Testicular Cancer Incidence in Eight Northern European Countries: Secular and Recent Trends

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Abstract

Objective: **Striking geographic variation and marked increasing secular trends characterize the incidence of testicular cancer. However, it is not known whether these patterns have attenuated in recent years and whether they are similar for seminomas and nonseminomas, the two main histologic groups of testicular cancer.**
Method: **Cancer registry data, including 27,030 testicular cancer cases, were obtained from Denmark, Estonia, Finland, Latvia, Lithuania, Norway, Poland, and Sweden. Between 57 (Denmark) and 9 (Poland) years of registration were covered. Country-specific temporal trends were estimated, with focus on the last decade and seminomas and nonseminomas. Data from the Nordic countries were further analyzed using an age-period-cohort approach.**
Results: **Age-standardized incidence rates increased annually by 2.6% to 4.9% during the study period, with marginal differences between seminomas and nonsemi-**nomas. In the last decade, the increasing trend attenuated only in Denmark (annual change, −0.3%; 95% confidence interval, −1.5 to 0.9). In 1995, the highest and the lowest age-standardized incidence rates (per 10^5) were 15.2 in Denmark and 2.1 in Lithuania. Incidence rates (i.e., for all cancers and for seminomas and nonseminomas, separately) depended chiefly on birth cohort rather than on calendar period of diagnosis (although both birth cohort and period determined the Danish incidence rates).**
Conclusions: **Testicular cancer incidence is still increasing, with the exception of Denmark, and a large geographic difference exists. The increasing trend is mainly a birth cohort phenomenon also in recent cohorts. Temporal trends for seminomas and nonseminomas are similar, which suggests that they share important causal factors.**   (Cancer Epidemiol Biomarkers Prev 2004;13(12):2157–66)

Introduction

A secular increasing trend in the incidence of testicular cancer has been shown in Northern Europe (1-3), United Kingdom (4-6), Canada (7, 8), New Zealand (9), Australia (10), and the United States (11, 12), with the possible exception of Switzerland (13). An attenuation of the increasing trends was recently shown in Denmark (1), perhaps in the United States (12), but not in Canada (7), England or Wales (5). In the early 1990s, we carried out a collaborative study involving nine countries around the Baltic Sea and found that testicular cancer incidence doubled in 15 to 20 years, with an ~10-fold

geographic variation in incidence between participating countries (2). In the same study (14), as well as in studies of other populations (1, 7, 11, 12), the increasing trend seemed to be mainly a birth cohort phenomenon.

Despite efforts of analytic studies to investigate possible risk factors (mainly those acting early in life), causes of testicular cancer remain largely unknown and there are no satisfactory hypotheses to explain the trends in incidence nor in the geographic variations (15). Understanding testicular cancer etiology is complicated because two major histologic groups, seminomas and nonseminomas, peak in incidence at different ages: nonseminomas before 30 years of age and seminomas after age 30 (3, 6, 7, 10-12, 16). Hence, etiologic heterogeneity may exist between the two forms of testicular cancer. Some analytic studies have investigated seminomas and nonseminomas separately, but with conflicting results (17-31). Analogously, trend analyses have reported both similarities (11, 16) and differences (4, 7, 12) between the two histologic groups.

Comparing results from different countries is a valuable approach to understand whether the epidemic

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of testicular cancer is abating and whether nonseminomas and seminomas have different temporal trends. We, therefore, updated our earlier collaborative study (2, 14), analyzing, in a standardized fashion, data on >27,000 testicular cancer cases diagnosed among men ages 15 to 64 years recorded up to 1998 to 2000 in cancer registries of eight Northern European countries. We investigated recent and secular trends in incidence, we disentangled between birth cohort and period effects, and we analyzed seminomas and nonseminomas separately.

Materials and Methods

Characteristics of Cancer Registries. The eight cancer registries included in our analyses are all population based, with different covered periods (Table 1). In Poland, compulsory cancer notification was established in 1952, but a satisfactorily complete nationwide registration is available from 1990. Although the Estonian Cancer Registry was founded formally in 1978, reliable centralized registration was present already in 1968. In Lithuania, a population-based registration of cancer covering the entire country started in 1964 and a cancer registry was established in 1975. Since 1990, the registration was considered complete enough to be included in the present study. For the other countries, we analyzed the entire available period of cancer registration, after excluding the first years, when some underreporting might have existed. We obtained data up to the last available year, which varied between 1998 and 2000 in different registries.

Detailed information on each of the eight cancer registries is available in publications of the IARC (32-34) and in national publications and Web sites (Denmark: http://www.cancer.dk/; Estonia: ref. 35; Finland: http://www.cancerregistry.fi/; Lithuania: http://www.is.lt/cancer_reg/; Norway: http://www.kreftregisteret.no/; Poland: ref. 36; Sweden: http://www.sos.se/epc/). A comprehensive comparison of the cancer registries of Denmark, Finland, Norway, and Sweden was published in 2000 (37).

Cancer and Population Data. Data on all cases of testicular cancer diagnosed among men ages 15 to 64 years were obtained from the cancer registries in the form of a list of anonymous individual records, including year of diagnosis, age at diagnosis, year of birth, and histologic codes. Data on histopatologic type of testicular cancer were, however, not available in the Polish Cancer Registry. Population data were provided in the form of 5-year age groups by Baltic countries, Finland, and Poland, whereas data in 1-year age groups were available in Denmark, Finland (since 1975), Norway, and Sweden. We report the total number of testicular cancer cases analyzed and the estimated male population by country (Table 1).

