

# Trend Dynamics of Thyroid Cancer Incidence among China and the U.S. Adult Population from 1992-2017: A Join-point and Age-Period-Cohort

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## Research article

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# Abstract

**Purpose:** Based on the previously published reports, the incidence of thyroid cancer (TC) has been increasing in the past 25 years, and the reason for the increase is not yet clear. The present study aims to reveal the long-term trends and age–period–cohort effects for the incidence of TC in China and the U.S. from 1992 to 2017.

**Patients and methods:** We examined the trends of TC incidence in the two countries, for the different genders (men/women) in the Global Burden of Disease (GBD 2017). We further used an age-period-cohort model to analyze age-period-cohort effects on TC incidence, and the average annual percentage change (AAPC) of rates was estimated by Join-point regression analysis.

**Results:** TC increased with the age and period. Aging was one of the most influential factors of TC in China. The age effect increased markedly in the U.S. compared with China. The period effect showed an increase in China while that tended to grow steadily during 1992-2017 in the U.S. The cohort effect peaked in 1963-1967 birth cohorts for men and women in China and declined consistently in the birth cohort in the U.S.

**Conclusion:** From 1992 to 2017, due to ionizing radiation and over-diagnosis, age-standardized TC incidence rates in both genders rose in China and the U.S. The standardized incidence rate of women is higher than that of men. It is necessary to provide women with reasonable prevention and protection measures for TC. We need to apply for health services and screening to reduce ionizing radiation.

## Background

Due to the rapid increase for incidence of thyroid cancer (TC), TC is now considered as a major public health problem worldwide [1–3]. From a clinical perspective, TC is also a malignant tumor caused by follicular or parathyroid thyroid cells. In the recent past decades, the incidence of TC has been steadily increasing globally, especially among women [3–7]. Previous studies also indicated a significant increase in the incidence of TC in the Chinese population [8]. The incidence of TC in women is higher (3.8 per 100,000) than that in Chinese men (1.1 per 100,000). This difference may be attributed to female reproductive hormones. It is speculated that the increased levels of the female hormone caused by reproductive events trigger the thyroid hormone levels, which can cause thyroid dysplasia and eventually lead to cancer outbreaks [9]. In many middle and high-income countries, the incidence of TC has been growing rapidly, the incidence of thyroid cancer has risen sharply in the U.S, from 3.6 cases per 100,000 in 1973 to 15 cases per 100,000 in 2014. About, 62,450 new cases in the U.S. of TC are reported by the American Cancer Society [10]. In the U.S., women have doubled or tripled in just a few decades. According to some reports, the recent incidence has increased slightly in the U.S. [6, 11].

Many studies have different opinions about the influence of age, period and cohort on the incidence of TC. It is believed that the increase in the incidence of TC may be due to over diagnosis [12, 13], however, environmental factors may lead to an increase in the incidence of TC [14, 15]. In order to assess the trend

dynamic of TC incidence due to underlying reasons, we analyzed the temporal changes of TC from 1992–2017, stratified by sex and age group using Join-point and age-period-cohort model in China and the U.S population.

## **Material And Methods**

### **Data Sources**

The data was obtained from the global burden of disease (GBD) 2017. TC data by age groups (ranging from 20 to 79 years) from two representative countries (such as China and the U. S.) can be obtained from the Global Health Data Exchange (GHDx) website of the Institute for health metrics and evaluation (IHME). IHME is an independent global health research center at the University of Washington. The incidence rate of TC [International Classification of Diseases (ICD)-10 code] from GBD 2017 provides a comprehensive upshot for the 354 causes in 195 countries and territories from 1990 to 2017 [16]. GBD 2017 estimated annual results for metrics of incidence, prevalence, death, Years of Life Lost (YLLs), Years Lived with Disability (YLDs), and Disability Adjusted Life Years (DALYs) from 1990 to 2017. The study includes the burden of disease for global populations among all age groups, different causes, locations, and sexes [17]. Despite the no longer time span of data (1992–2017), the period span of study for each country from ages 20–79 years, and the data were aggregated and analyzed by a 5-year period.

### **Statistical Analysis**

#### **Join-point Regression Analysis**

The incidence rate of TC can be estimated by Join-point Regression Software. In the regression analysis, the annual percentage change (APC), the average annual percentage change (AAPC), and the 95% confidence interval (CI) for each segment were estimated. We discussed the numbers of TC change-points and estimated the model parameters by their associated p-values using Join-point Regression Analysis. We also used Monte Carlo methods to find each p-value and maintain the overall asymptotic significance level through Bonferroni correction. This analysis was conducted using the Join-point regression program version 4.6.0.0 (April 2018) from the Surveillance Research Program of the U.S. National Cancer Institute.

#### **Age–Period–Cohort Analysis**

Collinearity is a common problem in the application of APC models, it has  $age_1 = period_1 - cohort_1$ . The APC model is affected by the linearity between the two, so it is impossible to determine the three independent linear APC variables of age, period, and cohort. Now, the APC model is dedicated to the innovation of the traditional linear regression model: the intrinsic estimator (IE) is also a new method of coefficient estimation in our study. The APC model with the intrinsic estimator (IE) method is used to solve the collinearity problem [18].

In the APC model using the IE method, the age-specific rate was appropriately categorized into a continuous 5-year-old age group (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 years). It has 5-year intervals of periods (1992–1997, 1997–2002, 2002–2007, 2007–2012, and 2012–2017) and 18 cohorts of birth (i.e., 1913–1917, 1918–1922, ..., 1988–1992, 1993–1997). The general form of APC is written as

$$Y = \log(M) = \mu + \alpha_{age_1} + \beta_{period_1} + \gamma_{cohort_1} + \varepsilon,$$

where,  $M$  is defined as the incidence of the age group,  $\alpha$ ,  $\beta$ , and  $\gamma$  represent the functions of age, period and cohort effect,  $\mu$  and  $\varepsilon$  are the intercept item and the random error.

APC analysis was used to decompose the three trends and provides relatively efficient estimation results [19]. In this analysis, age reflects changes in vital rates, the risk of incidence increases with the age groups. Period effect represents influencing factors, including a series of historical events and environmental factors. Exposure to risk factors is different in different generations. Cohort effects show variations across groups of individuals born during the same period and changes in different lifestyles.

