Meta-analysis Study for One Year Effects of a Nicotine Patch

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Smoking is a risk factor for various disorders. Strategies have been established in various countries. To support smoking cessation, the nicotine patch was developed, and various clinical studies have been conducted to evaluate its effects. However, its long-term effects remain to be clarified. We conducted a meta-analysis based on the results of randomized, comparative studies, with high-level scientific reliability, to investigate the long-term efficacy of the nicotine patch. We reviewed the 1-year results of nicotine-patch use in 18 studies using a fixed effect model via the PubMed and Cochrane Library. The combined odds and risk ratios were 1.753 [95% confidence interval (CI): 1.520–2.021] and 1.594 (95% CI: 1.406–1.806), respectively. In the nicotine-patch group, the success rate for smoking cessation was significantly higher than that in the nicotine-patch-free group. Furthermore, the combined risk difference was 5.33% (95% CI: 3.99–6.66%); nicotine-patch prescription increased the rate at which smoking cessation was successfully achieved, by approximately 5%. The number of persons requiring treatment after 1 year was 19. Based on the results of RCTs, we calculated the combined odds ratio, combined risk ratio, combined risk difference, and number needed to treat (NNT). The nicotine patch significantly increased the success rate for smoking cessation after 1 year. The possibility of publication bias cannot deny completely because the funnel plots were not symmetrical.

Key words —— smoking cessation, meta-analysis, nicotine replacement therapy, nicotine patch, number needed to treat

INTRODUCTION

Smoking is a risk factor for various disorders. Strategies have been established in various studies. To support smoking cessation, the nicotine patch was developed, and various clinical studies have been conducted to evaluate its effects. A review of these studies has been published in the Cochrane Library,[1)] demonstrating marked effects. However, the review involves short- to long-term follow-up and comparative studies in which no placebo was prescribed in the control group, with low-level scientific reliability. In addition, some studies evaluated continuous smoking cessation from its start until the survey as successful (no lapses), whereas others regarded smoking cessation at the time of the survey as successful. Therefore, the long-term effects of the nicotine patch have not always been scientifically demonstrated.

In this study, we investigated its long-term efficacy via a meta-analysis.

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MATERIALS AND METHODS

The procedures for the literature search are shown in Fig. 1. We employed PubMed in addition to articles quoted in "Nicotine replacement therapy for smoking cessation" in the Cochrane Library,[1)] and searched the literature using the following formula: "nicotine patch" [All fields] AND "smoking cessation" [All fields] AND Randomized Controlled Trial [ptyp] AND (English [lang] OR Japanese [lang]) AND "humans" [MeSH Terms].

Our criteria for literature selection included a randomized controlled trial (RCT) design, comparison between active and placebo patches, and the description of the number (or rate) of persons achieving smoking cessation after 1 year. However, concerning the timing "after 1 year," many studies (n = 17) reported results 1 year after the start of treatment, and we investigated them; however, we also employed another study presenting results 1 year after the end of treatment.

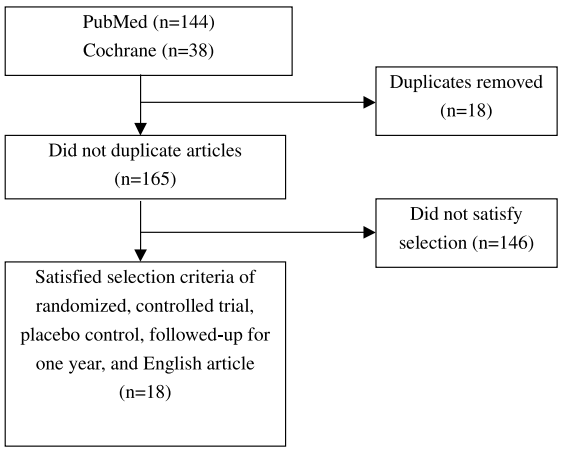

Fig. 1. Flow Chart of Literature Search and Meta-analysis

In these studies, we extracted the numbers of subjects and those achieving smoking cessation after 1 year in active- and placebo-patch groups. Some studies reported only the number of persons achieving smoking cessation after 1 year; therefore, when both the number of persons achieving continuous smoking cessation and that of persons achieving it after 1 year were published, we employed the latter. Although the definition of smoking cessation varied among the studies, many studies confirmed it based on the concentration of carbon monoxide in expired air (less than 10 ppm).

