Age-period-cohort analysis of cervical cancer incidence in Hong Kong from 1972 to 2001 using maximum likelihood and Bayesian methods

Gabriel M Leung, Pauline P S Woo, Sarah M McGhee, Annie N Y Cheung, Susan Fan, Oscar Mang, Thuan Q Thach and Hextan Y S Ngan

Updated information and services can be found at:
http://jech.bmj.com/cgi/content/full/60/8/712

These include:

References	This article cites 28 articles, 6 of which can be accessed free at: **http://jech.bmj.com/cgi/content/full/60/8/712#BIBL**
Rapid responses	You can respond to this article at: **http://jech.bmj.com/cgi/eletter-submit/60/8/712**
Email alerting service	Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article
Topic collections	Articles on similar topics can be found in the following collections Cancer: gynecological (252 articles) Bayesian statistics: examples (15 articles) Bayesian statistics: descriptions (19 articles)

Notes

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to *Journal of Epidemiology and Community Health* go to:
http://www.bmjjournals.com/subscriptions/

RESEARCH REPORT

Age-period-cohort analysis of cervical cancer incidence in Hong Kong from 1972 to 2001 using maximum likelihood and Bayesian methods

Gabriel M Leung, Pauline P S Woo, Sarah M McGhee, Annie N Y Cheung, Susan Fan, Oscar Mang, Thuan Q Thach, Hextan Y S Ngan

....

See end of article for authors' affiliations
....

Correspondence to:
Dr G M Leung, Department of Community Medicine, 21 Sassoon Road, Faculty of Medicine Building, University of Hong Kong, Pokfulam, Hong Kong, China; gmleung@hku.hk

Objective: To examine the secular effects of opportunistic screening for cervical cancer in a rich, developed community where most other such populations have long adopted organised screening.
Design, setting, and participants: The analysis was based on 15 140 cases of invasive cervical cancer from 1972 to 2001. The effects of chronological age, time period, and birth cohort were decomposed using both maximum likelihood and Bayesian methods.
Results: The overall age adjusted incidence decreased from 24.9 in 1972–74 to 9.5 per 100,000 in 1999–2001, in a log-linear fashion, yielding an average annual reduction of 4.0% (p<0.001) during the 30 year period. There were two second order and thus identifiable changes: (1) around the mid-1920s cohort curve representing an age-period interaction masquerading as a cohort change that denotes the first availability of Pap testing during the 1960s concentrated among women in their 40s; (2) a hook around the calendar years 1982–83 when cervical cytology became a standard screening test for pregnant women.
Conclusions: Hong Kong's cervical cancer rates have declined since Pap tests first became available in the 1960s, most probably because of increasing population coverage over time and in successive generations in a haphazard fashion and punctuated by the systematic introduction of routine cytology as part of antenatal care in the 1980s.

Analysis of secular trends in cancer epidemiology is important to the understanding of disease aetiology and for the assessment of public health control policy. Despite the availability of effective primary and secondary prevention—that is, cytological screening since the 1960s—cervical cancer remains an important cause of morbidity and mortality worldwide. Hong Kong provides a contemporary setting to study the secular effects of opportunistic screening for cervical cancer. It is one of very few communities worldwide at an advanced stage of socioeconomic development and with some of the best basic health indices in the world,[1] but does not have an organised population based screening programme. Thus Hong Kong's experience may illustrate the population impact of opportunistic uptake of cervical cytological smears. It can also act as a reliable epidemiological harbinger for mainland China as it rapidly transits through socioeconomic development in the coming decades.

Age-period-cohort (APC) models, as well as age-period (AP) and age-cohort (AC) models, have been used extensively in the literature to describe disease trends in populations,[2–6] and in particular for cervical cancer.[7 8] We present here a longitudinal analysis of cervical cancer incidence rates in Hong Kong from 1972 through 2001, using APC methods to decompose the independent effects of chronological age, time period, and birth cohort. In particular, we analysed the data using both the frequentist maximum likelihood approach as well as Bayesian methods.

METHODS

Sources of data

Data on cervical cancer incidence were obtained from the Hong Kong Cancer Registry. Details of the history, objectives, logistics, and registration coverage of the cancer registry are reported elsewhere.[9] Briefly, the Hong Kong Cancer Registry is a population based registry covering the entire resident population of Hong Kong. Information on cervical cancer cases were collected from both the private and public service sectors (mainly through departments of clinical and radiation oncology and histopathology), and from the government's Births, Deaths and Marriages Registry, as well as voluntary notification from all medical practitioners. The completeness and quality of the data has been reported to be good, with over 95% coverage for most cancers although there has not been detailed audits for each cancer specifically, especially in the past 20 years although like most other such registries worldwide there was probably relative underreporting in the 1970s compared with the post-1980 period.[9] The Hong Kong Cancer Registry is an accredited member of the International Association of Cancer Registries. Data on mid-year population statistics were derived from the government's Census and Statistics Department.

These analyses were based on 15 140 cases (of a total of 15 238 cases where the age at diagnosis was unknown in 98 cases) of invasive cervical cancer (*International Classification of Disease 8th edition* (ICD-8) and ICD-9 code 180) reported from all medical institutions in Hong Kong during a 30 year period from January 1972 to December 2001.

Statistical analysis

Age adjusted incidence rates were calculated by direct standardisation according to the World Standard Population and expressed per 100 000 female population.[10] To explore the effects of calendar time period and cohort on disease trends, we plotted age specific incidence by year of diagnosis (that is, cancer registration) and of birth.

Table 1 Age specific average annual percentage change (AAPC) of cervical cancer incidence in Hong Kong, 1972–2001

Age (years)	Linear model		Model with a quadratic trend term	
	AAPC for 1972–2001 (%)	p value	Sign of the second order term	p Value
25–29	−3.54	0.001	−	0.51
30–34	−4.10	<0.001	+	0.68
35–39	−3.99	<0.001	−	0.87
40–44	−4.32	<0.001	−	0.36
45–49	−4.75	<0.001	−	0.14
50–54	−4.34	<0.001	−	0.84
55–59	−4.65	<0.001	−	0.001
60–64	−4.16	<0.001	−	<0.001
65–69	−2.99	<0.001	−	0.18
70–74	−2.23	<0.001	−	0.001
75–79	−1.20	0.02	+	0.15
80–84	0.001	0.90	−	0.06
85+	−2.12	0.01	+	0.38
25–84	−4.20	<0.001	−	0.46
Age standardised	−3.95	<0.001	−	0.01

Maximum likelihood approach

Secular trends in cervical cancer incidence based on annual data were first examined with a simple log-linear regression model. This model formed the basis for the estimates of average annual percentage change (AAPC) in incidence rates with time periods. A two tailed test of statistical significance was applied to the AAPC.[11] The second order polynomial model with a quadratic trend term was also constructed to test for possible non-linear trends.

