

# Do Testicular Seminoma and Nonseminoma Share the Same Etiology? Evidence from an Age-Period-Cohort Analysis of Incidence Trends in Eight European Countries

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## Abstract

The incidence of the two main clinical subentities of testicular germ cell cancer (seminoma and nonseminoma) is increasing throughout Europe. Most studies have revealed little variation in risk factors between the two subtypes. This study compared generation-specific trends in eight European countries, hypothesizing that similar temporal pattern by birth cohort implied that seminoma and nonseminoma had a largely comparable etiology. The results are presented using the age-period-cohort model and the nonidentifiability problem highlighted by partitioning the age, period, and cohort effects in terms of their linear and curvature component parts, assuming a priori that cohort effects predominated. Despite uniform overall increases by calendar period, declining rates of nonseminoma but not pure seminoma were observed in the majority of countries during the 1990s. The subtype trends were, however, largely analogous

on a birth cohort scale. Notable observations were a decline in rates of both subtypes among recent birth cohorts in Switzerland and a short-term wartime effect in several countries, involving an attenuation of increasing risk of both subtypes in men born in 1940 to 1945. Departures from the steady increases in testicular cancer over time were likely to occur for nonseminomas some years ahead of seminoma on a period scale. The importance of birth cohort coincided with the view that given a short time interval of susceptibility to exposures earlier in life and a biologically constant time to diagnosis, all temporal changes in rate-limiting exposures should appear as generational effects. Trends in seminoma and nonseminoma conform to largely the same temporal patterns on this scale, implying that they share important etiologic factors. (Cancer Epidemiol Biomarkers Prev 2006;15(4):652–8)

## Introduction

Testicular cancer, the most common tumor in young men in many countries, has a very distinct epidemiology but a largely unexplained etiology. Descriptive epidemiology has revealed considerable geographic, ethnic, and temporal variations in incidence: at least a 30-fold variation in risk worldwide; rates ranging from 0.3 in Beijing, China to 12.5 in Zurich, Switzerland (1); with men of European origin in the United States having rates five times higher than their African origin counterparts (2). In many high-risk areas, such as Europe and North America, uniform increases in incidence between 3% and 6% per annum have been reported in long-term trends (2-7).

Several risk factors associated with prenatal and perinatal exposures have been suggested for testicular cancer (8-16), although aside from cryptorchidism, few risk determinants are well established. These and other possibly causal factors, such as low birth weight and low maternal parity, can only account for a small fraction of the total incidence. Previous studies have examined etiologic differences in the two main clinical subentities of testicular germ cell cancer: seminoma and nonseminoma (10, 11, 16-21). Despite well-documented

differences in the peak age of incidence (18), most studies have revealed little variation in risk factors between the two subtypes and, where particular associations have been found, they have been inconsistent across studies.

The increasing incidence in both seminoma and nonseminoma is unlikely to be explained by changes in disease classifications or diagnostic activities (22, 23). Studies that have examined trends in the two subtypes have observed strong but homogenous cohort patterns (7, 23-27), although a recent Canadian report indicated there were differences in cohort-specific risk (27), whereas another study, using U.S. (Surveillance, Epidemiology, and End Results) data, suggested some important temporal differences by subtype and within subtype by race (23).

This study examines time trends in seminoma and nonseminoma using cancer registry data in eight European countries. We focus our analysis on a comparison of the heterogeneity of generation-specific trends, hypothesizing that similar temporal patterns in the cohort dimension imply that the etiologies of seminoma and nonseminoma are largely similar if not identical.

## Materials and Methods

**Incidence Data.** The registry incidence and population data sets were taken from the EUROCIM software package and database (28) by registry, topography (International Classification of Diseases-Oncology, 2nd edition), histology (International Classification of Diseases-Oncology, 2nd edition), year of diagnosis, and 5-year age group. A minimum requirement for a registry's inclusion in the analysis was their consecutive

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compilation in the last three volumes (VI-VIII) of *Cancer Incidence in Five Continents* (CI5) covering the period of 1983 to 1997 (1, 29, 30). This criterion was chosen as a general marker of each registry's data quality over time, given that the editorial process involves a detailed assessment of the comparability, completeness, and validity of the submitted incidence data sets (1). In addition, each data set was required to span a minimum of 15 years to enable the fit of age-period-cohort (APC) models to equally spaced incidence data in 5-year groups of period and age.

The main histologic grouping (germ cell tumors, International Classification of Diseases-Oncology codes 9060-9102), usually comprising 95% to 99% of all testicular cancers in men under age 60, was abstracted for analysis, as were the subtypes seminoma (codes 9060-9064) and nonseminoma (including embryonal carcinoma, codes 9070-9073; malignant teratoma, codes 9080-9085 and 9102; choriocarcinoma, codes 9100-9101; and mixed tumors). The data set was restricted to the age group 15 to 54 to provide a well-defined grouping for the study of trends of histologic subtypes of germ cell cancers (18).

Given the relative paucity of incident cases after stratifying germ cell cancers into seminoma and nonseminoma, countries with less than an average of five cases per period in any age stratum were excluded. Eight countries were included in the final analyses (Table 1). In France, Italy, and Switzerland, a number of cancer registries were aggregated to obtain estimates of national incidence. The varying span of data available from registries led to a pragmatic aggregation of the data, maximizing the registration period and the number of registries represented within a country. We sought to ensure the same registries were used throughout the elected time period, although in practice, some registries did not cover the whole span (Table 1).

