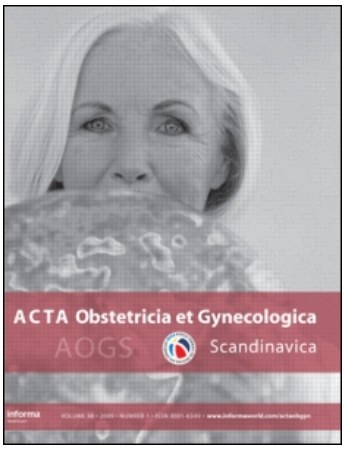

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ORIGINAL ARTICLE

Age-period-cohort analysis of cervical cancer mortality in Taiwan, 1974–1992

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Objectives. To develop a hypothesis about the carcinogenesis of cervical cancer from a descriptive analysis.
Methods. The mortality data of cervical cancer were analyzed over the period from 1974 to 1992 among Taiwanese women using a log-linear Poisson model modified from the method of Osmond and Gardner to examine the effects of age, calendar period of death, and birth cohort on cervical cancer mortality.
Results. This age-period-cohort model provides a summary guide for interpretation of cancer mortality trends. According to this model, age was found to be the strongest factor predicting cervical cancer mortality. Women in 50–54 age group have 89.3-fold risk of cervical cancer compared to those in the 30–34 age group. The cohort effect is also of particular interest because the generation at greatest risk for cervical cancer is the one born between 1893 and 1938, and a dramatically declining trend is observed thereafter for 1938–1963 birth cohort. Interest has emerged about the increasing trend in recent cohorts (after 1963 birth cohort). However calendar time only has a slight effect in the APC analysis. The model also identified a possible role of female sex hormones as the age effect, promiscuous sexual activity as the period effect (promoter) and the change in reproductive behavior as the cohort effect (initiator).
Conclusions. These results may help to develop a hypothesis of carcinogenesis of cervical cancer in Taiwan.

Key words: age-period-cohort analysis; cervical cancer

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Although the rates of cervical cancer have declined significantly in Western countries over the last several decades; cervical cancer remains one of the most common female cancers in developing countries (1, 2). In Taiwan, as recently as the early 1990's, cervical cancer still remains the most frequent neoplasm, accounting for more than 30% of all cancer among this population (3). The annual age-adjusted mortality rate of cervical cancer in Taiwan increased from 6.06 per 100,000 in 1974 to 10.02 per 100,000 in 1993, a 1.4-fold increase (4). The reasons for the long-term upward trend in mortality from cervical cancer in Taiwan have not been elucidated. Undoubtedly, environmental factors (e.g., sexual behavior, reproductive pattern and screening practices) have contributed in some populations within the past 20 years. However, it is urgent to provide more useful information to factors affecting cervical cancer mortality from age-period-cohort analysis, since these three temporal factors are particularly sensitive indicators of a changing environment.

Secular trends in the occurrence of cancer are prone to be linked to changes in the prevalence of risk factors (5). Thus, the study of secular trends can provide epidemiologists with valuable clues related to cancer etiology or hypotheses for testing the etiology (6). Age, period (year of death), and cohort (year of birth) are three separate time factors related to the cancer mortality (7). Each of these factors has a different biological meaning in the process of carcinogenesis. For example, under

the multistage theory of carcinogenesis (8), age represents biological aging process and birth cohort reflects early nurture (initiators), whereas period of death captures the effect of later environment (promoters) (9). However, cross-sectional analyses of cancer mortality have not simultaneously considered the effects of age, period and cohort. In addition, the traditional cohort analysis remains a graphic technique and fails to adjust the period effect while studying the cohort phenomenon (10). To characterize the effects due to age, period and cohort, a log-linear Poisson model (the age-period-cohort model, APC model) has been developed within the past 20 years and applied to analyze the secular trends of various diseases (11–13). However, it is well-known that such a model suffers from an identifiability problem due to the exact linear dependence between age, period and cohort (cohort=period − age). Although several methods have been proposed to solve the problem of non-identifiability inherent in the APC model by introducing suitable constraints on the parameters in the model (14,15), the method of Osmond and Gardner (16) was adopted in the present study since they have the advantage of quantifying the separate effect of the three factors: age, period and cohort.

This study applied a log-linear Poisson regression approach to show the secular trends of mortality from cervical cancer between 1974 and 1992 through age, period and cohort indices. The relative effects of these variables on mortality rate of cervical cancer and possible hypotheses of the observed trends are discussed.

