Whether iodized salt consumption increases thyroid cancer incidence

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ABSTRACT

Background and Objectives: This study aimed to explore the correlation between population-based iodine intake from iodized salt (iodine-IS) and thyroid cancer (TC) incidence. **Methods and Study Design:** The TC incidence data were collected from the annual reports issued by *China's National Central Cancer Registry*. The iodine-IS data were extracted from the *National Iodized Salt Surveys and National IDD Surveys* (NIDDs). The time lag effect of iodine-IS on TC incidence was examined by using a polynomial distributed lag (PDL) model. **Results:** Iodine-IS consumption peaked in 1999, declined to approximately 60% of 1999 in 2018, but remained close to 142.2 μg/person/day. After 2000, TC incidence increased notably on an annual basis. Iodine-IS and the age-standardized rate adjusted to the world population of TC incidence were significantly negatively correlated ($p<0.05$). The PDL model revealed that iodine-IS had a significant 6-year time lag effect on TC incidence ($p<0.05$). **Conclusions:** Iodine nutrition, as indicated by iodine-IS, exhibited a steady decline. The population-based iodine-IS was adequate, however, TC incidence continued increasing. Although the 6-year cumulative effect of iodine-IS was considered, a negative correlation between iodine-IS and TC incidence was observed. Iodine-IS may not be a major risk factor for TC because universal salt iodization is maintaining adequate iodine nutrition in the population. The increasing TC incidence may reduce public willingness to consume iodized salt.

Key Words: thyroid cancer, iodized salt consumption, iodized salt, polynomial distributed lag model

INTRODUCTION

Thyroid cancer (TC) incidence has been on the rise in most countries such as South America and Australia, especially in women.[1] In China, the incidence tripled between 2005 and 2015.[2] This increase is partially attributable to the widespread application of improvement in the precision of ultrasound technologies for detecting thyroid nodules.[3] The growth in iodine intake also constitutes a potential factor.[3] After universal salt iodization (USI) was achieved in 1994, iodine deficiency disorders (IDD) have been controlled in China and continually managed since 2004.[4] However, household-level consumption of adequately iodized salt has notably declined. In Shanghai and Tianjin, the household-level coverage does not exceed 90% as recommended by WHO/UNICEF/the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) because of residents' belief that excessive iodine intake caused by the consumption of iodized salt may lead to the development of TC.[5-7] Moreover, iodine intake among women (including pregnant women) is lower than the median urinary iodine concentration (mUIC) of 150 µg/L recommended by WHO/UNICEF/ICCIDD.[8] Recently, Fan et al collected data from the *2018 Annual Report to the Nation on the Status of Cancer* and the *2018 National Iodine Deficiency Disorders (IDD) surveillance*, observing that appropriate iodine intake can reduce TC incidence by the cross-sectional study.[9] However, it is well known that the impact of certain factors on the incidence of cancer cannot be assessed in cross-sectional studies; the longitudinal time horizon and the cumulative effect must be considered. To overcome this problem, the present study used an econometric model for analysis. The abundance of systematic data that China has collected from *Cancer Registry Annual Reports* (CRAR) since 1988 and from the *National Iodized Salt Surveys* (NISSs) and *National IDD Surveys* (NIDDs) since 1995 enable the examination of population-level association. The present study revealed an association between the population-based iodine intake from iodized salt (iodine-IS) and TC incidence and analyzed the time lag effect between them.

MATERIALS AND METHODS

TC incidence

TC incidence data were sourced from CRAR, reports published by the National Cancer Center (NCC), including the *1993–1997 volume* and *1998–2002 volume* and annual volumes since 2003. Following the method used by Sun,[10] we formulated a regression equation to estimate the annual age-standardized rate of TC from 1993 to 2002 according to the age-standardized rate adjusted to the world population (ASRW). The ASRW of TC after 2003 was taken directly from the CRAR issued by the NCC. The actual observation period was from 1995 to 2015. The diagnostic criteria of TC from 1993 to 1997 and after 1998 were based on those outlined in the *International Classification of Diseases, 9th Revision and the International Classification of Diseases, 10th Revision*, respectively, as cited by the NCC. Various types of TC, such as papillary TC, were not within the scope of this study because the available data did not provide sufficient detail.

