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Risk of Acute First Myocardial Infarction and Use of Nicotine Patches in a General Population

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OBJECTIVES To determine if nicotine patches, both as prescribed and used over-the-counter, increase the risk of first myocardial infarction (MI).

BACKGROUND Although nicotine patches improve smoking cessation rates, case reports have raised the hypothesis that they may increase the risk of MI.

METHODS A population-based case-control study among 68 hospitals in an eight-county region surrounding Philadelphia was performed to determine if nicotine patches increase the risk of first MI. Cases were smokers (current or within the prior year) admitted to all hospitals in the region with a first MI. Controls were smokers (current or within the prior year) without prior MI selected from the same region using random-digit dialing. Data were collected by telephone interviews and chart reviews. The study had 80% power to detect an odds ratio (OR) of 2.5.

RESULTS A total of 653 cases and 2,990 controls were interviewed. There was no association between nicotine patches and MI (OR 0.46; 95% CI: 0.09, 1.47), and the confidence interval (CI) excluded an effect from nicotine patches equal to that from cigarette smoking itself (OR < 2.5). Among those who abstained from smoking, the OR for use of nicotine patches was 0.25 (95% CI: 0.01, 1.67); among those who smoked concomitantly, the OR for patch use was 0.83 (95% CI: 0.09, 3.81). Adjustment for confounding did not alter the study's findings (OR adjusted for confounders that could mask a harmful effect of patches: 0.70; 95% CI: 0.20, 2.46).

CONCLUSIONS Nicotine patches, as used in actual practice, do not appear to be associated with an increased risk of MI. (J Am Coll Cardiol 2001;37:1297–302) © 2001 by the American College of Cardiology

Despite the fact that cigarette smoking accounts for more than 400,000 deaths (1) and billions of dollars of health care expenditures (2) each year in the U.S., an estimated 48 million Americans continue to smoke (3). Cigarette smoking increases the risk of acute myocardial infarction (MI) by about two- to fivefold (4), with a greater relative risk among younger people (5).

Nicotine replacement therapy has been shown to increase smoking cessation rates, particularly when combined with counseling (6). However, in 1992, five cases of MI were reported among nicotine patch users, raising concerns that nicotine patch use might increase the risk of MI (7). Others have since reported cases of MI among patch users (8–10). These reports have fueled the debate over the safety of nicotine patches (9,11–14) and led to calls both for careful monitoring and selection of patients who might benefit from the patch (10,14) and for studies to further investigate the effects of nicotine patches on MI risk (8). These concerns have become even more important with the recent increase in the use of nicotine patches (15).

Data from several recent studies have suggested that nicotine replacement therapy (nicotine gum or patches) does not increase the risk for cardiovascular events, even in people with underlying coronary disease (16–19). These studies, although valuable, were limited in their ability to draw conclusions about the risk of MI because their primary end points were a composite of different clinical events (18), they had few or no patients with MI (17–19), they were not designed (17) or sufficiently powered (16,17) to examine cardiovascular effects, they had high rates of discontinuation of therapy (17,18) and they examined mostly short-term nicotine replacement therapy (16,18,19). Equally important, controlled trials may not be representative of a more general population of nicotine replacement users, especially given the relatively recent introduction of over-the-counter therapy. Thus, the safety of nicotine patches as they are currently used by the population has remained unknown.

The specific aim of this study was to examine the effects of nicotine patches on the risk of first MI.

METHODS

Study site and identification and definition of cases. The study was conducted in the Philadelphia metropolitan area, using the population-based Delaware Valley Case-Control

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Abbreviations and Acronyms
CI = confidence interval
MI = myocardial infarction
OR = odds ratio

Network; that is, all 68 acute-care hospitals in an eight-county region (see Appendix).

Cases were current or recent smokers between the ages of 30 and 65 with a first MI who were hospitalized at one of the network hospitals from September 1995 through December 31, 1997. Because smokers may use nicotine replacement therapy for an extended period of time after stopping smoking, some recent smokers may be exposed to the patch. Therefore, cases were included if they had smoked cigarettes within one year before their MI (whether or not they had used a patch). In order to maximize case identification, hospital-specific systems of case ascertainment were developed and hospitals were contacted on at least a monthly basis.

