

## TREND OF CERVICAL CANCER MORTALITY IN BELGIUM (1954–1994): TENTATIVE SOLUTION FOR THE CERTIFICATION PROBLEM OF UNSPECIFIED UTERINE CANCER

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**We investigated the evolution of mortality from cervical cancer in Belgium between 1954 and 1994 in terms of absolute number of deaths, and standardised and age-specific mortality rates. Changes over generations were summarised using the standardised cohort mortality ratio. Trend studies of cervical cancer mortality were hampered by certification problems. The number of deaths due to cancer of the uterine cervix is not known exactly since a substantial proportion of death causes are coded as cancer of the uterus without specifying the anatomic site: cervix or corpus uteri. This inaccuracy in codification has been corrected using distribution tables derived from countries where this certification problem is minimal. Trends in mortality from certified and corrected cervical cancers were compared. The corrected age-standardised mortality rate decreased continuously over the last 4 decades, from over 14 to 5 per 100,000 woman-years (slope  $-0.26/100,000$  woman-years, 95% CI  $-0.28$  to  $-0.24$ ). Its slope is 3.1 times (95% CI 2.9–3.5) more important than for the rate of mortality from certified cervical cancer. In addition to the almost linear decrease, substantial nonlinear cohort influences were observed in certified and corrected mortality rates. The tendency of increasing mortality in women born after 1935 required particular attention. Nevertheless, the slope of the corrected recent cohort effect remained limited in Belgium, probably as a consequence of screening.**

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**Key words:** cervical cancer; death certificate; mortality; trend analysis

In an earlier study covering the period 1954–1989, it was shown that the age-standardised mortality from certified cervical cancer was decreasing almost linearly.<sup>1</sup> Behind this monotonous variation, a complex of influences is hidden, which requires the study of age-specific rates as a function of birth cohort and calendar time. Recognising birth-cohort effects, reflecting the historic changes in exposure to etiologic factors, is indispensable in distinguishing screening effects. Special attention must be given to the quality of death certification and coding, to avoid consideration of spurious trends.<sup>2,3</sup> A methodology already used to study mortality from uterine cancer in the Flemish region (northern Belgium) was further refined and applied to the whole of Belgium.<sup>4,5</sup> We therefore used a number of descriptive and graphic statistical techniques based on the 3 inherent components of vital statistics: age, calendar time at death and epoch of birth or cohort.

We do not consider here the simultaneous estimation of age-cohort-period effects by log-linear Poisson models.<sup>6,7</sup> The spatial variation of mortality within Belgium is not examined either. These are the subjects of ongoing studies.

### MATERIAL AND METHODS

#### Number of deaths

The annual number of deaths from uterine cancer, aggregated over 5-year age groups, in women resident in Belgium between 1954 and 1994 was provided by 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). Corpus uteri cancer was coded as 172 (ICD-6 and 7) or 182 (ICD-9). Not otherwise specified (NOS) uterine cancer

was coded as 174 (ICD-6 and -7) or 179 (ICD-9). The 8th edition of ICD has caused problems since cancer of the corpus uteri and NOS uterine cancer were classified together under code 182. Both could still be distinguished with the fourth digit (182.0 for corpus cancer, 182.9 for NOS uterine cancer), but these latter subcodes were applied inconsistently.

#### Population data

Data concerning the female population over the same period were provided by the National Institute of Statistics as well. The total number of women resident in Belgium increased from 4.9 million in 1954 to 5.2 million in 1994.

#### Mortality rates

We successively computed trends of the number of deaths for each anatomic subsite and the age-standardised mortality rates from cervical cancer, expressed as the number of deaths per 100,000 woman-years. The European standard population was used as reference.<sup>8</sup> We calculated 95% confidence intervals (CIs) on the basis of a Poisson distribution.<sup>9,10</sup>

Age-specific rates were calculated over 5-year periods to stabilise random variation.<sup>11</sup> We defined 8 periods beginning in 1955, to allow comparisons with previous publications.<sup>1,12</sup> Cohort-specific mortality rates were studied as well. Cohorts included women born in the same period and, hence, ageing together and exposed to similar risks. Since age groups and periods span 5 years, the corresponding birth cohorts are necessarily 10 years wide. Successive cohorts overlap partly and are indicated by their central year.<sup>11–13</sup>

#### Cohort effects

The cohort effect, or standardised cohort mortality ratio, represents the relative risk in a certain cohort of dying from cervical cancer compared to the mean mortality rate of all generations together. This cohort effect is calculated by an indirect standardisation method.<sup>14,15</sup> It consists of the ratio of the number of observed deaths in a given cohort,  $k$ , over the number of expected deaths if the average age-specific mortality rates are applied to the respective age segments of the population in cohort  $k$ .

