

Cigarette Yield and the Risk of Myocardial Infarction in Smokers

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Background: Although cigarette smoking is a major risk factor for acute myocardial infarction (MI), cigarette tar yield has not been clearly demonstrated to affect MI risk.

Methods: A case-control study of first MI in smokers aged 30 through 65 years was conducted among 68 hospitals in an 8-county area during a 28-month period. Case subjects were smokers hospitalized at any of the area hospitals with a first MI. Approximately 4 community control smokers per case subject were randomly selected from the same geographic area using random digit dialing. Detailed data on smoking history and cigarette brand were collected.

Results: We identified 587 case subjects and 2685 controls who smoked cigarettes with known tar yields. After adjustment using multivariable logistic regression, the odds ratios (ORs) for subjects smoking medium- and high-

compared with low-tar-yield cigarettes were 1.86 (95% confidence interval [CI], 1.21-2.87) and 2.21 (95% CI, 1.47-3.34), respectively. The adjusted OR increased as tar per day intake increased ($P < .001$ for the trend); compared with the lowest category of tar per day, the ORs (95% CIs) for increasing tar per day were 1.16 (0.83-1.62), 1.85 (1.35-2.52), 2.42 (1.54-3.78), and 2.50 (1.78-3.52). There was a similar trend of increasing ORs as tar per day increased in smokers of lower-yield cigarettes ($P < .001$ for the trend) and when low-yield cigarette smokers were excluded ($P < .001$ for the trend).

Conclusions: Smoking higher-yield cigarettes is associated with an increased risk of MI, and there is a dose-response relationship between total tar consumption per day and MI.

Arch Intern Med. 2002;162:300-306

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SINCE THE FIRST observational study linking tobacco and heart disease in 1940,¹ numerous studies have confirmed the association between cigarette smoking and an increased risk of myocardial infarction (MI).²⁻⁴ Smoking cessation dramatically decreases this risk to the level of nonsmokers within 3 years.^{5,6} Despite these compelling data and great efforts by public health officials to educate smokers, an estimated 1.1 billion people worldwide continue to smoke.⁷ Regulatory efforts to limit the tar and nicotine content of cigarettes have been proposed in many countries,⁸ based primarily on the effects of higher cigarette yield on the risk of malignancy⁹⁻¹² and mortality from some smoking-related diseases.^{13,14} Several countries have recently adopted or proposed legislation that limits the amount of tar and nicotine in cigarettes,^{8,15,16} and the European Union, which already has a 12-mg tar limit, recently passed legislation that will reduce the upper limit of tar to 10 mg.¹⁷ Similar regu-

lations have not been enacted in the United States.

While reductions in cigarette yield (eg, reductions in nicotine, carbon monoxide, and tar) may reduce the risk of some smoking-related malignancies,⁹⁻¹⁴ the effects on MI are unknown. Because the absolute increase in risk of MI from cigarette smoking is greater than that for lung cancer,² a better understanding of the effects of cigarette yield on MI risk is critically important to worldwide regulatory efforts. Although prior investigations have failed to identify a clear difference in MI risk by cigarette yield,^{12,18-21} most of these studies were performed more than a decade ago, before low-tar cigarettes became popular, and therefore may have had limited ability to detect an effect of higher- vs lower-yield cigarettes.¹⁸⁻²⁰ The only study to suggest an increase in the occurrence of nonfatal MI from higher-tar-yield cigarettes did not specifically include data for smokers of the lowest-yield cigarettes.²¹ Therefore, the specific aims of this case-control study were to

SUBJECTS AND METHODS

SOURCE POPULATION

We performed a case-control study of MI in smokers from an 8-county region of eastern Pennsylvania (Philadelphia, Montgomery, Bucks, Chester, Delaware, Camden, Gloucester, and Burlington counties). The primary objective of the study was to examine the effect of nicotine patch exposure and the risk of MI in smokers.²² This study also collected detailed information on smoking habits and therefore permitted a secondary post hoc evaluation of the role of tar yield in MI.