We used histologic information obtained from the registries to identify testicular cancers occurring in the germ cells and we classified them into seminomas and nonseminomas. A more detailed analysis of trends of different histologies was not feasible, because the cancer registries used different morphologic classifications with some changes over time (33, 35-37). Table 1 reports, for each country, the number of seminomas and nonseminomas analyzed.

Statistical Analyses. We analyzed the observed trends of age-standardized (world standard population; ref. 32) incidence of testicular cancer by country and histologic group. We estimated average annual changes and corresponding 95% confidence interval (95% CI) by fitting a linear regression model where the logarithm of the age-standardized incidence was assumed to be linearly dependent on calendar time. We also carried out Poisson regression models of age-adjusted (5-year age groups) incidence rates by calendar year. Because estimates from the Poisson and the linear regression models were similar, we decided to present average annual changes in the age-standardized incidence rate only (Table 2). We used linear splines, with a unique knot at year 1990, to better investigate late changes in the temporal distribution. Statistical analyses were conducted using STATA version 8.1.

We did age-period-cohort (APC) analyses by using Poisson regression, limiting our attention to Denmark, Finland, Norway, and Sweden, all of which had both a sufficiently long period of registration and a large number of recorded cases (38, 39). We analyzed ten 5-year age groups (15-64 years) and eight (Sweden: 1960-1964,

Table 1. Characteristics of the study populations

Country	Study period	Male population*	All testicular cancers†	Germ cell tumors‡	
				Seminomas	Nonseminomas
Denmark	1943-1999	2.58	9,138	4,929 (54%)	3,833 (42%)
Norway	1955-1998	2.16	4,888	2,501 (51%)	2,240 (46%)
Sweden	1960-1999	3.93	5,830	3,094 (53%)	2,644 (45%)
Finland	1953-1999	2.49	1,842	931 (51%)	792 (43%)
Poland	1990-1998	18.57	4,388	—§	—
Estonia	1968-1998	0.69	293	163 (56%)	110 (38%)
Lithuania	1990-1999	1.75	259	120 (46%)	100 (39%)
Latvia	1980-2000	1.16	392	199 (51%)	168 (43%)

*In 1995, in millions.
†All testicular cancers occurring in patients aged between 15 and 64 years at diagnosis, including germ cell tumors, non-germ cell tumors, and testicular tumors with unspecified histology.
‡Seminomas and nonseminomas were defined according to the codes/recodes of the following classifications: Denmark, modified *ICD-7* (67); Norway, *Manual of Tumor Nomenclature and Coding* (68) and *ICD for Oncology-2* (*ICDO-2*) (since 1993) (69); Sweden, C24 (WHO/HS/CANC/24.1); Finland, *Manual of Tumor Nomenclature and Coding* (70); Estonia, *ICDO-2* (69); Lithuania, *ICDO-2* (69); Latvia, *ICDO-2* (69).
§Not applicable. Information on histology was not available in the Polish Cancer Registry.

Table 2. Average annual change in age-standardized (world standard population) incidence of testicular cancer by country, period, and histological type

Country	Histological group	Annual change (%) (95% CI)*			Incidence in 1995	
		Entire period	<1990	>1990	Observed	Estimated (95% CI)*
Denmark	All[†]	2.6 (2.4-2.8)	2.8 (2.7-3.0)	−0.3 (−1.5 to 0.9)	15.0	15.4 (14.6-16.2)
	Seminomas	2.4 (2.2-2.7)	2.6 (2.3-2.8)	0.9 (−1.2 to 2.9)	8.3	8.0 (7.3-8.7)
	Nonseminomas[†]	3.4 (3.1-3.6)	3.9 (3.6-4.3)	−3.5 (−5.8 to −1.2)	6.2	6.9 (6.2-7.5)
Norway	All	3.0 (2.7-3.3)	3.0 (2.6-3.4)	2.9 (0.5-5.2)	11.3	13.5 (12.3-14.8)
	Seminomas	2.6 (2.2-3.0)	2.6 (2.1-3.0)	2.7 (0.0-5.4)	4.7	6.4 (5.7-7.1)
	Nonseminomas	3.7 (3.2-4.1)	3.7 (3.2-4.3)	2.8 (−0.6 to 6.1)	6.3	6.8 (5.9-7.7)
Sweden	All	3.2 (3.0-3.5)	3.3 (3.0-3.7)	2.5 (1.1-3.9)	8.6	9.3 (8.9-9.9)
	Seminomas[†]	3.1 (2.8-3.4)	2.8 (2.3-3.2)	5.0 (3.4-6.7)	5.3	4.8 (4.5-5.1)
	Nonseminomas[†]	3.4 (3.0-3.9)	4.0 (3.4-4.5)	0.0 (−2.3 to 2.4)	3.2	4.4 (4.0-4.8)
Finland	All	3.9 (3.4-4.3)	3.8 (3.2-4.4)	4.6 (1.4-7.9)	3.0	3.1 (2.8-3.5)
All types	Seminomas	3.1 (2.4-3.7)	3.0 (2.1-3.8)	3.8 (−0.9 to 8.6)	1.1	1.2 (1.1-1.5)
	Nonseminomas	6.0 (5.2-6.8)	6.3 (5.3-7.4)	3.3 (−2.3 to 9.0)	1.7	1.6 (1.3-2.0)
Poland	All	4.3 (2.4-6.3)	—	—	2.6	2.7 (2.6-2.8)
Estonia	All	3.2 (1.7-4.7)	3.2 (1.0-5.4)	3.1 (−4.0 to 10)	5.3	2.6 (2.0-3.3)
	Seminomas	2.4 (0.3-4.5)	2.0 (−1.0 to 5.0)	4.4 (−5.4 to 14)	1.9	1.3 (0.9-1.8)
	Nonseminomas	6.7 (4.2-9.1)	7.5 (3.9-11)	2.9 (−8.9 to 15)	2.6	1.2 (0.8-1.8)
Lithuania	All	4.9 (0.0-10.0)	—	—	1.6	2.1 (1.8-2.4)
	Seminomas	6.3 (−1.2 to 14)	—	—	1.1	0.9 (0.8-1.1)
	Nonseminomas	7.8 (−2.8 to 18)	—	—	0.3	0.8 (0.6-1.0)
Latvia	All	4.2 (2.1-6.2)	3.0 (−1.6 to 7.6)	5.3 (0.7-10)	2.3	2.6 (2.2-3.0)
	Seminomas	4.0 (−0.3 to 8.4)	−3.2 (−12 to 6.1)	11 (1.9-20)	0.7	1.2 (0.9-1.6)
	Nonseminomas[†]	6.8 (2.3-11)	16 (7.7-25)	−2.8 (−12 to 6.0)	1.5	1.2 (0.9-1.5)