#### Redistribution of NOS uterine cancers

Finally, we present a tentative solution for the classification problem of NOS uterine cancers (ICD-6 and -7 = 174, ICD-8 =

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TABLE I—PROPORTION OF UTERINE CANCERS OF CERVICAL ORIGIN AS DERIVED FROM CERTAIN EUROPEAN COUNTRIES WITH LOW PERCENTAGES OF NOS CANCER

Age group	Norway, 1955–1969		Finland, the Netherlands, Norway, Scotland, 1970–1994					
	Proportion	(95% CI)	1970–1979		1980–1989		1990–1994	
			Proportion	95% CI	Proportion	95% CI	Proportion	95% CI
≤ 30	0.990	0.972–1.000	0.950	0.921–0.979	0.961	0.940–0.982	0.955	0.923–0.988
35–39	0.979	0.958–0.999	0.940	0.911–0.970	0.962	0.942–0.982	0.967	0.941–0.993
40–44	0.919	0.885–0.953	0.893	0.864–0.922	0.898	0.869–0.928	0.870	0.825–0.916
45–49	0.877	0.842–0.911	0.850	0.826–0.874	0.792	0.759–0.824	0.828	0.783–0.874
50–54	0.803	0.761–0.844	0.765	0.742–0.788	0.687	0.654–0.721	0.717	0.666–0.768
55–59	0.641	0.597–0.686	0.655	0.632–0.677	0.594	0.565–0.623	0.529	0.480–0.577
60–64	0.559	0.513–0.604	0.589	0.567–0.612	0.569	0.545–0.593	0.495	0.453–0.536
65–69	0.544	0.494–0.594	0.516	0.494–0.538	0.531	0.509–0.554	0.459	0.425–0.493
70–74	0.576	0.525–0.627	0.493	0.470–0.515	0.481	0.459–0.503	0.409	0.378–0.440
75–79	0.530	0.466–0.594	0.463	0.438–0.488	0.435	0.413–0.458	0.455	0.423–0.488
80–84	0.503	0.423–0.584	0.469	0.439–0.499	0.388	0.363–0.413	0.409	0.375–0.443
≥85	0.550	0.424–0.676	0.454	0.416–0.492	0.367	0.340–0.394	0.361	0.328–0.394

182 (partly), ICD-9 = 179). We therefore constructed a repartition table with the age-specific proportion of uterine cancer mortality that is probably of cervical origin. Jensen *et al.*<sup>4</sup> were the first to apply such a method in a study on cancer-related mortality in the 11 member states of the European Community in 1980. The age-specific repartition of, respectively, cervical and corpus uteri cancer was derived from countries with a low proportion of NOS uterine cancer mortality. However, Jensen *et al.*<sup>4</sup> did not specify the involved countries and did not present standard errors. Therefore, we downloaded files from the WHO Mortality Database (<http://www.who.int/whosis/mort>), selected data concerning uterine cancer from European countries and recoded causes of death into the codes of the ICD-9. Subsequently, we identified countries with a percentage of NOS uterine cancer mortality lower than or equal to 11% over at least 2 recent decades. In the period 1970–1994, Finland, the Netherlands, Norway and Scotland matched these criteria. Before that period, a low proportion of NOS uterine cancer was observed only in Norway. We excluded Iceland and Luxembourg because of their small population sizes. The age-specific proportion of cervical cancer among uterine cancers with known origin did not vary substantially over time in the 4 selected countries, but since this variation was significant, we constructed different period-specific repartition tables (Table I). Using Table I, we redistributed the sum of the number of all uterine cancer deaths within the corresponding age and period groups in Belgium, which yielded the corrected number of deaths from cervical cancer. We calculated 95% CIs for the corrected cervical cancer mortality using the delta method for a product of 2 parameters, being the number of deaths from uterine cancer, following a Poisson distribution, and the proportion of uterine deaths originating from the cervix uteri, following a binomial distribution.<sup>16</sup>

The trends of the certified and corrected cervical cancer mortality rates were subsequently compared. To facilitate visual comparison, we opposed systematically both sets of mortality indicators in double plots using identical y axes.

## RESULTS

The proportion of uterine cancers without specification among all cancers of the uterus, shown in Figure 1, was highest during the period that the ICD-8 classification was applied (53.0%). This was, respectively, 46.1% and 39.3% for ICD-6/-7 and ICD-9.

The column diagram in Figure 2a shows the absolute number of deaths due to cancer of the cervix, corpus and NOS uterus that occurred in 5-year periods. The number of deaths from certified cervical cancer fluctuated between 1,559 and 950. The total number of deaths due to cancer of the cervix + NOS uterus varied between 3,832 and 2,151. The total number of uterine cancer deaths ranged from 5,210 to 2,882. By redistributing deaths from NOS uterine cancer into cervix- and corpus carcinoma, we obtained the corrected or probable number of deaths due to the 2

