Patterns of and hypotheses for infection-related cancers in a Chinese population with rapid economic development

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SUMMARY

With economic development, non-communicable diseases replace infectious diseases as the leading cause of death; how such transition occurs for infectious diseases with long latency has rarely been considered. We took advantage of a Chinese population with rapid economic development in the mid-20th century to study changing patterns of infection-related cancers. We used sex-specific Poisson regression to estimate age, period and cohort effects on adult deaths 1976–2005 from eight infection-related cancers in Hong Kong. Cervical, head and neck, and oesophageal cancers, associated with sexually transmitted infections, decreased for the first birth cohorts with sexual debut in a more developed environment. Leukaemia and non-Hodgkin’s lymphoma, associated with vertically transmitted infections, decreased for the first cohorts born into a more developed environment. Birth cohort patterns were unclear for nasopharyngeal, stomach and liver cancers. Mortality rates for cancers related to early infections may depend on population history, with delayed reductions for some infection-related cancers.

Key words: Economic development, human papillomavirus, hepatitis B virus, Epstein–Barr virus infections, human T lymphotropic virus, Helicobacter pylori, cancer, mortality, Chinese.

INTRODUCTION

With economic development and epidemiological transition, non-communicable diseases replace infectious diseases as the leading causes of death [1]. However, the epidemiological transition classically describes a process since the start of the industrial revolution in long-term developed countries, while much more rapid economic development is currently taking place in many developing countries. How such rapid economic development affects patterns of infectious diseases with a long latency period has rarely been considered. Nevertheless, rapid and recent economic transition may be contributing to the relatively high rates of diseases such as tuberculosis [2], viral hepatitis [3], or infection-related cancers [4] in populations with a recent history of economic development or in migrants from poor to rich countries [5–7]. Here, we took advantage of a Chinese population with a recent and rapid epidemiological transition to delineate the impact on infection-related cancers, and thus to forewarn future disease patterns in other populations currently undergoing rapid economic development.

Uniquely, the Chinese population of Hong Kong is one of the first populations to experience very rapid economic transition from pre-industrial to post-industrial living conditions over a lifetime, i.e. the last
70 years. The Hong Kong population was formed by mass migration in the mid-20th century (1945–1955) from pre-industrial China to relatively developed Hong Kong [8, 9], where rapid development to a post-industrial economy continued [9]. As a result of this mass migration, the population experienced a ‘step-change’ in living conditions in the mid-1940s. A comparison between different birth cohorts shows the effect of this ‘step-change’ at different ages. In this unique setting, we used age-period-cohort (APC) models to estimate the effects of age, calendar period, and birth cohort on death from infection-related cancers. To provide aetiological insight, we hypothesized that cancers related to sexually transmitted infections with human papillomavirus (HPV) (cervical [10], head and neck [11] and oesophageal [12]) should decrease for the first birth cohorts with sexual debut in better living conditions, corresponding to the late 1920s birth cohorts. Cancers related to early childhood infection with Epstein–Barr virus (EBV) (nasopharyngeal) [13, 14] or Helicobacter pylori (stomach) [15] should decrease for the first birth cohorts in childhood in better living conditions, corresponding to the late 1930s/early 1940s birth cohorts. Finally, cancers related to vertically transmitted infections, such as human T-lymphotropic virus (HTLV) (leukaemia [16], non-Hodgkin’s lymphoma [17, 18]) or hepatitis B virus (HBV) (liver) [3] should decrease for the first birth cohorts born into better living conditions, corresponding to the late 1930s/early 1940s birth cohorts. We also considered two other cancers, colorectal and lung, specifically because these are not thought to be associated with infections. In this paper, we first explain the modelling approach; second, we give APC models for all the cancers considered; and third, we compare the observed cohort effects for each infection-related cancer with those expected in our setting given their mode of transmission.

