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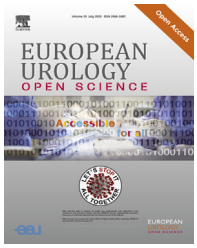

European Association of Urology

Testis Cancer

Long-term Testis Cancer Survivors in Canada—Mortality Risks in a Large Population-based Cohort

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Abstract

Background: Testis cancer (TC) patients are young with excellent cancer prognosis. Hence, the risk of late-onset treatment-related morbidity and mortality is of concern due to longer survival after treatment.
Objective: We set to characterize long-term survival of TC patients through a Canadian population dataset.
Design, setting, and participants: We used a population-based dataset, the Canadian Census Health and Environment Cohort (CanCHEC), to identify individuals diagnosed with TC between 1991 and 2010. We compared them with all other male individuals without TC.
Outcome measurements and statistical analysis: The primary outcome was mortality due to cardiovascular disease (CVD) or nontesticular malignancy. Mann-Whitney or chi-square test was used where applicable. Data were analyzed using a Cox proportional hazard model with and without matching.
Results and limitations: We identified 1950 individuals with TC. We compared them with 1 300 295 men with no TC. There were 335 deaths in the study group during the study period (17.2%) with a mean follow-up of 19.6 yr. TC patients were at increased risk of death from secondary malignancies (hazard ratio [HR] 1.63, 95% confidence interval [CI] 1.39–1.91; $p < 0.0001$) with specific risks for hematologic neoplasms (HR 3.86, 95% CI 2.78–5.37; $p < 0.001$) and other malignancies (HR 2.41, 95% CI 1.76–3.29; $p < 0.001$). Gastrointestinal, hematologic, and respiratory toxicities were the most common secondary malignancies leading to death. When stratified according to histology, nonseminoma (NS) patients were at significantly increased risk of death from CVD (HR 2.03, 95% CI 1.27–3.25; $p = 0.0032$). Individuals with seminoma were at increased risk of death from other nontestis neoplasms (HR 1.46, 95% CI 1.17–1.82; $p = 0.0007$), specifically hematologic neoplasms (HR 2.09, 95% CI 1.18–3.72; $p = 0.0118$).

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Conclusions: NS patients are at increased risk of CVD-related death, whereas seminoma patients are at increased risk of death from non–testis-related malignancies.

Patient summary: We report long-term mortality following diagnosis of testis cancer. Nonseminoma patients have an increased risk of death from cardiovascular disease, while seminoma patients have an increased risk of death from secondary malignancies.

1. Introduction

In Canada, testis cancer accounts for 1% of malignancies among men and 13% of cancer cases in young males [1]. Patients with higher-risk disease require systemic therapy. The discovery of cisplatin-based chemotherapy and its use in clinical trials 40 yr ago revolutionized the treatment of testicular cancer from carrying a 1-yr survival rate of 5% for metastatic testis cancer to achieving the current 10-yr overall survival rate of 95% [2,3].

Additional postorchiectomy treatments depend on the International Germ Cell Cancer Collaborative Group risk classification of advanced germ cell tumor risk group, patients, and physician preferences [4]. Treatment options broadly include surveillance, retroperitoneal lymph node dissection (RPLND), radiotherapy, and/or chemotherapy. Short- and long-term adverse events following the various treatments for testicular cancer have been reported. Late complications of RPLND include incisional hernias and bowel obstruction [5], while those of radiotherapy include gastrointestinal toxicity and secondary malignancy [6]. Long-term effects of chemotherapy include peripheral neuropathy, Reynaud's phenomenon, ototoxicity, hypogonadism, infertility, secondary malignancies, and cardiovascular disease (CVD) [7,8]. Radiation exposure during diagnostic imaging of patients on surveillance for testis cancer carries a lifelong risk of secondary malignancies ranging between 1.2% and 2.6% [9,10].

With early cohorts receiving cisplatin chemotherapy now reaching the middle and later stages of their lives, there is growing interest in the very-long-term testicular cancer survivorship. Early (<5 yr) and long-term (~10 yr) sequelae of treatment and survivorship have been well defined. CVD morbidity risk among testis cancer survivors has been reported to be significantly higher than that in the general population, with a 1.9–3.1-fold increased risk for patients receiving cisplatin chemotherapy compared with the general population at median observation of 18.4–19 yr [11,12]. Another concerning long-term sequela of testis cancer survivors is the increased risk (1.4–1.9) for secondary malignancies [13–15].

