Research Article

Historical Long-term Exposure to Pentachlorophenol Causing Risk of Cancer - A Community Study

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Abstract

Background: Pervious studies suggested occupational workers exposure to pentachlorophenol (PCP) might contribute to increased risk of cancer. However, few studies have focused on associations between PCP and cancer risk at the community level. Objective: The present study was to explore the cancer risk for the community population living long-term in a PCP contaminated area. Methods: All the cancer cases diagnosed in 2009-2011 in Tongling City were collected. The cancer patients' residences were geo-referenced in each district. The historical PCP usage for each district of Tongling was calculated as the PCP pollution index, which was further used to divide into PCP exposure categories. Standardized rate ratios (SRRs) of cancer incidence were applied to detect the cancer risk as exposure grade elevated. Correlation analysis was performed to analyze the relationship between PCP pollution and cancer incidence. Results: A total of 5,288 cancer cases (3,451 male and 1,837 female) were identified. PCP usage was correlated with the incidence of leukemia (r=0.88, P=0.002) for males, and with cancer of the esophagus for males (r=0.83, P=0.008) and females (r=0.71, P=0.020). Compared with the low exposure category, significant SRRs for total cancer sites was obtained for high PCP exposure category (SRR=1.61, 95%CI=1.59-1.62). Most SRR values of the cancer sites were significantly increased as exposure grade elevated and exposure time extended. Conclusion: The present study found that community residents living in the PCP contaminated area had increased risk of cancers. Leukemias, lymphomas and nasopharyngeal and esophageal cancers are most possibly associated with PCP exposure.

Keywords: Incidence - pentachlorophenol - exposure - cancer risk

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Introduction

Pentachlorophenol(PCP) has been widely used as wood preservative, herbicide and insecticide in western countries since 1940s; and also it has been used for killing oncomelania in some areas of China where schistosomiasis is epidemic (Zheng et al., 2011). Since the toxicity and carcinogenicity of PCP has been discovered, the International Agency for Research on Cancer (IARC) classified PCP as a group 2B carcinogen in 1991 for inadequate evidence in humans but sufficient evidence in animal studies (IARC, 1991). PCP is restricted or banned to use in many countries in 1990s (Muir et al., 1999).

PCP has been used since 1936, its effect on cancer has been studied in several countries after 1970s. And on account of there is no community population exposing to PCP in western countries, thus the study population are the workers in manuscript plants and sawmills. Case reports and case–control studies of hematopoietic cancers published in the 1980s and 1990s indicated the risk of non-Hodgkin lymphoma, soft-tissue sarcoma and multiple myeloma in relation to pentachlorophenol exposure for occupational workers (Greene et al., 1978; Bishop et al., 1981; Pearce et al., 1986; Smith et al., 1992; Hardell et al., 1994; Hardell et al., 1995; Kogevinas et al., 1995). In the 1990s and 2000s, four cohort studies reported the results between cancer risk and PCP exposure, and most of them reported weak or no risk of exposure to PCP, the authors infer the non-significant results might due to the less study population and healthy worker effects (Hertzman et al., 1997; Demers et al., 2006; Ramlow et al., 1996; Ruder et al., 2011).

After it has been forbidden to use in many countries, a worldwide research suggests that in indoor air, bodies of water, and freshwater sediments around the world, PCP levels has declined over time (Zheng et al., 2011). However, in Chinese surface water/sediments, PCP levels increase over time (Zheng et al., 2012). The causes were that since 1960 the sodium pentachlorophenate(Na-PCP) had been extensively sprayed to control the spread of snailborne schistosomiasis, and also the forbidden using PCP in China is later than other counties. Because of the re-emergence of schistosomiasis causing the adding consumption of PCP in several provinces in China, it...
indicates an aggravating trend of PCP pollution. And also, the Na-PCP is still used for fish pond cleaning in China, in many sampling sites, the long-term using Na-PCP for killing oncomelania and for fish pond cleaning induce a nearly two-fold risk of PCP contamination of the environment (Tan et al., 2008; Yang et al., 1996; Ge et al., 2007). The PCP level is also detected in human body that lives in PCP pollution area. Relatively high concentration of PCP has been found in human urine (Wang et al., 1998), adipose tissue (Zheng et al., 1997), blood lipids (Zhou, 2007), and breast milk fat (Chen et al., 2006). Although Na-PCP has been replaced by some new mollusacides in China, the persistence of PCP and its derivatives has resulted in serious pollution in the schistosomiasis epidemic area, and the human has severely suffered long history of PCP burden. Therefore, even for the populations exposed to low levels of PCP, their health risk is not negligible.