METHODS

Data sources


Outcomes

We considered as the primary outcomes death from cancers related to sexually transmitted infections with HPV, to childhood infections with EBV or Helicobacter pylori and to vertical infections with HTLV or HBV. Cancers classified as related to sexually transmitted infections with HPV were cervical (ICD-8 and ICD-9 180, ICD-10 C53), head and neck excluding nasopharyngeal (140–146, 148–149, 160–161; C00–C10, C12–C14, C30–C32) and oesophageal (150, C15). Cancer classified as related to childhood infections with EBV or H. pylori were nasopharyngeal (147, C11) and stomach (151, C16), respectively. Cancers classified as related to vertical infection with HTLV were leukaemia (204–208, C91–C95) and non-Hodgkin's lymphoma (200, 202, C82–C85) and to vertical infection with HBV was liver (155, C22). For comparison, we also considered death from two major lifestyle-related cancers, i.e. colorectal (153–154, C18–C20) and lung (162, C33–C34) cancers.

Data analysis

Mortality rates for the population were expressed per 100 000 people, and directly standardized to the World Standard Population [19]. We used thirteen 5-year age groups from 25–30 years to 85 years and six 5-year calendar periods from 1976–1980 to 2001–2005, producing 18 birth cohorts from 1889–1893 to 1974–1978.

We used Poisson APC models to estimate relative risks by age, calendar period and birth cohort, with 95% confidence intervals. Under these models the numbers of new cases of each cancer were assumed to follow a Poisson distribution, where the incidence rates in the population were regressed on age, period, and cohort variables with a log link. APC models are a standard demographic tool to examine patterns in disease incidence at a population level [20]. We used Akaike’s Information Criterion (AIC) and likelihood-based tests to evaluate goodness-of-fit of models with age, period, and cohort variables with a log link. APC models are a standard demographic tool to examine patterns in disease incidence at a population level [20]. We used Akaike’s Information Criterion (AIC) and likelihood-based tests to evaluate goodness-of-fit of models with age, period, and cohort variables with a log link. APC models are a standard demographic tool to examine patterns in disease incidence at a population level [20].
varied within a group of cancers we compared a model which had one common birth cohort effect for all the cancers in the group with a model allowing the birth cohort effect to vary with cancer type (i.e. an interaction term for cancer type by birth cohort within group) from which we reported the $P$ values for the interaction terms [21] as shown in Table 1. We also similarly examined whether the birth cohort effects for each cancer differed from the birth cohort effects for colorectal or lung cancers as shown in Table 2.

A fundamental problem inherent in APC models is that age, period, and cohort are linearly dependent [22]. There are several ways to overcome this non-identifiability problem, including using an arbitrary additional reference constraint, estimating slopes (curvature) rather than regression coefficients, and fitting nonlinear effects for $\geq 1$ components [22]. The first method allows presentation of estimated effects as relative risks on age and time scales, although the non-identifiability problem remains and interpretation should focus on second-order changes (i.e. changes in slopes or inflection points) rather than the absolute values of the estimated risks. The second method directly estimates the slopes (curvature) and is useful in identifying inflection points but has only recently come into use. The third method is appropriate only when there is biological evidence of nonlinear effects [22]. We adopted the commonly used technique of constraining the second (1981–1985) and penultimate (1996–2000) periods to be reference categories [2, 23]. Similar results were obtained with different reference categories (data not shown). We also used the 55–59 years age group and the 1934–38 birth cohort as reference categories. Also due to linear dependency of age, period, and cohort, only second-order changes (i.e. changes in slopes or inflection points) are interpretable, rather than the absolute value of individual estimates [22]. We plotted the estimates for age, period, and cohort to facilitate visual identification of second-order changes, with women relative to men on the same graph. To confirm our interpretations, we also plotted the estimated curvature components, which clarify when second-order changes occur [22].

All analyses were implemented in R version 2.5.0 (R Development Core Team, Austria).

**RESULTS**

**Age-standardized mortality rates**

Figure 1 shows the observed age-standardized mortality rates in Hong Kong from 1976 to 2005.

