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ORIGINAL PAPER

Spatiotemporal analysis and risk assessment of thyroid cancer in Hangzhou, China

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Abstract Thyroid cancer (TC) incidence in China has increased rapidly in recent years. Hangzhou is one of the areas with the highest TC incidence in China. However, the composite space–time variation and risk factors of TC are rarely investigated. We acquired 7147 TC cases from 2008 to 2012 in Hangzhou. Descriptive statistics were employed to compare the incidence disparities in different sub-populations. Geographical information systems were used to create spatial distribution maps. Hotspot analysis was applied to detect high/low incidence clusters, and the GeogDetector model was implemented to investigate the relationship between TC incidence and environmental factors. TC incidence in Hangzhou increased dramatically from 2008 to 2012: a noticeable 244.9 % increase, from 10.04 to 34.63 per 100,000 individuals, with a female to male ratio of 3.0, an urban to rural ratio of 3.2 and iodine sufficient to iodine deficient ratio of 3.5. Significantly high TC cluster was detected in the northeast area of Hangzhou. Elevation was found to be the most powerful determinant of TC distribution, followed by soil parent materials and slope. TC incidence decreased as elevation and slope increased. Concerning soil parent materials, deposited materials were generally linked to higher TC incidence than were eluvium ones. The spatial/temporal pattern of TC incidence is affected by geomorphology and soil property variations. Excessive iodine exposure may be a TC risk factor. Health research and management should pay sufficient attention to the improved understanding and prediction of the composite space–time distribution of the quickly increasing TC incidence described in this study.

Keywords Thyroid cancer · Spatiotemporal pattern · Iodine sufficient · Spatial analysis · Risk factors

1 Introduction

Thyroid cancer (TC), which has been associated with the highest incidence among human endocrine malignancies, has increased dramatically worldwide during the recent decades, with a female-to-male ratio of about 3 (Nikiforov et al. 2013; Chen et al. 2009; Enewold et al. 2009; Kilfoy et al. 2009; Kolonel et al. 1990). In the United States, the annual percentage change (APC) for TC primary tumors <1.0 cm was about 10 (both genders) (Chen et al. 2009). In China, only a limited number of publications have reported TC cases before 1990, but during the last decade the disease has caught wide attention and great concern. In Chinese registry areas, the age-standardized TC incidence was 4.80/100,000 individuals in 2009, a 49.5 % increase since 2005, with an urban-to-rural ratio of about 2.5 (Fei et al. 2014).

While many studies have discussed a variety of potential pathogenic factors for TC, actually, the only established factors are ionizing radiation (Hatch et al. 2005), and benign proliferative thyroid disease (Kolonel et al. 1990). Other potential factors worth of further investigation include vitamins and minerals (Zhang et al. 2013a, b), ethnic background (Soloway et al. 2011), fish and shellfish consumption (Mack et al. 1999), alcohol intake (Allen

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et al. 2009), diabetes (Chen et al. 2013), genetic aspects (Zhu et al. 2014), vegetable consumption (Dal Maso et al. 2009) and body mass index (BMI) (Peterson et al. 2012). Moreover, the lack of sufficient evidence has made it impossible to draw a unanimous conclusion concerning factors like smoking (Hallquist et al. 1993), and occupation exposure to chemicals and industrial pollutants (Lope et al. 2005).

Some earlier studies considered the relationship between iodine intake and TC risk, but the conclusions have been rather contradictory and inconclusive: in Hawaii, the TC cases were characterized by iodine intake greater than that of healthy people (Kolonel et al. 1990), whereas in French Polynesia a decreased TC risk was associated with increasing dietary iodine intake (Clero et al. 2012). Some other studies showed that follicular TC cases mainly existed in iodine deficient areas, whereas papillary TC cases were observed in iodine sufficient areas (Lind et al. 1998; Kalk et al. 1997). Several scientists have pointed out that endocrine disrupting compounds such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and pesticides, which can disturb thyroid function are linked to carcinogenesis through a variety of mechanisms (Freeman et al. 2011; Solan et al. 2013; Leux and Guenel 2010).

Interestingly, only a few studies exist concerning the spatial/temporal TC distribution and the role of geomorphology and soil properties as TC risk factors (Amin and Burns 2014; Amphlett et al. 2013; Pellegriti et al. 2009; Minelli et al. 2013). Since geomorphology and soil properties have great impact on the migration and preservation of most chemicals (such as iodine, and endocrine disrupting compounds), the present study assumed that the distribution of geomorphology and soil properties may influence the spatial pattern of TC incidence. The focus of the study is Hangzhou city (China). According to the Chinese Cancer Registry (CCR) annual report, in recent years the age-standardized TC incidence has increased considerably in the city. Specifically, during 2004–2009 incidence increased from 1.93 to 4.46 per 100,000 individuals (males), and from 7.16 to 14.20 per 100,000 individuals (females) (Chinese National Cancer Center 2008–2012). The main goals of the present work then are to study the spatiotemporal distribution of TC incidence in Hangzhou city and to assess whether geomorphology and soil properties are significant TC risk factors.

2 Materials and methods

2.1 Study area

Being one of the most developed cities in China, Hangzhou is located in the southeast coast of China (E 118°21′–120°30′, N 29°11′–30°33′), having a population of about 6.78 million inhabitants (according to the 2011 Hangzhou statistics book). Hangzhou includes 8 districts and 5 counties. The districts of Shangchen, Xiachen, Jianggan, Gongshu, Xihu, and Binjiang are located in the metropolitan Hangzhou area and have a higher population density (4498 people per square kilometer) than the rest (294 people per square kilometer). Accordingly, we classified them as urban areas (denoted as “Downtown areas” in Fig. 1a). Approximately 2.20 million people live in urban areas and 4.58 million people live in rural areas. Notice that previous study has used endemic goiter prevalence as an iodine status indicator (Galanti et al. 1995), where high goiter prevalence areas (before the national salt iodization program was implemented) were classified as iodine deficient areas. In accordance with the 1980–1984 endemic goiter distribution data (Tan et al. 1989), the present study classified Hangzhou into iodine sufficient versus iodine deficient areas (Fig. 1a). The towns of Xiaoshan, Yuhang, Fuyang and Downtown, having nearly 72 % of the population, were considered iodine sufficient areas (with endemic goiter prevalence lower than 3 %); and the towns located mainly in southwest Hangzhou were considered as iodine deficient areas (with endemic goiter prevalence higher than 3 %, or even higher than 10 % in some cases).

2.2 Data

All new TC cases [International Classification of Disease 10th edition (ICD-10) code: C73] diagnosed in Hangzhou during 2008–2012 were obtained from the Center for Disease Control and Prevention (CDC), Hangzhou city. Hangzhou as a monitored city of the Chinese National Cancer Center, the completeness and reliability of cancer data were checked and evaluated by Chinese National Cancer Center. The registered population (2011) at each township was obtained from the Hangzhou Public Security Bureau (PSB). All cases were allocated to 201 townships according to household register data. There are totally 7147 patients (5385 female and 1762 male) newly diagnosed with TC during the period from Jan. 1, 2008 to Dec. 31, 2012. The registered population was about 6.78 million.