We further analysed the independent effects of chronological age, time period, and birth cohort on cervical cancer incidence trends using APC modelling. Cases were grouped into five year age groups (from 25–29 years to 80–84 years). There were very few cases in the age groups below 25 years or above 85 years and resultant rates were unstable, we therefore omitted these age groups from the analysis. Similarly, the time period of diagnosis were divided into five year intervals from 1972–76 to 1997–2001. A two way table of age group by time period was constructed giving a total of 12 age groups, six time periods, and 17 synthetic birth cohorts (on the diagonals from left to right, starting with each of the 12 age groups in the earliest time period of 1972–76, then five additional birth cohorts for each of the remaining time periods) (table A1 in the appendix).

To obtain the effects of age, period, and cohort, a log-linear model was fitted to the data by assuming a Poisson distribution for the observed number of cervical cancer cases, and that incidence rates are a multiplicative function of the model parameters.[12–15] Let c_{ij} be the observed cases for age group i in time period j. We assumed that it follows a Poisson distribution with mean μ_{ij}, that is, $c_{ij} \sim Poisson\ (\mu_{ij})$ and we modelled the mean as:

$$\log(\mu_{ij}) = \log(n_{ij}) + \alpha_i + \beta_j + \gamma_k + \varepsilon_{ij}$$

where α_i is the age effect ($i = 1, \ldots, I$), β_j is the period effect ($j = 1, \ldots, J$) and γ_k is the cohort effect ($k = 1, \ldots, K$ where $k = I+j−i$ and $K = I+J−1$); n_{ij} denotes the total number of person years for age group i in time period j; and ϵ_{ij} is the random error term.

The parameter estimates were the maximum likelihood estimates. In our study, the calendar period 1977–81 and birth cohort with central year of birth 1922 were adopted as reference categories. A sequence of models was fitted to the data, starting with the single factor age model, then the two factor age drift, AP and AC model and the full three factor APC model.

A fundamental problem of the APC modelling is the non-identifiability problem when all the three variables, namely, age, period, and birth cohort are included into the model simultaneously. The three variables are not independent (cohort = period – age) such that the chosen solution to the model is not unique, although each set of solution produces the same fitted rates. The technique adopted in this paper had been commonly used in several previous studies.[6 16 17] Specifically, the regression coefficients of the first and last period were both constrained to be zero, the first order relative risk estimates for the cohort effects can thus be estimated for a particular set of APC parameters. Likewise, the regression coefficients of the first and last cohorts were constrained to equal zero thereby obtaining relative risks for the period effects.

The deviance of the model was used as a measure of the goodness of fit. It is the log-likelihood ratio statistic

Table 2 Summary statistics comparing goodness of fit for different cervical cancer maximum likelihood models

Model	Degrees of freedom	Deviance	p Value*	Adjusted R²†
Age	60	1805.2		
Age drift ‡	59	270.9		0.85
Age period	55	214.6	<0.001	0.87
Age cohort	44	111.0	<0.001	0.92
Age-period-cohort	40	68.5		0.94

*p Values are based on the F test for comparisons between two factor model with the full age-period-cohort model.[18] †Adjusted R² measures how much of the variability that is explained by factors other than age, taking into account the difference in the numbers of degrees of freedom.[15] ‡The ''drift'' parameter represents a log-linear change in rate not exclusively identifiable as a period or cohort effect.

comparing the fitted model with the model with a perfect fit (one parameter per observation in the dataset). The presence of second order period or cohort effects was tested by comparing the change in deviance between the respective models and the full APC model using the F test.[18] For instance, when testing for the importance of cohort effects, a substantial change in the deviance between the AP model and the APC model implies a significant contribution of cohort effects; and similarly for testing the added contribution of period effects. This set of statistical analyses was performed using SAS version 8.02.

Bayesian approach

For comparison purposes, we also applied the Bayesian framework to the APC modelling. The Bayesian approach combines prior knowledge with observed data to derive a posterior distribution (posterior distribution $\propto$ prior distribution $\times$ likelihood), from which we can draw inferences about parameters or functions of the parameters. The analysis was based on single calendar years (but still five year age groups).

A hierarchical model was assumed with a binomial model in the first stage: $c_{ij} \sim Binomial\ (n_{ij},\ \pi_{ij})$ such that the classic APC model could be adopted which decomposes the log odds

$\eta_{ij} = \log\left(\dfrac{\pi_{ij}}{1 - \pi_{ij}}\right)$ additively into an overall μ level, age effects α_i ($i = 1, \ldots, I$), period effects β_j ($j = 1, \ldots, 5J$) and cohort effects γ_k ($k = 1, \ldots, K$ where $k = 5(I-i)+j$ and $K = 5(I+J-1)$:

$$\log\left(\frac{\pi_{ij}}{1 - \pi_{ij}}\right) = \eta_{ij} = \mu + \alpha_i + \beta_j + \gamma_k$$

The parameters α, β, and γ were given prior distributions to obtain posterior distributions through simulations rather than analytically. Trends corresponding to age, period, and birth cohort were smoothed using a first order random walk model to constrain parameter estimates from deviating

excessively from those in adjacent time bands[19]:

$$\alpha_i \sim Normal\left(\alpha_{i-1}, \frac{1}{\kappa}\right),\ i = 2, \ldots, I$$

with a flat prior for α_1 and $\kappa \sim\ Gamma(a, b)$

where the hyperparameter κ was a precision parameter determining the smoothness of the age effects. The same type of prior was used for the period and cohort parameters β and γ with precision parameters λ and ν respectively. The full conditionals for the age, period, and cohort effects thus followed a multivariate Gaussian distribution. These distributions were rewritten into a linear Gaussian state space model for efficient implementation.[19]

This model was implemented using the software BAMP (BAMP v1.3.0). Parameter estimates and 90% credible intervals were obtained by Markov chain Monte Carlo simulations in state-space models. The simulations were run for 1 010 000 iterations with the initial 10 000 iterations used as burn-in to minimise the effect of initial values. Highly non-informative values were chosen for the hyperpriors of the precision parameters κ, λ and ν, namely, $Gamma(1, 0.0005)$.

