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Description of the influence of age, period and cohort effects on cervical cancer mortality by loglinear Poisson models (Belgium, 1955-94)

by

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Abstract

Background: *Cervical cancer mortality in Belgium has been decreasing continuously over the last forty years. This might generate the impression that the trend has hardly been influenced by changing exposure to etiologic factors or by increasing attendance to screening conducted since twenty years. It is important to separate out the role of ageing, period of death and period of birth (cohort).*

Method: *An age-period-cohort analysis, based on Poisson regression, was performed on cervical cancer mortality in Belgium between 1955 and 1994 in women between 20 and 79 years. The method of model building as proposed by Clayton (1, 2) is used. A linear secular trend (drift) can be isolated but not attributed to either period- or cohort-effects. Only the non-linear deviations are estimable using second differences contrasts. Over-dispersion is allowed.*

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Results: *The mortality decreased with about 50% over the last four decades. A full age-period-cohort model, adjusted for extra-Poisson variation, was necessary to adequately describe the trends. Strong cohort-effects were observed, besides age and drift. The non-linear period effect was significant but limited in magnitude.*

Conclusions: *The cohort effects seem to coincide with changing sexual behaviour of successive generations. The existence of a substantial negative drift factor shows that the decrease of mortality cannot be ascribed simply to prevention by Papanicolaou testing. Otherwise it does not provide evidence that screening was not influential. It is possible that screening further prolonged the effect of earlier clinical diagnosis and treatment due to improved access to health care.*

Keywords

Age-period-cohort models, trend analysis, Poisson regression models, mortality, cervical cancer, Belgium.

Introduction

Age standardised mortality rate (ASMR) due to cervical cancer in Belgium decreased continuously since registration of death causes was initiated in 1954, long before prevention by Pap-smear became important (3, 4). This rather monotonous trend may suggest a regular decrease in risk, which was hardly influenced by phenomena such as the progressive introduction of screening or the changing exposure to etiologic factors. The ASMR is a rough summary parameter obtained by age adjustment of cross-sectional data from different generations (direct standardisation). Older age groups, experiencing higher mortality, dominate the ASMR, thereby masking the relevance of events occurring in recent cohorts. By referring to a standard population it makes comparison of mortality possible among areas with different age structures. Nevertheless its relevance in analytical epidemiology is limited. The same can be said of indirectly standardised mortality ratios (SMR).

The tabular or graphical representation of age-specific rates, arranged by calendar period or age of birth, allows qualitative understanding of the

impact of preventive or therapeutic measures and the influence of changing exposure to carcinogenic agents (5, 6). This was the object of an earlier study (4). When several time-related factors in complex combinations are into play, it becomes difficult to discern clear patterns in the temporal variation in mortality rates, without using statistical modelling techniques to separate *a*ge, *p*eriod (secular influences) and *c*ohort (generational factors) on mortality *(APC-models)*. To this end, Poisson models will be used (1, 2). The mathematical basis of APC-modelling and its intrinsic methodological problems will be elaborated shortly.

Materials and methods

Source of data

Data on deaths due to cervical cancer and on the composition of the female population in Belgium between 1955 and 1994 were obtained from the National Institute of Statistics. Deaths from cervix uteri cancer were coded as 171 for the period 1954-1968 (ICD-6 and -7) and as 180 for the period 1969-1994 (ICD-8 and 9).

Identification of age groups, calendar periods and birth cohorts

Analysis is limited to the age range of 20 to 79 years, since mortality at younger age is extremely rare (only one case in the category 15 to 19 years in 1959) and the reliability of death cause certification in the elderly is limited (7, 8). Deaths and population are grouped in A quinary age groups *(A = 12)* indexed *a (a = 1, ..., A)* and in *P* quinquenial periods *(P = 8)* indexed *p (p = 1, ..., P)*. Data are assembled in a two-way *A* by *P* table with *A* rows representing the categories of age and *P* columns defining the calendar periods. Mortality rates (M_{ap}) are derived from the number of deaths (D_{ap}) occurring in age group *a* during the period *p* over N_{ap}, the corresponding number of person-years (see Table 1).

Birth cohorts are defined by the *K (K = A + P – 1 = 19)* diagonals in the A × P contingency table.

Cohorts are indexed by *k (k = 1, ..., K; K = 19)*. The three indices are related by

$$k = A - a + p. \qquad \text{(Equation 1)}$$

TABLE 1

Cervical cancer mortality rates (deaths/100 000 women-years) arranged by 5-year age groups (columns) and 5 year periods (rows). Cohorts are 10 years wide and can be distinguished following diagonals.

	Age group (a)												
Period (p)	20 1	25 2	30 3	35 4	40 5	45 6	50 7	55 8	60 9	65 10	70 11	75 12	Cohort (k)
1955 1	0,07	0,56	2,46	3,11	8,24	10,46	10,95	15,35	16,10	17,69	20,59	18,43	
1960 2	0,07	0,20	1,60	3,17	7,32	8,94	11,37	14,04	15,10	16,44	16,03	20,21	1880 1
1965 3	0,07	0,35	0,52	2,26	4,80	9,89	9,90	9,98	12,65	13,91	17,89	17,95	1885 2
1970 4	0,00	0,26	0,56	1,75	4,61	6,52	11,76	10,27	11,55	13,84	15,88	19,69	1890 3
1975 5	0,11	0,06	0,59	1,97	3,20	5,17	8,04	10,21	11,39	12,07	17,29	19,33	1895 4
1980 6	0,10	0,27	1,08	1,91	2,77	4,98	6,23	8,41	10,49	14,61	16,13	20,22	1900 5
1985 7	0,00	0,51	0,54	1,89	3,73	5,48	4,74	6,01	10,69	13,82	12,68	16,80	1905 6
1990 8	0,06	0,15	1,18	2,23	3,04	4,84	6,37	5,12	5,48	7,77	11,13	10,23	1910 7
Cohort k	1970 19	1965 18	1960 17	1955 16	1950 15	1945 14	1940 13	1935 12	1930 11	1925 10	1920 9	1915 8	

Because intervals for age and period categories are both 5 years wide, a birth cohort spans 10 years. Successive cohorts are overlapping partially and can be identified by the mid-year of the interval. For example, women aged 40-44 years (a = 5) in 1965-69 (p=3), were between 30-34 years (a=3) in 1955-59 (p=1) and will be between 60-64 years ($a = 9$) in 1985-89 ($p = 7$). They belong to the cohort born between 1920 and 1929 and can be identified as the 1925 cohort (k=10). Women who are on average 5 years younger in the same period (situated one cell to the left in the $A \times P$ table, age = a-*1* and period = p) belong to the generation born between 1925 and 1934 and are identified as the 1930 cohort ($k = 11$).

