Occupational exposure to *N*-nitrosamines and pesticides and risk of pancreatic cancer

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Running title: Occupation and pancreatic cancer

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What this paper adds

Pancreatic cancer has very poor prognosis and affects one in 60, thus primary prevention is a crucial approach to explore.

Little is known about occupational causes of pancreatic cancer.

This case-control study used case-by-case expert assessment of occupational histories to estimate lifetime exposures to *N*-nitrosamines and pesticides.

No association was found for either type of exposure.

Abstract

Objectives

Animal evidence shows that *N*-nitrosamines and similar xenobiotic compounds are pancreatic carcinogens. We aimed to determine whether occupational exposure to *N*-nitrosamines or to pesticides increases risk of pancreatic cancer development.

Methods

Participants (504 cases, 643 controls) in a population-based case-control study (The Queensland Pancreatic Cancer Study) provided data on demographic, medical and lifestyle factors and lifetime job histories. Specific questions were asked regarding work in rubber and leather industries, metal-working jobs and occupational or direct use of pesticides on animals or crops. An occupational hygienist reviewed this information (blind to case status) to assess likelihood of exposure to *N*-nitrosamines and pesticides and estimated level and frequency of such exposures.

Results

No associations were found for risk of pancreatic cancer and occupational exposure to *N*-nitrosamines (OR=0.85, 95% CI 0.51-1.42) and no associations were seen with level or frequency of exposure. No associations were observed for ever exposure to pesticides in general (OR=0.90, 95% CI 0.61-1.33) or to any of the pesticide subgroups. Stratification by history of cigarette smoking did not change these results.

Conclusions

This comprehensive analysis of a large case-control study does not support an association between occupational exposure to *N*-nitrosamines or pesticide use and risk of pancreatic cancer.

Keywords: pancreatic cancer, occupation, case-control, nitrosamines, pesticides, work

Background

Pancreatic cancer, while only the 14th most common cancer in the more developed regions of the world, affects one in 60 of the population over the lifetime(1) . It has the lowest 5-year survival of any cancer and is thus the 4th or 5th most common cause of cancer death. It is therefore important to find preventable causes of this disease. Identifying and subsequently reducing exposures that increase the risk of pancreatic cancer may offer a preventive approach, however few such risk factors have been determined to date.

N-nitrosamines are organic nitrogen-based xenobiotics. Fifteen *N*-nitrosamines and *N*-nitrosamides have been classified as "reasonably anticipated to be a human carcinogen" by the US Department of Health and Human Services (2). The documentation for this classification cites experimental evidence of *N*-nitrosamines causing pancreatic adenocarcinoma in fish (*N*-nitrosodiethylamine, NDEA), Syrian golden hamsters and in mice with human tissue explants (*N*-nitrosomethylamino-1-(3-pyridyl)-1-butanone, NNK) but no direct human evidence. The International Agency for Research in Cancer has classified these and several more *N*-nitrosamines as probable or possible carcinogens, but none of these were so categorized on the basis of effects on development of pancreatic cancer (3).

Risch has hypothesized that risk of pancreatic cancer in humans is also increased by *N*-nitrosamine or *N*-nitrosamide exposures (4). Experimental studies have shown that carcinogenic *N*-nitrosamines are not directly mutagenic but first must be metabolized to their mutagenic forms (4). In the hamster-BOP model, low subcutaneous doses of the pancreatic ductal hormone secretin have been shown to potentiate strongly the development of pancreatic ductal carcinomas (5). Pancreatic ductular and ductal cells metabolize *N*-nitrosamines to mutagens (6) and such conversion is believed to be enhanced by secretin stimulation (5), establishing a potential role of *N*-nitrosamine exposures in pancreatic carcinogenesis.

Humans are exposed to *N*-nitrosamines primarily through cigarette smoke and occupational sources. Cigarette smoking increases the risk of developing pancreatic cancer (7), although *N*-nitrosamines, particularly NNK, are but one of the many carcinogens contained in cigarette smoke. Pancreatic duct fluid of smokers contains NNK at 7-fold higher levels than in non-smokers (2). Compared to active smoking, environmental tobacco smoke exposure is associated with weaker increased risk of pancreatic cancer development (8).