The APC analysis was done using Stata 15.0 software (College Station, TX, USA). Furthermore, a Wald test was carried out peculiarly based on the outcomes of the APC model, due to the corresponding value of  $P < 0.05$ , which represents a vivid significance statistically. Moreover, the Akaike information criterion (AIC), Bayesian information criterion (BIC), and Deviance were used to estimate and analyze the degree of fitting of the model.

## Results

### Descriptive analysis of TC Incidence in China and the U.S.

The trends of the crude incidence rate (CIR), age-standardized incidence rate (ASIR) at all ages from 1992 to 2017 for TC in China and the U.S were presented as shown in Fig. 1. CIR for men and women experienced increased from 1992 to 2017 in China and the U.S. The ASIR in men increased from 0.56 in 1992 to 1.72 in 2017 per 100,000 persons, and the ASIR in women increased slowly from 1.71 to 2.63 per 100,000 during the same period in China. Overall, in both populations (China and the U.S), compared to men, the higher CIR and ASIR of women has been observed from 1992 to 2017. The ASIR of the U.S. increased before 2009 and declined thereafter, with an average annual percent change (AAPC) values of  $-0.5\%$  (95% CI:  $-0.9\%$ ,  $-0.1\%$ ) for women during 2009–2017.

### Temporal trends of TC incidence in different time segments

APC and AAPC of TC incidence by gender from 1992 to 2017 in China and the U.S. are reported in Table 1. The regression model showed a significant increasing trend in China between 1992 and 2017. This trend displayed from 1992 to 2017 in both men and women, with overall AAPC values of  $4.7\%$  ( $4.3\%$ ,  $5.1\%$ ) for men and  $1.7\%$  ( $1.5\%$ ,  $2.0\%$ ) for women. In the U.S., Join-point regression results for men showed

that the ASIR declined from 2001 to 2004, and then rose until 2017. However, the results of women described that the ASIR increased from 1992 to 2009 and then declined until 2017 in the U.S. ASIR significantly increased in men (AAPC = 1.3%; 95% CI = 0.7, 1.9) and in women (AAPC = 1.3%; 95% CI = 0.8, 1.8) in the U.S. population (Table 1).

Table 1  
Trends in Thyroid cancer incidence rates by gender in China and the U.S. 1992–2017.

Segments	China		the U.S.	
	Year	APC * (95% CI)	Year	APC * (95% CI)
<b>Men</b>				
Trend1	1992-2002	2.9*(2.7,3.1)	1992-1995	4.9(3.1,6.7)
Trend2	2002-2006	5.6* (4.5,6.8)	1995-1998	1.4(-1.8,4.7)
Trend3	2006-2011	10.3* (9.5,11.0)	1998-2001	2.7*(-0.4,5.9)
Trend4	2011-2014	4.7*(2.1,7.3)	2001-2004	-1.0(-3.9,2.0)
Trend5	2014-2017	0.6(-1.1,2.3)	2004-2017	0.7(0.5,0.9)
AAPC *	1992-2017	4.7*(4.3,5.1)	1992-2017	1.3*(0.7,1.9)
<b>Women</b>				
Trend1	1992-1998	1.9*(1.5,2.2)	1992-1995	3.5*(1.9,5.1)
Trend2	1998-2003	-1.9*(-2.5,-1.3)	1995-1998	1.2(-1.8,4.2)
Trend3	2003-2006	0.5*(-1.4,2.4)	1998-2001	3.9*(1.0,6.9)
Trend4	2006-2015	4.3*(4.1,4.4)	2001-2009	1.3*(0.9,1.7)
Trend5	2015-2017	1.2*(0.1,2.3)	2009-2017	-0.5*(-0.9,-0.1)
AAPC *	1992-2017	1.7*(1.5,2.0)	1992-2017	1.3*(0.8,1.8)
Note: * APC, annual percentage change; AAPC, average annual percent change; CI, confidence interval;				
*Significantly different from 0 at alpha = 0.05 (p < 0.05)				

## The Age, Period, and Cohort Effects on TC Incidence

We reported the incidence of specific TC in the age and birth cohort (Fig. 2). The incidence of a specific age group had different peaks in different age groups, as given below: Chinese men have two peak periods, 55 to 59 years and 75 to 79 years. They also had a turning point in birth cohorts. Chinese women have risen from 20 to 70, with the highest age being 65–69 years. The cohort of each age group showed that the incidence of the earlier period was lower than the incidence of later. In the U.S., the maximum age for men and women is 65 to 69 years. There is no turning point for birth cohorts of every age. Among

men and women of all ages in China and the U.S. with the exception of a few individual cohorts, the incidence of birth cohorts in other specific populations was still increasing.

The APC model was listed for men and women separately. The relative risk of TC caused by age, period, and cohort is given in Table 2. The APC-IE method showed the estimated coefficients of age, period, and cohort effects (Table 3).

Table 2  
 Thyroid cancer incidence relative risks (RR) of 95% confidence interval (CI) due to age period cohort.

Variables	The U.S.(RR 95%CI)		China(RR 95%CI)	
	Men	Women	Men	Women
<b>Age</b>				
20-24	1.00	1.00	1.00	1.00
25-29	1.67(2.77,1.01)	1.52(2.04,1.13)	1.46(1.91,1.12)	1.41(1.67,1.20)
30-34	2.68(5.43,1.32)	3.96(6.84,2.30)	3.00(4.83,1.87)	3.77(5.34,2.66)
35-39	3.02(6.44,1.41)	3.64(6.32,2.10)	4.52(7.99,2.56)	4.98(7.35,3.38)
40-44	3.80(8.87,1.63)	5.29(10.01,2.80)	5.97(11.25,3.17)	5.42(8.17,3.59)
45-49	5.45(14.19,2.09)	3.91(7.22,2.12)	9.71(19.95,4.73)	7.96(12.66,5.01)
50-54	7.08(19.76,2.53)	4.42(8.44,2.32)	13.19(28.73,6.06)	7.93(12.84,4.90)
55-59	8.29(24.36,2.82)	4.40(8.45,2.29)	14.89(33.73,6.57)	9.10(15.14,5.47)
60-64	4.33(11.53,1.63)	5.19(10.30,2.62)	13.44(30.94,5.84)	9.60(16.24,5.68)
65-69	4.65(12.86,1.68)	5.70(11.41,2.85)	14.71(34.40,6.29)	9.14(15.50,5.39)
70-74	5.06(14.43,1.78)	5.54(10.94,2.80)	12.40(28.48,5.40)	8.67(14.63,5.13)
75-79	12.58(39.74,3.98)	5.44(10.42,2.85)	13.04(29.09,5.84)	7.68(12.64,4.67)
<b>Period</b>				
1992	1.00	1.00	1.00	1.00
1997	1.15(1.21,1.10)	1.10(1.12,1.08)	1.30(1.36,1.24)	1.23(1.26,1.19)
2002	1.40(1.53,1.28)	1.11(1.14,1.09)	1.54(1.65,1.44)	1.51(1.57,1.45)
2007	2.00(2.31,1.73)	1.23(1.27,1.19)	1.66(1.77,1.55)	1.68(1.75,1.61)
2012	3.28(4.03,2.68)	1.56(1.65,1.48)	1.89(1.99,1.78)	1.83(1.90,1.76)
2017	3.81(4.70,3.09)	1.90(2.02,1.79)	2.13(2.22,2.05)	1.95(2.01,1.89)
<b>Cohort</b>				
1913-1917	1.00	1.00	1.00	1.00
1918-1922	0.99(1.24,0.79)	0.90(1.15,0.71)	0.93(1.09,0.80)	0.94(1.09,0.80)
1923-1927	1.05(1.56,0.71)	0.89(1.27,0.62)	0.86(1.10,0.68)	0.88(1.11,0.71)
1928-1932	1.09(1.83,0.65)	0.92(1.42,0.60)	0.81(1.08,0.61)	0.85(1.10,0.65)

