Determining the effects of exercise after smoking cessation therapy completion on continuous abstinence from smoking: Japanese study protocol

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Abstract

Background: Despite a steady world-wide decline over recent decades, the smoking rates remain high in developed countries. In Japan, the smoking rate is 30% for men and 10% for women. Based on these rates, Japan's smoking population is estimated to be 18.8 million (14.06 million for men and 4.74 million for women). The rate of success for smoking cessation has recently improved due to the widespread availability of drug therapy; however, the success rate for quitting smoking one year after beginning therapy is only around 50%. Previous studies have demonstrated that exercise can relieve mental stress during continuous abstinence from smoking and curb smoking resumption. To date, no large-scale randomized controlled trials have examined the effects of exercise on smoking cessation. The present study aims to determine the effects of implementing an intervention in the form of exercise instruction after smoking cessation therapy completion on continuous abstinence from smoking. Methods: This is a multicenter, prospective, parallel-group, randomized controlled trial in Japan. We will enroll 300 individuals visiting a smoking cessation clinic (over three months) who have abstained from smoking in the second month after their initial visit as potential participants. Participants will not habitually exercise and will consent to participate. Participants will be randomly assigned to the exercise intervention group or control group. The intervention group will receive instruction on exercises that can be incorporated into their daily lives. The control group will be followed during the standard smoking cessation support program. The primary endpoint will be the continuous abstinence rate, and secondary endpoints will be weight, blood pressure, exhaled carbon monoxide concentration, psychological state, and blood test results. These indices will be compared between the intervention and control groups, with follow-up periods of nine months for both groups. Discussion: By examining the effects of exercise instruction after completion of a 12-week smoking cessation therapy, this study should yield quality information that can be used to develop protocols to improve the continuous abstinence rate and inhibit weight gain after smoking cessation therapy.

Background

Smoking is a major health issue in Japan

Smoking is a major health issue that is associated with the development of malignancies and respiratory diseases, as well as the development of cardiovascular diseases such as cerebrovascular disease and ischemic heart disease. The Japan Collaborative Cohort Study of 95,000 Japanese participants indicated that smoking increases the risk of death due to cardiovascular disease by 1.6–2.0-fold. Moreover, numerous Japanese cohort studies have reported that the population attributable risk of cardiovascular disease due to smoking is approximately 20% for men and >5% for women\(^1\). In Japan, the current smoking rate is 30% for men and 10% for women. Despite a steady decline over the last few decades, smoking rates remain high in developed countries\(^2\). In Japan, >1 million people suffer from smoking-related conditions such as malignancies, cerebrovascular diseases, or cardiovascular diseases, and the medical expenses attributed to smoking (and passive smoking) are estimated to be as high as 1.49 trillion Yen\(^3\).
Quitting smoking promotes public health

Quitting smoking has numerous preventive effects, such as an improved prognosis for cardiovascular disease\(^4\). Furthermore, symptoms of chronic bronchitis improve one to two months after smoking cessation; patients with mild-to-moderate chronic obstructive pulmonary disease have improved pulmonary function one year after quitting smoking; risk of coronary artery disease decreases within two to four years; patients with a history of coronary artery disease have a 35% lower risk of recurrence or death; former smokers have a rate of diminished pulmonary function equivalent to that of nonsmokers after five years. Moreover, individuals aged 40–59 years who attempt to quit smoking have a significantly lower risk of incurring massive medical expenses in the future compared with continuing smokers, and individuals attempting to quit smoking have a reduced risk of massive medical expenses similar to that of lifetime nonsmokers\(^5\). Thus, actively promoting smoking cessation should significantly inhibit the development of cardiovascular disease and greatly reduce medical expenses.

Smoking cessation aids lack sufficient long-term effectiveness

Many people smoke again within one year after the initial consultation to the smoking cessation clinic, even if they quit smoking successfully. However, if they could continue quitting smoking for more than one year, fewer people would smoke again. Since the term of the smoking cessation therapy at clinics in Japan is 3 months, it is necessary to follow up for the remaining 9 months after the 3-month therapy (Total of one year). In April 2006, the Japanese national health insurance started to include smoking cessation treatment. The national health insurance covers treatment for 3 months. The rate of success for individuals quitting smoking has recently improved due to the widespread availability of drug therapy at smoking cessation clinics. Since its introduction to the Japanese market in 2008, varenicline tartrate, an oral smoking cessation aid, increased the success rate of smoking cessation treatment immediately after completion to approximately 70%. However, the continuous abstinence rate dropped to approximately 50% one year after therapy initiation\(^6\). This highlights the urgent requirement for medical personnel to provide support to individuals attempting to quit smoking to help them avoid resuming the habit.