NOTE: Observed and estimated incidence (per 100,000) in 1995.
*Estimated with a linear regression model using age-standardized incidence and linear splines with one knot at 1990.
[†]Two-sided test for difference in linear trend before and after 1990: $P < 0.05$.

..., 1995-1999) to 11 (Denmark: 1945-1949, ..., 1995-1999) 5-year periods. The first two years of registration in Denmark and in Finland were excluded to have similar complete 5-year periods in all countries. In Norway, the 4-year period 1995 to 1998 was considered to be representative of the 5-year period 1995 to 1999. Ten-year-wide overlapping birth cohorts were obtained by the difference between the middle year of each period and the middle year of each age group. Hereafter, birth cohorts are denoted by their central birth year. For example, we obtained 20 cohorts in Denmark (1885-1980) and 17 cohorts in Sweden (1900-1980).

Due to the linear dependency among age, period, and cohort, the full APC model is not identifiable (39), meaning that no unique set of regression parameters for the linear effect of age, period, and cohort can be found when the three factors are analyzed simultaneously. Different strategies of analysis are proposed in literature, with two main possible approaches. One is trying to solve the identifiability problem, with, for example, the penalty function approach (40). A second approach, the one that we followed, is based on the reparameterization of estimable effects (38).

We fitted four partial models including (1) age-only, (2) age-period, (3) age-cohort, and (4) age-drift (where drift denotes a trend in incidence, which is linear on a log scale and therefore equally described by period and cohort effects). We did goodness-of-fit tests, based on Pearson statistic, to assess the ability of the model to reproduce the observed rates. It should be noted that the age-cohort model includes more parameters than the other ones and thus has an intrinsic tendency to have a better fit than the other models (38). A full APC model can be fitted by forcing two effects for one of the temporal factors to be equal, implying that two period parameters and/or (depending on the inclusion of the drift variable) two cohort parameters had a relative risk of one (39). Although this method allows solving the identifibiality problem, the resulting coefficients are not directly interpretable unless a strong a priori hypothesis on which parameters should be forced exists. However, it is still possible to estimate the contrasts between relative risks associated with adjacent periods or birth cohorts (corresponding to the second differences on a logarithmic scale), which are measures of curvature, and interpret them in terms of acceleration or attenuation of the increasing trend in incidence (39). For instance, the curvature at the birth cohort 1960 is obtained by comparing the ratio between the relative risks for the cohorts 1965 and 1960 with the ratio between the relative risks for the cohorts 1960 and 1955. It follows that a contrast of one indicates the lack of nonlinear effects, an estimate above unity indicates acceleration and finally an attenuation of the increasing trend in incidence is associated with a contrast estimate below unity.

The approach that we used in the present study differs from our previous APC analysis on testicular cancer incidence in Nordic countries (14). In the earlier study, data were fitted using an age-cohort model, but nonlinear period and cohort effects were not evaluated.

APC analyses were done for all testicular cancers and for seminomas and nonseminomas separately. Given the difference in median age at diagnosis between the two histologic forms, analyses were restricted to 20 to 64 years of age and 15 to 59 years of age for seminomas and nonseminomas, respectively.

Results

Trend Analyses. The age-standardized incidence of testicular cancer increased over time in all countries, although patterns for the three Baltic countries are less clear due to the small number of cases (Fig. 1). The increasing trend was evident both for seminomas and nonseminomas. The highest incidence was found in Denmark followed by Norway and Sweden.

