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SMOKING CESSATION AFTER GENOTYPE NOTIFICATION: PILOT STUDIES OF SMOKERS EMPLOYED BY A MUNICIPAL GOVERNMENT AND THOSE ON NAGOYA UNIVERSITY MEDICAL CAMPUS

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ABSTRACT

In order to examine whether a notification of genotypes related to a susceptibility to smoking has any influence on an intention to quit, a pilot study was conducted for 61 smokers out of 66 municipal government employees who attended an anti-smoking seminar in November 2005 or January 2006 (MG), and for 46 smokers (employees and students) on a medical campus (Tsurumai Campus) of Nagoya University (TC), who voluntarily responded to the study enrollment notice in August 2006. They were genotyped for four polymorphisms; *GSTM1* null/present, *GSTT1* null/present, *NQO1* C609T, and *CYP1A1* Ile/Val. For the MG group, their smoking habits were ascertained three times; at enrollment, one month later just before the genotype notification by in-house mail, and three months after the notification. The smoking cessation rate was 8.2%. For the TC group, their genotypes were mailed two weeks after blood sampling. The follow-up questionnaire three months after the genotype notification found a 10.9% cessation rate. Their stage of smoking cessation significantly improved after the genotype notification. This study demonstrated that the effects of the genotype notification in this context of smoking cessation were moderate and less remarkable than might have been expected. Although the genotype notification in TC improved their stage of readiness to quit smoking, additional skills or tools in support of the notification are needed to achieve a higher cessation rate.

Key Words: Smoking cessation, Genotype notification, *GST, NQO1, CYP1A1*

INTRODUCTION

Tobacco smoking is one of the most preventable causes of various diseases. A large-scale population-based cohort study in Japan showed that 29% of male and 3% of female cancers might have been prevented by the avoidance of smoking.[1)] Those statistics indicate that about 90,000 people could have avoided cancer by quitting smoking.

Though most people now recognize the health risks from tobacco, the recent prevalence of current smokers has remained at 45.8% in males and 13.8% in females.[2)] Accordingly, the

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mere awareness of those risks is not sufficient to induce smoking cessation. Generally speaking, changing smoking behavior is so difficult that educational programs on the harmful effects of smoking have only had a limited impact. The development of effective tobacco control measures is essential to reduce smoking rates and subsequent disease risks.

Personalized genotype notification to smokers may provide a powerful motivation to quit. To date, two randomized controlled trials in the United States, one trial at a cancer hospital in Japan, and two case series studies at Japanese worksites have been reported.[3-7] While no effect was observed in one of the randomized controlled trials,[4] the other two trials seemed to be promising, a significantly elevated cessation rate among low income African-American smokers, and an improved (but insignificant as a whole) rate among first-visit outpatients at a Japanese cancer hospital.

The present study aimed to examine the effects of a genotype notification among smokers in two different groups. One was among municipal government employees (MG) who attended a seminar against smoking, and the other was among smokers including employees and students on a medical campus (Tsurumai campus) of the Nagoya University School of Medicine (TC). The notified genotypes were: *glutathione S-transferase M1* (*GSTM1*) null/present, *GSTT1* null/present, *NAD(P)H: quinone oxidoreductase 1* (*NQO1*) C609T, and *cytochrome P450 1A1* (*CYP1A1*) Ile/Val. The *GSTM1 null type*, *GSTT1 null type*, and *NQO1 609TT* genotypes lack the enzyme activity needed to detoxify carcinogenic compounds in tobacco smoke. On the other hand, *CYP1A1 Val/Val* exhibits high enzyme activity to oxygenate tobacco smoke carcinogens, resulting in their metabolic activation. Therefore, smokers with the above genotypes are considered to be at higher risk of tobacco-related cancers.[8-10]

MATERIALS AND METHODS

Although this study was conducted among two different populations under different settings, the overall purposes and framework were similar. The MG group was comprised of municipal government employees at an annual health checkup including managers, officials, technicians, manual workers, and nurses, who stated they were smokers. The government's health management section made a list of newly employed smokers and those with a history of smoking for more than 45 pack-years. Listed were 71 smokers under 40 years and 114 smokers over 40 years, respectively (Table1). An educational session was provided for newly employed smokers on November 29, 2005, and for heavy smokers on March 9, 2006. A total of 66 smokers attended the 3-hour sessions, which explained the hazardous effects of smoking and relevant genetic susceptibility. An 8-page color pamphlet on polymorphism genotypes as well as a study description and questionnaire on smoking habits was given to all participants. The questionnaire included a disease history, Fagerström test for nicotine dependence (FTND), and stage to quit smoking. Of 66 smokers who attended the sessions, 61 agreed to participate in the study. After a written informed consent form was provided, blood was drawn in the session room.

