ARTICLE

Noncancer Causes of Death in Survivors of Testicular Cancer

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Background Although modern treatments for testicular cancer are associated with increased survival, the long-term health effects of these treatments are unclear. We conducted a population-based study to quantify the long-term risks of mortality from noncancer causes among men with testicular cancer.

Methods We identified 38 907 one-year survivors of testicular cancer within 14 population-based cancer registries in North America and Europe (from 1943 through 2002). We used data from these registries to calculate standardized mortality ratios (SMRs) for noncancer deaths and to evaluate associations between histology, age at testicular cancer diagnosis, calendar year of diagnosis, and initial treatment and the risk of noncancer mortality. All statistical tests were two-sided.

Results A total of 2942 deaths from all noncancer causes were reported after a median follow-up of 10 years, exceeding the expected number of deaths from all noncancer causes in the general population by 6% (SMR = 1.06, 95% confidence interval [CI] = 1.02 to 1.10); the noncancer standardized mortality ratios did not differ statistically significantly between patients diagnosed before and after 1975, when cisplatin-based chemotherapy came into widespread use. Compared with the general population, testicular cancer survivors had higher mortality from infections (SMR = 1.28, 95% CI = 1.12 to 1.47) and from digestive diseases (SMR = 1.44, 95% CI = 1.26 to 1.64). Mortality from all circulatory diseases was statistically significantly elevated in men diagnosed with testicular cancer before age 35 years (1.23, 95% CI = 1.09 to 1.39) but not in men diagnosed at older ages (SMR = 0.94; 95% CI = 0.89 to 1.00). Men treated with chemotherapy (with or without radiotherapy) in 1975 or later had higher mortality from all noncancer causes (SMR = 1.34, 95% CI = 1.15 to 1.55), all circulatory diseases (SMR = 1.58, 95% CI = 1.25 to 2.01), all infections (SMR = 2.48, 95% CI = 1.70 to 3.50), and all respiratory diseases (SMR = 2.53, 95% CI = 1.26 to 4.53). Testicular cancer patients who were younger than 35 years at diagnosis and were treated with radiotherapy alone in 1975 or later had higher mortality from all circulatory diseases (SMR = 1.70, 95% CI = 1.21 to 2.31) compared with the general population.

Conclusion Men who have survived for at least 1 year after being diagnosed with testicular cancer have a slightly higher risk of dying from noncancer causes, including infections, digestive diseases, and circulatory diseases, than the general population. Men treated with chemotherapy in 1975 or later may be at particularly high risk.

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The high survival rates associated with modern treatments for testicular cancer have been accompanied by increasing concern about the long-term adverse health effects of these treatments, including the development of second malignancies, cardiovascular morbidity, and infertility (1–5). Several reports (6–9) have evaluated the risks of death from non-neoplastic causes among men treated for testicular cancer compared with men in the general population. However, those studies were limited by the small number of cases

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See "Notes" following "References."

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CONTEXT AND CAVEATS

Prior knowledge

Modern treatments have improved the survival of men diagnosed with testicular cancer, raising concerns about the long-term health effects of these therapies with respect to the risk of death from noncancer causes.

Study design

A population-based study using data from cancer registries in North America and Europe to evaluate long-term trends in noncancer–specific mortality among men who had survived for at least 1 year after being diagnosed with testicular cancer.

Contribution

Compared with the general population, testicular cancer patients treated with chemotherapy in 1975 or later had higher risks of death from all noncancer causes, infections, circulatory diseases, and respiratory diseases. Patients who were diagnosed before age 35 years (regardless of treatment) had higher risks of death from all noncancer causes, infections, and circulatory diseases.

Implications

Additional investigations that include detailed information on treatment and comorbid conditions are needed to assess the incidence of the late effects of testicular cancer and its treatment. In addition, evidence-based studies are needed to develop optimal guidelines for patient follow-up and possible interventions aimed at reducing death rates from infection, digestive diseases, and circulatory diseases.

Limitations

The registry data lacked detailed information on radiotherapy fields and chemotherapeutic regimens and had no information on relapse therapy. Misclassification of cause of death could limit mortality estimates for specific disease subcategories, such as human immunodeficiency virus or hypertensive disorders.

in each series, which precluded precise quantification of those risks; moreover, all four studies focused on cardiovascular deaths. In this study, we analyzed the long-term risk of cause-specific, noncancer mortality among 38 907 one-year survivors of testicular cancer reported to population-based cancer registries, focusing on the impact of age at testicular cancer diagnosis, testicular cancer histology, calendar year of testicular cancer diagnosis, and initial treatment.

Patients and Methods

Patients

Men who were diagnosed with testicular cancer as a first primary malignancy from January 1, 1943, through December 31, 2001, and who survived for at least 1 year (n = 38 907) were identified from nationwide cancer registries in Denmark (inclusive period from 1943 through 1998), Sweden (from 1958 through 2000), Norway (from 1953 through 1999), and Finland (from 1953 through 2001); the Ontario (Canada) Cancer Registry (from 1964 through 2000); and from nine registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (from 1973 through 1999, except where noted), including those in Connecticut, Hawaii, Iowa, New Mexico, Utah, and the metropolitan areas of San Francisco–Oakland, Detroit, Seattle–Puget Sound (from 1974 through 1999), and Atlanta (from 1975 through 1999). Only men with seminomatous and nonseminomatous testicular tumors were included, and all other inclusion criteria have previously been described in detail (1). A subset of the patients included in this study (3378 men with testicular germ cell tumors reported to the Norwegian Cancer Registry from 1962 through 1997) were included in a previous report (9) that examined mortality rates; this study extended follow-up of those men and included another 989 patients who were reported to the Norwegian Cancer Registry.

Follow-up for each patient (except those from Norway) began 1 year after testicular cancer diagnosis; follow-up for patients from Norway began 1 year after testicular cancer diagnosis or January 1, 1961 (the date that cause-of-death information became available in Norway), whichever occurred later. Follow-up ended on the date of death, the last date the patient was known to be alive (for patients who were lost to follow-up before the study end date), or the study end date, whichever occurred first. The study end dates varied by registry and were December 31, 1999, for Denmark; December 31, 2000, for the SEER Program and Norway; December 31, 2001, for Ontario and Sweden; and December 31, 2002, for Finland.

Treatment

All registries, except those in Sweden and Ontario, routinely record information on the initial course of cancer therapy, which we categorized as "surgery only," "radiotherapy only," "chemotherapy only," "radiotherapy and chemotherapy," or "other/not specified." Standard initial treatment for testicular cancer consists of orchiectomy, and treatment after orchiectomy varies according to tumor histology [seminoma versus nonseminoma (10)] and extent of disease (1,11). Before 1975, the standard treatment after orchiectomy for seminoma patients who did not have metastases consisted of infradiaphragmatic radiotherapy (at doses of 30–40 Gy) targeted to fields that covered the para-aortic and ipsilateral iliac regions. A small number of seminoma patients without metastases were also given mediastinal irradiation, which was the standard therapy for patients with retroperitoneal lymph node metastases (6,7). Nonseminoma patients were also treated with infradiaphragmatic irradiation, but at higher target doses (45–50 Gy) and with or without retroperitoneal surgery. Treatment options for patients with distant metastases or disease relapse included combinations of various cytotoxic drugs (which frequently included cyclophosphamide, vinblastine, bleomycin, and doxorubicin), radiation, and/or surgery. However, few testicular cancer patients who presented with distant metastases at diagnosis and were treated with chemotherapy drugs that were available before 1975 survived for 1 year or longer.

