Effects of screening on cervical cancer incidence and mortality in New South Wales implied by influences of period of diagnosis and birth cohort

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Abstract:
***Study objectives*—Cervical cancer incidence and mortality in NSW during 1972–1996 is examined under counterfactual assumptions to estimate the number of new cervical cancer cases averted and deaths avoided, with projections to 2006.**
***Setting*—Cervical cancer incident cases and deaths in NSW for 1972–96 were obtained from the NSW Central Cancer Registry, Sydney, Australia.**
***Design*—Data were analysed by age-period-cohort (APC) modelling, using Poisson regression. Projection of incidence to 2006 was based on a linear trend for period effects. A counterfactual scenario was constructed assuming stable period effects (1972–74), but modelled cohort effects. Modelled rates were converted to cases and deaths (using mortality:incidence ratios for cervical cancer), and compared with actual data to estimate cancers prevented and deaths averted due to screening.**
***Results*—Rising cohort effects with recency of birth were found after controlling for age and period of diagnosis, and declining period effects were identified after controlling for age and birth cohort. The estimated cumulated number of new cases of cervical cancer prevented during 1972–1996 was 3440. The cumulated number of averted deaths over 1972–1996, derived from incident cases, was estimated to be 1610 (including actual declines in the M/I ratio). With no change in the M/I ratio from 1972, estimated cumulated mortality averted due to cervical cancer for 1972–1996 was 1210 deaths.**
***Conclusions*—Cervical screening has prevented a substantial number of new cases of cervical cancer and deaths. In addition, secondary prevention and improved treatment has contributed further to cervical cancer deaths averted.**
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Cervical cancer is a significant gynaecological cancer in women in most populations, and is preventable by regular screening by exfoliative cytology using the Papanicolaou technique. Screening identifies cervical intraepithelial neoplasia (CIN), which conveys a risk of development into invasive carcinoma; these lesions can then be removed or ablated, which reduces population incidence of invasive cervical carcinoma. Screening can also detect early asymptomatic invasive carcinoma and produce lower case fatality and improved survival.[1 2] Declines in cervical cancer mortality in populations over time is a consequence of declines in both incidence and case fatality.

CIN and invasive carcinoma are consequences of causes that operate over years, often decades. The most important cause is probably infection with human papilloma virus (HPV), which is spread by sexual contact. Cervical cancer incidence and mortality shows generational (birth cohort) trends as successive cohorts are differentially affected by exposure to causative influences,[3–5] especially to the number of sexual partners during young adulthood, the primary source of infection with HPV. Strong birth cohort effects are characteristic of the epidemiology of most cancers because cancer is usually a consequence of long term cumulative exposures from youth that derive from structural aspects of the physical, sociocultural and economic environment, which change slowly over generations.[6]

Age, period, and cohort (APC) models, as well as age-period and age-cohort models,[7–10]

