Incidence Trends of Adenocarcinoma of the Cervix in 13 European Countries

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Abstract

Rapid increases in cervical adenocarcinoma incidence have been observed in Western countries in recent decades. Postulated explanations include an increasing specificity of subtype—the capability to diagnose the disease, an inability of cytologic screening to reduce adenocarcinoma, and heterogeneity in cofactors related to persistent human papillomavirus infection. This study examines the possible contribution of these factors in relation to trends observed in Europe. Age-period-cohort models were fitted to cervical adenocarcinoma incidence trends in women ages <75 in 13 European countries. Age-adjusted adenocarcinoma incidence rates increased throughout Europe, the rate of increase ranging from around 0.5% per annum in Denmark, Sweden, and Switzerland to ≥3% in Finland, Slovakia, and Slovenia. The increases first affected generations born in the early 1950s through the mid-1940s, with risk invariably higher in women born in the mid-1960s relative to those born 20 years earlier. The magnitude of this risk ratio varied considerably from around 7 in Slovenia to almost unity in France. Declines in period-specific risk were observed in United Kingdom, Denmark, and Sweden, primarily among women ages >30. Whereas increasing specificity of subtype with time may be responsible for some of the increases in several countries, the changing distribution and prevalence of persistent infection with high-risk human papillomavirus types, alongside an inability to detect cervical adenocarcinoma within screening programs, would accord with the temporal profile observed in Europe. The homogeneity of trends in adenocarcinoma and squamous cell carcinoma in birth cohort is consistent with the notion that they share a similar etiology irrespective of the differential capability of screen detection. Screening may have had at least some impact in reducing cervical adenocarcinoma incidence in several countries during the 1990s.

Introduction

There is consensus that screening by conventional cytology within high-quality programs can reduce the incidence of invasive cervical cancer by >80% (1). Epidemiologic studies have shown that women with cancer of the cervix typically have been less adequately screened than corresponding women free of the disease (1-3). Where population-based screening has been routinely practiced, large declines in both cervical cancer incidence and mortality have been reported (4-8), with a result that it is now a relatively uncommon form of cancer (9).

Numerous studies in the last two decades have, however, reported increasing rates of cervical adenocarcinomas relative to squamous cell carcinomas (10-25). Most studies have noted increasing rates of adenocarcinoma among younger women, particularly under the age of 40. Global estimates indicate that adenocarcinomas now comprise up to one quarter of cervical cancer cases in some Western countries (9).

The differential in the temporal profile of the two main subtypes of invasive cervical cancer may reflect the relative inability of cytologic screening to reduce the rates of invasive adenocarcinoma. Cytologic screening has been shown to effectively detect squamous cell carcinoma in early stages, whereas adenocarcinomas have been reported to be less detectable by screening (26-28). However, recent work by Mitchell and colleagues in Australia, investigating the efficacy of cytologic examinations in the 1990s, reported that screening has offered an increasing level of protection against adenocarcinoma (29), citing improved endocervical sampling and the recognition that adenocarcinoma in situ is the precursor to invasive adenocarcinoma as responsible (30).

The changing prevalence of oncogenic types of human papillomavirus (HPV) may have contributed to the increase in adenocarcinoma. Persistent viral infection with the high-risk types of HPV is established as a necessary cause of both cervical cancer subtypes (31, 32). There may be also some heterogeneity in the cofactors associated with the two histologic subtypes (33-40), such as smoking for which risk is elevated for squamous cell carcinoma but not for adenocarcinoma in several recent studies (36, 38, 40).

This study examines secular trends in the incidence of adenocarcinoma of the cervix uteri in women ages <75 in 13 European countries using an age-period-cohort model. For each country, we evaluate the extent to which an increasing capability to diagnose the disease has affected the trends, and assess the evidence of changes in risk in successive generations and the impact of the diverse cytologic screening policies currently in place in Europe (41).

Materials and Methods

We extracted registered cases of cervical cancer in women ages <75 and corresponding population-at-risk data from the...
EUROCIM database (42). To ensure consistently high-quality data over a sufficient length of time, the final data set was restricted to those cancer registries included in the last three volumes of *Cancer Incidence in Five Continents* (9, 43, 44). The time span of available registry data varied from 15 to 47 years among the 13 countries. In France, Spain, Italy, and Switzerland, a number of regional registries were aggregated to estimate national incidence trends. The varying intervals of years available for these registries led to a selection of registries and years to ensure that the same populations and years within one country were included where possible in building the final data set.

