Solid waste and pancreatic cancer: an ecologic study in Florida, USA

Gary G Schwartz, Halcyon G Skinner and Robert Duncan

Background
Other than cigarette smoking, modifiable risk factors for pancreatic cancer have not been consistently identified. This study explored the ecologic relationship between pancreatic cancer incidence and measures of cigarette smoking, income, and solid waste collection for Florida's 67 counties.

Methods
We used Florida's population-based cancer registry to compare county-specific incidence rates of pancreatic cancer among Whites to median household income, the per county prevalence of cigarette smoking, and to measures of per capita municipal solid waste collected.

Results
County-specific incidence rates for pancreatic cancer ranged from 0 to 8.1 per 100 000 per year and were significantly correlated with income ($r = 0.35$), cigarette smoking ($r = 0.39$), and solid waste ($r = 0.47$). The correlation between pancreatic cancer and solid waste was largely attributable to one sub-component of solid waste, yard trash (grass clippings, and tree and shrub trimmings) ($r = 0.42$). Using a stepwise regression procedure, only cigarette smoking and yard trash remained significant in the model.

Conclusions
These data suggest that some factor associated with grass and tree trimmings, e.g. insecticides and herbicides, may increase the risk for pancreatic cancer. This hypothesis is consistent with several reports of pancreatic cancer and insecticide exposure in individuals and may suggest new avenues for research in pancreatic cancer.

Keywords
Pancreatic cancer, epidemiology, pesticides, Florida, solid waste, incidence rates

Cancer of the pancreas accounted for approximately 26 300 incident cases and 27 800 deaths in the US in 1996. The similarity in incidence and mortality rates reflects the high lethality of this neoplasm. The median survival of patients with newly diagnosed pancreatic cancer is about 3 months and fewer than 5% of such patients are expected to survive 5 years.

The aetiology of pancreatic cancer is very poorly understood (see Anderson et al. for a comprehensive review of the epidemiology). Despite considerable epidemiological study, the only modifiable risk factor that has been identified consistently is cigarette smoking. However, the increased risk associated with smoking is only about twofold. Thus, the occurrence of pancreatic cancer among non-smokers and among many smokers must be attributed to other factors. These factors are unknown.

We conducted a hypothesis-generating study using county-specific incidence rates for the state of Florida and observed a positive correlation between pancreatic cancer and indices of municipal solid waste, particularly yard trash (grass clippings, and tree and shrub trimmings). This association appears to be independent of the effect of cigarette smoking and supports a link between pancreatic cancer and exposure to insecticides/herbicides. Because there are few leads to the aetiology of this fatal neoplasm, we report our findings in the hope of stimulating further investigation into this association.

Materials and Methods
Incidence data
Age-adjusted incidence rates for pancreatic cancer by county for the period 1981–1994 were obtained from the Florida Cancer Data System (FCDS). Briefly, FCDS was established in 1981 and is the statewide population-based cancer registry for Florida's 67 counties. The FCDS collects information on malignant neoplasms diagnosed in all Florida hospitals and has been estimated to be successful in capturing greater than 95% of cancers diagnosed in Florida. Of the cases of pancreatic cancer reported to FCDS during this time period, 80% were confirmed pathologically. Because countywide data for pancreatic cancer in non-Whites were very sparse, the analyses were restricted to Whites.
Exposure data

Florida law defines ‘solid waste’ to include: ‘garbage, refuse, yard trash, clean debris, white goods (inoperative and discarded refrigerators, ranges, and other large appliances), special wastes, ashes, sludge, or other discarded material, including solid, liquid, semisolid, or contained gaseous material resulting from domestic, industrial, commercial, mining, agricultural or governmental operations’. Yard trash refers to ‘vegetative matter resulting from landscaping maintenance or land clearing operations and includes materials such as tree and shrub trimmings, grass clippings, palm fronds, trees and tree stumps’ (p.42). Data on solid waste per county were obtained from the Florida 1996 Solid Waste Management Report (via the Internet), and the 1996 Florida Statistical Abstract. We calculated the variable, ‘per capita solid waste’, as the average of municipal solid waste in tons collected in each county for the years 1994 and 1995, divided by the county population, as reported in the 1990 Florida Census Handbook. Because the category ‘solid waste’ is very heterogeneous, we examined the data on solid waste stratified by four of its major sub-components: paper, construction and demolition debris, yard trash, and food waste. These categories comprise (respectively) 27, 24, 14, and 5% of solid waste collected in Florida by weight (total, 70%). The remaining categories of solid waste are metals (10%), miscellaneous (7%), plastics (5%), glass (3%), textiles (3%), and tyres (1%).