The number of subjects in the selected literature markedly differed; we cannot simply review these data. We calculated the combined odds ratio using the Mantel-Haenszel method, a standard meta-analysis method as a fixed effect model. We also calculated the combined risk ratio and difference using the general variance-based method. Furthermore, the uniformity of the data on the odds and risk ratios as well as risk differences was examined using the Q statistic for Homogeneity (Q-H) method. The publication bias was investigated, as described by Begg. Funnel plotting was performed.[2,3] The number needed to treat (NNT) was calculated using the following formula: NNT = 1/risk difference.[3,4] $P < 0.05$ was regarded as significant.

RESULTS

We selected 144 reports from PubMed and 38 articles from the Cochrane Library.[1] Of these 182 reports, 18 were duplicated, and 146 did not meet the selection criteria (Fig. 1). A summary of 18 selected articles is shown in Table 1. In most studies, the subjects' ages were over 18 years. In one study, the subject was pregnant. The existence of Japanese persons as study subjects was not described. The doses of the nicotine patch immediately after the start of treatment ranged from 15 to 30 mg/day. The treatment period ranged from 8 to 24 weeks.

Of the 18 extracted studies, 3 were large-scale RCTs (Nos. 2, 7, and 14) involving more than 1000 persons, and 2 were RCTs (Nos. 4 and 12) involving less than 100 persons. In many studies, the intervention-to-control group ratio was 1 : 1. However, in 2 studies, the ratio was 2 : 1 (Nos. 7 and 10).

The data published in the 18 studies are shown in Table 2. The intervention and control groups consisted of 4385 (632+3753) and 3629 (338+3291) persons, respectively. The success rates for smoking cessation were 14.41% [95% confidence interval (CI): 13.37–15.45%] and 9.31% (95% CI: 8.37–10.26%) in the intervention and control groups, respectively, according to simple calculation. The difference was 5.10%. These rates were weighted with the respective variance's inverse, and the estimated values were 13.05% (95% CI: 12.06–14.04%) and 7.64% (95% CI: 6.78–8.49%), respectively. The difference was 5.41%.

The odds ratio in each study with its 95% CI and combined odds ratio, which was calculated using the Mantel-Haenszel method, also with its 95% CI, are shown in Fig. 2. The minimum and maximum odds ratios were 0.943 and 5.829, respectively. The 25%, 50%, and 75% tile values were 1.476, 1.732 (median), and 2.757, respectively. In one study (No. 8), the odds ratio was less than 1. In 7 studies (Nos. 4, 6, 7, 9, 11, 13, and 15), it exceeded 2. Furthermore, the 95% CI strided across 1 in 7 studies (Nos. 1, 5, 8, 12, 16, 17, and 18). The combined odds ratio was 1.753 (95% CI: 1.520–2.021). The null hypothesis of "odds ratio = 1" was rejected ($p < 0.0001$). When the uniformity was tested (Q-H), the χ^2 value was 23.34 ($p = 0.138$); the uniformity hypothesis was not rejected. The Kendall correlation coefficient, calculated using Begg's method, was 0.1895 ($p = 0.272$). The hypothesis that there was no publication bias was not rejected. The Funnel plot for the odds ratios is shown in Fig. 3. The plot was a symmetrical funnel type in which the left area was lacking.

