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Breast cancer mortality in Chinese women: Does migrant status play a role?

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Abstract

***Background*:** It is unclear whether migration would affect the mortality risk of breast cancer. In this study, we compared breast cancer mortality among three Chinese populations: Guangzhou (GZ) or Hong Kong (HK) born women and HK residents who were born outside HK (HK-immigrant), with the aim to explore the impact of migrant status on breast cancer mortality.

***Methods*:** We applied an age-period-cohort (APC) model to annual age-specific mortality rates of breast cancer among GZ-born (2003-2016), HK-born and HK-immigrant women (2003-2016), respectively. We also projected annual mortality rates of breast cancer from 2017 to 2030 for the 35-64 and 65+ age groups of these populations.

***Results*:** The annual age-standardized mortality rate of breast cancer in women aged 35 years or over was 9.18, 9.17 and 9.83 per 100,000 population, for GZ-born, HK-born and HK-immigrant women, respectively. A decreasing trend was found in the post-1950s cohorts of GZ-born women, and in the post-1960s cohorts of two HK populations. Annual mortality rates of breast cancer in these populations were projected to decrease among the 35-64 age group and increase among the 65+ age group in 2017-2030.

***Conclusions*:** We found higher age-specific mortality rates of breast cancer in HK-immigrant women compared with HK- and GZ-born women, suggesting that immigration status might have an impact on breast cancer mortality.

Keywords: Breast cancer, age-period-cohort model, immigration, Chinese women, demographic epidemiology, mortality.

Background

Breast cancer is one of the most common cancers in women. Globally, it was estimated that 2.09 million women were newly diagnosed with breast cancer, and 0.63 million died from breast cancer in 2018 [1]. Previous studies have identified several risk factors of breast cancer incidence and mortality, including genetic factors such as family history, BRCA1/2 carrier and estrogen [2]; reproductive and hormonal factors such as menstrual life, nulliparity, first live birth age and breastfeeding [3-5]; lifestyle factors such as obesity [6-8], physical activity, dietary habits [9] and smoking [10]. Besides these risk factors, migrant status has also been proposed to associate with breast cancer. For example, one early study in Sweden showed that the attack rate of breast cancer tended to be different between immigrants and native Caucasian populations [11]. A study in Canada found that Asian immigrants less likely received mammography screening than did non-immigrants [12]. Moreover, similar breast cancer survival rates for Asian immigrants and native Caucasian women were reported by a US study [13], but another study reported that the survival rates of Asian immigrants were worse than those of native Asian women [14]. However, no studies have been conducted to compare breast cancer mortality between immigrant and non-immigrant women within the same ethnicity and culture, to our best knowledge.

Breast cancer is now the fourth leading cause of death among cancers in Chinese women, and the age standardized mortality rate increased from 5.7 to 8.8 deaths per 100,000 women throughout the past ten years in China [1, 10, 15]. The incidence rate and prognosis of breast cancer showed great heterogeneity in mainland China. Economically developed urban areas in China had higher incidence rates of breast cancer and better prognoses than underdeveloped urban and rural areas [10]. It has been reported that the 5-year survival rate of breast cancer patients in Shanghai, one of the most industrialized cities in China, was 78% in 1992-95 [16], much higher than the survival rate in a rural area near Shanghai (58% in 1992-2000) [17]. Both rates were significantly lower than the rate of 89% reported for US women in 1999-2005 [18].

In this study, we compared the mortality rates of breast cancer between Chinese women in Hong Kong (HK) and Guangzhou (GZ). Both cities share similar ethnicity (>90% of female residents are Chinese) [19], culture and dietary habits. Multiple migration waves from mainland China to HK occurred in the last century, including a major migration inflow during the Chinese Civil War (from 1945 to 1950), and several small-scale inflows in the 1950s, 1970s and 1990s [22-25]. 87.8% of these immigrants were Chinese originally from the Guangdong province where GZ is the capital city [26]. Previous studies found that child immigrants in Hong Kong had a higher risk of cardiovascular diseases [27] and wheezing disorders [28]. However, to date there are no studies that have compared the breast cancer mortality of immigrants and HK origin residents, although such comparison could provide important evidence to understand the role of immigration in cancer mortalities.

