Understanding sociohistorical imprint on cancer risk by age–period–cohort decomposition in Hong Kong

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Accepted 29 June 2009

ABSTRACT

Background Research on trends in cancer incidence has usually examined single sites in populations that long ago completed the economic transition. The trends in 11 cancers in three groups in the recently transitioned Hong Kong Chinese population were examined to delineate the effects of economic transition and provide generalised aetiological insights.

Methods Sex-specific Poisson models were fitted to cancer incidence in Hong Kong (1974–2003) to examine age, period and birth cohort effects. Cancers were grouped as: hormonally modulated (including breast, endometrium, ovary and prostate), infection-related (cervix, liver, nasopharynx, lymphoma and stomach) and lifestyle-related (colorectum and lung).

Results Age-standardised incidence of hormonally modulated female cancers increased for the first generation (women born ~1940) to experience puberty in the transitioning environment of Hong Kong. Prostate cancer incidence increased, despite a downturn for the first generation growing up in Hong Kong. Incidence of infection-related cancers decreased, mainly due to birth cohort effects; coinciding with birth for liver cancer and lymphoma, with reaching adulthood for cervical and male nasopharyngeal cancers, and with a generation for stomach cancer. Lifestyle-related cancers had sex-specific declines by birth cohort.

Conclusion With economic transition and the associated lifestyle changes, environmentally determined levels of pubertal female hormones may drive intergenerational increases in hormonally related female cancers. Economic development, via improved living conditions, may also reduce infection-related cancers, possibly including prostate cancer; however, the effects depend on transmission dynamics and perhaps specific public health initiatives. In traditional societies, males may benefit from economic development sooner than females.

INTRODUCTION

Age–period–cohort (APC) models have long been deployed to elucidate the different biological and environmental causes of cancer by examining trends over time,[1] mainly focusing on single sites in populations with a long history of economic development.[2–4] However, with economic development, and the associated improvements in nutrition, living conditions and medical care, patterns of disease change radically. To provide insight into the impact of economic development on the incidence of cancer, 11 major cancers were investigated in the Hong Kong Chinese population, which has a unique history of recent, rapid economic transition in the past 60 years (ie, within two or three generations) from essentially preindustrial conditions to 'First World' living conditions (figure 1).[5–12] Moreover, patterns of smoking may be culturally specific regardless of economic development. In Hong Kong, like much of Asia, smoking rates have remained low with economic development, particularly in women.[13] Much of developing Asia has since followed Hong Kong's developmental trajectory, thus the present findings may portend future epidemiological changes and inform public health responses in those and other emerging economies.

To provide aetiological insight, the cancers were grouped according to current understanding of their major causes, although, as with any multifactorial diseases, these groupings may be an over-simplification. A priori, the three groups were: 1. hormonally modulated (breast, endometrium, ovary and prostate), 2. infection-related (cervix, liver, lymphoma, nasopharynx and stomach) and 3. lifestyle-related (colorectum and lung), because economic development would be expected to have different impacts by group. Specifically, it was hypothesised that hormonally modulated cancers, including prostate cancer,[14–16] would increase with each generation born into a more economically developed environment, because of intergenerational increases in hormone levels with economic development,[17–19] and the pattern with 'Third World' to 'First World' migration.[20 21] Conversely, it was hypothesised that infection-related cancers should decrease with socioeconomic development via improved living conditions and preventive healthcare reducing the spread of infections. Finally, it was hypothesised that the lifestyle-related cancers would reflect secular trend in behaviours such as smoking. The incidence of these 11 cancers was statistically decomposed into APC effects, to assess the differential epidemiological imprint of population history on secular trends.

METHODS

Data were obtained on cancer incidence for 1974–2003 from the population-based Hong Kong Cancer Registry, an accredited member of the International Association of Cancer Registries. Information on all newly diagnosed cancers was collected from the private and public sectors, the government's death registry, plus voluntary notifications from all medical practitioners, with over 95% capture for most cancers. Multiple cancers for the same person are counted separately (ie, not only primary cancers were included). Midyear population figures were obtained from the Census and Statistics Department.

