Table 1 Brief Strategies to Help the Patient Willing to Quit Tobacco Use—The "5 A's"

Step	Strategies for implementation
Step 1: Ask (systematically identify all tobacco users at every visit)	· Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented. · Expand the entries of vital signs (blood pressure, pulse, weight, etc.) to include tobacco use (current, former, never) or use an alternative universal identification system (e.g., placing tobacco-use status stickers on all patient charts).
Step 2: Advise (Strongly urge all tobacco users to quit (in a clear, strong, and personalized manner))	Advice should be: · Clear: "I think it is important for you to quit smoking now and I can help you." "Cutting down while you are ill is not enough." · Strong: "As your clinician, I want you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you." · Personalized: Tie tobacco use to current health/illness, and/or its social and economic costs, motivation level/readiness to quit, and/or the impact of tobacco use on children and others in the household.
Step 3: Assess (determine willingness to make a quit attempt)	· Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days). If the patient is willing to make a quit attempt at this time, provide assistance. If the patient is unwilling to make a quit attempt at this time, provide a motivational intervention.
Step 4: Assist (aid the patient in quitting)	A patient's preparations for quitting:
• Help the patient with a quit plan.	· Set a quit date (ideally, the quit date should be within 2 weeks). · Tell family, friends, and coworkers about quitting and request understanding and support. · Anticipate challenges to planned quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. · Remove tobacco products from your environment. Prior to quitting, avoid smoking in places where you spend a lot of time (e.g., work, home, car).
• Provide practical counseling (problem solving/skills training).	· Abstinence: Total abstinence is essential. "Not even a single puff after the quit date." · Past quit experience: Identify what helped and what hurt in previous quit attempts. · Anticipate triggers or challenges in upcoming attempt: Discuss challenges/triggers and how patient will successfully overcome them. · Alcohol: Since alcohol can cause relapse, the patient should consider limiting/abstaining from alcohol while quitting. · Other smokers in the household — Quitting is more difficult when there is another smoker in the household. Patients should encourage housemates to quit with them or not smoke in their presence.
• Provide intra-treatment social support.	· Provide a supportive clinical environment while encouraging the patient in his or her quit attempt. "My office staff and I are available to assist you."
• Help patient obtain extra-treatment social support.	· Help patient develop social support for his or her quit attempt in his or her environments outside of treatment. "Ask your spouse/partner, friends, and coworkers to support you in your quit attempt."
• Recommend the use of approved pharmacotherapy, except in special circumstances.	· Recommend the use of pharmacotherapies found to be effective. Explain how these medications increase smoking cessation success and reduce withdrawal symptoms. The first-line pharmacotherapy medications include: sustained-release bupropion hydrochloride (not approved in Japan), nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch.
• Provide supplementary materials.	· Provide supplementary materials appropriate for the patient (Sources—Governmental agencies, nonprofit agencies, or local/state health departments).
Step 5: Arrange (Schedule followup contact)	· Timing: Followup contact should occur soon after the quit date, preferably during the first week. A second followup contact is recommended within the first month. Schedule further followup contacts as indicated. · Actions during followup contact: Congratulate success. If tobacco use has occurred, review circumstances and elicit recommitment to total abstinence. Remind patient that a lapse can be used as a learning experience. Identify problems already encountered and anticipate challenges in the immediate future. · Assess pharmacotherapy use and problems. Consider use or referral to more intensive treatment.

(AHRQ: The Agency for Healthcare Research and Quality, 2000)

Table 2 Brief Strategies to Enhance Motivation to Quit Tobacco Use—The "5 R's"

Relevance	Encourage the patient to indicate why quitting is personally relevant, being as specific as possible. Motivational information has the greatest impact if it is relevant to a patient's disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).
Risks	The clinician should ask the patient to identify potential negative consequences of tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient.
Rewards	The clinician should ask the patient to identify potential benefits of stopping tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient.
Road blocks	The clinician should ask the patient to identify barriers or impediments to quitting and note elements of treatment (problem solving, pharmacotherapy) that could address barriers.
Repetition	The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting.

(AHRQ, 2000)

limiting or abstaining from alcohol particularly immediately after the quit date; learning how to deal with other smokers, if any, in the household; identifying what interfered with previous quit attempts and providing advice on how to succeed), (3) by providing advice about the use of social support (concerning the use of support from healthcare professionals, family, friends, and coworkers), (4) by implementing pharmacotherapy, and (5) by providing supplementary educational materials on smoking cessation.

In Step 5 (Arrange), the procedure is to schedule follow-up contact for the patient with a quit plan to help him or her succeed in the quit attempt. It is recommended that the first follow-up contact occur soon after the quit date, preferably within the first week, and that a second follow-up contact take place within the first month. Congratulating the patient on his or her sustained abstinence provides great encouragement.

Role and Practical Aspects of Specialized Smoking Cessation Clinics

The role of outpatient clinics that specialize in helping patients overcome nicotine dependence is to provide special treatment to patients for whom brief intervention at a general outpatient clinic is insufficient to produce successful abstinence. Nicotine gum and the nicotine patch were introduced as a prescription drug to Japan in 1994 and 1999, respectively. As a result of these opportunities, an increasing number of outpatient clinics that specialize in treating nicotine dependence have been set up. A total of 247 institutions in this country as of January 2002 have such clinics (a list of outpatient clinics specializing in nicotine dependence in Japan is available at the URL of the Osaka Medical Center for Health Science and Promotion: http://www.kenkoukagaku.jp).

We opened a clinic specializing in the treatment of nicotine dependence in the Osaka Cancer Prevention and Detection Center in October 1998, and are continuing to treat patients in the clinic, which moved to the Osaka Medical Center for Health Science and Promotion in July 2001. More than 1,500 smokers have visited our clinic to date. In this clinic, a physician and counselor team is assigned to a particular patient, and methodology based on the results of research in two scientific fields, behavioral science and drug dependence, is used. A flowchart of the initial and subsequent visits to the clinic is shown in Fig. 1. The patient is interviewed individually for about 1 hour at the time of the first visit and for about 30–40 minutes at

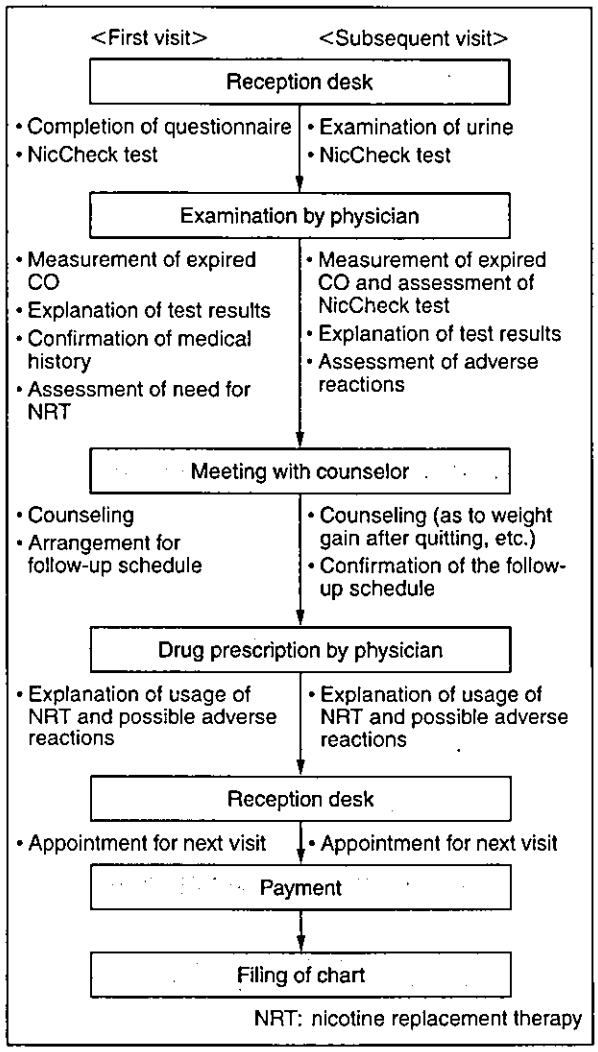


Fig. 1 Flowchart of treatment in the specialized smoking cessation clinic of the Osaka Medical Center for Health Science and Promotion

subsequent visits.

Patient visits to the clinic are scheduled using an appointment system, with the date of visits scheduled at times convenient for the patient. Most patients attend the clinic once every 2–3 weeks during the first few months after the quit date, because they usually use nicotine replacement therapy and therefore require assessment of its efficacy and possible adverse reactions as well as additional prescriptions at such intervals. The frequency of visits decreases to once every 1–2 months after three months of abstinence, when prescriptions for nicotine replacement therapy are generally terminated. In this clinic, patients "graduate" when abstinence from smoking has been maintained for 6 months from the quit date. On the day of the graduation ceremony, a photograph of the patient together with the physician and counselor is taken and placed on the certificate of course completion. This certificate is given to the patient to encourage continued abstinence.

