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Cardiovascular Disease in Survivors of Adolescent and Young Adult Cancer: A Danish Cohort Study, 1943–2009

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Background Cardiovascular disease has emerged as a serious late effect in survivors of adolescent and young adult cancer, but risk has not been quantified comprehensively in a population-based setting.

Methods In the Danish Cancer Registry, we identified 43 153 1-year survivors of cancer diagnosed at ages 15 to 39 years (1943–2009) and alive in 1977; from the Danish Civil Registration System, we randomly selected a comparison cohort of the same age and sex. Subjects were linked to the Danish Patient Register, and observed numbers of first hospitalizations for cardiovascular disease (*International Classification of Diseases, Tenth Revision* codes I10–I79) were compared with the expected numbers derived from the comparison cohort. We calculated the absolute excess risks attributable to status as a survivor of cancer and standardized hospitalization rate ratios (RRs). All statistical tests were two-sided.

Results During follow-up, 10 591 survivors (24.5%) were discharged from the hospital with cardiovascular disease, whereas 8124 were expected (RR = 1.30; 95% confidence interval [CI)] = 1.28 to 1.33; $P < .001$). The absolute excess risks were 400 and 350 extra cases of cardiovascular disease per 100 000 person-years for people aged 20 to 59 and 60 to 79 years at discharge, respectively. Survivors of Hodgkin lymphoma experienced high risks for being hospitalized with valvular disease (RR = 12.2; 95% CI = 9.9 to 15.0; $P < .001$). Survivors of leukemia had high risks for cerebral hemorrhage (RR = 10.3; 95% CI = 5.5 to 19.1; $P < .001$) and cardiomyopathy (RR = 8.6; 95% CI = 4.3 to 17.3; $P < .001$).

Conclusions Survivors of adolescent and young adult cancer are at increased risk for cardiovascular disease throughout life, although each main type of adolescent and young adult cancer had its own risk profile.

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Patients treated for cancer during adolescence and young adulthood, defined as ages 15 to 39 years, are at risk for late complications of treatment. The 5-year survival of patients in Europe with any type of cancer diagnosed at age 15 to 24 years is 87% (1), indicating that most have a long life expectancy. The most frequently reported physical late effects are second primary cancers, cardiovascular and pulmonary complications, endocrine and metabolic disorders, and fertility problems (2,3).

Information on the long-term outcomes of survivors of adolescent and young adult cancer, diagnosed at ages 15 to 21 years, comes from the North American Childhood Cancer Survivor Study (4). The cancer pattern of patients at ages 15 to 39 years differs from those of children and of older adults (eg, testicular cancer, lymphomas, and tumors of the brain and nervous system are more frequent in men and cervical cancer, malignant melanoma, and cancer of the breast are more frequent in women) (5). Further, the biology of site-specific cancers among adolescents and young adults is distinct from that of children and older adults (6).

Although several studies have assessed long-term outcomes among survivors of Hodgkin lymphoma and testicular cancer among patients with adolescent and young adult cancer (ages 15–39 years) (2), the long-term outcomes of survivors of other cancers occurring in young adulthood, such as cervical cancer, breast cancer, malignant melanoma, and brain tumor, remain understudied. We therefore conducted a population-based cohort study of 1-year survivors of adolescent and young adult cancer and assessed the rates of hospitalization for various cardiovascular conditions and compared them with those of a cancer-free subset of the Danish population.

Methods

Cancer Survivors and Comparison Cohort

The basic adolescent and young adult cancer cohort was comprised of 53 212 people who had been reported to the Danish Cancer Registry with a first primary cancer diagnosed at aged 15 to 39 years during 1943–2009 and who were alive on April 2, 1968, when the Danish Civil Registration System was started. The Danish Cancer Registry has recorded incident cases of cancer nationwide since 1943, with diagnostic information from multiple

sources, ensuring close to 100% coverage (7). Cancers were classified according to the *International Classification of Diseases, Seventh Revision* in the period from 1943 to 1977, *International Classification of Diseases for Oncology* in the period from 1978 to 2003, and according to the *International Classification of Diseases, Tenth Revision* (ICD-10) thereafter. Since the start of the Civil Registration System, all inhabitants of Denmark have been given a 10-digit personal identification number that incorporates sex and date of birth and permits accurate linkage of population and outcome registers (8).

Because we were not assigned permission to receive identifiers for all Danish inhabitants in the age range 15 to 39 years (approximately 1.8 million persons in 2000), we estimated rates of morbidity of cardiovascular disease in the general Danish population by use of a comparison cohort taken at random from the Civil Registration System; for each survivor of adolescent and young adult cancer, we chose five cancer-free comparison subjects who were born in Denmark, alive at the date of diagnosis of their respective survivor, and of the same sex and year of birth (ie, a total of 266 060 comparison subjects). Information on vital status and migration during follow-up was obtained from the Civil Registration System for both cohorts.

Before linking survivors and comparison subjects to the Danish Patient Register, we excluded those who had died or emigrated before the start of this register on January 1, 1977 (n = 4114 survivors; n = 2058 comparison subjects) and those who had died or emigrated during the first year after the cancer diagnosis or an equivalent period for the population comparison cohort (n = 4114; n = 1089). This resulted in a cohort of 44 984 1-year survivors of adolescent and young adult cancer and a comparison cohort of 262 913 individuals in the general population of Denmark (Figure 1).

Hospital Contacts for Cardiovascular Disease

The Patient Register contains individual information on virtually all nonpsychiatric hospital admissions in Denmark since January 1, 1977, and since 1995, all outpatient activities and emergency room contacts have been included (9). Each admission initiates a record, which includes the personal identification number, dates of admission and discharge, a primary discharge diagnosis, and up to 19 supplementary diagnoses coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) and ICD-10. For adolescent and young adult cancer survivors and population comparison subjects, we identified all hospital admissions with a primary or supplementary discharge diagnosis of cardiovascular disease (ICD-8 codes: 400–448; ICD– 10 codes: I10–I79). Linkage to the Patient Register revealed that 1545 survivors and 6152 comparison subjects were admitted to hospital for a cardiovascular condition before the date of cancer diagnosis or the equivalent date for the corresponding comparison subjects, and these were excluded from the study. Furthermore, we excluded people who were notified as having a chromosome abnormality (ICD-8: 759.3–759.5; ICD– 10: Q90–Q99) (n = 47 survivors; n = 251 comparison subjects) or a congenital heart malformation (ICD-8: 746, 747; ICD-10: Q20–Q28) (n = 239 survivors; n = 997 comparison subjects) because it was considered that these conditions might confound any causal association between cancer treatment and cardiovascular late effects. Thus, 43 153 1-year survivors of adolescent and young adult cancer and 255 513 population comparison subjects remained for analysis; see also the flow chart in Figure 1. Table 1 shows the distribution on type of cancer by age at cancer diagnosis. Supplementary Table 1 (available online) shows characteristics of the survivors of adolescent and young adult cancer.