1933-1937	1.01(1.89,0.53)	0.95(1.54,0.59)	0.77(1.05,0.56)	0.81(1.09,0.61)
1938-1942	0.80(1.56,0.41)	0.91(1.52,0.54)	0.71(0.98,0.51)	0.77(1.05,0.57)
1943-1947	0.73(1.25,0.43)	0.99(1.63,0.60)	0.64(0.86,0.48)	0.73(0.97,0.55)
1948-1952	0.81(1.36,0.49)	1.10(1.80,0.67)	0.58(0.75,0.46)	0.67(0.86,0.51)
1953-1957	0.84(1.38,0.52)	1.04(1.65,0.66)	0.52(0.64,0.43)	0.63(0.80,0.50)
1958-1962	0.80(1.28,0.50)	0.94(1.44,0.61)	0.47(0.55,0.41)	0.59(0.72,0.48)
1963-1967	0.88(1.36,0.57)	0.98(1.49,0.65)	0.44(0.48,0.40)	0.54(0.65,0.46)
1968-1972	0.79(1.13,0.56)	0.84(1.22,0.58)	0.40(0.40,0.39)	0.48(0.55,0.42)
1973-1977	0.66(0.81,0.53)	0.68(0.92,0.51)	0.36(0.34,0.39)	0.45(0.49,0.42)
1978-1982	0.62(0.68,0.56)	0.61(0.72,0.51)	0.36(0.30,0.43)	0.45(0.45,0.44)
1983-1987	0.61(0.58,0.64)	0.56(0.58,0.54)	0.35(0.24,0.51)	0.45(0.41,0.49)
1988-1992	0.55(0.33,0.90)	0.42(0.24,0.73)	0.31(0.13,0.70)	0.42(0.27,0.65)
1993-1997	0.43(0.05,4.00)	0.30(0.04,2.43)	0.27(0.03,2.09)	0.37(0.11,1.29)
AIC	3.19	3.91	4.48	4.92
BIC	-170.03	-169.73	-170.30	-170.68
Deviance	1.04	1.34	0.77	0.39

Table 3

Thyroid cancer incidence rates estimated coefficients and 95% confidence interval (CI) for the age, period and cohort effects

Variables	The U.S.(Coef,95%CI)		China(Coef,95%CI)	
	Men	Women	Men	Women
<b>Age</b>				
20-24	-1.41(-3.02,0.21)	-1.32(-2.39,-0.26)	-1.90(-2.97,-0.81)	-1.67(-2.40,-0.94)
25-29	-0.89(-2.00,0.22)	-0.91(-1.68,-0.14)	-1.51(-2.33,-0.69)	-1.32(-1.88,-0.76)
30-34	-0.42(-1.33,0.49)	0.05(-0.47,0.57)	-0.79(-1.40,-0.19)	-0.34(-0.72,0.04)
35-39	-0.30(-1.16,0.56)	-0.03(-0.54,0.48)	-0.38(-0.89,0.13)	-0.06(-0.40,0.28)
40-44	-0.07(-0.84,0.70)	0.34(-0.08,0.77)	-0.11(-0.55,-0.34)	0.02(-0.29,0.34)
45-49	0.29(-0.37,0.95)	0.04(-0.41,0.49)	0.38(0.02,0.74)	0.41(0.14,0.67)
50-54	0.55(-0.04,1.14)	0.16(-0.26,0.58)	0.68(0.39,0.99)	0.40(0.16,0.65)
55-59	0.71(0.17,1.25)	0.16(-0.25,0.57)	0.91(0.55,1.07)	0.54(0.32,0.76)
60-64	0.06(-0.58,0.70)	0.32(-0.06,0.70)	0.71(0.46,0.95)	0.60(0.39,0.80)
65-69	0.13(-0.47,0.73)	0.42(0.05,0.79)	0.80(0.57,1.03)	0.55(0.35,0.75)
70-74	0.22(-0.35,0.79)	0.39(0.00,0.77)	0.63(0.38,0.87)	0.49(0.29,0.70)
75-79	1.13(0.66,1.59)	0.37(-0.04,0.79)	0.68(0.40,0.95)	0.37(0.14,0.60)
<b>Period</b>				
1992	-0.62(-1.18,-0.05)	-0.25(-0.57,0.07)	-0.43(-0.68,-0.18)	-0.40(-0.59,-0.21)
1997	-0.48(-0.99,0.04)	-0.16(-0.46,0.14)	-0.17(-0.37,0.03)	-0.20(-0.37,-0.03)
2002	-0.28(-0.75,0.19)	-0.14(-0.44,0.15)	0.00(-0.18,0.18)	0.01(-0.14,0.16)
2007	0.08(-0.34,0.50)	-0.04(-0.32,0.24)	0.07(-0.11,0.25)	0.12(-0.03,0.27)
2012	0.57(0.21,0.93)	0.20(-0.07,0.46)	0.20(0.01,0.39)	0.20(0.05,0.36)
2017	0.72(0.37,1.08)	0.39(0.13,0.65)	0.33(0.12,0.53)	0.27(0.10,0.43)
<b>Cohort</b>				
1913-1917	0.25(-0.96,1.46)	0.24(-0.71,1.19)	0.63(0.04,1.23)	0.48(-0.05,1.01)
1918-1922	0.23(-0.75,1.22)	0.14(-0.57,0.84)	0.56(0.13,1.00)	0.41(0.04,0.79)
1923-1927	0.30(-0.51,1.12)	0.12(-0.47,0.72)	0.48(0.13,0.84)	0.35(0.05,0.66)