**APC Model.** We assumed that incidence rates were constant within 5-year age classes ( $a = 1, 2, \dots, A$ ) and 5-year periods of diagnosis ( $P = 1, 2, \dots, P$ ), leading to a likelihood for the observations that is proportional to a Poisson likelihood for the counts, with the log of the person-years at risk specified as an offset. The magnitude of the rates were described by a full APC model:

$$\log(\lambda(a, p)) = \alpha_a + \beta_p + \gamma_c$$

which can be fitted under the application of generalized linear model theory (31), with birth cohort derived from period and age such that  $c = p - a + A$  for  $c = 1, 2, \dots, C$  with  $C = A + P - 1$ . The variables  $\alpha_a$ ,  $\beta_p$ , and  $\gamma_c$  refer to the fixed effects of age group  $a$ , period  $p$ , and birth cohort  $c$ . The models were

fitted using Stata 8 (32). Tests for the net drift, the sum of the period and cohort slopes, and the separate effects of period and cohort curvature were obtained using the standard analysis of deviance of nested models (33, 34).

To allow a systematic evaluation of the histologic trends across countries, the results are presented using the full APC model and the nonidentifiability problem highlighted by partitioning the age, period, and cohort effects in terms of their linear and curvature component parts, according to the method of Holford (35). Holford showed that whereas the overall slopes are unrestricted, they do not vary independently, given that the three linear slopes from an arbitrary APC model (indexed  $L$ ) can be represented by  $\alpha_L' = \alpha_L + \rho$ ,  $\beta_L' = \beta_L - \rho$ , and  $\gamma_L' = \gamma_L + \rho$ , where  $\alpha_L$ ,  $\beta_L$ , and  $\gamma_L$  are the true values for the slopes according to age, period, and cohort, respectively, and  $\rho$  is an unknown constant that may result in increasing or decreasing trends of each slope (35).

The major contribution of cohort effects has been consistently shown in previous reports describing the increasing incidence of testicular cancer with time in Europe (3, 6, 7, 36). Birth cohort effects are considered a consequence of the changing prevalence of known and/or putative risk factors for the disease in successive generations. We have, therefore, a priori assumed that cohort effects predominate, and the underlying cohort slope is nonnegative. Fixing the period slope to zero for both histologies allows the cohort slope to take up the entire linear component but still permits nonlinear period effects, such that  $0 \leq \gamma_L \leq \beta_L + \gamma_L$  (37). The results are presented as incidence rate ratios with country-specific reference cohort  $c = A + P - 7$ . Due to small numbers in the cells comprising the youngest and oldest cohorts, the corresponding birth cohort effects are not displayed.

## Results

Figure 1 compares the age-truncated (ages 15-54 years) standardized rates (European standard) of seminoma and nonseminoma in the eight countries (1994-1996). Rates of seminoma tend to be about a third higher than nonseminoma, but there is a clear relationship between the absolute magnitude of the two, with rates of seminoma increasing proportionally with rates of nonseminoma in low risk (e.g., Italy and France) through to intermediate risk (Czech Republic and Norway) to high-risk countries (Denmark and Switzerland).

There are clear increases in the incidence of both histologies with calendar period in each European country, with the magnitude of the slopes similar across populations

**Table 1. Testicular germ cell incidence: populations included in the trend analysis by histologic subtype**

European area	Country	Calendar period*	Person-years <sup>†</sup>	Incidence (seminoma) <sup>‡</sup>	% Germ cell <sup>§</sup>	Incidence (nonseminoma) <sup>‡</sup>	% Germ cell <sup>§</sup>	Person-years <sup>†</sup>
Eastern	Czech Republic	1985-1999 ( $n = 3$ )	3.1	179	54.8	148	45.2	3,071,444
Northern	Denmark	1979-1998 ( $n = 4$ )	1.5	154	58.9	108	41.1	1,530,603
	Norway	1953-1997 ( $n = 9$ )	1.3	88	57.2	66	42.8	1,251,442
	Sweden	1964-1998 ( $n = 7$ )	2.4	116	56.4	90	43.6	2,426,688
	United Kingdom <sup>  </sup>	1978-1997 ( $n = 4$ )	15.1	792	58.3	567	41.7	15,089,155
Southern	Italy <sup>**</sup>	1983-1997 ( $n = 3$ )	1.3	48	61.7	30	38.3	1,238,491
Western	France <sup>**</sup>	1978-1997 ( $n = 4$ )	1.2	56	54.4	47	45.6	1,162,916
	Switzerland <sup>††</sup>	1983-1997 ( $n = 3$ )	0.8	85	60.9	55	39.1	834,828

\*Data available according to period of diagnosis (number of 5-year periods available in the analysis).

<sup>†</sup>Average annual male population expressed in million person-years at risk obtained from most recent 5-year period.

<sup>‡</sup>Annual number of incident cases obtained from most recent 5-year period.