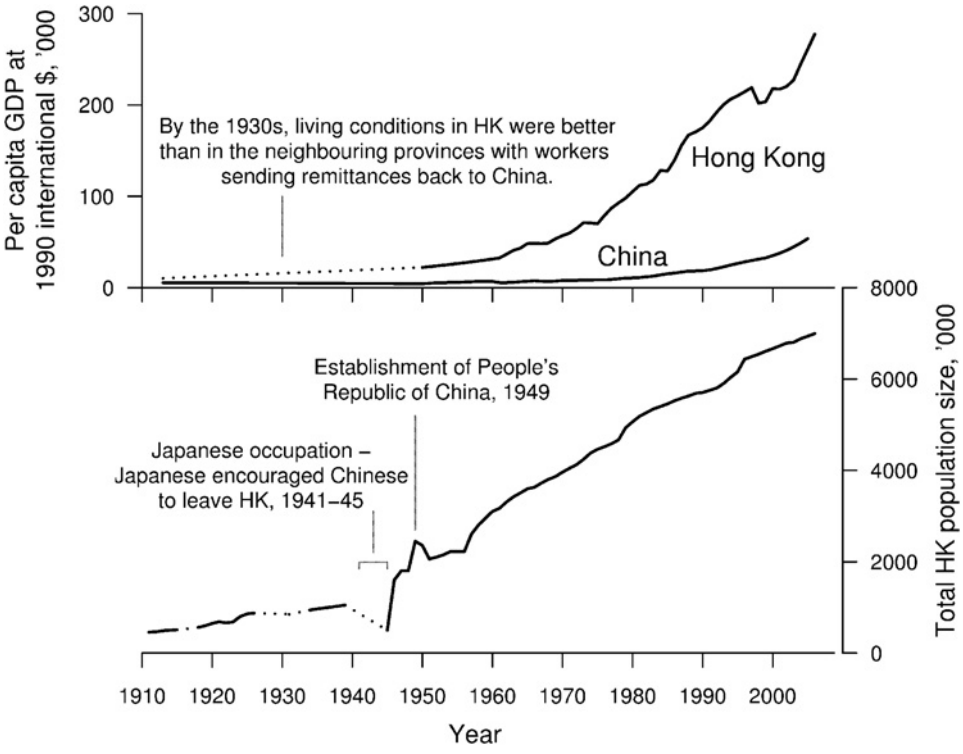

Figure 1 Levels of per capita Gross Domestic Product in China (1913–2005) and Hong Kong (1950–2006) (dotted line represents extrapolation from 1950 back to 1914), and total population size in Hong Kong (1911–2006) (dotted line represents interpolation during periods when data were unavailable).

For breast, cervical, endometrial, ovarian, colorectal, liver, lung, lymphoma and stomach cancers, ten 5 year age groups were used from 35–39 years to 80 or above, that is 15 birth cohorts centred at 5 year intervals. However, for nasopharyngeal and prostate cancers, sparse age groups with very low incidence rates were dropped (75+ and 35–44 years respectively), giving 13 birth cohorts. Six 5 year calendar time periods from 1974–1978 to 1999–2003 were used. Incidence rates were directly standardised by age using the World Standard Population[22] and expressed per 100 000 population consistent with routine local statistics.

Sex-specific Poisson regression models were fitted to estimate cancer incidence by age and relative risks by period and birth cohort with 95% CIs. The second and the penultimate periods and the central birth cohort were chosen as the reference categories, to generate identifiable estimates for birth cohort and period.[23] Due to the inherent linear dependency between the three components (ie, birth cohort=period–age), only second-order changes (ie, changes in slopes or inflection points) are interpretable, rather than absolute value.[1] Second-order changes can be inspected visually from plots of the estimates. The contribution of age, period and birth cohort was assessed from the Akaike Information Criterion. Age-specific incidence rates were also plotted by birth cohort and period to check the interpretations. Statistical analyses were conducted using R version 2.4.0.[24]

RESULTS

Age-standardised incidence rates for all 11 cancers in Hong Kong

Figure 2 shows the observed age-standardised incidence rates from 1974 through 2003. Hormonally modulated cancers increased in incidence, particularly breast and prostate cancers. Infection-related cancers were more heterogeneous. Cervical and nasopharyngeal cancers decreased steeply, with a modest decrease for stomach cancer. Liver cancer decreased recently, whereas lymphoma increased. Lung cancer incidence peaked in the mid-1980s. Colorectal cancer rose substantially, although the rate of growth may be slowing.

Age, birth cohort and period effects

Hormonally modulated cancers

Figure 3 shows the APC plots for the hormonally modulated cancers. The left-hand panels show estimated incidence by age, from which it can be observed that the increase in incidence with age had a slight deflection around the menopause (~50–55 years) for breast cancer, a larger deflection for ovarian cancer and a downturn for endometrial cancer. In contrast, prostate cancer increased exponentially with age. The right-hand panels show relative risks by birth cohort and period, from which inflection points can be identified. Most obvious are upward inflections in the birth cohort curves around 1935–1940 for the three female cancers, but a downward inflection in the same birth cohort for prostate cancer. There were possibly also downward inflections around 1955–1960 for breast and endometrial cancers. The period curves do not have obvious inflections for the three hormonally modulated female cancers, but prostate cancer had a U-shaped period curve with the nadir at 1990.

