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EXOCRINE PANCREATIC CANCER AND LIVING NEAR TO WASTE SITES CONTAINING HAZARDOUS ORGANIC CHEMICALS, NEW YORK STATE, USA – AN 18-YEAR POPULATION-BASED STUDY

BAYARMAGNAI WEINSTEIN[1], ALAN DA SILVA[2], and DAVID O. CARPENTER[1,3]

[1] University at Albany, Rensselaer, NY, USA

Department of Environmental Health Sciences, School of Public Health

[2] University of Brasília, Brasília, Brazil

Department of Statistics

[3] University at Albany, Rensselaer, NY, USA

Institute for Health and the Environment

Abstract

Objectives: The etiology of exocrine pancreatic cancer (EPC) remains unknown except for family history and smoking. Despite recent medical advances, rates of pancreatic cancer incidence and mortality are increasing. Although existing evidence suggests a potentially causal relationship between environmental chemical exposures and pancreatic cancer, whether residential exposure impacts pancreatic cancer rates remains unknown. **Material and Methods:** The authors identified 28 941 patients diagnosed with exocrine pancreatic cancer in New York State exclusive of New York City for the years 1996–2013. Descriptive statistics and negative binomial regression were used in this ecological study to compare pancreatic cancer hospitalization rates among patients who lived in zip codes with hazardous waste sites (HWSs) containing persistent organic pollutants (POPs) and volatile organic pollutants (VOCs) compared with clean zip codes with no identified hazardous waste sites. The authors assessed the effect of selected known and suspected human carcinogens on the EPC hospitalization rates by subgroup analyses. **Results:** Compared with the clean sites, the pancreatic cancer hospital discharge rate in the "VOCs without POPs" and "VOCs and POPs" sites, after adjustment for potential confounders were 1.06 (95% CI: 1.03–1.09) and 1.05 (95% CI: 1.01–1.08), respectively. In the analysis by specific chemicals, rate ratios (RR) for the benzene (RR = 1.12) and ethylbenzene (RR = 1.34) in the non-chlorinated VOCs group, trichloroethylene (RR = 1.07) and tetrachloroethylene (RR = 1.11) in the chlorinated VOCs group, chlorinated pesticides (RR = 1.11) and PCBs (RR = 1.05) in the POPs groups were statistically significant (p-values <0.05) compared with clean sites. **Conclusions:** Residential exposure to both volatile and semi-volatile organic compounds coming from identified HWSs is associated with elevated risk of being hospitalized for exocrine pancreatic cancer. The authors attribute the exposure to inhalation. These results are important because while the exposures are much lower than seen in occupational settings, residential exposure in continuous, and the authors have identified several specific chemicals showing significant associations. Int J Occup Med Environ Health. 2022;35(4):459–71

Key words:
benzene, pancreatic cancer, pesticides, residential exposure, VOCs, PCBs

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Corresponding author: David O. Carpenter, University at Albany, Institute for Health and the Environment, 5 University Place, Room A 217, Rensselaer, NY 12144, USA (e-mail: dcarpenter@albany.edu).

INTRODUCTION

Exocrine pancreatic cancer (EPC) is a rapidly fatal malignancy with a 5-year survival rate of 10 % and is the third leading cause of cancer mortality in the USA [1]. According to the latest cancer statistics, overall cancer incidence in the U.S. has declined during 2012–2016 except for the increased rate for the 5 cancers including pancreatic cancer [2]. The reason for the increasing trend is not understood. The same increasing trend for pancreatic cancer was seen in New York State (NYS), in which the 5-year average incidence rate (14.4%) was even higher than the national rate (12.7%) during the same period.

The etiology of EPC remains largely unknown. Less than 10% of all pancreatic cancers are estimated to be associated with genetic factors [3] and about 25% of new cases have been attributed to smoking [4]. Specific medical conditions and lifestyle-related risk factors have been suggested (diabetes mellitus, chronic pancreatitis, obesity, poor diet, excess alcohol consumption, poor oral hygiene, infections of *H. pylori*, hepatitis B and C), but there is a lack of consistency across studies. Evidence for an effect of poverty on pancreatic cancer incidence is inconsistent, ranging from having little effect [5] to being an important determinant dependent on race [6].

Chemical exposures and EPC

Several occupational, hospital-based case-control, and agricultural studies have reported some evidence of an association between environmental chemical exposures and EPC. A large meta-analysis [7] of 92 occupational studies and 23 occupational chemicals reported excess pancreatic cancer risk from occupational exposure to chlorinated hydrocarbons, nickel and chromium compounds.

