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# Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors

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**Abstract** ***Background:*** Cervical cancer trends in a given country mainly depend on the existence of effective screening programmes and time changes in disease risk factors, notably exposure to human papillomavirus (HPV). Screening primarily influences variations by period of diagnosis, whereas changes in risk factors chiefly manifest themselves as variations in risk across successive birth cohorts of women.

***Methods:*** We assessed trends in cervical cancer across 38 countries in five continents, age group 30–74 years, using age-standardised incidence rates (ASRs) and age-period-cohort (APC) models. Non-identifiability in APC models was circumvented by making assumptions based on a consistent relationship between age and cervical cancer incidence (i.e. approximately constant rates after age 45 years).

***Findings:*** ASRs decreased in several countries, except in most of Eastern European populations, Thailand as well as Uganda, although the direction and magnitude of period and birth cohort effects varied substantially. Strong downward trends in cervical cancer risk by period were found in the highest-income countries, whereas no clear changes by period were found in lower-resourced settings. Successive generations of women born after 1940 or 1950 exhibited either an increase in risk of cervical cancer (in most European countries, Japan, China), no substantial changes (North America and Australia) or a decrease (Ecuador and India).

***Interpretation:*** In countries where effective screening has been in place for a long time the consequences of underlying increases in cohort-specific risk were largely avoided. In the absence of screening, cohort-led increases or, stable, cervical cancer ASRs were observed. Our study underscores the importance of strengthening screening efforts and augmenting existing cancer control efforts with HPV vaccination, notably in those countries where unfavourable cohort effects are continuing or emerging.

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## 1. Introduction

Invasive cervical cancer (ICC) is the third most common cancer in women worldwide, with an estimated 529,000 new cases in 2008. The burden of cervical cancer varies considerably worldwide, with more than 85% of the global burden occurring in low-to-medium-resource countries, where it is still in many instances the most common malignancy in women.[1] Incidence and mortality rates of ICC have fallen over the past decades in a number of countries, mainly in high-resource countries following the introduction of screening programmes for cervical cancer.[2–5] However, stable or even rising trends have been observed in countries where screening activity is either lacking or suffers from low-quality and low-coverage.[2,4,6]

Persistent infection with oncogenic human papillomavirus (HPV) is considered a necessary cause of ICC.[7] Other cofactors, such as high number of sexual partners, young age at first sexual intercourse,[8] multiparity,[9] oral contraceptive use,[10] smoking[11] and HIV infection,[7] influence either the risk of acquisition of HPV infection or the progression to ICC. HPV infection could not be accurately detected in large epidemiological studies until the 1980s, and little is known on time trends of HPV prevalence in different populations.[12,13]

The comparison of ICC trends in different countries offers, therefore, an opportunity to assess the impact of screening efforts set against background changes in ICC risk factors.[2] For this purpose, we performed age-period-cohort (APC) analyses using incidence data from high-quality and longstanding population-based cancer registries from 38 countries to examine ICC patterns and trends across the major world regions.

## 2. Methods

### 2.1. Incidence data

New cases of ICC by age and calendar year of diagnosis were obtained from population-based cancer registries from the series *Cancer Incidence in Five Continents* (CI5) Volumes I to IX.[14] Population data were obtained from the same sources. Registries were included in our study if there was availability of at least 15 consecutive years of data and they were included in the last volume of CI5. The last year of diagnosis available in Volume IX of CI5 was 2002, but more recent data accessible online, up to 2010, were added, where available (Table 1).

National data were available for 22 of the 38 eligible countries. For the remaining populations, regional registries were aggregated to obtain a proxy of the national incidence. The time span of observations at the country level varied from 15 to 55 years and analyses were restricted to ages 30 to 74 (Table 1).

### 2.2. Statistical analysis

Age-standardised incidence rates (ASRs) per 100,000 person-years were calculated by the direct standardisation method, using the World standard population as a reference.[15] ASRs were displayed on a semi-log plot by 5-year time periods.

We obtained birth cohorts by subtracting age (midpoint of 5-year age band) from the central year of 5-year calendar period of diagnosis, and plotted trends in incidence rates *versus* birth cohort and calendar period by age on a logarithmic scale. APC models were used to summarise time trends in terms of cohort and period effects.[16–18] For each 5-year age-class $a = 1, 2,\ldots, A$ and 5-year period of diagnosis $p = 1, 2,\ldots, P$, the number of events and person-years $(D, Y)$, corresponded to $5 \times 5$ year subsets of a Lexis diagram. Under the assumption of a constant incidence rate $\lambda$ within the 5-year age classes and 5-year period the likelihood of the contribution from each subset is proportional to the likelihood for a Poisson observation $D$ with mean $\lambda Y$. The magnitude of the rates $\lambda(a, p)$ can be therefore described as a function of age $(a)$, period $(p)$ and cohort $(c)$ using a log-linear model, with Poisson errors and a logarithmic link function and with the log of the person-years at risk $\log(Y)$ as an offset. The nine distinct values of $a$ were 30–34, 35–39,..., 70–74 years, corresponding to midpoints: 32.5, 37.5,..., 72.5 years, whereas the number of distinct values of $p$ and $c$ varied across registries (Table 1).

The APC model is a generalised linear model,[18] and the full model can be represented as:

$$\log\ \lambda(a,\ p) = \alpha_a + \beta_p + \gamma_c = \log\left[\lambda(a,\ p)Y_{ap}\right] = \alpha_a + \beta_p + \gamma_c + \log(Y_{ap})$$

The model suffers from the problem of non-identifiability on account of the inherent linear interdependency between the three variables. It is impossible to determine the independent linear effects (slopes) of the three APC variables. Only the curvature effects, which represent departures from the linear trend, are uniquely estimable for the three APC variables. The age-adjusted sum of the period and cohort slopes, i.e. the drift[16] was used to estimate the annual percentage change of the regular trend, a quantity that cannot be attributed specifically to period or cohort. We computed the overall trend 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.

The age distribution of ICC is influenced by screening practice. In countries with little or no cervical cancer screening, ICC incidence rates rapidly increase until the time premenopausal hormonal changes usually start, at around the age of 45 years.[8,19] Conversely, in screened populations, incidence rates peak at approximately age