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Long-term health effects among testicular cancer survivors

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Abstract
Purpose Testicular cancer is diagnosed at a young age and survival rates are high; thus, the long-term effects of cancer treatment need to be assessed. Our objectives are to estimate the incidence rates and determinants of late effects in testicular cancer survivors.
Methods We conducted a population-based cohort study of testicular cancer survivors, diagnosed 1991–2007, followed up for a median of 10 years. We identified 785 testicular cancer patients who survived ≥5 years and 3323 men free of cancer for the comparison group. Multivariate Cox regression analysis was used to compare the hazard ratio between the cases and the comparison group and for internal analysis among case patients.
Results Testicular cancer survivors experienced a 24 % increase in risk of long-term health effects >5 years after diagnosis. The overall incidence rate of late effects among testicular cancer survivors was 66.3 per 1000 person years. Higher risks were observed among testicular cancer survivors for hypercholesterolemia, infertility, and orchitis. Chemotherapy and retroperitoneal lymph node dissection appeared to increase the risk of late effects. Being obese prior to cancer diagnosis appeared to be the strongest factor associated with late effects.
Conclusions Testicular cancer survivors were more likely to develop chronic health conditions when compared to cancer-free men.
Implications for Cancer Survivors While the late effects risk was increased among testicular cancer survivors, the incidence rates of late effects after cancer diagnosis was fairly low.

Keywords Testicular cancer · Late effects · Cardiovascular disease · Obesity

Introduction

Approximately 244,110 men in the USA today are testicular cancer survivors [1]. Worldwide, approximately 52,549 cases

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and 9906 deaths occur due to testicular cancer each year [2]. Within the USA, the incidence rate for testicular cancer in Utah is among the highest [3]. The testicular cancer incidence rates have been increasing in the USA and most other regions of the world including Europe, Asia, and South America [4]. The 5-year relative survival rate among testicular cancer patients ≥20 years was 96.0 % for 1988–2001 [5].

Previous studies on late effects following testicular cancer treatment focused on death due to disease as the outcome rather than the incident disease [6]. Additionally, few studies have been population-based and instead focused on clinical populations that may not be representative of all testicular cancer patients. Previous studies included testicular cancer patients diagnosed up to the mid-1990s, and thus, analyses of a more contemporary cohort of testicular cancer patients who underwent more recent treatment regimens are needed. The aim of our study is to assess the incidence rates and potential determinants of late effects in a population-based cohort of testicular cancer survivors in Utah.

Methods

The Utah Population Database (UPDB) links data from the Utah Cancer Registry, part of the Surveillance, Epidemiology, and End Results (SEER) Program registries, to electronic medical records (EMR; 1991–present), driver licenses, voter registration, genealogical data, and vital records. We used the UPDB to identify patients (1) diagnosed with first primary testicular cancer (International classification of disease (ICD-O3) codes 62.0, 62.1, and 62.9) between 1991 and 2007; (2) survived ≥5 years following diagnosis; and (3) were ≥15 years old at the time of the diagnosis. Of the 1136 first primary testicular cancer patients diagnosed from 1991 to 2007 and were ≥15 years old at diagnosis, 1074 patients had survived for ≥5 years (94.5 %). Late-effect diseases and conditions of interest were assessed by linkage to electronic medical records from the University of Utah Health Sciences Center data warehouse (UUHSC) or Intermountain Healthcare hospital system data warehouse (Intermountain), which provide care to 85–90 % of patients in Utah. Of the 1074 testicular cancer survivors eligible for our study, 995 survivors had follow-up time for more than 1 year after diagnosis. Approximately 917 survivors had medical records in the UUHSC or Intermountain and were followed up for various diseases and conditions after cancer diagnosis (92.2 %). We also linked statewide ambulatory surgery and statewide inpatient hospital data to the testicular cancer cases and the cancer-free men.

