# Increase in Testicular Cancer Incidence in Six European Countries: a Birth Cohort Phenomenon

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***Background:*** **For unknown reasons, the age-standardized incidence of testicular cancer has shown a rapid increase in virtually all countries (mostly Western) studied. For populations with a sufficiently long period of cancer registration, this development can be traced back to the first half of this century.** ***Purpose:*** **By evaluating data from six countries with long periods of cancer registration (Denmark, Norway, Sweden, the former German Democratic Republic [East Germany], Finland, and Poland), we sought to determine whether the increase in testicular cancer risk follows a birth cohort pattern and, if so, to quantify and compare any birth cohort effects.** ***Methods:*** **A total of 30 908 incident cases of testicular cancer, diagnosed from 1945 through 1989 in men who were 20-84 years of age, were identified in population-based cancer registries in the six countries. In addition to performing simple trend analyses, we fitted several Poisson regression models (with the explanatory variables age, time period [calendar time], and birth cohort) to the data. Individual models were estimated by the maximum likelihood method.** ***Results:*** **The age-standardized incidence of testicular cancer was found to vary among the six populations and, on the basis of total registration data, increased annually at rates ranging from 2.3% (in Sweden) to 5.2% (in East Germany). A comparison of several regression models indicated that birth cohort was a stronger determinant of testicular cancer risk than was calendar time for all six populations. Within each population, little variation in testicular cancer risk was observed for men born between 1880 and 1920; thereafter, the risk began to increase. Among men born in Denmark, Norway, and Sweden between 1930 and 1945 (the period encompassing the Second World War), the increasing trend in risk was interrupted (i.e., a leveling in risk occurred). After 1945, an uninterrupted increase in risk was observed for all six populations. With men born around 1905 as the reference group, the relative risk of testicular cancer for those born around 1965 varied from 3.9 (95% confidence interval [CI] = 2.7-5.6) in Sweden to 11.4 (95% CI = 8.3-15.5) in East Germany.** ***Conclusions and Implications:*** **The increasing trend in testicular cancer risk observed for these six populations follows a birth cohort pattern. This distinct risk pattern provides a framework for the identification of specific etiologic factors. [J Natl Cancer Inst 1996;88:727-33]**

The evidence is overwhelming that testicular cancer incidence has increased rapidly in virtually all countries (mostly western) studied (*1-3*). For populations with a sufficiently long period of cancer registration, notably in Connecticut (*4*) and Denmark (*1,5*), this development can be traced back to the first half of this century. A doubling in incidence was documented in Denmark within 25 years following the initiation of cancer registration in 1943 (*5*). The causes of these trends, notwithstanding their strength and consistency, are unknown and remain elusive (*2,6,7*).

Our aim is to describe the pattern of testicular cancer occurrence by age and time in several different high- and low-risk populations. Such a description could provide a framework for the critical assessment of old and new etiologic hypotheses. Future analytic epidemiologic studies could then focus on factors with an exposure pattern—by age, time period, and geographic area—that tallies with the descriptive epidemiology. Previously, we performed simple trend analyses of testicular cancer incidence in Germany (the former German Democratic Republic [East Germany] and Saarland), Poland, the Nordic countries (Denmark, Finland, Norway, and Sweden), and the Baltic countries (Estonia, Latvia, and Lithuania). These analyses confirmed the almost 10-fold variation in age-standardized incidence and revealed strong persistent upward trends (*8*). The specific purpose of the investigation reported here was to clarify whether the trends in testicular cancer occurrence follow a birth cohort pattern—as suggested by a few studies (*3,5,9,10*)—in six countries with a sufficiently long period of cancer registration, and, if so, to quantify and compare any birth cohort effects.