Iodine-IS

Iodine-IS, defined as population-based iodine intake from iodized salt, was calculated from the national iodized salt sale (ISS), the population covered by the surveyed area (SP), the national population (NP), and the salt iodine concentration (SIC). The ISS, SP, and NP data were extracted from the *statistical yearbook* issued by the National Health Commission of the People's Republic of China, with 2003–2018 as the observation period. The SP data from 1995 to 2002 were fitted on the basis of the actual proportion of the SP during the observed period. The ISS before 2002 was calculated according to the daily salt intake level per person (DSI). According to the 1992 and 2002 statistical yearbooks, the DSI was assumed to be 13.9 g/person/day in and before 2001 and 12.0 g/person/day in 2002. It was calculated as follows:

ISS (g) = DSI (g/person/day) * NP * 365 -------------Equation 1

where 365 was taken as the number of days in each year.

The SIC data were collected from the NISSs (1996–2011) or NIDDs (1995, 1997, 1999, 2002, 2005, 2011, 2014, 2017, 2018). Specifically, the SIC was determined from the median or mean concentration of iodine in iodized salt, with the mean used as a replacement for missing data. The SIC missing data (1996, 1998, 2000, 2001, 2003, and 2013) were calculated on the basis of the neighboring year. We supposed that the iodine intake level of the uncovered population in the NISSs and NIDDs data was adequate, and the iodine-IS was calculated according to the 150 μg/person/day WHO/UNICEF/ICCIDD recommendation.[8] In addition, iodine loss from iodized salt during transport from the production site to the household was estimated to be approximately 20%, as was the percentage lost in cooking (before consumption).[8] Equation 2 contains equation 1, as follows:

Iodine – IS (μg/person/day) = <[(ISS (kg) * SIC (mg/kg) * 1000 + (NP-SP) * 150(μg/D/per) * 365)] / (NP*365) > * 60%-------Equation 2

where the 60% term accounts for the 40% loss of iodine from iodized salt between production and consumption. Furthermore, 365 was taken as the number of days in a year.

Iodine intake in school-aged children: mUIC

The data on the mUIC of school-aged children were extracted from the NIDDs (1995, 1997, 1999, 2002, 2005, 2011, 2014, 2017, 2018).

Time lag effect of iodine-IS on TC incidence

The lag effect was examined by using a polynomial distributed lag (PDL) model, which is suitable for determining the effect of a single independent variable on a single dependent variable. The general form of the PDL model is as follows:

$$Y_t = \alpha + \beta_0 X_t + \beta_1 X_{t-1} + \cdots + \beta_k X_{t-k} + \mu_t$$

where X and Y denote the independent and dependent variables, respectively; k is the lag order; α is a constant; β_k is the lag coefficient; μ_t is the error; and t is the time series.

The PDL model was visualized by using the polyDlm function in the dLagM package in R 4.0.2 software. Iodine-IS and the ASRW of TC incidence were the independent and dependent variables, respectively. We supposed that TC incidence was not only affected by the level of iodine supplementation during the same period but also by the cumulative effect of iodine supplementation over the past few years (the reference manual is available at dLagM.pdf. https://CRAN.R-project.org/package=dLagM). The command code is as follows:

```
# Load package “dLagM”
> install.packages(“dlagm”)
> library(dLagM)
> data(data1)
# Finite polyDlm. (n represents the lag time, n=3,4,5…(n>k))
> model.poly = polyDlm(x = data1$iodine_intake, y = data1$TC_incidence , q = n , k = 2 ,
show.beta = TRUE)
# Generate AIC and displays sorted AIC
> aic = AIC(model.poly$model)
> sortscore(aic , score = "aic")
```

Statistical analysis

The Shapiro.test() and cor() functions in R were used to perform the Shapiro–Wilk normality test[11] and correlation analysis, respectively, with the level of significance set at $p<0.05$. The Shapiro–Wilk test revealed that the ASRW of TC incidence was completely nonnormally distributed. A normal distribution was noted after the natural logarithmic transformation was accepted ($p>0.05$).