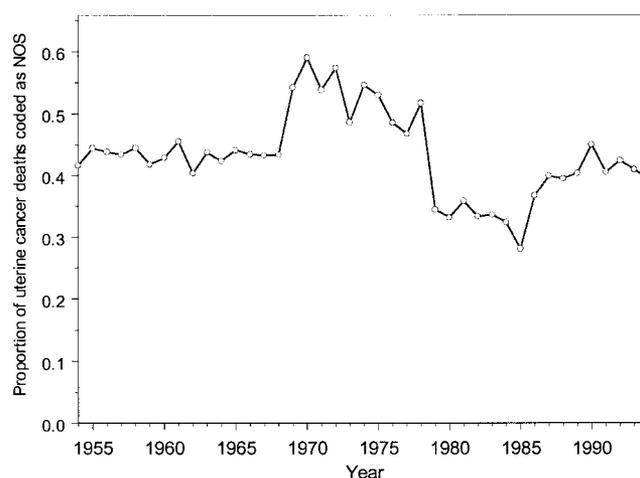
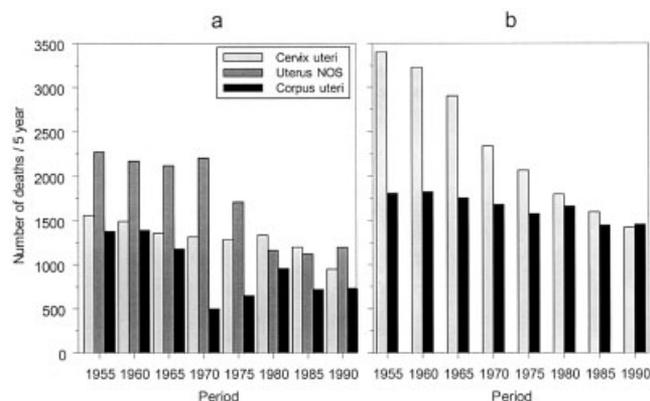


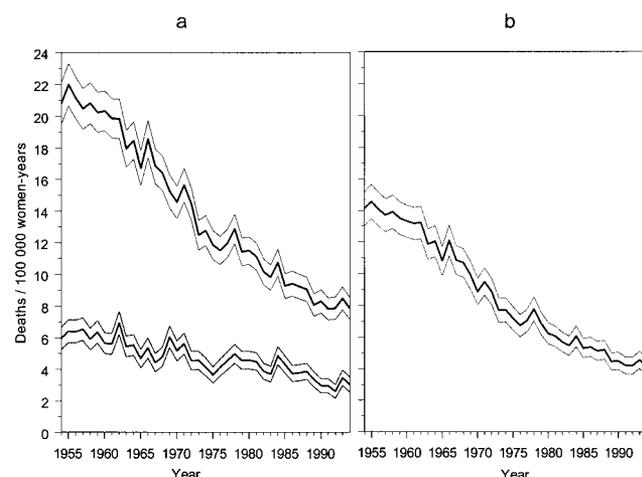
FIGURE 1—Proportion of uterine cancer deaths for which the topographic origin is not specified, Belgium, 1954–1994.

respective cancers (Fig. 2b). The corrected number of deaths from cervical cancer in Belgium varied between 3,401 (in the period 1955–1959) and 1,423 (in the period 1990–1994). The trend was decreasing with on average 680 deaths per year in the 1950s and 285 deaths in the 1990s. In 1994, 286 women probably died from cancer of the cervix uteri and 299 from cancer of the corpus uteri.

Figure 3a displays the trend of the age-standardised mortality rate for certified cervical cancer and for all uterine cancers combined. Both curves show an almost linear decline over time, with slopes of, respectively,  $-0.08/100,000$  woman-years (95% CI  $-0.10$  to  $-0.07$ ) for cervical cancer and  $-0.38$  (95% CI  $-0.41$  to  $-0.36$ ) for uterine cancer. The standardised rate for cervical cancer decreased from 6.3 (95% CI 5.6–7.0) in the 1950s to 3.0 (95% CI 2.6–3.5) per 100,000 in the 1990s, a reduction of 52.4%. The rate for all uterine cancer deaths dropped over the same period from 20.9 (95% CI 19.6–22.2) to 8.1 (95% CI 7.4–8.8) per 100,000, a decline of 61.3%. The right panel in Figure 3 shows the evolution of the age-standardised mortality rate for corrected cervical cancer. The linear regression line fits better to the corrected rate ( $R^2 = 0.96$ ) than to the rate of certified cervical cancer mortality ( $R^2 = 0.80$ ). The slope of the corrected rate is  $-0.29/100,000$  (95% CI  $-0.30$  to  $-0.26$ ). This corresponds with a drop of 67.5% over a time span of 41 years. However, when only the last 5 years are considered, the standardised corrected rate remains stable around 4.9/100,000 woman-years, with a slope very close to 0 ( $b = 0.02$ , 95% CI  $-0.22$ –0.18).



**FIGURE 2** – (a) Number of deaths occurring in 5-year periods due to cancer originating from the cervix uteri, the corpus uteri or NOS uterus in Belgium between 1955 and 1994, as registered by the National Institute of Statistics. (b) Probable number of deaths by cancer of the cervix and corpus uteri, calculated by repartition of NOS uterine cancers. Periods are indicated by the first year of the interval.



**FIGURE 3** – (a) Trend of the standardised mortality rate for certified cervical cancer (lower curves) and for total uterine cancer (upper curves), Belgium, 1954–1994, European reference population. (b) Standardised mortality rate for corrected cervical cancer. Bold lines represent the standardised rate; thin lines on both sides correspond to the respective 95% CIs.

The linear age-specific trends are shown in Table II. A model with separate slopes for each age group (containing the interaction age  $\times$  time) fitted significantly better than a model with one common slope. The slopes for noncorrected cervical cancer were most pronounced in the age group 40–69. The drop in the rate was insignificant for women in age groups <40 and >80 years. The decrease of the corrected rates was systematically steeper for all age groups, and the intensity of the negative slopes increased with age.

