

Table 3. Summary of the association between tobacco smoking and colorectal cancer risk, cohort study

References	Study period		Study population			Magnitude of association*			
	Sex	Number of subjects	Age	Event	Number of incident cases or deaths	Colon	Rectum	Colorectum	
Kono et al. 1987 (9)	Men	5477	27-89 years	Death	39	NA	NA	-	
Akiba and Hirayama 1990 (10)	Men	122 261	40+ years	Death	444	-	↑	NA	
	Women	142 857	40+ years	Death	468	-	↑	NA	
Akiba 1994 (11)	Men and women	61 505	Not specified	Incidence	542	-	-	NA	
	Men	13 392	35+ years	Incidence	161	-	↑↑↑	NA	
Shimizu et al. 2003 (12)	Women	15 659	35+ years	Incidence	134	-	-	-	
	Men	42 540	40-69 years	Incidence	447	-	-	↑	
Orani et al. 2003 (13)	Women	47 464	40-69 years	Incidence	259	NA	NA	-	
	Men	25 260	40-79 years	Incidence	366	-	-	NA	
Wakai et al. 2003 (14)	Women	34 619	40-79 years	Incidence	246	-	-	NA	

NA, not available. \*↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; -, no association (see text for more detailed definition).

Giovannucci (6) proposed a hypothesis that smoking is involved in cancer initiation and long induction period is needed before the appearance of the carcinogenic effects of smoking, which may be detected by recent studies including a sufficient number of long-term smokers. In line with the hypothesis, recent cohort studies in Japan (12-14) reported a 20-40% increased risk of colon cancer associated with current smoking in men. These studies probably include many long-term smokers, because most Japanese smokers started smoking around 20 years of age and participants in these studies were relatively old: 35 years or older (12), 40-69 years (13) and 40-79 years (14).

We identified a significant, or marginally significant, increased risk of rectal cancer associated with smoking in all case-control studies published after 1994 (23-29) and in some cohort studies (10,12,13). No study in this review reported a significant inverse association between smoking and rectal cancer. A clearer association of smoking with rectal cancer than with colon cancer has also been noted in several studies outside Japan (6). Furthermore, a Japanese study indicated that smoking is more strongly associated with rectal adenomas than with colon adenomas (30).

We should mention methodological issues. Several Japanese studies (9,12-14,26,29) controlled for alcohol drinking, a probable risk factor for colorectal cancer (8) and closely correlated with smoking behavior. However, few controlled for other dietary factors (14). According to a Japanese national survey on nutrition (31), there is a substantial difference between smokers and non-smokers in diet including the intake of calcium and folate, which are potentially associated with reduced risk of colorectal cancer (32,33). As a result, such confounding cannot be excluded from the results of Japanese studies.

In summary, epidemiological evidence for the association with smoking among Japanese population appears to be stronger for rectal cancer than for colon cancer. A consistent positive association between smoking and rectal cancer was observed among several recent case-control studies. However, since earlier case-controls studies and several cohort studies did not show a significant association between smoking and rectal cancer, it would therefore be appropriate to classify their association as 'possible'. For colon cancer, epidemiological studies have provided mixed results; namely, several earlier case-control studies reported a decreased risk with smoking, whereas recent cohort studies showed a non-significant increased risk with smoking. Therefore, evidence among Japanese population is insufficient to establish any clear association between smoking and colon cancer.

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From these results and based on assumed biological plausibility, we conclude that tobacco smoking may possibly increase the risk of colorectal cancer among the Japanese population.

Table 4. Summary of the association between tobacco smoking and colorectal cancer risk. case-control study

References	Study period			Study subjects			Magnitude of association*			
	Sex	Age	Number of cases	Number of controls	Colon	Rectum	Colorectum	Colon	Rectum	Colorectum
Haenszel et al. 1980 (16)	Men and women	Not specified	284	571	NA	NA	-	NA	NA	-
Watanabe et al. 1984 (17)	Men and women	Not specified	203 (M: 110, F: 93)	203 (M: 110, F: 93)	↓↓↓	-	NA	-	-	NA
Tajima et al. 1985 (18)	Men	40-79 year	52	111	↓	-	NA	-	-	NA
Kato et al. 1990 (19)	Men	20 yr or older	3327	16600	↓	-	NA	-	-	NA
Kato et al. 1990 (20)	Men and women	Not specified	223	578	↓	-	NA	-	-	NA
Yoshida et al. 1992 (21)	Men and women	25-79 year	330 (M: 171, F: 159)	660	-	-	-	-	-	-
Hoshiyama et al. 1993 (22)	Men and women	40-69 year	181 (M: 98, F: 83)	653 (M: 343, F: 310)	↓↓↓	-	NA	-	-	NA
Kotake et al. 1995 (23)	Men and women	Not specified	363 (M: 214, F: 149)	363 (M: 214, F: 149)	-	↑↑	NA	↑↑	↑↑	NA
Inoue et al. 1995 (24)	Men	Not specified	257	8621	-	↑↑	NA	↑↑	↑↑	NA
Murata et al. 1996 (25)	Women	Not specified	175	23161	-	↑↑	NA	↑↑	↑↑	NA
Yamada et al. 1997 (26)	Men	Not specified	104	208	-	↑↑	NA	↑↑	↑↑	NA
Murata et al. 1999 (28)	Men and women	34-80 year	66 (M: 55, F: 11)	132 (M: 110, F: 22)	NA	NA	-	NA	NA	↑↑
Minami et al. 2003 (29)	Men	Not specified	267	395	-	-	-	-	-	-
	Men	40 year or older	288	1222	-	↑	NA	↑	↑	NA
	Women	40 year or older	200	1222	-	↑	NA	↑	↑	NA

NA, not available

\*↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; -, no association (see text for more detailed definition).

More specifically, tobacco smoking may possibly increase the risk of rectal cancer; however, the epidemiologic evidence remains insufficient to demonstrate any clear association with colon cancer.

### Acknowledgments

The authors gratefully acknowledge the assistance of Ms Tamami Hatano. This work was supported by the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare, Japan.

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Research article

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## Public awareness of risk factors for cancer among the Japanese general population: A population-based survey

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Published: 10 January 2006

Received: 23 June 2005

*BMC Public Health* 2006, **6**:2 doi:10.1186/1471-2458-6-2

Accepted: 10 January 2006

This article is available from: <http://www.biomedcentral.com/1471-2458/6/2>

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### Abstract

**Background:** The present study aimed to provide information on awareness of the attributable fraction of cancer causes among the Japanese general population.

**Methods:** A nationwide representative sample of 2,000 Japanese aged 20 or older was asked about their perception and level of concern about various environmental and genetic risk factors in relation to cancer prevention, as a part of an Omnibus Survey. Interviews were conducted with 1,355 subjects (609 men and 746 women).

**Results:** Among 12 risk factor candidates, the attributable fraction of cancer-causing viral and bacterial infection was considered highest (51%), followed by that of tobacco smoking (43%), stress (39%), and endocrine-disrupting chemicals (37%). On the other hand, the attributable fractions of cancer by charred fish and meat (21%) and alcohol drinking (22%) were considered low compared with other risk factor candidates. For most risk factors, attributable fraction responses were higher in women than in men. As a whole, the subjects tended to respond with higher values than those estimated by epidemiologic evidence in the West. The attributable fraction of cancer speculated to be genetically determined was 32%, while 36% of cancer was considered preventable by improving lifestyle.

**Conclusion:** Our results suggest that awareness of the attributable fraction of cancer causes in the Japanese general population tends to be dominated by cancer-causing infection, occupational exposure, air pollution and food additives rather than major lifestyle factors such as diet.

### Background

In Japan, cancer has been recognized as a major component of the overall pattern of disease for decades. Thus, the importance of cancer prevention by lifestyle modification should now be strongly acknowledged.

