Review

Impact of environmental factors on gastric cancer: A review of the scientific evidence, human prevention and adaptation

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Abstract

Globally, gastric cancer (GC) ranks fifth in prevalence and third in fatalities, and shows a distinct geographical distribution in morbidity and mortality. Such a spatial pattern indicates that environmental factors could be an important contributor to GC. We reviewed a total of 135 relevant peer-reviewed articles and other literature published 1936–2019 to investigate the scientific evidence concerning the effects of environmental factors on GC worldwide. Environmental factors affect GC from the aspects of water, soil, air, radiation, and geology. Risk factors identified include water type, water pollution, water hardness, soil type, soil pollution, soil element content, climate change, air pollution, radiation, altitude, latitude, topography, and lithology; and most of them have an adverse impact on GC. Furthermore, we found that their effects followed five common rules: (1) the leading environmental factors that affect GC incidence and mortality vary by region, (2) the same environmental factors may have different effects on GC in different regions, (3) some different environmental factors have similar effects on GC in essence, (4) different environmental factors often interact to have combined or synergistic effects on GC, and (5) environmental factors can affect human factors to have an impact on GC. Environmental factors have a great impact on GC. Human beings may prevent GC by controlling carcinogenic factors, screening high-risk populations and providing symptomatic and rehabilitative treatments. Furthermore, adaptation measures are recommended to reduce GC risk on private and public levels. Future studies should transcend existing empirical studies to develop causal relationship models and focus on vulnerable population analysis.

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Introduction

Gastric cancer (GC) is a highly malignant, fast-growing, mucinous adenocarcinoma (originating from gastric mucosal epithelial cells), and many patients with GC already have partial metastasis at diagnosis. GC was the most common malignancy worldwide according to the first estimates of worldwide frequency of the twelve major cancers in 1975 (Parkin et al., 1984). Although GC incidence has declined in recent decades, it still ranks fifth among the most prevalent cancers (after lung, breast, colorectum and prostate cancers) and is the third most common cause of death from cancer (after lung and colorectal cancers) worldwide (Bray et al., 2018). An estimated 1033,701 new GC diagnoses (5.7% of overall cancer incidence) and 782,685 deaths from GC (8.2% of all cancer mortality) were reported in 2018 (Bray et al., 2018).

GC shows distinct geographical distributions for both morbidity and mortality. Firstly, on a global scale, Eastern Asia, Eastern Europe, and South America have higher GC incidence than Northern Europe, Africa, and North America (Parkin et al., 1984; Bray et al., 2018). Eastern Asia was estimated to have the highest GC incidence (32.1 per 100,000 in men, 13.2 per 100,000 in women), whereas Northern Africa had the lowest (4.7 and 3.0, respectively) in 2018 (Bray et al., 2018). Half of the world’s GC cases occur in East Asia (Ferlay et al., 2015); Korea, Japan, Mongolia, and China have notably high GC incidence rates (Torre et al., 2015). GC mortality follows a similar pattern. East Asia also had the highest GC mortality (28.1 per 100,000 in men, 13.0 per 100,000 in women), whereas North America had the lowest (2.8 and 1.5, respectively) in 2008 (Ferlay et al., 2010). Mid-East Europe and Central and South America also have high GC mortality (for both genders) (Ferlay et al., 2010). In South America, GC mortality is higher in the mountainous regions near the Pacific Ocean and the Andes (Torres et al., 2013). Secondly, GC incidence and mortality also vary on a national/regional scale. For example, in China in 2015, new GC cases are the lowest in the south (24,300) and highest in the east (179,500); GC deaths are the lowest in the south (18,000) and highest in the southwest (141,000) (Chen et al., 2016). Regionally, since 2004, obvious GC clusters have been reported in some “cancer villages” in the Huai River Basin (Yang and Zhuang, 2014). The geographical distribution of GC is also evident in Brazil (Amorim et al., 2014), Spain (Aragones et al., 2009) and Ecuador (Montero-Olas et al., 2017).

GC is a multifactorial disease, and both environmental and human factors are important to its pathogenesis (Freedman et al., 2007; Guggenheim and Shah, 2013). Previous studies pointed out that human factors mainly include diet (Gao et al., 2011; Karimi et al., 2014), socioeconomic level (Nyström et al., 2009; Guggenheim and Shah, 2013), infectious agents (Wu et al., 2015).
et al., 2005; Karimi et al., 2014; Lahmidani et al., 2018) and population characteristics (Straif et al., 1999; You et al., 2000; Bray et al., 2018). Abundant evidence shows that environmental factors are key determinants for GC distribution. First, early studies identified the geographical distribution of GC and pointed out environmental factors that affect GC. The 1936 British Empire Cancer Campaign annual report showed that cancer mortality in England and Wales varied by region, and it speculated that high GC mortality in the adjoining counties of northwest England was related to high precipitation (None, 1936).

![Diagram of environmental factors and human response to gastric cancer]