The risk ratio in each study with its 95% CI and combined risk ratio, also with its 95% CI, are shown in Fig. 4. The minimum and maximum risk ratios were 0.950 and 5.297, respectively. The 25%,

Table 1. Characteristics of Studies on Nicotine-patch Therapy in Review

No.	Trial	Population	Interventions
1	Jorenby, D. E., *et al.* (1999)[5]	Participants aged ≥ 18 years who smoked ≥ 15 cigarettes per day.	Participants were divided into 4 groups: placebo tablet, active patch, bupropion, and active patch + bupropion.
2	Tonnesen, P., *et al.* (1999)[6]	Participants aged 20–70 years who smoked > 14 cigarettes per day for at least 3 years.	Participants were divided into 5 groups: placebo and either standard- or high-dose nicotine patch (15 and 25 mg daily, respectively), each given for 8 or 22 weeks.
3	Daughton, D., *et al.* (1998)[7]	Participants aged 19–65 years who smoked at least 20 cigarettes per day.	Participants were divided into two groups: placebo and active patches, for 10 weeks.
4	Perng, R. P., *et al.* (1998)[8]	Participants who smoked more than 20 cigarettes per day for more than a year.	Participants were divided into two groups: placebo and active (30 mg) patches, for 6 weeks.
5	Killen, J. D., *et al.* (1997)[9]	Participants aged ≥ 18 years.	Participants were divided into 4 groups: placebo and active (21 mg) patches, each with or without video-enhanced, self-help treatment.
6	Paoletti, P., *et al.* (1996)[10]	Participants aged ≥ 20 years who smoked ≥ 10 cigarettes per day for at least 3 years.	Participants were divided into two groups by plasma cotinine levels, and then were subdivided into two groups: placebo and active patches.
7	Stapleton, J. A., *et al.* (1995)[11]	Participants aged 20–60 years who smoked ≥ 15 cigarettes per day.	Participants were divided into 3 groups: placebo patch, active (15 mg) patch with standard dose, and active (15 mg) patch with dose increase pm (10 mg).
8	Kornitzer, M., *et al.* (1995)[12]	Participants aged 20–65 years who smoked ≥ 10 cigarettes per day for at least 3 years.	Participants were divided into 3 groups: placebo patch + placebo gum, active (15 mg) patch + placebo gum, and active (15 mg) patch + active gum.
9	Hurt, R. D., *et al.* (1994)[13]	Participants aged 20–65 years who smoked ≥ 20 cigarettes per day for the past year.	Participants were divided into two groups: placebo and active (22 mg) patches.
10	Russell, M. A., *et al.* (1993)[14]	Participants aged 20–60 years who smoked ≥ 15 cigarettes per day.	Participants were divided into 3 groups: placebo patch, active (15 mg) patch with standard dose, and active (15 mg) patch with dose increase pm (10 mg).
11	Tonnesen, P., *et al.* (1991)[15]	Participants aged ≥ 20 years who smoked ≥ 10 cigarettes per day for at least 3 years.	Participants were divided into two groups: placebo and active (15 mg) patches.
12	Hurt, R. D., *et al.* (1990)[16]	Participants aged 20–65 years who smoked ≥ 10 cigarettes per day for at least the preceding year.	Participants were divided into two groups: placebo and active (30 mg) patches.
13	Sachs, D. P., *et al.* (1993)[17]	Participants aged ≥ 18 years who smoked ≥ 10 cigarettes per day for at least 3 years.	Participants were divided into two groups: placebo patch and active (15 mg) patch.
14	Imperial Cancer Research Fund General Practice Research Group (1994)[18]	Participants aged 25–64 years who smoked ≥ 15 cigarettes per day.	Participants were divided into 4 groups: active (21 mg) patch + pamphlets, active (21 mg) patch + booklet, placebo patch + pamphlet, and placebo patch + booklet.
15	Richmond, R. L., *et al.* (1997)[19]	Participants in which of the mean age was 42 years, mean cigarette consumption was 29 cigarettes per day, and mean duration of smoking was 24 years.	Participants were divided into two groups: placebo and active (21 mg) patches.
16	Wisborg, K., *et al.* (2000)[20]	Participants who were healthy, pregnant women and smoked ≥ 10 cigarettes per day.	Participants were divided into two groups: placebo and active (15 mg) patches.