After the widespread introduction of cisplatin-based chemotherapy for the treatment of testicular cancer in the mid-1970s, an increasing proportion of nonseminoma patients had retroperitoneal surgery alone or combined with chemotherapy after orchiectomy, and treatment with radiotherapy was gradually abandoned. However, infradiaphragmatic radiotherapy remained the most common treatment modality for seminoma even after 1975, although the typical doses were reduced from 30–40 Gy to 20–30 Gy and the size of the target field was reduced (12,13). Mediastinal irradiation was gradually omitted. Starting in the 1980s, increasing proportions of orchiectomized patients with seminoma or nonseminoma without metastases have been followed with a surveillance strategy as an alternative to infradiaphragmatic radiotherapy or retroperitoneal surgery (14,15).

All study registries collect data on the underlying cause of death as classified by International Classification of Disease (ICD) codes (Revisions 7–10) (16–20). Categories for nonmalignant causes of death were defined a priori as part of a common coding scheme that was used in an earlier mortality study reported by our group (21). We used ICD-7 and ICD-8 classifications to establish broad disease categories (e.g., infectious disease, cardiac diseases, respiratory diseases) because they included more broadly defined disease categories than later ICD versions. We then identified specific disease entities within each of the broad groups that were common to all ICD versions to create subcategories of disease (listed in the Appendix). All female-specific sites were excluded.

Statistical Methods

Person-years of follow-up and deaths from various causes were categorized by initial treatment (surgery only, radiotherapy only, chemotherapy only, radiotherapy and chemotherapy, or other/not specified), country, testicular germ cell tumor histology (seminoma versus nonseminoma), calendar year of testicular cancer diagnosis (before 1975 versus 1975 or later), and by 5-year categories of attained age, attained calendar year, age at diagnosis, and time since testicular cancer diagnosis. For categorical analyses of the influence of age at testicular cancer diagnosis, 35 years was used as the cut point because it was the approximate mean age of the cohort. General population mortality rates specific for each disease category, each registration area, male sex, and 5-year age and calendar-year intervals were multiplied by the person-years at risk to estimate the number of expected deaths. The observed and expected numbers of deaths were then summed over the appropriate subcategories, and the standardized mortality ratio (SMR) was calculated as their ratio (i.e., observed/expected). The 95% confidence intervals (CIs) were obtained by using an approximation that was based on the assumption of a Poisson regression model for the risk of mortality, as previously described by Liddell (22); exact methods were used when the observed number of deaths was five or fewer. Tests for differences in standardized mortality ratios or heterogeneity among several standardized mortality ratios were based on likelihood ratio methods. Two-sided *P* values are presented, and *P* value of .05 or less was considered to be statistically significant.

Results

Patient Characteristics

Among 38 907 one-year testicular cancer survivors in the study cohort, the median follow-up time was 10 years (range = 1–55 years), and 20 633, 7985, and 2142 patients were followed for at least 10, 20, and 30 years, respectively (Table 1). More than 80% of the men were diagnosed with testicular cancer after 1975, and approximately 50% of this subgroup was followed for at least 10 years. There were 7197 deaths among all patients, 2942 of which were due to noncancer causes. The cause of death was not known for 295 deaths (4.1%).

Overall Standardized Mortality Ratios and Latency

Mortality from all noncancer causes combined in the study cohort was slightly but statistically significantly higher than that expected in the general population (SMR = 1.06, 95% CI = 1.02 to 1.10) (Table 2). There was no indication that mortality from all noncancer causes declined with increasing time since testicular cancer diagnosis. Among all patients, the risk of dying from infections was higher than expected (SMR = 1.28, 95% CI = 1.12 to 1.47), and statistically significantly more deaths were observed than expected for all subcategories of infections evaluated. The risk of dying from intestinal infections was especially large (SMR = 9.10, 95% CI = 4.73 to 16.00), but this result was based on only 12 cases. Excess deaths due to all infections were highest 1–4 years after testicular cancer diagnosis (SMR = 1.60, 95% CI = 1.20 to 2.11) but were also evident in later time periods. Of the 68 deaths from viral infections, 57 were attributed to human immunodeficiency virus (HIV) (SMR = 1.34, 95% CI = 1.02 to 1.74); 49 deaths from HIV were reported in North American registries (43 in the SEER Program and six in Ontario; SMR for North America = 1.27, 95% CI = 0.94 to 1.68) and eight deaths from HIV were reported in European registries (SMR for Europe = 2.14, 95% CI = 0.92 to 4.21) (*P* for difference in standardized mortality ratios between continents = .20).

In this cohort, overall mortality from all digestive diseases was statistically significantly higher than that in the general population (SMR = 1.44, 95% CI = 1.26 to 1.64), but the excess deaths were not apparent until 10 years after testicular cancer diagnosis. Overall mortality from circulatory diseases did not exceed expectations; however, overall mortality from hypertensive disorders was statistically significantly increased compared with the general population (SMR = 1.39, 95% CI = 1.01 to 1.89). Mortality from all respiratory diseases, all genitourinary tract diseases, and all endocrine and metabolic diseases was higher than expected but not statistically significantly so. There was no evidence of excess mortality from external causes, including suicide.

Histology, Age at Diagnosis, and Calendar Year of Diagnosis

The standardized mortality ratios for most noncancer causes of death were generally higher for nonseminoma patients than for seminoma patients, but the differences were statistically significant only for mortality from other digestive diseases (i.e., digestive diseases other than gastric/duodenal ulcer or liver disease) ($P = .010$) (Table 3). Differences of marginal statistical significance ($P<.10$) were observed for all circulatory diseases ($P = .064$), ischemic heart disease ($P = .054$), endocrine and metabolic diseases ($P = .073$), and diabetes mellitus ($P = .096$).

In general, patients who were younger than 35 years when diagnosed with testicular cancer had higher standardized mortality ratios for most causes of death than patients who were 35 years or older at diagnosis. Among the major cause-of-death categories evaluated, these differences were statistically significant for mortality from all noncancer causes ($P = .006$), all infections ($P = .032$), and all circulatory diseases ($P<.001$). For mortality from all infections, statistically significant differences by age-group at diagnosis were seen for seminoma patients ($P = .05$) but not for nonseminoma patients ($P>.5$) (data not shown). Compared with the general population, mortality from all infections was statistically

Table 1. Description of population-based cohort of 38907 one-year survivors of testicular cancer*