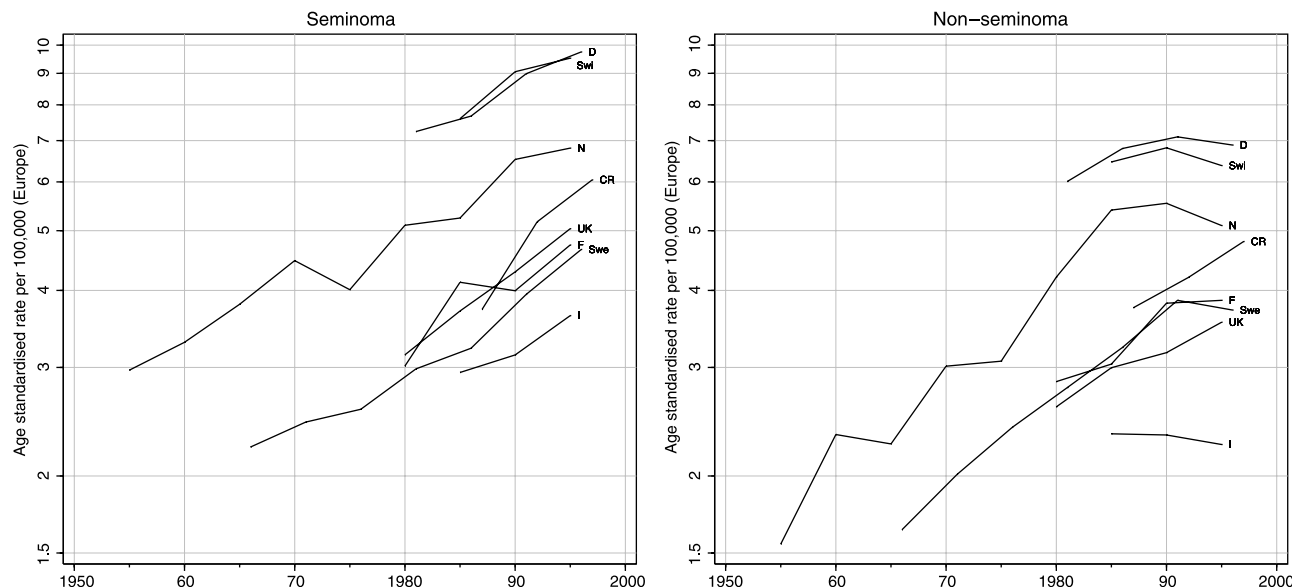
<sup>§</sup>Proportion based on cases in most recent 5-year period.

<sup>||</sup>Aggregation of England (1978-1997) and Scotland (1978-1997).

<sup>\*\*</sup>Aggregation of Florence (1985-1997), Varese Province (1983-1997), Parma Province (1983-1997), Ragusa Province (1983-1997), and Turin (1985-1997).

<sup>\*\*</sup>Aggregation of Bas-Rhin (1978-1997), Calvados (1978-1997), Doubs (1978-1997), Isere (1979-1997), Somme (1982-1997), and Tarn (1982-1997).

<sup>††</sup>Aggregation of Basel (1983-1997), Geneva (1983-1997), Neuchatel (1983-1996), St. Gall-Appenzell (1983-1997), Vaud (1988-1996), and Zurich (1983-1996).



**Figure 1.** Truncated age-standardized rates (European) of pure seminoma (*left*) and nonseminoma (*right*) in men aged 15 to 54 years in eight European countries by 5-year period of diagnosis (CR, Czech Republic; D, Denmark; F, France; I, Italy; N, Norway; Swe, Sweden; Swi, Switzerland; UK, United Kingdom).

(Fig. 2). The overall ranking of rates between countries is retained over time. A notable feature of the trends is the decline in nonseminoma rates observed in some but not all countries in the last 5-year period in the 1990s. This pattern is seen in high-risk Switzerland and Denmark as well as lower-risk Norway, Italy, and Sweden but not in the Czech Republic and the United Kingdom. In France, nonseminoma trends seem to have reached a plateau during the latest period.

No such declines are observed in the seminoma trends (Fig. 2). The relative proportions of seminoma and nonseminoma are largely similar between countries, despite the 3-fold variation in risk. Seminoma comprises the larger share with 55% to 60% of germ cell cancers, leaving 40% to 45% nonseminomas (Table 1). The proportion that were seminomas is slightly higher in low-risk Italy and high-risk Switzerland.