Table 1. Continued

No.	Trial	Population	Interventions
17	Glavas, D., *et al.* (2003)[21]	Participants aged ≥ 18 years who smoked ≥ 1 cigarette per day for at least 12 months.	Participants were divided into two groups: placebo and active (21 mg for heavy smokers, 14 mg for medium smokers, and 7 mg for light smokers) patches.
18	Campbell, I. A., *et al.* (1996)[22]	Participants aged 18–75 years who smoked > 1 cigarette per day within one week.	Participants were divided into two groups: placebo and active (28 mg for high and 14 mg for low Fagerstrom scores) patches.

Table 2. Summary Table

Study number	Success in the intervention group	Success in the control group	No change in the intervention group	No change in the control group	Total number	Odds ratio	Risk ratio	Success rate in the intervention group	Success rate in the control group	Difference
1	40	25	204	135	404	1.059	1.049	0.164	0.156	0.008
2	110	71	605	643	1429	1.647	1.547	0.154	0.099	0.054
3	27	16	157	169	369	1.816	1.697	0.147	0.086	0.060
4	9	3	21	29	62	4.143	3.200	0.300	0.094	0.206
5	20	14	83	90	207	1.549	1.442	0.194	0.135	0.060
6	17	5	43	55	120	4.349	3.400	0.283	0.083	0.200
7	77	19	723	381	1200	2.136	2.026	0.096	0.048	0.049
8	19	10	131	65	225	0.943	0.950	0.127	0.133	−0.007
9	33	17	87	103	240	2.298	1.941	0.275	0.142	0.133
10	37	10	363	190	600	1.937	1.850	0.093	0.050	0.043
11	16	3	129	141	289	5.829	5.297	0.110	0.021	0.090
12	9	8	22	23	62	1.176	1.125	0.290	0.258	0.032
13	28	10	85	97	220	3.195	2.651	0.248	0.093	0.154
14	91	65	751	779	1686	1.452	1.403	0.108	0.077	0.031
15	43	18	110	134	305	2.910	2.373	0.281	0.118	0.163
16	19	18	105	108	250	1.086	1.073	0.153	0.143	0.010
17	13	9	43	47	112	1.579	1.444	0.232	0.161	0.071
18	24	17	91	102	234	1.582	1.461	0.209	0.143	0.066

50%, and 75% tile values were 1.413, 1.622 (median), and 2.287, respectively. In one study (No. 8), the risk ratio was less than 1. In 6 studies (Nos. 4, 6, 7, 11, 13, and 15), it exceeded 2. Furthermore, the 95% CI strided across 1 in 10 studies (Nos. 1, 3, 4, 5, 8, 10, 12, 16, 17, and 18). The combined risk ratio was 1.594 (95% CI: 1.406–1.806). The null hypothesis of "risk ratio = 1" was rejected ($p < 0.0001$). When the uniformity was tested (Q-H), the χ^2 value was 22.51 ($p = 0.166$); the uniformity hypothesis was not rejected. The Kendall correlation coefficient, calculated using Begg's method, was 0.2026 ($p = 0.240$). The hypothesis that there was no publication bias was not rejected. The Funnel plot for the risk ratios is shown in Fig. 5. The plot was a symmetrical funnel type in which the left area was lacking.

The risk difference in each group with its 95% CI and combined risk difference, also with its 95% CI, are shown in Fig. 6. The minimum and maximum risk differences were −0.667% and 20.625%, respectively. The 25%, 50%, and 75% tile values were 3.48%, 5.99% (median), and 12.24%, respectively. In one study (No. 8), the risk difference was a negative value. In 5 studies (Nos. 4, 6, 9, 13, and 15), it exceeded 10%. Furthermore, the lower limit of the 95% confidence interval was a negative value in 8 studies (Nos. 1, 3, 5, 8, 12, 16, 17, and 18). The combined risk difference was 5.33% (95% CI: 3.99–6.66%). The null hypothesis of "risk difference = 0" was rejected ($p < 0.0001$). When the uniformity was tested (Q-H), the χ^2 value was 28.23 ($p = 0.042$); the uniformity hypothesis was rejected. The Kendall correlation coefficient, calculated us-