Cervical adenocarcinoma was classified according to the IARC/WHO histologic groupings (45). Cancers of the cervix uteri with unspecified or ill-defined histology were not reallocated to specified histologic subtypes on the grounds that there was insufficient external information on which to base a rule for reallocation. In particular, the strong assumption that the unspecified group represent a random sample of those subjects with histology specified was not considered as justified.

**Statistical Analysis.** According to the data resolution available in EUROCIM, each 5-year age-class and 1-year period, the number of events and person-years (D, Y), corresponded to 5 × 1 year subsets of a Lexis diagram. It is well known that under the assumption of a constant incidence rate λ, the likelihood contribution from each subset is proportional to a likelihood for a Poisson observation well known that under the assumption of a constant incidence rate λ, the likelihood contribution from each subset is proportional to a likelihood for a Poisson observation. The number of distinct values of p was typically 5 × 5 age by period classes (46, 47).

The parametric form for f, g, and h was taken as cubic splines, functions that are third-degree polynomials in each of a sequence of intervals defined by a set of points (knots). The parameters were constrained to have 0th, 1st, and 2nd derivatives identical at the knots. We used natural splines constrained to be linear beyond the outermost (boundary) knots using R (48). We chose the knots as points on the scales for age, period, and cohort that divided the number of recorded cases equally in the intervals between knots. In the age-period-cohort model, there is a well-known identification problem because c = p − a and, hence, two constants and a linear term can be moved between the three functions f, g, and h that still produce the same sum. To circumvent this problem, we first fitted an age-cohort model:

\[
\log \lambda_{a,c} = f(a) + h(c)
\]

where h is chosen so that \(h(c_0) = 0\) for a reference cohort \(c_0\) (in this case, the 1945 cohort). This means that \(f(a)\) will correspond in this parameterization to log-incidence rates in the cohort \(c_0\) and \(h(c)\) will be the rate-ratio of cohort \(c\) relative to cohort \(c_0\).

Subsequently, we fitted a period effect to the residuals by using a Poisson model for \(D\), but with the log of the fitted values from the age-cohort model as offset. This gives period effects conditional on the estimated age and cohort effects. The fitted values from this approach will be very close to those obtained by maximum likelihood estimation in the full age-period-cohort model. In so doing, all secular trend is explicitly put in the cohort term in a well-defined way. Furthermore, the SE values of the estimated values of f, g, and h are easily derived. The resulting period-effect is in spirit (and in practice) very close to the “detrending” approach suggested by Holford (49). We present these age, period, and cohort effects together with their associated 95% confidence intervals for each of the 13 countries, and, where informative, the observed age-specific period and cohort trends in selected countries.

**Table 1. Time trends in the crude rates (per 100,000 person-years) of cervical adenocarcinomas, combined categories of unspecified cervical carcinoma and cervical unspecified cancers, and cervical adenocarcinomas if all cervical cases unspecified were truly adenocarcinomas**

<table>
<thead>
<tr>
<th>European area</th>
<th>Country</th>
<th>Cervical adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>Denmark</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Estonia</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Norway</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
<td>1.7</td>
</tr>
<tr>
<td>Eastern</td>
<td>Czech Republic</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Slovakia</td>
<td>1.6</td>
</tr>
<tr>
<td>Southern</td>
<td>Italy</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Slovenia</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>1.5</td>
</tr>
<tr>
<td>Western</td>
<td>France</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Results

