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A CASE-CONTROL STUDY OF SELF-REPORTED EXPOSURES TO PESTICIDES AND PANCREAS CANCER IN SOUTHEASTERN MICHIGAN

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A case-control study of pancreas cancer in residents, aged 30–79 years, of 18 counties in southeastern Michigan was conducted to investigate the risks of exposure to DDT and related materials in the general population. Sixty-six people with cytologically diagnosed pancreas cancer were identified using 7 participating hospitals in metropolitan Detroit and Ann Arbor. One hundred and thirty-one controls were frequency-matched to the cases on age, sex, ethicity and county of residence by random-digit dialing. All study participants were administered a questionnaire to assess life-time exposure to pesticides from both environmental and occupational sources, family history of cancer, past medical history, smoking history and demographic information. A statistically significant increased risk was found for self-reported exposure to ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane). Increased odds ratios were observed for self-reported exposures to chloropropylate and DDT, as well as for the summary group of organochlorine pesticides which included all of these materials, though these associations were not significant. ***Int. J. Cancer*** **72:62–67, 1997.**

Pancreas cancer is the 5th leading cause of cancer mortality, preceded only by lung, colorectal, prostate and breast cancers. It has the poorest survival rate of any major malignancy, with only 4% of pancreas cancer patients surviving for 5 years (American Cancer Society, 1996). The etiology of pancreas cancer is poorly understood. Cigarette smoking is the only risk factor consistently associated with pancreas cancer in epidemiologic research, accounting for approximately 14% of all cases (Fernandez *et al.,* 1996). Other potential risk factors (diet, coffee consumption, diabetes, pancreatitis, allergies, tonsillectomy and family history of pancreas cancer) are inconsistently associated with pancreas cancer across studies, and some of these factors (*e.g.,* diabetes) may be early signs of clinical disease rather than etiologic risk factors (Fernandez *et al.,* 1996). If these factors are involved in the etiology of pancreas cancer, it is unlikely that they account for a large percentage of cases.

Garabrant *et al.* (1992) reported a strong association between occupational exposure to DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) and pancreas cancer in a case-control study of chemical manufacturing workers. In that study, they also observed an independent association of pancreas cancer with 2 closely related materials, DDD (1,1-dichloro-2,2-bis(4-chlorophenyl)-ethane) and ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl)ethane). DDD is one of the major metabolites of DDT. Analyses by duration of exposure and by latency since first exposure further substantiated these associations and demonstrated a 7-fold risk among those with the highest exposure to DDT.

Although DDT was banned from use in 1972 in the United States, exposure to the general population remains a concern. DDT is a persistent environmental pollutant and is present in the food chain through sources such as fish and game (U.S. Department of Health and Human Services, 1992; Evans *et al.,* 1991). DDT continues to be manufactured in other countries and is an important insecticide for malaria control (U.S. Department of Health and Human Services, 1992). Furthermore, a number of chemically related organochlorines are currently in use in the United States (methoxychlor, dicofol). Studies of breast cancer risk related to DDE, which is the major DDT metabolite stored in adipose tissue, illustrate that ongoing concern about health effects is justified (Wolff *et al.,* 1993). All of these issues suggest that exposure of the general population to DDT and related organochlorine compounds is an ongoing concern.

We have completed a case-control study of pancreas cancer in the general population of southeastern Michigan. Sixty-six people with pancreas cancer and 131 controls were interviewed in person to ascertain smoking behaviors, past medical conditions, family history of cancers, demographics and life-time exposure to pesticides. The primary goal of our study was to examine the risks associated with self-reported exposure to organochlorines and pancreas cancer.

DDT and related compounds were the major pesticides of interest in this research. Specifically, these compounds included DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane), bulan (2-nitro-1,1-bis(4-chlorophenyl) butane), chlorfenethol (1,1-bis(4-chlorophenyl) ethanol), chloropropylate (isopropyl 4,4′-dichlorobenzilate), dicofol (2,2,2-trichloro-1,1-bis(4-chlorophenyl) ethanol), ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane), methoxychlor (1,1,1-trichloro-2,2-bis(4-methoxyphenyl) ethane and TDE (1,1-dichloro-2,2-bis(4-chlorophenyl) ethane). All of these compounds were used primarily for the control of insects in the home and on crops. They were chosen for study based on the high probability that these insecticides were used in southeastern Michigan.