Each testicular cancer case was matched to 4–5 cancer-free men on birth year, birth region, and the date of last residence in Utah (equal or later than case). Cancer-free men were thus alive at the time of the case's cancer diagnosis and have similar follow-up times since their last residence date in Utah was matched on. The cancer-free men were randomly selected from men in the UPDB, who have medical records at the UUHSC or Intermountain system.

The clinical characteristics, first course cancer treatment information, demographics and vital status of the cases and the cancer-free men were retrieved from the UPDB, the hospital electronic medical records and the Utah Cancer Registry. Body mass index (BMI) was calculated from the height and weight information from Driver's License Division data linked to the UPDB. Pre-diagnosis BMI (>1 year before cancer diagnosis) and post-diagnosis BMI were calculated for the testicular cancer survivors. For the comparison group, the BMI prior to entering the study and BMI after entering the study were calculated. Family history of testicular cancer and family history of any cancer (excluding skin cancer) was assessed for first-degree relatives, second-degree relatives, and cousins in the family history data within the UPDB.

A specific query of the medical conditions was conducted using ICD-9 and CPT (current procedural terminology) codes. We focused on conditions diagnosed 5 years after the testicular cancer diagnosis for myocardial infarction (MI), angina pectoris (AP), cardiomyopathy, heart failure, pericarditis, acute renal failure, chronic renal failure, nonspecific renal failure, restrictive pulmonary disease, infertility (azospermia, oligospermia and hypognadism-related infertility), dyslipidemia (hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein (HDL)), hypertension, hearing loss, peripheral neuropathy, osteoporosis, and orchitis. Metabolic syndrome was assessed by combining individuals who had BMI > 30 kg/m^2, high blood pressure, diabetes, and hypercholesterolemia. For the combined outcome of any late effects (from the list above), we did not include obesity since it was fairly common and was not identified to be a high-risk outcome among testicular cancer survivors in our data. This project was approved by the University of Utah and Intermountain Healthcare IRBs.

Statistical analyses were conducted in SAS version 9.3 and STATA version 12.1. The aims of our analysis were to (1) compare the incidence rates of each medical condition between the cases and the comparison group, and estimate the corresponding hazard ratio (HR); and (2) conduct an internal analysis among case patients to estimate the hazard ratios (HR) of the outcomes of interest (separately and combined) in association with clinical and demographic characteristics. The person-time at risk was defined from the date starting follow-up (date of cancer diagnosis or date of study entry for cancer-free men) to the date of developing an outcome, death or the last known date of residence in Utah. The last known date of residence in Utah is determined by whether the individual was observed in one of these records in Utah: birth certificate (for a child of the individual), marriage, divorce, hospital admissions, and cancer registry. Individuals who had the medical condition of interest before the date of cancer

diagnosis were not included in the analysis for that specific outcome since they had a prevalent condition. Multivariate Cox regression analysis with time since diagnosis or entry was used to compare the hazard ratio between the cases and the cancer-free men and for internal analysis among case patients. We adjusted on race as a potential confounder and stratified on race to account for matching.

For the internal analysis among the case patients, we presented the crude HR and the models adjusted for age at diagnosis, stage, histology, year of diagnosis, cancer treatment (orchiectomy, radiation, chemotherapy, retroperitoneal lymph node dissection (RPLND)) where appropriate. We selected these factors as potential confounders a priori. Of the 917 testicular cancer survivors, 132 were excluded from the analysis because they had less than 5 years of follow-up (n=785 included). An additional 172 were excluded from the case-only analysis because they had one of the diseases/conditions of interest as a comorbidity (prevalent case). An additional 27 testicular cancer survivors were excluded because their cancer stage was in situ or they had missing BMI. Thus, 588 testicular cancer survivors were included in the analysis of late effect determinants (Table 4). Cumulative incidence of late effects taking into account competing risks due to death was estimated in STATA [7]. To assess hazard ratio changes over follow-up time, we used the restricted cubic spline proportional hazards model [8].