Changing Rates of Adenocarcinoma Relative to Unspecified Carcinomas and Unspecified Cancers. The rates of adenocarcinoma have tended to increase in successive decades in most countries studied, although trends were rather stable in Estonia, France, and Sweden. In parallel, declines in the rates of unspecified cervical cancer and unspecified cervical carcinomas were observed, notably within the last two decades in Southern Europe but also in United Kingdom, Denmark, and France (Table 1). The historical data from Finland, Norway, and Sweden indicate that the rates of unknown histology were large, often exceeding those of adenocarcinoma from the 1950s and 1960s, but in the 1970s, unspecified histology rates were vastly reduced, remaining steady (and of a low order of magnitude) thereafter. High rates of unspecified cervical cancers/carcinomas were observed in Slovakia and United Kingdom in the mid-1970s, although this decreased rapidly with time in Slovakia; however, in United Kingdom, the unspecified rate was still among the highest (second only to Estonia) in the mid-1990s. Large declines in unspecified rates were also seen in Southern Europe, notably in Italy and Slovenia from the mid-1980s to the mid-1990s. Conversely, the rates of unspecified were stable and minor in Switzerland in the same time period.

Geographic Variations in Age-Adjusted Rates 1993 to 1997. There was a 3-fold variation in the age-standardized rates of adenocarcinoma in the European populations (Table 2). Rates varied from relatively low (1.3-1.5 per 100,000) in Estonia, Spain, Italy, France, and Finland, through intermediate (1.9-2.2) in Sweden, Czech Republic, Slovakia, and United Kingdom. The highest rates were recorded in Norway (2.6), Denmark (2.8), and Slovenia (3.5).

Regular Trend. Figure 1 and Table 2 present the estimated annual percentage change per year in the regular trend in each European country across the whole study period, and for the 15 most recent years available, based on the age-drift model. Only in France was a mean decline in the recent trend of adenocarcinoma observed, the annual change estimated at –1.1% per year between 1983 and 1997. The mean rates of increase during the most recent 15 years were rather modest (≤0.5% per annum) in Denmark, Sweden, and Switzerland; they were more substantial in the majority of countries studied (Table 2). Increases ranged from around 1% to 2% in Estonia and Italy, to increases of 2.4% in United Kingdom and Spain, 2.8% in Finland, 3.4% in Slovakia, and 4.6% in Slovenia.

Where the span of data was limited or close to 15 years, recent trends were obviously of similar magnitude to the overall trend, although some discrepancies emerged in Northern Europe, where longer periods of data were available (Fig. 1). In Finland and Estonia, the modest overall declines contrasted with recent annual increases. In Norway, Sweden, and United Kingdom, the temporal changes were in opposite directions, with a reduction in the rate of increase observed during the most recent 15 years.

Table 1. Time trends in the crude rates (per 100,000 person-years) of cervical adenocarcinomas, combined categories of unspecified cervical carcinoma and cervical unspecified cancers, and cervical adenocarcinomas if all cervical cases unspecified were truly adenocarcinomas (Cont’d)

<table>
<thead>
<tr>
<th>Unspecified cervical carcinomas and unspecified cervical cancer</th>
<th>Cervical adenocarcinoma if all unspecified cervical carcinoma or unspecified cervical cancers were adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Figure 1. Drift estimates (and corresponding 95% confidence intervals) of cervical adenocarcinoma incidence over the most recent 15-year period available in 13 European countries in women aged <75, expressed as the mean annual percentage change.
Table 2. Trends in adenocarcinoma of the cervix: populations included in the analysis, recent age-standardized rates, the estimated percentage change in the regular trend, and model characteristics and characteristics of cohort trends by country