However, occupational studies usually lack statistical power due to small sample size, and are prone to the "healthy workers effect," and exposure misclassifications. A few hospital-based case-control [8,9] and self-reported exposure studies [10,11] reported varying findings, but these types of studies are prone to information bias and misclassification in the control and case ascertainment processes. The Agricultural Health Study Cohorts reported significantly elevated rate ratios for pancreatic cancer associated with exposure to the pesticides, S-ethyl-N,N-dipropylthiocarbamate and pendimethalin, but the results remain inconclusive given the potential exposure misclassification [12]. Reasonable consistency has been seen in a few studies reporting a positive association between pancreatic cancer and exposures to chlorinated solvents, organochlorine pesticides, polychlorinated biphenyls (PCBs), and polyaromatic hydrocarbons (PAHs) [13–18].

The relationship between long-term residential exposure to organic chemicals and pancreatic cancer remains unknown. Moreover, there is an increasing need for scientific inquiry given the increasing incidence of this cancer, and the ubiquity of exposure to these chemicals. The situation is further complicated by the long latency period between exposure and development of cancer which necessitates an extended follow-up time and individual-level data

The authors examined the association between residential exposure to different groups of organic chemicals and pancreatic cancer hospitalization rates among NYS residents using state-wide population-based hospital discharge data recorded over an 18-year period. The authors have used several datasets maintained by NYS to explore associations, if any, between residence near hazardous wastes containing known contaminants and pancreatic cancer. The New York State Department of Environmental Conservation (NYSDEC) maintains a listing of hazardous wastes sites (HWS) that pose "a threat to public health." The listing include the geographical location of the HWS along with the major hazardous chemicals contained in each site.

For the statewide pancreatic cancer data, the New York State Cancer Registry (NYSCR) is the principal source

of information on cancer incidence and mortality and provides residential address, sociodemographic, and tumor-specific data for all NYS residents diagnosed with cancer. However, accessibility to the registry is limited due to patient confidentiality concerns, and the publicly available format of the registry data for pancreatic cancer is only at the county-level. As an alternative data source, the Statewide Planning and Research Cooperative System (SPARCS) can be used. The SPARCS contains hospital discharge data that is mandated to be reported by all state-regulated hospitals to the New York State Department of Health (NYSDOH), so does not include Veterans Administration or Indian Health Services facilities. Statewide Planning and Research Cooperative System data provides all diagnoses (≥15), procedures, demographic information (age, sex, race and ethnicity), and patient's residential address upon hospital discharge. The publicly available SPARCS data used in this study included the 5-digit zip codes of the patients' residential addresses, but not the patient's name or street address. The authors have matched the hospitalization rate for pancreatic cancer by zip codes to the zip codes containing HWS with different contaminants.

The validity of using SPARCS data as hypothesis-generating information that is subsequently confirmed in studies with individual-level exposure assessment has been demonstrated for 2 different diseases. Kouznetsova et al. [19] and Huang et al. [20] reported significant elevations in hospitalization rates for diabetes mellitus and hypertension, respectively, among individuals living in zip codes containing POPs waste sites. Most POPs sites contained primarily PCBs, but some also had chlorinated pesticides and dioxins or furans. Subsequent studies by Aminov et al. [21] and Goncharov et al. [22] confirmed these associations with direct measurement of diabetes markers and blood pressure, respectively, in relation to serum PCB concentrations. A further test of the usefulness of SPARCS was that Boberg et al., found statistically significant increases in hospital discharge rates for chronic lymphocytic leukemia and lymphoma among people who lived in zip codes containing benzene waste sites [23]. This corroborated known association between the benzene and hematological malignancies.

MATERIAL AND METHODS

Study population

The authors conducted a population-based cross-sectional study. In the state-wide SPARCS data, the authors identified a total of 107 572 hospital discharge records of patients diagnosed with EPC in 1996–2013. The EPC cases were identified using the international classification of diseases ICD-9-CM codes initialized with "157" excluding the records of "1574" for the malignancy of Langerhans islets (endocrine tumors).

