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Breast cancer incidence and mortality in a transitioning Chinese population: current and future trends

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Background: Projections of future trends in cancer incidence and mortality are important for public health planning.

Methods: By using 1976–2010 data in Hong Kong, we fitted Poisson age-period-cohort models and made projections for future breast cancer incidence and mortality to 2025.

Results: Age-standardised breast cancer incidence (/mortality) is projected to increase (/decline) from 56.7 (/9.3) in 2011–2015 to 62.5 (/8.6) per 100 000 women in 2021–2025.

Conclusions: The incidence pattern may relate to Hong Kong's socio-economic developmental history, while falling mortality trends are, most likely, due to improvements in survival from treatment advancement and improved health service delivery.

Breast cancer is the most common malignancy and the leading cause of cancer-related death in women, accounting for 10% of new malignancies worldwide annually, and ~22% of malignancies among women (Ferlay *et al*, 2004). In Hong Kong (HK) the most westernised and urbanised city in China, breast cancer is the most common cancer and the third leading cause of cancer-related mortality among women (Cancer Statistics, 2013). There are clear differences between populations in the East and the West in terms of breast cancer incidence and mortality (Figure 1), the precise aetiology of which remains unclear.

Age-period-cohort (APC) models allowing examination of trends in disease rates over time (Holford, 1991, 1992) have long been deployed to further understanding of the biologic and environmental causes of cancer (Holford, 1991, 1992). By using APC methods, we estimated the relative contribution of effects from age, period and birth cohort to trends in breast cancer incidence and mortality, and projected future trends to the medium term.

MATERIALS AND METHODS

We obtained age-specific breast cancer incidence, death data (defined according to the International Classification of Diseases

(ICD) codes as ICD-8 174, ICD-9 174 and ICD-10 C50, C50.0–C50.9) and mid-year population figures for the years 1976–2010 from the HK Cancer Registry (2013), the Death Registry and the Census and Statistics Department, respectively. We calculated the age-standardised incidence and mortality rates in HK according to the World Standard Population in 2000. Non-linearities in trends of varying time periods were characterised using segmented annual percent change from segmented regression (Clegg *et al*, 2009) or join-point regression analysis (Kim *et al*, 2000).

We modelled breast cancer incidence and mortality using APC models (details in Supplementary Information 1) (Clayton and Schifflers, 1987; Holford, 1991, 1992). We grouped the mortality/incidence and population data into fourteen 5-year age groups from 20–24 years to 85 or above, and seven 5-year periods from 1976–1980 to 2006–2010. This classification resulted in 20 birth cohorts centred at 5-year intervals beginning in the 1890s. The second and the penultimate periods and the central birth cohort were defined as reference groups to generate identifiable estimates. We used Bayesian inference to estimate the model parameters (Bray *et al*, 2000; Bray, 2002; Brennan and Bray, 2002; Baker and Bray, 2005). We used the resulting models to project age-standardised breast cancer incidence and mortality rates to medium term (until 2021–2025), with 95% projection intervals.

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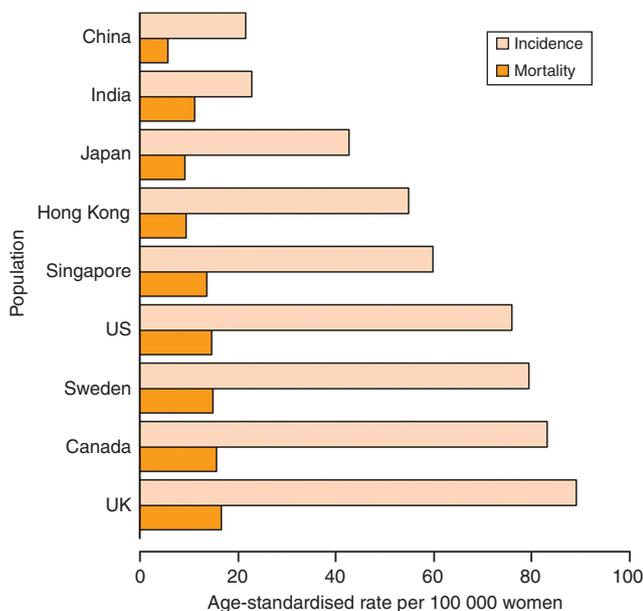


Figure 1. Age-standardised rates of female breast cancer incidence and mortality for women in 2008 (Data source: GLOBCAN 2008).