Since information about the age-distribution of the TC cases is not available, the TC incidence at the town level was estimated as the number of cases divided by the population. When calculating the 5-year average incidence, the person-years for each township were calculated by multiplying their 2011 populations by 5.

Given that cancer etiology usually includes physical, biological, chemical, social and cultural factors, many of these direct determinants are difficult to measure. However, the direct determinants impact on cancer through

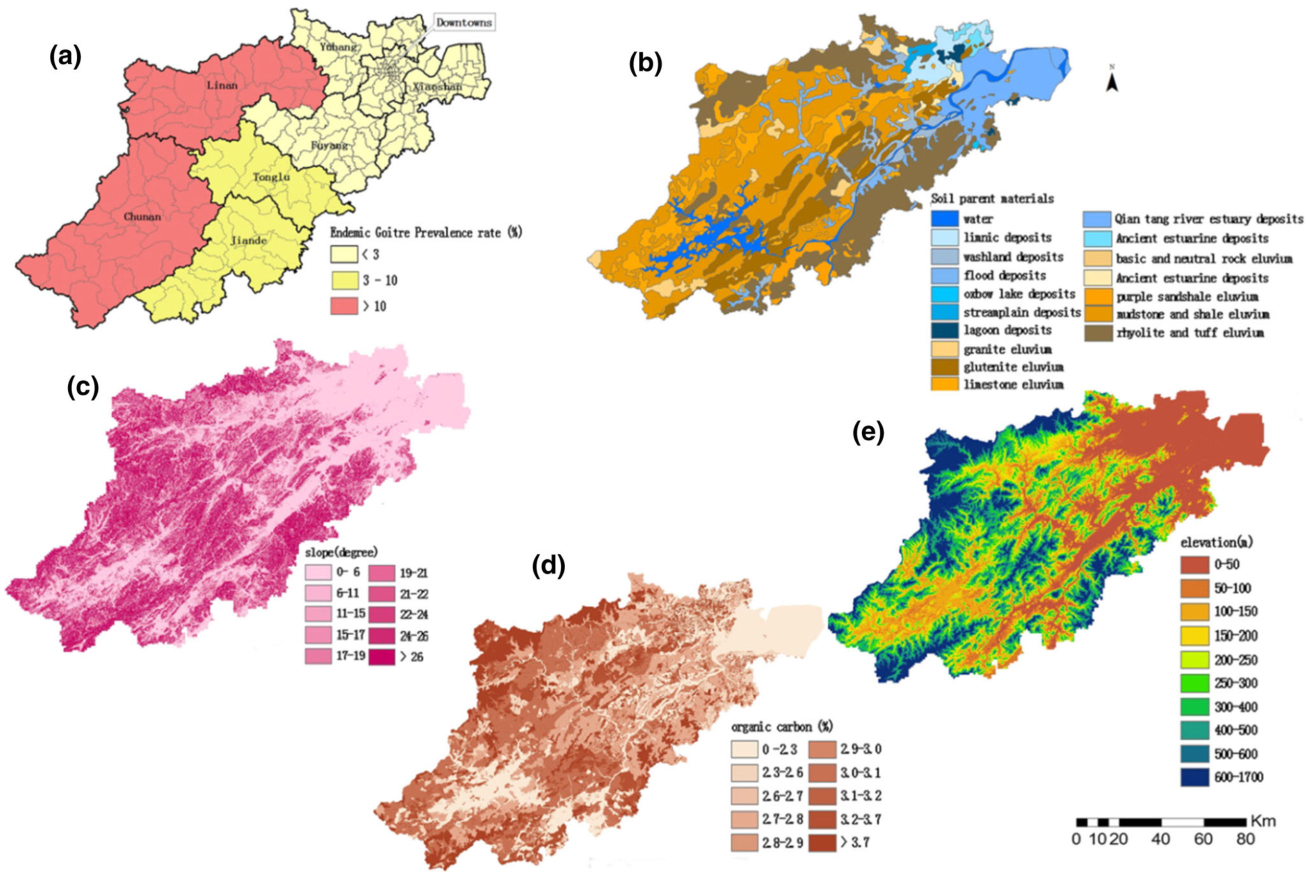

Fig. 1 Maps of the distribution of environmental factors

explicit geographical factors, which are easier to obtain using geographical information system (GIS) techniques (Wang et al. 2010a, b). The explicit factors considered in this research are as follows: Topographic elevation and slope distribution data were obtained from the Advanced Spaceborne Thermal Emission and Reflection Radiometer Global Digital Elevation Model (ASTER GDEM) (30 m spatial resolution) (http://datamirror.csdb.cn/index.jsp/). Information about soil organic carbon and parent materials was obtained from the Zhejiang Soil Survey Geographic Database (Fig. 1b–e) (Wu et al. 2013). Figure 2 shows the conceptual framework about the explicit geomorphology and soil properties proxies and the implicit direct TC determinants. The Geographical Detector (GeogDetector) Model was employed to analyze the association between explicit proxies and TC incidence, and the implicit direct TC determinants were used to interpret the association.

2.3 Statistical analysis

Descriptive statistics and the Student's t test were used to evaluate the incidence disparities between male versus female populations, urban versus rural regions, and iodine sufficient versus deficient areas. GIS mapping techniques were employed to provide visualization distribution maps, and Hotspot analysis (Getis and Ord 1992) was used to analyze the spatial clustering of TC incidence, for both genders during the period 2008–2012.

The aim of Hotspot analysis is calculating the Getis-Ord G_i^* statistic (z score) for each attribute feature, which enables the detection of hidden spatial associations. Cluster structures can be detected on the basis of their z values, thus making the Getis-Ord G_i^* statistic a widely used method of spatial analysis. The G_i^* statistic is computed by

$$Z(G_i^*) = \frac{\sum_{j=1}^{n} w_{ij}x_j - \bar{x}\sum_{j=1}^{n} w_{ij}}{SW} \tag{1}$$

where $Z(G_i^*)$ is the z score, x_j is the TC incidence value at location j, w_{ij} is the weight of neighbor i to location j which was calculated through the inverse distance weighted method, and n is the total number of samples (i.e., this tool works by looking at each feature within the context of neighboring features). The $\bar{x}$, S, and W in Eq. (1) are calculated by

