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A population-based age-period-cohort study of colorectal cancer incidence comparing Asia against the West

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most common cancer worldwide but incidence varied widely. Despite the role of genetics, CRC is also sensitive to macro-environmental factors. Few studies have ever compared across different countries/regions to suggest possible macro-environmental risk factors of CRC. We estimated the effects of age, period and cohort on the changes of incidence of colorectal cancer across different countries/regions.

Methods: Poisson regression age-period-cohort (APC) models were conducted to estimate the age, period and cohorts effects on CRC incidence across the West (i.e., the UK, the US and Australia) and Asia (i.e. Japan, Hong Kong, Shanghai, Singapore and India). We maximized the length of the study period according to each country's data availability.

Results: Western populations show upward inflections for their 1950s–1960s cohorts, while Asian populations (except India) show downward inflections for their 1950s cohorts. Japanese population also shows upward inflections for its 1960s cohorts, similar to the Western populations. There are apparent upward inflections towards the more recent cohorts for Hong Kong, Shanghai and Singapore; nevertheless, the confidence intervals are wider towards the more recent cohorts.

Conclusion: Our findings imply an increasing risk of CRC in both Western and Asian populations as their younger cohorts reach older ages. These findings are consistent with the life course argument that macro-environmental changes associated with socio-economic development have specific effects that extend over the life course. Actions that pertain to altering lifestyle-related exposures over the life course are of great importance in combating young CRC risks in the future.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast cancers, with over 1 million new cases being detected yearly [1]. It is also the third leading cause of cancer death with 880,792 deaths recorded in 2018 [2]. CRC has traditionally been more prevalent among developed countries, contributing to around 60% of global CRC cases [1]. However, incidence varied widely across the globe, with low rate traditionally observed in India [3].

While genetic factors are known to play an important role, CRC is highly sensitive to non-genetic, macro-environmental factors, in particular modifiable risk factors associated with lifestyle, including low fruit and vegetable intake, high-fat diet, overweight and obesity, sedentary lifestyle, tobacco use and alcohol consumption [4]. Another well-known example that demonstrated the impact of macro-environmental changes on CRC is the rapid increase of the CRC incidence rates of immigrants to reach those of the host country [5,6]. Other important risk factors include increasing age, male gender, positive family history of inflammatory bowel diseases and adenoma or CRC [4,7,8].

To date, there is scarcity of studies comparing different countries to give a coherent story of the temporally related macro-environmental risk factors of CRC. Previous studies have demonstrated the importance of considering the effects of biological age, calendar period and birth cohort to identify temporally related macro-environmental risk factors of CRC [9–15]; however, the conclusions were inconsistent.

In this study, we aimed to give clues on possible broad, macro-environmental risk factors associated with the changes in CRC incidence across different countries. We used age-period-cohort (APC) modeling

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which is a powerful method to identify risk factors that are temporally coincided with, and potentially contribute to, the changes in patterns of disease by decomposing incidence rates into the contributions of age, calendar period and birth cohort effects [16]. Age is the surrogate of the natural aging process [17]. Period is the surrogate of contemporary population-wide influences that affect all population under study – e.g. implementation of health interventions on the population at risk [17], or more general population-wide exposures that see no age limit (e.g. regional wars, financial setbacks or population-wide policies). Cohort is the surrogate of long-term life course influences that affect different generations differentially, because the same generations may have very similar macro-environmental exposures at critical periods of their lives such as during gestation, early childhood, adolescence or early adulthood [17,18]. As such, this study adopts a cross-country comparative study design, which will enable us to observe both the commonalities and dissimilarities in the patterns of age, period and cohort effects across different countries. With this intention, for each country included in our analysis, we estimated the relative contributions of age, period and cohort to the CRC incidence trends for their corresponding observed periods.

We hypothesized increasing age effects on CRC incidence across all observed countries, period effects that correspond to changes of the macro-environment of the populations, and increasing cohort effects for the generations who were increasingly exposed to more westernized living environments.