RESULTS

The trends in age-standardised breast cancer incidence and mortality rates by 5-year periods from 1976 and 2010 are shown in Figure 2 and Supplementary Table 1. The fourth period centred at 1993 was marked by a join-point at which the slope changed significantly for incidence and mortality trends in 1976–2010.

The estimated parameters for the age, period and cohort components for incidence (upper panels) and mortality (lower panels) models are shown in Figure 3. Due to the well-known identifiability problem of APC models, where the effects of the three components are linearly dependent, only second-order changes (i.e., inflection points) are interpretable. Figure 3 shows clear second-order changes are visible for both the age effects and the cohort effects for incidence and mortality with negligible second-order changes in period effects. Downward inflections in the age-specific breast cancer rates occurred at around 45–50 years for incidence and 65–70 years for mortality. The first two inflection points for the cohort curves have similar downturns around 1910 and upturns around 1930 for both incidence and mortality, but the third inflection points differ, with a downturn around 1960 for incidence and around 1950 for mortality.

Age-standardised incidence rate rose on average 1.69% per annum in the three decades between 1976 and 2010. On the basis of these trends, we predicted that age-standardised breast cancer incidence rates would increase from 56.7 cases in 2011–2015 to 62.5 per 100 000 women in 2021–2025. In contrast, age-standardised mortality rates decreased on average 0.02% per year between 1976 and 2010. The rate is projected to decline from 9.3 deaths in 2011–2015 to 8.6 deaths per 100 000 women in 2021–2025.

Disparities in the disease rates by age group were observed (Supplementary Figure 1). Incidence is projected to increase into the near future for women ≥55 years, while mortality is projected to decline for women aged <65 years but increase for women aged ≥65 years.

DISCUSSION

We predict that age-standardised breast cancer incidence in HK will continue to increase at a rate of 0.65% per annum, while

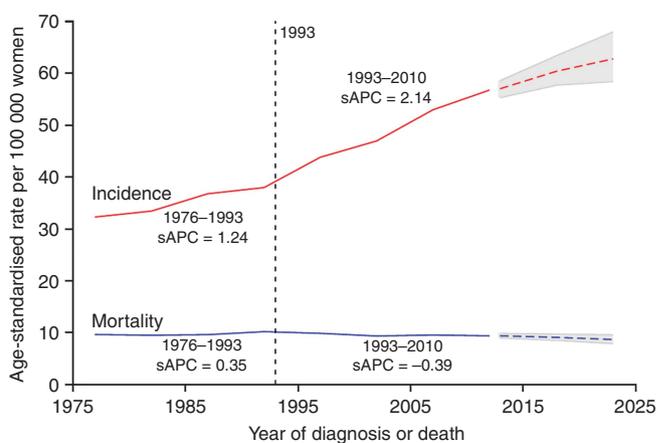


Figure 2. Annual age-standardised female breast cancer incidence (red line) and mortality (blue line) rates in Hong Kong from 1976 to 2010 and projected incidence and mortality (dotted lines) to 2025 with 95% credible intervals (grey area). Notes: The sAPC (annual percent change from segmented analysis) is significantly different from zero ($P < 0.05$), from which the period centred at 1993 (vertical dotted line) was marked by a join-point at which the slope changed significantly in both the incidence and mortality trends.

age-standardised mortality will decrease at 0.56% per annum over the next 15 years. Cumulatively, this represents a projected increase of 10.2% in incidence and a decrease of 7.5% in mortality rates during 2010–2025. Similar to our previous findings (Wong *et al*, 2007), the rising incidence trends seem to have been driven mainly by ageing and cohort effects, with no clear trends by calendar time period. On the other hand, we observed that the overall mortality trends appeared to be relatively stagnant over the last three decades. Given that HK does not operate a mass mammographic screening and only the low levels of mammography screening in our population occur (Leung *et al*, 2008), these trends could be most likely attributed to improvements in survival including advances in treatment care such as use of Paclitaxel from the 1990s and adjuvant hormonal (Early Breast Cancer Trialists’ Collaborative Group, 2005; Gibson *et al*, 2009; Burstein *et al*, 2010; Cuzick *et al*, 2010) from the 1970s and targeted immunotherapy (Slamon *et al*, 2001; Madarnas *et al*, 2008; Costa *et al*, 2010) in the 2000s, or a different case-mix. We expect mortality to continue to decrease in the future. These findings might also serve as a reliable epidemiological sentinel for the rest of developing China.