## Subjects and Methods

### Cancer Registration

We analyzed cancer incidence data from six population-based cancer registries. Essential information about these registries is described in Table 1; more complete information about them has been documented (*11*). Further

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*See* "Notes" section following "References."

description of the Nordic registries and of cancer registration in East Germany can be found in incidence publications (*12-15*) and collaborative monographs (*1,16,17*). By and large, cancer registration in the Nordic countries, dating back to 1943 in Denmark and to the 1950s in Finland, Norway, and Sweden, is considered almost complete and reliable. In East Germany, an obligatory system established in 1953 included both the notification of new cases and annual status reports during the first 5 years after a case patient's initial diagnosis; additional links between cancer registration and social services helped to reach an estimated completeness of about 95% (*8*). Cancer registration in Poland, compulsory nationwide since 1952, became more formalized following governmental instruction in 1962. Twelve regional registers, coordinated by a National Cancer Registry, were gradually introduced during the 1960s (*11*); the completeness of registration, facilitated by centralized treatment of testicular cancer since the mid-1970s, was estimated to be 90% overall (Table 1) and 95% during the last decade (*18,19*).

## Statistical Methods

Data from all registries included the age-adjusted incidence rates [world standard population (*11*)] for each year and the number of testicular cancer cases plus the population denominator by 5-year age group. We excluded the first few years of cancer registration (when underreporting might have been most marked) to obtain complete 5-year periods through 1989 for analyses; 30 908 incident cases of testicular cancer (in patients who were 20-84 years of age at diagnosis) could be included in our analyses (Table 1).

In addition to simple trend analyses, we fitted Poisson regression models to the data. In age–period–cohort analyses, we assumed that the number of incident cases is a variable with a Poisson distribution that has a mean depending multiplicatively on the number of person-years and the explanatory variables age, time period, and birth cohort (*20,21*). The models were estimated by the maximum likelihood method, using the GLIM software package (*22*). Submodels with the combination of age and period or age and cohort were fitted in addition to the full age–period–cohort model. The special case in which the effect of period or cohort on the logarithmic rates in age–period and age–cohort models was assumed to be linear was also considered. In this case, it is impossible to distinguish period effects from cohort effects, and the linear effect is denoted as "drift" (*20*).

The basic measure used in the evaluation of the models was the deviance, defined as twice the difference between the log likelihood value of a perfectly fitting model and the current model. Different nested models were compared by determination of the difference in deviance, which is asymptotically, chi-square distributed. A large reduction in deviance compared with the reduction in degrees of freedom when, for example, an age and an age–cohort model are compared, indicates that an important factor has been added. In the assessment of absolute fit, the Pearson chi-squared statistic is usually preferred to the deviance. The results obtained were similar; therefore, Pearson statistics are not shown. When the Pearson statistic, and also (usually) the deviance, is of the same order of magnitude as the number of degrees of freedom, the fit may be considered adequate.

The number of 5-year periods available for analysis for the individual registries varied between five and nine; the number of testicular cancer cases ranged from 1174 to 10 051 (Table 1). The number of age groups for all countries was 13 (i.e., 20-24, . . ., 80-84 years). In the end, there were 21 partially overlapping birth cohorts (defined by 10-year intervals) in Denmark (i.e., 1860-1869, 1865-1874, . . ., 1960-69) and fewer in the other countries. We denote the cohorts by the middle year of birth as: 1865, . . ., 1965. To obtain reasonably stable estimates, the 1905 cohort was used as the reference.

All reported *P* values are from two-sided tests.

# Results

## Simple Trend Analyses

As reported earlier (*8*), the age-standardized incidence of testicular cancer in 1980 varied sixfold, from 1.3 per $10^5$ males in Finland to 7.8 per $10^5$ males in Denmark (Table 1). On the basis of data from the entire period of registration, the average annual increase in incidence was lowest in Sweden (2.3%), intermediate (2.7%-3.4%) in the other Nordic countries, and highest in Poland (4.8%) and East Germany (5.2%). Fig. 1 shows plots of age-specific incidence rates by birth cohort for each country. Besides illustrating the geographic variation in age-specific rates, the plots reveal that the incidence rate at younger ages increased markedly for each successive birth cohort. In East Germany, the incidence at age 35-39 years almost doubled for each decade from 1930 to 1950. Likewise, the men born between 1955 and 1964 (the 1960 birth cohort) experienced a dramatic, further increase in incidence at ages 20-29 when compared with those born about 1950. A development of this kind took place in all countries (Fig. 1). In contrast, incidence trends at higher ages were generally weak and inconsistent; these trends could be studied mostly in men born in 1920 and earlier. There is evidence of a separate pattern at higher ages in Finland and Poland, with a second peak in incidence among men aged 70-80 years. In Finland, lymphomas of the testis (which occur largely in old men) are coded as testicular cancers, probably explaining the observed pattern. In Denmark, East Germany, Norway, and Sweden, testis lymphomas were definitely not coded as testicular cancers, although they may have been coded as testicular cancer in Poland. To distinguish and quantify cross-sectional and birth cohort effects more clearly, we fitted various age–period–cohort regression models to the data.

