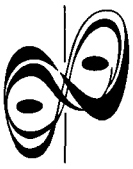

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Cigarette Smoking As a Cause of Lung Cancer and Coronary Heart Disease. A Study of Smoking-Discordant Twin Pairs

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Abstract. Despite increasing scientific evidence for a causal role of tobacco smoking in lung cancer and coronary heart disease, an alternative hypothesis was put forward several decades ago. The constitutional hypothesis has stated that there are genetic or other common factors, which predispose both to smoking and disease. A critical test of this hypothesis was considered the pattern of occurrence of disease in monozygotic (MZ) twin pairs in which one is a smoker and the other never has been a smoker. Initial twin studies found only small differences in the mortality of smoking and nonsmoking twins of discordant pairs. In the Finnish Twin Cohort, a population-based panel of adult like-sexed twin pairs, a questionnaire study carried out in 1975 permitted identification of 2488 twin pairs discordant for cigarette smoking. Analyses of total mortality and mortality due to coronary heart disease and lung cancer indicate that the smoking members of discordant MZ pairs are at higher risk than their nonsmoking cotwins; increased mortality of smoking cotwins was also found on 21-year follow-up of smoking-discordant pairs in Sweden. Incidence data and noninvasive studies of atherosclerosis in the Finnish sample provide confirmatory evidence for the causal role of smoking in the etiology of coronary heart disease and lung cancer.

Key words: Twins, Smoking, Mortality, Coronary heart disease, Lung cancer, Prospective studies, Causality

INTRODUCTION

The first epidemiological data on the increased health risks of smokers became available over three decades ago [38,40]. Since then, critics of the causal hypothesis, such as R.A.Fisher and H.J. Eysenck [1,7,9,37], have pointed out inconsistencies in the data and indicated the lack of known pathogenetic mechanisms. An alternative explanation was offered: the constitutional hypothesis stated that there were underlying genetic or other predispositions that led to both smoking and the disease. The study of monozygotic (MZ) twins discordant for smoking was proposed to test this hypothesis. Such studies were first initiated in Denmark and Sweden and somewhat later in the United States during the 1960s [5]. These studies have not shown differences with respect to manifest coronary heart disease (CHD) in the smoking and nonsmoking cotwins [3,4,16,17,18,32,33]. Various deficiencies in study design may explain why differences were not found. These include the low power of the studies due to relatively small numbers of discordant pairs and the low amount of smoking discordance as well as the cross-sectional nature of the studies.

Early mortality studies found only a slightly increased risk of death in the smoking cotwin compared to the nonsmoking cotwin. The initial reports from the Swedish study of smoking-discordant pairs indicated little, if any, excess mortality of the smoking MZ male cotwins [6,11,12]. Also the Danish study of 904 smoking-discordant pairs showed a slight excess mortality during the first six-year follow-up [16]. A second brief report [17] was based on 1584 discordant pairs; no overall difference in mortality was found nor were any cause-specific differences reported. Detailed smoking habits and other characteristics of the Danish series have not been reported. The most recent report on the Swedish series [10] is based on 21 years of follow-up. Now an increased mortality risk for smokers was found among male MZ pairs discordant for tobacco use (relative risk, or RR = 1.6, P = 0.06).

Finland has had very high mortality rates of CHD and lung cancer, especially among men. Also smoking was very common from the 1920s onwards until the 1960s, after which it has somewhat declined. Thus, a study of smoking-discordant twins seemed feasible in Finland and was started in 1974. This paper will review a series of studies we have carried out on this sample; the original work has been published elsewhere [14,20,26,27,28,29,30,31]. Additional data on the incidence of CHD and lung cancer are provided. Where appropriate, we will compare our results with those obtained by the Swedish study [10].

METHODS AND SUBJECTS

The Finnish Twin Cohort was compiled from the national population registry of all Finnish citizens in 1974 [21]. It consists of all like-sexed pairs born prior to 1958 with both members of a pair alive in 1967. The selection procedures, determination of twinship and assessment of representativeness are described in detail elsewhere [22,23]. The present study population as well as the Swedish twin pairs have been drawn from population-based twin panels representing nearly all living twins in the

country. The response rates in the questionnaire studies in these twin panels were high and therefore there should be few of the biases found in studying volunteer samples.