We used a second-order polynomial to determine the optimal lag time according to the Akaike information criterion (AIC), adjusted r^2, and the p-value of the lag coefficient.[12] The optimal model was defined as that in which the AIC and adjusted r^2 were minimized and maximized, respectively, with the p-value of the lag coefficient below 0.05.[13]

RESULTS

Iodine-IS, and mUIC of school-aged children

Iodine-IS, and mUIC of school-aged children were significantly positively correlated ($r=0.94$, $p<0.05$).

Iodine-IS and ASRW of TC over time

Iodine-IS peaked in 1999 and declined to approximately 60% of the 1999 in 2018. Compared with 20 years ago, the TC incidence increased by about 5 times in 2015. The results were presented in Figure 1.

Iodine-IS and ASRW of TC

Iodine-IS and the ASRW of TC were significantly negatively correlated ($p<0.05$; Table 1).

Iodine-IS and ASRW of TC across genders

Iodine-IS and the ASRW of TC were significantly negatively correlated between men and women ($p<0.05$; Table 1).

Time lag effect of iodine-IS on the ASRW of TC

In the sixth year, the AIC and adjusted r^2 were the lowest and highest, respectively ($p<0.05$; Figure 2); the optimal results were observed when a second-order polynomial and 6-year lag were used. The results indicated that the effect of iodine-IS on the ASRW of TC could be maintained for 6 years (Table 2).

Time lag effect of iodine-IS on the ASRW of TC across genders

Optimal results were observed when a second-order polynomial and 6-year lag were used (Table 2).

DISCUSSION

The mUIC of school-aged children can be used to represent iodine nutrition in the population. In the present study, iodine-IS was significantly correlated with mUIC, suggesting that iodine-IS was indicative of population iodine status in the same period.

As mentioned, China achieved USI in 1994. The upper limit of SIC, adjusted from 40 mg/kg in 1994 to 60 mg/kg in 1996, was lowered to 50 and 39 mg/kg in 2000 and 2012, respectively, as a means of reducing the risk of excessive iodine intake. The present results indicate that iodine-IS peaked in 1999 and declined to approximately 60% of the 1999 in 2018. Nevertheless, it remained close to the WHO/UNICEF/ICCIDD recommendation.[8] Similarly, the NIDDs revealed that iodine nutrition was adequate in the population, as indicated by an mUIC between 100 and 299 μg/L in school-aged children.[14]

After 2000, TC incidence increased notably on an annual basis under iodine adequacy. Although the 6-year cumulative effect of iodine-IS was taken into account, a negative correlation between the iodine-IS level and TC incidence was observed. The clear increase in TC incidence may influence the public's willingness to purchase and consume iodized salt.

The relationship between iodine nutrition and TC is U shaped.[15] Both iodine excess and iodine deficiency are associated with TC, with papillary and follicular TCs being particularly strongly correlated with excess and deficiency, respectively.[16] Regardless of the implementation of salt iodization, an increasing trend in TC incidence is observable in most countries. Salt iodization has not yet been implemented in Japan and South Korea. By contrast, it is mandatory in China and Switzerland.[17] The continued increase in TC incidence might be correlated with improvements in diagnostic techniques as well as with overdiagnosis.[18] A Danish study reported a significant increase in TC incidence and an increase in the incidence of papillary TC before and after the implementation of salt iodization, respectively.[19] In the present study, the increase in TC incidence over the observation period occurred during a period of iodine adequacy in the Chinese population. Although the cumulative effect of iodine-IS was considered and despite the reduction of iodine-IS, TC incidence continued to increase over the observation period. Iodine intake was not the most pivotal factor responsible for this upward trend in TC incidence.