This study was aimed to assess the age, period and cohort effects on breast cancer mortality during the study period of 1998-2017, as well as to project mortality rates up to 2030, in three Chinese populations: GZ- or HK-born women, and HK women who were born outside HK (HK-immigrant). We chose these three populations based on the following reasons: 1) they are ethnically homogeneous and share the same culture and dietary habits; 2) GZ-born and HK-immigrant women had similar early life experiences; 3) HK-immigrant and HK-born women likely share similar screening and healthcare

seeking behavior. Specifically, we hypothesize that if migrant status plays an important role in breast cancer mortality, HK-immigrant women could show different patterns of age, period and cohort effects from the homeland population (represented by GZ) and HK-born population.

Methods

Data source

The HK and GZ population data by age, gender, ethnicity and birthplace were obtained from the Census and Statistics Department (CSD) of Hong Kong and the Guangzhou Municipal Centre for Disease Control and Prevention (GZCDC) respectively. The Hong Kong data were divided into HK-born and HK-immigrants who were born outside HK (including mainland China, Macau and Taiwan). The death registry data of Hong Kong in 2003-2016 were obtained from the CSD. GZ is the capital city of the nearest province (Guangdong province) in mainland China to HK. Compared to the majority of the other parts in mainland China, GZ has similar environmental conditions and living habits as in HK. The death registry data of GZ in 2003-2016 were obtained from GZCDC. Breast cancer mortality data were retrieved from the death registry data using the International Classification of Diseases version 10 (ICD-10) codes C50, C50.0-C50.9 after 2000 for both GZ and HK. Given the low incidence of breast cancer in men and young women, only the mortality data from women aged 35 years or over were included in this study. Annual mortality rate was calculated for single-year age groups, and age-standardized mortality rates were calculated based on the WHO world standard population in 2000 [29]. We also did a stratified analysis for the age groups of 35-64 and 65+ years. The cutoff age at 65 was selected since nearly 50% of the breast cancer incidences aged above 65 years [30].

Statistical analysis

We applied an APC model with a Poisson distribution to annual mortality rates of breast cancer by single-year age groups from 35 to 85+ years, for GZ-born, HK-born and HK-immigrant women, respectively. The APC model has long been applied to incidence or mortality data of cancers and chronic diseases, and more technique details can be found in a review by Holford [31]. The best-fit APC model was selected by minimizing the deviance and the Akaike Information Criteria (AIC) [32]. We bootstrapped the sample data from the whole datasets 100 times and fitted an APC model to each sample to check the sensitivity and fitting performance of the final APC model. A probability map was also plotted in Figure S1 to show the percentile of all the fitting values that observed data fell at for each data point [33, 34]. Overall all the models achieved the satisfactory goodness of fit.

It is well known that the APC model has an identifiability problem due to the linear correlations between age, period and cohort variables, therefore only the second-order differences could be estimated from this model [35, 36]. Statistical significance of age, period and cohort effects was tested by log-likelihood ratio tests between the full models and nested sub-models of age-period, age-cohort and period-cohort effects. Furthermore, *t*-tests were applied to test the statistical significance of the age effect difference between the three populations. We did not test for the period effects and the effects of pre-1930 cohorts, because the data of early cohorts could be imprecise due to insufficient data sample. Further details of this limitation can be found in the discussion section.

By fixing the period effect at its average level, we used the age-cohort sub-model to project the trend of mortality rates in those aged 35 or over from 2017 to 2030 [37, 38]. We used the second-order autoregressive time series to extrapolate the cohort effects, in which each point estimate was derived from the data of two preceding cohorts. The 95% credible intervals was estimated by using a chain-ladder model with a Poisson distribution [33, 34, 39].

The p-value < 0.05 indicated statistical significance. All the analyses were conducted by the package "apc" of R software version 3.4.3 [40].

Results

During the study period, annual age-standardized mortality rate of breast cancer was 9.83, 9.17 and 9.18 per 100,000 women, for HK-immigrant, HK-born and GZ-born women aged 35 years or over, respectively (Table 1). An increasing trend of mortality rates over age was observed for all these populations, with occasional exceptions. Women in HK had significantly higher mortality rates than GZ-born women among most the age groups, and the largest difference was found in those age 70+ years (Table 2). HK-immigrant women had a higher mortality risk than HK-born women in younger and older age groups, whereas no significant difference was found in the age groups of 35-39 and 55-69 years, and a significant lower rate in the 45-54 age group.

