Published in final edited form as:
Int J Cancer. 2009 May 15; 124(10): 2495–2500. doi:10.1002/ijc.24185.

Agricultural Pesticide Use and Pancreatic Cancer Risk in the Agricultural Health Study Cohort

Gabriella Andreotti[1,*], **Laura E. Beane Freeman**[1], **Lifang Hou**[2], **Joseph Coble**[1], **Jennifer Rusiecki**[3], **Jane A. Hoppin**[4], **Debra T. Silverman**[1], and **Michael Alavanja**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

[2]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[3]Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

[4]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, DHHS Research Triangle Park, NC

Abstract

Pancreatic cancer is a rapidly fatal disease that has been linked with pesticide use. Previous studies have reported excess risks of pancreatic cancer with organochlorines such as DDT, however, many other commonly used pesticides have not been examined. To further examine the potential associations between the use of a number of pesticides and pancreatic cancer, we conducted a case-control analysis in the Agricultural Health Study, one of the largest prospective cohorts with over 89,000 participants including pesticide applicators and their spouses in Iowa and North Carolina. This analysis included 93 incident pancreatic cancer cases (64 applicators, 29 spouses) and 82,503 cancer-free controls who completed an enrollment questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides was assessed. Risk estimates were calculated using unconditional logistic regression controlling for age, smoking, and diabetes. Among pesticide applicators, two herbicides (EPTC and pendimethalin) of the 13 pesticides examined for intensity-weighted lifetime use showed a statistically significant exposure-response association with pancreatic cancer. Applicators in the top half of lifetime pendimethalin use had a 3.0-fold (95% CI 1.3-7.2, p-trend=0.01) risk compared to never users, and those in the top half of lifetime EPTC use had a 2.56-fold (95% CI=1.1-5.4, p-trend=0.01) risk compared to never users. Organochlorines were not associated with an excess risk of pancreatic cancer in this study. These findings suggest that herbicides, particularly pendimethalin and EPTC, may be associated with pancreatic cancer.

Keywords

pancreatic cancer; pesticides; agriculture

[*]Correspondence to: Gabriella Andreotti, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS 8011, MSC 7240, Bethesda, MD 20892. Fax: 301-402-1819; E-mail: andreotg@mail.nih.gov.

Introduction

Pancreatic cancer is a rare, but rapidly fatal disease. It is currently the fourth leading cause of cancer death among both men and women in the U.S.1 Cigarette smoking is the best established risk factor, yet only explains about 25% of the cases.2 Other suggested risk factors for pancreatic cancer include diabetes, obesity, black race, pancreatitis, family history of pancreatic cancer, and possibly, pesticide use.3

Several epidemiological studies have reported excess risks of pancreatic cancer in relation to agricultural occupations.4-6 Exposure to organochlorines, including DDT, DDD and ethylan have been associated with excess risks of pancreatic cancer in two case-control studies,7, 8 and significantly higher serum concentrations of organochlorine compounds were found among pancreatic cancer cases compared to controls.9, 10 To further explore specific pesticide use and pancreatic cancer risk, we conducted a case-control analysis in the Agricultural Health Study (AHS) cohort, one of the largest prospective cohort studies of pesticide applicators and their spouses.

Materials and Methods

Study Subjects

The AHS cohort with over 89,000 participants includes licensed private and commercial pesticide applicators, and spouses of private applicators residing in Iowa and North Carolina. Applicators were enrolled between December 13, 1993 and December 31, 1997 at pesticide licensing facilities in each state; 82% of applicators seeking licensing were enrolled in the study (57,311 applicators). Spouses of enrolled applicators were asked to complete a questionnaire provided by the enrolled applicator, and return it by mail or complete it over the phone, generally within one month of applicator enrollment. Of all spouses 75% (32,347 spouses) chose to participate. The study protocol was approved by all appropriate institutional review boards.

