

Occupational Exposures and Risk of Gastric Cancer in a Population-based Case-Control Study¹

Anna Mia Ekström,² Mikael Eriksson, Lars-Erik Hansson, Anders Lindgren, Lisa Beth Signorello, Olof Nyrén,³ and Lennart Hardell

Department of Medical Epidemiology, Karolinska Institutet, S-171 77 Stockholm, Sweden [A. M. E., L. B. S., O. N.]; Department of Oncology, University Hospital, S-221 85 Lund, Sweden [M. E.]; Department of Surgery, Mora Hospital, S-792–85 Mora, Sweden [L. E. H.]; Department of Pathology, Falu Hospital, S-791 82 Falun, Sweden [A. L.]; and Department of Oncology, Örebro Medical Center, S-701 85 Örebro, Sweden [L. H.]

ABSTRACT

Gastric cancer trends seem to follow improvements in the environment of blue-collar workers, but the etiological role of occupational exposures in gastric carcinogenesis is scantily investigated. The risk of gastric adenocarcinoma in 10 common occupational industries, and particularly the long-term effects of asbestos, organic solvents, impregnating agents, insecticides, and herbicides, were evaluated in a population-based case-control study, including data on most established risk factors. The study base included all individuals of ages 40–79, born in Sweden and living in either of two areas (total population, 1.3 million) with differing gastric cancer incidences, from February 1989 through January 1995. We interviewed 567 cases classified to site (cardia/noncardia) and histological type, and 1165 population-based controls, frequency-matched for age and sex. Metal workers had a 46% excess gastric cancer risk [adjusted odds ratio (OR), 1.46; 95% confidence interval (CI), 1.10–1.94], increasing to 1.65 (95% CI, 1.17–2.32) for >10 years in the industry. The elevated risk after exposure to herbicides (OR, 1.56; 95% CI, 1.13–2.15) was attributable to phenoxyacetic acids (adjusted OR, 1.70; 95% CI, 1.16–2.48), similarly across tumor subtypes, and not modified by smoking, body mass index, or *Helicobacter pylori*. The absence of interaction was demonstrated by the pure multiplicative effect found among those exposed to both *H. pylori* and phenoxyacetic acids (OR, 3.42; 95% CI, 1.41–8.26). Organic solvents, insecticides, impregnating agents, and asbestos were not associated with gastric cancer risk. Employment in the metal industry and exposure to phenoxyacetic acids were both positively and independently associated with gastric cancer risk. The fractions of all gastric cancers attributable to these job-related exposures were small but not negligible (7 and 5%, respectively) in the Swedish population.

INTRODUCTION

The links, if any, between occupational exposures and gastric cancer remain poorly understood. Because gastric cancer is more prevalent among blue-collar workers and the slope in incidence started in the industrialized world (1, 2), it seems reasonable to study occupational exposures that have declined concomitantly with gastric cancer because of the increased awareness of hazards in the workplace.

Occupational exposures of interest range from substances with primarily promoting effects to potent initiators, including dusts, asbestos and other insulating material, impregnating agents, organic solvents, and pesticides (herbicides, insecticides, and fungicides).

Dust and particulate matter, swallowed after respiratory clearance (3, 4), could cause irritation and subsequent cell proliferation in the gastric mucosa and also function as carriers of other carcinogenic substances. Certain herbicides have been associated with cancer, such as phenoxyacetic acids, with soft tissue sarcomas and lymphomas (5,

6). The potential carcinogenicity and the timing of their commercial upswing and decline made them interesting for evaluation in our study.

Because of diverging incidence trends and demographic differences (7, 8), there is emerging wariness of assuming a common etiology for tumors located in the gastric cardia and distal gastric cancer. The two major histological subtypes (9), diffuse and intestinal, also appear to be epidemiologically distinct because the latter is allegedly more linked to environmental factors (10, 11). Therefore, both anatomical subsite and histological type should be taken into account in etiological research.

Acknowledging this, we took advantage of the high-quality population registration in Sweden when designing a population-based case-control study to investigate the effect of occupational exposures on gastric cancer risk.

MATERIALS AND METHODS

Setting. This study was conducted in two geographic areas (total population, 1.3 million) in Sweden with differing gastric cancer incidence. The incidence rate in the three counties representing the south-central area (9 per 100,000 person-years in 1992⁴) is close to the national average, whereas the northern area, represented by two other counties, has the country's highest incidence (17 per 100,000 person-years in 1992⁴). The study base consisted of all individuals of ages 40–79, born in Sweden and living in one of the above-mentioned counties during the study period, *i.e.*, from February 1989 through January 1995.

Cases. We identified all new cases diagnosed in the study period with histologically confirmed gastric adenocarcinoma via clinicians enrolled as contact persons at all hospitals in the study area. This reporting was supplemented by: (a) continuous surveillance of all definite or suspected cases whose specimens were evaluated at the county pathology departments; (b) monthly double-checks with all regional cancer registries; and (c) a final check with the national Cancer Register 30 months after the end of the study period to identify cases notified with long delays.

Those who met the above-mentioned eligibility criteria ($n = 908$) were asked by their clinician to participate in an interview performed by Statistics Sweden. The median time that elapsed between cancer diagnosis and interview was 32 days, and 90% were interviewed within 3 months. In total, 567 cases (33.3% women) with a mean (SD) age of 67.9 (9.1) years were interviewed. The reasons for nonparticipation were early death or very advanced disease in 270 (29.7%), mental or physical illness other than gastric cancer in 40 (4.4%), patient refusal in 28 (3.1%), and 3 (0.3%) could not be located. An important reason for the seemingly low participation rate (62.4%) was the extremely thorough case ascertainment; all cases resident in the population under study were identified, even when managed outside of the study area, and the number in the denominator exceeded that recorded in the Swedish Cancer Register (100% compared 98%; Ref. 12).