Hazardous waste refers to solid waste defined as ‘hazardous’ by Florida Administrative Code Rule 62-730.020. In general, this category includes (among other things), biomedical waste, laboratory discharge, solvents, heavy metals, and mercury-containing devices. Data on hazardous waste were obtained from the 1991–1993 Biennial Hazardous Waste Report Data for Florida Large Quantity Generator Sites (via the Internet). We calculated the variable, ‘hazardous waste per capita’, as the total tons of reportable hazardous waste per county divided by the county population (as above).

Potential confounders

The only established behavioural risk factor for pancreatic cancer is cigarette smoking. Socioeconomic status has been implicated in some studies of pancreatic cancer, although the data are inconsistent. Both smoking status and socioeconomic status were considered potential confounders.

We used two measures of smoking status: lung cancer incidence rates per county, and the percentage of smokers among pancreatic cancer patients per county. Data on county-specific lung cancer incidence rates for the period 1981–1994 were obtained from FCDS. Data on the smoking status of individual patients with pancreatic cancer were abstracted from patients’ medical records by trained abstractors who were unaware of the hypothesis under study. Smoking was classified as ‘Yes’ (for presently a cigarette smoker), ‘No’ (not presently a cigarette smoker), and ‘Unknown’. We defined the variable, ‘per cent smokers’, as the percentage of all pancreatic cancer cases per county who were presently cigarette smokers. ‘Per cent smokers’ were also calculated separately by gender.

‘Median household income’ per county among Whites was used as the measure of socioeconomic status. These data were obtained from the 1990 Florida Census Handbook. Three counties without reported income data (Dixie, Gilchrist, Lafayette) were censored from the analyses.

Linear models

We calculated Pearson correlation coefficients (r) between pancreatic cancer incidence rates by county and county data for per capita collected municipal solid waste, per capita generated hazardous waste, smoking status, and median household income. Correlation coefficients were generated for each independent variable using both sexes combined and for each sex separately. In order to assess possible non-linear relationships, scatter plots were examined between pancreatic cancer incidence rates and each independent variable.

Results

During 1981–1994, a total of 18 050 incident cases of pancreatic cancer among Whites were reported to FCDS, for a state rate of 7.20 per 100 000 per year (age-adjusted, both sexes combined). For males, the rate was 8.46 per 100 000 (N = 9126 cases) and for females, the rate was 6.18 per 100 000 (N = 8924). Age-adjusted incidence rates for pancreatic cancer in Florida’s 67 counties are shown in Figure 1. These rates range from 0 per 100 000 per year to 8.1 per 100 000 per year (based on 14 cases) (Hamilton and Franklin Counties, 1990 populations: 11 918 and 9995 respectively).

Among pancreatic cancer cases, 40.2% were classified as smokers, and 40.3% as non-smokers. The smoking status for 19.5% of cases was unknown.

Incidence rates for pancreatic cancer were not significantly correlated with hazardous waste (r = 0.11, P = 0.40). Conversely, pancreatic cancer was significantly correlated with per cent smokers, median household income, and solid waste (Table 1).

All of the variables that were significantly correlated with pancreatic cancer incidence for both sexes combined showed similar relationships for males and females separately. Of the individual sub-components of solid waste, neither construction and demolition debris nor food waste was significantly correlated with pancreatic cancer (r = 0.02 and 0.10, respectively). Conversely, significant correlations were observed for both paper and yard trash (r = 0.25 and 0.42, respectively).

Regression analysis

Inspection of the scatter plot between pancreatic cancer incidence rates and yard trash indicates that the relationship between these variables is curvilinear and is not greatly influenced by the presence of one or two extreme values (Figure 2). We explored this relationship by adding a squared term, [yard trash]², to the linear model of pancreatic cancer versus yard trash. After fitting the linear term, yard trash, [yard trash]² showed a significant negative regression (β₂ = -16.65, P = 0.04). In order to examine the influence of yard trash on pancreatic cancer using linear regression, we created the linearized variable ‘linear yard trash’ = β₀ + β₁ [yard trash] + β₂ [yard trash]².