MATERIAL AND METHODS

Recruitment of cases and controls began on September 1, 1994. The data presented here include all cases and controls identified through August 15, 1995.

Case ascertainment

Patients with exocrine pancreas cancer were identified in 5 large hospitals in the Detroit metropolitan area and in the 2 teaching hospitals of the University of Michigan in Ann Arbor. A rapid case-finding system was built on hospital tumor registries, pathology departments and physicians' offices of the participating hospitals, allowing newly diagnosed cases to be contacted and interviewed within a short time of diagnosis. Fifty percent of the eligible cases were interviewed within 2 weeks of their identification, 73% within 3 weeks and over 80% within 4 weeks. Eligible

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cases included those with a cytologically diagnosed adenocarcinoma of the exocrine pancreas (topography codes C25.0–C25.3 and C25.7), aged 30–79 years, who were residents of southeastern Michigan at the time of diagnosis (specifically, Hillsdale, Lenawee, Monroe, Jackson, Washtenaw, Wayne, Ingham, Livingston, Oakland, Macomb, Shiawassee, Genesee, Lapeer, St. Clair, Bay, Gratiot, Midland, or Saginaw counties), who spoke English and who had a working telephone number. Of the 107 people with pancreas cancer who were eligible for study, 22 had died before contact could be made and 3 were not contacted because their physicians refused. The remaining 82 people were invited to join the study, of whom 66 (80.5%) agreed.

Control ascertainment

Population-based controls were selected during the same time period that cases were identified. To be eligible for the study, controls were 30–79 years old, residents of southeastern Michigan (in the same 18 counties as cases), English-speaking and living in a household with a working telephone number. Controls were frequency-matched to cases by age group (30–44, 45–59, 60–69, 70–79), gender, ethnicity (African-American *vs.* other) and county group of residence (counties were grouped into 9 different areas based on population size and proximity to each other). Standard random-digit dialing techniques based on the Waksberg method (Groves *et al.*, 1988) were used to recruit controls. Once a residential number was reached, a household census was taken to determine if any eligible control resided in the home. If more than one eligible control was present in a household, one was randomly chosen. The eligible control was then given a brief summary of the study protocol and invited to join the study. Those who refused were mailed a letter which explained the study protocol in more detail and were then recontacted and encouraged to participate. Less than 5 refusals actually were converted to participants. Since it was imperative that cases were interviewed as quickly as possible due to the short survival of pancreas cancer patients, we attempted to secure the consent of the eligible controls as quickly as possible. Over 70% of the controls were interviewed within 2 weeks of their identification and over 90% within 3 weeks. A total of 482 households were identified through random-digit dialing to contain at least one eligible control. Thirty percent (146/482) of the eligible controls agreed on the phone to participate in the study, and in-person interviews were completed with 89.7% (131/146) of these.

Questionnaire

Life-time exposure to pesticides was measured using a structured questionnaire. The interviewer first created a time line of major events in the subject's life (*i.e.,* completion of school, marriages, births of children, purchase of homes or farms, deaths) to help them increase their ability to recall specific past exposure by establishing the temporal relationships among pesticide-exposure events. Within this time framework, the interviewer asked the subject to recall specific activities which may have involved pesticide exposures, such as housework, gardening and yard work. Subjects were then asked if they had used any pesticides during these activities to kill insects, mice or weeds. Next, subjects were questioned about their use of DDT and other specific organochlorines during these activities. To facilitate their recall, subjects examined a series of cards containing the trade names and commercial names of the pesticides of interest (DDT and chemically related organochlorines). Subjects were further asked to indicate if they had used any other pesticides not mentioned on the series of cards. Next, an occupational history was taken to examine job-associated pesticide exposures. For each job held for at least 6 months after age 18, subjects were questioned on dates of employment, employer, occupation, tasks performed, specific materials used and frequency of specific materials used. For each pesticide the subject had used, the interviewer probed further to determine the frequency and duration of use.