**Fig. 1** – Main environmental factors and human response to gastric cancer.

<table>
<thead>
<tr>
<th>Set</th>
<th>Type</th>
<th>Sub-type</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>Gastric cancer</td>
<td>Condition</td>
<td>Cancer, gastric cancer, stomach cancer, gastric carcinoma, gastric adenocarcinoma, gastrointestinal cancer, digestive tract cancer, upper gastro intestinal cancers, major cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incidence</td>
<td>Gastric cancer incidence, gastric cancer morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>Gastric cancer death, gastric cancer mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk</td>
<td>Gastric cancer cluster, gastric cancer risk</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Water</td>
<td>Water type</td>
<td>Drinking water source, pond water, river water, mountain spring water, deep ground water, salinity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water pollution</td>
<td>Water pollution, heavy metal pollution, organic matter, wastewater, arsenic (As), lead (Pb), cadmium (Cd), chromium (Cr), selenium (Se), zinc (Zn), nitrate, nitrite, nitrate/nitrite exposure, nitrate/nitrite levels, nitrate/nitrite content</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water hardness</td>
<td>Drinking water hardness, calcium (Ca) ions, magnesium (Mg) ions</td>
</tr>
<tr>
<td></td>
<td>Soil</td>
<td>Soil type</td>
<td>Soil type, river clay soil, sea clay soil, sandy soil, peat soils, reclaim peat soil, porous subsoil, sandstone, red soil, high-reducing soil, flooded soil</td>
</tr>
<tr>
<td></td>
<td>Soil pollution</td>
<td>Soil pollution</td>
<td>Soil pollution, heavy metal element, cadmium (Cd), lead (Pb), chromium (Cr), arsenic (As), organic matter, pesticide, chemical fertilizer, landhill</td>
</tr>
<tr>
<td></td>
<td>Soil element content</td>
<td>Soil element content</td>
<td>Selenium (Se), molybdenum (Mo), iron (Fe), zinc (Zn), cobalt (Co), copper (Cu), zinc/copper ratio (Zn/Cu)</td>
</tr>
<tr>
<td>Air</td>
<td>Climate change</td>
<td>Climate change</td>
<td>Climate change, climate zone, meteorological factor, temperature, humidity, wind speed, precipitation, moisture</td>
</tr>
<tr>
<td></td>
<td>Air pollution</td>
<td>Air pollution</td>
<td>Air pollution, suspended particulate, carcinogenic particle, PM_{2.5}, PM_{10}, nitrogen dioxide (NO_{2}), sulfur dioxide (SO_{2}), petrol station density, vehicle exhaust emissions, coal mine dust, carbon black</td>
</tr>
<tr>
<td>Radiation</td>
<td>Altitude</td>
<td>Altitude</td>
<td>Altitude, elevation</td>
</tr>
<tr>
<td></td>
<td>Latitude</td>
<td>Latitude</td>
<td>Latitude</td>
</tr>
<tr>
<td></td>
<td>Topography</td>
<td>Topography</td>
<td>Topography, landform, plain, mountain, hill, land, sea, geological fault, dipping strata, sloping topography</td>
</tr>
<tr>
<td></td>
<td>Lithology</td>
<td>Lithology</td>
<td>Volcano, granite, limestone, loose rock, volcanic rocks, metamorphic rock, Cambrian strata, tertiary strata, quaternary red sub-sand, sub-clay, Devonian stratum</td>
</tr>
</tbody>
</table>

Table 1 – The list of keywords used to select the literature.
A study found that soil drainage and topography affected GC mortality in Wales (Legon, 1951). Second, previous literature examined the correlation between GC and environmental factors, including multifactor and one-factor correlation. A comprehensive investigation studied the effects of altitude, climate and other environmental factors on GC in Eastern Transylvania, Romania (Málási et al., 1976). A study on the US and Chinese population indicated a positive correlation between latitude and GC mortality (Archer, 1989). Third, some studies used statistical analyses to quantify specific relationships between environmental factors and GC. A study in Spain used Poisson regression analysis to investigate the relationships between GC mortality and altitude, latitude, as well as two human factors (per capita income and diet) (Vioque et al., 1995). Extensive existing literature focuses on correlations between certain environmental factors and GC in some areas, or reviews literature evidence on GC and some environmental factors (also including human factors) in a typical nation (Torres et al., 2013; Ghaffari et al., 2019). However, a comprehensive review focusing on “the impact of the natural environment on GC” is still lacking. This study comprehensively reviewed the effects of environmental factors on GC worldwide and discussed human prevention and adaptation, aiming to provide enlightenment for future prevention of GC and directions for future research.

1. Materials and methods

The review research was directed by a framework (Fig. 1). A one-way arrow represents that the former environmental factor can affect the latter environmental factor, and a two-way arrow represents an interactive effect between two environmental factors, which is derived from a summary of the literature results. A comprehensive literature search was conducted in 2019, using Web of Science/Knowledge, PubMed, Google Scholar, Baidu Scholar, and CNKI. Two sets of terms were used to formulate the searching keywords to select the literature; the returned records include at least one of the two sets (Table 1). The first set depicts basic conditions and aspects of GC such as gastric cancer, gastric cancer incidence, death, risk, and distribution. The second set describes environmental factors including water, soil, air, radiation, and geology.

Fig. 2 – Literature identification, screening, eligibility and inclusion criteria.
Table 2 – Empirical studies concerning effects of trace elements on GC.

