Twenty-Four Year Mortality in World War II US Male Veteran Twins Discordant for Cigarette Smoking

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Background. This study was undertaken to test the constitutional hypothesis which attributes the association of tobacco smoking with morbidity and mortality to genetic predispositions to smoking and/or disease.

Methods. Subjects were World War II veterans, born in the US between 1917 and 1927, and surveyed at mean age 47 for present and past smoking habits. Twenty-four year mortality follow-up data were available for 1515 male twin pairs discordant for lifelong cigarette smoking. Using the first or only death of a smoking-discordant pair, 24-year relative risks of mortality were calculated by zygosity, cause of death, amount smoked, and age at death.

Results. We found that active smokers at baseline, regardless of zygosity, had a higher risk of death than their co-twins who had never smoked or quit smoking (monozygotic pairs: relative risk [RR] = 2.5; 95% confidence interval [CI]: 1.3-6.1 and RR = 1.7; 95% CI: 1.2-2.5; dizygotic pairs: RR = 2.4; 95% CI: 1.4-3.8 and RR = 2.0; 95% CI: 1.7-3.3). The elevated risk of death among smokers was due to deaths from lung cancer (monozygotic pairs: RR = 5.0; 95% CI: 2.6-15.0; dizygotic pairs: RR = 11.0; 95% CI: 4.3-45.0) or deaths from cardiovascular diseases (monozygotic pairs: RR = 3.9; 95% CI: 1.9-11.5; dizygotic pairs: RR = 2.8; 95% CI: 1.7-4.9). Apart from these findings the relationship of smoking with all-cause mortality was stronger for earlier/younger deaths and for heavy to moderate smoking.

Conclusions. The present results, from the largest and longest-studied series of smoking-discordant twins negate the constitutional hypothesis that genetic or early shared familial influences underlie the significant association between tobacco smoking and premature mortality.

From the time the first epidemiological data on the association between tobacco smoking and chronic diseases became available,1-3 critics of a causal explanation of this relationship have offered the constitutional hypothesis as an alternative explanation.4-6 According to this hypothesis, genetic predispositions to smoking and/or chronic diseases explain in part the smoking-disease association. A simple test of the constitutional hypothesis is the study of monzygotic twins discordant for smoking behaviours. When the association is as strong in smoking-discordant monozygotic twins as in the population as a whole, the causal hypothesis is supported. A weaker or non-existent association among smoking-discordant twins, who are completely matched on their genetic endowments, will negate the causal hypothesis in support of a mediating effect of genetic and/or shared environmental influences. Beginning in the early 1960s, the Danish and Swedish twin registries— and later the Finnish twin registry—were used to test the constitutional hypothesis. Because of deficiencies in study design, including small numbers of smoking-discordant pairs, low levels of smoking, cross-sectional comparisons, and short periods of follow-up, no significant relationships with mortality from lung cancer, cardiovascular disease, or all-cause mortality were found.7-10 More recently, however, a report from the Swedish twin registry,11 based on 21 years of follow-up, did find that male monozygotic smokers of smoking-discordant pairs had an increased mortality risk that approached significance (risk ratio [RR] = 1.6, P < 0.06). Another report, from a 12-year prospective study of the Finnish twin registry,12 found 13 deaths among male smokers of smoking-discordant monozygotic pairs and only one death among their non-smoking co-twins (RR = 13.0, P < 0.01). In a combined analysis of the Swedish and Finnish series, the risk ratios for deaths from cardiovascular disease were RR = 3.9 (P < 0.001) in monozygotic discordant pairs and RR = 2.0 (P < 0.001) in dizygotic pairs. For lung cancer, there were six cases among monozygotic
smoking twins and none among their non-smoking co-twins ($P < 0.05$) and 15 cases among dizygotic smoking twins and two cases among the non-smoking co-twins ($P < 0.01$). These results, to our knowledge, were the first to negate the constitutional hypothesis in a population-based series of smoking-discordant twins.

The objective of the present study was to verify the results from the Swedish and Finnish twin series for a cohort of male twins born in the US between 1917 and 1927 who are members of the National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry. Available 24-year mortality data for these subjects make this study the longest prospective study of smoking-discordant twins and the first US population-based study. Other unique characteristics of this cohort include the large number of smoking-discordant twin pairs and the high levels of tobacco exposure for this cohort (cigarettes were distributed free during military service and resulted in a prevalence of 80% of ever smokers).