Other information collected by the interviewer included the subject's cigarette smoking history, demographic information (age, sex, ethnicity, marital status, education and income), self-reported medical conditions (including diabetes, allergies, tonsillectomy, pancreatitis, abdominal surgery, gastro-intestinal disease, frequent loose stools, constipation, laxative use and antacid use) and family history of cancer. A family history of pancreas cancer, leukemia, lymphoma, soft-tissue sarcoma or breast cancer was of particular interest since these tumors have been associated with DDT exposure in other studies (Wolff *et al.*, 1993; Woods *et al.*, 1986).

Statistical methods

Statistical analyses were performed using the Statistical Analysis System (SAS Institute, 1988). Crude odds ratios (ORs) and 95% test-based confidence intervals were calculated for each of the major independent variables (insecticide, herbicide and rodenticide use in each 10-year time period, as well as any exposure to bulan, chlorfenethol, chloropropylate, dicofol, ethylan, methoxychlor or TDE). Co-variates were considered to be potential confounders if they were known or strongly suspected *a priori* to cause pancreas cancer (*e.g.,* smoking) or if they were associated with both pancreas cancer and the exposure of interest in the data. Factors were regarded as effect modifiers if stratification on the factor produced associations between the major independent variable and pancreas cancer which differed across the strata. Exposures investigated as confounders and effect modifiers included age, sex, ethnicity, ever smoked cigarettes, family history of cancer, family history of breast cancer and a physician-diagnosed stomach ulcer at least 5 years prior to interview.

Unconditional logistic regression analyses were conducted to explore relationships between the co-variates and pancreas cancer and to estimate ORs and 95% confidence intervals (CIs) (Breslow and Day, 1980). Multiple logistic regression models were built for the main effects of the major independent variables, with significant interaction terms and potential confounding variables included. Final adjusted odds ratios (aORs) were derived from the logistic regression model which best fit the data (as determined by the -2 log likelihood statistic). Both ORs and aORs are reported.

Logistic regression analyses were employed to test the association between pancreas cancer and general pesticide exposures (ever use of any insecticide, rodenticide or herbicide) for 5 time periods (1945–1955, 1956–1965, 1966–1975, 1976–1985, 1986–1995). Data on specific residential and occupational organochlorine pesticide exposures were combined due to the small number of subjects reporting work-related pesticide exposures. For the initial analyses of specific pesticides, DDT and other organochlorine exposures were categorized as ever *vs.* never used. Further analyses were conducted on DDT and ethylan to determine the association between low and high exposure to the pesticide and pancreas cancer. Dose was calculated by multiplying the frequency of exposure by the duration of exposure. Low- and high-exposure categories were calculated using the frequency distribution of the cases and controls combined. Those individuals who used the pesticide and who fell below the mean dose level were categorized as low-exposure, while those individuals above the mean were categorized as high-exposure.

RESULTS

Study subject characteristics

Cases were slightly older than controls (62.7 *vs.* 59.5 years, $p = 0.04$) (Table I). However, the proportion of cases in each age category did not differ significantly from the controls ($p = 0.47$). Cases and controls did not differ appreciably on gender, ethnicity, income, education or county group.

Life-style factors, medical conditions and family history of cancer

Pancreas cancer cases were 2 times more likely to smoke than controls. This effect was greatest in cases who currently smoked (OR = 2.5, 95% CI = 1.1–5.4). Cases had significantly increased

TABLE I – CHARACTERISTICS OF PANCREAS CANCER CASES AND CONTROLS IN SOUTHEASTERN MICHIGAN, 1994–1995

	Case (n = 66)	Control (n = 131)
Age (years)		
30–44	3 (4.6%)	11 (8.4%)
45–59	22 (33.3%)	46 (35.1%)
60–69	21 (31.8%)	46 (35.1%)
70–79	20 (30.3%)	28 (21.4%)
Mean age (SD)[1]	62.7 (10.2)	59.5 (11.4)
Gender		
Male	31 (47.0%)	64 (48.9%)
Female	35 (53.0%)	67 (51.2%)
Ethnicity		
African-American	9 (13.6%)	14 (10.7%)
Other	57 (86.4%)	117 (89.3%)
Education (years)		
0–8	3 (4.5%)	9 (6.7%)
9–12	36 (54.6%)	46 (35.1%)
>12	26 (39.4%)	76 (58.1%)
Refusal	1 (1.5%)	0 (0.0%)
Income		
0–$14,000	7 (10.6%)	19 (14.5%)
15–$24,000	16 (24.2%)	25 (19.1%)
25–$39,000	8 (12.1%)	22 (16.8%)
40–$69,000	12 (18.2%)	28 (21.4%)
$70,000+	19 (28.8%)	32 (24.4%)
Refusal	4 (6.1%)	5 (3.8%)