Infection-related cancers

Liver, lymphoma and stomach cancers increased exponentially with age (figure 4), but cervical and nasopharyngeal incidence peaked around 45 years. The birth cohort curves mainly had downward inflections but for different birth cohorts. Stomach cancer had an additional inflection around 1940 for women representing a temporary halt in the downward trajectory, which accelerated in both sexes from 1955 to 1960. Liver cancer showed a single downward inflection around 1940 in both sexes. Lymphoma had a similar downward inflection around 1945 in both sexes, but also a deceleration about 20 years later, around 1965. Cervical cancer had an acceleration in the downward trajectory around 1925 but a deceleration around 1960. Nasopharyngeal cancer in men showed a similar decreasing trend with the acceleration and deceleration about 5 years later (1930 and 1965). There was no apparent period effect for nasopharyngeal, cervical or male stomach cancer, but there was a downturn around 1985–1990 for liver, lymphoma and female stomach cancer.

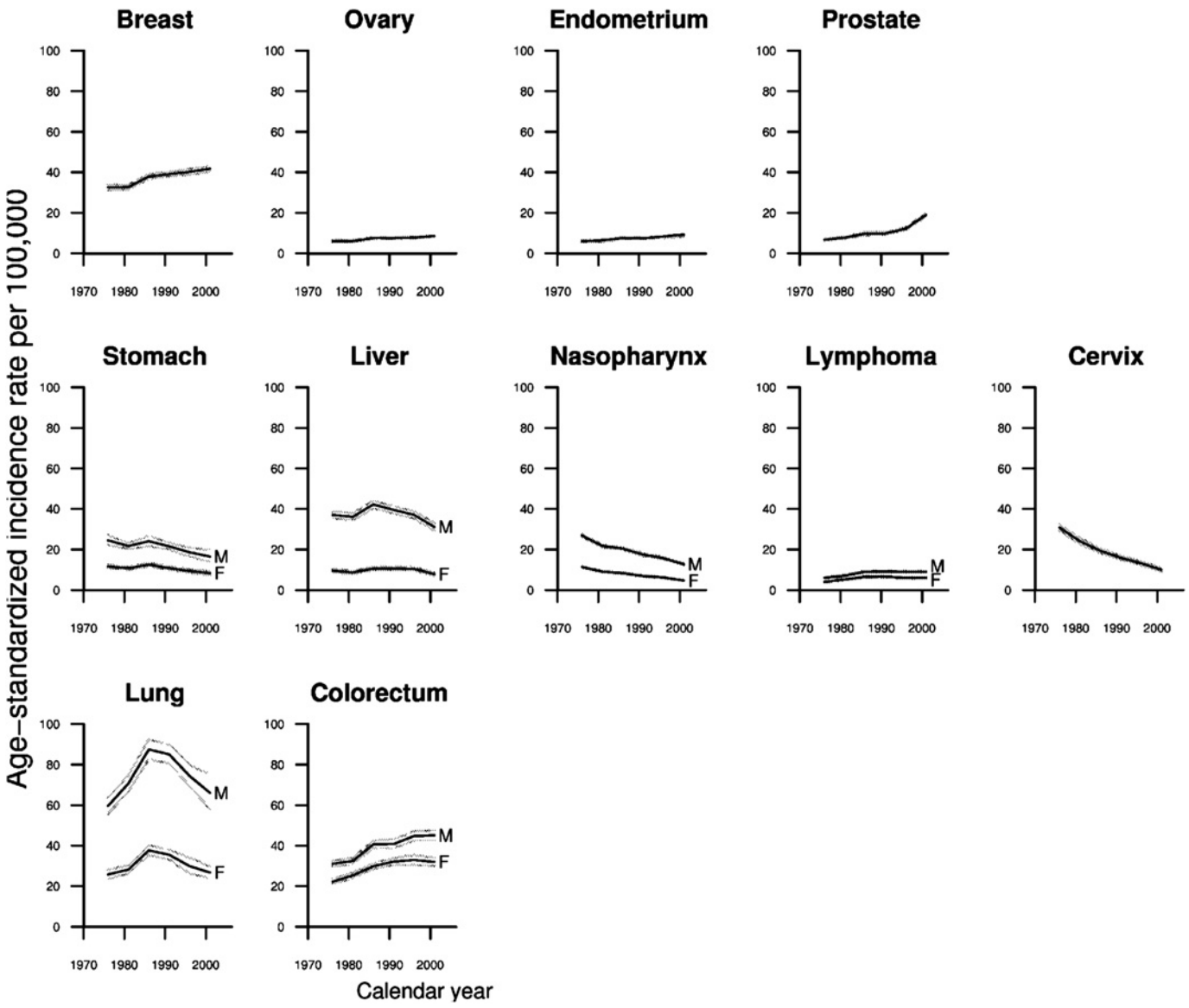

Figure 2 Age-standardised incidence rates for 11 cancers in Hong Kong from 1974 to 2003 with 95% CIs.