The contributions of smoking status, socioeconomic status, paper waste, and linear yard trash were examined by stepwise linear regression using an α level of >0.05 to reject a variable from the model. Because the variable, ‘per cent cigarette smokers’, was based on individual (rather than group) level data, we used this variable as the measure of smoking status.

The variables income (P = 0.08) and paper waste (P = 0.80) were rejected from the model; per cent smokers (P = 0.004) and linear yard trash (P = 0.0001) were retained (Table 3).
1. Escambia 24. Gilchrist 47. Hillsborough
2. Santa Rosa 25. Levy 48. Polk
5. Holmes 28. Union 51. St. Lucie
11. Gadsden 34. Putnam 57. Desoto
12. Liberty 35. Flagler 58. Charlotte
14. Wakulla 37. Volusia 60. Martin
15. Leon 38. Seminole 61. Palm Beach
17. Madison 40. Orange 63. Lee
18. Taylor 41. Lake 64. Collier
19. Dixie 42. Sumter 65. Broward
21. Suwanee 44. Hernando 67. Monroe
22. Hamilton 45. Pasco
23. Columbia 46. Pinellas

Figure 1 County-specific incidence rates for pancreatic cancer in Florida, 1981–1994, Whites, both sexes combined

Table 1 Pearson correlation coefficients versus pancreatic cancer incidence, stratified by gender

<table>
<thead>
<tr>
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<th>Men</th>
<th>Women</th>
<th>All</th>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Lung cancer incidence</td>
<td>0.3799</td>
<td>0.0020</td>
<td>0.3027</td>
</tr>
<tr>
<td>Per cent cigarette smokers</td>
<td>0.2389</td>
<td>0.0573</td>
<td>0.5085</td>
</tr>
<tr>
<td>Median household income</td>
<td>0.3339</td>
<td>0.0070</td>
<td>0.2564</td>
</tr>
<tr>
<td>Solid waste</td>
<td>0.4218</td>
<td>0.0004</td>
<td>0.3905</td>
</tr>
<tr>
<td>Hazardous waste</td>
<td>0.1275</td>
<td>0.3315</td>
<td>0.1875</td>
</tr>
</tbody>
</table>

Table 2 Pearson correlation coefficients and P-values of sub-components of solid waste versus pancreatic cancer incidence, stratified by gender

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<th>Men</th>
<th>Women</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Construction &amp; demolition</td>
<td>0.0746</td>
<td>0.5580</td>
<td>-0.0265</td>
</tr>
<tr>
<td>Food</td>
<td>0.1179</td>
<td>0.3536</td>
<td>0.0435</td>
</tr>
<tr>
<td>Paper</td>
<td>0.2649</td>
<td>0.0344</td>
<td>0.1804</td>
</tr>
<tr>
<td>Yard trash</td>
<td>0.3687</td>
<td>0.0027</td>
<td>0.3513</td>
</tr>
</tbody>
</table>
Examination of the stepwise linear regression between linear yard trash and pancreatic cancer by sex indicated similar effects for each sex with no evidence of effect modification ($r = 0.433$, $P = 0.0004$; $r = 0.370$, $P = 0.003$, males and females, respectively, Table 4).

**Discussion**

County-specific incidence rates of pancreatic cancer among Whites in Florida ranged from 0.0 to 8.1 cases per 100 000 per year. If counties with rates that are possibly statistically unstable are excluded (i.e. excluding counties that had fewer than 5 cases each, $[N = 5]$), the incidence rates for pancreatic cancer among Whites in Florida range fourfold, from 2.1 to 8.1 cases per 100 000 per year. Considering that the variation in pancreatic cancer incidence rates worldwide is about 30-fold, a fourfold variation within one race, within a relatively small geographical area, and over a relatively long period of time (14 years), is remarkable. These data appear to contrast with those reported by Blot et al. who noted little regional variation in pancreatic cancer mortality rates during 1950-1969 for the US as a whole. It is probable that this discrepancy, at least in part, reflects differences in scale. Blot et al. sought to identify broad regional differences in mortality rates whereas we sought to explore variability within a small area.