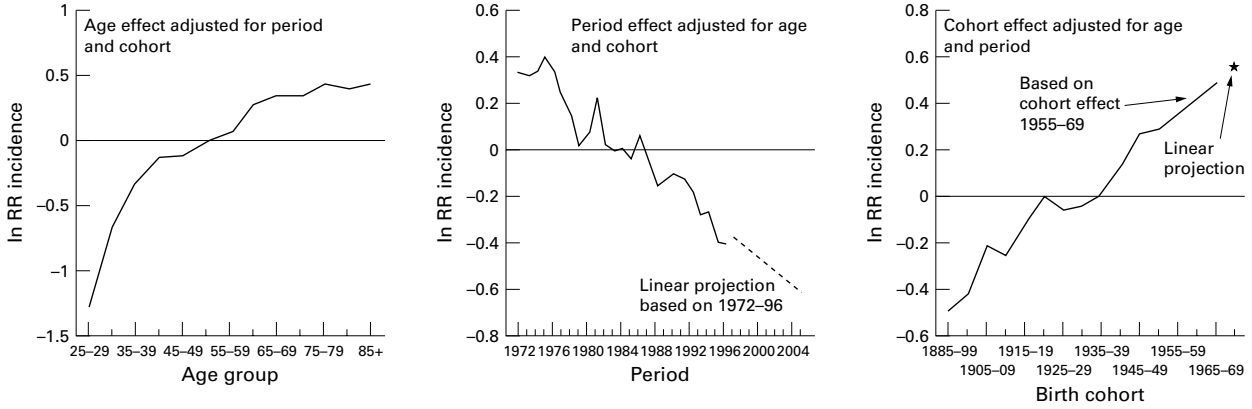

Figure 1 Cervical cancer incidence in New South Wales 1972–96. Effects of age and period of diagnosis and birth cohort, and projections.

have been used in the descriptive analysis of disease trends in populations,[11] especially cancer,[6 12–17] including cervical cancer,[3–5] and as an aid to understanding the evolution of cancer incidence and mortality over time. APC models are particularly useful for extrapolating incidence or mortality trends since generational cohort effects naturally project themselves into the future.

Cervical cancer incidence and mortality have been decreasing in Australia for some time. In NSW the incidence rate fell by 1.3% per year and mortality fell by 3.6% per year over 1973–82.[18] Similar trends have continued into the mid-1990s in NSW and Australia.[19–23]

Analysis of case-control and cohort studies have documented the effectiveness of regular cervical screening in preventing squamous cancer of the cervix.[24] Evidence for effectiveness of screening in populations relies on time trends in cervical cancer incidence and/or mortality (by age group) in relation to the introduction and intensity of cervical screening[25–32]; and on comparison of trends in cervical cancer incidence or mortality between populations with different dates of introduction or intensities of cervical screening.[30 33–35]

This analysis uses changes in period effects as a surrogate for the influence of primary prevention through cervical screening, and changes in the mortality:incidence (M/I) ratio as an indicator of secondary prevention via screening and improved treatment outcomes in cancer cases.

Methods

DATA

Since 1972, notification of malignant neoplasms to the NSW Central Cancer Registry has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes, and for pathology and outpatients departments since 1985.[23] Primary site of cancer is coded according to the International Classification of Diseases, 9th revision (ICD-9). Annual numbers of new cases and deaths from cervical cancer in NSW female residents by five year age group and year of diagnosis for 1972 to 1996 were obtained for this analysis.

Annual population estimates for 1972 to 1996 by sex and five year age group were obtained from the Australian Bureau of Statistics (ABS). Annual female population projections by five year age group from 1996 to 2006 were obtained from Australian Bureau of Statistics estimates, using interpolation and extrapolation where necessary.

MODELLING

APC modelling suffers the problem of non-identifiability, when age, period and cohort are modelled together. This can be solved in a technical sense by imposing constraints on the variables in the model; a minimal set of constraints entails aggregating the youngest and older cohorts and using one year periods but five year birth cohorts.

Data on cervical cancer incidence (new cases) and population were stratified by five year age group and single year of diagnosis. Age groups 25 years or over were used to limit instances with zero cases in the analysis. Five year birth cohorts were used for the analysis. These can be identified as cells running diagonally through the age-period data matrix.

APC modelling was by Poisson regression, which is a multiplicative model using a logarithmic link transformation and a Poisson error distribution.[36] The Poisson model took the following form:

$$\log_e (c/p) = \beta_1 \text{ age} + \beta_2 \text{ period} + \beta_3 \text{ cohort} + k$$

where c = cases, p = population, k = constant, and the βs are the regression coefficients ($\log_e$ relative risk) for the model.

The β coefficients for age, period, and cohort from the APC regression were plotted to show the separate effects of age, period, and cohort in the model, each controlling for the effect of the other two variables. The contribution of each variable to the model was assessed by backwards deletion from the full model and the resulting change in deviance was assessed as an approximate χ^2 distribution using the change in the model degrees of freedom to obtain the p value.

PROJECTIONS AND COUNTERFACTUAL SCENARIO

Projections of cervical cancer incidence rates to 2006 were made by a linear projection of the period effect ($\log_e$ RR) using data from 1972–96, then combining the age, period, and cohort effects in the above model. The projected annual age specific incidence rates were applied to projected populations to produce expected new cases of cervical cancer to 2006.