Most studies reported cancer risk of exposing to PCP for occupational workers, but few studies detect the cancer risk for community population who long term lived in PCP contaminated area. To perform a risk assessment of cancer for community population, we collect all the cancer cases in a PCP contaminated area and calculate the cancer incidences. PCP pollution is assessed by collecting the data of PCP usage, so as to investigate the link between human environmental exposing to PCP and risk of cancer.

Materials and Methods

Study area

Tongling was the smallest prefecture-level city in China, located in the east longitudes 117°42’00”-118°10’6” and north latitude 30°45’12”-31°07’56” . It comprised 720 thousands inhabitants living in an area of 1113 km². Its geographic character was locating in south-side of the midstream and downstream of Changjiang River. And the suitable environment gave rise to abundantly snail propagation, which further led to the schistosomiasis epidemic.

Digital map of the regionalism of Tongling

The 1:200,000 digital map of Tongling were provided by State Bureau of Surveying and Mapping. Our purpose of the study was to detect the correlation between the PCP pollution and the cancer incidences in each district, thus the digital map was simply divided by administrative district boundaries. The Tongling City was divided in ten districts, including an urban area and nine countries (Datong, Wusong, Xilian, Donglian, Xuba, Laozhou, Tianmen, Shunan, Zhongming). The location of the districts had been labeled on the map. Each district was treated as a unit and processed in Geographic Information System in the analysis.

The collection of case records

This study utilized cancer registry system which had collected cancer cases in Tongling city. The cancer registry system was implemented in 2007. The registries identified new cancer cases from all hospitals, community health centers, death registries. The study population included all cancer patients in Tongling city. The database of cancer registry contained individual level data of cancer patients, including name, date of birth, race, sex, county, residence address and cancer site (coded using ICD-10). If some information of cancer cases was unavailable, households interview or telephone call were applied to investigate the information. And all the cancer cases had been localized in each district according to their residence addresses (if the patient had two or more residences in the past, we chose the address which he or she had lived for longer time). Population information of each district was obtained from official registration records.

Owing to the population in the involved district was small, and cancer was a rare disease, we merged cancer data from 2009 to 2011 and calculated average cancer incidence, in order to obtain a relatively stable incidence rate for each district. This study applied incidence data rather than mortality data because incidence data was more closely related to the cause and was not influenced by different effects due to the progress of treatment in different places.

Exposure assessment

We interviewed the Schistosomiasis Control Centre of Tongling, and obtained the historical data of PCP usage in killing oncomelania. According to the PCP usage data, it had been used to kill oncomelania for all the districts in Tongling City, and it was almost constantly sprayed in each district from 1960 to 2002.

We used the PCP usage per square meter as the pollution index. Firstly, we calculated the average usage of PCP per year for each district. Next, the PCP usage per square meter in each district was computed as index to categorize the exposure grade. Exposure categories based on quartiles of reported PCP spray were created. The <25th percentile of PCP pollution index (corresponding to <2.117 mg/m² per year) was designated the “low” exposure category, and districts that were in the >75th percentile of PCP pollution index (corresponding to >34.002 mg/m² per year) were designated as “high” exposure category. The rest districts that were between 25th percentile and 75th percentile were designated as “medium”. According

We firstly calculated the average age-standardized incidence rates* for each district and for each exposure category, using the world population in 2000-2025 as the standard population. Pearson correlation analysis was conducted to test the association between PCP usage and cancer incidences. And then the standardized rate ratios (SRR) of the cancer incidence for PCP exposure category of medium and high were calculated relative to low exposure category. Statistical stability was evaluated with a 95% confidence interval (CI). The data analysis was completed using Stata11.0 Software.