### Table 1. Comparison of birth cohort effects for different cancers within mode of transmission group

<table>
<thead>
<tr>
<th>Transmission group</th>
<th>Infection</th>
<th>Cancer</th>
<th>Men</th>
<th>Women</th>
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<tr>
<td>Sexual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-related cancers in women</td>
<td>HPV</td>
<td>Cervical</td>
<td>n.a.</td>
<td>0·13</td>
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<tr>
<td></td>
<td>HPV</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>Oesophageal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-related cancers in men</td>
<td>HPV</td>
<td>Oesophageal</td>
<td>0·39</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>Head and neck excluding NPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV-and $H. pylori$-related cancers</td>
<td>EBV</td>
<td>Nasopharyngeal</td>
<td>&lt;0·001</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>$H. pylori$</td>
<td>Stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTLV-related cancers</td>
<td>HTLV</td>
<td>Leukaemia</td>
<td>0·045</td>
<td>0·088</td>
</tr>
<tr>
<td></td>
<td>HTLV</td>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTLV- and HBV-related cancers</td>
<td>HTLV</td>
<td>Leukaemia</td>
<td>0·45</td>
<td>0·36</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTLV-and HBV-related cancers</td>
<td>HTLV</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>0·0028</td>
<td>0·037</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>Liver</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPC, Nasopharyngeal cancer; HPV, human papillomavirus; EBV, Epstein–Barr virus; $H. pylori$, Helicobacter pylori; HTLV, human T-lymphotropic virus; HBV, hepatitis B virus.
Mortality rates declined for cancers related to HPV and EBV as well as for stomach cancer, but less so for leukaemia or liver cancer. In contrast, there were increases in mortality rates for non-Hodgkin’s lymphoma and colorectal cancer.

Age, period, and cohort effects

Age and cohort contributed to all cancers considered with a clear additional contribution from the period effect for cervical, oesophageal in men, stomach in men, colorectal in women and lung cancers (Appendix Table A1). There was an increase with age in mortality rates for most cancers. However, HPV-related cancers (cervical, head and neck, oesophageal), nasopharyngeal and liver had decelerations in middle age and lung cancer slightly later (Appendix Fig. A1). For the period, effects, there was clearly a downturn in the early 1990s for cervical cancer and an upturn in the early 1980s for stomach cancer in men (Fig. 2).

Figure 2 shows the relative risks by birth cohort, from which second-order changes (inflection points) were confirmed by examination of the curvature components (Appendix Fig. A2). There was a fairly systematic downward inflection for the 1910s birth cohorts (Fig. 2). These birth cohorts mainly migrated from China in the late 1940s and had exceeded contemporary Chinese life expectancy at migration and may represent strongly selected survivors or ‘healthy’ migrants.

Table 1 shows that in both men and women the birth cohort effects for HPV-related cancers (cervical, head and neck, oesophageal) were similar, because the P values for interaction between cancer type and cohort effect within cancer group were not significant. For these cancers, there were downward inflections for the 1920s to 1930s birth cohorts followed by upward inflections for the 1950s to 1960s birth cohorts (Fig. 2a–c, Appendix Fig. A2a–c).

Nasopharyngeal and stomach cancer did not have similar birth cohort effects in either men or women (Table 1). For nasopharyngeal cancer, there was a downward inflection for the early 1930s birth cohorts in men and late 1930s birth cohorts in women followed by a deceleration for the 1960s birth cohorts in women (Fig. 2d, Appendix Fig. A2d). However, the birth cohort effect for nasopharyngeal cancer in men did not differ from that for the HPV-related cancers (P > 0.12). Stomach cancer had an upward inflection for the mid-1930s birth cohort in both sexes, followed by a downturn for the 1940s birth cohort in men and for the mid-1950s birth cohorts in women (Fig. 2e, Appendix Fig. A2e).

Leukaemia and non-Hodgkin’s lymphoma did not have completely similar birth cohort effects in men (Table 1). There was a downward inflection for both cancers in the early 1940s birth cohorts, but an upturn in leukaemia for the 1970s birth cohorts and in non-Hodgkin’s lymphoma for the 1960s birth cohorts (Fig. 2f, g, Appendix Fig. A2f, g). The birth cohort effect for leukaemia was more similar to that for liver cancer (Table 1). Liver cancer had a downturn for the 1930s birth cohorts followed by an upturn for the 1960s birth cohorts. In addition, liver cancer in men had a similar birth cohort effect to HPV-related cancers (P > 0.12).