Classification of Histopathological Type and Site. To uniformly classify each case with regard to histological type [according to Laurén (9)] and tumor subsite, the clinicians continuously sent us standardized reports of the tumor location relative to anatomical landmarks, hospital case records were scruti-

Received 9/2/99; accepted 10/4/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ Supported by Grant R01 CA 50959 from the National Cancer Institute.

² To whom requests for reprints should be addressed, at the Department of Medical Epidemiology, Karolinska Institutet, Box 281, S-171 77 Stockholm, Sweden. E-mail: Annamia.Ekstrom@mep.ki.se.

³ Principal investigator.

⁴ A. M. Ekström, L. E. Hansson, L. B. Signorello, A. Lindgren, R. Bergström, and O. Nyrén. Decreasing incidence of both major subtypes of gastric adenocarcinoma. A population-based study in Sweden, submitted for publication.

nized, and histological slides (both biopsy and resection specimens) were reevaluated by one pathologist (A. L.).

Intestinal differentiation was considered to be present when malignant cells formed definite glandular patterns ($n = 337$). Poorly differentiated cells, often signet ring shaped and rarely forming glandular patterns, characterized the diffuse type ($n = 184$). The tumors were classified according to their predominant pattern, and only when these patterns were exhibited equally were they classified as being of mixed type ($n = 37$). In 1.6% ($n = 9$) of the cases, the histological type could not be determined with certainty. The stainings used were H&E and van Giesson, supplemented with Alcian blue-periodic acid Schiff in biopsy specimens. Cancer of the gastric cardia ($n = 90$) was defined as an adenocarcinomatous lesion with its center located within 1 cm proximal and 2 cm distal to the gastroesophageal junction (13). For a small fraction (0.9% of the cases, $n = 5$) the exact site origin could not be determined.

Controls. Two controls per case were randomly selected (and successively interviewed during the study period) by Statistics Sweden from age and gender strata in the continuously updated computerized population register to mimic the distribution of cases (frequency matching). Of the 1534 control subjects that were contacted, 1165 were interviewed (participation rate, 75.9%). The mean (SD) age was 67.0 (9.8) years, and 33.1% were women. The reasons for nonparticipation were refusal in 245 (16.0%), mental or physical illness (other than gastric cancer) in 90 (5.9%), and 34 (2.2%) could not be located for interview.

Interviews. Professional interviewers from Statistics Sweden conducted face-to-face interviews. Because of the severity of the disease, it was impossible to conceal case/control status, but the interviewers were blinded to the study hypotheses and trained to treat all subjects uniformly. Cases were interviewed in the hospital (44%), in their homes (53%), or elsewhere (3%); controls were interviewed in their homes (93%) or elsewhere (7%). The mean interview duration was 1.5 h for the cases (range, 35 min to 2 h and 10 min) and 1.4 h for the controls (range, 30 min to 2 h and 25 min). The investigators scrutinized the questionnaires shortly after interview, and subjects were recontacted regarding unclear answers through a blinded coordinator at Statistics Sweden.

Explanatory Variables. All employment of at least 1-year duration was coded using a 5-digit classification of occupational titles as devised by the Nordic Classification of Occupations (1983), based on the International Standard Classification of Occupations (International Labor Office of the United Nations, 1958). The first two digits were used to summarize the total duration of work within each of the 10 most frequent industries. Work in each industry was analyzed as ever (minimum duration of employment was 1 year) *versus* never but was also stratified by duration (1–10 years *versus* >10 years).

Interviewers inquired in open-ended questions about exposures (including duration and calendar time of exposure) to mining, paper mill, or pulp-mill work, asbestos and other insulating materials, organic solvents *e.g.*, white spirit and tri-chloro-ethylene, pesticides, impregnating agents, and paint. Using these self-reports on exposure, taking job histories as well as calendar year into account, two experienced occupational epidemiologists (M. E., L. H.), blinded to any information that might disclose case-control status, assessed type of exposure, assigned every subject an exposure status (never/ever), and estimated the cumulative duration of each exposure under consideration. Pesticides were subdivided into herbicides (phenoxyacetic acids and other herbicides), insecticides (DDT and other insecticides), and fungicides, while considering year of withdrawal/banning whenever applicable. Impregnating agents were similarly subdivided into chlorophenols, creosote, arsenic, and tar. To evaluate the reproducibility of the exposure assessment, we used an occupational hygienist, blinded to case-control status, unaware of any focus of the reassessment and of the previous evaluations, to estimate the exposure to specific compounds by using the original data records in a sample of 201 individuals. The κ -coefficient of observer agreement was 0.89 (95% CI,⁵ 0.82–0.96), indicating almost perfect agreement between observers (14).