**Results**

For the study period a total of 5288 cases (3451 male and 1837 female cases) were collected. The age distribution was skewed, the median was 65 year-old, and the 25 percentile and 75 percentile of age distribution was 55 and 73 year-old, respectively.

The results of the incidence for the cancers grouped by pathogenetic site between 2009 and 2011 in Tongling City are shown in Table 1.

**Table 1. Cancer Incidences in Males and Females in Tongling City**

<table>
<thead>
<tr>
<th>Cancer sites</th>
<th>Male</th>
<th>Female</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer incidence rates*</td>
<td></td>
<td>Cancer incidence rates**</td>
<td></td>
</tr>
<tr>
<td>Oral Cavity, Pharynx (C00-10,C12-14)</td>
<td>1.71</td>
<td>1.33</td>
<td>0.57</td>
</tr>
<tr>
<td>Nasopharynx (C11)</td>
<td>3.15</td>
<td>2.40</td>
<td>1.42</td>
</tr>
<tr>
<td>Esophagus (C15)†</td>
<td>51.99</td>
<td>36.16</td>
<td>11.80</td>
</tr>
<tr>
<td>Stomach (C16)†</td>
<td>77.67</td>
<td>54.06</td>
<td>29.26</td>
</tr>
<tr>
<td>Colon, Rectum, Anus (C18-21)</td>
<td>28.11</td>
<td>20.35</td>
<td>21.42</td>
</tr>
<tr>
<td>Liver (C22)</td>
<td>25.59</td>
<td>18.67</td>
<td>7.64</td>
</tr>
<tr>
<td>Gallbladder (C23-24)</td>
<td>3.60</td>
<td>2.55</td>
<td>6.23</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
<td>6.49</td>
<td>4.52</td>
<td>5.57</td>
</tr>
<tr>
<td>Trachea, Bronchus, Lung (C33-34)</td>
<td>65.23</td>
<td>45.82</td>
<td>23.12</td>
</tr>
<tr>
<td>Breast (C50)†</td>
<td>0.54</td>
<td>0.46</td>
<td>22.08</td>
</tr>
<tr>
<td>Ovary (C56)</td>
<td>-</td>
<td>-</td>
<td>4.34</td>
</tr>
<tr>
<td>Kidney, Urinary Organs (C64-66,68)</td>
<td>4.23</td>
<td>3.17</td>
<td>1.51</td>
</tr>
<tr>
<td>Bladder (C67)†</td>
<td>6.40</td>
<td>4.50</td>
<td>1.70</td>
</tr>
<tr>
<td>Brain, Central Nervous System (C70-72)</td>
<td>4.32</td>
<td>3.26</td>
<td>2.45</td>
</tr>
<tr>
<td>Thyroid Gland (C73)</td>
<td>0.36</td>
<td>0.29</td>
<td>2.27</td>
</tr>
<tr>
<td>Lymphoma (C81-85, 88, 90, 96)</td>
<td>5.23</td>
<td>4.01</td>
<td>3.87</td>
</tr>
<tr>
<td>Leukemia (C91-95)</td>
<td>3.69</td>
<td>3.18</td>
<td>4.06</td>
</tr>
<tr>
<td>Total (C00-C97)</td>
<td>308.96</td>
<td>219.77</td>
<td>182.05</td>
</tr>
</tbody>
</table>

†Significant different incidences between men and women, P<0.05; * per 100000 population; ** World population per 100000
were summarized in Table 1. The age-standardized incidence in males was greater than that in females with a sex standardized incidence ratio(SIR) of 159 males per 100 female. And significant incidence ratios were also detected in the cancer sites of breast, liver, stomach, lung and esophageal, bladder.