Acute MI was defined using the criteria from the Minnesota Heart Survey (20). Eighty-four percent of subjects identified (778 subjects) had their medical records reviewed for confirmation of their MI. Of the 729 records (94%) with sufficient information available to verify MI, 85% had MIs that met the study criteria. Given this high rate of confirmation, the 145 subjects for whom charts were not available are included in the primary study analyses; a separate analysis excluded these subjects.

Cases were excluded if they 1) had never smoked cigarettes or last smoked cigarettes more than one year before their MI, 2) had an MI as a complication of a hospitalization for a different condition (e.g., postoperatively), 3) had a history of prior MI, 4) were pregnant or nursing (a relative contraindication to nicotine patch use), 5) did not have telephones or did not speak English or 6) did not live in one of the eight counties of the network.

The participation rate among eligible cases was 68%, and the charts of 79% of eligible nonparticipants were reviewed to determine basic demographic characteristics.

Identification and selection of controls. Approximately four community controls with no history of MI were selected for each case using a modification of the Waksberg random-digit dialing method (21). Each randomly derived telephone number was dialed up to nine times (three attempts each during the day, evening and weekend) in order to maximize participation. If there was more than one eligible person living in a single household, one was chosen at random. Controls were also smokers (current or recent, as defined for cases) and met the same exclusion criteria as cases. The participation rate among known eligible controls was 51%.

An additional study of nonparticipant controls was conducted over an eight-month period. Two hundred fourteen consecutive control subjects who refused to participate in the study were called again, and 85 agreed to answer two questions (not specified until the subject agreed to participate) regarding patch use either within the prior day or the prior week.

Definition of exposure. Because patients with MI may delay presentation to the hospital (22) and because it is possible that an effect of nicotine may manifest itself clinically several days after the patch is discontinued, the a priori primary definition of exposure to nicotine patches was any patch use within one week of the index date (the date of MI for cases and the date of the telephone interview for controls). Additional analyses considered exposure only if nicotine patch use occurred one day before the index date.

Data collection. Exposure and covariate data were collected for all subjects by telephone interview. Subjects were not told of the study hypothesis at any point during the study.

In order to maximize the validity of nicotine patch exposure information, cases were interviewed only if they could be reached within six months of their MI. Controls also were interviewed only within six months of being identified in order to prevent selection bias. To further maximize recall (23,24), all subjects were prompted for exposure information with indication-specific questions about smoking cessation, reading of all nicotine patch names and examination of photographs with pictures of all available nicotine patches (which all subjects were sent by mail prior to the interview). One hundred eighty-three subjects also were reinterviewed to determine reliability of exposure information, and agreement on patch use was 99%.

Sample size. The study was designed to have 80% power to detect an odds ratio (OR) for MI among patch users relative to nonusers of 2.5 (an OR equal to that of smoking itself) (4), based on an estimated prevalence of patch use in the control group of 1%, a two-tailed alpha of 0.05, and a control:case ratio of 4:1 (estimated 691 cases needed). Because more cases than expected did not meet our criteria for MI, we had 653 completed cases. However, by recruiting more controls, we were able to maintain a detectable OR of 2.5.

Analysis. Exact p-values and 95% confidence intervals (CIs) were calculated for all ORs. Because of the small number of exposed cases, we first performed exact stratified analyses for each possible confounder. Confounding was considered present if the summary OR from the stratified analyses was at least 10% different from the unadjusted OR (25). We then performed logistic regression to adjust simultaneously for those confounders that would mask a harmful effect of nicotine patches on MI (i.e., those confounders that increased the OR in stratified analyses).

The study was approved by the Institutional Review Boards of all participating hospitals.