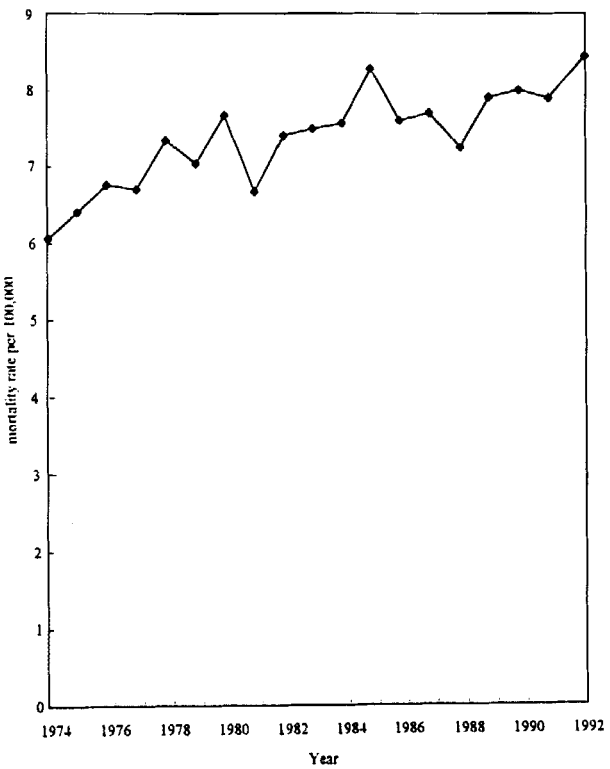

Fig 1. Age-adjusted mortality rates of cervical cancer in Taiwan from 1974 to 1992.

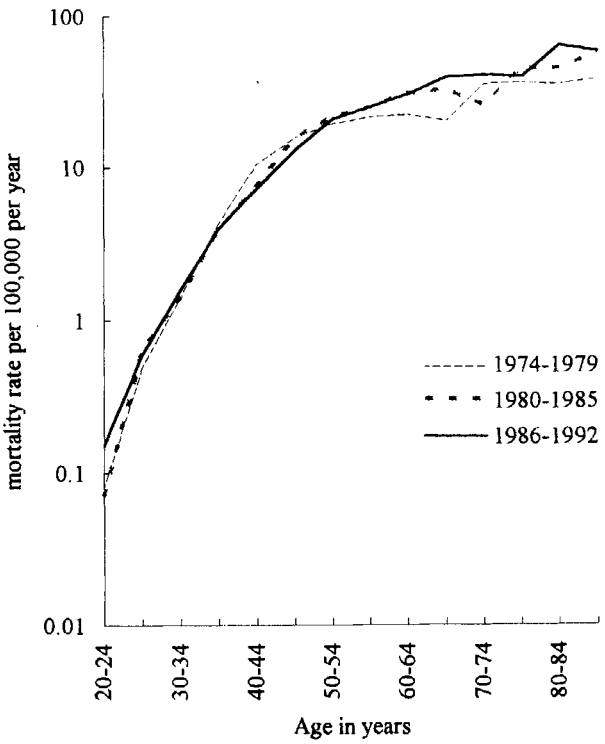

Fig 2. Age-specific mortality rates of cervical cancer in Taiwan from 1974 to 1992.

Materials and methods

Mortality data and population

Data of cervical cancer deaths from 1974 through 1992 were obtained from the computer center of the Taiwan Provincial Department of Health (17). Each cervical cancer death was characterized by detailed demographic data including age at death, year of death, and residential area. Cervical cancer cases were identified as code number 180 in both International Classification of Disease, 8th and 9th revisions (ICD-8 and ICD-9 code 180). A total of 9720 cervical cancer cases with complete records were collected for the period 1974–1992. The mortality rates were classified by 5-year age groups. Age specific midyear population estimations were obtained from data published by the Ministry of the Interior in Taiwan (18).

Descriptive analysis

The secular trends of age-specific and age-adjusted mortality rates of cervical cancer during the period

from 1974 to 1992 were described in this study (age-standardized to the 1976 World Population in order to minimize the effect of difference in age composition for different periods) (19).

Traditional birth cohort analyses were also used to show the birth-cohort phenomenon in the study (20). These cohorts were designated by median-year of birth.

Statistical age-period-cohort analysis

From the matrix of the age-specific death rates were calculated for each 5-year period intervals, beginning with 1974 to 1978 and 5-year age intervals, beginning with age 20 to 24. The effect of age, period and birth cohort were examined using a log-linear Poisson regression model, modified from Osmond and Gardner's method (16). The statistical model used in these analyses was:

$$\log [R_{ijk}] = K + A_i + P_j + C_k + E_{ijk},$$

where R_{ijk} represents the observed mortality rate in a particular age-period-cohort category, K is a constant, A_i, P_j and C_k represent the age, period and cohort effects respectively; and E_{ijk} represents random error. The mortality from cervical cancer is assumed to follow a Poisson distribution.