The flowchart, Figure 1, shows the record selection process. Since New York City (NYC) operates an independent hospital discharge data system, the authors excluded 47 201 records of the NYC. There were 51 867 records after restricting data to the non-Hispanic white population ("whites") and African Americans ("blacks"). The resulting data was deduplicated to 29 527 to achieve a record per patient. Details for the deduplication method and algorithms are described below. The records-data was linked to the U.S. Decennial Census 2000 and Census 2010 datasets for the proxy of person-years corresponding with the hospital discharges in 1996–2004 and 2005–2013, respectively, in the SPARCS data based on the 5-digit zip codes. A total of 571 records without matching zip codes to the Census zip codes were eliminated as these were post office box zip codes that did not reflect site of residence. Zip code area-poverty level was assigned to each record based on the Summary Files of Census 2000 and 2010 to determine the percentage of people in the zip codes below the federally defined poverty line. The area-poverty categories used were: <5%, 5 to <10%, 10 to <20%, and >20% to create a categorical area-poverty indicator. There were

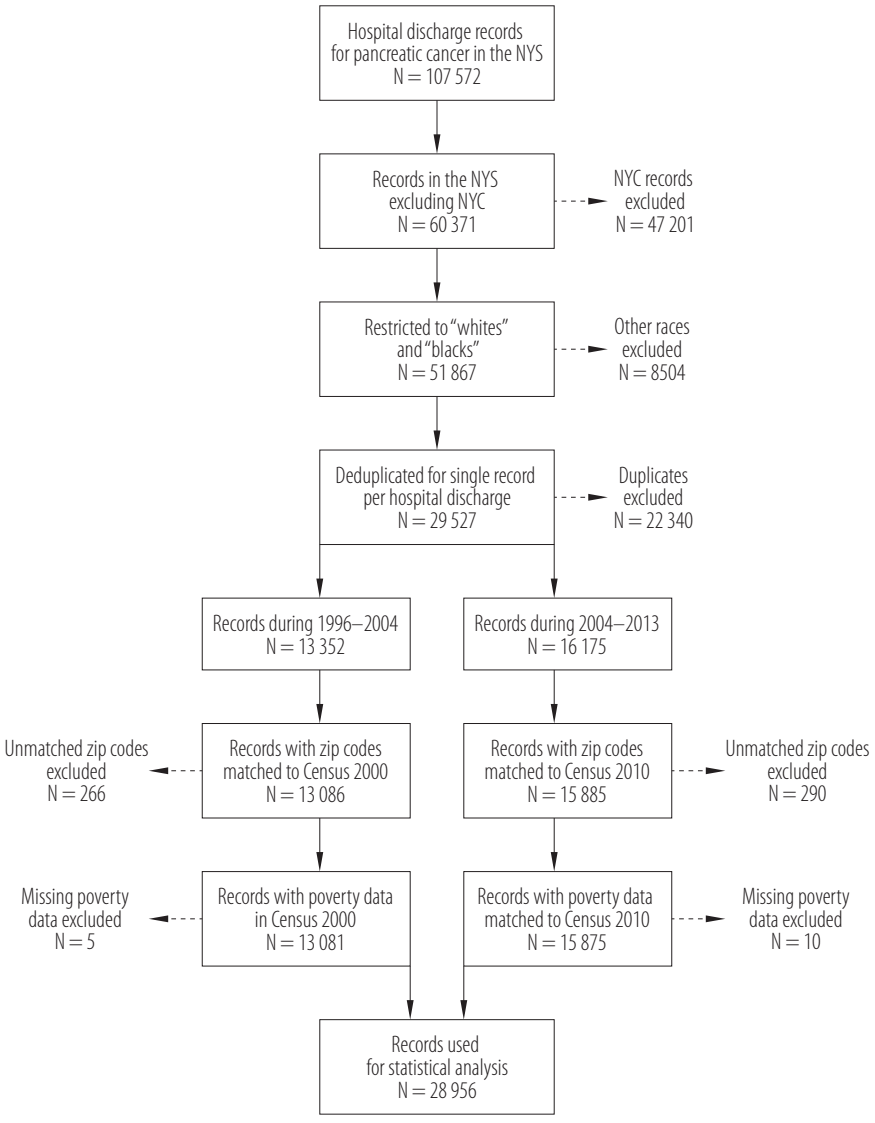

Figure 1. Flowchart illustrating the record selection process for study on exocrine pancreatic cancer in New York State (NYS) exclusive of New York City (NYC) in 1996–2013

15 records with no poverty data and they were excluded, which led to 28 941 records in the final analytical dataset. The SPARCS data version used in this study does not identify patients with multiple hospitalizations. To distinguish multiple hospitalizations of the same patient and select the earliest single hospitalization record for each patient, the authors deduplicated the multiple hospitalizations per patient data (Figure 1) by the deterministic linkage method based on the key variables, such as 5-digit zip code of residential address, patient's birth year, birth month, race, sex, and calendar year of hospital discharges. The authors used the NYSCR's publicly available incidence case data for pancreatic cancer as a gold-standard (reference) to assess the accuracy of the deduplication process. The combination of variables used for deduplication that approached closest to the NYSCR incidence data by calendar years, 5-year age groups, sex, and the race was used to produce the final record per patient hospital discharge data.