The subjects of the TC group were employees and students on the medical campus of the Nagoya University School of Medicine. Forty-six smokers participated in this study of their own accord. The enrollment was conducted on two occasions (August 29 and 30, 2006). The enrollment was similar to that for the MG group as described above, except that subjects were individually briefed concerning the hazardous effects of smoking and related genetic susceptibility one by one for several minutes after blood was drawn. The blood samples were anonymized with numbers matched to the participants, and genotyped at the Department of Preventive Medicine/Biostatistics and Medical Decision Making of the Nagoya University Graduate School of Medicine.

Table 1 Age and sex distributions of smokers: municipal government employees (MG), and employees and students in medical campus (Tsurumai campus; TC)

	MG	TC
Listed	185	–
Attended	66	–
Participated	61	46
Males	52	38
Females	7	8
No answer	2	0
Age		
20–29	18	16
30–39	5	10
40–49	3	13
50–59	35	6
60–69	0	1

As for the MG group, the genotypes sealed in an envelope were sent to the health management section of the municipal government one month after each session, and then sent to each participant by in-house mail within a week. The TC group genotypes were sent directly to participants by regular mail or by in-house mail from the study office of the Department of Preventive Medicine of Nagoya University. A questionnaire to be completed before opening the envelope was attached only for the MG group. The staff had no knowledge of the genotypes of individual participants. Three months after the genotype notification, a follow-up questionnaire probing their current smoking status was distributed and collected through the health management section (the MG group) or directly from the study office of the Department of Preventive Medicine (the TC group). In the MG group, anonymized questionnaires at enrollment, one month later just before genotype notification, and at the follow-up three months after genotype notification were sent to the study office. The questionnaires were matched with the subject numbers put on the cover sheet of each one.

The stage of smokers concerning smoking cessation was classified into four categories; unconcerned, concerned but have no intention to quit, intend to quit but not in one month, and intend to quit smoking within one month.[11] The middle two categories were combined into "no intention to quit" in the analysis. Anxiety and regret were evaluated by two questions. One was "How did you feel when notified of your genotype?" The choices were: 1) relieved, 2) nothing, 3) became slightly anxious, 4) became very anxious, 5) became anxious enough to feel disturbed in my daily life ("seriously anxious" in Table 4), and 6) cannot remember the genotype or forgot how I felt ("not remember" in Table 4). The other question concerned satisfaction/regret for genotype testing in the expression shown in Table 4. FTND consisted of eight questions for the MG group and six for the TC group. FTND scores were classified into three categories, 0–3; low, 4–6; intermediate, and 7–11; high.

GSTM1, *GSTT1*, *NQO1* C609T and *CYP1A1* Ile/Val were genotyped by polymerase chain reaction with confronting two-pair primers.[12] All statistical analyses in this study were performed using STATA statistical software, version 7 (STATA Corporation Inc., College Station, TX, USA). Characteristics of both quitters and non-quitters were compared by a χ^2 statistic. Changes in stage of smoking cessation after genotype notification were evaluated by a Wilcoxon signed-rank test.

A probability value of $p<0.05$ was considered significant.

This study was approved by the Ethics Committee of the Nagoya University School of Medicine (Approval numbers: 98 issued on December 5, 2003, and 98-3 issued on July 11, 2006).

RESULTS

The participants of the MG group numbered 61 smokers (52 males, 7 females, and 2 non-responders) out of 66 attendants. The questionnaire distributed before the genotype notification found that the great majority understood genotype testing as explained via the lecture and pamphlet either completely (37.7% or partly 50.9%). Among 46 subjects (38 males, 8 females) of the TC group, 30 participants responded to the questionnaire.