Table 3 Meta-Analysis of Studies on the Efficacy of Nicotine Replacement Therapy

Nicotine replacement therapy (No. of trials)		Quit rate odds ratio (95% CI)
Gum	(48)	1.63 (1.49–1.79)
Patch	(31)	1.75 (1.57–1.94)
Intranasal spray	(4)	2.27 (1.61–3.20)
Inhaler	(4)	2.08 (1.43–3.04)
Sublingual tablet	(2)	1.73 (1.07–2.80)
All formulations		1.71 (1.60–1.83)

(Lancaster, 2000)

Pharmacotherapy for Nicotine Dependence—Nicotine Replacement Therapy

Various drugs have been examined as pharmacotherapy for nicotine dependence. Among them, nicotine replacement therapy has been established as safe and efficacious and is in widespread use throughout the world.

Nicotine replacement therapy using chewing gum or other formulations of nicotine supplies the patient with nicotine to relieve the withdrawal symptoms that occur during abstinence. With this therapy, the patient initially is weaned from psychological dependence, then from physical dependence through adjustment of the nicotine supply. According to a meta-analysis of studies on the effect of nicotine replacement therapy carried out in various countries, the therapy increased the chances of quitting 1.7-fold in comparison with placebo, as shown in Table 3.[3]

Table 4 Characteristic Features of Nicotine Gum and Patch

	Nicotine gum	Nicotine patch
Advantages	1. Allows self-regulation of the nicotine dose. 2. Is short-acting. 3. Offers both oral and tactile gratification.	1. Easy to use. 2. Allows maintenance of stable nicotine concentrations in blood.
Disadvantages	1. Requires instructions on proper use. 2. May cause nausea and irritation of the mouth and throat.	1. Cannot handle abrupt surges of craving. 2. May cause skin reddening or rash, and sleep disorder.

In Japan, chewing gum and patches are the currently available formulations of nicotine replacement therapy. The greatest merit of the nicotine patch is that it provides stable blood concentrations of nicotine when renewed every morning. On the other hand, nicotine gum is advantageous in that it provides a more rapid increase in the nicotine concentration in blood than the nicotine patch, so that it can better handle abrupt surges of craving for tobacco. Based on the characteristic features of these two formulations (Table 4), our clinic uses the nicotine patch as the basic formulation, and adds nicotine gum as supplementary dosing for surges of craving or for times when the effect of the nicotine patch is not adequate in the morning. In addition, we recommend concomitant use of nicotine gum for patients in whom the nicotine patch with the highest dose of nicotine (Nicotinel TTS30®) is considered to be insufficient. In selecting the dose of the nicotine patch, it is convenient to use a color test paper, NicCheck [Dynagen Inc., USA], which allows semi-quantitative measurement (0–14, 15 levels) of nicotine and its metabolites in urine. According to data from patients in our clinic who used the patch for 7 consecutive days without smoking, Nicotinel TTS30® (nicotine content 52.5 mg) provides a 4.8 ± 1.3 (mean ± standard deviation) NicCheck level of nicotine, TTS20® provides a 3.4 ± 1.4 level, and TTS10® provides a 1.8 ± 0.7 level.[4] When the nicotine patch is prescribed to the patient at the first examination, these data are used as a yardstick, based on the NicCheck level determined.

In Japan, nicotine gum was formerly a prescription drug that was not covered under national health insurance. However, it was approved as an over-the-counter drug in June 2001, and has been available in drugstores since September 2001. Readers are referred to two of the author's papers for detailed usage of the nicotine patch and nicotine gum.[5,6]

Conclusion

Although tobacco epidemic became prevalent in Japan about 30 years later than in the West, its epidemic was substantial by the 1970s, and Japan currently has the highest level of tobacco consumption among the developed countries. It is therefore easy to predict that health hazards caused by tobacco use will become a serious social problem as the population ages.

Nicotine dependence treatment is an anti-smoking measure that can be implemented by healthcare professionals in routine clinical settings. The efficacy and cost-effectiveness of such intervention have been demonstrated by scientific evidence, and it is expected to have greater immediate effects on reducing smoking prevalence than smoking prevention. Health hazards caused by tobacco use in the first half of the 21st century occur mainly in those who are current smokers. Therefore, comprehensive anti-smoking measures, including nicotine dependence treatment, are urgently needed.

We have developed educational materials for medical institutions and healthcare profes-

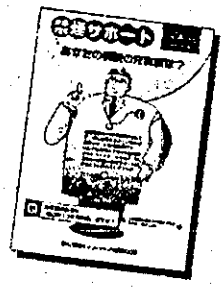
♦ Osaka Prefecture's guidelines for tobacco control (for medical institutions) [digest edition]

In May 2000, the Osaka Prefectural government developed guidelines to curtail tobacco use in medical institutions, with the goal of achieving the smoking ban or complete isolation of smokers in specified areas and providing support for smoking cessation in all medical institutions by 2005. The guidelines propose specific activities for this purpose.

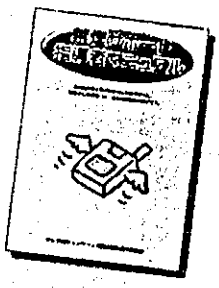
●Osaka Prefecture's guidelines for tobacco control (for medical institutions) [digest edition]

♦ Educational materials useful for the support of smoking cessation

Material that allows medical institutions to self-assess the extent of their support for smoking cessation is available as well as various other materials including an instructor's manual describing how to provide support and leaflets to patients.



●Checking smoking cessation support activities
"What is the level of preparedness and achievement in your institution?"



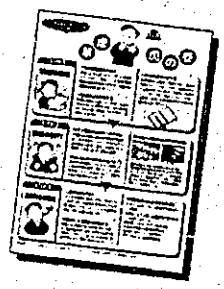
●Smoking cessation support: instructor's manual

♦ Educational materials useful for promoting the smoking ban or isolation of smoking in medical institutions

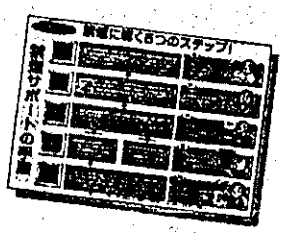
A pamphlet is available that allows individual medical institutions to self-assess their progress in smoking ban or isolating smoking in the institution.
Also available is illustrated material that introduces important points in promoting the smoking ban or isolation of smoking, specific practical procedures, and successful examples.

●Checking smoking restriction in medical institution
"Is your institution progressing with the isolation of smoking?"

●Manual for smoking restriction in medical institutions



●Leaflet for patients
"Keys to successful smoking cessation"



●Smoking cessation support procedures sheet
"Five steps leading to successful smoking cessation"

Fig. 2 Educational materials for the promotion of tobacco control in medical institutions

sionals under the Osaka Executive Committee of the Cancer Prevention Campaign, which aims to promote the control of tobacco use in medical facilities (Fig. 2). Smoking ban in a medical institution provides "a cleaner, more comfortable hospital environment" and is also expected to increase the motivation of patients and personnel who smoke to give up the habit. To give greater credence to medical programs aimed at treating nicotine dependence, smoking ban in medical institutions needs to be addressed. These educational materials are available for reading and downloading on the URL of the Osaka Cancer Prevention and Detection Center (http://www.gan-osaka.or.jp) (in Japanese only).

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Special Issue

Original Article

Effects of Stage-matched Repeated Individual Counseling on Smoking Cessation: A Randomized Controlled Trial for the High-risk Strategy by Lifestyle Modification (HISLIM) Study

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Abstract

Objective: The purpose of this study was to evaluate the effects of stage-matched repeated individual behavioral counseling as an intervention for the cessation of smoking.

Methods: We conducted a multisite randomized controlled trial that enrolled smokers unselected for their readiness to quit. There were 979 smokers with hypertension or hypercholesterolemia recruited from 72 study sites and randomly allocated to the intervention or control group. Smokers in the intervention group received stage-matched individual counseling consisting of a 40 minute initial session and four 20–30 minute follow-up sessions. Smokers in the control group received individual behavioral counseling for hypertension or hypercholesterolemia.

Results: The point prevalence abstinence rate at 6 months, validated by carbon monoxide testing, in the intervention group (13.6%) was 5.4 times higher ($p<0.001$) than that in the control group (2.5%). When the data were analyzed based on the baseline stage of change, there were significant differences in the abstinence rates at 6 months in smokers versus controls with each stage of change except in immotives. The odds ratio was 6.4 ($p<0.001$) in precontemplators, 6.7 ($p<0.001$) in contemplators, and 6.2 ($p<0.01$) in preparators. There was a positive, consistent effect of the intervention regardless of study site (worksite or community) or the presence of hypertension or hypercholesterolemia.

Conclusions: We showed the effects of an intervention with repeated individual behavioral counseling on the cessation of smoking in smokers unselected for their readiness to quit. This result suggests that stage-matched individual counseling, based on the transtheoretical model, is effective in smokers with a lower motivation to quit as well as those ready to quit.