RESULTS

Age standardised as well as age specific trends in incidence rates over the entire period of observation were plotted on a logarithmic scale in figure 1. For clarity of presentation, only data for every other five year age group are shown. The overall age adjusted incidence decreased from 24.9 in 1972–74 to 9.5 per 100 000 in 1999–2001, in a log-linear fashion. This incidence decline in time was evident in all age groups (except in those 80 years and above). Figure 2 presents the age specific incidence by 10 year birth cohorts where the parallelism in the curves shows decreasing incidence with each successive generation.

Assuming that the rate of change was constant throughout the observed period, we computed the AAPC from a simple log-linear regression model (table 1). The overall age
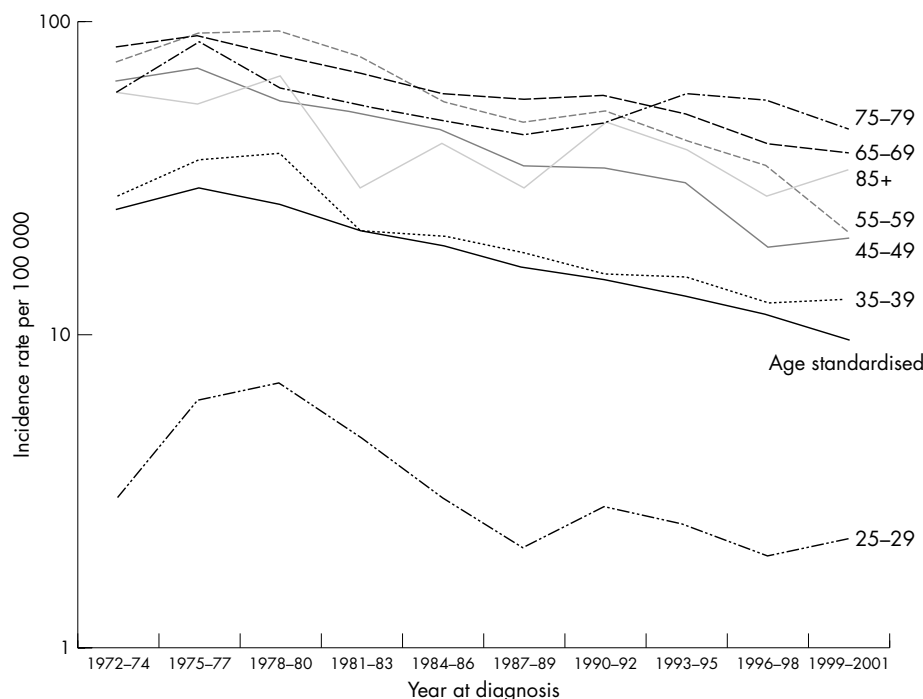

Figure 1 Age standardised (world standard population) and selected age specific incidence rates for cervical cancer by year of diagnosis in Hong Kong, 1972–2001.
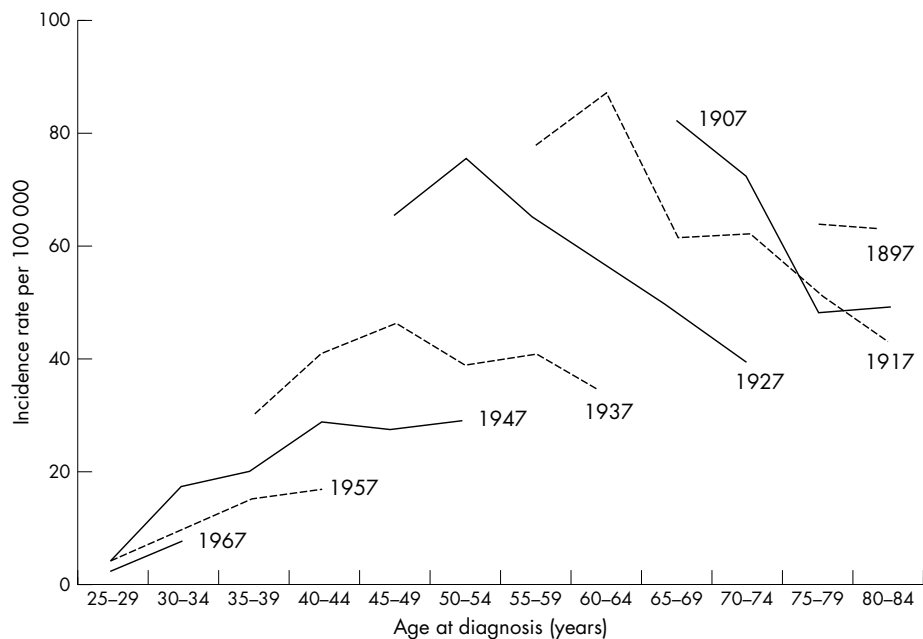
Figure 2 Age specific incidence of cervical cancer by birth cohort.

standardised incidence decreased annually by 4.0% during the 30 year period. Significant negative changes were registered in almost all age groups ranging from −4.8% to −1.2%, except for the 80 and above age group. With non-statistically significant exceptions in only two age groups, the second order quadratic terms were uniformly negative for all other age specific strata and overall. The negative coefficient of the quadratic term attempts to take into account the initial increase in rates in the early 1970s (and subsequent steady decrease after around 1977).

Maximum likelihood APC models were fitted to the data from 1972 to 2001. Table 2 shows the change in deviance (that is, showing goodness of fit) in the sequential building of the models. Both the AP and AC models significantly improved the fit over the age only and age drift models. The full three factor model was in turn significantly better than the two factor AP (p<0.001) and AC (p<0.001) models as shown by the *F* test.

Figure 3 compares relative risks calculated by time period and birth cohort based on two separate full APC models with period and cohort constraints imposed with Bayesian posterior estimates of the APC parameters. The slope of the time period effects curve decreased in the late 1970s. Similarly, with the exception of the earliest birth cohort with central year of birth in 1892, the slope of the birth cohort effects curve also declined. We obtained mostly consistent results under the Bayesian analytical framework. The age parameter shows the typical decelerating rise where the slopes were steepest for young women and progressively levelled off in the older age groups. Period effects show a log-linear decline from the second five year period beginning in 1977. The Bayesian estimates suggest that there may have been an additional short term second order, and thus identifiable, change in period effects—the hook caused by an upturn in rates in 1982 and 1983. Both the maximum likelihood and Bayesian birth cohort curves show one other clear identifiable change—that is, the decrease in slope around 1920. The possible increase in cohort slope in the early 1960s is not as evident in the maximum likelihood estimates as in the Bayesian estimates (the smoothing of the Bayesian method makes this change look much more evident than is warranted based on age specific rates), and given the variability of estimates for recent cohort effects because of

the comparatively smaller number of cases as these women would not have borne the full potential cancer burden yet, may or may not reflect an actual change.