<table>
<thead>
<tr>
<th>Element</th>
<th>Region</th>
<th>Factor</th>
<th>Relation</th>
<th>Empirical evidence and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se</td>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>–</td>
<td>There is a significant negative correlation between Se and GC mortality in men (Nakaji et al., 2001).</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Soil</td>
<td>–</td>
<td>The loose combination of selenite and soil in low GC incidence area is more conducive to Se absorption by plants and water systems (Weerasooriya et al., 1989).</td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td>Soil</td>
<td>–</td>
<td>Low Se level in soil correlates with high GC risk areas (Armijo et al., 1981).</td>
<td></td>
</tr>
<tr>
<td>the United States</td>
<td>Soil</td>
<td>–</td>
<td>Decreased GC mortality occurs in areas with high Se levels (Shamberger et al., 1976).</td>
<td></td>
</tr>
<tr>
<td>Mo</td>
<td>China</td>
<td>Soil</td>
<td>–</td>
<td>High Se exposure has been found to reduce GC risk (Vinceti et al., 2014).</td>
</tr>
<tr>
<td>Fujian, China</td>
<td>Soil</td>
<td>–</td>
<td>Mo content of soil is low in areas with high GC incidence (Chen, 2008).</td>
<td></td>
</tr>
<tr>
<td>Changle, Fujian</td>
<td>Soil</td>
<td>–</td>
<td>Mo content of soil is low in areas with high GC incidence (Chen, 2009).</td>
<td></td>
</tr>
<tr>
<td>Jiangxi, China</td>
<td>Soil</td>
<td>–</td>
<td>Available Mo content in soil is negatively correlated with GC mortality (Wu et al., 1996).</td>
<td></td>
</tr>
<tr>
<td>Fe</td>
<td>Costa Rica</td>
<td>Soil</td>
<td>+</td>
<td>GC incidence is positively correlated with Fe concentration in soil (Sierra and Barrantes, 1983).</td>
</tr>
<tr>
<td>Fujian, China</td>
<td>Soil</td>
<td>–</td>
<td>Fe has an important inhibitory effect on GC (You et al., 1995).</td>
<td></td>
</tr>
<tr>
<td>Soil</td>
<td>–</td>
<td>Plant ferritin is affected by Fe content in soil, and can reduce the risk of GC in consumers (Zielinska-Dawidziak, 2015).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co</td>
<td>North Wales and Cheshire</td>
<td>Soil</td>
<td>+</td>
<td>GC incidence is positively correlated with Co content in soil (Stocks and Davies, 1960).</td>
</tr>
<tr>
<td>Zn</td>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>–</td>
<td>There is a significant negative correlation between Zn and GC mortality in men (Nakaji et al., 2001).</td>
</tr>
<tr>
<td>North Wales and Cheshire</td>
<td>Soil</td>
<td>+</td>
<td>GC incidence is positively correlated with Zn content in soil (Stocks and Davies, 1960).</td>
<td></td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Soil</td>
<td>–</td>
<td>GC incidence is negatively correlated with Zn concentration in soil (Sierra and Barrantes, 1983).</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Soil</td>
<td>–</td>
<td>There is a negative correlation between GC mortality and available Zn in soil (Jackson et al., 1986).</td>
<td></td>
</tr>
<tr>
<td>Cu</td>
<td>Wales</td>
<td>Soil</td>
<td>+</td>
<td>People in areas with copper-deficient soil may be more susceptible to GC (Legon, 1952).</td>
</tr>
<tr>
<td>Cr</td>
<td>Liaoning, China</td>
<td>Water</td>
<td>+</td>
<td>GC mortality is directly proportional to exposure to hexavalent chromium in water (Beaumont et al., 2006).</td>
</tr>
<tr>
<td>North Wales and Cheshire</td>
<td>Soil</td>
<td>+</td>
<td>GC incidence is high in areas with high Cr content in soil (Stocks and Davies, 1960).</td>
<td></td>
</tr>
<tr>
<td>Isfahan, Iran</td>
<td>Soil</td>
<td>+</td>
<td>High Cr levels in soil exist in areas with high GC incidence (Mohajer et al., 2013).</td>
<td></td>
</tr>
<tr>
<td>Pb</td>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>+</td>
<td>There is a significant positive correlation between Pb content and GC mortality in men (Nakaji et al., 2001).</td>
</tr>
<tr>
<td>Guangdong, China</td>
<td>Water</td>
<td>+</td>
<td>Long-term exposure to Pb will increase GC mortality (Wang et al., 2011b).</td>
<td></td>
</tr>
<tr>
<td>Dabaoshan, Guangdong</td>
<td>Water</td>
<td>+</td>
<td>Pb exposure is positively correlated with GC mortality (Wang et al., 2011a).</td>
<td></td>
</tr>
<tr>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>–</td>
<td>There is a significant negative correlation between Pb content and GC mortality in women (Nakaji et al., 2001).</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>Soil</td>
<td>+</td>
<td>Pb concentration in soil was positively correlated with GC incidence (Türkdogan et al., 2003).</td>
<td></td>
</tr>
<tr>
<td>Anhui, China</td>
<td>Soil</td>
<td>+</td>
<td>Pb concentration in soil was positively correlated with GC risk (Zhao et al., 2014).</td>
<td></td>
</tr>
<tr>
<td>As</td>
<td>Simav Plain, Turkey</td>
<td>Water</td>
<td>+</td>
<td>GC risk is positively correlated with As concentration in drinking water (Gunduz et al., 2009).</td>
</tr>
<tr>
<td>Suzhou, China</td>
<td>Soil</td>
<td>+</td>
<td>As concentration in soil can increase GC mortality (Chen et al., 2015).</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Soil</td>
<td>+</td>
<td>As concentration in soil was positively correlated with GC mortality (Nunez et al., 2016).</td>
<td></td>
</tr>
<tr>
<td>Kurdistan, Iran</td>
<td>Soil</td>
<td>+</td>
<td>As concentration in soil was positively correlated with GC mortality (Eskandari et al., 2015).</td>
<td></td>
</tr>
<tr>
<td>Antofagasta, Chile</td>
<td>Soil</td>
<td>+</td>
<td>High As exposure in areas is associated with low GC risk (Armijo et al., 1981).</td>
<td></td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>Turkey</td>
<td>Soil</td>
<td>+</td>
<td>Cd concentration in soil was positively correlated with GC incidence (Türkdogan et al., 2003).</td>
</tr>
<tr>
<td>Guangdong, China</td>
<td>Water</td>
<td>+</td>
<td>Long-term exposure to Cd will increase GC mortality (Wang et al., 2011b).</td>
<td></td>
</tr>
<tr>
<td>Dabaoshan, Guangdong</td>
<td>Water</td>
<td>+</td>
<td>Cd exposure is positively correlated with GC mortality (Wang et al., 2011a).</td>
<td></td>
</tr>
<tr>
<td>Strontium (Sr)</td>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>+</td>
<td>There is a significant positive correlation between Sr content and GC mortality (Nakaji et al., 2001).</td>
</tr>
<tr>
<td>Au</td>
<td>Aomori Prefecture (Japan)</td>
<td>Water</td>
<td>+</td>
<td>There is a significant positive correlation between Au content and GC mortality in women (Nakaji et al., 2001).</td>
</tr>
<tr>
<td>Thorium (Th)</td>
<td>Qingzhou City</td>
<td>Soil</td>
<td>–</td>
<td>High Th levels in soil exist in areas with low GC incidence (Mao, 2012).</td>
</tr>
</tbody>
</table>

+: positive correlation; --: negative correlation.
Three criteria were primarily used when selecting literature from search results. First, this review mainly includes peer-reviewed articles. Some highly relevant reports, books, and websites are also included, even though they are in small quantity. Second, the selected literature focused on the relationship between environmental factors and GC, including multiple study types, such as observational studies and experimental studies. Third, we mainly searched newly published studies but also included some early milestone papers. The finally included papers were published from 1936 to 2019.