The Pearson correlation analysis showed that the PCP usage was correlated with leukemia (r=0.88, P=0.002) for male, and with cancer of esophageal for male (r=0.83, P=0.008) and female (r=0.71, P=0.020).

Standardized rate ratios(SRR) was calculated according to the age-standardized incidences by using the incidence in the low PCP spray districts as the reference. Without considering the exposure time, significant SRRs for total cancer sites was obtained with high exposure category (SRR=1.61, 95%CI=1.59-1.62). As shown in Table 2, we detected that most SRR values of cancer sites were significantly increased as exposure grade elevated. The SRRs of leukemia in high exposure for male (SRR=27.97, 95%CI=24.60-31.79) and lymphoma in high exposure for female (SRR=9.37, 95%CI=8.41-10.45) indicated strong association between leukemia of male and lymphoma in female with PCP exposure.

Most of the cancer incidences appeared to increase consistently with the SRR grouped by exposure time (Table 3 and Table 4). And it also corroborated the association between leukemia and lymphoma with PCP. In the longer term exposed strata some prominent elevated cancer incidences were observed for nasopharyngeal cancers that were less considered a priori to be associated with PCP. Of these, nasopharyngeal cancer exhibited the most consistent pattern as exposure time extended and exposure level rose.

**Discussion**

Different with the results of previous similar studies of occupational workers exposing to PCP, the present study detected significant cancer risk for community population long term exposed to PCP. The occupational workers in former studies were almost male and in the middle-age, which contained healthy worker effect. That might limit those studies to obtain statistical significant result. The present study was to detect the cancer incidence of the
whole city residents in all age groups. And by dividing exposure categories, we had found that the people lived in PCP pollution area had excess risk of occurring cancers.

The present study discovered the PCP exposure was associated with cancer of esophageal, which had not been found in previous studies. The significantly raised SRR values of cancer in esophageal also indicated the risk when people exposing to higher concentration of PCP. And, the incidence ratio of cancer of esophageal (male: female=4.33, 95%CI=3.21-5.83) indicated the higher incidence was more attributed to male. The standardized cancer incidences of esophageal (29.66 per 105) and stomach (50.13 per 105) in Tongling were almost twice than that in national average level. Although the correlation analysis did not show PCP exposure was significant associated with cancer of stomach, the SRR values of it suggested more than two-fold risk in high exposure category. We surmised the PCP might contribute to the results. As we investigated to all the area of Tongling, its geographic character was that the communities and countries were surrounded by natural water networks, such as rivers, ponds and ditches. And the PCP was sprayed into these water networks which were also used as drinking water for the local residents. This might provide the direct pathway of exposing and ingesting to PCP, which was different with mainly though inhalation and less from dust deposition in occupational workers (Greene et al., 1978). In addition, many studies regarded that PCP was persistent, toxic, anthropogenic chemicals. Its bio-accumulate in humans, because humans resided at the top of the “food chain”, thus mostly (>90%) intake of PCP was through contaminated foods, such as meat and fish, and particularly from food of animal origins (Hong et al., 2005).

The PCP exposure was also associated with incidence of leukemia in male. The PCP associated with the leukemia in male were much evident (high exposure category SRR=27.97, 95%CI=24.60-31.79). The association with female was significant in lymphoma (high exposure category SRR=9.37, 95%CI=8.41-10.45). To explain the association, we interviewed the staff of Schistosomiasis Control Centre and local residents of high exposure category districts. These districts were almost farmland, and the farmers used the water of Changjiang River, which was contaminated by PCP, to irrigate the field. PCP was also sprayed along the canals and ditches around the field. People were undertaken the agricultural work which provided the opportunity to directly expose to PCP. Especially, when PCP is exposure to intense solar radiation, it could result to even greater toxicity and carcinogenicity (Agbo et al., 2011). There was one cohort study had similar result with us, it reported increased risk of leukemia associated with people directly exposing to PCP in occupational workers (Ruder et al., 2005). They discovered that among the male workers, except white races, had increased leukemia mortality (SMR=4.57, 95%CI=1.25-11.7).