$$\bar{x} = \frac{1}{n}\sum_{j=1}^{n} x_j \tag{2}$$

$$S = \sqrt{\frac{1}{n}\sum_{j=1}^{n} x_j^2 - \bar{x}^2} \tag{3}$$

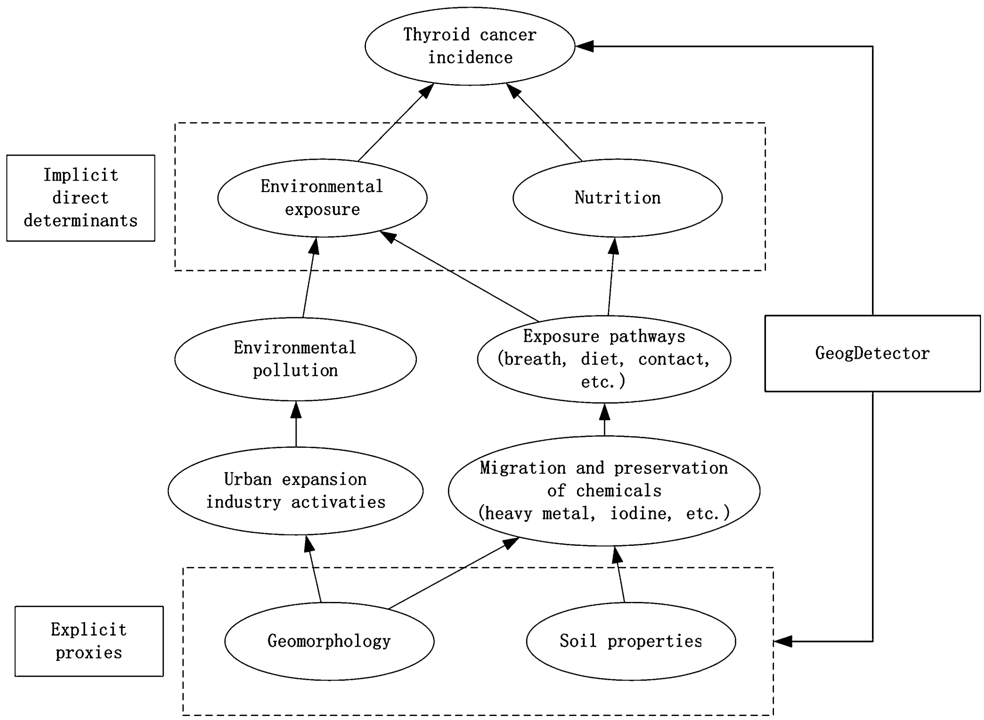

Fig. 2 Association between direct thyroid cancer determinants and their proxy factors

$$W = \sqrt{\frac{1}{n-1}\left[n\sum\nolimits_{j=1}^{n} w_{ij}^{2} - \left(\sum\nolimits_{j=1}^{n} w_{ij}\right)^{2}\right]} \quad (4)$$

Methodologically, according to the analysis above, two criteria are used to decide whether a location is a statistically significant hotspot or not: (*a*) the location of interest has a high attribute value; and (*b*) the location is surrounded by other locations with high attribute values.

Technically, the location of interest and its neighbors are the units of the G_i^* statistic, and the *z*-score is calculated by Eq. (1) so that the local sum of TC incidence values at these units is compared proportionally to the sum at all locations. If the difference between the local sum and its expected value is too large to be viewed as a result of random chance, the *z* score is considered statistically significant. There are positive and negative *z* scores, implying hotspots and coldspots, respectively. In numerical terms, if the absolute *z*-score values are greater than 2.58, between 1.96 and 2.58, and between 1.65 and 1.96, they imply, respectively, statistical significant clusters at the 0.01, 0.05, and 0.10 level. A *z*-score between −1.65 and 1.65 infers a random TC incidence distribution. Detailed information about the Getis-Ord G_i^* could be found in Getis and Ord (1992).

In order to reduce the random effects caused by small samples, GeogDetector model and software (GeogDetector; http://www.sssampling.org/Excel-GeoDetector/) were used to determine the association between 5-year average TC incidence (2008–2012) and environmental risk factors. The basic idea of this model is to detect the consistency of the spatial distribution of TC incidence with that of environmental health risks. The environmental risk factors considered in the present research are the topographic elevation, slope, soil organic carbon and soil parent materials. We used three geographical detectors, viz. risk detector, factor detector, and ecological detector to identify, respectively, the potential risk area, the responsible factors and the relative importance factors. Detailed information about the GeogDetector model and software could be found in Li et al. (2013) and Wang et al. (2010a, b).

The fact that GeogDetector determines the relationships between disease and environmental health risks based on spatial variation analysis makes it suitable for detecting TC risk factors, since it doesn't require stochastically homoscedastic incidence, and it can handle categorical factors such as soil parent materials. The basic methodological assumption is that if the environmental factor is a disease risk, the spatial distribution of the disease should be similar to the factor's geographical distribution (Li et al. 2013). Figure 3 outlines the principles of GeogDetector analysis. Briefly, the 5-year (2008–2012) averaged TC incidence (*I*) data was converted into raster form (the spatial resolution of the grid was 1000 m × 1000 m in the present work). Environment risk factors detected in this study (topographic elevation, slope, soil organic carbon, and soil parent materials) were used to stratify the entire study region into sub-regions according to the principle of maximizing/minimizing the dispersion variance of a risk