SES was estimated from the occupational titles reported in the job histories

⁵ The abbreviations used are: CI, confidence interval; OR, odds ratio; SES, socioeconomic status; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; MCPA, 4-chloro-2-methyl-phenoxyacetic acid; DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; BMI, body mass index; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

as devised by Statistics Sweden (15) and classified as follows: (1) unskilled manual worker; (2) skilled manual worker; (3) lower nonmanual worker; or (4) higher nonmanual worker. To achieve a long-term estimate of socioeconomic living standards, a weighed lifetime average of the above-mentioned SES scores was computed according to Hansson *et al.* (16) and used for multivariate adjustments. Level of education was classified into <9 years, 9 years, other postcompulsory training, secondary school, higher secondary school, and university. Further covariates included number of siblings (1–2, 3–4, 5–6, or ≥ 7 , including self), area of residence (north *versus* central Sweden), alcohol intake (grams per month), and smoking habits (nonsmoker, cigarette smoker for <30 years, cigarette smoker for ≥ 30 years). Subjects described their typical diet 20 years prior to their interview by answering 59 food frequency questions, including fruit and vegetable intake (divided into quartiles based on the frequency distribution among controls).

Serological Data. During the last years of fieldwork, we also collected blood samples from interviewed cases ($n = 298$) and controls ($n = 244$; participation rate, 70.5% of those asked to provide a blood sample). Serum IgG antibodies to *Helicobacter pylori* were determined using HM Cap ELISA [sensitivity, 94–98% (17); specificity, 92–97% (18)] to evaluate whether the effects of the occupational exposures were modified by this infection or *vice versa*.

Statistical Methods. Occupational data were missing for 2 cases and 1 control, leaving 565 cases and 1164 controls for the analyses. Duration of exposure to phenoxyacetic acids could not be determined in 1 case. Three cases and 1 control also had missing data on debut of this exposure. Cases with undetermined anatomical site (0.9%) or histopathological type (1.6%) were not included in the subtype-specific analyses.

Unconditional logistic regression was used in both univariate and multivariate analyses. Model parameters were estimated by the maximum likelihood method (19). As measures of the relative risk, ORs and 95% CIs were calculated on the basis of the estimated β -parameters and their SEs. All baseline models were adjusted for age and sex. In the multivariate analyses, only variables considered to be of primary biological and statistical importance were kept in the final model.

RESULTS

Education was strongly inversely associated with risk of gastric cancer (P for trend, <0.0001). University-educated persons had a 60% lower risk than those did with <9 years of schooling (OR, 0.40; 95% CI, 0.24–0.66). Compared with unskilled manual workers, the risk of gastric cancer was 15% lower among skilled manual workers (OR, 0.85; 95% CI, 0.65–1.11) and 45% lower among nonmanual workers (OR, 0.55; 95% CI, 0.42–0.73).

Table 1 shows the association between work in the 10 most common industries and overall gastric cancer risk. Farming, the most common occupation among men in our study, was not associated with gastric cancer. Housekeeping, predominating among women, displayed no duration-risk relationship with the disease, although a moderate excess risk was seen before adjusting for SES. Among forestry workers, a 30% increased risk of developing gastric cancer (OR, 1.33; 95% CI, 1.02–1.74) was attenuated after control for SES. An association with ever-exposure to metalwork remained significant (OR, 1.38; 95% CI, 1.05–1.83) after adjustments, displaying a clear trend toward increasing risk with time in the metal industry. Further adjustments for geographic area, siblings, and fruit and vegetable intake strengthened the association (OR, 1.46; 95% CI, 1.10–1.94). After 10 years of metal-related work, the relative risk was 1.65 (95% CI, 1.17–2.32). This effect was not modified by smoking (adjusted ORs for ever-exposure to metalwork among nonsmokers and smokers: 1.48; 95% CI, 0.93–2.37; and 1.45; 95% CI, 1.00–2.09, respectively), and there was no confounding by alcohol intake, smoking, or *H. pylori* infection. The proportion of gastric adenocarcinomas attributable to metalwork (20) was 32% among the exposed (*i.e.*, workers in the metal industry) and 7% in the mixed Swedish population (exposed and nonexposed).

Table 1 ORs and 95% CI for developing gastric adenocarcinoma after exposure to work in the 10 most common industries among 565 cases and 1164 controls

Code ^a	Industry	Duration	Cases _{exposed} / Controls _{exposed} (n)	OR ^b	95% CI ^b	OR ^c	95% CI ^c
41	Farm workers	Ever	145/308	0.92	0.73–1.17	0.86	0.68–1.10
		1–10 years	87/203	0.84	0.64–1.12	0.81	0.61–1.08
		>10 years	58/105	1.07	0.76–1.51	0.97	0.68–1.39
92	Housekeeping service workers	Ever	127/218	1.45	1.02–2.07	1.25	0.87–1.80
		1–10 years	41/73	1.43	0.89–2.30	1.35	0.84–2.18
		>10 years	86/145	1.46	1.00–2.16	1.21	0.81–1.80
44	Forest workers	Ever	122/202	1.33	1.02–1.74	1.17	0.89–1.54
		1–10 years	58/106	1.22	0.86–1.73	1.11	0.78–1.58
		>10 years	64/96	1.45	1.02–2.05	1.23	0.86–1.77
75	Shop and construction metal workers	Ever	115/185	1.42	1.08–1.86	1.38	1.05–1.83
		1–10 years	40/78	1.18	0.79–1.78	1.17	0.78–1.76
		>10 years	75/107	1.59	1.15–2.20	1.55	1.11–2.17
79	Masonry, concrete, and all-around construction work	Ever	101/168	1.32	1.00–1.76	1.20	0.90–1.62
		1–10 years	39/65	1.33	0.87–2.02	1.26	0.82–1.93
		>10 years	62/102	1.34	0.95–1.90	1.17	0.82–1.67
64	Motor vehicle drivers for urban and road transport	Ever	85/183	0.97	0.73–1.29	0.89	0.67–1.20
		1–10 years	48/112	0.89	0.62–1.28	0.88	0.61–1.27
		>10 years	37/71	1.09	0.72–1.66	0.92	0.59–1.41
33	Salesmen and shop clerks	Ever	82/182	0.91	0.68–1.21	0.94	0.70–1.26
		1–10 years	37/77	1.00	0.66–1.50	1.04	0.69–1.58
		>10 years	45/104	0.86	0.59–1.24	0.87	0.59–1.27
40	Farmers	Ever	68/152	0.88	0.65–1.20	1.07	0.70–1.65
		1–10 years	14/27	1.04	0.54–2.00	1.04	0.54–2.02
		>10 years	54/125	0.84	0.60–1.19	1.09	0.63–1.89
77	Wood workers	Ever	60/115	1.09	0.78–1.53	1.00	0.71–1.41
		1–10 years	34/65	1.11	0.72–1.72	1.02	0.66–1.58
		>10 years	26/49	1.10	0.67–1.80	0.98	0.59–1.61
00	Technicians/Engineers	Ever	52/120	0.90	0.63–1.28	1.17	0.80–1.71
		1–10 years	18/32	1.17	0.65–2.12	1.39	0.76–2.54
		>10 years	34/88	0.80	0.53–1.22	1.08	0.69–1.69