As shown in Table 2, five smokers in the MG group had already quit smoking before the genotype notification. Among five quitters, two who quit before the genotype notification continued to abstain, while the other three resumed smoking. Another three smokers quit after the genotype notification, resulting in five quitters at the follow-up three months after the notification. Out of five quitters as a whole at the follow-up, one had no concern about quitting at enrollment (16.7% of 6), and the other four had no intention to quit but felt concern about quitting (7.8% of 51). One of the five quitters was a female. After the genotype notification, the stage to smoking cessation improved in eleven smokers, was unchanged in forty-one, and worsened in seven, though two smokers failed to respond about their stage. The changes were not statistically significant.

Table 2 Stage of smokers at the enrollment, one month later just before genotype notification, and at three months after genotype notification.

	MG* (n=61)	TC* (n=46)
At enrollment		
No concern	6	5
No intention	51	37
Wish to quit	3	4
No answer	1	0
Just before the genotype notification		
Not quit	55	–
No concern	4	–
No intention	46	–
Wish to quit	5	–
No answer	1	–
Quit	5	–
Three months after the notification		
Not quit	56	25
No concern	7	1
No intention	45	20
Wish to quit	3	3
No answer	1	1
Quit	5	5

* The abbreviations are the same as in Table 1.

In the TC group, five smokers had quit smoking three months after the notification. Among them, three stated in the follow-up questionnaire that they had quit before the genotype notification, and two had quit after. Another two smokers who had quit before the genotype notification

Table 3 Characteristics of quitters and non-quitters*[1]

Characteristics		MG*[2]			TC*[2]		
		Quit (n=5)	Not quit (n=56)	p	Quit (n=5)	Not quit (n=41)	p
Age	20–29	4	14		2	14	
	30–39	0	5		3	7	
	40–49	0	3	0.08	0	13	0.18
	50–59	1	34		0	6	
	60–69	0	0		0	1	
Sex	Males	4	48		4	34	
	Females	1	6	0.56	1	7	0.87
	No answer	0	2		0	0	
FTND score*[3]	Low	3	8		2	13	
	Intermediate	2	32	**0.03**	3	24	0.75
	High	0	15		0	4	
	No answer	0	1		0	0	
Stage at the enrollment	No concern	1	5		0	5	
	No intention	4	47	0.66	3	34	**0.027**
	Wish to quit	0	3		2	2	
	No answer	0	1		0	0	
Genotype	GSTM1						
	Present	0	25	0.052	3	20	0.64
	Null	5	31		2	21	
	GSTT1						
	Present	3	33	0.96	1	22	0.16
	Null	2	23		4	19	
	NQO1						
	609CC	0	20		1	14	
	609CT	2	27	**0.04**	3	21	0.81
	609TT	3	9		1	6	
	CYP1A1						
	IleIle	2	30		0	26	
	IleVal	3	24	0.73	5	15	**0.007**
	ValVal	0	2		0	0	
Sensitive genotypes*[4]	0	0	11		0	10	
	1	2	27	0.42	3	18	0.58
	2	2	15		2	11	
	3	1	3		0	2	

*[1] Participant failed to return the follow-up questionnaire in TC group was treated as a non-quitter.
*[2] Abbreviations are the same as in Table 1.
*[3] FTND with eight questions for MG group and six for TC group. Low; 0–3, intermediate; 4–6, high; 7–11.
*[4] *GSTM1 null* type, *GSTT1 null* type, *NQO1 609TT*, *CYP1A1 Val/Val* were considered sensitive genotypes.

Table 4 Quitters at the follow-up three months after genotype notification according to anxiety and regret for attending genotype testing.

	MG*	TC*
How did you feel when your genotypes were notified?		
Relieved	0/16 (0.0)	1/7 (14.3)
Nothing	2/22 (9.1)	1/9 (11.1)
Slightly anxious	3/18 (16.7)	3/11 (27.3)
Very anxious	0/0 (0.0)	0/1 (0.0)
Seriously anxious	0/0 (0.0)	0/0 (0.0)
Not remember	0/3 (0.0)	0/2 (0.0)
No answer	0/2 (0.0)	0/0 (0.0)
Are you satisfied with or do you regret the genotype testing?		
Satisfied	4/37 (10.8)	2/17 (11.8)
Rather Satisfied	1/18 (5.6)	2/12 (16.7)
Rather regret	0/3 (0.0)	0/0 (0.0)
Regret	0/1 (0.0)	1/1 (100)
No answer	0/2 (0.0)	0/0 (0.0)

* The abbreviations are the same as in Table 1.

had resumed smoking. Out of five quitters at the follow-up, three had no intention to quit smoking at enrollment (10.0% of 30), and the other two wished to quit (28.6% of 7). One of five quitters was a female. The stage to smoking cessation improved in nine smokers, remained unchanged in nineteen and worsened in one. One smoker who returned the questionnaire didn't respond to queries about his stage. The stage to smoking cessation in the TC group significantly improved after the genotype notification.