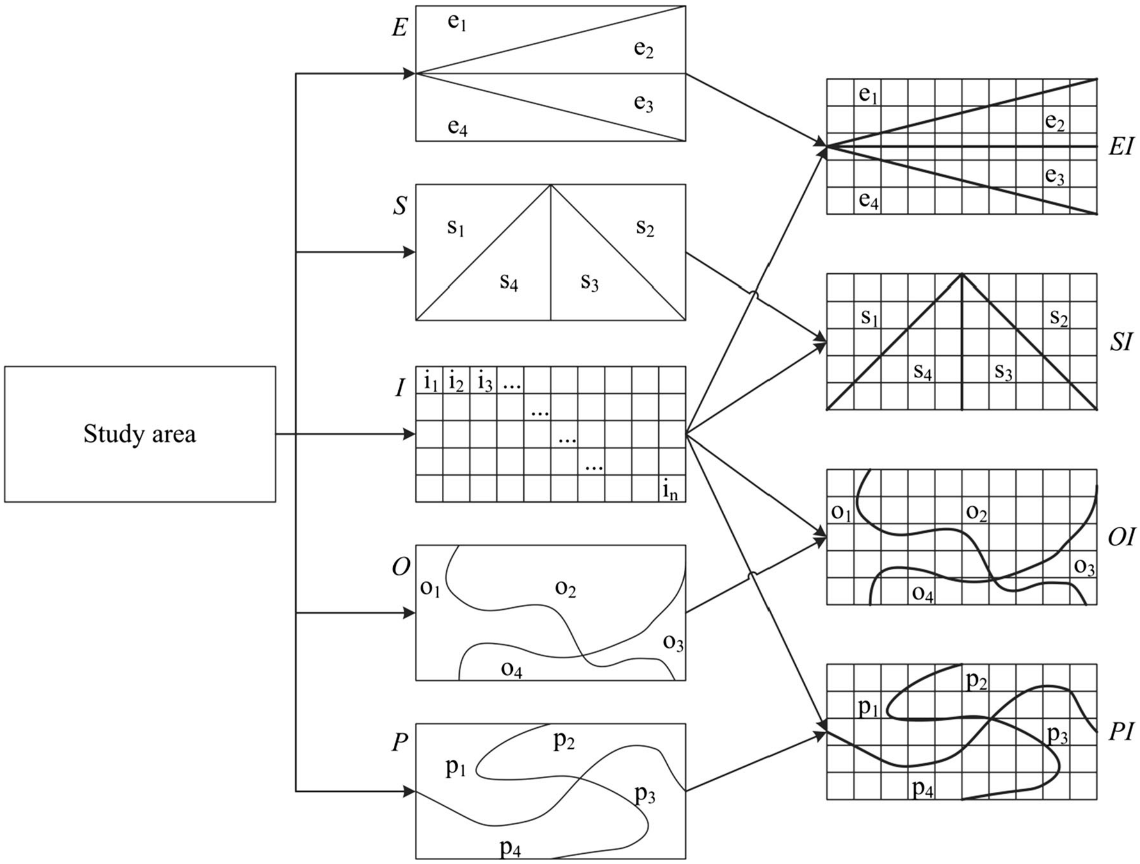

Fig. 3 The flow chart of GeogDetector

factor between and within sub-regions. The stratifications associated with the factors of topographic elevation (E), slope (S), soil organic carbon (O), and soil parent materials (P) are denoted in Fig. 3 as $\{e_1, e_2, e_3, e_4\}$, $\{s_1, s_2, s_3, s_4\}$, $\{o_1, o_2, o_3, o_4\}$ and $\{p_1, p_2, p_3, p_4\}$, respectively. Then, the TC incidence data (I, in grid form) were overlapped by the environmental factors data, and the means and dispersion variances of TC incidence were calculated in the entire study region and within each sub-region (Fig. 3). The notion of power determinant (PD) was introduced to determine the effect of environmental factors on disease distribution. PD was calculated by

$$PD = 1 - \frac{1}{AV}\sum_{i=1}^{N} A_i V_i \tag{5}$$

where A is the total area of the study region; V is the total TC incidence dispersion variance within the study region; the subscript $i = 1,2,\ldots N$ represent different sub-regions (N is the total number of sub-regions); A_i and V_i denote, respectively, the area and TC incidence dispersion variance within sub-region i.

For illustration purposes, consider the topographic elevation (E) factor in Fig. 3. The TC incidence data in the study area were converted into grid form $\{i_1, i_2, i_3,\ldots, i_n\}$. According to the elevation distribution, the study area was stratified into sub-regions denoted as $\{e_1, e_2, e_3, e_4\}$, see above. After overlaying the TC incidence layer I with the elevation layer E, the final overlaid layer EI was obtained. In layer EI, the means and dispersion variances of TC incidence in the corresponding sub-regions (denoted by $\bar{I}_{ei}$ and V_{ei}, respectively), and of the entire study area (denoted by $\bar{I}_E$ and V_E, respectively) can be calculated. A_E and A_{ei} ($i = 1, 2, 3, 4$) represent the areas of the entire study region and the sub-regions e_i, respectively. Then, from Eq. (5) the power determinant is computed by

$$PD_E = 1 - \frac{\sum_{i=1}^{4} A_{ei} V_{ei}}{A_E V_E} \tag{6}$$

If the TC incidence distribution is completely determined by an environmental factor, the corresponding dispersion variance $V_i = 0$, in which case $PD = 1$. Whereas, if the incidence distribution is completely unrelated to this factor, then $\sum A_i V_i = AV$ in which case $PD = 0$. Thus, PD which changes from 0 to 1, is a measure of the effect of a risk factor on disease distribution.

In sum, in the present study the t test was performed with the help of the SPSS 19.0 software. Risk factors were detected using the GeogDetector model. P values less than

0.05 were considered as statistically significant, whereas all tests of statistical significance were two-sided. Hotspot analysis maps estimated using the Getis-Ord G_i^* tool and the distribution maps of TC incidence were generated by ArcGIS 9.3 (http://www.esri.com/).

3 Results

3.1 Thyroid cancer incidence in Hangzhou

In Hangzhou, a total of 7147 patients were newly diagnosed with TC during the period from Jan 1, 2008 to Dec 31, 2012 (specifically, 742, 901, 1202, 1876 and 2426 cases during the years 2008, 2009, 2010, 2011 and 2012, respectively). The number of women patients diagnosed with TC (553, 687, 913, 1402 and 1830, respectively) was about 3 times more than that of men patients (189, 214, 289, 474 and 596, respectively). It is noteworthy that in Hangzhou the TC incidence increased sharply by 244.9 %, from 10.04 to 34.63/100,000 during the period 2008–2012. In particular, male incidence increased from 5.46 to 17.00/100,000 with an APC of about 32.8 %; and female incidence increased from 14.09 to 52.30/100,000 (i.e., a threefold increase compared to that of male incidence) with an APC of about 38.8 % (Table 1).

TC incidence was significantly higher in urban areas than in rural areas ($P = 0.013$ for both genders). In urban areas, TC incidence among women increased from 27.31 to 84.58/100,000, with a 5-year average incidence of 49.72/100,000; and among men, incidence increased from 9.49 to 30.19/100,000, with a 5-year average incidence of 17.94/100,000. In rural areas, TC incidence among women increased from 11.16 to 36.44/100,000 with a 5-year average incidence of 14.23/100,000; and among men, incidence rose from 3.53 to 10.36/100,000 with a 5-year average incidence of 6.28/100,000 (Table 1), i.e., TC incidence in urban areas was about 3.2 times higher than in rural areas. When comparing the TC incidence observed in iodine deficient versus sufficient areas, we found that TC incidence in iodine sufficient areas was significantly higher than in iodine deficient areas ($P = 0.013$ and 0.011 for male and female respectively). In iodine sufficient areas, a 5-year average incidence among women was 38.80/100,000, an increase from 20.67 to 65.49/100,000 during 2008–2012; and the 5-year average incidence among men was 12.71/100,000, an increase from 6.74 to 21.44/100,000 during the same period. In iodine deficient areas, a 5-year average incidence among women was 10.85/100,000, an increase from 5.07 to 16.37/100,000, and a 5-year average incidence among men was 3.39/100,000, an increase from 2.29 to 5.21/100,000 during 2008–2012 (see Table 1).

The distribution of TC incidence in Hangzhou was spatially heterogeneous (non-homogeneous variation with distinct local trends, Fig. 4). Incidence in northeast towns, exhibiting a faster growth, was higher than that in southwest towns; and there was a definite trend from the southwest low incidence region to the northeast high incidence region, especially for the female population that had a considerably higher incidence. Hotspot analysis provided additional information about the spatial heterogeneity of TC incidence (Fig. 5). Higher TC clusters were located in northeast of Hangzhou (see, e.g., the Downtowns, Xiaoshan and Yuhang districts). However, lower TC clusters were all located in southwest of Hangzhou (e.g., Chunan, Jiande, Tonglu, and Linan counties).

3.2 GeogDetector modeling of risk factors

The distribution of TC incidence in Hangzhou is spatially heterogeneous, see Figs. 4 and 5, which may be due to the uneven distribution of the specific environmental factors.