We observed a significant effect for smoking, a finding consistent with most studies of pancreatic cancer. The smoking variable we used was relatively crude, since it represented present, rather than past smoking. However, we observed similar results using lung cancer incidence rates, which have been shown to be a good surrogate for past cigarette smoking.

Pancreatic cancer incidence rates were significantly correlated with median household income. However, this effect did not remain significant in the multiple regression model. Both positive, negative, and no effect for socioeconomic status have been reported for pancreatic cancer. Although some more recent studies have found an association with higher social class, socioeconomic status generally is not considered to be a strong or consistent risk for pancreatic cancer.

We observed a significant correlation between pancreatic cancer incidence and per capita solid waste. This finding was not predicted a priori and may be due to chance. However, chance seems an unlikely explanation because significant correlations of similar magnitude were found separately for each sex between solid waste and pancreatic cancer, and between sub-components of solid waste and pancreatic cancer. Of the
sub-components of solid waste, significant correlations were observed for paper and for yard trash. However, only linear yard trash and smoking remained significant following a stepwise regression procedure that included income. Because only three correlations were made with the data on pancreatic cancer before the finding for solid waste was observed, these findings are not the fortuitous results of many statistical tests (i.e. multiple comparisons).

This study is subject to several potential biases. Chief among these is the ecological fallacy, i.e. the possibility that associations observed at the level of the group do not reflect associations at the level of the individual. To our knowledge, no previous studies have examined the risk of pancreatic cancer in relation to yard trash in individuals. However, a significantly increased 3.6-fold risk for pancreatic cancer was reported for male gardeners and groundsman in Finland, an occupational group likely to have high exposure to yard trash. The association between employment as a gardener and groundsman remained significant after adjustment for potential confounders including age, smoking, alcohol consumption and diabetes.

Another potential sources of bias is the misclassification of disease and exposure. Because there are no effective treatments for most cases of pancreatic cancer, many people seriously ill with a presumed cancer of the pancreas are not subjected to biopsy. This has resulted in pancreatic cancer having the lowest rate of biopsy-confirmed cancer for any major neoplasm. The mean rate of biopsy-confirmed pancreatic cancer in Florida, 80%, compares favourably with the national average (77%), and did not show appreciable differences by county. Thus, any misclassification caused by the inaccurate identification of cases is likely to be non-directional and thus to underestimate the true size of the correlation coefficients. This study assumes that the exposure, county of residence, reflects residence at a time that is causally important for the development of pancreatic cancer. The residential history of people in this study was unknown. Because Florida is a popular destination for migrants (e.g. retirees and immigrants), it is likely that some aetiological exposures for pancreatic cancer occurred prior to migration. However, our data do not support the hypothesis that the high rates observed in many Florida countries are the result of migration. For example, the highest rates of pancreatic cancer in Florida occur in Franklin, Hendry, and Gadsden counties. During the period 1970–1980, these counties experienced 54, 74 and 0% population growth due to migration (respectively), compared to 92.0% for Florida overall.

Lastly, it is possible that the findings for linear yard trash are the result of confounding. The only known confounder for pancreatic cancer is cigarette smoking. The addition of linear yard trash to a regression model containing smoking added significantly to the model's predictive power for both males and females. Thus, we conclude that the effect for linear yard trash is unlikely to be the result of confounding by smoking. However, because the information on smoking was relatively crude (Yes/No for presently a smoker), some residual confounding by smoking can not be excluded.

Despite the limitations inherent in ecological studies, this study has several strengths. Unlike many ecological studies in which the ecological units are large, e.g. countries, we studied relatively homogeneous units, counties, within a single state. This would tend to minimize misclassification of disease caused by factors such as unequal access to medical facilities and variation in diagnostic practices. Additionally, because of regulatory aspects of solid waste disposal (disposers of solid waste in Florida are taxed according to the type and amount of waste), records on solid waste are exceptionally detailed. This is likely that some aetiological exposures for pancreatic cancer may be able to detect other risk factors that have not yet been established. What hypothesis might these findings suggest? We consider that yard trash per se is unlikely to be a pancreatic carcinogen. However, in a sub-tropical region like Florida, yards are often