Lifestyle-related cancers

Colorectal and lung cancers generally increased exponentially with age (figure 5). The birth cohort curves had downward inflections in colorectal cancer for men born around 1940 and women around 1955. For lung cancer, among men and women born about 1950 there was a deceleration in men and an upturn in women. There was a downward turn in the period effect for lung cancer in both sexes and female colorectal cancer around 1985–1990.

Comparisons of model fit (appendix table AI) and plots of age-specific incidence by period and birth cohort confirm these interpretations (appendix figures AI,AII,AIII).

DISCUSSION

Common, population-wide exposure to radically improved living conditions over a compressed time frame during the mid-20th century exerted opposite effects, which were generally as expected. There were birth cohort-driven increases in female hormonally modulated cancers, but not for prostate cancer. There were also largely birth cohort-driven decreases in infection-related cancers, albeit in different birth cohorts.

Hormonally modulated cancers

The female hormonally modulated cancers show similar patterns suggesting, as hypothesised, a common endocrine aetiology moderated by living conditions at critical life stages. All three cancers demonstrated similar 'stepped' patterns by birth cohort at dates corresponding to key historical events. The increase around 1935–1940 coincides with the first birth cohorts that migrated to more economically developed Hong Kong before puberty (mainly during 1946–1955). The deceleration around 1960 coincides with the last birth cohorts to have more than a few experience puberty in China. Older age at first birth and decreasing parity in Hong Kong (appendix figure AIV)[25 26] may also have contributed to the subsequent increase for ovarian cancer. The levelling off in breast and endometrial cancer risk in the birth cohorts from the 1960s onwards could indicate an upper threshold to the effects of economic transition. However, the 1960s and 1970s birth cohorts mainly experienced puberty in Hong Kong, but their mothers mainly did not. The first birth cohorts with mothers who also experienced puberty in Hong Kong were born from around the mid-1970s and it is too early to detect any associated changes in cancer risk.[23] Migration studies