The estimates derived from the model, including the three time factors, that minimized the weighted sum of the Euclidean distances from the three possible two-factor model (age/period; age/cohort; period/cohort) based on the goodness-of-fit of each one. In the study, these measures were taken as the inverse of the deviance statistics. The sum of each of the three effects was constrained to be zero. These effects can be interpreted as logarithms of relative risks. The computer program SAS/IML was used for the computation (21).

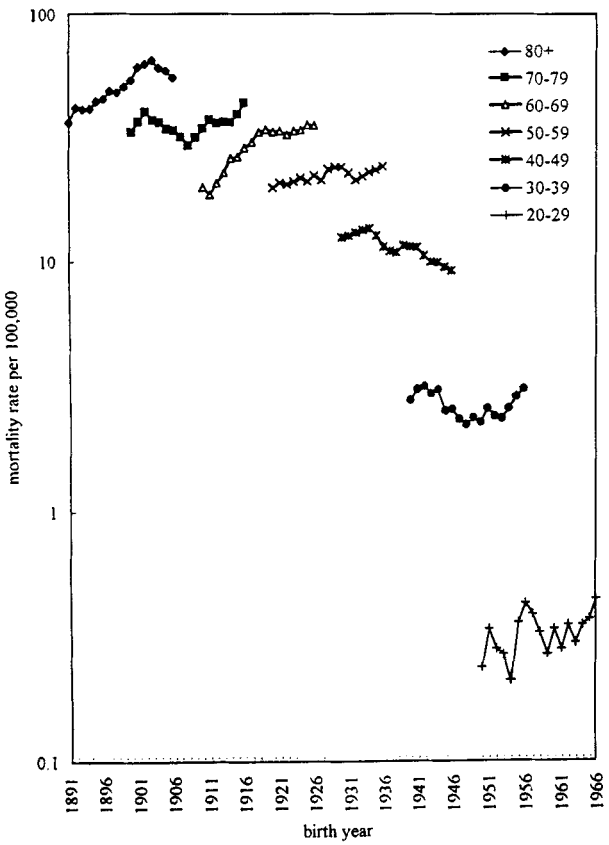

Fig 3. Age-specific mortality trends of cervical cancer in Taiwan for birth cohort from 1891 to 1966.

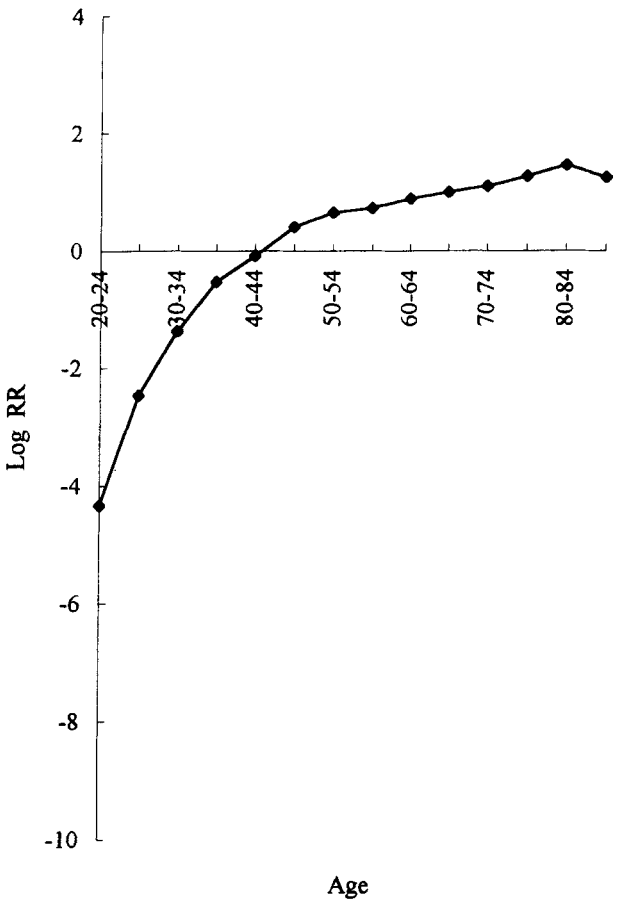

Fig 4. Age effects on cervical cancer mortality in Taiwan from 1974 to 1992.

