 (5, 42)[†]	114/1566	42	19	23 (3, 43)[†]		
2000–2007	324/6696	32	22	10 (0, 20)	315/6390	28	19	9 (-1, 19)		
Education										
≤ 9 years	92/1198	64	50	14 (-12, 40)	91/1140	56	45	11 (-14, 36)		
10–12 years	240/4477	29	19	10 (-1, 21)	231/4314	29	17	11 (0, 23)		
> 12 years	101/2520	13	6	7 (-3, 118)	100/2411	11	7	4 (-6, 14)		
Sick-leave/disability pension year -2 to -1										
No	371/6995	20	8	12 (5, 20)[†]	362/6717	19	9	10 (3, 18)[†]		
Yes	40/883	174	128	46 (-6, 98)	38/833	158	103	55 (3, 107)[†]		

^aSurveillance/radiotherapy/chemotherapy 1–3 courses.

^bChemotherapy ≥ 4 courses.

[†]*p*-value > 0.05.

[‡]*p*-value > 0.01.

of chemotherapy until the fifth year after diagnosis (Figure 2). No differences were observed in any other group versus comparators beyond the first year (Figure 2, Supplementary Figure 2 available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>).

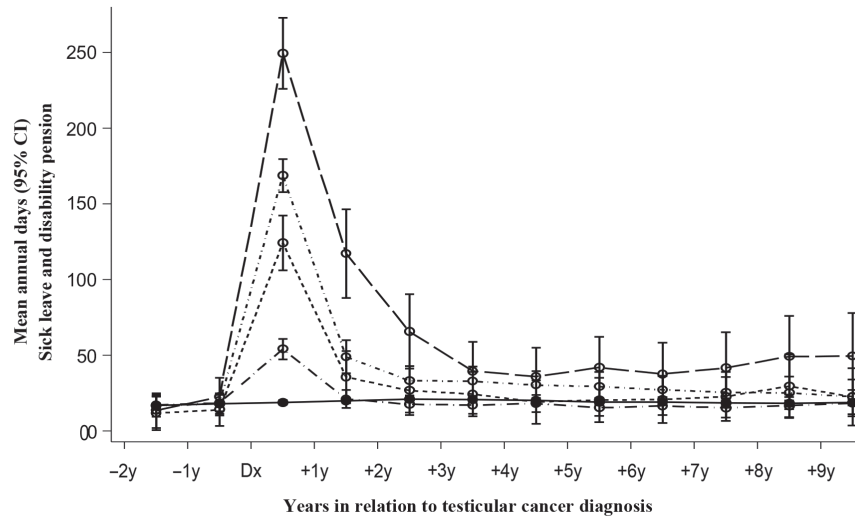
In analysis of risk of disability pension, registered from Day 1, a similar pattern in risk by treatment was observed. Thus, extensively treated patients were at increased risk of disability pension [4 courses: HR 1.93 (95% CI 1.01, 3.71); > 4 courses HR 5.16 (95% CI 2.00, 10.3)], while patients on surveillance or with limited treatment were not at risk (Table IV).

Discussion

In this large nationwide population-based study, we observed an increased annual risk of sick leave and

disability pension up to the third year after diagnosis among all TCSs in comparison to a matched general population sample. Specifically, TCSs who had received four or more courses of chemotherapy had more annual days of sick leave and/or disability pension persisting for several years after diagnosis, and the increase was not explained by high-dose chemotherapy, metastatic surgery or relapse. Importantly however, most TCSs treated with no or limited treatment, including radiotherapy and 1–3 chemotherapy courses, were not at increased risk of work loss beyond the first year following diagnosis.

We are unaware of any previous nationwide studies of work loss encompassing virtually all TCSs with detailed information on stage and treatment modality and long follow-up. In a previous Norwegian study, including 2008 cancer survivors of whom 155 were TCSs [12], most cancer survivors were on sick



