Trends in Cervical Squamous Cell Carcinoma Incidence in 13 European Countries: Changing Risk and the Effects of Screening

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Abstract

Despite there being sufficient evidence for the effectiveness of screening by cytology in preventing cancer of the cervix uteri, screening policies vary widely among European countries, and incidence is increasing in younger women. This study analyzes trends in squamous cell carcinoma (SCC) of the cervix uteri in 13 European countries to evaluate effectiveness of screening against a background of changing risk. Age-period-cohort models were fitted and period and cohort effects were estimated; these were considered as primarily indicative of screening interventions and changing etiology, respectively. A unique set of estimates was derived by fixing age slopes to one of several plausible age curves under the assumption that the relation between age and cervical cancer incidence is biologically determined. There were period-specific declines in cervical SCC in several countries, with the largest decreases seen in northern Europe. A pattern emerged across Europe of escalating risk in successive generations born after 1930. In the western European countries, a decrease followed by a stabilization of risk by cohort was accompanied by period-specific declines. In southern Europe, stable period, but increasing cohort trends, were observed. Substantial changes have occurred in cervical SCC incidence in Europe and well-organized screening programs have been highly effective in reducing the incidence of cervical SCC. Screening and changing sexual mores largely explain the changing period- and cohort-specific patterns, respectively. The increasing risk in recent cohorts is of obvious concern particularly in countries where no screening programs are in place. Further investigation of the effectiveness of opportunistic screening is warranted as is the observation of differing risk patterns in young cohorts in countries with relatively similar societal structures. (Cancer Epidemiol Biomarkers Prev 2005;14(3):677–86)

Introduction

Cervical cancer is the second most common cancer in women worldwide (1) and ranks third in Europe (2). A recent evaluation by IARC concluded that there is sufficient evidence that screening women ages 35 to 64 for cervical cancer precursors by conventional cytology every 3 to 5 years within high-quality programs reduces incidence of invasive cervical cancer by at least 80% among those screened (3). There are however large variations in current screening policies in Europe and in organizational aspects of established programs (4, 5); whereas cervical cancer incidence and mortality has been declining in many European populations in the last few decades (6, 7), upward trends have been reported in younger women in several countries (8-17). Time trend studies at the population level are therefore a critical element in evaluating the effectiveness of cervical screening against a backdrop of changes in risk.

In this study, we examine trends in incidence of cervical squamous cell carcinoma (SCC) by period of diagnosis and birth cohort in European women of screening age (ages 30-64) in 13 countries with high-quality incidence data. Cervical SCC is the dominant histologic subtype, currently accounting for 75% to 90% of cervical neoplasms in developed countries (18). Historically, susceptibility to detection by cytology has been much greater for cervical SCC (19), although it is possible that this distinction is becoming less apparent as our understanding of precursors to adenocarcinoma increases and methods for detecting endocervical lesions improve (20, 21). Additionally, there is some evidence that the etiology of cervical SCC and adenocarcinoma may be different (22-25).

We make the assumption that the relationship of incidence of cervix cancer to age is determined by the natural history of the disease and that this is constant over time; time trends in incidence can thus be partitioned into the effects of birth cohort and period of diagnosis. Period effects can be viewed as the result of interventions, such as cervical screening that should deflect trends downward among targeted age groups over the same period of time. Cohort effects may arise from changing exposure to etiologic factors in successive generations of women and these may point to modifications in the population prevalence of persistent infection with oncogenic types of sexually transmitted human papillomavirus (26, 27). This temporal analysis of 13 European populations aims therefore to evaluate the effectiveness of cytologic screening in countries with diverse screening policies and implementation strategies (5) against the background of changing risk patterns that will also have affected the incidence trends.

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Table 1. Populations included in the analysis (A-E), estimated percentage change in the regular trend (F-G), model characteristics (H-L), and summary of the identifiable attributes of the period and cohort trends (M-N) by country

A	B	C	D	E	F	G
European area	Country	Period*	Incidence†	Person-years†,‡	Overall trend [%§ (95% CI)]	Recent trend [%‖ (95% CI)]
Northern	Denmark	1979-1998 (4)	225	1,216,706	−2.4 (−2.8 to −2.0)	−3.3 (−4.6 to −1.9)
	Estonia	1971-2000 (6)	99	337,550	−0.6 (−1.0 to −0.2)	2.8 (0.0 to 5.8)
	Finland	1955-1999 (9)	65	1,225,829	−4.7 (−4.8 to −4.5)	8.2 (3.8 to 13.4)
	Norway	1953-1997 (9)	185	933,595	−1.1 (−1.2 to −0.9)	−1.2 (−2.9 to 0.6)
	Sweden‡	1964-1998 (7)	215	1,943,275	−4.2 (−4.3 to −4.0)	−0.8 (−2.3 to 0.9)
	United Kingdom‖	1978-1997 (4)	1360	11,982,152	−2.3 (−2.5 to −2.2)	−5.6 (−6.0 to −5.1)
Eastern	Czech Republic	1985-1999 (3)	651	2,366,652	−0.6 (−1.1 to −0.2)	−2.0 (−2.8 to −1.1)
	Slovakia	1968-1997 (6)	384	1,180,261	1.5 (1.2 to 1.8)	1.1 (−0.2 to 2.6)
Southern	Italy¶¶	1983-1997 (3)	119	1,118,959	−1.4 (−2.5 to −0.2)	−0.8 (−2.9 to 1.7)
	Slovenia	1985-1999 (3)	126	475,358	3.5 (2.1 to 5.0)	5.3 (2.5 to 8.5)
	Spain##	1983-1997 (3)	72	692,076	0.7 (−0.8 to 2.4)	1.0 (−1.8 to 4.2)
Western	France[a]	1978-1997 (4)	115	896,132	−4.2 (−4.8 to −3.7)	−3.8 (−5.5 to −1.9)
	Switzerland[b]	1983-1997 (3)	73	702,021	−3.7 (−4.8 to −2.5)	−0.5 (−3.1 to 2.4)