1928-1932	0.33(-0.36,1.02)	0.16(-0.36,0.68)	0.43(0.12,0.73)	0.31(0.05,0.57)
1933-1937	0.25(-0.32,0.83)	0.19(-0.27,0.66)	0.37(0.09,0.65)	0.27(0.03,0.51)
1938-1942	0.02(-0.52,0.57)	0.15(-0.29,0.58)	0.29(0.02,0.56)	0.22(-0.01,0.45)
1943-1947	-0.06(-0.74,0.61)	0.23(-0.22,0.68)	0.20(-0.11,0.50)	0.17(-0.08,0.41)
1948-1952	0.04(-0.66,0.74)	0.34(-0.12,0.79)	0.10(-0.25,0.44)	0.07(-0.20,0.34)
1953-1957	0.08(-0.64,0.79)	0.28(-0.21,0.77)	-0.02(-0.41,0.38)	0.02(-0.28,0.31)
1958-1962	0.02(-0.71,0.75)	0.18(-0.34,0.70)	-0.12(-0.56,0.32)	-0.06(-0.38,0.27)
1963-1967	0.12(-0.66,0.89)	0.22(-0.31,0.76)	-0.19(-0.70,0.31)	-0.13(-0.49,0.23)
1968-1972	0.01(-0.84,0.87)	0.07(-0.51,0.65)	-0.29(-0.87,0.28)	-0.25(-0.65,0.14)
1973-1977	-0.17(-1.17,0.83)	-0.14(-0.80,0.52)	-0.38(-1.05,0.30)	-0.31(-0.77,0.14)
1978-1982	-0.24(-1.35,0.88)	-0.26(-1.04,0.52)	-0.40(-1.18,0.38)	-0.33(-0.84,0.18)
1983-1987	-0.24(-1.50,1.01)	-0.34(-1.26,0.58)	-0.42(-1.39,0.55)	-0.33(-0.95,0.30)
1988-1992	-0.35(-2.06,1.35)	-0.62(-2.13,0.88)	-0.55(-2.00,0.87)	-0.39(-1.35,0.57)
1993-1997	-0.59(-4.02,2.84)	-0.96(-4.00,2.08)	-0.69(-3.34,1.97)	-0.50(-2.27,1.26)

## Age-period-cohort Analysis

### Age Effect

After controlling for period and cohort effects, we found that the age effect on TC showed that risk ratios (RRs) of incidence slightly increased with age for men (Fig. 3), except for the 55–59 age group in China, with a slowly decrease for 55–59 and 65–69 age groups in the U.S. The TC incidence of China and U.S. in the 75–79 age group was about 12.58 and 13.04 times higher than that of the 20–24 age group for men. In women of RRs incidence, it was about 5.44 and 7.68 times higher, which indicated that the incidence of TC increased slowly with advancing age. Overall, the RRs of men and women in the U.S. were higher than that in China.

### Period Effect

In addition to the effect of age on the incidence of disease, we observed that time is highly dependent on the disease. Hence, it is very crucial to express the effect of the period with regard to the GBD. Periodic RRs of TC incidence in China and the U.S. are plotted in Fig. 3. Generally, the risk of TC incidence substantially increased with the period for both genders in China and the U.S. Compared to the period group in 1992, the RRs of China incidence in the period group in 2017 in men and women were 3.81 and 1.95, respectively. Among the periods for Chinese men, the RRs of incidence markedly increased by

39.02% from 2007 to 2012. For women, the period effects of TC incidence were relatively stable in the U.S.

## Cohort Effect

We demonstrated the cohort RRs of TC incidence in China and the U.S. as shown in Fig. 3. The curves displayed a downward trend for both genders in general. In terms of TC incidence in China, the risk spiral increased before 1967 and then declined after 1967 for both genders, Chinese men had risen quickly since 1913, and then displayed a sharp decline from 1932 to 1947. The associated curve of Chinese women showed a gradual increase to the highest point, then had a gentle decline for the 1962 birth cohort, and finally displayed a sharp decline in the birth cohort. Compared to China, the patterns were found to have different behavior in U.S. Later birth cohorts showed lower RRs than early birth cohorts did in the U.S. The cohort RRs of TC incidence in the U.S. showed a declining trend among the cohorts for both genders; while in general, men had always been lower than women in all birth cohorts had.

## Discussion

We found that from 1992 to 2017, the incidence of ASIR of TC in China and in the U. S. was higher in women than in men and still at a relatively higher level. We observed the incidence of TC varies by gender, and estrogen levels of women may be one of the risk factors for TC [20]. Join-point regression analysis presented incidence rates increased in both men and women from 1992 to 2017, while incidence rates obviously increased in Chinese men mainly from 2006 to 2011. Due to the interaction between age, period and cohort effect, we use an age-period-cohort regression model and internal estimator algorithm to analyze and estimate the change of TC. In addition, the incidence of TC in the model is significantly related to the age effects and cohort effects. Therefore, it is necessary to further analyze the causes and differences of these trend changes in the model, and further discuss the risk factors leading to the occurrence of TC disease. In general, the incidence of TC increases with age and period, especially the 40–75 age groups of men in the U.S. The men showed a significant upward trend from 2007 to 2017, but decreased with the birth cohort in China.

Based on our findings, the incidence of TC increased with the age of men and women, and China's aging may exacerbate this situation [21]. Chinese men have a higher risk of TC in the 40–55 age group, probably because residents between the ages of 40–59 paid more attention to physical examination, and the detection rate in cities are higher than in rural areas [22]. The rapid rise in age RRs of Chinese men for the 70–79 age group is due to the most variability of cancer prognosis in the old ages and the highest risk of TC treatment. Among the female population in China, the fastest growth was in women of childbearing age, which is consistent with the results of other countries [13]. The rapid increase RRs of 20–30 age groups of women may be an annual obstetric and gynecological examination during reproduction in China. The risk of TC in women increases during puberty, but decreases after menopause. Among young women, the incidence of TC ranks first among malignant tumors. It is suggested that hormone factors are involved in TC, and estrogen increases thyroid growth [23]. According to our results, old age people had a higher risk of TC than young people did. The age effects may increase the risk of

illness in the elder people. In addition, increased complications of TC are existed in older TC patients than in younger patients. China's aging is growing faster than the U.S., the trend of population growth and aging is increasing in China [24]. Therefore, we may pay more attention to prevention and control the occurrence of TC in the old age people.