**Table 1.** Characteristics of six population-based cancer registries with the number of testicular cancer cases—patients 20-84 years of age at diagnosis—included in the analysis, along with age-standardized (world standard population) incidence rates per $10^5$ males in 1980

| Country/ area | Population, mill* | Year when registry started | Years analyzed | Estimated completeness of registration | No. of cases analyzed | Age-standardized incidence in 1980† |
|---|---|---|---|---|---|---|
| Denmark | 5.11 | 1943 | 1945-1989 | 97 | 6352 | 7.8 |
| Finland | 4.89 | 1952 | 1955-1989 | 99 | 1174 | 1.3 |
| German Democratic Republic | 16.66 | 1953 | 1965-1989 | 95 | 10 051 | 5.9 |
| Norway | 4.20 | 1952 | 1955-1989 | 100 | 3111 | 5.4 |
| Poland | 37.20 | 1952 | 1965-1989 | 90 | 6450 | 1.7 |
| Sweden | 8.34 | 1958 | 1960-1989 | 96 | 3770 | 3.6 |
| Total | 76.40 | | | | 30 908 | |

*Estimates from the mid-1980s, as given in (*1*); mill = million.
†*From* ref. (*8*).

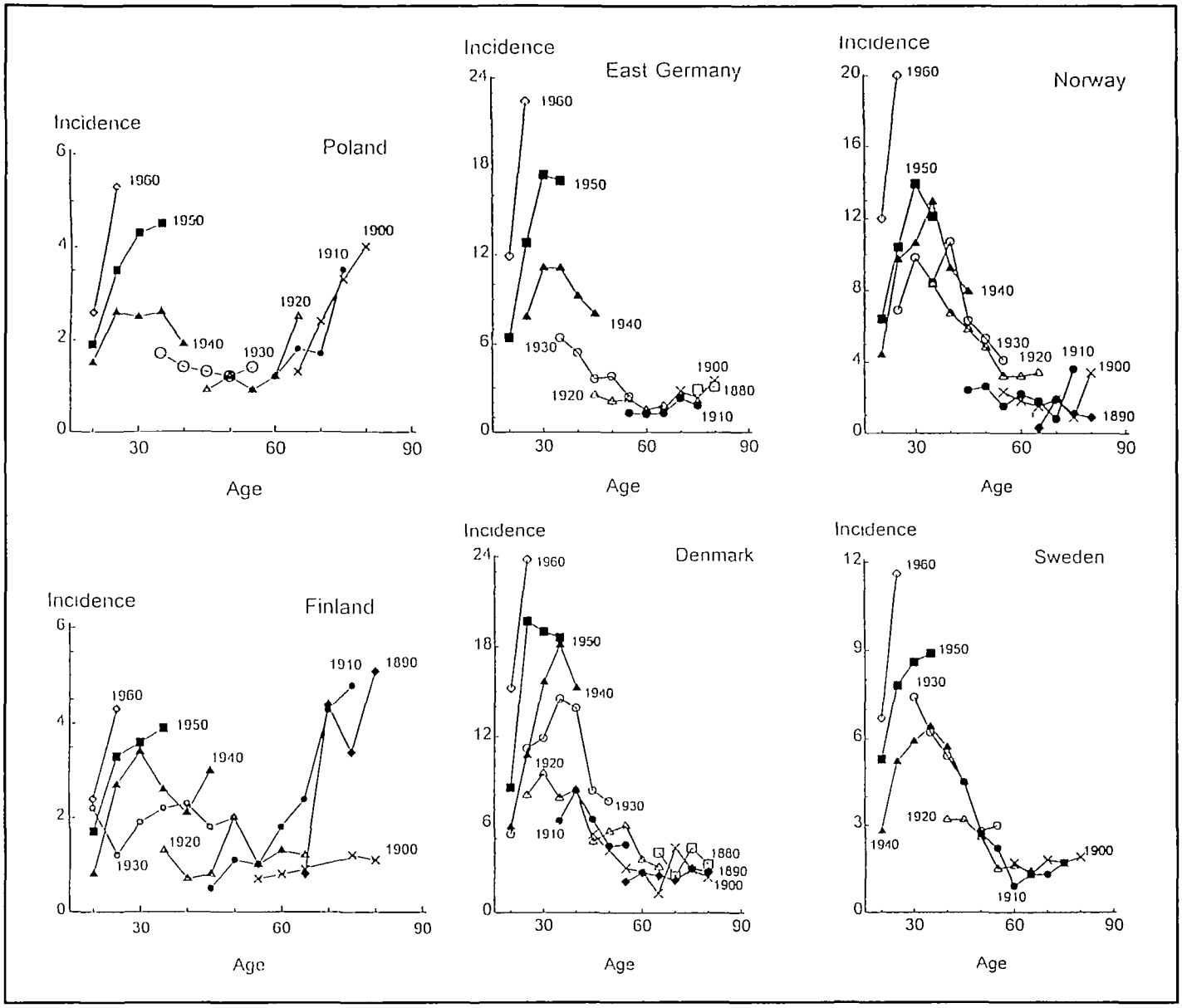


**Fig. 1.** Observed age-specific incidence of testicular cancer in selected birth cohorts by country.

## Age–Period–Cohort Models

Table 2 contains results of the modeling. An age–drift model always reduced the deviance of the basic age model considerably. An age–period model was a marginal improvement on the age–drift model in Denmark. There was no evidence of nonlinear period effects in any other country. On the other hand, the age–cohort model was always a vast improvement on the age–drift model. The full age–period–cohort model gave an adequate representation of the data in all six populations—with the