Estimated incidence and average annual changes by country and histologic group are summarized in Table 2. In 1995, highest and lowest age-standardized incidences
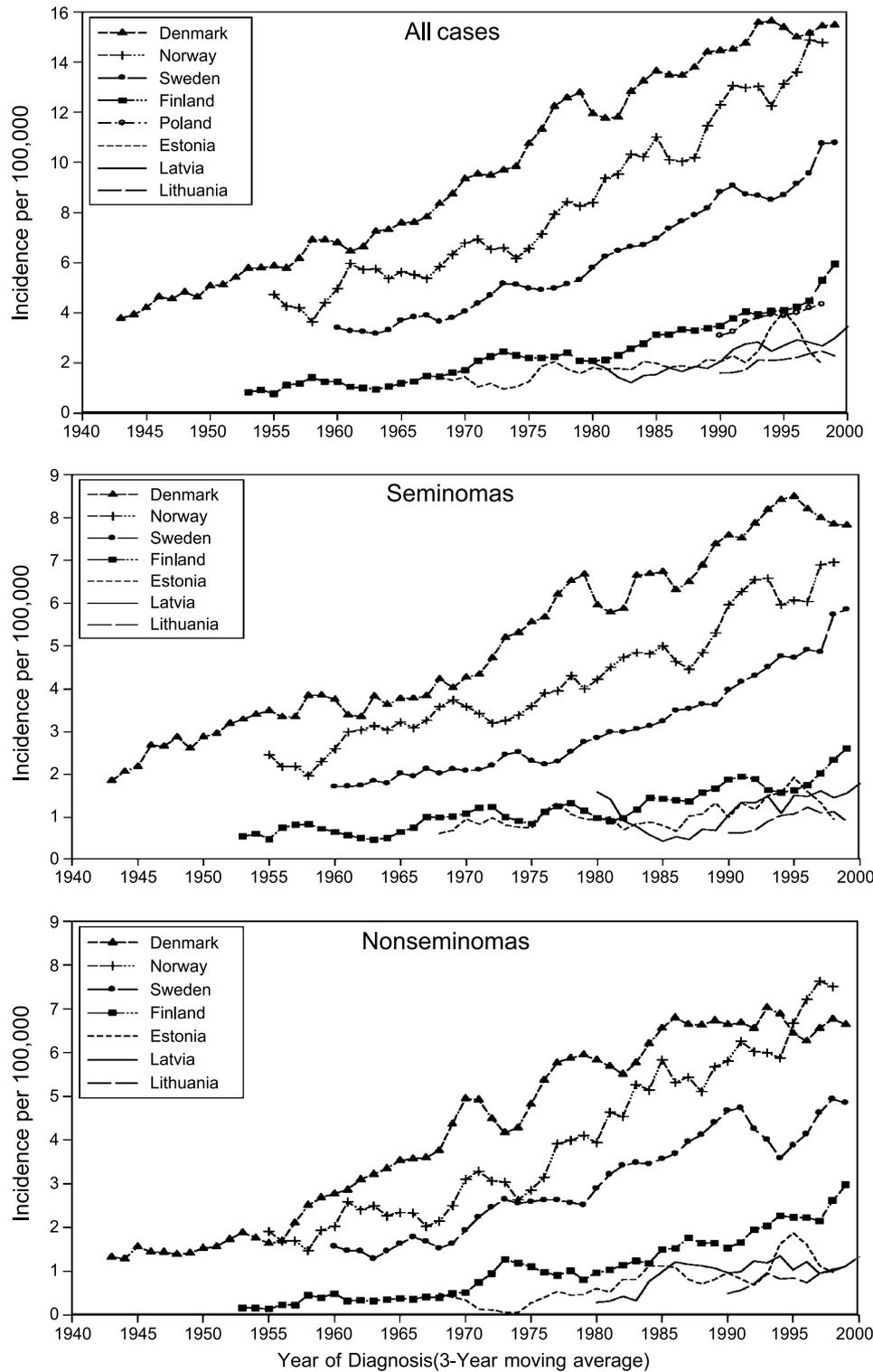

Figure 1. Age-standardized (world standard population) incidence of testicular cancer by year of diagnosis, country, and histological type.
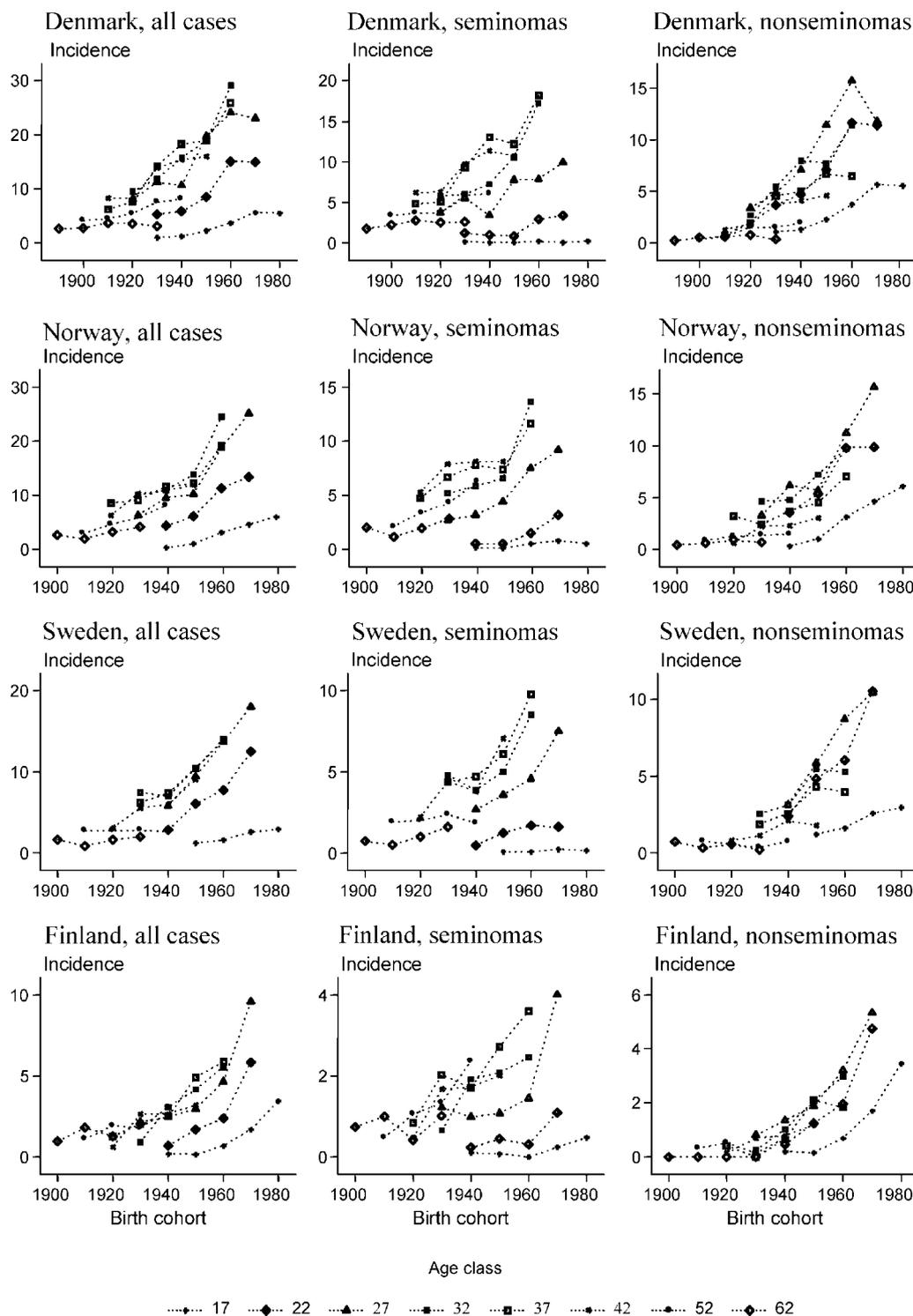
Figure 2. Trends in selected observed age-specific incidence (per 100,000) by selected cohort of birth, country, and histological type. Birth cohorts and age groups are denoted by their middle year.