Since 1980s, the descriptive and analytical epidemiology of exposure to PCP causing human cancer had been extensively studied in developed countries. Most population-based studies conducted in developed countries used occupational workers as the study population to analysis the relationship between PCP exposure and cancers. The previous case-control studies and recent cohort studies were mainly concerning to lymphoma, and strong evidence had been provided to substantiate the association between exposure to PCP and Non-Hodgkin’s lymphoma (Demers et al., 2006). In our study, we also detected the statistical significant SRRs for lymphoma as exposure grade elevated. And a similar study conducted in Finland observed increased incidence of Non-Hodgkin’s lymphoma in community population who lived in PCP-contaminated area (Lampi et al., 1992).

In the large cohort study of Demers et al., 2006, the sawmill workers exposed to PCP with 2-5 exposure years had an increased risk of liver cancer(RR=8.47, 95%CI=2.21-32.45). In present study, the significant SRRs value of liver cancer also showed increased risk as the exposure time extended. But the effect-response relationship between PCP exposure and liver cancer might be confounded by other factors, which weakened the association. In schistosomiasis epidemic area, the schistosomal infection could promote developing liver cancer. It could accelerate progression to hepatitis C-associated fibrosis and made quicker progression to Hepatocellular carcinoma (Kamel et al., 1992; Hassan et al., 2001). But we had not collected the clinic data of the liver cancer patients, in further investigation with detailed exposure information would be helpful to detected the association between PCP exposure and liver cancer.

The study found significant association with nasopharyngeal cancer. When the exposure over 40 years, for high exposure category the SRR was 20.98 (95%CI=16.04-27.46). Evidence of an excess of nasal and nasopharyngeal cancer had been observed in another study of chlorophenol and wood preservative exposed workers (Mirabelli et al., 2000). They obtained elevated risk for nasopharyngeal who held jobs assigned high intensity chlorophenol exposure (OR=9.07, 95%CI=1.41-42.9).

We recognized that the study had several limitations. Firstly, imprecision existed in calculating average cancer incidences. The development of cancer from exposure to environmental pollutants was a long-term event, and yet in this study the number of cancer cases for the years 2009-2011 collected from available sources was slightly insufficient. And this might be the reason of failing to detect significant SRRs value of soft-tissue sarcoma and multiple myeloma which were considered to be associated with PCP exposure. In addition, the small population in this city might be another reason for the fewer cases.

The exposure occurred during 1960-2002. Changes in population characteristics due to migration or other dynamics might influence cancer estimates separately from PCP pollution. However, that might not have impact on our study. As we interviewed bureau of census, we were told that there was no large-scale migration happened in the history of Tongling City after 1960.

Lastly, the study was also limited by the ecological design, because no direct person-level measures of environmental exposure were available. And all individuals in a given district were assigned to the same exposure category, without regard for proximity to other
carcinogens exposure and individual behavior, which could cause individual variations. For instance, commercial grade PCP contained a variety of contaminants and by-products of the manufacturing process, the primary contaminants were hexa-, hepta-, and octa-chlorinated dibenzodioxins, and higher-chlorinated dibenzofurans. In Canada, polychlorodibenzo-p-dioxins and furans (PCDD/Fs) were detected in the place where emission from pentachlorophenol (PCP)-treated wooden poles in service (Bulle et al., 2010). And in further study, the measurement of PCP concentration and other carcinogens in human body and environment would be advantageous to better realize the carcinogenicity of PCP to the community residents who were long-term living in PCP pollution area.

In summary, by assessing the PCP pollution for the districts in Tongling city, we had established a practical approach to reveal the impact of environmental PCP exposure on community population developing cancers. Study results suggested that community residents living in the PCP contaminate area had increased risk of developing cancers, and also the PCP exposure might associate with the leukemia, lymphoma, esophageal and nasopharyngeal cancer.

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References