Results

The median follow-up times were 10.0 years for the 785 testicular cancer survivors and 11.8 years for men in the comparison group. Of the 785 testicular cancer survivors, the majority was diagnosed at <35 years of age (median 31 years old) and at localized stage (Table 1). A higher proportion of testicular cancer survivors did not have any children (31.0 %) in comparison with the cancer-free men (26.6 %, Table 2).

The risk of late effects among testicular cancer survivors was increased by 24 % for conditions diagnosed >5 years after cancer diagnosis (Table 3). Five-year testicular cancer survivors did not have higher risks of cardiac diseases or cerebrovascular diseases compared to cancer-free men. Restricting the analysis to individuals who were followed up for at least 15 years did not yield different results (251 testicular cancer survivors and 997 men in the comparison group; results not shown). Higher risks were observed among testicular cancer survivors for the following diseases 5 years after cancer diagnosis: hypercholesterolemia, infertility, and orchitis.

Although treatment appeared to be a risk factor for late effects risks, the HR estimates changed between the crude and adjusted models, suggesting that the estimates are not stable. Older age at diagnosis (50+ years) was associated with an increased late effects risk (HR = 4.39, 95 % CI = 1.66–11.67) than younger age at diagnosis (<35 years; Table 4). Being obese at baseline was also associated with an increased risk of late effects (HR = 2.87, 95 % CI = 1.78–4.63).

All analyses were repeated restricting to the white population to assess any influence or race/ethnicity on our results; the results were consistent with those including all race/ethnicity groups.

Table 1 Characteristics of testicular cancer 5 years survivors diagnosed in Utah between 1991 and 2007 ($n = 785$)

	Number	Percent
Diagnosis year		
1991–1995	159	20.3
1996–2000	243	
2001–2005	292	37.2
2006–2007	91	11.6
Age at diagnosis		
15 - 25	495	63.1
25–29	120	15.3
30–34	80	10.2
35–39	61	7.8
40–58	29	3.7
Cancer stage at diagnosis		
Localized	563	71.7
Regional	132	16.8
Advanced/metastatic	80	10.2
Unknown	10	1.3
Histology		
Seminoma	429	54.7
Non-seminoma	161	20.5
Mixed germ cell tumors	195	24.8
Treatment		
Radical orchiectomy only	291	37.1
Radical orchiectomy + chemotherapy	168	21.4
Radical orchiectomy + radiotherapy	302	38.5
Other treatment[a]	24	3.1
Retroperitoneal lymph node dissection		
No	628	80.0
Yes	157	20.0

[a] Unknown, radiotherapy only, chemotherapy only, or radiation + chemotherapy + orchiectomy

Discussion

In our study, we observed a 24 % increase in late effects >5 years after cancer diagnosis among testicular cancer survivors. While testicular cancer survivors had an incidence rate of late effects of 66.3 per 1000 person years, men in the comparison group experienced an incidence rate of 57.1 per 1000.

Table 2 Characteristics of testicular cancer cases diagnosed in Utah between 1991 and 2007 and cancer-free men

	Testicular-cases (785)		Cancer-free (3323)	
	N	%	*N*	%
Birth year				
1943–1949	32	4.1	125	3.8
1950–1959	146	18.6	616	18.5
1960–1969	255	32.5	1090	32.8
1970–1979	271	34.5	1159	34.9
1980–1991	81	10.3	333	10.0
Race				
White	777	99.0	3122	94.0
Non-white	8	1.0	85	2.6
Unknown	0	0.0	116	3.5
Vital status				
Alive	766	97.6	3256	98.0
Dead	19	2.4	67	2.0
Age attained at the end of follow-up				
22–35	143	18.2	532	16.0
35–44	265	33.8	1166	35.1
45–54	249	31.7	1053	31.7
55–69	128	16.3	572	17.2
Follow-up period (years)				
5 to 10	281	35.8	1105	33.3
11 to 14	253	32.2	1221	36.7
15 to 19	200	25.5	877	26.4
20–21	51	6.5	120	3.6
Number of children				
0	243	31.0	883	26.6
1	114	14.5	512	15.4
2	168	21.4	691	20.8
3	129	16.4	596	17.9
4+	131	16.7	641	19.3
Body mass index at baseline[a]				
16–25 kg/m^2	284	36.2	1179	35.5
25–29.9 kg/m^2	348	44.3	1447	43.5
30–54 kg/m^2	141	18.0	675	20.3
Missing	12	1.5	22	0.7
Family history of testicular cancer				
No	758	96.6	3278	98.7
Yes	27	3.4	45	1.3
Family history of any cancer				
No	381	48.5	1586	47.7
Yes	404	51.5	1737	52.3