The change in cervical cancer mortality by age is plotted for distinct cohorts in Figure 4a. Intervening curves are omitted for graphic clearness. Mortality rose with age up to a maximum and then dropped slightly. This maximum was reached at subsequently higher ages in older cohorts. There is considerable overlap between successive cohorts. Only from cohort C1920 up to C1935 there was a continuous fall in age-specific mortality. From C1940 mortality did not further decline. Moreover, a discrete tendency of increase could be suspected for the youngest cohorts. Corrected mortality rates were lifted substantially in the older cohorts, which

are clearly separated (Fig. 4b). In the central cohorts, containing 8 observations, a peak was reached around the age of 50 years. The corrected rate did not level off thereafter but remained high at a plateau.

The evolution of mortality as a function of the birth cohort is summarised by the cohort effect (Fig. 5a). We observed discrete peaks of the mortality risk for the cohorts C1885, C1895 and C1920 and a progressive decrease for the cohorts C1920–C1935 followed by a continuous rise. The tendency over the last 3 cohorts was very unstable because it was based only on younger age ranges, where mortality rates are low. This is illustrated by the very wide CIs beyond C1960 in Figure 5.

The corrected cohort effect in the right panel of Figure 5 displays again remarkable differences. The older cohorts expressed a relatively higher than average risk, which declined more markedly in subsequent cohorts. The peak around C1920 was still obvious, but the smaller peaks in women born at the end of the nineteenth century had disappeared. The increasing trend observed in the younger cohorts is less obvious than in the uncorrected cohort effect, but it is still clear that beyond C1935 the falling trend stopped.

## DISCUSSION

Trend studies of cervical cancer mortality are complex since several factors interfere simultaneously: quality of vital statistics, changing exposure to risk factors and protective effects from screening and treatment. The frequency of total hysterectomy is an additional complicating element that influences the denominator (the number of woman-years at risk).<sup>17</sup> The prevalence and incidence of hysterectomy in Belgium was described earlier.<sup>18</sup> The other influences are discussed below.

### Quality of mortality statistics

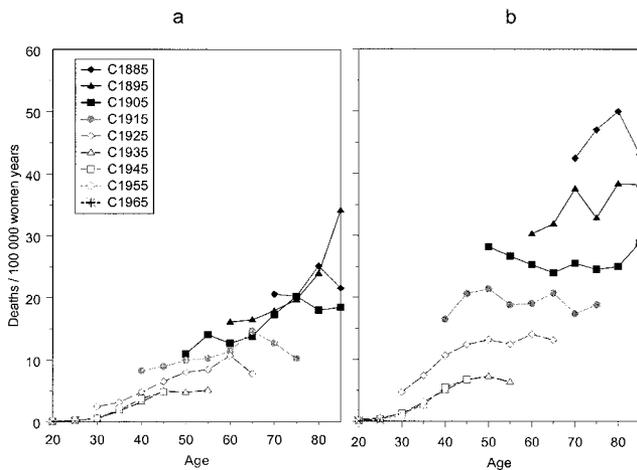
The inaccuracy in the exact determination of the anatomic origin of uterine cancer is essentially due to insufficient training of physicians completing death certificates. Administrators, in charge of codification, could contact certifying doctors for additional information, but unfortunately this is rarely done (H. Van Oyen, personal communication, 2002). This classification problem seriously complicates trend studies. The question of NOS uterine cancer mortality is addressed in different ways throughout the literature. The Centre for Operational Research (Scientific Institute of Public Health, Brussels), which produces regular overviews of cause-specific mortality in Belgium, presents the sum of mortality due to cancer of the cervix and NOS uterus.<sup>19</sup> Vyslouzilova *et al.*<sup>1</sup> included only certified cervical cancer deaths coded ICD-6/7 = 171 and ICD-8/9 = 180. In atlases of cancer mortality in Europe, certified cervical cancer and total uterine cancer were mapped separately.<sup>20,21</sup> Death from uterine cancer between 15 and 54 years is a component of “avoidable death,” which is used as a measure of the effectiveness of preventive and curative health care.<sup>21–23</sup> La Vecchia *et al.*<sup>24</sup> studied only trends of mortality due to all uterine cancers combined. Levi *et al.*<sup>25</sup> considered total uterine cancer mortality trends limited to the age group 20–44 years, where the majority of deaths are due to cervical cancer. Devesa *et al.*<sup>26</sup> combined NOS uterine cancer with corpus cancer deaths, to analyse mortality trends for endometrial cancer and he studied certified cervical cancer mortality as such. Swerdlow *et al.*<sup>27</sup> followed the same approach, arguing that corpus cancer and NOS uterine cancer mortality show similar age patterns. In the last overview of cancer mortality in the European Union in 1995, cancer deaths coded as unspecified were treated as random and reallocated to cervical or corpus uteri cancer according to the age-specific proportions of death causes certified as ICD-9 180 or 182.<sup>28</sup>