The extreme birth cohorts ($k = 1$ or $= 19$), born respectively around 1880 and 1970, contain information of only one cell respectively at the upper right and lower left corner.

Log-linear modelling

Rates are nonnegative and therefore are naturally modelled on the log-scale. The temporal variation of mortality can be explained by variables such as age at death, period at death and epoch of birth. The logarithmic transformation of the mortality rate allows the formulation of a generalised linear model (9, 10) such as:

$$Ln\,(M_{ap}) = \mu + \alpha_a + \pi_p + \kappa_k$$

where α_a, π_p, κ_k are respectively the *fixed* age, period and cohort effects or values. μ represents a constant corresponding to the log-rate for the reference levels (when a, p or $k = 0$).

Poisson variability can reasonably be assumed for the observed number of deaths, which means that the variance of the logarithm of the mortality rate is the inverse of the expected number of deaths (1). Parameters can be estimated by means of maximum likelihood using statistical packages able to perform generalised linear modelling (1, 11-13).

The logarithm of the person-years, $Ln\,(N_{ap})$, is declared as the *offset*, which means that its coefficient is put to unity, and hence does not need to be estimated (9).

$$\hat{M}_{ap} = \hat{D}_{ap} / N_{ap}$$

$$Ln\,(\hat{M}_{ap}) = Ln\,(\hat{D}_{ap}) - Ln\,(N_{ap})$$

$$Ln\,(\hat{D}_{ap}) = Ln\,(N_{ap}) + \mu + \alpha_a + \pi_p + \kappa_k$$

Assessment of the goodness of fit

The goodness of fit is assessed by the deviance *(D)*, which is based on the ratio between the likelihoods (L) of the current and the saturated model *(D = – 2Ln (L {model$_i$} / L {saturated model})* (9). This log likelihood ratio statistic provides an overall measure of the adequacy of the model. It follows approximately a chi-square distribution whose number of degrees of freedom equals the amount of observations less the number of parameters included in the model (14). The contribution of an additional term to the current model is evaluated by comparing the change in deviance with the chi-square value for the difference in degrees of freedom (9). The goal is to find a model with deviance close to its residual degrees of freedom.

Over-dispersion

If the actual variance of the observed number of deaths is larger than expected under the Poisson assumption, the model is said to exhibit over-dispersion or in this case extra-Poisson variation. This is not uncommon when counts are large, for instance when data at national level are studied. One way to cope with over-dispersion in aggregated counts or rates is to modify the fixed relationship between the mean and the variance in the Poisson distribution by including a proportionality constant, called the heterogeneity factor (15). The factor can be estimated from the deviance of the most complex model one is prepared to consider, provided that it contains all appropriate explanatory variables (16).

The method for correcting for over-dispersion by Williams (17), adapted by Breslow (18) for the particular case of Poisson distributions, takes into account the following relationship:

$$\sum_{a,p=1}^{A,P} \frac{(y_{ap} - \hat{y}_{ap})^2}{(\sigma_{EP}^2 + \tau_{ap}^2)} = \text{number of residual df,}$$

where y_{ap} and $\hat{y}_{ap}$ are the observed and fitted log rates for age a and period p; τ_{ap}^2 is the expected variance corresponding to $1/\hat{D}_{ap}$ and σ_{EP}^2 represents the extra-Poisson variance to be estimated in an iterative procedure so that the deviance approximates the number of residual degrees of freedom. The procedure by Breslow (18) was implemented here by means of a GLIM macro written by Lindsey (16) and adapted to our needs. It can be obtained from the authors upon request.

Description of the log-linear models

The expected rates $(\hat{M}_{ap})$ are obtained by the exponentiation of the sum of the estimated effects or by multiplying the antilogs:

$$\hat{M}_{ap} = e^{\mu + \alpha_a + \pi_p + \kappa_k} = e^{\mu} \cdot e^{\alpha_a} \cdot e^{\pi_p} \cdot e^{\kappa_k}$$

By back transformation of lograte the more familiar multiplicative parameters or relative risks are obtained. The antilogs of the effects α_a, π_p or κ_k are to be interpreted as the adjusted rate ratios with respect to the reference categories for a, p or k.

The constant parameter μ is added to α_a, so that the age value takes the form of an age specific mortality rate (expressed as number of deaths by 100 000 women-years in category a).

Hierarchical loglinear models will be analyzed in terms of age, drift, period or cohort in the order as proposed by Clayton (2). This generally applied method is extended by introducing *drift*age* interactions in order to study age specific evolutions (19, 20).

As age is a fundamental biological determinant of cancer incidence and mortality, it is obvious to introduce it as first factor to a null model.

$$Ln\,(\hat{M}_a) = \mu + \alpha_a \qquad \text{(Model 1).}$$

Model 1 implies absence of temporal change in age specific rates.

Next, calendar time is added as a continuous variable to verify if the different age specific curves show a common constant linear slope or *drift* over time. Year at occurrence of death (Model 2a) or year of birth (Model 2b) can be used equally.

$$Ln\,(\hat{M}_{ap}) = \mu + \alpha_a + \delta_p^{*}\,(period_p - period_1) \qquad \text{(Model 2a),}$$

$$Ln\,(\hat{M}_{ap}) = \mu + \alpha_a + \delta_c^{*}\,(cohort_k - cohort_1) \qquad \text{(Model 2b).}$$

If the age-drift model fits well, it should imply that the logarithm of the mortality rate is changing at a constant rate for all age groups over time. The constants δ_p and δ_c are the slopes of the log-linear regression equations. The age-values represent fitted age-specific rates in respectively the reference period (p_1) (model 2a) or the reference cohort (c_1) (model 2b).

It is possible that age groups express different linear changes. This implies an interaction between age and drift:

$$Ln\,(\hat{M}_{ap}) = \mu + \alpha_a * \delta_{pa}^{*}\,(period_p - period_1) \qquad \text{(Model 3a).}$$

A significant *P effect* means that a non-linear temporal deviation from the regular trend line is observed across all age groups. Age specific log-mortality curves plotted against calendar period should be irregular but parallel, if the AP- model fits well. The respective log-linear equation can be formulated as:

$$Ln\ (\hat{M}_{ap}) = \mu + \alpha_a + \pi_p \qquad \text{(Model 3b).}$$

The mortality rates of the first period, 1955-59, are taken as reference set. π_1 is put at zero, so π_p expresses the difference in lograte occurred in the interval between the initial and the considered period *p*. $e^{\pi p}$ is the multiplicative period parameter which expresses the relative risk respective to the standard period ($p = 1$) and can be interpreted as the indirectly standardised mortality ratio (SMR) (21, 22).