[a] BMI for controls is >1 year prior to study entry. BMI for cases is >1 year prior to cancer diagnosis

These differences suggest that although long-term health effects are fairly rare among testicular cancer survivors, they are nonetheless at a significantly increased risk for late effects.

Table 3 Late effects among testicular cancer survivors ($n = 785$) and cancer-free men ($n = 3323$), >5 year after diagnosis/ascertainment

	Incidence rate per 1000 PY			
	Cases	Cancer-free men	HR[a]	95 %CI
Any late effect	66.3	57.1	*1.24*	*(1.1,1.39)*
Number of any late effects				
1	3.8	4.0	1.02	(0.66,1.57)
2	5.9	5.3	1.28	(0.92,1.79)
3+	52.4	44.8	*1.22*	*(1.08,1.39)*
Cardiac diseases	22.2	19.8	1.15	(0.94,1.41)
Coronary heart disease[b]	1.2	1.3	0.93	(0.46,1.88)
Coronary heart disease[c]	1.3	1.4	0.88	(0.44,1.75)
Myocardial infarction	0.9	1.0	0.86	(0.39,1.89)
Angina	0.2	0.5	0.49	(0.11,2.17)
Heart failure	0.9	0.9	0.73	(0.29,1.79)
Cardiomyopathy	0.3	0.4	0.29	(0.04,2.24)
Cerebrovascular disease	0.6	0.9	0.67	(0.23,1.95)
Stroke	0.1	0.4	0.53	(0.07,4.24)
Transient ischemic attack	0.3	0.2	1.17	(0.24,5.76)
Aortic aneurysm	0.2	0.3	0.67	(0.08,5.86)
Diabetes	3.3	4.0	0.63	(0.39,1.00)
Hypertension	11.7	11.1	0.99	(0.77,1.28)
Hypercholesterolemia	6.3	3.9	*1.70*	*(1.19,2.41)*
Hypertriglyceridemia	0.7	0.6	1.00	(0.37,2.70)
Metabolic syndrome	1.7	1.1	0.97	(0.48,1.98)
Obesity	3.9	4.2	0.93	(0.61,1.42)
Osteoporosis	0.2	0.2	0.79	(0.17,3.73)
Peripheral neuropathy	4.4	3.0	1.29	(0.84,1.98)
Hearing loss	0.6	0.2	1.79	(0.57,5.64)
Restrictive lung disease	0.7	0.4	1.27	(0.49,3.31)
Pulmonary embolism	1.2	1.0	1.30	(0.62,2.74)
HIV	0.1	0.1	1.73	(0.1,30.76)
Renal failure	1.4	1.6	0.79	(0.4,1.55)
Infertility	1.7	0.5	*3.13*	*(1.48,6.61)*
Dyslipidemia	9.7	8.7	1.14	(0.86,1.49)
Orchitis	1.4	0.7	*2.52*	*(1.1,5.79)*