Exposure assessment

The NYSDEC maintains a listing of all hazardous waste sites within the State. This listing contains the location of the site and lists the major chemicals found within that hazardous waste site. The authors have used these data to characterize each zip code based on whether it contains a hazardous waste site, and, if so, which are the major chemicals found within that site. The authors assume that the major route of exposure is inhalation of volatile or semi-volatile chemicals. Each zip code area was categorized as containing volatile organic compounds (VOCs), persistent organic pollutants (POPs), other, or clean based on the major contaminant list provided by the NYSDEC. The authors further refined the zip codes with "VOCs without POPs" (228 zip codes), "POPs without VOCs" (85 zip codes), "VOCs and POPs" (110 zip codes), "other" (32 zip codes), and "clean" (1169 zip codes) to reduce the cross contaminations. "Clean" is not meant to indicate that that zip code had no sources of contamination but only that it did not contain an identified hazardous waste site.

Statistical analysis

The authors calculated EPC hospitalization rates per 100 000 population as the number of hospital discharge diagnoses of EPC divided by the total population residing in the zip codes at each category of age, race, sex, and area-poverty status. The authors modeled the rates of pancreatic cancer hospitalization in the exposure categories of "VOCs without POPs," "VOCs and POPs," "POPs without VOCs," and "other" in comparison to the zip codes with no identified HWSs ("clean") using negative binomial process adjusting to age, race, sex, and area-poverty status. The models calculated 95% confidence intervals (CI) of rate ratios (RRs) for each exposure category accounting for the effects of the potential confounders including age, race, sex, and area-poverty status. Given that epidemiological studies and meta-analyses have reported that both race and poverty impact pancreatic cancer rates [15], the authors assessed pancreatic cancer hospitalization rates by race and poverty status by including the interaction term in the models.

The negative binomial model was set as:

$$\begin{aligned}&\text{Number of pancreatic cancer discharges} = \\ &\text{exponent}\,(\beta_0 + \beta_1\,\text{exposure} + \beta_2\,\text{age} + \beta_3\,\text{race} + \\ &\beta_4\,\text{sex} + \beta_5\,\text{area-poverty status} + \beta_6\,\text{race} * \\ &\text{area-poverty (interaction term)} + \varepsilon\end{aligned} \quad (1)$$

where,

$\beta_0, \ldots, \beta_6$ – the intercept and regression coefficients,

ε – the model random error.

Variable levels and reference groups were defined as:

- exposure levels: "clean," "VOCs without POPs," "VOCs and POPs," "POPs without VOCs," and "other" using "clean" group for a reference;
- age: <54 years, 54–74 years, and ≥75 years using <54 years group for a reference;
- race: "whites" and "blacks" using "whites" for a reference;
- sex: "males" and "females" using "females" for a reference;
- area-poverty status were: <5%, 5 to <10%, 10 to <20%, and ≥20% using <5% group for a reference.

RESULTS

Figure 2 compares the deduplicated hospital discharge records of pancreatic cancers in the SPARCS and the incident cases of pancreatic cancers in the NYSCR during 1996–2013. The overall difference between the 2 datasets was only 199 for the entire study period. These results indicate that with the deduplication procedures applied, use of the SPARCS data provides comparable information to that of the NYSCR, at least for rapidly fatal cancers such as pancreatic cancer, and that this can be done without having access to unique identifying information.