Originally, 2868 publications in all were identified based on the search keywords. Based on the inclusion criteria of affecting factors for GC, 1835 references were retained for further review. Afterward, 1548 references were excluded after further review of the title and abstract. Finally, 135 articles were selected for this review research based on the full text of the remaining papers. Most of these articles focus on the effects of environmental factors on GC in high-risk areas such as Europe, Asia, and South America, and relatively low-risk effects of environmental factors on GC in high-risk areas such as the remaining papers. Most of these articles focus on the effects of environmental factors on GC in high-risk areas such as Europe, Asia, and South America, and relatively low-risk regions including North America, Africa, and Australia. The process of literature identification, screening and inclusion, and reasons for exclusion at each step are shown in Fig. 2.

2. Results

2.1. Water and GC

2.1.1. Water type

The relationship between drinking water type and GC incidence has been widely studied (Allenprice, 1960; Zhang et al., 1999). Drinking pond water, river water or shallow groundwater was found to increase GC incidence in Zanhuang County, Hebei Province of China (Zhang et al., 1999) and Eastern Transylvania (Málnási et al., 1976), whereas low GC incidence occurs in some areas with deep groundwater in France (Tromp and Diehl, 1954). In addition, long-term consumption of highly saline drinking water can damage the gastric mucosa and trigger GC (Chen, 2008).

2.1.2. Water pollution

Water pollution is an important contributor to GC. The geographical distribution of Chinese “cancer villages” is highly associated with polluted rivers. Nearly 60% of “cancer villages” are within 3 km of the rivers and 81% within 5 km (Gong and Zhang, 2013). GC incidence was found to be related to water pollution in some areas of the Huai River Basin (Wan et al., 2011), and GC mortality tended to rise in counties with severe water pollution (Ren et al., 2014). In Shijiazhuang, Hebei Province of China, GC mortality in waste-water areas is higher than in clean-water areas (Massagué et al., 2015). Some specific substances in contaminated water also reportedly affect GC incidence. A study of eleven counties in Fujian Province found that contamination of water with organic matter could cause high GC incidence (Wang et al., 1997). In addition, many studies examine the effects of heavy metal pollution in water on GC, as listed in Table 2. The ability of GC cells to invade and metastasize is enhanced when exposed to heavy metals (Yuan et al., 2016). Some heavy metal elements in water were found positively correlated with GC incidence/mortality, such as cadmium (Cd), lead (Pb), arsenic (As) and chromium (Cr); while others were negatively correlated with GC mortality in men, including selenium (Se) and zinc (Zn). For example, GC risk is positively correlated with As concentration in drinking water supply areas in villages of the Simav Plain in Turkey (Gunduz et al., 2009, 2015). Some studies on water and crop heavy metal pollution revealed a correlation between GC risk and long-term environmental exposure to Pb and Cd (Wang et al., 2011a, 2011b). In addition, in Liaoning Province, GC mortality is directly proportional to exposure to hexavalent Cr in water (Beaumont et al., 2006). Furthermore, the contamination of nitrate/nitrite content in drinking water can also affect GC incidence and mortality (Jensen, 1982; Sandor et al., 2001). Nitrate and nitrite can be converted into nitrosamines in the stomach, which are potent carcinogens (Jensen, 1982). A higher level of nitrate content in drinking water is consistent with higher GC incidence in northern Jutland of Denmark (Jensen, 1982), Colombia (Cuello et al., 1976), and Zanhuang County (Zhang et al., 1998). Specifically, long-term exposure to drinking water with nitrate concentrations above 45 mg/L increased GC incidence in Central India (Taneja et al., 2017); in Taiwan, when the nitrate concentration in drinking water was greater than 0.45 mg/L, the odds ratio of GC was 1.14 (Yang et al., 1998); and when the nitrate exposure in drinking water was greater than 0.38 ppm, the OR was 1.16 (Chiu et al., 2012). In the Baranya County of Hungary, when water nitrate content was higher than 88 mg/L, GC risk was significantly increased (Sandor et al., 2001). Furthermore, nitrate/nitrite content in drinking water is closely related to the occurrence and development of GC (Zhang et al., 1998). Gastric histology changes were found to be related to drinking water quality and nitrate levels in Moping county of Shandong Province (Xu et al., 1992). Besides, high nitrate content in water was related to pre lesions of suspected GC in Colombia (Cuello et al., 1976).

2.1.3. Water hardness

Water hardness is also an important indicator reflecting drinking water’s effect on GC. WHO reported that hard water has no known adverse effects on human health (Sengupta, 2013), and many studies pointed out a prominently negative correlation between drinking water hardness and GC mortality in Taiwan (Yang et al., 1997, 1998; Chiu et al., 2012). GC mortality in soft-water areas is higher than in hard-water areas in England and Wales (Turner, 1962). The same result is found in Zanhuang County. Drinking water hardness in high-GC risk areas is lower than that in the low-risk areas (Zhang et al., 1999). Water hardness is measured by concentrations of calcium (Ca) and magnesium (Mg) ions in water. Ca and Mg ions are reportedly protective against GC (Blondell, 1980; Lipkin and Newmark, 1985), and softer water will enhance the dissolution of toxic substances in the pipelines into drinking water (Yang et al., 1997). These partly explain the effect of drinking water hardness on GC.