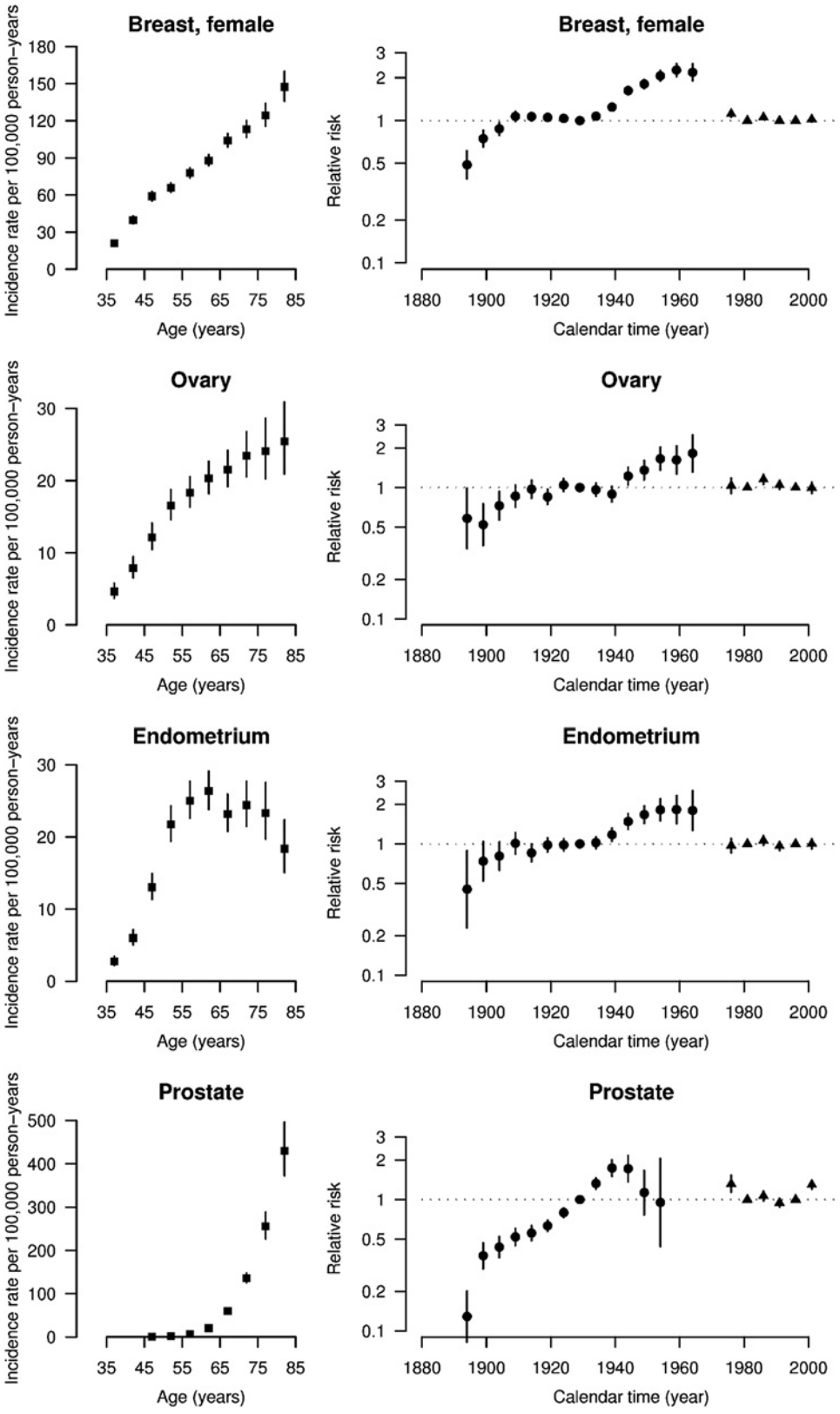

Figure 3 Parameter estimates and 95% confidence bars of age (squares in left-hand panels), period (triangles) and cohort (circles) effects (right-hand panels) for four hormonally modulated cancers in Hong Kong.

suggest that it takes several generations for the full effects of economic transition to be evident for breast and endometrial, though not ovarian cancer.[20 21]

Mechanistically, the present findings suggest that puberty may be a critical developmental window for the three female hormonally modulated cancers, because living conditions around puberty set lifetime hormone levels.[17] In addition, living conditions during maternal puberty may also be a developmental window for her offspring's risk,[18] via circulating maternal oestrogen levels during pregnancy.[19]

In contrast, birth cohort effects for prostate cancer share temporal parallels with the female hormonally modulated cancers, but in an