Years in relation to testicular cancer diagnosis												
No at risk:	-2y	-1y	Dx	+1y	+2y	+3y	+4y	+5y	+6y	+7y	+8y	+9y
1 courses (621) - - -	608	618	619	603	601	594	591	568	477	372	282	237
2-3 courses (118) - - -	113	117	118	114	114	114	113	109	101	87	79	65
4 courses (384) - - -	368	381	382	365	360	353	351	343	303	263	232	192
>4 courses (102) - - -	97	101	102	92	91	90	90	88	81	73	66	60
Comparators (8467) —	8109	8344	8418	8448	8381	8302	8243	8006	6993	6064	5248	4312
Mean difference (95% CI):												
1 course vs comp	0	0	35	0	-4	-4	-2	-4	-3	-3	-1	-1
	(-5,6)	(-5,6)	(28,43)	(-5,7)	(-10,2)	(-10,2)	(-9,3)	(-9,2)	(-9,5)	(-10,3)	(-9,6)	(-10,9)
2-3 courses vs comp	-4	-3	105	14	6	3	-1	2	2	4	12	3
	(-16,8)	(-14,8)	(87,124)	(-2,32)	(-11,22)	(-11,19)	(-15,13)	(-13,16)	(-14,18)	(-12,21)	(-10,33)	(-16,23)
4 courses vs comp	-1	0	150	28	13	12	10	10	8	7	7	4
	(-8,6)	(-6,7)	(138,161)	(17,38)	(3,22)	(2,22)	(0,19)	(0,20)	(-2,18)	(-2,17)	(-4,18)	(-8,16)
>4 courses vs comp	-2	6	232	96	46	19	16	24	18	23	31	30
	(-15,10)	(-7,18)	(208,256)	(66,126)	(21,70)	(0,38)	(-4,36)	(2,45)	(-2,40)	(0,46)	(4,57)	(2,59)

Abbreviations: Comp = Comparators

Figure 2. Mean annual days of sick-leave or disability pension from 2 years before, up to maximum 10 years after diagnosis (Dx) among TCSs treated with chemotherapy and population comparators. The numbers at risk and differences in mean annual days between TCSs and comparators, with 95% confidence intervals (CI), are displayed below the graph.

leave the first year after diagnosis. Sick leave-levels then decreased within the next four years but stayed significantly higher than for comparators. However, TCSs had fewer sick leave episodes than their comparators five years post-diagnosis [12]. Similarly, in another Nordic study by Lindbohm et al., no difference in work ability was detected in a cross-sectional study of 380 TCSs with a follow-up of between one and eight years after diagnosis in comparison to age-matched reference individuals [10]. That study was restricted to TCSs with low-stage disease, and no obvious differences were observed for TCSs who had received chemotherapy compared to those who had not, although the number of chemotherapy courses was not considered. Hence, these two studies are broadly in line with our results of no increased risk of work loss among low-stage patients treated with no or limited treatment.

Among cancer patients overall, treatment modality, stage of disease, recurrence of cancer and other chronic conditions have been reported to affect employment and work loss although few studies have assessed risks long term [8,10,19,20]. Also, several studies on work loss in cancer survivors have been

based on self-reported questionnaires, and could therefore be affected by misclassification as well as non-response [10,19,21]. Swedish population-based health care and labor market registries with prospectively recorded lost work days with high coverage and minimal loss to follow-up provide a unique opportunity for longitudinal investigation of work loss following a cancer diagnosis. Another strength of the present study is the access to detailed register-based information on clinical stage, treatment and relapse on all TCSs nationwide. We were able to identify subgroups of TCSs who are at high risk of work loss, but also to reliably confirm the lack of an increase among patients receiving limited treatment.

Among the most extensively treated patients, our results showed an increased risk of sick leave and/or disability pension up to the fifth year after diagnosis, with more mean days of sick leave and/or disability pension up to the 10th year. This was not fully explained by high-dose chemotherapy or relapse. One weakness of this study was that we did not have information on pre-existing comorbidity either in TCSs or among the comparators, although we did have information about prior sick leave and disability

Table IV. Hazard ratio (HR) and 95% confidence intervals (CI) of disability pension among testicular cancer survivors (TCSs) compared with matched population comparators. First, patients are grouped by tumor subtype and clinical stage (CS) and second by treatment modality. Follow-up is censored at relapse.

	Disability pension N/Total (%)	Crude HR (95% CI)	Adjusted HR ^a (95% CI)	Forest plot ^a
Tumor subtype/clinical stage				
Comparator cohort	209/8140 (3)	Ref.	Ref.	
TCSs	76 2073 (4)	1.49 (1.15, 1.94)[†]	1.48 (1.08, 2.01)[†]	
Seminomas	27/889 (3)	1.06 (0.68, 1.63)	1.07 (0.64, 1.79)	
Non-seminomas	49 1148 (4)	1.88 (1.34, 2.63)[†]	1.80 (1.22, 2.67)[†]	
CS I	40/1462 (3)	1.16 (0.82, 1.63)	0.98 (0.64, 1.50)	
CS II-IV, Mk+	36 611 (6)	2.28 (1.50, 3.47)[‡]	2.65 (1.65, 4.28)[‡]	
Treatment modality				
Comparator cohort	209/8140 (3)	Ref.	Ref.	
Surveillance	21/580 (4)	1.69 (1.00, 2.86)	1.67 (0.87, 3.19)	
Radiotherapy	7/291 (2)	0.45 (0.20, 1.00)	0.75 (0.19, 1.15)	
Chemotherapy				
1 course	13/603 (2)	1.23 (0.65, 2.32)	0.73 (0.33, 1.63)	
2-3 courses	4/115 (4)	1.74 (0.53, 5.64)	2.02 (0.52, 7.84)	
4 courses	19 370 (5)	1.80 (1.02, 3.20)[†]	1.93 (1.01, 3.71)[†]	
> 4 courses	12 98 (12)	4.44 (1.92, 10.30)[‡]	5.16 (2.00, 10.3)[‡]	