*Data available according to period of diagnosis; figure in parentheses represent number of 5-year periods available in the analysis.
†Average annual number of cases/person-years obtained from most recent 5-year period.
‡Aggregation of England and Scotland.
§Estimated annual percentage change based on the trend variable from the net drift for the whole study period (95% CI).
‖Estimated annual percentage change based on the most recent two 5-year periods (95% CI).
¶¶Aggregation of Florence, Varese Province, Parma Province, Ragusa Province, and Turin.
##Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, and Zaragoza.
[a]Aggregation of Bas-Rhin, Calvados, Doubs, Isère, Somme, and Tarn.
[b]Aggregation of Basel, Geneva, Neuchatel, St. Gall-Appenzell, Vaud, Zurich.

Materials and Methods

Incidence Data. We extracted registered cases of cervical cancer and population-at-risk data from the EUROCIM database (28). The analysis was restricted to cancer registries accepted in the last three volumes of *Cancer Incidence in Five Continents* (18, 29, 30), with data spanning at least 15 years, to ensure consistently high-quality data over a sufficient length of time. Cervical SCC was classified according to the IARC/WHO histologic groupings (31). Cancers of the cervix uteri with unspecified or ill-defined histology (<10% of all cervix cancer cases) were not reallocated to one of the known histologies, although carcinomas of squamous cell origin coded as ''uterus unspecified'' (<1% of all uterine cancer cases) were included as cervical SCC.

For the 13 countries, the time span of registry data available varied from 15 to 45 years (Table 1, *columns A-E*). Several regional registries in France, Spain, Italy, and Switzerland were aggregated to estimate national incidence trends. The varying intervals of years available for registries within one country led to a pragmatic selection of registries and years to ensure that the same populations were included throughout the study period.

Statistical Analysis. We obtained birth cohorts by subtracting age (midpoint of 5-year age band) from the central year of the 5-year period of diagnosis. To distinguish the effects of time period and birth cohort on the time trends in each population, age-period-cohort (APC) models were fitted (32-36) using Stata (37). The model suffers from the well-known problem of nonidentifiability (32-36, 38, 40) a result of linear interdependency arising from cohort being entirely defined in terms of period and age. Commonly, the problem is specified in terms of an estimable linear function of the slopes and the corresponding curvature effects, the identifiable changes in each slope (33, 34). The age-adjusted sum of the period and cohort slopes, the drift (33), is used in this study to convey the magnitude of the regular trend, a quantity that cannot be attributed specifically to period or cohort. We make a distinction between the overall trend (the drift over the whole time period available) and the recent trend (the relative change in the last two 5-year periods). A two-sided 95% confidence interval (95% CI) for each estimate was also calculated.

Although the individual slopes for age, period, and cohort cannot be uniquely determined, Holford (32, 39) has shown that they do not vary independently, fixing the value of any one of the slopes leads to automatic estimation of the slopes of the other two time components. We adopt Holford's method to obtain a unique set of age, period, and cohort effects by using supporting evidence of a unique age curve for cervical SCC (41), fixing the slope for age to determine the magnitudes of the period and cohort slopes (see Appendix 1).

Evidence for a Unique Age-Incidence Curve for Cervical SCC. For most epithelial cancers, risk increases as a power of age (42), and this has been interpreted in terms of a multistage model for carcinogenesis (43, 44). Cervical cancer is an exception in that risk increases until around the age of menopause and reaches a plateau or declines thereafter. As infection with the human papillomavirus has been identified as a necessary etiologic agent in cervix cancer (27, 45), the underlying age pattern may be linked to the natural history of human papillomavirus infection and its accompanying carcinogenic mechanisms.

Gustafsson et al. analyzed age-specific cervical cancer incidence rates, selecting populations where screening activity was either minimal or had not become common (41), because the age distribution in postscreened populations changes markedly (46). After scaling the rates to account for differing orders of magnitude, Gustafsson et al. (41) found that most populations fitted one of two reference curves. Reference curve type I, including Denmark, the Netherlands, Norway, Slovenia, and Sweden, was characterized by an onset at about age 25, a rapid increase between ages 30 and 40, and a peak at ages 44 to 49. After the peak, the decline in subsequent age groups was fairly rapid. Reference curve type II included Finland and had an onset at approximately the same age but a slower increase to a peak (for Finland) at an age ~53 years followed by a decline similar to reference type I. Data from the United Kingdom did not fit either curve probably due to the effect of large variations in risk by birth cohort distorting the cross-sectional curves (8, 10). Gustafsson et al. showed that birth cohort trajectories of the same shape could generate cross-sectional age curves of both reference types dependent on the direction and magnitude of the cohort trend (41). These curves

Table 1. Populations included in the analysis (A-E), estimated percentage change in the regular trend (F-G), model characteristics (H-L), and summary of the identifiable attributes of the period and cohort trends (M-N) by country (Cont'd)