Although the risk of CVD and secondary malignancies is higher in testis cancer patients, it is unclear whether this translates into differences in overall survival. The objective of this study was to explore disease-specific mortality in testis cancer patients in comparison with the general male population.

2. Patients and methods

2.1. Study design, setting, and data source

We conducted a population-based retrospective cohort study using administrative data from Statistics Canada: the 1991 Canadian Census Health and Environment Cohort (CanCHEC). The 1991 CanCHEC is based on approximately 2.7 million people aged ≥25 yr who responded to the 1991 long-form census questionnaire. Individuals in this census cohort were linked to their tax, cancer registry, and mortality records. The 1991 CanCHEC comprises the 1984–2011 Historical Tax Summary Files, the 1969–1991 Canadian Cancer Database, the 1992–2010 Canadian Cancer Registry, and the 1991–2011 Canadian Mortality Database, with baseline characteristics coming from the 1991 census (Supplementary Fig. 1).

2.2. Population

We used the CanCHEC database to identify individuals who were diagnosed with testis cancer between 1991 and 2010 (ICD9 = 186.0/186.9 or ICD-O3-T = C62). These patients were compared with all other men found in the CanCHEC database who were not diagnosed with testis cancer. Participants with missing data were excluded.

2.3. Outcome, exposure, and covariates

Our primary outcome was mortality due to either CVD or nontesticular malignancy. The cause of death was determined from the CanCHEC. Secondary malignancies were subcategorized by the site of malignancy. The following demographic characteristics were included: patient age, marital status, education level, subcountry region of residence, urbanicity, and minority status (Supplementary Table 1). Some information regarding cancer characteristics (stage and grade) is available in the CanCHEC for select years, but the sample size was too small and the information was not permitted to be released for confidentiality purposes. The different types of cancer treatments received (radiation and chemotherapy) are not reported in the CanCHEC.

2.4. Statistical analysis

Baseline variables are reported as medians (interquartile range [IQR]) or counts (percentages), and were compared using a Mann-Whitney or chi-square test. Population weighting to account for sampling error was applied according to standard protocols. A two-sided p-value of <0.05 was considered significant. Data were analyzed using a Cox proportional hazard model with and without matching. Unadjusted and adjusted (for the above baseline characteristics) hazard ratios (HRs), p values, and 95% confidence intervals (CIs) are reported. Privacy regulations do not allow releasing the size of any group under six people, so these groups were not

Table 1 – Demographic baseline characteristics.

	Cohort (n = 1 302 245)	Testis cancer (n = 1950)	Nontestis cancer (n = 1 300 295)	p value
Age (yr), median (IQR)	43 (25)	36 (15)	43 (25)	<0.0001
Marital status (count), n (%)				<0.0001
Single	259 555 (19.9)	535 (27.4)	259 020 (19.9)	
Married	890 970 (68.4)	1220 (62.3)	889 745 (68.4)	
Divorced	119 265 (9.2)	175 (9)	119 090 (9.2)	
Widow	32 455 (2.5)	15 (0.7)	32 440 (2.5)	
Education, n (%)				<0.0001
No high school	469 810 (36.1)	525 (26.7)	469 285 (36.1)	
High school	482 875 (37.1)	790 (40.4)	482 085 (37.1)	
Postsecondary, nonuniversity	156 855 (12)	280 (14.4)	156 575 (12)	
University	192 710 (14.8)	360 (18.5)	192 350 (14.8)	
Region, n (%)				<0.0001
Ontario	479 515 (36.8)	785 (40.3)	478 730 (36.8)	
Quebec	333 430 (25.6)	310 (15.9)	333 120 (25.6)	
West Coast (BC)	162 690 (12.5)	265 (13.6)	162 425 (12.5)	
Prairies (Man, Sask, Alb)	215 200 (16.5)	410 (21)	214 790 (16.5)	
Atlantic Canada (NB, NFLD, PEI, NS)	107 755 (8.3)	170 (8.7)	107 585 (8.3)	
Territories (NWT, Yuk)	3655 (0.3)	10 (0.5)	3645 (0.3)	
Urbanicity, n (%)				0.1086
Rural	311 575 (23.9)	445 (22.8)	311 130 (23.9)	
Small urban (<30 000)	173 770 (13.3)	255 (13.1)	173 515 (13.3)	
Urban (30 000–99 999)	116 205 (8.9)	190 (9.7)	116 015 (8.9)	
Urban (100 000–499 999)	135 250 (10.4)	235 (12.1)	135 020 (10.4)	
Urban (500 000+)	565 445 (43.4)	825 (42.3)	564 620 (43.4)	
Immigration status, n (%)				<0.0001
Canadian born	1 014 090 (77.9)	1665 (85.4)	1 012 425 (77.9)	
Immigrant	288 155 (22.1)	285 (14.6)	287 870 (22.1)	

