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Disparity of nitrate and nitrite in vivo in cancer villages as compared to other areas in Huai River Basin, China

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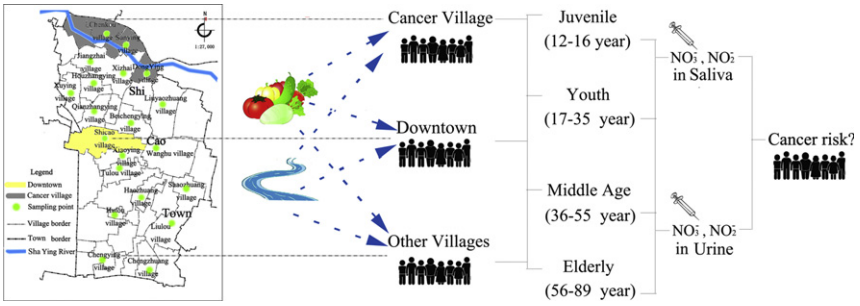
HIGHLIGHTS

- Higher levels of nitrate/nitrite concentration in saliva and urine samples are found in cancer villages.
- Nitrite content in saliva samples of the youth group was found to be more than two times higher than that of the average level in the control group.
- The level of nitrate and nitrite content in sample increases with age, peaks in the middle-age group and decreases in the elderly group.
- The intense use of chemical fertilizer in cancer villages is suspected to be the cause of high nitrate and nitrite in local environments.

GRAPHICAL ABSTRACT



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ABSTRACT

Saliva and Urine samples were collected for the study on how nitrate and nitrite concentration in human body may be related to the corresponding health risk in a high cancer incidence area. The study area includes three known cancer villages in Huai River basin, China. The results of analyzing collected sample show that there are higher levels of nitrate and nitrite concentration in human saliva and urine sample collected in the study area as compared to those collected in other areas. In addition, levels of nitrate and nitrite concentration in saliva and urine sample change significantly with the ages of sampled population. NO3-concentrations in saliva and urine sample are the most outstanding among the middle-aged and elderly populations. It means that the middle-aged and elderly populations have relatively high vivo nitrate reductive transformation rates and they also have higher N-nitroso compounds synthesis risks in the studied cancer villages.

1. Introduction

Nitrate pollution has been a common and important global environmental problem (Pérez-Martína et al., 2016; Zirklea et al., 2016). While there is no clear evidence from toxicology experiments to support a definitive relationship between human body's exposure to nitrate and nitrite and the formation of cancer (Forman, 1987; Knekt et al., 1999;

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National Toxicology Program, 2001; Ward et al., 2005; Frerart et al., 2009;Muntané and la Mata, 2010; Bryan et al., 2012; Zirklea et al., 2016), results from existing environmental and epidemiological studies have shown that exposure to an environment that is rich in nitrate and nitrite is closely related to the cancer incidence and mortality (Ward et al., 2007; Coulter et al., 2008; Catsburg et al., 2014). Health concerns for intakes of excessive nitrate and nitrite have caused problems in regulatory actions because of perceived risk of methemoglobinemia in infants and gastrointestinal cancer risk in adults (Obek, 2009; Walkuska et al., 2010). In areas with a high incidence rate of esophageal cancer, the dietary intake and total N-nitroso compounds in urine were found to be significantly higher than in those sampled in low esophageal cancer-prone areas (Lin et al., 2002; Lin et al., 2009). To that end, Bryan and Loscalzo (2011) recommended that comprehensive, systematic review of the potential risks and benefits of food sources of nitrates and nitrites be studies by experts from academia, industry, and governmental and non-governmental sectors.

Based on relevant literature, there are two views on how nitrate and nitrite may be related to cancer occurrences. One view is that, after nitrate enters the human body, it is reduced to nitrite by the bacteria in the digestive system. It is then combined with secondary amines to form carcinogenic substances such as N-nitrosomines (NAD) and other N-nitroso compounds (NOC) (Ward et al., 2007; Frerart et al., 2009; Catsburg et al., 2014). The second view is that; nitrite provides the raw material/nourishment for nitrite respiration of tumor cells. At the same time, it offers a NO-signaling molecule, which is necessary for the growth of tumor cells. Nitrite doesn't necessarily lead to cancer directly, but it can accelerate the proliferation and malignant transformation of cancer cells. It acts as a cancer-promoting agent (Vanin et al., 2007; Frrart et al., 2008; Hunagfu et al., 2010).

Clinical tests and laboratory experiments (Dejam et al., 2004; Suzuki et al., 2005; Ward, 2009; Wang et al., 2012; Catsburg et al., 2014) have showed that, after nitrite in water and vegetable enters the human digestive system, it typically enters the bloodstream through the gastrointestinal circulation, which is about 98% of the total nitrate intake. Meanwhile, it is secreted by the salivary glands into the mouth. Nitrate reductase, produced by nitrate reduction bacteria in the mouth, reduces nitrate to nitrite, which then enters the gastrointestinal digestive system. About 80% of nitrite found in the human body comes from nitrate reductive conversion in saliva. Therefore, the content of nitrate and nitrite in human saliva and in urine can reflect the nitrate and nitrite transformation and metabolism in the human body, NOC formation, and the increase in cancer risk.