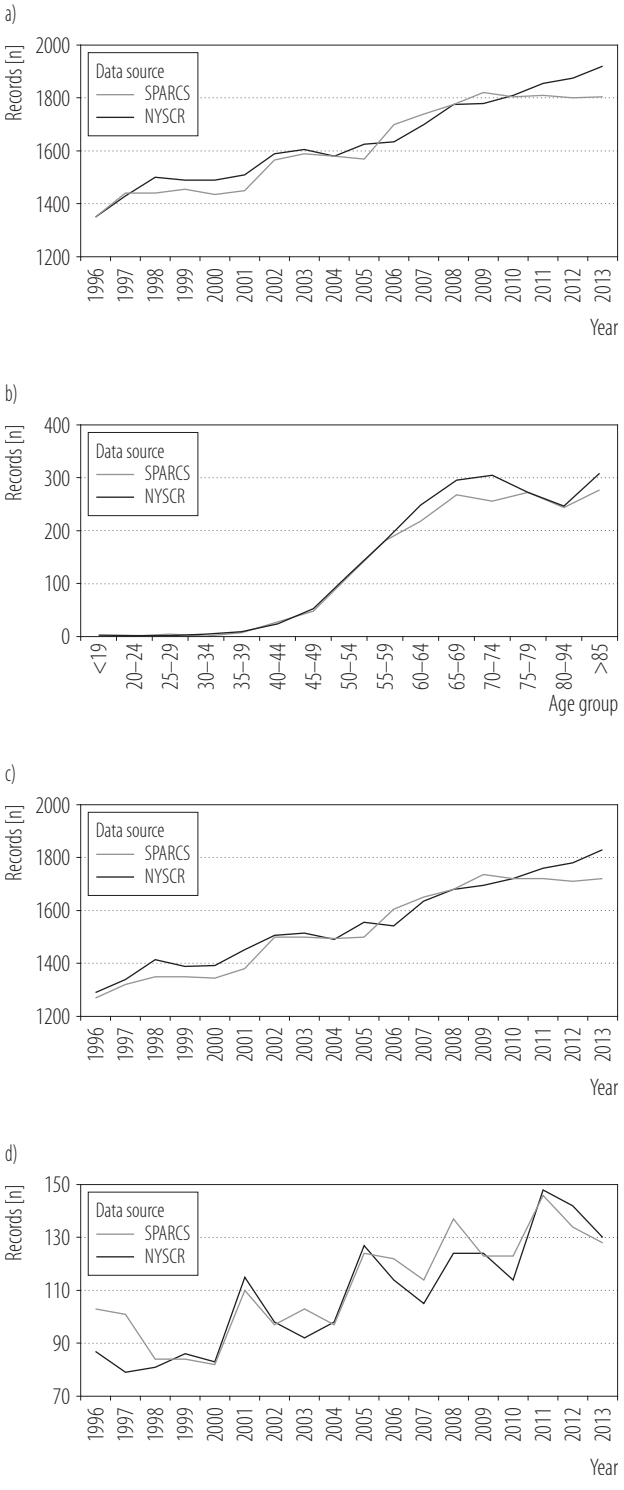

Figure 2. Deduplicated Statewide Planning and Research Cooperative System (SPARCS) data compared to the New York Cancer Registry (NYSCR) by: a) calendar year, b) age groups, c) race and year ("whites"), d) race and year ("blacks")

Descriptive analysis

Table 1 compares crude and age-adjusted rates of pancreatic hospital discharge rates by exposure groups and key socio-demographics. Both crude and age-adjusted rates were lowest in the "clean" exposure group, whereas the highest rates were observed in the "VOCs without POPs" group followed by "VOCs and POPs" and "POPs without VOCs" groups. The "other" group (HWSs with only metals and some nuisance materials) had only 733 cases over the 18 years, thus these rates lacked meaningful interpretation. As expected for pancreatic cancer, the majority of patients were >54 years. In record per patient data, age ranged 3–107 years with an average of 70 years and median of 71 years. Among the cases used in the study, 93% were non-Hispanic white, 7% were African Americans ("blacks"). The age-adjusted rate is higher among "blacks" whereas the crude rate is higher among "whites." The sex-specific crude rate ratio is almost one whereas the age-adjusted rate is higher among males after adjusting to age, probably because of higher rates of smoking among men. The area-poverty level-specific rates stratified by race shows that both crude and age-adjusted rates are highest in the wealthiest group (percentage below poverty <5%) among "whites." In contrast, the rates were highest in the poorest group (percentage below poverty >20%) among the "blacks." The observed trends were not linear and were slightly more prominent in the crude rates. The disparity between the crude and age-adjusted rates within the same groups shows that the age distribution of "whites" and "blacks" is substantially different. Thus, age-adjustment is necessary for a valid comparison across the groups.