Detailed information about the model goodness of fit and prediction performance is shown in Supplementary Table S1-S3. The APC models generally fitted well to annual single-year mortality rates of breast cancer among the three Chinese female populations (Figures 1 and 2). In women aged 35-64 years, a slow rising trend of breast cancer mortality was observed before 2014 among all the populations, but a clear declining trend was found post 2014. The projection to year 2030 shows that breast cancer mortality rate decreases in this younger age group, and the most dramatic change occurs in HK-born women. The trends of mortality in older women aged 65+ years were less consistent. The mortality rates of GZ-born women consistently increased after 2003, but a turnover point was found in 2009 and the rates increased since 2012. The mortality rates of HK-born and HK-immigrant women remained relatively stable in older women, while GZ-born older women had a lower mortality rate, which is projected to surpass the former around 2025. In both age groups combined, annual mortality rates of age 35 or over are projected to remain stable in 2017-30, with an average annual rate of 32, 22 and 27 deaths per 100,000 women among the HK-immigrant, HK-born and GZ-born populations.

The effect estimates of age, period and cohort for GZ-born, HK-immigrant and HK-born women are shown in Figure 2. The trend of the age effects is consistent between HK-born and GZ-born women, with a fast rising trend for those aged 35-50 years, a plateau for 50-75 years and a rising trend again in 75 years and above. The period effects are largely consistent between the three populations. The cohort effects show an inverse "U" shape in all three populations with a peak clearly observed in the 1930s, whereas multiple peaks were found in HK-immigrant and HK-born women. A decreasing trend was found among the post-1960s cohorts of GZ-born women, and in the post-1950s cohorts for two HK populations. For the 1941-50 cohort, breast cancer mortality risk was relatively lower for GZ-born than

HK-immigrant and HK-born women, whereas the 1956-65 GZ-born cohort has a relatively higher risk than HK-immigrant and HK-born women (Table 3).

Discussion

In this study, we projected the trend of age-specific mortality rates up to year 2030 in the age groups of 35-64, 65+ years and both combined, separately for these populations. In the combined group, the projection shows a steady trend, which is consistent with another study in HK [41, 42]. The mortality rate of breast cancer is projected to continuously increase in older women but simultaneously decrease in the 35-64 age group. Projected increase in the elderly could be associated with more frequent diagnosis of cancer at advanced stages resulting in poorer survival [42, 43]. A similar situation was reported in the US and the UK, which could also be applied to the HK context [38]. Increased awareness against breast cancer, early diagnosis and improved cancer therapies in both HK and GZ could possibly explain the projected trends [10, 44-46], but further investigations on the underlying reasons are needed.

Interestingly, we observe a higher mortality rate among HK-immigrant women than the other two, particularly in older women (Figure 1). Consistently, in the cohort effects we identified a faster increasing trend in the 1920-1930 cohorts and multiple peaks in the 1940-1950 cohorts in HK-immigrant women (Figure 2). These cohorts correspond to the first immigration wave during the Chinese Civil War (1945 to 1950s), and the second during the Culture Revolution (late 1960s to 1970s) [47]. Hence, we speculate that many of the 1940-1950 cohorts of HK-immigrants had probably suffered from the Chinese Civil War and the Great Chinese Famine between 1959 and 1961 during their puberty and adolescence before they fled to HK [22-25]. Those who moved from mainland China to HK after the famine could have worse early-life experience and less healthy physical conditions than the HK-born population, which could affect the survival odds from breast cancer in their later life. Our findings echo the previous findings that women who experienced severe famine during their childhood and early adulthood had a higher risk of breast cancer than those without famine exposure [48]. Another possible explanation is the implementation of the one-child policy in the late 1970s [49, 50], which has been found to be associated with increased breast cancer risk in mainland China [10]. It is of note that mortality rates might also be affected by many other factors such as socioeconomic status, lifestyle (obesity, smoking), mammography screening, early diagnosis of breast cancer, and accessibility to effective treatments. In the past decades, the mainland China has experienced a fast economic growth, and an epidemiological transition has been found in cardiovascular diseases since more people adopted westernized lifestyle [51]. This could also explain the rapid increase of breast cancer mortality among GZ-born women in this study. Therefore, further studies are warranted to explain the high mortality rate in the HK-immigrants.