Colorectal and lung cancers had downward inflections for the early 1920s birth cohorts, followed by a
Fig. 1. Age-standardized cancer mortality rates in Hong Kong, 1976–2005, for men (dashed line), women (dotted line), and both sexes (solid line), for: (a) cervical, (b) head and neck excluding nasopharyngeal, (c) oesophageal, (d) nasopharyngeal, (e) stomach, (f) leukaemia, (g) non-Hodgkin’s lymphoma, (h) liver, (i) colorectal, (j) lung. Bars, 95% confidence interval.
Fig. 2. Parameter estimates for cohort (filled circles) and period (open circles) effects on cancer mortality in Hong Kong, 1976–2005, in men (circles) and women (triangles), for: (a) cervical, (b) head and neck excluding nasopharyngeal, (c) oesophageal, (d) nasopharyngeal, (e) stomach, (f) leukaemia, (g) non-Hodgkin’s lymphoma, (h) liver, (i) colorectal, (j) lung. Bars, 95% confidence interval.
downturn in colorectal cancer in men and in lung cancer in women for the late 1940s birth cohorts and in lung cancer in men and colorectal cancer in women for the 1950s birth cohorts, as well as an acceleration in lung cancer around the 1960s birth cohorts in men and the 1950s birth cohorts in women. The birth cohort effects for colorectal and lung cancers differed from those of almost all other cancers, with significant \( P \) values for the interaction of the cohort effect for each group of infection-related cancers with the cohort effects for both colorectal and lung cancers in men and women (Table 2). However, in men the birth cohort effects for HPV-related cancers, nasopharyngeal, leukaemia and liver cancers were similar to those for colorectal cancer, in women the birth cohort effects for leukaemia and non-Hodgkin’s lymphoma were similar to those for colorectal cancer and finally in men, the birth cohort effects for leukaemia were similar to those for lung cancer (Table 2).

**DISCUSSION**

Consistent with our hypothesis, the same exposure, i.e. a ‘step-change’ in living conditions in the late 1940s, had different effects on infection-related cancers with long latency, which corresponded in some cases to the mode of transmission. Cancers related to sexually transmitted infections, i.e. cervical, head and neck, and oesophageal, had downward inflections by birth cohort about 15–20 years before the ‘step-change’ in living conditions, i.e. for those with sexual debut in a more economically developed environment. Similarly, cancers due to vertically transmitted infections, i.e. leukaemia, non-Hodgkin’s lymphoma and perhaps liver had downturns proximate to the ‘step-change’ in living conditions for the 1940s birth cohorts. However, cancers related to early childhood exposures, i.e. nasopharyngeal and stomach cancers, had downturns in different birth cohorts.

Despite taking advantage of a unique setting, using population-level data for 30 years and using a novel approach to compare infection-related cancers grouped by mode of transmission, there are some limitations. First, this is an ecological study. Nevertheless, APC models are particularly valuable in recently developing and developed locations, where long-term records or cohort studies may be lacking. Second, our results depend on the quality of the mortality and population data, as do all other studies of this type. Most deaths in Hong Kong have taken place in hospital (certainly since 1970), thus facilitating accurate ascertainment of cause of death; nevertheless, as in many developed countries, autopsy rates are falling and some misdiagnoses are inevitable [24], although unlikely to be systematic. Many Hong Kong residents born before the 1960s lack birth certificates, so age may be slightly inaccurate, but any such inaccuracies would be largely removed by grouping into 5-year age groups. Third, the low number of deaths in recent cohorts impaired precision and the power to detect differences between some cancers, so we are cautious in the relevant interpretations. Finally, case-fatality rate of some cancers may have decreased between 1976 and 2006 due to improvements in treatment, so changes in incidence and mortality may not be parallel. However, improvements in treatment are most likely population-wide and as such reflected in period effects rather than cohort effects because there is no reason to believe that improvements in cancer treatments for adults were age-specific.