The APC model was used to estimate the annual age specific incidence rate of cervical cancer for 1972–2006 if the period effect had remained constant at the 1972–74 level (that is, no change in primary prevention), but the cohort effect had applied, as indicated by the model. New cases of cervical cancer per year were estimated by applying age specific incidence rates to age specific annual populations and their projections.

Mortality from cervical cancer was used in conjunction with incidence to compute mortality/incidence (M/I) ratios for 1972–96. Because of small numbers, M/I ratios were smoothed using moving averages over three adjacent five year age groups and seven annual periods. Linear projection of M/I ratios to 2006 by age group was based on 1992–96 data. Cervical cancer deaths were then estimated from incidence using these age and period specific M/I ratios for the counterfactual scenario and projections. Although cervical cancer survival is available for NSW,[20 37] estimation of the annual stream of deaths from incident cases in each year by age would entail even smaller numbers, and was considered unfeasible. A counterfactual scenario that included a constant M/I ratio from 1972–74 was also examined; this corresponds to no change in secondary prevention (early diagnosis) and no improvement in stage specific treatment outcomes. Cervical cancer deaths by age were combined with populations to

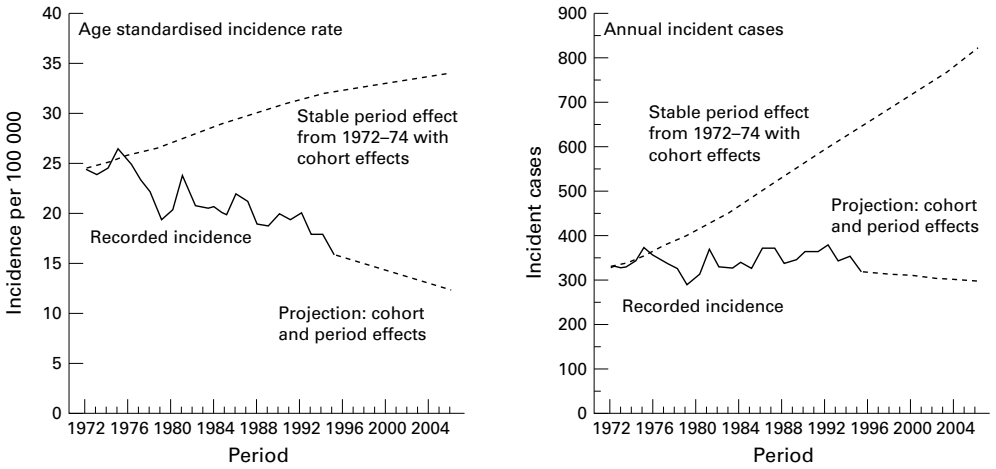

Figure 2 Cervical cancer incidence in NSW 1972–2006. Actual and counterfactual scenarios with projections.

produce age specific and age standardised mortality rates.

Incident cases prevented and deaths averted by cervical screening, by age group, were estimated from the difference between the recorded incidence or mortality (and projections), and the counterfactual incidence scenario. These data are displayed as annual numbers, and cumulative numbers since 1972.

Age standardised incidence and mortality rates were calculated using the direct method,[38] using the 1996 NSW census population as a standard.