IDENTIFICATION AND DEFINITION OF CASE SUBJECTS

Case subjects were between the ages of 30 and 65 years with a first MI who were hospitalized at any of the 68 acute care hospitals in the 8-county region from September 1995 through December 31, 1997. To maximize the completeness of case subject identification, hospital-specific systems of case subject ascertainment were developed, and the person responsible for case subject ascertainment at each hospital was contacted on at least a monthly basis.

Acute MI was defined using the criteria from the Minnesota Heart Survey.²³ Of potentially eligible subjects (N=778), 84% had their medical records reviewed for confirmation of their MI, and 85% had MIs that met the study criteria. Given this high rate of confirmation, the 140 eligible subjects for whom charts were not available are included in the primary analyses; a separate analysis excluded these subjects.

Subjects were excluded if (1) they were not current smokers (defined as abstinence from cigarettes for at least 1 week prior to their MI); (2) they had the MI as a complication of a hospitalization for a different condition (eg, postoperatively); (3) they had a prior MI; (4) they were pregnant or currently nursing (an exclusion criterion used in the primary data set²²); (5) they did not have telephones or did not speak English; (6) they did not live in 1 of the 8 counties; or (7) the brand of cigarette smoked by the participant was not tested by the Federal Trade Commission.

The participation rate among eligible case subjects was 68%; among all potential case subjects (known eligible and potentially eligible), participation was estimated to be 61%.²⁴ The charts of 349 nonparticipant eligible case subjects (79% of the known eligible nonparticipants) were reviewed to collect basic demographic information (age, sex, and insurance). The only difference between participants and nonparticipants was insurance status ($P<.01$), with nonparticipants more likely to be receiving medical assistance (13.1% vs 5.1%).²²

IDENTIFICATION AND SELECTION OF CONTROLS

Approximately 4 community control subjects were selected for each case subject using a modification of the Waksberg random digit dialing method.²⁵ Each randomly derived telephone number was dialed up to 9 times (3 attempts each during the day, evening, and weekend) to maximize participation and avoid the bias of using daytime only calls. Any household with a subject who refused to participate received up to 2 follow-up "conversion" telephone calls.

If there was more than 1 eligible person living in a single household, one was chosen at random. Controls were between the ages of 30 and 65 years and were subject to the same exclusion criteria as case subjects.

The participation rate among known eligible controls was 51%. A study was performed to estimate the use of nicotine patches (one marker of trying to quit smoking) among nonparticipants. Of the 214 subjects who refused to participate, 85 agreed to answer 2 questions, which were not specified until the subject agreed, about patch use. Two (2.4%; 95% confidence interval [CI], 0.3%-8.2%) of the 85 had used a nicotine patch within the prior week compared with 1.0% (95% CI, 0.7%-1.4%) of participant controls.²²

DATA COLLECTION

Exposure and covariate data were collected using a structured telephone interview for both case subjects and controls. The study hypothesis was not revealed to subjects at any time. To maximize the validity of exposure information, case subjects were interviewed only if they could be reached within 6 months of their MI. Controls were also interviewed only within 6 months of being identified to prevent the potential selection bias that could result if subjects who could not be reached within this time frame differed from those who could. Detailed information was obtained regarding tobacco use (including most recent brand of cigarette smoked, frequency and duration of smoking, and prior attempts to quit) and other clinical and demographic characteristics. All data were collected relative to the index date: the date of MI for case subjects and the date of the telephone interview for controls.

CIGARETTE YIELD CLASSIFICATION

Tar yield was used as a measure of cigarette yield because (1) it is directly proportional to the amount of nicotine, carbon monoxide, and other potentially toxic substances produced by a cigarette; (2) it is the measure being used for regulatory limitations in many countries^{8,15-17}; and (3) it is the basis for the labeling of cigarettes as *ultralight*, *light*, or *regular*. The tar yield of each brand of cigarettes smoked by patients was determined from data published by the Federal Trade Commission.²⁶ From these data, 3 categories of cigarettes (low tar, medium tar, and high tar) were derived, which correspond to ultralight (≤ 6 mg of tar), light (7-12 mg), and regular (>12 mg). A measure of tar consumed per day also was calculated for each participant by multiplying the tar yield of the cigarette smoked by the quantity of cigarettes smoked per day during the week prior to the index date. Quintiles were created to ensure an equal number of control group participants in each category.