Occupational exposures to *N*-nitrosamines occur in rubber processing and tyre manufacture (particularly in curing areas) and possibly in leather tanneries. *N*-nitrosamines were also contaminants in synthetic and soluble cutting oils used in metal-working prior to the 1970s (9). Mutagenicity of metabolized *N*-nitrosamines lies in their ability to produce DNA adducts (10), and substantially increased levels of adducts are seen in peripheral blood of cigarette smokers and highly exposed rubber workers (4). However, evidence that occupational exposure to *N*-nitrosamines increases risk of pancreatic cancer is sparse , with small numbers of cases in cohort studies and few exposed subjects in case control studies (11-13).

Many pesticides, particularly herbicides, also contain *N*-nitrosamines, although reductions in amounts of *N*-nitrosamines in pesticides have occurred since the 1980s(14). The Agricultural Health Study reported statistically significant exposure-response relationships between risk of pancreatic cancer and exposure to two herbicides that form *N*-nitrosamines (15). Organochlorine insecticides may also be associated with pancreatic cancer risk (16) and various organochlorines have been categorized as "Reasonably Anticipated to be Human Carcinogens (2).

A review of relevant studies published since 1998 noted the small numbers of exposed cases in most studies and concluded that "the magnitude of the effect that occupational exposure to *N*-nitrosamines has on pancreatic cancer has not been evaluated to date"(16). In this context of uncertainty, we conducted a case-control analysis to examine whether occupational exposures to *N*-nitrosamines or pesticides were associated with risk of pancreatic cancer.

Methods

Participants

The Queensland Pancreatic Cancer Study (QPCS) is a population-based case-control study (17). Cases were Queensland residents aged over 18 years old with pancreatic cancer diagnosed histologically or clinically between 1st January 2007 and 30th June 2011. Controls were randomly selected from the Australian Electoral Roll and frequency-matched to cases by sex and 5-year age group at diagnosis. We excluded potential cases and controls who could not give informed consent or for whom telephone numbers could not be located.

Forty-six percent (n = 711) of potential controls and 37% (n = 705) of potential cases completed interviews. Reasons for case nonparticipation were: patient died before invitation (56%); refusal by doctor (12%) or patient (18%); unable to contact (13%); cognitive impairment (1%). A further 269 participants (68 controls and 201 cases) did not provide

complete occupational histories, leaving 643 controls and 504 cases for the present analysis. We selected 2172 controls. We could not find telephone numbers for 629 (29%) in the online white pages directory and these were therefore not approached. We approached 1543 potential controls by letter, followed by an attempted telephone call. Of these, 86 were ineligible or dead, 596 declined and 127 were unable to be contacted. Of eligible controls, 711 (49%) returned the questionnaire

Amongst cases, occupational history was more likely to be missing if the participants were over 80 years of age, or had a diagnosis of diabetes in the previous 3 years. Risk of missingness increased with increasing alcohol intake. Among controls no demographic variables were associated with missing occupational history.

The study was approved by the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute and participating hospitals and each participant gave written informed consent

Data collection

Participants completed face-to-face (84% of cases; 29% of controls) or telephone interviews, undertaken by trained interviewers. We collected information about socio-demographic and lifestyle factors, medical history and history of cancer in first degree relatives. Participants who had cumulatively smoked more than 100 cigarettes, cigars or pipes over their lifetime were asked detailed questions about their smoking history (17). We developed the following variables to characterize smoking: smoking status at time of interview (never, former, current); cigarette pack years as a continuous variable and in 4 categories (0-10, >10 to 20, >20 to 30, >30); cigarettes per day; time since quitting smoking; total years smoking.

Occupational exposure data

Participants were also asked about their lifetime job history including job title, industry, location, main tasks, and ages at start and finish. If the participant had ever worked in the rubber or leather industries or in a metal working job before 1970 (e.g. machinists, fitters, boilermakers) they were asked further questions about specific tasks related to nitrosamine exposure within the relevant industry. For example a rubber worker was asked in which processes he or she had worked (e.g. the breakdown mill) and a leather worker was asked if he or she had worked on animal hides or synthetic leather). Copies of the study questionnaires are available upon request to the corresponding author.