Statistical Analyses

To avoid inclusion of most acute, nonpersistent, treatment-induced cardiovascular conditions, follow-up for a diagnosis of cardiovascular disease began 1 year after the date of diagnosis of cancer and the corresponding date for the equivalent comparison subjects or January 1, 1977, whichever occurred latest, and ended on the date of death (n = 11 648 survivors; n = 25 840 population comparison subjects), date of emigration (n = 308; n = 3381), disappearance (n = 15; n = 61), or the closing date of December 31, 2010 (n = 25 879; n = 199 225). Follow-up was also ended if a second primary cancer was diagnosed in a survivor (n = 5303) or a first primary cancer was diagnosed in a population comparison subject (n = 27 006). Diagnostic categories of ICD-8 were adapted to the categories of ICD-10 to the extent possible. For study subjects hospitalized more than once for a certain cardiovascular disease, only the first record was retained because it was presumed to reflect the date of diagnosis.

Risk analyses were carried out for any cardiovascular disease, for each of nine main diagnostic categories, and for each of a selected set of diagnostic entities within the main diagnostic categories. The observed numbers of first hospitalizations for each diagnosis among survivors were compared with expected numbers derived from the sex-, age-, and calendar period–specific morbidity rates of the comparison cohort. The statistical significance and 95% confidence intervals (CIs) of the standardized hospitalization rate ratio (RR; observed-to-expected hospitalizations for each disease entity) were estimated assuming that the observed number of first hospitalizations follows a Poisson distribution. The absolute excess risks (AERs; ie, the survivors' additional risks for a hospital discharge diagnosis of cardiovascular disease) were derived as the difference between observed and expected first hospitalization rates for cardiovascular disease among the survivors per 100 000 person-years of follow-up with corresponding 95% confidence intervals. The choice of five times as many comparison subjects as survivors in our study yielded a statistical power close to that of a full-scale study (ie, a study based on the entire Danish population).

Because a portion of cardiovascular disease among survivors of cancer might be secondary to other treatment-related or disease-related diseases, such as diabetes mellitus (ICD-10: E10–E14), chronic obstructive pulmonary disease (ICD-10: J40–J44), and chronic kidney disorders (ICD-10: N18), we also report rate ratios for those conditions. The cumulative risk was calculated as $100 \times (1 - \exp(-\text{cumulative rate}/100))$. The statistical analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-sided. This study was approved by the Danish Data Protection Agency (J. no. 2011-41-6351).

Results

The cohort of 43 153 1-year adolescent and young adult cancer survivors (60.2% women) was followed up in the Patient Register for a total of 627 455 person-years (mean = 15 years; range = 0–34 years),

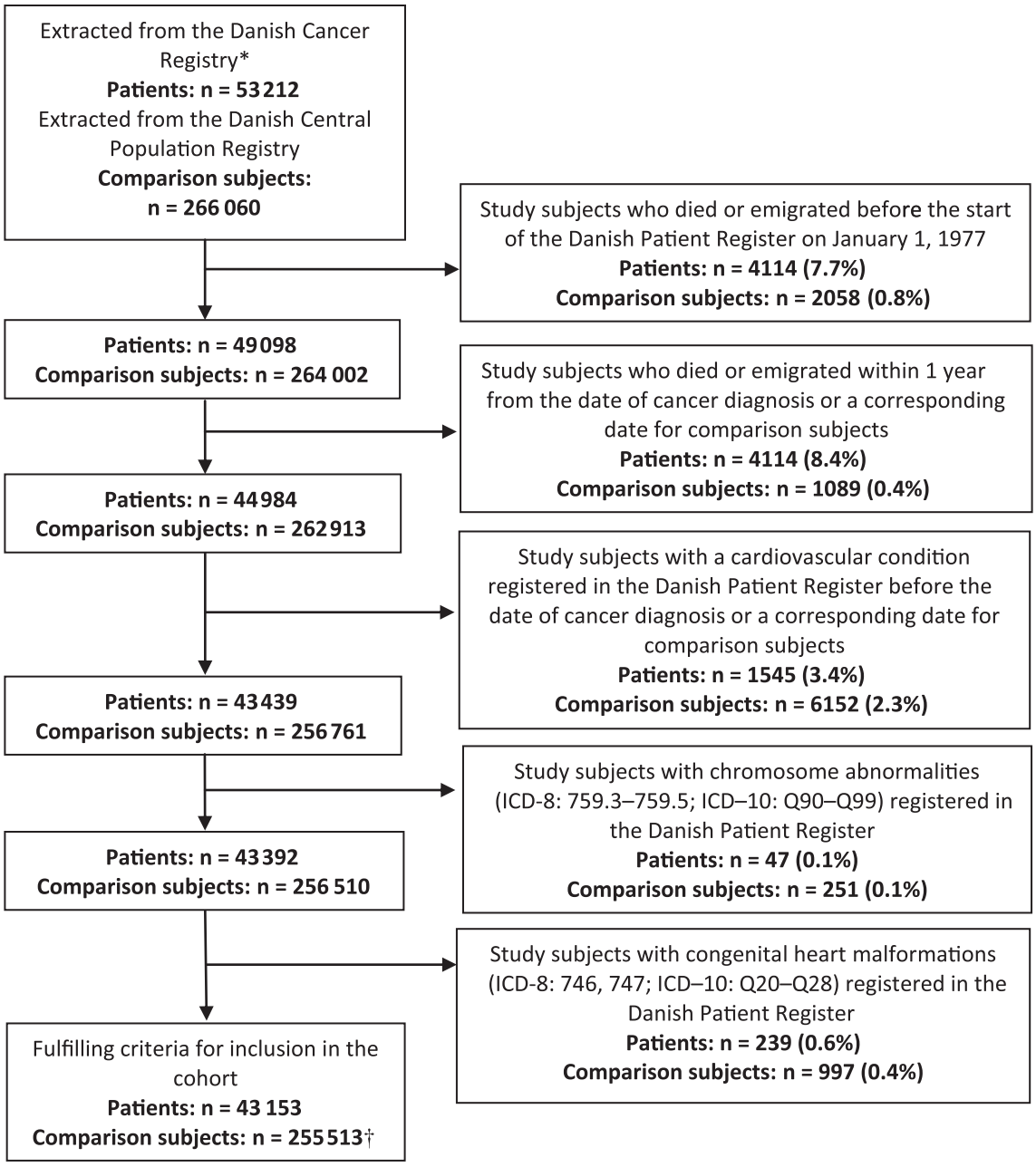

Figure 1. Flow chart for the cohort of adolescent and young adult cancer patients and their population comparison subjects. *Patients were diagnosed with a first primary cancer at age 15 to 39 years in the period from 1943 to 2009 and were alive on April 2, 1968, when the Civil Registration System was started. †Selection of comparison subjects with replacement. ICD-8 = *International Classification of Diseases, Eighth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*.