Internationally, several studies have estimated the proportion of total cancer deaths attributable to various risk factors based on epidemiologic evidence [1,2], and various international guidelines and recommendations derived from these have appeared [3-6]. Not surprisingly, domestic guidelines and recommendations for cancer prevention in Japan such as the 'Twelve recommendations for

**Table 1: Survey response rate**

	Number of samples	Number of responses	%
Total	2000	1355	67.8
Gender			
Men	977	609	62.3
Women	1023	746	72.9
Age			
20–29	284	175	61.6
30–39	351	247	70.4
40–49	369	257	69.6
50–59	411	282	68.6
60–69	349	228	65.3
70≤	236	166	70.3
Region			
Hokkaido and Tohoku	245	169	69.0
Kanto (Kanto and Keihin)	646	425	65.8
Chubu (Koshinetsu, Hokuriku and Tokai)	366	261	71.3
Kinki (Kinki and Hanshin)	325	222	68.3
Chugoku, Shikoku and Kyushu	418	278	66.5
City scale			
14 metropolises*	458	325	71.0
Other cities	1122	736	65.6
Towns and villages	420	294	70.0

\* Sapporo, Sendai, Saitama, Chiba, Tokyo, Kawasaki, Yokohama, Nagoya, Kyoto, Osaka, Kobe, Hiroshima, Kitakyushu and Fukuoka.

cancer prevention [7]' and 'Healthy People Japan 21 [8]' have been significantly influenced by these reports.

Public awareness of risk factors in relation to cancer prevention has been surveyed in only a few countries [9,10], and results have demonstrated poor awareness. Other studies focusing on specific cancers only have also appeared [11-14]. However, none of these studies quantitatively evaluated public awareness of the attributable fraction of individual risk factors.

In Japan, it appears that most people are aware of the major risk factors of cancer. Although we are unaware of any published evidence, however, public knowledge and information on cancer prevention now seems influenced largely by the mass media and other sources, rather than by information provided directly by health professionals, resulting in a distorted picture of causation. Cancer control policy therefore urgently requires a clarification of the discrepancies which now exist between ideal levels of public concern about risk factors and the current reality, particularly public health policy makers in their formulation of cancer control measures. To address this need, the present study was designed to provide information on awareness of the attributable fraction of cancer causes among the Japanese general population. Since we are interested in quantitatively estimating the awareness of preventability, we placed special emphasis on gauging awareness by attributable fraction of cancer.

## Methods

The study was conducted as a part of an omnibus survey in December, 2003, by commission to a polling agency. The omnibus survey is a monthly multipurpose cross-sectional survey which includes public opinion research, social research, scientific research, market research, and others. Using a stratified two-stage sampling method, a total of 2,000 people aged 20 or older were randomly selected as study subjects, from 160 districts selected from area units representing 12 geographical blocks (Hokkaido, Tohoku, Kanto, Keihin, Koshinetsu, Hokuriku, Tokai, Kinki, Hanshin, Chugoku, Shikoku, Kyushu) and 3 types of city scale (14 metropolises, other cities, towns and villages) in proportion to the population distribution as at March 2002. After an initial visit to obtain oral informed consent and schedule a visit for the interview, the survey was conducted by face-to-face interview using trained interviewers in each district. The omnibus survey does not collect any personally identifiable information such as name, date of birth or address details at interview. For the present report, we obtained the electronic data file for the relevant interview component, with no personal identifiers. Ethical approval was not applicable to the present study under the Japanese ethical guidelines for epidemiologic studies, which comply with the declaration of Helsinki.

Among the 2,000 people selected for survey (977 men, 1,023 women), interviews were successfully obtained

**Table 2: Respondent characteristics**

	Total			Male			Female		
	Number	%	(SE)	Number	%	(SE)	Number	%	(SE)
Total	1355	100		609	44.9		746	55.1	
Educational status									
Junior high school	202	14.9	(1.0)	93	15.3	(1.5)	109	14.6	(1.3)
Senior high school	693	51.2	(1.4)	273	44.9	(2.0)	420	56.3	(1.8)
College or higher	459	33.9	(1.3)	242	39.8	(2.0)	217	29.1	(1.7)
Occupation									
Agriculture, forestry and fisheries	35	2.6	(0.4)	17	2.8	(0.7)	18	2.4	(0.6)
Labor	276	20.4	(1.1)	127	20.9	(1.6)	149	20.0	(1.5)
Service, clerk, management, others	659	48.6	(1.4)	439	72.1	(1.8)	220	29.5	(1.7)
Homemaker	351	25.9	(1.2)	0	0.0	(0.0)	351	47.1	(1.8)
Student	34	2.5	(0.4)	26	4.3	(0.8)	8	1.1	(0.4)
Habitual smoking									
Never	724	53.4	(1.4)	158	25.9	(1.8)	566	75.9	(1.6)
Former	256	18.9	(1.1)	186	30.5	(1.9)	70	9.4	(1.1)
Current (<20 cigarettes per day)	245	18.1	(1.0)	149	24.5	(1.7)	96	12.9	(1.2)
Current (≥20 cigarettes per day)	130	9.6	(0.8)	116	19.0	(1.6)	14	1.9	(0.5)
Habitual drinking									
Never	640	47.2	(1.4)	177	29.1	(1.8)	463	62.1	(1.8)
Former	34	2.5	(0.4)	19	3.1	(0.7)	15	2.0	(0.5)
Current (≤4 times per week)	423	31.2	(1.3)	209	34.3	(1.9)	214	28.7	(1.7)
Current (almost everyday)	258	19.1	(1.1)	204	33.5	(1.9)	54	7.2	(0.9)

SE: Standard error

from 1,355 (67.8%). The remaining 645 did not respond because of change of address after sampling ( $n = 29$ ), absence from home in the survey period ( $n = 295$ ), refusal to participate ( $n = 303$ ), and other undetermined reasons ( $n = 18$ ).

The questionnaire of this survey comprised questions on the awareness of various environmental and genetic risk factors in relation to cancer prevention by enquiring about the attributable fraction of cancer. Fractions were: 1) 12 risk factor candidates, namely alcoholic beverages, unbalanced diet, use of food additives and pesticide chemicals, charred fish and meat, tobacco smoking, obesity, physical inactivity, endocrine-disrupting chemicals, air pollution such as diesel emissions, occupational exposure, cancer-causing viral and bacterial infection, and stress; 2) genetic factors in general; and 3) the preventable fraction of cancer occurrence by lifestyle modification [see Additional file 1].

The first question asked about the preventable fraction of cancer which would result in Japan if each factor were completely and totally eliminated, using the fine categories of <5%, 5 to <10%, 10 to <15%, 15 to <20%, 20 to <25%, 25 to <30%, 30 to <40%, 40 to <50%, 50 to <60%, 60 to <70%, 70 to <80%, 80 to <90%, and 90 to 100%. These categories were exhibited together on a pie chart.

These risk factor candidates were selected with reference to previous international and domestic recommendations and guidelines [1-8]. The second question asked about the fraction of cancer genetically predetermined using the same categories as the first, while the third asked about the preventable fraction of cancer by modification of lifestyle using estimation of an actual percent value. In addition to these questions, subjects were also asked about their smoking and drinking practices, and occupational and educational status.

Mean values of the attributable fractions were calculated for each risk factor of cancer and compared by demographic and habitual smoking and drinking status. For analyses, the mid-values of each category were assigned for categorical variables. All analyses were performed using Stata statistical software, S/E Version 8 [15].

