Arh. hig. rada toksikol., **30** *(1979) suppl. pp. 69–78.*

CIGARETTE SMOKING AND CHEMICAL CARCINOGENESIS IN POPULATION STUDIES

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ABSTRACT

In view of the causal contribution of cigarette smoking to cancer, especially respiratory cancer, it is difficult to assess the role of occupational exposures to chemicals or physical agents. Asbestos[6] exposures appear to be strongly and positively interactive with cigarette smoking in prospective cohort studies.

Large-scale population studies, for which smoking data were not available show significant and consistent associations with industrial[2] or occupational[7] exposures. Such studies have been given less recognition because of suggestions that the results could have been produced by population variations in smoking.

Three large scale population studies for which smoking data were available are presented and reviewed[3,5,13]. Analyses of interview data from the Third National Cancer Survey, controlling for cigarette smoking with or without other variables, did not alter associations of industry and occupation with cancer. Current smoking data for 25 occupational categories are correlated with lung cancer Standard Mortality Rate (SMR) observed in the British Registrar-General's Decennial Supplement (Occupational Mortality), but smoking adjustment by regression makes only trivial changes in the rank order of occupation by lung cancer SMR. In a large cancer center, occupational associations were unaltered when adjustments were made for smoking.

Generalizing, it seems unlikely that variation in smoking is an adequate explanation for cancer associated with occupational and industrial chemical exposure. This generalization is consistent with a causative role for smoking in cancer and with smoking and occupational interacting in carcinogenesis.

The more than additive contribution of smoking to asbestos-associated lung cancer is widely accepted[6,9], and the role of smoking in cancer of the bladder,[8] in radon-associated lung cancer[1] and BCME related lung cancer have been reported[11]. Smoking has been implicated in augmenting respiratory dosage of materials, some of which are carcinogens. In such cohort studies the role of smoking can be defined, but in population studies where it is hard to define, uncertainty about effects of smoking has clouded evidence that some occupations are at exceptional risk of cancer.

In seven large population studies, excess respiratory cancer risks have been shown consistently, for example, for painters and metal workers. Of these, two

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recent population studies, Williams and co-workers[13] and Fox[5] include data on smoking. A third study[3] analyses data for occupation among persons referred to a large regional cancer treatment and research center. Each study uses different methods.

MATERIALS AND METHODS

Williams and co-workers[13] report data from a sample of the U.S. National Cancer Survey, which included about one-tenth of the incident cancer cases in the U.S.A., 1969 – 1971. Interviews with a random 10% sample were sought; this if completed would reflect 13 179 patients. Of these, 7 518 were completed, including questions on smoking, alcohol consumption, occupation and industry. Other than occupation and industry, Table 1 shows the significant positive and negative associations found. Smoking and tobacco use are strongly associated with cancer of several sites. Mantel-Haenszel odds ratios were computed by cancer site for occupations and industries having adequate numbers, and analyses were stratified by smoking and other variables.

Fox presents[5] standard lung cancer mortality ratios for men aged 15 – 64 in 25 occupational orders based on British Registrar-General's Decennial Supplement on Occupational Mortality. Along with this is shown a smoking score representing the proportion in a separate survey currently smoking cigarettes as a percentage of the expected proportion, standardized for age. Table 2 shows the observed lung cancer SMR and the smoking score along with computed deviations from regression, discussed below.

Decoufle and co-workers[3] studied men and women admitted to Roswell Park Memorial Institute in Buffalo New York. All individuals completed a detailed questionnaire including demographic, medical and lifetime occupational history information. Cases were collected during 1956 – 1965; of 25 416 individuals admitted, 6 434 white males and 7 515 white females with one of 22 kinds of cancer were selected for study. Persons admitted with non-neoplastic diseases formed the "control" population. On the assumption that clerical occupations are free of carcinogenic hazard, a group of persons whose lifetime exposures were to clerical jobs were used to compare with, both for neoplastic and non-neoplastic admissions. Such a procedure could produce elevated relative risks if either the occupation has excess cancer, (true positive) or if clerical workers were admitted in augmented numbers for non-neoplastic conditions, compared to admissions for non-neoplastic disease among the occupation of interest (false positive). For selected sites the Relative Risks (Age adjusted) are shown in Table 3 both with and without smoking adjustment, along with the numbers of cancer cases.