during which time 10 591 (24.5%) survivors were hospitalized for at least one cardiovascular disease; 8124.2 would have been expected, yielding a statistically significantly increased rate ratio of 1.30 (95% CI = 1.28 to 1.33; $P < .001$) (Table 2). The observed and expected overall hospitalization rates for cardiovascular disease were 1688 and 1294.8 per 100 000 person-years, respectively, and the absolute excess risk was 393 (Table 2). Thus, for each additional year of follow-up, a cardiovascular disease, attributable to status as a survivor of cancer, was diagnosed in an average of four of 1000 survivors.

In each age group, the hospitalization rate for cardiovascular disease among survivors was higher than expected (Figure 2), indicating that the risk remains markedly increased throughout life (Table 2). The extent of increase diminished considerably with increasing age on a relative scale (reflecting the increase in background disease rates with age), from a rate ratio of 6.7 in the group aged 16 to 19 years at follow-up to 1.1 in those aged 70 to 79 years. However, the absolute burden of excess disease did not vary notably over ages at observation. The age-specific absolute excess risk was approximately 800 extra cardiovascular hospitalizations per 100 000 person-years for survivors aged 16 to 19 years, and then stabilized at approximately 400 extra cases for those aged 20 to 59 years, with a modest drop to 350 at 60 to 79 years (Table 2).

Table 1. Distribution of the 10 most frequent sites of cancer among 43 153 1-year survivors of adolescent and young adult cancer diagnosed at ages 15 to 39 years in Denmark, 1943–2009

		Age at diagnosis, y				
	All patients	15–19	20–24	25–29	30– 34	35–39
Site of cancer (ICD-10)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Cervix (C53)	7093 (16.4)	7 (0.3)	270 (6.2)	1241 (16.1)	2343 (19.8)	3232 (19.3)
Testis (C62)	6479 (15.0)	313 (12.7)	1000 (22.8)	1677 (21.7)	1900 (16.1)	1589 (9.5)
Breast (C50)	5731 (13.3)	5 (0.2)	57 (1.3)	435 (5.6)	1515 (12.8)	3719 (22.2)
Malignant melanoma of skin (C43)	5668 (13.1)	228 (9.2)	650 (14.9)	1218 (15.8)	1616 (13.7)	1956 (11.7)
Brain (C71, C751–C753, D330–D332, D430–D432, D352–D354, D443–D445)	2922 (6.8)	470 (19.0)	453 (10.3)	584 (7.6)	716 (6.1)	699 (4.2)
Hodgkin lymphoma (C81)	2123 (4.9)	354 (14.3)	509 (11.6)	518 (6.7)	403 (3.4)	339 (2.0)
Non-Hodgkin lymphoma (C82–C85, C883–C889)	1336 (3.1)	146 (5.9)	141 (3.2)	233 (3.0)	330 (2.8)	486 (2.9)
Ovary (C56, C570–C574)	1148 (2.7)	77 (3.1)	161 (3.7)	179 (2.3)	285 (2.4)	446 (2.7)
Thyroid (C73)	1053 (2.4)	87 (3.5)	141 (3.2)	205 (2.7)	296 (2.5)	324 (1.9)
Leukemia (C91–C95)*	963 (2.2)	188 (7.6)	146 (3.3)	162 (2.1)	205 (1.7)	262 (1.6)
Other sites†	8637 (20.1)	599 (24.2)	849 (19.5)	1268 (16.4)	2221 (18.7)	3700 (22.0)
Total, % of total	43 153 (100)	2474 (5.7)	4377 (10.1)	7720 (17.9)	11 830 (27.4)	16 752 (38.8)

* Lymphatic leukemia, myeloid leukemia, monocytic leukemia, other and unspecified leukemia.

† Cancers of the colon (n = 869), urinary bladder (n = 808), connective tissue (n = 779), spinal cord, cranial nerves and other and unspecified parts of the central nervous system (n = 643), meninges (n = 593), bones, joints, and articular cartilage (n = 536), rectum and anus (n = 486), corpus uteri (n = 445), salivary glands (n = 388), lung (n = 304), and sites with fewer than 300 cases (n = 2786).

Table 2. Observed and expected numbers of first hospitalizations for cardiovascular disease of any type by sex and attained age among 43 153 1-year survivors of adolescent and young adult cancer (17 185 men and 25 968 women)*

	All cardiovascular disease					
	No. of first hospitalizations			Hospitalization rate†		
Study group	Observed	Expected	RR (95% CI)	Observed	Expected	AER† (95% CI)
Both sexes	10 591	8124.2	1.30 (1.28 to 1.33)	1688	1294.8	393 (359 to 427)
Men	3998	2977.5	1.34 (1.30 to 1.39)	1633	1216.0	417 (364 to 470)
Women	6593	5146.7	1.28 (1.25 to 1.32)	1723	1345.2	378 (334 to 422)
Attained age, y						
16–19	22	3.3	6.7 (3.7 to 12.2)	951	141.9	809 (408 to 1211)
20–29	288	124.4	2.3 (2.0 to 2.7)	731	315.8	415 (328 to 502)
30–39	1520	891.9	1.7 (1.6 to 1.8)	1068	626.4	441 (385 to 497)
40–49	2721	1903.6	1.4 (1.4 to 1.5)	1407	984.1	423 (367 to 478)
50–59	2399	1928.3	1.2 (1.2 to 1.3)	1881	1511.8	369 (290 to 448)
60–69	1929	1666.8	1.2 (1.1 to 1.2)	2512	2170.2	341 (223 to 459)
70–79	1286	1159.5	1.1 (1.1 to 1.2)	3621	3264.2	356 (147 to 565)
Years since diagnosis						
<5	1404	698.7	2.0 (1.9 to 2.1)	1210	602.2	608 (544 to 672)
5–9	1294	898.1	1.4 (1.4 to 1.5)	1092	758.1	334 (274 to 395)
10–19	2538	1955.0	1.3 (1.3 to 1.4)	1408	1084.8	324 (268 to 379)
20–29	2435	1926.8	1.3 (1.2 to 1.3)	2074	1641.0	433 (350 to 516)
30–39	1823	1566.9	1.2 (1.1 to 1.2)	2814	2418.8	395 (266 to 525)
40–49	881	857.5	1.0 (1.0 to 1.1)	3493	3399.5	93 (-138 to 324)
50–59	209	209.4	1.0 (0.9 to 1.1)	4123	4130.6	-8 (-567 to 551)

* AER = absolute excess risk; CI = confidence interval; RR = standardized hospitalization rate ratio.