2. Materials and methods

2.1. Study design and data sources

We conducted a population-based study using APC modeling, and included all men and women in the population over the study period for each country. Age- and sex-specific annual number of new CRC cases and annual population data are used to estimate the incidence. Age- and sex-specific annual population and incidence data for each country were obtained from the Cancer Incidence in Five Continents Time Trends (CI5plus) databases of the World Health Organization (WHO) International Agency for Research on Cancer (IARC) [19]. CI5plus provides access to various databases containing information on the occurrence of cancer worldwide held and managed by the Section of Cancer Surveillance of IARC. While no large-scale database can be perfect, quality control procedures are instituted to ensure the quality of the data, identify the areas and degree of imperfection, and assist in data interpretation [20]. The CI5plus system also ensures that the data items recommended for registration to be kept minimal, with emphasis on the quality rather than the volume of information [20]. Moreover, intensive and extensive use of the registry's data tends to maintain and improve their quality [20].

From the data source, we chose representative Asian countries/regions including Japan, China (Hong Kong, Shanghai), Singapore and India and compared them against representative western countries including the UK, the US and Australia. We selected these countries for their representativeness of the different models of the epidemiologic transition [21]. While the UK, the US and Australia represent well-established Western populations, the Asian populations represent the accelerated epidemiologic transition model. Shanghai is a representation of the Chinese populations that are recently undergoing accelerated socio-economic development; Hong Kong and Singapore represent mature Asian economies; and Japan has the most established economy with high incidence of the disease. On the other hand, India with a low CRC incidence is included for comparative purposes. Due to data availability and completeness, selected regions of some countries were included, while population-wide data were used for all the others. We included Merseyside and Cheshire, North Western, South and Western Regions, Birmingham and West Midlands Region, Yorkshire of England and Scotland for the UK; the Surveillance, Epidemiology, and End Results (SEER) Regions for the US; New South Wales, Queensland, South Australia, Tasmania, Victoria and Western Australia for Australia; Miyagi and Osaka Prefectures for Japan; and Mumbay and Chennai for India. Details of the registries included in this study are also shown in Supplementary Table 1.

2.2. Statistical analysis

CRC incidence rates were presented per 100,000 people, and directly age-standardized to the WHO World Standard Population [22] for international comparison. We grouped the incidence data into five-year age groups in order to control for potential inconsistency and fluctuating data noise. We maximized the length of the study period; i.e., to maximize the number of five-year age groups and the number of five-year periods according to each country's data availability. We used data of 1983–2007 for the UK, 1978–2007 for the USA, 1983–2007 for Australia, 1978–2007 for Japan, 1983–2007 for Hong Kong, 1988–2007 for Shanghai, 1968–2007 for Singapore and 1983–2007 for India. Cases below the age of 20 were excluded due to low-to- zero incidence in younger ages. Number of CRC cases over the last four five-year periods in each country is shown in Supplementary Table 2. For the observed periods, we modeled CRC incidence using Poisson APC regression models to decompose rates over time by age, period and cohort, with 95% confidence intervals.

We applied Poisson age-period-cohort (APC) models using maximum likelihood method to estimate the relative risks (rate ratios) by age groups, calendar period and birth cohort, with 95% confidence intervals. Under the full age-period-cohort model, the mean is specified as follows:

$$\log(\mu_{ij}) = \alpha_{age_i} + \beta_{period_j} + \gamma_{cohort_k} + \log(n_{ij}),$$

where α_{age_i} $(i = 1, ..., I)$ is the age effect, β_{period_j} is the period effect $(j = 1, \cdots, J)$, γ_{cohort_k} is the cohort effect $(k = 1, ..., K, k = I + j - i)$, and $\log(n_{ij})$ is the offset term.

We adopted the common method of including an arbitrary reference constraint in the model to overcome the "non-identifiability" of APC model due to the linear dependency between the three components (i.e., cohort = period – age) [23,24]. For age effect, we used age group 40–44 as the reference; for period effect, we used the second and penultimate periods to be references [25,26]; and for cohort effect, we used cohort centered at 1943 as reference.