While the Decoufle and co-workers study[3] used a relative risk procedure, capable of being influenced by the uneven distribution of non-malignant cases by occupation, the Williams study[13], also based on a universe of cancer patients, permits interaction between industries and occupations, especially those with a high proportion of the population (wholesale and retail trade has about 25 per cent of the females and manufacturing about 25 per cent of the males), since the experience of each industry and occupation is compared to all others.

TABLE 1

Summary of associations: Third National Cancer Survey Interview Study[a]. Before examination for effects of occupation and industry[14].

"Exposure" variables	Significant positive associations	Significant inverse associations
Cigarette smoking	Lip-tongue Larynx[b] Lung[b] Pharynx[b] Esophagus[b] Bladder[b] Cervix (F)[b] Gum-mouth Stomach Pancreas Kidney	(Colon)
Other tobacco (cigar, pipe, chew-snuff)	Gum-mouth[b] Cervix (F) Larynx (M) Lung (only in males not using cigarettes)	Lung (only in males using cigarettes)
Alcohol (wine, beer hard, all)	Pharynx[b] Gum-mouth Larynx[c] Lip-tongue[c] Breast[b] Esophagus Colon[c] Rectum (F) Thyroid (Lung)	(Prostate) (Bladder)
College and/or high income	Breast[c] Corpus (F) Melanoma (M) Thyroid	Cervix[c] Stomach[c] Lung Lip-tongue Colon (F)

[a] Significant $P \leq 0.05$ for regular or extension M-H chi-square in any contingency tables for male, female, or both sexes. (M) or (F) indicates associations observed only in one sex; (site) designates sites whose association was likely spurious, since it weakened considerably or disappeared in analyses employing appropriate exclusions or control variables.

[b] Strong dose-response gradient in increasing relative odds and multiple regression, both "significant".

[c] Significant linear slope in multiple regression analysis.

Table 4 gives an example of the adjustment procedure used for a single site and industry in the Williams study. In this example the significant ratio of 2.50 based on 32 females is not altered by computing a Mantel-Haenszel relative odds, stratified by education although the p value is less significant partly because of

TABLE 2
Lung cancer mortality and smoking habit by occupation order. Deviations from smoking predicted regression.

Order	Lung cancer SMR (O)	Smoking score*	Predicted lung cancer SMR** (P)	O−P
I. Farmers, foresters, fishermen	84	77	80.9	+ 3.1
II. Miners and quarrymen	116	137	146.1	− 30.1
III. Gas, coke and chemicals makers	123	117	124.4	− 1.4
IV. Glass and ceramics makers	128	94	99.3	+ 28.7
V. Furnace, forge, foundry, rolling mill workers	155	116	123.3	+ 31.7
VI. Electrical and electronic workers	101	102	108.0	− 7.0
VII. Engineering and allied trades workers, n.e.c.	118	111	117.8	+ 0.2
VIII. Woodworkers	113	93	98.3	+ 14.7
IX. Leather workers	104	88	92.8	+ 11.2
X. Textile workers	88	102	108.0	− 20.0
XI. Clothing workers	104	91	96.1	+ 7.9
XII. Food, drink and tobacco workers	129	104	110.2	+ 18.8
XIII. Paper and printing workers	86	107	113.5	− 27.5
XIV. Makers of other products	96	112	118.9	− 22.9
XV. Construction workers	144	113	120.0	+ 24.0
XVI. Painters and decorators	139	110	116.7	+ 22.3
XVII. Drivers of stationery engines, cranes, etc.	113	125	133.0	− 20.0
XVIII. Labourers, n.e.c.	146	133	141.8	+ 4.2
XIX. Transport and communications workers	128	115	122.2	+ 5.8
XX. Warehousemen, storekeepers, packers, bottlers	115	105	111.3	+ 3.7
XXI. Clerical workers	79	87	91.7	− 12.7
XXII. Sales workers	85	91	96.1	− 11.1
XXIII. Service, sport and recreation workers	120	100	105.9	+ 14.1
XXIV. Administrators and managers	60	76	79.8	− 19.8
XXV. Professional, technical workers, artists	51	66	68.9	− 17.9

*Observed proportion currently smoking cigarettes as percentage of expected proportion, standardized for age.
**Predicted rates based on linear regression computation of lung cancer on smoking scores.

two cases which are excluded because of lack of data on education. Smoking stratification does not influence the odds ratio or its significance in any appreciable way. Similar analyses including location, and alcohol consumption also had no influence on the significant odds ratio. But the analysis also reveals the distinctive characteristics within strata which contribute to the odds ratios. In this example they are women over 70 and light smokers.