2.2. Soil and GC

The relationships among soil, vegetation and food (Tromp and Diehl, 1955) imply that substances in soil are transmitted through the food chain, and accumulate in consumers’ bodies, with possible effects on carcinogenesis (Fei et al., 2018). Soil
impacts GC through soil type, soil pollution, and soil element content.

2.2.1. Soil type
A survey in the Netherlands found that the GC mortality followed the order of “river clay soil < sandy soil < peat soil < sea clay soil < reclaimed peat soil” (Tromp and Diehl, 1955). Some studies in London indicated that GC incidence was high in peat soil areas, which have poor soil drainage and generally grow crops with fewer nutrients and copper (Cu) deficiency (Legon, 1951; Legon, 1952). In areas with relatively good drainage, such as those with porous subsols (including sandstone and limestone), GC incidence is lower (Tromp and Diehl, 1954; Malmäsi et al., 1976). Several counties with calcareous soils in the western United States and others with acidic sandy soils in north Wisconsin have high GC incidence, and most of the soils have low available Zn (Jackson et al., 1986). Other studies showed that GC mortality in red soil areas was low, but was higher in areas with soils rich in decaying organic matter or flooded soil (Legon, 1951, 1952).

2.2.2. Soil pollution
Two types of soil pollution have been found to be correlated with GC. First, exposure to heavy metal contaminated soil can increase GC incidence and mortality, especially As, Cd, Pb, and Cr (Zhao et al., 2014; Nunez et al., 2016). In Suzhou of China, an increase in As concentration in soil by 1 ppm was positively associated with a 11.1% increase in GC mortality (Chen et al., 2015). This positive correlation also exists in Kurdistan, Iran (Eskandari et al., 2015; Nunez et al., 2016). The levels of Cd and Pb in soil are positively correlated with GC incidence in Turkey (Türkdoğan et al., 2003). A statistically significant correlation of Pb topsoil levels with GC risk was also observed in Anhui Province, China (Zhao et al., 2014). Second, soil pollution by organic matter also leads to increased GC incidence and mortality (Bhat et al., 2015; Ciaula, 2016). A study in Kashmir showed that 22.3% of GC patients suffered from soil pollution, of which 21.6% and 38.6% of patients were respectively exposed to fertilizers and pesticides almost every day (Bhat et al., 2015). In agricultural provinces of Chile, the consumption of nitrate fertilizers is proportional to GC mortality (Zaldivar and Wetterstrand, 1975), and GC mortality is positively correlated with cumulative exposure to nitrogen fertilizers per capita (Armiño and Coulson, 1975). Furthermore, long-term use of chemical fertilizers may cause the accumulation of heavy metal elements in soil (Mohajer et al., 2013). In the Apulia region of southern Italy, men living in communities near landfills had an increased risk of GC, which is probably due to some toxic chemicals and microbes in the surrounding environment, including soil (Ciaula, 2016). In Sydney, some high-risk populations for GC were found to be affected by long-term exposure to industrial emissions and toxic waste (Burnley, 1991).

2.2.3. Soil element content
Elements in soil affect GC incidence and mortality, especially the trace elements needed by the human body. For example, Se required by the human body is derived from plants, so it is very dependent on the element content in soil (Ryan-Harshman and Aldoori, 2005). Trace elements have complex biochemical functions that synergize or inhibit each other to maintain a balanced state, and their absence or excessive intake can cause diseases, including cancers (Liu et al., 2006). Based on the reviewed literature, the effect of trace elements in soil on GC was also summarized as shown in Table 2. The analysis showed that some trace elements had a consistent effect on GC in most study areas, such as molybdenum (Mo); but such effect for other elements is inconsistent in varying regions, such as iron (Fe) and Zn. Firstly, the contents of some trace elements in soil were found to be negatively correlated with GC. For example, high Se exposure in soil could reduce GC risk in Sri Lanka (Weerasooriya et al., 1989) and Chile (Armiño et al., 1981), because Se can restrain tumor cell proliferation, and acts synergistically with vitamin E to reduce damage by free radicals in human tissue (Thompson, 1984; Chen, 2008). Mo can inhibit the carcinogenic effect of nitrates and nitrates, and Mo deficiency in soil can weaken nitrite fixation in plants, leading to increased human nitrite intake and storage, which may increase GC risk (Jackson et al., 1986; Chen, 2008, 2009). Zn, almost all coming from food, is an essential component of many enzymes in the human body (Prasad, 1985), and its deficiency leads to poor immune function and increases cancer incidence (Liu et al., 2006). Secondly, some other trace elements in soil are positively correlated with GC incidence and mortality, especially heavy metal elements, which has been elaborated above. Thirdly, the effects of trace elements in soil on GC are usually dependent on the combined action of elements rather than a single one. A study found that single heavy metal elements did not significantly affect GC incidence, but would do so in synchronization, such as Cr–Cd, Cr–Pb, and Cd–As (Yuan et al., 2016; Fei et al., 2018). In another study, Zn and Cu were found to have antagonistic effects, and the Zn/Cu ratio was positively correlated with GC mortality (Stocks and Davies, 1964; Rose and Sarner, 1965). The effects of trace elements in soil on GC are complex and may have synergistic or antagonistic effects. Therefore, discussion on the effects of a single element on GC may be insufficient and sometimes even misleading (Yan et al., 2009).