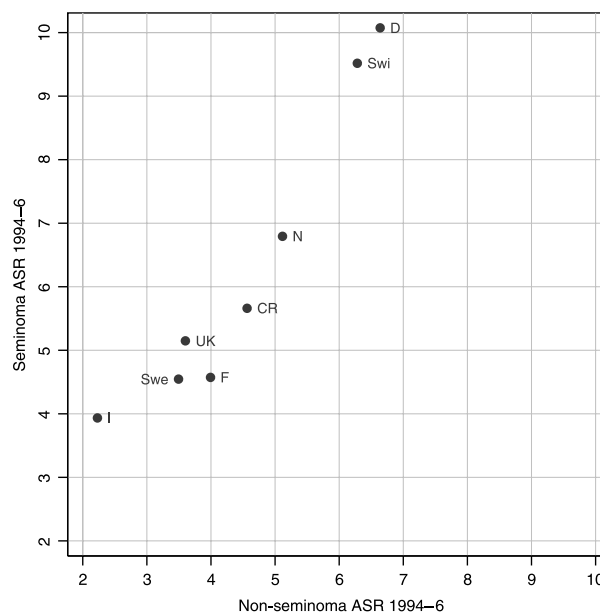
For the seminoma trends, a sufficient amount of variation in each country was explained either by a model representing the linear trend adjusted for age (in France, Italy, and the United Kingdom) or with additional cohort curvature (the Czech Republic, Denmark, Norway, Sweden, and Switzerland; data not shown). The nonlinear effects of cohort over and above the drift provided a statistically significant contribution to the seminoma trends in four of the eight countries (Norway, Sweden, Denmark, and the Czech Republic) and of borderline significance in two (Italy and Switzerland; Table 2A). In contrast, period curvature was not required in describing the seminoma trends in any European country (Table 2A).

None of the population-based trends for nonseminoma suffered from a significant lack of fit, although the required complexity of the model varied by population (data not shown). In Italy and Switzerland, only age effects were required, whereas both age and period were necessary in Denmark and France. Cohort curvature was necessary in explaining the nonseminoma incidence trends in three countries (the Czech Republic, the United Kingdom, and Denmark) and of borderline significance in Switzerland (Table 2B). Period curvature significantly improved the fit of nonseminoma trends in Norway (Table 2B).

Figure 3 displays the incidence rate ratios from the APC model according to birth cohort. The incidence trends of seminoma and nonseminoma in successive generations are

similar, although the trends tend to be more heterogeneous in the most recently born cohorts, where data are more sparse, and most of the cases are nonseminomas. The exception is Italy, where the trends in histology diverge in generations born after 1945.

In Switzerland, there is a strong indication that cohort-specific declines in both seminoma and nonseminoma rates in consecutive cohorts born since the 1960s. There is also some indication of a plateau in the trends in recent generations born in France and Denmark, but the observation is more evident for seminoma (Fig. 3).



**Figure 2.** Scatterplot of truncated age-standardized rates (European) of seminoma versus nonseminoma in men aged 15 to 54 years and diagnosed from 1994 to 1996 in eight European countries (CR, Czech Republic; D, Denmark; F, France; I, Italy; N, Norway; Swe, Sweden; Swi, Switzerland; UK, United Kingdom).

**Table 2. Period and cohort curvature over and above net drift**

European area	Incidence population	Period curvature			Cohort curvature		
		$\Delta$ Deviance*	$\Delta$ <i>df</i> <sup>†</sup>	<i>P</i> <sup>‡</sup>	$\Delta$ Deviance <sup>§</sup>	$\Delta$ <i>df</i> <sup>  </sup>	<i>P</i> <sup>¶</sup>
<b>A. Seminoma trends</b>							
Eastern	Czech Republic	3.1	1	0.08	17.5	8	0.02
	Northern	Denmark	1.3	2	0.52	22.6	9
	Norway	6.2	7	0.52	60.9	14	<0.01
	Sweden	5.8	5	0.32	43.7	12	<0.01
	United Kingdom**	0.2	2	0.88	7.0	9	0.63
Southern	Italy <sup>††</sup>	0.2	1	0.64	15.5	8	0.05
Western	France <sup>**</sup>	3.5	2	0.17	11.8	9	0.22
	Switzerland <sup>¶</sup>	1.2	1	0.28	15.6	8	0.05
<b>B. Nonseminoma trends</b>							
Eastern	Czech Republic	0.0	1	0.88	21.2	8	0.01
Northern	Denmark	3.6	2	0.16	16.6	9	0.05
	Norway	30.3	7	<0.01	11.8	14	0.62
	Sweden	11.0	5	0.05	15.4	12	0.22
	United Kingdom**	3.3	2	0.19	17.4	9	0.04
Southern	Italy <sup>††</sup>	0.0	1	0.85	6.5	8	0.60
Western	France <sup>**</sup>	1.6	2	0.45	13.0	9	0.16
	Switzerland <sup>¶</sup>	0.8	1	0.38	15.6	8	0.05

Abbreviation: *df*, degree of freedom.

\*Represents the difference in the deviance of the age + drift model and the age + drift + period model.

<sup>†</sup>Represents the difference in the degrees of freedom of the age + drift model and the age + drift + period model.

<sup>‡</sup>To determine the goodness-of-fit, the change in deviance was compared with the  $\chi^2$  distribution on the change in degrees of freedom between the models.

<sup>§</sup>Represents the difference in the deviance of the age + drift model and the age + drift + cohort model.

<sup>||</sup>Represents the difference in the degrees of freedom of the age + drift model and the age + drift + cohort model.

<sup>¶</sup>Aggregation of Basel (1983-1997), Geneva (1983-1997), Neuchatel (1983-1996), St.Gall-Appenzell (1983-1997), Vaud (1988-1996), and Zurich (1983-1996).

\*\*Aggregation of England (1978-1997) and Scotland (1978-1997).

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<sup>\*\*</sup>Aggregation of Bas-Rhin (1978-1997), Calvados (1978-1997), Doubs (1978-1997), Isere (1979-1997), Somme (1982-1997), and Tarn (1982-1997).