† Per 100 000 person-years.

We stratified the cohort into survivors of cancer diagnosed in 1943 to 1959 (n = 3786; 71 894 person-years), 1960 to 1974 (n = 6006; 142 519 person-years), 1975 to 1989 (n = 13 151; 243 861 person-years), and 1990 to 2009 (n = 20 210; 169 180 person-years). Data derived from outpatient visits (available since 1995) were not included in Figure 3, A and B. For the same attained ages, the cumulative risks for a hospital diagnosis of cardiovascular disease were not statistically significantly different; however, survivors of both sexes diagnosed with cancer in the earliest calendar period (years 1943–1959) tended to have a slightly higher cumulative risk when compared with the other calendar period (years 1960–2009) (Figure 3, A and B).

Male survivors whose cancers were diagnosed when they were aged 15 to 19 years had the highest cumulative risk of hospitalization

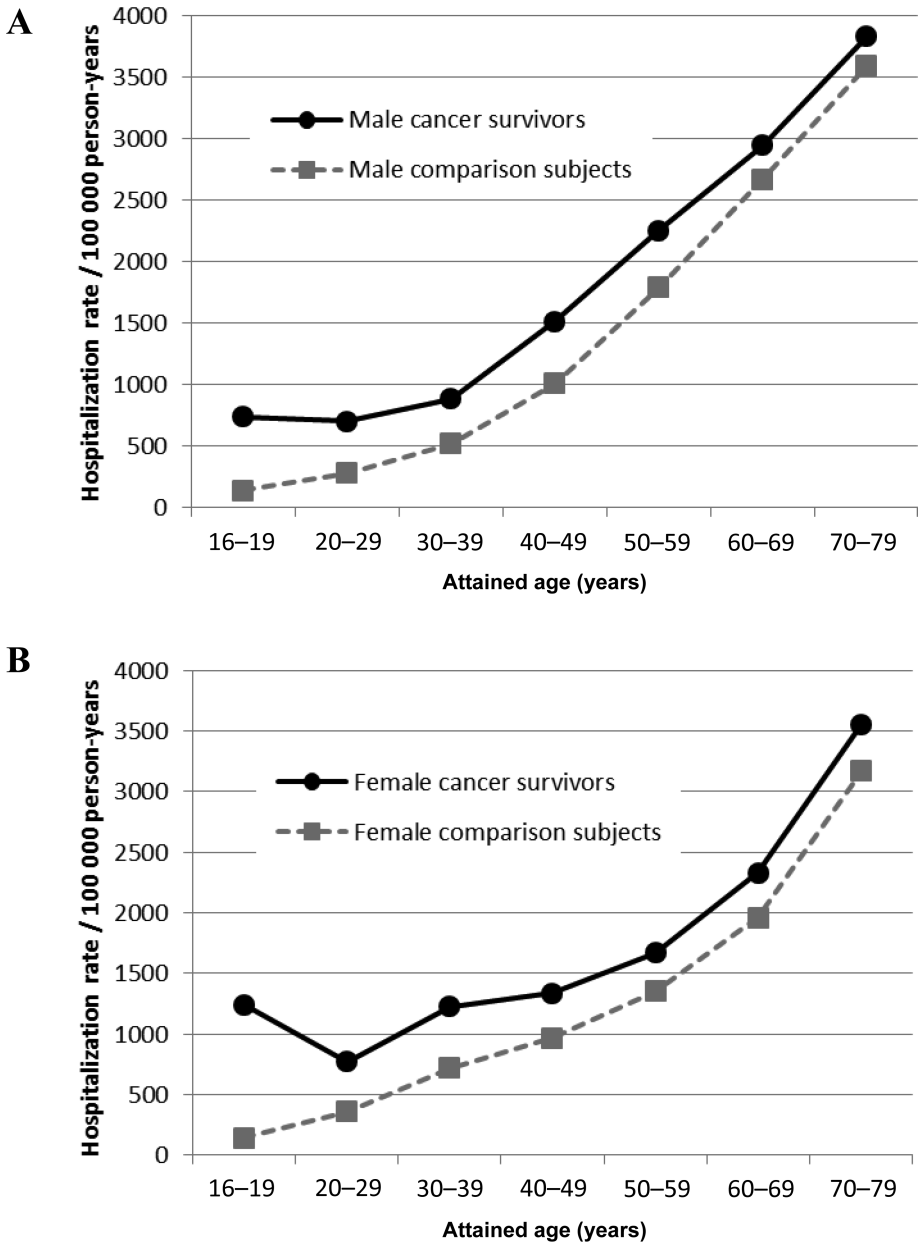

Figure 2. Hospitalization rate per 100 000 person-years among survivors of adolescent and young adult cancer and among population comparison subjects. **A**) Male cancer survivors and male comparison subjects. **B**) Female cancer survivors and female comparison subjects.

for cardiovascular disease (61% at age 70); the corresponding cumulative risk among women was 47%. Generally the cumulative risk was higher among male survivors than among female survivors (aged 20–24 years at cancer diagnosis: men = 59%, women = 51%; aged 25–29 years at cancer diagnosis: men = 55%, women = 51%; aged 30–34 years at cancer diagnosis: men = 54%, women = 48%; aged 35–39 years at cancer diagnosis: men = 55%, women = 51%; data not shown). Supplementary Table 2, A–K (available online) shows the standardized hazard rate ratios for attained age at cardiovascular disease by age at cancer diagnosis for all cancer types combined and for each of the 10 most frequent cancer types. Further, Supplementary Tables 3 and 4 (available online) give the cumulative risk for the main categories of cardiovascular disease by attained age and years since cancer diagnosis, respectively, for all adolescent and young adult cancer survivors and separately for survivors of the 10 most common adolescent and young adult cancers.