Alb = Alberta; BC = British Columbia; IQR = interquartile range; Man = Manitoba; NB = New Brunswick; NFLD = Newfoundland; NS = Nova Scotia; NWT = North West Territories; PEI = Prince Edward Island; Sask = Saskatchewan; Yuk = Yukon.

reported. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

We identified 1950 individuals who had a testis cancer diagnosis and met our inclusion criteria (Table 1). Median age at diagnosis of testis cancer was 36 (IQR: 15) yr. Mean follow-up was 19.6 yr.

The most common testis cancer histology was seminoma (n = 1170, 60%). We identified 1 300 295 men not diagnosed with testis cancer, who comprised the unexposed cohort. Importantly, the testis cancer patients were younger ($p <$ 0.0001) and more highly educated ($p <$ 0.0001) than the comparison group.

There were 335 deaths (17.2%) among the testis cancer group during the follow-up period (Table 2). The most common cause of death was nontesticular neoplasm (n = 150, 7.7%). There were significant differences between testis cancer and nontestis cancer individuals in overall death rate, death from CVD, respiratory disease, and subcategories of nontesticular neoplasms. After adjusting for demographic parameters, testis cancer patients were found to have a higher risk of death from nontestis cancer malignancy (HR 1.63, 95% CI 1.39–1.91; $p <$ 0.0001), hematologic neoplasms (HR 3.86, 95% CI 2.78–5.37; $p <$ 0.0001), and other malignancies (HR 2.41, 95% CI 1.76–3.29; $p <$ 0.0001; Table 3). The most common secondary malignancy–related deaths were from gastrointestinal, hematologic, and respiratory malignancies.

We further stratified the cause of death by seminoma versus nonseminoma (NS) histology (Table 4). On multivariate analysis, individuals with NS testicular cancer were at significantly increased risk of death from CVD (HR 2.03, 95% CI 1.27–3.25; p = 0.0032). Individuals with seminoma did not have an increased risk of CVD-related death but were at increased risk of death from other nontestis neoplasms (HR 1.46, 95% CI 1.17–1.82; p = 0.0007), specifically hematologic neoplasms (HR 2.09, 95% CI 1.18–3.72; p = 0.0118).

4. Discussion

We conducted a large cohort study of very-long-term testis cancer survivorship and demonstrated that these individuals are at significantly increased risk of death from secondary malignancies and CVDs. While our study is observational and we cannot infer causality from these results, it is possible that treatment with chemotoxic agents and radiotherapy mediates this relationship. Regardless of the etiology, our study demonstrates that long-term testis cancer survivors require additional surveillance for secondary malignancies and CVD. As testis cancer patients survive longer, patient cohorts mature and the disease, once regarded as the hallmark model for curable cancer, now serves as a prototype model for assessing long-term cancer survivorship outcomes [16–18].

Table 2 – Overall death during study.

	Cohort (n = 1 302 245)	Testis cancer (n = 1950)	Nontestis cancer (n = 1 300 295)	p value
Overall during study period	331 705	335 (17.2%)	331 370 (25.5%)	<0.0001
Cardiovascular	108 960	80 (4.1%)	108 880 (8.4%)	<0.0001
All nontesticular neoplasms	113 575	150 (7.7%)	113 420 (8.7%)	0.1498
Infectious and parasitic	6625	10 (0.5%)	6615 (0.5%)	0.3335
Respiratory	28 530	15 (0.8%)	28 510 (2.2%)	<0.0001
GI neoplasms [a]	30 260	35 (1.8%)	30 230 (2.3%)	0.0582
Genitourinary neoplasm (nontesticular) [a]	19 855	20 (1%)	19 835 (1.5%)	0.0483
Hematologic neoplasm [a]	10 780	35 (1.8%)	10 745 (0.8%)	<0.0001
Respiratory and thoracic neoplasm [a]	34 510	25 (1.3%)	34 485 (2.7%)	0.0002
Other and nonspecified neoplasm [a]	18 170	40 (2.1%)	18 130 (1.4%)	0.0157

[a] Subdivision of "all nontesticular neoplasms".

Table 3 – Association between testis cancer and cause of death.