Characteristic	No. of patients	Person-years of follow-up	No. of deaths by cause: All causes†	Testicular cancer	Nontesticular cancer	Noncancer
All testicular cancer patients	38907	451678	7197	2337	1623	2942
Germ cell tumor, seminoma‡	22328	267769	4429	849	1224	2199
Germ cell tumor, nonseminoma§	16579	183909	2768	1488	399	743
Age at testicular cancer diagnosis, y						
<20	1932	22981	246	158	35	40
20–29	12311	146199	1450	792	194	343
30–39	13744	161064	1967	669	445	753
40–49	6813	80300	1607	359	448	770
≥50	4107	41134	1927	359	501	1036
Calendar year of testicular cancer diagnosis						
Before 1975	6340	138352	3693	1156	906	1565
1975 or later	32567	313326	3504	1181	717	1377
Population-based cancer registry‖						
SEER Program (1973–1999)	13314	129195	1557	458	317	620
Denmark (1943–1998)	7610	102637	2264	685	546	942
Sweden (1958–2000)	5844	75308	1177	384	272	520
Ontario (1964–2000)	5985	70742	867	336	195	299
Norway (1953–1999)	4367	53108	965	322	229	410
Finland (1953–2001)	1787	20687	367	152	64	151
Follow-up interval entered, y¶						
1–4	38833	133376	2723	1909	219	495
5–9	29189	123761	1056	228	213	537
10–14	20633	84246	944	108	275	521
15–19	13380	52756	796	58	268	442
20–24	7985	29496	591	23	226	309
25–29	4167	14951	446	6	183	247
30–34	2142	7821	295	4	117	170
35–39	1070	3541	203	1	71	130
40–44	434	1277	97	0	35	62
≥45	167	454	46	0	16	29
Initial treatment for testicular cancer#						
Surgery only	8802	86226	1040	280	189	494
Radiotherapy only	12454	167636	3183	800	852	1413
Chemotherapy only	4586	38042	619	376	61	133
Radiotherapy and chemotherapy	777	7990	218	129	31	51
Other/not specified	459	5734	93	32	23	32

* All patients were diagnosed with testicular cancer as a first primary cancer and survived 1 year or more. SEER = Surveillance, Epidemiology, and End Results.

† Includes 295 deaths for which cause of death was missing.

‡ International Classification of Diseases for Oncology (ICD-O) (10) morphology codes 9060–9063.

§ ICD-O (10) morphology codes 9070–9073, 9080–9085, and 9100–9102.

‖ Inclusive of calendar years of testicular cancer diagnosis.

¶ In Norway, information on cause of death was not available until 1961. One-year survivors of testicular cancer in Norway who were diagnosed from January 1, 1953, through December 31, 1955, and who were alive on January 1, 1961, entered the cohort in the 5-9–year follow-up period. Therefore, the number of patients entering the 1-4–year follow-up interval (n = 38833) differs from the total number of patients in the cohort (n = 38907).

\# Numbers include only those patients reported to registries that collect data on initial course of cancer treatment (SEER Program, Denmark, Finland, and Norway). Data on subsequent therapy were not available in the registry records.

significantly elevated among patients diagnosed before age 35 years (SMR = 1.57, 95% CI = 1.25 to 1.96) and marginally statistically significantly elevated among those diagnosed at older ages (SMR = 1.15, 95% CI = 0.97 to 1.37, P = .10). A statistically significantly increased risk of death due to pneumonia was observed in patients diagnosed below the age of 35 years (SMR = 2.08 95% CI = 1.25 to 3.25). The standardized mortality ratio for all circulatory diseases was 1.23 (95% CI = 1.09 to 1.39) for patients diagnosed before age 35 years, but there was no evidence of excess mortality for patients who were diagnosed at older ages (SMR = 0.94, 95% CI = 0.89 to 1.00). The standardized mortality ratios for circulatory diseases were statistically significantly higher for patients diagnosed before the age of 35 years than for patients diagnosed at older ages for both seminoma (P = .022) and nonseminoma (P = .004). Among patients diagnosed with testicular cancer before age 35 years, standardized mortality ratios for circulatory disease were elevated primarily for patients at younger attained ages; the standardized mortality ratio for circulatory disease before age 50 years was 1.47 (95% CI = 1.23 to 1.76), whereas that for patients at attained ages of 50 years or older was 1.09 (95% CI = 0.93 to 1.28). (The 50-year cut point was used because of the similar number of deaths before and after this age among men

Table 2. SMR for noncancer causes of death according to time since testicular cancer diagnosis*