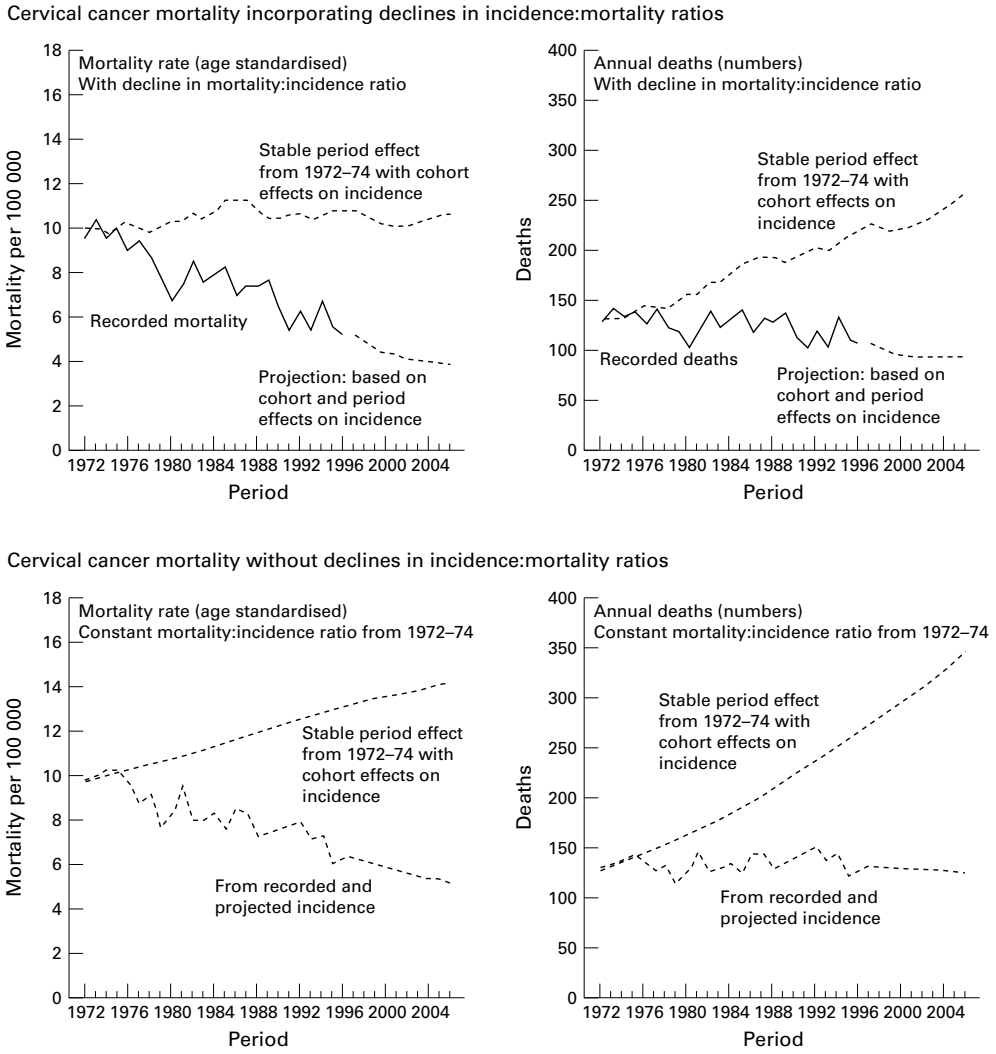

Figure 3 Cervical cancer mortality in NSW 1972–2006. Actual and counterfactual scenarios with projections.