The shape and direction of changes in cervical cancer mortality should not be biased by studying only deaths certified as such, if the proportion of cervical cancers coded as NOS uterine cancer was constant over time. In Belgium, however, the proportion of NOS uterine cancer deaths reattributed to cervical cancer varied

**TABLE II** – AGE-SPECIFIC SLOPES (CHANGE IN NUMBER OF DEATHS/100 WOMAN-YEARS) AND 95% CIs OF THE LINEAR TREND FOR MORTALITY FROM CERTIFIED VS. CORRECTED CERVICAL CANCER IN BELGIUM BETWEEN 1954 AND 1994

Age group	Certified cervical cancer		Corrected cervical cancer	
	Slope	95% CI	Slope	95% CI
20–29	–0.002	–0.009 to –0.004	–0.017	–0.030 to –0.003
30–39	–0.031	–0.068 to –0.005	–0.123	–0.212 to –0.034
40–49	–0.161	–0.225 to –0.010	–0.464	–0.617 to –0.312
50–59	–0.233	–0.296 to –0.170	–0.676	–0.759 to –0.594
60–69	–0.221	–0.334 to –0.109	–0.604	–0.698 to –0.509
70–79	–0.185	–0.322 to –0.047	–0.860	–1.022 to –0.699
80+	–0.039	–0.319 to –0.241	–0.927	–1.101 to –0.753
	$p = 0.001^1$		$p = 0.000^1$	

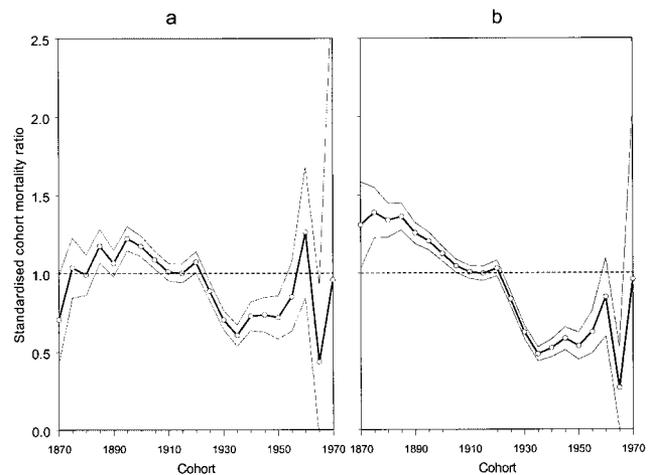
<sup>1</sup>Test for difference between models with common and age-specific linear time trends.



**FIGURE 4** – (a) Cohort-specific mortality rate by cervical cancer as a function of age, Belgium, 1955–1994. For graphic reasons, intervening curves are omitted. Age groups are indicated by the first year of the 5-year interval; the cohort is labelled with the central year of the corresponding 10-year interval. (b) Corrected cohort-specific mortality rate by age group.

over time. It was on average 80.2% when ICD-6/7 codes were used and 54.2% when ICD-9 codes were applied. In addition, the percentage of NOS uterine cancer deaths changed clearly according to the ICD code (Fig. 1), and there exist important regional differences. The percentage of NOS deaths in 1994 was only 26.4% in the Flemish region, 33.8% in the capital of Brussels and 60.3% in the Walloon region.<sup>29</sup> Belgium currently ranks in the intermediate group of west European countries. Around 1995, the proportion of NOS deaths was lower than 10% in Norway (4.8%), Finland (7.7%) and Scotland (8.9%); in certain south European countries, this percentage was quite high: Greece (60.4%), France (59.4%), Italy (65.4%).<sup>25</sup>

Correction of the classification problem was, at least for Belgium, necessary to appreciate real trends. Systematic attribution of NOS cancers to either cervical or corpus cancer should yield substantial over- and underestimation, respectively. Allocation of NOS deaths according to the mutual proportion of cervical and corpus cancers, as proposed by Bray *et al.*,<sup>28</sup> would have led to an implausible increase of cervical cancer mortality in the ICD-8 period. Because of lack of reliable cancer incidence and survival data for Belgium, the redistribution of NOS uterine cancers, based on a documented repartition table, is currently the only available method to rectify somehow the misclassification in mortality statistics. Of course, we must assume that the repartition is representative of Belgium. In Finland, the Netherlands and parts of Scotland, well-organised screening at the population level has been done for at least 2 decades.<sup>30–33</sup> These programmes possibly have



**FIGURE 5** – (a) Standardised cohort mortality ratio: relative risk of mortality from cervical cancer for a given cohort with respect to the average mortality of all cohorts, Belgium, 1955–1994. (b) Corrected cohort mortality ratio. Bold lines, estimate of the cohort effect; thin lines, corresponding 95% CIs.

had more impact than in Belgium, where screening was essentially opportunistic.<sup>34</sup>

By the correction, we probably obtained a more realistic picture of the evolution of cervical cancer mortality over time and over generations. The declining trends became more pronounced, some artefacts were smoothed away and the magnitude of the cohort effects could be estimated more exactly. In a later stage, we will verify the robustness and generalisability of alternative methods for reallocation of deaths by NOS uterine cancer in European countries where the possibility of data linkage exists to adjust mortality statistics from reliable cancer registries.<sup>35</sup>