Questionnaire

Applicators completed a self-administered questionnaire at enrollment eliciting information on demographics, lifestyle factors, medical histories, ever/never use of 50 pesticides, and comprehensive pesticide use (i.e., years and days per year applied pesticides, personal protective equipment, and application methods) on 22 of the 50 pesticides. All enrolled applicators were given a self-administered take-home questionnaire, which collected comprehensive pesticide exposure data on the other 28 pesticides; 40% of the enrolled applicators returned the take-home questionnaire. No meaningful differences in demographics, medical histories or farming practices were found between those who completed and did not complete the take-home questionnaire.11 For spouses of enrolled applicators, information on demographics, lifestyle factors, medical histories, and ever/never use of the same 50 pesticides was obtained from a self-administered questionnaire (81%) or telephone interview (19%). For this analysis, we report results for pesticides with at least 10 exposed pancreatic cases, or at least 5 organochlorine-exposed cases (because of the prior findings for this chemical group), which totaled 24 pesticides examined for ever/never exposure, and 13 pesticides for intensity-weighted lifetime exposure days.

Pesticide Exposure

For pesticide applicators, lifetime exposure days through enrollment were calculated as: [(years applied each pesticide) × (days applied each pesticide in an average year)]. Using lifetime exposure days and an intensity score, the intensity-weighted lifetime exposure days was calculated as: [(lifetime exposure days) × (intensity score)]. The intensity score was

computed from an algorithm that took into account exposure-modifying factors such as how the pesticide was used and applied, and the protective equipment that was used.12 For spouses, only ever/never pesticide use was available.

Pancreatic Cancer Identification

Pancreatic cancer (ICD-10 = C25.0-C25.9) cases were identified using population-based state cancer registries. Incident pancreatic cancer cases diagnosed between enrollment and December 31, 2004 (over 9 years of follow-up time) were included in the analysis. Participants with any type of prevalent cancer at enrollment were excluded from the analysis. Vital status was obtained from the state death registries and the National Death Index. Participants who moved out of North Carolina or Iowa were not followed for cancer occurrence after moving.

Statistical Analysis

This analysis included cases with incident primary carcinoma of the pancreas (93 cases: 64 applicators, 29 spouses), and controls without a history of cancer (52,721 applicators, 29,782 spouses). All but one of the 93 cases were exocrine tumors, with 47% located in the head of the pancreas. Pancreatic cancer risk in relation to selected characteristics and pesticide use was estimated by unconditional logistic regression controlling for age group (< 50, 50-59, 60-69, ≥ 70), cigarette smoking (never, past, current), diabetes (no, yes), and subject type for ever/never pesticide exposure (applicator, spouse). Pesticide use was assessed using ever/never use for applicators and spouses and intensity-weighted lifetime exposure days for applicators. Intensity-weighted lifetime exposure days was categorized into never use, low use (< median days) and high use (≥ median days) using the median value of each pesticide among the controls as the cutoff between low and high use. A test of trend was calculated using an ordinal variable for never, low, and high use. Family history of pancreatic cancer could not be considered a potential confounder since only 10 cases reported a family history of “other cancer,” which may or may not have included pancreatic cancers. SAS version 9.1 (Cary, NC) and the AHS data release PIREL0612 were used to conduct all analyses.

Results

As shown in Table 1, age was positively associated with pancreatic cancer among applicators and spouses. Also, compared to applicators who never smoked cigarettes, past smokers had a 1.5-fold (95% CI=0.8-2.8) risk and current smokers had a 3.3-fold (95% CI=1.7-6.4) risk. Applicators with diabetes had a 3.3-fold (95% CI=1.6-6.9) risk compared to non-diabetics. Among spouses, cigarette smoking, diabetes, and obesity (≥ 30 kg/m^2) were associated with excess, although not statistically significant, risks of pancreatic cancer.

Applicators and spouses had similar risk factors for pancreatic cancer, therefore the risk estimates for ever/never pesticide use are shown for both combined (Table 2). Associations for pesticides with at least 10 exposed cases, or at least 5 organochlorine-exposed cases (because of the prior findings for this chemical group), are reported. Among the 24 pesticides examined for ever/never use, ever use of five (pendimethalin, trifluralin, EPTC, chlorimuron-ethyl, and heptachlor) were associated with excess risks of pancreatic cancer adjusting for age group, cigarette smoking, diabetes and subject type, with ORs greater than or equal to 1.4, although the associations were not statistically significant. Ever use of DDT and malathion were significantly inversely associated with pancreatic cancer risk. These results were not considerably changed when the associations were examined only among applicators.