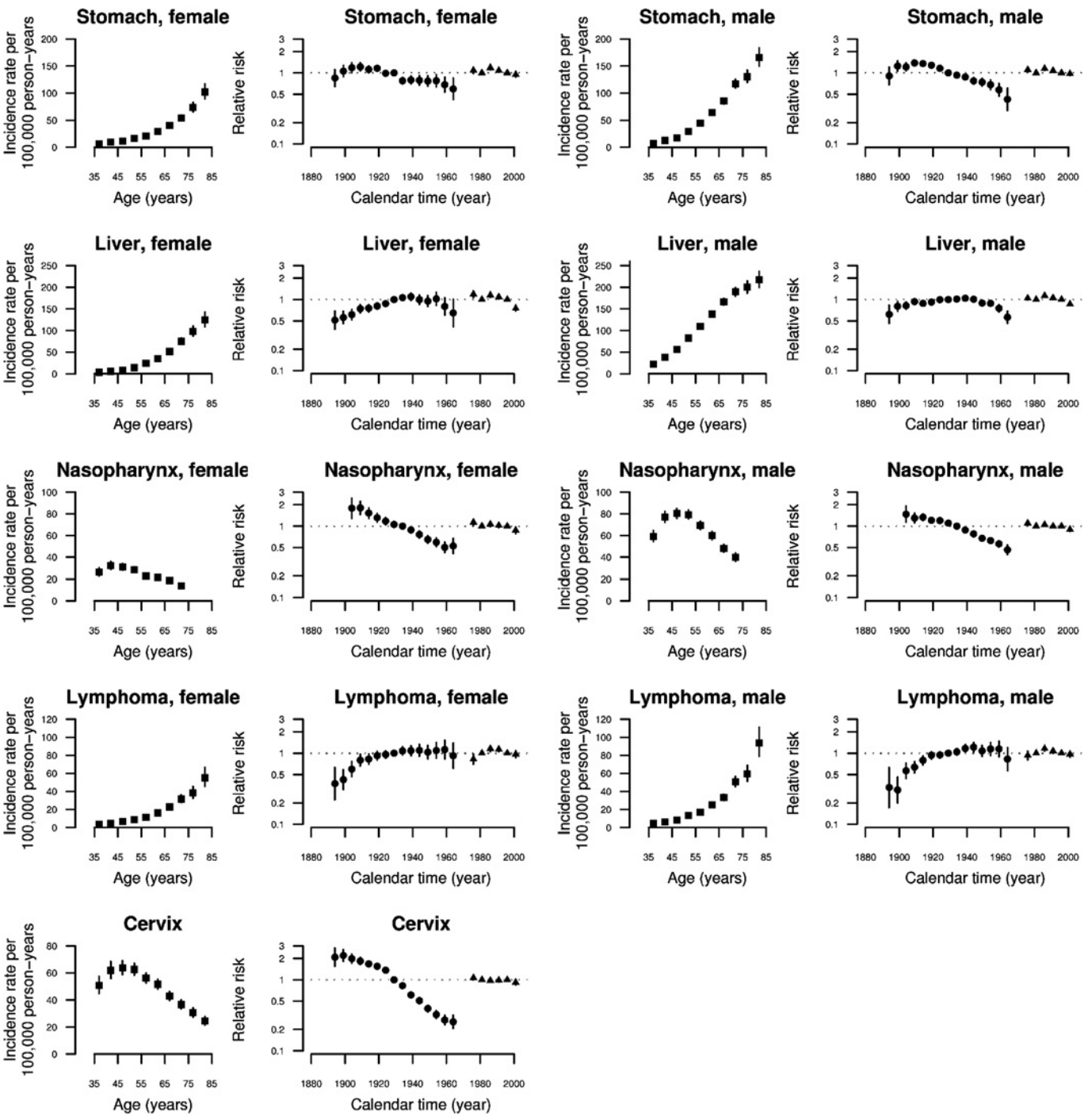

Figure 4 Parameter estimates and 95% confidence bars of age (squares), period (triangles) and cohort (circles) effects for five infection-related cancers in Hong Kong.

opposite direction, with a decrease around 1940. This difference could be chance; however, there was a similar decline around the 1940s in Taiwan.[27] As with breast cancer, the rise in prostate cancer with migration to Westernised countries occurs over several generations.[28] Nevertheless, these opposite patterns by birth cohort imply that a conceptualisation of breast and prostate cancers as similarly driven by sex-steroids[14] may be unhelpful. The birth cohort effects for prostate cancer are more compatible with recent speculation that infection, perhaps with propionibacterium acnes at puberty, may be relevant,[29 30] and that transmission may have been reduced by better hygiene facilitated by migration to Hong Kong in the mid-20th century.

Infection-related cancer

The infection-related cancers showed heterogeneity by age and birth cohort. Liver cancer and lymphoma decreased for the first birth cohorts with more births in Hong Kong, thereby possibly implicating an early life exposure, perhaps hygiene or nutrition. Hepatitis B virus (HBV) infection is usually bloodborne; however, infection in early life from prolonged and low intensity exposure to saliva and cutaneous exudates is possible,[31] particularly in areas of high prevalence. A reduction in vertical and horizontal transmission of HBV, before universal vaccination for newborns was introduced in 1988,[32] might be relevant to the reduction for liver cancer and is consistent with a step change in