Key words: smoking cessation, individual counseling, stage of change, intervention study, effect, randomized ontrolled trial

Introduction

Tobacco use is the single most important preventable health risk in developed countries, and a major cause of premature death and disability worldwide (1, 2). In 2000, tobacco smoking accounted for an estimated 113,000 of the total 962,000 deaths in Japan (3). Thus, tobacco smoking is responsible for approximately one in every eight to nine deaths in Japan. Although the prevalence of smoking among men has gradually decreased to 45.9% in 2000 (4), the absolute number of annual tobacco-attributed deaths among men in Japan is still increasing as a consequence of high-level tobacco consumption over several decades (3). Smoking is uncommon among Japanese women, with only about 10% currently smoking; however, smoking is increasing among younger women (4).

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Therefore, it is easy to predict that the health burden caused by tobacco use will become a more serious social problem in the future. The burden of tobacco-caused diseases in the first half of the 21st century occurred mainly in those who were current smokers (5). Thus, comprehensive tobacco control measures to reduce smoking prevalence are urgently needed.

The essence of tobacco use is nicotine dependence (6). Nicotine dependence is a chronic disease that often requires repeated intervention (7). Environmental change strategies for tobacco control, such as tobacco taxation and smoking restriction in public places, can be effective in reducing tobacco use (8, 9), but smokers often find it difficult to overcome their dependence without help (10). Effective treatments to promote smoking cessation need to be implemented in various health care settings as part of a comprehensive tobacco control measure.

There is clear evidence that various interventions for the treatment of tobacco dependence are both effective and cost-effective compared to other medical and disease prevention interventions (11–13). In Western countries, evidence-based guidelines for treating tobacco dependence were developed for health professionals as well as health commissioners and managers (7, 12), and many efforts have been made to implement these guidelines into health care settings.

However, in Japan, there have been a limited number of studies on smoking intervention. Seven intervention studies with a controlled trial design examined the effects of individual counseling or a combined intervention format including individual counseling (14–20). Although some have shown the intervention to be effective (14–17), others failed to show a significant difference, mainly due to a small sample size (18) or a small effect of the intervention (19, 20). These previous studies had limitations in that only a few used a biochemical test to validate self-reports of smoking status (17, 18) and only three assigned the subjects to study groups by random allocation (17–19).

From a theoretical perspective, most previous studies did not include a description of the theoretical background of behavioral science for the design of the smoking intervention. The transtheoretical model (stages-of-change model) (21, 22) proposes that interventions should take into account the current stage (readiness) of the individual to change. We have developed a smoking cessation intervention that utilizes repeated individual counseling based on the transtheoretical model. We have also developed a training program to teach health care providers a behavioral approach to use in counseling smokers. The purpose of this study was to perform a multisite, randomized, controlled trial to examine the effects of a smoking intervention with repeated individual counseling by trained health care providers.

Methods

Overview

A multisite randomized controlled trial (the High-risk Strategy by Lifestyle Modification, HISLIM study) was organized to examine the effects of individual counseling for behavior change among high-risk subjects aged 20 to 69 who had two of three risk factors: hypertension (systolic BP of 135 to 179 or diastolic BP of 85 to 104), hypercholesterolemia (total cholesterol of 220 to 300 mg/dl), and smoking. To be eligible for enrollment, subjects were required to have smoked for at least 1 year before recruitment. Pipe or cigar smokers were excluded from the study.

Study subjects consisted of three subgroups: the smoking and hypertension group (SHT), the smoking and hypercholesterolemia group (SHC), and the hypertension and hypercholesterolemia group (HTHC). Subjects of each subgroup (SHT, SHC, HTHC) were individually assigned at random to the two intervention groups within each study center. Subjects assigned to the intervention A or B group received a behavioral intervention for risk factor A or B, respectively. In evaluating the effect of the behavioral intervention for risk factor A, the intervention B group was treated as a control group ("positive control group"). The main outcome criteria of the trial were changes in the risk factors at 6 months.

The original sample size estimate of 220 in each group provided the study with 80% power to detect a 4 mmHg decrease in systolic BP in the intervention group compared with the control group. This power analysis was calculated using a 2-sided test with the probability level (α) being set at 0.05 and standard deviations of 15.0 for SBP. The number of participants in our study was also considered to be sufficient for detecting differences between the two groups for both total cholesterol reduction (8 mg/dl) and the abstinence rate (10%).

All of the survey and intervention procedures were examined and approved by the Medical Science Ethics Review Board of Shiga University of Medical Science.

Recruitment of the study site

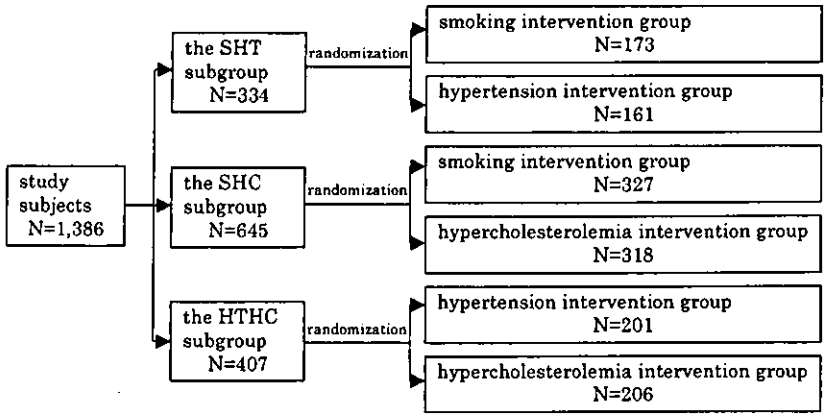
Two-day research workshops were held in the Kanto and Kansai districts for over 200 health care providers working for communities or worksites that were interested in participating in the study. In the workshops, the study purpose and protocols were explained.

As a result, 72 sites participated in the study. The 72 study sites consisted of 26 communities and 46 worksites. Among the 26 communities, there were 7 prefectural health centers and 19 municipal health centers or offices. Among 46 worksites, there were 28 private companies, 4 public worksites, and 14 medical facilities providing worksites with health check-up services.

Subject recruitment and randomization

Study subjects were recruited from the 72 sites. Each study site was requested to select one of three risk-factor subgroups (SHT, SHC, HTHC) and recruit 20 subjects who met the inclusion criteria. All subjects were informed of the study and gave their written consent.

A total of 1,386 subjects were recruited by the study sites: 334 subjects in the SHT subgroup, 645 in the SHC subgroup, and 407 in the HTHC subgroup (Fig. 1). The subjects were stratified by study site and randomly assigned to either one of the two intervention groups in each subgroup. As a result of randomization, 173 of 334 subjects in the SHT subgroup were assigned to the smoking intervention group and 161 subjects were assigned to the hypertension intervention subgroup. Among



Note. SHT: smoking and hypertension group, SHC: smoking and hypercholesterolemia group, HTHC: hypertension and hypercholesterolemia group.

Fig. 1 Outline of randomization assignment of study subjects

the 645 subjects in the SHC subgroup, 327 and 318 subjects were assigned to the smoking and hypercholesterolemia interventions, respectively. Among the 407 subjects in the HTHC subgroup, 201 and 206 subjects were assigned to the hypertension and hypercholesterolemia interventions, respectively.

Among the 1,386 subjects, 399 subjects (28.8%) had all three risk factors (hypertension, hypercholesterolemia, and smoking). The percentage of those who had all three risk factors was 27.2% in the SHT subgroup, 42.6% in the SHC subgroup, and 8.6% in the HTHC subgroup. There were no statistical differences in the percentage of those who had all three risk factors among intervention groups in the SHT, SHC, and HTHC subgroups. A total of 979 smokers (334 in SHT, 645 in SHC) were selected for the present study to examine the effects of stage-matched smoking intervention. Among 334 subjects in the SHT subgroup, two subjects proved to be ex-smokers at randomization and were excluded from the analysis. Thus, 977 subjects (332 in SHT, 645 in SHC) were included in the final analysis. There were 500 subjects in the smoking intervention group (173 in SHT, 327 in SHC) and 477 in the control group (159 in SHT, 318 in SHC).

Health care provider training

One-day and consecutive two-day training seminars were provided for health care providers who participated in the study. To standardize our intervention protocol and method, the study sites were requested to send two staff members to participate in these seminars. The purpose of the seminars was to make participants understand the significance of risk factor interventions by behavioral counseling, and to demonstrate and practice the counseling. The participants received lectures on smoking intervention in the first seminar. The contents of the lectures were the health effects of smoking, the significance of smoking cessation, and the smoking intervention protocol of the study. In the second seminar, conducted 5 to 6 months after the first, the instructor presented the method used to counsel smokers according to their stage of change for smoking cessation and showed a videotape demonstrating successful stage-matched counseling interactions. The participants used role-playing to rehearse smoking cessation counseling.