The RRs of TC in women increased rapidly with the age of before 45-year-old age group in the U.S. However, the RRs of TC decreased rapidly after the 60-year-old, which may indicate that estrogen levels play a role in the development of TC. There was obvious gender differences in the incidence of TC. Women were 2–3 times more likely than men for TC incidence from 1992 to 2017. It further indicates that TC may be related to estrogen [25]. The age RRs of TC for U.S. men increased slowly from 20 to 49 years but increased rapidly after 50 years of age. Therefore, among men over 50 years old, the diagnosis rate of papillary TC is high, but over diagnosis is rare among men between 20 and 49 years old in the U. S. Among patients with TC in the U. S., the majority of patients in diagnosis were 45–49 age groups for women and 55–59 age groups for men [26]. The difference in age and gender may be that middle-aged women use more health care services than men. This difference is also a result of reproductive activity and menopause, leading to earlier diagnosis [7, 27]. Moreover, compared with women, men tend to pay more attention to their health when they get old. According to a study, the increased TC incidence rates have been reported among young people and adults in the U.S. [28], which shows that some risk factors, such as high body mass index (BMI), [29] ionizing radiation, [30] may have contributed to increasing TC incidence rate.

Period effects are usually affected by a complex set of historical events and environmental factors. Environmental factors are closely related to TC, that is, exposure to ionizing radiation is one of the TC risk factors [31, 32]. On the whole, the period RRs of men and women in China is on the rise. From 1992 to 2008, the frequency of medical diagnostic and therapeutic nuclear medicine in China has been increasing, resulting in a significant increase in the annual personal radiation dose [33]. It is not difficult to find that the period effect of men and women after 2007 in China has a clear rising trend. Among them, men showed a slow upward trend after 2012, while women increased significantly from 2007 to 2017. A previous study conducted in China reported that in 2008, about 17% of people over the age of 15 had regular physical examinations, 68% had a physical examination every 7–12 months, and one-third of the population conducted X-rays [34]. More frequent nuclear medical examinations may lead to increasing radiation exposure, resulting in an increased incidence of TC. With the acceleration of China's industrialization process, the exposure to risk factors is becoming more and more obvious [35]. From 1992 to 2017, men's carcinogens increased significantly. The rising incidence of men may be due to cancer caused by occupational diseases [16]. Over the past 25 years, environmental exposure caused by industrial activities of industrial density may have affected the incidence of TC, which is an occupational carcinogen. TC is considered a cancer that can be affected by occupational exposure. In addition, the GBD study also showed that cancer death and disability-adjusted life years (DALYs) due to occupational risks began to increase around 2007. In fact, occupational exposure has increased since 2007 [36]. Especially, male workers who are exposed to certain solvents and pesticides have an increased risk of developing thyroid tumors. Period RRs showed a remarkable increasing trend of Chinese men, which may

be caused by occupational carcinogens. Therefore, it is necessary to minimize the exposure of men to occupational carcinogens in China [37].

In the U. S., men and women period effects have a similar upward trends. TC is one of the ten most common cancers in the U.S. From 1990 to 2017, the incidence of TC has been increasing at a higher rate than any other malignant tumor. The survey data of the U.S. from 2003 to 2009, revealed that the 5-year survival rate of TC reached up to 98.2% [38]. The steady growth trend of men and women may be due to the rise in the economy of the U.S. The increased incidence of TC was caused by over diagnosis from 1990 to 2000 [26]. The socio-economic development of the U.S. is rapidly increased. In general, people with higher socioeconomic status are more likely to access health care services, and have increased contact with the health care system, leading to an increased risk of over diagnosis. A positive correlation is existed between socioeconomic status and TC risk [39].

The cohort effect reflects the influencing factors that appear early in life. Exposure to certain risk factors early in life may adversely affect future life [40]. The birth cohort effect obtained through the APC model is the net effect after excluding the age effect and the period effect. Men and women simultaneously increased the risk of morbidity in the cohort effect. This may be linked to China's historical background and economic development. One stage was from 1943–1947 to 1948–1952, which was considered to be related to the Japanese invasion over China and plunged China into a long war. People's living environment has deteriorated, medical and health services have been severely damaged, and health cannot be guaranteed. Moreover, during the periods of 1958–1962 and 1963–1967, China experienced a series of social and economic system changes, plus the three years of famine from 1959 to 1961, the food shortage was very serious and health risk factors have increased significantly [41]. In terms of gender differences in China, we found that in the early cohort women had a lower risk of incidence than men. After the birth cohort in 1933–1937, the risk of women in the incidence began to be higher than that of men, and in the birth cohort after 1978–1982, the risk of women began to be lower than that of men. It is clear that women greatly reduced the risk of the birth cohort after 1952. It may be due to China has established a medical insurance system for employees, including the public medical system in 1952 and the labor insurance medical system in 1953 [42, 43]. After the Second Domestic Revolutionary War, China launched a patriotic public health campaign, which greatly improved the health environment and public health, and also reduced the risk of TC [44]. The increased risk of incidence in later-born men is related to social disintegration and later-born men are more likely to be exposed to smoking, drinking, and other risk factors that lead to higher risk levels. Complex interactions between these risk factors may lead to increasing TC risk of Chinese men [45]. In the U. S., ultraviolet radiation may be one of the risk factors for TC. Because, since 1960s, the availability of medical services in the U.S., new equipment and complex diagnostic tests has increased, the number of X-rays for medical examinations and care has significantly increased [46]. We found that people over the age of 40 are more likely to be exposed to ultraviolet radiation than younger people. It reflects that the cohort effect of TC is on declining trend [47]. During 1913–1917 and 1993–1997, the incidence of TC for men and women showed a continuous downward trend in the U.S. The possible reason is that the recently born cohort is well-educated and has a better understanding of health and disease prevention [48].

## Limitations

We acknowledge that our research has certain limitations. Firstly, the data used in this study are based on the latest data from GBD 2017, which uses incidence data from the Cancer Registry. The accuracy of the diagnosis is still biased, which will lead to the problem of decreased data accuracy. Secondly, our research on TC had no specific cancer subdivisions or in-depth research on the factors that lead to changes in TC, so we cannot make causal inferences. Despite its limitations, our study is still an indispensable national study, which aims to compare the trends and changes in the incidence of TC in China and the U.S.