## Discussion

This study provides broad support for the hypothesis that generation-specific trends in testicular seminomas and nonseminoma conform to largely the same temporal patterns, implying that they share important etiologic factors. Trends in pure seminomas and nonseminomas are increasing with calendar time in most of the countries studied, although there are recent plateaus or minor declines in cross-sectional age-adjusted rates of nonseminoma in Denmark and Switzerland. Declines in incidence rates of both subtypes are also evident among recent birth cohorts in the latter country.

Despite differences in morphologic manifestation and in prognosis and treatment, there are many indications that the origin and pathogenesis of seminoma and nonseminoma are similar (38, 39). Both subtypes arise from the fetal population of primordial germ cells, also called gonocytes, which migrate to the developing gonad in weeks 5 to 6 of gestation. Both subtypes develop through a premalignant stage known as testicular carcinoma *in situ* or testicular intraepithelial neoplasia (40).

Morphologically and biochemically, seminoma cells resemble carcinoma *in situ* cells and primordial germ cells. Nonseminomas can show all stages of embryonic development, including embryoid bodies, which mimic the earliest stages of growth of the developing zygote, and fully differentiated tissues of any type in teratomas. Seminoma and nonseminoma are aneuploid. There is typically loss of material from chromosomes 4, 5, 11, 13, 18, and Y and gain of chromosome 7, 8, 12, and X material. In particular, gain of chromosome 12 material in the form of a 12p isochromosome is associated with the transformation from carcinoma *in situ* to the invasive phenotype of seminoma or nonseminoma.

Analytic studies of the causes of testicular cancer have often sought to identify separate risk factors for seminoma and nonseminoma, but no such difference has been established with consistency (10, 11). The current consensus is that

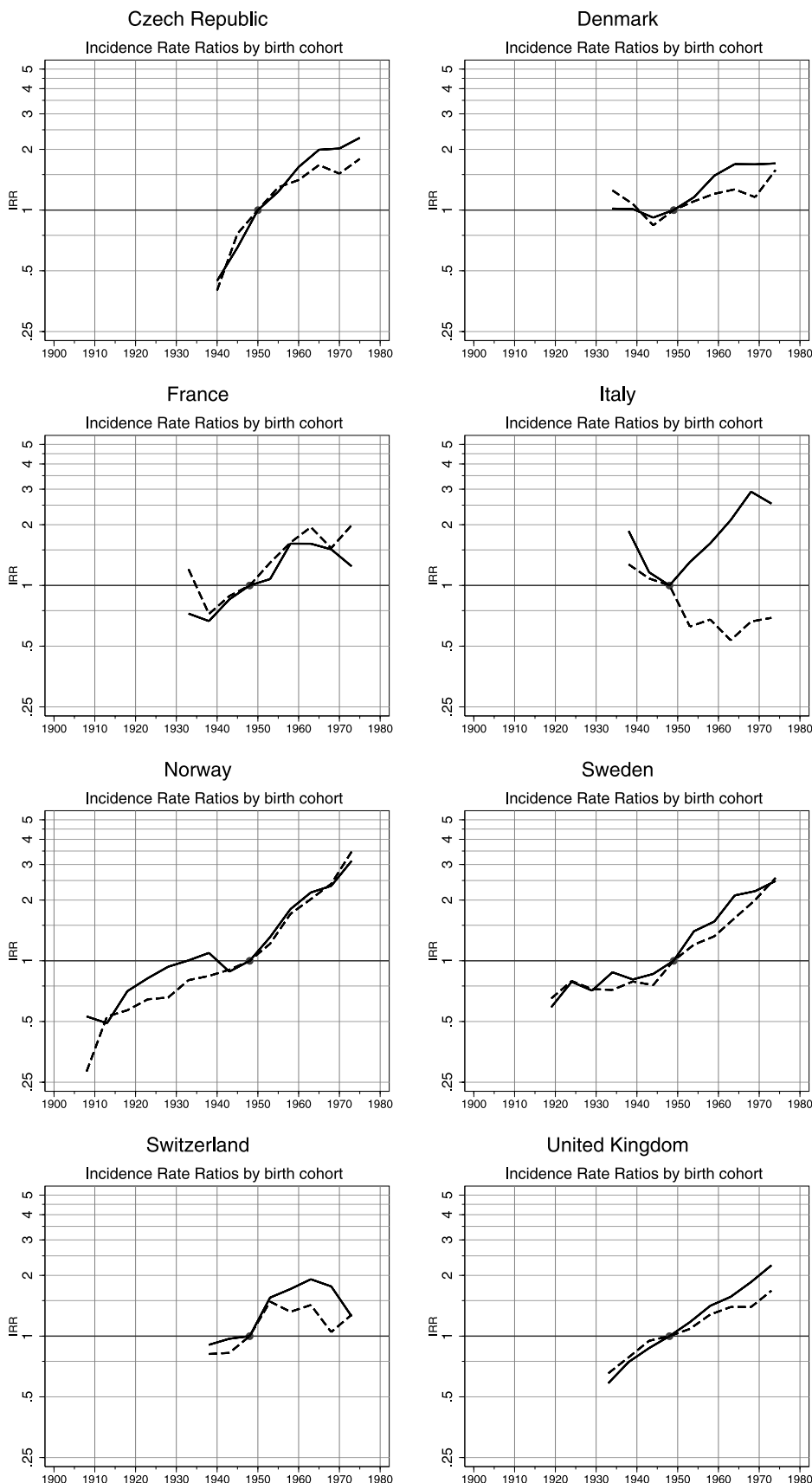
seminoma and nonseminoma are more likely to have similar rather than different causes (41, 42).