2.3. Air and GC

2.3.1. Climate change
GC incidence is clearly related to climate change. First, the zonal distribution of GC is related to the climate zone. In China, the provinces with higher GC mortality are located in the climate zones of the Qinghai–Tibet Plateau and arid or semi-arid temperate zone; the provinces with lower rates are located in tropical and subtropical humid regions, except Beijing, located in the semi-humid warm temperate zone (Lin and Zhang, 1985). Second, some meteorological factors affect regional GC incidence. Meteorological factors related to high GC incidence in coastal areas include temperature, wind speed and humidity (Liu, 2002). GC incidence in cold areas is higher than in warm areas of Eastern Transylvania, Romania (Malmäsi et al., 1976). High GC mortality in the counties of northwest England is related to high precipitation. The coastal Fujian Province, a high-risk area for GC, is affected by the warm and humid southeast wind all year round, with more precipitation in spring and summer (Liu, 2002). According to a
Air pollution is positively associated with GC incidence and mortality, and it impacts GC mainly through suspended particles, which can be directly inhaled and enter the stomach. A positive correlation existed between PM$_{2.5}$ and GC incidence, and an increase of 5.0 $\mu$g/m$^3$ PM$_{2.5}$ increased GC risk by 38% (Nagel et al., 2018), probably due to sulfur (S) in PM$_{2.5}$ (Weinmayr et al., 2018). In the Cancer Prevention Study II, near-source PM$_{2.5}$ was found to be positively associated with GC mortality (Turner et al., 2017). In Buffalo of New York, areas with high particulate pollution had twice the GC mortality of low-pollution areas, regardless of economic and ethnic influences (Winkelstein and Kantor, 1969). Besides, people living in areas with high petrol station density, an indicator of traffic air pollution, had an increased risk of death from GC in Taiwan (Chiu et al., 2011). Vehicle exhaust emissions increased inhalable carcinogenic particles in the air, thus delivering carcinogens directly to the stomach. Furthermore, GC is positively correlated with dusty occupations (Meyer et al., 1983). High GC mortality in rubber workers is associated with dust exposure in Germany (Straif, 2000). Similar studies found that high GC incidence in coal miners may be related to the inhalation of coal mine dust (Ames, 1983; Ong et al., 1983). Workers with long-term exposure to carbon black have a higher GC incidence (Gold, 1975).

2.4. Radiation and GC

Radiation exposure is an invisible risk factor for GC (Lee and Derakhshan, 2013). First, the presence of a radiation source is a risk factor for GC. For German uranium miners, even exposure to low doses of radiation was a risk factor for GC (Kreuzer et al., 2012). GC mortality in uranium mines in New Mexico is also high (Wilkinson, 1985). Alpha and beta radiation are both high in all lakes around Van City, a high-risk area for GC in Turkey (Akan et al., 2014). The higher GC morbidity in volcanic areas may be related to the high radiation level of volcanic soil (Amani et al., 2015). Second, radiation has a long-term effect on GC incidence and mortality. Studies on survivors of the atomic bombings in Hiroshima and Nagasaki in Japan showed that exposure to ionizing radiation increased GC risk, and survivors had a higher mortality rate from cancers, including GC (Sauvaget et al., 2005; Goto et al., 2012).

2.5. Geology and GC

2.5.1. Altitude

Altitude is conceived as a very important environmental factor for GC. Abundant literature has discussed the association between altitude and GC incidence and mortality (Bonequi et al., 2013; Torres et al., 2013). Higher GC incidence is seen at higher areas in Spain (Vioque et al., 1995); and GC incidence increases with altitude in the Ardabil Province of Iran (Amani et al., 2015). A positive correlation was indicated between altitude and GC risk in Latin America (Torres et al., 2013). Higher GC incidence and mortality are also found in high-altitude areas of Ecuador (Carrido and Carrido, 2018). The same pattern also exists in eastern Kenya (Mcfarlane et al., 2001). Altitude affects GC both directly and indirectly. The direct effect is reflected in many studies. In Ecuador, high-altitude provinces have the highest standardized GC mortality (Montero-Oleas et al., 2017). GC incidence increases with altitude in Qingzhou City, Shandong Province, China (Mao et al., 2011). Altitude also affects GC indirectly by impacting its important risk factors. Firstly, food limitation (such as insufficient consumption of fresh fruits and vegetables), nutritional deficiency, and low soil Se content in high-altitude areas are promoting factors for GC (Kabuto et al., 1994; Vioque et al., 1995). Cows in highlands of the Andes of Venezuela usually eat bracken fern and people ingest ptaquiloside through milk, which increases GC risk (Alonso-Amelot and Avendano, 2001). Secondly, Helicobacter pylori is recognized by the WHO as a primary carcinogen (Pounder and Ng, 1995), and its prevalent genotypes and haplotypes vary by altitude. Most $H$. pylori strains in the Tumaco region on the Pacific coast are of African origin, whereas those in the neighboring Andean Pasto region of Colombia have a more severe European ancestry (Sablet et al., 2011). Thus, severe $H$. pylori strains may cluster in high-altitude mountainous areas and lead to higher GC risk (Torres et al., 2013). Lastly, altitude may be a surrogate for host cytokine genotypes. Riskier genotypes may easily cluster in isolated mountains in western Honduras (Morgan et al., 2006).

2.5.2. Latitude

Higher GC incidence occurs in high-latitude areas, which may be due to geography and solar exposure (Adeola et al., 2018). GC mortality among Caucasian Americans is highest in the northwestern and northern central states, and lowest in the southwestern states (Ren et al., 2007). In Japan, northern and central counties have higher GC mortality rates. The United Kingdom, Iceland, Italy, and Spain have similar patterns (Vioque et al., 1995; Ren et al., 2007). In China, most areas with high GC incidence are located above 30°N, and low-incidence areas are located below 30°N (Lin and Zhang, 1985).