^a Occupational classification codes as devised by the Nordic Classification of Occupations (NYK 1983) based on the International Standard Classification of Occupations (International Labor Office of the United Nations, 1958).

^b Adjusted for age and gender. Reference group: all unexposed to the industry of interest.

^c Adjusted for age, gender, and lifetime average socioeconomic status.

For the remaining industries, masonry and construction, transport, sales, wood, and technical engineering, we found no significant associations with gastric cancer.

Because an association with industry is determined both by the likelihood and the intensity of exposure to hazardous substances, we proceeded to analyze some occupational exposures of particular interest (Table 2).

We found that exposure to herbicides was significantly associated with risk of gastric cancer (OR, 1.56; 95% CI, 1.13–2.15). Further stratification by herbicide type revealed that those ever-exposed to phenoxyacetic acids had an 80% excess risk (OR, 1.80; 95% CI, 1.26–2.57) compared with those never exposed to any herbicides. The majority had been exposed to Hormoslyr, a combination of 2,4-D and 2,4,5-T, used against weeds and bushy vegetation (OR, 1.73; 95% CI, 1.16–2.58). Only 3 cases and no controls were exposed to 2,4-D only. The OR (1.84; 95% CI, 0.82–4.10) for MCPA did not reach statistical significance. The risk associated with exposure to herbicides was entirely driven by phenoxyacetic acids, and there was no association with other herbicides (OR, 0.96; 95% CI, 0.49–1.85).

Gastric cancer was not associated with other pesticides, such as insecticides (including DDT, the most common insecticide in Sweden, followed by organophosphates; OR, 0.75; 95% CI, 0.52–1.07) and fungicides (OR, 0.76; 95% CI, 0.24–2.41). Nor did we observe any association with organic solvents or impregnating agents such as chlorophenols (Table 2). Exposure to paper pulp conferred a statistically nonsignificant 67% excess risk (OR, 1.67; 95% CI, 0.95–2.96). We found no significant associations with asbestos or other insulating materials.

The risk increase associated with phenoxyacetic acids remained strong after adjustment for SES, geographic area, siblings, and fruit and vegetable intake (overall gastric adenocarcinoma OR, 1.70; 95% CI, 1.16–2.48; Table 3). Stratifying by tumor site and histological type, we found the subtype-specific ORs to be of similar magnitude,

although somewhat lower among cardia cases (Table 3) and not confounded by either alcohol intake or smoking.

Despite a statistically significant trend ($P = 0.03$), there was no clear relationship with cumulative duration of exposure to phenoxyacetic acids (Table 4) because the highest risk was observed at 1–6 months duration of exposure (OR, 1.86; 95% CI, 1.10–3.15). An

Table 2 ORs and 95% CIs for developing gastric adenocarcinoma after exposure to specific occupational compounds among 565 cases and 1164 controls

Compound	Exposure	Cases (n)	Controls (n)	OR ^a	95% CI ^a
Pesticides (all)	No	462	960	1.00	
	Yes	103	204	1.05	0.81–1.37
Herbicides (all)	No	490	1057	1.00	
	Yes	75	107	1.56	1.13–2.15
Phenoxyacetic acids (all) ^b	Yes	62	77	1.80	1.26–2.57
	2, 4, 5-T and 2, 4-D ^{b,c}	48	61	1.73	1.16–2.58
MCPA ^b	Yes	11	14	1.84	0.82–4.10
Other herbicides ^b	Yes	13	30	0.96	0.49–1.85
Insecticides (all)	No	521	1046	1.00	
	Yes	44	118	0.75	0.52–1.07
DDT ^d	Yes	23	54	0.86	0.52–1.42
	No	561	1153	1.00	
Fungicides	Yes	4	11	0.76	0.24–2.41
	No	333	700	1.00	
Organic solvents	Yes	232	464	1.08	0.87–1.33
	No	453	957	1.00	
Impregnating agents	Yes	112	207	1.16	0.89–1.51
	Yes	28	56	1.05	0.66–1.68
Paper pulp	No	543	1136	1.00	
	Yes	22	28	1.67	0.95–2.96
Insulating materials	No	380	807	1.00	
	Yes	185	357	1.16	0.91–1.47
Asbestos	No	410	861	1.00	
	Yes	155	303	1.11	0.87–1.42

^a Adjusted for age and gender.