possible exception of Poland—as indicated by deviances of the same size as the number of degrees of freedom. A comparison of the age–period model with the full age–period–cohort model entailed significant improvement ($P<.001$) in all countries, indicating strong birth cohort effects. In contrast, a comparison of the age–cohort model with the full age–period–cohort model led to substantial improvement only in Denmark, marginal improvements in Finland and Poland, and no significant improvement in the other three populations. The age–cohort model was chosen as an adequate representation of the data, since, even in Denmark, it was markedly superior to the age–period model.

## Birth Cohort Representation

Fig. 2 shows birth cohort effects obtained from the age–cohort models defined in Table 2. Before 1905, the pattern was irregular, with only moderate, mostly nonsignificant differences in relative risks (RRs) compared with the reference cohort, which was born between 1900 and 1909 (Table 3). When cancer registration started, men in these early birth cohorts had all passed the age of 25-34 years, i.e., the age when testicular cancer incidence peaks. From about 1905 to 1920, the RRs started to increase in all countries except Sweden (Fig. 2, A) and East Germany (Fig. 2, B). In the latter country, a rapid increase took place beginning with the 1930 cohort; for the 1965 cohort, the RR compared with the reference group (the 1905 cohort) was

Table 2. Characteristics of different age–period–cohort models for testicular cancer incidence in six populations analyzed separately during the time periods shown in Table 1