Adolescent and young adult cancer survivors were at substantially increased risk for hospitalization for nearly all of the 26 diagnoses of cardiovascular disease (Table 3). The risks were particularly high for endo-, peri-, and myocarditis, arterial thrombosis, and cerebral hemorrhage and extraordinarily high for lymphedema and other and unspecified lymphatic disease (Table 3). Venous and lymphatic disease was the leading reason for hospitalization (AER = 133 per 100 000 person-years), constituting, with cardiomyopathy and arrhythmia, 35% of all cardiovascular hospitalizations among survivors. Supplementary Table 5, A–J (available online) gives equivalent estimates for each of the 10 most frequent cancer types.

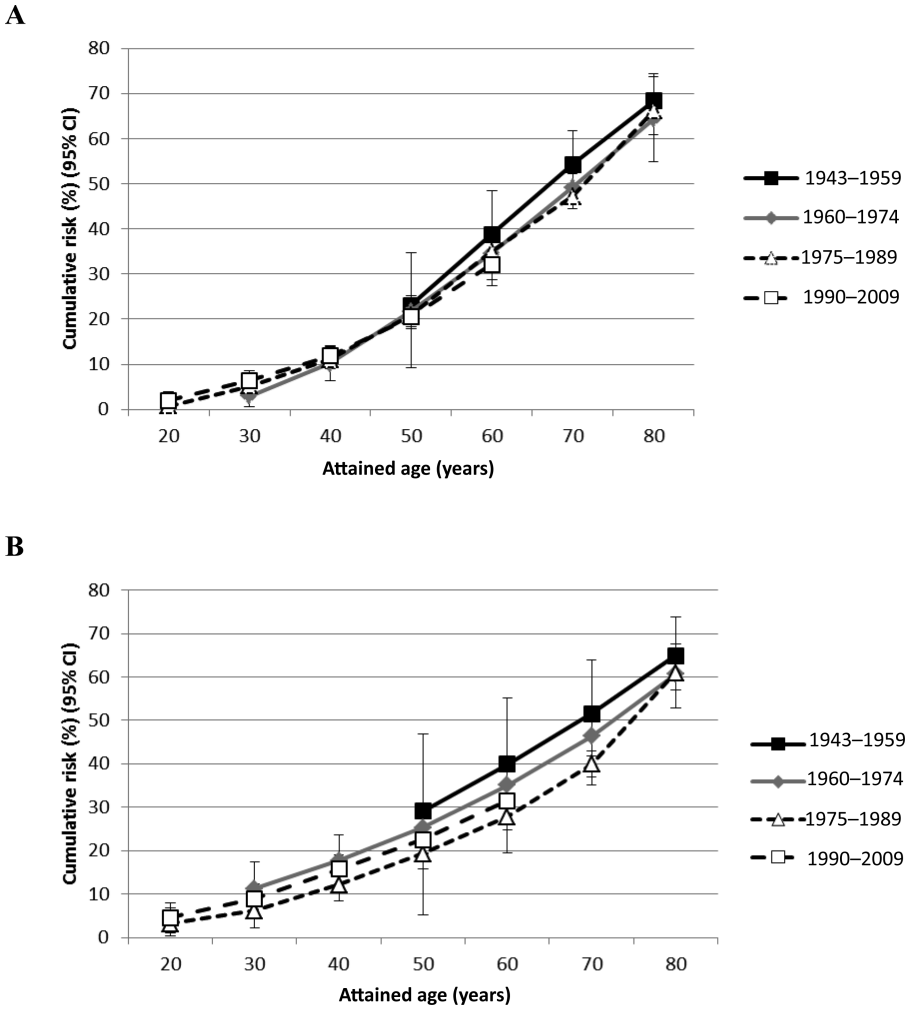

Figure 3. Cumulative risk (%) with 95% confidence intervals (CIs) for a first hospitalization for cardiovascular disease among survivors of adolescent and young adult cancer by attained age at cardiovascular disease diagnosis and calendar period of cancer diagnosis. Outpatient visits for cardiovascular disease added to the Danish Patient Register in 1995 onwards are not included. **A**) Male survivors of adolescent and young adult cancer. **B**) Female survivors of adolescent and young adult cancer.

Survivors of each of the 10 most frequent adolescent and young adult cancers had a markedly increased risk for a subsequent hospital diagnosis of cardiovascular disease (Table 4). Survivors of leukemia had the highest risk, followed by survivors of Hodgkin lymphoma and brain tumors. Table 4 also lists the relative risks for specific cancer–outcome combinations for which the lower 95% confidence limit was 1.5 or greater. The risk for lymphedema was high in survivors of breast cancer (RR = 63.3), cervical cancer (RR = 21.5), malignant melanoma (RR = 15.9), Hodgkin lymphoma (RR = 5.8), and brain tumors (RR = 5.1). The risk for cardiomyopathy was high in survivors of leukemia (RR = 8.6; 95% CI = 4.3 to 17.3), non-Hodgkin lymphoma (RR = 6.5), breast cancer (RR = 5.3), and Hodgkin lymphoma (RR = 4.8). In addition, survivors of Hodgkin lymphoma were at markedly increased risk for subsequent valvular disease (RR = 12.2; 95% CI = 9.9 to 15.0; $P < .001$). The risk for cerebral hemorrhage was extraordinarily high in survivors of leukemia (RR = 10.3; 95% CI = 5.5 to 19.1; $P < .001$), although the estimate was based on only 10 patients.

Survivors of adolescent and young adult cancer were also at increased risks for diabetes mellitus (RR = 1.23; 95% CI = 1.17 to 1.30), chronic obstructive pulmonary disease (RR = 1.24; 95% CI = 1.17 to 1.31), and chronic kidney disease (RR = 2.30; 95% CI = 2.04 to 2.60).

Discussion

In this population-based follow-up study of more than 40 000 1-year survivors of adolescent and young adult cancer, one of four had been admitted to the hospital for cardiovascular diseases and at a 30% higher rate of first hospitalization than that of the general population.

The risk for cardiovascular disease was substantially elevated in all ages of observation up to 70 years, suggesting that the cardiotoxic effects of cancer treatment, the underlying cancer, and/or lifestyle factors peculiar to survivors of adolescent and young adult cancer manifest themselves many decades after initial diagnosis. The absolute excess risk for survivors aged 20 to 59 years was relatively stable, with approximately 400 new cases of cardiovascular disease per 100 000 person-years, leading to overall cumulative risks of 45% at age 60 years and 52% at age 70 years.