Second-order changes of slopes instead of the absolute risk ratios were interpreted [16]. Akaike Information Criterion (AIC) was used to compare the models, including age, age-drift, age-period, age-cohort and age-period-cohort models; a lower AIC indicates a better fitting model, and hence a significant change in effect through time for the relevant component. All analyses were implemented using R software (R Development Core Team, Vienna, Austria).

3. Results

3.1. Age-standardized incidence rates

Overall, the age-standardized incidence rates are higher for men than women across all countries (Fig. 1). All populations except Shanghai and India have similar CRC incidence towards the most current years – i.e., around 40 new cases per 100,000 person-years. Regarding trends of CRC incidence, only the US shows a decline. Incidence rates are relatively stable for the UK, Australia and Hong Kong, throughout their respective observed periods. Singapore's incidence rates have also increased to a comparable level as Hong Kong around the late 1980s and did not see much of an increase afterwards. Japan has seen its incidence rates arisen from 1978 to the zenith around the 1990s and plateaued thereafter. Shanghai, albeit having lower incidence rates than most other countries, still sees its CRC incidence

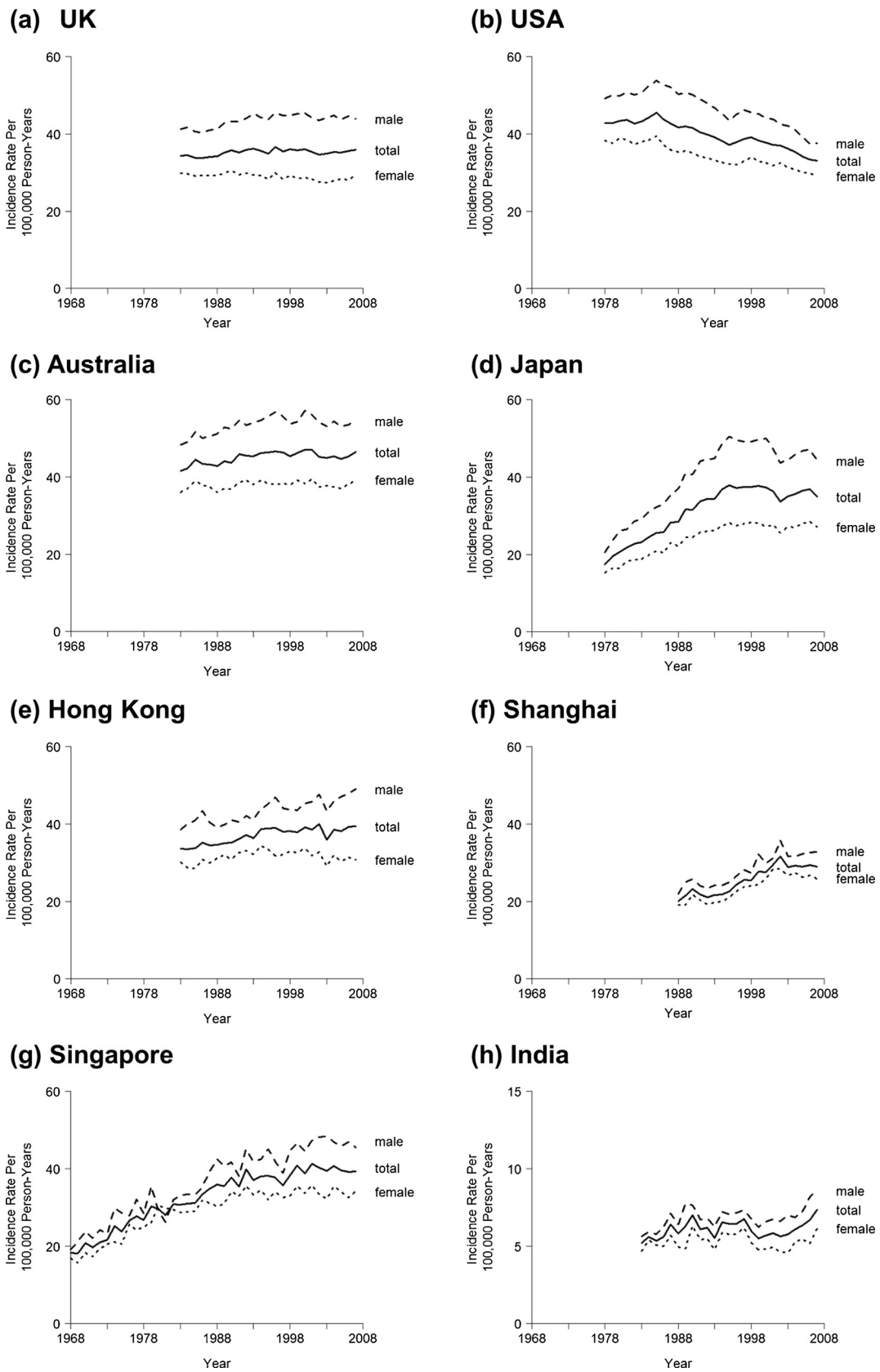

Fig. 1. Age-standardized incidence rates across (a) UK (1983–2007), (b) USA (1978–2007), (c) Australia (1983–2007), (d) Japan (1978–2007), (e) Hong Kong (1983–2007), (f) Shanghai (1988–2007), (g) Singapore (1968–2007), and (h) India (1983–2007).

Table 1
Akaike information criteria (AIC) of age, age-drift, age-period, age-cohort and age-period-cohort models for risk of colorectal incidence across all populations under study.

Populations	Age	Age-drift	Age-period	Age-cohort	Age-period-cohort
UK	1446.8	1412.8	1343.0	981.7	840.3
USA	5438.1	2594.3	2325.9	1451.8	1010.7
Australia	1803.2	1674.5	1591.9	923.6	880.9
Japan	6102.7	2657.9	1441.3	2074.9	1031.0
Hong Kong	1063.5	963.1	936.6	732.5	721.8
Shanghai	2124.0	1326.0	1277.4	604.2	564.4
Singapore	1891.8	1248.2	1144.5	975.7	944.4
India	587.1	572.0	543.9	573.1	538.4