## Results

A total of 1,355 (67.8%) subjects responded to the survey, with a higher response rate in women (72.9%) than in men (62.3%). Response rate was lower in the 20s age strata than in the other age groups, but no trend to an increase in response rate with increasing age was observed. Overall, no significant difference in area and age distribution was seen between the sampled population and survey respondents. Response rate tended to be

**Table 3: Awareness of attributable fraction of cancer causes among the Japanese general population**

	Total		Men		Women	
	Mean %	(95%CI)	Mean %	(95%CI)	Mean %	(95%CI)
Preventable fraction of cancer (%) by eliminating:						
Cancer-causing viral and bacterial infection	51.3	(49.5- 53.0)	48.7	(46.1- 51.3)	53.4	(51.1- 55.6)
Tobacco smoking	43.0	(41.6- 44.4)	40.1	(38.1- 42.2)	45.4	(43.6- 47.3)
Stress	39.0	(37.6- 40.4)	35.8	(33.7- 37.9)	41.6	(39.7- 43.5)
Endocrine-disrupting chemicals	37.1	(35.7- 38.5)	34.9	(32.8- 37.0)	38.9	(37.1- 40.8)
Occupational exposure	36.0	(34.5- 37.4)	33.2	(31.1- 35.4)	38.2	(36.3- 40.2)
Air pollution	34.7	(33.4- 36.0)	32.5	(30.5- 34.5)	36.6	(34.7- 38.4)
Food additives and pesticides	31.4	(30.2- 32.7)	28.7	(26.9- 30.5)	33.7	(32.0- 35.4)
Unbalanced diet	28.8	(27.6- 30.0)	26.1	(24.4- 27.7)	31.0	(29.4- 32.7)
Obesity	28.2	(27.0- 29.4)	25.4	(23.6- 27.1)	30.6	(28.9- 32.3)
Physical inactivity	26.0	(24.8- 27.1)	23.8	(22.1- 25.5)	27.8	(26.2- 29.4)
Alcohol drinking	21.7	(20.7- 22.7)	19.2	(17.8- 20.6)	23.7	(22.3- 25.1)
Charred fish and meat	21.4	(20.3- 22.5)	20.1	(18.4- 21.8)	22.5	(21.0- 23.9)
Fraction of cancer genetically determined (%)	31.5	(30.2- 32.9)	32.0	(30.0- 34.1)	31.1	(29.4- 32.8)
Fraction of cancer preventable by improving lifestyle (%)	35.5	(34.6- 36.5)	33.7	(32.3- 35.2)	37.0	(35.7- 38.3)

CI: Confidence interval

lower among subjects who reside in the Kanto region and in cities other than the 14 metropolises than among other subjects (Table 1).

Characteristics of the 1,355 respondents (609 men, 746 women) are presented in Table 2. The proportion of current smokers was 44% in men and 15% in women, and decreased with age in both genders. In female subjects aged in their 20s, 26% currently smoke and 49% drink alcohol beverages at least 4 times a week.

Awareness of the attributable fraction of cancer causes among the Japanese general population is presented in Table 3. Among the 12 risk factor candidates, the attributable fraction was considered highest for cancer-causing viral and bacterial infection (51.3%), followed by tobacco smoking (43.0%), stress (39.0%), and endocrine-disrupting chemicals (37.1%). In contrast, the attributable fraction of charred fish and meat (21.4%) and alcohol drinking (21.7%) were considered low compared with other risk factor candidates. The attributable fraction of other risk factor candidates such as occupational exposure, air pollution, food additives and pesticides, unbalanced diet, obesity and physical activity ranked between the high and low fractions. The attributable fraction responses tended to be higher in women than in men, and were increased among inhabitants of larger cities and in homemakers and decreased in those engaged in agriculture, forestry and fisheries. In contrast, risk factor candidate rankings were similar by gender, age group, city scale, and educational and occupational status. In men, those who neither smoke nor drink tended to consider the preventive fraction of the risk factors higher than those who

both smoke and drink, whereas in women, the former subjects considered the values lower than the latter.

The speculated fraction of cancer which is genetically determined was 31.5% as an average (Table 3). This fraction was higher in current heavy smokers and former drinkers, and lower in homemakers and students. On the other hand, an average 35.5% of cancer were considered preventable by lifestyle improvement, with this ratio being higher in homemakers, former smokers, and never and former drinkers.

## Discussion

The present survey, targeted at the Japanese general population, showed that the attributable fraction of cancer among Japanese tended to be higher for cancer-causing infection, occupational exposure, air pollution and food additives than major lifestyle factors such as dietary factors. In addition, the attributable fraction of cancer estimated by the Japanese general population was higher than that derived from epidemiologic evidence in the West, which is frequently quoted as 30% for tobacco smoking and 30% for food as a whole [1,2].

Some of the major cancers in Japan, including gastric and liver cancers, are known to be related to cancer-causing viral and bacterial infection, and a higher level of concern about such infection among Japanese than in Western populations would therefore be understandable [9]. Notwithstanding the validity of such concern, however, the high level of concern for infection, as well as for endocrine-disrupting chemicals, identified in the present survey was most likely due to the severe acute respiratory

syndrome (SARS) epidemic which occurred just prior to it, as well as a focus on endocrine-disrupting chemicals in the Japanese mass media in recent years. Both of these resulted in a surge of interest in these issues, even if their relationship with cancer is less likely.

Likewise, a high level of concern for tobacco smoking was also observed, in spite of a relatively dull reduction in the rate of male current smokers in past decades compared with the U.S. This was probably due to recent enactment of the Health Promotion Law, which curbs passive smoking in public spaces.

Respondent estimates for attributable fractions were generally high. This may be in part due to anchoring and adjustment effects of the response categories used and the tendency of people to respond near the middle of the scale. Given that responses tended to be generally high, concern over the present results should probably be focused on rankings rather than absolute values per se. Although tobacco smoking ranked among the top factors, risk factor candidates whose actual contribution is considered to be low, such as endocrine-disrupting chemicals, occupational exposure, air pollution such as diesel emissions and the use of food additives and pesticide chemicals ranked higher than previous estimates of the attributable fraction of cancer causes [1,2]. In contrast, this should be compared with the results for unbalanced diet, which ranked at only 8th among the 12 risk factor candidates despite an actual ranking which is estimated to be as high as that for tobacco smoking. Particularly in light of findings on long-term exposure to common lifestyle factors such as diet as a cause of cancer, these results suggest that public awareness of cancer prevention is still insufficient.

We are unaware of any previous studies aimed at determining public awareness of the attributable fraction of cancer as a whole or at gauging the level the awareness of cancer prevention by attributable fraction. Accordingly, to our knowledge, this is the first attempt to discover the level of awareness for each risk factor candidate, and the questionnaire used has hence not been fully validated. In addition, as indicated above, responses to this type of cross sectional survey are subject to social conditions such as information from the mass media and other sources on disease epidemics and other putative risk factors. Thus, the results might not necessarily reflect actual public awareness. However, the study subjects were recruited from among a nationally representative random sample, and the response rate was similar to that of recent omnibus surveys in other countries [16-19]. Nevertheless, the exclusion of non-respondents may have distorted the results.

## Conclusion

In conclusion, awareness of the attributable fraction of cancer causes among the Japanese general population tended to be dominated by infection, occupational exposure, air pollution and food additives rather than dietary factors. The results of the present survey provide valuable clues and perspectives toward the formulation of relevant cancer prevention strategies in Japan.

## Competing interests

The author(s) declare that they have no competing interests.

## Authors' contributions

MI developed the concept and design of the study, analyzed the data and wrote the paper. MIw, TO and SS participated in the design of the study, interpretation of the data and revision of the paper. ST developed the concept and design of the study and revision of the paper. All authors read and approved the final manuscript.

## Additional material

### Additional File 1

Questionnaire in the omnibus survey on the awareness of risk factors and prevention of cancer

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## Acknowledgements

This work was supported by the Health and Labour Sciences Research Grants, the Research on Health Services and the Third Term Comprehensive 10-year Strategy for Control Research for Cancer, from the Ministry of Health, Labour and Welfare, Japan.

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### Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1471-2458/6/2/prepub>

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## ORIGINAL ARTICLE

# Effect of vitamin C on common cold: randomized controlled trial

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**Objective:** To investigate the relationship between the common cold and vitamin C supplementation.

**Design:** A double-blind, 5-year randomized controlled trial.

**Setting:** A village in Akita prefecture, one of the regions in Japan with the highest mortality from gastric cancer.

**Subjects:** Participants in annual screening programs for circulatory diseases conducted under the National Health and Welfare Services Law for the Aged, and diagnosed as having atrophic gastritis. Of the 439 eligible subjects, 144 and 161 were assigned to receive 50 or 500 mg of vitamin C, respectively, after protocol amendment. During the supplementation phase, 61 dropped out, and 244 completed the trial.