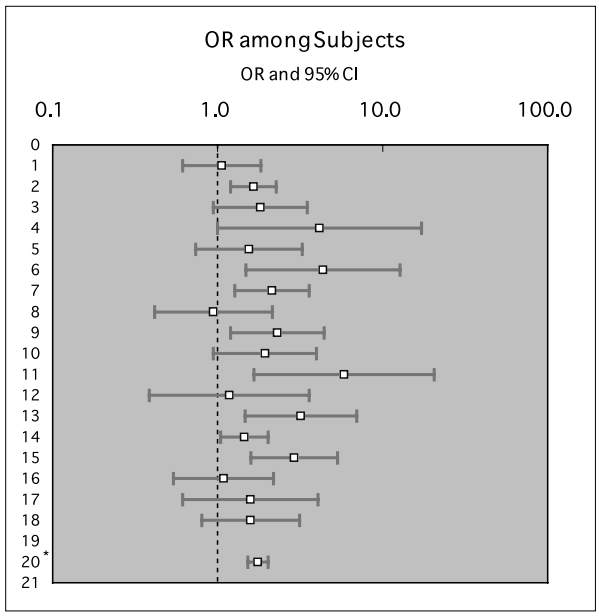

Fig. 2. Odds Ratios (OR) and 95% CI of Each Study and Combined OR and 95% CI
*Combined OR and 95% CI are shown on line 21 in the figure.

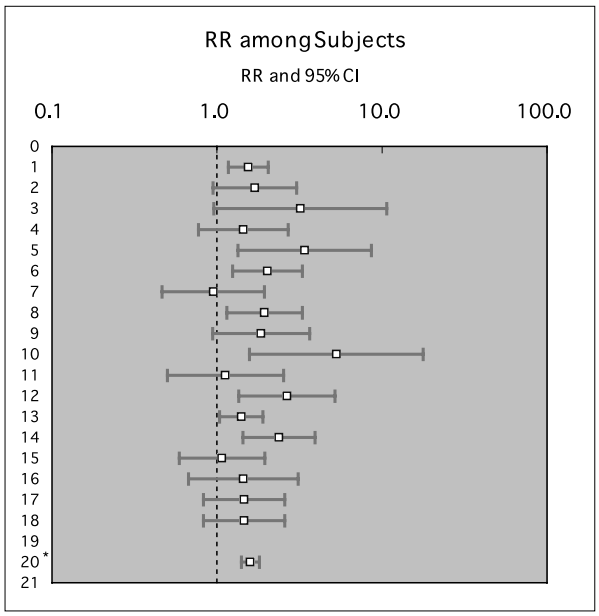

Fig. 4. Risk Ratios (RR) and 95% CI of Each Study and Combined RR and 95% CI
*Combined RR and 95% CI are shown on line 21 in the figure.