B	H	I	J	K	L	M	N
Country	APC model¶	Residual deviance**	*df***	*P***	Reference type††	Direction (midyear) period trend‡‡	Direction (midyear) cohort trend§§
Denmark	APC	12.7	10	0.24	I	– (*)	+ (1949)
Estonia	AC	34.6	24	0.07	II	0 (*)	+ (1936)
Finland	APC	78.2	35	<0.05	I	– (1967)	+ (1945)
Norway	APC	69.3	35	<0.05	I	– (1975)	0 (1943)
Sweden‡	APC	71.4	25	<0.05	I	– (*)	0 (1934), 0 (1954)
United Kingdom‖	APC	51.2	10	<0.05	I	– (1985)	+ (1933)
Czeck Republic	APC	9.5	5	0.09	I	0 (*)	0 (1945)
Slovakia	APC	38.9	20	<0.05	I/II	– (1985)	+ (1938)
Italy‖‖	AD	14.5	13	0.34	I/II	– (*)	+ (1948)
Slovenia	AC	5.4	6	0.49	I/II	0 (*)	+ (1940)
Spain¶¶	AC	9.0	6	0.18	II	0 (*)	+ (1938)
France[a]	APC	24.1	10	<0.05	I	– (*)	0 (1938)
Switzerland[b]	AP	20.5	12	0.06	I	– (*)	0 (1948)

¶Refers to the most parsimonious final model providing a good fit: AD: age + drift; AC: age + drift + cohort; AP: age + drift + period; APC: age + drift + period + cohort.
**To determine the goodness-of-fit, the deviance was compared with the χ^2 distribution on the *df* determined by the model (see Appendix 1). $P < 0.05$ denotes that the full APC model does not yield an adequate fit.
††Age curve of reference type used (see Materials and Methods).
‡‡Estimated direction of trends by period of diagnosis (+, positive trends; –, negative trend; 0, stable trend or difficult to interpret). Major changes in the direction noted in parentheses as the midyear of the 5-year period (* denotes change throughout study period).
§§Estimated direction of trends by birth cohort (–, negative trend; 0, stable trend or difficult to interpret). Major changes in the direction noted in parentheses as the midyear of the 10-year birth cohort.
‖‖Aggregation of Florence, Varese Province, Parma Province, Ragusa Province, and Turin.
¶¶Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, and Zaragoza.
[a]Aggregation of Bas-Rhin, Calvados, Doubs, Isère, Somme, and Tarn.
[b]Aggregation of Basel, Geneva, Neuchatel, St. Gall-Appenzell, Vaud, Zurich.

must largely reflect cervical SCC incidence, given that in unscreened populations in Europe cervical SCC comprises ~90% of all cervical neoplasms.

Presenting Unique Variable Estimates of Age, Period, and Cohort. We circumvented the nonidentifiability problem of the APC model by specifying *a priori* age-specific curves of cervical SCC analogous to the reference types suggested by Gustafsson et al. (41). Starting with a base value of 0 for the age slope, the APC model was refitted with age slope increases of 0.2% per year until the ratio of the age variables in the last (60-64) to first (30-34) strata were equal to or greater than 1.5, 4.9, and 3.2. The first two ratios (called types I and II) match the ratios (and hence resemble the age curves) proposed by Gustafsson et al. The ratio was lowered to 1.2 to obtain more plausible type I curves for the Czech Republic, Denmark, and Sweden, because a ratio of 1.5 produced curves showing a progressively increasing risk after age 50. The third (type I/II) is the average of the types I and II ratios and serves as an intermediate age curve. As an example, Fig. 1 displays three sets of age, period, and cohort effects for Slovakia produced by fixing the age structures to resemble types I, II, and I/II. Assuming particular magnitudes of the age slope from the full APC model yields unique period and cohort slopes additional to the identifiable curvature of each effect.

From the three possible sets of estimated age, period, and cohort variables for each country, a single set was selected based on the plausibility of the age curves and the level of agreement between the model variables and the observed age, period, and cohort trends. The final set of chosen variables,

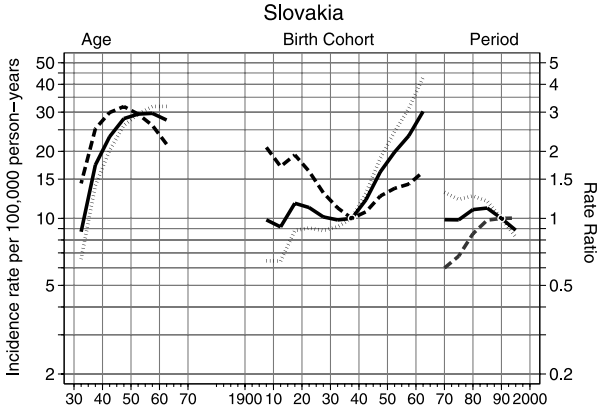

Figure 1. Cervical SCC incidence trends, Slovakia 1968-1997, with age reference type I (*dashed line*), type II (*dotted*), and type I/II (*solid*) imposed. Age is on a rate scale. Reference points for period and cohort rate ratios are marked.

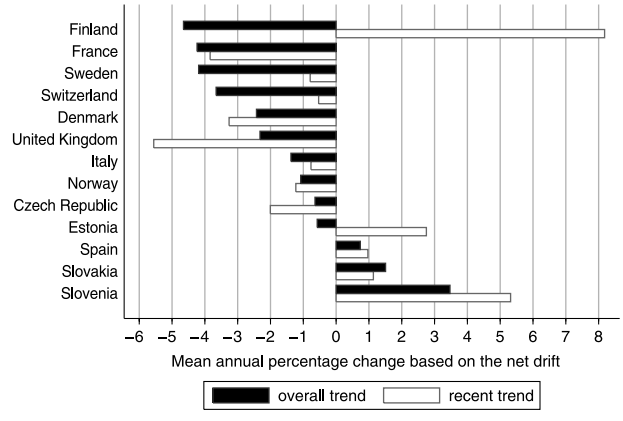

Figure 2. Regular trend over the whole study period and in the last two periods: cervical SCC incidence in 13 European countries for women ages 30-64, sorted by magnitude of overall trend, expressed as the mean annual percentage change.