**SUBJECTS AND METHODS**

**Study Subjects**

The sample for this study was the NAS-NRC Twin Registry. The methods used to construct this twin panel have been described elsewhere.\(^1^3\),\(^1^4\) Briefly, multiple births of white males occurring in the continental US from 1917 to 1927 were identified by searching birth certificates. About 93% of all such births estimated from national statistics to have occurred during those years were found. These records were linked to the Master Index File of the Department of Veterans Affairs (VA), yielding 15,948 pairs of twins in which both had served in the military, mostly during World War II.

Zygosity classification was determined from the self-reports of twin brothers regarding their degree of similarity or dissimilarity. Later assessments of the accuracy of these reports based on fingerprints, physical characteristics, and blood typing estimated the classification to be correct in approximately 95% of the twin pairs.\(^1^4\)

An epidemiological questionnaire was mailed to these twins between 1967 and 1969 in a collaborative study with investigators of the Swedish Twin Registry. The English-language questionnaire was essentially a translation of one used in Sweden and later adopted in the Finnish twin registry.\(^1^5\),\(^1^6\) The objective of the survey was to evaluate the prevalence of coronary and respiratory disease and to obtain a history of health practices, including eating habits and tobacco and alcohol consumption. The overall response rate to the 1967–1969 epidemiological questionnaire was 78%. Due to a higher enrolment into the registry of monozygotic as compared to dizygotic pairs responses to the epidemiological survey were obtained from 2305 monozygotic and 2470 dizygotic twin pairs.

**Smoking Variables**

A detailed self-report history of current and past smoking, separately for cigarette, pipe, and cigar smoking, was obtained at baseline in 1967 through 1969. The amount smoked, the age smoking started, and information about cessation were asked of all the individuals who reported ever smoking.\(^1^7\) Excluding pipe and cigar smokers twin subjects were classified as active smokers if they smoked daily during the year preceding the year the epidemiological survey was conducted. Former cigarette smokers were those who had smoked in the past but were currently non-active smokers. Never smokers were subjects who were lifelong non-smokers.

Based on this classification, all pairs in which one member was an active cigarette smoker and his co-twin was a non-smoker (never or former smoker) in 1967 through 1969 were considered smoking discordant. In addition, former smoking discordant pairs (i.e. former versus never smokers) were considered as a separate group.

**Mortality Follow-up**

Periodic mortality reviews in the twin registry are performed through the computer-based Beneficiary Identification and Records Locator Subsystem (BIRLS) of the VA. Many veterans are eligible for a burial allowance, and the VA is notified of 95% of deaths among World War II veterans by relatives or morticians claiming this allowance. The BIRLS file locates the VA claims folder, which usually contains a copy of the death certificate so that claimed benefits can be assigned or paid. The Medical Follow-Up Agency (MFUA) at the National Academy of Sciences routinely requests a copy of these death certificates as part of its update of vital status of the twin registry. These are then sent to a trained nosologist for coding of underlying and associated causes of death using the ICD-8 coding system. Death certificates not available from BIRLS are requested from state vital statistics offices. Through 31 December 1990, a total of 9364 deaths were ascertained, or 29.4% of the original cohort of 31,898 twin subjects. Survival for veterans is slightly better than that of the US population of the same sex and age.\(^1^8\)

**Statistical Analysis**

To test the hypothesis of no difference in the mortality of the smoking and non-smoking twins we used the McNemar matched pair test. This test based on the first
or only death in a pair, can be performed without adjustment for survival times. Since the primary interest in the present study was the test of the null hypothesis and not estimation of the relative risks (RR) we always report the significance level and calculate the 95% confidence intervals (CI) in some cases to allow comparisons to previous other studies.

RESULTS
In the present sample of twins, 52% of monozygotic twins and 53% of dizygotic twins were cigarette smokers in 1967 through 1969. Among current smokers, 26% of monozygotic twins and 28% of dizygotic twins were heavy smokers (>30 cigarettes per day); 13% and 10% respectively, were light smokers (≤10 cigarettes per day).