Age class

····•···· 17   ····◆···· 22   ····▲···· 27   ····■···· 32   ····□···· 37   ····•···· 42   ····▲···· 52   ····◇···· 62

were 15.4 per 100,000 (95% CI, 14.6-16.2) in Denmark and 2.1 per 100,000 (95% CI, 1.8-2.4) in Lithuania. During the entire period of analysis, the lowest increase in incidence was found in Denmark (2.6%; 95% CI, 2.4-2.8), whereas the annual change was above 3% in all other countries. We found no major differences between seminomas and nonseminomas.

When trend analyses were focused on the last decade (after 1989), we found evidence of a leveling off of incidence in Denmark, where the estimated annual change was −0.3% (95% CI, −1.5 to 0.9). Trend appearances did not change substantially in the other countries during the last decade, with the exception of Sweden, where we found a markedly stronger annual

Table 3. Goodness-of-fit of partial age-period-cohort models by country and histological type

Country	Model											
	Age			Age-drift			Age-period			Age-cohort		
	df	$\times^2$	P	df	$\times^2$	P	df	$\times^2$	P	df	$\times^2$	P
Denmark												
All cancers	100	1,334	<0.001	99	225.9	<0.001	90	185.8	<0.001	81	162.0	<0.001
Seminomas	90	709.7	<0.001	89	153.3	<0.001	80	138.8	<0.001	72	116.2	<0.001
Nonseminomas	90	789.2	<0.001	89	202.1	<0.001	80	114.8	0.007	72	154.4	<0.001
Norway												
All cancers	80	752.8	<0.001	79	147.7	<0.001	72	138.1	<0.001	63	66.2	0.37
Seminomas	72	335.2	<0.001	71	106.8	0.004	64	94.7	0.008	56	49.4	0.72
Nonseminomas	72	453.2	<0.001	71	89.9	0.06	64	—*		56	—†	
Sweden												
All cancers	70	831.2	<0.001	69	135.1	<0.001	63	125.2	<0.001	54	69.4	0.08
Seminomas	63	504.7	<0.001	62	112.7	<0.001	56	100.4	<0.001	48	60.4	0.11
Nonseminomas	63	409.3	<0.001	62	101.6	0.001	56	82.8	0.01	48	78.7	0.003
Finland												
All cancers	80	480.8	<0.001	79	117.1	0.004	72	100.1	0.02	63	70.3	0.25
Seminomas	72	176.1	<0.001	71	75.5	0.39	64	—‡		56	—§	
Nonseminomas	72	356.3	<0.001	71	101.5	0.01	64	88.3	0.02	56	72.8	0.07

NOTE: Based on Pearson statistics.
*P = 0.20, comparison of the age-drift-period model with the age-drift model.
†P = 0.05, comparison of the age-drift-cohort model with the age-drift model.
‡P = 0.40, comparison of the age-drift-period model with the age-drift model.
§P = 0.06, comparison of the age-drift-cohort model with the age-drift model.

change for seminomas (5.0%; 95% CI, 3.4-6.7) than for nonseminomas (0.0%; 95% CI, −2.3 to 2.4).

Age-Period-Cohort Analyses. We plotted age-specific rates by birth cohort for each of the four Nordic countries and different histologic entities (Fig. 2). For almost any birth cohort, the highest incidences were found in the age groups 25 to 29 for nonseminomas and 30-34/35-39 for seminomas. Rates increased with successive birth cohorts among all age groups and countries but Denmark, where the increase leveled off in the most recent cohorts. For instance, incidence of nonseminomas peaked in the 1970 cohort among those ages 15 to 19 and in the 1960 cohort among those ages 20 to 24 and 25 to 29 years.