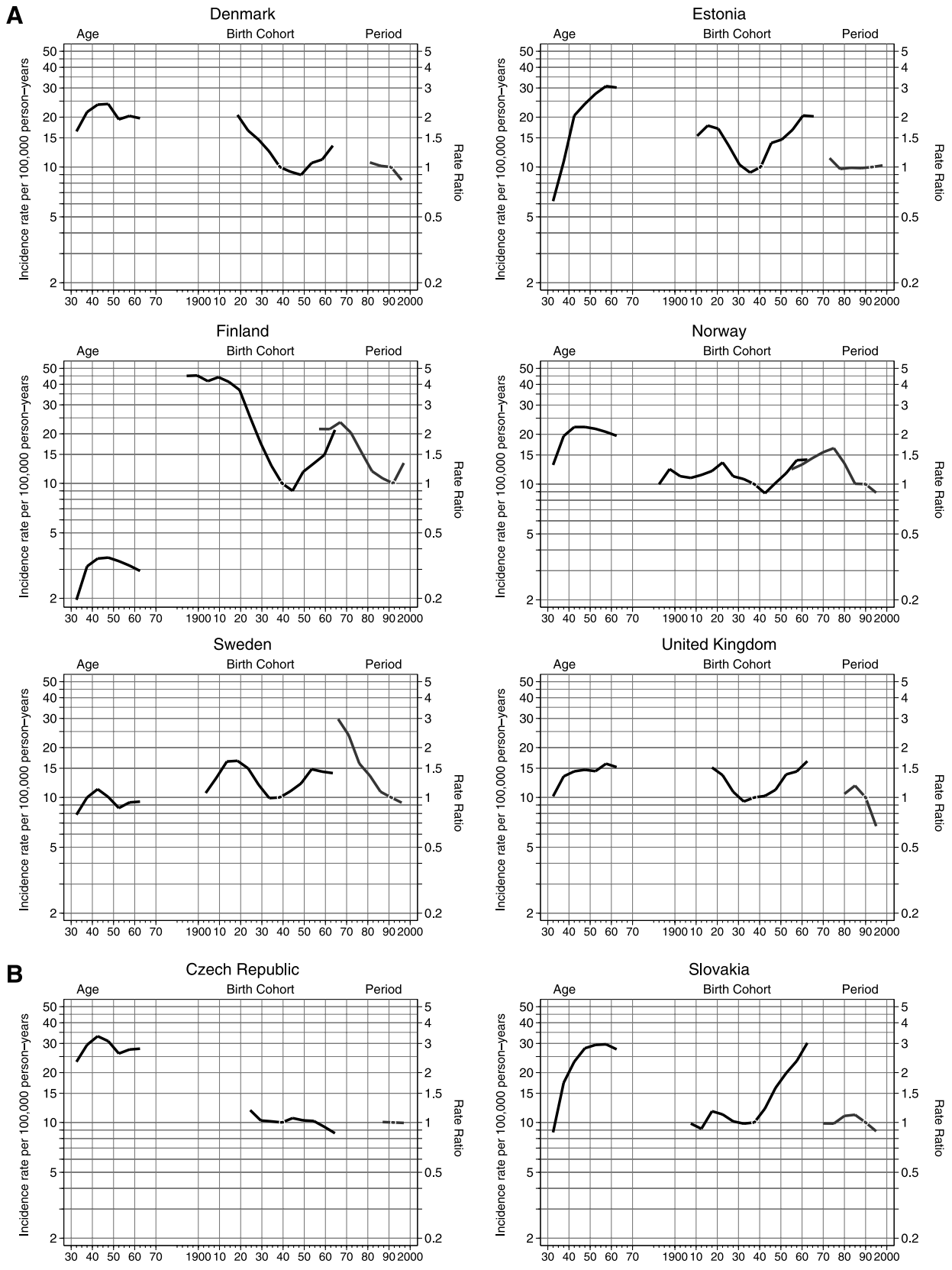

Figure 3. Cervical SCC incidence trends in 13 European countries for women ages 30-64: (**A**) northern European countries, (**B**) eastern European countries, (**C**) southern European countries, and (**D**) western European countries. Age is on a rate per 100,000 scale. Reference points for period and cohort rate ratios are marked.