**Intervention:** Daily vitamin C supplementation of 50 mg (low-dose group) or 500 mg (high-dose group).

**Results:** Total number of common colds (per 1000 person-months) was 21.3 and 17.1 for the low- and high-dose groups, respectively. After adjustment for several factors, the relative risks (95% confidence interval (CI)) of suffering from a common cold three or more times during the survey period was 0.34 (0.12–0.97) for the high-dose group. No apparent reduction was seen for the severity and duration of the common cold.

**Conclusion:** A randomized, controlled 5-year trial suggests that vitamin C supplementation significantly reduces the frequency of the common cold but had no apparent effect on the duration or severity of the common cold. However, considering several limitations due to protocol amendment, the findings should be interpreted with caution.

**Sponsorship:** This study was supported in part by Grants-in-Aid for Cancer Research and for the Second Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.

*European Journal of Clinical Nutrition* (2006) **60**, 9–17. doi:10.1038/sj.ejcn.1602261; published online 24 August 2005

**Keywords:** vitamin C; common cold

## Introduction

Many experimental studies have indicated that vitamin C affects the immune system. Vitamin C increases the proliferative responses of T lymphocytes and the production of interferon, and prevents defects in neutrophils (Hemila, 1996, 1997). However, the extent of the physiologic

relevance of these effects on the susceptibility of human beings to infection is not well understood.

The effect of vitamin C on common cold incidence remains unclear. Numerous intervention studies have investigated the relationship between vitamin C supplementation and the incidence of common cold episodes. Six, large randomized trials of normally nourished subjects in Western countries, whose supplementation period ranged from 2 to 9 months, revealed no effect of vitamin C on common cold incidence (Anderson *et al.*, 1972; Karlowski *et al.*, 1975; Elwood *et al.*, 1976; Ludvigsson *et al.*, 1977; Pitt and Costrini, 1979; Briggs, 1984). However, studies of specific groups, such as subjects under heavy acute physical stress (Hemila, 1996) or British males with extremely low levels of vitamin C intake (Glazebrook and Thomson, 1942; Charleston and Clegg, 1972; Clegg and Macdonald, 1975; Baird *et al.*, 1979), revealed significant reduction in common cold incidence

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Contributors: The study was designed and supervised by YT, SS and ST. SO, and MH coordinated the fieldwork and advised on the study design. SS analyzed the data, interpreted the current findings, and wrote the paper.

Received 21 September 2004; revised 15 June 2005; accepted 29 June 2005; published online 24 August 2005

with vitamin C supplementation. In addition, studies have consistently found reduced duration or severity of the common cold with vitamin C supplementation (Hemila and Douglas, 1999). Thus, studies to clarify both the preventive and the therapeutic effects of vitamin C on the common cold are needed. In this study, we examined the effect of 5-year vitamin C supplementation on common cold incidence, duration, and severity in a population-based, double-blind, randomized controlled trial.

## Methods

### Subjects

The initial aim of this study was to examine the effects of supplementation of  $\beta$ -carotene and vitamin C on the incidence of gastric cancer. Target subjects were men and women aged 40–69 years living in four municipalities of the Yokote Public Health Center District in the Akita prefecture, a region in Japan with one of the highest mortality rates from gastric cancer. The subjects were recruited through annual health checkup programs for circulatory diseases conducted during June–September 1995 by each municipality under the National Health and Welfare Services Law for the Aged. The rationale, design, and methods of the study have been described in detail elsewhere (Tsubono *et al.*, 1997). Subjects with a diagnosis of chronic atrophic gastritis (defined as pepsinogen (PG) I < 70 ng/ml and PG I/PG II ratio < 3.0); no history of gastric cancer, gastric surgery, liver cancer, cirrhosis, or other cancers within the previous 5 years; no abnormal liver function (aspartate aminotransferase > 100 IU/l, alanine aminotransferase > 100 IU/l, or alkaline phosphatase > 800 IU/l); no use of diet supplements containing  $\beta$ -carotene or vitamin C; and no expectation of moving outside the study area within 1 year were regarded as eligible. Written informed consent was obtained from each participant, and the Ethics Committee of National Cancer Center approved the protocol.

### Study design and procedures

We first conducted a run-in phase, providing full doses of  $\beta$ -carotene (15 mg/day) and vitamin C (500 mg/day) to all participants for 4 weeks to identify and exclude at an early stage the subjects who either did not comply or showed side effects. All participants had started taking run-in capsules by December 1995. Participants were then randomized in a double-blind manner to one of four groups by using a 2 × 2 factorial design (0 or 15 mg/day  $\beta$ -carotene and 50 or 500 mg/day vitamin C) for the 5-year supplementation period. The assignment was based on simple randomization by using a table of random sampling numbers. The allocation of resources, participant enrollment, and group assignment were completed by one of the co-authors (YT). Participants were asked to visit community centers every 3 months, at which time public health nurses checked clinical

symptoms and compliance by counting the number of unconsumed capsules, and then provided more capsules. At the baseline and fifth year of the study, participants also were asked to fill out a questionnaire inquiring about smoking habits, alcohol consumption, and medical history. A semiquantitative food frequency questionnaire with 108 items also was included in the main questionnaire.

In response to a US National Cancer Institute press release of January 18, 1996, indicating that two  $\beta$ -carotene trials had shown no benefit but had shown potential harm (Anon-ymous, 1996), we were obliged to amend the study protocol. Supplementation of  $\beta$ -carotene was stopped, but the prescription of vitamin C was continued for 5 years. The primary end point was altered from the 10-year cumulative incidence rate of gastric cancer to the 5-year change in serum levels of PGs, *Helicobacter pylori* infection, oxidative stress markers, and so on. On February 9 and 16, 1996, we invited the participants to community centers, explained in detail the results of the two US studies and the amendment of the study protocol, and collected the discontinued capsules from each participant. Signed consent was obtained again from individuals willing to remain in the study ( $N = 244$ ), and new capsules containing vitamin C only (50 or 500 mg/day) were provided. Although we estimated that a minimum of 1812 participants would be needed for the trial to detect a 40% reduction of the incidence of gastric cancer in the intervention group, the study area was restricted to the village from which participants had already been recruited; no new participants were recruited from the three other municipalities.

Vitamin C was expected to have a preventive or therapeutic effect on the common cold through effects on the immune system. In this report, we aim to evaluate the effect of vitamin C on the incidence, duration, and severity of the common cold.

### Common cold survey

Episodes of the common cold were surveyed during the supplementation period (from years 2 to 5) and 1 year after the intervention was completed. Participants visited the community center every 3 months for new capsules and checkups by public health nurses who were blinded to the group assignment; the participants also were asked if they had caught a cold since the date of the previous visit. Thus, the information on the common cold covered all seasons. The first survey for the common cold was conducted during January–March 1997. All data were available to participants while they participated in the trial.

At 1 year after the supplementation phase was completed, a self-administered questionnaire was mailed to the participants inquiring about their history of diseases, endoscopy, and surgery, as well as episodes of the common cold during the previous year. The number of common colds (i.e., a cold so severe that the subject had to be in bed) during the period was determined by precoded answers: none, 1, 2, 3, 4, 5, and

**Table 1** A typical scoring system in common cold trials<sup>a</sup>

	0	1	2	3
Cough	Nil	Mild	Troublesome and/or significant clear sputum	Incapacitating cough and/or purulent sputum
Nasal symptoms	Nil	Mild discharge	Heavy, clear discharge and/or stuffiness	Yellow or green nasal discharge
Throat symptoms	Nil	Mild sore throat only	Moderate sore throat and/or hoarseness	Severe sore throat
Systemic symptoms	Nil	Some aches and/or slight fever	Definite elevation of temperature, moderate aches, headache	Severely incapacitated by general symptoms

<sup>a</sup>Scoring system is based on Hemila (1999).