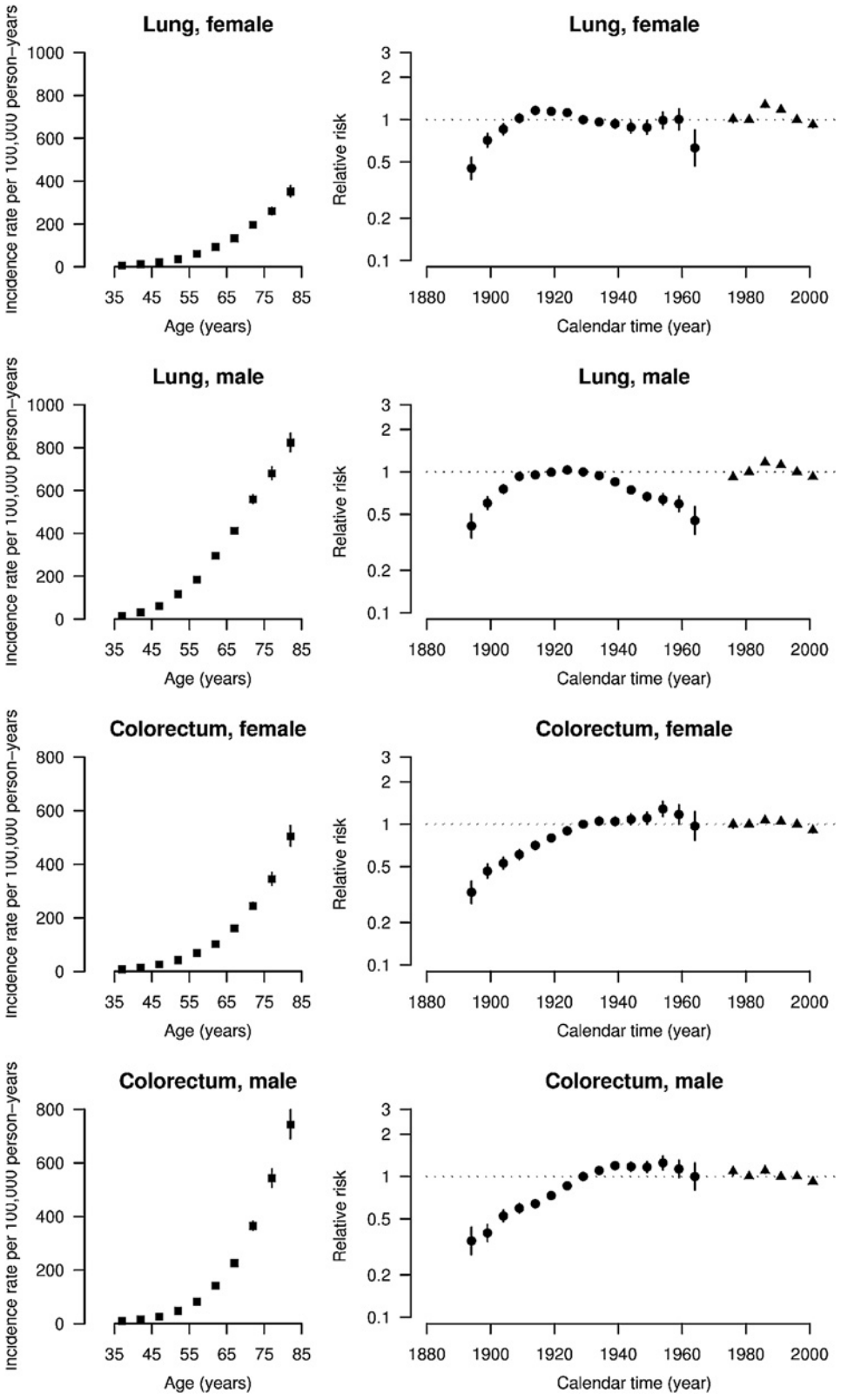

Figure 5 Parameter estimates and 95% confidence bars of age (squares in left-hand panels), period (triangles) and cohort (circles) effects (right-hand panels) for two lifestyle-related cancers in Hong Kong.

the prevalence of HBV surface antigen for people born before and after 1948.[33] Lymphomas encompass several cancers caused by potentially different infectious agents including Epstein-Barr virus (EBV), hepatitis C, *Helicobacter pylori*and *Campylobacter jejuni*.[34] The different cohort effects for nasopharyngeal and stomach cancers make it unlikely that EBV or *H pylori*are relevant to the decrease for lymphoma. There is little evidence that the other infections are vertically transmitted, suggesting that some other mechanism associated with birth in a more hygienic environment may be relevant to lymphoma as the decrease ceased once the proportion born in Hong Kong reached about 80% in the 1960s.[35]

Cervical, nasopharyngeal and stomach cancers show different decreasing birth cohort effects. The decline in cervical cancer

accelerated for the first birth cohorts (~1925) to have been sexually active in Hong Kong rather than China. Greater availability of condoms in Hong Kong or altered sexual habits in a legally more settled, monogamous community could have reduced sexual transmission of human papillomavirus (HPV), until the liberalisation of sexual mores for the 1960s birth cohorts. The decline in male nasopharyngeal cancer accelerated for the first birth cohorts (~1930) to reach adulthood in Hong Kong making early life EBV infection or weaning with salted fish[36] an unlikely explanation. Infection with EBV is ubiquitous, why reactivation occurs and which cofactors promote nasopharyngeal cancer is unclear[36] - a sexually transmitted cofactor has never been considered; however, the similar age and birth cohort effects for cervical and nasopharyngeal cancers might support such a speculation.

In contrast, although *H pylori* is usually associated with poor childhood conditions,[37] the decline in stomach cancer accelerated about a decade after migration to Hong Kong (1955–1960 birth cohorts), similar to another chronic bacterial disease, tuberculosis.[38] *H pylori* prevalence declined for births from the 1930s to the 1950s, without a 'step' change.[39] Transmission of *H pylori* could have reduced in the 1950s, but been offset by other factors including population mixing or food sharing, particularly for girls. Alternatively, public health measures, such as the 'Public Health and Urban Services Ordinance' in 1960 including regular inspections of food and domestic premises or the introduction of the public housing programme in the 1950s replacing squatter camps might have reduced *H pylori* transmission.

Different patterns of decline for the infection-related cancers with economic development are consistent with different infectious agents and transmission dynamics. However, the heterogeneity indicates that economic development alone may not suffice because some infections have a critical window of vulnerability (eg, around birth for liver cancer), others are affected by the accumulation of years in a developed environment or by specific public health measures (such as stomach or nasopharyngeal cancers).

Lifestyle-related cancers

The lifestyle-related cancers had sex-specific declines. The birth cohort curves for lung cancer are consistent with the gradual decline in smoking prevalence in Hong Kong over the last three decades (appendix figure AV).[13] As elsewhere the rise and fall of the smoking epidemic took place initially in men and subsequently in women,[40] with a relatively early decline in female smoking. In 1982, 15% of older women (≥60 years) were smokers whereas by 1998 this was only 4%.[13]

Colorectal cancer decreased by birth cohort from about 1935 in men and 1955 in women. There is little consistent pattern by birth cohort elsewhere.[4 41] Chinese-born migrants to the USA have similar colorectal cancer rates to US-born second-generation Chinese migrants.[42] It has been suggested that colorectal cancer is related to *H pylori* infection;[43] however, the different birth cohort effects from stomach cancer and differences by sex suggest otherwise. Traditionally, in Chinese culture, men eat first, which may have given males earlier access to some protective 'delicacy', newly available with growing prosperity.