Table 1 Thyroid cancer incidence in Hangzhou

	Characteristics	2008[a]	2009	2010	2011	2012	P[b]
Male	Overall	5.46	6.24	8.37	13.58	17.00	
	Rural	3.53	4.25	4.80	8.25	10.36	
	Urban	9.49	10.26	15.54	24.23	30.19	0.013
	Iodine deficiency	2.29	2.29	2.19	4.99	5.21	
	Iodine sufficiency	6.74	7.77	10.74	16.84	21.44	0.013
Female	Overall	14.09	20.27	26.68	40.48	52.30	
	Rural	7.33	10.07	12.28	18.05	23.44	
	Urban	27.31	29.37	40.97	66.47	84.58	0.013
	Iodine deficiency	5.07	7.09	10.72	15.03	16.37	
	Iodine sufficiency	20.67	25.27	32.66	49.92	65.49	0.011

[a] Thyroid cancer incidence in every year (1/100,000)

[b] Two-sided test from *t* test

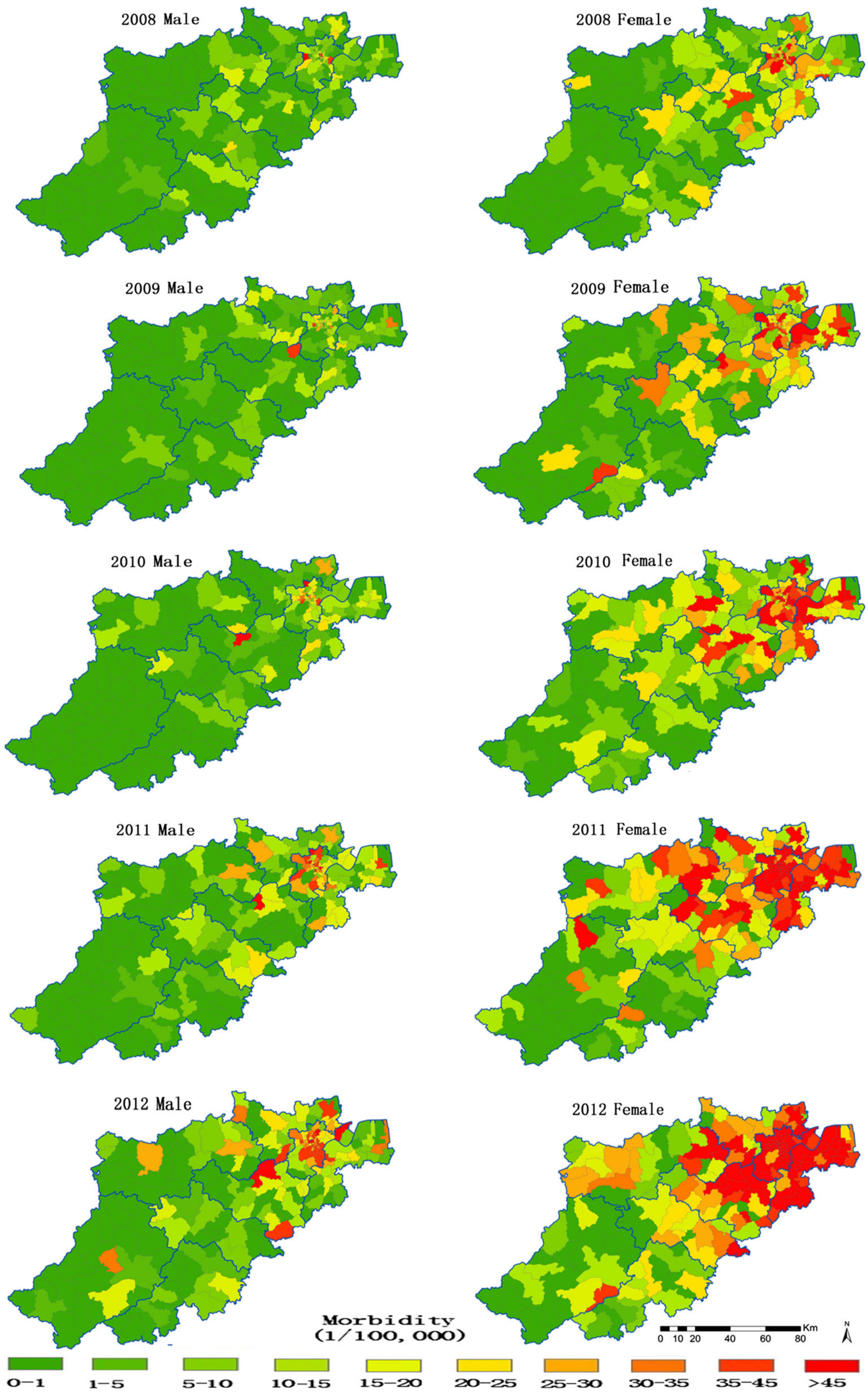

Fig. 4 Distribution of male versus female thyroid cancer incidence during 2008–2012

So, the GeogDetector was employed to assess the relationships between TC incidence and the relevant environmental factors (Table 2). According to their *PD*-values, elevation was the most important and statistically significant factor of TC distribution, followed by soil parent materials (significant), slope (significant), and soil organic carbon (non-significant) (this ranking is valid for both genders).