The importance of birth cohort effects in this study is in accordance with many prior reports of combined or subtype-stratified testicular cancer trends in Europe (3, 6, 7, 36), the United States (2), and Canada (26, 27). Nonlinear cohort effects significantly improved the fit of the APC model in six countries for both subtypes, indicating the importance of generational influences, whereas period curvature was not required in the majority. Furthermore, short-term attenuations of increasing risk in men born around 1940 to 1945 were evident in Denmark (for both histologies) and Norway (seminoma only) and less unequivocally in Sweden and France, but for both subtypes. Such observations have been reported previously for incidence trends in the Scandinavian countries, either in testicular germ cell trends overall or for both subtypes (6, 24, 25, 36, 43). In Denmark, the temporary irregularity has been hypothesized to be at least partially a result of specific events (e.g., dietary changes or tobacco consumption) at the time of German occupation during the Second World War (25). The similarity of the subtype trends implies such a wartime effect would act in an identical manner on seminoma and nonseminoma.

The observed lag of ~10 years in the age at peak incidence of subtypes has been consistently reported in Western populations, with nonseminomas peaking earlier, in men aged in their late 20s (18). The differential age profile may perhaps reflect that nonseminomas are more aggressive and rapidly growing than seminomas at diagnosis; the proportion of metastatic to localized tumors is often higher for nonseminomas than seminomas (25). Any departure from the steady increases in testicular cancer over time is, therefore, likely to occur for nonseminomas some years ahead of seminoma. This seems as an artifact of analysis on the period scale, not present on the birth cohort scale. With a narrow time window of susceptibility to exposures earlier in life, and a biologically constant time to diagnosis, all temporal changes in rate-limiting exposures should appear as cohort effects.

Some evidence of a plateau in the cohort-specific risk of both types is observed among recent cohorts in some populations (Czech Republic, Denmark, and France), although it unknown whether there will be subsequent

declines. With the exception of Italy, the subtype trends followed a rather similar generational course, and the homogeneity mirrors several previous observations reported for temporal variations in testicular germ cell incidence. The



**Figure 3.** Incidence rate ratios of testicular germ cell seminoma (solid line) and nonseminoma (dashed line) by birth cohort in eight European countries, assuming an overall period slope of zero. •, reference category (IRR, incidence rate ratio = 1), corresponding to birth cohort  $A + P - 7$ .



period-specific decline in nonseminoma (but not seminoma) seen in Switzerland in the 1990s is in agreement with reports describing trends in the Vaud region (44). However, our observation that there is a diminution in risk of both histologies for consecutive Swiss cohorts most evident since the mid-1960s adds weight to the hypothesis that only a delay of around a decade in clinically manifest cancer distinguishes seminomas from nonseminomas.

In the unavoidable presence of nonidentifiability of the three effects, the linear interdependency arising from cohort being entirely defined in terms of period and age, analyzing, and interpreting variable estimates via the APC model is inherently problematic. In circumventing the problem using Holford's method (35), and setting the period component of the net drift to zero in each country, we have assumed that the increasing regular trend is exclusively the result of a birth cohort phenomenon, and that there are no diagnostic or coding artifacts that would lead to increases or decreases in rates with calendar time. The prominence paid to the operation of cohort effects would seem a reasonable assumption given that carcinogenic development of both seminoma and nonseminoma are likely mediated through early-in-life or *in utero* exposures (25, 40). If left untreated, testicular cancer is highly fatal, and diagnostic or coding artifacts seem unlikely to be responsible for much of the rapid increases in the regular trend (18).

Diagnostic changes in one or both subtypes cannot be entirely excluded however. In Italy, the cohort effects, in discordance with other countries, diverge after the late 1940s. The recent seminoma/nonseminoma incidence ratio is unusually high in Italy, whereas the trends in nonseminoma are rather flat. However, nonlinear period effects, a potential indicator of temporal changes due to artifact, were not significant for either subtype, although this may be due to a lack of power to reject simpler models (45). It is possible that artifactual changes were in operation throughout the study period, and that they differed by subtype; this would have led to divergent period slopes but more consistency between cohort effects for seminoma and nonseminoma.