The cohort effects became consistent across the three populations in the post-1960 cohorts, but inconsistent for the pre-1960 cohorts. This could be due to fast economic development of mainland China after 1980s, with an annual increase rate of 8.5% in mainland China [52, 53]. The consistency of the post-1960 cohorts could also be (partly) due to an increased age at first child-birth among the GZ-born women [54]. We also projected that the older GZ-born women had a faster increase in mortality rates in next fourteen years (Figure 1). The HK-born women had a higher mortality rate than the GZ-born women among those aged over 70 years, but the two mortality rates appear similar among younger

age groups (Table 2). This might be the result of rapid development in living conditions among the younger generation of GZ-born women during the economic boom after the 1980s [52, 53].

Breast cancer mortality is determined by both survival profile and incidence rate. In our data, age-standardized mortality rates were found similar between the three populations. Age-standardized incidence rate in 2008 was 45.8 and 46.6 per 100,000 women in HK and GZ, respectively [21]. There is no strong evidence to suggest distinctive survival profiles between HK-born and GZ-born women. One study of the US Asians from 1988 to 2005 demonstrated that immigrant status could partially explain the disparities in breast cancer survival rates between immigrants and local born people, although they had different ethnicities [55]. Unfortunately we do not have the incidence rate in HK-immigrants. Future work is warranted when individual data become available for migrant status, cancer incidence and mortality.

The strengths of our study lie in several aspects. First, we compared the immigrants with the other two ethnically homogeneous Chinese populations, and these three populations share similar culture and dietary habits. However, most previous studies often compared the data of minority immigrants to those of local populations with different ethnicities [11-14]. Second, our data was from two large and representative Chinese cities, and divided into three groups according to birthplace and immigration status. We were able to compare the age, period and cohort effects of immigrants with those in local born populations and also with a representative population from the place of origin.

Our study has some limitations. First, ecology fallacy cannot be avoided in this ecological study. Second, we do not have the records of the exact immigration time for individual subjects, so the assumption that the immigrants had similar early-life exposure to the origin populations might not hold in some HK-immigrants who came to HK in their early childhood. Third, there are many other factors that could have driven the temporal change of breast cancer mortality but remained unadjusted in our model, such as screening programs, promotion of the public awareness of breast cancer, and health services. Last but not least, due to the lack of incidence rate and individual data, and the descriptive nature of the APC model, further individual-based research is needed to elucidate the mechanisms behind the discrepant patterns across these Chinese populations.

Conclusions

Using the APC model, we found that HK-immigrant women had slightly higher age-specific mortality rates among three populations of Chinese women that share similar culture. The findings suggest that migrant status might somehow have affected the breast cancer mortality of Chinese women.

List of abbreviations

HK: Hong Kong; GZ: Guangzhou; APC: age-period-cohort; AIC: Akaike information criterion; CSD: the Census and Statistics Department of Hong Kong; GZCDC: the Guangzhou Municipal Centre for Disease Control and Prevention; ICD: the International Classification of Diseases.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the Census and Statistics Department (CSD) of Hong Kong and the Guangzhou Municipal Centre for Disease Control and Prevention (GZCDC) but restrictions apply to the availability of these data, which were used under license for the current study, and thus are not publicly available. However, data are available from the corresponding authors upon request and with permissions from the CSD of Hong Kong and GZCDC.

Competing interests

None.

Funding

Not applicable.

Authors' contributions

S.Z. and L.Y. conceived, and designed the work.

L.Y., G.L. and H.D. acquired the data.

S.Z. carried out the analysis in this work.

S.Z., L.Y. and D.H. interpreted data, and drafted the manuscript.

All authors revised the manuscript, and approved the final version.

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Table 1. Age-specific mortality rates of breast cancer and age-standardized mortality rates (per 100000 female population) in Hong Kong (HK) from 2003-2016, and in Guangzhou (GZ) from 2003-2016.