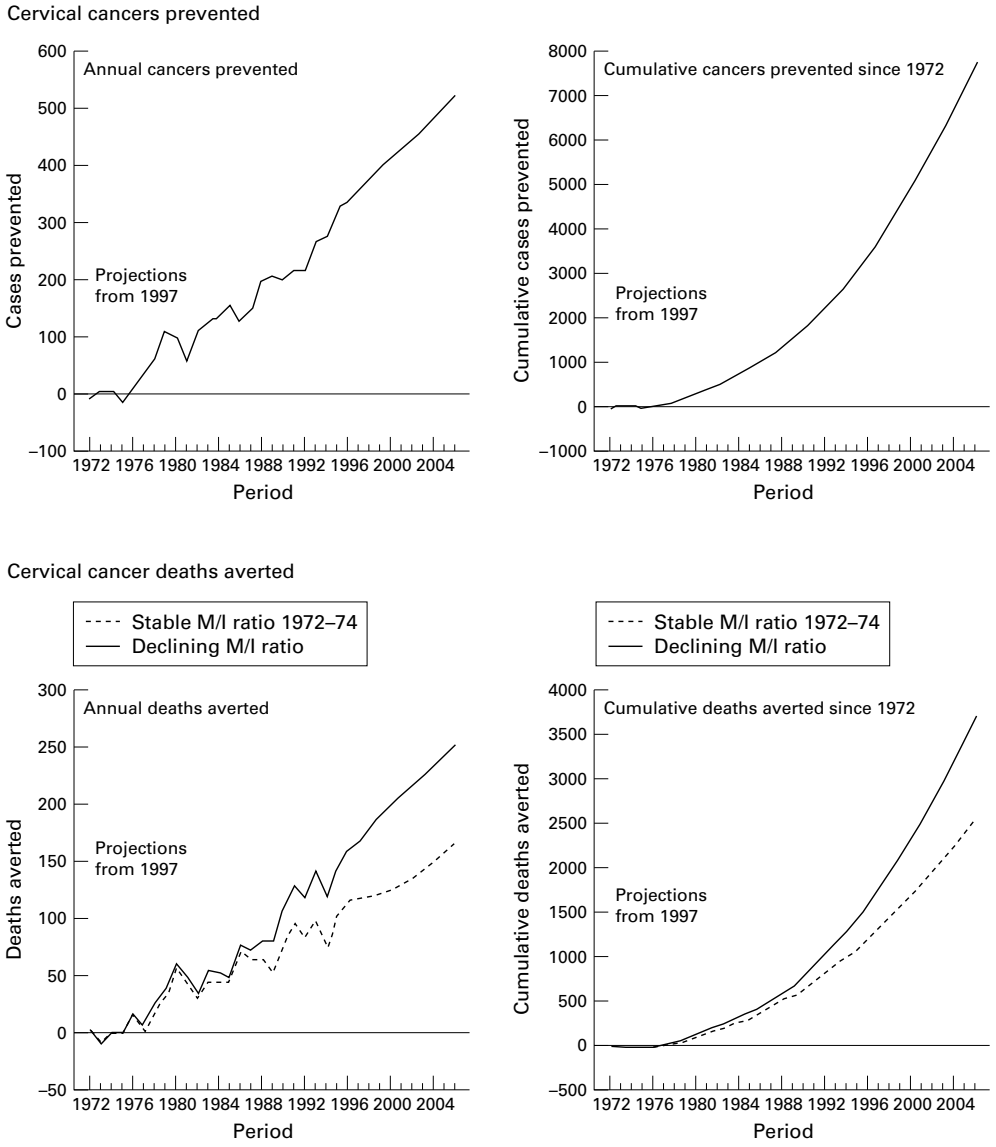

Figure 4 Estimated cervical cancers prevented and cervical cancer deaths averted by cervical screening in NSW 1972–2006.

Results

The APC model revealed the expected effect of age on cervical cancer with an increase of log(RR) for incidence to age 40–44 years, a lesser rise to 60–64 years, and a levelling off thereafter (fig 1). The period effect revealed a near linear decrease in log(RR) from 1972 to 1996 (fig 1). The generational cohort effect showed a general increase of log RR in five year birth cohorts from 1885 to 1969; a pause and slight decrease for women born during 1910–1914 (aged 20 years in 1930–1934), and for women born during 1925–1939 (aged 20 years in 1945–1959); and steep increases in women born during 1915–1924 (aged 20 years in 1935–44), 1940–1949 (aged 20 years in 1960–69), and after 1955 (fig 1).

Actual and projected new cervical cancer cases and incidence rates for 1972–2006, and those for the counterfactual scenario, are displayed in figure 2. Incidence rates and numbers of new cases of cervical cancer from 1972–74 increase for a scenario of stable period effects and including cohort effects.

Actual and projected cervical cancer mortality rates and deaths (1972–2006), and those for the counterfactual scenario, are displayed in figure 3, for both declining and stable M/I ratios. For declining (observed) M/I ratios, the counterfactual scenario indicates cervical cancer mortality rates would remain stable, whereas annual deaths would increase in line with these trends and population increase. For the additional counterfactual scenario of stable M/I ratio (at 1972–74 level), higher annual mortality rates and more deaths are estimated than if the M/I ratio had declined as observed (fig 3).