Our observations are in broad agreement with a number of previous studies examining cohort trends in the two main subtypes. Using a varying level of analytic sophistication, a general consensus has emerged of increasing trends of similar magnitude by subtype, based on European reports in Denmark (25), Norway (24), England, and Wales (46), and more recently, in a number of Northern European countries (7), and on reports in Canada (Ontario; ref. 26) and the United States (Connecticut; ref. 2). A study found increasing trends between 1963 and 1984 in Scotland for both histologies, with nonseminomas increasing more rapidly than seminomas (47). Some differences in trends in the subtypes have been found by two recent studies analyzing testicular cancer data up to 1998 in the United States (23) and up to 1995 in Canada (27). In the U.S. study (based on Surveillance, Epidemiology, and End Results data), nonseminomas reached a plateau in White men, with seminoma/nonseminoma ratios of 50:50 in the mid-1970s comparing with 60:40 some 20 years later (23). The Canadian study argues that the subtype trends differ by both age and birth cohort. Using a method analogous to ours, the authors suggest there are distinct cohort patterns in aggregated data from Ontario, Saskatchewan, and British Columbia (27). The subtype trends they plot from the APC model, however, are similar in successive cohorts born after 1920 and could be interpreted as indicators of homogeneity in the seminoma and nonseminoma trends.

Further evidence that the subtypes share the same etiologic factors comes from several analytic studies examining prenatal and perinatal exposures and the risk of testicular cancer. A Danish study (10) argued that seminoma and nonseminoma have similar causes, finding that whereas cryptorchidism, birth

weight, and maternal age were all independent risk factors for testicular cancer, only the latter differed by subtype, with higher maternal age being more strongly associated with seminoma. Recent studies in Canada (14), the United States (48), and Sweden (16) have generally upheld the hypothesis of a similar etiology: despite markers of high estrogen levels consistently increasing the risk of germ cell cancer, little evidence of heterogeneity on stratification by histologic group emerged.

Some studies have reported statistically significant heterogeneity in risk factors for seminoma and nonseminoma, but these have not been found consistently across studies. Thus, Sabroe and Olsen (12) found elevated risks of seminoma in Danish men of a lower birth order, whereas a Swedish study (11) found that markers of estrogen during pregnancy, higher maternal age, higher placental weight, and lower parity affected seminomas, and factors related to neonatal growth retardation, specifically lower maternal age, and lower placental weight increased the risk of nonseminoma. In a U.K. report, a history of sexually transmitted disease and participation in certain sports was linked to a higher risk of nonseminoma cancers (21). The effect of socioeconomic status on testicular cancer is not conclusive, although men belonging to higher socioeconomic groups are often reported to be higher risk of testicular cancer relative to less-privileged groups (49, 50). As with other variables, the risk estimates tend not, however, to be consistent by subtype (50).

Difficulties in achieving sufficient statistical power to detect truly significant effects in analytic studies make such investigations problematic, whereas the multiple testing of candidate risk factors increases the likelihood of finding statistically significant effects by chance. In parallel, statements as to the degree of homogeneity of seminoma and nonseminoma trends must be equivocal, given that nonidentifiability precludes the possibility to present and compare unique estimates of the cohort trends. Nevertheless, assuming that only generational influences operate, the incidence trends are rather similar in this time dimension for most European countries studied, indicative that the subtypes share largely the same distribution of causal factors within a number of diverse populations. Where the subtype trends substantially diverge, they may be explained by the presence of linear period effects, implicating diagnostic or coding artifacts with calendar time.

In conclusion, epidemiologic studies of testicular cancer will continue to be fundamental in gaining insight into a disease with few known causal determinants, and at present, little scope for primary prevention. This study provides further evidence of the etiologic similarity of testicular seminoma and nonseminoma.