<table>
<thead>
<tr>
<th>European area</th>
<th>Country</th>
<th>Period (no. years)*</th>
<th>Annual no. cases¹</th>
<th>Person-years⁷</th>
<th>ASR (0-74) 1993-1997 per 100,000⁷</th>
<th>Overall trend, %¹ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>Denmark</td>
<td>1978-1998 (21)</td>
<td>73</td>
<td>2.4</td>
<td>2.8</td>
<td>0.7 (−0.2-1.5)</td>
</tr>
<tr>
<td></td>
<td>Estonia</td>
<td>1968-2000 (33)</td>
<td>10</td>
<td>0.7</td>
<td>1.3</td>
<td>−0.6 (−1.8-0.6)</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>1953-1999 (45)</td>
<td>39</td>
<td>2.4</td>
<td>1.5</td>
<td>−0.2 (−0.6-0.2)</td>
</tr>
<tr>
<td></td>
<td>Norway</td>
<td>1953-1997 (45)</td>
<td>55</td>
<td>2.0</td>
<td>2.6</td>
<td>2.1 (1.7-2.5)</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>1960-1998 (39)</td>
<td>82</td>
<td>4.0</td>
<td>1.9</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Eastern</td>
<td>United Kingdom*</td>
<td>1974-1997 (24)</td>
<td>391</td>
<td>25.1</td>
<td>2.2</td>
<td>3.2 (2.9-3.5)</td>
</tr>
<tr>
<td></td>
<td>Czech Republic</td>
<td>1985-1999 (15)</td>
<td>104</td>
<td>5.0</td>
<td>2.0</td>
<td>1.7 (0.5-2.9)</td>
</tr>
<tr>
<td></td>
<td>Slovakia</td>
<td>1968-1997 (30)</td>
<td>53</td>
<td>2.6</td>
<td>2.1</td>
<td>2.0 (1.3-2.7)</td>
</tr>
<tr>
<td>Southern</td>
<td>Italy**</td>
<td>1981-1997 (17)</td>
<td>37</td>
<td>2.1</td>
<td>1.4</td>
<td>1.5 (−0.7-3.8)</td>
</tr>
<tr>
<td></td>
<td>Slovenia</td>
<td>1983-1999 (15)</td>
<td>36</td>
<td>1.0</td>
<td>3.5</td>
<td>4.4 (2.4-6.4)</td>
</tr>
<tr>
<td></td>
<td>Spain†</td>
<td>1980-1997 (18)</td>
<td>20</td>
<td>1.5</td>
<td>1.3</td>
<td>1.9 (−0.6-4.5)</td>
</tr>
<tr>
<td>Western</td>
<td>France²</td>
<td>1978-1997 (20)</td>
<td>27</td>
<td>1.9</td>
<td>1.4</td>
<td>0.5 (−2.0-3.0)</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>1981-1997 (17)</td>
<td>22</td>
<td>1.3</td>
<td>1.5</td>
<td>−1.4 (−3.0-0.2)</td>
</tr>
</tbody>
</table>

NOTE: Adapted from the European Cervical Cancer Screening Network questionnaire survey (see ref. 41).
Abbreviations: 95% CI, 95% confidence interval; ASR, truncated age-standardized rate in women ages <75 (European standard) in most recent 5-year period.

*Data available according to period of diagnosis. Numbers in parentheses represent number of years available.
¹Average annual number of cases per person-years (the latter expressed per 1 million) obtained from most recent 5-year period for women ages <75.
²Estimated annual percentage change based on the trend parameter from the net drift for the whole study period.
³Estimated annual percentage change based on the most recent 15-year period.
⁴Estimated direction of recent trends by birth cohort (+: positive trend; 0: relatively stable trend or difficult to interpret). Time in parentheses is year of birth when change in direction of trend first noted (to the nearest 5 years); ——, change in trends is not apparent.
⁵Aggregation of England, Scotland.
⁶Aggregation of Florence, Varese province, Parma province, Ragusa province, Turin.
⁷Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza.
⁸Aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn.
⁹Aggregation of Basel, Geneva, Neuchatel, St. Gall-Appenzell, Vaud, Zurich.

their magnitude and the time at which successive generations were first observed to be at increasingly higher risk of developing the disease. The starting point of the escalation varied from generations born in early-1930s through the mid-1940s. The risk of adenocarcinoma was elevated in women born in the mid-1960s compared with those born in the mid-1940s, although the magnitude of the increase varied considerably across countries. Assuming the observed data and model specification are correct, Slovenian women born around 1965 had seven to eight times higher risk of adenocarcinoma compared with those born two decades earlier. In contrast, in France, the relative rate in the later birth period was only ~20% above that in women born around 1945 (Fig. 3).

In Northern Europe (Fig. 3, 1-6), the increases were seen mainly in women born after around 1940, although the effect was possibly observed earlier in Norway (early-1930s) and later in Denmark (around 1950). The largest increase in risk among recent generations was seen in Estonia and Finland. A lesser degree of acceleration in risk was seen in Sweden than elsewhere in the region. Increases were observed in the Eastern European countries represented (Fig. 3, 7-8).