Of the nine diagnostic categories investigated, diseases of the venous and lymphatic system—complications of surgery and

Table 3. Standardized hospitalization rate ratios and absolute excess risks for nine categories of cardiovascular disease and for a selected number of diagnostic entities among 43 153 1-year survivors of adolescent and young adult cancer

Category of cardiovascular disease and diagnostic entity (ICD-10)	No. of cases among survivors†	RR (95% CI)	AER (95% CI)	% total AER
Hypertension (I10–I15)	3187	1.20 (1.16 to 1.25)	86 (68 to 105)	12.6
Essential hypertension (I10)	3082	1.20 (1.15 to 1.24)	80 (62 to 99)	
Hypertension with complications (I11–I15)	310	1.53 (1.36 to 1.73)	17 (11 to 23)	
Ischemic heart disease (I20–I25)	2823	1.23 (1.18 to 1.28)	85 (67 to 102)	12.4
Angina pectoris (I20)	1596	1.26 (1.19 to 1.33)	52 (39 to 65)	
Myocardial infarction (I21–I22)	1301	1.20 (1.13 to 1.27)	34 (23 to 46)	
Chronic ischemic heart disease (I25)	1578	1.27 (1.20 to 1.33)	53 (40 to 66)	
Pulmonary heart disease (I26–I28)	440	1.49 (1.35 to 1.65)	23 (16 to 30)	3.4
Pulmonary thrombosis (I26)	320	1.52 (1.34 to 1.71)	17 (12 to 23)	
Endo-, peri-, and myocarditis and valvular heart disease (I30–I41)	789	1.89 (1.75 to 2.05)	59 (50 to 68)	8.6
Pericarditis (I30) and myocarditis (I40–I41)	126	1.94 (1.60 to 2.36)	10 (6 to 13)	
Endocarditis (I33)	60	2.16 (1.62 to 2.88)	5 (3 to 8)	
Valvular heart disease (I34–I39)	559	1.71 (1.56 to 1.88)	37 (29 to 45)	
Cardiomyopathy and arrhythmia (I42–I50)	2828	1.30 (1.25 to 1.35)	103 (86 to 121)	15.1
Cardiomyopathy (I42–I43)	213	1.95 (1.67 to 2.26)	16 (12 to 21)	
Heart failure (I50)	1266	1.37 (1.29 to 1.45)	54 (43 to 66)	
Conduction disorders (I44–I45)	300	1.43 (1.26 to 1.61)	14 (9 to 20)	
Cardiac arrest (I46)	182	1.29 (1.10 to 1.51)	7 (2 to 11)	
Disturbances of heart rhythm (I47–I49)	1682	1.20 (1.14 to 1.26)	45 (31 to 58)	
Cerebrovascular disease (I60–I69)	2045	1.33 (1.27 to 1.40)	82 (67 to 96)	12.0
Subarachnoid hemorrhage (I60)	162	1.40 (1.19 to 1.66)	7 (3 to 12)	
Cerebral hemorrhage (I61–I62)	323	1.68 (1.49 to 1.90)	21 (15 to 27)	
Cerebral infarction (I63)	719	1.26 (1.16 to 1.36)	23 (15 to 32)	
Apoplexia cerebri (I64)	974	1.34 (1.26 to 1.44)	40 (29 to 50)	
Other undefined cerebrovascular disease (I65–I69)	892	1.33 (1.24 to 1.43)	36 (26 to 45)	
Arterial disease (I70–I79)	1514	1.55 (1.47 to 1.64)	86 (73 to 99)	12.6
Atherosclerosis (I70)	836	1.57 (1.46 to 1.69)	48 (39 to 58)	
Aneurysm (aortic and other) (I71–I72)	192	1.30 (1.11 to 1.51)	7 (2 to 12)	
Arterial thrombosis (I74)	205	1.78 (1.52 to 2.07)	14 (10 to 19)	
Venous and lymphatic disease (I80–I89, I97.2)	3421	1.32 (1.27 to 1.37)	133 (113 to 152)	19.4
Phlebitis (I80)	774	1.65 (1.53 to 1.78)	49 (39 to 58)	
Disease of veins (I83–I87)	2219	1.05 (1.00 to 1.09)	15 (1 to 31)	
Lymphedema (I89.0, I97.2)	391	18.6 (15.5 to 22.3)	59 (53 to 65)	
Other and unspecified lymphatic disease (I88, I89.1–I89.9)	179	3.25 (2.72 to 3.87)	20 (15 to 24)	
Other and undefined circulatory disease (I01, I05–I09, I51, I52, I95–I99 excluding I97.2)	461	1.57 (1.42 to 1.74)	27 (20 to 34)	3.9

* AER = absolute excess risk; CI = confidence interval; RR = standardized hospitalization rate ratio.

† Numbers do not add up to total because the same patient could be classified in several categories and entities.

possibly radiation—predominated, with 3421 affected survivors, representing close to 20% of all treatment-related cardiovascular disorders. The risk for lymphedema among survivors was high, particularly after breast cancer, cervical cancer, and malignant melanoma. Other high-risk outcomes were valvular disease in Hodgkin lymphoma survivors, cerebral hemorrhage and cardiomyopathy in survivors of leukemia, and cardiomyopathy in survivors of non-Hodgkin lymphoma; all of these conditions are known complications of radiotherapy and chemotherapy including anthracyclines.

A Dutch study of 1474 5-year survivors of Hodgkin lymphoma who were aged less than 41 years at the time of treatment (years 1965–1995) found a statistically significantly increased relative risk for angina pectoris, ranging from 2.6 to 6.2 for survivors treated at four age groups within the age range 21 to 40 years (10). In our study, for 2072 1-year survivors of Hodgkin lymphoma diagnosed in the period from 1960 to 2009, the equivalent overall risk estimate of 2.5 was statistically significant, although slightly lower than that for the Dutch survivors. The relative risks for myocardial infarction and congestive heart failure in the Dutch study were 2.6 to 5.9 and 2.5 to 7.0, respectively, comparable with the overall estimates of 3.0 and 5.9 in our study.

De Bruin et al. reported substantially increased relative risks for stroke of 2.0 and 3.1 among survivors of Hodgkin lymphoma treated at age 21 to 30 years and 31 to 40 years, respectively (11). The hospital discharge diagnoses of survivors of Hodgkin lymphoma in our study were cerebral hemorrhage in eight cases (relative risk = 1.6), cerebral infarction in 22 (relative risk = 1.6), and apoplexia cerebri in 27 (relative risk = 1.8).