^b Reference group: unexposed to all herbicides.

^c 2,4,5-Tri-chloro-phenoxyacetic acid (2,4,5-T), 2,4-Di-chloro-phenoxyacetic acid (2,4-D).

^d Reference group: unexposed to all insecticides.

^e Reference group: unexposed to all impregnating agents.

Table 3 ORs and 95% CIs of developing gastric adenocarcinoma by subsite and histological subtype derived from multivariate logistic regression analyses of exposure to phenoxyacetic acids among 565 cases and 1164 controls

Subtype	Exposure to phenoxyacetic acids	Cases (n)	Controls (n)	OR ^a	95% CI ^a	OR ^b	95% CI ^b
Overall	No ^c	490	1057				
	Yes	62	77	1.80	1.26–2.57	1.70	1.16–2.48
Cardia ^d	No ^c	77	1057				
	Yes	11	77	1.66	0.84–3.29	1.55	0.74–3.26
Noncardia ^d	No ^c	409	1057				
	Yes	51	77	1.86	1.27–2.72	1.76	1.18–2.63
Intestinal ^d	No ^c	228	1057				
	Yes	29	77	1.74	1.10–2.78	1.71	1.04–2.79
Diffuse ^d	No ^c	145	1057				
	Yes	16	77	1.84	1.02–3.30	1.67	0.90–3.10

^a Adjusted for age and gender.

^b Adjusted for age, gender, lifetime average SES, area of residence (north/south), number of siblings, and fruit and vegetable intake.

^c The reference group consisted of subjects unexposed to all herbicides, *i.e.*, it did not include the 13 cases and 30 controls exposed to herbicides other than phenoxyacetic acids (see Table 2).

^d Cases of unspecified site (cardia/noncardia) or unspecified histological type (intestinal/diffuse) are not included.

excess risk of gastric cancer was noted already 10 years after first exposure to phenoxyacetic acids but with nonsignificant point-estimates varying between 49 and 59% until 40 years after first exposure, when the risk more than doubled (OR, 2.14; 95% CI, 1.00–4.58), *P* for trend = 0.01.

In the subset with data on *H. pylori* serology (positive/negative), a stratified analysis in the *H. pylori*-positive and -negative strata resulted in identical ORs for ever-exposure to phenoxyacetic acids when adjusting for all confounders (OR, 2.09; 95% CI, 0.89–4.89; and OR, 2.09; 95% CI, 0.60–7.22, respectively). This suggests that *H. pylori* does not modify the effect of phenoxyacetic acids. Using seronegative individuals never exposed to herbicides as reference, *H. pylori* seropositivity approximately doubled the risk of gastric cancer (OR, 1.82; 95% CI, 1.21–2.74), as did exposure to phenoxyacetic acids only (OR, 2.05; 95% CI, 0.65–6.50), adjusted for all confounders. The highest risk was found among those exposed to both *H. pylori* and phenoxyacetic acids (OR, 3.42; 95% CI, 1.41–8.26), indicating a multiplicative effect of two independent risk factors and, again, absence of interaction.

We also investigated whether adipose storage of herbicide contaminants such as dioxins (PCDDs) and dibenzofurans (PCDFs; Ref. 21) modified the effect. An analysis within strata below and above the median BMI [(weight (kg)/height (m)²] did not indicate any significant interaction between phenoxyacetic acids and BMI (OR, 1.52; 95% CI, 0.82–2.80; and OR, 1.72; 95% CI, 1.05–2.80; in the low and high BMI strata, respectively). Cigarette smoking did not modify the effect of phenoxy herbicides on gastric cancer risk.

The proportion of gastric adenocarcinoma attributable to phenoxyacetic acids (20) was 41% among the exposed and 5% in a mixed Swedish population of exposed and nonexposed.

Table 4 ORs and 95% CIs for developing any subtype of gastric adenocarcinoma by cumulative duration of exposure to phenoxyacetic acids derived from multivariate logistic regression analyses including 565 cases and 1164 controls

Cumulative duration of phenoxyacetic acid exposure	Cases ^a (n)	Controls (n)	OR ^b	95% CI ^b
Unexposed to all herbicides ^c	490	1057	1.00	
<1 month	11	18	1.57	0.72–3.45
1–6 months	30	33	1.86	1.10–3.15
7–12 months	7	10	1.74	0.64–4.73
>1 year	13	16	1.38	0.63–3.01
			(<i>P</i> for trend = 0.03)	

^a One case exposed to phenoxyacetic acid was not included because of missing data on duration of exposure.

^b Adjusted for age, gender, lifetime average SES, area of residence (north/south), number of siblings, and fruit and vegetable intake.

^c The reference group was subjects unexposed to all herbicides, *i.e.*, it did not include the 13 cases and 30 controls exposed to herbicides other than phenoxyacetic acids (see Table 2).

DISCUSSION

Several investigators have found elevated risks of gastric cancer associated with the metal industry (22, 23, 24). We observed a 46% excess risk among metal workers. Unfortunately, we could not obtain reliable quantitative data on metal dust exposure through interviews, but unlike earlier studies, we had information on important cofactors such as dietary habits, lifetime SES, smoking, alcohol intake, and infection by *H. pylori*.