Associations between intensity-weighted lifetime days of pesticide use and pancreatic cancer risk among applicators are shown in Table 3 for pesticides with at least 10 exposed cases and 5 cases per exposure group. Of the 13 pesticides examined for intensity-weighted lifetime days of exposure, 2 herbicides, pendimethalin and EPTC, had statistically significant exposure-response associations with pancreatic cancer adjusting for age group, cigarette smoking, and diabetes. For pendimethalin, low users had a 1.4-fold risk (95% CCI = 0.5-3.9) and high users had a 3.0-fold (95% CI 1.3-7.2) risk (p-trend = 0.01) compared to never users. For EPTC, low users had a 1.8-fold risk (95% CI = 0.7-4.3) and high users had a 2.5-fold (95% CI = 1.1-5.4) risk (p-trend = 0.01) compared to never users. The risk estimates and exposure-response association between intensity-weighted lifetime days of pendimethalin and pancreatic cancer were not measurably changed after adjusting for ever/never use of EPTC (low pendimethalin use: OR = 1.4, 95% CI = 0.5-3.9; high pendimethalin use: OR = 2.6, 95% CI = 1.0-6.5; p-trend = 0.03). In contrast, the association between intensity-weighted lifetime days of EPTC and pancreatic cancer after adjusting for ever/never use of pendimethalin was attenuated and no longer statistically significant; however this model was limited to the subset who completed the take-home questionnaire (40% of the applicators) since data for pendimethalin was only available from the take-home questionnaire. Restricting to participants who completed the take-home questionnaire (5 EPTC exposed cases), the association between EPTC and pancreatic cancer (not adjusting for pendimethalin) was attenuated and not statistically significant (data not shown). This suggests the attenuation may not be due to confounding by pendimethalin, but rather the reduced number of cases. In order to further explore possible confounding by multiple pesticide use, the following additional analyses were conducted. Among applicators in the AHS cohort, pendimethalin and EPTC were not highly correlated to each other (r=0.19) or to the other pesticides examined for intensity-weighted lifetime days of exposure (r < 0.36). Also, we considered the lifetime use of all pesticides among applicators, and found no considerable change in the associations for pendimethalin and EPTC (less than 5% change in risk estimates (data not shown)), suggesting that confounding due to multiple use of more than one pesticide was not likely.

Discussion

In this case-control analysis of pancreatic cancer in the AHS, we found statistically significant exposure-response associations for 2 herbicides, pendimethalin and EPTC. Our finding of an excess pancreatic cancer risk for these two herbicides, but not for insecticides, is consistent with the results from a case-control study of pesticide exposed workers that found an excess pancreatic cancer risk with herbicide, but not insecticide, use.6 Pendimethalin (*N*-[1-ethylpropyl]-2,6-dinitro-3,4-xylidine) is a widely used dintroaniline herbicide, classified as a Group C possible human carcinogen by the United States Environmental Protection Agency (U.S. EPA).13 It has been associated with an increased risk of lung14 and rectal cancers15 among applicators in the AHS, and with thyroid tumors in rodents.16 The thiocarbamate EPTC (*S*-ethyl-*N*,*N*-dipropylthiocarbamate) is a Group E non-likely carcinogen with moderate acute toxicity based on the U.S. EPA classification.13 It has been linked with an increased risk of colon17 and prostate cancer18 in the AHS, as well as NHL among farmers using the herbicide for less than 7 years.19 Due to the small number of pancreatic cancer cases, previous studies of pendimethalin15 and EPTC18 in the AHS did not examine pancreatic cancer risk.

The biological mechanisms by which pendimethalin or EPTC may be linked with pancreatic cancer have not been described. Pendimethalin contains N-nitrso-compounds or nitrosamine impurities,20 and EPTC has been classified as a nitrosatable pesticide (able to form N-nitroso compounds in reaction with nitrite).21 Nitrosamines are potent animal carcinogens and are considered suspected human carcinogens.22 Nitrosamine compounds, such as those

found in tobacco products, have been implicated as significant causes of cancer, including pancreatic cancer.23, 24 Although regulations were implemented by the US EPA to reduce nitrosamine contamination in pesticides in the 1980s,20 it may be biologically plausible that moderate nitrosamine exposure in pesticides prior to the US EPA reduction and subsequent lower levels of nitrosamine exposure may have a carcinogenic effect in regularly exposed individuals. To note, three other pesticides, trifluralin, atrazine, and dicamaba, which are also nitrosatable pesticides, were not associated with pancreatic cancer. Further investigation of the mechanisms of individual pesticides is warranted.