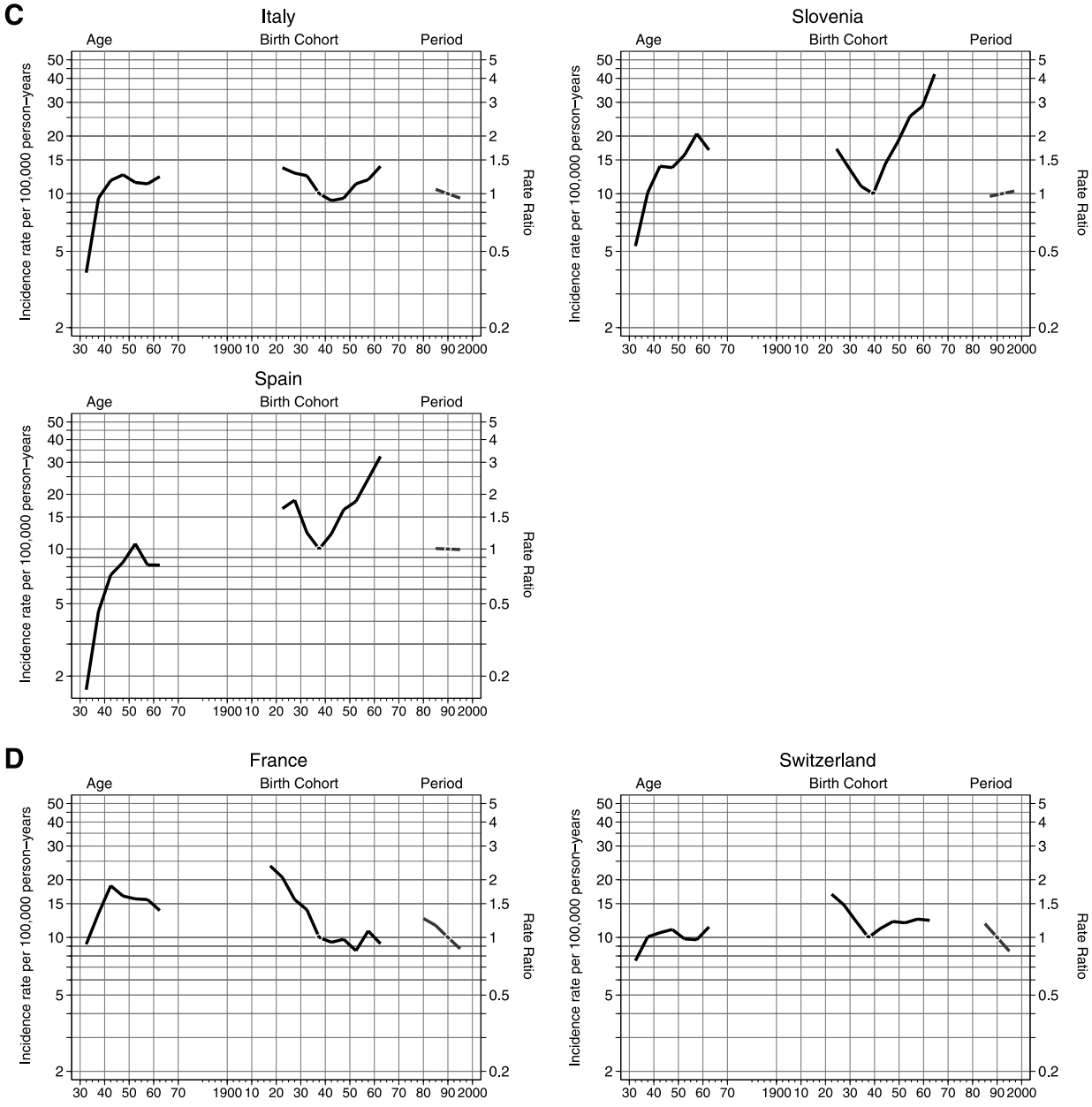

Figure 3. Continued

although still arbitrary, are derived from an informed decision on the biological evidence of a steady-state age effect that cannot be directly observed due to the effects of screening and changes in risk factors.

As well as presenting the risk patterns in terms of age, period, and birth cohort effects, we calculated the second differences (34), identifiable indicators of local departures from the linear trend, to detect when the major changes (accelerations or decelerations) in the period and cohort trends occurred. We also attempted to indirectly assess the contribution of the period slope (assumed to be driven by screening) to the net drift, the combined period and cohort slopes from the full APC model, and essentially equivalent to the drift variable, described above (see Appendix).

Results

Regular Trend. Figure 2 and Table 1 (*columns F-G*) show the regular trend in each country across the whole study period and within the 10 most recent years. There have been large mean decreases in cervical SCC in several northern and western European countries over the whole time period: ~4% per year in Finland (95% CI, −4.8 to −4.5), France (95% CI, −4.8 to −3.7), Sweden (95% CI, −4.3 to −4.0), and Switzerland (95% CI, −4.8 to −2.5). Average declines of >2% per year were seen in Denmark (95% CI, −2.8 to −2.0) and the United Kingdom (95% CI, −2.5 to −2.2) In contrast, mean annual increases have been observed in Slovenia of 3% per year (95% CI, 2.1-5.0) and in Spain and Slovakia, with nonsignificant positive trends of 0.7% (95% CI, −0.8 to 2.4) and 1.5% (95% CI, −0.2 to 2.6) per year, respectively.

For countries with a limited span of data, recent trends were of similar magnitude to the overall trends, although some interesting discrepancies do emerge between countries with longer periods of observation (Fig. 2). In Sweden, the (nonsignificant) decline of 0.8% per year (95% CI, −2.3 to 0.9) in the 1990s was modest compared with the 4.2% (95% CI, −4.3 to −4.0) decrease over the whole period (1964-1998). In Finland, the direction as well as the magnitude of the trend has changed, with the large drop in cervical SCC of

4% per year over several decades replaced by increases of >8% (95% CI, 3.8-13.4) per year in the 1990s. The decrease of 5.6% (95% CI, −6.0 to −5.1) per year in the United Kingdom between 1988 and 1997 was double that of the overall decline between 1978 and 1997.

