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BMJ 2005;330:277-; originally published online 28 Jan 2005;
doi:10.1136/bmj.38327.648472.82

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Abstract

Objectives To investigate the association between environmental tobacco smoke, plasma cotinine concentration, and respiratory cancer or death.

Design Nested case-control study within the European prospective investigation into cancer and nutrition (EPIC).

Participants 303 020 people from the EPIC cohort (total 500 000) who had never smoked or who had stopped smoking for at least 10 years, 123 479 of whom provided information on exposure to environmental tobacco smoke. Cases were people who developed respiratory cancers or died from respiratory conditions. Controls were matched for sex, age (plus or minus 5 years), smoking status, country of recruitment, and time elapsed since recruitment.

Main outcome measures Newly diagnosed cancer of lung, pharynx, and larynx; deaths from chronic obstructive pulmonary disease or emphysema. Plasma cotinine concentration was measured in 1574 people.

Results Over seven years of follow up, 97 people had newly diagnosed lung cancer, 20 had upper respiratory cancers (pharynx, larynx), and 14 died from chronic obstructive pulmonary disease or emphysema. In the whole cohort exposure to environmental tobacco smoke was associated with increased risks (hazard ratio 1.30, 95% confidence interval 0.87 to 1.95, for all respiratory diseases; 1.34, 0.85 to 2.13, for lung cancer alone). Higher results were found in the nested case-control study (odds ratio 1.70, 1.02 to 2.82, for respiratory diseases; 1.76, 0.96 to 3.23, for lung cancer alone). Odds ratios were consistently higher in former smokers than in those who had never smoked; the association was limited to exposure related to work. Cotinine concentration was clearly associated with self reported exposure (3.30, 2.07 to 5.23, for detectable/non-detectable cotinine), but it was not associated with the risk of respiratory diseases or lung cancer. Frequent exposure to environmental tobacco smoke during childhood was associated with lung cancer in adulthood (hazard ratio 3.63, 1.19 to 11.11, for daily exposure for many hours).

Conclusions This large prospective study, in which the smoking status was supported by cotinine measurements, confirms that environmental tobacco smoke is a risk factor for lung cancer and other respiratory diseases, particularly in ex-smokers.

Introduction

Environmental tobacco smoke, or involuntary smoking, comprises sidestream smoke from the smouldering tobacco between puffs and exhaled mainstream smoke from the smoker. More than 50 investigations, mostly case-control studies, have shown that involuntary smoking is associated with an increased risk for lung cancer.^{1 2} In 2002, a working group of the International Agency for Research on Cancer evaluated the epidemiological evidence and included environmental tobacco smoke in group I (human carcinogen).^{3 4} Few cohort studies are available, however, with accurate information on potential confounders or effect modifiers. We analysed data from the large European prospective investigation into cancer and nutrition (EPIC) to assess the relation between environmental tobacco smoke and lung cancer, upper respiratory cancers, and death from chronic obstructive pulmonary disease (COPD) or emphysema, limiting our analysis to never smokers and people who had not smoked for more than 10 years. The advantage of the cohort design is the lack of recall bias as information about exposure was collected before onset of disease.

Methods

The EPIC cohort

EPIC is a multicentre study, coordinated by the International Agency for Research on Cancer (Lyons), in which more than 500 000 healthy volunteers were recruited in 10 European countries (Sweden, Denmark, Norway, the Netherlands, United Kingdom, France, Germany, Spain, Italy, Greece).⁵ The cohort includes men and women, mostly in the age range 35-74 at recruitment. Recruitment took place between 1993 and 1998. Diet was measured by questionnaires specific for each country, designed to address local dietary habits and to provide high compliance. Six countries administered a dietary questionnaire, which provided data on up to 350 food items per country. In France, Spain, and Ragusa (Italy) similar dietary questionnaires but structured by meals were used. The centres in Spain and Ragusa performed a face-to-face dietary interview with a computerised dietary programme, the others used a self administered questionnaire. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC.