STATISTICAL ANALYSIS

The odds ratio (OR) was used to estimate the relative risk of MI from smoking higher-yield cigarettes vs lowest-yield cigarettes. Multivariable logistic regression analysis was performed to control for possible confounding. The method of Hosmer and Lemeshow²⁷ demonstrated good fit for all models ($P>.05$). The multivariable model included

Continued on next page

variables that are known risk factors for MI and any potential confounding variable that changed the crude OR by more than 10% after adjustment.²⁸ These covariates included sociodemographic and lifestyle traits (age, sex, race, any degree of exercise within the past year, vitamin use, education, years smoking, and number of cigarettes smoked per day during the index week) and clinical characteristics (body mass index; history of coronary disease, hypertension, diabetes mellitus, or hypercholesterolemia; and any family history of coronary disease). Other potential confounding variables tested (total household income, marital status, caffeine and alcohol consumption, type of insurance, prior attempts to quit, use of any nicotine replacement therapy, aspirin or β -blocker use, patient concerns for MI, and a validated physical activity score²⁹) did not significantly affect any of the tar-yield ORs and were therefore not included.

Dose-response relationships were tested by including the tar variables, both as continuous and categorical variables, in multivariable models. Additional quadratic terms were included to test for nonlinearity. Separate analyses using nicotine or carbon monoxide instead of tar as a marker for cigarette yield produced similar results. Analyses including any subject who smoked within the last year, using the lifetime average smoking frequency as a covariate and excluding the 140 case subjects with unverified MI, were performed with no meaningful change in the results. In addition, interactions were tested between each variable and tar yields; none was significant ($P > .10$). Statistical analyses were performed using the SPSS statistical program (version 9.0, SPSS Inc, Chicago, Ill), and statistical significance was defined as a 2-sided P value lower than .05.

determine if smoking higher-yield cigarettes is associated with an increased risk of first nonfatal MI and to examine the contribution of tar yield to MI risk.

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS

A total of 609 eligible case subjects and 2739 eligible controls were identified. Of these, 22 case subjects and 54 controls were excluded because they smoked cigarettes with unknown tar yields. The characteristics of smokers in the control group, listed by type of cigarette smoked, are given in **Table 1**.

ASSOCIATION BETWEEN CIGARETTE TYPE AND MI

In the unadjusted analysis, smokers of medium- and high-yield cigarettes had a higher OR for MI than low-yield smokers (**Table 2**). The confounding variables that increased the ORs after adjustment were age, quantity smoked per day, and history of diabetes, coronary artery disease, hypertension, or hypercholesterolemia. The

confounders that decreased the ORs after adjustment were vitamin use, education, and exercise. After adjustment for all confounders, the ORs increased for smokers of medium- and high-yield cigarettes, and the associations remained significant (Table 2). When we controlled for all sociodemographic and lifestyle factors, the ORs for smokers of medium- and high-yield cigarettes increased relative to the unadjusted results: 1.61 (95% CI, 1.09-2.39) and 2.00 (95% CI, 1.38-2.91), respectively. When we controlled for all clinical factors, the ORs also increased (medium-yield OR, 1.95; 95% CI, 1.29-2.95; high-yield OR, 2.67; 95% CI, 1.81-3.92).

DOSE-RESPONSE RELATIONSHIP BETWEEN TAR AND MI

Tar Yield per Cigarette

The association between tar yield per cigarette (using quintiles) and MI is given in **Table 3**. Compared with the lowest group (≤ 5 mg tar), the multivariable-adjusted ORs for each of the categories of tar were sequentially higher ($P < .001$ for the trend). When tar yield was treated as a continuous variable, the estimated risk for MI increased by 4% for each 1-mg increase in tar yield (adjusted OR, 1.04; 95% CI, 1.01-1.06; $P = .002$). In addition to this linear association, there was a nonlinear relationship for continuous tar (adjusted for quadratic term, $\beta = -0.003$; $SE = 0.0015$; $P = .05$).