2.5.3. Topography

Topography affects GC incidence from three aspects. First, some geological structures could affect GC incidence. Most high-incidence areas in China are located at geologic fault zones, which may affect drinking water (Yang et al., 1987), or cause the formation of fault basins with high levels of mercury (Hg), gold (Au) and barium (Ba) (You et al., 1995). Furthermore, GC incidence is relatively low in dipping strata and sloping topography due to their good drainage (Tromp and Diehl, 1954), but generally high in low-lying areas because of their poor drainage and moist soil (Segi and Kurihara, 1960). Second, land and sea location is also...
important. In Fujian Province, the high-GC incidence areas are mostly located in coastal plains, possibly because low-lying land and poor water flow easily lead to water pollution and high contents of nitrite in water (You et al., 1995), which both contribute to GC incidence. However, GC mortality in the inland areas is higher than in the coastal areas of Spain (Palmeiro et al., 1988). Furthermore, landform types are also related to GC incidence, and high GC incidence is mostly found in hill or mountain areas. GC incidence tends to decrease from the southwest hills to the northeast plains in Qingzhou City (Mao et al., 2011), and from mountain areas to plain areas in the Romagna region of Italy (Mancini et al., 2015). A similar discovery was found in the Taihang Mountains, a high-GC risk region in Northern China (Deng et al., 2010).

2.5.4. Lithology
Lithology could affect GC from two perspectives. First, GC incidence is closely related to rock types, as different rock types can affect local soil and water. In China, most high-GC incidence areas are concentrated in volcanic and metamorphic regions, whereas low-GC incidence areas are mostly located in limestone regions (Ren et al., 2007). In Fujian Province with high GC incidence, the geological background is volcanic rocks and granite of similar components (You et al., 1995). GC incidence in Huaxi District of Guiyang in China is low, where 70% of the local geology is limestone (Ren et al., 2007). Furthermore, adjacency to a volcano can increase GC risk in the Ardabil province of Iran (Amani et al., 2015). Second, different strata affect GC incidence and mortality. In Qingzhou City, most areas with high GC incidence are covered with Cambrian strata, whereas low-incidence areas are covered with quaternary red sub-sand and sub-clay (Mao et al., 2011). GC mortality is higher in areas with highly mineralized Devonian stratum in West Devon (Allenprice, 1960). In Henan Province of China, exposed tertiary strata are highly correlated with GC mortality (Yang et al., 1988).

The reviewed literature indicates some general patterns concerning the effects of environmental factors on GC. First, the leading environmental factors that affect GC incidence and mortality vary by region. For example, water pollution is the leading factor in the “cancer villages” of China (Yang and Zhuang, 2014), but adjacency to a volcano is a predominant factor in volcanic areas (Amani et al., 2015). Second, in different regions, the same environmental factors may have different effects on GC. This may be because the risk of GC in

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<td>Latitude</td>
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different regions is determined by many factors, and only studying the relationship between one factor and GC incidence cannot reflect the real situation. For example, GC incidence increases with altitude in Spain, but altitude has no definite effect on GC in Chile, where the risk of GC is more related to ethnicity and socio-economics (Torres et al., 2013; Vioque et al., 1995). Diversity of exposure ranges and different data grouping criteria might be a reason for the heterogeneity of different research results such as in Taiwan (Yang et al., 1997) and Santiago (Zaldívar and Wetterstrand, 1978). There is a negative correlation between Zn concentration in soil and GC incidence in Costa Rica (Sierra and Barrantes, 1983), but a positive correlation in North Wales and Cheshire (Stocks and Davies, 1960). This may be due to the influence of other substances in soil. For example, Cu in soil can act in conjunction with Zn to affect GC (Stocks and Davies, 1960). Third, some different environmental factors have similar effects on GC in essence. Water systems originate from strata and sedimentary soil, so they have a similar effect on GC (Allenprice, 1960; Oliver, 1997). Some studies found that heavy metal pollution increased GC risk, whether in soil or water (Wang et al., 2011a, 2011b). These findings imply that some substances in the environment are key determinants for local GC conditions. Fourth, although studies usually investigate the effects of a single or one type of environmental factor on GC, different environmental factors often interact to have combined or synergistic effects on GC. Altitude, latitude, and topography all have an impact on the climate, topography and lithology also affect water and soil, and these factors influence GC through such complex relationships. The interactive effect of environmental factors on GC is shown in Fig. 1 and summarized in detail in Table 3. Geological faults often cause loss of deep groundwater (Yang et al., 1986). In Jiyuan County, Henan Province, GC incidence for residents who drank shallow surface water was higher than that of residents who drank mountain spring water or deep groundwater (Yang et al., 1987). Some elements in the environment also interact to affect GC (Table 2). Iron group elements have an obvious inhibitory effect on GC, especially Fe with cobalt (Co) (You et al., 1993). Last, environmental factors could affect human factors to affect GC. Altitude impacts both H. pylori and host cytokine genotypes, and thus exerts an effect on GC incidence (Torres et al., 2013). Regional differences could affect local residents’ eating habits. Residents of arid regions may eat more preserved foods (e.g., pickles) and fewer fresh fruits and vegetables, whereas residents of some coastal areas tend to eat salted fish and fish sauce, leading to a higher GC incidence in both types of areas (Hu et al., 1984; Ye et al., 1994). In addition, the elemental content in soil would also affect local food quality. A study in the Hunan Province of China indicated that white rice grown in soil contaminated with heavy metals also contained excessive heavy metal elements, which could affect consumers’ health through the food chain (Lei et al., 2015).

3. Human prevention and adaptation

Environment will continue to influence the health risk for GC, through the effect of a single factor or the combined effect of multiple factors. For human society, taking prevention and adaptation measures is one of the most effective ways to control health effects. Prevention means to take measures in advance to ensure that GC will not occur, and adaptation means to take measures in many ways to cope with changes in the natural environment and human society to reduce the risk of GC.