Lifestyle questionnaires included questions on reproductive history, use of oral contraceptives and hormone replacement

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therapy, education, physical activity, history of previous illness or surgical operations, and history of consumption of tobacco and alcoholic beverages. Eleven centres (in France, Italy, Denmark, Sweden, the Netherlands, and Potsdam, Germany) collected data on exposure to environmental tobacco smoke, by asking about any exposure, place of exposure, and exposure during childhood. This resulted in a subgroup of 123 479 (only never smokers or former smokers who had stopped for at least 10 years), most of whom had information on any exposure and place of exposure.

The follow up was based on data from population cancer registries in seven of the participating countries: Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. In France, Germany, and Greece we used a combination of methods including health insurance records, cancer and pathology registries, and active follow up through study participants and their next of kin. Mortality data were also obtained from the cancer registries or mortality registries at the regional or national level. Follow up was virtually 100% complete. We used ICD-10 (international classification of diseases, 10th revision). The median follow up time was seven years.

Design of the nested case-control study (GenAir)

The nested case-control study (GenAir) studied the relation between air pollution or environmental tobacco smoke and newly diagnosed cancers of the bladder, lung, oral cavity, pharynx, or larynx, or leukaemia. The study also identified and included deaths from respiratory diseases (chronic obstructive pulmonary disease and emphysema). We included only people who had never smoked or who had stopped smoking for at least 10 years.

We matched three controls per case for assessment of exposure and the analysis of questionnaire data and two controls per case for laboratory analyses. Matching was introduced to allow strict control of potentially confounding variables because other risk factors may be stronger than environmental tobacco smoke. In addition, matching was needed for laboratory analyses, to avoid differential sample degradation between cases and controls. Controls were matched for sex, age (plus or minus 5 years), smoking status (never/former smoker), country of recruitment, and time elapsed since recruitment (months). To identify controls we randomly sampled the study base (whole cohort at inception ($n = 500\ 000$)) on the basis of the characteristics of each case until we found three subjects who matched; 66 cases were matched to 198 controls, while 40 cases were matched to two controls only (total 80 controls), and eight to one control (total 286 controls) (for 17 we were unable to find a control to match).

Laboratory analyses

Cotinine was extracted from plasma by ion exchange chromatography and analysed by liquid chromatography-atmospheric pressure ionization-tandem mass spectrometry (API LC-MS/MS) at the Mario Negri Institute (Milan) in 1574 participants, irrespective of the information available on environmental tobacco smoke. These were all the cases included in GenAir and their matched controls (2:1) for whom serum and DNA samples were available.

Polymorphisms in genes involved in carcinogenesis were analysed by Taqman in white blood cells. We developed a score for the number of "at risk polymorphisms" in the genes GSTM1, GSTM3, GSTP1, GSTT1, CYP1A1, NAT2, MnSOD, MPO, NQO1, and CYP1B1. "At risk polymorphisms" are gene variants with impaired function.⁶

Statistical analyses

We analysed the whole cohort with Cox's proportional hazards models, using age at diagnosis (cases) or at last contact as the dependent variable, as suggested by Korn et al.⁷ Hazard ratios were adjusted by sex, smoking habit (former or never smoker), country, education in four levels, energy intake, consumption of fruit and vegetables, and physical activity. Energy, dietary items, and physical activity were used as continuous variables or in quarters (models using quarters gave virtually identical results and are not shown). In the nested case-control study we computed odds ratios and 95% confidence intervals in conditional logistic regression models⁸ that included educational level, energy intake, fruit and vegetables consumption, and physical activity as further adjustment variables in addition to matching variables. Matched pairs were inherently matched by batch. We also performed unconditional logistic regression analyses, which were based on the whole set of controls and gave results virtually identical to those based on conditional analysis (when not otherwise specified). We assessed interaction by creating indicator variables for the combination of single variables (for example, environmental tobacco smoke and country) and by the Breslow-Day test for heterogeneity.⁸ Analyses were performed with the SAS package (Cary, NC, USA) for a personal computer.

Results

Information on exposure to environmental tobacco smoke was collected from 123 479/303 020 (40.8%) participants who had never smoked or former smokers in the EPIC cohort. Of these 97 people developed lung cancer, 20 developed upper respiratory cancers (pharynx, larynx), and 14 died from chronic obstructive pulmonary disease or emphysema during the seven years of follow up. Table 1 shows details for cases, controls, and the whole cohort.