The slightly lower risk estimates in our study than in the two Dutch studies (10,11) might be because of differences in information on outcomes. We included cases of cardiovascular disease that

Table 4. Standardized hospitalization rate ratios (RRs) with 95% confidence intervals (CIs) for cardiovascular disease of any type and for selected diagnostic entities distinguished by a lower 95% CI ≤ 1.5 by specific cancer among the survivors of adolescent and young adult cancer*

Site of cancer†	Cardiovascular disease	No. of hospitalizations	RR (95% CI)	AER (95% CI)
Leukemia (n = 963)	Any	142	2.5 (2.1 to 2.9)	1244 (900 to 1588)
	Cerebral hemorrhage	10	10.3 (5.5 to 19.1)	133 (42 to 224)
	Cardiomyopathy	8	8.6 (4.3 to 17.3)	104 (23 to 186)
	Heart failure	13	4.6 (2.6 to 7.9)	149 (45 to 253)
	Phlebitis	15	4.2 (2.6 to 7.0)	169 (57 to 280)
	Cerebral infarction	10	3.9 (2.1 to 7.3)	110 (18 to 201)
	Disturbance of heart rhythm	24	3.1 (2.1 to 4.6)	240 (98 to 381)
	Essential hypertension	37	2.4 (1.7 to 3.2)	313 (137 to 488)
Hodgkin lymphoma (n = 2123)	Any	522	1.7 (1.6 to 1.9)	666 (529 to 803)
	Valvular disease	100	12.2 (9.9 to 15.0)	280 (221 to 340)
	Other and unspecified lymphatic disease	23	7.8 (5.2 to 11.9)	61 (33 to 90)
	Lymphedema	5	5.8 (2.4 to 14.2)	13 (-1 to 26)
	Heart failure	93	4.9 (4.0 to 6.0)	226 (168 to 284)
	Cardiomyopathy	24	4.8 (3.2 to 7.2)	58 (29 to 87)
	Other and undefined circulatory disease	40	4.6 (3.4 to 6.3)	96 (58 to 134)
	Chronic ischemic heart disease	131	3.7 (3.1 to 4.4)	291 (222 to 360)
	Myocardial infarction	91	2.8 (2.3 to 3.4)	178 (120 to 235)
	Phlebitis	50	2.8 (2.1 to 3.7)	98 (56 to 141)
	Angina pectoris	113	2.5 (2.1 to 3.0)	205 (142 to 269)
	Disturbance of heart rhythm	91	2.1 (1.7 to 2.6)	148 (90 to 205)
Brain (n = 2922)	Any	534	1.6 (1.5 to 1.8)	602 (468 to 736)
	Lymphedema	5	5.1 (2.1 to 12.5)	12 (-1 to 25)
	Other and undefined cerebrovascular disease	89	4.5 (3.6 to 5.5)	204 (149 to 259)
	Apoplexia cerebri	55	2.7 (2.0 to 3.5)	101 (58 to 144)
	Phlebitis	44	2.2 (1.7 to 3.0)	71 (33 to 110)
Non-Hodgkin lymphoma (n = 1336)	Any	307	1.5 (1.4 to 1.7)	613 (415 to 810)
	Other and unspecified lymphatic disease	23	14.7 (9.7 to 22.3)	123 (69 to 177)
	Cardiomyopathy	22	6.5 (4.3 to 9.9)	107 (54 to 160)
	Valvular disease	21	3.0 (1.9 to 4.6)	80 (28 to 132)
	Heart failure	44	2.3 (1.7 to 3.0)	141 (66 to 215)
	Phlebitis	26	2.2 (1.5 to 3.3)	82 (24 to 139)
Breast (n = 5731)	Any	1340	1.4 (1.4 to 1.5)	594 (489 to 698)
	Lymphedema	178	63.3 (51.7 to 77.6)	254 (216 to 292)
	Cardiomyopathy	44	5.3 (3.9 to 7.2)	52 (33 to 71)
	Other and unspecified lymphatic disease	29	4.4 (3.0 to 6.4)	32 (17 to 48)
Testis (n = 6479)	Any	1487	1.3 (1.2 to 1.3)	293 (218 to 368)
	Other and unspecified lymphatic disease	21	2.7 (1.7 to 4.3)	13 (4 to 22)
	Valvular disease	99	2.4 (2.0 to 3.0)	56 (37 to 75)
	Atherosclerosis	160	2.2 (1.9 to 2.6)	85 (60 to 109)
	Other and undefined circulatory disease	87	2.1 (1.7 to 2.7)	45 (27 to 63)
Cervix (n = 7093)	Any	2381	1.2 (1.2 to 1.3)	330 (253 to 407)
	Lymphedema	106	21.5 (16.5 to 28.1)	80 (64 to 96)
	Other and unspecified lymphatic disease	24	2.4 (1.6 to 3.6)	11 (3 to 19)
	Atherosclerosis	315	2.1 (1.8 to 2.3)	129 (101 to 156)
	Phlebitis	187	1.7 (1.5 to 2.0)	60 (38 to 81)
Malignant melanoma of skin (n = 5668)	Any	992	1.2 (1.1 to 1.2)	184 (101 to 267)
	Lymphedema	43	15.9 (11.4 to 22.2)	54 (36 to 71)
	Other and unspecified lymphatic disease	21	2.5 (1.6 to 3.8)	17 (5 to 28)
Ovary (n = 1148)	Any	309	1.2 (1.1 to 1.4)	290 (111 to 470)
Thyroid (n = 1053)	Any	214	1.2 (1.0 to 1.4)	212 (38 to 387)
	Other and unspecified lymphatic disease	9	4.8 (2.5 to 9.2)	43 (7 to 79)

* AER = absolute excess risk; CI = confidence interval; RR = standardized hospitalization rate ratio.

† Sites of cancer at which there were five or fewer cases are not included even if the lower confidence interval was 1.5 or greater.

led to a hospital contact, whereas the data for the Dutch cohort were collected from the medical records of general practitioners and attending physicians (10,11).