6 or more. When subjects reported one or more episodes of the common cold, they were asked about the duration and severity of specific symptoms for the most severe cold. Duration of cough, nasal symptoms, sore throat, fever, headache, or muscular pain; days in bed; days absent from work; and total duration of the episode were ascertained. Severity of the cold was measured by using a typical scoring system introduced by Hemila (Hemila and Douglas, 1999; Table 1). For cough, nasal, throat, and systemic symptoms, a score of 0–3 was assigned according to the severity of each; then the total severity score was calculated. For those subjects who had not responded, two reminders with a new questionnaire were sent at 4 and 7 months after the first contact.

#### Laboratory analysis

Fasting blood samples collected at baseline and after 5 years were analyzed for serum ascorbic acid levels, PG I, and PG II. All samples were stored at –70 to –85°C and were analyzed simultaneously after completion of the 5-year supplementation. All assays were conducted by persons who were blinded to the intervention assignment and the questionnaire data. The serum for ascorbic acid measurement was stabilized by the addition of meta-phosphoric acid. The level of serum ascorbic acid was analyzed fluorometrically (iodine oxidation and condensation with 1,2-phenylenediamine). Serum levels of PG I and PG II were measured by radioimmunoassay in a commercial laboratory (Dinabot, SRL Co. Ltd, Tokyo).

#### Statistical analysis

At each survey point, we calculated the incidence of the common cold (number of subjects; Figure 2) and total number of common colds (per 1000 person-months; Table 3). Person-months of follow-up were calculated from the date of the previous visit of the first common cold survey until the last survey. For those who withdrew from the trial, the date of dropout was treated as censoring. The Cox proportional hazards regression model was used to estimate the relative risks (RRs) of the common cold occurring one, two, or three or more times during the survey period. Age, sex, body mass index, smoking status, alcohol drinking, and the dietary

intake of vitamin C, green or yellow vegetables, other vegetables, and fruits were included as covariates. Analysis of variance and analysis of covariance were conducted to investigate differences in the duration or severity of symptoms across supplementation groups. Age, sex, body mass index, past history of respiratory diseases, smoking status, alcohol drinking, and the dietary intake of vitamin C, green or yellow vegetables, other vegetables, and fruits were included as covariates. The analyses were conducted for subjects who completed the 5-year supplementation (completed group analysis;  $n=120$  for the low-dose group and  $n=124$  for the high-dose group), including those who dropped out after the protocol amendment (intention-to-treat analysis;  $n=144$  for the low-dose group and  $n=161$  for the high-dose group). Since the common cold survey began in the second year of the supplementation, the intention-to-treat cohort analyzed in this report consisted of 133 and 140 subjects in the low- and high-dose groups, respectively. Reported  $P$ -values are two-sided, and all statistical analyses were carried out by using the Statistical Analysis System (SAS) version 8.2 (SAS Institute, Inc., Cary, NC, USA).

## Results

Of 1231 subjects screened through annual health checkup programs (June–September 1995), 1214 provided a blood sample for serum PG measurement (Figure 1). Among these subjects, 635 (52%) were diagnosed with chronic atrophic gastritis on the basis of serum PG level. A total of 33 people were ineligible since they did not meet the inclusion criteria. Of the remaining 602 eligible subjects, 439 (73%) consented to take part in the trial. Of the 439 subjects who initially participated in the study, 42 dropped out before the study was altered. Of the 397 remaining subjects, 305 (77%) consented to take part in the modified trial. After amendment of the protocol, 61 people withdrew for the following reasons: death ( $n=4$ ), lost to follow-up ( $n=2$ ), unknown ( $n=4$ ), refusal ( $n=51$ ). Refusal included other illness, minor side effect such as constipation or diarrhea ( $n=8$ ; five for low-dose group, three for high-dose group), and heartburn ( $n=4$  for high-dose group). A total of 244 subjects (80% of the subjects included in the modified trial) completed the

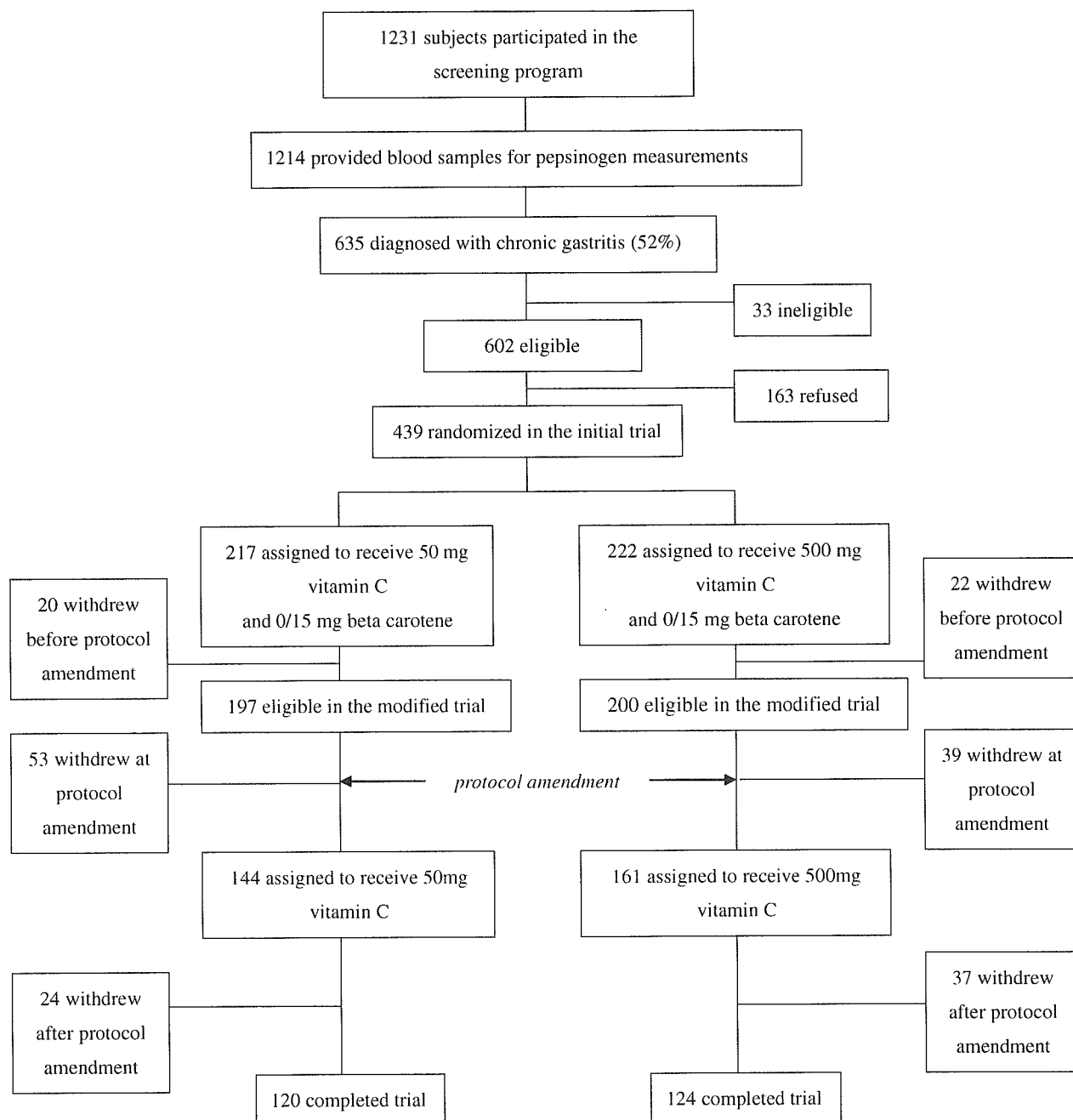


Figure 1 Study flow.

5-year supplementation. Table 2 shows baseline characteristics for the supplementation groups. No statistical difference except that for age was found between the low-dose (50 mg) and high-dose (500 mg) groups.