			Time since testicular cancer diagnosis, y									
	All patients		1–4		5–9		10–19		20–29		≥30	
Cause of death	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
Noncancer, all	2942	1.06 (1.02 to 1.10)	495	1.06 (0.97 to 1.16)	537	1.01 (0.93 to 1.10)	963	1.10 (1.04 to 1.18)	556	1.01 (0.93 to 1.10)	391	1.08 (0.98 to 1.19)
Infections, all	211	1.28 (1.12 to 1.47)	52	1.60 (1.20 to 2.11)	35	0.96 (0.67 to 1.34)	72	1.40 (1.10 to 1.77)	34	1.30 (0.91 to 1.83)	18	0.99 (0.59 to 1.58)
Intestinal infections	12	9.10 (4.73 to 16.00)	4	20.50 (5.59 to 52.52)	2	10.01 (1.21 to 36.12)	2	5.72 (0.69 to 20.70)	3	10.61 (2.19 to 30.98)	1	3.43 (0.05 to 19.19)
Viral infections	68	1.40 (1.09 to 1.79)	26	1.92 (1.26 to 2.82)	12	0.80 (0.41 to 1.40)	27	1.60 (1.06 to 2.33)	2	0.76 (0.09 to 2.77)	1	3.11 (0.08 to 17.36)
HIV	57	1.34 (1.02 to 1.74)	24	1.95 (1.25 to 2.92)	9	0.66 (0.30 to 1.26)	23	1.56 (0.99 to 2.35)	1	0.54 (0.01 to 3.04)	0	0.00 (0.00 to 29.75)
Pneumonia	102	1.27 (1.04 to 1.54)	15	1.24 (0.70 to 2.05)	16	1.16 (0.66 to 1.89)	35	1.51 (1.05 to 2.10)	22	1.27 (0.80 to 1.92)	14	1.00 (0.55 to 1.68)
Digestive diseases, all	222	1.44 (1.26 to 1.64)	27	1.04 (0.69 to 1.51)	33	1.04 (0.72 to 1.47)	85	1.62 (1.30 to 2.01)	53	1.85 (1.39 to 2.43)	24	1.54 (0.99 to 2.30)
Gastric/duodenal ulcer	32	1.67 (1.14 to 2.36)	3	1.08 (0.22 to 3.19)	6	1.85 (0.68 to 4.03)	12	2.09 (1.08 to 3.66)	8	1.96 (0.85 to 3.88)	3	0.89 (0.18 to 2.62)
Diseases of the liver	73	0.91 (0.72 to 1.16)	12	0.84 (0.43 to 1.47)	13	0.72 (0.39 to 1.24)	37	1.27 (0.90 to 1.75)	8	0.59 (0.25 to 1.16)	3	0.64 (0.13 to 1.88)
Other digestive diseases†	117	2.11 (1.75 to 2.53)	12	1.34 (0.69 to 2.35)	14	1.33 (0.73 to 2.24)	36	2.05 (1.44 to 2.84)	37	3.38 (2.38 to 4.67)	18	2.40 (1.43 to 3.80)
Circulatory diseases, all	1498	0.98 (0.94 to 1.04)	163	0.76 (0.66 to 0.90)	252	0.96 (0.85 to 1.09)	522	1.08 (1.00 to 1.18)	323	0.95 (0.85 to 1.07)	238	1.04 (0.91 to 1.18)
Heart disease, all	1117	0.97 (0.92 to 1.03)	126	0.78 (0.65 to 0.93)	192	0.95 (0.83 to 1.10)	411	1.11 (1.01 to 1.23)	230	0.90 (0.79 to 1.03)	158	0.96 (0.82 to 1.13)
Ischemic heart disease	911	0.93 (0.88 to 1.00)	106	0.78 (0.64 to 0.95)	157	0.93 (0.80 to 1.10)	334	1.06 (0.96 to 1.19)	193	0.87 (0.76 to 1.01)	121	0.87 (0.73 to 1.05)
Noncardiac circulatory diseases, all	298	0.98 (0.88 to 1.11)	29	0.71 (0.48 to 1.02)	52	1.06 (0.80 to 1.40)	82	0.91 (0.73 to 1.14)	72	1.04 (0.82 to 1.32)	63	1.16 (0.90 to 1.50)
Hypertensive disorders	42	1.39 (1.01 to 1.89)	3	0.61 (0.13 to 1.81)	5	0.83 (0.27 to 1.95)	14	1.37 (0.75 to 2.31)	10	1.73 (0.83 to 3.19)	10	3.02 (1.45 to 5.57)
Respiratory diseases, all	174	1.15 (0.99 to 1.34)	17	0.97 (0.57 to 1.56)	31	1.36 (0.93 to 1.94)	49	1.06 (0.79 to 1.41)	42	1.16 (0.84 to 1.58)	35	1.22 (0.86 to 1.71)
Chronic lower respiratory diseases	126	1.01 (0.84 to 1.21)	10	0.75 (0.36 to 1.39)	20	1.12 (0.68 to 1.73)	34	0.90 (0.63 to 1.27)	30	0.97 (0.66 to 1.40)	32	1.27 (0.87 to 1.80)
Other respiratory diseases§	48	1.94 (1.43 to 2.58)	7	1.78 (0.72 to 3.68)	11	2.40 (1.20 to 4.31)	15	1.89 (1.06 to 3.12)	12	2.37 (1.23 to 4.15)	3	0.94 (0.19 to 2.77)
Genitourinary tract diseases, all	54	1.27 (0.96 to 1.66)	6	0.86 (0.32 to 1.89)	11	1.39 (0.70 to 2.50)	22	1.68 (1.06 to 2.55)	6	0.71 (0.26 to 1.55)	9	1.47 (0.67 to 2.80)
Glomerular and tubulointerstitial diseases	20	1.45 (0.89 to 2.25)	2	0.73 (0.09 to 2.65)	7	2.29 (0.92 to 4.73)	6	1.30 (0.48 to 2.85)	3	1.23 (0.25 to 3.59)	2	2.20 (0.27 to 7.96)
Endocrine and metabolic disorders	93	1.17 (0.95 to 1.44)	10	0.80 (0.38 to 1.47)	16	1.04 (0.60 to 1.70)	34	1.28 (0.89 to 1.80)	20	1.25 (0.77 to 1.94)	13	1.44 (0.77 to 2.48)
Diabetes mellitus	70	1.14 (0.89 to 1.44)	6	0.66 (0.24 to 1.45)	10	0.88 (0.42 to 1.63)	27	1.31 (0.87 to 1.92)	14	1.07 (0.59 to 1.80)	13	1.71 (0.91 to 2.93)
External causes of mortality	391	0.97 (0.88 to 1.08)	119	1.02 (0.85 to 1.23)	111	1.05 (0.86 to 1.27)	108	0.91 (0.75 to 1.10)	30	0.70 (0.47 to 1.00)	23	1.25 (0.80 to 1.88)
Suicide and self-inflicted injury	135	0.99 (0.83 to 1.18)	43	1.14 (0.83 to 1.54)	45	1.24 (0.91 to 1.67)	36	0.85 (0.60 to 1.19)	9	0.60 (0.27 to 1.14)	2	0.39 (0.05 to 1.42)

* Specified causes of noncancer deaths not included in the table for which 20 or more deaths were reported included the following: mental disorders (number of deaths = 43, SMR = 0.71, 95% CI = 0.52 to 0.96); nervous system disorders (number of deaths = 63, SMR = 1.14, 95% CI = 0.88 to 1.47); diseases of the skin, subcutaneous tissue, and musculoskeletal system (number of deaths = 63, SMR = 5.52, 95% CI = 4.25 to 7.07); and senility (number of deaths = 73, SMR = 0.70, 95% CI = 0.56 to 0.89). Not all cause-of-death subcategories are specified, thus explaining differences in numbers. SMR = standardized mortality ratio; CI = confidence interval; HIV = human immunodeficiency virus.

† The most common causes of death were vascular disorders of the intestine (n = 27), diseases of the pancreas (n = 17), and cholelithiasis/cholecystitis/obstruction of the bile duct (n = 12).

§ The most common causes of death were pulmonary fibrosis/pneumoconiosis (n = 16) and pneumonitis due to inhalation of food or vomitus (n = 10).

Table 3. Standardized mortality ratio of death due to nonmalignant causes according to histology and age at and calendar year of testicular cancer diagnosis*