An increased gastric cancer risk among forestry workers has also been reported (22, 25, 26). Herbicide exposure, poor food storage facilities (27), and wood dust (28) are other characteristics of forestry work that potentially could contribute to this effect. Contrary to some previous investigations (29, 30, 31), we found no increased risk associated with asbestos or other insulating material, despite relatively large numbers of exposed subjects. Albeit borderline significant, the 67% risk increase associated with paper pulp exposure does support earlier findings (32). Although organic chlorines are used in this industrial processing, individual exposure assessments of specific compounds are lacking (32).

In our population-based study, exposure to phenoxyacetic acids increased gastric cancer risk ~70%, regardless of tumor subtype and, after adjustment for conceivable confounders.

Phenoxy herbicides were introduced in Sweden in the late 1940s and became popular for combating shrubs along railways, in forestry, and in agriculture. The commercial use declined after 1977 when 2,4,5-T was banned because of contamination with the toxic TCDD (33–35). In 1990, 2,4-D was withdrawn from the Swedish market, whereas MCPA is still used as a herbicide, across the world. Several case-control studies have linked soft-tissue sarcoma and malignant lymphoma with exposure to phenoxyacetic acids and the contaminating dioxins (PCDDs) and dibenzofurans (PCDFs; Refs. 5 and 36). The IARC classified TCDD as a Human Group I carcinogen (34), but the evidence of 2,4-D, MCPA, and 2,4,5-T as human carcinogens was considered to be limited (37).

Few have found associations between herbicides and gastric adenocarcinoma. In a large meta-analysis of farmers, Blair *et al.* (38) observed a small but significant excess of gastric cancer. Although herbicide exposure was one possible explanation, specific data were not available (38). A cohort study of Swedish railroad workers showed slightly elevated gastric cancer mortality among those exposed to phenoxyacetic acids (39). A review of health outcomes after the wartime use of Agent Orange (containing 2,4,5-T and 2,4-D) found no association with gastrointestinal cancers, but reviewers did point out shortcomings in exposure definition and quantification (40).

The toxicity of phenoxy herbicides depends on the composition of

the product (33, 34). Hence, solvents and impurities may be independent risk factors of cancer (35). The phenoxy herbicide 2,4,5-T, as well as the chemically related chlorophenols, were contaminated with PCDDs and PCDFs (41). Lower chlorinated PCDDs have been found in 2,4-D (42). Because impurities are rarely taken into account, variations in their occurrence might explain inconsistencies among studies. Two German cohort studies showed a nonsignificant increased risk among dioxin-exposed workers (43, 44), whereas a review made by IARC declared evidence insufficient to support an association between phenoxy herbicides, TCDD, and gastric cancer (34). No increased mortality in gastric cancer was observed in a recently published study on a cohort of United States males manufacturing TCDD-contaminated products (45). Even if dioxins would increase the risk of gastric cancer, it is unlikely that this impurity alone explains our results, because we found a similar effect of MCPA, which is not contaminated by PCDDs and PCDFs. Furthermore, we failed to find an increased risk for exposure to chlorophenols that do contain these contaminants.

H. pylori, a human carcinogen (46), has repeatedly been associated with gastric cancer (47). Although limited by rather small numbers, the identical phenoxy effects among both seropositives and -negatives indicate that *H. pylori* infection and phenoxy herbicides are independent risk factors, where the former does not modify the effect of the latter.

Because 10 industries and 15 specific substances were analyzed, the risk of observing significant results by chance was inflated. However, the consistency in our findings and the support of the literature, albeit weak, increased our confidence. Because the higher nonresponse rate among cases was mainly attributable to the severity of disease, selection bias would result if the exposures (metal, herbicides) were associated with the rate of disease progression. However, this would probably underestimate the associated risk. Differential misclassification could occur if cases were more likely than controls to recall the exposure. However, null associations with exposures commonly conceived as harmful (e.g., asbestos and DDT) and the absence of any linkage between phenoxy herbicides and gastric cancer in popular media somewhat reduce this concern. Bias arising from the classification of specific exposures was curbed by the blinding of case-control status and became even less of a concern after an independent and blinded reevaluation revealed excellent agreement between observers. Important confounding is unlikely, because we controlled for most known risk predictors of gastric cancer including age, gender, *H. pylori*, fruit and vegetable intake, SES, BMI, and smoking.

Considering the consistency across subgroups, the persistence of an effect after adjustment for known risk factors, and the tendency toward a dose-response relationship, it appears that exposure to phenoxy herbicides, even when uncontaminated by dioxins, could increase the risk of gastric cancer. Yet, the biological plausibility of the association remains uncertain. Peroxisome proliferators, a diverse group of chemicals including phenoxyacetic acids (48, 49, 50), may stimulate growth factors, activate cell cycle S-phase ploidy changes (49), and induce liver tumors in rodents (50), possibly through the production of free radicals (48, 51). Whether this evidence applies to humans has not been substantiated (50).

ACKNOWLEDGMENTS

We are indebted to Jan Dich (Cancer Epidemiology Unit, Department of Oncology and Pathology, Karolinska Institutet and Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden) for reevaluation of exposure assessment.