In contrast to previous findings, we found no association between organochlorines and pancreatic cancer, as well an inverse association for DDT. It is possible that the inverse association for DDT may in part be due to a healthy survivor effect among those who had used DDT before it was banned in the 1970's. The case-control study of pancreatic cancer conducted by Garabrant et al that found statistically significant effects of DDT, DDD, and ethylan7 was conducted among chemical manufacturing workers who likely had higher levels of exposure to the pure product than those who used or applied these pesticides. Furthermore, the U.S. population-based case-control study that reported higher median serum concentration of organochlorine compounds among pancreatic cancer cases compared to controls,10 also found that the association with DDE was attenuated after controlling for polychlorinated biphenyls (PCBs), suggesting possible confounding by PCBs. The hospital-based case-control study conducted in Spain that observed an exposure-response association between serum concentrations of DDT and pancreatic cancer risk was only statistically significant for those cases with a K-*ras* mutation.9 These previous findings suggest that organochlorines may be associated with pancreatic cancer, but only among certain populations or conditions. It is unlikely that pendimethalin or EPTC are surrogates for DDT as neither is highly correlated with DDT in the AHS (pendimethalin r=0.14, EPTC r=0.03).

Several strengths of this study should be mentioned. Selection bias should be minimal due to the high cohort recruitment (82% of applicators, 75% of spouses) and the low loss to follow-up (less than 2%). Misclassification of pancreatic cancer diagnosis is unlikely given the data linkage to population-based state cancer registries. Pesticide use data, although self-reported, has been shown to be reliable,25 and due to the prospective study design, any misclassification of pesticide use should be non-differential and therefore unlikely to create false-positive associations. Also, we were able to control for several important risk factors including, age, cigarette smoking, and diabetes.

A few limitations should also be noted. We were unable to evaluate certain pesticides and did not have sufficient statistical power to estimate statistical interactions due to the limited number of exposed cases, however, it is important to note that these cases were drawn from one of the largest prospective cohorts of pesticide exposed subjects, thus no other study would have a larger sample size. While the response rate to the take-home questionnaire was 40%, an evaluation of the potential biases related to this response rate concluded that there was little meaningful opportunity for confounding.11 Our findings may have limited generalizability due to the predominantly white male study population. Because we examined several pesticides with biological effects in humans that are unclear, and are the first to report associations for pendimethalin and EPTC with pancreatic cancer, these findings should be considered hypothesis generating and in need of confirmation.

In conclusion, we found statistically significant exposure-response associations for pendimethalin and EPTC on pancreatic cancer risk among pesticide applicators in the AHS cohort. Pendimethalin and EPTC are able to form N-nitroso-compounds, thus, our findings are consistent with evidence suggesting a carcinogenic effect of nitrosamines on the

pancreas. Future studies with a larger number of pancreatic cancer cases are needed to confirm our findings and to evaluate the effect of other nitrosamine carrying pesticides.