The incidence (%) of the common cold during the supplementation period for those who completed the supplementation is shown in Figure 2. For most of the survey period, the incidence of the common cold was higher

in the low-dose than in the high-dose group. When the survey was conducted during April–June 1999, the incidence was 9.2% for the low-dose and 3.2% for high-dose group ( $P=0.05$ ). The peaks of incidence (March–May 1998, December 1998–March 1999, February–April 2000) were as high as the incidence of the first survey (January–April 1997) for the low-dose group, whereas the peak incidence was consistently lower than that of the first survey for the

Table 2 Baseline characteristics by randomized group<sup>a</sup>

	Intervention group			Dropout (n = 134)
	Low dose (vitamin C 50 mg/day) (n = 120)	High dose (vitamin C 500 mg/day) (n = 124)	P for difference <sup>b</sup>	
Age	58.7 (0.7)	56.3 (0.7)	0.02	57.8 (0.7)
Male/female	41/79	45/79	0.73	50/84
Current smoker (%)	10.0	15.3	0.21	13.4
Alcohol drinker, 1+ /week (%)	36.7	40.3	0.56	24.6
Body mass index (kg/m <sup>2</sup> )	23.4 (0.3)	23.2 (0.2)	0.60	24.0 (0.3)
<i>Dietary intakes</i>				
Vitamin C (mg/day)	150.8 (9.5)	149.9 (9.4)	0.94	133.8 (8.5)
Fruit (g/day)	205.8 (19.8)	207.1 (19.6)	0.96	157.9 (12.5)
Green or yellow vegetables (g/day)	56.5 (5.2)	55.6 (5.1)	0.91	50.9 (4.2)
Other vegetables (g/day)	140.6 (13.4)	148.5 (13.3)	0.68	128.6 (12.1)
Serum ascorbic acid (mg/dl)	1.38 (0.03)	1.35 (0.03)	0.48	1.4 (0.03)

<sup>a</sup>Values are means (s.e.) unless otherwise specified.

<sup>b</sup>Difference between low-dose and high-dose group is based on one-way analysis of variance or chi-square test.

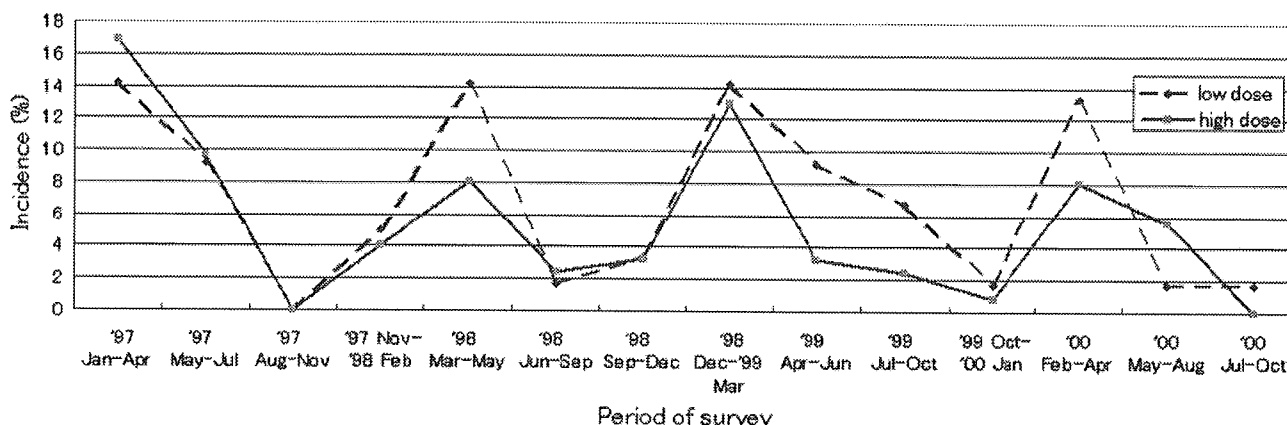


Figure 2 Common cold incidence, by supplementation group, during vitamin C supplementation.

high-dose group. The results were nearly identical for the intention-to-treat group.

On the basis of those subjects who completed the supplementation, total number of common colds (per 1000 person-months) during the supplementation was 21.3 for the low-dose group and 17.1 for the high-dose group (Table 3). Estimates of RRs were obtained for the common cold defined as one, two, or three or more times, with adjustment for potential confounding factors. When the common cold was defined as occurring three or more times during the survey period, an approximately 70% reduction in RR was observed (0.34, 95% CI: 0.12–0.97,  $P=0.04$ ). The corresponding value for the common cold defined as occurring four or more times was 0.28 (95% CI: 0.06–1.28,  $P=0.10$ ), for which only 10 events were observed. The results were essentially the same in the intention-to-treat groups.

The occurrence of common cold episodes also was surveyed after completion of the supplementation phase. Among those who completed the supplementation, 240 subjects received the self-administered questionnaire (four had died or moved). A total of 228 subjects (95%) returned their questionnaire; 146 (61%), 67 (28%), and 15 (6%) responded on first, second, or third contact, respectively. Among the 113 subjects in the low-dose and 115 in the high-dose group, 25 (25.7%) and 20 (17.4%), respectively, reported having caught cold during the previous year ( $P=0.13$ ). The corresponding values for those who responded on first contact were 19 (24.7%) and 12 (17.4%), respectively ( $P=0.28$ ).

Crude and adjusted means of duration (days) of common cold and specific symptoms for the two groups are shown in Table 4. After several factors were adjusted, the duration of cough, runny nose, sore throat, and total duration were

**Table 3** Relative risks of common cold incidence, by intervention group, on the basis of surveys during the supplementation period

Intervention group	Person-months	Total no. of common colds	Total no. of common colds/1000 person-months	Adjusted RR <sup>a</sup> (95% CI)	Adjusted RR <sup>b</sup> (95% CI)	Adjusted RR <sup>c</sup> (95% CI)
<i>Completed group analysis</i>						
Low dose (n = 120)	5396.75	115	21.3	1.0	1.0	1.0
High dose (n = 124)	5606.43	96	17.1	0.93 (0.65–1.34)	0.85 (0.47–1.53)	0.34 (0.12–0.97)
<i>Intention-to-treat analysis</i>						
Low dose (n = 133)	5715.28	120	21.0	1.0	1.0	1.0
High dose (n = 140)	5901.77	103	17.5	0.98 (0.69–1.40)	0.86 (0.48–1.56)	0.36 (0.13–0.99)

<sup>a</sup>RR for the common cold occurring one time during the whole survey period versus fewer occurrences.

<sup>b</sup>RR for the common cold occurring two times during the whole survey period versus fewer occurrences.

<sup>c</sup>RR for the common cold occurring three times during the whole survey period versus fewer occurrences.

<sup>a-c</sup>Adjusted for age, sex, body mass index, cigarette smoking, alcohol drinking, dietary intake of green or yellow vegetables, other vegetables, fruits, and vitamin C.

**Table 4** Duration (in days) of the common cold and specific symptoms for the most severe cold in the two groups, measured after the supplementation period

Symptoms	Supplementation group	Crude mean (s.e.)	P for difference	Adjusted mean (s.e.) <sup>a</sup>	P for difference
Cough	Low dose	1.6 (1.1)	0.19	1.9 (1.4)	0.30
	High dose	3.9 (1.3)		4.6 (1.9)	
Runny nose	Low dose	1.2 (0.5)	0.19	0.9 (0.5)	0.03
	High dose	2.1 (0.5)		3.1 (0.7)	
Sore throat	Low dose	1.1 (0.4)	0.50	1.1 (0.6)	0.48
	High dose	1.5 (0.5)		1.9 (0.8)	
Fever, headache, or muscular pain	Low dose	2.1 (0.4)	0.72	2.2 (0.5)	0.62
	High dose	1.8 (0.5)		1.8 (0.7)	
Days in bed	Low dose	1.6 (0.3)	0.59	1.8 (0.4)	0.46
	High dose	1.3 (0.4)		1.3 (0.6)	
Days absent from work	Low dose	0.9 (0.3)	0.88	1.0 (0.3)	0.68
	High dose	1.0 (0.3)		0.7 (0.4)	
Total duration	Low dose	5.9 (1.1)	0.57	5.9 (1.5)	0.48
	High dose	7.0 (1.4)		7.9 (2.0)	

<sup>a</sup>Data are based on analysis of covariance, including age, sex, body mass index, smoking status, alcohol drinking, past history of respiratory diseases, dietary intake of vitamin C, green or yellow vegetables, other vegetables, and fruits as covariates.

longer in the high-dose group than in the low-dose group, although the difference was statistically significant only for runny nose. In contrast, duration of fever, headache, and muscular pain; days in bed; and days absent from work were longer in the low-dose group, although the differences were not statistically significant. When the analysis was repeated for those who responded on first contact, the observed difference in duration by group was more pronounced, although it still did not reach the level of statistical significance (data not shown).