[1]SD, standard deviation.

odds of being diagnosed with a stomach ulcer at least 5 years prior to interview (OR = 3.9, 95% CI = 1.6–10.0). Pancreas cancer cases were more likely to have a first-degree relative with cancer compared to controls (OR = 1.9, 95% CI = 1.0–3.6). A suggestive but non-significant OR was found for cases having a first-degree relative with pancreas cancer (OR = 3.1, 95% CI = 0.5–18.9). Cases were no more likely than controls to have a first-degree relative with lymphoma, leukemia or soft-tissue sarcoma; however, subjects with pancreas cancer were 2.9 times (95% CI = 1.3–6.9) more likely to have a relative with breast cancer than controls (Table II).

Pesticide exposures

After adjusting for a stomach ulcer 5 years prior to interview and a first-degree relative with breast cancer, the largest ORs for insecticide, rodenticide and herbicide exposures occurred in the earliest time period. The aOR for pancreas cancer cases reporting insecticide exposure was significantly increased in the 1945–1955 time period (aOR = 2.6, 95% CI = 1.3–5.0). The aORs for insecticides and rodenticides decreased sequentially in more recent periods, while the ORs for herbicides suggest risk even in later periods (Table III). This effect was not confounded by age.

None of the variables investigated as potential confounders or effect modifiers (age, sex, ethnicity, ever smoked cigarettes, family history of cancer, family history of breast cancer and a physician-diagnosed stomach ulcer at least 5 years prior to interview) appreciably altered the crude estimate of the association between pancreas cancer and specific organochlorine insecticides.

Non-significantly increased ORs were found for the association between pancreas cancer and chloropropylate, DDT, dieldrin and any organochlorine use (Table IV). A large and statistically significant risk was found for subjects who had ever used ethylan. Cases were 10.7 (95% CI = 1.2–93.2) times more likely to report exposure to ethylan compared to controls. The interaction between DDT and ethylan was also examined (Table V). Three of the cases and no controls reported exposure to both DDT and ethylan (OR = ∞). The OR for DDT exposure alone (no ethylan) was 1.4, while that for ethylan was 4.5. These relationships suggest that interaction between DDT and ethylan may take place. However, caution should be used in the interpretation of these results as the number of individuals is quite small (n < 25).

TABLE II – UNIVARIATE ANALYSIS OF LIFE-STYLE FACTORS, MEDICAL CONDITIONS AND FAMILY HISTORY OF CANCER, 1994–1995

	Case/ control	OR[1]	95% CI
Never smoked cigarettes	19/59	1.0	Reference
Ever smoked cigarettes	47/72	2.0[2]	1.1–3.8
Former smoker	28/48	1.8	0.9–3.6
Current smoker[2]	19/24	2.5*,[4]	1.1–5.4
History of stomach ulcer at least 5 years prior to interview	12/7	3.9*	1.6–10.0
Family history of cancer[3]			
All cancers combined	46/71	1.9*	1.0–3.6
Pancreas cancer	3/2	3.1	0.5–18.9
Lymphoma, leukemia, or soft-tissue sarcoma	2/5	0.8	0.2–4.3
Breast cancer	14/11	2.9*	1.3–6.9

[1]Crude odds ratio.–[2]Includes subjects who quit smoking within 1 year of the interview.–[3]Cancer in first-degree relatives.–[4]Two-tailed test for trend (never, former, current smoker), $p = 0.02$.
*Significant at $p < 0.05$.