Plasma cotinine was measured in 1574 GenAir subjects (with or without information on environmental tobacco smoke). The method was highly specific and sensitive with a detection limit of 0.05 ng of cotinine per ml of plasma in 50 μ l samples. We excluded 47 participants with values > 10 ng/ml because they were likely to be active smokers ($n = 41$) or sniffers/chewers ($n = 6$). Of the 1527 remaining subjects, 461 (30%) had detectable concentrations of plasma cotinine with an overall mean value of 0.92 ng/ml (SD 0.96 ng/ml). Table 2 shows the mean cotinine concentrations in the 374 people with information on environmental tobacco smoke. Cotinine concentrations were clearly associated with self reported exposure to environmental tobacco smoke (odds ratio 3.30, 95% confidence interval 2.07 to 5.23, for detectable/non-detectable cotinine, $P < 0.0001$). We did not reassess environmental tobacco smoke after cotinine measurements—that is, these are two independent sources of information.

Table 3 shows results for the whole cohort (Cox's proportional hazards model) and for the nested case-control study (conditional regression models). Increased odds ratios and hazard ratios were associated with environmental tobacco smoke exposure at recruitment for all respiratory diseases and for lung cancer alone in the whole cohort and in the nested study. Higher odds ratios were observed separately in each country (data not shown; test for heterogeneity, $P = 0.08$). The differences observed in risks associated with environmental tobacco smoke between sexes were not significant (test for heterogeneity $P = 0.66$).

Former smokers had higher risks for respiratory disease (attaining significance) than those who had never smoked in

Table 1 Distribution of cases and controls by relevant variables

	Lung cancer (n=97)	Upper respiratory cancer (n=20)	COPD deaths (n=14)	Controls (n=286)	Whole cohort (n=123 479)
Men	27	15	7	105	27 532
Women	70	5	7	181	95 947
Mean (SD) age (years)	58.0 (7.5)	59.4 (6.4)	59.1 (7.2)	57.9 (7.6)	53.2 (8.3)
School level attained:					
None or primary	34	10	7	75	27 819
Secondary/technical	39	6	4	141	52 975
University degree	23	3	3	66	32 782
Missing values	1	1	-	4	9 903
Smoking:					
Former smokers	38	7	8	113	20 556
Never smokers	59	13	6	173	102 923
ETS exposure:					
Home and/or work:					
Yes	57	11	10	153	71 722
No	40	9	4	133	51 757
Home:					
Yes	20	4	5	56	23 396
No	49	9	6	136	58 675
Missing*	28	7	3	94	41 408
Work:					
Yes	49	10	9	123	58 653
No	22	3	2	72	28 620
Missing*	26	7	3	91	36 206

*For these subjects we investigated home and work exposures combined.

both the whole cohort and the case-control analyses. The raised risks in both analyses, were limited to exposures related to work, with significant risk estimates around 1.5 to 2.0. Cotinine was not associated with lung cancer or other diseases. The odds ratio for detectable versus undetectable cotinine concentrations and respiratory disease/cancer was 0.9 (0.5 to 1.8).

Table 4 shows the distribution of self reported exposure to environmental tobacco smoke during childhood in those who had never smoked, in the centres where information was

collected (n=60 182). Increased risks were present for the categories "daily" and "daily, many hours," with significant confidence intervals for the latter.

We analysed the role of environmental tobacco smoke in lung cancer according to the score of "at risk" alleles for polymorphisms in metabolic genes. The odds ratio associated among carriers of at least three of the at risk polymorphisms was 2.86 (0.79 to 10.35), while for those with one or two alleles it was 1.33 (0.82 to 2.18). This difference was detected in unconditional analysis because numbers were too small for conditional analysis.

Table 2 Cotinine measurements in 374 people* with information on exposure to environmental tobacco smoke

ETS status	Mean (SD)†	Cotinine	
		Detectable (>0.05 ng/ml)	Undetectable
Yes (n=189)	0.55 (0.96)	89	100
No (n=174)	0.17 (0.49)	37	137

*Eleven people with cotinine concentration >10 ng/ml excluded.