Age group (years)	HK-immigrant				HK-born				GZ-born			
	2003-2007	2008-2012	2013-2016	Whole period	2003-2007	2008-2012	2013-2016	Whole period	2003-2007	2008-2012	2013-2016	Whole period
35-39	5.83	7.18	3.51	5.67	5.36	4.5	5.12	5.95	5.55	5.19	5.49	5.4
40-44	10.93	13.14	10.62	12.11	11.7	10.11	11.09	11.61	11.33	9.7	8.6	9.91
45-49	17.44	17.04	17.68	17.06	18.02	17.19	18.61	18.83	21.17	16.09	18.32	18.39
50-54	25.08	29.35	22.61	24.38	28.31	25.92	28.82	27.32	27.16	24.19	28.94	26.68
55-59	27.37	34.97	33.72	30.61	26.66	28.93	32.82	30.46	28.16	27.63	34.5	30.29
60-64	33.86	36.62	37.37	34.26	38.31	34.36	36.79	35.06	24.81	27.94	31.56	28.76
65-69	25.95	31.46	37.26	29.07	35.8	25.21	29.41	29.56	28.92	25.42	33.14	29.43
70-74	31.18	29.48	32.68	30.91	31.69	26.43	35.83	28.47	34.54	37.38	31.32	34.59
75-79	38.9	35.26	39.33	39.26	22.65	24.92	29.45	28.8	34.86	38.03	33.75	35.69
80-84	59.01	56.68	43.42	56.1	38.88	39.48	41.87	43.06	40.05	43.95	53.24	46.86
85+	86.53	86.83	70.24	82.8	44.88	38.61	40.77	43.67	51.52	62.87	52.47	55.83
Age-standardized	9.6	10.28	9.61	9.83	9.34	8.45	9.73	9.17	9.18	8.66	9.56	9.18

Note: Age-standardization was based on the WHO world standard population in 2000 [29].

Table 2. Comparison of age-specific mortality rates of breast cancer (per 100000 female population) between the HK-born, HK-immigrant and GZ-born women.

Age group	HK-immigrant VS. HK-born			HK-immigrant VS. GZ-born			HK-born VS. GZ-born		
	Diff	95% CI	*p*-value#	Diff	95% CI	*p*-value#	Diff	95% CI	*p*-value#
35-39	0.09	[0.06, 0.13]	<0.0001	0.03	[0, 0.07]	0.0672	-0.06	[-0.08, -0.03]	<0.0001
40-44	0.1	[0.05, 0.15]	0.0001	0.2	[0.15, 0.25]	<0.0001	0.1	[0.05, 0.14]	<0.0001
45-49	-0.05	[-0.12, 0.02]	0.1454	-0.15	[-0.23, -0.07]	0.0002	-0.1	[-0.17, -0.03]	0.0033
50-54	-0.22	[-0.31, -0.13]	<0.0001	-0.07	[-0.16, 0.02]	0.1417	0.15	[0.09, 0.22]	<0.0001
55-59	0.34	[0.26, 0.42]	<0.0001	0.25	[0.18, 0.33]	<0.0001	-0.09	[-0.15, -0.02]	0.0066
60-64	0.08	[-0.01, 0.18]	0.0967	1.09	[1, 1.18]	<0.0001	1.01	[0.9, 1.12]	<0.0001
65-69	0.13	[0.03, 0.23]	0.0144	0.17	[0.06, 0.28]	0.0025	0.04	[-0.08, 0.16]	0.5358
70-74	0	[-0.13, 0.13]	0.9756	-0.47	[-0.58, -0.36]	<0.0001	-0.47	[-0.62, -0.32]	<0.0001
75-79	1.7	[1.57, 1.84]	<0.0001	0.32	[0.19, 0.44]	<0.0001	-1.39	[-1.51, -1.26]	<0.0001
80-84	1.84	[1.6, 2.09]	<0.0001	0.98	[0.82, 1.15]	<0.0001	-0.86	[-1.11, -0.61]	<0.0001
85+	5.88	[5.74, 6.02]	<0.0001	3.77	[3.62, 3.92]	<0.0001	-2.11	[-2.28, -1.95]	<0.0001

Abbreviation: HK, Hong Kong; GZ, Guangzhou; Diff, difference; and CI, confidence interval.

p-value of *t*-test

Table 3. Comparison of cohort-specific mortality rates of breast cancer (per 100000 female population) between the HK-born, HK-immigrant and GZ-born women.