Prevention is the best way to reduce GC incidence and mortality and can be conducted at three levels. Primary prevention refers to the control of GC carcinogenic factors, which is closely related to the environmental factors mentioned earlier. Risk factors considered in primary prevention are divided into changeable and unchangeable ones (Sitaz et al., 2018). Changeable factors include diet, tobacco, alcohol, and obesity for patients, H. pylori eradication and medication such as aspirin and Non-Steroidal Anti-inflammatory Drugs for doctors (Karimi et al., 2014). People should focus on improving personal hygiene and drinking water quality (such as not drinking raw water and river water), installing household water purification devices, and appropriately improving the diet according to the local soil conditions, such as supplementing the beneficial trace elements that are deficient in the soil. Unchangeable factors include family history, occupational exposure, and comorbidities (Sitaz et al., 2018). Workers in special occupations, such as rubber workers and coal miners, should strengthen protective measures to reduce exposure to dust and other harmful substances. In addition, the government should actively manage environmental pollution and reduce the emergence of “cancer villages”, and improve the living and working environment of the high-risk population for GC. It is necessary to strengthen the detection of environmental contaminants, especially the control of heavy metal pollution and the emission of pollutants (Wang et al., 2011b; Yuan et al., 2016; Fei et al., 2018). Secondary prevention refers to the screening of high-risk populations for GC. High-risk patients with family histories of GC, or people in high-risk areas but without clear chronic gastric symptoms, must be screened. In high-GC risk areas, any H. pylori infection should be documented and instantly treated (Correa and Piazuelo, 2010). Secondary prevention may be suitable for areas with high GC incidence (such as Japan), but might be unnecessary in low-GC incidence areas, such as the USA (Correa et al., 2004). Tertiary prevention improves the patients’ condition mainly through symptomatic treatment and rehabilitation, to finally enhance the survival rate of GC (Fock, 2014). For example, people could take proactive measures to improve the living quality of patients in high-risk areas, such as supplementing the nutrients that are lacking in the area or avoiding exposure to a harsh environment favorable for GC incidence.

The risk of GC may be reduced with appropriate adaptation measures on private and public levels. On the one hand, keeping a healthy lifestyle is recommended for individuals or families in high-risk or GC-prone areas, including maintaining a healthy diet (such as quitting drinking and smoking) and insisting on regular stomach checkups (Karimi et al., 2014). For example, residents of the coastal areas of Fujian Province, a high-risk area for GC in China, should reduce their consumption of fish sauce. On the other hand, the local or national governments should formulate relevant policies for screening of high-risk populations for GC, because only early detection and treatment can reduce GC mortality (Leung et al.,...
2008). Some successful policies in Japan on GC screening have proved this. Since 1960, various laws and regulations have been formulated to guide GC screening (Oshima, 1994; Asaka and Mabe, 2014; Hamashima, 2018a); for example, the Law on the Health and Medical Services for the Aged, established in 1983 (Oshima, 1994), and the guidelines for screening GC, introduced in 2003 (Hamashima, 2018a). Therefore, the proportion of GC deaths in all cancer deaths decreased from 45.6% in 1960 to 13.6% in 2012 (Oshima, 1994; Hamashima, 2014). Besides, establishing special gastroenterology clinics and regularly following up on susceptible patients can facilitate early detection, diagnosis, and treatment of GC (Cancer Health Center, 2012). However, the specific choice of GC screening is dependent on the population size and economic status of a country. For China, with large population and high GC incidence, it is very difficult to widely popularize GC screening. So, presently only two economical and simple methods are used in initial screening for examiners to determine whether an X-ray or gastroscopy is further needed (Liang, 2009). One is to use computer models to recognize patterns of medical history and symptoms (Liang, 2009), and the other is to collect gastric juice first and then conduct occult-blood or biochemical examination (Li, 2018). The “two-round screening method” was conceived as an economical GC screening program worthy of promoting in high-risk areas (Liang, 2009). In Zhuanghe City of Liaoning Province of China, the cost-benefit ratio for GC screening using this method is 1:2.6 (Pan et al., 2005). Considering the cost-effectiveness of GC screening, the target age group and screening interval must be clearly defined to optimize the allocation of medical resources (Leung et al., 2008; Hamashima, 2018a). Some studies showed that the initial age of GC screening could be defined as 50 years old, and the screening interval could be defined as 2–3 years, but these results require further research to clarify (Jun et al., 2017; Hamashima, 2018b).

4. Discussion

Although many previous studies have investigated the relationship between environmental factors and GC, there are still two main challenges: inadequate inter-disciplinary collaboration, and studies that are mainly empirical. Therefore, for future research, three aspects should be given priority. First, scientific advances are needed to transcend empirical observations of the relationship between environmental factors and changes in GC and to reach more expositive conclusions. This improvement to the interpretative approach is subject to our knowledge about the net-result of health implications on GC; it is also subject to our comprehension of the net-health effects incurred by changes in various environment variables. Second, developing reliable models that describe the effects of key environmental factors on GC requires quantifying causal relationships. Based on such models, the health impacts (such as disease burden and relative risk) of key environmental factors for GC could be predicted. The models also set a foundation for the adoption of proper prevention measures. Third, the analysis of vulnerable populations for GC should be paid due attention since it could provide a valuable reference to reasonably allocate medical resources. So, identifying high-risk groups and adopting suggestions derived from projections based on developed models could realize the prevention of GC at its earliest stage and to the maximum extent.

5. Conclusions

GC is a malignant tumor with distinct geographical distribution in the world. This review summarizes the effects of environmental factors on GC worldwide and nationwide, including water, soil, air, radiation, and geology. Risk factors identified include water type, water pollution, water hardness, soil type, soil pollution, soil element content, climate change, air pollution, radiation, altitude, latitude, topography and lithology; and most of them have an adverse impact on GC. Furthermore, we found that the effect of environmental factors on GC followed five common rules. Despite the fact that environmental factors have a significant or adverse effect on GC, human beings may take appropriate preventive and adaptive measures to reduce GC risk.

Declaration of interest

None.

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