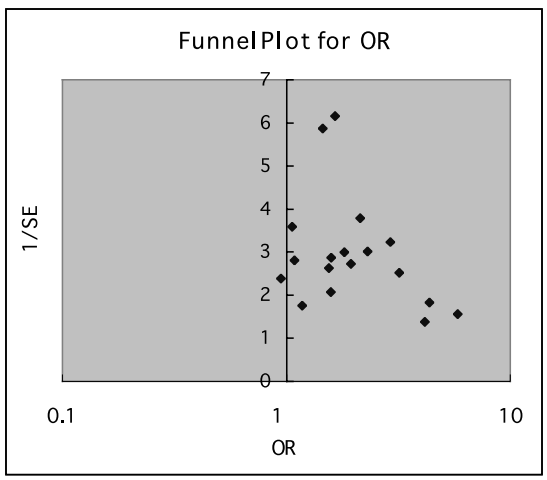

Fig. 3. Funnel Plot for OR

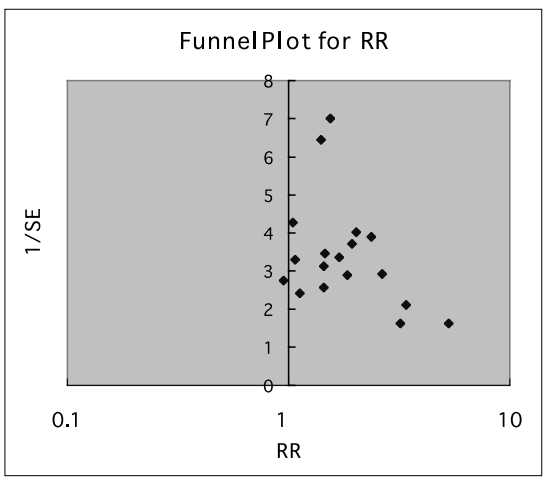

Fig. 5. Funnel Plot for RR

ing Begg's method, was 0.2810 (p = 0.103). The hypothesis that there was no publication bias was not rejected. The Funnel plot for the risk differences is shown in Fig. 7. The plot was a symmetrical funnel type in which the left area was lacking.

The minimum and maximum numbers of persons requiring treatment were 4.8 and 130.1, respectively. In one study (No. 8), the success rate for smoking cessation was higher in the control group. In 8 studies (Nos. 1, 3, 5, 8, 12, 16, 17, and 18), the lower limit of the 95% confidence interval was a negative value. Based on the combined risk difference, the number of persons requiring treatment was calculated as 18.8 (95% CI: 15.0–25.1, Table 3).

DISCUSSION

This study is the first meta-analysis demonstrating a significant nicotine-patch-related increase in the success rate for smoking cessation after 1 year and the risk difference. Smoking is a risk factor for various disorders, and strategies have been established in various countries. To support smoking cessation, the nicotine patch was developed, and various clinical studies have been conducted to evaluate its effects. A review of these studies has been published in the Cochrane Library,[1)] demonstrating marked effects. However, the review involves short- to long-term follow-up and comparative stud-

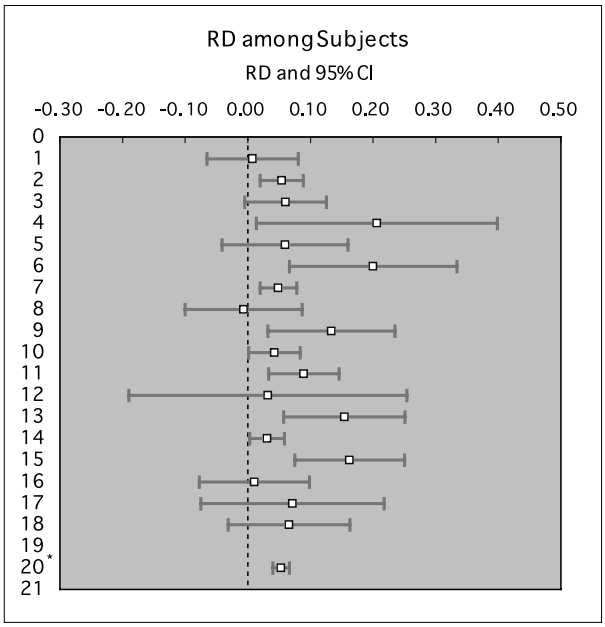

Fig. 6. Risks Differences (RD) and 95% CI of Each Study and Combined RD and 95% CI

*Combined RD and 95% CI are shown on line 21 in the figure.