Another Dutch study of 2512 five-year survivors of testicular cancer treated during the period from 1965 to 1995 reported non-statistically significantly increased relative risks for myocardial infarction of 1.4 and 1.1 for survivors treated at less than 30 years and at 30 to 39 years, respectively; the estimates were based on 19 and 41 cardiovascular outcomes verified as described in the studies of Hodgkin lymphoma (12). These estimates fall

within the 95% confidence limits of the statistically significantly increased risk of 1.3 (95% CI = 1.1 to 1.5) for myocardial infarction in our study. The similar risks for myocardial infarction in Danish and Dutch survivors of Hodgkin lymphoma and testicular cancer are probably because symptoms of myocardial infarction lead to hospital treatment and thus inclusion of these cases in both studies.

Swerdlow et al. (13) followed a cohort of 7033 Hodgkin lymphoma patients who were treated in Britain at a broad range of ages. A little more than 4000 were adolescents or young adults when treated. The highest relative risk for death due to myocardial infarction was seen among the adolescent and young adult cancer survivors compared with survivors of cancer diagnosed at an older age; in contrast, the lowest absolute excess risk was observed among the adolescent and young adult patients (13). Radiotherapy and treatment with anthracyclines are important determinants of subsequent death due to myocardial infarction, but the concomitant influence of other known cardiac risk factors such as cigarette smoking and hyperlipidemia is not well studied (14).

Prasad et al. (15) followed 9245 5-year cancer survivors diagnosed before age 35 years and treated during the period from 1966 to 1999 in Finland. This is one of the first population-based studies to show an increase in cardiovascular disease mortality in long-term survivors of pediatric and adolescent and young adult cancer. The standardized mortality ratio for circulatory disease was 1.9 (95% CI = 1.5 to 2.3) (15). Similar to our investigation, important differences were noted among patient subgroups, with risk greatest for survivors of central nervous system cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma.

We started follow-up of study subjects 1 year after date of diagnosis or the equivalent date for the corresponding comparison subjects. We judged that this date was the optimal compromise between two different objectives: on one hand, we wanted to obtain the most valid date of diagnosis of a cardiovascular outcome; on the other hand, we also wanted to avoid inclusion of nonpersistent cardiovascular side-effects due to ongoing cancer treatment. By choosing the 1-year point for start of follow-up, the date of diagnosis was reasonably precise at the same time as most survivors had passed the period of cytostatic treatments

Cancer treatment can cause hormonal and metabolic changes that in turn lead to increased occurrence of classical cardiovascular risk factors, such as hypertension, hyperlipidemia, obesity, and type 2 diabetes, sometime clustered in the metabolic syndrome (12,16). We saw moderate but statistically significantly increased risks for hypertension and diabetes and other adverse conditions known to predispose to cardiovascular disease, such as chronic obstructive pulmonary disease and chronic kidney disorder, which occurred at statistically significantly increased rates among the adolescent and young adult cancer survivors. We were unable to differentiate the proportions of cardiovascular late effects due to a direct damaging effect of treatment on the tissues of the circulatory system from those due to indirect effects on other organ systems. Likewise, other factors besides adverse chronic conditions may predispose to cardiovascular disease in adolescent and young adult cancer survivors, such as prevalence of overweight, level of physical activity, dietary habits, and other aspects of lifestyle. However, in this study describing the full range of cardiovascular disease attributable to the status as adolescent and young adult cancer survivor, we regard the above-mentioned chronic conditions and survivors' particular lifestyle as mediators rather than confounders, and we did not adjust for such factors.

The strengths of this study include the high quality of the Danish Cancer Registry, dating back to 1943 (17), the completeness of the Danish Patient Register, initiated in 1977 (18,19), and the existence of a central civil registration system (8), which enabled us to gather large cohorts of survivors of adolescent and young adult cancer and population comparison subjects, to establish a long-term follow-up of study subjects with minimal loss to follow-up, and to establish a personal hospital history with discharge diagnoses of cardiovascular disease issued by treating physicians.

The usefulness of the Danish Cancer Registry files in research on late effects in survivors of adolescent and young adult cancer is, however, limited by insufficient information on treatment variables in patient records. Another potential limitation of this study is that less severe cardiovascular outcomes handled exclusively by general practitioners were not ascertained completely, so that the pattern of late effects in patients treated for adolescent and young adult cancer is related mainly to serious heart conditions requiring hospitalization. This limitation applies to members of the population comparison cohort as well, indicating the comparability of the generated hospitalization rates. Surveillance bias may arise if survivors of adolescent and young adult cancer have easier access to hospital treatment for minor health problems than population comparison subjects, which might lead to overestimates of the associated risks. Comparison of the Danish and Dutch risk estimates for angina pectoris does not, however, support the existence of this type of bias in our data. The size of the cohort, the relative consistency of the pattern of late effects with those found in other large studies, and the completeness of cancer registration in Denmark convince us that the risk pattern for cardiovascular disease among survivors of adolescent and young adult cancer described here is reasonably valid with precise estimates of risk over the period of follow-up to age 70 years. The relatively high occurrence of heart disease over all ages of observation indicates that long-term follow-up care should include monitoring for heart disease for early detection, intervention, and health preservation.

References

1. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer*. 2009;45(6):992–1005.
2. Coccia PF, Altman J, Bhatia S, et al. Adolescent and young adult oncology. *J Natl Compr Canc Netw*. 2012;10(9):1112–1150.
3. Woodward E, Jessop M, Glaser A, Stark D. Late effects in survivors of teenage and young adult cancer: does age matter? *Ann Oncol*. 2011;22(12):2561–2568.
4. Armstrong GT, Liu Q, Yasui Y et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27(14):2328–2338.
5. van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0–34 years: historical and actual status in Denmark. *Int J Cancer*. 2006;118(11):2816–2826.
6. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer*. 2008;8(4):288–298.
7. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health*. 2011;39(7 Suppl):42–45.

8. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22–25.
9. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30–33.
10. Aleman BM, van den Belt-Dusebout AW, de Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. 2007;109(5):1878–1886.
11. de Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst*. 2009;101(13):928–937.
12. van den Belt-Dusebout AW, Nuver J, de WR, et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*. 2006;24(3):467–475.
13. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst*. 2007;99(3):206–214.
14. Boice JD, Jr. An affair of the heart. *J Natl Cancer Inst*. 2007;99(3):186–187.
15. Prasad PK, Signorello LB, Friedman DL, Boice JD, Jr., Pukkala E. Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland. *Pediatr Blood Cancer*. 2012;58(3):421–427.
16. de Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT, Gietema JA. The metabolic syndrome in cancer survivors. *Lancet Oncol*. 2010;11(2):193–203.
17. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull*. 1997;44(5):535–539.
18. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263–268.
19. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56(2):124–130.

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