An experienced occupational hygienist (GB) reviewed this information (blinded to case status) to determine the likelihood, level and frequency of occupational exposure to *N*-nitrosamines based on existing literature information (18, 19). Likelihood of exposure was rated as probable when most people doing a particular task would be expected to have some exposure to *N*-nitrosamines. A likelihood rating of possible was used when it was likely that some people doing the task would be exposed to *N*-nitrosamines but information was insufficient to determine whether the particular worker had been exposed. In most of these cases, the hygienist considered it unlikely that the worker would have been exposed.

We decided a priori that low level of exposure to *N*-nitrosamines would represent <1 microgram/m^3, medium would be 1-2 microgram/m^3 and high would be >2 microgram/m^3. Frequency estimates were used in order to differentiate those who were only rarely exposed to *N*-nitrosamines (less than or equal to 4 days per year) from those who were exposed more frequently (more than 4 days per year).

Assessment of likelihood, level and frequency of pesticide exposure was also carried out. Participants were also asked whether or not, over their lifetime they had ever mixed, loaded, or applied any pesticides as part of their work. We also assessed fumigation tasks with phosphine for weevils and with methyl bromide but did not assess exposure to workers re-entering fields where spraying had taken place. If any pesticide tasks were performed, the subjects were asked about the type of pesticide used, the pest involved, the crop or animal and the application method of the pesticide.

Using a pesticide matrix which contained information on crop, target pest, and usage date, the hygienist assessed likelihood of exposure to pesticides. Assessments were made for organochlorine insecticides, organophosphate insecticides, phenoxy herbicides, other herbicides, fumigants, fungicides and other pesticides. For organochlorine pesticides we complied with the definition described in Brooks, 1975 (20) and included the chlorinated insecticides of the DDT group, the diene-organochlorine group, and the hexachlorocyclohexane and toxaphene groups. Organophosphate insecticides were more loosely defined as any insecticide or nerve agents acting on the enzyme acetylcholinesterase (the pesticide group carbamates were also included).

For level of exposure, the pesticide matrix was used in combination with an algorithm based upon personal protection equipment (PPE) use, and how the pesticide was mixed and applied. For example, if the subject reported using DDT without any PPE, mixed indoors and applied

by tractor with mist blower then the exposure level was assessed as High. Conversely, full PPE, no mixing and tractor driver of hand sprayer configuration was assessed as Low. Frequency of exposure was categorized as less than or equal to 4 days per year or more than 4 days per year. For nine participants the fact of exposure to pesticides was determined but not the type of pesticide used. These nine participants were omitted from the subanalyses of pesticide type.

Data were combined across jobs, with each person allocated the highest likelihood, level and frequency of exposure in any of their jobs. Those with only possible exposure to the agents of interest were excluded from the analyses (four controls and one case for *N*-nitrosamines and one control and three cases for pesticides).

Statistical analysis

We used unconditional logistic regression methods to calculate odds ratios (ORs) and 95% confidence intervals (95%CIs) for the risk of pancreatic cancer associated with the occupational exposures. All models were adjusted for the matching variables age (in 10-year age groups) and sex. We used the "chest" command in Stata 13 to examine the change in estimate when the following variables were added to the model: all the variables for smoking defined above; average weekly alcohol intake; level of education; country of birth; BMI categories; history of diabetes; and first-degree family history of pancreatic cancer. We retained variables that changed main effects by more than 5% (pack years as a continuous variable for *N*-nitrosamines and no variables for pesticides).

Results

Because of differential completion of job history questions, slightly more female controls than cases were included, and controls tended to be older than cases (Table 1). Cases were more likely than controls to be current smokers, drink more alcohol, weigh more, have diabetes and have a family history of pancreatic cancer.

In total, 107 reported jobs in 70 individuals were found to have exposures to *N*-nitrosamines including 35 metalworking jobs, 12 mechanic jobs, 7 rubber worker jobs, 5 electrical jobs, 4 farmer/gardener jobs, 2 leather worker jobs, and 2 printer jobs. High level exposures were mainly found in the rubber and leather worker jobs, and medium levels in some metal working jobs. Virtually no variation in frequency of exposure to *N*-nitrosamine was seen, with almost all workers being exposed most working days.

After adjusting for age, sex, and cigarette pack years, no associations were seen between occupational exposure to *N*-nitrosamines and pancreatic cancer risk (OR = 0.85, 95% CI 0.51-1.42), and no trend with level of exposure (Table 2). Among non-smokers the risk of pancreatic cancer with exposure to *N*-nitrosamines was 1.00 (95% CI 0.34-2.92) and among ever smokers it was 0.98 (95% CI 0.56 – 1.73).