The analysis of the alternative *AC model* (3c) allows verifying the contribution of generational κ_k effects.

$$Ln\ (\hat{M}_{ak}) = \mu + \alpha_a + \kappa_k \qquad \text{(Model 3c).}$$

The default choice of the first cohort (women born around 1880) as standard is not indicated for statistical reasons. The observed mortality might not be very stable as deaths are only observed for one age group ($a = 12$; women of 75 to 79 years). Therefore, we have recoded the cohort index. The most recent complete generation (observed over the 8 periods), born around 1935, is given the index of one, so that it is considered as reference. The AC-model implies that age-specific mortality curves plotted on a logarithmic scale by birth cohort show a parallel pattern. The multiplicative cohort effects ($e^{\kappa k}$) are similar to the standardized cohort mortality ratios (SCMR) described by Beral (23). They represent the changing risk that successive generations exhibit throughout their lives relative to the 1935 cohort.

Period- and cohort effects should be considered as sudden temporal deviations from a straight line, while a drift expresses a monotone continuous change over time. $e^{\delta p}$, the antilog of the slope parameter in model 2a expresses the constant relative risk of dying by cervical cancer for adjacent periods just as in the AP-model. The equation for Model 2a describing the age-drift including the numeric period variable can be written as a special age-period model:

$$Ln\ (\hat{M}_{ap}) = \mu + \alpha_a + \pi_p^{*}\ (period_p - period_1) \qquad \text{(Equation 2).}$$

The period at death can be derived from the age and the birth date (1): $p = c + a - A$ and $p_1 = c_1 + a_1 - A$. By replacing the p-terms in the drift model, we can reformulate Model 2a as an age-cohort model, where the age effect should be corrected accordingly (Equation 3):

$$Ln\,(\hat{M}_{ac}) = \mu + \alpha_a + \delta_p^* [(c + a - A - (c_1 + a_1 - A)] \text{ or}$$

$$Ln\,(\hat{M}_{ac}) = \mu + \alpha_a + \delta_p^* (a - a_1) + \delta_p^* (c - c_1) \qquad \text{(Equation 3).}$$

The α_a values in (Equation 2) are called "cross-sectional" age-effects, while the values $\alpha_a + \delta_p^*(a - a_1)$ in (Equation 3) are termed "longitudinal" age-effects.

The linear drift cannot be attributed purely to neither period at death or epoch of birth, the mathematical formulations (Equation 2) and (Equation 3) being equivalent. The same argumentation can be applied, starting from the drift-model based on the numeric cohort-time variable, by replacing now the terms c and c_1.

Only when neither the age & period nor the age & cohort terms provide a satisfying fit, the full APC-model (Model 4) can be conceived.

$$Ln\,(\hat{M}_{ac}) = \mu + \alpha_a + \pi_p + \kappa_k \qquad \text{(Model 4).}$$

The APC-model allows for non-parallel age-specific mortality curves as a function of birth cohort or calendar period.

Identifiability problem

A complex identifiability question arises, because the tree factors are not independent but mutually linked by the relation described by equation (1). Drift can be partitioned arbitrarily among period and/or cohort influences with resultant alteration of the age curve. An infinite number of different parameterisations can be formulated that predict the mortality rate similarly. Nevertheless, all the sets of non-drift effects have the so-called contrast of second differences in common. They are defined by the relative position of a parameter compared to the preceding and the following one. For three adjacent period effects, such a contrast is formulated as:

$$(\pi_{p+1} - \pi_p) - (\pi_p - \pi_{p-1}) = \pi_{p+1} - 2\pi_p + \pi_{p-1} \qquad \text{(Equation 4).}$$

These identifiable contrasts determine the curvatures of secular trends. A negative value implies a sudden acceleration (concave curve) at time p and a positive value a brusque downward bending of the mortality rate

(convex curve), while zero means absence of change of the local trend. In a multiplicative form we have to consider the ratios of three consecutive relative risks:

$$(e^{\pi p+1} / e^{\pi p}) / (e^{\pi p} / e^{\pi p-1}) = (e^{\pi p+1} \cdot e^{\pi p-1}) / (e^{2\pi p}) \qquad \text{(Equation 5).}$$

Presentation of different models

For the successive models we will show the predicted and observed age-specific mortality rates as a function of period or cohort. The estimated multiplicative parameters (the antilogs of the additive values) will be presented graphically as age-specific rates, or as relative risks with respect to the standard period, 1955-59 or cohort, 1930-39. The estimated effects and the second order differences for complex APC-model will be displayed in tabular and graphical form.

Results

Tabular and graphical presentation

The trend over 5 year periods of age-specific mortality rates is given in Table 1 and graphed in Figure 1a.

The age adjusted rate, calculated by the method of direct standardisation and based on the European reference population, is included in the same graph as solid bold line. Figure 1b shows the evolution of age specific rates as a function of birth cohorts. Alternated series are omitted in the graph for reasons of presentation. The mortality rate increases obviously with age. The standardised rate declined almost linearly from 6.3 to 3.0 by 100 000 women- years over the 40 years of observation (reduction of 52%; slope of the linear regression line of $-0.09/10^5$ women-years; $R^2 = 0.97$). Most age-specific rates decreased also. The curve corresponding to the oldest group (> = 75 years) increased gently until 1985-89 but started declining thereafter. Mortality among the youngest groups (< = 39 years) remained rather stable. The decreasing slopes of the intermediate age groups tend to become less noticeable over the last 10 to 15 years. There was little change over the cohorts born before 1920. Discrete upward peaks can be observed for the generations C1895 and C1920. For four successive cohorts (C1920 through C1935) an important continuous