CS, Clinical stage; HR, Hazard ratio.

^aHRs adjusted for education, sick-leave 1–2 years prior to diagnosis, unemployment >50% 0–1 years prior to diagnosis and region of residence in Sweden. Patients with relapse were censored 3 months before the event. Patients with disability pension before testicular cancer diagnosis were excluded from the analysis.

[†]p-value>0.05.

[‡]p-value>0.01.

[‡]p-value>0.001.

pension. Taskila et al. reported that comorbidity was a risk factor for impaired work ability in cancer survivors [19,20]. Our results support this observation in showing that patients with prior work loss experienced a much greater mean number of lost work days following cancer diagnosis than those without such history. Importantly however, in our study, heavily treated patients lost significantly more days than comparators also in the absence of a history of work loss before diagnosis.

We found that TCSs had more days with work loss the year before diagnosis in comparison to comparators. This is likely explained by the delay between the initiation of examinations and orchietomy/date of diagnosis.

Possible explanations for the increased risk in the most extensively treated TCSs are long-standing treatment side effects [5,6,22,23]. Most of the severe long-term effects, such as secondary cancer and cardiovascular disease after TC treatment have been reported to occur more than 10 years after treatment [22,24] and therefore could not readily explain the observed risks up to 10 years. In patients with other cancer types, chemotherapy has been associated with reduced cognitive function [25]. This has also been reported in TCSs [26], with possible effects on work ability. TCSs may also experience somatic complications, such as gonadal dysfunction [5,23,27], oto- and

neurotoxicity [28] and pulmonary toxicity [6], but it remains unclear to what extent these complications interfere with work ability.

A weakness of our study is that we only had records of sick-leave episodes registered by the Social Insurance Agency, beyond 14 days (if not repeated within a short time frame). This has led to an underestimation of the total work loss due to sickness among TCSs. However, this also applies to the population comparators and hence should not have affected the comparison between the two groups. If patients have had more frequent short (<14 days) periods of sick leave than comparators (starting later than 5 days of a previous sick-leave episode), the ratios may also be somewhat underestimated. Reassuringly, in analysis of disability pension only (recorded from the first day), similar risk patterns were observed, strengthening the overall results. The welfare system in Sweden differs to those in other countries which could make this study less applicable internationally, but the terms and conditions for sick leave and disability pension were also equal to both TCSs and comparators. On a different note, the fact that TC treatment is relatively uniform worldwide increases the value of our findings.

In conclusion, we have shown that most TCSs, receiving no or limited treatment, do not have an increased risk of work loss in comparison to the gen-

eral population beyond the first year after diagnosis. However, extensively treated TCSs have a prolonged increased risk of sick leave and/or disability pension, especially those who have received more than four cycles of chemotherapy, which cannot be explained by cancer relapse. Further studies are needed to investigate underlying reasons for the increased risk of work loss among the most heavily treated patients. Physicians should be aware of this risk in order to provide optimized support and early work-related rehabilitation.