Smoking intervention protocol

Based on a smoking cessation program for health check-up settings that we developed (23), standardized intervention protocols and manuals were arranged to guide health care providers in delivering smoking cessation counseling. The smoking intervention consisted of a 40 minute initial counseling session and four 20–30 minute follow-up counseling sessions at 1, 2, 4, and 6 months after the initial session. These sessions were conducted face-to-face by individual counselors. If a smoker established a quit date, there was an additional follow-up 1 week after the initial session by telephone call or letter. The initial session consisted of stage-matched individual counseling with the feedback of expired carbon monoxide (CO) testing (24) and provision of a self-help guide that described the stages of change for smoking cessation (25). The stage-matched individual counseling included: 1) assessing the smoker's stage of change, 2) providing counseling about smoking cessation that differed according to the smoker's stage of change, 3) recommending that smokers willing to quit smoking set a quit date. A smoker's stage of change was categorized into four categories: the immotive stage (not interested in quitting smoking and not thinking about quitting in the next 6 months), the precontemplation stage (interested in quitting smoking but not thinking about quitting in the next 6 months), the contemplation stage (planning to quit within the next 6 months), and the preparation stage (planning to quit in the next month) (22, 26, 27).

With smokers in the immotive stage (immotives), the immediate goal of smoking intervention is to help them begin to think about quitting (28). The counselor's task is to raise the client's awareness of risks and problems with smoking behavior. With smokers in the precontemplation stage (precontemplators) and the contemplation stage (contemplators) who are ambivalent about changing their smoking behavior, the counselor's task is to help them make the decision to quit smoking by providing individualized information on the potential risks of smoking, and by identifying the barriers to quitting and offering potential solutions. With smokers in the preparation stage (preparators), who are ready to quit smoking and seeking cues for action, the counselor's task is to help them plan the quit

attempt by setting a quit date and providing individualized information on cognitive and behavioral strategies for quitting.

At follow-up counseling sessions, if smokers succeeded in quitting smoking, the counselor first congratulated them on their efforts to quit, then talked with them about the withdrawal symptoms and the urge to smoke, and provided information on solutions to prevent relapse. At the latter part of the follow-up sessions, if quitters experienced weight gain, the counselor advised them on methods of weight control. If smokers failed to quit smoking or relapsed, the counselor discussed with them the reasons for their behavior, and encouraged them to try to quit smoking again if they were willing.

The smoking intervention in our study was conducted by health care providers including public health nurses, nurses, physicians, nutritionists, and medical technologists. In the intervention at worksites, the number of public health nurses and nurses was the largest, about 80% of the total number. In the intervention at communities, the largest number of health care providers consisted of public health nurses, at about 70% of the total, followed by nutritionists at about 20% of the total.

Nicotine replacement therapy was not used in this study as clearly stated in the intervention protocols. Health care providers were also informed about not using nicotine replacement therapy at the training seminars.

Baseline assessment and outcome measures

A baseline assessment was scheduled in each subject 3 weeks before the initial intervention session. The subjects who attended the baseline assessment session received: 1) a screening test including systolic and diastolic blood pressure, serum cholesterol, and expired CO concentration; 2) a food survey for dietary assessment; and 3) a self-administered questionnaire survey on lifestyle and medical history, followed by an interview with the study providers. After baseline assessment, the same assessments were also conducted at the initial intervention session and the follow-up intervention sessions at 1, 2, 4, and 6 months.

In the self-administered questionnaire surveys at the baseline session, questions on smoking were asked concerning daily cigarette consumption, age at start of smoking, stage of change, Fagerstrom Test for Nicotine Dependence (FTND) score, number of quit attempts, and confidence in quitting. Questions on smoking status, daily cigarette consumption, and stage of change were also asked at the five consecutive intervention sessions.

Smoking status was validated by measurement of the expired CO concentration with a Micro Smokerlyzer (29). If the concentration of CO in expiratory air exceeded 8 ppm, the subject was classified as a smoker (30).

The main outcome measure was the CO-validated abstinence rate at 6 months. We defined smoking cessation in three different ways. Our primary definition of smoking cessation was the CO-validated point prevalence abstinence rate at 6 months. The other two outcome measures with more stringent criteria were the CO-validated two-point consecutive abstinence rate at 2 and 6 months and the four-point consecutive abstinence rate at all four follow-up sessions (at 1, 2, 4, and

Table 1 Comparison of the baseline characteristics of male and female smokers aged 20–69 years old between the intervention and the control groups

	Intervention group (N=500)	Control group (N=477)	p-value
Age (years)	44.5	44.8	0.616
Sex (%)			
Male	98.6	98.1	0.549
Female	1.4	1.9	
Stage of change (%)			
Immotive	27.3	26.9	0.828
Precontemplation	53.0	51.9	
Contemplation	12.0	14.0	
Preparation	7.7	7.1	
Age at the start of smoking (years)	20.4	20.4	0.837
Daily cigarette consumption	25.2	24.9	0.682
FTND score	4.6	4.7	0.528
Expired carbon monoxide (ppm)	26.0	25.6	0.607
Number of attempts to quit (%)			
Never quit	46.8	52.4	0.115
Quit once	20.2	20.6	
Quit 2 ~ 3 times	26.0	19.5	
Quit 4+ times	7.1	7.5	
Confidence in quitting (%)			
Almost none	55.2	58.4	0.364
Some	31.0	30.8	
A lot	13.8	10.8	

Note. FTND: Fagerstrom Test for Nicotine Dependence

Table 2 CO-validated abstinence rates at 6 months according to three different criteria

	Intervention group (N=500)	Control group (N=477)	Odds ratio	Test for significance
Abstinent at 6 months	13.6%	2.5%	5.4	p<0.001
Abstinent at both 4 months and 6 months	10.0%	1.9%	5.3	p<0.001
Abstinent at all four points (1, 2, 4, and 6 months) after initial intervention	3.6%	0.8%	4.5	p<0.005

6 months).

Subjects lost to follow-up and those whose report of cessation could not be confirmed biochemically were classified as current smokers. The percentages of those lost to follow-up at the initial intervention and the four follow-up sessions were 2.2%, 1.4%, 2.4%, 4.0%, and 4.8% in the smoking intervention group and 6.7%, 5.9%, 5.9%, 4.4%, and 6.3% in the control group, respectively. The percentage of those whose report of cessation could not be confirmed biochemically at the five consecutive sessions were 1.0%, 2.8%, 4.6%, 3.4%, and 4.6% in the smoking intervention group and 0.0%, 0.2%, 0.2%, 0.2%, and 0.6% in the control group, respectively.

Statistical analysis

Baseline characteristics by study groups were examined using chi-square for categorical variables and Student's t test for continuous variables. Associations of smoking intervention with outcome measures were examined through the use of chi-square tests. In cases in which the number of samples in a cell was small (less than 5) in 2 x n contingency tables to compare the categorical data, Fisher's exact test was used. All statistical analyses were performed using SPSS 10.0.

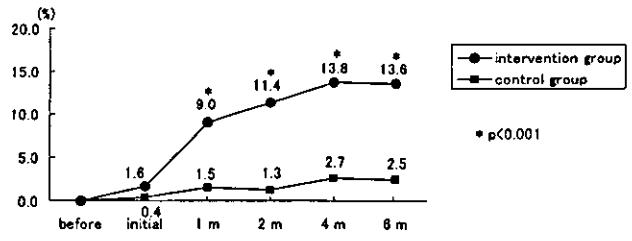
Results

Baseline characteristics of study groups

There were no differences between the intervention and control groups in baseline characteristics, including age, sex, stage of change, age at the start of smoking, daily cigarette consumption, FTND score, expired CO, number of attempts to quit, and confidence in quitting (Table 1).

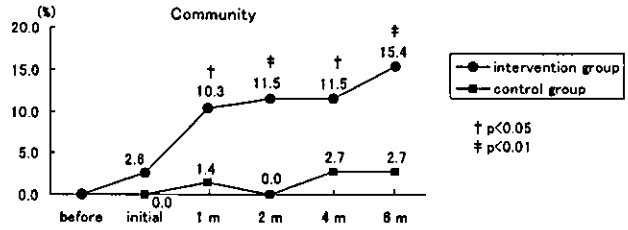
Smoking status outcomes

The point prevalence abstinence rate at 6 months in the intervention group (13.6%) was 5.4 times higher (p<0.001) than that in the control group (2.5%) (Table 2). When more stringent criteria of abstinence were applied in calculating the abstinence rate at 6 months, the differences were also significant, with odds ratios that remained almost constant as the stringency of abstinence increased.

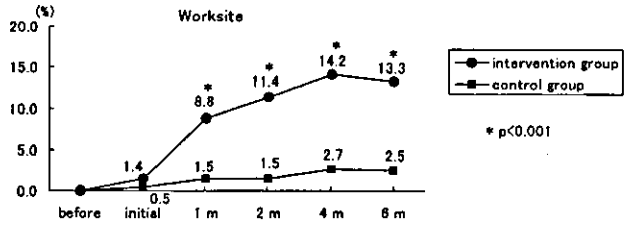


Note. Odds ratios of the abstinence rates were 6.0, 8.8, 5.1, and 5.4 at the four points from 1 to 6 months after the initial intervention, respectively.