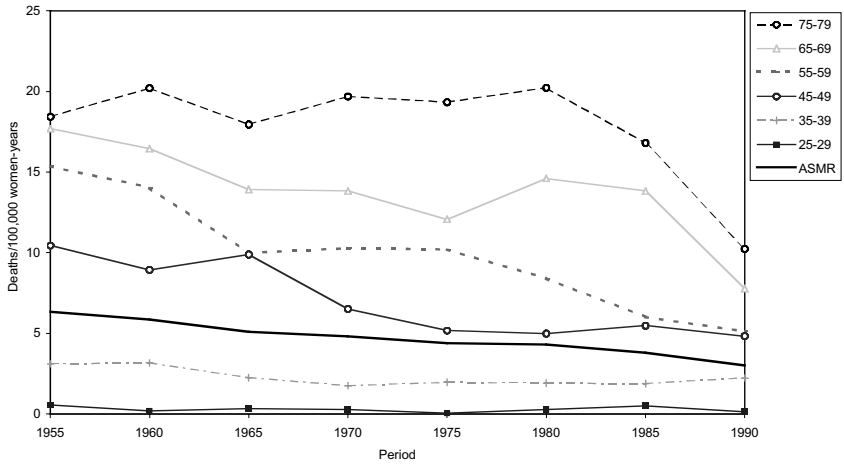


Fig. 1a: Age specific and standardised mortality rates from cervical cancer in Belgium between 1955 and 1994 in function of period.
The periods are 5 years wide and indicated by the first year.

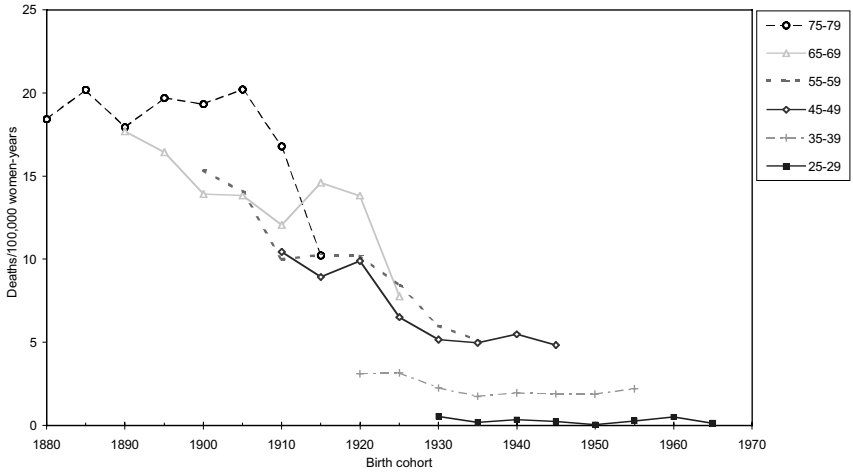


Fig. 1b: Age specific mortality rates from cervical cancer in Belgium between 1955 and 1994 in function of birth cohort.
The birth cohorts are 10 years wide and indicated by the mid-year.

reduction in mortality is noticed. On the contrary, the curves for the next generations follow a horizontal course with a slight tendency of increase.

Deviance analysis

The contribution of explanatory variables to the prediction of the mortality rate is assessed by the analysis of the deviance, which is presented in Table 2.

The inclusion of age (1) as first term is evident, as it provokes a large jump in deviance. Addition of the numeric drift factor (2) further forces the deviance to decrease with 452 at the expense of only one degree of freedom. Inclusion of period (3b), cohort (3c), or the interaction between age and drift (3a) each further ameliorates the model significantly. Even the full Age-period-cohort model (4) provides a more adequate fit than the previous combinations. The model (3a), containing the product $\alpha_a * \delta$, is not further developed for reasons of interpretability.

The residual deviance of the final APC model (4) is 100.1 for df = 60. The corresponding χ^2 test (p = 0.0009) indicates a still unsatisfactory prediction of the observed number of deaths assuming only Poisson variation. However, allowance for over-dispersion yields a deviance of 62.2, approximating the number of degrees of freedom and indicating an acceptable fit (p = 0.398).

Observed and predicted mortality rates

The trends of observed (points) and modelled (curves) age specific rates are shown for different considered models in figure 2. For reasons of graphical visibility only the second age groups of each tenth are traced (25-29, 35-39, and so on). Predictions from the six following models are presented successively: (1) age-model (parallel horizontal regression lines), (2) age-drift (parallel lines with common constant slope), (3a) age-age*drift (non parallel straight lines with age-specific slopes), (3b) age-period and (3c) age-cohort (parallel non-linear curves), and finally (4) age-period-cohort (non-linear age-specific curves changing irregularly with cohorts and periods). The first four graphs of figure 2 are plotted on a logarithmic ordinate scale. Lower mortality rates (< $10/10^5$ women-years) currently observed in the younger age groups are obviously separated. The graphs with cohort effects are traced on a linear Y-axis, allowing more distinct mortality curves for older age groups. Going down progressively from fig-

TABLE 2

Deviance, degrees of freedom and significance of progressively more complex APC-models.
The contribution of an extra term is evaluated by the change in deviance (col 6) with the χ^2 corresponding with the number of lost df (7).
The corresponding p-value (col 8) should be < 0.05. The adequacy of the model is assessed by comparing the residual deviance (3)
with the χ^2 for the resting df (4). The corresponding p-value is presented in column 9

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
		Residual					p value	
N°	Model	deviance (D)	df	Comparison with model	Δ D	Δ df	addition of terms	model versus observed data
0	Null	8108,1	95					
1	Age	703,9	84	0	7404,2	11	0,000	0,0000
2	Age-drift	252,1	83	1	451,8	1	0,000	0,0000
3a	Age-Age*drift	198,8	72	2	53,3	11	0,000	0,0000
3b	Age-Period	230,4	77	2	21,7	6	0,001	0,0000
3c	Age-Cohort	127,0	66	2	152,0	17	0,000	0,0000
4	Age-Cohort-Period	100,1	60	3c	26,9	6	0,000	0,0009
	ACP with extra-Poisson	62,2	60					0,3978

ure 2.1 to 2.4, the predicted curves more accurately approximate the observed rates.

The age-specific curves are vertically separated and, in general, are decreasing over the considered periods. Among the youngest and oldest age categories an almost horizontal trend is observed. Until the birth cohort of 1920, there is little variation at the exception of some discrete peaks for the cohorts 1895 and 1920. From then onwards a continuous decline can be distinguished until the epoch of 1935. For more recent cohorts, the trend becomes horizontal or even increasing.

Estimation of the parameters

The estimated parameters belonging to different models are presented graphically in Figures 3.1 to 3.4.

Age model

The age effect in a simple *A*-model (figure 3.1), represents the general average of fitted age specific rates over the 8 periods. It increases from 0.06 (95% confidence interval = CI: 0.03 – 0.12) for the youngest to 17.7 for the oldest age category (CI: 16.7 – 18.8) by 100 000 person-years.