## Conclusion

In summary, the incidence of TC in men and women in China and in the U.S. from 1992 to 2017 was attributed to the following factors: over diagnosis and screening, a significant increase in ionizing radiation, and the effect of estrogen on TC. We observe that period effect has a growth trend in China, while it is steadily increasing in the U. S. The cohort effect shows a downward trend, but China's fluctuations are observable. The age effect may be a critical factor affecting the incidence of TC, but the peaks of different age groups in both China and the U.S are different. China's population growth and aging have an impact on the incidence of TC. Therefore, it is necessary to provide reasonable health services and screening to reduce ionizing radiation. At the same time, we need strengthen the prevention and protection of TC for women.

## Declarations

## Authors' contribution

YC and CY performed the study design, data collection. YC completed first draft of the manuscript. SM completed final version of the manuscript and supervised all of the work. RL and NS checked and revised the manuscript. All authors read and approved the final manuscript.

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## Disclosure

The author reports no conflicts of interest in this work.

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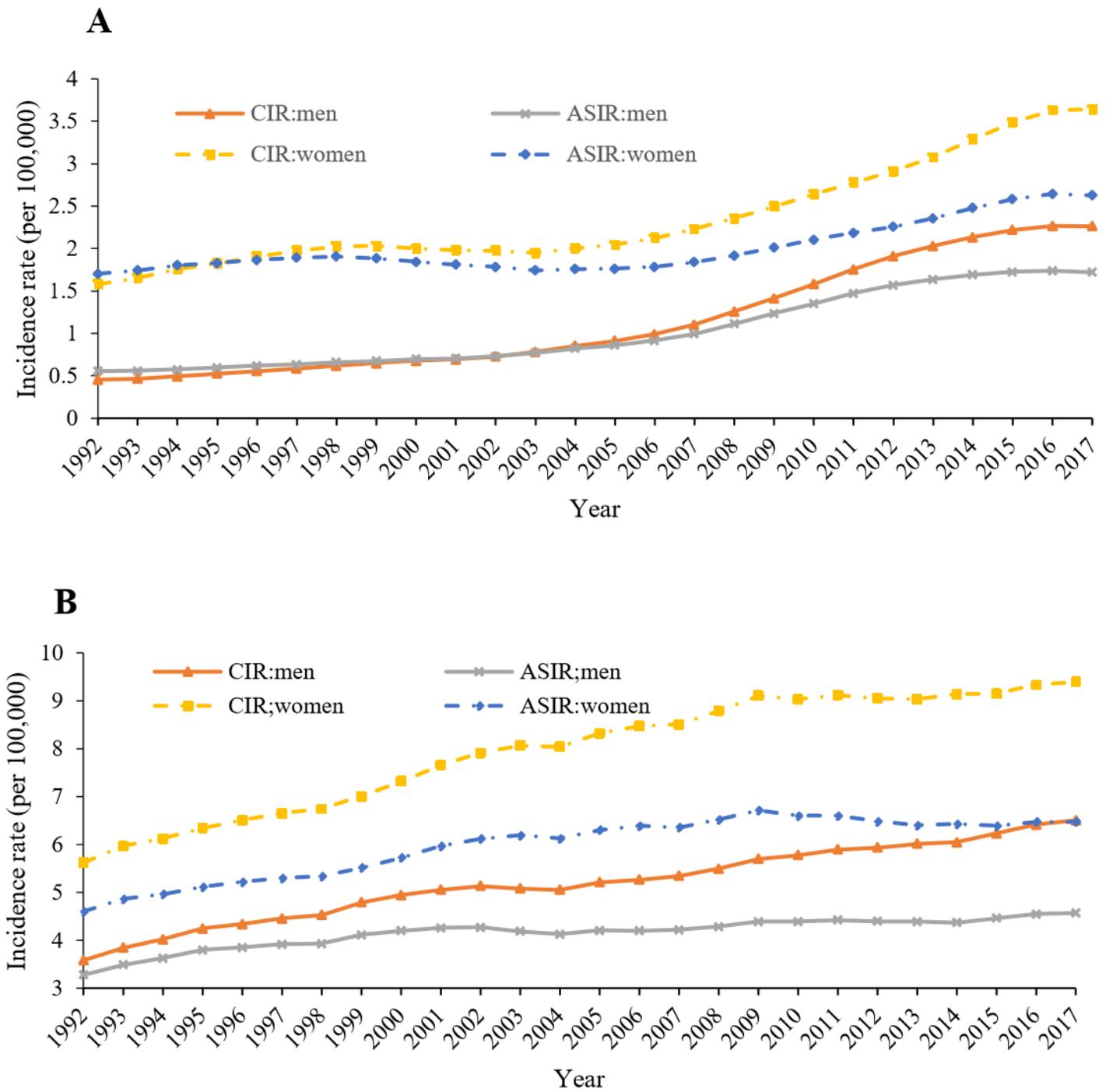
## References