<p>| Table 3 | Stepwise linear regression using the variables: smoking, income, linear yard trash, and paper waste versus pancreatic cancer incidence rates, both genders combined |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>Student's t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>2.21223</td>
<td>0.60744</td>
<td>3.64</td>
<td>0.0006</td>
</tr>
<tr>
<td>Per cent smokers</td>
<td>0.03964</td>
<td>0.01321</td>
<td>3.00</td>
<td>0.0039</td>
</tr>
<tr>
<td>Linear yard trash</td>
<td>0.89803</td>
<td>0.21860</td>
<td>4.11</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

| r = 0.5770 |

<p>| Table 4 | Results of a stepwise linear regression using the variables: smoking, income, linear yard trash, and paper waste versus pancreatic cancer incidence rates, stratified by gender |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
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<tr>
<td>Coeff.</td>
<td>SE</td>
<td>Student's t</td>
<td>P</td>
<td>Coeff.</td>
<td>SE</td>
<td>Student's t</td>
<td>P</td>
<td></td>
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</tr>
<tr>
<td>Per cent smokers</td>
<td>0.03080</td>
<td>0.01429</td>
<td>2.15</td>
<td>0.0351</td>
<td>0.05223</td>
<td>0.01258</td>
<td>4.15</td>
<td>0.0001</td>
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<tr>
<td>Linear yard trash</td>
<td>1.2585</td>
<td>0.30772</td>
<td>4.08</td>
<td>0.0001</td>
<td>0.56617</td>
<td>0.23400</td>
<td>2.42</td>
<td>0.0185</td>
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<td></td>
</tr>
<tr>
<td>r = 0.5092</td>
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Women | 0.5688
treated with insecticides and herbicides. For example, a survey of surface water and soil samples from Florida counties indicated that the pesticides Atrazine, DDT, and DDE, are common environmental contaminants. Pesticides have been associated with an increased risk of pancreatic cancer in several epidemiological studies. For example, in an exploratory case-control study, Friedman et al. reported a significant association between pancreatic cancer and exposure to ‘insect or plant sprays’. Alavanja et al. reported a significantly increased risk for pancreatic cancer among workers in flour mills, a job site where pesticides are used more frequently than in other branches of the grain industry. Garabrant et al. reported a 4.8-fold increased risk of pancreatic cancer among individuals exposed to DDT. Similarly, among farmers in Italy, Forastiere et al. found a significantly elevated odds ratio for pancreatic cancer among licensed pesticide users. Conversely, a significantly decreased standardized incidence ratio for pancreatic cancer was observed for licensed applicators in Sweden. However, the mean follow-up for that cohort (12.2 years) was very short. A significant fivefold risk of pancreatic cancer was reported in male chlorohydrin production workers exposed to ethylene dichloride, a constituent of liquid fumigants used to control insects. Finally, Fryzek et al. reported a 10.7-fold significantly increased odds of exposure to the organochlorine pesticide Ethylan among pancreatic cancer cases in Michigan.

Laboratory evidence supports the hypothesis that some insecticides may be pancreatic carcinogens. For example, dichlorvos (dichlorovinyl dimethyl phosphoric acid ester) is a cholinesterase inhibitor used widely in indoor and outdoor areas as an insecticide. Neoplasms of the exocrine pancreas have been reported following dichlorvos administration by gavage to Fischer rats and to B6C3F1 mice. Mutations in the p16, p53, and DPC4 tumour suppressor genes, and in the K-ras oncogene have been associated with pancreatic cancer and may be influenced by environmental exposures. For example, piperonyl butoxide (α-[2-(2-butoxyethoxy) ethoxy]-4,5-methylenedioxy-2-propyltoluene) (PB), an insecticide synergist, is known to induce mutations in codon 12 of the K-ras gene. Mutations in the K-ras gene, in the 12th codon in particular, are found in the vast majority of human adenocarcinomas of the pancreas and are believed to represent an early event in pancreatic carcinogenesis. Thus, insecticides are a biologically plausible cause of pancreatic cancer. However, the route(s) of exposure by which these agents could influence pancreatic (or other) cancer in non-occupationally exposed people is unknown.

In conclusion, we observed a positive correlation between yard trash per capita and countywide incidence rates for pancreatic cancer in Florida counties. This relationship is not explainable by known risk factors for pancreatic cancer and suggests a link between pancreatic cancer and exposure to insecticides and/or herbicides. It would be valuable to attempt to replicate these findings using similar data from locations, e.g. other US states. Further study of the risk of pancreatic cancer among workers in the lawn care industry and among members of garden clubs would be especially informative.

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References