Cause of death	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Cardiovascular	0.47	0.38–0.58	<0.0001	1.02	0.82–1.27	0.856
All non-testicular neoplasms	0.85	0.72–1	0.0442	1.63	1.39–1.91	<0.0001
Infectious and parasitic	1.14	0.62–2.08	0.677	1.78	0.97–3.26	0.0636
Respiratory	0.37	0.23–0.59	<0.0001	0.88	0.54–1.43	0.6018
GI neoplasms [a]	0.69	0.49–0.97	0.0312	1.29	0.91–1.81	0.1514
Genitourinary neoplasm (nontesticular) [a]	0.62	0.39–0.96	0.0316	1.36	0.87– 2.13	0.1829
Hematologic neoplasms [a]	2.11	1.52–2.93	<0.0001	3.86	2.78–5.37	<0.0001
Respiratory and thoracic neoplasm [a]	0.46	0.31–0.68	<0.0001	0.87	0.59–1.29	0.496
Other and nonspecified neoplasm [a]	1.39	1.02–1.89	0.0396	2.41	1.76–3.29	<0.0001

CI = confidence interval; GI = gastrointestinal; HR = hazard ratio.
[a] Subdivision of "all nontesticular neoplasms".

Table 4 – Cause of death stratified by testicular histology.

Cause of death	Univariate analysis						Multivariate analysis					
	Nonseminoma			Seminoma			Nonseminoma			Seminoma		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Cardiovascular	0.48	0.3–0.77	0.0021	0.45	0.33–0.6	<0.0001	2.03	1.27–3.25	0.0032	1.04	0.78–1.39	0.7647
All nontesticular neoplasms	0.43	0.26–0.7	0.0006	0.73	0.59–0.91	0.0057	1.36	0.83–2.21	0.2178	1.46	1.17–1.82	0.0007
Infectious and parasitic	NR			NR			1.57	0.33–7.46	0.568	1.38	0.56–3.4	0.4782
Respiratory	NR			NR			1.079	0.23–4.98	0.9223	0.688	0.33–1.44	0.3209
GI neoplasms [a]	NR			NR			1.04	0.36–2.95	0.9456	1.26	0.8–1.98	0.3202
Genitourinary neoplasm (nontesticular) [a]	–	–	–	0.73	0.59–0.91	0.0057	–	–	–	1.56	0.91–2.7	0.1093
Hematologic neoplasms [a]	–	–	–	1.13	0.63–2	0.6821	–	–	–	2.09	1.18–3.72	0.0118
Respiratory and thoracic neoplasm [a]	NR			NR			0.73	0.22–2.45	0.6041	1.12	0.71–1.77	0.6382
Other and nonspecified neoplasm [a]	1.69	0.92–3.11	0.0933	1.05	0.67–1.67	0.8212	4.27	2.31–7.89	<0.0001	1.87	1.18–2.95	0.0073

CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; NR = not reported (models could not be run due to small numbers [n < 6]); – = no deaths recorded for this cause.
[a] Subdivision of "all nontesticular neoplasms".

Given the large size of our study and its length of follow-up, we were able to perform important subgroup analyses. During the 19.6-yr follow-up, there was an increased rate of CVD-related deaths in the NS group (HR 2.03 for NS). The seminoma group did not have increased CVD-related deaths. A possible explanation for the increased risk of CVD-related death in the NS group only is higher (double) exposure to chemotherapy than seminoma patients [19]. The proposed mechanism for CVD morbidity among testis cancer survivors is believed to be an increased prevalence of the metabolic syndrome. Chemotherapy exposure in testis cancer patients led to a 2.3-fold increased risk of metabolic syndrome compared with the general population [20]. The risk of CVD morbidity reported is up to 1.5–3.1-fold higher among testis cancer patients receiving chemotherapy [11,12,20]. Even so, Fung et al [21] reported an increased risk (HR 4.86) of CVD mortality during the 1 st year after chemotherapy, probably making the argument for

a multifactorial cause of CVD among testis cancer patients. Several reports suggested different ways to deal with this issue. In order to control CVD risk, Adams et al [22] evaluated high-intensity aerobic training for testis cancer patients and observed a 20% reduction in CVD risk. Feldman et al [23] applied the Framingham risk score to better assess at-risk testis cancer survivors who would benefit from closer screening and counseling.