The twins were mailed a questionnaire in the autumn of 1975 to obtain baseline characteristics of the cohort. The response rate was 89%. Responses from over 12,000 pairs, with both twins responding, were obtained. Zygosity diagnosis was by the questionnaire method, and validated in a subsample of > 100 pairs [36]. In the entire twin cohort there are over twice as many DZ like-sexed pairs as there are MZ pairs. This ratio corresponds closely to that computed from the ratio of like-sexed to unlike-sexed twin births indicating little selection by zygosity [24]. Because MZ pairs have more similar smoking habits than DZ pairs [2,15,18,22,34,35], the proportion of MZ twins was lower than expected among smoking-discordant pairs.

A detailed smoking history was obtained. Smoking-discordant pairs were selected from respondent pairs on the basis of cigarette smoking status in 1975. All pairs in which one member was a never or occasional smoker and in which the other was a regular smoker (current or former) were considered discordant. The pairs were then further divided into current smoker (CS) discordant and former smoker (FS) pairs. In most analyses the pairs in which the nonsmoker was an occasional smoker were included. A detailed description of the methods and subjects may be found elsewhere [20].

Mortality follow-up was done by computer record-linkage of the twin cohort to the national population registry, at regular intervals and copies of death certificates were obtained. Hospital inpatient record abstracts, disability pension records and information on use of medications for coronary heart disease were obtained from centralized computer registers. Cancer incidence data was obtained from the Finnish Cancer Registry. In the analysis of disease occurrence in the smoking discordant pairs, a null hypothesis of no difference in the disease incidence or mortality of the smoking and non-smoking twins in MZ pairs is used. Thus a simple matched pair analysis using McNemar's test can be done without need to adjust for survival times [19]. The analysis is based on the first or only death or disease occurrence in a pair. The numerical value of the risk estimate was not of primary interest, but rather whether the null hypothesis could be rejected.

RESULTS AND DISCUSSION

The smoking twins were divided into 1278 current smokers (CS)(143 MZ and 598 DZ males and 171 MZ and 585 DZ females) and 1210 former smokers (FS)(129 MZ and 408 DZ males and 113 MZ and 341 DZ females). The pairs are relatively young with 45.1% of males and 48.3% of females aged 18-29 and the remainder aged 30 or more years; each smoker is, however, age and gender-matched to a nonsmoker.

Smoking Habits

In the study of the health consequences of smoking crucial issues are adequate exposure among the smokers and valid measurement of exposure. While many of the smokers were relatively light smokers, sufficient numbers of smokers with a long smoking history could be identified. Both the daily cigarette consumption and the number of years smoked were computed from the questionnaire data. These were then multiplied together to yield a summary measure of exposure: pack-years of smoking. In the male MZ CS group, 26.8% had smoked 15 or more pack-years. For the female MZ CS group, only 8.3% had smoked 15 or more pack-years. Exposure to tobacco was much higher among males: over 25% of men smoked 20 or more cigarettes daily compared to less than 10% of women. Older (aged 30 or more) men and women reported smoking more daily than younger persons: among male MZ CS twins aged 30 or more, 32% smoked 20 cigarettes or more daily compared to 17% of 18-29 year olds.

Misclassification of smoking history would reduce the risk estimates from this kind of study. Long-term follow-up and urinary cotinine measurement in a subsample of the pairs confirmed that the discordance for smoking persists over many years [14]. In the present study, there are much higher levels of smoking than reported by the Swedish study [6]: for male MZ pairs 14.6 cigarettes/day in the present study and 7.3 cigarettes daily for Swedish pairs. The level of smoking was not reported in the Danish study of discordant pairs [17].

Mortality and Morbidity

For death from all causes, male current smokers, both MZ (RR = 13.0) and DZ (RR = 2.43), had a greater risk of death than their nonsmoking twin brothers during the twelve-year follow-up period (Table 1). No excess risk was observed for former male smokers. Among women the number of deaths was small: no statistically significant excess mortality was observed for either former or current smokers. The excess mortality was clearer among men than women; men had higher mean lifetime exposure to tobacco. Also there were more deaths among men than women, which means that the risk estimates for men are statistically more stable. The mortality rates among individual smokers, who belong to discordant pairs did not differ from that of all smokers in the twin cohort [20]. Also the mortality rates of nonsmokers from the discordant pairs was similar to those of all nonsmokers [20].