Tar Dose Per Day

There was a significant increase in ORs with increasing tar consumption per day within each subgroup of cigarette type (**Figure**). This trend was also seen in the unadjusted analysis for each individual subgroup of smokers (low, $P = .002$; medium, $P < .001$; high, $P < .001$). Multivariable adjustment did not alter the results for smokers of medium-tar ($P = .005$) or high-tar ($P = .01$) cigarettes; however, we could not fit reliable multivariable models for smokers of low-tar cigarettes because of the small number of exposed individuals in the higher-tar-per-day categories within this group.

COMMENT

STUDY RESULTS

Using tar as a marker for cigarette yield, the results of this study show that smoking higher-yield cigarettes is associated with an increase in the odds of MI. In addition, increasing amounts of tar inhaled per day was associated with increased risk. Although a dose-response relationship between smoking and risk for MI has been clearly demonstrated in previous studies,^{2,4} this relationship was only explained in terms of the number of cigarettes smoked per day. The results of our study demonstrate that, among people smoking the same number of cigarettes per day, tar yield is an independent risk factor for MI, and that people who consume more tar, regardless of cigarette type, have an increased risk for MI.

Table 1. Characteristics of Smokers in the Control Group*

Characteristic	Cigarette Type		
	Low Tar (n = 302)	Medium Tar (n = 927)	High Tar (n = 1456)
Tar, mg	4.42 ± 1.38	9.54 ± 1.07	16.37 ± 2.03
Nicotine, mg	0.448 ± 0.130	0.779 ± 0.084	1.158 ± 0.140
Carbon monoxide, mg	5.17 ± 1.48	10.81 ± 1.60	15.75 ± 1.85
Tar dose per day, mg	90.35 ± 62.43	172.77 ± 104.68	297.39 ± 211.06
Cigarettes smoked per day	20.88 ± 12.10	18.06 ± 10.67	18.12 ± 12.01
Smoking duration, y	26.35 ± 9.67	23.19 ± 9.86	24.20 ± 9.94
Ever attempted to quit	263 (87.4)	764 (82.4)	1117 (77.0)
Age, y	46.94 ± 8.16	42.91 ± 8.62	43.53 ± 8.64
Race			
White	275 (91.4)	802 (86.9)	951 (65.8)
Black	21 (7.0)	97 (10.5)	436 (30.2)
Other	5 (1.7)	24 (2.6)	58 (4.0)
Female sex	194 (64.2)	569 (61.4)	781 (53.6)
BMI, kg/m ²	26.14 ± 5.16	25.66 ± 5.03	26.45 ± 5.36
College education	214 (70.9)	492 (53.1)	617 (42.4)
Exercised in the past year	191 (63.2)	575 (62.0)	809 (55.6)
History of CAD	10 (3.3)	14 (1.5)	34 (2.3)
Hypercholesterolemia	58 (19.2)	153 (16.5)	229 (15.7)
Hypertension	52 (17.2)	140 (15.1)	280 (19.2)
Diabetes mellitus	15 (5.0)	33 (3.6)	51 (3.5)
Family history of MI	126 (41.7)	354 (38.2)	544 (37.4)
Vitamin use	125 (41.4)	335 (36.1)	435 (29.9)
Aspirin use for prevention of MI	13 (4.3)	38 (4.1)	41 (2.8)
Medical assistance recipient	0	15 (1.6)	71 (4.9)
Patient concerned about MI	120 (39.7)	328 (35.4)	498 (34.2)

*Data are given as mean ± SD or number (percentage) of smokers. BMI indicates body mass index; CAD, coronary artery disease; and MI, myocardial infarction. Number of subjects for some variables may not add up to the total study population because of missing or unknown data.

Table 2. Association Between Cigarette Type and Myocardial Infarction

Cigarette Type	Cases	Controls	Odds Ratio (95% Confidence Interval)	
			Bivariable*	Multivariable†
Low tar (≤6 mg)	42	302	1.0 (Reference)	1.0 (Reference)
Medium tar (7-12 mg)	163	927	1.26 (0.88-1.82)	1.86 (1.21-2.87)
High tar (>12 mg)	382	1456	1.89 (1.34-2.66)	2.21 (1.47-3.34)

* $P < .001$ for overall comparison.