Acknowledgments

This paper has been supported by the Intramural Research Program of the NIH, National Cancer Institute (Z01 CP010119) and National Institute of Environmental Health Sciences (Z01-ES049030-11). We thank the Agricultural Health Study participants for their participation, and the field station and coordinating center staff for their efforts.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics. CA Cancer J. 2008; 58:71–96.
2. Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, Brown LM, Greenberg RS, Hayes RB, Swanson GM. Cigarette smoking and pancreas cancer: A case-control study based on direct interviews. J Natl Cancer Inst. 1994; 86:1510–1516. [PubMed: 7932805]
3. Anderson, K.; Mack, T.; Silverman, DT. Pancreatic cancer. In: Schottenfeld, D.; Fraumeni, J., editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006. p. 721-762.
4. Kauppinen T, Partanen T, Degerth R, Ojajarvi A. Pancreatic cancer and occupational exposures. Epidemiology. 1995; 6:498–502. [PubMed: 8562625]
5. Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965-1988. Am J Ind Med. 1999; 36:239–47. [PubMed: 10398932]
6. Ji BT, Silverman DT, Stewart PA, Blair A, Swanson GM, Baris D, Greenberg RS, Hayes RB, Brown LM, Lillemoe KD, Schoenberg JB, Pottern LM, Schwartz AG, Hoover RN. Occupational exposure to pesticides and pancreatic cancer. Am J Ind Med. 2001; 39:92–9. [PubMed: 11148019]
7. Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. DDT and related compounds and risk of pancreatic cancer. J Natl Cancer Inst. 1992; 84:764–71. [PubMed: 1573662]
8. Fryzek JP, Garabrant DH, Harlow SD, Severson RK, Gillespie BW, Schenk M, Schottenfeld D. A case-control study of self-reported exposures to pesticides and pancreas cancer in southeastern Michigan. Int J Cancer. 1997; 72:62–7. [PubMed: 9212224]
9. Porta M, Malats N, Jariod M, Grimalt JO, Rifa J, Carrato A, Guarner L, Salas A, Santiago-Silva M, Corominas JM, Andreu M, Real FX. Serum concentrations of organochlorine compounds and K-ras mutations in exocrine pancreatic cancer. PANKRAS II Study Group. Lancet. 1999; 354:2125–9. [PubMed: 10609819]
10. Hoppin JA, Tolbert PE, Holly EA, Brock JW, Korrick SA, Altshul LM, Zhang RH, Bracci PM, Burse VW, Needham LL. Pancreatic cancer and serum organochlorine levels. Cancer Epidemiol Biomarkers Prev. 2000; 9:199–205. [PubMed: 10698482]
11. Tarone RE, Alavanja MC, Zahm SH, Lubin JH, Sandler DP, McMaster SB, Rothman N, Blair A. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. Am J Ind Med. 1997; 31:233–42. [PubMed: 9028440]
12. Dosemeci M, Alavanja MC, Rowland AS, Mage D, Zahm SH, Rothman N, Lubin JH, Hoppin JA, Sandler DP, Blair A. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg. 2002:245–260. [PubMed: 12074034]
13. EPA. Prevention, Pesticides, and Toxic Substances. United States Environmental Protection Agency; 1999. p. 1-8.
14. Alavanja MC, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, Barker J, Hoppin JA, Sandler DP, Coble J, Thomas K, Blair A. Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol. 2004; 160:876–85. [PubMed: 15496540]
15. Hou L, Lee WJ, Rusiecki J, Hoppin JA, Blair A, Bonner MR, Lubin JH, Samanic C, Sandler DP, Dosemeci M, Alavanja MC. Pendimethalin exposure and cancer incidence among pesticide applicators. Epidemiology. 2006; 17:302–7. [PubMed: 16452832]

16. Hurley PM. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ Health Perspect. 1998; 106:437–45. [PubMed: 9681970]

17. van Bemmel DM, Visvanathan K, Beane-Freeman LE, Coble J, Hoppin JA, Alavanja MC. S-ethyl-N,N-dipropylthiocarbamate (EPTC) Exposure and Cancer Incidence among Male Pesticide Applicators in the Agricultural Health Study, a prospective cohort. Environmental Health Perspectives. Accepted.

18. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol. 2003; 157:800–14. [PubMed: 12727674]

19. Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J Occup Environ Med. 2001; 43:641–9. [PubMed: 11464396]

20. Zweig, G.; Garner, W. Policy and regulatory aspects of N-nitroso contaminants in pesticide products. In: Scanlan, RA.; Tannenbaum, SR., editors. N-nitrso compounds. Washington, DC: American Chemical Society; 1981. p. 383-9.

21. Lee WJ, Lijinsky W, Heineman EF, Markin RS, Weisenburger DD, Ward MH. Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus. Occup Environ Med. 2004; 61:743–9. [PubMed: 15317914]

22. Preston-Martin S, Correa P. Epidemiological evidence for the role of nitroso compounds in human cancer. Cancer Surv. 1989; 8:459–73. [PubMed: 2696590]

23. Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS. Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and Areca-derived N-nitrosamines. Cancer Res. 1988 Dec 1.48:6912–7. [PubMed: 3180100]

24. Hecht SS, Hoffmann D. N-nitroso compounds and tobacco-induced cancers in man. IARC Sci Publ. 1991:54–61. [PubMed: 1855913]

25. Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, Steen WC, Samanic C, Dosemeci M, Alavanja MC. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. 2002; 13:94–9. [PubMed: 11805592]

Table 1

Odds Ratios and 95% confidence intervals (CI) for pancreatic cancer in relation to selected characteristics among applicators and spouses in the Agricultural Health Study, 1993-2004