increasing over its relatively short period (1988–2007). India has had the lowest incidence among all countries with no apparent increase over the years.

3.2. Age, period and cohort effects

For all countries, age, period and cohort contribute to the observed changes in CRC incidence. Models including all three components fit best (Table 1). Age-drift models generally have lower AICs than age models, but higher AICs than age-period and age-cohort models. Age-cohort models generally have lower AICs than age-period models – i.e., cohort effects tend to contribute more than period effects to the observed changes, but with the exceptions of Japan and India.

3.2.1. Age effects

In general, the CRC incidence increases across age with slight downturn toward older ages in all populations (Fig. 2). UK, US and Australia display more apparent downturn towards the older age groups as compared to Japan, HK, Shanghai, Singapore and India.

3.2.2. Period effects

In general, the period effects reflect the trend of the age-standardized incidence rates of each country (Fig. 3). Japan displays a sharp downturn at around 1993–1997, which then continue in its decline till the end of observation period. There is also a sharp increase in the period effects of CRC incidence in India around 2003–2007; however, no apparent trend can be concluded from this single-period increase without a longer observation beyond 2007. These observations are consistent with the AICs, where period effects cannot explain all the observed changes of CRC incidence in general, and also the exceptions of Japan and India having significant period effects.

3.2.3. Cohort effects

All the Western populations (i.e., UK, US and Australia) had upward inflections observed as their last inflection direction of cohort effects and no downturns are observed for their younger cohorts (Fig. 3). The upward inflections happen in different cohorts among these countries, with the US displaying the earliest upward inflection with its 1940s cohorts. The patterns of cohort effects are quite similar for the UK and Australia, with the UK displaying upturn for cohorts born around the mid-1960s, and Australia displaying upturn for cohorts born around the late 1950s.