It was estimated that, in China in 2015 alone, there were 4.3 million diagnosed cancer cases, with 2.8 million of them dying because of cancer. This was equivalent to having 12,000 new cancer patients and 7500 passed away each day in 2015 because of cancer. Among the different types of cancer, lung cancer was the deadliest one. Stomach cancer, esophagus cancer, and liver cancer were the next most frequently diagnosed types of cancer that also had high death rates. In rural China in 2015, diagnosed cancer cases were 213.6 per 100,000 population (or 213.5/100 K) and the death rate was 149/100 K. Both were higher than those in urban China, which were 191.5/100 K and 109.5/100 K, respectively (Chen et al., 2016a).

At provincial level, Henan Province had 250/100 K cancer cases with a death rate of 161/100 K, both were higher than those of national figures in 2015 (Chen et al., 2016b). These translated to approximately 250,000 cancer cases per year and 160,000 deaths caused by cancer.

In this article, we report a study that was designed to confirm the suspected links between human body's exposure to nitrate and nitrite and the formation of cancer. To do this, we collected sample in well-known cancer villages in China and compared the sample to those collected in non-cancer villages at locations nearby sampled cancer villages. Results from analyzing the samples reveal that there is indeed a trend that human body's exposure to nitrate and nitrite in cancer villages is higher than those sampled in non-cancer villages. Furthermore, such exposure seems to vary among different age groups.

2. Study area

In 2005, China's Center for Disease Control followed 50,000 residents in Shenqiu in Henan for 3 years and found that the age-adjusted death rates due to lung cancer rose by 1400% for men and 2000% for women between 1973 and 2005. The death rates due to liver cancer rose 523% for men and 480% for women in Shenqiu for the same time period. Comparing to other regions in China where the death rates due to cancer typically showed declining trends, Shenqiu area is indeed an area to be further studied. In this area of 1,293,100 population, approximately 2000 residents died because of cancer (Xinjing News, 2013) each year. Moreover, according to Yang and Zhuang (2014) and a study by China Center for Disease Control (Xinhua News, 2013), water pollution was positively linked to high cancer incidents in a number of Cancer Villages across Henan Province, Jiangsu Province, and Anhui Province.

Nitrate nitrogen pollution and the high incidence of cancer and mortality have been identified as prominent problems in Huai River Basin by many studies (Tan et al., 2005; Bai and Shi, 2006;Guo et al., 2008; Wang et al., 2010; Zhang et al., 2010; Wan et al., 2011; Chen et al., 2013; Meng et al., 2013; Zhao et al., 2014; Ren et al., 2015). In early 2010′s, the cancer incidence rates were more than 400 per 10 million population (or 400/10mln) in some severely affected areas. Locally, these are called *cancer villages* (Liu, 2010; Ebenstein, 2012; Tian et al., 2013).

Within Huai River Basin, areas located in the northern side of Huai River, such as Shicao Town of ShenQiu County, were found to have notable high cancer incidence rates than the national average. The higher-than-average cancer incidence rates in Shicao Town have been reported on many websites by autoreactive news media, including http://news.sina.com.cn/c/2013-06-28/075327520830_2.shtml, which reported annual deaths due to cancer to be over 2000 (http://www.ln.xinhuanet.com/newscenter/2013–06/28/c_116324331.htm and http://fuding.fjsen.com/2013-06/28/content_11770255_2.htm). It is for this reason that this study selected Shicao Town as the study area.

Shicao Town practices intensive farming of wheat, corn, and vegetables (Zuo and Wang, 2004), all relying on heavy fertilization of the soil. Shicao Town is adjacent to Sha Ying River, which is the largest tributary of Huai River. Sha Ying River has been seriously polluted with >50% of the river classified as Grade V class or worse. The Grade V classification is considered to be a severe level of pollution, according to the scales by China's national standards for drinking water quality established in 2006 (GB-5749-2006). Sha Ying River is the biggest branch of the Huai River but with the worst water quality. Its drainage area is approximately 40,000 km^2, which is only 14% of that of Huai River. Based on Ni et al. (2011) and Dong & Mao (2005). However, Sha Ying River contributes the most pollution (more than 1/3 of the total COD and ammonia nitrogen) to Huai River (Dong & Mao, 2005) (Fig. 1).

In 2010, the nitrogen fertilizer application rate in Shicao Town was >380 kg/hm^2 (in N gauge) (Chen et al., 2016a). The application rate of nitrogen fertilizer for vegetables was >750 kg/hm^2 (in N gauge). Our field surveys of the study area in 2010 detected severe nitrate pollution in water and vegetables. Based on our surveys, the nitrate and nitrite daily exposure doses in the drinking water and produces were 0.343–5.069 mg/Kg d^{-1} and 0.0064–0.0496 mg/Kg d^{-1}, respectively. The cancer villages included in this study are Sun Ying, Chen Kou, and Dong Ying, which are in Shicao Town and are adjacent to coasts of Sha Ying River. The cancer incidence rates in these villages reached up to 516/10 million in 2010 (Chen et al., 2016). The incidence rates of cancer reached 390/10 million for the studied villages, which were far higher than the national average of 286/10 million. Among the different types of cancer that residents in this area have, gastrointestinal cancer was the most prevalent.