A total of 1515 pairs were discordant for smoking at baseline. These pairs further divide into 424 pairs discordant for current versus never smoking, 801 pairs discordant for current versus former smoking, and 290 pairs discordant for former versus never smoking. The 24-year mortality experience of these pairs by zygosity is presented in Table 1. We first observe that, regardless of zygosity, active smokers in 1967 through 1969 were at significantly higher risk of death from all causes than were co-twins who had never smoked (RR = 2.5 and RR = 2.4 in monozygotic and dizygotic pairs, respectively, both \( P < 0.01 \)). Second, the higher risk of active smokers in 1967-1969 persisted independent of zygosity compared to the risk of co-twins who quit smoking. Third, former monozygotic smokers reduced their mortality risk to the risk of their brothers who had never smoked (RR = 0.7; \( P > 0.20 \)).

We now turn to analyses that stratified pairs by age at death (≥65 and <65) and smoking intensity (moderate to heavy smokers, >10 cigarettes per day; light smokers, ≤10 cigarettes per day). As shown in Table 2, regardless of zygosity, more early/younger deaths were experienced by smokers than by their never-smoking co-twins (RR = 2.7 versus 2.0 in monozygotic pairs; RR = 2.8 versus 1.8 in dizygotic pairs). Similarly, among smoking-discordant pairs whose co-twins were former smokers, more earlier/younger deaths were observed among continuing smokers of dizygotic pairs but not among the monozygotic pairs. Stratified by amount smoked, a dose-response relationship with smoking intensity was evident regardless of zygosity or whether the non-smoker twin was a never smoker or a former smoker. As Table 2 shows, the relative risks for heavier smokers are consistently higher than those for light smokers.

Cause-specific mortality rates in smoking-discordant pairs (former and never combined) in 1967 through 1969 are shown in Table 3. For cardiovascular disease, we found an RR of 3.9 (95% CI: 1.9–11.5) in monozygotic smokers compared with the risk of their never or former smoker co-twins. The corresponding RR in dizygotic twins was 2.8 (95% CI: 1.7–4.9). For cancers of all sites, we observed an RR of 2.7 (95% CI: 1.4–6.7) in the monozygotic smoking-discordant pairs, the excess mortality being due to five lung cancer cases in the smoking twins and one in the non-smoking co-twins. The corresponding RR for cancers of all sites in dizygotic pairs was 1.6 (95% CI: 1.0–2.9).
with the risk for lung cancer deaths being 11.0 (95% CI: 4.3–45.0). No excess mortality from trauma was found in smokers compared with their non-smoking co-twins.

**DISCUSSION**

The present study, the largest and longest study of smoking-discordant twins, found that rates of mortality from all causes of death were more than twice as high in twin smokers as in co-twins who did not smoke. The elevated risk ratio in smoking-discordant pairs was independent of zygosity and of the same order of magnitude as that of all individual smokers to non-smokers in this cohort (RR = 2.5 in monozygotic smoking-discordant pairs; RR = 2.4 in dizygotic smoking-discordant pairs, RR = 2.6 for the whole cohort). Apart from this finding, we confirmed in the present series the dose-response relationship with smoking intensity and found, as in many other studies of unrelated

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**TABLE 2 Relative risks (RR) in smoking-discordant twins, by age at death, and smoking intensity in 1967–1969**

<table>
<thead>
<tr>
<th>Category</th>
<th>MZ twins</th>
<th>DZ twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoker/Never smoker</td>
<td>Smoker/Former smoker</td>
</tr>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>S/NS</td>
</tr>
<tr>
<td>Age at death &gt;65</td>
<td>2.0 (0.7–15.7)</td>
<td>8/4</td>
</tr>
<tr>
<td>Age at death &lt;65</td>
<td>2.7 (1.3–9.0)</td>
<td>19/7</td>
</tr>
<tr>
<td>Moderate to heavy (&gt;10 cigarettes/day)</td>
<td>2.8 (1.3–8.1)</td>
<td>22/8</td>
</tr>
<tr>
<td>Light smoker (&lt;10 cigarettes/day)</td>
<td>1.7 (0.4–24.0)</td>
<td>5/3</td>
</tr>
</tbody>
</table>

*Monozygotic.
* Dizygotic.
* S number of pairs in which the first or only death was a current smoker.
* NS number of pairs in which the first or only death was a never smoker or former smoker.