This study has several limitations. First, we assumed iodine adequacy in the population in the areas not addressed in the NIDDs, and the population was not grouped. Second, we did not take into account sources of iodine supplementation other than iodized salt. Third, because of the limitations of the available data, we examined only one of the numerous factors related to TC incidence. Fourth, various types of TC, such as papillary TC, were not assessed because data of sufficient detail were not available. Finally, the stability of the PDL model, which involves econometrics, may have been affected by the fact that only one independent variable, iodine-IS (for which relatively scant data were available) was considered.

Conclusion

Iodine intake from iodized salt consumption, as assessed by using iodine-IS, decreased gradually over time. Although iodine nutrition in the population was adequate, TC incidence continued increasing over time. Although the 6-year cumulative effect of iodine-IS was considered, a negative correlation between the iodine-IS level and TC incidence was observed. Iodine-IS may not be a major risk factor for TC because USI is maintaining adequate iodine nutrition at the population level. The observable increase in TC incidence might reduce the public's willingness to consume iodized salt.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Khodamoradi F, Ghoncheh M, Mehri A, Hassanipour S, Salehiniya H. Incidence, mortality, and risk factors of thyroid cancer in the world: a review. World Cancer Research Journal. 2018;5:e1093. doi: 10.32113/wcrj_20186_1093.
2. Wang J, Yu F, Shang Y, Ping Z, Liu L. Thyroid cancer: incidence and mortality trends in China, 2005-2015. Endocrine. 2020;68:163-73. doi: 10.1007/s12020-020-02207-6.
3. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133. doi: 10.1089/thy.2015.0020.
4. Sun D, Codling K, Chang S, Zhang S, Shen H, Su X, Chen Z, Scherpbier RW, Yan J. Eliminating iodine deficiency in China: achievements, challenges and global implications. Nutrients. 2017;9:361. doi: 10.3390/nu9040361.
5. Chen C, Xu H, Chen Y, Chen Y, Li Q, Hu J et al. Iodized salt intake and its association with urinary iodine, thyroid peroxidase antibodies, and thyroglobulin antibodies among urban Chinese. Thyroid. 2017;27:1566-73. doi: 10.1089/thy.2017.0385.
6. Liu ZH, Wang Y, Cui YS, Fu G, Hou CC. Survey on iodine intake from salt and iodine nutrition in pregnant women in Tianjin during December,2013 and August, 2014. Practical Preventive Medicine. 2016;23:1436-9. doi: 10.3969/j.issn.1006-3110.2016.12.008. (In Chinese)
7. Zhou L, Qian M, Chen QG,Liang LF, Gao Y, Di M, Wang SY, Zhang JQ, Li XL. An online survey on iodine deficient disorders knowledge and its control in urban doctors and nurses. 2018;37:557-61. doi: 10.3760/cma.j.issn.2095-4255.2018007.009. (In Chinese)
8. WHO, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd ed. Geneva: WHO; 2007.
9. Fan LJ, Meng FG, Gao YY, Liu P. Insufficient iodine nutrition may affect the thyroid cancer incidence in China. Br J Nutr. 2021;18:1-9. doi: 10.1017/S0007114521000593.
10. Sun JW, Xu XJ, Cai QM, Xu YJ, Gu J. Epidemiological study on thyroid cancer in China. China Cancer. 2013;22. doi: 10.11735/j.issn.1004-0242.2013.09.A002 (In Chinese)
11. Royston, J. An extension of Shapiro and Wilk's W test for normality to large samples. Journal of the Royal Statistical Society. Series C (Applied Statistics). 1982;31:115-24. doi: 10.2307/2347973.