Among discordant pairs with former smokers, there was not much difference in the mortality of smoking and nonsmoking twins, which may be due to a number of effects. The elevated risk associated with smoking lessens upon quitting, sooner for CHD than cancer [38]. One reason for quitting can be signs and symptoms of disease, and therefore the causal relationships between smoking and disease can be obscured when studying former smokers. Former smokers also differ from current smokers in other characteristics [13,25], which confounds comparisons between current and former smokers.

Table 1 - All causes mortality in smoking discordant twins by zygosity, smoking status and gender during 1976-1987 in Finland and during 1961-1981 in Sweden[a]

Country	Smoking status	Zygosity	No. of first or only deaths in twin pair among		RR	P
			Smokers	Nonsmokers		
Male						
Finland	CS	MZ	13	1	13.0	<0.01
		DZ	34	14	2.43	<0.01
	FS	MZ	9	16	0.56	ns
		DZ	31	25	1.24	ns
Sweden	AS	MZ	35	22	1.6	0.056
		DZ	102	72	1.4	0.014
Female						
Finland	CS	MZ	4	4	1.0	ns
		DZ	15	12	1.25	ns
	FS	MZ	4	1	4.0	ns
		DZ	12	6	2.0	ns
Sweden	AS	MZ	37	32	1.2	ns
		DZ	105	83	1.3	0.063

[a] Based on references 10 and 26.
RR: relative risk; CS: current cigarette smokers; FS: former cigarette smokers; AS: all cigarette smokers.

Table 2 - Mortality from coronary heart disease in smoking discordant twins by zygosity and smoking status during 1976-1987 in Finland and during 1961-1981 in Sweden[a]

Country	Smoking status	Zygosity	No. of first or only deaths in twin pair among		RR	P
			Smokers	Nonsmokers		
Finland	CS	MZ	9	0		0.003
		DZ	18	8	2.25	0.05
	FS	MZ	3	8	0.40	ns
		DZ	15	6	2.50	0.049
Sweden	AS	MZ	18	7	2.57	0.028
		DZ	62	32	1.94	0.002

[a] Based on references 10 and 26.
RR: relative risk; CS: current cigarette smokers; FS: former cigarette smokers; AS: all cigarette smokers.

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When the analysis was restricted to moderate and heavy smokers, relative risks were higher than when all cases were analysed [26]. Thus an effect of dose can be observed in the Finnish sample. Significant excess mortality was observable in the Swedish sample as well (Table 1), so when both samples are considered together, there is clear evidence for an overall increased mortality risk among smokers compared to nonsmokers matched for age, gender, and genetic constitution.

Cause-specific analyses were done for CHD and lung cancer. In Finland, for MZ CS pairs there were 9 CHD deaths in the smokers with none in the nonsmokers (Table 2). For DZ pairs RRs greater than 2 were observed for CHD. Thus CHD deaths were more frequent among the current smoking twins than among their nonsmoking cotwins. The combined risk ratio for CHD deaths from the Finnish current smoking discordant pairs and the Swedish data set is 3.9 ($P < 0.001$) for MZ pairs and 2.0 ($P < 0.001$) for DZ pairs.

In the subset of initially disease-free pairs, the incidence of CHD (hospitalisations and deaths due to CHD) was higher in the smokers during a six-year follow-up period [20], and this effect persists when ten-year follow-up data is considered (Table 3). We have also investigated the status of peripheral arteries by duplex ultrasound techniques in 49 smoking-discordant MZ pairs [14] and significantly more atherosclerotic lesions were found in the smokers. Smoking-discordant MZ pairs are also a powerful model for elucidating metabolic and physiological effects of smoking [27-31]. Thus the results from all the latest studies on smoking-discordant pairs confirms the role of smoking as a major causal risk factor for CHD.

Table 3 - Coronary heart disease (CHD) incidence in smoking discordant twins[a] initially free of CHD by zygosity during 1976-1987 in Finland

Gender	Zygosity	No. of pairs[b]	No. of first or only events[c] in twin pair among		RR[d]	P
			Smokers	Nonsmokers		
Male	MZ	138	10	3	3.33	0.052
	DZ	585	23	9	2.56	0.013
Female	MZ	169	3	2	1.50	ns
	DZ	576	17	12	1.42	ns

[a] Current smoking discordant pairs only.
[b] Pairs with either member hospitalized for CHD or on disability pension prior to 1976 excluded.
[c] Events from death certificates (1976-1987), hospitalisations (1976-1985) and disability pensions and medication records (1976-1987).
[d] Relative risk.