Results of the goodness-of fit tests for the partial APC models are reported in Table 3. The age-cohort model fitted the observed counts in Finland for all testicular cancers and nonseminomas, in Norway for all histologic entities, and in Sweden for all testicular cancers and seminomas. The age-only model fitted the data in none of the countries. When we analyzed seminomas in Finland and nonseminomas in Norway, the age-drift model gave a good fit to the data, with a further improvement after the inclusion of cohort parameters (P for comparison between age-drift-cohort model and age-drift model, 0.06 and 0.05, in Finland and Norway respectively). None of the partial models fitted Danish data, and the exclusion of the first 10 years of registration (between 1945 and 1954) did not improve the fit of the age-cohort model.

The estimable birth cohort effects obtained from the full APC models are reported in Fig. 3. Consistent with previous findings (14), there was an attenuation of the increase in incidence of testicular cancer among men born during the Second World War in Denmark,

Norway, and Sweden, but not Finland, as shown by contrasts below unity for those born in the 1935 cohort in Denmark and Norway, and for those born in the 1930 cohort in Sweden. This means that in Denmark, for instance, the ratio between the relative risks for the cohorts 1940 and 1935 was smaller than the ratio between the relative risks for the cohorts 1935 and 1930. In Denmark, Norway, and Sweden, there was an acceleration in the increasing in incidence rate, indicated by contrast estimates and confidence intervals above unity, among men born around 1950 (1940 in Sweden). In Denmark, the increasing trend in incidence leveled off again among men born in the 1965 and 1970 cohorts.

Seminomas and nonseminomas had similar patterns in all four countries (Fig. 4). Particularly in Denmark and Norway, the war time effect on incidence was evident for both histologic entities.