No statistically significant difference between groups was observed in the severity of the cold or each symptom (Table 5). The adjusted total severity score was 4.3 for the

low-dose group and 4.2 for high-dose group ( $P = 0.91$ ). The results were similar when the analysis was restricted to those who responded at the first approach.

## Discussion

In this population-based, double-blind, randomized controlled trial, vitamin C supplementation was inversely related with common cold incidence, defined as a common cold episode occurring three or more times, while it had no effect on common cold duration or severity. Although vitamin C was supplemented for 5 years, the common cold

**Table 5** Severity of the common cold and each symptom for the most severe cold in two groups, measured after the supplementation period

Symptoms (severity score)	Supplementation group	Crude mean (s.e.)	P for difference	Adjusted mean <sup>a</sup> (s.e.)	P for difference
[a] Cough (0–3)	Low dose	0.9 (0.2)	0.33	1.1 (0.2)	0.65
	High dose	1.2 (0.2)		1.3 (0.3)	
[b] Nasal symptoms (0–3)	Low dose	0.7 (0.1)	0.27	0.7 (0.1)	0.87
	High dose	0.9 (0.2)		0.8 (0.2)	
[c] Throat symptoms (0–3)	Low dose	0.7 (0.2)	0.40	1.0 (0.2)	0.65
	High dose	1.0 (0.2)		0.8 (0.2)	
[d] Systemic symptoms (0–3)	Low dose	1.5 (0.1)	0.46	1.6 (0.2)	0.18
	High dose	1.4 (0.2)		1.2 (0.2)	
Total severity score ([a] + [b] + [c] + [d])	Low dose	3.8 (0.5)	0.41	4.4 (0.5)	0.67
	High dose	4.4 (0.6)		4.0 (0.6)	

<sup>a</sup>Data are based on analysis of covariance, including age, sex, body mass index, past history of respiratory diseases, dietary intake of vitamin C, green or yellow vegetables, other vegetables, and fruits as covariates.

survey period began in the second year and covered the period of 3½ years. Thus, a common cold episode occurring three or more times during the survey corresponds to about one time or more per year. However, our study has several disadvantages such as relatively small sample size, no clear definition of common cold, large drop out at protocol amendment, and lack of placebo arm. These points should be discussed before interpreting the present findings.

As mentioned above in the Method section, the sample size was calculated in accordance to the initial protocol that aimed to detect the reduction in gastric cancer rate. However, because of the protocol amendment, we restricted the subjects to one village and also 92 subjects dropped out from the trial at the time, which finally left 120 subjects for the low-dose group and 124 subjects for the high-dose group in the modified trial. Based on this sample size, standardized effect size of 0.30–0.40 can be detected by a setting of two-tailed test with  $\alpha = 0.05$ ,  $1 - \beta = 0.80$ . The observed standardized effect ranged from about 0.05 to 0.2 from our results in Tables 4 and 5. Consequently, the sample size in our study was considered to be not enough to detect the small effect of vitamin C on common cold duration or severity.

We did not set a clear definition of the common cold. On surveys done during the supplementation period, participants were asked if they had caught cold since the date of the previous visit. The definition of common cold fully depends on each participant's interpretation. Although the survey conducted after the supplementation phase limited the reporting of a common cold to those 'so severe that had to be in bed,' it still did not define what the common cold is. Thus, the present study possibly suffered some misclassification as regards disease status, which frequently masks the true association. There is no generally accepted definition of common cold. Except for a few studies (Karlowski *et al.*, 1975; Ludvigsson *et al.*, 1977; Pitt and Costrini, 1979), previous studies did not provide a clear definition of the

common cold. Also, as in previous studies, the diagnosis was based on self-reports. Some studies have emphasized the use of seropositivity in the diagnosis (Cohen *et al.*, 1993). However, a high proportion of common cold episodes that were not clinically detectable (i.e., false positive) were included in these studies (Takkouche *et al.*, 2002).

Finally, only slightly more than half of the subjects randomized to the initial trial completed the supplementation; therefore, our findings should be interpreted cautiously. However, the protocol amendment (cessation of  $\beta$ -carotene supplementation and change in the end point from gastric cancer incidence to biomarkers) is not directly related to respiratory disease, including the common cold, or interest in vitamin C. In fact, there was no difference in baseline characteristics between the low-dose group ( $n = 144$ ) and high-dose group ( $n = 161$ ) who participated in the modified trial (Kim *et al.*, 2004), which means that the randomization almost was maintained even though 134 subjects dropped out early in the study before and at the time of protocol amendment. Of the 305 subjects who participated in the modified trial, 244 (80%) subjects completed the trial. Moreover, as shown in Table 2, the baseline characteristics of the completed group were similar except for age; thus, it is unlikely that the dropout at the protocol amendment markedly reduced the scientific meaning of our results.

Although the role of vitamin C in the prevention and treatment of the common cold remains controversial, emerging evidence shows that vitamin C reduces mortality from heart disease or can reduce oxidative stress and lower the risk of age-related degenerative changes (Bsoul and Terezhalmay, 2004). Thus, although it is ideal to set a placebo arm, the vitamin C dosage of 50 mg, which corresponds to the recommended dietary allowance (Kurita, 1994) at that time, was set as low-dose group in our study. Furthermore, on the basis of our pilot study of 3-month supplementation



of  $\beta$ -carotene and vitamin C (Sasaki *et al.*, 2000), the serum level of ascorbic acid acted simultaneously for the placebo and 50-mg supplemented groups; the percent changes in serum ascorbic acid from baseline for the placebo and 50-mg groups were 31 and 23% at 1 month, 37 and 23% at 2 months, and 31 and 29% at 3 months, respectively. In comparison with previous studies, the supplementation amount of 500 mg per day for the high-dose group in our study does not seem large. According to a report (Levine *et al.*, 1996), safe doses of vitamin C are less than 1000 mg daily, while bioavailability declines and the absorbed amount is largely excreted at single doses of 500 mg and higher. Thus, we set 500 mg as the dosage for the high-dose group. In fact, our previous report revealed a statistically significant difference in serum ascorbic acid level in the two groups after 5 years of supplementation (1.48 mg/dl for low-dose group, 1.73 mg/dl for high-dose group,  $P=0.0001$ ) (Sasazuki *et al.*, 2003). We did not assume that the dietary intake from food is nil. As shown in Table 2, the daily vitamin C intake from food is calculated as 150.8 and 149.9 mg among low-dose and high-dose group, respectively ( $P$  for difference = 0.94). Also, the serum level of vitamin C did not differ between the group and this means that the background level of vitamin C is similar for low-dose and high-dose group. In our setting, we aimed to investigate the difference in effect of additional supplementation of vitamin C with 50 and 500 mg.

Potential bias is inevitable in any study. Although the subjects were randomized to each group and data were analyzed by considering several factors, the effect of unmeasured factors such as physical and psychologic stress may be important in evaluating the role of vitamin C on the common cold (Hemila, 1996; Takkouche *et al.*, 2001). The findings in this study must be interpreted in light of possible sample selection bias, which may affect the ability to apply our results to other populations. Subjects of this trial were chosen on the basis of a diagnosis of atrophic gastritis by serum PG level (52% of those screened initially). In another village within the same district, the prevalence of atrophic gastritis was 55.4% among participants aged 40–59 years. Although the prevalence of atrophic gastritis was relatively higher in our study subjects than in other areas (Kabuto *et al.*, 1993), our subjects do not represent a special group in Japan.