Similar notable birth cohort effects occurred for both breast cancer incidence and mortality in the first half of the 20th century. Here, we attempt to interpret the cohort-driven trends and to generate hypotheses based on the relevance of social history in the evolution of population disease risk, in addition to from the perspective of well-known contemporaneous determinants such as lifestyle factors. Deceleration for the 1910s birth cohorts may be an artefact of HK’s migration history. Acceleration for the 1930s birth cohorts coincided with the first cohort of women who by migrating from China to HK in 1945–1955 were the first generation to reach maturity in comparatively developed HK, where gross domestic product per head in 1951 was about five times higher than in China (Maddison, 2001). The deceleration for the birth cohorts a generation later around 1960 could represent an upper threshold in the population effects of transitioning to a developed society for East Asians, despite lower fertility, delayed childbearing (Herrinton *et al*, 1994; Liao *et al*, 2003) (Supplementary Figure 2) and increased oral contraceptive use for women born after 1960. On the other hand, migration studies suggest it takes several generations for the full effects of economic transition to become

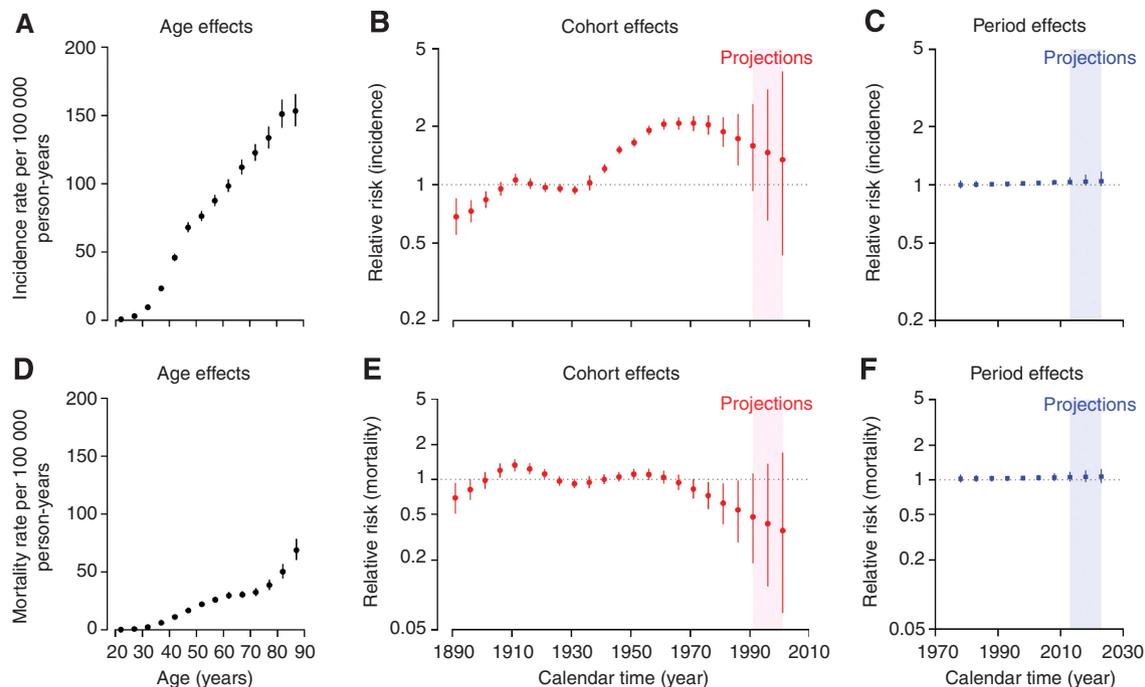


Figure 3. Parameter estimates of age (black), period (blue) and cohort (red) effects from two age-period-cohort models for *female incidence* (upper panels) and *mortality* (lower panels) trends due to breast cancer (DIC = 916.60 for incidence rate model; DIC = 737.44 for mortality rate model) with projections (shaded area). Leftmost upper panel (A): Estimated age-specific annual *female incidence* rates due to breast cancer in 5-year age groups in Hong Kong with 95% credible intervals. Middle and rightmost upper panel (B, C): Estimated relative risks for 10-year birth cohort (beginning in the calendar year 1889) and 5-year calendar period (beginning from 1976) effects associated with the *incidence* cases with 95% credible intervals, including projected cohort effects for birth cohorts centred on the years 1993, 1998 and 2003 (shaded areas) and projected period effects for periods centred on the years 2013, 2018, 2023 (shaded area). Leftmost lower panel (D): Estimated age-specific annual *female mortality* rates due to breast cancer in 5-year age groups in Hong Kong with 95% credible intervals. Middle and rightmost lower panels (E, F): Estimated relative risks for 10-year birth cohort (beginning in the calendar year 1889) and 5-year calendar period (beginning from 1976) effects associated with the *deaths* with 95% credible intervals, including projected cohort effects for birth cohorts centred on the years 1993, 1998 and 2003 (shaded area) and projected period effects for periods centred on the years 2013, 2018, 2023 (shaded area).

evident for female hormonal-related cancers (Herrinton *et al*, 1994; Liao *et al*, 2003). Notably, the mortality deceleration started earlier for generations born around 1950s, perhaps due to generational differences in awareness and inclination to seek screening and treatment. Conversely, if survival remains high for these women as they get older, then this would point to the existence of an unidentified protective factor which has counteracted the mortality associated with changing socio-economic and demographic patterns.