Exercise can improve the rate of quitting smoking

Exercise can relieve mental stress, during continuous abstinence from smoking, and curb smoking resumption\(^7\). A systematic review of the efficacy of exercise on curbing the resumption of smoking showed that exercise helped to curb smoking resumption in 12 out of 14 studies\(^8\). Similarly, a meta-analysis also indicated that exercise, as part of a cardiac rehabilitation program, significantly reduced the smoking rate\(^9\). Active incorporation of exercise may improve the rate of quitting smoking.

Exercise can inhibit weight gain after quitting smoking

Weight gain typically occurs after smoking cessation. A recent meta-analysis reported an average weight gain of 4.7 kg one year after quitting smoking\(^10\). Weight gain after smoking cessation may lead to the resumption of smoking, and preventing weight gain is a vital aspect of smoking cessation support.
Japanese smoking cessation programs using drug therapy provide instruction primarily in the form of diet and cognitive behavioral therapy; however, several studies have reported that such programs may not result in adequate weight control\textsuperscript{11,12}. Explaining specific forms of exercise to individuals who are attempting to quit smoking and do not exercise may help to improve the success rate for quitting smoking and help manage subsequent weight control.

Several intervention studies have examined the effects of combining exercise instruction with drug therapy. In a systematic review of 20 studies (including 5870 participants) examining the effectiveness of exercise interventions, the largest of the 20 studies was an Internet trial of 2318 individuals. Of the 20 studies, 8 had fewer than 30 subjects, 9 included only women, and 1 included only men. Although 4 of 20 studies reported adequate sample size and the effectiveness of exercise in smoking cessation, the effect of exercise instruction on smoking cessation remains unclear\textsuperscript{13}.

**Study objective**

The present study aims to determine the effects of exercise instruction provided after completion of a 12-week smoking cessation therapy (covered by the national health insurance) on continuous abstinence from smoking.

**Methods/design**

**Study design**

This will be a multicenter intervention study with a centralized enrollment (open-label, prospective, parallel-group randomized controlled trial). Three institutions participated in this study (Kyoto Medical Center, Kumamoto Red Cross Hospital, Komoro Kosei Hospital). The two facilities are located on the west side of Japan and one on the east side.

**Sample size**

The previous study showed, the addition of exercise instruction increased the odds ratio of successful smoking cessation 3-fold after six months. Of the 306 people screened by phone in this study, eligibility for study participation was determined and eventually consented from 40 people. After the two-week run-in period, 26 individuals were randomized to the intervention and control groups, including 13 women and 12 men (excluding one participant who developed lung cancer)\textsuperscript{14}. Assuming that the addition of exercise instruction after the anticipated conclusion of drug therapy is estimated to increase the odds ratio 2-fold after nine months, and the standard therapy group is estimated to successfully quit smoking at a rate of 50%, then a power of $1-\beta = 0.8$ and a type I error of $\alpha = 0.05$ would indicate that the minimum sample size required would be 134 participants per group, making a total of 268 participants. Assuming a dropout rate of 10% during the study, a randomized intervention study with 150 participants per group will require a total of 300 participants\textsuperscript{25}. Study participants will be allocated to one of two groups: an exercise intervention group, who will receive additional exercise instruction in addition to the standard instruction,
and a control group, who will receive the standard instruction. Participants will be followed for nine months after enrollment. The target number of participants to be enrolled is 300 (150 in each group).

**Participants**

Study participants will include individuals who have abstained from smoking during the last month while undergoing a standard smoking cessation therapy (three months after the initial visit).

**Inclusion criteria**

Individuals who have abstained from smoking during the last month while undergoing a standard smoking cessation therapy (three months after the initial visit) and fulfilling the following will be included: (1) individuals who do not exercise (those who do not answer “I have continued to exercise 30 min a day at least twice a week for over a year” in a questionnaire); (2) age 20–75 years; (3) individuals who agree to the purpose of this study and who provide written consent.

**Exclusion criteria**

Individuals fulfilling any of the following items will be excluded: (1) those prohibited from exercising by their physician (individuals for whom exercise is contraindicated); (2) those who would have difficulty exercising due to conditions, such as an orthopedic disorder, neuromuscular disease, or peripheral vascular disease; (3) pregnant women; (4) in-patients or residents of a facility; (5) individuals whose participation in this study has been deemed inappropriate by their primary physician.

**Discontinuation criteria**

This study will be discontinued in the event of any of the following: (1) continuation of the study is not feasible due to adverse events; (2) the study cannot be continued due to participant withdrawal or withdrawal of consent; (3) participants meet the exclusion criteria or are deemed ineligible after enrollment; (4) females who are pregnant; (5) marked noncompliance; (6) the study itself is discontinued; (7) if an investigator otherwise deems that continuing this study is not feasible.