Modelled results

Table 2 presents the results of a multiple negative binomial regression model. The authors found a 6% and 5% increase in pancreatic cancer hospitalization rates in the population in the "VOCs without POPs" and

Table 1. Inpatient hospital discharge rate for pancreatic cancer during 1996–2013 in New York State excluding New York City

Variable	Patients [n (%)]		
	hospital discharge	person-years	hospital discharge rate per 100 000 population
Gender			
male	14 124 (49)	85 012 839 (49)	16.6
female	14 817 (51)	89 607 546 (51)	16.5
Race/ethnicity			
whites	26 919 (93)	157 835 898 (90)	17.1
blacks	2 022 (7)	16 784 487 (10)	12.0
Age			
≤54 years	3 475 (12)	127 542 060 (73)	2.7
55–74 years	13 596 (47)	33 824 727 (19)	40.2
≥75 years	11 870 (41)	13 253 598 (8)	89.6
Poverty level			
whites			
<5%	11 520 (43)	61 235 694 (39)	18.8
5–9%	8 085 (30)	49 803 606 (32)	16.2
10–20%	5 954 (22)	38 616 948 (24)	15.4
>20%	1 360 (5)	8 179 650 (5)	16.6
blacks			
<5%	276 (14)	2 293 173 (14)	12.0
5–9%	467 (23)	3 985 857 (24)	11.7
10–20%	645 (32)	5 616 369 (33)	11.5
>20%	634 (31)	4 889 088 (29)	13.0

"VOCs and POPs" groups, respectively, compared with "clean" sites after adjusting for the potential confounders (age, race, sex, and area-poverty). The association for the "POPs without VOCs" group was marginally significant (p-value 0.110). As expected, the adjusted RRs significantly increased among the elderly. Males had a 24% excess rate compared with females. This result is consistent with existing evidence that smoking is a pancreatic cancer risk factor and more prevalent among men. The authors observed a monotonic increase in rate ratios across increasing area-poverty levels among "blacks" peaking at 1.29 (95% CI: 1.11–1.50) in the poorest group (percentage of people living below poverty >20%). However, RRs across area-poverty levels among "whites" were not linear in trend but were consistently lower compared with the reference group (the wealthiest area).

Table 3 presents the sub-group analyses to assess the relationship between the EPC hospitalization rates and selected human carcinogens as identified by the International Agency for Research on Cancer (IARC). Data shown in Table 2 for the "VOCs without POPs" and "POPs without VOCs" groups are also included in Table 3 for compari-

Table 2. Hospitalization for pancreatic cancer during 1996–2013 in New York State excluding New York City

Variable	RR	95% CI	p
Exposure (ref. clean)			
VOCs without POPs	1.06	1.03–1.09	<0.001
VOCs and POPs	1.05	1.01–1.08	0.008
POPs without VOCs	1.04	0.99–1.09	0.110
other	0.94	0.87–1.01	0.091
Gender (ref. female)			
male	1.24	1.21–1.27	<0.001
Age (ref. ≤54 years)			
55–74 years	14.9	14.4–15.5	<0.001
>75 years	34.1	32.8–35.4	<0.001
Poverty			
whites (ref. < 5%)			
5–9%	0.88	0.85–0.91	<0.001
10–20%	0.83	0.80–0.86	<0.001
>20%	0.91	0.86–0.96	0.002
blacks (ref. < 5%)			
5–9%	1.13	0.97–1.31	0.132
10–20%	1.17	1.01–1.36	0.031
>20%	1.29	1.11–1.50	0.001

POPs – persistent organic pollutants; RR – rate ratio; VOCs – volatile organic compounds.
Negative binomial regression model results.

son purposes. Any VOCs or Any POPs groups represent the zip codes that contain HWSs with VOCs and POPs, respectively, without excluding the cross-contaminations of POPs or VOCs. EPC hospitalization rate for any VOCs group was significant (1.06, 95% CI: 1.03–1.08), similar to "VOCs without POPs" group (1.06, 95% CI: 1.03–1.09). The association for any POPs was statistically significant (1.05, 95% CI: 1.02–1.08) and slightly higher than the association for "POPs without VOCs" group.

For chlorinated and non-chlorinated VOCs, non-chlorinated VOCs had a slightly higher RR (RR = 1.09, 95% CI: 1.05–1.13) than chlorinated VOCs (RR = 1.06, 95% CI: 1.03–1.09). From non-chlorinated VOCs, the authors selected benzene, a known carcinogen, and ethylbenzene, a possible carcinogen to humans for further analysis. The authors found a statistically significant association for benzene at 1.12 (95% CI: 1.07–1.16) and an even stronger association for ethylbenzene at 1.34 (95% CI: 1.26–1.42).