TABLE III – NUMBER OF CASE AND CONTROL SUBJECTS AND ODDS RATIOS FOR GENERAL MEASURES OF PESTICIDE EXPOSURES IN DEFINED TIME PERIODS, 1994–1995

Time period	Case/ control	Crude OR	Adjusted OR[1]	95% CI
Ever use insecticides				
1945–1955	35/47	2.2	2.6*	1.3–5.0
1956–1965	38/66	1.4	1.3	0.7–2.4
1966–1975	45/91	1.0	1.0	0.5–2.0
1976–1985	45/96	0.8	0.7	0.4–1.5
1986–1995	42/100	0.5	0.5	0.2–1.0
All years	56/114	0.8	0.8	0.3–1.8
Ever use herbicides				
1945–1955	14/17	1.8	1.9	0.8–4.2
1956–1965	20/37	1.1	1.1	0.6–2.2
1966–1975	25/54	0.9	0.8	0.4–1.6
1976–1985	29/59	1.0	1.0	0.5–1.8
1986–1995	29/68	0.5	1.6	0.8–3.0
All years	42/85	0.9	0.9	0.7–1.8
Ever use rodenticides				
1945–1955	14/17	2.0	2.0	0.8–5.2
1956–1965	20/37	1.7	1.8	0.8–4.0
1966–1975	25/54	1.1	1.0	0.5–2.1
1976–1985	29/59	1.1	1.2	0.6–2.4
1986–1995	29/68	0.8	0.8	0.4–1.7
All years	42/85	0.9	0.9	0.7–1.8

[1]Adjusted for stomach ulcer 5 years prior to interview and first-degree relative with breast cancer.
*Significant at $p < 0.05$.

TABLE IV – NUMBER OF CASE AND CONTROL SUBJECTS AND ODDS RATIOS FOR EVER *VS.* NEVER USE OF ORGANOCHLORINES, 1994–1995

	Case/control	OR[1]	95% CI
Bulan	0/1	—	—
Chlorfenethol	1/0	—	—
Chloropropylate	2/2	2.0	0.3–14.6
DDT	17/23	1.6	0.8–3.1
Dicofol	0/3	—	—
Ethylan	5/1	10.7*	1.2–93.2
Methoxychlor	3/7	0.8	0.2–3.4
TDE	0/2	—	—
Any organochlorine	21/31	1.5	0.8–2.9

[1]Crude odds ratio.
*Significant at $p < 0.05$.

The association between pancreas cancer and low and high exposure to DDT and ethylan is given in Table VI. The data suggest that a dose–response relationship may exist for both DDT and

TABLE V – ODDS RATIOS FOR INTERACTION BETWEEN DDT AND ETHYLAN, 1994–1995

	DDT		No DDT		Case/control	OR (95% CI)
	Case/control	OR (95% CI)	Case/control	OR (95% CI)		
Ethylan	3/0	∞	2/1	4.5 (0.4–51.5)	5/1	10.7 (1.2–93.2)
No ethylan	14/23	1.4 (0.7–2.9)	47/107	1.0 (reference)		
	17/23	1.6 (0.8–3.3)				

TABLE VI – DOSE–RESPONSE FOR DDT[1] AND ETHYLAN, 1994–1995

Compound	Case/control	OR	95% CI
Low DDT exposure	5/10	1.1	0.4–3.3
High DDT exposure	7/9	1.7	0.6–4.8
Low ethylan exposure	2/1	4.3	0.4–47.9
High ethylan exposure	3/0	∞	

[1]Missing values for 5 cases and 4 controls.

ethylan. The risks are higher for both pesticides in the high-exposure groups.

DISCUSSION

Our study demonstrates that past use of DDT-related organochlorine pesticides may be associated with pancreas cancer in the general population. Cases had increased odds of insecticide, rodenticide and herbicide exposure in the earliest time period. This association was significant for insecticide use in the 1945–1955 time period and remained elevated in the 1956–1965 time period. It is noteworthy that ORs for insecticide, herbicide and rodenticide exposures were highest in the time period from 1945–1965, when DDT was at its peak usage. Suggestive risks for pancreas cancer were detected for subjects who were ever exposed to chloropropylate, DDT and dieldrin, as well as for the summary group of organochlorine pesticides which included all of these pesticides, while a large, significant risk was observed for exposure to ethylan. However, the number of subjects studied to date is small, and caution should be used in the interpretation of the estimates.