Italicized HRs are statistically significant

[a] Adjusted for race, stratified on matched group

[b] Includes angina and myocardial infarction

[c] Includes angina, myocardial infarction and heart failure

Previous studies on cardiovascular disease among testicular cancer patients reported increased risks of myocardial infarction [9], angina pectoris [9, 10], and associations between chemotherapy/radiation therapy and cardiovascular disease [11] and between coronary artery disease and chemotherapy [12]. These studies had median follow-up times of 18.4 years [10], 10.2 years [11] and 19 years [12]. Perhaps the length of follow-up (median 10.0 years, range of 5 to 21 years) was not

Table 4 Treatment, demographic factors and the risk of hypothesized late effects among testicular cancer survivors diagnosed in Utah between 1991 and 2007

	No event	Event	Crude HR (95 % CI)	Adjusted HR[a] (95 % CI)
Treatment				
Radical orchiectomy only	186	48	1.00	1.00
Radical orchiectomy and chemotherapy	83	32	1.33 (0.85,2.08)	*1.92 (1.06,3.47)*
Radical orchiectomy and radiotherapy	165	64	*1.47 (1.01,2.14)*	1.04 (0.61,1.78)
Other therapies[b]	6	4	1.49 (0.54,4.15)	1.6 (0.53,4.88)
Retroperitoneal lymph node dissection				
No	344	136	1.00	1.00
Yes	96	12	0.98 (0.54,1.79)	1.17 (0.62,2.23)
Stage				
Localized	328	111	1.00	1.00
Regional	72	23	0.96 (0.61,1.51)	1.12 (0.7,1.8)
Advanced	40	14	0.8 (0.46,1.39)	1.01 (0.54,1.88)
Year of diagnosis				
1991–1995	74	66	1.00	1.00
1996–2000	137	55	1.08 (0.73,1.6)	0.99 (0.67,1.47)
2001–2005	174	26	1.14 (0.68,1.93)	0.95 (0.54,1.65)
2006–2007	55	1	0.43 (0.06,3.2)	0.33 (0.04,2.63)
Age at cancer diagnosis				
<35	307	78	1.00	1.00
35–39	66	27	*1.55 (1,2.41)*	1.33 (0.85,2.09)
40–44	32	23	*2.18 (1.37,3.47)*	*1.99 (1.23,3.25)*
45–49	27	15	*2.06 (1.18,3.58)*	*1.93 (1.09,3.41)*
50+	8	5	*5.29 (2.12,13.19)*	*4.39 (1.66,11.67)*
Race				
White	436	147	1.00	1.00
Non-White	4	1	0.72 (0.1,5.17)	0.55 (0.08,4.04)
BMI				
<25 kg/m^2	191	37	1.00	1.00
25–29.9 kg/m^2	197	77	*1.85 (1.25,2.74)*	*1.65 (1.1,2.47)*
30+ kg/m^2	52	34	*2.88 (1.81,4.61)*	*2.87 (1.78,4.63)*
Marital status				
Divorced, widowed, unmarried	156	49	1.00	1.00
Married	284	99	1.06 (0.75,1.49)	0.98 (0.69,1.39)
Family history of any cancer				
No	221	73	1.00	1.00
Yes	219	75	0.84 (0.6,1.15)	0.82 (0.59,1.14)
Family history of testicular cancer				
No	428	142	1.00	1.00
Yes	12	6	1.91 (0.84,4.33)	1.81 (0.76, 4.31)

Italicized HRs are statistically significant

[a] Adjusted for age at diagnosis, stage, histology, year of diagnosis, treatment, RPLND where appropriate

[b] Unknown, radiotherapy only, chemotherapy only, or radiation + chemotherapy + orchiectomy

long enough in our study since testicular cancer patients are diagnosed at young ages and cardiovascular and cerebrovascular diseases are conditions associated with older age groups. Additionally, since the majority of testicular cancer patients (71.7 % in our patient group) are diagnosed at localized stage, perhaps the treatment regimens were not as severe as for other cancers; and thus, the risk of cardiovascular disease was not as high as expected. Another issue is the low tobacco prevalence in the Utahn population (10.6 % current smokers in 2012) [13], which may lead to lower cardiovascular disease risk among testicular cancer survivors than in other survivors that are from populations with higher smoking prevalence. Another reason may be the inclusion of more recent diagnosis years in our study (1991–2007). There has been a focus on adjusting testicular cancer treatments to minimize the long-term effects, such as restricting the areas of radiation exposure [14], which may have resulted in less cardiovascular disease risk. Consistent with our study, studies including more recently diagnosed patients did not report increased risks of cardiovascular disease death [15] or differences in the Framingham Risk Score for cardiovascular disease [16].