It is obvious that multiple test (202 employment categories tested against 29 cancer sites yields 5 858 tests) will, due to random processes alone yield a number of results within the usual bounds of statistical significance; for example 59 tests are expected with $p < 0.01$ on a random basis from 5 828 tests performed.

TABLE 3

The effect of smoking adjustment on the relative risks for cancer for males ever employed in selected occupations. Roswell Park Memorial Institute, Buffalo, New York[3].

	Occupation	Number of cases	Relative risks: With smoking adjustment	Relative risks: Unadjusted
LUNG CANCER	Barbers	8	1.23	0.96
	Carpenters	43	1.22	1.12
	Cranemen, derrickmen and hoistmen	20	0.97	1.06
	Electricians	20	2.22*	2.10*
	Deliverymen and routemen	20	0.97	1.06
	Excavating, grading and road machine operators	6	1.02	0.85
	Farmers and managers in general, crop, and livestock farms	51	0.70	0.68
	Filers, grinders, and polishers, metal	71	0.89	0.83
	Foremen, all industries	40	0.85	0.94
	Furnacemen, smeltermen, and pourers	13	1.34	1.62
	Kitchen workers, except private household	7	1.04	1.20
	Laborers, fabricated metal industry	9	1.25	1.21
	Laborers, miscellaneous manufacturing industry	21	0.81	0.92
	Laborers, paper industry	7	0.81	1.35
	Laborers, primary metal industry	24	0.98	0.99
	Locomotive engineers and firemen	12	0.94	1.00
	Machinist	20	1.11	1.26
	Mechanics and repairmen	84	1.12	1.12
	Millwrights	7	1.06	0.84
	Mine operatives and laborers	17	1.09	1.07
	Molders metal	16	1.91	1.60
	Operatives, fabricated metal industry	11	0.65	0.61
	Operatives, miscellaneous manufacturing industry	58	0.89	0.95
	Operatives, paper industry	8	1.06	0.94
	Operatives, primary metal industry	28	1.54	1.53
	Operatives, textile industry	9	1.53	1.49
	Painters	42	1.90*	1.71*
	Plumbers and pipe fitters	17	1.36	1.55
	Stationary engineers	6	0.66	.65
	Stationary firemen	14	1.59	1.31
	Toolmakers, diemakers and setters	7	0.59	0.82
	Welders and flamecutters	11	0.67	0.85
BLADDER CANCER	Barbers	5	1.79	1.49
	Carpenters	13	0.85	0.81
	Deliverymen and routemen	8	1.13	1.13
	Electricians	6	1.87	1.78
	Farmers and managers, dairy farms	7	2.88*	3.15*
	Farmers and managers, general crop, and livestock farms	19	0.75	0.57
	Filers, grinders and polishers, metal	7	0.84	0.99
	Foremen, all industries	16	0.91	1.02
	Furnacemen, smeltermen and pourers	7	2.60*	2.40*
	Laborers, primary metal industry	9	1.06	0.97
	Locomotive engineers and firemen	8	1.63	1.65
	Machinist	7	1.04	1.13
	Mechanics and repairmen	38	1.21	1.40
	Millwrights	5	1.83	1.40
	Mine operatives and laborers	8	1.38	1.29
	Operatives, fabricated metal industry	13	1.86	2.12*
	Operatives, leather industry	11	3.96**	6.77**
	Operatives, miscellaneous manufacturing	15	0.60	0.78
	Operatives primary metal industry	5	0.84	0.73
	Painters	16	1.72	1.62
	Plumbers and pipefitters	7	1.80	1.57

*Probability of the relative risk being different from 0 is between $p = 0.01$ and $p = 0.05$; **$p \leq 0.01$

TABLE 4
Example of data and computations used in Occupational and Industrial Cancer Study based on Third National Cancer Survey Interviews (Leukemia in Sales Industry).