Results

Secular trends

During the period 1974–1992 the age-adjusted mortality rate of cervical cancer showed a slight increase, with 6.06 per 100,000 in 1974 compared to 8.28 per 100,000 in 1992 (Fig.1). During this study period the average annual increase of cervical cancer mortality rate was 0.09%. Further analyses on the age-specific mortality rate in three

periods of the calendar years between 1974 and 1992 are presented in Fig. 2. There was no significant difference in the age-specific mortality rates within the past 20 years. In the same figure, however, it can be seen that the age-specific mortality rates of cervical cancer increase rapidly with age between 20 and 50 years of age and, thereafter, show an increase again in mortality with a smaller slope. Fig. 3 depicts the results of the traditional birth cohort analysis. The effects of birth cohort are noticeable. The mortality rates increased slowly by birth cohort for older age groups (>50 years). For 35–49 age groups, however, they are decreasing by birth cohort. For the youngest group (20–29), the mortality rate increases again by birth cohort. In addition, there is clear evidence of a cohort-based decrease in mortality among women born from 1938 to 1963, and thereafter, increases in mortality.

Age-period-cohort analysis

A goodness-of-fit test of the APC model shows that the fit is good. The separate effects due to age, cohort and period indices, respectively, (Figs. 4–6) were estimated from the APC model and were all statistically significant ($p<0.01$) as judged by the likelihood ratio test. Fig. 4 demonstrates the age effects of cervical cancer mortality presented in the form of the logarithm of relative risks in different age groups as derived from the APC model. Prior to the age group of 50–54, there is a approximate linear trend of age effect on cervical cancer mortality (50–54 age group having a risk of cervical cancer 89.3-fold as compared to those 30–34 age group). Thereafter, however, the effect of age resumes with an increase exhibited by a smaller slope. These results are consistent with previous analysis on secular trends (Fig. 2). Fig. 5 depicts the period effect. There is a slight increase in secular trend of age-adjusted cervical cancer mortality in Taiwan (Fig. 1) reproduced in the APC analysis. However, the period effect was less striking than the age effect. As regards cohort effects, Fig. 6 displays the cohort effect in cervical cancer mortality from 1893 to 1968. It can be seen that, in the earlier birth cohorts, the cohort effect fluctuates and remains above the average; however, they decline dramatically after the birth cohort of 1938. It is of interest to note that the relative risk increased again after the birth cohort of 1963. These findings are also comparable to the analysis in Fig. 3.

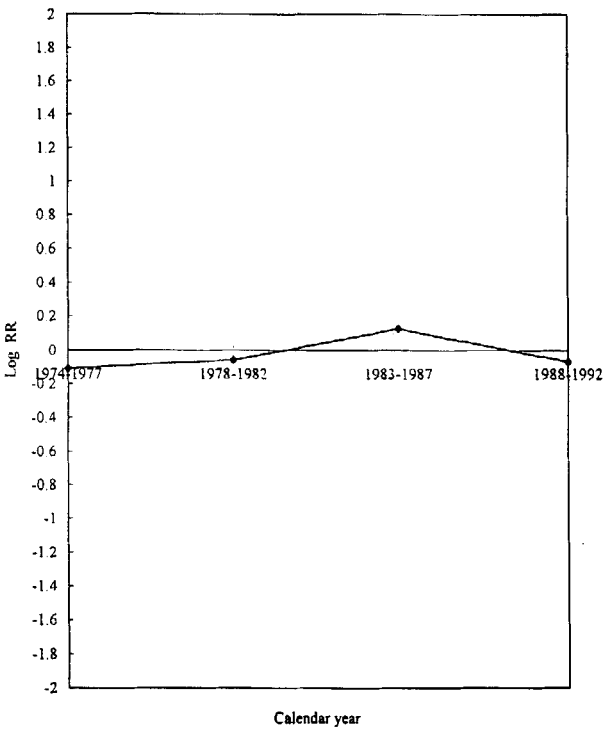

Fig 5. Period effects on cervical cancer in Taiwan from 1974 to 1992.