	Applicators						Spouses					
	Controls		Pancreatic Cancer Cases				Controls		Pancreatic Cancer Cases			
Selected Characteristics	**n**	**(%)**	**n**	**(%)**	**OR[1]**	**95% CI[1]**	**n**	**(%)**	**n**	**(%)**	**OR[1]**	**95% CI[1]**
All subjects	52,721	(100.0)	64	(100.0)	-	-	29,782	(100.0)	29	(100.0)	-	-
Applicator type												
Private	48,027	(91.1)	60	(93.8)	1.0	-	-	-	-	-	-	-
Commercial	4,694	(8.9)	4	(6.2)	-	-	-	-	-	-	-	-
Sex												
Male	51,258	(97.2)	62	(96.9)	1.0	-	197	(0.7)	0	0	1.0	-
Female	1,462	(2.8)	2	(3.1)	-	-	29,585	(99.3)	29	(100.0)	-	-
Age at interview												
< 50	33,462	(63.4)	10	(15.6)	1.0	-	18,365	(61.7)	4	(13.8)		
50 - 59	10,546	(20.0)	22	(34.4)	6.4	3.0-13.6	6,783	(22.8)	12	(41.4)	8.0	2.6-24.8
60 - 69	6,521	(12.4)	22	(34.4)	8.6	3.9-18.8	3,749	(12.5)	10	(34.5)	12.4	3.8-39.9
≥ 70	2,189	(4.2)	10	(15.6)	12.5	4.8-32.2	885	(3.0)	3	(10.3)	11.0	2.0-61.31
p-trend						*<.0001*						*<.0001*
Race												
White	50,111	(97.4)	61	(98.4)	1.0	-	28,347	(98.3)	27	(93.1)	1.0	-
Other	1,355	(2.6)	1	(1.6)	-	-	502	(1.7)	2	(6.9)	-	-
Education												
High school or less	28,479	(56.5)	45	(72.6)	1.0	-	11,737	(45.3)	17	(70.8)	1.0	-
Beyond high school	21,927	(43.5)	17	(27.4)	0.8	0.4-1.4	14,151	(54.7)	7	(29.2)	0.5	0.2-1.3
State of residence												
Iowa	34,144	(64.8)	33	(51.6)	1.0	-	20,007	(67.2)	18	(62.1)	1.0	-
North Carolina	18,577	(35.2)	31	(48.4)	0.9	0.6-1.6	9,775	(32.8)	11	(37.9)	0.9	0.4-1.9
Smoke cigarettes												
Never	27,423	(53.8)	20	(32.3)	1.0	-	20,298	(72.3)	21	(72.4)	1.0	-
Past	14,849	(29.2)	25	(40.3)	1.5	0.8-2.8	4,831	(17.2)	3	(10.3)	0.6	0.2-2.2
Current	8,668	(17.0)	17	(27.4)	3.3	1.7-6.4	2,953	(10.5)	5	(17.2)	2.3	0.8-6.2

	Applicators						Spouses					
	Controls		Pancreatic Cancer Cases				Controls		Pancreatic Cancer Cases			
Selected Characteristics	**n**	**(%)**	**n**	**(%)**	**OR[1]**	**95% CI[1]**	**n**	**(%)**	**n**	**(%)**	**OR[1]**	**95% CI[1]**
p-trend						*0.001*						*0.28*
Other tobacco use												
Never	29,739	(56.4)	30	(46.9)	1.0	-	26,434	(88.8)	25	(86.2)	1.0	-
Past or current	22,981	(43.6)	34	(53.1)	1.0	0.6-1.7	3,348	(11.2)	4	(13.8)	1.3	0.4-3.8
Drank alcohol												
Never	15,602	(31.7)	28	(47.5)	1.0	-	12,813	(45.0)	20	(69.0)	1.0	-
Ever	33,540	(68.3)	31	(52.5)	0.8	0.5-1.4	15,650	(55.0)	9	(31.0)	0.6	0.3-1.3
Diabetes												
No	48,555	(97.0)	49	(84.5)	1.0	-	27,549	(96.8)	25	(89.3)	1.0	-
Yes	1,515	(3.0)	9	(15.5)	3.3	1.6-6.9	924	(3.2)	3	(10.7)	2.0	0.6-6.8
Body mass index (kg/m^2)												
<25	9,339	(26.2)	10	(23.8)	1.0	-	10,220	(50.6)	10	(47.6)	1.0	-
25-29	17,991	(50.4)	25	(59.5)	1.3	0.6-2.9	6,342	(31.3)	4	(19.1)	0.6	0.2-1.8
≥30	8,361	(23.4)	7	(16.7)	1.0	0.4-2.7	3,653	(18.1)	7	(33.3)	1.9	0.7-5.0
p-trend						*0.94*						*0.34*

[1] Adjusted for age group, smoking (never, past, current), diabetes. Estimates for smoking are adjusted for age group and diabetes, and estimates for diabetes are adjusted for age group and smoking.