There were also increases in risk of cervical adenocarcinoma in Southern Europe, although the changing rates of cervical cancers/carcinomas warrants a cautious interpretation. Among successive generations of Italian and Spanish women, increases from around 1940 were indicated (Fig. 3, 9-11). In Slovenia, consecutive cohorts born from around 1930 were affected, where the risk increased much more rapidly. In Western Europe (Fig. 3, 12-13), the cohort trends in Switzerland were rather flat up to around 1955, with increasing risk thereafter, although the rates are based on few cases. The generation-specific increases among French women (from around 1945) were minor compared with other European countries.

Period-Specific Trends from the Age-Period-Cohort Models. Whereas the assumption of a period slope of zero precluded the possibility to assess the magnitude of trends on this time scale, curvature, in the form of accelerations or decelerations in period-specific risk, are identifiable and were noted in some countries (Fig. 3). Declines in period-specific risk were most evident in United Kingdom, beginning around 1990 (Fig. 3, 6), although a decline in Denmark (Fig. 3, 1) around the same time was also suggested, and in Sweden (Fig. 3, 5), possibly slightly earlier, during the late-1980s.

The age-specific trends in Fig. 2 indicate a stabilization or decline in rates in women ages >30 in Denmark, Sweden, and United Kingdom, and these seem more related to period of diagnosis than birth cohort. Cohort-specific increases were observed in women ages <30 in Denmark and United Kingdom, corresponding to generations born from the mid-1960s onward (Fig. 2). In contrast, the observed rates in Swedish women born after 1960 seem to consecutively decline, although, as a result of smoothing, the model parameters displayed in Fig. 3 do not exhibit such a trend.

Discussion

This study examined temporal patterns of cervical adenocarcinoma incidence using good-quality data from population-based cancer registries in 13 European countries. The interpretation of the trends are clearly complex in light of a number of plausible factors that may explain them. We assess below the relative contribution of diagnostic and coding artifacts, a changing distribution and prevalence of risk factors, and the impact of cytologic screening. The temporal patterns of cervical adenocarcinoma are then discussed in relation with those previously reported for squamous cell carcinoma (50).

Are the Increases in Adenocarcinoma a Result of an Increasing Specificity of Cervical Cancer Histologic Subtypes Over Time? Increasing cervical adenocarcinoma rates could reflect an increasing ability to diagnose the disease over time. A recent study from England and Wales apportioned the unspecified cases to adenocarcinoma or squamous cell carcinoma according to their relative proportions by age and period of diagnosis (19). We did not take this approach,
Table 2. Trends in adenocarcinoma of the cervix: populations included in the analysis, recent age-standardized rates, the estimated percentage change in the regular trend, and model characteristics and characteristics of cohort trends by country (Cont’d)

<table>
<thead>
<tr>
<th>Country</th>
<th>Recent trend, % (95% CI)</th>
<th>Direction, year (cohort trend)</th>
<th>Year of onset of organized screening program, type of screening system, area covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>0.4 (–0.7–1.6)</td>
<td>+ (1945)</td>
<td>1967 (achieved national coverage recently)</td>
</tr>
<tr>
<td>Estonia</td>
<td>1.0 (–1.8–3.9)</td>
<td>+ (1935)</td>
<td>No screening program</td>
</tr>
<tr>
<td>Finland</td>
<td>2.6 (1.0–4.3)</td>
<td>+ (1945)</td>
<td>1963 (national coverage)</td>
</tr>
<tr>
<td>Norway</td>
<td>1.1 (–0.4–2.7)</td>
<td>+ (1930)</td>
<td>1995 pilot 1992 (program in one county 1959-1977)</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.4 (–0.6–1.5)</td>
<td>+ (—)</td>
<td>1967-1973 in different counties, Gothenburg 1977</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2.4 (1.9–2.8)</td>
<td>+ (1940)</td>
<td>1988 (national coverage)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1.7 (0.5–3.0)</td>
<td>+ (—)</td>
<td>Opportunistic since 1966 (screening in two districts, beginning 2004)</td>
</tr>
<tr>
<td>Slovakia</td>
<td>3.4 (1.7–5.1)</td>
<td>+ (1935)</td>
<td>(intention to initiate program)</td>
</tr>
<tr>
<td>Italy</td>
<td>1.6 (–0.8–4.0)</td>
<td>+ (1940)</td>
<td>Florence (1985), Parma (1998), Ragusa (no data), Turin (1992), Varese (no data)</td>
</tr>
<tr>
<td>Slovenia</td>
<td>4.5 (2.4–6.6)</td>
<td>+ (1940)</td>
<td>Opportunistic until 2003</td>
</tr>
<tr>
<td>Spain</td>
<td>2.6 (–0.2–5.4)</td>
<td>+ (1940)</td>
<td>Catalonia (opportunistic until 1993)</td>
</tr>
<tr>
<td>France</td>
<td>−1.1 (–3.1–1.0)</td>
<td>0 (1945)</td>
<td>Bas-Rhin (1994), Doubs (1995), Isère (1990)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.4 (–2.2–3.1)</td>
<td>0 (1955)</td>
<td>Opportunistic (no data)</td>
</tr>
</tbody>
</table>