Figure A1 in the appendix shows the observed and fitted number of incident cervical cancer cases with associated 90% credible regions by alternate five year age groups in different panels. Visual inspection shows that the model fit was generally good, except in the extremes of age where there were comparatively fewer cases. Quantitatively assessing model fit,[19] the median posterior deviance ranged from 351 to 396, which were very close to the asymptotically optimal value of 360 (= 12×30)—that is, the number of observations entered into the model.

DISCUSSION

We found that the overall age standardised incidence of cervical cancer had recorded statistically significant average annual decreases of 4.0% in the period of observation. The reduction was more pronounced for those aged 30 to 65 years although women of all ages showed some incidence decline. While age is positively associated with cancer rates, figures 1 and 2 confirm that both calendar period and birth cohort trends have been decreasing throughout the duration of observation. Thus although the linear period and cohort slopes in the full APC models are not identifiable because they were separately constrained to be zero in the methods to derive the other set of estimates, we can conclude that the observed negative trends for calendar period and birth cohort in figure 3 are in fact real.

Interpretation of APC analyses is difficult largely because of the lack of good data on trends in risk factors or medical practice. While definitive inferences about the impact of Pap testing on cervical cancer rates should ideally be based on both additional years of incidence data (for example, incidence rates beginning in 1960 or earlier) and detailed quantitative information on secular trends in Pap test use by age, neither are available in Hong Kong (or indeed most countries) for such a long time series but this should not preclude educated postulation of plausible hypotheses as we set out as follows.

Two second order and thus identifiable changes in the period and cohort effect curves merit special attention, as indicated by the inflection points (1) centred around the
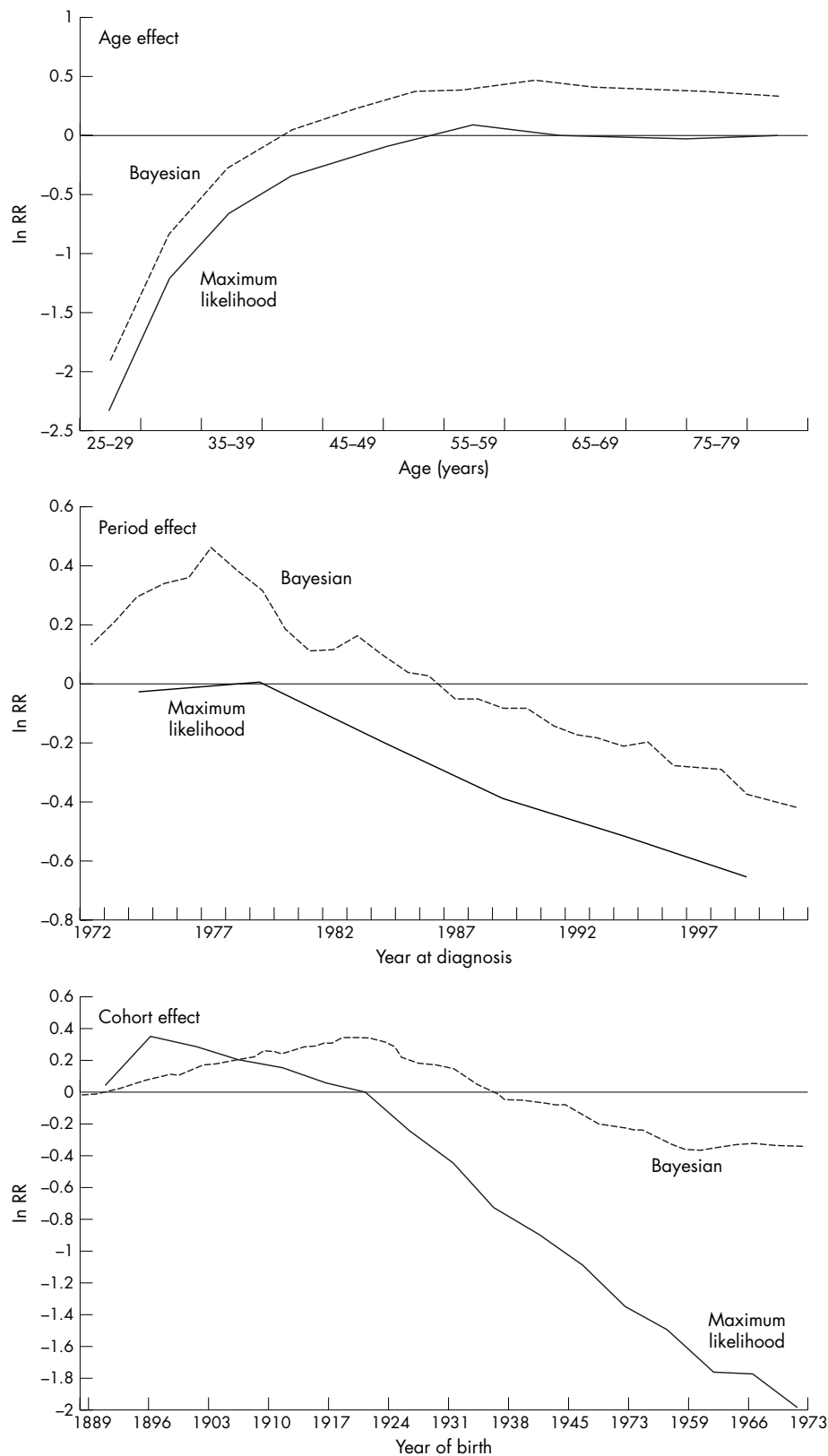
Figure 3 Maximum likelihood and Bayesian posterior median estimates for age, period, and cohort parameters in the cervical cancer incidence model. RR, relative risk.

mid-1920s on both the maximum likelihood and Bayesian birth cohort curves and (2) for the calendar years 1982–3 on the Bayesian period curve (fig 3).