With adjustment for age, and sex, no association was observed between occupational exposure to pesticides in general and risk of pancreatic cancer (OR = 0.90, 95% CI 0.61-1.33) and no trend with either level or frequency of exposure (Table 2). No statistically significant associations were found with exposure to any of the individual pesticide groups, although numbers of exposed cases were low. There were no suggestions of increased risk by level or frequency of exposure to individual pesticide groups (data not shown). Among non-smokers the risk of pancreatic cancer with exposure to pesticides was 1.00 (95% CI 0.48-2.06) and among ever smokers it was 0.82 (95% CI 0.51-1.32).

Restricting analyses just to men made no substantial difference to any of the results. Restricting analysis to those who had face to face interviews (444 cases and 189 controls) resulted in ORs which were not statistically significantly different to the original results.

Discussion

Our study found no association between occupational exposure to either *N*-nitrosamines or pesticides and risk of pancreatic cancer.

N-nitrosamines and pancreatic cancer

For *N*-nitrosamines, our overall OR was below unity with confidence intervals that included unity and we did not detect higher risk in those with higher exposures. To our knowledge, no previous case-control studies of pancreatic cancer have been able to assess occupational exposures specifically to the *N*-nitrosamines.

Evidence that occupational exposure to *N*-nitrosamines increases risk of pancreatic cancer is sparse and inconsistent. Case-control and cohort studies of workers, in either the rubber or the leather industries, have had few exposed cases of pancreatic cancer. A cohort study specifically examining *N*-nitrosamine exposure and cancer mortality in the rubber industry included 15 pancreatic cancer deaths and found no associations (21). A cohort study in the leather industry found no increased risk of pancreatic cancer mortality (n = 27 deaths) (13).

Analysis of pancreatic cancer incidence data from over 15 million people in the Nordic countries, showed few statistically significantly increased risks by occupation, with the highest risks in beverage workers, waiters, cooks, and chimney sweeps (12). Shoe and leather workers had no increased risk (SIR = 1.00 95% CI 0.86-1.15) and rubber industry workers were not identified separately. A 1998 review of five cohort studies of metal-workers (who were possibly exposed to *N*-nitrosamines) reported that two studies found significant excess mortality from pancreatic cancer, but there were small numbers of cases in these studies, and inconsistencies between the studies (11).

In our study about 6% of the participants were exposed to *N*-nitrosamines at some time during their working life. This proportion is likely to decrease over time, as cutting oils no longer contain *N*-nitrosamines, and the rubber and leather industries have declined in size in developed countries. A recent survey found that about 0.3% of the Australian working population were exposed to *N*-nitrosamines in their current jobs (22). Our higher exposure prevalence of 6% is likely to be primarily due to the fact that we included exposures in all jobs that a person had ever done (i.e. a lifetime prevalence of any exposure). For example, a person who is now in management in a rubber company may have previously been a maintenance worker. Such individuals would be positive for lifetime exposure to *N*-nitrosamines but negative for current exposure. In addition, changes in the industrial landscape in Australia over the previous 50 years have led to exposure declines, in particular reductions in heavy industries such as the rubber manufacture and leather tanneries. Lastly, current workers using cutting oils are no longer exposed to *N*-nitrosamine preservatives.

Pesticides and pancreatic cancer

We found no association between overall pesticide exposure and risk of pancreatic cancer nor with specific pesticides, although numbers of cases were small in some groups . A meta-analysis in 2000 found no associations between pancreatic cancer risk and herbicides (Meta Risk Ratio = 1.0 95%CI 0.8-1.3) or insecticides (MRR = 1.5 95% CI 0.6-3.7) (23). A case-control study in Spain applied a job exposure matrix to two main occupations for each participant and found a non statistically significant increased risk of pancreatic cancer for exposure to any pesticide (OR = 3.54 95%CI 0.83-15.21) (24). One of the few studies that has been able to examine individual pesticide subgroups and pancreatic cancer risk is the Agricultural Health Study Cohort (15). Of the 13 individual pesticides that they examined, two were associated with pancreatic cancer (pendimethalin OR = 3.0 95% CI 1.3-7.2 and a thiocarbamate (EPTC) OR = 2.56 95% CI 1.1-5.4) and both of these can contain or be

metabolized to *N*-nitroso compounds. We did not have sufficient information or sample size to be able to examine exposure to these specific pesticides.