†P<0.0001 for difference (Wilcoxon Rank sum test).

Discussion

Environmental tobacco smoke and risk of cancer

We followed up the EPIC cohort for a median of seven years and identified incident cases of lung cancer and upper respiratory cancer and deaths from respiratory conditions among former smokers and those who had never smoked. We found that respi-

Table 3 Environmental tobacco smoke (ETS) exposure (home and/or work) and respiratory disease (including deaths from lung cancer, larynx or pharynx cancer, and deaths from chronic obstructive pulmonary disease) or lung cancer alone, in whole cohort (n=123 479, 131 cases) and in nested case-control study (n=114 cases, 286 controls)

	Hazard ratios (95% CI)		Odds ratios* (95% CI)	
	Respiratory disease	Lung cancer	Respiratory disease	Lung cancer
Exposure to ETS at home and/or at work (yes/no):				
Model I†	1.21 (0.82 to 1.78)	1.25 (0.80 to 1.96)	1.64 (0.99 to 2.69)	1.75 (0.96 to 3.18)
Model II‡:				
All	1.30 (0.87 to 1.95)	1.34 (0.85 to 2.13)	1.70 (1.02 to 2.82)	1.76 (0.96 to 3.23)
Former smokers	2.32 (1.07 to 5.01)	2.32 (0.94 to 5.71)	3.11 (1.06 to 9.18)	NA
Never smokers	1.02 (0.63 to 1.66)	1.05 (0.60 to 1.82)	1.45 (0.75 to 2.80)	1.42 (0.63 to 3.20)
Men	1.72 (0.81 to 3.66)	1.96 (0.68 to 5.67)	1.79 (0.63 to 5.09)	NA
Women	1.15 (0.71 to 1.86)	1.20 (0.71 to 2.02)	1.46 (0.76 to 2.80)	NA
ETS only at home	1.11 (0.71 to 1.74)	1.03 (0.60 to 1.76)	1.10 (0.60 to 2.02)	0.82 (0.37 to 1.82)
ETS only at work	1.55 (1.03 to 2.32)	1.65 (1.04 to 2.63)	2.05 (1.22 to 3.47)	2.17 (1.16 to 4.08)

*Computed by conditional logistic regression analysis.

†Adjusted by sex, age (plus or minus 5 years), smoking (former or never smoker), country, and school years.

‡Additionally adjusted by energy intake, fruit and vegetables consumption, and physical activity.

Table 4 Cox's proportional hazards model for relation between exposure to environmental tobacco smoke in childhood and risk of lung cancer in whole cohort in 60 182 people who have never smoked

Exposure to ETS in infancy	Whole cohort	No of cases	HR* (95% CI)
Never (reference)	29 164	15	1.0
Seldom	12 376	8	1.08 (0.45 to 2.59)
Few times/week	8 360	7	1.45 (0.59 to 3.61)
Daily	8 063	8	2.04 (0.85 to 4.94)
Daily, many hours	2 219	4	3.63 (1.19 to 11.11)

*Adjusted for sex, country, education, vegetables, fruit, total energy, physical activity. P value for trend 0.018.

ratory conditions and lung cancer alone were associated with self reported environmental tobacco smoke exposure at the time of recruitment. The association was consistently observed after we stratified by country. The association was stronger in the nested case-control study than in the whole cohort. This observation has two possible explanations: chance or better adjustment for confounders through careful matching. The association, however, was limited to exposures related to work, possibly because of higher levels of exposure.

Advantages and limits of the study design

Our study design had several advantages: its prospective nature—that is, the fact that exposure was investigated years before the onset of disease (so that recall bias can be excluded); accurate ascertainment of disease through cancer registries and clinical records, with histological confirmation whenever available; the relatively large number of cases accrued among former smokers and never smokers; and the availability of blood samples that allowed validation of questionnaire information by cotinine measurement.

One limitation, however, was the lack of detailed information on environmental tobacco smoke exposure (with scanty data, for example, on the number of hours of exposure) and the fact that information was collected only once. Concerning the quality of information on environmental tobacco smoke, it is, however, unlikely that people who reported that they were former smokers were actually current smokers as we excluded those with cotinine concentrations > 10 ng/ml (n = 47).