#### Changing exposure to risk factors

The sexually transmissible human papillomavirus (HPV) is the main etiologic factor for cervical cancer.<sup>36–38</sup> Changes in sexual behaviour of distinct generations are reflected in cohort-specific mortality rates. Beral<sup>14</sup> illustrated the association between enhanced incidence of sexually transmitted diseases among young women during the Second World War and the subsequent increase of mortality by cervical cancer in the same generation in England and Wales. In Belgium as well, an increased risk is noticed for the cohorts C1920 and, to a lesser extent, C1895. It concerns women who were between 15 and 30 years old during the world wars. From C1920 until C1935, we observed a continuous decline in cervical cancer mortality. Since C1940 (this concerns generations of women who reached the age of 20 years after 1960), mortality has been rising again or at least not further declining. This is probably a result of changes in sexual behaviour since the 1960s,

yielding enhanced transmission of HPV. The increased frequency of smoking and oral contraception, both risk factors for cervical cancer, may have contributed to the rise of the cohort effect.<sup>33,39</sup> These abrupt generational effects are not disturbed by the inaccuracy in cause-of-death certification. However, the continuous marked decrease in cohorts born between the end of the nineteenth century up to 1935, only temporarily interrupted for women born around 1920, was for a major part masked in the noncorrected data. Presumably, other etiologic and poorly understood (co-) factors, linked to improved social conditions and access to health care, may explain this historic phenomenon.<sup>40</sup>

#### Screening effects

The declining trend of cervical cancer mortality was initiated before Pap smear screening became general practice. The progressive achievement of high coverage among the target population<sup>18,41</sup> did not bring about a more pronounced decrease. Certain epidemiologists deduce from this fact that cytologic screening was hardly effective<sup>42-44</sup> and certainly did not have the same impact as in some Nordic countries, such as Finland.<sup>43,45</sup>

Recent rises in cervical cancer mortality in younger women were first noted in England and Wales<sup>46-50</sup> and described later in several other countries, even in Finland.<sup>12,30,51-56</sup> The increase in England and Wales revealed poor organisation during the 1970s and 1980s, characterised by low population coverage combined with overscreening in low-risk groups and moderate technical quality of screening process parameters.<sup>16,57</sup> This situation prompted health authorities to reorganise screening by installing a nationwide call-recall system, incentives for general practitioners and stringent quality-assurance procedures.<sup>58</sup> These measures resulted quickly in a substantial decline of mortality in all age groups in the target population.<sup>59-62</sup>

In Belgium, the rise of the cohort effect since C1935-40 was not as steep as in England and Wales. It is possible that the limited increase is the net result of increased risk counterbalanced to a certain extent by screening. Quality of screening, reaching a steadily growing part of the female population, was not so poor as in England in the 1970s and 1980s. Otherwise, the substantial drop in mortality observed in the 1990s in England did not occur in

Belgium because no serious efforts to organise screening more efficiently were undertaken.<sup>34</sup>

Several influences might have contributed to varying degrees to changes in cervical cancer mortality. Formal statistical models can assess age, period and cohort effects in routinely collected demographic databases. The impact of these influences can be plausibly explained in qualitative terms from historic facts, but it is hard to quantify. The role of screening parameters concerning population compliance and quality of screening, if available, can be included as explanatory parameters in statistical models.<sup>63,64</sup> Unfortunately, in Belgium and several other European countries, historic background data are lacking.

Screening coverage in Belgium, defined as the proportion of women between 25 and 64 years having had a Pap smear taken less than 3 years ago, was estimated to be 78% in 1996.<sup>34,65</sup> Reaching currently unscreened groups, which are concentrated essentially in lower socioeconomic categories,<sup>18</sup> is an important task for health professionals and authorities. It is probably this category that determines the increasing slope in recent age-specific mortality trends. Quality assurance of the whole screening process should result in further reduction of mortality in participating women.

In Belgium, about 3.5 million euros are spent annually in opportunistic cytologic screening, but there is no possibility to assess its impact.<sup>34,66</sup> The Belgian Parliament has launched an appeal to the federal government to organise early detection of cervical cancer more efficiently and to install formal registration of screening parameters.<sup>67</sup> In this framework, analysis of real mortality trends should constitute the final piece in the comprehensive evaluation of cervical cancer screening.