Period Trends from the APC Models. Figure 3 displays the model estimates by European area. A complete graphical overview of the observed and modeled trends is available online (47). In northern European countries, there is clear evidence of large period-specific declines in cervical SCC, most notably in Sweden and Finland since the mid-1960s but also in Norway since the mid-1970s, in the United Kingdom since the mid-1980s, and in Denmark throughout the study period (data available from 1979). Within these countries, there is some indication of accelerations in the declining trends in Norway and Sweden from the 1980s and clear evidence of an increasing trend in Finland during the 1990s. Estonia is the exception within northern Europe: there is no trend discernible in the period variables. In France and Switzerland (western Europe) and in Italy (southern Europe), there are negative period variables in recent periods, whereas in Spain and Slovenia no such period trends are apparent. In eastern Europe, the trends are slightly different: period effects are largely flat in the Czech Republic, whereas in Slovakia there is suggestion of a deceleration in cervical SCC incidence detectable from the mid-1980s.

Birth Cohort Trends from the APC Models. A notable feature of the variables displayed in Fig. 3 are the similar birth cohort patterns that emerge across several European countries. The declines in risk seen in generations born in the first three decades of the 20th century have often been replaced by successive increases in risk of cervical SCC in women born thereafter. The timing of the change varies between countries, but in each the escalation of risk begins in generations born in the early 1930s through to the late 1940s (Table 1, *column N*). In northern Europe, this characteristic is evident in the cohort trends in Denmark and Finland, whereas in Estonia and the United Kingdom the generational increases start somewhat earlier. The increasing cohort variables in Norway and Sweden are however less open to inference, with even a suggestion of a deceleration in the trend in the most recent generations.

In several southern and eastern European countries, the risk in women born since around 1940 is clearly increasing in Spain, Slovakia, and Slovenia. In Italy too, the trend is less marked and starts a little earlier, whereas in the Czech Republic there is little change in risk in successive birth cohorts. In France and Switzerland, declines in cervical SCC risk in the 1920 and 1930 cohorts have been followed by rather constant level in more recent generations.

Contribution of Period Slope to the Net Drift. Figure 4 compares the contribution of the period slope to the net drift—the combined effects of period and cohort slopes from the full APC model. The bottom left quadrant includes nine countries in which the downward trend in cervical SCC is accompanied by a decrease attributed to a linear period effect. The negative period slope takes up most of the negative regular trend where the observations are reasonably close to the superimposed $y = x$ line, with the extent of the period-specific reduction large in certain countries (e.g., Sweden and Switzerland) and minimal in others (e.g., the Czech Republic). Four countries are characterized by increasing regular trends (Fig. 4, *top*) accompanied by period slopes of negligible magnitude. The increase is most notable in Slovenia and Spain.

Screening in European Countries. Table 2 summarizes the screening programs or policies (5) in countries (and regions of countries, where relevant) for which we have examined the time trends. The table is alluded to in the commentary below.

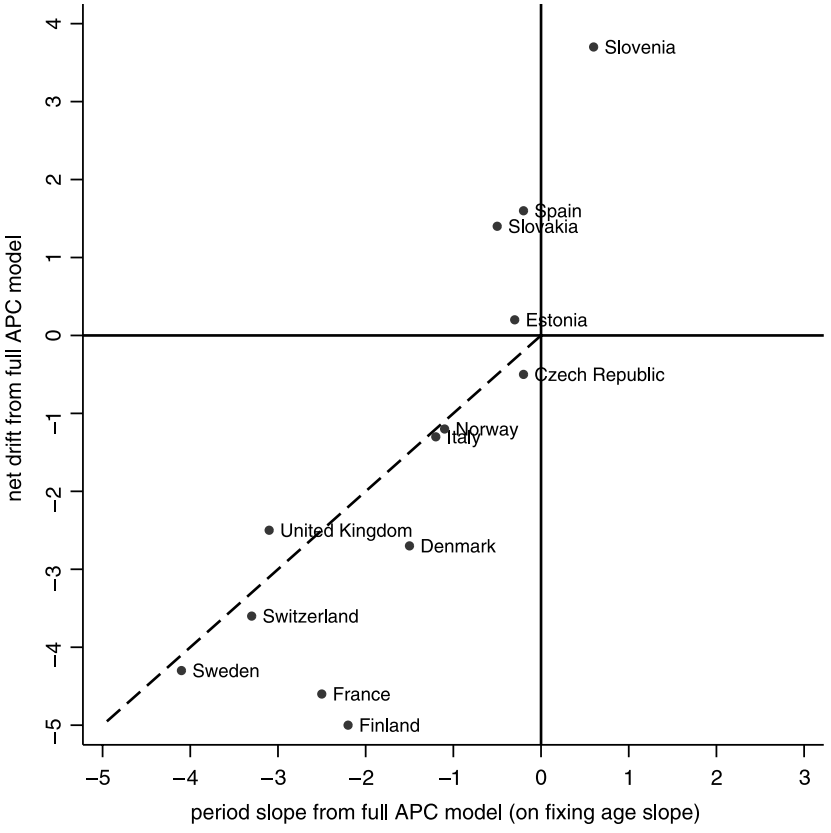

Figure 4. Scatterplot comparison of the net drift and the contribution of the period slope alone. Both are generated from the full APC model and expressed as the mean annual percentage change in cervical SCC incidence in each country.