Variables and stratification	Mantel-Haenszel relative odds		Number of leukemia cases[a]	
	Males	Females	Males	Females
Age and race, total	1.16	2.50***	21	32
< 30	–	–	1	0
30–49	1.08	2,58	3	5
50–69	0.83	1.84	7	12
> 70	1.47	3.88**	10	15
Education, age, race, total[b]	1.12	2.51**	19	30
< 9yrs education	0.67	2.22	5	11
9–12yrs education	1.17	3.09*	7	15
> 12yrs education	2.22	2.03	7	4
Smoking, age race and education, total[b]	1.12	2.82**	15	27
Non-smokers	1.63	2.25*	7	14
< 20 pack-years	2.18	20.98	5	6
21–40 pack-years	0.61	3.18	1	5
> 40 pack years	0.43	1.66	2	2

[a] The numbers given are the smallest number in a 2 × 2 contingency table of which the marginals are the numbers with leukemia, and the numbers with all cancer in the sales industry: viz the total Female 2 × 2 table is

	Leukemia	Other cancer	
Sales industry	32	585	617
Other industries	28	1769	1797
	60	2354	2414

[b] The numbers available decrease as completeness of interview data is taken into account. For example education is not codable for two women, and smoking for three more.

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

The relatively low proportion of responses is discussed more fully by Williams and co-workers[13]. However, with patients as sick as many cancer patients interviews are not possible, even with family members. Different regions of the country had different proportions of successful interviews. The industries located in places with a low proportion interviewed are more likely to be influenced by non-reporting biases. Only seven areas are included, the SMSA's (Standard Metropolitan Statistical Areas) of Atlanta, Birmingham, Dallas-Ft. Worth, Detroit, Minneapolis – St. Paul, Pittsburgh, and San-Francisco – Oakland, and one state, Colorado. Only one occupation and industry was coded, whereas Decoufle and Houten coded all lifetime occupations and tabulated those with 5 years or more or any exposure. Thus in their study one person could appear in more than one occupation. They did not analyse their data by industry.

RESULTS

Lung cancer patients were found by Williams and co-workers[13] more often than expected in trucking, air transport, wholesale, painting, building construction and building maintenance industries and in manufacture of furniture, transportation equipment and food products. Controlling for cigarette smoking did not change these associations. Leukemia and multiple myeloma were associated with sales personnel of both sexes, whereas lymphomas and Hodgkin's disease were excessive among women working in the medical industry. Other associations included rectum cancer with several retail industries; prostate cancer with ministers, farmers, plumbers, and coal miners; malignant melanoma with school teachers, and invasive cervical cancer with women working in hotels and restaurants. Breast cancer patients were more common among women who were teachers or other professionals and who worked in bussiness and finance (even after controlling for education and for cigarette smoking).

An example of the type of calculation used in the analysis is that for painters and lung cancer (Table 5).

TABLE 5
Incidence of lung cancer in painters: observed versus expected.

	Lung cancer	Other cancer	Total
Painters	12/5.6	15/21.4	27
Other occupations	420/426.4	1 618/1 611.6	2 038
All occupations	432	1 633	2 065
	$\chi^2 = 9.35$ $p < 0.005$		

The only association to be altered downward by adjustment for smoking and drinking was the apparent association of oral cancer among men employed in water transportation, or in restaurants and bars, and this was due to increased alcohol consumption, with which increased tobacco use was associated. Thus despite significantly higher consumption of tobacco by cancer patients employed in construction, trucking, and water transportation, and low tobacco use among professionals, analysis for associations of cancer by site in these industries and occupations were not decreased by stratifying on tobacco consumption.

Fox's data in Table 2, while also showing that some occupations with high Lung Cancer SMR also have high smoking scores, a finding replicated in the U.S. by Sterling and Wenkman[10], nevertheless ranks the occupation orders with a high SMR corresponding to comparable deviations from the smoking-adjusted lung cancer prediction line (Table 6). Further data from the Registrar General's Decennial Supplement can amplify the method of estimating Lung cancer SMR.

TABLE 6

Ranks of lung cancer SMR by occupation order from Great Britain and ranks of deviations from smoking regression. Source: Fox[5].