The results of this study support the earlier results of Garabrant *et al.* (1992) on the role of DDT-related compounds and pancreas cancer. In this nested case-control study among chemical manufacturing workers, a history of occupational exposure to DDT and 2 of its derivatives, DDD and ethylan, was strongly associated with pancreas cancer. Few other studies have investigated the role of pesticides in the etiology of pancreas cancer. An exploratory study by Friedman and van den Eeden (1993) found a small, significant risk for pancreas cancer in people who had used insect or plant sprays earlier than 1 year before they were interviewed, but information on the type of pesticides used was not gathered. Three occupational studies found a significant excess of pancreas cancer in workers handling pesticides (Kauppinen *et al.,* 1995), workers employed in flour mills (Alavanja *et al.,* 1990) and nurserymen (Milham, 1983). Workers in all of these studies had the potential for extensive insecticide exposures, but, similar to the study of Friedman and van den Eeden (1993), information on specific pesticide exposures was not available in any of the studies.

As DDT use increased from 1945 to 1970, some tumor registries have shown an increase in pancreas cancer in the same time period. The incidence of pancreas cancer has remained constant in men since the 1970s and has risen slightly in women. A study based on the Connecticut Tumor Registry found that the age-adjusted incidence of pancreas cancer increased in both males and females beginning in 1935 (Roush *et al.,* 1987). Since the mid-1970s, however, there has been a continuing upward trend in the incidence of pancreas cancer among females (black and white) 65 years old and older, while the incidence of pancreas cancer among men in this age group has remained constant since the mid 1970s.

Ethylan (1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane) is the *p, p′* analog of DDD and is more commonly known by its trade name, Perthane. Introduced in 1950, ethylan was used to control pear psylla, leaf-hoppers, various larvae on vegetables and moths and carpet beetles on clothes and other textiles. After a hepatocarcinogenic effect was observed in mice, ethylan was banned in 1980 (Smith, 1991). Due to its potential use as a product for the home environment and its structural similarity to DDT, it is reasonable to assume that ethylan exposure did occur in the general population and that its association with pancreas cancer detected in this study may be real and deserves further study.

Our study also demonstrated that pancreas cancer cases had an increased risk of having first-degree relatives who had been diagnosed with any cancer, breast cancer or pancreas cancer. Case reports have indicated that pancreas cancer may cluster in certain families (Lynch *et al.,* 1989). Falk *et al.* (1988) evaluated family history in their case-control study of life-style risk factors for pancreas cancer in Louisiana. Among persons reporting any cancer in a close relative, a significant risk for pancreas cancer was observed. Most notably, when persons reported pancreas cancer in a close relative, their risk for pancreas cancer increased greatly (OR = 5.3, 95% CI 2.1–13.2). In a population-based case-control study conducted in Canada, Ghadirian *et al.* (1991) also demonstrated a significant risk associated with a family history of pancreas cancer. In this study, people with pancreas cancer were almost 3 times more likely to report a history of breast cancer in first-degree relatives. A study among breast cancer families has shown that a family history of pancreas cancer predicted the presence of a *BRCA*2 mutation (Phelan *et al.,* 1996). Since both pancreas cancer (Garabrant *et al.,* 1992) and breast cancer (Wolff *et al.,* 1993) were shown to be associated with DDT in past studies, exploration of the relationship between mutations in the *BRCA*2 gene and organochlorine pesticide exposure in pancreas cancer would be valuable.

Case-control studies are useful for studying risk factors for rare events. However, they are often subject to recall bias, where subjects who have the disease may report events more accurately or completely than subjects without the disease. Two methods were used to reduce the possibility of recall bias for the pesticide exposures in our study: a standardized questionnaire was used for both the cases and controls to identify specific pesticides and subjects were given cards which listed the common name and trade names of all pesticides of interest. These methods ensured that all study subjects had comparable opportunity to recall the pesticides of interest. We also were able to measure the possibility of differential recall in the analysis. Included among the group of pesticide cards were 2 fictitious pesticides. None of the cases and one of the controls reported exposure to these pesticides, indicating that cases were probably not over-emphasizing their pesticide exposures. Furthermore, subjects were asked to list any pesticides that they had ever used, even those not mentioned on the pesticide cards. The mean number of pesticides reported by the cases was 4.0, while the mean number of pesticides reported by the controls was 5.1. This difference was not significant ($p = 0.06$), suggesting that it is unlikely that recall bias influenced the study results in any appreciable way.