Women born in the 1920s were the first to have had an opportunity to be screened when they were in their 40s (around 1960s) with the advent of the Pap smear that was available in Hong Kong soon after its introduction in the West. This is the same age group who are the most likely to have been screened (fig A2 in the appendix). Therefore, although the introduction of an efficacious detection method such as screening Pap smear would ordinarily be expected to appear as a change in the period effects curve, it is possible

that an age-period interaction masqueraded as the observed cohort change if most of those screened (and benefited from such) when Pap smears became available in the 1960s were concentrated in the then 40 year olds (that is, belonging to the 1920s birth cohorts). Moreover, the time series of cancer registration did not stretch back far enough to the 1960s to detect this expected change in the period slope. We are additionally hampered by underregistration of cases in the early years of operation of the Hong Kong Cancer Registry. Probable underregistration of cancer cases in the 1970s could explain the consistent observation in both the Bayesian and maximum likelihood models that period effects in the early to mid-1970s seemed to be more dampened than would otherwise be expected if recent trends were backwards extrapolated. Such underreporting has been widely recognised and previously acknowledged. Nevertheless, such a phenomenon would most probably have been non-differential given Hong Kong's universal access to and market share dominance of the public sector since the 1960s and therefore would not have posed any significant threat to validity. However, given the lack of detailed coverage data from audits over time, it is impossible to adjust our results to formally take this into account.

Regarding the second identifiable change in the period slope, it probably represents an initial, transient increase in rates due to ''harvesting'', coinciding with the time of the introduction of systematic antenatal screening in the early 1980s and therefore a sudden surge in population coverage. This period change in screening practice punctuates a sustained log-linear decrease in cancer rates since the 1970s (more probable since the 1960s although there are no data to quantitatively substantiate such as discussed above) up to the present (fig A1 and table A1 in the appendix).

According to the 2003 population household survey,[20] only 42.3% of local women aged at least 21 years reported ever being screened by cytological smear, of whom 99.6% were tested in the previous five years and 57.2% attended on a regular basis. Two other independent population surveys in 1997–8[21] and 2003[22] corroborate these statistics. However, there is strong qualitative evidence to suggest that starting from the early 1980s most Hong Kong women had received a Pap smear as part of routine antenatal care, although a substantial number did not apparently realise it. Given that over 90% of all local pregnant women had received at least one episode (median roughly 2.5) of antenatal care since the early 1980s,[23] we adjusted the proportion ever screened to take into account this probable underreporting by reassigning a positive ever screened response to all women who reported no screening, were ever pregnant resulting in a live birth since 1980, and belonged to birth cohorts with central year of birth in 1950 or later, assuming a median age of first pregnancy at 29 years.[24] Figure A2 in the appendix shows that the potential magnitude of underreporting was large where the overall adjusted ever screening rate increased to 60.6%. This figure represents an upper limit because not all pregnant mothers received antenatal care, nor would every one have received a Pap smear during antenatal visits, and not all women would have underreported Pap screening as part of routine antenatal care. In comparison, screening penetration rates had reached 75% (enrolled in national every five year screening program) in Finland by 1975,[25] 85% (ever screened among those aged at least 15 years) in Canada by 1985,[26] 88% (ever screened among those aged at least 18 years) in the USA by 1987,[27] and 85% (screened at least once within five years) in the UK by 1995.[28]

Since the establishment of human papillomavirus (HPV) as a necessary cause of cervical cancer in the 1990s,[29] disease risk should be examined from the perspective of mediating viral infection or modulating events in the natural history of cervical neoplasia after HPV acquisition.[30] Considering relevant markers of sexual activity, in Hong Kong as elsewhere, the mean age of first sexual activity has been decreasing while the number of premarital sexual partners and the proportion who reported having premarital sex both increased, according to routine sexual health surveys conducted by The Family Planning Association of Hong Kong since the late 1960s.[31] In tandem with progressively more liberal sexual practices, current male condom use has increased by a whole order of magnitude from 3.5% among 15 to 49 year olds in 1972 to 37.8% in 1997.[32] This might have buffered against an even bigger epidemic of HPV infection, which is as common in Hong Kong women as for others worldwide where a bimodal age dependent point prevalence profile is characteristic. In Hong Kong and other western countries, about one fifth of young women in their 20s are typically infected; the prevalence then declines through their 30s and 40s only to peak again during the sixth decade to about 10%.[33][34] In terms of the distribution of HPV subtypes in Hong Kong, HPV-16 were isolated in 61.7% and HPV-18 in 14.8% of cervical cancer patients in a large consecutive case series,[35] which are similar to overseas figures reported by the International Biological Study on Cervical Cancer (IBSCC) study group.[36] However, subtypes 58 and 52, comparatively rare in the rest of the world, were found to be the third and fourth commonest genotypes in Hong Kong and China.[35] These two strains are phylogenetically similar to subtypes 16, 31, 33, 35, and 67, which may show similar pathogenic

What this paper adds

- Whereas most rich, developed countries have long adopted organised cervical cytology screening, Hong Kong provides a unique, contemporaneous setting to study the secular effects of opportunistic screening that can be compared with overseas settings at an advanced stage of socioeconomic development as well as forewarn the coming epidemiological transition facing mainland China.

- The secular decline of cervical cancer rates in Hong Kong can be similarly attributed to both period and cohort effects, in contrast with the dominant impact of inter-generational change in most other populations.

- We propose that Hong Kong's cervical cancer rates have declined since Pap tests first became available in the 1960s because of increasing population coverage over time and in successive generations largely in a haphazard fashion and punctuated by the systematic introduction of routine cytology as part of antenatal care in the 1980s.

Policy implications

Hong Kong's experience bears enormous policy significance for mainland China as modernisation and rapid socio-economic transition, from the eastern coastal provinces moving westwards inland, will probably bring about increasing availability of opportunistic screening. However, while overall population coverage is an important indicator of public health success, policymakers should be sensitive to and guard against the potential for the inverse care law in screening uptake.

potential. Thus the higher sexual behavioural risk in successive generations (resulting in similar profiles of HPV infection prevalence in the general population and specific subtypes among cancer patients between Hong Kong and other western populations) in itself would have led to an increase in cervical cancer rates in contrast with the overall decline as seen. This suggests the presence of other counter-effects, such as screening as shown by the two identifiable changes as previously explained, on the population level that have been driving down cervical cancer rates.

Therefore, we propose that Hong Kong's cervical cancer rates have come down steadily since the 1960s when Pap tests first became available, because of increasing population coverage over time and in successive generations largely in a haphazard fashion and punctuated by the systematic introduction of routine cytology as part of antenatal care in the 1980s. It has long been argued that opportunistic screening can reduce cervical cancer rates, but probably not to the extent of organised programmes.[37][38] It is unclear by how much Hong Kong's incidence will further decrease after the introduction of the population based recall programme in 2004 (that is, its marginal effect in addition to the population impact of the status quo of opportunistic screening) although we do not anticipate the magnitude to be as substantial as historically (see appendix for further details on the recall programme). Taking reference from the experience of England and Wales, Peto and colleagues[39] argued that the 42% decrease in cervical cancer incidence between 1988 and 2000 in the UK was directly attributable to its National Health Service Cervical Screening Programme launched in 1988. Whether Hong Kong can achieve a similar relative decrease in incidence rates after organised screening should be prospectively evaluated.