| Terms in model | Denmark | | | Finland | | | German Democratic Republic | | | Norway | | | Poland | | | Sweden | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *df** | dev† | *P* | *df** | dev† | *P* | *df** | dev† | *P* | *df** | dev† | *P* | *df** | dev† | *P* | *df** | dev† | *P* |
| Age | 104 | 834.9 | | 78 | 218.5 | | 52 | 1341.0 | | 78 | 329.5 | | 52 | 773.4 | | 65 | 272.3 | |
| Age–drift | 103 | 204.0 | | 77 | 115.6 | | 51 | 151.0 | | 77 | 123.2 | | 51 | 129 0 | | 64 | 133.8 | |
| Age–period‡ | 96 | 188.6 | <.05 | 72 | 106.6 | NS§ | 48 | 150.4 | NS | 72 | 116.3 | NS | 48 | 123.0 | NS | 60 | 126.6 | NS |
| Age–cohort‖ | 84 | 118.8 | <.001 | 60 | 75.5 | <.005 | 36 | 32.5 | <.001 | 60 | 57.7 | <.001 | 36 | 56.7 | <.001 | 48 | 52.7 | <.001 |
| Age–period–cohort¶ | 77 | 85.7 | <.001<br><.001 | 55 | 64.0 | <.001<br><.05 | 33 | 30.1 | <.001<br>NS | 55 | 50.5 | <.001<br>NS | 33 | 47.5 | <.001<br><.05 | 44 | 49.4 | <.001<br>NS |

*Degrees of freedom.
†Deviances from standard Poisson estimation of model.
‡*P* values refer to a comparison of the age–period model with the age–drift model.
§NS = not significant.
‖*P* values refer to a comparison of the age–cohort model with the age–drift model.
¶*Two P values refer to a comparison of the full age–period–cohort model with the age–period and the age–cohort models, respectively.*

about 11, the same as in Poland and similar to that in Finland (Table 3). In Sweden, an increase occurred between the 1920 and 1930 cohorts; the increase in risk, however, was slow for men born before 1945. In Denmark and Norway, there was a leveling of risk between 1935 and 1945 in the otherwise general increase in RRs. A more detailed age–cohort modeling of non-overlapping 5-year birth cohorts, confined to data from the Nordic countries, substantiated this pattern further. Although the increasing trend appeared uninterrupted in Finland, a leveling took place in Sweden among men born between 1926 and 1940. Men born in 1941 through 1945 in Denmark and Norway may have even experienced a reduction in testicular cancer risk compared with those born during the preceding 5-10 years (data not shown). In all countries, the risk increased among men born after 1945, but the rate of increase was much slower in the Scandinavian countries than in East Germany, Finland, and Poland. Point estimates with 95% confidence intervals are shown for selected birth cohorts in Table 3.

## Age Effects

In all six countries, the age effects obtained from the age–cohort models (Fig. 3) had peak values for the group aged 35-39 years, with RRs between 2.2 and 2.8 (the reference group was men aged 20-24 years). The RRs then diminished with increas-