The analysis on periods did not suggest relevant nonlinear effects, with two main exceptions (Fig. 3). First, the increase in incidence of testicular cancer attenuated in Denmark starting from the 1980 to 1984 period. This pattern was evident both for seminomas and nonseminomas, whereas it did not apply to non germ cell tumors. Due to these specific nonlinear period effects, we fitted Danish data with separate models for men diagnosed before 1980 and those diagnosed after that. The age-cohort models fitted the observed counts for all testicular cancers (before 1980, P = 0.18; after 1980, P = 0.63), for nonseminomas (before 1980, P = 0.59; after 1980, P = 0.12), and for seminomas (before 1980, P = 0.08; after 1980, P = 0.67). The second exception regards Finland, where we found attenuation of the increasing trend in incidence in two consecutive periods between 1975 and 1984. This nonlinear period effect was confined to nonseminomas.
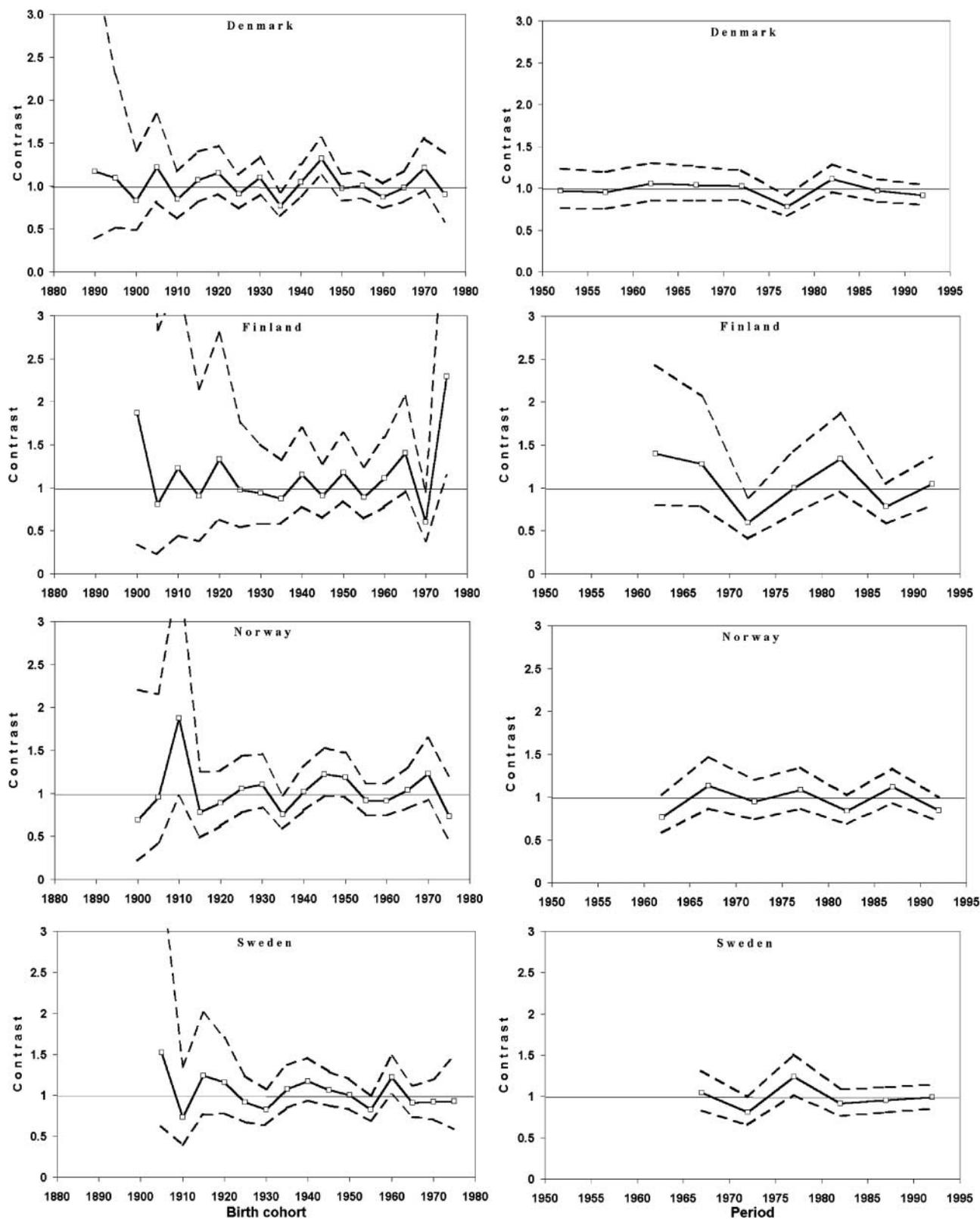
Figure 3. Estimable birth cohort and period effects on incidence of testicular cancer (mutually and age adjusted) and corresponding 95% CIs, by country (results for older Finnish birth cohorts are not reported because of instability of the estimates). Birth cohorts and periods are denoted by their middle year. Contrasts are second differences between successive birth cohorts or periods on a logarithmic scale.
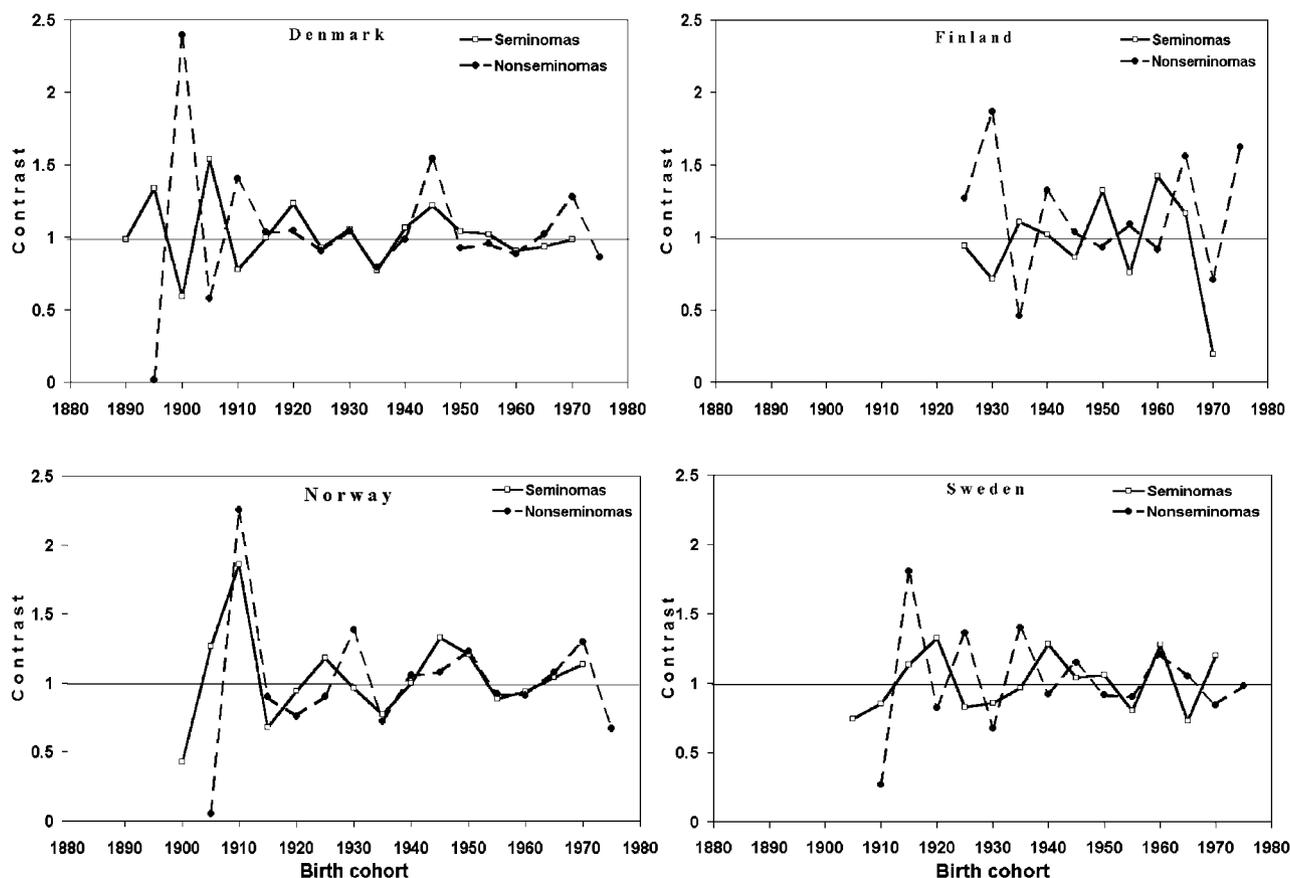
Figure 4. Estimable birth cohort effects on incidence of testicular cancer (adjusted for age and period) by country and histological type (results for older Finnish birth cohorts are not reported because of instability of the estimates). Birth cohorts are denoted by their middle year. Contrasts are second differences between successive birth cohorts on a logarithmic scale.

Discussion

Methodologic Considerations. We analyzed temporal trends in incidence of testicular cancer in eight populations, allowing direct assessment of the consistency of trend patterns. The reliability of our results depends on the quality of cancer registration in each of the participating countries. Testicular cancer occurs in young men and is generally easily diagnosed, suggesting that virtually all testicular tumors in the population are clinically detected and histopathologically verified. Furthermore, the completeness of the registry data in this study is high, and we have no reasons to believe that testicular cancer registration has been worse than for other cancers. However, changes in completeness of registration over time may have artificially influenced temporal trends to some extent. The consistency of our findings between countries and the general lack of nonlinear period effects suggest that such artifact had marginal, if any, effect on the registration of testicular cancer.