	Testicular cancer histology				Age at testicular cancer diagnosis (y)				Year of testicular cancer diagnosis			
	Seminoma		Nonseminoma		<35		≥35		Before 1975		1975 or later	
Cause of death	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**
Noncancer, all	2199	1.04 (1.00 to 1.09)	743	1.11 (1.04 to 1.20)	736	1.16 (1.08 to 1.25)	2206	1.03 (0.99 to 1.07)	1565	1.07 (1.02 to 1.13)	1377	1.04 (0.99 to 1.10)
Infections, all	145	1.22 (1.03 to 1.44)	66	1.45 (1.13 to 1.85)	79	1.57 (1.25 to 1.96)	132	1.15 (0.97 to 1.37)	81	1.22 (0.97 to 1.52)	130	1.32 (1.11 to 1.57)
Intestinal infections	9	8.69 (3.99 to 16.59)	3	10.59 (2.19 to 30.98)	5	21.59 (7.03 to 50.51)	7	6.44 (2.60 to 13.36)	4	5.13 (1.40 to 13.15)	8	14.86 (6.50 to 29.74)
Viral infections	34	1.25 (0.87 to 1.75)	34	1.60 (1.11 to 2.25)	47	1.46 (1.08 to 1.95)	21	1.29 (0.80 to 1.98)	7	1.99 (0.80 to 4.11)	61	1.36 (1.04 to 1.75)
HIV	30	1.29 (0.87 to 1.84)	27	1.40 (0.93 to 2.05)	40	1.34 (0.96 to 1.84)	17	1.33 (0.78 to 2.13)	4	1.92 (0.52 to 4.93)	53	1.31 (0.98 to 1.72)
Pneumonia	80	1.22 (0.97 to 1.53)	22	1.44 (0.91 to 2.19)	19	2.08 (1.25 to 3.25)	83	1.16 (0.93 to 1.45)	56	1.22 (0.93 to 1.59)	46	1.32 (0.97 to 1.77)
Digestive diseases, all	161	1.40 (1.19 to 1.64)	61	1.55 (1.19 to 2.00)	65	1.63 (1.26 to 2.08)	157	1.37 (1.17 to 1.61)	111	1.53 (1.26 to 1.84)	111	1.36 (1.12 to 1.64)
Gastric/duodenal ulcer	27	1.75 (1.16 to 2.56)	5	1.32 (0.43 to 3.10)	3	1.00 (0.21 to 2.97)	29	1.79 (1.20 to 2.58)	17	1.34 (0.78 to 2.15)	15	2.31 (1.30 to 3.82)
Diseases of the liver	56	0.98 (0.75 to 1.28)	17	0.74 (0.43 to 1.20)	26	1.00 (0.66 to 1.48)	47	0.87 (0.64 to 1.17)	26	0.82 (0.54 to 1.21)	47	0.98 (0.72 to 1.30)
Other digestive diseases	78	1.82 (1.44 to 2.28)	39	3.07 (2.19 to 4.21)	36	3.24 (2.27 to 4.49)	81	1.82 (1.45 to 2.27)	68	2.39 (1.86 to 3.04)	49	1.81 (1.34 to 2.40)
Circulatory diseases, all	1172	0.96 (0.91 to 1.02)	326	1.08 (0.97 to 1.21)	265	1.23 (1.09 to 1.39)	1233	0.94 (0.89 to 1.00)	885	0.97 (0.92 to 1.05)	613	0.99 (0.92 to 1.08)
Heart diseases, all	881	0.95 (0.90 to 1.02)	236	1.03 (0.90 to 1.17)	197	1.19 (1.03 to 1.37)	920	0.93 (0.88 to 1.00)	635	0.93 (0.86 to 1.01)	482	1.02 (0.94 to 1.13)
Ischemic heart disease	709	0.90 (0.84 to 0.98)	202	1.05 (0.92 to 1.22)	151	1.11 (0.95 to 1.31)	760	0.90 (0.84 to 0.97)	537	0.90 (0.83 to 0.98)	374	0.99 (0.90 to 1.10)
Noncardiac circulatory diseases, all	234	0.95 (0.84 to 1.09)	64	1.11 (0.86 to 1.42)	47	1.26 (0.93 to 1.68)	251	0.94 (0.84 to 1.07)	201	1.07 (0.93 to 1.23)	97	0.84 (0.69 to 1.04)
Hypertensive disorders	31	1.32 (0.90 to 1.87)	11	1.66 (0.83 to 2.98)	8	1.54 (0.66 to 3.04)	34	1.36 (0.95 to 1.91)	22	1.47 (0.93 to 2.24)	20	1.31 (0.80 to 2.03)
Respiratory diseases, all	143	1.17 (0.99 to 1.39)	31	1.06 (0.73 to 1.52)	23	1.18 (0.75 to 1.79)	151	1.15 (0.98 to 1.35)	98	1.14 (0.93 to 1.40)	76	1.16 (0.92 to 1.46)
Chronic lower respiratory diseases	107	1.06 (0.87 to 1.28)	19	0.80 (0.49 to 1.26)	13	0.84 (0.45 to 1.45)	113	1.03 (0.85 to 1.25)	79	1.09 (0.86 to 1.36)	47	0.90 (0.66 to 1.20)
Other respiratory diseases	36	1.84 (1.29 to 2.56)	12	2.30† (1.19 to 4.04)	10	2.67 (1.28 to 4.93)	38	1.81 (1.28 to 2.49)	19	1.55 (0.93 to 2.43)	29	2.33 (1.56 to 3.35)
Genitourinary diseases	45	1.31 (0.96 to 1.76)	9	1.09 (0.50 to 2.08)	7	1.31 (0.53 to 2.70)	47	1.26 (0.93 to 1.69)	32	1.26 (0.86 to 1.78)	22	1.29 (0.81 to 1.95)
Glomerular and tubulointerstitial diseases	14	1.30 (0.71 to 2.19)	6	2.01 (0.74 to 4.38)	4	1.75 (0.47 to 4.51)	16	1.39 (0.80 to 2.27)	10	1.47 (0.71 to 2.72)	10	1.44 (0.69 to 2.65)
Endocrine and metabolic disorders	62	1.04 (0.80 to 1.34)	31	1.56 (1.07 to 2.23)	21	1.09 (0.68 to 1.67)	72	1.20 (0.94 to 1.52)	42	1.19 (0.86 to 1.61)	51	1.16 (0.87 to 1.53)
Diabetes mellitus	47	1.00 (0.74 to 1.34)	23	1.55 (0.99 to 2.34)	14	1.03 (0.56 to 1.73)	56	1.17 (0.88 to 1.52)	36	1.28 (0.90 to 1.78)	34	1.01 (0.71 to 1.42)
External causes	256	1.03 (0.91 to 1.16)	135	0.88 (0.74 to 1.05)	180	0.85 (0.74 to 0.99)	211	1.10 (0.96 to 1.26)	154	1.08 (0.92 to 1.27)	237	0.91 (0.80 to 1.04)
Suicide and self-inflicted injury	83	0.97 (0.78 to 1.21)	52	1.02 (0.76 to 1.34)	68	0.95 (0.74 to 1.21)	67	1.03 (0.81 to 1.32)	41	0.80 (0.58 to 1.09)	94	1.11 (0.90 to 1.36)

* Not all cause-of-death subcategories are specified, thus explaining differences in numbers. SMR = standardized mortality ratio; CI = confidence interval; HIV = human immunodeficiency virus.

diagnosed with testicular cancer before the age of 35 years.) Standardized mortality ratios for external causes were statistically significantly lower in patients diagnosed before the age of 35 years than in patients who were 35 years or older at diagnosis ($P = .014$).

The standardized mortality ratios for men diagnosed with testicular cancer before 1975 did not differ statistically significantly from those for men diagnosed in 1975 or later for any of the cause-of-death categories shown in Table 3. The standardized mortality ratios for all noncancer conditions combined were 1.07 (95% CI = 1.02 to 1.13) for patients diagnosed before 1975 and 1.04 (95% CI = 0.99 to 1.10) for those diagnosed in 1975 or later ($P = .45$). Analyses restricted to the first 25 years of follow-up yielded similar results (data not shown). Standardized mortality ratios from all infections and from all digestive diseases were statistically significantly elevated among patients who were diagnosed with testicular cancer in 1975 or later. For all noncancer causes of death and all circulatory diseases, patterns of risk by age-group at diagnosis were similar for men diagnosed before and after 1975 (data not shown). Among patients who were diagnosed with testicular cancer before age 35 years in 1975 or later, mortality from all noncancer causes (SMR = 1.12, 95% CI = 1.01 to 1.24) and from all circulatory diseases (SMR = 1.43, 95% CI = 1.17 to 1.75) was statistically significantly elevated (data not shown).