In addition, our study showed that only seminoma patients had a significantly increased risk of nontestis cancer death (HR 1.46). This was particularly for hematologic neoplasms (HR 2.09). Travis et al [13] was the first to report medium- to long-term risks of secondary malignancies (relative risks of 1.5–3.6) with an average follow-up of 10.2–11.3 yr. Gastric and connective tissue cancers were the most prevalent secondary malignancies [13,14]. Fosså et al [24] noted an increased risk for secondary malignancies, but follow-up periods were not reported. Secondary malignancies following different cancer treatments are not limited to testis cancer. Increased secondary malignancies have been reported following radiation for Hodgkin's lymphoma and breast cancer [25–28]. This may explain the increased risk of secondary malignancies among seminoma patients in our study, as they are more likely to be exposed to radiation, either by radiation therapy or by surveillance scans.

Our study has yielded similar results to those published previously. Fung et al [21] demonstrated an increased risk of CVD, but only within the 1 st year after treatment. Haugnes et al [11] had a longer follow-up period of 20 yr and again showed an association between treatment for testis cancer using radiotherapy and/or chemotherapy and long-term increased risk of CVD. These results were again demonstrated in a study by van den Belt-Dusebout et al [12], who showed that even within their 5-yr follow-up, these individuals were at risk of experiencing myocardial infarction, which would be extremely rare among the general population. The increased risk of secondary malignancies was demonstrated in a medium-term follow-up study, which demonstrated an increased risk of death from hematopoietic malignancies as well as CVD [29]. Zagars et al [30] showed that secondary malignancy risk was elevated, but could be demonstrated only with 15 yr of follow-up. Fosså et al [31] demonstrated that beyond these previously mentioned outcomes, testis cancer survivors are also at increased risk of death from infections, digestive disease, and circulatory diseases when followed for >1 yr. The advantage of our study over those previously published is that we are able to capture the cause of death data encompassing many of these previously identified outcomes within one cohort and have follow-up matching the longest of these aforementioned studies.

The time lag from the initial treatment of testis cancer to the emergence of treatment-related mortality can be decades. The treating physicians may not be dealing directly with the late complications as it may be outside their specialty or time frame of practice (retired when complications occur). Thus, the risks of these late treatment side effects may be undervalued during shared decision-making and planning of testis cancer treatment. We believe that these risks of late-onset CVD and secondary malignancies should be discussed during initial patient counseling and surveillance. While others have proposed more rigorous measures [22,23], simple patient counseling regarding the importance of maintaining a healthy lifestyle with emphasis on physical activity can, and should, be a part of every patient encounter.

Our study is limited by its retrospective and population-based design. A major limitation of this study is the lack of data on adjuvant treatments, such as chemotherapy, radiation exposure, or retroperitoneal node dissection. NS patients have a poorer prognosis when matched for stage and have higher exposure to systemic chemotherapy; therefore, it may be assumed that the increased CVD risk in our study is secondary to chemotherapy exposure. Similarly, seminoma patients were more likely to be treated with radiation, which have been shown in previous studies to increase the risk of secondary malignancies.

Limitations of the CanCHEC database have been reported previously and include a selection bias influencing socioeconomic status, which possibly affects mortality rates [32]. Furthermore, information within the CanCHEC database is dependent on the accuracy of data coding. The absence of data regarding the different treatments for testis cancer within the cohort limits the conclusive relationship between treatment and specific mortality, as we could not perform a subgroup analysis with regard to different treatment groups. Moreover, the CanCHEC database lacks accurate data on confounding variables, such as smoking.

5. Conclusions

Long-term CVD mortality following the diagnosis of NS testis cancer has increased. The long-term risk of mortality from secondary malignancies is increased following the diagnosis of seminoma testis cancer. The findings of this study should be discussed as part of pretreatment patient counseling and follow-up patient encounters, with the aim of minimizing CVD risk factors and pursuing specific screening measures for secondary malignancies in these populations.

Author contributions: Nicholas E. Power 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: Lavi, Clark, Nair, Hetou, Power.
Acquisition of data: Lavi, Clark, Ly, Haan.
Analysis and interpretation of data: Ly, Haan, Lavi, Clark.
Drafting of the manuscript: Lavi, Clark, Nair, Hetou, Power.
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CRediT authorship contribution statement

Arnon Lavi: Conceptualization, Methodology, Investigation, Writing - original draft, Visualization, Project administration. **Roderick Clark:** Conceptualization, Methodology, Investigation, Writing - original draft, Project administration. **Tina Luu Ly:** Data curation, Formal analysis, Methodology, Resources, Software, Validation, Writing - original draft, Writing - review & editing. **Shiva M. Nair:** Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Khalil Hetou:** Conceptualization, Investigation, Methodology, Project administration, Validation, Writing - review & editing. **Michael Haan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - review & editing. **Nicholas E. Power:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2020.10.005.

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