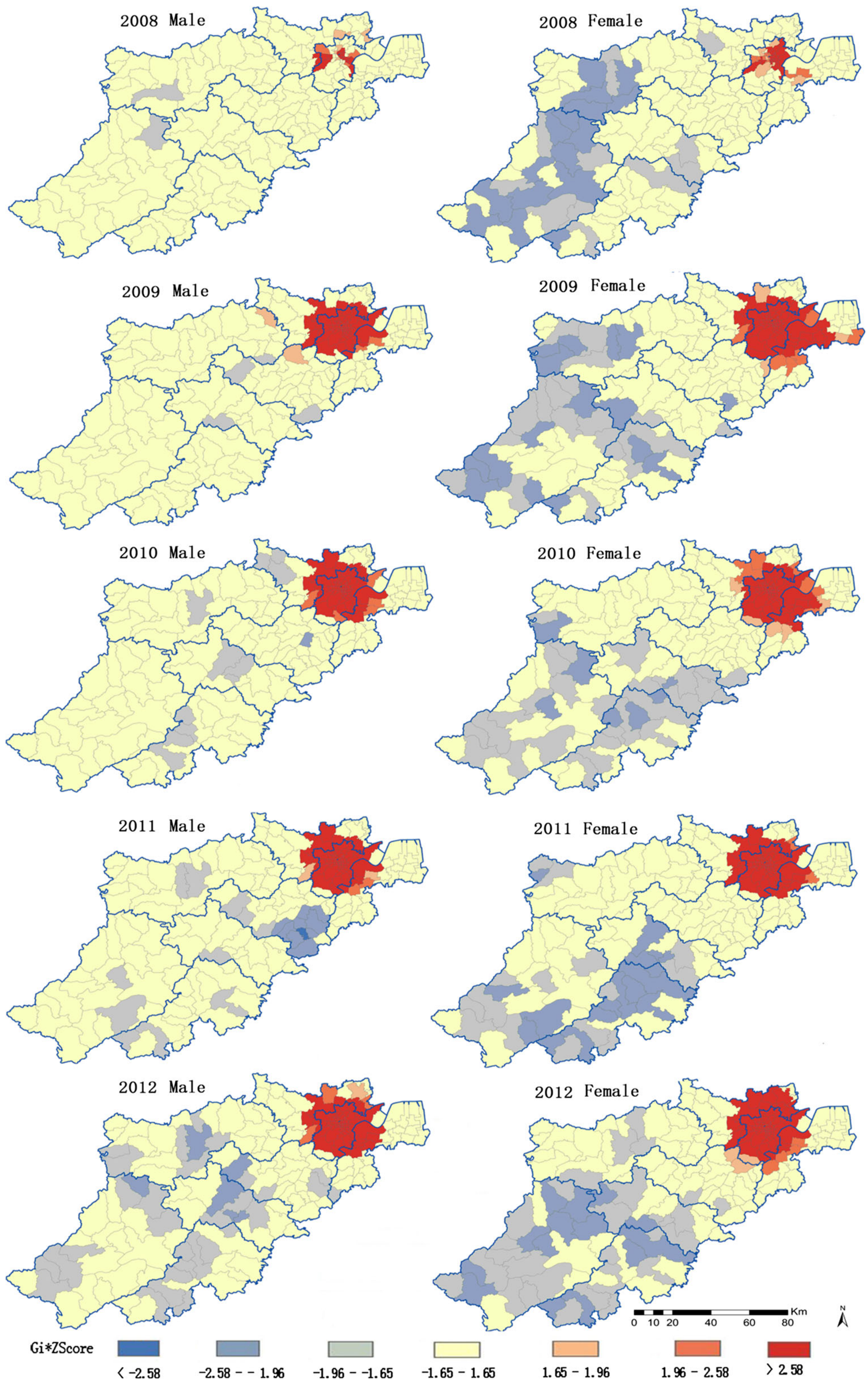

Fig. 5 Hotspot analysis of male versus female thyroid cancer incidence during 2008–2012

Moreover, Fig. 6 presents the relationships between TC incidence and the different environmental factors. TC incidence showed a dramatic decline with increasing topographic elevation and slope. In regions with elevation between 0 and 50 m the incidence was about 3 times greater than in regions with elevation higher than 600 m. In addition, TC incidence in regions with a 0°–6° slope was about two times larger than that in regions with a slope

Table 2 Power determination (PD)[a] values of different environmental factors

Gender	Elevation	Soil parent material	Slope	Soil organic carbon
Male	0.251	0.245	0.197	0.147
Female	0.329	0.306	0.256	0.193

[a] PD varies between 0 and 1 representing the weakest to the strongest effect of a risk factor on thyroid cancer distribution

greater than 15°. When soil organic carbon content increased, TC incidence declined dramatically at first, and then it remained at relative low levels. Table 3 describes the variation of TC incidence in regions with different soil parent materials. In general, TC incidence in areas where the subsurface consisted of deposited layers was statistically greater than that in areas with eluvium layers, with the exception of areas in which the basic and neutral rock eluvium was greater than in some deposited layers (e.g., river-valley, wash-land, and flood deposits). However, since basic and neutral rock eluvium occupied a relative small area in Hangzhou, TC incidence in this area may be less relevant.

4 Discussion

This ecological study revealed a quickly increased TC trend in Hangzhou from 2008 to 2012, with a female versus male ratio of 3.0, urban versus rural ratio of 3.2 and iodine sufficient areas versus iodine deficient areas ratio of 3.5. The distribution of TC incidence was spatially heterogeneous at the township level, a significantly high cluster was located in the northeast coastal areas of Hangzhou, and a low cluster was located in the southwest mountainous areas. Risk factor detection showed that elevation had the greatest influence on the TC distribution, followed by soil parent materials, slope and soil organic carbon.

The analysis of the available evidence demonstrates that TC incidence in Hangzhou city increased at an accelerated pace in the last decade or so:

(a) According to the 2000 report of the Tumor Registration Association (TRA), in Hangzhou the TC incidence for men and women was only 1.2 and 3.0/100,000, respectively.
(b) According to the annual report of the National Central Cancer Registry (NCCR), during 2004–2008 the male TC incidence in Hangzhou increased from 2.42 to 5.13/100,000, whereas the female incidence increased from 8.65 to 14.72/100,000 (Chinese National Cancer Center 2008–2012).
(c) During the period 2008–2012, the TC incidence in Hangzhou increased from 10.04 to 34.63/100,000 (female incidence, in particular, increased from 14.09 to 52.3/100,000, with an APC of about 38.8 %), which was the highest incidence level ever observed.

According to our literature search, there were few reported TC cases in Hangzhou city before 1990. As its incidence grew faster in recent years, TC became one of the top 5 malignant tumors in the area, following lung, liver, stomach, and breast malignant tumors. It's worth noticing that, given that the other four tumors had a relative stable incidence in Hangzhou during recent years (according to the CDC data), if TC incidence keeps increasing at the same rate, within a few years it will become the top malignant tumor in Hangzhou.

Concerning urban versus rural factors, we found that the TC incidence in urban areas was about 3.2 times higher than in rural areas, which is in agreement with previous studies (Fei et al. 2014; Soloway et al. 2011). In particular, Fei et al. (2014) found that the TC incidence in China increased by 49.5 % from 2005 to 2009, with an urban–rural ratio of 2.5. And, Soloway et al. (2011) pointed out that in recent years, TC incidence increased quickly in New York city, especially in its metropolitan area. There are many factors that may affect the urban–rural disparity of TC incidence. People living in urban areas usually have a higher socioeconomic status, better education, better access to health services, dietary pattern with more fish and meat consumption, higher BMI, higher industrial pollution exposure etc. (Enewold et al. 2009; Kilfoy et al. 2009; Fei et al. 2015), which are all possible TC risk factors.

Furthermore, we found that the female incidence with larger percentage change was about three times higher than the male incidence, a finding that is also consistent with other studies. Specifically, Fei et al. (2014) noticed that the TC incidence had a female to male ratio of about 3.0 in China. Enewold et al. (2009) illustrated that papillary carcinoma rates increased most rapidly among females during 1980–2005. And, Kilfoy et al. (2009) remarked that the average increase rate of TC incidence was 48.0 % for the male and 66.7 % for female population, respectively, from 1973–1977 to 1998–2002. In addition to the common risk factors of both genders mentioned above (Enewold et al. 2009; Kilfoy et al. 2009; Fei et al. 2015), recent studies assumed that higher female TC incidence and increase rate may be attributed to female reproductive and