Treatment

To evaluate the effects of more recent therapies for testicular cancer on noncancer mortality, we calculated the standardized mortality ratios for noncancer causes of death in testicular cancer patients who were diagnosed in 1975 or later (Table 4). Among all 1-year testicular cancer survivors, mortality from all noncancer causes of death and from all circulatory diseases was statistically significantly increased in patients whose treatment included chemotherapy, and there was no indication of an increased mortality risk for patients treated with radiotherapy only or surgery only. Among patients who received chemotherapy with or without radiotherapy, the standardized mortality ratios (data not shown) were 1.34 (95% CI = 1.15 to 1.55) for all noncancers; 1.58 (95% CI = 1.25 to 2.01) for all circulatory diseases; 2.48 (95% CI = 1.70 to 3.50) for all infections, and 2.53 (95% CI = 1.26 to 4.53) for all respiratory diseases. Compared with the general population, patients who were younger than 35 years at diagnosis and were treated with radiotherapy only had statistically significantly increased mortality from all noncancer causes (SMR = 1.21, 95% CI = 1.01 to 1.44) and from all circulatory diseases (SMR = 1.70, 95% CI = 1.21 to 2.31). Mortality from all noncancer causes (SMR = 1.31, 95% CI = 1.15 to 1.50) and from all circulatory diseases (SMR = 1.36, 95% CI = 1.14 to 1.63) was also increased for patients who were younger than 35 years at diagnosis, diagnosed before 1975, and treated with radiotherapy only. The standardized mortality ratios for all infections were highest among men whose treatment included chemotherapy, regardless of their age at diagnosis, and were also statistically significantly elevated for all men treated with surgery alone. Among men who received radiotherapy only, the standardized mortality ratio for all infections was higher in patients diagnosed before age 35 years than in patients diagnosed at age 35 years or older ($P = .10$). Compared with the general population, mortality from all digestive diseases was statistically significantly higher among all patients who received radiotherapy alone (SMR = 1.61, 95% CI = 1.21 to 2.10) and among patients diagnosed before age 35 years who received surgery alone (SMR = 2.08, 95% CI = 1.03 to 3.71). The highest standardized mortality ratios for respiratory diseases were observed in men whose treatment included chemotherapy.

Table 4. Standardized mortality ratios for nonmalignant causes of death in 1-year survivors of testicular cancer diagnosed in 1975 or later according to initial therapy for testicular cancer*

	Surgery only		Radiotherapy only		Chemotherapy only		Radiotherapy and chemotherapy	
Cause of death, age at diagnosis (y)	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**
Noncancer, all	307	1.05 (0.93 to 1.17)	523	1.00 (0.91 to 1.09)	131	1.26 (1.05 to 1.49)	41	1.65 (1.18 to 2.24)
<35	107	1.20 (0.98 to 1.45)	127	1.21 (1.01 to 1.44)	60	1.12 (0.85 to 1.44)	14	1.50 (0.82 to 2.51)
≥35	200	0.98 (0.85 to 1.13)	396	0.94 (0.85 to 1.04)	71	1.41 (1.10 to 1.78)	27	1.75 (1.15 to 2.54)
Infections, all	36	1.45 (1.02 to 2.01)	43	1.14 (0.82 to 1.53)	28	2.48 (1.64 to 3.58)	4	2.51 (0.68 to 6.43)
<35	17	1.43 (0.83 to 2.30)	20	1.55 (0.94 to 2.39)	20	2.61 (1.59 to 4.03)	1	1.15 (0.03 to 6.42)
≥35	19	1.46 (0.88 to 2.29)	23	0.93 (0.59 to 1.39)	8	2.20 (0.95 to 4.33)	3	4.13 (0.85 to 12.08)
Digestive system diseases, all	27	1.48 (0.98 to 2.15)	55	1.61 (1.21 to 2.10)	5	0.74 (0.24 to 1.74)	4	2.21 (0.60 to 5.66)
<35	11	2.08 (1.03 to 3.71)	13	1.66 (0.88 to 2.84)	2	0.70 (0.08 to 2.52)	3	4.29 (0.89 to 12.54)
≥35	16	1.24 (0.71 to 2.01)	42	1.60 (1.15 to 2.16)	3	0.78 (0.16 to 2.28)	1	0.90 (0.02 to 5.01)
Circulatory diseases, all	115	0.91 (0.76 to 1.10)	245	0.95 (0.84 to 1.08)	48	1.44 (1.06 to 1.91)	21	2.06 (1.27 to 3.14)
<35	18	1.18 (0.70 to 1.86)	40	1.70 (1.21 to 2.31)	15	1.69 (0.94 to 2.78)	3	1.53 (0.32 to 4.48)
≥35	97	0.88 (0.71 to 1.07)	205	0.88 (0.76 to 1.01)	33	1.35 (0.93 to 1.89)	18	2.18 (1.29 to 3.45)
Respiratory diseases, all	16	1.11 (0.63 to 1.80)	30	0.99 (0.67 to 1.42)	9	2.66 (1.21 to 5.04)	2	2.09 (0.25 to 7.54)
<35	2	1.78 (0.22 to 6.43)	2	1.24 (0.15 to 4.47)	2	2.94 (0.36 to 10.61)	1	7.58 (0.19 to 42.21)
≥35	14	1.05 (0.58 to 1.77)	28	0.98 (0.65 to 1.42)	7	2.59 (1.04 to 5.33)	1	1.21 (0.03 to 6.75)

* SMR = standardized mortality ratio; CI = confidence interval.

Heterogeneity Between North America and Europe

There was no evidence of statistically significant heterogeneity in the standardized mortality ratios for all noncancer causes of death (P = .31) between North America and Europe or among the six countries whose cancer registries were used to identify testicular cancer survivors (P = .45). The standardized mortality ratios for all noncancer causes of death were 1.03 (95% CI = 0.97 to 1.10) for North America and 1.07 (95% CI = 1.03 to 1.12) for Europe. There was little evidence of heterogeneity between continents for the overall standardized mortality ratios for all infections (P = .48), all circulatory diseases (P>.5), all digestive diseases (P = .20), or all respiratory diseases (P = .14); there was also no statistically significant heterogeneity among countries (P>.15 for all comparisons).

Among patients who were diagnosed with testicular cancer before age 35 years, the standardized mortality ratios for all noncancer causes of death were 1.06 (95% CI = 0.94 to 1.20) for patients in North America and 1.22 (95% CI = 1.12 to 1.34) for patients in Europe (P for difference = .065); the standardized mortality ratios for all circulatory diseases were 1.32 (95% CI = 0.04 to 1.65) and 1.20 (95% CI = 1.04 to 1.39), respectively (P for difference>.5). Standardized mortality ratios for all infections did not differ statistically significantly (P>.5) between the two continents. However, patients diagnosed with testicular cancer before age 35 years showed statistically significant heterogeneity among countries in the standardized mortality ratios for all noncancer causes of death combined (P = .04) and in the standardized mortality ratios for circulatory diseases (P = .037).

Discussion

This is, to our knowledge, the first large international population-based study to evaluate long-term trends in cause-specific mortality among testicular cancer patients during three decades of follow-up. More than 2900 noncancer deaths formed the basis of our comparisons to nonmalignant causes of mortality among men in the general population. New findings include increased risks of dying from noncancer causes among patients whose treatment included chemotherapy and among patients who were diagnosed with testicular cancer before age 35 years, regardless of the treatment they received. In particular, we found that patients treated with chemotherapy had statistically significantly higher risks of death from all noncancer causes, infections, circulatory diseases, and respiratory diseases and that patients diagnosed before age 35 years had statistically significantly higher risks of death from all noncancer causes, infections, and circulatory diseases. Overall, the excess risk of death from all noncancer causes was slightly (6%) but statistically significantly higher than expected, and there was no evidence that any of the standardized mortality ratios differed by calendar year period of testicular cancer diagnosis (pre-1975 versus 1975 or later).

Four investigations (6–9) have examined mortality from noncancer causes in testicular cancer survivors. Limitations of these studies included not only the focus on cardiovascular causes but also the small numbers of deaths from noncancer causes (range = 23–181), the inclusion of irradiated seminoma patients only (6–8), the restriction to one referral center (6), and the exclusion of patients older than age 55 years (9). Any discrepancies among these studies (6–9) are likely explained, at least in part, by these limitations. To our knowledge, no study has evaluated the influence of chemotherapy or surgery on noncancer mortality in testicular cancer survivors.