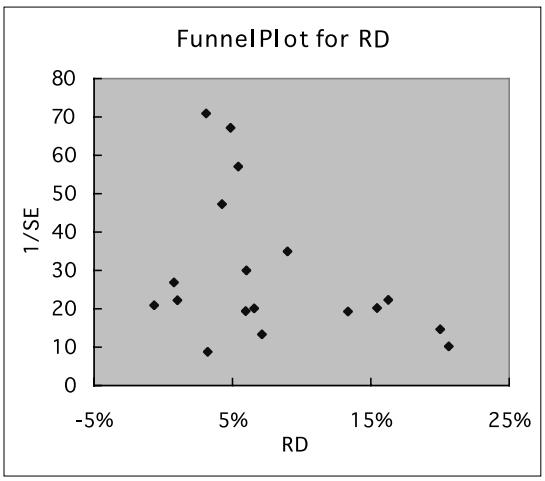

Fig. 7. Funnel Plot for RD

ies in which no placebo was prescribed in the control group, with low-level scientific reliability. In addition, some studies evaluated continuous smoking cessation from its start until the survey as successful, whereas others regarded smoking cessation at the time of the survey as successful. Therefore, the long-term effects of the nicotine patch have not always been scientifically demonstrated.

The success rates for smoking cessation were 14.41% and 9.31% in the intervention and control groups, respectively, according to simple calculation. However, these rates were weighted with the respective variance's inverse, and the estimated values were 13.05% and 7.64%, respectively. In the two groups, the values calculated simply were slightly higher. The differences were because individually conducted surveys were regarded as a large-scale survey on simple calculation, whereas the reliability of each survey was reflected in the weighted method.

Table 3. Number Needed to Treat (NNT)

Study No.	NNT	95% CI for NNT	
		Lower limit	Upper limit
1	130.1	12.4	−15.3
2	18.4	11.3	49.9
3	16.6	8.0	−201.0
4	4.8	2.5	73.2
5	16.8	6.2	−24.3
6	5.0	3.0	15.1
7	20.5	12.8	51.1
8	−150.0	11.5	−10.0
9	7.5	4.3	31.3
10	23.5	11.9	956.9
11	11.2	6.9	29.9
12	31.0	3.9	−5.3
13	6.5	4.0	17.4
14	32.2	17.0	291.2
15	6.1	4.0	13.4
16	96.4	10.2	−12.9
17	14.0	4.6	−13.3
18	15.2	6.1	−31.8
20	18.8	15.0	25.1

According to simple calculation, the difference in the success rate for smoking cessation between the intervention and control groups was 5.10%. The 95% CIs in the two groups were not overlapped, suggesting the efficacy of the nicotine patch. In the method in which the ratios in the two groups were weighted with the number of persons investigated, the difference in the success rate for smoking cessation was 5.41%. The 95% CIs in the two groups were not overlapped. In addition, the combined risk difference was 5.33% (95% CI: 3.99–6.66%), the CI did not stride across 0% , suggesting the marked effects of the nicotine patch. These results suggest that the nicotine patch increases the success rate for smoking cessation after 1 year by approximately 5% in comparison with the control group. The 5% of this risk difference seemed to be small. However, it is not a small value at all when the success rate for smoking cessation of the control group is about 8%.

Meta-analysis is classified into a fixed effect model analysis, in which the status of data is analyzed, and random effect model analysis, in which the future is predicted based on the data. However,

the purpose of this study was to investigate the status of the data presented in each article; therefore, we calculated the combined odds ratio, risk ratio, and risk difference using various procedures of a fixed effect model. The odds ratio represents the ratio of an odds value of the success rate for smoking cessation (success-to-failure ratio) in the intervention group to that in the control group. The combined odds ratio was 1.753 (95% CI: 1.520–2.021); the CI significantly exceeded 1. The risk ratio represents the ratio of the success rate for smoking cessation in the intervention group to that in the control group. The combined risk ratio was 1.594 (95% CI: 1.406–1.806); the CI significantly exceeded 1. The risk difference represents variation in the success rate for smoking cessation between the intervention and control groups. As described above, the combined risk difference was 5.33% (95% CI: 3.99–6.66%); the CI significantly exceeded 0%. Concerning the risk difference, the hypothesis regarding data uniformity was rejected, and, for analysis, we employed the DerSimonian-Laird method as a random effect model. In our results, the combined risk difference was 6.17% (95% CI: 4.12–8.22%); the CI significantly exceeded 0%. Thus, from several perspectives, the efficacy of the nicotine patch was demonstrated.