Rank	Lung cancer SMR		Positive deviations from lung cancer – smoking score regression	
1	Furnace, forge, foundry, rolling mill workers	155	Furnace, forge, foundry and rolling mill workers	31.7
2	Laborers, n.e.c.	146	Glass and ceramic makers	28.7
3	Construction workers	144	Construction workers	24.0
4	Painters and decorators	139	Painters and decorators	22.3
5	Food, drink, and tobacco workers	129	Food, drink and tobacco workers	18.8
6	Glass and ceramic makers	128	*Woodworkers	14.7
7	Transport and communications workers	128	Service, sport and recreation workers	14.1
8	Gas, coke and chemical makers	123	*Leather workers	11.2
9	Services, sport and recreation workers	120	*Clothing workers	7.9
10	Engineering and allied trade workers	118	Transport and communication workers	5.8

*Not in high SMR set.

Table 3 for lung and bladder cancer for males shows that in the Buffalo area, electricians and painters have elevated lung cancer risks, unaffected by smoking adjustments; for bladder cancer dairy farmers, furnacemen, smeltermen and pourers, and leather industry operatives have elevated risks unaffected by smoking adjustment. Operatives in the fabricated metal industry have significantly high risks and the significance is lost by smoking adjustment, the risk dropping by but a small amount.

DISCUSSION

We are left with an apparent paradox that while various studies of occupational cancer tend to point to occupations with excess cancer, cigarette smoking is often elevated in at least some of them. Cigarette smoking is known to be a causal factor in lung cancer, which occupational exposures also seem to influence, and smoking is at least a suspected causal factor in bladder cancer. Yet statistical adjustment for smoking makes very little difference.

First, there are unquestionably specific occupational exposures which increase cancer risks. Schneiderman arguing from the general population trend data on cancer makes a good case for the likelihood of occupational cancer, without recourse to the population studies referred to here[8]. The paradox can be resolved if we consider the multistage theory and a few reasonable figures. Whittemore[12] and her colleagues present models based on a number of data sets which permits us to estimate the separate effects of exposures at various stages.

Assume that respiratory cancer is eight times as likely to occur among smokers as non-smokers and four times as likely among persons in a given occupation as among unexposed, independent of smoking. For every million males, 10 000 of whom are in the occupation of interest, and an assumed 10 cases per million among the non-exposed non-smokers, then the situation would be as in Table 7, if 40% are smokers, in exposed and total population.

TABLE 7
Expected cancer in total population and in occupationally exposed persons.

	Non-exposed			Occupationally-exposed		
	N	Expected cancer	Rate	N	Expected cancer	Rate
Non-smokers	600 000	6	1×10^{-5}	6 000	0.24	4×10^{-5}
Smokers	400 000	32	8×10^{-5}	4 000	1.28	32×10^{-5}
Total	1 000 000	38		10 000	1.52	

Without an occupational effect, these 10 000 would have had 0.38 cancer cases. Suppose that there are now in the occupationally exposed group, 60% smokers and 40% non-smokers, the expected cancer cases are now 0.16 in 4 000 non-smokers, and 1.92 among 6 000 smokers, for a total incidence of 2.08 compared to 1.52 when smoking prevalence was standard. The difference this makes in the total cancer incidence is trivial in relation to the high multiplication factors associated with smoking and occupation. The ratio would be 5.5 instead of 4.0. Thus lack of effect of smoking adjustment means only that changes in the effect of smoking differences by occupation are small compared to effects of smoking itself and occupation itself.

Indeed there may even be an effect of cardio-vascular disease among smokers which tends to cause its highest mortality in a period of life before lung cancer occurs. Thus it is possible that smoking and occupation strongly interact biologically, and adjustment procedures as used in these studies might show little differences if the smoking prevalence in the given occupation is similar to that among the rest of the occupations.

The preferable way to study smoking and occupational interactions remains the use of cohort and case-control studies. It is these types of study which have identified both occupational-cancer associations, and smoking-cancer once[1,4,6,11]. However population studies point toward unidentified agents and interactions; they cannot be dismissed because "Most of the environmental cancers are the result of the habit of cigarette smoking" as one consultant proposes.

These findings strongly contraindicate a dismissal of occupational cancer association merely because smoking has a strong carcinogenic effect. Thus these population studies now answer the question first posed by Dunn and co--workers[4] in their pioneering cohort studies over a decade ago, "Can the relatively weak effect of occupation on carcinogenesis be detected in the presence of the stronger effect of smoking?" It can. It is now time to act on this evidence.

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