

## Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study

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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. 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) between 1993 and 1998.<sup>1</sup>

The follow up was based on data from population cancer registries and other sources (see [bmj.com](http://bmj.com)). Mortality data were also obtained at the regional or national level. Follow up was virtually 100% complete. The median follow up time was seven years.

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**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

ETS=environmental tobacco smoke; COPD=chronic obstructive pulmonary disease.

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

### 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. 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).

### Laboratory analyses

Cotinine was analysed in 1574 participants, irrespective of the information available on environmental tobacco smoke. 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.<sup>2</sup>

### 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. 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. In the nested case-control study we computed odds ratios and 95% confidence intervals in conditional logistic regression models that included educational level, energy intake, fruit and vegetables consumption, and physical activity as further adjustment variables in addition to matching variables.

### 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 and 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).

Increased odds ratios and hazard ratios were associated with environmental tobacco smoke exposure at recruitment for all respiratory diseases and for lung

**Table 2** 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 3** Cox's proportional hazards model for relation between exposure to environmental tobacco smoke (ETS) 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.

cancer alone in the whole cohort and in the nested study (table 2).

Former smokers had a higher relative risk for respiratory disease (attaining significance) than those who had never smoked in both the whole cohort and the case-control analyses. The raised risks, in both analyses, were limited to exposures related to work, with significant relative risk ratios 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 3 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).

## Discussion

### 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 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).

### 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

### Former smokers

Former smokers had a higher relative risk 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. 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 polymorphic genes increases the odds ratio to 2.86. This, if confirmed, would be an example of "mendelian randomisation."<sup>3</sup> Previous studies have found that the association between environmental tobacco smoke and lung cancer was stronger in subjects with polymorphisms in GSTM1,<sup>4,5</sup> but one study had negative results, although statistical power was limited.<sup>6</sup>

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.<sup>7</sup> 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.<sup>7,8</sup>

### 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.<sup>9-10</sup> 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 children exposed to environmental tobacco smoke is widespread and quantitatively important.<sup>11</sup>

### Conclusions

Our study contributes to the existing literature reinforcing the conclusions of the IARC Monograph Working Group<sup>7-8</sup> that there is sufficient evidence on the carcinogenicity of environmental tobacco smoke in humans.

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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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## Q&A

### Penis enlargement

#### Question

Can a man increase the size of his penis?

Frank Martin, *student*

#### Answer

I presume you are asking about increasing the size of the erect phallus rather than asking about erectile dysfunction.

It is possible to surgically increase the size of an erect (and flaccid, for that matter) penis, but it should not be undertaken lightly, as it is by no means guaranteed to produce the result one might be hoping for.

Length can be added by division of the penile suspensory ligament that tethers the penis to the pubic arch. This sounds like a simple solution, but remember the ligament was there for a reason. Dividing it will allow the penis to fall away from the pubis, giving some length (a couple of centimetres), but at a loss of the normal "angle" at erection. Also, this does not lengthen the skin, and so the peripenile pubic skin is often pulled onto the shaft of the penis, resulting in pubic hair growing from the penile shaft.

Another surgical technique is "enhancement" of penile girth by the injection of harvested adipose tissue (fat) from elsewhere. This has significant risks of

resulting in uneven, lumpy appearance, and patient satisfaction is not assured.

What is important to remember is that there is wide natural variation in penis size, as in height, weight, and many other human physical characteristics. Thus, what may seem small is probably normal. Surgery is fraught with uncertainties about results, and, like other forms of medically "unnecessary" cosmetic surgery, people often have unrealistic expectations and are disappointed as a result.

And don't believe any advertisements found in the back of top shelf publications or try any "DIY" methods. They don't work. I have spent the odd night in accident and emergency trying to undo these "efforts"; it is embarrassing for the patient, and the penis is never larger, once the pain and swelling have subsided.

John F Bolton, *clinical fellow in urology, Bristol Royal Infirmary, Bristol*

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