†Model included the following potential confounding variables: age; sex; race; body mass index; history of coronary disease, hypertension, diabetes mellitus, or hypercholesterolemia; any family history of coronary disease; exercise within the past year; vitamin use; education; years smoking; and number of cigarettes smoked per day. $P = .001$ for overall comparison.

PRIOR INVESTIGATIONS OF TAR YIELD AND MI

There are relatively few, and somewhat contradictory, epidemiological data on the association between tar and MI. One large case-control study conducted in England concluded that smokers of medium-tar cigarettes (≥ 10 mg, the highest tar yield studied) had modestly increased (10%) odds for MI when compared with smokers of low-tar cigarettes (≥ 10 mg).²¹ Our study demonstrates not only a greater increase in risk from greater than 10-mg tar yield, but also an increased risk from even a 6- to 10-mg tar yield. The lesser OR in the previous study²¹ may have resulted from the selection of controls who were relatives of the case subjects. These controls may have been more likely to smoke similar tar-yield cigarettes because of their relationship, potentially biasing the results toward the null. In

addition, because this study,²¹ as well as other European studies,^{12,18} did not specifically include data on the lowest-yield cigarettes (< 6 mg), the effects of lower-yield cigarettes could not be studied.

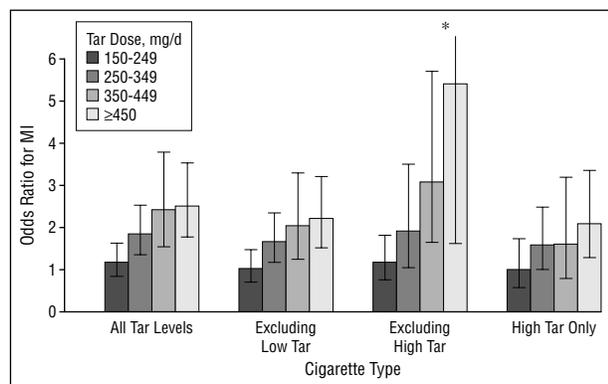
Two prior studies examining yield of American cigarettes did not demonstrate an association between increasing yields of nicotine or carbon monoxide and MI^{19,20} relative to nonsmokers. Although tar was not specifically studied, the results for tar yield would be expected to be related to nicotine and carbon monoxide, as the tar yield is proportional to these compounds in all cigarettes. The apparent discrepancy with our study could be explained by the use of hospital-based controls and of nonsmokers as the reference group in the prior studies.^{19,20} Hospitalized patients may not accurately reflect the general population from which our case subjects were drawn, and the comparison with those who

Table 3. Association Between Tar Yield per Cigarette and Myocardial Infarction

Tar Yield, mg	Cases	Controls	Odds Ratio (95% Confidence Interval)	
			Bivariable*	Multivariable†
≤5	36	278	1.0 (Reference)	1.0 (Reference)
6-10	147	849	1.34 (0.91-1.97)	2.05 (1.30-3.23)
11-15	114	409	2.15 (1.44-3.23)	2.16 (1.34-3.48)
16-20	247	1098	1.74 (1.20-2.52)	2.36 (1.51-3.69)
>20	43	51	6.51 (3.82-11.10)	2.42 (1.28-4.56)

* $P < .001$ for overall comparison.

†Adjusted for the same confounding variables listed in the second footnote to Table 2. $P = .006$ for overall comparison; $P < .001$ for trend.



Multivariable odds ratios were adjusted for the same confounding variables listed in Table 2, excluding cigarettes smoked per day. The reference group comprises those subjects who consume less than 150 mg of tar per day. $P = .001$ for the trend; $P = .001$ for all tar levels; $P < .001$ for the category excluding low-tar cigarettes; $P < .001$ for the category excluding high-tar cigarettes; and $P < .001$ for high-tar cigarettes only. Brackets indicate 95% confidence intervals (CIs). The asterisk indicates that the upper limit of the 95% CI for the group consuming more than 450 mg of tar per day in the category excluding high-tar cigarette smokers is 17.9.

have never smoked may have diminished any relative dose-response relationship that cigarette yield has among smokers. In addition, these studies were conducted more than 10 years ago, when low-tar cigarettes were only beginning to gain popularity. Most of the smokers of the lowest-yield cigarettes were likely to have recently switched to these brands, perhaps preventing a clear distinction from smokers of higher-yield cigarettes.