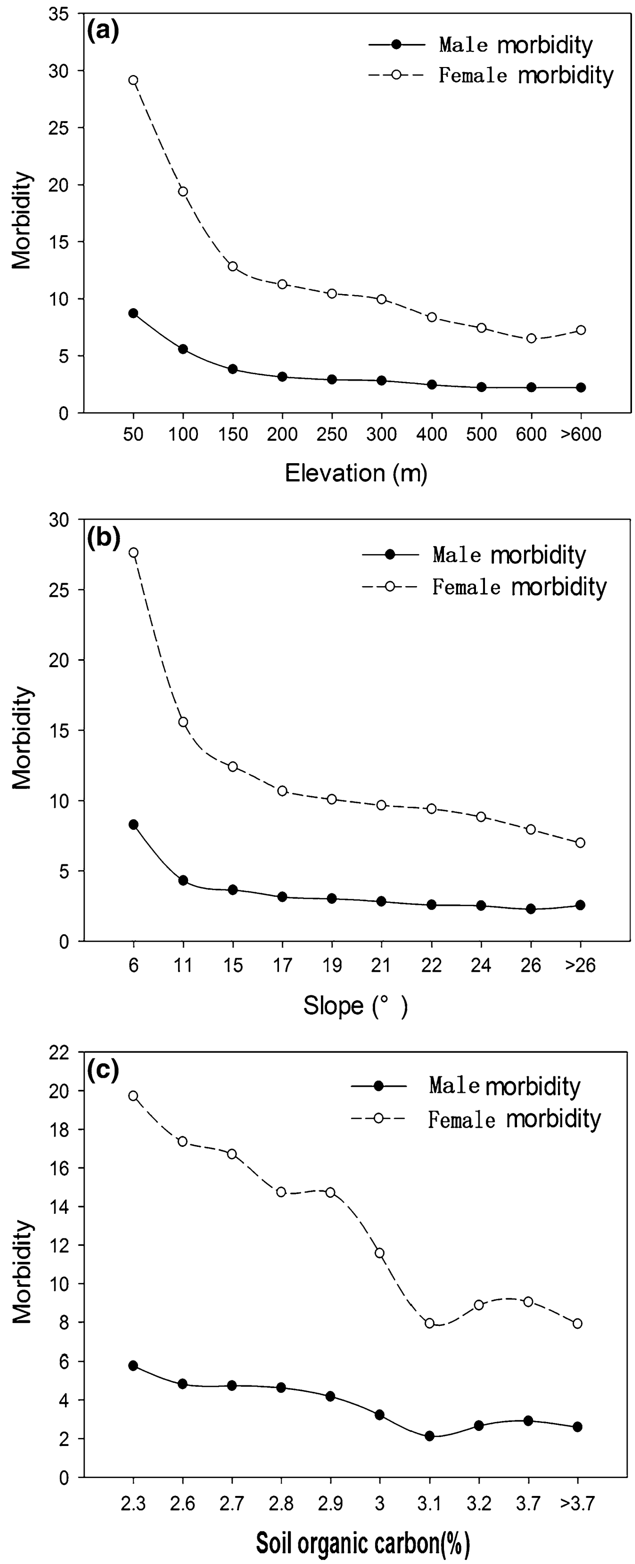

Fig. 6 Relationships between different environmental factors and thyroid cancer incidence (1/100,000)

menstrual factors (pregnancy, menopausal status, exogenous hormone use etc.) (Rahbari et al. 2010; Zamora-Ros et al. 2015).

Concerning iodine sufficiency and spatial heterogeneity, our results showed that TC incidence in iodine sufficient areas was about 3.5 times higher than that in iodine deficient areas. Iodine is an important thyroid trace element, which influences thyroid function, in both a direct and an indirect manner, by means of hormone metabolism (Dal Maso et al. 2009). As mentioned earlier, there is no definitive agreement in the literature regarding the impact of iodine on TC [e.g., epidemiological studies in French Polynesia and California have noticed a reduced risk of TC with high dietary iodine intake (Clero et al. 2012; Horn-Ross et al. 2001), whereas other studies in Hawaii and elsewhere revealed a positive association between iodine sufficient areas and high TC incidence (Kolonel et al. 1990; Lind et al. 1998)]. In fact, our findings support the latter conclusion. Iodine distribution in Hangzhou was spatially heterogeneous (non-homogeneous variation with distinct local trends). Southwest Hangzhou was iodine deficient, which lead to higher prevalence of endemic goiter, whereas northeast Hangzhou was iodine sufficient (Tan et al. 1989). To prevent goiter, a program of iodine supplementation by salt iodization was implemented nationwide in the 1990s. As a result of this program and the heterogeneous iodine variation, people living in the iodine sufficient northeast Hangzhou area may have experienced high iodine exposure that lead to increased TC incidence. In fact, during recent years China has been classified as an iodine-included hyperthyroidism risk area (Andersson et al. 2005; De Benoist et al. 2008); and it has been argued that excessive iodine exposure may turn out to be a national health problem. Hence, it is urgent to adjust the program of universal iodine supplementation, e.g., the salt iodine content for coastal residents could be reduced, and even the iodine supplementation program in the iodine sufficient region should be suspended.

Concerning spatial clustering, as noted earlier, according to the incidence maps and the results of Hotspot analysis, the distribution of TC incidence was spatially heterogeneous, experiencing considerable clustering. Previous studies have also emphasized the spatial clustering of TC incidence. In Florida, Amin and Burns (2014) found significant TC clusters in the southern and northwestern parts of the study area at the county level (adolescents and young adults). Amphlett et al. (2013) collected a total of 1747 thyroid cases in Wales during 1985–2010, and concluded that TC incidence has increased, although the spatial distribution was inconsistent with the radioactive fallout. Compared to these earlier studies, data for many more cases (totally, 7147 thyroid cancer cases) were collected in the present study and spatial clusters were detected at a smaller administrative level (township). Thus, we could produce more stable and detailed maps of TC distribution and clusters, which is an advantage of the present study, as regards the spatial variation of the disease.

Table 3 5-years average thyroid cancer incidence in different soil parent materials regions

Soil parent materials	Female incidence[a]	Male incidence
Ancient estuarine deposits	40.51	13.03
Quaternary red earth	39.59	11.52
Qian tang river estuary deposits	32.27	9.31
Lagoon deposits	30.33	8.74
Oxbow lake deposits	28.32	8.39
Basic and neutral rock eluvium	25.95	7.72
Limnic deposits	22.21	5.51
Streamplain deposits	20.70	5.04
Washland deposits	18.87	4.16
Rhyolite and tuff eluvium	13.03	3.67
Flood deposits	12.90	3.46
Glutenite eluvium	12.61	2.93
Mudstone and shale eluvium	8.66	2.48
Limestone eluvium	8.53	2.37
Granite eluvium	6.32	1.93
Purple sandshale eluvium	5.34	1.62

[a] 5-years average thyroid cancer incidence during 2008–2012 (1/100,000)

GeogDetctor has been used to analyze the influence of vegetable planting models (categorical variables) and planting age (continuous variable) on fluoroquinolone residues in the soil, and provide effective suggestions to control fluoroquinolone residues pollution (Li et al. 2013). It also could be used in environmental health risk assessment. Wang et al. (2010a, b) used this model to estimate the risk of neural tube defects in different environments (elevation, slop, watershed, soil, etc.). In view of the distinct ability of spatial variation analysis to combine continuous variables (elevation, slope, soil organic carbon) with categorical variables (soil parent materials), GeogDetector was first used in this work to determine the relationship between chronic disease incidence and long-time existing environmental factors, which may offer valuable insight to disease control and prevention. Several previous studies have analyzed the geomorphology and soil risk factors for TC, providing considerable methodological support to the present study. Among others, Pellegriti et al. (2009) found that people lived in the volcanic soil of the Catania province experienced a higher papillary TC incidence than in other places in Sicily; Minelli el al. (2013) pointed out that people residing in the mountainous areas of Italy had a higher TC mortality.