Circulatory Diseases

Several recent studies (3,23–26) and a review article (27) have documented the heightened cardiovascular risk profiles (e.g., increased serum levels of lipids and/or inflammatory markers) and increased cardiac morbidity in testicular cancer patients who have undergone modern chemotherapy. Cisplatin-based chemotherapy for testicular cancer may be associated with systemic endothelial cell dysfunction (24) and cardiovascular morbidity (2,3,23,25,27). Excess deaths due to hypertension, which can be related to cisplatin-associated renal dysfunction (28) or the development of the metabolic syndrome (23,26), may have contributed to the excess deaths due to circulatory diseases that we observed among the testicular cancer patients who were treated with chemotherapy in 1975 or later. Associations between radiotherapy for testicular cancer and cardiac mortality have been previously reported (2,3,6–9,29). For example, Fosså et al. (9) found a small increased risk of death from circulatory disorders (SMR = 1.21, 95% CI = 1.0 to 1.5) among testicular cancer survivors, the majority of whom were treated with radiotherapy. Hanks et al. (7), Zagars et al. (6), and Lederman et al. (29) observed a statistically significant twofold increase in the risk of cardiac death among testicular cancer patients, particularly among those who received mediastinal radiotherapy. A recent Dutch study (2) documented an increased incidence of cardiac complications after mediastinal radiotherapy for testicular cancer. Increased cardiac morbidity and mortality following thoracic irradiation has also been described in survivors of Hodgkin lymphoma or breast cancer (30,31). Mediastinal radiation adversely affects the myocardium, epicardium, and autonomic nervous system and may enhance arteriosclerosis in coronary vessels (32). Variations in the use of mediastinal radiotherapy in different series may explain, in part, the range of reported estimates for cardiac complications. Mediastinal radiotherapy was, for example, used to treat 40% of patients in the series by Hanks et al. versus an estimated 16% of the patients in this study (33).

We observed excess mortality from circulatory diseases in testicular cancer patients who were younger than 35 years at diagnosis and were treated with radiotherapy alone. Age and radiation dose are important risk factors for cardiovascular disease. Two reviews (32,34) have documented the association between younger age at the time of radiation exposure and the increased risk of developing heart disease in patients treated for Hodgkin lymphoma and breast cancer. In addition, Carr et al. (35) evaluated the risk of coronary heart disease after radiotherapy for peptic ulcer disease and found that the risk of coronary heart disease increased progressively with age at exposure (35). Although our finding of statistically significantly increased risks of death due to circulatory diseases in irradiated patients below the age of 35 years is consistent with those reported in other studies of cancer survivors (32,34), it is possible that the discordant findings between patient populations reflect differences in the doses of cardiac radiation. After 1975, radiotherapy for testicular cancer consisted largely of irradiation to infradiaphragmatic fields, in which only the most inferior parts of the heart received exposure, resulting in an average cardiac dose of 0.7 Gy (3). Excess cardiac morbidity has been reported at radiation doses as low as 0.5 Sv (comparable to 0.5 Gy) in the Japanese atomic bomb survivors (36); however, the magnitude of the increased risk at such low doses is currently uncertain. It is also possible that the radiation-related excess of circulatory deaths observed among patients treated before 35 years of age could have been mediated in part by damage to the renin–angiotensin system, resulting from renal doses of 6–10 Gy received during infradiaphragmatic radiotherapy (1,28,37).

After chemotherapy with or without radiotherapy, we observed a statistically significantly increased risk of death due to circulatory diseases. Cardiotoxic chemotherapy agents, such as doxorubicin, increase the risk of cardiomyopathy, in particular after radiation (38,39). This cytotoxic drug was frequently used alone or in combination with radiotherapy to treat metastatic and relapsing testicular cancer in the 1970s and early 1980s, a practice (40,41) that may explain, in part, the statistically significantly increased mortality from circulatory diseases we observed in patients whose treatment included chemotherapy. Cardiotoxicity associated with anthracyclines is also related to the cumulative dose, with the risk increasing with increasing age (38).

Infections

Excess mortality due to infection has not been previously reported in 1-year survivors of testicular cancer. Our finding of statistically significantly increased risks of HIV-related deaths may reflect previously reported associations between HIV infection and testicular cancer (42–48). Although testicular cancer is not an acquired immunodeficiency syndrome–defining malignancy, it occurs with increased frequency in individuals with HIV infection (42), and some (44,45), although not all (46), studies have described a statistically significantly increased risk of testicular cancer in HIV patients. The clinical behavior of testicular cancer in patients with HIV does not appear to differ from that of testicular cancer in the general population, and 5-year testicular cancer–free survival is similar among both groups (47). However, compared with testicular cancer survivors without HIV infection, worse overall survival has been reported in HIV patients with germ cell tumors due to HIV-related mortality (43,48), and this finding was supported by the results of our study.

Not surprisingly, we observed the highest risk (SMR = 1.60, 95% CI = 1.20 to 2.11) of death due to all infections in the 1- to 4-year period after chemotherapy. This increased mortality risk may reflect persistently reduced bone marrow reserves after prolonged intensive primary treatment or the administration of salvage chemotherapy after the first year (49). For example, in the 1970s and early 1980s, most patients with metastatic testicular cancer received maintenance chemotherapy for more than 1 year (50,51). The increased mortality from infection we observed in patients treated with surgery only for testicular cancer may reflect possible underreporting of adjuvant chemotherapy, but it could also be due to postoperative complications resulting from more extensive surgery in patients who relapsed after the introduction of cisplatin-based chemotherapy (52). The persistence of excess deaths from infections in the second and third decades after testicular cancer diagnosis likely reflects the administration of salvage chemotherapy. In addition, although chronic lung fibrosis after mediastinal radiotherapy and/or bleomycin-containing chemotherapy is most often asymptomatic in long-term testicular cancer survivors, it may result in an increased risk of death due to infectious pneumonia many years after treatment (53,54). The more frequent use of bleomycin in nonseminoma patients may explain, in part, the statistically significant standardized mortality ratio for pneumonia we observed in patients diagnosed before age 35 years.

Diseases of the Digestive System

The increased incidence of gastric and duodenal ulcers in irradiated testicular cancer patients is well established (55–57), and we observed statistically significant excess deaths due to these conditions in our cohort. These ulcers reflect the fact that abdominal radiotherapy induces chronic atrophy of the gastrointestinal mucosa and/or intestinal ischemia due to thickening of the intimae of large and small vessels, followed by necrosis and perforation of the bowel wall and hemorrhage (58–61). Typically, these anatomical changes develop over several years, and as a result, increased mortality due to radiation-induced arterial stenosis has not been observed until 10 or more years after radiotherapy (62). Postradiation fibrosis in the upper retroperitoneal space (63) may also lead to life-threatening dysfunction of the bowel, liver, and/or pancreas. The statistically significantly increased risks of death from digestive disorders after surgery for testicular cancer in 1975 or later that we observed were largely restricted to men who were younger than 35 years at diagnosis, a finding that should probably be viewed in the context of the increased use of more extensive surgery, particularly among younger nonseminoma patients, from 1975 onward.