Limitations

Some potential shortcomings should be noted. First, the present study is descriptive and it can only be speculate about the aetiologies of the changes observed. APC analysis can be valuable in generating hypotheses, particularly in developing or recently developed populations, where other sources of information or long-running cohort studies, may be lacking. Moreover, aetiological groupings were used to explore some hypotheses. Second, the categorisation into three aetiological groups is an oversimplification, because the causes of many cancers are multifactorial. Moreover, the relative importance of each contributing factor may be context-specific. Where a necessary infection is ubiquitous, lifestyle may be the distinguishing factor, and conversely where behaviour is homogeneous, infectious pathogens or changes in transmission dynamics may be key. Hence, the importance of evidence from populations is different to the more commonly studied industrialised countries with a long history of economic development since the Industrial Revolution. Third, the present interpretation depends on understanding of migration patterns into Hong Kong. Unfortunately, place of birth and age at migration are not available for cancer registrations, precluding direct comparison by migrants status. However, it is known that the Hong Kong population was largely formed by migration from China in the mid-20th century from a variety of contemporary and historic sources[5–12 35] and from analysis of population-based samples by migrant status and age.[44] Fourth, the present results depend on the quality of incidence data. The Hong Kong Cancer Registry is the most carefully validated source locally.[45] Two internationally accepted indicators of data quality in cancer registries are high morphological verification and few death certificate only (DCO) cases. In Hong Kong currently over 85% of cases are morphologically verified and only 1.4% DCO (in 2004). However, DCO cases have only been included since 1983, when 13.3% of cases were DCOs, which could have influenced the apparent upward 'blip' in the period effect for the deadlier cancers (lung, liver and lymphoma) without a real change in incidence. Fifth, the present observations could have been contaminated by screening for breast or prostate cancer. However, only 6.9% of local women regularly attended mammography screening by 2003–2004.[46] Earlier estimates of screening prevalence are unavailable, but were probably lower. In contrast, the introduction of the prostate specific antigen (PSA) screening test and increased use of transurethral resection of the prostate,[47] might have resulted in period effects around 1990 for prostate cancer, although there are few data on these procedures. PSA uptake can usually be detected by birth cohort, where baby boomers were the first generation to take the test.[48] A negative inflection point was observed instead, the magnitude of which might perhaps have been even larger. Sixth, inevitably there have been improvements in cancer diagnosis during the period, which may have generated apparent period effects indicating rising incidence. In addition, cancer may have been underascertained in older people, in the early cohorts, which may have generated apparent cohort effects indicating rising incidence. The early birth cohorts largely represent people who survived early 20th century China and migrated in middle age or later and may, as such, be strongly selected 'healthy migrants'. Hence, the period effects and early birth cohorts should be interpreted with caution.

CONCLUSION

The history of very recent and rapid economic development in Hong Kong, coupled with this decomposition of the incidence of 11 aetiologically grouped cancers, has produced several novel hypotheses. First, improved living conditions during a critical developmental window at puberty (of the current and previous generations) may increase the risk of breast cancer, and also of other female hormonally modulated cancers, that is ovarian and endometrial. Second, risk of prostate cancer may be affected by an infection at puberty. Third, economic development may be beneficial for infection-related cancers, although the impact may

What is already known on this subject

- Previous research on secular changes in cancer incidence has sought to understand disease aetiology by examining each cancer site separately, mainly in populations that long since completed the economic transition.
- Trends in 11 cancers in three groups (ie, hormonally, infection- and lifestyle-related) were examined in the recently transitioned Hong Kong Chinese population to delineate the effects of economic transition on cancer and to provide generalised aetiological insights.

What this study adds

- With economic development, higher levels of pubertal female hormones may drive intergenerational increases in endometrial and ovarian cancer as well as breast cancer.
- Economic development, via improved living conditions, may also reduce infection-related cancers, possibly including prostate cancer; however, the effects are heterogeneous reflecting varying transmission dynamics and perhaps specific public health initiatives.
- In traditional societies, females might take longer to benefit from economic development than males.

depend on the introduction of effective public health measures and the infection-specific transmission dynamics. Fourth, in societies with traditional preferences for boys, girls may take longer to benefit from economic development. These observations, if confirmed, may be relevant to cancer aetiology and to informing public health policies to reduce the risk of cancer in developing populations.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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