1. Davies, L. and H.G. Welch, *Increasing incidence of thyroid cancer in the United States, 1973-2002*. *Jama*, 2006. **295**(18): p. 2164-7.
2. Pandeya, N., et al., *Increasing thyroid cancer incidence in Queensland, Australia 1982-2008 - true increase or overdiagnosis?* *Clin Endocrinol (Oxf)*, 2016. **84**(2): p. 257-264.
3. Vigneri, R., P. Malandrino, and P. Vigneri, *The changing epidemiology of thyroid cancer: why is incidence increasing?* *Curr Opin Oncol*, 2015. **27**(1): p. 1-7.
4. Enewold, L., et al., *Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005*. *Cancer Epidemiol Biomarkers Prev*, 2009. **18**(3): p. 784-91.
5. Finlayson, A., et al., *Incidence of thyroid cancer in England by ethnic group, 2001-2007*. *Br J Cancer*, 2014. **110**(5): p. 1322-7.
6. La Vecchia, C., et al., *Thyroid cancer mortality and incidence: a global overview*. *Int J Cancer*, 2015. **136**(9): p. 2187-95.
7. Pellegriti, G., et al., *Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors*. *Journal of cancer epidemiology*, 2013. **2013**: p. 965212-965212.
8. Wang, Y. and W. Wang, *Increasing Incidence of Thyroid Cancer in Shanghai, China, 1983-2007*. *Asia-Pacific Journal of Public Health*, 2015. **27**(2).
9. Bray, F., et al., *Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration*. *Int J Cancer*, 2015. **137**(9): p. 2060-71.
10. Ries, L.A.G., et al., *Cancer Survival and Incidence from the Surveillance, Epidemiology, and End Results (SEER) Program*. *Oncologist*, 2003. **8**(6): p. 541-552.
11. Vaccarella, S., et al., *Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis*. *N Engl J Med*, 2016. **375**(7): p. 614-7.
12. McNally, R.J.Q., et al., *Increasing incidence of thyroid cancer in Great Britain, 1976–2005: age-period-cohort analysis*. *European Journal of Epidemiology*, 2012. **27**(8): p. 615-622.
13. Liu, S., et al., *Increasing thyroid cancer incidence in Canada, 1970-1996: time trends and age-period-cohort effects*. *British journal of cancer*, 2001. **85**(9): p. 1335-1339.
14. Zhu, C., et al., *A Birth Cohort Analysis of the Incidence of Papillary Thyroid Cancer in the United States, 1973-2004*. *Thyroid : official journal of the American Thyroid Association*, 2009. **19**: p. 1061-6.
15. Zheng, T., et al., *Time trend and age-period-cohort effect on incidence of thyroid cancer in Connecticut, 1935-1992*. *Int J Cancer*, 1996. **67**(4): p. 504-9.

16. *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017*. Lancet, 2018. **392**(10159): p. 1789-1858.
17. Murray, C.J., A.D. Lopez, and D.T. Jamison, *The global burden of disease in 1990: summary results, sensitivity analysis and future directions*. Bulletin of the World Health Organization, 1994. **72**(3): p. 495-509.
18. Yang, Y., W.J. Fu, and K.C. Land, *A Methodological Comparison of Age-Period-Cohort Models: The Intrinsic Estimator and Conventional Generalized Linear Models*. Sociological Methodology, 2010. **34**(1): p. 75-110.
19. Keyes, K.M. and R. Miech, *Age, period, and cohort effects in heavy episodic drinking in the US from 1985 to 2009*. Drug and alcohol dependence, 2013. **132**(1-2): p. 140-148.
20. Kilfoy, B.A., et al., *International patterns and trends in thyroid cancer incidence, 1973-2002*. Cancer causes & control : CCC, 2009. **20**(5): p. 525-531.
21. Kanasi, E., S. Ayilavarapu, and J. Jones, *The aging population: demographics and the biology of aging*. Periodontol 2000, 2016. **72**(1): p. 13-8.
22. Du, L., et al., *Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China*. BMC Cancer, 2018. **18**(1): p. 291-291.
23. Fontham, E.T.H., *Cancer Epidemiology and Prevention. Third Edition: Edited by David Schottenfeld and Joseph F. Fraumeni, Jr*. American Journal of Epidemiology, 2008. **168**(4): p. 469-469.
24. Lutz, W., W. Sanderson, and S. Scherbov, *The coming acceleration of global population ageing*. Nature, 2008. **451**(7179): p. 716-719.
25. Machens, A., S. Hauptmann, and H. Dralle, *Disparities between male and female patients with thyroid cancers: sex difference or gender divide?* Clinical Endocrinology, 2006. **65**(4): p. 500-505.
26. Davies, L. and H.G. Welch, *Current Thyroid Cancer Trends in the United States*. Archives of Otolaryngology-head & Neck Surgery, 2014. **140**(4): p. 317-322.
27. Dal Maso, L., et al., *Incidence of thyroid cancer in Italy, 1991–2005: time trends and age–period–cohort effects*. Annals of Oncology, 2011. **22**(4): p. 957-963.
28. Hogan, A.R., et al., *Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients*. J Surg Res, 2009. **156**(1): p. 167-72.
29. Peterson, E., P. De, and R. Nuttall, *BMI, diet and female reproductive factors as risks for thyroid cancer: a systematic review*. PLoS One, 2012. **7**(1): p. e29177.
30. Richardson, D.B., *Exposure to ionizing radiation in adulthood and thyroid cancer incidence*. Epidemiology (Cambridge, Mass.), 2009. **20**(2): p. 181-187.
31. Dal Maso, L., et al., *Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors*. Cancer Causes & Control, 2009. **20**(1): p. 75-86.
32. Marcello, M., et al., *The influence of the environment on the development of thyroid tumors: A new appraisal*. Endocrine-related cancer, 2014. **21**.