arguing that we did not have sufficient evidence to conclude that age and period-specific proportions of unspecified and specified cases were not in some way interrelated. As way of example, in Finland, a sudden drop in the number of unspecified cases was observed in 1968, likely due to structural changes in the way pathology data was coded, with the quality of the data pre-1968 considered of relatively poor quality in general. The Finnish data is, therefore, regarded at its most reliable if only cases coded as adenocarcinoma are included, and more recent trends were the focus of our analysis. Our analysis adhered to this criterion for all 13 countries and the evaluation of recent trends was given priority.

Caution in interpretation of the cervical adenocarcinoma trends must be exercised where the order of magnitude of both the absolute rates of unspecified cancers/carcinomas and their relative rate of increase are large compared with those of adenocarcinoma. Following the alternative scenario that all unknown cases were truly adenocarcinoma, the recent increases in adenocarcinoma rates in Denmark, Czech Republic, Italy, Slovenia, Spain, and United Kingdom could be explained by an increasing specificity in pathologic diagnosis of subtype with time. It is worth noting that the reallocation approach in the recent England and Wales study (19) yielded similar results to that of United Kingdom as reported in our study on the basis of the unadjusted data. An increasing specificity of subtype with time would explain at least part of the adenocarcinoma increase in Denmark. An earlier study reported proportional decreases in unspecified and unknown type, and increases in adenocarcinomas from the period 1943 to 1947 through 1978 to 1982. However, observed increases in adenocarcinoma rates among recent cohorts were also reported (51).

Data and Modeling Considerations. Our main focus has been on the description of trends by birth cohort and identification of deviations by period of diagnosis. To achieve a unique solution from the infinite number possible (47), the period slope was constrained to zero and assumed to reflect the well-documented historical inability to screen for adenocarcinoma. Other solutions, such as fixing the age structure as was done previously for squamous cell carcinoma (50), were considered less reasonable for adenocarcinoma. There is little background knowledge regarding the latent age curve for adenocarcinoma, whereas it is possible that error may be introduced should segments of the age profile be over-compensated or undercompensated by an age-related misclassification of adenocarcinomas.

In some countries, the trends are based on relatively few cases and have shorter follow-up time, reflecting the present status of good-quality cancer registry data in Europe. Clearly, the description of the period and cohort-specific trends is open to less interpretation than for countries with long-standing registries with larger population coverage.

Is the Increasing Risk in Recent Successive Generations Real? What Are the Causes? We observed recent statistically significant increases in cervical adenocarcinoma rates of at least ≥2% per annum in Finland, United Kingdom, Slovakia, and Slovenia. Positive but nonsignificant trends of a lesser magnitude were observed in most other countries. That cervical adenocarcinoma is increasing in recent years in Europe, particularly among young women, has been consistently reported in several countries (11, 14-20, 23, 25). This study establishes that the increases in incidence refer mainly to generations born since the epoch 1930 to 1945. The risk in cohorts born in the 1960s relative to the 1940s varied 7-fold, from high-incidence Slovenia to low-incidence France, where, uniquely, the risk seemed to be reasonably stable among recent generations.