Fig. 2 CO-validated abstinence rates by time from start of the intervention (n=500 for the intervention group, n=477 for the control group) in 72 study cites.

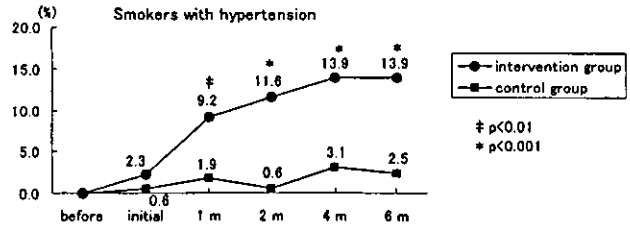


Note. Odds ratios of the abstinence rates were 7.4, ∞, 4.3, and 5.7 at the four points from 1 to 6 months after the initial intervention, respectively.

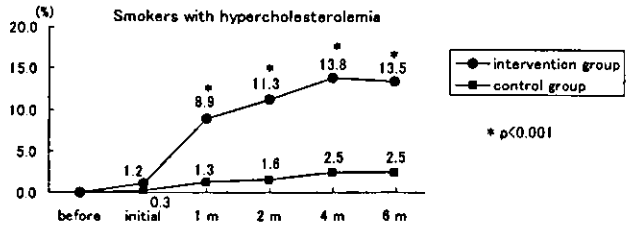


Note. Odds ratios of the abstinence rates were 5.9, 7.6, 5.3, and 5.3 at the four points from 1 to 6 months after the initial intervention, respectively.

Fig. 3 CO-validated abstinence rates by study site

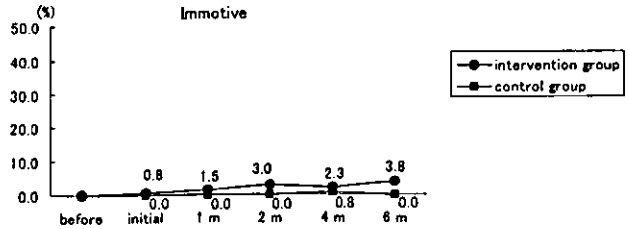


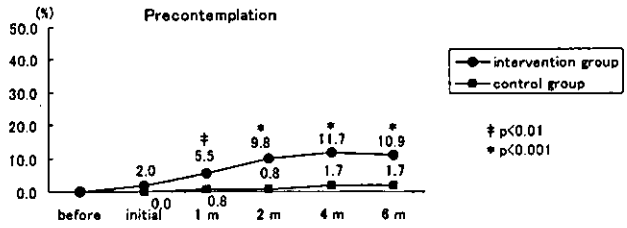
Note. Odds ratios of the abstinence rates were 4.8, 19.3, 4.5, and 5.6 at the four points from 1 to 6 months after the initial intervention, respectively.



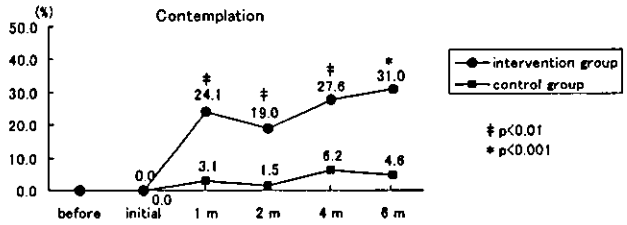
Note. Odds ratios of the abstinence rates were 6.8, 7.1, 5.5, and 5.4 at the four points from 1 to 6 months after the initial intervention, respectively.

Fig. 4 CO-validated abstinence rates by study subgroup

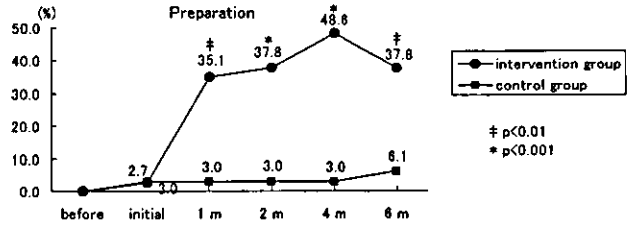




Note. Odds ratios of the abstinence rates were 6.9, 12.3, 6.9, and 6.4 at the four points from 1 to 6 months after the initial intervention, respectively.



Note. Odds ratios of the abstinence rates were 7.8, 12.7, 4.5, and 6.7 at the four points from 1 to 6 months after the initial intervention, respectively.



Note. Odds ratios of the abstinence rates were 11.7, 12.6, 16.2, and 6.2 at the four points from 1 to 6 months after the initial intervention, respectively.

Fig. 5 CO- validated abstinence rates by stage of change

The point prevalence CO-validated abstinence rates at each period from 1 month to 6 months in the intervention group were 5.1–8.8 times higher than those in the control group (Fig. 2). All the differences were significant.

The smoking outcomes at 6 months did not differ by study site (community, worksite) or by study subgroup (smokers with hypertension, smokers with hypercholesterolemia) (Figs. 3, 4). The odds ratios of point prevalence CO-validated abstinence rates at 6 months by study site were 5.7 at community ($p<0.01$) and 5.3 at worksite settings ($p<0.001$). The odds ratios were 5.6 among smokers with hypertension ($p<0.001$) and 5.4 among smokers with hypercholesterolemia ($p<0.001$).

The point prevalence CO-validated abstinence rates by stage of change at each period from 1 to 6 months in the intervention group were significantly higher than those in the control group among all stages of change except immotives, with the abstinence rates in both groups increasing as the stage of change shifted towards smoking cessation (Fig. 5). The odds ratios of the point prevalence abstinence rates at 6 months among smokers in precontemplation, contemplation, and preparation were 6.4 ($p<0.001$), 6.7 ($p<0.001$), and 6.2 ($p<0.01$), respectively.

Discussion

This is the first multisite randomized controlled study in Japan that has demonstrated the effects of a moderately intensive smoking intervention based on the transtheoretical model and implemented by trained health care providers. This study showed that repeated individual counseling to smokers unselected for their readiness to quit significantly increased by 5.4 times the point prevalence abstinence rate at 6 months. The intervention was effective despite stringent evaluation criteria at 6 months. There was a positive, consistent effect regardless of study site or subgroup. Therefore, these effects appear to be directly attributable to the intervention. Our intervention also succeeded in increasing the abstinence rates during the study period among smokers with a lower motivation to quit (precontemplators and contemplators) as well as those ready to quit (preparators). From the viewpoint of public health, this is significant because most existing smoking-cessation interventions target only motivated smokers, with few interventions having a positive effect in smokers with a lower motivation to quit.

There was no statistical difference in the abstinence rates among immotives between the intervention and control groups during the study period. This may be related to the characteristics of the immotives, who have decided to keep on smoking (26) and do not recognize smoking as a problem.

The odds ratio for smoking cessation in our study was higher compared to that in the two previous studies (11, 31), although nicotine replacement therapy was not used as part of the protocol in this study and the distribution of Japanese smokers by stage of change was shifted to a lower stage compared to smokers in the United States and other developed countries (32, 33). According to a recent meta-analysis of 18 randomized or quasi-randomized trials of the effects of individual behavioral counseling by the Cochrane Review (31), the odds ratio for smoking cessation was 1.62, which was significant (95% CI 1.35 to 1.94). This result was consistent with the review undertaken for the updated United States clinical practice guideline for treating tobacco use and dependence (11). The US review included an analysis of 58 trials and estimated the odds ratio to be 1.7 (95% CI 1.4 to 2.0) for smoking cessation with individual counseling compared to that with no intervention.