Age-drift model (figure 3.2)

The age effect represents now the fitted age-specific rate for the first period (1955-59) chosen as reference epoch. The period-drift assumes a continuous linear decrease of the log rate with slope, $\delta = -0.098$. This means that the relative mortality risk for a period with respect to the previous one is $e^{\delta} = 0.906$ (CI: 0.898-0.915). From the first up to the last period the mortality declined regularly to 50.3% ($= e^{(P-1)*\delta}$) of its original value. $e^{\delta} - 1 = -0.009$ (CI: $-0.010 - -0.008$) represents the slope of the regression line through the age standardised rates.

Parameters can also be estimated, considering the birth cohort as a continuous independent variable. This yields the same $\delta = -0.098$ but implies modification of the age-effects, which are shifted upwards with a factor $(e^{-0.098*(a-a1)})$. These longitudinal age-effects are shown as a dashed curve in Figure 3.2.

The inclusion of the numerical cohort variable instead of period-drift yields the same predicted rates and shows an identical deviance (= 252.1 for 83 degrees of freedom, Table 2).

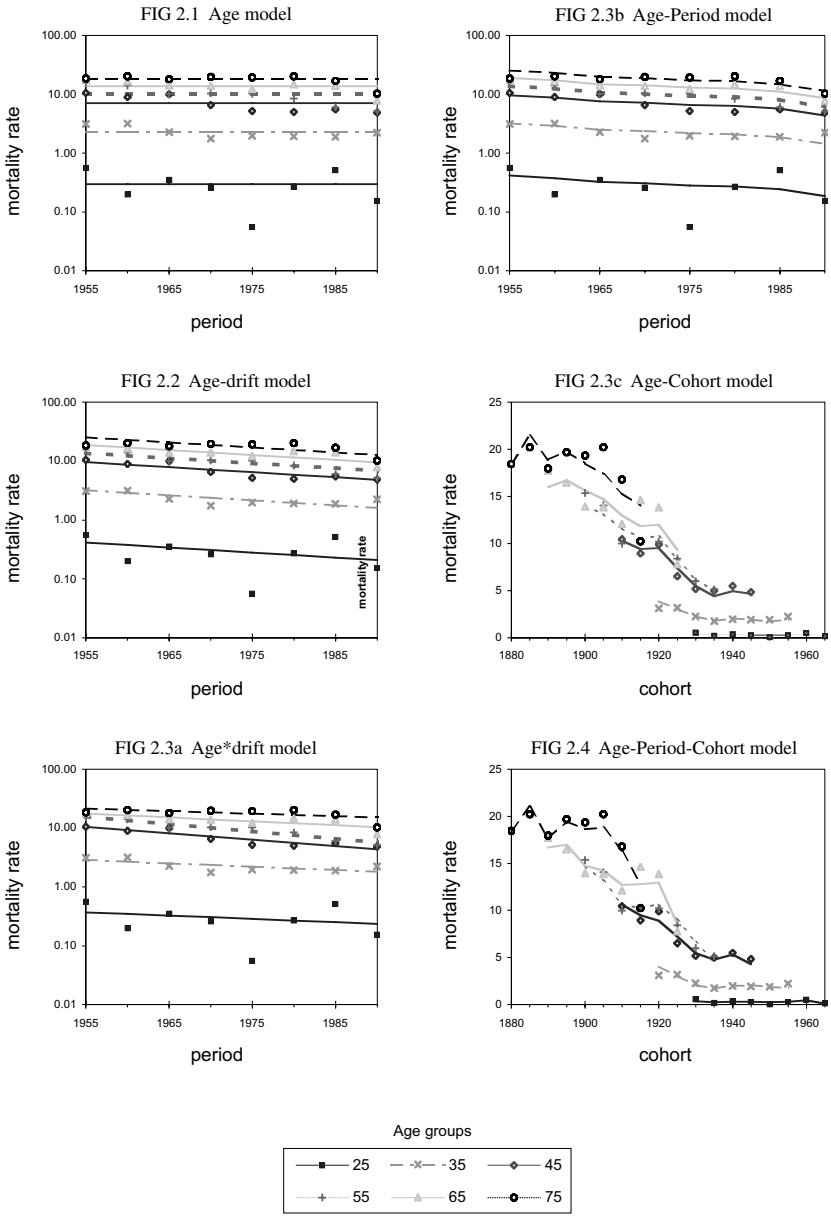


Fig. 2: Observed (points) and fitted age specific mortality rates for different Poisson models.

Remark: more clear graphs in colour can be obtained at:
http://www.iph.fgov.be/epidemio/epien/cervixen/aph2002_MA.pdf

Interaction between age group and drift

In Figure 3.3a multiple age-specific periodic drifts are drawn. The steepest linear decrease is observed in the intermediate age groups 45-59 years, while the less pronounced slopes are in the younger (25-29 years) and older age groups (> = 70 years).

Forcing all age groups expressing a regular trend over the complete period has a distorting effect on the curve of the age effects, which shows now a less smoothed course.

FIG 3.1 Age model

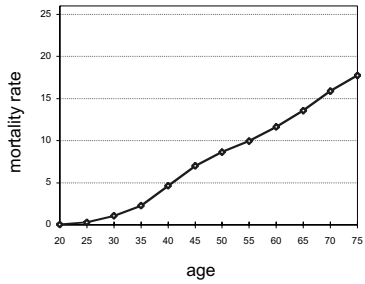
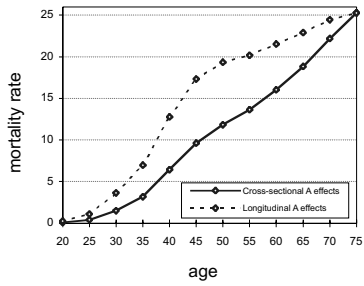


FIG 3.2 Age-drift model



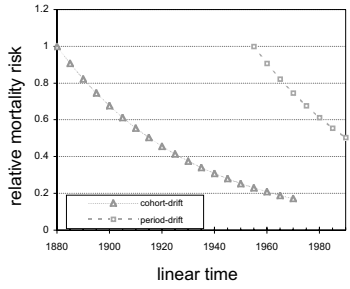
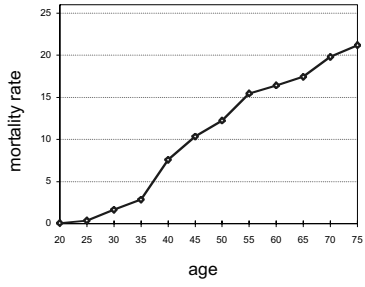


FIG 3.3a Age*drift model



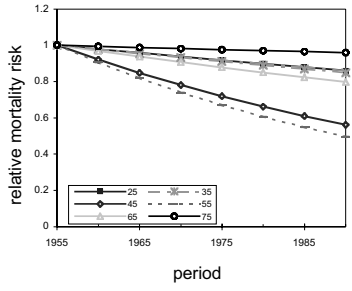


Fig. 3: Estimated effects from different models,
at left the age effects are plotted as age specific mortality rates;
at right the time related effects (drift, period or cohort) are plotted as relative risks.
See remark in Fig. 2.