Table 3 shows the characteristics of quitters and non-quitters of both the MG and TC groups. The MG group FTND score and *NQO1* C609T were significantly related to smoking cessation. In the TC group, the stage at enrollment and *CYP1A1* Ile/Val were significantly related to smoking cessation. Among males in the TC group, age was significantly related to smoking cessation (p=0.04).

Table 4 demonstrates the responses to genotype testing, as well as the cessation rate according to the response. In the MG group, two males with two null genotypes at 20s "became slightly anxious," but were satisfied with the genotype testing, and quit smoking. One male and one female with one null genotype at 20s felt "nothing," but they also quit smoking. Another quitter with three null genotypes at 50s, "became slightly anxious," but was "satisfied with the genotype testing." Although the great majority of participants were either "satisfied" or "rather satisfied" with the genotype testing (90.2%, 55/61), two newly employed smokers and one heavy smoker "rather regretted," and one heavy smoker "regretted" the testing because he couldn't quit smoking. In the TC group, two males with two null genotypes and one female with one null genotype "became slightly anxious", but were satisfied (or rather satisfied) with the genotype testing, and they quit smoking. One male with one null genotype felt "relieved," but he also quit smoking. Another quitter with one null genotype felt "nothing," but "regretted" his involvement in the genotype testing since he suffered an internal hemorrhage in his arm after blood was drawn.

DISCUSSION

The smoking cessation rate of the MG group was 8.2% and that of the TC group was 10.9%. The FTND score and *NQO1* C609T polymorphism were significantly related to smoking cessation in the MG group. In the TC group, the stage at the enrollment and *CYP1A1* Ile/Val polymorphism were significantly related to smoking cessation.

Among males in the TC group, age was significantly related to smoking cessation. The stage to smoking cessation in the TC group significantly improved after the genotype notification.

The present study showed a similar cessation rate to our previous studies using a genotype notification; 7.9% among 101 health checkup examinees,[7] 8.5% among 106 different employees of the same municipal government enrolled in 2004–05,[6] and 12.7% among 245 outpatients at a cancer hospital.[5] These figures suggested that genotype information was influential for one out of ten Japanese smokers. Those informed of genotypes susceptible to tobacco smoke tended to quit smoking in both this and our previous studies.[5,7] In the study which showed a higher cessation rate than their controls for U.S. smokers notified of a *GSTM1* genotype (19% and 10% six months after notification, and 15% and 10% at twelve months after, respectively), the difference in the cessation rates between those with *null* type (17% at six months and 18% at twelve months) and those with *present* type (23% at six months and 15% at twelve months) was not significant.[3]

When compared with other methods to motivate people to quit, the cessation rate in this study was not worse, but hardly remarkable. Intensive educational sessions achieved an 8% cessation rate six months later among health checkup examinees (4% for controls),[13] 10% one year later among male checkup examinees (4% for controls),[14] and 20% five months later among outpatients of a cancer hospital (9% for controls).[15] A randomized clinical trial of 258 smokers to evaluate the effect of brief advices of a physician showed an 8.8% cessation rate for the intervention group and 6.8% for the control group.[16]

Although we observed a moderate effect for genotype notification as a potential tool for discouraging smoking, further consideration of possible effect modifiers is needed. Age, sex, nicotine dependence, and the stage of smoking cessation were important factors for cessation.[17] Although the subject numbers were limited, the FTND score and *NQO1* genotype in the MG group, and the stage and *CYP1A1* genotype in the TC, as well as age in TC males were significantly associated with the quitting. Because of the small sample size, an incomplete follow-up of the TC group, and a relatively short follow-up period, detailed interpretations may be difficult. Since people who had successfully quit smoking were limited, multivariate analysis by a logistic model was not conducted.