Table 2

Odds ratios and 95% confidence intervals for pancreatic cancer in relation to ever/never pesticide exposure[1] among applicators and spouses in the Agricultural Health Study, 1993-2004

	Controls		Pancreatic Cancer Cases			
Pesticides	**Never**	**Ever**	**Never**	**Ever**	**OR[2]**	**95% CI[2]**
All pesticides	17,259	65,244	23	70	0.7	0.4-1.4
Herbicides[3]	22,612	59,891	26	67	1.0	0.5-1.9
Dinitroanilines						
Pendimethalin[7]	41,034	9,237	43	14	1.7	0.8-3.3
Trifluralin	49,460	26,411	48	32	1.4	0.8-2.4
Thiocarbamate						
EPTC	64,896	10,114	65	14	1.8	1.0-3.3
Phenoxy						
2,4,-D	37,240	41,935	42	48	0.9	0.5-1.5
Triazine						
Atrazine	43,145	36,126	54	37	0.7	0.4-1.2
Cyanazine	55,299	20,499	61	21	1.0	0.6-1.8
Metribuzin[7]	41,479	8,688	47	10	1.0	0.5-2.2
Chloroacetanilide						
Alachlor	49,828	26,102	58	26	0.8	0.5-1.3
Metolachlor	52,711	23,097	61	23	1.0	0.6-1.7
Imidazolinone						
Imazethypyr	54,109	21,215	62	20	1.1	0.6-1.9
Phosphinic						
Glyphosate	31,282	48,461	35	55	1.1	0.6-1.7
Benzoic						
Dicamba	50,606	25,000	57	23	0.9	0.6-1.6
Urea						
Chlorimuron-ethyl[7]	42,479	7,750	46	11	1.4	0.7-3.0
Insecticides[4]	30,510	51,993	45	48	0.6	0.4-0.9

	Controls		Pancreatic Cancer Cases			
Pesticides	**Never**	**Ever**	**Never**	**Ever**	**OR[2]**	**95% CI[2]**
Organochlorines						
Aldrin[7]	46,295	3,531	49	8	1.2	0.5-2.7
DDT[7]	44,550	5,387	51	6	0.4	0.2-0.9
Heptachlor[7]	47,239	2,619	50	7	1.6	0.7-3.8
Toxaphene[7]	47,334	2,492	50	5	1.2	0.5-3.2
Organophosphates						
Chlorpyrifos	56,941	22,084	72	17	0.6	0.4-1.1
Fonofos	65,332	10,336	71	12	1.2	0.6-2.2
Malathion[7]	31,260	19,357	41	15	0.4	0.2-0.9
Phorate[7]	43,363	6,746	46	11	1.4	0.7-2.9
Terbufos	57,226	18,534	62	22	1.2	0.7-2.1
Carbamates						
Carbaryl[7]	32,489	18,197	40	17	0.6	0.4-1.1
Carbofuran	62,596	12,756	68	14	0.8	0.5-1.6
Pyrethroids						
Permethrin used on crops and animals	69,578	12,925	83	10	0.9	0. 5-1.8
Fungicides[5]	69,035	13,468	80	13	0.7	0.4-1.4
Fumigants[6]	72,743	9,760	81	12	0.7	0.4-1.4

[1] Pesticides with at least 10 7exposed cases, or for organochlorines at least 5 exposed cases, are reported

[2] Adjusted for age group, cigarette smoking (never, past, current), diabetes, and applicator type

[3] Additionally includes: butylate, 2,4,5-TP, 2,4,5-T, Paraquat, Petroleum oil

[4] Additionally includes: Lidane, Chlordane, Dieldrin, Trichlorofon, Parathion, Diazinon, Coumaphos, Dichlorvos

[5] Includes: Benomyl, Chorothalonil, Captan, Maneb/Mancozeb, Metalaxyl, Ziram

[6] Includes: Methyl bromide, Aluminum phosphide, Carbon tetrachloride, Ethylene dibromide

[7] Data available from take-home questionnaire only

Int J Cancer. Author manuscript; available in PMC 2010 May 15.