12. Lepeule J, Rondeau V, Filleul L, Dartigues JF. Survival analysis to estimate association between short-term mortality and air pollution. Environ Health Perspect. 2006;114:242-7. doi: 10.1289/ehp.8311
13. Demirhan H. dLagM: An R package for distributed lag models and ARDL bounds testing. PLoS One. 2020;15:e0228812. doi: 10.1371/journal.pone.0228812.
14. Zimmermann MB, Aeberli I, Andersson M, Assey V, Yorg JAJ, Jooste P et al. Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100-299 µg/L: a UNICEF/ICCIDD study group report. J Clin Endocrinol Metab. 2013;98:1271-80. doi: 10.1210/jc.2012-3952.
15. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3:286-95. doi: 10.1016/S2213-8587(14)70225-6.
16. Barrea L, Gallo M, Ruggeri RM, Di Giacinto P, Sesti F, Prinzi N et al. Nutritional status and follicular-derived thyroid cancer: An update. Crit Rev Food Sci Nutr. 2021;61:25-59. doi: 10.1080/10408398.2020.1714542.
17. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. Thyroid Res. 2015;8:8. doi: 10.1186/s13044-015-0020-8.
18. Ahn HS, Welch HG. South Korea's thyroid-cancer “Epidemic”--turning the tide. N Engl J Med. 2015;373:2389-90. doi: 10.1056/NEJMc1507622.
19. Blomberg M, Feldt-Rasmussen U, Andersen KK, Kjaer SK. Thyroid cancer in Denmark 1943-2008, before and after iodine supplementation. Int J Cancer. 2012;131:2360-6. doi: 10.1002/ijc.27497..

Table 1. Correlations between population-based iodine intake from iodized salt (iodine-IS) and the age-standardized rate adjusted to the world population of thyroid cancer incidence

Variables	Pearson r	*p*
Iodine-IS: LN_Men†	-0.571	0.007
Iodine-IS: LN_Women‡	-0.603	0.004
Iodine-IS: LN_Total§	-0.564	0.008

†LN_Men: the natural logarithmic transformation was accepted for the age-standardized rate adjusted to the world population (ASRW) of thyroid cancer (TC) incidence in men.
‡LN_Women: the natural logarithmic transformation was accepted for the ASRW of TC incidence in women.
§LN_Total: the natural logarithmic transformation was accepted for the ASRW of total TC incidence

Table 2. Time lag effect between population-based iodine intake from iodized salt (iodine-IS) and the age-standardized rate adjusted to the world population of thyroid cancer incidence

Variables	Lag time (years)	AIC	Adjusted R-squared	*p*
Iodine-IS: LN_Men†	6	-23.1	0.964	0.000
Iodine-IS: LN_Women‡	6	-29.7	0.978	0.000
Iodine-IS: LN_Total§	6	-29.3	0.975	0.000

†LN_Men: the natural logarithmic transformation was accepted for the age-standardized rate adjusted to the world population (ASRW) of thyroid cancer (TC) incidence in men.
‡LN_Women: the natural logarithmic transformation was accepted for the ASRW of TC incidence in women.
§LN_Total: the natural logarithmic transformation was accepted for the ASRW of total TC incidence