**Ethical considerations**

All procedures will be carried out in accordance with the ethical standards of the facilities involved and those of domestic research councils and in accordance with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards.

**Study protocol**

An overview of the proposed study protocol is shown in Fig. 1.

**Allocation**
Participants will be centrally allocated using the electronic data capture (EDC) system of the University Hospital Medical Information Network.

After written consent is obtained from participants who meet the selection criteria, the lead investigator will verify that the participants meet all of the eligibility criteria and none of the exclusion criteria, and their information will be registered in the EDC system. After registration, the EDC system will assign patient numbers that do not include a patient’s personal information. Immediately after entry, the EDC system will randomly assign participants to one of two groups (exercise intervention or control groups) via dynamic allocation.

**Allocation and allocation adjustment factors**

Confounding factors [age, sex, number of cigarettes smoked per day, Fagerstrom test for nicotine dependence (FTND) score, and self-rating depression scale (SDS) score will be adjusted between the two groups via registration in the EDC system. Participants will be randomized by minimization, which is a method of dynamic allocation.

**Intervention**

**Acquisition of data at the beginning of the study**

Patient characteristics (sex, age, medical history, history of present illness, alcohol consumption, type of medications taken, and psychological state), blood chemistry (white blood cell count, red blood cell count, hemoglobin level, hematocrit, platelet count, fasting blood glucose level, and total cholesterol [T-cho], high-density lipoprotein cholesterol [HDL-cho], and triglyceride [TG] levels), and measurements (height, weight, blood pressure, and concentration of exhaled carbon monoxide) at the beginning of the study will be examined. Smoking status (number of years of smoking, number of cigarettes smoked, tobacco dependence screener score, FTND score, age the individual started smoking, smokers in the family, and number of previous attempts to quit smoking) will be recorded during an interview at the initial visit to the smoking cessation clinic.

**Exercise intervention group**

After completion of the smoking cessation therapy, participants will be informed of the significance of active exercise while attempting to quit smoking. Participants will receive an activity tracker for the duration of the study and will be instructed on exercises to increase and maintain their physical activity as part of their daily lives.

**Setting of exercise goals**

During the follow-up, participants will individually record their daily step count, level of activity, and weight. A regular follow-up will be conducted approximately 2–4 times over nine months. During regular follow-up, participants will receive feedback based on their individual logs, exercise goals will be adjusted, and will be encouraged to maintain their amount of physical activity and control their weight. Exercise instruction will
be provided in accordance with an exercise instruction manual compiled under the supervision of a certified fitness instructor and a certified cardiac rehabilitation specialist.

**Standard therapy (control) group**

The control group will be followed during the course of the standard smoking cessation program. After completing the smoking cessation therapy, participants will not be actively advised to exercise; therefore, further exercise instruction will not be provided.

Participants will receive an activity tracker immediately after completing the smoking cessation therapy and eight months after beginning the study. They will return the tracker one month later in both instances. Regular follow-up will be performed 2–4 times over nine months. During regular follow-up, it will be confirmed whether smoking cessation continues, and participants will not receive active instructions for exercise.

**Items studied during the study and follow-up periods**

The study will begin on the day the participant is given an activity tracker. The follow-up period will be nine months for both groups. In addition to face-to-face meetings, follow-up may be conducted by mail, telephone, or online. Participant status will be ascertained at the beginning of the study and one, eight, and nine months after beginning the study.

Continuous abstinence from smoking, psychological state, type of medications taken, blood chemistry (white blood cell count, red blood cell count, hemoglobin level, hematocrit, platelet count, fasting blood glucose level, and T-cho, HDL-cho, and TG levels), and measurements (height, weight, blood pressure, and concentration of exhaled carbon monoxide) will be assessed in both groups after nine months.

**Items observed and studied**

**Primary endpoint:** Continuous abstinence rate

An individual is deemed to have continuously abstained from smoking when they report that they have not smoked in the past week when interviewed and if the concentration of exhaled carbon monoxide is \( \leq 7 \text{ ppm} \).

**Secondary endpoints:** Changes in metabolic indices (height, weight, blood pressure, exhaled carbon monoxide concentration, red blood cell count, white blood cell count, hemoglobin level, hematocrit, platelet count, fasting blood glucose level, and T-cho, HDL-cho, and TG levels) and changes in an individual's psychological state (SDS score, depressive tendencies, and patient activation measure score).