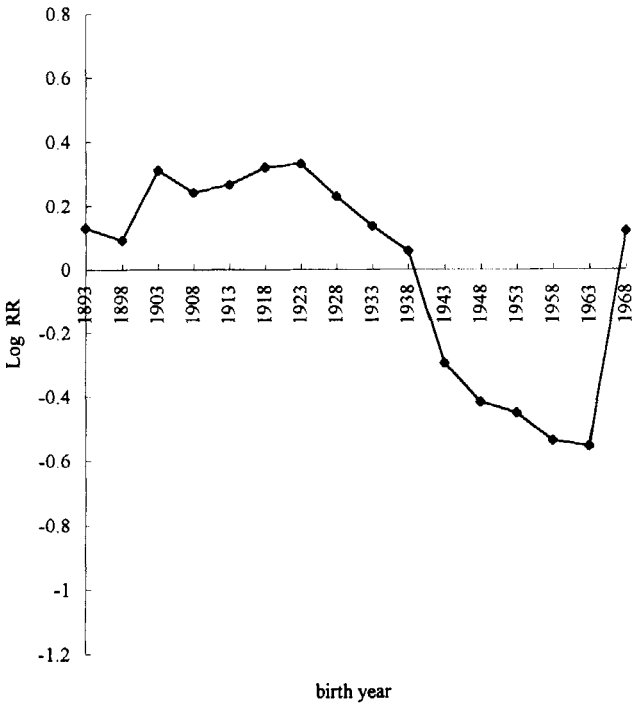

Fig 6. Cohort effects on cervical cancer mortality in Taiwan from 1974 to 1992.

Discussion

Time trend of mortality rate for a particular disease can provide an epidemiologist with valuable clues or hypotheses for disease etiology (10). Three temporal factors which are often considered in

such an investigation are age, period (year of death) and cohort (year of birth). In 1939, Frost first employed these three factors on mortality rates from tuberculosis in Massachusetts (22).

This technique was adopted further by Case to establish the value of cohort analysis (23), but the technique remained a graphical one and the contributions of various time factors determined visually to examine patterns in disease rates over time (20). In contrast, statistical age-period-cohort (APC) analysis has been developed in an attempt to overcome these drawbacks and to quantify the separate effects of the age, period and cohort variables, provided suitable constraints are imposed (24). The constraints proposed by Osmond and Gardner were determined solely within the data and yielded an objective indication of the statistical significance of a particular pattern (16). Although the limitation of this technique was subsequently pointed out by Holford, and a more objective method among the APC models proposed (10).

In applying the APC analysis to mortality trends in the present study, all three temporal effects revealed useful information. The age effect reflects largely the change of the biological aging process (9). One of the peaks in the age effect within the age group of 50-54 is comparable to the descriptive analysis of age-specific mortality (Fig. 2). It is possible that occurrence of cervical cancer is influenced by female sex hormones such that mortality stops linear increase after menopause. This explanation is consistent with the patterns observed in UK and USA (25).

The female population in Taiwan has been made more aware of cervical cancer. Since 1974, a campaign for Pap smear screening was launched by the Taiwan Cancer Society. However, the period effect discovered in this study rose slightly over the past two decades. It is possible that Pap smear activity may be too low in Taiwan to induce a screening-like effect whereby the mortality would have decreased. However, another factor may relate to the increasing sexual freedom which has been postulated as a cause and is supported by the paralled trends between rates of sexually transmitted disease (26) and incidence from cervical cancer in Taiwan (3). Increasing mortality from cervical cancer among women over the past 20 years has serious implications since it implies either that exposure to factors that increase the risk of the disease is continuing or that current control programs are not fully effective. An explanation for these trends in cervical cancer mortality in Taiwan should be urgently sought.

In addition to age and period effects, the cohort phenomena in this study were the most intriguing findings since Levi et al. suggested that the cohort effect is an important factor in understanding time trends for many diseases (27). These findings imply that some important determinants of the disease may occur in early life, which express their effects some time later. In this study, we noted that fluctuations of the mortality from cervical cancer in successive generations of women in Taiwan was interrupted by dramatically declined rates in women born between 1938 and 1963. Women born during this period spent part of their child-bearing lives during the 1960–80 family planning and birth control campaign, when the fertility rate and birth rate decreased sharply since the total fertility rate had fallen rapidly from 1960 to 1980 in Taiwan: 5.75 in 1960 and 2.50 in 1980. The rate was almost fixed around 2.50 in the early 1980s, and then showed a gradually declining trend, and in 1992 it was 1.80. This coincidence, in time, may imply that the reproductive factors are one of the most possible sources of the cohort effect. Moreover, it is somewhat contrary to expectation that an increasing risk was observed in the recent birth cohort (after 1963 birth cohort). There is also a suggestion of similar patterns in several countries, especially the United States, United Kingdom and Australia (28–30). The reasons for recent increases in mortality in younger cohort are poorly understood. It could also easily be a statistical artefact. Thus, a further study to continue monitoring the mortality may provide further insight regarding the true trend of cervical cancer in Taiwan (31–33).

Acknowledgments

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