The impact of our intervention may be related to four factors. First, the intensity of our intervention was classified as moderately intensive, since it consisted of five sessions and an additional telephone follow-up contact to smokers who set a quit date (31). The intensity of the smoking intervention in previous studies varied and included a single session intervention (11, 31). In the Cochrane Review, 7 of the 18 studies used a brief

intervention with only a single session (31). There is a dose-response relationship between the intensity of the smoking intervention (e.g., number of intervention sessions and session lengths) and successful intervention outcome (11). Thus, the difference in the intensity of the interventions may account for the difference in the abstinence rates between our study and the results of the meta-analysis. Second, the duration of follow-up in our study was 6 months, which was shorter than that in previous studies. The previous studies provided outcome data with follow-up for at least 6 months or more after the initial intervention (31) or at least 5 months or more after the designated quit date (11). The shorter periods of our follow-up could yield higher abstinence rates. Since smokers are likely to relapse during follow-up periods, a short length of follow-up period is usually related to high abstinence rates. Third, the smokers in the control group had little chance to receive even a minimum smoking intervention or to quit voluntarily, because we used a "positive control group" as our control group. They, therefore, concentrated on other lifestyle changes for reducing hypertension or hypercholesterolemia. Studies designed with a "positive control" group may decrease the point prevalence abstinence rate in the control group to 2.5% at 6 months. Furthermore, in the studies included in the Cochrane Review (31), most control groups received the usual care or minimal intervention for smoking cessation by brief advice or self-help materials. This may account for the difference in results between our study and previous studies. Fourth, as the smoking prevalence in Japanese men is still higher than that in populations in other developed countries (4, 34), Japanese smokers may be more likely to quit smoking than those in other developed countries, although the level of motivation to quit smoking in Japanese smokers was lower compared to that in other developed countries (32, 33). Successful tobacco control is thought to result in a higher dependence among the remaining smokers due to selective quitting by low-dependent smokers (35). At the level of countries, the degree of nicotine dependence was negatively correlated with the prevalence of smoking (35). In addition to the level of nicotine dependence, the relative proportion of other types of "hard-core smokers" with comorbid psychological or psychiatric conditions among the total smoking population may increase with the success of tobacco control at a national level (36). Therefore, these differences in the characteristics of smokers between our study and the previous studies may extend to differences in the odds ratios.

Our study had methodological strengths. First, it was performed in a population recruited from smokers who received health check-ups in communities or worksites. Therefore, the study subjects did not actively volunteer to take part in the smoking intervention and had no special motivation to quit smoking. Second, a randomized controlled study design was used. The study groups were well matched at baseline, and follow-up rates were quite high and similar in the study groups. Fairly good adherence with the intervention was also obtained. Therefore, we consider that we could evaluate the effects of repeated individual counseling in an ideal setting. Third, we used an intention-to-treat analysis, except for two subjects who did not satisfy the inclusion criteria, with all subjects lost to follow-up being classified as smokers. As a result, a modest abstinence rate was estimated. Fourth, self-reports of smoking status were biochemically validated using expired CO. Biochemical markers for smoking are used to validate self-reports of smoking cessation in intervention studies. CO and cotinine are popular markers. Although cotinine has a higher sensitivity and specificity than CO, CO is more convenient to measure and is only modestly less useful (37, 38).

Our study also had some limitations. First, the duration of the follow-up was relatively short and limited to the treatment period. Most relapses take place within 3 months of cessation (6, 39). A point prevalence measure taken at 6 months would certainly capture the great majority of those relapse events (11). However, it is desirable to conduct a follow-up survey after an intervention-free period. Second, there were few female subjects in our study. It is uncertain whether the study results would be applicable to a female smoking population. Further research is needed to clarify the intervention effect on female smokers. Third, our smoking cessation program was effective, but moderately intensive. Considering its dissemination into health care settings, it will be difficult for health care providers to use it in routine health services such as at an outpatient clinic or health check-up setting, because the time allotted for behavioral counseling in these settings is limited. From a public health perspective, health care settings have an excellent potential to yield many quitters if effective programs are successively combined into routine health services. Therefore, further research is needed on the development of a brief smoking intervention program tailored for use in an outpatient clinic or health check-up setting, and the development of a training program for health care providers. Intervention studies are also needed to examine the effects of the programs.

In conclusion, we showed the effects of repeated individual behavioral counseling to smokers unselected for their readiness to quit. This result suggests that stage-matched individual counseling based on the transtheoretical model is effective in smokers with a lower motivation to quit, as well as in those ready to quit.

Acknowledgements

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Blood pressure response after two-step exercise as a powerful predictor of hypertension: the Osaka Health Survey

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Objective To investigate the relationship between blood pressure at 4 min after exercise using a Master's two-step and the risk for hypertension.

Design Prospective cohort study.

Setting Work site in Osaka, Japan.

Participants A total of 6557 Japanese men, aged 35–63 years with systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg, and no history of hypertension or diabetes at baseline.

Main outcome measures Blood pressure was measured by standard techniques, using 160/95 mmHg for diagnosis of hypertension. Normotension was defined as no history of hypertension, and SBP < 130 mmHg and DBP < 85 mmHg. High normal blood pressure was defined as no history of hypertension and SBP ≥ 130 and < 140 mmHg or DBP ≥ 85 and < 90 mmHg.

Results During the 63 696 person-years follow-up period, we confirmed 660 cases of hypertension. SBP and DBP after exercise were associated with an increased risk for developing hypertension. The multiple-adjusted relative risk for SBP and DBP after exercise were 1.55 per 10 mmHg (confidence interval, 1.42–1.69) and 1.55 per 10 mmHg (confidence interval, 1.42–1.69), respectively. These associations were independent of resting SBP and DBP. Even after stratifying subjects according to blood pressure at rest, SBP or DBP at 4 min after exercise was associated with an increased risk for hypertension in subjects with normotension or high normal blood pressure at rest.

Conclusions The blood pressure response after exercise with a two-step was associated with an increased risk for hypertension, independently of resting blood pressures.
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Keywords: exercise, hypertension, prospective studies, middle age, blood pressure

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See editorial commentary page 1507

Introduction

Hypertension is a well-known risk factor for coronary heart disease and stroke. As organ damage is observed even in the early stages of hypertension [1,2], early identification of hypertension and the effective management of individuals with hypertension are of great importance to prevent complications. An exaggerated blood pressure response to exercise has been reported to be one of the useful indicators for the development of hypertension [3–10]. As these studies evaluated the risk using treadmill or ergometer tests, it is difficult to perform population-based studies for primary prevention of hypertension because the cost and demands on participants' time can be excessive. The Master's double two-step exercise test has recently not been used to examine for ischemic heart disease, and has been replaced by the treadmill and ergometer test. Nevertheless, the Master's method requires only simple and inexpensive apparatus for exercise and it can be performed with less labor compared with a treadmill or ergometer bicycle test [11].

The present study prospectively examined the relationship between blood pressures after exercise using the Master's double two-step exercise test and the development of hypertension in 6557 men over a 5-year to 16-year follow-up period.

Methods

Description of the Osaka Health Survey

The Osaka Health Survey is an ongoing cohort investigation of risk factors for chronic diseases, including hypertension and diabetes. Study subjects are male employees of a gas company in Osaka, Japan. Japanese

law requires all employers to conduct annual health screenings for all employees. In addition to these annual screenings for the purpose of the study, all employees in this company aged 35 years or older undergo more detailed biennial medical check-ups and they complete questionnaires on health-related behaviors including exercise.

Selection of the study population

Between 1981 and 1991, 8410 Japanese white-collar men aged 35–63 years at entry were enrolled in the study. We excluded 1738 men because they took antihypertensive medicine or had systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, diabetes [fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l)], an oral glucose tolerance test with a 2-h post-load plasma glucose level ≥ 200 mg/dl (≥ 11.1 mmol/l), or men with history of diabetes at study entry. Therefore, the study population consisted of 6672 men.

Data collection and measurements

The biennial clinical examination consisted of a medical history, a physical examination, blood pressure measurement, anthropometric measurements, the Master's double two-step exercise test, measurements of the fasting plasma glucose levels, and questionnaires on health-related behaviors such as physical activity, smoking, and daily alcohol consumption. Trained nurses took all measurements. Participants were asked to fast for 12 h and to avoid smoking and heavy physical activity for more than 2 h before the examinations. After a 5-min rest in a quiet room, the SBP and DBP were measured in the sitting position twice at an interval of a few minutes on the right arm with a standard mercury sphygmomanometer, and the subject's blood pressure was defined as the average of two readings. A sound of Korotkov phase V was used as a DBP. The blood pressure in the follow-up period was measured in the same way. Anthropometric measurements included height and body weight, which were measured while the subject was wearing light clothing without shoes. The body mass index was calculated as the weight in kilograms divided by the height in metres squared.

The questionnaire completed by each individual related to physical activity elicited information on leisure-time physical activity and the duration of the walk to work. Leisure-time physical activity was defined as physical activity unrelated to their work. The questions about leisure-time physical activity were as follows: 'do you engage in any regular physical exercise, such as jogging, bicycling, swimming, and tennis, long enough to "work up a sweat" (lasting 30 min or more)?'; 'If yes, how many times per week?'; 'What exercise is this?'. The questions about regular physical exercise have been validated as a measure of physical exercise [12]. In the analysis, subjects were classified as engaging in regular physical exercise at least once per week or less than once per week. The question about the duration of the walk to work was as follows: 'How long does it take you to walk to this office?'.

Questions about alcohol intake included items about the type of alcoholic beverage, the weekly frequency of alcohol consumption, and the usual amount consumed daily. Alcohol intake was converted to total alcohol consumption (in millilitres of ethanol per day) using standard Japanese tables. Current and past smoking habits were classified according to the type and quantity of cigarettes smoked daily. Subjects were classified as current smokers, past smokers, or non-smokers.