Our observation of an increased risk of hypercholesterolemia among testicular cancer patients was consistent with previous studies [17–19]. Peripheral neuropathy is a well-known acute adverse effect of testicular cancer treatment, but did not appear to be persistent after 5 years in our study [20]. Several studies focusing on peripheral neuropathy as a long-term effect have reported increased risk in contrast to our study [21–24].

Similar to the previous studies on hypercholesterolemia and peripheral neuropathy, studies on hearing loss, restrictive lung disease, pulmonary embolism, and infertility among testicular cancer patients have largely focused on reporting prevalence and have not reported on the risk of these long-term effects. We showed increased risks for infertility and orchitis in our population-based cohort of testicular cancer survivors.

An unexpected result in our study was that treatment and stage were not clear determinants of late effects in the long term. Further treatment details such as chemotherapy agent and dose may help to elucidate the association in future studies. Obesity, on the other hand, was a determinant of late effects, conferring an approximate twofold increase in late effects among testicular cancer survivors.

A limitation of the study is that misclassification of late effects may be possible if the ICD coding was not conducted consistently. Although the methodology to assess long-term effects among cases and cancer-free men were the same, it is likely that the testicular cancer survivors were more closely monitored in their follow up care for recurrences as well as general health. If this contributed to our results, we may expect to observe increases in risk for a wider variety of diseases, perhaps including cardiovascular disease. However, we did not observe such increases for various disease groups and we did not observe an association with cardiovascular disease risk. We also did not have data on quality of life or lifestyle factors such as tobacco, alcohol, and physical activity. BMI may act as a marker for physical activity, but it is drawn from the driver's license records, which are self-reported. However, we would not expect the reporting of height and weight to be different in the cases and comparison groups, particularly for the pre-diagnostic BMIs. Assessment of the risk of second primary tumors was difficult due to low numbers of cases ($n=25$). The use of electronic medical records excludes the possibility of recall bias, but if an individual leaves Utah, we would not be able to follow them up. However, our medical record linkage for late effects of 93.2 % is very high. Additionally, the emigration out of Utah is approximately 2.5 % according to the 2014 census estimates on state to state and moving abroad [25]. Finally, we did not have data on the chemotherapeutic agent in our study nor whether patients underwent multiple lines of chemotherapy, although cisplatin-based chemotherapy has been the standard of care for the testicular cancer survivors diagnosed during the period of our cohort.

Some strengths of our study include the population-based design covering the Utah population of approximately 2.9 million individuals. To our knowledge, this is one of the first population-based studies of testicular cancer survivors in the USA, which had incident disease information. We did not rely on patient recall since our study is based on electronic medical records; thus, recall bias is not an issue in our study. Our medical record linkage of 93.2 % is very high and difficult to achieve in other population-based cohort studies of cancer survivors or studies that rely on questionnaires. We also had long-term follow-up of 22 years (maximum) since the electronic medical records date back to 1991–1994. We are able to thus assess long-term effects of cancer treatment.

In conclusion, testicular cancer survivors in Utah were more likely to develop several chronic health diseases or conditions when compared to testicular cancer-free men, although the incidence rates were fairly low. Further studies to assess the quality of life and lifestyle behaviors such as smoking, drinking, and physical activity as potential determinants of late effects among of testicular cancer survivors would be of interest.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent The study used secondary data and did not involve any contact of participants. We obtained a waiver of consent for all individual participants included in the study with our IRB.

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