An international study of time trends of adenocarcinoma incidence 1973 to 1991 (15) described increasing risk in cohorts born after the mid-1930 in England, Scotland, Denmark, Sweden, Slovenia, and Slovakia. Our study replicated these findings, although having data spanning the 1990s, we reported also increases in Estonia, Spain, Finland, and Italy (starting in cohorts born between 1935 and 1945), countries previously reported to have either stable or decreasing trends by cohort. Our own findings for United Kingdom are replicated by studies in England and Wales reporting generational increases in adenocarcinoma (18, 19). The authors found risk to be ~14 times greater in women born in the early 1960s relative to those born before 1935.

Persistent infection with sexually transmitted high-risk HPV types is established as the necessary cause of cervical cancer (52) and its main histologic subtypes (53). The widespread increases in cervical adenocarcinoma in Europe among recently born cohorts reported in this study and others (15, 18, 19, 23, 25) suggest that an increasing number of women are becoming HPV carriers of high-risk HPV types in many European countries. These cohorts may be defined by generational changes in sexual behavior that increase the risk of HPV infection, among them younger age at first intercourse, increased number of sexual partners, and increasing risk that each sexual partner is HPV positive.

Cofactors may modify the probability of HPV exposure and infection, and the residual effects of high parity, oral contraceptive use, and tobacco smoking on risk of cervical cancer have been reported in a number of epidemiologic studies (38, 39, 54-56). A recent meta-analysis of six case-control
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Whereas effective cytologic screening may have had a recent effect. Five-year age-specific rates are plotted against birth cohort and period of diagnosis for women ages 20 to 49, with the midpoint of age groups on the cohort scale labeled.

Adenocarcinoma is associated more with acquisition of HPV-18 than squamous cell carcinomas, which in turn is more linked to HPV-16 than adenocarcinoma (57, 58). The reasons for this specificity remain unidentified (53). The overall prevalence of high-risk HPV DNA has been found to be lower in adenocarcinoma than in squamous cell carcinoma in a number of studies (e.g., ref. 59), which may indicate a subset of women developed the disease through mechanisms unrelated to HPV infection, but artifactual explanations are possible and include the testing of inadequate samples, sampling errors of HPV detection in biopsies, and misclassification of adenocarcinomas of the endometrium as of the cervix (60). More recent studies are estimating the proportion of adenocarcinomas harboring high-risk HPV types to be close to 100% (1).

There are a few studies reporting trends in HPV incidence or prevalence either overall or by subtype, and these have been cross-sectional in nature. Increases in the incidence and seroprevalence of HPV-16 have been reported in Finland in women in their 20s (61), whereas in Sweden the main increases in HPV-16 during the period 1969 and 1989 occurred during the 1970s and early-1980s in women ages <35 (62). It has been suggested that the lifetime number of sexual partners is the strongest marker for oncogenic HPV infection, whereas a history of condyloma is associated more with acquiring benign HPV types (63). It may be of utility from a public health perspective to examine the prevalence and distribution of HPV and its markers in birth cohorts to better understand the behavioral aspects that places women at a higher average risk of cervical cancer in certain countries relative to others.

Has Cytologic Screening Had an Impact on Cervical Adenocarcinoma Trends? Whereas effective cytologic screening has led to declines in cervical squamous cell carcinoma incidence and mortality rates among targeted age groups over the same time period, the intervention has been considered less effective at reducing the incidence of cervical adenocarcinoma (64). Some authors have, however, suggested that screening may have been responsible in some reductions in adenocarcinoma during the 1990s (15, 29). Mitchell et al. (29) observed decreases among Australian women who had a pap smear with endocervical material within 1 year, or with an increasing number of pap smears with an endocervical component. One explanation for an increasing ability to detect endocervical lesions in cervical screening involves the improved diagnostic yield via use of the extended tip spatula or the Cervix (endocervical) brush, or a combination of both (65), as well as an understanding and recognition of adenocarcinoma in situ (30). Nevertheless, in the province of Florence, Italy, the extended tip spatula has been in common use since the 1980s (66), and has had little impact on the increasing adenocarcinoma rates in women ages ≤55 (67), whereas in a case-control study within the same region, the use of the cytobrush did not seem to offer any significant protection from adenocarcinoma (28).