POTENTIAL LIMITATIONS

The potential limitations of observational research and secondary post hoc analyses must be considered in interpreting the results of this study. Because this study only included patients with nonfatal MI, we cannot draw conclusions regarding fatal MIs. A false association could be created if smokers of lower-yield cigarettes were more likely to develop silent MI or sudden death after an MI. However, there are no data to suggest that lower-yield cigarettes would increase the likelihood of developing either of these clinical outcomes, and thus this potential bias is unlikely.

A low participation rate could have created a false association if nonparticipant controls were more likely to smoke higher-yield cigarettes, or if nonparticipant case subjects were more likely to smoke lower-yield ciga-

rettes, than participants. Although response bias is difficult to assess, the information that was obtained from nonparticipant controls and case subjects suggests that this bias is unlikely. Because the prevalence of nicotine patch use among nonparticipant controls seemed to be higher than that of participants (although this could be a chance finding), nonparticipant controls may have been more likely to attempt to quit, a characteristic associated with smokers of lower-yield cigarettes in our data. In addition, although insurance status of nonparticipant controls is unknown, nonparticipant case subjects were more likely to be receiving medical assistance, a characteristic that was strongly associated with smoking higher-yield cigarettes in our study. These characteristics of nonparticipants would falsely diminish an association between tar yield and MI.

Uncontrolled confounding (eg, lifestyle factors and depression) is another potential limitation of our study. It has been postulated that the low-yield-cigarette smoking population is likely to choose this type of cigarette as a way to minimize the damaging health consequences of smoking³⁰ and that the marketing of low-tar cigarettes targets more educated and health-conscious smokers.³¹ However, adjustment for numerous markers of low-risk individuals (eg, vitamin use, education, exercise) did not alter the study results. In addition, low-yield smokers may have been at higher, rather than lower, risk because they tended to have more traditional risk factors for MI. In fact, adjustment for all measured potential confounders increased, rather than decreased, the ORs for smokers of medium-tar and high-tar cigarettes. In addition, several subanalyses, including those that excluded smokers of low- and medium-yield cigarettes, continued to demonstrate a clear association between increasing tar and MI. Therefore, uncontrolled confounding is unlikely to have explained the study results.

The inability to accurately measure the amount of tar exposure of an individual smoker could have affected our results in several ways. First, we only collected information on the most recent brand of cigarette. However, we believe it is more likely that high-yield smokers would have switched to low-yield brands, diminishing the association between tar and MI. Second, individual smoking behavior can alter the delivery of the proposed dose of tar,³² especially among those who switch to lower-yield cigarettes but titrate the amount of tar delivered through “vent-blocking” and other smoking behavior modifications.³³⁻³⁵ This may be of greater im-

Study Participants

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portance right after switching than with longer-term use.³⁵⁻³⁹ Regardless, individual smoking behavior that increased actual exposure to tar in the lower-yield groups, relative to what was predicted, would have biased our results toward the null. Finally, smokers may have changed their quantity of smoking in the index week; however, calculations of tar per day using lifetime averages did not alter the results.

CONCLUSIONS

This study demonstrated a significant association between smoking higher-yield cigarettes and first nonfatal MI, independent of the quantity of cigarettes smoked, and a consistent dose-response relationship between tar intake per day and MI, regardless of the type of cigarette smoked. Tar yields above 10 mg per cigarette, and even

above 6 mg, were associated with a significant increase in MI. Therefore, legislation aimed at reducing the amount of tar in cigarettes could have additional benefits, above and beyond reducing smoking-related cancers and other morbidities. Of course, smoking cessation should remain the goal of all smokers, as it is the only way to abolish the increased risk of MI from smoking,^{5,6} even among smokers of low-yield cigarettes.^{19,20}

Accepted for publication April 14, 2001.

This study was supported by grants from Aventis Pharmaceuticals (formerly Hoechst Marion Roussel Inc), Parsippany, NJ; Novartis Consumer Health, Summit, NJ; and McNeil Consumer Products Co, Fort Washington, Pa.

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