For cancers of all sites there was a relative risk of 3.0 among MZ CS pairs, the excess mortality being due to 2 lung cancer cases in the smoking cotwins. For all MZ pairs the RR was 2.0, while DZ pairs had no excess cancer mortality. A total of 8 lung cancer cases were observed in the smoking-discordant pairs, all of them in the smoking cotwins. Thus, for lung cancer, both men and women had a clear excess mortality in smokers in a pattern similar to that found for the Swedish

data [10]. If we combine the results for lung cancer in the two data sets (Table 4), there were 6 cases in the smoking cotwins of MZ pairs and no cases in their nonsmoking cotwins ($P < 0.05$). Correspondingly, for DZ pairs there were 21 cases among smokers and two among their non-smoking cotwins ($P < 0.01$). It is unlikely that diagnostic errors could explain these differences, because total mortality was also much greater in the smoking twins than in their nonsmoking cotwins. Cancer incidence data (1976-1989) for the Finnish sample supports the mortality results, with all but 1 of 14 new cases of lung cancer occurring in smokers (Table 4).

Table 4 - Lung cancer mortality (1976-1987) and incidence (1976-1989) in smoking discordant twins by zygosity and smoking status during 1976-1987 in Finland and corresponding lung cancer mortality during 1961-1981 in Sweden

Country	Zygosity	No. of first or only deaths in twin pair[a] among		Incident cases of lung cancer[b] (first or only case in twin pair)	
		Smokers	Nonsmokers	Smokers	Nonsmokers
Finland	MZ	2	0	2	0
	DZ	4	0	11	1
Sweden	MZ	4	0		
	DZ	17	2		

[a] Based on references 10 and 26.
[b] Finnish Cancer Registry data; pairs with any cancer diagnosed 1953-1975 are excluded.

Could the mortality differences between smoking and nonsmoking cotwins be due to other factors than smoking? In order to explain the difference in disease occurrence, the factor should be associated with increased risk of disease and should be more common among smokers. Family history of disease is often a major predictor of disease; in this unique study design both the exposed and nonexposed have the same family history, in addition to sharing all (for MZ pairs) or part of (for DZ pairs) their genes. Thus, other explanatory factors have to be environmental. Various possibilties were considered for the present data set [19]. Significant differences were found for relative weight, use of alcohol and leisure-time physical activities among male MZ CS pairs. The smokers weighed less than their cotwins: this should lessen their CHD risk, not increase it, and should not affect their lung cancer risk. The smokers used more alcohol, but only on average 4-5 drinks per month more. This would increase the risk of lung cancer very little, if at all [39]. Smokers also engaged in less physical activity, which could explain some of their increased CHD risk as physical inactivity increases risk moderately, but it cannot explain the increased lung cancer risk.

Eysenck [7,8] has suggested that personality differences between smokers and nonsmokers are the cause of differences in disease risk and that smoking is not a causal agent. In the present study, personality factors (including measures of extraversion, neuroticism and perceived stress of daily life), life-changes and Type A behavior, occupational class, marital status and educational level were equally distributed among smokers and nonsmokers. This suggests that once genetic factors

are controlled, personality differences between smokers and nonsmokers no longer account for morbidity differences. In 49 pairs of smoking-discordant MZ pairs [14] representing a subgroup of pairs with greater than average discordance for smoking, there were no differences between smokers and nonsmokers in systolic and diastolic blood pressure, serum cholesterol, history of diabetes, body mass index, coffee use, or hostility score. In a clinical study of a subsample of the Swedish discordant pairs [33], little differences between smokers and nonsmokers were found. It is unlikely that any factor other than smoking explains the observed increased mortality, particularly for CHD and lung cancer.

This study and the Swedish series now have sufficient exposure history, adequate sample sizes and long follow-up time. The results for coronary heart disease and lung cancer are consistent with other epidemiological literature and we may thus reject the constitutional hypothesis. This adds further support to the evidence that smoking has a major causal role in lung cancer and coronary heart disease.

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