Former smokers

Former smokers had higher risks for respiratory disease than those who had never smoked. Although the difference between former and never smokers might be due to chance (P = 0.58, test for heterogeneity), the observation suggests that former smokers might be more susceptible to the effects of environmental tobacco smoke. Three centres collected information on duration of smoking and number of cigarettes smoked for former smokers. In these centres the odds ratio for respiratory diseases and environmental tobacco smoke exposure, adjusted for all variables indicated above, plus duration and number of cigarettes smoked, was 1.5 (0.5 to 4.5), based on 24 cases, identical to the unadjusted estimate (1.5, 0.5 to 4.6). Therefore, the fact that the association with lung cancer is stronger in former smokers is difficult to understand. While bias is unlikely, one possible explanation is that former smokers are more susceptible to low level exposure to environmental tobacco smoke because they already have mutations in their cells.

Biomarkers

The biological plausibility of a causal association between environmental tobacco smoke exposure and lung cancer is reinforced by the suggestion that having more than three polymor-

What is already known on this topic

Environmental tobacco smoke has been recognised as a human carcinogen by a working group of the International Agency for Research on Cancer

What this study adds

In a large European prospective study (EPIC) exposure to environmental tobacco smoke was confirmed with plasma cotinine measurement

There was an increased risk in association with exposure to environmental tobacco smoke for respiratory diseases, specifically lung cancer

The risk was higher among former smokers (stopped for at least 10 years) than among never smokers, which could indicate the greater susceptibility of former smokers due to already existing mutations

The association was limited to exposure related to work, which was particularly important in European countries

phic genes increases the odds ratio to 2.86 instead of 1.76. This, if confirmed, would be an example of "mendelian randomisation."⁹ Previous studies have found that the association between environmental tobacco smoke and lung cancer was stronger in subjects with polymorphisms in GSTM1,^{10 11} but one study had negative results, although statistical power was limited.¹²

Cotinine concentrations were not associated with the risk of lung cancer. This could be expected, as previous studies have stressed the limitations of cotinine as a biomarker of exposure.³ Cotinine is an expression of the past 24 hours of exposure and is valuable mainly to exclude current smoking rather than estimating long term exposure to environmental tobacco smoke.^{3 4} However, we found a non-significant association in those with three or more polymorphic alleles (data not shown).

Childhood exposure

Environmental tobacco smoke exposure during childhood showed an association with lung cancer, particularly among those who had never smoked; the association was significant for daily exposure for many hours. The observation is not new, but the literature is not entirely consistent.^{13 14} To our knowledge, ours is the first prospective study to report such association. Of course, the reliability of information on exposure to environmental tobacco smoke in childhood can be questioned, although most people should be able to recall whether their parents smoked. The uptake of carcinogens in exposed children is widespread and quantitatively important.¹⁵

Conclusions

Our study contributes to the existing literature reinforcing the conclusions of the IARC Monograph Working Group^{3 4} that there is sufficient evidence on the carcinogenicity of environmental tobacco smoke in humans.

Mortality data for the Netherlands were obtained from Statistics Netherlands.

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Funding: European Community (5th Framework Programme) (grant QLK4-CT-1999-00927), Compagnia di San Paolo, Europe Against Cancer Programme of the European Commission (SANCO), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, German Federal Ministry of Education and Research, Danish Cancer Society, Health Research Fund (FIS) of the Spanish Ministry of Health, Spanish Regional Governments of Andalusia, Asturias, Basque Country, Murcia, and Navarra, Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, Wellcome Trust, Greek Ministry of Health, Greek Ministry of Education, Italian Association for Research on Cancer (AIRC), Italian National Research Council, Dutch Ministry of Public Health, Welfare and Sports, World Cancer Research Fund, Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skåne, Sweden, Norwegian Cancer Society, Research Council of Norway.

Competing interests: None declared.

Ethical approval: GenAir was approved by the ethical committee of the International Agency for Research on Cancer and by all the local ethical committees of the participating centres.

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(Accepted 23 November 2004)

doi 10.1136/bmj.38327.648472.82

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