REFERENCES

- Parkin, D. M., Pisani, P., and Ferlay, J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int. J. Cancer*, *54*: 594–606, 1993.
- Howson, C. P., Hiyama, T., and Wynder, E. L. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol. Rev.*, *8*: 1–27, 1986.
- Meyer, M. B., Luk, G. D., Sotelo, J. M., Cohen, B. H., and Menkes, H. A. Hypothesis. The role of the lung in stomach carcinogenesis. *Am. J. Respir. Dis.*, *121*: 887–891, 1980.
- Neugut, A. I., and Wylie, P. Occupational cancers of the gastrointestinal tract. *Occup. Med.*, *2*: 109–135, 1987.
- Hardell, L., Eriksson, M., Axelson, O., and Zahm, S. H. Cancer epidemiology. In: A. Schecter (ed.), *Dioxins and Health*, pp. 525–547. New York: Plenum Publishing Corp., 1994.
- Dich, J., Zahm, S. H., Hanberg, A., and Adami, H.-O. Pesticides and cancer. *Cancer Causes Control*, *8*: 420–443, 1997.
- Blot, W. J., Devesa, S. S., Kneller, R. W., and Fraumeni, J. F., Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *J. Am. Med. Assoc.*, *265*: 1287–1289, 1991.
- Powell, J., and McConkey, C. C. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur. J. Cancer Prev.*, *1*: 265–269, 1992.
- Lauren, P. The two main histological types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. *Acta Pathol. Microbiol. Scand.*, *64*: 31–49, 1965.
- Lauren, P. A., and Nevalainen, T. J. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. *Cancer (Phila.)*, *71*: 2926–2933, 1993.
- Correa, P., and Shiao, Y. Phenotypic and genotypic events in gastric carcinogenesis. *Cancer Res.* *54* (Suppl.): 1941s–1943s, 1994.
- Ekström, A. M., Signorello, L. B., Hansson, L. E., Bergström, R., Lindgren, A., and Nyrén, O. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. *J. Natl. Cancer Inst.*, *91*: 786–790, 1999.
- Misumi, A., Murakami, A., Harada, K., Baba, K., and Akagi, M. Definition of carcinoma of the gastric cardia. *Langenbecks Arch. Chir.*, *374*: 221–226, 1989.
- Fleiss, J. L. In: *Statistical Methods for Rates and Proportions*, p. 321. New York: John Wiley & Sons, 1981.
- Swedish Socioeconomic Classification, Statistics Stockholm, Sweden 1982; vol. 4, 1984.
- Hansson, L. E., Baron, J., Nyren, O., Bergstrom, R., Wolk, A., Lindgren, A., and Adami, H.-O. Early-life risk indicators of gastric cancer. A population-based case-control study in Sweden. *Int. J. Cancer*, *57*: 32–37, 1994.
- Graham, D. Y., Evans, D. G., and Evans, D. J. An accurate, rapid and convenient physician-office serologic test for detection of *H. pylori* infection. *Am. J. Gastroenterol.*, *89*: 1305, 1994.
- Marchildon, P., Ciota, L., Smith, J., Zamaniyan, F., and Peacock, J. Evaluation of three EIAs for detection of *H. pylori* infection when compared to the C13 urea breath test. *Am. J. Gastroenterol.*, *89*: 1341, 1994.
- Hosmer, D. W., and Lemeshow, S. Model-building strategies and methods for logistic regression. In: V. Barnett, R. A. Bradley, S. K. Hunter, J. B. Kadane, D. G. Kendall, A. F. M. Smith, S. M. Stigler, G. S. Watson (eds.), *Applied Logistic Regression*, pp. 82–118. New York: John Wiley & Sons, Inc., 1989.
- Rothman, K. J. Measures of effect. In: *Modern Epidemiology*, pp. 38–39. Boston: Little, Brown and Company, 1986.
- Hardell, L., Fredriksson, M., Eriksson, M., Hansson, M., and Rappe, C. Adipose tissue concentrations of dioxins and dibenzofurans in patients with malignant lymphoproliferative diseases and in patients without malignant disease. *Eur. J. Cancer Prev.*, *4*: 225–229, 1995.
- Chow, W. H., McLaughlin, J. K., Malker, H. S., Weiner, J. A., Ericsson, J. L., Stone, B. J., and Blot, W. J. Occupation and stomach cancer in a cohort of Swedish men. *Am. J. Ind. Med.*, *26*: 511–520, 1994.
- Cocco, P., Ward, M. H., and Buiatti, E. Occupational risk factors for gastric cancer: an overview. *Epidemiol. Rev.*, *18*: 218–234, 1996.
- Xu, Z., Brown, L. M., Pan, G. W., Liu, T. F., Gao, G. S., Stone, B. J., Cao, R. M., Guan, D. X., Sheng, J. H., Yan, Z. S., Dosemeci, M., Fraumeni, J. F., Jr., and Blot, W. J. Cancer risks among iron and steelworkers in Anshan, China. Part II. Case-control studies of lung and stomach cancer. *Am. J. Ind. Med.*, *30*: 7–15, 1996.
- Parent, M. E., Siemiatycki, J., and Fritsch, L. Occupational exposures and gastric cancer. *Epidemiology*, *9*: 48–55, 1998.
- Cocco, P., Palli, D., Buiatti, E., Cipriani, F., DeCarli, A., Manca, P., Ward, M. H., Blot, W. J., and Fraumeni, J. F., Jr. Occupational exposures as risk factors for gastric cancer in Italy. *Cancer Causes Control*, *5*: 241–248, 1994.
- Hansson, L. E., Nyren, O., Bergstrom, R., Wolk, A., Lindgren, A., Baron, J., and Adami, H.-O. Diet and risk of gastric cancer. A population-based case-control study in Sweden. *Int. J. Cancer*, *9*: 181–189, 1993.
- Siemiatycki, J., Richardson, L., Gerin, M., Goldberg, M., Dewar, R., Desy, M., Campbell, S., and Wachholder, S. Associations between several sites of cancer and nine organic dusts: results from a hypothesis-generating case-control study in Montreal, 1979–1983. *Am. J. Epidemiol.*, *123*: 235–249, 1986.
- Frumkin, H., and Berlin, J. Asbestos exposure and gastrointestinal malignancy: review and meta-analysis. *Am. J. Ind. Med.*, *14*: 79–95, 1988.
- Kang, S. K., Burnett, C. A., Freund, E., Walker, J., Lulich, N., and Sesito, J. Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. *Am. J. Ind. Med.*, *31*: 713–718, 1997.
- Selikoff, I. J., Hammond, E. C., and Seidman, H. Mortality experience of insulation workers in the United States and Canada 1943–1976. *Ann. NY Acad. Sci.*, *330*: 91–116, 1979.
- Hogstedt, C. Cancer epidemiology in the paper and pulp industry, pp. 382–389. IARC Sci Publ. No. 104. Lyon, France: IARC, 1990.