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## References

- Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Vol. VIII. IARC Scientific Publications No. 155 ed. Lyon: IARC Press; 2002.
- Zheng T, Holford TR, Ma Z, et al. Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935–1992. *Int J Cancer* 1996;65:723–9.
- Coleman MP, Esteve J, Damiacki P, Arslan A, Renard H. Trends in cancer incidence and mortality. Lyon: IARC; 1993.
- Adami HO, Bergstrom R, Mohnner M, et al. Testicular cancer in nine northern European countries. *Int J Cancer* 1994;59:33–8.
- Forman D, Moller H. Testicular cancer. *Cancer Surv* 1994;19/20:323–41.
- Bergstrom R, Adami HO, Mohnner M, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. *J Natl Cancer Inst* 1996;88:727–33.
- Richiardi L, Bellocchio R, Adami HO, et al. Testicular cancer incidence in eight northern European countries: secular and recent trends. *Cancer Epidemiol Biomarkers Prev* 2004;13:2157–66.
- Swerdlow AJ, Stiller CA, Wilson LM. Prenatal factors in the aetiology of testicular cancer: an epidemiological study of childhood testicular cancer deaths in Great Britain, 1953–73. *J Epidemiol Community Health* 1982;36:96–101.
- Swerdlow AJ, Huttly SR, Smith PG. Prenatal and familial associations of testicular cancer. *Br J Cancer* 1987;55:571–7.
- Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. *Cancer Causes Control* 1997;8:904–12.
- Akre O, Ekbohm A, Hsieh CC, Trichopoulos D, Adami HO. Testicular nonseminoma and seminoma in relation to perinatal characteristics. *J Natl Cancer Inst* 1996;88:883–9.
- Sabroe S, Olsen J. Perinatal correlates of specific histological types of testicular cancer in patients below 35 years of age: a case-cohort study based on midwives' records in Denmark. *Int J Cancer* 1998;78:140–3.
- Wanderas EH, Grotmol T, Fossa SD, Tretli S. Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective population- and register-based study on Norwegian males born between 1967 and 1995. *Cancer Causes Control* 1998;9:475–86.
- Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int J Cancer* 2000;87:438–43.
- Dieckmann KP, Endins G, Pichlmeier U. How valid is the prenatal estrogen excess hypothesis of testicular germ cell cancer? A case control study on hormone-related factors. *Eur Urol* 2001;40:677–83.
- Richiardi L, Akre O, Bellocchio R, Ekbohm A. Perinatal determinants of germ-cell testicular cancer in relation to histological subtypes. *Br J Cancer* 2002;87:545–50.
- Depue RH, Pike MC, Henderson BE. Estrogen exposure during gestation and risk of testicular cancer. *J Natl Cancer Inst* 1983;71:1151–5.
- Pike MC, Chilvers CED, Bobrow LG. Classification of testicular cancer in incidence and mortality statistics. *Br J Cancer* 1987;56:83–5.
- Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case-control study. *Am J Epidemiol* 1986;124:39–52.
- Prener A, Hsieh CC, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes Control* 1992;3:265–72.
- Coupland CA, Chilvers CE, Davey G, et al. Risk factors for testicular germ cell tumours by histological tumour type. United Kingdom Testicular Cancer Study Group. *Br J Cancer* 1999;80:1859–63.
- Stone JM, Sandeman TF, Ironside P, Cruickshank DG, Matthews JP. Time trends in accuracy of classification of testicular tumours, with clinical and epidemiological implications. *Br J Cancer* 1992;66:396–401.
- McGlynn KA, Devesa SS, Sigurdson AJ, et al. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer* 2003;97:63–70.
- Wanderas EH, Tretli S, Fossa SD. Trends in incidence of testicular cancer in Norway 1955–1992. *Eur J Cancer* 1995;31A:2044–8.
- Moller H. Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. *Eur Urol* 1993;23:8–13.
- Weir HK, Marrett LD, Moravan V. Trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, 1964–1996 [see comments]. *CMAJ* 1999;160:201–5.
- Liu S, Semenciw R, Waters C, et al. Clues to the aetiological heterogeneity of testicular seminomas and non-seminomas: time trends and age-period-cohort effects. *Int J Epidemiol* 2000;29:826–31.
- European Network of Cancer Registries. EUROCIM version 4.0. Lyon: European Network of Cancer Registries; 2001.
- Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. Cancer Incidence in five continents. Vol. VI. Lyon: IARC Press; 1992.
- Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents. Vol. VII. Lyon: IARC Press; 1997.
- McCullagh P, Nelder JA. Generalized linear models. 2nd ed. London: Chapman and Hall; 1989.
- Stata Statistical Software. Version 8.0. College Station (TX): Stata Corp. LP; 2003.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: age-period and age-cohort models. *Stat Med* 1987;6:449–67.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: age-period-cohort models. *Stat Med* 1987;6:469–81.
- Holford TR. The estimation of age, period and cohort effects for vital rates. *Biometrics* 1983;39:311–24.
- Moller H. Decreased testicular cancer risk in men born in wartime. *J Natl Cancer Inst* 1989;81:1668–9.
- Holford TR. Age period cohort analysis. *Encyclopedia of biostatistics*. Chichester: John Wiley & Sons; 1998. p. 82–99.
- Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. *Nat Rev Cancer* 2005;5:210–22.
- Looijenga LH, Oosterhuis JW. Pathobiology of testicular germ cell tumors: views and news. *Anal Quant Cytol Histol* 2002;24:263–79.
- Skakkebaek NE, Berthelsen JG, Giwercman A, Muller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. *Int J Androl* 1987;10:19–28.
- Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: an overview. *Int J Cancer* 2005;116:331–9.
- Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. *World J Urol* 2004;22:2–14.
- Moger TA, Aalen OO, Halvorsen TO, Storm HH, Tretli S. Frailty modelling of testicular cancer incidence using Scandinavian data. *Biostatistics* 2004;5:1–14.
- Levi F, Te VC, Randimbison L, la Vecchia C. Trends in testicular cancer incidence in Vaud, Switzerland. *Eur J Cancer Prev* 2003;12:347–9.
- Kaldor JK, Day NE. Mathematical models in cancer epidemiology. 2nd ed. In: Schottenfeld D, Fraumeni-JF J, editors. *Cancer epidemiology and prevention*. New York: Oxford; 1996. p. 127–37.
- dos Santos Silva I, Swerdlow AJ, Stiller CA, Reid A. Incidence of testicular germ-cell malignancies in England and Wales: trends in children compared with adults. *Int J Cancer* 1999;83:630–4.
- Boyle P, Kaye SB, Robertson AG. Changes in testicular cancer in Scotland. *Eur J Cancer Clin Oncol* 1987;23:827–30.
- English PB, Goldberg DE, Wolff C, Smith D. Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). *Cancer Causes Control* 2003;14:815–25.
- Pearce N, Sheppard RA, Howard JK, Fraser J, Lilley BM. Time trends and occupational differences in cancer of the testis in New Zealand. *Cancer* 1987;59:1677–82.
- Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971–95. *Int J Cancer* 2002;102:643–8.

## Do Testicular Seminoma and Nonseminoma Share the Same Etiology? Evidence from an Age-Period-Cohort Analysis of Incidence Trends in Eight European Countries

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