Strengths and limitations

A potential limitation of our study concerns the low response fraction for both cases and controls which may have resulted in some selection bias. Both younger and female cases appeared less likely to participate. This may have artificially increased the proportion of exposed cases as *N*-nitrosamine exposure occurs in heavy industries in which more men than women tend to work and older people are also more likely to have had opportunities to work in these industries. If this is so, a real effect of exposure may have been masked by such bias although we consider the likelihood of major bias is unlikely given that there was no effect seen in only men and that we adjusted for age. It is also possible that associations are restricted to people with particular genotypes or with other exposures such as *H pylori* colonization (25) but we did not have sufficient statistical power to conduct stratified analyses.

A second limitation of our study is potential misclassification of exposures. We had no actual measurement data as it is not possible to obtain such information in the Australian context over many jobs and many decades. We used individual assessments of exposures based on the tasks that a person did, rather than assuming all workers in a job had the same exposures (26). However we had only one expert reviewing the job histories and some studies have suggested that a panel of experts gives a more robust assessment (27, 28). Considering the low prevalence of exposure and our study sample size it is likely that some misclassification may have occurred, most probably toward false negatives (28). However, our expert has had personal experience with both the rubber and leather industries and has a high level of understanding of the ways in which *N*-nitrosamine exposure may occur in these and other industries. He has also had considerable experience with assessing pesticide exposure and has consulted widely with people who have worked in pesticide regulation in Australia over many years.

The assessment for pesticide exposure depended on the reporting by the participants and quality of such reporting was variable. Some subjects gave the names of all pesticides used, others just trade names, whilst others could only remember the type of crop that they sprayed. Nearly all organochlorine use was reported for jobs prior to the 1980s. However, some subjects reported DDT use through 1990 (well after the official cessation of use). To

moderate the reported data we used a pesticide matrix with details on dates of pesticide availability over the various eras.

Strengths of our study include the appreciable numbers of exposed cases, the individual level occupational exposure assessment, and the good information on confounding variables, particularly smoking.

In conclusion, this analysis of occupational exposure in a large case-control study does not support associations between *N*-nitrosamines or pesticide use and risk of pancreatic cancer. Misclassification of exposure and other factors in our study may have biased our results toward the null, however, our results still imply it is unlikely that any large associations with risk of pancreatic cancer exist.

Acknowledgements: The Queensland Pancreatic Cancer Study was funded by a National Health and Medical Research Council Australia (NHMRC) project grant. P. Webb, L. Fritschi, and R Neale are funded by NHMRC Fellowships and D. Whiteman is funded by an Australian Research Council fellowship. This study would not have been possible without the invaluable contribution of the research nurses, Fran Millar and Lisa Ferguson.

Table 1. Demographic and lifestyle characteristics of pancreatic cancer cases (n = 504) and controls (n = 643) from the Queensland Pancreatic Cancer Study.

		Cases		Controls		OR^	95%CI
		N	%	N	%		
Sex	Male	314	62.3	383	59.6	1.00	
	Female	190	37.7	260	40.4	0.91	0.71-1.16
Age group (years)	30-39	10	2.0	5	0.8	1.00	
	40-49	34	6.8	38	5.9	0.44	0.14-1.42
	50-59	98	19.4	109	17.0	0.44	0.14-1.33
	60-69	198	39.3	233	36.2	0.42	0.14-1.24
	70-79	123	24.4	166	25.8	0.36	0.12-1.09
	80+	41	8.1	92	14.3	0.23	0.07-0.72
Smoker	Never	182	36.1	318	49.5	1.00	
	Former	203	40.3	269	41.8	1.31	1.00-1.72
	Current	119	23.6	56	8.7	3.54	2.42-5.19
Education	High school	219	43.5	282	43.9	1.00	
	Technical college	114	22.6	97	15.1	1.47	1.06-2.05
	Trade qualifications	74	14.7	119	18.5	0.72	0.51-1.03
	University	65	12.9	104	16.2	0.72	0.50-1.04
	Other	31	6.2	39	6.1	0.94	0.56-1.56
	Missing	1	0.2	2	0.3	0.41	0.03-4.96
Country of birth	Australia and NZ*	381	75.6	516	80.3	1.00	
	UK and USA*	70	13.9	66	10.3	1.49	1.03-2.15
	Other Europe	34	6.8	34	5.3	1.36	0.82-2.23
	Other	19	3.8	27	4.2	0.89	0.48-1.63
Body Mass Index (kg/m^2)	<25	140	28.8	229	35.9	1.00	
	25 to <30	197	40.5	250	39.2	1.20	0.90-1.61
	30 to <35	105	21.6	112	17.6	1.36	0.96-1.93
	>=35	45	9.2	47	7.4	1.33	0.83-2.13
Diabetes	None	412	81.8	557	86.6	1.00	
	Diagnosis >=3 yrs ago	67	13.3	67	10.4	1.40	0.97-2.03
	Diagnosis <3 ys ago	23	4.6	19	3.0	1.49	0.80-2.79