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#### REFERENCES

- Vyslouzilova S, Arbyn M, Van Oyen H, Drieskens S, Quataert P. Cervical cancer mortality in Belgium, 1955-1989. A descriptive study. *Eur J Cancer* 1997;33:1841-5.
- Kelson M, Farebrother M. The effect of inaccuracies in death certification and coding practices in the European Economic Community (EEC) on international cancer mortality statistics. *Int J Epidemiol* 1987;16:411-4.
- Percy C, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981;71:242-50.
- Jenssen OM, Estève J, Moller H, Renard H. Cancer in the European Community and its member states. *Eur J Cancer* 1990;26:1167-256.
- Arbyn M. Trend analysis of mortality from cervical in the Flemish region (1969-1997) [in Dutch]. In: Aelvoet W, Cloots H, eds. *Gezondheidsindicatoren 1998*. Brussels: Ministerie van de Vlaamse Gemeenschap, 2000. 98-114.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. *Stat Med* 1987;6:449-67.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. *Stat Med* 1987;6:469-81.
- Waterhouse JAH, Muir CS, Shanmugaratnam K, eds. *Cancer incidence in five continents*. Lyon: IARC, 1976.
- Doll R, Smith PG. Comparison between registries: age-standardised rates. In: Waterhouse JAH, Muir CS, Shanmugaratnam K, Powell J, eds. *Cancer incidence in five continents*. vol. 4. Lyon: IARC, 1982. 671-5.
- Estève J, Benhamou E, Raymond L. Statistical methods in cancer research. *Descriptive epidemiology*. Vol. 4. Lyon: IARC, 1994.
- Moolgavkar SH. Analysis of vital statistics data. In: Rothman KJ, Greenland S, eds. *Modern epidemiology*. Philadelphia: Lippincott-Raven, 1998. 481-97.
- Arbyn M, Van Oyen H, Sartor F, Tibaldi F, Molenberghs G. Description of the influence of age, period and cohort effects on cervical cancer mortality by log linear Poisson models (Belgium, 1955-94). *Arch Public Health* 2002;60:73-100.
- Kupper LL, Janis JM, Karmous A, Greenberg BG. Statistical age-period cohort analysis: a review and critique. *J Chronic Dis* 1985;38:811-30.
- Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974;1:1037-40.
- Osmond C, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. *Stat Med* 1982;1:245-59.
- Ebeling K, Nischan P. Organization and results of cervical cancer screening in the German Democratic Republic. *IARC Sci Publ* 76. Lyon: IARC, 1986. 251-66.
- Miller AB, Visentin T, Howe GR. The effect of hysterectomies and screening on mortality from cancer of the uterus in Canada. *Int J Cancer* 1981;27:651-7.
- Arbyn M, Quataert P, Van Hal G, Van Oyen H. Cervical cancer screening in the Flemish region (Belgium): measurement of the attendance rate by telephone interview. *Eur J Cancer Prev* 1997;6:389-98.
- Centrum voor Operationeel Onderzoek en Volksgezondheid. Mortality and cause-specific mortality in the Flemish community, 1989-91 [in Dutch]. Brussels: Ministerie Vlaamse Gemeenschap, Administratie van Volksgezondheid van de Vlaamse Gemeenschap, Wetenschappelijk Instituut voor Volksgezondheid, 1997.
- Smans M, Muir CS, Boyle P. Atlas of cancer mortality in the European Economic Community. Lyon: IARC, 1992.
- Holland WW, EC Working Group on Health Services and Avoidable Deaths. *European Community atlas of "avoidable deaths"*. Commission of the European Communities. Oxford: Oxford University Press, 1997.
- Rutstein D, Berenberg W, Chalmers R. Measuring the quality of medical care. *N Engl J Med* 1976;297:582-8.
- Lagasse R, Humblet PC, Hooff P, Van de Voorde H, Wollast E. Atlas