On the other hand, most other Asian populations (Japan, Hong Kong, Shanghai and Singapore) show downward inflections for birth cohorts born around the 1950s. Despite having similar downward inflections with most of the other Asian populations. Japan also has upward inflections for its cohorts born around the 1960s, similar to the Western populations. There are also some apparent upward inflections toward the more recent cohorts for Hong Kong, Shanghai and Singapore. Nevertheless, the confidence intervals are wider toward the more recent cohorts, rendering the interpretations less definite. There are no significant changes in the cohort effects for India.

4. Discussion

This is the first comparative population-based study that examined the age, period and cohort effects on CRC incidence across different countries representing the West versus the East.

First, regarding the age-standardized incidence rates across the countries, we observed that the incidence rates had stabilized in the UK and Australia, and even had declined in the US during the past 30 years. These happened to be the long-term developed Western countries, which also shared more similar socio-cultural and lifestyle background than the other non-Western countries. At the other end, Shanghai, being the most economically developed city in Mainland China, has an increasing CRC incidence rate during the past 20 years, which also coincides with its more current rapid socio-economic development after the implementation of the Open Door Policy in China [27]. It is also noteworthy that Japan has witnessed both a steady increase in the CRC incidence rates from 1970s to early 1990s, and a plateau afterwards, and its pattern of CRC incidence seems to coincide with its pattern of socio-economic development, where its economy rapidly grew in the 1960s and slowed down in the 1990s [28,29]. Similar pattern of growth and plateau of CRC incidence can also be observed in Singapore, which also experienced socio-economic development after the 1960s [29,30]. It is also interesting that Hong Kong, sharing similar socio-cultural and lifestyle background with Singapore [30], witnessed a rather similarly stable pattern of CRC incidence as Singapore from the 1980s onwards; however, due to the relatively shorter length of data for Hong Kong, we were unable to observe whether the CRC incidence was also rapidly increasing as in Singapore during the 1960s and 1970s. Given these observations, one can speculate that there may somehow be association between CRC incidence and general socio-economic development; however, longer period of data is needed to confirm such relationship.

Second, the age effects of incidence generally increase across all populations. This is consistent with the literature that CRC is a disease of the advancing age [31]. Particularly interesting is the slight decline of age effects toward the older age groups in the West, which is not apparent in the Asian populations. This may be reflective of the increased proportion of adults over 50 years undergoing CRC screening with the launch of nation-wide programs during the past several decades in these countries [32–35].

Third, there are no apparent second-order change in period effects with the exception of Japanese and Indian. However, out of almost all the populations under study, the observed periods are relatively short; longer period of observation is warranted for further interpretations.

Finally, there are differential cohort effects on CRC incidence between the Western populations (UK, US and Australia) and the Asian populations (Japan, Hong Kong, Shanghai and Singapore). There is generally an increased cohort effects for cohorts born after the 1950s and 1960s in the UK, the US and Australia. On the contrary, a generally declined cohort effects for the 1950s generations in the Asian populations is observed. In other words, there is a phenomenon of increased CRC cohort effects being shifted toward the younger generations in the Western populations, while this increase is not as apparent for the 1950s generations of the Asian populations. Two possible explanations are offered here.

First, the application of screening strategies and colonoscopic polypectomy may reduce CRC in the West. Nevertheless, since CRC screening is usually recommended to those aged 50 years old or above [10,34], the impact of screening towards the current younger age groups (who by definition also belong to the younger cohorts) would be smaller than that towards the older age groups/generations. The alternative explanation is related to the inherent difference in terms of macro-environmental exposures between the Western and the Asian populations. Westernized lifestyle factors (including low fruit and vegetable intake, high-fat diet, overweight and obesity, sedentary