The Master's double two-step exercise test was performed according to the standard protocol [11]: the 'two-step' apparatus has each of the two steps 23 cm high and is shaped like a winners' podium. The age, sex, and weight of each subject dictate the exact number of trips to be performed, and this information is indicated on the published 'two-step' chart. The double test is performed in 3 min. The subject ascends to the top of the 'two-step' and walks down the other side. This is counted as one trip. He then reverses the direction of turn at the end of each trip. When exercise has been completed, the subject immediately lies down.

Blood pressure was measured at 4 min after exercise in the supine position. The blood pressure at rest was measured as already described in a separate room.

All subjects underwent medical screenings by a physician at least once annually in this company, and the diagnosis of hypertension was made on the basis of blood pressure measurements conducted in these annual medical screenings. Hypertension was defined using World Health Organization criteria as physician-diagnosed hypertension (SBP ≥ 160 mmHg and/or DBP ≥ 95 mmHg) or taking antihypertensive medication [13].

Statistical analysis

For each man, person-years of follow-up were counted from the date at study entry to the date of diagnosis of hypertension or 1 April 1997, whichever came first. The follow-up rate was 94% of the total potential person-years of follow-up. Subjects were classified into the quintile of SBP or DBP at 4 min after exercise. The multivariate Cox proportional hazards regression model was used to evaluate the simultaneous effects of SBP or DBP at 4 min after exercise, age, body mass index, daily alcohol consumption, the level of leisure-time physical activity (regular physical exercise at least once

per week or less than once per week), the duration to walk to work, smoking status (current smokers, past smokers, or non-smokers), and the fasting plasma glucose level (impaired fasting glucose or normoglycemia). Baseline SBP and DBP at rest were not included in our primary analyses because they were highly correlated with SBP and DBP at 4 min after exercise. However, we included SBP and DBP at rest in further models to assess the effects of SBP and DBP at 4 min after exercise on the risk for developing hypertension independent of their effects on SBP and DBP at rest. The linear trends in risks were evaluated by entering indicators for each categorical level of exposure, using the median value for each category. As a reference category, we used men with the lowest level of blood pressure at 4 min after exercise. Furthermore, we examined whether blood pressure at rest modified the association between blood pressure at 4 min after exercise and the risk for developing hypertension in stratified analysis according to blood pressure at rest, such as normotension (no history of hypertension, SBP $<$ 130 mmHg, and DBP $<$ 85 mmHg) and high normal blood pressure (no history of hypertension, and SBP $\geq$ 130 and $<$ 140 mmHg or DBP $\geq$ 85 and $<$ 90 mmHg). We examined two models to analyse the risk (see Table 3 later). In model 1, each quintile 1 in the group of normal blood pressure at rest or high normal blood pressure at rest was the reference category; and in model 2, quintile 1 in the group of normal blood pressure at rest was the common reference category in the group of normal blood pressure at rest and high normal blood pressure at rest.

We calculated the 95% confidence interval (95% CI) for each relative risk and all P values are two-tailed. Statistical analyses were performed using the SPSS 9.0 software package (SPSS Inc., Chicago, Illinois, USA).

Results

Of the 6672 men eligible for this study between 1981 and 1991, 115 men who did not undergo medical check-ups during the follow-up period were excluded. The study population for analysis ultimately consisted of 6557 men (Table 1). During the 63696 person-years follow-up period between 1981 and 1997, 660 men developed hypertension.

Blood pressure at 4 min after exercise

Higher SBP at 4 min after exercise was associated with an increased risk for developing hypertension after the multiple adjustment (Table 2). The multiple-adjusted relative risk for hypertension was 11.72 (95% CI, 8.17–16.80) for men with quintile 5 (130–176 mmHg) of SBP at 4 min after exercise compared with men with quintile 1 (80–110 mmHg) of SBP at 4 min after exercise. For every 10 mmHg increase in SBP at 4 min after exercise, the multiple-adjusted relative risk for hypertension was 1.99 (95% CI, 1.86–2.12). Adjustments for other factors, including SBP and DBP at rest, did not influence our estimates of the relative risks.

Table 1 Subject characteristics

Number of subjects	6557
Age (years)	41.4 ± 6.4
Systolic blood pressure (mmHg)	121.7 ± 10.6
Diastolic blood pressure (mmHg)	67.5 ± 10.0
Body mass index (kg/m^2)	22.7 ± 2.6
Alcohol drinkers (%)	82.4
Alcohol intake (ml/day)	37.4 ± 25.9
Smokers' habits	
Lifelong non-smokers (%)	20.8
Former smokers (%)	17.6
Current smokers (%)	61.5
Regular physical exercise at least once weekly (%)	35.3
Fasting plasma glucose (mmol/l)	5.06 ± 0.5

Data are the mean ± standard deviation, except for alcohol drinkers, smokers, and regular physical exercise at least once weekly.

Higher DBP at 4 min after exercise was associated with an increased risk for developing hypertension after the multiple adjustment (Table 2). The multiple-adjusted relative risk for hypertension was 11.55 (95% CI, 7.94–16.82) for men with quintile 5 (77–137 mmHg) of DBP at 4 min after exercise compared with men with quintile 1 (8–59 mmHg) of DBP at 4 min after exercise. For every 10 mmHg increase in DBP at 4 min after exercise, the multiple-adjusted relative risk for hypertension was 2.02 (95% CI, 1.89–2.16). Adjustments for other factors, including SBP and DBP at rest, did not influence our estimates of the relative risks.

Blood pressure at 4 min after exercise in relation to blood pressure at rest

To examine whether blood pressure at rest modified the association between SBP at 4 min after exercise and the risk for hypertension, we stratified subjects according to blood pressure at rest, normotension and high normal blood pressure (model 1 of Table 3). After data were adjusted for age, body mass index, daily alcohol consumption, leisure-time physical activity, the duration of the walk to work, smoking status, and fasting plasma glucose level, among both men with normotension and high normal blood pressure at rest, higher SBP at 4 min after exercise was associated with an increased risk for hypertension ($P < 0.001$ for trend). To examine the effects of clustering risk factors, such as SBP at 4 min after exercise and blood pressure at rest on the risk for hypertension, we used men with normotension at rest and quintile 1 (80-108 mmHg) of SBP at 4 min after exercise as a reference category (model 2 of Table 3). Men with high normal blood pressure at rest and quintile 5 (137–169 mmHg) of SBP at 4 min after exercise had a multiple-adjusted relative risk of hypertension of 25.62 (95% CI, 15.22–43.12).

Table 2 Relative risks for hypertension according to blood pressures at 4 min after exercise

	Person-years of follow-up	Cases of hypertension	Age-adjusted relative risk (95% CI)	Multivariate relative risk (95% CI)[a]	Further multivariate relative risk (95% CI)[b]
Systolic blood pressure at 4 min after exercise					
Quintile 1 (80–110 mmHg)	14 086	34	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (111–117 mmHg)	14 194	74	2.49 (1.66–3.74)	2.27 (1.51–3.41)	1.53 (1.01–2.32)
Quintile 3 (118–122 mmHg)	11 448	104	4.51 (3.08–6.65)	4.17 (2.83–6.15)	2.28 (1.52–3.41)
Quintile 4 (123–129 mmHg)	12 548	165	7.00 (4.83–10.12)	6.26 (4.32–9.08)	2.66 (1.91–4.27)
Quintile 5 (130–178 mmHg)	11 440	283	13.87 (9.71–19.82)	11.72 (8.17–16.80)	4.12 (2.73–6.21)
P for trend			< 0.001	< 0.001	< 0.001
Systolic blood pressure as a continuous variable (per 10 mmHg)			2.07 (1.94–2.21)	1.99 (1.86–2.12)	1.55 (1.42–1.69)
Diastolic blood pressure at 4 min after exercise					
Quintile 1 (8–59 mmHg)	14 464	31	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (60–65 mmHg)	14 252	74	2.47 (1.62–3.78)	2.37 (1.56–3.61)	1.98 (1.30–3.01)
Quintile 3 (66–70 mmHg)	12 262	92	3.73 (2.48–5.60)	3.48 (2.31–5.23)	2.30 (1.53–3.48)
Quintile 4 (71–76 mmHg)	12 170	165	6.67 (4.54–9.79)	5.92 (4.03–8.71)	3.21 (2.16–4.77)
Quintile 5 (77–137 mmHg)	10 548	298	13.62 (9.39–19.74)	11.55 (7.94–16.82)	4.60 (3.09–6.84)
P for trend			< 0.001	< 0.001	< 0.001
Diastolic blood pressure as a continuous variable (per 10 mmHg)			2.07 (1.95–2.20)	2.02 (1.89–2.16)	1.55 (1.42–1.69)

Data are relative risks (95% confidence intervals) or *n*. [a] Adjusting for age, body mass index, alcohol consumption, leisure-time physical activity (regular physical activity at least once weekly or less than once weekly), the duration of the walk to work, smoking status (current smoker, past smoker, non-smokers), and fasting plasma glucose level (impaired fasting glucose or normoglycemia). [b] Adjusting for age, body mass index, alcohol consumption, leisure-time physical activity (regular physical activity at least once weekly or less than once weekly), the duration of the walk to work, smoking status (current smoker, past smoker, non-smokers), fasting plasma glucose level (impaired fasting glucose or normoglycemia), systolic blood pressure, and diastolic blood pressure.