The annual and cumulative (since 1972) new cases prevented and deaths averted of cervical cancer for the counterfactual scenario for 1972–2006 are set out in figure 4. The cumulated number of cases of cancer prevented during 1972–1996 was estimated as 3440. The estimate for 1972–2006 was 7840 cancers prevented.

KEY POINTS
- For the period 1972–1996, Pap screening in NSW has been found to be associated with prevention of approximately 3440 cases of cervical cancer.
- Cumulated cervical cancer mortality averted in NSW during 1972–1996 was estimated to be 1610 deaths. Part of this is attributable to secondary prevention and improved treatment.
- Age-period-cohort modelling of cancer incidence and mortality in conjunction with counterfactual scenarios is useful particularly when over an extended time period there are incremental changes in secondary prevention and treatment.

Cumulated cervical cancer mortality averted for 1972–1996 was estimated to be 1210 assuming a constant M/I ratio (at 1972–74 level). For 1972–2006 the estimate was 2580 deaths averted. Incorporating the observed declining M/I ratio over 1972–1996, the estimated cumulated number of averted deaths from cervical cancer was 1610, and for 1972–2006, the estimate was 3720.

Discussion

Evaluation of the effects of the availability of preventive measures or programmes in populations are of considerable interest, not least for the health services that fund them. Preventive programmes must report on their effectiveness if they are to ensure that they will be adequately supported, or expanded as required. As prevention programmes are applied to whole populations without control conditions, they must be assessed in relation to what would have happened if preventive measures or programmes had not been implemented, or had been implemented to a lesser extent. This requires the construction of realistic counterfactual scenarios for comparison with observed incidence and mortality.

As no randomised control trials have been conducted of cervical screening, our understanding of the effectiveness of cervical screening in the control of cervical cancer comes from meta analyses of observational studies of individuals.[24] Another approach to estimating the effectiveness of cervical screening on cervical cancer incidence relies on comparing aggregate changes in cervical cancer incidence in relation to the introduction and intensity of cervical cancer screening.[1 25–35] In NSW, statewide data are only recently available on Pap test screening because the NSW Pap Test Register (PTR) has only functioned since 1996, thus precluding a time series analysis of aggregate cervical cancer incidence rates and cervical screening. Pap tests as recorded in Health Insurance Commission (Medicare) data could be used to assess population cervical screening but these data exclude public sector provision and are usually reported as Pap tests rather than women screened.

Another approach to estimating the effectiveness of cervical screening in populations is to apply screening data to populations using component models that incorporate assumptions regarding disease causality and progression,[39 40] effectiveness of cervical screening (sensitivity and specificity), and the progression, regression and treatment of pre-cancerous abnormalities. This approach requires detailed data or estimates of screening participation by subgroup over extended periods. A version of this approach is to use the proportion of pre-cancerous lesions detected in a screened population, and the proportion of these that would have progressed to cervical cancer.[28] This approach requires population-based data on pre-cancerous lesions by type that may not be available, or are available for a short period only. Moreover, the accuracy of such progression rate estimates are based on the natural histories of the different pre-cancerous lesions that are not well known. In order to establish these, however, it must also be assumed that screen detected abnormalities are not treated, which is implausible. At present, meta-analytical estimates of progression rates from pre-cancerous lesions to invasive cervical cancer are highly variable and not sufficiently reliable over extended periods for estimating a time distribution of progression.[41] As a consequence of the unreliability of these assumptions for component modelling, the effects of interventions on cervix cancer incidence and mortality have been based on statistical modelling of age adjusted period and cohort trends in cervical cancer incidence.

APC analysis can be affected by the "non-identifiability" of the three parameters, as each can be described by the other two if the data are classified symmetrically. That is, a given age and period "defines" a cohort; a given age and cohort the period; and a given cohort and period "defines" the age if the time intervals are the same (for example, five years). This problem can be alleviated to some extent by making the time intervals for periods different from the time interval for age and cohort groups. Such constraints were imposed in the present analysis by using five year birth cohorts and age groups with single period years in the models. Although data by age are available by period, for the oldest and youngest cohorts cervix cancer incidence rates are only available for some age groups. To deal with this problem in its extreme form, the youngest and oldest three cohorts were aggregated.