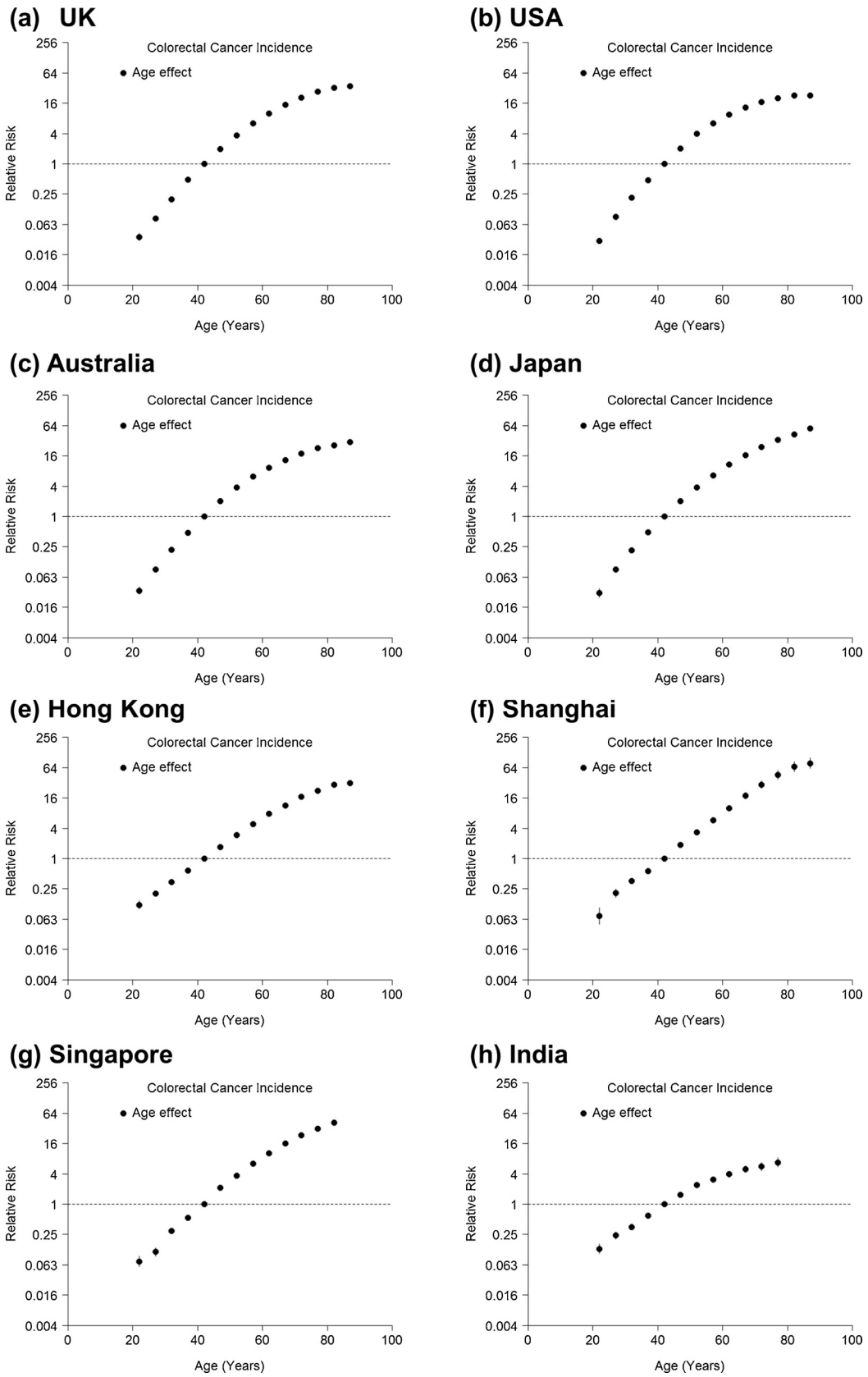

Fig. 2. Parameter estimates and 95% confidence intervals of age effects for colorectal cancer incidence in (a) UK, (b) USA, (c) Australia, (d) Japan, (e) Hong Kong, (f) Shanghai, (g) Singapore, and (h) India.