Cohort	HK-immigrant VS. HK-born			HK-immigrant VS. GZ-born			HK-born VS. GZ-born		
	Diff	95% CI	*p*-value#	Diff	95% CI	*p*-value#	Diff	95% CI	*p*-value#
1931-1935	1.69	[1.58, 1.8]	<0.0001	1.06	[0.94, 1.18]	<0.0001	-0.63	[-0.75, -0.52]	<0.0001
1936-1940	1.14	[1.01, 1.28]	<0.0001	0.77	[0.67, 0.86]	<0.0001	-0.38	[-0.52, -0.24]	<0.0001
1941-1945	1.15	[1.02, 1.28]	<0.0001	-0.2	[-0.34, -0.12]	0.0001	-1.38	[-1.5, -1.26]	<0.0001
1946-1950	-0.21	[-0.35, -0.07]	0.0026	-0.5	[-0.64, -0.42]	<0.0001	-0.32	[-0.46, -0.18]	<0.0001
1951-1955	0.61	[0.49, 0.73]	<0.0001	0.68	[0.57, 0.78]	<0.0001	0.07	[-0.04, 0.18]	0.2344
1956-1960	0.36	[0.26, 0.46]	<0.0001	0.76	[0.66, 0.86]	<0.0001	0.4	[0.31, 0.49]	<0.0001
1961-1965	0.11	[0.03, 0.18]	0.0078	0.34	[0.25, 0.42]	<0.0001	0.23	[0.17, 0.3]	<0.0001
1966-1970	0.19	[0.11, 0.27]	<0.0001	-0.2	[-0.25, -0.09]	<0.0001	-0.36	[-0.42, -0.29]	<0.0001
1971-1975	-0.27	[-0.32, -0.21]	<0.0001	0.02	[-0.04, 0.08]	0.5636	0.28	[0.22, 0.35]	<0.0001
1976-1980	0.12	[0.05, 0.19]	0.001	-0.2	[-0.32, -0.16]	<0.0001	-0.36	[-0.43, -0.29]	<0.0001

Abbreviation: HK, Hong Kong; GZ, Guangzhou; Diff, difference; and CI, confidence interval.

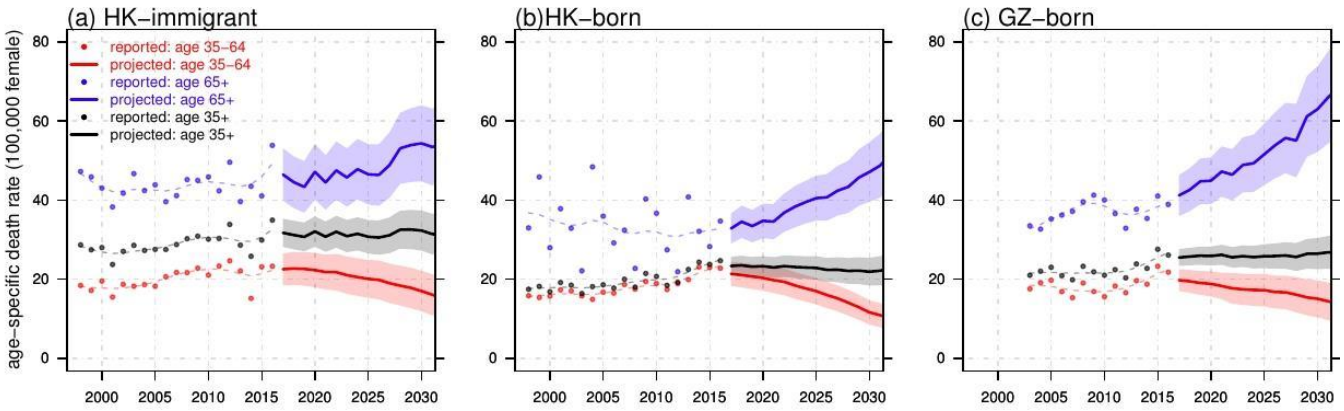
p-value of *t*-test

Figure legends

Figure 1. Observed and projected age-specific mortality rates of breast cancer in 2003-2030, among (a) HK-immigrant, (b) HK-born and (c) GZ-born women, by the 35-64 (red), 65+ age groups (blue) and both combined (black). In each panel, observed data are plotted as dots, *LOESS* smoothed data as broken line, projected rates as solid line, and the shaded areas are 95% credible intervals of projected rates.