Table 1. Distribution of Risk Factors Among Cases and Controls*

	Cases (n = 653) Number With Factor/Total (%)	Controls (n = 2,990) Number With Factor/Total (%)	Exact OR (95% CI)
Age ≥50 yrs	391/653 (60%)	713/2,990 (24%)	4.77 (3.97, 5.72)†
Body mass index ≥25.2 kg/m^2‡	451/650 (69%)	1,480/2,963 (50%)	2.27 (1.89, 2.74)†
Cigarette ≥19 pack-years‡	520/637 (82%)	1,457/2,895 (50%)	4.39 (3.53, 5.48)†
Diabetes mellitus	123/643 (19%)	117/2,977 (4%)	5.78 (4.37, 7.64)†
Family history of coronary disease	272/577 (47%)	841/2,740 (31%)	2.01 (1.67, 2.43)†
Female gender	210/652 (32%)	1,721/2,990 (58%)	0.35 (0.29, 0.42)†
Family income <$30,000/yr	303/612 (49%)	1,273/2,814 (45%)	1.19 (0.99, 1.42)‖
History of angina or coronary disease	70/643 (11%)	63/2,960 (2%)	5.62 (3.89, 8.12)†
History of high cholesterol	232/650 (36%)	497/2,981 (17%)	2.77 (2.29, 3.36)†
Hypertension	265/649 (41%)	522/2,981 (17%)	3.25 (2.69, 3.92)†
Private health insurance	530/631 (84%)	2,378/2,838 (84%)	1.02 (0.80, 1.30)‖
Race			
White	515/650 (76%)	2,266/2,974 (76%)	1.0 (reference)‖
Black	108/650 (20%)	603/2,974 (20%)	0.79 (0.62, 0.99)
Other	27/650 (4%)	105/2,974 (4%)	1.06 (0.65, 1.68)

*Numbers may be less than total because subjects reported "don't know" for risk factors or data missing. †$p < 0.001$. ‡The median value in the control group. ‖$p > 0.05$.
CI = confidence interval; OR = odds ratio.

RESULTS

Study population. A total of 653 cases of first MI and 2,990 controls participated in the study. The distribution of their clinical characteristics is shown in Table 1.

Association between nicotine replacement therapy and MI. Table 2 presents the association between nicotine patch use and the risk of MI. There was no statistically significant association between nicotine patch use and MI (OR 0.46; 95% CI: 0.09, 1.47). Excluding cases without medical records to confirm MI did not substantively change the results (Table 2); the upper limit of the 95% CI still excluded the a priori OR of 2.5. Including exposure to both nicotine patch and gum (any nicotine replacement therapy), the OR was 0.47 (95% CI: 0.15, 1.19). Patch use within the prior day also was not associated with MI (OR 0.59; 95% CI: 0.11, 1.98).

Among subjects who smoked any time during the index week, the use of the patch was not associated with an increased risk of MI relative to those who smoked but did not use the patch (OR 0.38; 95% CI: 0.04, 1.54; $p = 0.26$). Comparing those who reported specifically that they smoked on the same day that they used the patch with those who smoked cigarettes but did not use the patch, the OR was 0.83 (95% CI: 0.09, 3.81; $p = 1.0$). When comparing those who used the patch without concurrent smoking with those who did not use the patch or smoke (i.e., estimating the effects of using the patch alone without smoking relative to not smoking and not using the patch), the OR was 0.25 (95% CI: 0.01, 1.67; $p = 0.25$).

The effects of adjustment for potential confounders using exact stratified analysis are shown in Table 3. Five confounders actually reduced the OR (i.e., moved it further away from 1): body mass index, pack-years of smoking, income, gender and a history of high cholesterol. Adjustment for age, family history, hypertension and insurance increased the OR by more than 10%. However, for no analysis did the point estimate of the OR exceed 1.0, nor did the upper limit of the 95% CI exceed the a priori limit of 2.5. Stratification by the number of the above risk factors present (0–1, 2, 3, >3) produced an exact OR of 0.35 (95% CI: 0.04, 1.46; $p = 0.19$). Logistic regression adjusting simultaneously for age, family history, hypertension and insurance (i.e., all confounders increasing the OR) produced an OR of 0.70 (95% CI: 0.20, 2.46), again excluding an OR of 2.5.

Participants versus nonparticipants. Participant cases did not differ from nonparticipants with respect to age (mean age 51.1 vs. 51.9, respectively; $p = 0.16$) or gender (32% vs.