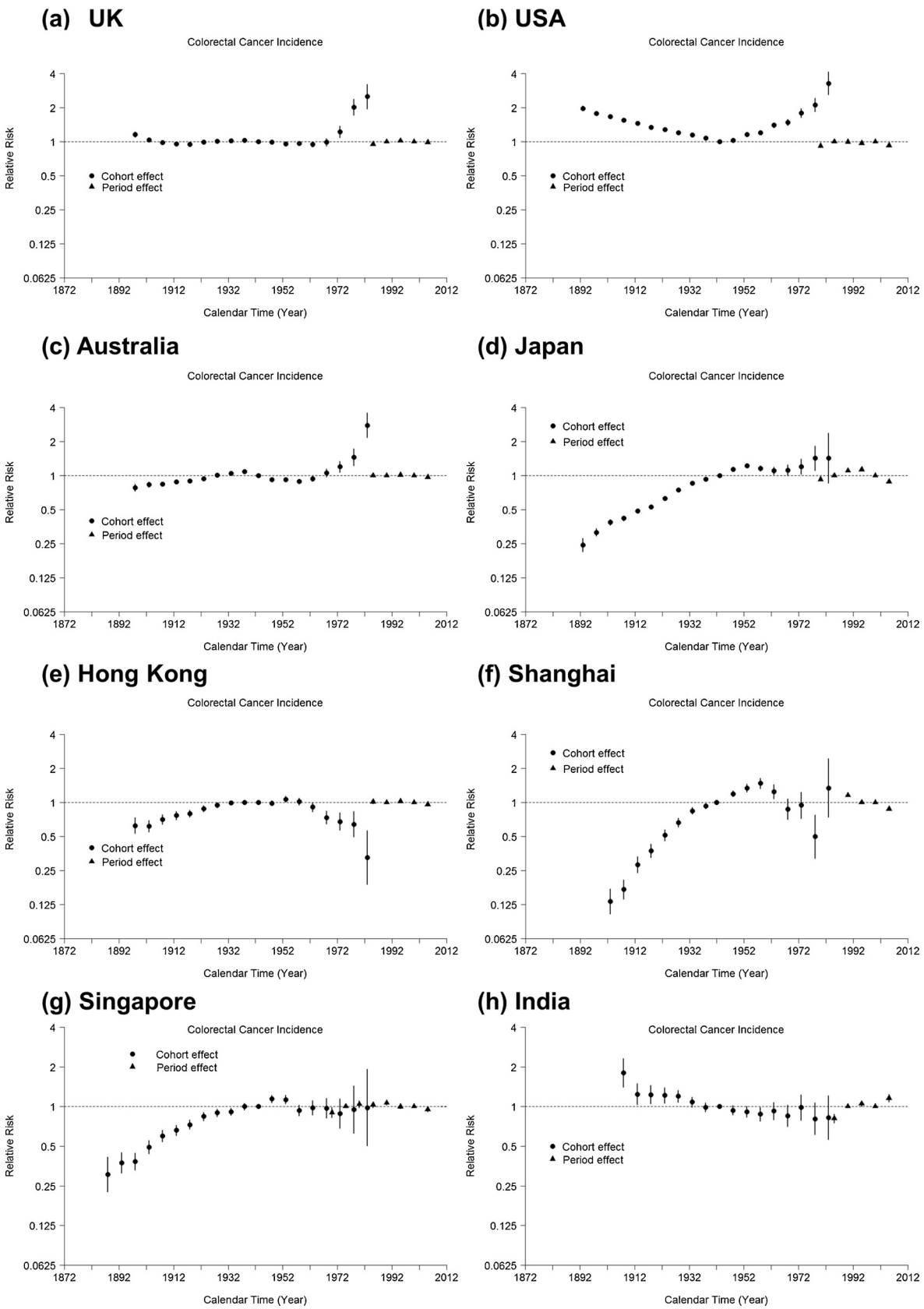

Fig. 3. Parameter estimates and 95% confidence intervals of period (triangles) and cohort (circles) effects for colorectal cancer incidence in (a) UK, (b) USA, (c) Australia, (d) Japan, (e) Hong Kong, (f) Shanghai, (g) Singapore, and (h) India.

lifestyle, tobacco use and alcohol consumption) are well-established risk factors of CRC [4]. The differential observation between the Western and the Asian populations may imply that despite continuous socio-economic development to adopt more western-like lifestyles, there may still be deep-rooted traditions among these Asian populations that may protect them against CRC, especially for those generations (i.e., 1950s cohorts) who still grew up in a macro-environment that largely consumed traditional non-Western diet [36]. Further analytical epidemiological studies are needed to clarify the specific dietary habits that contribute to this effect.