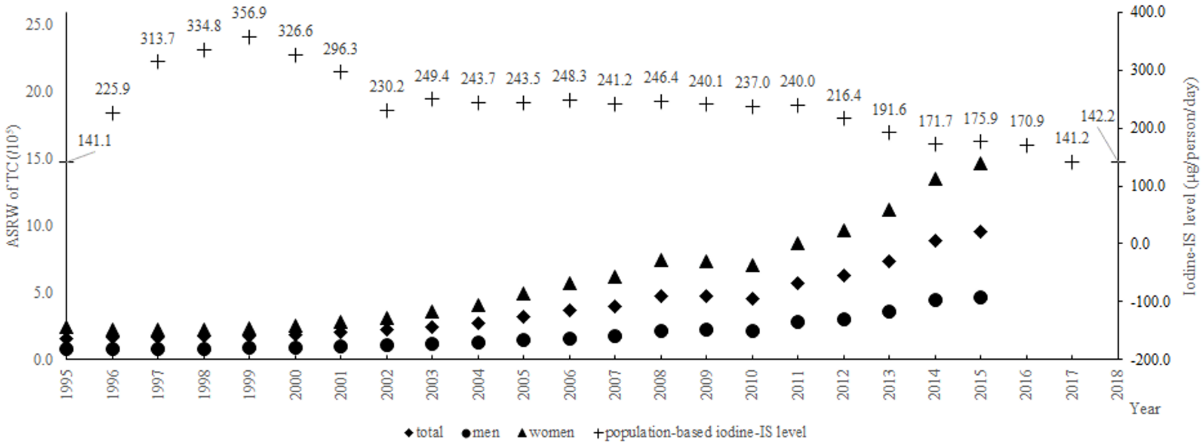

Figure 1. Trend of the iodine-IS (μg/person/day, +) and the ASRW of TC incidence in men (/10^5, ●), women (/10^5, ▲), and total (/10^5, ♦) from 1995 to 2018.

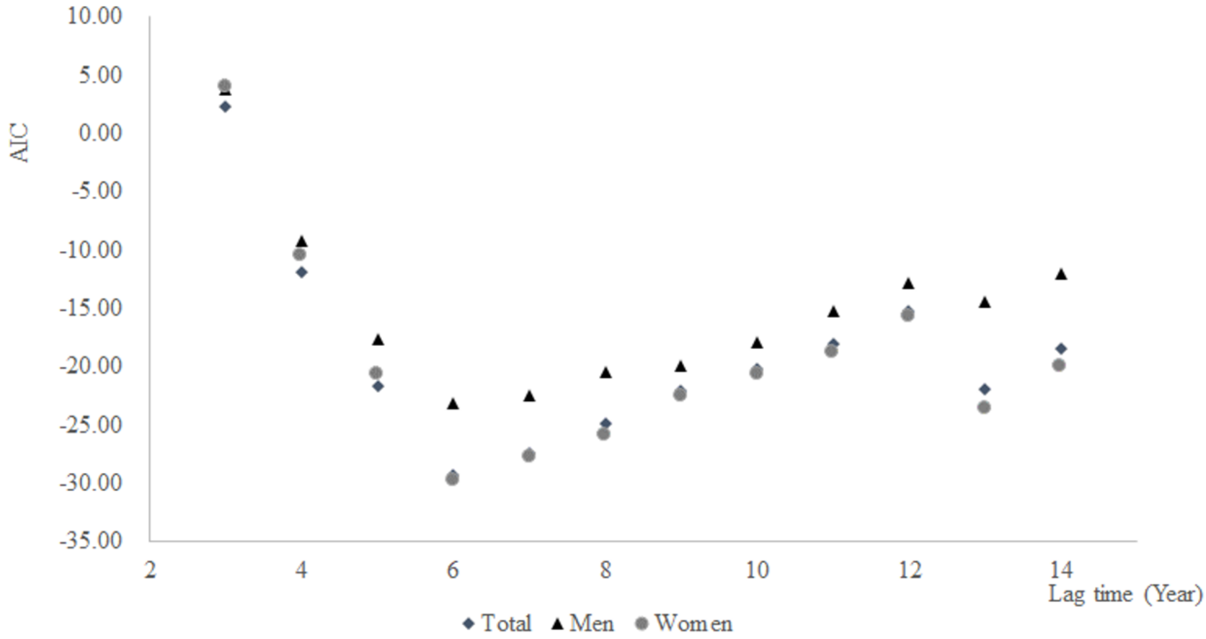

Figure 2. AIC results with varying lag times (years).