**TABLE 3 Relative risks (RR) in twin pairs discordant for smoking in 1967–1969, by zygosity and cause of death**

<table>
<thead>
<tr>
<th>Category</th>
<th>MZ twins</th>
<th>DZ twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S/NS</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>All causes</td>
<td>84/43</td>
<td>2.0 (1.4–2.9)</td>
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<tr>
<td>All natural causes</td>
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<td>2.5 (1.6–4.0)</td>
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<tr>
<td>Trauma</td>
<td>2/4</td>
<td>0.5</td>
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<tr>
<td>Cardiovascular disease</td>
<td>31/8</td>
<td>3.9 (1.9–11.5)</td>
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<tr>
<td>Cancer (all sites)</td>
<td>30/11</td>
<td>2.7 (1.4–6.7)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>5/1</td>
<td>5.0 (2.6–15.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6/8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Monozygotic.
* Dizygotic.
* S number of pairs in which the first or only death was a current smoker.
* NS number of pairs in which the first or only death was a never smoker or former smoker.
individuals, that these occurred at earlier/younger ages rather than older ages.\(^{20-22}\) Specifically, the elevated risks of death among active cigarette smokers were due to deaths from lung cancer and cardiovascular disease. The RR for death from lung cancer was 5.0 in monozygotic smoking-discordant pairs and 11.0 in dizygotic smoking-discordant pairs; the corresponding RR for deaths from cardiovascular disease were 3.9 and 2.8, respectively, in monozygotic and dizygotic smoking-discordant pairs. Taken together, the present results confirm the most recent findings from the Swedish and Finnish twin series, thus definitely negating the constitutional hypothesis that attributes the smoking-mortality relationship to inherited predispositions or shared environmental experiences. The finding, however, that smoking was associated with premature mortality in this twin study does not eliminate the important role of gene-environment interaction effects. The substantial heterogeneity in risk associated with cigarette smoking among individuals of different cultural backgrounds can be explained in part as due to the modifying effect of cigarette smoking on specific genes.

The present study population, like the Swedish and Finnish twin series, was drawn from a population-based twin panel representing a substantial proportion of US twins of this age group. Because the response rate in twin studies is relatively high, there should be less bias in the present study from non-response to the survey than is found in other studies of non-twin samples. Smoking discordance status, however, required responses from both twins, thus, the number of smoking-discordant pairs available for analyses may have been lower because of death or attrition of the smoking cotwin. Furthermore, those who smoked at baseline may have quit smoking during the lengthy period of follow-up and the association may have been changed depending on how long ago this change in smoking pattern occurred. Interestingly, a recent study found that premature mortality as measured by the difference in all-cause mortality death rates between active cigarette smokers and lifelong non-smokers continued unabated in men from the 1960s to the 1980s.\(^{23}\)

In the Swedish and Finnish series, the reported levels of smoking were lower than those in the present study (average of 19 cigarettes per day in the NAS-NRC Twin Registry, 14.6 cigarettes per day in the Finnish series, and 7.3 cigarettes per day in the Swedish series). Despite these and other cultural differences between the US and the Swedish and Finnish twin series, the strength of the association of tobacco smoking with lung cancer, cardiovascular disease, and all-cause mortality is similar. In the Finnish study, however, there was no reduction in mortality risk for former smoking twins when compared with their never-smoking brothers. This finding may be due to a number of factors, including a smaller number of such discordant pairs, the time since quitting, and smoking cessation occurring after the manifestation of disease symptoms.

We found in the present study that former smokers who quit smoking before 1967 through 1969 were at significantly lower risk of mortality than their brothers who continued to smoke. In addition, we found that monozygotic twins who quit smoking prior to the 1967–1969 survey reduced their mortality rates to those of their co-twins who had never smoked. The absence, however, of this relationship for dizygotic pairs, who share only half of their genes, may suggest in part a role for genetic factors in the recovery process that follows smoking cessation.

Over the past decade, major innovations in the diagnosis and treatment of chronic diseases have occurred. None of these advances, however, offer as much benefit as avoiding or quitting smoking. Because of the proven causal effect of tobacco smoking on disease and the ability to eliminate it as a risk factor, smoking remains an important public health challenge that deserves the highest priority in current preventive campaigns.

ACKNOWLEDGEMENT
This study was supported by ADAMHA grant AA08925 and contract N01CP-95647-56 from the National Cancer Institute.

REFERENCES


(Revised version received October 1995)