However, an upturn of cohort effects among the younger 1960s–1970s generations in these Asian populations (Japan, Hong Kong, Shanghai and Singapore) is also observed. In fact, the timing of the upturn for these younger cohorts coincide with their greater early life exposures to westernized diet and lifestyle that came with rapid socio-economic development. This upturn is especially obvious for Japan, which experienced socio-economic development earliest in Asia. Our findings are consistent with the life course framework to understanding the risk factors of lifestyle-related chronic, non-communicable diseases, which postulates that exposures to living conditions and macro-environmental changes throughout the life course are important driver of changes in population health. Early life exposure is considered to be a critical period that impacts the risk of non-communicable diseases during later life [37]. Despite wide confidence intervals toward the younger cohorts for these Asian populations (Hong Kong, Shanghai and Singapore), the upturn of cohort effects implies that if the life course explanation holds true, there will be an increased CRC risk for these cohorts as they grow older in the future. A longer period of observation will be needed to confirm this notion.

There are limitations to our study. First, routinely collected data has its limitation by nature – since CRC incidence increases with age, many people of younger age may not have lived up to the normal age range that the disease is typically developed yet. Since the cohort effect of younger generations are based on incidence in the younger age groups, there are more uncertainties towards the more recent birth cohorts as shown by the overlapping confidence intervals. A longer period of data collection would help clarify the effects on the more recent generations. Also, the observed age range and lengths of period varied across different populations under study. Even so, the time periods are long enough to generate reliable and comparable cohort estimates that generally went back to the turn of the 20th century. Second, the three components of age, period and cohort are linearly dependent on each other, making the full model with all three components non-identifiable without an additional reference constraint. Even with an additional constraint, only second-order changes in slope can be interpreted. To confirm our results, we also conducted APC modeling using the alternative method of partial least squares regressions [38], and found the same inflection points for all three effects (data not shown). Third, while we cannot rule out differences in reporting across years, hence a possible presence of the period effect, there is no reason to believe that these differences would occur in a systematic manner. Moreover, the present study used the most up-to-date data leading up to year 2007 for analysis. Since the lengths of follow-up period are longer for the older birth cohorts, there is stronger power and confidence to the findings of these older cohorts, thus enhancing robustness of our findings for international comparison. Last, this study treated CRC as one disease cluster, while in reality risk factors may differentially affect the various sub-sites (colon vs rectum, left colon vs right colon). Any future study would benefit from analysis by the different sub-sites. Nevertheless, the present study is a necessary first step to delineate the complex etiological risk factors of CRC with a global perspective.

5. Conclusions

Despite overall stagnant or even declining CRC incidence among the classically developed Western countries, the cohort effects for CRC incidence increased as the generations became younger, thereby signaling a potential threat of a future CRC resurgence as these younger cohorts reach older ages. On the other hand, upturn of cohort effects among the younger 1960s–1970s cohorts are also observed in the Asian populations, indicating a possible increased risk of CRC for these younger Asian cohorts. Actions that pertain to altering lifestyle-related exposures especially during early life are of great importance in addition to genetic studies and improved screening and diagnostic procedures in combating young CRC risks in the future.

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Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

Author statement

CHUNG Roger Yat-Nork oversaw the successful implementation of the study, the conception and design of the study, acquisition and analysis of the data, interpretation of the results and report writing.

TSOI Kelvin, KYAW Moe Htet, LUI Abdul Rashid and SUNG Joseph Jao-Yiu supervised the conception and design of the study, interpretation of the results and report writing.

LAI Francisco TT conducted APCs using partial least square to confirm the results of the APCs using Maximum Likelihood method.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.01.007.

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