With respect to the age curves, downward inflection points in incidence and mortality rates were around 45–50 years and 65–70 years, respectively. The downward inflection in incidence at the age of menopause coincides with Clemmesen's hook, which is classically recognised in developed countries (Clemmesen, 1948). The subsequent downward inflection in mortality may represent the lag between incidence and mortality.

In most Caucasian populations in the developed West, increases in breast cancer incidence have mainly occurred in women aged ≥ 50 years, whereas reductions have been observed in those aged 35–49 years (Hery *et al*, 2008). We observed similar patterns, although only sporadic, opportunistic mammography screening occurs with relatively low and socially patterned coverage in HK (Leung *et al*, 2008).

We also projected a reduction in age-specific breast cancer mortality rates for women aged < 65 years, and a rising trend in the rates among women ≥ 65 years in the next 15 years. When comparing our trends with western countries, a reduction in mortality trends has been observed in the younger age group (< 50

years) in countries where screening of young women is rare (Denmark, Finland, Netherlands, Norway, UK) but also in those where screening is common (France, Germany, Sweden) (Autier *et al*, 2010). The relatively larger reduction in younger women involved may reflect more effective cancer treatment and better response to treatment (Autier *et al*, 2010). Similarly, the breast cancer deaths in United States and United Kingdom decreased at ages 20–69 years in the recent decade, probably due to many factors including increased use of hormonal and cytotoxic treatments for both early and advanced disease and increased awareness of breast cancer (Peto and Boreham, 2000). These same factors could apply in the HK context. Increased mortality projections for older women could be due to less frequent diagnostic activity, less intensive treatment and more frequent diagnosis of cancer at advanced stages resulting in poorer survival (Eaker *et al*, 2006; Autier *et al*, 2010). Investigation of the underlying reasons is needed.

There are two potential limitations in this study. First, APC analyses are descriptive in nature and we can only speculate the aetiologies of the changes observed. Second, we cannot quantify the survival benefit due to progress in early detection and treatment care in reducing disease risk in past trends, due to lack of relevant survival data in our Chinese population. We however estimated the complement of the mortality to incidence ratio ($1 - (M/I)$ ratio) as a proxy indicator of 5-year relative survival of breast cancer (Supplementary Figure 3) (Asadzadeh Vostakolaei *et al*, 2011). The proxy shows improved survival from breast cancer over times, as the curve of $1 - (M/I)$ ratio appears to be increasing.

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