For the chemicals in the chlorinated VOCs group, the authors found statistically significant associations for trichloroethylene RR = 1.07 (95% CI: 1.04–1.11), tetrachloroethylene RR = 1.11 (95% CI: 1.07–1.15), and marginally significant association for the vinyl chloride. Chlorinated benzenes were not associated with an increased EPC rate. Chlorinated pesticides (chlordane, DDE, DDD, DDT, dieldrin, endosulfan, endrin, and heptachlor) and PCBs showed increased RRs, respectively, RR = 1.11 (95% CI: RR = 1.05–1.18) and R = 1.05 (95% CI: 1.01–1.09). There was no significant association for PAHs. The quality of fit of the negative binomial model was satisfactory given the value of the Pearson χ^2 and

Table 3. Subgroup analysis, hospitalization for pancreatic cancer during 1996–2013 in New York State excluding New York City

Pollutant	RR	95% CI	Zip codes [n]	p
VOCs				
any	1.06	1.03–1.08	338	<0.001
without POPs	1.06	1.03–1.09	228	0.001
non-chlorinated	1.09	1.05–1.13	111	<0.001
benzene	1.12	1.07–1.16	62	<0.001
ethylbenzene	1.34	1.26–1.42	22	<0.001
chlorinated	1.06	1.03–1.09	261	<0.001
trichloroethylene	1.07	1.04–1.11	101	<0.001
tetrachloroethylene	1.11	1.07–1.15	83	<0.001
vinyl chloride	1.05	1.00–1.11	22	0.07
chlorinated benzenes*	0.99	0.92–1.06	16	0.73
POPs				
any	1.05	1.02–1.08	195	0.002
without VOCs	1.04	0.99–1.09	85	0.110
chlorinated pesticides**	1.11	1.05–1.18	25	0.004
PCBs only	1.05	1.01–1.09	186	0.013
PAHs (non-chlorinated)	1.00	0.90–1.10	19	0.93

PAHs – polyaromatic hydrocarbons; PCBs – polychlorinated biphenyls.
Other abbreviations as in Table 2.
* Chlorinated benzenes included chlorobenzene, dichlorobenzene and monochlorobenzene.
** Chlorinated pesticides included chlordane, DDE, DDD, DDT, dieldrin, endosulfan, endrin, and heptachlor.
Negative binomial regression model results.

the deviance divided by the number of degrees of freedom was close to 1. All statistical analyses were conducted as two-sided with an α level of 0.05 using the Proc Genmod procedure in SAS software v. 9.4.

DISCUSSION

The authors assessed whether living near to a hazardous waste site containing volatile and persistent organic pollutants is associated with rates of pancreatic cancer in the general population, as this has not been studied before. The authors have evidence that residence within a zip code containing HWSs with specific VOCs and POPs is associated with an elevated risk of EPC after adjustment for age, sex, race, and area-poverty status. Overall, the strength of association for VOCs was stronger than POPs, although this must be considered in light of the fact that VOCs are much more volatile than the semi-volatile POPs. Noticeably the strongest associations were found for ethylbenzene and benzene. IARC classified ethylbenzene as "possibly carcinogenic to humans." Ethylbenzene is found at the highest concentration in styrene and plastic production industries and it is one of the most commonly found substances at HWSs. A dose-response relationship between the occupational exposure to ethylbenzene and excess pancreatic cancer risk was reported in a large cohort study among the workers in Denmark, Finland, Italy, Norway, Sweden, and the UK [24]. This finding was also corroborated by the Danish sub-cohort of the study with the significantly increased incidence rate ratio [25] and North American occupational study with increased standardized mortality ratio in styrene chemical

plants [26]. Other occupational studies based on styrene factories also reported suggestive evidence of excess death from pancreatic cancer in the U.S. [27,28].

Benzene is a known human carcinogen especially for hematological cancers. The result for benzene was consistent with major clinic-based case-control study in the U.S. [8] that reported statistically significant (OR = 1.7, 95% CI: 1.23–2.35) association between pancreatic cancer and benzene exposure. However, an occupational exposure study in Spain [13] did not find conclusive evidence (OR = 0.93, 95% CI: 0.47–1.83).

Pesticides, organochlorine insecticides, and PCBs

The authors found a significantly elevated risk of EPC hospitalization (RR = 1.11, 95% CI: 1.05–1.18) associated with chlorinated pesticides (chlordane, DDE, DDD, DDT, dieldrin, endosulfan, endrin, and heptachlor). An occupational study has reported an increased standardized mortality ratio among the workers exposed to DDT [14]. Two studies based on individual-level serum concentrations of specific organochlorines (DDE, DDT, and PCBs) in Spain [18] and the U.S. (DDE, PCB, and trans-nonachlor) [17] reported significantly elevated odds ratios of EPC among the patients with higher serum concentrations of these specific organochlorines compared to controls. However, confidence in the result is limited by the small number of zip codes that contained these chlorinated pesticides. Nevertheless, the observation corroborates existing evidence and is biologically plausible. Questions remain as to which of this group of chlorinated pesticides are responsible for the associations seen.