Age-period model

The period effect of the age-period model is shown in figure 3.3b in its two most extreme expressions: without drift containing exclusively non-linear changes (solid curve) and absorbing 100% of the linear drift (dotted curve). The deviations from the straight line are limited.

FIG 3.3b Age-Period model

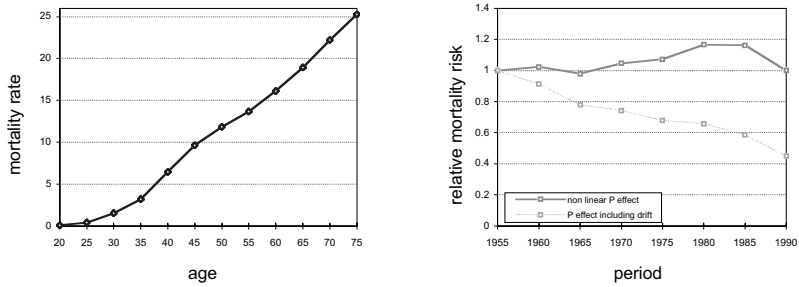


FIG 3.3c Age-Cohort model

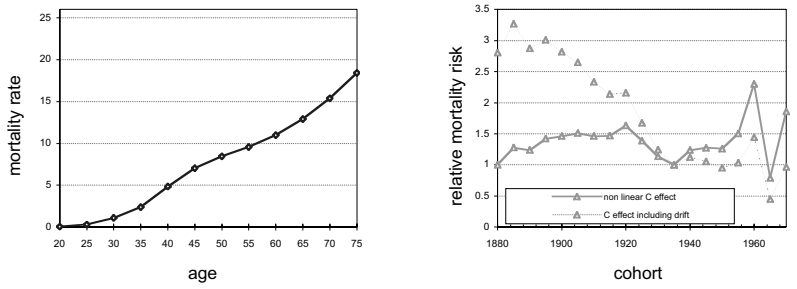


FIG 3.4 Age-Period-Cohort model

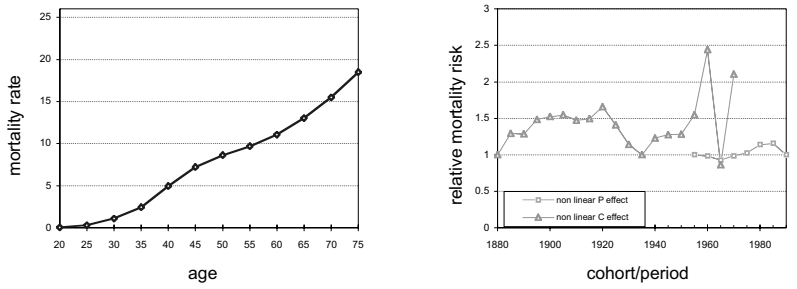


Fig. 3 (continued): Estimated effects from different models,
at left the age effects are plotted as age specific mortality rates;
at right the time related effects (drift, period or cohort) are plotted as relative risks.

TABLE 3

*Infinite alternative equations can be formulated by arbitrary repartitions of the net linear slope in period or cohort components. Three different sets of estimates *1, *2 and *3 from a multiplicative APC model are presented for age, drift, period and cohort. All predict the same fitted mortality rates. The common contrast of second differences is shown in the last column. The contrast is derived by calculating* $(*_{i-1} . *_{i+1}) / *_i^2$ *. For each set of parameters the contrast is the same*

Parameters	Parameter estimates (*1)	(*2)	(*3)	Second differences
Age group				
20-24	0.058	0.058	0.058	
25-29	0.310	0.278	0.310	0.664
30-34	1.102	0.885	1.102	0.624
35-39	2.442	1.758	2.442	0.913
40-44	4.943	3.193	4.943	0.723
45-49	7.228	4.183	7.228	0.816
50-54	8.627	4.472	8.627	0.940
55-59	9.679	4.499	9.679	1.019
60-64	11.067	4.613	11.067	1.029
65-69	13.026	4.864	13.026	1.011
70-74	15.501	5.191	15.501	1.002
75-79	18.484	5.551	18.484	
Drift	0.896	–	–	
Period				
1955-59	1.000	1.000	1.000	
1960-64	0.983	0.983	0.881	0.960
1965-69	0.928	0.928	0.745	1.127
1970-74	0.986	0.986	0.710	0.980
1975-79	1.028	1.028	0.664	1.065
1980-84	1.141	1.141	0.660	0.915
1985-89	1.158	1.158	0.601	0.851
1990-94	1.000	1.000	0.465	
Cohort				
1875-1884	1.000	3.330	1.000	
1880-1889	1.294	3.865	1.294	0.767
1885-1894	1.284	3.438	1.284	1.165
1890-1899	1.485	3.561	1.485	0.888
1895-1904	1.524	3.277	1.524	0.988
1900-1909	1.546	2.980	1.546	0.941
1905-1914	1.475	2.549	1.475	1.062
1910-1919	1.495	2.316	1.495	1.095
1915-1924	1.660	2.305	1.660	0.766
1920-1929	1.411	1.756	1.411	0.954
1925-1934	1.144	1.276	1.144	1.078
1930-1939	1.000	1.000	1.000	1.408
1935-1944	1.230	1.103	1.230	0.844
1940-1949	1.277	1.026	1.277	0.967
1945-1954	1.282	0.923	1.282	1.205
1950-1959	1.550	1.000	1.550	1.303
1955-1964	2.440	1.412	2.440	0.225
1960-1969	0.865	0.448	0.865	6.864
1965-1974	2.102	0.978	2.102	

Age-cohort model

The C effect in an AC model is presented in Figure 3.3c, again under two extreme versions, with and without linear trend. A discrete upward peak is observed for C1920. The three subsequent cohorts express a continuously lower mortality. This trend changes abruptly at C1935. Women born after this period seem exposed to increasing mortality risk. The variation at the right end is very large. It concerns mortality for the youngest generations where mortality is extremely low and consequently not stable. Therefore, no firm conclusions can be derived for the last two cohorts.