33. Buser, H. R., and Bosshardt, H. P. Determination of 2,3,7,8-tetrachlorinated dibenzo-1,4-dioxins at part-per-billion levels in technical grade 2,4,5-trichlorophenoxyacetic acid, in 2,4,5-T alkyl ester, and 2,4,5-T amine salt herbicide formulations by quadruple mass fragmentography. *J. Chromatogr.*, *90*: 71–77, 1974.
34. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 69: Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. Lyon, France: IARC, 1997.
35. Dich, J., and Wiklund, K. The use of phenoxy acid herbicides in Sweden. *Chemosphere*, *18*: 391–394, 1989.
36. Zahm, S. H., and Blair, A. Pesticides and non-Hodgkin's lymphoma. *Cancer Res.*, *52* (Suppl. 19): 5485s–5488s, 1992.
37. IARC. IARC Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, Vol. 1 to 42, and IARC Monographs, Evaluation of Carcinogenic Risks to Humans, Suppl. 7. Lyon, France: IARC, 1987.
38. Blair, A., Zahm, S. H., Pearce, N. E., Heineman, E. F., and Fraumeni, J. F., Jr. Clues to cancer etiology from studies of farmers. *Scand. J. Work Environ. Health*, *18*: 209–215, 1992.
39. Axelson, O., Sundell, L., Andersson, K., Edling, C., Hogstedt, C., and Kling, H. Herbicide exposure and tumor mortality: an updated epidemiologic investigation on Swedish railroad workers. *Scand. J. Work Environ. Health*, *6*: 73–79, 1980.
40. Institute of Medicine. Veterans and agent orange: health effects of herbicides used in Vietnam. Washington, DC: National Academy Press, 1996.
41. Hardell, L. Chlorophenols, phenoxyacetic acids, and dioxins. The chemical occupational environment. In: C. Zenz, O. B. Dickerson, E. P. Horvath Jr. (eds.), *Occupational Medicine*, pp. 654–660. St. Louis: Mosby, 1994.
42. Cochrane, W. P., Singh, J., Miles, W., Wakeford, B. Determination of chlorinated dibenzo-*p*-dioxin contaminants in 2,4-D products by gas chromatography-mass spectrometric techniques. *J. Chromatogr.*, *217*: 289–299, 1981.
43. Zober, A., Messerer, P., and Huber, P. Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *Int. Arch. Occup. Environ. Health*, *62*: 139–157, 1990.
44. Manz, A., Berger, J., Dwyer, J., Flesch-Janys, D., Nagel, S., and Waltsgott, H. Cancer mortality among workers in a chemical plant contaminated with dioxin. *Lancet*, *338*: 959–964, 1991.
45. Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M., and Chang, L. I. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J. Natl. Cancer Inst.*, *91*: 779–786, 1999.
46. IARC. Schistosomes, liver flukes and *Helicobacter pylori*: IARC working group on the evaluation of carcinogenic risks to humans, Lyon, France, June 7–14, 1994. IARC Monogr. Eval. Carcinog. Risks Hum., *61*: 1–241, 1994.
47. Huang, J. Q., Sridhar, S., Chen, Y., and Hunt, R. H. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology*, *114*: 1169–1179, 1998.
48. Vainio, H., Nickels, J., and Linnainmaa, K. Phenoxy acid herbicides cause peroxisome proliferation in Chinese hamsters. *Scand. J. Work Environ. Health*, *8*: 70–73, 1982.
49. Gibson, G. G. Peroxisome proliferators: paradigms and prospects. *Toxicol. Lett.*, *68*: 193–201, 1993.
50. Youssef, J., and Badr, M. Extraperoxisomal targets of peroxisome proliferators: mitochondrial, microsomal, and cytosolic effects. Implications for health and disease. *Crit. Rev. Toxicol.*, *8*: 1–33, 1998.
51. Rao, M. S., Lalwani, N. D., Watanabe, T. K., and Reddy, J. K. Inhibitory effect of antioxidants ethoxyquin and 2(3)-tert-butyl-4-hydroxyanisole on hepatic tumorigenesis in rats fed ciprofibrate, a peroxisome proliferator. *Cancer Res.*, *44*: 1072–1076, 1984.