Comparing the two statistical approaches undertaken in this study, a priori, Bayesian inference may offer a more robust approach to model estimation, especially when there are only sparse data, than the classic approach of maximum likelihood that depends on the assumption of asymptotic normality. The sampling based method of Bayesian estimation also provides a full distributional profile of the parameters and can take into account additional unstructured heterogeneity.[19] Empirically, we showed that our findings are consistent between and robust to the two estimation methods. Hence this lends added credence to the validity of our data.

A potential caveat regarding histological subtypes of cervical cancer and the interpretation of disease trends bears mention. It has been suggested that cytological screening may be less effective in detecting adenocarcinoma compared with squamous tumours.[40][41] Unpublished data from the American College of Pathologists accredited cervical cyto-pathology laboratory of Queen Mary Hospital, a high volume tertiary referral facility show that there was little difference in adenocarcinoma incidence as a proportion of all invasive cancers diagnosed between 1993–6 (22.2%) and 2000–3 (21.8%) (unpublished data from ANYC, gynaecological pathologist in charge of review of oncology cases). However, there was a relative increase in the proportion of carcinoma of mixed histological differentiation (adenosquamous) from 3.6% to 4.9% and other rare tumours (for example, mucoepidermoid tumours, melanoma, sarcoma) from 1.3% to 1.8% as a percentage of all invasive tumours. Although longer term or more population based data on histological subtypes are lacking, the available information do not seem to substantiate the previous observation although it could well be attributable to the as yet suboptimal impact of haphazard screening in reducing the burden of the dominant type squamous tumours, hence the relative

proportion of the much less common adenocarcinoma remains small and static in comparison.

It is important to bear in mind that our interpretation of the findings should be treated as hypotheses to be further examined with other study designs and in different settings because it is difficult to evaluate such on the basis of non-experimental evidence, especially on the ecological level. Nevertheless, Hong Kong's experience has provided informative lessons on the natural history of opportunistic screening and its secular effects in a developed Chinese population.

Finally, Hong Kong's experience bears enormous policy significance for mainland China. Given the present state of health care financing and delivery, which is mostly devolved and unregulated, China is unlikely to be able to centrally plan and implement an organised screening programme with adequate national or even regional coverage. Nevertheless, as modernisation and rapid socioeconomic transition from the eastern coastal provinces moving westwards inland will probably bring about increasing availability of opportunistic screening, our findings show that it may be possible to achieve a sustained reduction in cervical cancer incidence burden, given that an intact and functional management infrastructure for screen positive cases exists. However, while overall population coverage is an important indicator of public health success, policymakers should be sensitive to and guard against the potential for the inverse care law in screening uptake.

. . . .

Authors' affiliations

G M Leung, P P S Woo, S M McGhee, T Q Thach, Department of Community Medicine and School of Public Health, University of Hong Kong, Hong Kong, China
A N Y Cheung, Department of Pathology, University of Hong Kong
S Fan, The Family Planning Association of Hong Kong, Hong Kong, China
O Mang, Hong Kong Cancer Registry, Hospital Authority, c/o Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, China
H Y S Ngan, Department of Obstetrics and Gynaecology, Queen Mary Hospital, University of Hong Kong

REFERENCES

1 **Department of Health**. *Annual report 2002/2003*. Hong Kong: Government Printers, 2003.
2 **Osmond C**, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. *Stat Med* 1982;**1**:245–59.
3 **Zheng T**, Mayne ST, Holford TR, *et al*. The time trend and age-period-cohort effects on incidence of oesophageal cancer in Connecticut, 1935–89. *Cancer Causes Control* 1992;**3**:481–92.
4 **Adami HO**, Bergstrom R, Sparen P, *et al*. Increasing cancer risk in younger birth cohorts in Sweden. *Lancet* 1993;**341**:773–7.
5 **Persson I**, Bergstrom R, Sparen P, *et al*. Trends in breast cancer incidence in Sweden 1958–1988 by time period and birth cohort. *Br J Cancer* 1993;**68**:1247–53.
6 **Leung GM**, Thach TQ, Lam TH, *et al*. Trends in breast cancer incidence in Hong Kong between 1973 and 1999: an age-period-cohort analysis. *Br J Cancer* 2002;**87**:982–8.
7 **Wang PD**, Lin RS. Age-period-cohort analysis of cervical cancer mortality in Taiwan, 1974–1992. *Acta Obstet Gynecol Scand* 1997;**76**:697–702.
8 **Sasieni 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.
9 **Hong Kong Cancer Registry**. *Cancer incidence and mortality in Hong Kong 1995–1996*. Hong Kong: Hospital Authority, 1999.