Table 2. Association Between Nicotine Patch Use and Myocardial Infarction: Nicotine Patch Use in Index Week

	Cases Nicotine Exposed/ Total (%)	Controls Nicotine Exposed/ Total (%)	Exact OR (95% CI)	Exact p Value
All subjects	3/653 (0.46%)	30/2,990 (1%)	0.46 (0.09, 1.47)	0.26
Only subjects in whom MI was confirmed by chart review	3/505 (0.59%)	30/2,990 (1%)	0.59 (0.11, 1.91)	0.55

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

Table 3. Association Between Nicotine Patch Use and Myocardial Infarction: Effects of Adjustment by Potential Confounders

Stratification Variable	Adjusted Exact OR (Exact 95% CI)	Exact p Value
None (crude OR)	0.46 (0.09, 1.47)	0.26
Age (<50 versus ≥50 years)	0.51 (0.10, 1.75)	0.45
Body mass index ≥25.2 kg/m^2	0.40 (0.08, 1.32)	0.18
Cigarette ≥19 pack-years	0.36 (0.07, 1.18)	0.12
Cigarette smoking in index week	0.46 (0.09, 1.50)	0.25
Diabetes mellitus	0.45 (0.81, 1.50)	0.24
Family history of coronary disease	0.55 (0.11, 1.81)	0.46
Family income <$30,000	0.32 (0.04, 1.29)	0.15
Gender	0.40 (0.08, 1.32)	0.18
History angina/coronary disease	0.42 (0.08, 1.39)	0.17
History of high cholesterol	0.41 (0.08, 1.35)	0.17
Hypertension	0.52 (0.10, 1.70)	0.34
Private health insurance	0.52 (0.10, 1.69)	0.34
Race (black versus other)	0.45 (0.09, 1.47)	0.25

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

28% female; p = 0.21). The only significant difference was insurance status (p = 0.006); nonparticipants were more likely to be on medical assistance (13.1%) than were participants (5.1%).

Among 142 nonparticipant cases in whom prior medication data were noted from medical records, no subject had documented patch use. In contrast, two out of 297 (0.7%) participant cases had their patch use documented in the records. Both of these subjects had stated they used the nicotine patch in the index week during their study interview. No case subject who denied use of the nicotine patch in the index week had nicotine patch use documented in the medical record.

Among controls who refused to participate in the study but agreed to answer questions in the nonparticipation study, two (2.3%; 95% CI: 0.3%, 8.2%) had used a nicotine patch within the prior week. This is in comparison with the 1.0% (95% CI: 0.7%, 1.4%) of participant controls who used the patch within the prior week.

DISCUSSION

Study findings. This large multicenter case-control study did not detect an increased risk of first MI from nicotine patches as used by a diverse population in actual practice. Although the OR of 0.46 is consistent with prior hypotheses that nicotine patches may reduce the risk of cardiovascular events by reducing the amount and intensity of cigarette smoking (26), the results were not statistically significant. Therefore, the most important finding was that the upper limit of the 95% CI of the OR of MI from nicotine patches (1.47) was lower than the OR of MI from smoking alone (4,5). Even if nicotine patch users were at this somewhat increased relative risk of MI during their short-term use of the patch, this risk would be less than that of continuing to smoke, which would continue lifelong.

The lack of an association between patch use and MI was not due simply to the fact that patch users were not currently smoking; the risk of MI among patch users who were not smoking was not increased when compared with those who were not smoking and not using the patch. We also did not detect an increased risk among patch users who smoked on the same day as wearing the patch. However, we had limited power to examine this question, as reflected by the wide CI.

Comparison with previous studies. These findings add new evidence to those of previous clinical studies supporting the safety of nicotine patches (16–19). These prior studies, however, were not specifically designed or powered to examine the effect of nicotine patches on MI risk. For example, a randomized trial of patches did not demonstrate an increase in a composite cardiovascular event end point (including congestive heart failure and arrhythmias) among short-term users of the patch, but was not powered to examine the effects of patches on MI (18). Most of these prior studies also were performed under controlled clinical trial conditions. Our study adds to these studies by demonstrating no significant increased risk of MI from "real world" use of the nicotine patch.