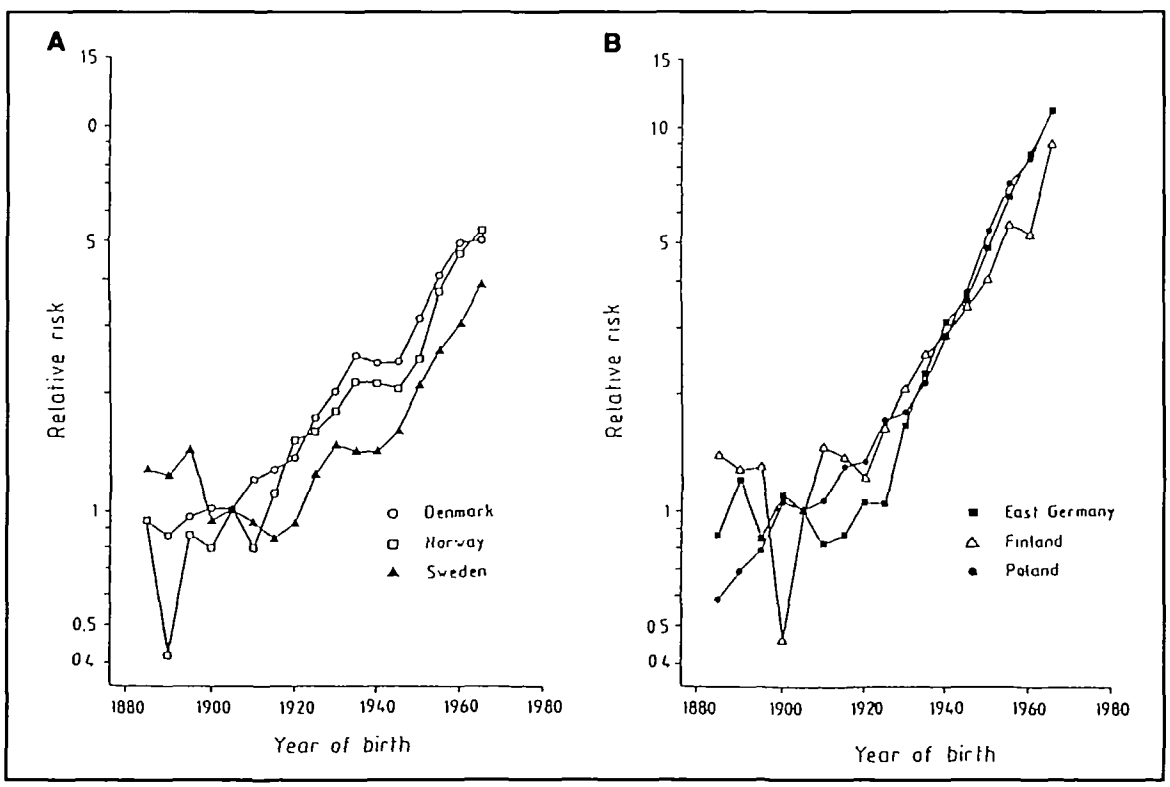


**Fig. 2.** Relative risk of developing testicular cancer by country and birth cohort, using men born between 1900 and 1909 as the reference. Results were obtained from age–cohort models defined in Table 2 Confidence intervals for selected cohorts are given in Table 3. Left panel = Denmark, Norway, and Sweden; right panel = German Democratic Republic, Finland, and Poland.

Table 3. Relative risk (RR) with 95% confidence interval (CI) of developing testicular cancer for selected 10-year birth cohorts by country (results were obtained from age–cohort models as defined in Table 2)

| Country | Central year of birth | | | | | |
|---|---|---|---|---|---|---|
| | 1890 | 1905 | 1920 | 1935 | 1950 | 1965 |
| Denmark | | | | | | |
| RR (95% CI) | 0.9 (0.6-1.2) | 1.0 ref* | 1.4 (1.1-1.6) | 2.5 (2.1-3.0) | 3.2 (2.6-3.8) | 5.1 (4.0-6.5) |
| Finland | | | | | | |
| RR (95% CI) | 1.3 (0.7-2.3) | 1.0 ref | 1.2 (0.8-2.0) | 2.6 (1.6-4.1) | 4.1 (2.5-6.5) | 9.3 (5.1-16.9) |
| German Democratic Republic | | | | | | |
| RR (95% CI) | 1.2 (0.8-1.8) | 1.0 ref | 1.1 (0.8-1.4) | 2.3 (1.7-3.1) | 4.9 (3.6-6.6) | 11.4 (8.3-15.5) |
| Norway | | | | | | |
| RR (95% CI) | 0.4 (0.2-0.8) | 1.0 ref | 1.6 (1.1-2.1) | 2.2 (1.6-2.9) | 2.5 (1.8-3.4) | 5.4 (3.7-7.9) |
| Poland | | | | | | |
| RR (95% CI) | 0.7 (0.4-1.1) | 1.0 ref | 1.3 (1.1-1.7) | 2.1 (1.6-2.8) | 5.4 (4.1-7.1) | 11.2 (8.3-15.3) |
| Sweden | | | | | | |
| RR (95% CI) | 1.2 (0.8-1.9) | 1.0 ref | 0.9 (0.7-1.2) | 1.4 (1.1-1.9) | 2.1 (1.5-2.8) | 3.9 (2.7-5.6) |

*ref = reference.

ing age in all countries. At high ages, two distinct patterns were revealed. In Finland and Poland, the RRs increased again and became substantially higher at older ages than the value of the reference group. In the remaining countries, the RRs showed weak increases at higher ages. It should be noted that Fig. 3 does not show absolute risks, which are highest in Denmark.