When converting the incidence data into raster format, water-covered areas were not accounted, plausibly assuming that these areas are not populated. When classifying different soil strata, zero soil property values were assigned to areas covered by buildings, denoting the lack of soil information in these areas. The PD values of topographic elevation were significantly larger than those of other environmental factors. TC incidence decreased with increasing elevation and slope, which may be due to two reasons:

(a) There are some chemicals in soils [heavy metals, environmental endocrine disruptors (EEDs) etc.] that are potentially carcinogenic (Solan et al. 2013; Soto and Sonnenschein 2010), or they play an important role in regular thyroid function (iodine etc.) (Peterson et al. 2012; Lind et al. 1998). These chemicals can easily move from high to low elevation areas, and accumulate in relatively flat area through water movement and soil erosion (Quinton and Catt 2007; Campbell et al. 2006). Moreover, iodine, which plays a key role in thyroid gland regulation, is movable rather easily from mountains and hills (higher elevation and slope) and accumulates in lowland and coastal regions (Tan et al. 1989), creating iodine-rich ecologies in areas with low elevation and slope. Following human intervention for endemic goiters (i.e., the national salt iodization program), these iodine-rich areas were exposed to even higher iodine levels, and after a relative long latent period, this excessive iodine exposure may lead to higher TC incidence (Kolonel et al. 1990; Lind et al. 1998).

(b) As previous studies have suggested, people tend to live and build factories in lower land and flat areas, rather than in high mountainous and hilly places (Zhang et al. 2013a, b). As a result, these areas would discharge larger amounts of environmental pollutants—such as heavy metals, PCBs and PBDEs through urban expansion, industrial activities and transportation (Zoeller 2005; Yuan et al. 2008). These chemicals especially the EEDs (PCB, PBDE, etc.) have direct impacts on thyroid hormone receptors, and they may disrupt the thyroid function through some unpredictable mechanisms (Moon et al. 2012). It was found that PBDE and Thyroid stimulating hormone (TSH) concentration and the number of micro-nucleated binucleated cells in serum were significantly higher in humans living in villages close to an electronic-waste site than in the control group located far away from the site (Yuan et al. 2008). Previous studies also found PCB exposure and plasma concentration of persistent organochlorines could alter thyroid function and TSH concentration (Persky et al. 2001; Osius et al. 1999). TSH is important to thyroid growth and normal function, and can affect cancer development significantly. Human populations with elevated serum TSH levels have a higher probability to suffer from TC, since TSH is important in thyroid cell proliferation (Yuan et al. 2008). Therefore, people living in low and flat urban areas may be exposed to higher EED concentration, which lead to TSH rise and a higher TC risk.

We noted aforementioned that TC incidence in areas with deposited layers was statistically greater than that of eluvium layers. The likely explanations could be similar to those associated with topographical elevation and slope described earlier. There are some chemicals (heavy metals etc.) in soil parent materials that are potentially carcinogenic, or they are important for regular thyroid function (iodine etc.) (Peterson et al. 2012; Lind et al. 1998). These chemicals could enter human body through the relevant exposure pathways (Wu et al. 2004). Furthermore, an interaction exists between topography factors and soil parent materials: chemicals in eluvium layers are easily removed via soil erosion, and are accumulated in deposited places that are often associated with a flat topography suitable for agriculture. Hence, it has been observed that it is easier for high concentration chemicals to enter human bodies living in areas with deposited materials, thus, causing higher TC incidence.

Since urban areas generally experience a higher TC incidence than rural areas (Fei et al. 2014), in the present Hangzhou study the built-up areas indeed experienced high TC incidence levels: about 29.27 and 8.72/100,000, respectively, for females and males. The influence of soil organic carbon on the distribution of TC incidence was rather small (PD < 0.2). Soil organic carbon has an impact on the adsorption and dynamics of certain chemicals (iodine, heavy metals, persistent organic pollutants etc.) (Dai et al. 2009; Nam et al. 2008; Sikorska-Sobiegraj and Zielinski 2005), which implies that its content affects TC incidence. The above considerations could be the focus of further experimentation and analysis.

As is the case with most similar studies, the present one has certain limitations too. These limitations, which are mainly due to lack of information (age and population mobility records, histological data), are discussed next. First and perhaps most important, the case data obtained from CDC was lacking age information, a fact that restricted our ability to calculate the age-standardized incidence and obtain an assessment of the exposure period. Therefore, the results obtained in this study may not be as conclusive as those that could have been derived using age-standardized incidence, only if the relevant information was available. Secondly, the available household registration information included case location and town population, but not population mobility. Thirdly, when assessing "soil properties-TC incidence" associations, the raster data covered by buildings were defined as "not available" strata, so certain of the results concerning the above associations may be more appropriate for rural rather than for urban regions. Finally as regards the ecological design of this study, it is difficult to adjust for potential confounding problems at the individual level, such as thyrotropin level, medical radiation, and obesity. On the other hand, better access to healthcare and the rising use of thyroid imaging could contribute to the increase of papillary thyroid microcarcinoma incidence, which partly explains the uptrend of TC incidence (Vigneri et al. 2015). However, due to lack of histologic information about TC, we could not measure the contribution of advances in diagnostic practice to the increased TC incidence.

TC etiology still remains largely unknown, although the findings of this study may provide some new hints concerning the matter, as the ecological design of this study, all the results should be explained with cautions and further studies are needed to validate those explanations. Low endemic goiter prevalence, low topographic elevation and low slope were linked to high TC incidence, a finding that implied that excessive iodine exposure could be an important TC risk factor in the study area, given that these variables are iodine status indices, directly or indirectly. Future studies should focus on the association between iodine exposure and TC risk at the individual level.

5 Conclusions

In conclusion, TC incidence in Hangzhou increased sharply in recent years, exhibiting considerable differences between (i) urban versus rural areas, (ii) iodine sufficient versus deficient areas, and (iii) male versus female populations. The distribution of TC incidence in Hangzhou during the time period of interest was spatially heterogeneous, towns in northeast Hangzhou showing a higher incidence than towns in southwest Hangzhou (for both male and female populations). The high TC incidence in Hangzhou was significantly correlated with lower topographic elevation and slope. Moreover, the TC incidence observed in areas with deposited layers was greater than that in areas with eluvium layers. This was particularly valid in rural Hangzhou. This study's findings suggest that excessive iodine exposure may be a risk factor for TC. Policy makers and scientists should pay sufficient attention to this serious disease and focus on the high TC incidence regions described above when attempting to determine disease cause and explore procedures to control and prevent TC. Additional research, including case–control/cohort studies, is needed to examine whether certain factors (e.g., environmental factors, advancing health services and socioeconomic status) are reasons of high TC prevalence. These factors may be also linked to cancerogenesis theories (Portier et al. 2000) when sufficient information becomes available, and also be considered in the context of disease decision-making in conditions of in situ uncertainty (Mikler et al. 2007).

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