10 **Segi M**. *Cancer mortality for selected sites in 24 countries (1950–1957)*. Sendai, Japan: Tohoku University Press, 1960.
11 **Tarone RE**, Chu K. Implications of birth cohort patterns in interpreting trends in breast cancer rates. *J Natl Cancer Inst* 1992;**84**:1402–10.
12 **Clayton D**, Schifflers E, Models for temporal variation in cancer rates I: age-period and age-cohort models. *Stat Med* 1987;**6**:449–67.
13 **Clayton D**, Schifflers E. Models for temporal variation in cancer rates II: age-period-cohort models. *Stat Med* 1987;**6**:469–81.
14 **Holford TR**. The estimation of age, period, and cohort effects for vital rates. *Biometrics* 1983;**39**:311–24.
15 **Holford TR**. Understanding the effects of age, period, and cohort on incidence and mortality rates. *Annu Rev Public Health* 1991;**12**:425–57.
16 **Tarone RE**, Chu K. Evaluation of birth cohort patterns in population disease rates. *Am J Epidemiol* 1996;**143**:85–91.
17 **Shahpar C**, Li G. Homicidal mortality in the United States, 1935–1994: age, period and cohort effects. *Am J Epidemiol* 1999;**125**:1213–22.
18 **McCullagh P**, Nelder J. *Generalised linear models*. 2nd ed. London: Chapman and Hall, 1983.
19 **Knorr-Held L**, Rainer E. Prognosis of lung cancer mortality in West Germany: a case study in Bayesian prediction. *Biostat* 2001;**2**:109–29.
20 **The University of Hong Kong**. *Population health survey report*. Hong Kong: Department of Health, Government of the Hong Kong Special Administrative Region, People's Republic of China, 2005.
21 **Adab P**, McGhee SM, Yanova J, *et al*. Effectiveness and efficiency of opportunistic cervical cancer screening: comparison with organized screening. *Med Care* 2004;**42**:600–9.
22 **Hong Kong Census and Statistics Department**. *Thematic household survey report no 12*. Hong Kong: Government Printers, 2003.
23 **Leung GM**, Lam TH, Thach TQ, *et al*. Rates of cesarean births in Hong Kong: 1987–1999. *Birth* 2001;**28**:166–72.
24 **Hong Kong Census and Statistics Department**. Total live births by age of mother. In: *Hong Kong annual digest of statistics 1972–2002*. Hong Kong: Government Printers, 1973–2003.
25 **Anttila A**, Nieminen P. Cervical cancer screening programme in Finland. *Eur J Cancer* 2000;**36**:2209–14.
26 **Snider J**, Beauvais J, Levy I, *et al*. Trends in mammography and pap smear utilization in Canada. *Chronic diseases in Canada* 1996;**17**:108–17.
27 **Breen N**, Kessler L. Trends in cancer screening—United States, 1987 and 1992. *MMWR Morb Mort Wkly Rep* 1995;**45**:57–61.
28 **Department of Health**. *Cervical screening programme, England: 1994–95 to 1996–97*. London Department of Health (Statistical bulletins 1996/3, 1996/26, 1997/27).
29 **Bosch FX**, Lorincz A, Munoz N, *et al*. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;**55**:244–65.
30 **Franco EL**, Schlecht NF, Saslow D. The epidemiology of cervical cancer. *Cancer J* 2003;**9**:348–59.
31 **The Family Planning Association of Hong Kong**. Report on the survey family planning in Hong Kong: knowledge, attitude and practice in 1967, 1972, 1977, 1982, 1987, 1992, 1997 and 2002.
32 **The Family Planning Association of Hong Kong**. Youth sexuality study reports in 1981, 1986, 1991, 1996 and 2001.
33 **Bekkers RLM**, Massuger LFAG, Bulten J, *et al*. Epidemiological and clinical aspects of human papillomavirus detection in the prevention of cervical cancer. *Rev Med Virol* 2004;**14**:95–105.
34 **Chan PK**, Chang AR, Cheung JL, *et al*. Determinants of cervical human papillomavirus infection: differences between high- and low-oncogenic risk types. *J Infect Dis* 2002;**185**:28–35.
35 **Lo KW**, Wong YF, Chan MK, *et al*. Prevalence of human papillomavirus in cervical cancer: a multicenter study in China. *Int J Cancer* 2002;**100**:327–31.
36 **Bosch FX**, Manos MM, Munoz N, *et al*. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst* 1995;**87**:796–802.
37 **Lynge E**, Madsen M, Engholm G. Effect of organized screening on incidence and mortality of cervical cancer in Denmark. *Cancer Res* 1989;**49**:2157–60.
38 **Nieminen P**, Kallio M, Anttila A, *et al*. Organized versus spontaneous pap-smear screening for cervical cancer, a case control study. *Int J Cancer* 1999;**83**:55–8.
39 **Peto J**, Gilham C, Fletcher O, *et al*. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004;**364**:249–56.
40 **Paloma VA**, Moreno V, Bosch F, *et al*. International trends in incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. *Int J Cancer* 1998;**75**:536–45.
41 **Paloma VA**, Moreno V, Bosch F, *et al*. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. *Int J Cancer* 2000;**86**:429–35.

APPENDIX

Hong Kong launched a quasi organised screening programme in March 2004 (http://www.cervicalscreening.gov.hk/). Because of resource constraints, this government operated programme mainly provides a prospective record and recall function for those who have ever been screened. The programme encourages women to undergo regular cytological examination through social marketing campaigns for the general public and via primary care and women's health providers to women on an opportunisitic basis. For those women who decide to get screened, they can seek to be tested at public or private care providers on a full fee for service basis using either traditional Pap smear or liquid based method with/without human papillomavirus (HPV) testing. These providers are then encouraged to enter the screened woman's details into a centralised database for subsequent automatic recall (every three years) and archiving of test results. Therefore, without explicitly anchoring the programme with proactive, personalised invitation to be screened (initial ''call'' function) and direct provision of Pap testing at dedicated facilities for a reasonable fee (as compared with full market rates), it is a suboptimal arrangement compared with standard practice in Canada, UK, and other European countries, for example. Nevertheless, referral for colpolscopy and subsequent management in the case of invasive disease are available in both the public and private sectors, where the former essentially provides universal access to all services with minimal copayments (amounting to an all inclusive daily charge of less than £7 or US$13) at the point of care. Indeed, the public sector provides 95% of total bed days for all inpatient care locally. As at March 2005 after 12 months in operation, just under 120 000 (4.8%) women out of a potentially eligible female population of 2.5 million aged 21 to 69 years have been registered, even though we know that between 42% to 60% of local women reported being ever screened in the past five years. It remains to be seen whether the projected benefits of organised screening can be realised, perhaps with modification and enhancements subsequently to the present programme arrangements.

Table A1 Age standardised (world standard population) and age specific incidence rates (per 100 000 women) of cervical cancer in Hong Kong, 1972–2001

Age (years)	Time period (calendar year)					
	1972–76	1977–81	1982–86	1987–91	1992–96	1997–2001
25–29	4.05 (28)	6.37 (66)	3.78 (52)	2.57 (39)	2.14 (31)	2.15 (31)
30–34	16.65 (76)	17.26 (129)	11.74 (131)	9.66(137)	6.25 (104)	7.49 (123)
35–39	29.81 (164)	35.07 (172)	20.28 (163)	16.43 (188)	15.17 (228)	12.54 (225)
40–44	51.17 (314)	40.90 (237)	33.63 (183)	28.99 (236)	21.06 (249)	16.82 (265)
45–49	65.45 (390)	58.87 (364)	46.08 (280)	34.30 (188)	27.54 (230)	19.76 (243)
50–54	76.57 (404)	75.55 (453)	61.60 (389)	38.76 (234)	34.00 (187)	29.04 (249)
55–59	77.64 (342)	89.17 (458)	64.68 (379)	50.25 (311)	40.76 (245)	25.93 (144)
60–64	84.58 (310)	86.66 (378)	83.29 (420)	56.18 (320)	43.98 (270)	33.35 (205)
65–69	82.47 (223)	79.45 (275)	61.21 (252)	57.87 (271)	48.18 (265)	38.82 (237)
70–74	70.62 (149)	72.00 (184)	62.47 (198)	62.20 (225)	48.80 (210)	39.18 (201)
75–79	63.73 (84)	70.74 (123)	47.96 (99)	46.52 (116)	51.58 (158)	50.61 (192)
80–84	40.35 (28)	63.05 (59)	51.24 (64)	48.95 (68)	48.34 (88)	42.52 (100)
Age standardised	25.90	26.02	20.21	15.81	12.94	10.29

Number of cases on which rates are based are in parentheses.