According to the Cochrane Library,[1)] a review of 38 studies involving 6 months to 1 year of follow-up after nicotine-patch prescription showed that the combined odds ratio was 1.81 (95% CI: 1.63–2.02). Wu *et al.*[23)] reviewed 70 studies involving follow-up after 1 year of nicotine-replacement therapy (NRT) with the nicotine patch or other materials, and reported that the combined odds ratio was 1.71 (95% CI: 1.55–1.88). In 23 of the 70 studies, with the nicotine-patch method, the combined odds ratio was 1.63 (95% CI: 1.41–1.89), which was consistent with our results (1.753, 95% CI: 1.520–2.021).

In this study, the success rate for smoking cessation after 1 year in the nicotine-patch prescription group was 13–14%. According to the Cochrane Library, the success rate for smoking cessation in the nicotine-patch prescription group was approximately 15%, slightly higher than the value in our study. This may have been because studies published in the Cochrane Library employed the success rate after 6 months, whereas we employed that after 1 year.

Concerning the long-term effects of the nicotine patch, some studies conducted follow-up for a long period, more than 1 year.[21,24)] As the number of studies was small, meta-analysis was not performed. However, Glavas *et al.*[21)] performed nicotine-patch therapy for 3 weeks, and examined the success rate regarding smoking cessation 5 years after the start of treatment. In the placebo- and nicotine-patch groups, the success rates were 14.3 and 17.8%, respectively, with no significant difference. Yudkin *et al.*[24)] conducted nicotine-patch therapy for 12 weeks, and reported that the success rates for smoking cessation after 8 years in the placebo- and nicotine-patch groups were 10.9 and 10.3%, respectively. Considering the results of these studies and our results (slight effects after 1 year), the efficacy of the nicotine patch may persist beyond 1 year, but its long-term effects remain to be clarified. As few studies have conducted more than 1-year follow-up, long-term follow-up should be performed.

In this study, we selected RCTs in which a placebo was prescribed in the control group. Concerning smoking cessation, placebo effects may be marked. Therefore, in this study, placebo effects were adequately considered. As our criteria for selecting the literature included English and Japanese articles, some other articles were not included. Since we selected RCTs, most studies involved residents in Europe and the United States. It is controversial whether the results apply to Japanese persons, as the social background regarding smoking in Japan differs from that in Europe and the United States; further investigation is needed.

Concerning publication bias, a hypothesis that there was no publication bias in the odds ratio, risk ratio, nor risk difference was not rejected on a test using Begg's method ($\alpha = 0.05$). However, the Funnel plots for the odds ratio, risk ratio, and risk difference (Figs. 3, 5, and 7) were classified as a symmetrical funnel type in which the left area was lacking, suggesting the possibility of publication bias. Briefly, marked effects of the nicotine patch have been published, but, possibly, its less marked effects were not presented.

The number of persons requiring nicotine-patch therapy, which was calculated based on the combined risk difference, was 18.8 (95% CI: 15.0–25.1). This indicates that the minimum and maximum 95% CIs for the number of persons requiring treatment after 1 year (number of treated persons required to achieve smoking cessation in 1 person) were 15 and 25, respectively, with a representative value of 19. This value was first obtained in this study, and may be a parameter used in future studies

regarding the effects of the nicotine patch on smoking cessation.

In conclusion, based on the results of RCTs, we calculated the combined odds ratio, risk ratio, and risk difference, and NNT. These values were 1.753 (95% CI: 1.520–2.021), 1.594 (95% CI: 1.406–1.806), and 5.33% (95% CI: 3.99–6.66%), respectively. The nicotine patch significantly increased the success rate for smoking cessation after 1 year. Furthermore, the number of persons requiring treatment after 1 year (number of treated persons required to achieve smoking cessation in 1 person) was 19.

The possibility of publication bias cannot deny completely because the funnel plots were not symmetrical. In several surveys involving a period of several years, the efficacy of the nicotine patch was not confirmed. Therefore, its long-term effects should be further investigated.

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