Table 3 Relative risks for hypertension according to resting blood pressures and blood pressures at 4 min after exercise

	Model 1		Model 2	
	Age-adjusted relative risk (95% CI)	Multivariate relative risk (95% CI)[a]	Age-adjusted relative risk (95% CI)	Multivariate relative risk (95% CI)[a]
Quintile of systolic blood pressure at 4 min after exercise				
Normal blood pressure at rest (n = 4657)				
Quintile 1 (80–108 mmHg)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (109–114 mmHg)	2.86 (1.63–5.01)	2.58 (1.47–4.54)	2.82 (1.61–4.94)	2.61 (1.49–4.59)
Quintile 3 (115–119 mmHg)	4.63 (2.69–7.96)	3.99 (2.31–6.88)	4.52 (2.63–7.78)	4.04 (2.35–6.96)
Quintile 4 (120–124 mmHg)	6.41 (3.76–10.92)	5.67 (3.32–9.69)	6.25 (3.67–10.63)	5.72 (3.36–9.75)
Quintile 5 (125–176 mmHg)	11.01 (6.61–18.35)	9.24 (5.52–15.47)	10.67 (6.40–17.77)	9.34 (5.59–15.59)
P for trend	< 0.001	< 0.001		
High normal blood pressure at rest (n = 1900)				
Quintile 1 (90–121 mmHg)	1.00 (reference)	1.00 (reference)	7.30 (4.14–12.84)	6.79 (3.85–11.96)
Quintile 2 (122–126 mmHg)	1.92 (1.29–2.85)	1.83 (1.23–2.72)	14.24 (8.31–24.39)	12.54 (7.31–21.52)
Quintile 3 (127–131 mmHg)	2.05 (1.39–3.02)	1.98 (1.34–2.92)	15.17 (8.92–25.80)	13.45 (7.89–22.93)
Quintile 4 (132–136 mmHg)	3.25 (2.24–4.71)	3.06 (2.11–4.45)	24.31 (14.45–40.91)	20.90 (12.38–35.28)
Quintile 5 (137–169 mmHg)	4.29 (2.98–6.16)	3.83 (2.64–5.54)	32.33 (19.33–54.06)	25.62 (15.22–43.12)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001
Quintile of diastolic blood pressure at 4 min after exercise				
Normal blood pressure at rest (n = 4657)				
Quintile 1 (8–58 mmHg)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 2 (59–63 mmHg)	3.72 (2.03–6.80)	3.49 (1.91–6.40)	3.71 (2.03–6.80)	3.51 (1.92–6.42)
Quintile 3 (64–68 mmHg)	3.69 (2.02–6.75)	3.43 (1.87–6.27)	3.69 (2.02–6.74)	3.49 (1.91–6.39)
Quintile 4 (69–73 mmHg)	6.10 (3.41–10.90)	5.47 (3.05–9.78)	6.09 (3.41–10.87)	5.58 (3.12–9.98)
Quintile 5 (74–137 mmHg)	12.83 (7.39–22.27)	10.66 (6.11–18.60)	12.85 (7.41–22.30)	11.11 (6.39–19.31)
P for trend	< 0.001	< 0.001		
High normal blood pressure at rest (n = 1900)				
Quintile 1 (15–64 mmHg)	1.00 (reference)	1.00 (reference)	7.88 (4.22–14.73)	7.33 (3.92–13.70)
Quintile 2 (65–70 mmHg)	1.34 (0.86–2.13)	1.35 (0.85–2.14)	10.59 (5.76–19.47)	9.76 (5.30–17.97)
Quintile 3 (71–75 mmHg)	2.31 (1.53–3.51)	2.22 (1.46–3.37)	18.40 (10.34–32.71)	16.01 (8.98–28.55)
Quintile 4 (76–81 mmHg)	3.17 (2.13–4.74)	3.03 (2.02–4.53)	25.05 (14.26–44.02)	21.54 (12.22–37.95)
Quintile 5 (82–101 mmHg)	5.19 (3.53–7.65)	4.84 (3.27–7.17)	41.17 (23.67–71.60)	34.47 (19.74–60.19)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001

Data are relative risks (95% confidence intervals) or *n*. In model 1, each quintile 1 in the group of normal blood pressure at rest or high normal blood pressure at rest was the reference category; and in model 2, quintile 1 in the group of normal blood pressure at rest was the common reference category in the group of normal blood pressure at rest and high normal blood pressure at rest. [a] Adjusting for age, body mass index, alcohol consumption, leisure-time physical activity (regular physical activity at least once weekly or less than once weekly), the duration of the walk to work, smoking status (current smoker, past smoker, non-smokers), and fasting plasma glucose level (impaired fasting glucose or normoglycemia).

To examine whether blood pressure at rest modified the association between DBP at 4 min after exercise and the risk of hypertension, we stratified subjects according to blood pressure at rest, normotension and high normal blood pressure (model 1 of Table 3). Among both men with normotension and high normal blood pressure at rest, higher DBP at 4 min after exercise was associated with an increased risk of hypertension ($P < 0.001$ for trend). When we used men with normotension at rest and quintile 1 (8–58 mmHg) of DBP at 4 min after exercise as a reference category (model 2 of Table 3), men with high normal blood pressure at rest and quintile 5 (82–101 mmHg) of DBP at 4 min after exercise had a multiple-adjusted relative risk of hypertension of 34.47 (95% CI, 19.74–60.19).

Discussion

Our prospective data demonstrated that both SBP and DBP at 4 min after exercise using the Master's double two-step exercise test were associated with an increased risk for developing hypertension in a dose-dependent manner. These associations persisted after age, body mass index, daily alcohol consumption, leisure-time physical activity, duration of the walk to work, smoking status, fasting plasma glucose level, and resting SBP and DBP were taken into account.

Although 'exaggerated' blood pressure response was shown to be the predictor of new-onset hypertension in the previous study, even mild elevation of blood pressure response to exercise could also predict new-onset hypertension in the present study. In this present study, as the blood pressure response was shown to have a linear association with the risk of hypertension, all ranges of elevation of SBP and DBP can provide a prediction of the risk of hypertension for subjects. Furthermore, the combination of blood pressure at rest and blood pressure response at 4 min after exercise could more powerfully identify the risk of hypertension than one of them alone. It has been shown that the blood pressure response to exercise is a predictor of hypertension, but in most studies the data were not adjusted for any confounding factors or the subjects consisted of a small population [3–8]. Two large prospective population-based studies, adjusting for several confounding factors and using the treadmill exercise test, analyzed the association between blood pressure response during and after exercise separately in men and women and new-onset hypertension [9,10]. In the CARDIA study, they concluded that exaggerated BP response to exercise was associated with an increase of SBP, but that it was not significantly associated with new-onset hypertension [9]. In the Framingham Heart study, they demonstrated that exaggerated DBP during exercise and SBP and DBP after exercise is the predictor of new-onset hypertension in men; and that exaggerated DBP during exercise is positively related to new-onset hypertension in women [10]. These are partly consistent with our data in men.

The treadmill or the ergometer used in all previous studies is expensive and complicated to use. The methods using such apparatus may be appropriate for small numbers of subjects in high-risk approaches, but not for large numbers in population-based approaches. On the contrary, the two-step exercise test is less expensive and more easily performed than the treadmill or the ergometer exercise test, and it is a suitable method for population-based approaches.

The mechanisms by which the blood pressure response to exercise predicts the development of hypertension have not been clarified. The structure of the systemic resistance vessels or sympathetic adaptation may have been changed before the appearance of hypertension [14–17].

Subjects in the present study underwent medical screening by a physician at least once annually, and cases of hypertension were diagnosed by the physician. Therefore, the data were not biased by a misdiagnosis of hypertension. All subjects were registered employees of a single company and thus are not representative of the general Japanese population. However, the relative homogeneity of the cohort may actually enhance the study's internal validity; because of the relatively uniform educational background and socioeconomic status of the men in this cohort, these variables were unlikely to represent confounding factors. There may be some concern about complications such as ischemic attack and arrhythmia during this procedure. However, if the detailed questionnaires cover the history of chest pain, the risk of cardiovascular accidents could be minimal even without electrocardiographic monitoring during the two-step exercise test. Recently, the definition of hypertension was recommended to change [18,19]. However, we began this study about 20 years ago when we used the old definition of hypertension according to the World Health Organization [13]. We dared to use the old one to unify the criteria of hypertension.

Both SBP and DBP at 4 min after exercise using the Master's double two-step exercise test were associated with an increased risk for hypertension, independently of resting blood pressures. This labor-saving and inexpensive method is useful for predicting the risk of hypertension in large-scale populations.

References

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