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References

- [1] Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Moller H. Trends in testicular cancer incidence and mortality in 22 European countries: Continuing increases in incidence and declines in mortality. *Int J Cancer* 2006;118:3099–111.
- [2] McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer* 2003;97:63–70.
- [3] SWENOTECA. Available from: <http://skane.se/sv/Webbplatser/tumorregistret/Patientprocessarbete/Testikelcancer/Vard-program/>.
- [4] Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: A review. *J Urol* 2003;170:5–11.
- [5] Nord C, Bjoro T, Ellingsen D, Mykletun A, Dahl O, Klepp O, et al. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. *Eur Urol* 2003;44:322–8.
- [6] Haugnes HS, Bosl GJ, Boer H, Gietema JA, Brydoy M, Oldenburg J, et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *J Clin Oncol* 2012;30:3752–63.
- [7] Torp S, Nielsen RA, Fossa SD, Gudbergsson SB, Dahl AA. Change in employment status of 5-year cancer survivors. *Eur J Public Health* 2013;23:116–22.
- [8] Marino P, Luis Sagaon T, Laetitia M, Anne-Gaelle le CS. Sex differences in the return-to-work process of cancer survivors 2 years after diagnosis: Results from a large French population-based sample. *J Clin Oncol* 2013;31:1277–84.
- [9] Gudbergsson SB, Torp S, Flotten T, Fossa SD, Nielsen R, Dahl AA. A comparative study of cancer patients with short and long sick-leave after primary treatment. *Acta Oncol* 2011;50:381–9.
- [10] Lindbohm ML, Taskila T, Kuosma E, Hietanen P, Carlsen K, Gudbergsson S, et al. Work ability of survivors of breast, prostate, and testicular cancer in Nordic countries: A NOCWO study. *J Cancer Surviv* 2012;6:72–81.
- [11] Smedby KE. Cancer survivorship and work loss – what are the risks and determinants? *Acta Oncol* 2014;53:721–3.
- [12] Torp S, Nielsen RA, Gudbergsson SB, Fossa SD, Dahl AA. Sick leave patterns among 5-year cancer survivors: A registry-based retrospective cohort study. *J Cancer Surviv* 2012;6:315–23.
- [13] Peckham MJ, Bagshaw KD, Blandy JP. Prognostic factors in advanced non-seminatous germ-cell testicular tumours: Results of a multicenter study. Report from the Medical Research Council Working Party on Testicular Tumours. *Lancet* 1985;1:8.
- [14] Register SC. Available from: <http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/inenglish>.
- [15] The Causes of Death Register S. Available from: <http://www.socialstyrelsen.se/register/dodsorsaksregistret>.
- [16] Sweden S. Available from: www.scb.se.
- [17] Agency TSI. Available from: <http://www.forsakringskassan.se>.
- [18] Neovius M, Simard JF, Askling J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? *Ann Rheum Dis* 2011;70:1010–5.
- [19] Taskila T, Martikainen R, Hietanen P, Lindbohm ML. Comparative study of work ability between cancer survivors and their referents. *Eur J Cancer* 2007;43:914–20.
- [20] Taskila T, Lindbohm ML. Factors affecting cancer survivors' employment and work ability. *Acta Oncol* 2007;46:446–51.
- [21] Bottcher HM, Steimann M, Ullrich A, Rotsch M, Zurborn KH, Koch U, et al. Work-related predictors of not returning to work after inpatient rehabilitation in cancer patients. *Acta Oncol* 2013;52:1067–75.
- [22] Haugnes HS, Wethal T, Aass N, Dahl O, Klepp O, Langberg CW, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: A 20-year follow-up study. *J Clin Oncol* 2010;28:4649–57.
- [23] Joly F, Heron JF, Kalusinski L, Bottet P, Brune D, Allouache N, et al. Quality of life in long-term survivors of testicular cancer: A population-based case-control study. *J Clin Oncol* 2002;20:73–80.
- [24] Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005;97:1354–65.
- [25] Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev* 2008;18:121–31.
- [26] Skoogh J, Steineck G, Stierner U, Cavallin-Stahl E, Wilderang U, Wallin A, et al. Testicular-cancer survivors experience compromised language following chemotherapy: Findings in a Swedish population-based study 3–26 years after treatment. *Acta Oncol* 2012;51:185–97.
- [27] Sprauten M, Brydoy M, Haugnes HS, Cvancarova M, Bjoro T, Bjerner J, et al. Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. *J Clin Oncol* 2014;32:571–8.
- [28] Sprauten M, Darrah TH, Peterson DR, Campbell ME, Hannigan RE, Cvancarova M, et al. Impact of long-term serum platinum concentrations on neuro- and ototoxicity in

- Cisplatin-treated survivors of testicular cancer. *J Clin Oncol* 2012;30:300–7.
- [29] Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–56.
- [30] Ibrahim A, Zambon E, Bourhis JH, Ostronoff M, Beaujean F, Viens P, et al. High-dose chemotherapy with etoposide, cyclophosphamide and escalating dose of carboplatin followed by autologous bone marrow transplantation in cancer patients. A pilot study. *Eur J Cancer* 1993;29A:1398–403.
- [31] Rodenhuis S, Baars JW, Schornagel JH, Vlasveld LT, Mandjes I, Pinedo HM, et al. Feasibility and toxicity study of a high-dose chemotherapy regimen for autotransplantation incorporating carboplatin, cyclophosphamide and thiotepa. *Ann Oncol* 1992;3:855–60.

Supplementary material available online

Supplementary Figures 1-3 and Table I available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1020967>