Diseases of the Respiratory System

The statistically significantly increased risk of death from respiratory diseases we observed among testicular cancer patients given chemotherapy in 1975 or later is noteworthy in view of the well-established association between bleomycin and pulmonary fibrosis (53). Although the overall finding was based on only nine patients, seven of the patients were 35 years or older at testicular cancer diagnosis, which is consistent with reports of enhanced pulmonary toxicity of bleomycin-containing chemotherapy in older patients (54).

Comments

Our study has several strengths. It included a large number of men who were diagnosed with testicular cancer for a 50-year period, which allowed us to evaluate the influence of testicular cancer histology, age at diagnosis, calendar year of diagnosis, and initial treatment on cause-specific mortality. The population-based nature of our investigation allowed comparisons with mortality rates among men in the general population. The limitations of our study include those inherent to investigations based on data from cancer registries, including a lack of detailed information on radiotherapy fields and chemotherapeutic regimens and no information on relapse therapy. Moreover, the findings we report are most appropriately interpreted as averages for all countries and do not necessarily apply to each of the individual countries. This interpretation is particularly appropriate for findings pertaining to patients who were younger than 35 years at testicular cancer diagnosis, for whom we found evidence of heterogeneity among countries in the standardized mortality ratios for all noncancers and for all circulatory diseases. In addition, because our analyses pertaining to initial treatment were, of necessity, restricted to the registries that collect such data (i.e., SEER, Denmark, Finland, and Norway), our results for younger patients may not be generalizable to patients in Ontario and Sweden. Finally, any misclassification of cause of death is most likely to be a limitation when calculating standardized mortality ratios for specific disease subcategories, such as HIV or hypertensive disorders, but less of a concern when comparing broad categories such as all infections or all circulatory diseases. Because cause of death was missing for 4.1% of the deaths, all the standardized mortality ratios are slightly biased downward.

In conclusion, we found that 1-year survivors of testicular cancer had a small increased risk of death from noncancer causes compared with the general population and that risks did not appear to decline during the three or more decades after the testicular cancer diagnosis. Overall, men treated for testicular cancer in 1975 or later experienced statistically significantly 1.3- to 1.4-fold increased risks of death from infections and digestive diseases compared with the general population, and the patterns of excess mortality differed according to their age at testicular cancer diagnosis and the initial therapy they received. The estimated excess absolute risk, calculated as (observed deaths – expected deaths)/(number of person-years), was 3.7 deaths per 10 000 person-years compared with 61.4 deaths per 10 000 person-years that would be expected if general population rates prevailed. Chemotherapy as applied in 1975 or later was associated with an increased risk of cardiovascular death. Patients diagnosed with testicular cancer in 1975 or later before age 35 years experienced excess mortality due to circulatory diseases following radiotherapy only in spite of reduced target doses and target fields. Additional long-term follow-up studies of testicular cancer patients that include detailed information on treatment and comorbid conditions will be required to adequately assess the incidence of the sequelae of testicular cancer and its treatment. Future evaluations should comprehensively analyze the interactions of therapy for testicular cancer with other genetic and environmental determinants in the development of late effects (64). Moreover, evidence-based studies are needed to develop optimal guidelines for patient follow-up and possible interventions aimed at reducing death rates from infection, digestive diseases, and circulatory diseases (64). In the interim, clinicians and patients should be aware of recently published strategies for the long-term medical care of testicular cancer survivors (65).

Appendix Table. International Classification of Disease (ICD) codes according to ICD version and disease category

	ICD			
Cause of death	**Revision 7**	**Revision 8**	**Revision 9**	**Revision 10**
Infectious diseases, all	001–008, 010–074, 080–096, 100–108, 110–117, 120–138, 340, 480–483, 490–493	000–027, 030–046, 050–057, 060–068, 070–117, 120–136, 320, 470–474, 480–486	001–018, 020–088, 090–139, 279.5, 279.6, 320–322, 480–487	A00–B99, G00, G03, J10–J18
Intestinal infections	040–043, 045–048	000–004, 006, 008–009	001–009	A00–A09
Viral diseases	080–085, 091, 092, 094	040–046, 050–057, 060–068, 071–079	042–075, 077–079, 138, 279.5, 279.6	A80, A82, A90–A99, B05, B15–B24
Human immunodeficiency virus infection	Not identified	Not identified	042–044, 279.5, 279.6	B20–B24
Pneumonia	490–493	480–486	480–486	J12–J18
Diseases of the digestive system, all	530–545, 550–553, 560, 561, 570–587	520–537, 540–543, 550–553, 560–577	520–579	K00–K92
Gastric and duodenal ulcer	540, 541	531–533	531–533	K25–K27
Diseases of the liver	581	571	571	K70–K76
Other digestive diseases	530–539, 542–545, 550–553, 560, 561, 570–580, 582–587	520–530, 534–537, 540–543, 550–553, 560–570, 572–577	520–530, 534–570, 572–579	K00–K24, K28–K69, K77–K92
Diseases of the circulatory system, all	330–334, 400–402, 410–416, 420–422, 430–434, 440–447, 450–456, 460–468	390–398, 400–404, 410–414, 420–438, 440–448, 450–458	390–398, 401–405, 410–438, 440–459	I00–I99
Rheumatic heart disease	400–402, 410–416	390–392, 393–398	390–398	I00–I09
Hypertensive heart disease	440–443, 444–447	400–404	401–405	I10–I13
Ischemic heart disease	420–422	410–414	410–414	I20–I25
Cerebrovascular disease	330–334	430–438	430–438	I60–I69
Diseases of arteries	450–456	440–448	440–444, 446–448	I70
Miscellaneous circulatory diseases	430–434, 460–468	420–429, 450–453, 454–458	415.1, 427, 415.0, 415.2–415.9, 416–426, 428, 429, 451–455, 445, 449, 450, 456–459	I26–I51, I71–I99
Diseases of the respiratory system, all	470–475, 500–502, 510–527	460–466, 490–493, 500–508, 510–519	460–466, 470–478, 488–519	J00–J09, J19–J98

(Appendix continues)

Appendix Table (continued).

Cause of death	ICD Revision 7	ICD Revision 8	ICD Revision 9	ICD Revision 10
Chronic lower respiratory diseases	501, 502	490–493	490–496	J40–J47
Other diseases of respiratory tract	511–527	501–508, 510–519	488, 489, 497–499, 500–519	J00–J06, J30–J39, J60–J98
Diseases of genitourinary system, all	590–594, 600–617, 620–637	580–584, 590–607, 610–629	580–608, 610–629	N00–N98
Glomerular, tubulointerstitial diseases	590–594	580–584	580–589	N00–N15
Endocrine, metabolic, and certain immune disorders, all	240–245, 250–254, 260, 270–277, 280–289, 294–299	240–246, 250–258, 260–279	240–259, 270–279.4, 279.7–279.9	E00–E88
Diabetes mellitus	260	250	250	E10–E14
External causes of morbidity and mortality, all	E800–E802, E810–E835, E840–E866, E870–E895, E900–E904, E910–E965, E970–E985, E990–E999	E800–E807, E810–E823, E825–E845, E850–877, E880–E887, E890–E978, E980–E999	E800–E848, E850–888, E890–E999	V01–Y89
Suicide and self-inflicted injury	E963, E970–979	E950–E959	E950–E959	X60–X84

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Notes

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