Previous studies of cervical cancer using APC modelling of counterfactual scenarios have made similar assumptions concerning the period effect representing the effect of screening, in both New Zealand and the UK.[3 5] However, some studies have only modelled cervical cancer mortality,[4 5] and the change in period effect in these circumstances could be due to both primary and secondary prevention, as well as improvements in stage specific survival because of improvement in treatment efficacy. The other major influence on the period effect are changes in the completeness of enumeration of cancer, but there are no indications that completeness of ascertainment of cervical cancer by the NSW Cancer Registry has declined

over 1972–96. In fact, the histological verification rate for cervical cancer increased from 84% in 1972–76 to 96% in 1995.[23 37]

Birth cohort effects are pronounced for many cancers because they represent the cumulative effects of exposures in generations.[6 14–17] Birth cohort effects have been documented for cervical cancer,[3–5] and these are presumably partly related to patterns of sexual behaviour in young adults of different generations, and the likelihood of human papilloma virus infection. The generational effect found in this study showed a progressive increase in log RR for cervical cancer for birth cohorts from 1885 to 1969. The pauses and increases are not inconsistent with possible variations in sexual activity patterns, especially the steepest rise for the cohorts of women aged 20 years in 1960–69, which was also found in a UK study of cervical cancer mortality.[5] However, the NSW data do not show the biphasic birth cohort effects demonstrated by the UK cervical cancer mortality data.[5]

Projections of cervical cancer incidence to 2006 were by linear projections of period and cohort effects, although the latter naturally project themselves into the future, and any additional projected value has very little effect on forecasts. This presumes that there are continued improvements in cervical screening and its consequences. The counterfactual scenario was an increased incidence of cervical cancer with recency of birth cohort (from the birth cohort effects found in the incidence data), but no change in primary prevention through cervical screening from 1972–74 (constant period effect). The difference between recorded and projected cancers and those estimated to occur under the counterfactual scenario indicate new cases averted though primary prevention by cervical screening.

Mortality for projections and counterfactual scenarios was modelled by using mortality to incidence (M/I) ratios by age group and period (after smoothing). Although cervical cancer survival for the population of NSW is available,[20 37] the small numbers causes problems in estimating deaths from new cases using an annual cohort approach. Survival analysis has shown improvement in five year survival during 1972–1995, although stage adjusted survival only increased during 1972–1981, and during 1985–1995, indicating improvement in the effectiveness of treatment during these periods. However, the degree of spread categories in routinely collected data on cervical cancer in NSW (localised, regional spread, metastatic) may be insufficiently detailed to detect change in stage at diagnosis that has prognostic significance, and thus the effect of earlier diagnosis (including secondary prevention) may be underestimated in these data.[20–37]

Reductions in the M/I ratio are both a consequence of earlier diagnosis (secondary prevention through cervical screening and earlier clinical presentation), and improved efficacy of stage specific treatment. An additional counterfactual scenario was constructed that assumed no decline in the M/I ratio from 1972–74, which implies no beneficial effects from secondary prevention or improvement in treatment efficacy by stage.

In the absence of reliable estimates of progression rates from pre-cancerous lesions to invasive cervical cancer, coupled with a small number of time points in which cervical screening rates are known in NSW, it was not possible to use component models or time series analyses to reliably estimate the effects of cervical screening on cervical cancer incidence or mortality. Moreover, cervical screening has been occurring in NSW since the 1960s, although it had not been put on an organised, programmatic basis until 1996. Thus a time series analysis would, at best, be able to gauge the effect of organised cervical screening versus unorganised cervical screening. The alternative approach of APC modelling allows estimates of the effects of screening to be derived indirectly, based on counterfactual scenarios. While this approach is not ideal, the derived estimates of the numbers of prevented cervical cancer cases and deaths can serve as approximations to be improved upon with the accumulation of further screening rate data and improvements in estimates of progression rates of pre-cancerous lesions to invasive cervical cancer.

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