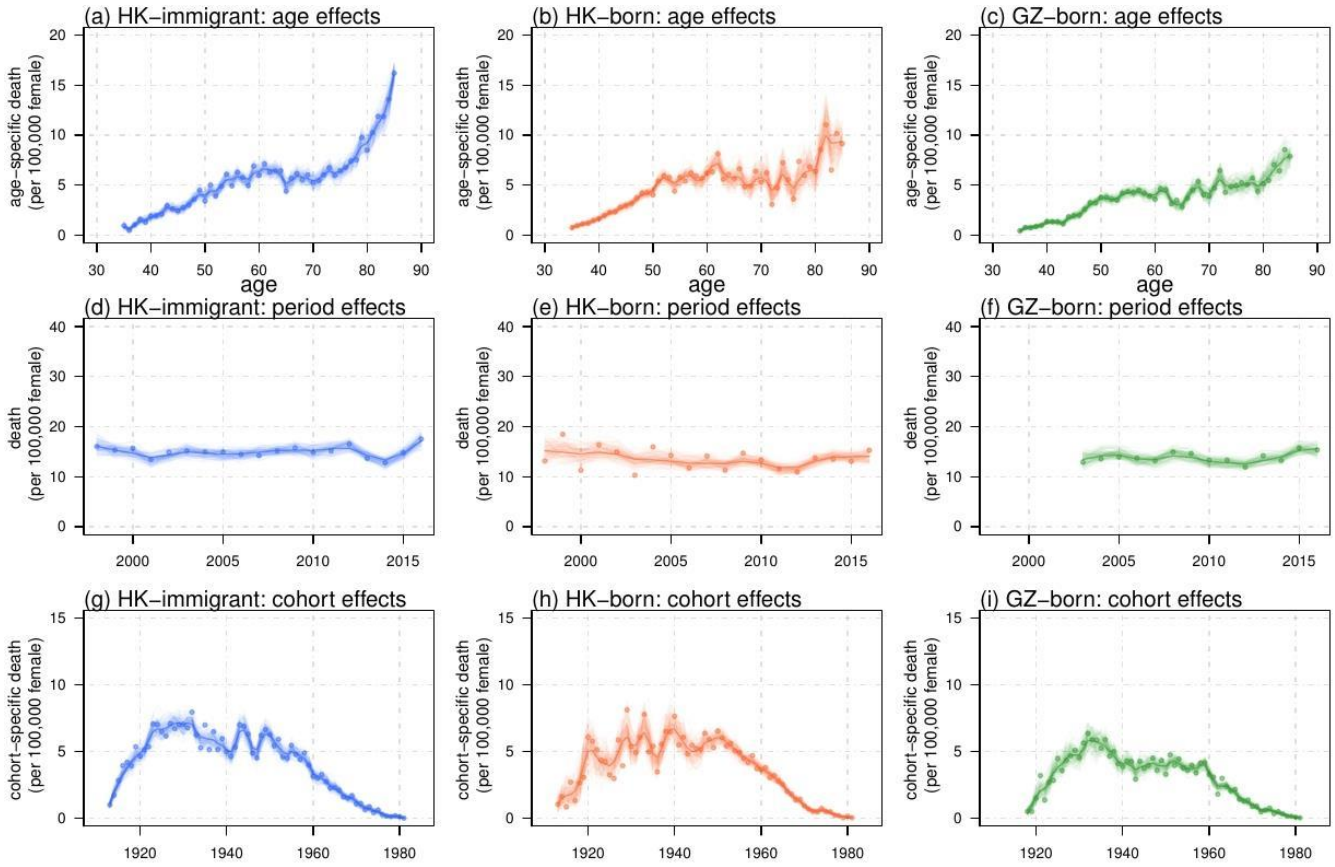
Figure 2. Estimates of the age, period and cohort effects on breast cancer mortality of HK-immigrant (panels a, d, g), HK-born (panels b, e, h) and GZ-born (panels c, f, i). In each panel, dots are observed age-specific mortality rates, thick lines are mortality rates predicted from the APC model, and thin lines are the estimated from the APC models fitted to the 100 sub-datasets randomly sampled by bootstrapping.

422


(a) HK−immigrant
(b)HK−born
(c) GZ−born
age−specific death rate (100,000 female)
reported: age 35−64
projected: age 35−64
reported: age 65+
projected: age 65+
reported: age 35+
projected: age 35+
0
20
40
60
80
2000
2005
2010
2015
2020
2025
2030

423

424


(a) HK–immigrant: age effects
(b) HK–born: age effects
(c) GZ–born: age effects
age–specific death (per 100,000 female)
age
(d) HK–immigrant: period effects
(e) HK–born: period effects
(f) GZ–born: period effects
death (per 100,000 female)
(g) HK–immigrant: cohort effects
(h) HK–born: cohort effects
(i) GZ–born: cohort effects
cohort–specific death (per 100,000 female)

425