**Analysis**

**Analysis set**
The two groups (exercise intervention and control groups) will be compared based on the intention-to-treat principle. All data for the metabolic indices and psychological states of the participants in each group obtained upon enrollment and nine months after enrollment will be analyzed. Individuals who quit smoking for a prolonged period will be similarly analyzed, and those who resume smoking will be excluded. Quitting smoking for a prolonged period is defined as not smoking for nine months since enrolling in the study (determined via an interview) and having exhaled carbon monoxide levels of ≤7 ppm. The continuous abstinence rate is defined as the proportion of participants who abstain from smoking with respect to the total number of participants in each group.

Items analyzed and analytical methods

The characteristics of the participants in both groups will be described statistically. Changes in the metabolic index and psychological state from the enrollment until nine months after enrollment will be compared between the two groups. The distribution of individual indices at the baseline and nine months after enrollment will be determined for the two groups, and a t-test or a Wilcoxon rank-sum test will be performed. For factor adjustment, analysis of covariance, multiple regression, or logistic regression will be used. In addition, Fisher’s exact test will be used to compare the continuous abstinence rate in the two groups. The level of significance will be ≤0.05. A two-tailed alpha of 5% and a two-sided 95% confidence level will be used. The statistical analysis will be performed by a statistician.

Early termination of this study

The trial will be discontinued in the event of any of the following situations: (1) if the trial cannot be safely conducted due to serious adverse events; (2) if it is not possible to enroll the planned sample size; or (3) if it is not feasible to continue the study.

Discussion

Exercise has various effects, including osteoporosis prevention due to improvements in cardiovascular, musculoskeletal, and pulmonary function, as well as increased muscle mass, obesity prevention due to fat reduction and increased muscle mass, dyslipidemia prevention due to reduced serum TG levels and increased HDL-cho levels, diabetes prevention due to the alleviation of insulin resistance, and hypertension prevention due to improved vascular endothelial function and reduced blood pressure. Exercise also relieves stress and is an effective treatment for depression as it alleviates anxiety. The 2013 Physical Activity Guidelines to Promote Health were formulated in Japan in 2013 and included exercise as an important component.

Weight gain is common after quitting smoking and impairs glucose tolerance, which may lead to smoking resumption. In this study, simple and safe exercises that can be easily performed by individuals who have gained weight after quitting smoking will be performed in accordance with a cardiac rehabilitation program. Participants will record their weight and step count, which should increase their self-efficacy. This study combines smoking cessation therapy and exercise therapy. If the study shows that...
exercise instruction improves the continuous abstinence rate, widespread implementation of the intervention is anticipated to reduce the public smoking rate, help to promote health, reduce medical expenses, and greatly benefit the public.

**Trial status**

This study protocol is the first version since December 10, 2015. Recruitment began on March 30, 2016, and the expected recruitment completion date is December 2019. At the time of manuscript submission, recruitment for this study is ongoing.

**Abbreviations**

EDC, electronic data capture; FTND, Fagerstrom test for nicotine dependence; SDS, self-rating depression scale; T-cho, total cholesterol; HDL-cho, HDL cholesterol; TG, triglyceride.

**Declarations**

**Ethics approval and consent to participate**

Informed written consent was obtained from all participants. The Ethical Review Board, National Hospital Organization, Kyoto Medical Centre approved the study protocol. Central ethical approval has been confirmed from The Ethical Review Board, National Hospital Organization, Kyoto Medical Centre (approval no. 14-090) and we will not begin recruiting at other trial centers until local ethical approval has been obtained.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that there are no conflicts of interest.

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**Author’s contributions**
YO, MK, KU, HI, SS, AM, MT, SN, YK, YK, and KH conceived and designed the study. YO, MK, YT, and KH acquired the data. YO drafted the manuscript and critical revision was performed by MK and KH. All authors reviewed and approved the final manuscript.

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Figures
Figure 1

Overview of the study protocol.
| STUDY PERIOD | Screening | Allocation | Visit 2 | Visit 3 | Close-out |
|--------------|-----------|------------|---------|---------|-----------|
|              | -4-0 weeks | 0 week     | 1 month | 8 months | 9 months |
| ENROLMENT:   |           |            |         |         |           |
| Eligibility screen | X         |            |         |         |           |
| Informed consent | X         |            |         |         |           |
| Allocation   |           | X          |         |         |           |
| INTERVENTIONS: |           |            |         |         |           |
| intervention group (Exercise guidance) |   | X          | X       |         |           |
| control group |           |            |         |         |           |
| ASSESSMENTS: |           |            |         |         |           |
| Physical examination | X         |            |         | X       |           |
| Laboratory examination |   | X          | X       |         |           |
| Self-rating Depression Scale |   | X          | X       |         |           |
| Questionnaire |           |            |         |         |           |
| Smoking status | X         |            |         | X       | X         |
| Exhaled carbon monoxide | X         |            |         |         | X         |

Figure 2

The schedule of enrolment, interventions, and assessments.

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