A significant association for PCBs in this study is consistent with the observations of Porta et al. [18] who reported excess pancreatic cancer incidence among individuals with higher serum PCBs. Hoppin et al. [17] also reported elevated risk of pancreatic cancer in relation serum PCB levels in a case-control study. PCBs as a group consists of a number of different congeners depending on the number of chlorines and their positions around the biphenyl rings. The authors assume the route of exposure in the study is inhalation, and it is the PCB congeners with fewer chlorines that are more volatile, whereas those with more chlorines are more persistent and more likely found in food. The results suggest that lower chlorinated, more volatile PCB congeners contribute to risk of EPC, not just the higher chlorinated congeners that dominate in serum samples. The authors have previously demonstrated elevated cancers due to inhalation of PCBs [15].

Chlorinated hydrocarbon solvents

Residential exposure to trichloroethylene, tetrachloroethylene, and vinyl chloride may constitute a non-negligible risk of EPC. Trichloroethylene and vinyl chloride are "human carcinogens" and tetrachloroethylene is a "probable human carcinogen" according to IARC. Meta-analyses have reported elevated EPC risk associated with chlorinated hydrocarbons (CHC) and weak associations for individual CHCs, trichloroethylene, vinyl chloride, and tetrachloroethylene [7,29,30]. Positive associations related to CHCs were also corroborated by more recent hospital based case-control studies in Spain and USA. The potentially causal effect of VOCs was suggested because KRAS mutated cases were more likely to have been occupationally exposed to chlorinated hydrocarbon solvents compared to non-mutated cases.

For comparison, the authors applied the same study design, statistical methods, and data deduplication algorithm to kidney cancer using the same SPARCS dataset. Hospital discharge cases for kidney cancer were identified by ICD-9-CM code (189) and resulting records were deduplicated by the residential zip, birth-year, birth-month, sex, race, and ethnicity to reduce the multiple hospital records per person. The authors conducted multiple negative binomial regressions adjusting to the same demographic variables used for pancreatic cancer. The authors did not find any statistically significant increase in the kidney

hospitalization rates associated with living in zip codes that contained HWS containing volatile and persistent organic pollutants in comparison to clean sites. While this study has not been published it provides assurance that the findings with pancreatic are not non-specific.

There are some significant limitations of the study. The exposure assessment is limited to residence in a zip code containing a HWS at the time of diagnosis. The authors have no information on occupational exposures, exposure coming from diet, household products and furniture. This is certainly poor exposure assessment, and its validity is not supported by any chemical measurements in the individuals. Moreover it does not account for residential movement. The VOCs, PAHs, and PCBs are ubiquitous in the ambient air as they are regularly produced from motor vehicle emissions, cigarette smoke, and polluted food and consumer production processes. Also, these chemicals occur in a mixture with other pollutants that make measuring and tracking these chemicals in a residential setting very difficult. This reduces the specificity of exposure classifications of the study. Also, the authors do not have individual-level smoking and food consumption data which would account for the significant amount of person-level exposure to PAHs and PCBs. Residential exposure is known to be many times lower than the occupational or point-source exposures such as direct handling of chemicals (i.e., pesticide applications). The exposure assessment is not inclusive of the baseline concentrations of these chemicals in the ambient air.

Despite these limitations, primarily due to poor exposure assessment, the strengths of the study out-way the limitations. Using the SPARCS dataset the authors have a large number of cases of EPC with demographic information that can be matched to the HWS exposure information. The conclusions are in general consistent but expand upon previous occupational studies. The results have important implications because the authors are studying low-level residential exposures that affect a large number of people. The results reported in this study are likely to be the underestimations of actual relationships between the exposure and pancreatic cancer hospitalizations. At minimum, the results demonstrate the need for additional study of the contribution of exposure to organic chemicals to EPC. The results also show the merit of using hospitalization data when cancer registry data is not available for discerning patterns of cancer. Furthermore, the result of this study is generalizable to other locals since there are HWSs everywhere.

CONCLUSIONS

Living near to a HWS containing hazardous organic chemicals is associated with a statistically significant elevation in rates of hospitalization for EPC after adjustment for some of the potential confounders. This finding is consistent with the hypothesis that inhalation of these volatile and semi-volatile chemicals poses an increased risk of development of EPC.

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