The findings of this study also are consistent with several physiologic and pharmacodynamic properties of nicotine and nicotine replacement therapy. First, although nicotine may cause coronary vasoconstriction and worsen myocardial dysfunction in stunned, ischemic myocardium (26), transdermal nicotine does not appear to increase platelet reactivity (27) or fibrinogen levels (at least in the short term) (28), potentially more important determinants of MI risk. Nicotine patches also appear to stimulate less catecholamine release than does cigarette smoking (27). Second, patch users who abstain from smoking typically have lower nicotine levels than those associated with smoking their usual number of cigarettes (29). Third, even when instructed to smoke ad libitum, smokers appear to reduce their intensity of smoke intake while wearing the nicotine patch, suggesting that patch use may reduce consumption of harmful

products other than nicotine in cigarette smoke even if people continue to smoke while wearing the patch (28,30).

Strengths and potential limitations. This study has several important strengths. First, it was population-based, thus minimizing the risk of selection bias. Second, the study reflects real-life use of the nicotine patch. Third, and most important, our study was large enough to exclude a relative risk from nicotine patches that is smaller than the relative risk from smoking; that is, it is riskier to continue to smoke than to use the nicotine patch.

However, several potential limitations of this study must be considered. First, there were only a few exposed cases. Although this finding is reassuring, because it reflects the lack of increased risk from patches, we could not adjust for all clinical variables simultaneously in multivariable analyses. Nonetheless, multivariable analysis that simultaneously included all variables that increased the OR for patches, the "worst-case scenario," found no suggestion of increased risk from nicotine patches, and the upper 95% CI still excluded an OR of 2.5.

Second, nonparticipation could have masked an association between nicotine patches and MI if nonparticipant controls were less likely and/or nonparticipant cases were more likely to use the patch. However, the study of nonparticipant controls suggested that the prevalence of patch use might have been higher than that for participants, and the nonparticipant cases were more likely to be on medical assistance and thus perhaps less likely to be able to buy nicotine patches (31). In addition, none of the nonparticipant cases whose medical records were reviewed had patch use documented. The potentially higher prevalence of patch use among nonparticipant controls and lower prevalence of patch use among nonparticipant cases suggested by these analyses would, if anything, have biased our results toward showing a harmful effect of nicotine patches.

Third, recall bias could have masked an association if cases were less likely than controls to recall patch use. However, the use of nicotine patches to stop smoking is a unique type of drug exposure that is unlikely to be forgotten, and drug histories were elicited using strategies that have been shown to improve the response rate to questions about medication use (23,24). Also, given the media attention about nicotine patches and MI (7), cases would, if anything, be more likely to recall patch use preceding their MI. In addition, chart review of subjects who denied nicotine patch use did not reveal any documented use of the patch.

Fourth, the study, by design, excluded persons dying of sudden cardiac death. Therefore, if nicotine patch users were more likely to suffer sudden death than nonusers, an association between nicotine patches and MI could have been masked. However, we are not aware of any data suggesting an increased risk of sudden death among users of nicotine replacement therapy. Regardless, for this bias to mask an OR of 2.5 and produce the OR of 0.46 observed in this study, nicotine patches would have to be associated with an almost 10-fold increased risk of sudden cardiac death (32–34), a risk more than five times that from cigarette smoking itself (35).

Conclusions. This study did not identify a statistically or clinically significant association between the use of nicotine patches and MI in an unselected population. These findings are consistent with the physiologic and pharmacodynamic properties of nicotine patches and with other studies that suggest no serious adverse cardiovascular effects among patch users. These results add further support to the safety of nicotine patches when users follow the recommended guidelines and abstain from cigarette smoking during patch use.

APPENDIX

Study Participants

Advisory Board Members: **Chair:** Robert Wallace, MD (University of Iowa, Iowa City, Iowa); Neal L. Benowitz, MD (University of California, San Francisco; San Francisco, California); Michael Criqui, MD, MPH (University of California San Diego School of Medicine, La Jolla, California); Paul D. Stolley, MD, MPH (University of Maryland School of Medicine, Baltimore, Maryland); Stephen Walter, PhD (McMaster University Health Sciences Center, Hamilton, Ontario, Canada).