Table 2. Overview of screening policy in countries and regions where cervical SCC incidence trends are presented: reported year of onset, age range targeted, and recommended screening interval

European area	Incidence population	Year of onset of organized screening program, type of screening system, and area covered	Age range targeted (year program began)	Recommended screening interval with normal result (y)
Northern	Denmark	1967 (achieved national coverage recently)	23-59 (1986)	3 (some counties 5 y in >45 or 50)
	Estonia	No screening program	No screening program	No screening program
	Finland	1963 (national coverage)	30-60 (1993)	5
	Norway	1995, pilot 1992 (program in one county 1959-1977)	25-69 (1992)	3
	Sweden	1967-1973 in different countries, Gothenburg 1977	23-60 (1999)	3 in ages 23-50; 5 in ages 51-60
	United Kingdom	1988 (national coverage)	20-64 (1988, reviewed 2003)	3-5 (currently 3 in ages 25-49 and 5 in ages 50-64)
Eastern	Czech Republic	Opportunistic since 1966 (screening in two districts, beginning 2004)	Not specified (1966)	1
	Slovakia	— (intention to initiate program)	25-64 (—)	3
Southern	Italy	Florence (1985)	25-60 (1985); (25-64 from 1995)	3
		Parma (1998)	25-64 (1998)	3
		Ragusa (no data)	25-64 (no data)	3
		Turin (1992)	25-64 (1992)	3
		Varese (no data)	25-64 (no data)	
	Slovenia	Opportunistic until 2003	20-64 (2003)	3
	Spain	Catalonia (opportunistic until 1993)	20-64 (1993)	3-5: initially 2 smears 1 y apart and then 3 y in ages 20-34 and 5 y in ages 35-64
Western	France	Bas-Rhin (1994)	25-65 (1990)	3
		Doubs (1993)	20-64 (1993)	3 (after 2 normal exams with 1-y interval)
		Isére (1990)	50-69 (1990)	3
	Switzerland	Opportunistic (no data)	18-69 (no data)	3

NOTE: Adapted from the European Cervical Cancer Screening Network questionnaire survey (5).

Discussion

In this study, we attempt to understand the risk of cervical SCC of the cervix uteri according to age, birth cohort, and period of diagnosis in 13 European countries for which high-quality incidence data are available for sufficiently long periods of time. The problem of nonidentifiability of the three variables is circumvented by considering *a priori* evidence of a constant pattern of age-specific risk over time. From a set of three candidate age curves, similar to those identified in unscreened populations by Gustafsson et al. (41), a fixed age slope was determined by taking into account the credibility of the age curves from a biological viewpoint, and on assuming the APC model was correctly specified, supporting evidence that the resultant period and cohort effects were not in disagreement with the observed age-specific trends. Although this does provide a unique solution, the true age-specific risk cannot be directly observed, and we interpreted the estimates with appropriate caution.

Although the deviance statistics in Table 1 (*columns H-J*) indicated the full APC model did not fit the data in several countries, the goodness-of-fit tests are of relatively minor consequence, given we used the model primarily as a descriptive tool to compare period- and cohort-specific risk patterns across Europe. Whether the deviance can capture the underlying reasons for the significant lack of fit, overdispersion, whereby the variance in the counts of incidence is larger than that of the Poisson assumption, is a likely determinant, given the large number of events being analyzed at the national level (48). Additionally, one may speculate that other complex factors than the effects of screening and changing risk patterns, spatial effects at the subnational level, and heterogeneity in the quality or completeness of cervical cancer registration, may also have contributed.

There has been a major decline in the incidence of cervical SCC over time in several European countries. Figure 4 shows that in most of them the decreased incidence is accompanied by a decline in the period slope, implying that it is the consequence of the implementation of effective cytologic screening. The absolute and relative magnitudes of the period and cohort slopes between countries should be interpreted with caution as they are dependent on both the available period of observed data (in relation to the initiation of screening) and the initial parameterization that yielded the particular set of estimates presented. Nevertheless, in most of the countries in which the period slope is of lower magnitude than the sum of the period and cohort slopes, notably in Finland and France, there are also declines in risk by birth cohort during the study period. In Finland, the moderation of the magnitude of the period slope relative to the net drift could be a consequence of the availability of data for over a decade before screening was officially implemented, thereby diminishing its effect. There has been almost no reduction in risk by time period in four countries, implying the absence of effective screening for these women who are at increasing risk in successive generations. The most obvious examples are Spain and Slovenia, where respective increases of 1% and >5% per year have been observed during the 1990s.

In light of the results, we can broadly dichotomize the European countries in terms of their historical screening activity and its impact on period-specific risk and changing etiology as described by trends in risk according to birth cohort.

Countries with Unequivocal Decreases in Period Risk, Varying Levels of Evidence of Increasing Cohort Risks. There is clear evidence that screening has been effective in reducing the incidence of cervical SCC in women in Finland (at least until 1990) and Sweden since the 1960s, reflecting the implementation of nationally organized programs in 1963 and 1964, respectively (49-51). In Denmark, the incidence data go as far back as 1979, and the declining period trend is evident throughout. Regional screening was introduced in 1967 in Denmark, initially covering 40% of the population (49, 52). Screening was introduced in Norway in a single county (5% of the population) in the same

year (49), and declines in cervical SCC incidence by period have been occurring since around 1975. A coordinated screening program has been in operation since the mid-1990s (53); therefore, the declines are probably a result of the increasing levels of opportunistic screening at least since the time of the period decline.

In the United Kingdom, incidence has been falling since the 1980s, particularly so during the 1990s, likely a result of improvements to the National Health Service Cervical Screening Programme from 1988 (54-59). Period-specific declines in risk are also evident throughout the study period in both France and Switzerland; in France, regional screening programs were implemented in the early to mid-1990s in three of the six registry areas represented in this analysis. Underlying the period-specific changes in risk in these populations, there are changes in risk of cervical SCC according to generation. Increasing cohort effects are most likely to be the result of changing sexual mores, resulting in an increased transmission of oncogenic types of human papillomavirus with corresponding increases in prevalence of persistent infection and dramatically increased risk (60-62). However, the possibility that women may have been screened differently from one cohort to another needs also to be considered.