Age-period-cohort model

In Figure 3.4 we show only the non-drift P- and C-effects adjusted for the presence of all influences together. The inclusion of period hardly alters the curve of the age- and cohort effects in comparison with the previous model. The P-curve fluctuates within a limited range around the unit line.

No unique set of parameters

According to distinct splits of the drift in a period or cohort component, different parameterisations are possible (see Table 3).

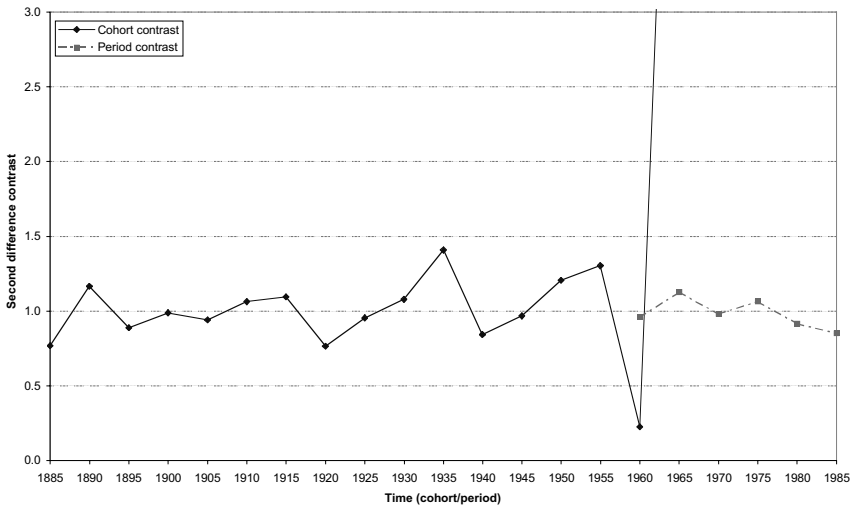


Fig. 4: Second differences contrasts for the period and cohort-parameters estimated from the age-period-cohort model.

The first set of parameters represents the situation plotted in Figure 3.4. Here, the drift is shown as periodic and completely separated from the other effects, for which only the non-linear deviations are estimated. In the second set the drift is absorbed in the cohort curve, which changes the age relations dramatically. In the third column, the P-effects have completely assimilated the linear trend.

The comparison of the change of slopes over adjacent age-, period or cohort groups in all possible sets leads to the definition of a unique set of second difference parameters (last column, Table 3). The curve with the period contrast balances around unity (Figure 4).

The negative peaks (values less than 1) for cohorts 1885, 1895 and 1920 indicate sudden changes: a convex curvature such as a temporary increase followed by a decrease of the risk. Contrasts above unity, indicating a concave bending of the mortality, are observed for the cohorts 1935 and 1955.

Discussion

General

The apparent monotone decrease of the mortality rate by cervical cancer over the last four decades is the result of a complex combination of counteracting events. Detailed observation of age specific rates as a function of the period of death or the period of birth reveals interesting patterns for which biological explanations can be sought. Age, period and cohort influences make up the essential constituents of vital rates. Clear examination of their interrelations and thorough understanding of the strengths and limits of the applied statistical methods protect against over-interpretation. The evolution of cervical cancer mortality is quite complicated. A full APC-model, allowing for extra-Poisson variation, is necessary to describe the trend.

Interpretation of the effects

The influence of age on mortality by cervical cancer is beyond any discussion for evident biological reasons and this fact is also corroborated by statistical arguments. Its addition as a factor provokes a reduction in

deviance of more than 7400. Nonetheless, further variation over time cannot be ignored.

Very often, the trend is explained as a period-related phenomenon. The striking decrease of the mortality in Belgium as well as in the rest of Western Europe and North-America is, in the medical literature, generally ascribed to the successful implementation of screening (24, 25). This interpretation implies the assumption of the drift as being (almost) completely periodic. Statistical and historical arguments can be retained against this simple hypothesis. The fall in mortality has already been observed since the 1950s, while screening became only important since the late 1960s (3). Since then, the coverage among the target population increased gradually (26, 27). The non-linear P-effect alone, the only part of the secular trend that is identifiable, is too weak to explain the observed variation. Moreover, no statistical arguments justify the assimilation of the drift within the period effect (1, 2).

The negative slope of the observed age-standardised mortality (fig 1) and of the fitted mortality in the AP-model (Figure 2.3b) does not show any further decline while the screening coverage increased. Certain epidemiologists considered screening with Pap smear as infective because of this fact (28, 29). Again this hypothesis starts from a simple age-period or age-periodical drift model.

The interaction between age and drift was not conceptualised in Clayton's general framework for APC-analysis (1, 2). The inclusion of A*drift was used by Bouchardy (19) and Estève (20) to verify age-specific changes of cervical cancer incidence rates subsequent to screening. They explained the decreasing linear trends in the age groups 30-64 years as a result of screening efficacy. The horizontal or even increasing trends in women less than 30 years old were interpreted as a possible result of exposure to risk factors linked with sexual behaviour. The explanation concerning the younger women is obviously a generational effect. The age* drift model shows a better fit than the alternative with age + drift. However, the assumption of a continuous regular change within all of the age groups looks implausible. The distorted aspect of the corresponding curve of age-effects (fig 3.3a) further enhances the impression this model is an artefact.