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REFERENCES

1. Smoking-attributable mortality and years of potential life lost—United States, 1984. MMWR Morb Mortal Wkly Rep 1997;46:444–51.
2. MacKenzie TD, Bartecchi CE, Schrier RW. The human costs of tobacco use (2). N Engl J Med 1994;330:975–80.
3. Cigarette smoking among adults—United States, 1994. MMWR Morb Mortal Wkly Rep 1996;45:588–90.
4. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. The Pooling Project Research Group. J Chronic Dis 1978;31:201–306.
5. Parish S, Collins R, Peto R, et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. Br Med J 1995;311:471–7.
6. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. JAMA 1994; 271:1940–7.
7. Associated Press. Nicotine patches' link to heart attacks probed. Safety of smoking during use questioned. The Washington Post, June 20, 1992.

8. Ottervanger JP, Festen JM, de Vries AG, Stricker BH. Acute myocardial infarction while using the nicotine patch. Chest 1995;107: 1765–6.
9. Warner JG, Jr., Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. Ann Intern Med 1994;120: 695.
10. Dacosta A, Guy JM, Tardy B, et al. Myocardial infarction and nicotine patch: a contributing or causative factor? Eur Heart J 1993;14:1709–11.
11. Kafka HP. Heart attacks, smoking, and the nicotine patch. Ann Intern Med 1994;121:389.
12. Arnaot MR. Treating heart disease. Nicotine patches may not be safe. Br Med J 1995;310:663–4.
13. Lee TS, Hou X. Nicotine is hazardous to your heart. Chest 1996;109: 584–5.
14. Warner JG, Jr., Little WC. Smoking while wearing a nicotine patch. Ann Intern Med 1995;122:477.
15. Use of FDA-approved pharmacologic treatments for tobacco dependence—United States, 1984–1998. MMWR Morb Mortal Wkly Rep 2000;49:665–8.
16. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Arch Intern Med 1994;154:989–95.
17. Sonderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. Am J Epidemiol 1997;145:309–18.
18. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 1996;335:1792–8.
19. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. J Am Coll Cardiol 1997;30:125–30.
20. Mascioli SR, Jacobs DRJ, Kottke TE. Diagnostic criteria for hospitalized acute myocardial infarction: the Minnesota experience. Int J Epidemiol 1989;18:76–83.
21. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
22. Gurwitz JH, McLaughlin TJ, Willison DJ, et al. Delayed hospital presentation in patients who have had acute myocardial infarction. Ann Intern Med 1997;126:593–9.
23. Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. Am J Epidemiol 1986;123: 670–6.
24. Beresford SAA, Coker AL. Pictorially assisted recall of past hormone use in case-control studies. Am J Epidemiol 1989;130:202–5.
25. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–37.
26. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol 1997;29:1422–31.
27. Benowitz NL, FitzGerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. J Am Coll Cardiol 1993;22:1159–67.
28. Zevin S, Jacob P, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther 1998; 64:87–95.
29. Hurt RD, Dale LC, Offord KP, et al. Serum nicotine and cotinine levels during nicotine-patch therapy. Clin Pharmacol Ther 1993;54: 98–106.
30. Foulds J, Stapleton J, Feyerabend C, Vesey C, Jarvis M, Russell MA. Effect of transdermal nicotine patches on cigarette smoking: a double blind crossover study. Psychopharmacology 1992;106:421–7.
31. Cummings KM, Hyland A, Ockene JK, Hymowitz N, Manley M. Use of the nicotine skin patch by smokers in 20 communities in the United States, 1992–1993. Tobacco Control 1997;6 Suppl 2:S63–70.
32. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research: Principles And Quantitative Methods. Belmont, CA: Lifetime Learning Publications, 1982.
33. White AD, Rosamond WD, Chambless LE, et al. Sex and race differences in short-term prognosis after acute coronary heart disease events: the Atherosclerosis Risk In Communities (ARIC) study. Am Heart J 1999;138:540–8.
34. American Heart Association. 2000 Heart And Stroke Statistical Update. Dallas, TX: American Heart Association, 1999.
35. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99:1978–83.