In studies of rapidly fatal disease, interview bias is also of concern. Because of the need to interview cases quickly, our interviewers conducted case interviews at the hospital or in the subject's home. It was not possible to mask the interviewers to the case/control status of the study subjects, and differential probing based on case status could have occurred. Intensive interviewer

training and unvarying use of a structured interview were used to minimize the occurrence of any such bias. Furthermore, as mentioned above, cases and controls reported similar pesticide-usage patterns for all pesticides, indicating that interview bias was probably not a major concern in this study.

We used the Michigan state cancer registry to compare the demographics of cases enrolled into the study with the demographics of all pancreas cancer diagnoses from the 18 study counties. There were no significant differences ($p < 0.1$) in age, sex or ethnicity between our cases and all cases of cytologically diagnosed pancreas cancer in the study area, indicating that selection bias among the cases was probably not important. One of the limitations of this study was the low participation rate among controls. Control participation may have been low in this study as a stipend for participation was not offered, in-home interviews were conducted and a blood draw was required. Selection bias may have taken place if the controls who refused differed from the controls who participated, especially if the refusals were older, male or African-American, characteristics which may be associated with pesticide exposures. One alternative approach which may increase participation in future studies is to eliminate the blood draw from the initial contact and interview. At the conclusion of the in-home interview, after a relationship had been established between the study personnel and the subjects, the interviewer would request a blood sample from the subject. The interviewer would then be present to address any questions or concerns the study subject has about the blood draw, which may help to alleviate any initial fears concerning the blood draw. Participation rates are declining as random-digit dialing is used more often in epidemiologic studies (Olson *et al.*, 1992), but the Waksberg method is still an efficient, effective sampling method for control selection (Perneger *et al.*, 1993). There is often concern that when the participation rate among controls is less than 50%, selection bias may have played a role. Specifically, controls may have agreed to participate (or not participate) based on their exposure status (pesticide use). This is unlikely to have happened in our study. A random sample of 30 control refusals who had completed the screening questionnaire were questioned about their basic demographic factors. Control refusals were similar to participants on age and ethnicity. However, compared to participants, slightly more control refusals were male (56.7% *vs.* 51.2% of participants). Given the similarity between participants and non-participants on most basic characteristics in the small refuser survey and the fact that study subjects did not know the hypothesis under study, selection bias among the controls is unlikely to have played a major role in our study.

Our study has many strengths. This is one of the few studies based on direct interviews of cases of pancreas cancer. Due to poor survival, most studies of pancreas cancer have relied on surrogate interviews, in which accurate exposure information is difficult to obtain. Our study was further strengthened by its strict case definition. All cases were required to have a cytological diagnosis of pancreas cancer. Pathology reports were reviewed by the study pathologist to ensure that diagnostic inclusion criteria were met. Finally, the study design incorporated important measures to reduce recall bias. Interviewer training, a structured interview and the inclusion of non-existent pesticides not only minimized recall bias but also allowed us to measure its potential impact.

A number of organochlorine pesticides are persistent environmental contaminants with long biological half-lives. They are readily absorbed into the blood from the gastro-intestinal tract, through the skin or by inhalation of vapor or dust and distributed to tissues with a high fat content, where an equilibrium is established (Tordoir and van Sittert, 1994). The exact nature of the biological mechanism by which certain organochlorines may be involved in the etiology of pancreas cancer is not clear. It is possible that some of the organochlorine compounds we studied may accumulate in the pancreas as it is a lipid-rich organ and its ductal epithelial cells may have prolonged exposure even in the absence of continuous external exposure. There is also evidence that DDT and DDE are excreted in the bile (Pashal *et al.*, 1974). Thus, direct exposure of the pancreatic ductal epithelium to these materials is possible.

The evidence provided by these analyses demonstrates that some organochlorines may be human carcinogens. Even though DDT was banned in the United States in 1972, DDT is still manufactured throughout the world and DDT-related compounds are still used in the United States. More than 50 years after its synthesis, the long-term health effects of DDT are unknown. Future studies are needed to clarify the associations between DDT-related compounds and pancreas cancer found in our study. One approach may be to investigate the association between DDT-related compounds and pancreas cancer in different populations, especially those populations where pancreas cancer rates are high (*e.g.*, African-Americans). Furthermore, the issues of latency and dose need to be more carefully evaluated to fully understand the relationship of pancreas cancer risk for different time periods and levels of exposure.

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