Despite a focus on cohort trends, an advantage of Holford’s approach to age-period-cohort modeling (49, 68) is that the period curvature is identifiable. The decelerations in period-specific risk indicate an intervention that affects all age groups at the same time, and we observed declining adenocarcinoma incidence rates during the 1990s in Sweden, United Kingdom, and Denmark in women ages >35. Cytologic screening may thus be starting to have a protective impact on adenocarcinoma, as has been postulated recently by Mitchell et al. (29), and by Sasieni and Adams (69) on the basis of the observed incidence trends in England.

A recent Swedish study described a lack of screening effect, citing uniform increases in period-specific risk from around 1975 to 1992 (16), although the risk was quite stable from 1983. In England and Wales, incidence has been reported to have possibly reached a peak in the late 1980s in women ages 25 to 39 (69). Our analysis concurs with theirs regarding the beneficial effects of screening in the last decade; although its effects seems restricted to women ages >30, there have been substantial increases in adenocarcinoma observed in younger women during the same period.

How Do the Time Trends of Adenocarcinoma Compare with Those of Squamous Cell Carcinoma? Much of the literature in Western countries in the last two decades has described a phenomenon of increasing adenocarcinoma in the face of overall decreases in cervical cancer incidence (10-25). We found possible instances of a period-specific decreases in adenocarcinoma in this study in Denmark, United Kingdom, and Sweden, although any such screening effect is very recent. In comparative terms, large period-related declines were noted for squamous cell carcinoma in 8 of the same 13 countries in line with the initiation of organized screening programs (in the mid-1960s in Finland and Sweden), whereas opportunistic screening may have also played a role (50). A comparison of this study with a recent analysis of squamous cell carcinoma trends in the same countries (50), however, supports the idea of considerable homogeneity in the cohort-specific trends of each subtype in Europe. The cohort-specific increases in Italy, Spain, United Kingdom, Norway, Estonia, Slovakia, Finland, and Slovenia in adenocarcinoma described in this paper are in accordance with the temporal patterns conveyed for squamous cell carcinoma, with risk of...
both subtypes accelerating among consecutive generations born in the 1930s and 1940s. The rapid increases in the drift estimates of adenocarcinoma noted in Finland and Slovenia in recent years match well those observed for squamous cell carcinoma. The more moderate generational increases in adenocarcinoma in Czech Republic, Sweden, and Switzerland also largely parallel those of squamous cell carcinoma trends as does the noted absence of an increase in recent generations in France of either subtype. The cohort-specific trends are, however, difficult to fully interpret for countries where the span of available data is short.

An increasing capability to correctly assign the histology of cervical cancer cases is unlikely to account for increases in squamous cell carcinoma, which still represent the vast majority of cervical malignancies (75-90%). That European women born in successive generations experienced an increasing risk of both major histologic forms of cervical cancer within the same time window—during the 1930s and 1940s—points to a homogeneity in the risk factors chiefly responsible for the increases, presumably linked to sexual activity and risk of HPV infection.

Prospects for Prevention of Adenocarcinoma. The increasing risk of adenocarcinoma in successive generations suggests a major role for an increasing prevalence of persistent oncogenic HPV infection and its cofactors, whereas the downturn in period effects in several countries during the 1990s provides at least some evidence that cytologic screening is detecting more preinvasive adenocarcinomas than in previous decades. HPV screening for high-risk HPV types—probably in combination with cytologic screening—may maximize the possibilities of having early lesions detected and treated.

Recent trials evaluating the efficacy of virus-like particle vaccines in prevention of persistent infection with HPV-16 and HPV-18 in young women have been shown to be highly effective.

Figure 3. Age, period, and cohort effects (and corresponding 95% confidence intervals) of cervical adenocarcinoma incidence in 13 European countries for women ages <75 by European region (Northern Europe, 1-5; Eastern Europe, 7-8; Southern Europe, 9-11; Western Europe, 12-13). The period effects are estimated as residual effects of period given the estimated age and cohort effects. The cohort effects are displayed for generations born up to 1975. Corresponding 95% confidence intervals are also displayed.
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efficacious (70, 71). There is, therefore, some expectation that cervical cancer generally, and adenocarcinomas of the cervix in particular, may be preventable by HPV vaccination. However, we believe that improved screening will continue to play an essential role in preventing occurrences of, and deaths from, cervical cancer in the decades to come.

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