To our knowledge, this is the first APC study to examine the effects of economic transition on mortality from infection-related cancers. Moreover, there are very few or no APC studies on mortality from oesophageal cancer [25–27], nasopharyngeal cancer, leukaemia [27–29], or non-Hodgkin’s lymphoma [29] but relatively more on the other cancers, especially cervical cancer.

The lower risk of death from cancers related to sexually transmitted infections (HPV) for the first birth cohorts with sexual debut in a more economically developed environment could be due to better protection, better hygiene or greater resistance to infection as a result of better nutrition in a more developed environment. Screening could also have contributed to the downward inflection in cervical cancer mortality for women in the 1920s birth cohorts, stemming from the first availability of Pap testing in the 1960s concentrated in women in their 40s [30]. There was a similar downward inflection in cervical cancer incidence in the 1920s in Hong Kong [30]. There was also a similar downward inflection for death from cervical cancer in cohorts born around the 1920s in Shandong, China, attributed to less exposure to sexually transmitted diseases with the banning of prostitution after the establishment of the People’s Republic of China [31]. Conversely, the upward inflections for HPV-related cancers in the 1950s and 1960s birth cohorts could be due to liberalization of sexual norms for these cohorts.
Nasopharyngeal cancer in men appears to have a similar birth cohort effect to sexually transmitted HPV-related cancers, consistent with transmission of HPV to men by their partners [32] and our previous observations for the incidence of nasopharyngeal cancer in this setting [23]. However, this birth cohort effect is less consistent with early life EBV infection [14] or weaning with salted fish [33] playing a role in nasopharyngeal cancer. \textit{H. pylori} is usually associated with poor childhood conditions, consistent with the downturn in stomach cancer for men in the early 1940s birth cohort. However, the lack of a similar downturn for women is not consistent with an immediate reduction in transmission with better childhood living condition unless other factors specific to girls emerged to play a role, such as declines offset by food sharing or caring for siblings. Alternatively, public health measures such as the ‘Public Health and Municipal Services Ordinance’ in 1960 (including regular food and housing inspections) and the introduction of a public housing programme in the 1950s replacing squatter camps might have been instrumental in reducing \textit{H. pylori} transmission. The differences between nasopharyngeal and stomach cancers could also be due to differences in the mode of transmission of viruses (EBV) compared to bacteria (\textit{H. pylori}) or in the aetiology of cancers related to viruses compared to bacteria.

The downturn for the 1940s birth cohort for leukaemia and non-Hodgkin’s lymphoma suggest that better infant living conditions reduced vertical transmission of an infection that can be transmitted through breastfeeding [34]. Why an upturn occurred for the recent birth cohorts (1960s for non-Hodgkin’s lymphoma and 1970s for leukaemia) is unclear. However, non-Hodgkin’s lymphoma includes several subtypes, some of which may be related to EBV [35] rather than HTLV [17] and there was also a turning point for nasopharyngeal cancer in the 1960s.

In contrast, liver cancer presents a more mixed picture with similarities to both cancers related to vertically transmitted infection with HTLV, i.e. leukaemia, and to cancers related to sexually transmitted infection with HPV, particularly for men. Reduced vertical HBV transmission during the 1940s is also consistent with a ‘step-change’ in HBV surface antigen prevalence for people born before and after 1948 [36]. However, HBV infection can also be transmitted through sexual contact [37]. There was a similar downturn for death from hepatocellular carcinoma in Taiwan for the 1930s birth cohorts [38]. It is also possible that higher levels of oestrogen from better pubertal nutrition reduced liver cancer in women for the late 1930s birth cohort [39], thus generating a different pattern in women. We have previously reported an increase in oestrogen-related cancers for this same birth cohort [23].