A certain degree of misclassification between seminomas and nonseminomas as well as between germ cell tumors and non-germ cell tumors has most likely occurred. If the level of misclassification changed over time, separate analysis of the histologic subgroups may have produced altered trend appearances. There are some particular periods in time when relevant changes occurred. At the end of the 1970s, the British Testicular Tumor Panel (41) and the WHO (42) introduced standards in the classification of testicular cancers. In the same years, advances in treatment, due to the introduction of cisplatinum-based chemotherapy for nonseminomas, increased the clinical importance of a precise histologic definition. With some possible exceptions, we did not find nonlinear period effects suggesting a relevant influence on temporal trends of changes either in histologic classifications or in pathologists' practice. These changes have affected to a greater extent the distribution of the different types of nonseminomas (choriocarcionmas, teratomas, and yolk sac tumors), rather than the proportion of the three main subgroups: seminomas, nonseminomas, and non-germ cell tumors. Another source of possible misclassification are lymphomas of the testis coded as testicular cancers. However, we restricted analyses to men ages <65 years at diagnosis, whereas lymphomas occur mainly at older ages.

We did not attempt to calibrate the different classifications used in different registries. Thus, although it is

possible to interpret geographic variations in incidence of testicular cancer as a single entity, similar comparisons are less meaningful when seminomas and nonseminomas are considered separately. For example, in the Danish Cancer Registry, the modified *International Classification of Diseases* (*ICD-7*) codes include chorionarcinomas and some types of non-germ cell tumors, as cancers occurring in Sertoli cells, in the same category. Translation of codes to an internally harmonizing classification would have lead to losses of information, and we therefore chose to prioritize comparability within countries over time, rather than between countries.

Main Findings. Our first main finding is that the incidence of testicular cancer is still increasing, and we ascribed this trend mainly to a birth cohort phenomenon in the Nordic countries. Moreover, the large geographic variation in incidence among countries around the Baltic Sea estimated in 1980 (2) is still present at the end of 1990s. In other words, the descriptive epidemiologic features of testicular cancer have not been changing substantially in recent times. Denmark is an exception, with its nonlinear period effects and its attenuated incidence trend from the early 1990s onwards. These results confirm findings of a previous Danish study based on incidence data up to 1996 (1). Relevant nonlinear period effects, indicating an attenuation of the increasing trend, have also been detected recently in the US (12) but not in the Canadian population (7).

In the search for risk factors that might explain the observed temporal trends, events early in life have been in focus. A causal role of such factors is supported by several pieces of evidence, including (i) testicular cancer peaks in incidence at early adulthood and may be already present at young ages; (ii) cancer *in situ* of the testis, a precursor of virtually all germ cell tumors, is believed to be generated *in utero* (43); (iii) the risk of testicular cancer is associated with the cohort of birth; analyses of Danish and Norwegian data using a frailty model fit with the hypothesis that testicular cancer occurs in a small proportion of men in the population, who acquires first germ cell damages early in life (44); and (iv) migration studies showed that men emigrating from countries with a high (or low) incidence of testicular to countries with a low (or high) incidence maintained their original risk (45, 46), irrespective of the age at immigration (45). Analytic studies investigating indicators of specific exposures acting prenatally or perinatally (possibly endogenous or exogenous estrogens 47), such as birth weight, birth order, maternal age, gestational age, have, however, not produced consistent findings (19-23, 25,27,28,30, 48-52). Cryptorchidism is associated with an increased risk of testicular cancer, but the etiologic fraction is only around 10%, and cannot thus explain the observed temporal trends (53). Maternal factors during pregnancy, in particular smoking (54, 55) and perhaps diet, deserve further investigation because they have changed over time. Moreover, subfertility has been linked to the risk of testicular cancer and the understanding of the causal pathway underlying this association may help in the search and study of candidate exposures (29, 56-58).

The nonlinear period effects in Denmark (and in Finland for nonseminomas) may suggest that postnatal exposures also affect the risk for testicular cancer,

perhaps acting as tumor promoters. Early age at puberty (18, 20, 57, 59), adult tallness (60-62), sedentary behavior (57, 63), and consumption of fats, milk, and diary products (31, 64-66) all have been associated with testicular cancer risk. However, for none of these factors has a causal association with testicular cancer been convincingly documented. The nonlinear period effect is an unexpected observation, for which we do not have a biological explanation.

A novel finding from the present study is that the temporal trends for seminomas and nonseminomas are similar, suggesting that the unknown cause(s) of the increasing trends are shared by the two main histologic forms. It has been debated whether etiologic heterogeneity exists and recent analytic studies included, whenever possible, separate analyses of seminomas and nonseminomas. In many instances, they have reported heterogeneities in some of the characteristics but no factor has been consistently associated with only one of the main histologic types (17-31). Reasons for inconsistent results might be a general problem of limited sample size to detect interactions in most of the studies, but also a true lack of a etiologic heterogeneity between the two histologic groups. Thus, although there is difference in age at peak in incidence between the two histologic forms, it seems that studies on testicular cancer etiology should primarily aim at testing candidate exposures responsible for increasing in incidence rather than at assessing etiologic heterogeneities.

In conclusion, in eight Northern European populations testicular cancer incidence is still increasing, with the possible exception of Denmark, and large geographic variations persist. APC analyses in Nordic countries revealed that the increasing trend is mainly a birth cohort phenomenon also in recent cohorts (with significant calendar period effects in Denmark). Finally, temporal trends for the two major histologic types of testicular cancer, seminomas and nonseminomas, are similar, which suggests that they have important causal factors in common.

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