Table 3

Odds ratios and 95% confidence intervals (CI) for pancreatic cancer in relation to intensity-weighted pesticide exposure[1] among applicators in the Agricultural Health Study, 1993-2004

Pesticides	Intensity-weighted pesticide exposure[2]	Controls	Pancreatic Cancer Cases	OR[2]	95% CI[2]
Herbicides					
Dinitroanilines					
Pendimethalin[4]	Never	13,725	14	1.0	-
	≤ 116	4,053	5	1.4	0.5-3.9
	≥ 117	4,038	9	3.0	1.3-7.2
	p-trend				*0.01*
Trifluralin	Never	22,908	22	1.0	-
	≤ 318	12,061	16	1.6	0.8-3.0
	≥ 319	12,040	10	1.1	0.5-2.2
	p-trend				*0.70*
Thiocarbamate					
EPTC	Never	37,342	36	1.0	-
	≤ 117	4,675	6	1.8	0.7-4.3
	≥ 118	4,709	8	2.5	1.1-5.4
	p-trend				*0.01*
Phenoxy					
2,4,-D	Never	13,218	17	1.0	-
	≤ 370	18,486	17	0.8	0.4-1.6
	≥ 371	18,333	24	0.9	0.5-1.7
	p-trend				*0.72*
Triazine					
Atrazine	Never	16,350	26	1.0	-
	≤ 336	17,056	20	0.8	0.5-1.5
	≥ 337	17,036	15	0.6	0.3-1.2
	p-trend				*0.12*
Cyanazine	Never	28,101	35	1.0	-
	≤ 180	9,573	8	0.8	0.4-1.7

Pesticides	Intensity-weighted pesticide exposure[2]	Controls	Pancreatic Cancer Cases	OR[2]	95% CI[2]
	≥ 181	9,562	9	1.0	0.5-2.0
	p-trend				*0.80*
Chloroacetanilide					
Alachlor	Never	23,020	31	1.0	-
	≤ 248	11,931	10	0.7	0.3-1.4
	≥ 249	11,936	11	0.7	0.4-1.5
	p-trend				*0.28*
Metolachlor	Never	25,658	34	1.0	-
	≤ 224	10,727	14	1.2	0.7-2.3
	≥ 225	10,732	6	0.6	0.2-1.4
	p-trend				*0.34*
Imidazolinone					
Imazethypyr	Never	26,998	34	1.0	-
	≤ 108	9,987	10	1.1	0.5-2.3
	≥ 109	9,791	8	1.0	0.5-2.3
	p-trend				*0.87*
Phosphinic					
Glyphosate	Never	12,477	11	1.0	-
	≤ 184	18,926	29	1.9	0.9-3.8
	≥ 185	18,909	19	1.2	0.6-2.6
	p-trend				*0.85*
Benzoic					
Dicamba	Never	23,697	29	1.0	-
	≤ 176	11,511	16	1.4	0.8-2.7
	≥ 177	11,575	5	0.5	0.2-1.3
	p-trend				*0.32*
Insecticides					
Organophosphates					
Chlorpyrifos	Never	30,111	44	1.0	-
	≤ 142	9,218	8	0.7	0.3-1.5
	≥ 143	9,275	5	0.4	0.1-1.0

Int J Cancer. Author manuscript; available in PMC 2010 May 15.

Pesticides	Intensity-weighted pesticide exposure[2]	Controls	Pancreatic Cancer Cases	OR[2]	95% CI[2]
	p-trend				*0.09*
Terbufos	Never	30,038	34	1.0	-
	≤ 189	8,557	10	1.3	0.7-2.7
	≥ 190	8,590	10	1.3	0.6-2.7
	p-trend				*0.38*

[1] Pesticides having at least 10 exposed cases and 5 cases per exposure group are shown.

[2] Intensity-weighted lifetime exposure days [(exposure days)×(intensity score)]; cutoffs based on median level among controls.

[3] Adjusted for age group, cigarette smoking (never, past, current), diabetes

[4] Data available from take-home questionnaire only