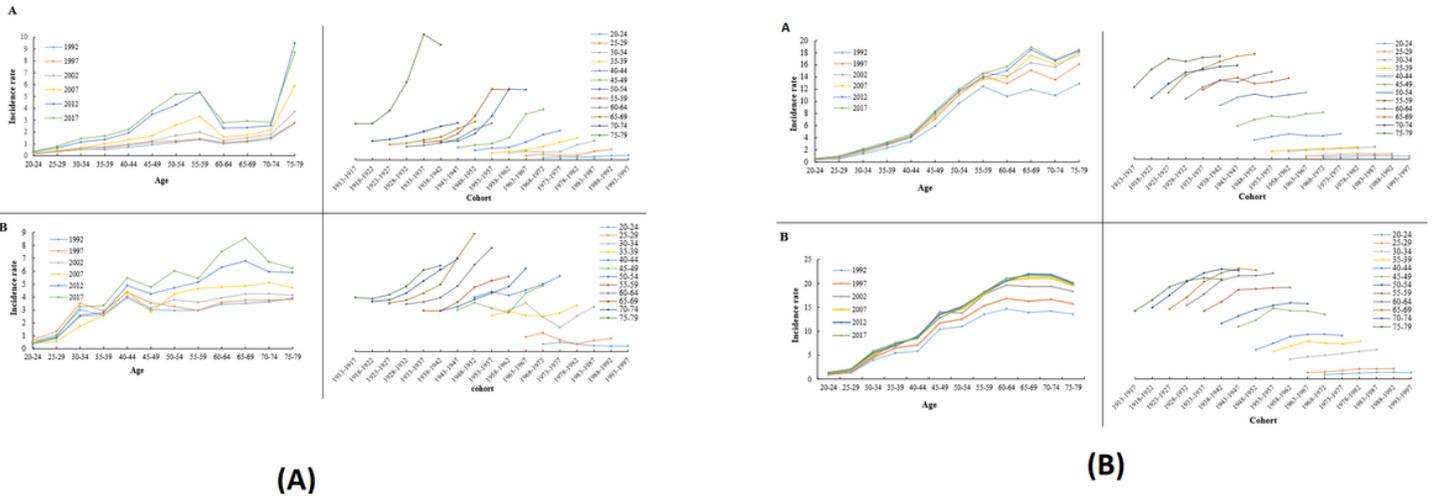
33. Yi, Y., et al., *Trends in radiation exposure from clinical nuclear medicine procedures in Shanghai, China*. Nuclear medicine communications, 2012. **33**(3): p. 331-336.
34. Xie, S.-H., et al., *Time trends and age-period-cohort analyses on incidence rates of thyroid cancer in Shanghai and Hong Kong*. BMC Cancer, 2014. **14**(1): p. 975.
35. Liu, X., et al., *Secular trends in incidence and mortality of bladder cancer in China, 1990–2017: A joinpoint and age-period-cohort analysis*. Cancer Epidemiology, 2019. **61**: p. 95-103.
36. Ding, Q., L. Schenk, and S.O. Hansson, *Occupational diseases in the people's Republic of China between 2000 and 2010*. American Journal of Industrial Medicine, 2013. **56**(12): p. 1423-1432.
37. Leux, C. and P. Guénel, *Risk factors of thyroid tumors: Role of environmental and occupational exposures to chemical pollutants*. Revue d'épidémiologie et de santé publique, 2010. **58**: p. 359-67.
38. Zeng, C., et al., *Disparities by race, age, and sex in the improvement of survival for major cancers: Results from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program in the United States, 1990 to 2010*. JAMA Oncology, 2015. **1**(1): p. 88-96.
39. Reitzel, L.R., et al., *Trends in Thyroid Cancer Incidence in Texas from 1995 to 2008 by Socioeconomic Status and Race/Ethnicity*. Thyroid, 2014. **24**(3): p. 556-567.
40. Janssen, F. and A.E. Kunst, *Cohort patterns in mortality trends among the elderly in seven European countries, 1950–99*. International Journal of Epidemiology, 2005. **34**(5): p. 1149-1159.
41. Li, C. and L.H. Lumey, *Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: a systematic review and meta-analysis*. Int J Epidemiol, 2017. **46**(4): p. 1157-1170.
42. Wang, F. and Y. Liang, *China's Rural Cooperative Medical Scheme: a type of health insurance or a type of health cooperative?* Prim Health Care Res Dev, 2017. **18**(2): p. 194-199.
43. Shi, L., *Health care in China: a rural-urban comparison after the socioeconomic reforms*. Bulletin of the World Health Organization, 1993. **71**(6): p. 723-736.
44. Zhang, J., et al., *Environmental health in China: progress towards clean air and safe water*. Lancet, 2010. **375**(9720): p. 1110-9.
45. Chen, L., et al., *Changes in the Sociodemographic Factors of Tobacco and Alcohol Consumption in Chinese Adolescents from 2004 to 2011*. Int J Environ Res Public Health, 2018. **15**(6).
46. *Radiation protection guidance for diagnostic x-rays. Federal guidance report No. 9*. 1976, ; Interagency Working Group on Medical Radiation, Washington, DC (USA). p. Medium: X; Size: Pages: 42.
47. Zamoiski, R.D., et al., *Prospective Study of Ultraviolet Radiation Exposure and Thyroid Cancer Risk in the United States*. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2017. **26**(5): p. 684-691.
48. Cohen, A.K. and S.L. Syme, *Education: a missed opportunity for public health intervention*. Am J Public Health, 2013. **103**(6): p. 997-1001.

# Figures



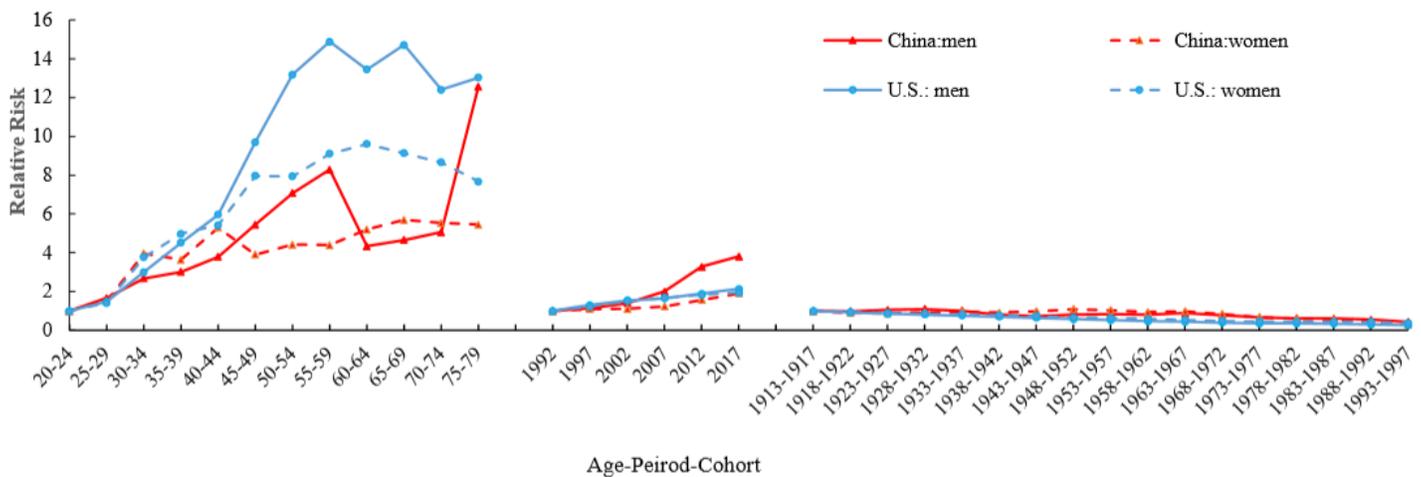
**Figure 1**

Trends of the crude incidence rates (CIR) and age-standardized incidence rates (ASIR) for thyroid cancer (TC) in men and women from 1992 to 2017 in (A) China and (B) the U.S.



**Figure 2**

2A) Age-standard incidence rates (ASIR) of thyroid cancer across ages and birth cohorts by periods and age groups among (A) men and (B) women in China. 2B) Age-standard incidence rates (ASIR) of thyroid cancer across ages and birth cohort by period and age group among (A) men and (B) women in U.S.



**Figure 3**

Thyroid cancer incidence relative risks due to age; period; and cohort effects for men and women using APC model