From Table 2, we learn that the addition of cohort, given age and drift, yields a more substantial reduction of the deviance than the inclusion of period or the interaction term. Of course, neither the AC, AP nor A*d cannot be distinguished using classical model comparison. Therefore, we can use the less formal Akaike's Information Criterion (AIC = deviance-2df)

for the judgment on the adequacy of the models described in table 2 at step 3 (30, 31). The AIC was lowest for the age-cohort (AIC = -5.0), followed by the age*drift (AIC = 54.8) and age-period (AIC = 76.4). Also in Figure 3, we observe larger deviations from linearity in the C- than in the P-effects. Plausible biological explanations can be given in terms of changing exposure of generations to etiological factors. Very strong associations have been observed between infection with sexually transmittable oncogenic types of human papillomavirus (HPV) and cervical cancer (32-35). Their etiologic role in carcinogenesis is nowadays generally accepted. Remarkable in this context is the increased mortality due to cervical cancer among the cohorts C1895 and C1920, that include women who were in their twenties during respectively the First and Second World War (36). Beral (23) illustrated the relation between the increased incidence of sexually transmitted diseases among women that were young during the period 1940-45 in England and Wales and the subsequent enhanced risk of mortality by cervical cancer. The increase of mortality for women, born after 1935, is ascribed to the higher promiscuity and, consequently, more intense HPV-transmission since the 1960s (25, 37, 38). The increase of mortality in younger cohorts seems in Belgium more limited than in some other West-European countries such as Great-Britain and Ireland (25). The recently increased prevalence of other less important risk factors, for instance smoking (39) and oral anti-conception (40-42), can have contributed for a minor extent to the enhanced cervical cancer mortality rate (25). The First World War effect is less clear. However, it must be stated that cohort effects, due to a short time increase of risk and overlap between adjacent cohorts, are smoothed somehow (6).

The AC-model (3c) turns out to be the most adequate alternative at step 3 (see Table 2). Non-linear P-elements further contribute as significant constituents of a full APC-model. The deviations of period effects from the straight line are limited in magnitude. Nonetheless, the existence of strong non-linear cohort effects, explainable as caused by changes in exposure to etiologic agents, and the lack of distinct period effects, do not exclude a favorable impact from secondary prevention. First of all, the evidence provided by numerous case-control, cohort and ecological studies is too overwhelming to deny protective effects resulting from screening (43, 44). Even in mortality data, arguments can be found to support the favorable effect of preventive activities. At least a part of the linear drift might be attributed to prevention. In the epoch that screening was not yet performed at large scale, access to health care increased and so the opportunity for diagnosis of cervical cancer at early treatable stages (45, 46). The lack of an obvious P-effect must not be interpreted as evidence for

lack of efficacy of the Pap smear campaigns. Attendance to screening differs significantly according to age (3, 26, 27). As a consequence, no pure P-effects can be distinguished anymore, since these imply uniform changes affecting all age groups in the same period, in the same direction and approximately the same amount. Consequently, protective actions with heterogeneous coverage in the population varying with age necessarily yield a cohort effect. It is possible that the limited recent increase of the cohort effect might be the net result of increased risk counterbalanced by screening.

Over-dispersion

The lack of fit of the final APC-model indicates heterogeneity in the mortality rates beyond Poisson variation. This could be due to specific spatial intra-country patterns or unmeasured covariates (16). Over-dispersion might simply be due to lack of quality of the data. Cervical cancer mortality is in this aspect an exceptionally difficult issue because of important death cause certification problems. In Belgium the proportion of not otherwise specified uterine cancer (ICD-9 = 179) among all deaths from uterus cancer varied between 54.9% and 33.7%. In a recent trend study of cervical cancer mortality over the last three decades in the Flemish Region (North Belgium), we focused on this particular certification problem (47). The adjustment for not specified cancer of the uterus made the linear downward trend for cervical cancer more steeply and smoothed some abrupt temporal changes principally due to 8th ICD codification (47). Nevertheless, the strong cohort effects, also observed in the Belgian data set, were maintained.

Hysterectomy

Varying hysterectomy rates, for neoplastic or other gynaecological indications, further complicates the story (48, 49). The prevalence and incidence of hysterectomy in Flanders and the rest of Belgium over the last 15 years were described earlier (50). Only recently, reliable age-specific data for Belgium became available that allow precise correction of population denominators corresponding to the women-years with a cervix uteri. Consequently, the possible impact of hysterectomy on cervical cancer mortality cannot be assessed. As described in studies from the USA (45), Canada (48, 51) and the Netherlands (52), we can expect that also in Belgium the increasing hysterectomy rates are not substantial enough to explain the observed decrease in mortality form cervix cancer.

Identification problem

The dependence between age, period and cohort (equation 1) is the root of the well-known problem of making the linear effect unidentifiable. Hence, considering isolated mortality data, derived from vital statistics, the drift factor can be attributed neither to cohort neither to period, or a determinable mixture of both.

Several attempts of solutions have been proposed (1, 2, 11, 53-55). Artificial constraints can be imposed on the parameter sets, allowing linear change being assigned to cohort- or period according to the relative magnitude of the non-linear deviations (11, 53); if individual records are available, age-period cells can be subdivided as belonging to two distinct non overlapping cohorts, which breaks the linear dependency (54) or the age-effects can be considered as fixed and calculable from multiple registers (56). All these methods lack a straightforward biological basis and generalisability (1, 2).

A thorough discussion of this question is beyond the scope of this study. Together with Clayton (2), we believe the problem of parameter estimation should be left, as it is, unresolved. The attention should be targeted to the derivation of irregular period and or cohort-effects beyond the regular continuous change over time.

Forecasting future trends

Extrapolation of π, δ and κ-values allows to some extent the prediction of future trends (57-59). The theoretical influences derived from Poisson-models should be corrected judiciously within realistic ranges for the main modifying factors: prevalence of HPV-infection, the participation to and quality of preventive activities. The most recent cohort values provide important clues for projections into the future, but it must be taken in mind, as mentioned before, that these estimations are unstable (57). The investigation of future trends of cervical cancer mortality in Belgium, adjusted for death-cause certification and hysterectomy, is the object of further research.

Conclusions

The impossibility to attribute the drift to respectively cohort- or period-related effects, because of their linear dependency, implies a serious prob-

lem in displaying and estimating the model parameters (2). Nevertheless, APC-modelling protects against over-interpretation of trends based on standardised rates or simple graphical presentation of age-specific curves. The existence of an important linear decrease of 9% per 5-year period or cohort and the absence of non-linear period effects indicate that Pap smear screening alone was not responsible for the decline. Neither does it provide evidence that screening did not imply any protection. Cytological detection and removal of precursor lesions probably might have prolonged the effect, already initiated by improved access to health care, allowing down-staging and consequent better survival of cervix cancer.

Identifiable, non-linear cohort effects further contribute substantially to the evolution of the mortality rate. The increased risk observed for the youngest cohorts prompts to supplementary caution from health authorities and warns against precocious relaxing of screening campaigns.

APC models of mortality data are essentially descriptive and the explanations given are partially speculative. Other reliable information systems linking screening histories, risk profiles, cancer diagnosis and death certification are needed to provide more causal evidence.

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