Generation-specific increases in risk are evident in Finland in women born since 1945. The increasing incidence among Finnish women age <55 since 1990 has been remarked on previously and attributed to changing sexual lifestyles and increased transmission of papillomaviruses in younger generations of women (63) and to shortfalls in screening attendance (63). A more recent study examining several Finnish cytologic laboratories suggested that other explanations are possible, linked to the quality and criteria of laboratory procedures during this time (64). In Denmark, some increases in cervical SCC are seen in women born since 1950, whereas in the United Kingdom there are increases in cohorts born since the mid-1930s as reported previously (58), although incidence rates in women age <55 seem to be deflected downward by period-related screening effects. Despite modest cohort-specific increases in risk in Sweden in generations born since 1940, suggested to be a consequence of organized and opportunistic screening efforts addressing these cohorts (51), there has been little or no increase in cervical SCC rates in young women.

There are no cohort-specific increases in risk among recent generations of women in France and Switzerland. It may be that women in these countries have had a different experience with respect to exposure to etiologic factors than other European women. On the other hand, screening has been mainly opportunistic in these countries and may have been accepted by successive generations of women (rather than women of all ages at a given period). In this instance, screening effects on risk would seem as a cohort effect and counter any underlying increase.

Countries with Little or No Changes in Period Risk, Increasing Cohort Risks. The decline in risk by period is small in Italy throughout the study period (1983 onward) and in Slovakia since around 1985. This may reflect sporadic screening at low intensity rather than organized screening effects given that the declines occur before any regional screening programs were in place in Italy, whereas screening policy in Slovakia is currently at the planning stage. In the Czech Republic, Estonia, Spain, and Slovenia, there is little or no trend in the period slope, in accordance with the minor screening efforts in these countries.

In several of these countries, there are accelerating incidence trends among recently born generations. There are large increases in cohort-specific risk in Slovenia, Slovakia, Spain, and, to a lesser extent, Estonia from around 1940 and in Italy beginning slightly later. The Czech Republic is an exception, in that there seems to be almost no change in the cohort-specific trends, but, as with several countries, they are difficult to interpret given the short period of observation. Most disturbing are the substantial cohort-led increases in countries where no programs are in place: in Spain and particularly in Slovenia, for which the recent regular increase amounts to >5% per year.

To conclude, the beneficial effects of organized screening programs can be deduced from the period-specific decreases in the Nordic countries and in the United Kingdom, which largely confirmed previously published results. The corresponding decline in France and Switzerland is consistent with the effectiveness of spontaneous screening in those countries. There are however competing generational increases in cervical SCC risk in younger women in many countries—irrespective of their screening policy—that deserve our particular attention. Most concerning are future prospects in countries like Slovenia, where there are rapid increases in risk in successive generations of women and a notable absence of any intervention-related declines.

Several observations deserve further investigation, particularly an assessment of the effectiveness and efficiency of spontaneous screening in certain European countries, where overscreening of low-risk women is established (65). Further, an exploration of differences in the trends in risk of cervical SCC in young cohorts between countries presumed to have relatively similar societal structures should be followed up: the implication of similar changes in sexual behavior seems to be at odds with the differing generation-specific risk patterns that have emerged.

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Appendix

We assumed that incidence rates were constant within the 5-year age classes $a = 1, 2, \ldots, A$ and 5-year periods of diagnosis $p = 1, 2, \ldots, P$ 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 (66), with birth cohort derived from period and age such that $c = p - a$ for $c = 1, 2, \ldots, C$ with $C = A + P - 1$. The variables α_a, β_p, and γ_c refer to the fixed effects of age group a, period p, and birth cohort c. The inclusion of an additional variable μ, the intercept, leads to an overparameterization of the model. As a consequence, linear constraints on the variables (e.g., $\Sigma_a\alpha_a = \Sigma_p\beta_p = \Sigma_c\gamma_c = 0$) have to be introduced to ensure estimation of all the variables.

To allow a systematic evaluation of the trends across countries, the results are presented using the full APC model, and the nonidentifiability problem was highlighted by partitioning the age, period, and cohort effects in terms of their linear and curvature component parts, according to the method of Holford (32). Holford showed that although 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 α_L, β_L, and γ_L are the true values for the slopes according to age, period, and cohort and ρ is an unknown constant that may result in increasing or decreasing trends of each slope (32). Based on assumptions on the age curve (see Materials and Methods), specification of α_L results in β_L and γ_L being immediately estimable. The effects for the individual categories can be found by adding together the corresponding linear and curvature components. The ath age effect can be expressed as $\alpha_a = [a - (A+1)/2] \times \alpha_L + \varphi_a$, with φ_a representing the departures from the linear trend. β_L and γ_L, the slopes for period and cohort, can be defined in the same way. The age effects in each country were anti–log transformed to rates per 100,000 person-years to allow absolute comparisons. The period and cohort effects were reparameterized to rate ratios with reference points $P - 1$ and $A + P - 6$, respectively; hence, the resultant midpoints of baseline risk were country dependent, varying from 1990 to 1993 for period and from 1938 to 1941 for birth cohort.

The sum of the period and cohort slopes, $\beta_L + \gamma_L$ called the net drift (33), is an estimable quantity, invariant to any APC model parameterization. To indirectly assess the contribution of the period slope to the net drift, a comparison of β_L with $\beta_L + \gamma_L$ was made via the above specification of α_L.

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