## Discussion

### Methodologic Considerations

As discussed in some detail (*23-25*), analysis of incidence data in age–period–cohort models is an advanced statistical methodology that requires careful, sometimes skeptical, interpretation. Nevertheless, such modeling may offer considerable advantages over the simple descriptive methods used in Fig. 1. With age–period–cohort models, it is possible to test whether a significant improvement is obtained when additional factors are included and to quantify any effects. Thus, it can be decided whether the full age–period–cohort model is an improvement on age–period or age–cohort models. However, individual parameters of the full age–period–cohort model cannot be uniquely identified, which makes interpretation difficult. With our data, the age–cohort model was found, in general, to adequately represent observed testicular cancer incidence rates; therefore, it was not necessary to identify the full model.

When one submodel is found to be superior to another (for example, the age–cohort model in comparison with the age–period model) and assumed to adequately describe the data, that submodel will be chosen to represent the data. It is often claimed explicitly or implicitly in such a case that cohort is the important factor. However, the linear effect may be due to period, even if the nonlinear effect is due to cohort (i.e., the correct representation could be a mixture of a linear period effect and a nonlinear cohort effect). However, similar to other investigators, we refer the linear effect primarily to the variable where a nonlinear effect could be established, although this cannot be formally proven to be correct due to the nonidentifiability problem. In certain situations, there may be biological reasons why one or the other of the two effects should be the dominant cause behind the drift term.

The situation created when data from more than one registry are present offers some further possibilities in the identification

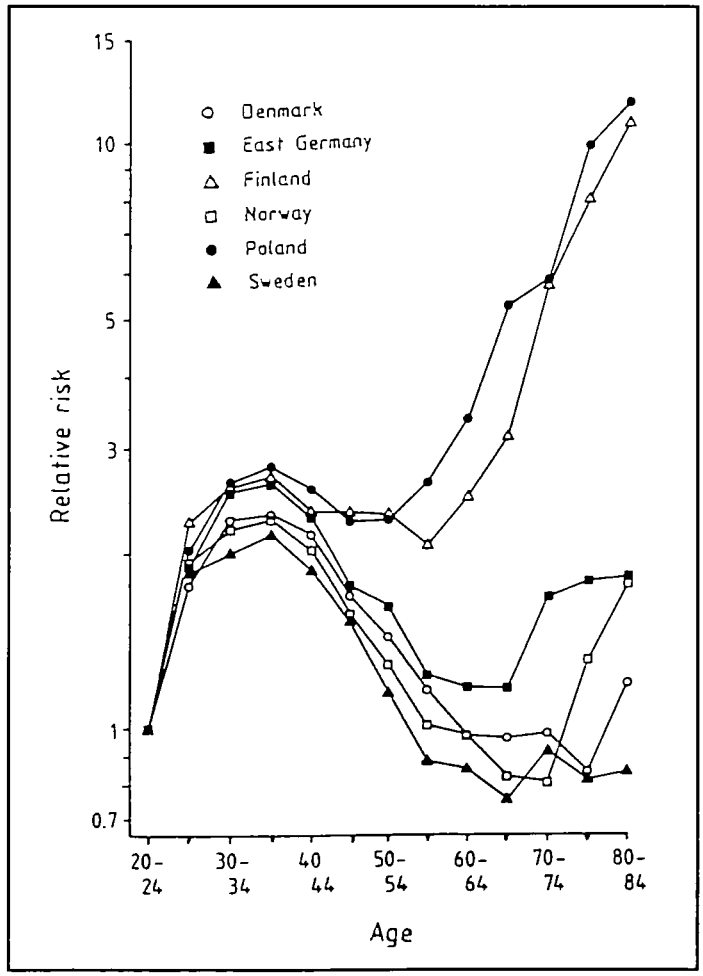


Fig. 3. Relative risk of developing testicular cancer by age, using the age group 20-24 years as the reference. Results were obtained from age–cohort models as defined in Table 2.

of the model. It is, for example, possible to study whether the period or the cohort effects, even if they are linear, are similar in the geographic areas included (*26*). The basic problem of whether the linear drift is due to cohort or period cannot, however, even in this situation, be resolved without further assumptions.