Finally, it is unlikely that changes in smoking, alcohol use or diet associated with economic development underlie the changes in infection-related cancers, because colorectal and lung cancers have completely different patterns from almost all the other cancers. The similar birth cohort effect of liver and colorectal cancers in men could suggest that colorectal cancer is related to HBV infection; however, there is little evidence on this point. It has also been suggested that colorectal cancer is related to \textit{H. pylori} infection [40] but the different birth cohort effects from stomach cancer suggest otherwise.

From a public health perspective, our findings clearly demonstrate the long-range effects of early living conditions on infection-related cancers, and provide a potential explanation for the continuing relatively high mortality rates from these cancers in populations with a recent history of economic development. Specifically, after 50 years of economic development, there have only been reductions in age-standardized mortality rates for infection-related cancers (cervical, head and neck, oesophageal, nasopharyngeal cancers) where transmission occurs relatively late (early adulthood) or death occurs at relatively young ages. In contrast, there has not yet been any decrease in age-standardized mortality rates for cancers with transmission early in life (leukaemia, non-Hodgkin’s lymphoma) or death at older ages (liver cancer). Moreover, in our setting we are essentially only seeing the effects in the first generation to experience economic development. To what extent rapid economic development has left residual reservoirs of infection that may have effects into succeeding generations could be further assessed from detailed modelling of the transmission dynamics of the relevant underlying infections. Nevertheless, our findings imply that the incidence of infection-related cancers may be contextually specific and depend not only on the current level of economic development but also on the population history. Public health policies designed to reduce mortality rates from these cancers might be more cost-effective if targeted at certain population subgroups, such as recent migrants, where these infections may be relatively more common.
CONCLUSION

With epidemiological transition as infectious diseases are replaced by non-communicable diseases as the leading cause of death, reservoirs of latent infections may prohibit immediate reductions in some infection-related cancers in populations currently experiencing rapid economic development. Public health policies and interventions to reduce mortality rates from infection-related cancers need to be contextually specific and perhaps targeted at certain subgroups because incidence may be related to population history.

ACKNOWLEDGEMENTS

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DECLARATION OF INTEREST

None.

REFERENCES


### Appendix Table A1. Akaike’s Information Criterion values for age, age-period, age-cohort, and age-period-cohort models for risk of mortality for different cancers, Hong Kong, 1976–2005

<table>
<thead>
<tr>
<th>Cancer</th>
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<th>Age cohort</th>
<th>Age-period cohort</th>
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<td>600.2</td>
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<td>Head and neck excluding NPC</td>
<td>Men</td>
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</tr>
<tr>
<td></td>
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<td>512.1</td>
<td>448.1</td>
<td>446.6</td>
<td>445.2</td>
</tr>
<tr>
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<td>Men</td>
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<td>625.3</td>
<td>562.4</td>
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<td>465.9</td>
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</table>

NPC, Nasopharyngeal cancer.
Appendix Fig. A1. Parameter estimates for age effects on cancer mortality in Hong Kong, 1976–2005, in men (circles) and women (triangles), for: (a) cervical, (b) head and neck excluding nasopharyngeal, (c) oesophageal, (d) nasopharyngeal, (e) stomach, (f) leukaemia, (g) non-Hodgkin’s lymphoma, (h) liver, (i) colorectal, (j) lung. Bars, 95% confidence interval.
Appendix Fig. A2. For legend see overleaf.

Sexual transmission

(a) Cervical

(b) Head and neck

(c) Oesophageal
Appendix Fig. A2 (cont.)
Appendix Fig. A2 (cont.)
Appendix Fig. A2. Curvature components for age effects (left hand panel) and cohort (filled) and period (outline) effects (right hand panel) on cancer mortality in Hong Kong, 1976–2005, stratified by men (circles) and women (triangles), for: (a) cervical, (b) head and neck excluding nasopharyngeal, (c) oesophageal, (d) nasopharyngeal, (e) stomach, (f) leukaemia, (g) non-Hodgkin’s lymphoma, (h) liver, (i) colorectal, (j) lung. Bars, 95% confidence interval. * Due to small number of cases, cohort effect was estimated for the 30 to ≥85 years group for head and neck cancer in women, and 35 to ≥85 years group for oesophageal cancer for both sexes.