- of avoidable death in Belgium, 1980–1984. *Arch Public Health* 1992; 50:1–97.
24. La Vecchia C, Lucchini F, Negri E, Boyle P, Maisonneuve P, Levi F. Trends of cancer mortality in Europe, 1955–1989. III: Breast and genital sites. *Eur J Cancer* 1992;28A:927–98.
  25. Levi F, Lucchini F, Negri E, Franceschi S, La Vecchia C. Cervical cancer mortality among young women in Europe: patterns and trends. *Eur J Cancer* 2000;36:2266–71.
  26. Devesa SS, Silverman DT, Young JL, Pollack ES, Brown CC, Horm JW, Percy CL, Myers MH, McKay FW, Fraumeni JF. Cancer incidence and mortality trends among whites in the United States, 1947–84. *J Natl Cancer Inst* 1987;79:701–45.
  27. Swerdlow A, dos Santos LR, Doll R. Cancer incidence and mortality in England and Wales: trends and risk factors. Oxford: Oxford University Press, 2001.
  28. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 2002;38:99–166.
  29. Arbyn M, Van Oyen H. Secondary prevention of cervical cancer in Flanders: facts and propositions for a structural approach. Memorandum addressed to the Minister of Welfare, Public Health and Equal Chances and the Administration of Health Care of the Flemish Community [in Dutch]. WIV/EPI-series 20. Brussels: Scientific Institute of Public Health, 1999.
  30. Macgregor JE, Campbell MK, Mann EM, Swanson KY. Screening for cervical intraepithelial neoplasia in northeast Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. *BMJ* 1994;308:1407–11.
  31. Anttila A, Nieminen P. Cervical cancer screening programme in Finland. *Eur J Cancer* 2001;36:2209–14.
  32. van Ballegooijen M, Hermens R. Cervical cancer screening in the Netherlands. *Eur J Cancer* 2000;36:2244–6.
  33. Szarewski A, Cuzick J. Smoking and cervical neoplasia: a review of the evidence. *J Epidemiol Biostat* 1998;3:229–56.
  34. Arbyn M, Van Oyen H. Cervical cancer screening in Belgium. *Eur J Cancer* 2000;36:2191–7.
  35. Zakej MP, Kirn VP, Skrlec F, Selb J. Can we rely on cancer mortality data? Checking the validity of cervical cancer mortality data for Slovenia. *Radiol Oncol* 2002;35:243–7.
  36. zur Hausen H. Molecular pathogenesis of cancer of the cervix and its causation by specific human papillomavirus types. *Curr Top Microbiol Immunol* 1994;186:131–56.
  37. Munoz N. Human papilloma virus and cervical cancer: epidemiological evidence. In: Franco E, Monsonego J, eds. *New developments in cervical cancer screening and prevention*. Oxford: Blackwell, 1997. 3–13.
  38. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244–65.
  39. Moreno V, Bosch FX, Munoz N, Meijer CJLM, Shah KV, Walboomers JMM, Herrero R, Franceschi S. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC Multicentric Case-Control Study. *Lancet* 2002; 359:1085–192.
  40. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2002;37:4–66.
  41. De Schryver A. Does screening for cervical cancer affect incidence and mortality trends? The Belgian experience. *Eur J Cancer Clin Oncol* 1989;25:395–9.
  42. Giard RWM, Coebergh JWW, Wijnen JA. Causes of low effectiveness of population screening for cervical cancer. *Ned Tijdschr Geneesk* 1996;141:317–21.
  43. Raffle AE, Alden B, Mackenzie EFD. Detection rates for abnormal cervical smears: what are we screening for? *Lancet* 1995;345:1469–73.
  44. Raffle AE. Deaths from cervical cancer began falling before screening programmes were established. *BMJ* 1997;315:953–4.
  45. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;1:1247–9.
  46. Hill GB, Adelstein AM. Cohort mortality from carcinoma of the cervix. *Lancet* 1967;2:605–6.
  47. Yule R. Mortality from carcinoma of the cervix. *Lancet* 1978;1031–3.
  48. Cook GA, Draper GJ. Trends in cervical cancer and carcinoma in situ in Great Britain. *Br J Cancer* 1984;50:367–75.
  49. Austoker J. Cancer prevention in primary care. Screening for cervical cancer. *BMJ* 1994;309:241–8.
  50. Anderson CM, Thornton JG. Screening for cervical cancer. Graphs may mislead. *BMJ* 1994;309:953–4.
  51. Armstrong B, Holman D. Increasing mortality from cancer of the cervix in young Australian women. *Med J Aust* 1981;1:460–2.
  52. Cox B, Skegg DC. Trends in cervical cancer in New Zealand. *N Z Med J* 1986;99:795–8.
  53. van der Graaf Y, Zielhuis GA, Vooijs GP. Cervical cancer mortality in the Netherlands. *Int J Epidemiol* 1988;17:270–6.
  54. Kirn VP, Kovacic J, Primic Zakej M. Epidemiological evaluation of cervical cancer screening in Slovenia up to 1986. *Eur J Gynaecol Oncol* 1992;13:75–82.
  55. Llorca J, Prieto MD, Delgado-Rodriguez M. Increase in cervical cancer mortality in Spain, 1951–1991. *J Epidemiol Community Health* 1999;53:408–11.
  56. Anttila A, Pukkala E, Soderman B, Kallio M, Nieminen P, Hakama M. Effect of organised screening on cervical cancer incidence and mortality in Finland, 1963–1995: recent increase in cervical cancer incidence. *Int J Cancer* 1999;83:59–65.
  57. Chamberlain J. Failures of the cervical cytology screening programme. *BMJ* 1984;289:853–4.
  58. Patnick J. Cervical cancer screening in England. *Eur J Cancer* 2000; 36:2205–8.
  59. Quinn M, Babb P, Jones J. Effect of screening on incidence and mortality from cancer of the cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;318:904–8.
  60. Sasiemi P, Cuzick J, Farmery E. Accelerated decline in cervical cancer mortality in England and Wales. *Lancet* 1995;346:1566–7.
  61. Sasiemi P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ* 1999;318:1244–5.
  62. Sasiemi PD, Adams J. Analysis of cervical cancer mortality and incidence data from England and Wales: evidence of a beneficial effect of screening. *J R Stat Soc A* 2000;163:191–209.
  63. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the “PSA era”. *Int J Cancer* 2001;92:893–8.
  64. Rostgaard K, Vaeth M, Holst H, Madsen M, Lyng E. Age-period-cohort modelling of breast cancer incidence in the Nordic countries. *Stat Med* 2001;20:47–61.
  65. van Ballegooijen M, van den Akker van Marle ME, Patnick J, Lyng E, Arbyn M, Anttila A, Ronco G, Habbema DF. Overview of important cervical cancer screening process values in EU countries, and tentative predictions of the corresponding effectiveness and cost-effectiveness. *Eur J Cancer* 2000;36:2177–88.
  66. Arbyn M, Van Oyen H. Cost-analysis of cervical cancer screening in the Flemish region: the spontaneous versus the organised approach. *Eur J Cancer* 1997;33:15–6.
  67. Arbyn M, Temmerman M. Belgian Parliament calls for organised cervical cancer screening and HPV research throughout Europe. *Lancet Oncol* 2002;3:74.