In addition to the analytic approach, the quality of the underlying incidence data remains crucial for valid conclusions. Because testicular cancer is a distinct clinical and histopathologic entity, overreporting is a limited concern, especially since the proportion of morphologically confirmed lesions was high (Table 1). Underreporting of incident cases may be a greater problem. In particular, increasing reporting completeness over time would spuriously inflate the positive incidence trends for testicular cancer. Such bias could conceivably contribute to the higher growth rate of the incidence in East Germany and Poland compared with the Nordic countries.

The multiplicative structure of the mathematical model required that the RRs between any two birth cohorts be the same at all ages. Since we had observations for a given birth cohort only during a limited age interval, the earliest cohorts were observed only at old ages, whereas the latest were observed only at young ages. The correctness of the multiplicative assumption is therefore difficult to judge. If the RR between two cohorts were to change with age, the results of our cohort modeling might not be valid.

## Findings and Implications

Our investigation shows unequivocally that birth cohort is a more important determinant of testicular cancer risk than is time period. Any concern about bias because of increasing completeness of the cancer registration is offset, for the most part, by this observation; such bias should cause time period rather than birth cohort effects. Although linear period effects could not be excluded for technical reasons, they may cause modest effects rather than the several hundred percent increases that we found. A weak nonlinear time period effect was found only in Denmark, where cancer registration is the longest and where completeness was assumed to be high several decades ago (*5*).

Apart from Denmark, we had limited ability to reveal trends in men born in 1920 and earlier in the five other countries; the statistical power was low because of the small numbers of cases. Therefore, the apparent lack of strong trends at high ages in the oldest birth cohorts (Fig. 1) does not exclude trends at younger ages in these cohorts. It is more apparent that an increasing trend took place among men born in 1920 and later and, furthermore, that this trend differs between the countries. The increase was dramatic and uninterrupted in East Germany, Finland, and Poland. In contrast, the growth rate was slower in the Scandinavian countries, notably in Sweden (Fig. 2). We found it particularly interesting that the increase in risk was arrested among men born in the late 1930s and in the early 1940s (i.e., the period before and during the Second World War) in the Scandinavian countries. We found no corresponding arrest outside Scandinavia. However, such a change in trend has been noted previously, not only in Denmark and Norway but also in British Columbia (*3,27*). With the exception of the "wartime effect," the results from the different countries included in this study show a surprisingly congruent pattern, especially considering the heterogeneity between the countries concerning incidence. Finally, the increasing trend in young age groups appeared to continue even in the most recent cohorts analyzed (i.e., among men born around 1960) (Fig. 1).

The generally high incidence of testicular cancer in Denmark might be explained by at least one of three factors: 1) a genetic predisposition among Danish men; 2) increased exposure to some etiologic factor in Denmark, both now and in the past; and 3) greater detection or registration of testicular cancer in Denmark, both now and in the past. There are no indications that the third factor provides the explanation, at least when the other Nordic countries are considered; nor does a different genetic disposition, at least relative to that in Sweden and Norway, seem plausible. Thus, we are left with a possible difference in etiologic factors.

A finding that cohort effects are important for the development of a cancer form does not automatically imply that the etiologic factors responsible for the disease occur very early in life. Any increase in lifetime exposure tied to birth cohort will be reflected as a birth cohort effect. However, for testicular cancer, most of the cancers occur at an early age, which means that any hypothesis on testicular carcinogenesis should take into account that major etiologic factors also operate early in life, perhaps even in utero. The few analytic studies (*28-35*) on perinatal characteristics of testicular cancer performed thus far show rather inconsistent results, possibly because of low statistical power and problems in assessing exposures; however, they do indicate that the perinatal period is important and, therefore, needs to be examined further in larger and more comprehensive studies.

In conclusion, several previous studies have documented the early age peak, temporal trends, and geographic variation in testicular cancer incidence. Our study further develops the benchmark of descriptive epidemiology. The underlying exposure(s) responsible for the temporal trends increased more rapidly, uninterrupted by wartime, in East Germany, Finland, and Poland than in the Scandinavian countries, which were much less affected by the war. It is a real challenge for epidemiologists, in their future etiologic studies, to identify exposures that tally with this paradoxical finding.

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## Notes

Supported by grants from the Swedish Cancer Society and Europe Against Cancer.

Manuscript received July 21, 1995; revised February 16, 1996; accepted March 8, 1996.