First degree family history of pancreatic cancer	No Yes	481 23	95.4 4.6	628 15	97.7 2.3	1.00 2.16	 1.09-4.26
Mean pack years among smokers	Pack years (standard deviation)	18.23 (28.6)		5.71 (16.1)		1.06	0.82-1.37
Average weekly alcohol intake	Standard drinks** (standard deviation)	13.56 (13.9)		9.88 (11.9)		1.02	1.01-1.04

* NZ = New Zealand, UK = United Kingdom, USA = United States of America.

** One standard drink contains 10g of alcohol.

^All adjusted for age and sex.

Table 2. Number and percent of cases (n = 504) and controls (n = 643) exposed to occupational *N*-nitrosamines and pesticides and odds ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer from the Queensland Pancreatic Cancer Study.

Agent	**Exposure**	**N cases (%)**	**N controls (%)**	**OR***	**95% CI**
Nitrosamines	Never (Reference)	471 (93.6)	601 (94.0)	1.0	
	Ever	32 (6.4)	38 (6.0)	0.85	0.51-1.42
	Level Low	23 (4.6)	29 (4.5)	0.83	0.46-1.50
	Medium	5 (1.0)	5 (0.8)	1.13	0.32-4.03
	High	4 (0.8)	4 (0.6)	0.65	0.15-2.81
Any pesticide	Never (Reference)	449 (89.6)	573 (89.3)	1.00	
	Ever	52 (10.4)	69 (10.7)	0.90	0.61-1.33
	Level Low	12 (2.4)	17 (2.7)	0.81	0.38-1.73
	Medium	16 (3.2)	21 (3.3)	0.91	0.47-1.79
	High	24 (4.8)	31 (4.8)	0.93	0.54-1.64
	Frequency<4 day/yr	15 (3.0)	24 (3.7)	0.74	0.38-1.44
	≥4 day/year	37 (7.4)	45 (7.0)	0.98	0.62-1.56
Organochlorine insecticides	Never	483 (97.2)	614 (96.5)	1.00	
	Ever	14 (2.8)	22 (3.5)	0.83	0.-1.65
Organophosphate insecticides	Never	478 (96.2)	615 (96.5)	1.00	
	Ever	19 (3.8)	22 (3.5)	1.07	0.57-2.01
Phenoxy herbicide	Never	478 (96.2)	614 (96.2)	1.00	
	Ever	19 (3.8)	24 (3.8)	0.93	0.50-1.74
Other herbicide	Never	480 (96.4)	610 (95.6)	1.00	
	Ever	18 (3.6)	28 (4.4)	0.76	0.41-1.39
Fumigants	Never	496 (99.4)	635 (99.4)	1.00	
	Ever	3 (0.6)	4 (0.6)	0.89	0.20-4.01
Fungicides	Never	494 (99.0)	628 (98.4)	1.00	
	Ever	5 (1.0)	10 (1.6)	0.62	0.21-1.83
Other pesticides	Never	488 (98.0)	618 (96.7)	1.00	
	Ever	10 (2.0)	21 (3.3)	0.56	0.26-1.22

*Adjusted for agegroup and sex for all analyses; additionally adjusted for cigarette pack years smoked for *N*-nitrosamine models Some cells do not sum to total counts because of missing values for exposure variables.

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