In conclusion, this study showed a certain effect of the genotype notification on smoking cessation similar to the past studies in Japan, as well as a shift in the stage to smoking cessation. In order to improve the cessation rate through genotype notification, other modes to strengthen the motivation linked to disease susceptibility and/or health consciousness should be developed. Combinations with other tools such as nicotine replacement therapy may be alternative approaches.

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REFERENCES

1) Inoue M, Hanaoka M, Sasazuki S, Sobue T, Tsugane S, the JPHC Study Group. Impact of tobacco smoking on subsequent cancer risk among middle-aged Japanese men and women: data from a large-scale population-based cohort study in Japan-the JPHC study. *Prev Med*, 2004; 38: 516–522.
2) Welfare Statistics Association. Health promotion and strategies against life-related diseases. *J Health Welfare Stat*, 2006; 53 (9): 75–88.
3) McBride CM, Bepler G, Lipkus IM, Lyna P, Samsa G, Albright J, Datta S, Rimer BK. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol Biomarkers Prev*, 2002; 11: 521–528.
4) Audrain J, Boyd NR, Roth J, Main D, Caporaso NE, Lerman C. Genetic susceptibility testing in smoking-cessation treatment: one-year outcomes of randomized trial. *Addict Behav*, 1997; 22: 741–751.
5) Ito H, Matsuo K, Wakai K, Saito T, Kumimoto H, Okuma K, Tajima K, Hamajima N. An intervention study of smoking cessation with feedback on genetic cancer susceptibility in Japan. *Prev Med*, 2006; 42: 102–108.
6) Hamajima N, Atsuta Y, Goto Y, Ito H. A pilot study on genotype announcement to induce smoking cessation by Japanese smokers. *Asian Pac J Cancer Prev*, 2004; 5: 409–413.
7) Hamajima N, Suzuki K, Ito Y, Kondo T. Genotype announcement to Japanese smokers who attended a health checkup examination. *J Epidemiol*, 2006; 16: 45–47.
8) Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*, 1997; 6: 733–743.
9) Siegel D, McGuiness SM, Winski SL, Ross D. Genotype-phenotype relationships in studies of a polymorphism in NAD(P)H: quinone oxidoreductase 1. *Pharmacogenetics*, 1999; 9: 113–121.
10) Hamajima N, Matsuo K, Iwata H, Shinoda M, Yamamura Y, Kato T, Hatooka S, Mitsudomi T, Suyama M, Kagami Y, Ogura M, Ando M, Sugimura Y, Tajima K. NAD(P)H: quinone oxidoreductase 1 (NQO1) C609T polymorphism and the risk of eight cancers for Japanese. *Int J Clin Oncol*, 2002; 7: 103–108.
11) Prochaska JO. Strong and weak principles for progressing from precontemplation to action on the basis of twelve problem behaviors. *Health Psychol*, 1994; 13: 47–51.
12) Kawase H, Hamajima N, Tamakoshi A, Wakai K, Saito T, Tajima K. Triplex polymerase chain reaction with confronting two-pair primers (PCR-CTPP) for *NQO1* C609T, *GSTM1*, and *GSTT1* polymorphisms: a convenient genotyping method. *Asian Pac J Cancer Prev*, 2003; 4: 67–70.
13) Shimizu H, Fukao A, Hisamichi S. A study of the effect of individual anti-smoking advice by physicians. *Nippon Koshu Eisei Zasshi*, 1985; 32: 698–702 (in Japanese).
14) Higashi A, Ozasa K, Watanabe Y, Hayashi K, Aoike A, Kawai K, Nakazawa A, Takahama S, Nishimura S. Efficacy of smoking cessation instruction for general smokers at an annual physical examination. *Nippon Koshu Eisei Zasshi*, 1995; 42: 313–321 (in Japanese).
15) Ogawa H, Tajima K, Kuroishi T. Practice of smoking cessation counseling for outpatients in hospital clinic. *Jpn J Cancer Clin*, 1993; 39: 435–441 (in Japanese).
16) Folsom AR, Grimm RH Jr. Stop smoking advice by physicians: a feasible approarch? *Am J Public Health*, 1987; 77: 849–850.
17) DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. *J Consult Clin Psychol*, 1991; 59: 295–304.