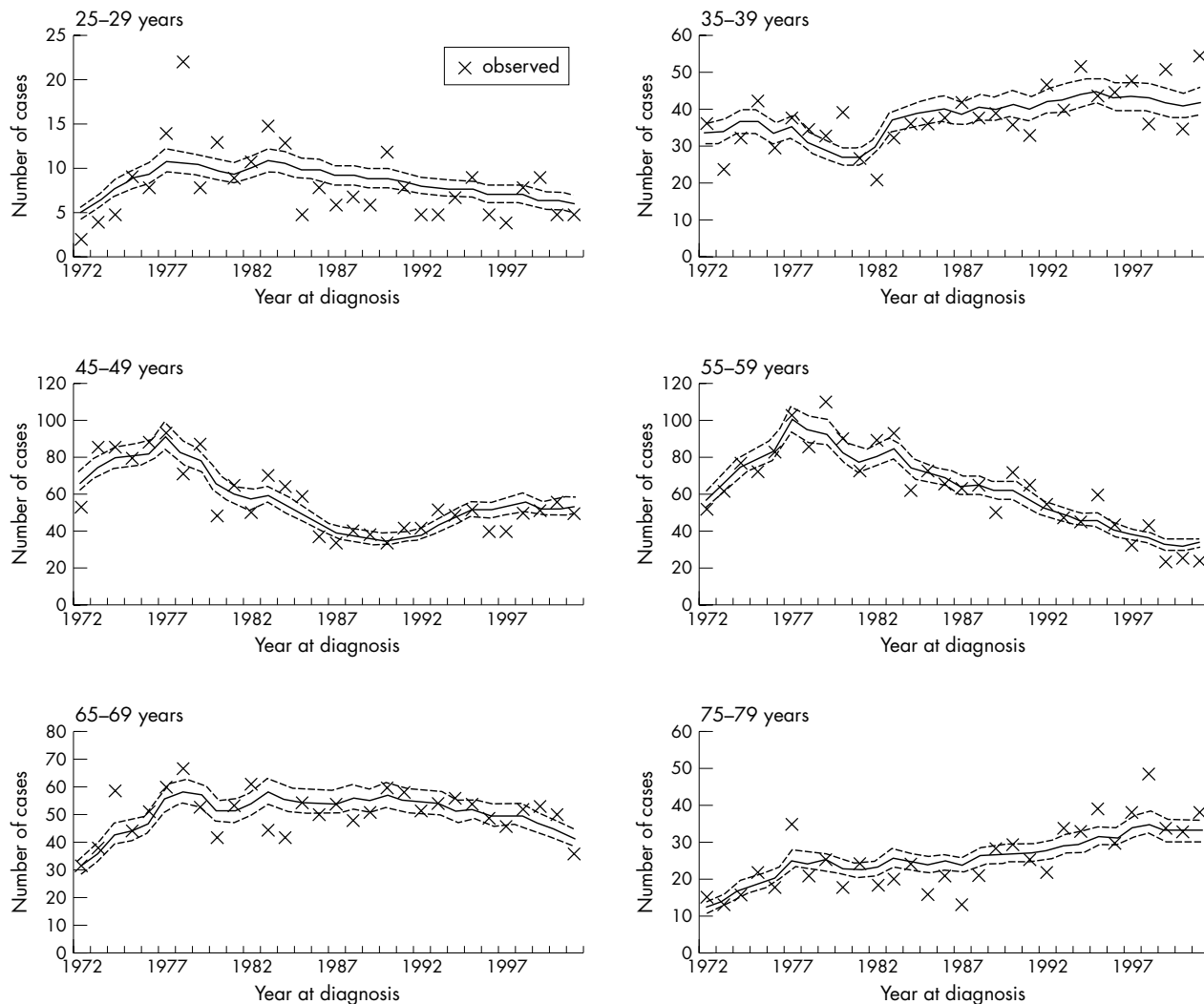Leung, Woo, McGhee, et al

Figure A1 Observed and fitted number of cervical cancer cases with associated 90% credible regions for selected age groups in Hong Kong, 1972–2001.
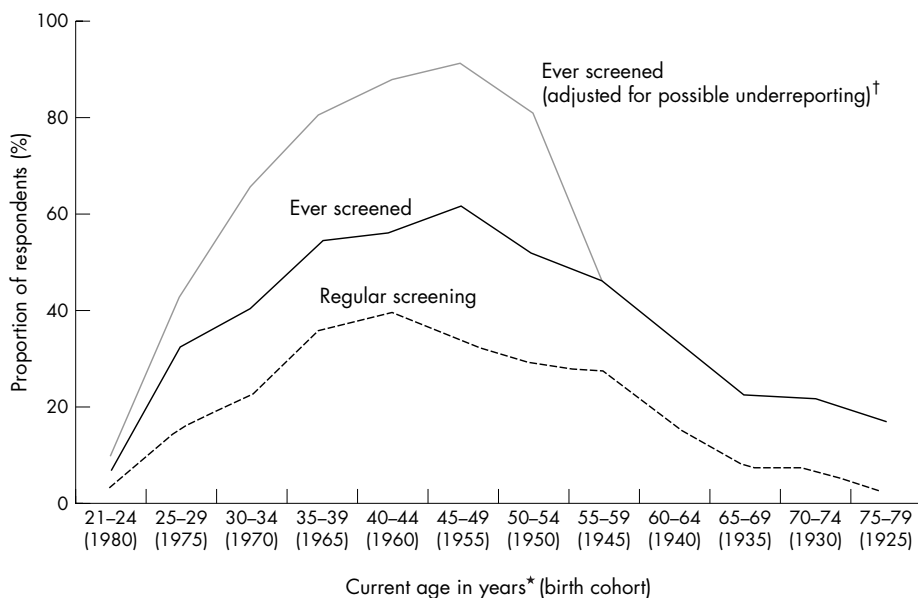

Figure A2 Proportion of Hong Kong female population ever screened and undergoing regular cytological examination by age (birth cohort). *As at 2003. †Assuming median age of first pregnancy is 29 years[24] and Pap smear became a routine part of antenatal diagnostics starting from 1980.