The initial trial started in September 1995, and all participants had started taking capsules by December 1995 and took them until the protocol amendment in February 1996. Thus, the period for which subjects took the initial capsule ranges from 2 to 5 months. On the basis of the results of our pilot study (Sasaki *et al.*, 2000), no statistically significant interaction between 3-month supplementation of  $\beta$ -carotene and vitamin C was seen either for serum  $\beta$ -carotene or for ascorbic acid. In fact, further adjustment for initial  $\beta$ -carotene treatment did not have any influence on the effect of vitamin C on common cold; adjusted RR and 95% CI for suffering from common cold three or more times

during the survey period was 0.35 (0.12–0.97) in high-dose group.

The effect of vitamin C supplementation on common cold incidence has been extensively studied. Pooled analysis of six major intervention trials of normally nourished subjects in Western countries showed that common cold incidence was not reduced in the vitamin C group, compared with the placebo group (pooled RR 0.99, 95% CI: 0.93–1.04) (Hemila, 1997). Our study differs from these previous studies in several ways. Our supplementation period was much longer than that of the six trials, which ranged from 2 to 9 months (Anderson *et al.*, 1972; Karlowski *et al.*, 1975; Elwood *et al.*, 1976; Ludvigsson *et al.*, 1977; Pitt and Costrini, 1979; Briggs, 1984). The long duration of supplementation may have resulted in the apparent reduction in incidence of the common cold. In fact, in a pilot supplementation study, the serum ascorbic acid level nearly reached a steady state and remained stable from 1 month onwards (Sasaki *et al.*, 2000). In addition, the season during which a study is conducted could affect the apparent role of vitamin C in susceptibility to the common cold. Since common cold viruses are subject to frequent mutations, the type of strain might differ across years. In our study, all seasons were covered for several years, which may have minimized any distortion of the results.

As shown in Table 2, the dietary intake of vitamin C was about 150 mg/day for our study subjects, which is higher than that reported for the UK (30–60 mg/day) and the US (90–120 mg/day) (Hemila, 1997). Neither dietary intake of vitamin C nor serum level of ascorbic acid has been examined in most of the previous vitamin C trials. Thus, we could not compare our subjects' initial vitamin C status with other studies. As we had information of both dietary intake and serum level of vitamin C, we were able to analyze the data precisely.

In placebo-controlled trials, researchers have found consistently that the duration and severity of the common cold is reduced by regular vitamin C supplementation (Hemila, 1997). In these trials, the effect on duration of the cold was slight, but a more marked benefit was observed for severity, measured either directly or indirectly. According to the four largest trials, the relative difference of duration of colds or specific symptoms between intervention groups ranged from 3 to 7%, and the differences in duration of days confined to the house or absent from school (indirect measures of severity) were 21 and 14%, respectively (Anderson *et al.*, 1972; Elwood *et al.*, 1976; Ludvigsson *et al.*, 1977; Pitt and Costrini, 1979). Our results are in line with the previous studies on the effect of vitamin C on common cold duration and severity, although our findings were not statistically significant.

A year after our subjects stopped vitamin C supplementation, the vitamin C group showed a limited immunity to the common cold. Complete elimination of vitamin C from the diet is reported to result in a zero level of ascorbate in serum within 35–40 days, in whole blood in about 80–90 days, and

in white blood cells in 100–120 days (Goodhart and Shils, 1980). Although results did not differ between those who replied on first contact or later, the sample size in our study was small as mentioned above and the ability to detect a long-term effect of vitamin C supplementation may be limited.

In summary, our randomized, controlled 5-year trial suggests that vitamin C supplementation reduces the frequency of the common cold but has no apparent effect on its severity and duration. However, considering the several limitations due to the protocol amendment, cautiousness must be needed in interpreting the results.

## Acknowledgements

We express our appreciation to the staff at Hiraka General Hospital and the public health nurses at the Sannai village office for their support and assistance with the study.

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# Blood pressure change in a free-living population-based dietary modification study in Japan

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**Objective** To assess whether dietary intervention in free-living healthy subjects is effective in improving blood pressure levels.

**Design** Open randomised, controlled trial.

**Setting** Free-living healthy subjects in two rural villages in north-eastern Japan.

**Participants** Five hundred and fifty healthy volunteers aged 40–69 years.

**Interventions** Tailored dietary education to encourage a decrease in sodium intake and an increase in the intake of vitamin C and carotene, and of fruit and vegetables.

**Main outcome measures** Blood pressure, dietary intake and urinary excretion of sodium, dietary carotene and vitamin C, and fruit and vegetable intake data were collected at 1 year after the start of the intervention.

**Results** During the first year, changes differed significantly between the intervention and control groups for dietary ( $P = 0.002$ ) and urinary excretion ( $P < 0.001$ ) of sodium and dietary vitamin C and carotene ( $P = 0.003$ ). Systolic blood pressure decreased from 127.9 to 125.2 mmHg (2.7 mmHg decrease; 95% confidence interval,  $-4.6$  to  $-0.8$ ) in the intervention group, whereas it increased from 128.0 to

128.5 mmHg (0.5 increase;  $-1.3$  to  $2.3$ ) in the control group. This change was statistically significant ( $P = 0.007$ ). In contrast, the change in diastolic blood pressure did not significantly differ between the groups. In hypertensive subjects, a significant difference in systolic blood pressure reduction was seen between the groups ( $P = 0.032$ ).

**Conclusion** Moderate-intensity dietary counseling in free-living healthy subjects achieved significant dietary changes, which resulted in a significant decrease in systolic blood pressure. *J Hypertens* 24:451–458 © 2006 Lippincott Williams & Wilkins.

*Journal of Hypertension* 2006, 24:451–458

**Keywords:** blood pressure, dietary, fruit and vegetables, intervention studies, randomized controlled trials, sodium

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Sponsorship: This study was supported in part by Grants-in-Aid for Cancer Research and for the Second- and Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.

Received 14 February 2005 Revised 11 October 2005 Accepted 14 November 2005

## Introduction

Stroke is the most common cardiovascular disease in Japan [1]. Hypertension is the major cause of stroke, making the control of hypertension an important factor in the prevention of stroke. Non-pharmacological treatment is recommended as the first line of management for elevated blood pressure (BP) [2], primarily composed of lifestyle and diet modification. Evidence indicates that lifestyle measures such as weight reduction [3], moderation of alcohol consumption [4] and reduction in salt intake [5,6] are both feasible and effective in lowering BP. The importance of dietary factors was demonstrated in the DASH (Dietary Approach to Stop Hypertension) study, in which a diet rich in fruits and vegetables, and utilizing low-fat dairy products and products low in saturated and total fat, decreased systolic and diastolic

BP compared with a diet representative of a typical diet for Americans [7].

Most clinical intervention trials targeted at the prevention and control of hypertension to date have been performed in academic study centers by expert personnel trained in the conduct of the trial. Because these studies were primarily designed to test the efficacy of their interventions, the intervention programs themselves were intensive. Due to the limited resources of the public health sector, however, broad implementation of such intensive lifestyle modification programs is difficult. Only a few lifestyle interventions have been performed in primary health care settings, and although most involved patients with hypertension, the interventions themselves were of low intensity and their effect was small.

Moreover, these studies have frequently lacked evaluations of dietary compliance using validated measures.

The Hiraka Dietary Intervention Study [8] was a moderate-intensity, community-based randomized controlled trial designed to develop an effective dietary modification tool and system in an area with high mortality for stomach cancer and stroke. The dietary intervention was designed to decrease sodium (salt) and increase vitamin C and carotene intakes, with an emphasis on a decrease in salted foods and an increase in fruits and vegetables. The effects of the intervention were assessed not only using responses to a self-administered questionnaire but also the corresponding biomarkers. Here, we examine the effects of this dietary intervention on BP.

## Methods

### Study subject and design

The Hiraka Dietary Intervention Study was a community-based, randomized, cross-over trial held in 1998–2000 in two rural villages in Akita Prefecture, Japan.

Participants were recruited through public magazines and posters, in which potential respondents were asked to participate in a research project. Eligibility criteria for this study were: (1) age 40–69 years; and (2) physician permission to participate for those under medical treatment or dietary control. We expected to detect a difference in mean salt intake of 2.0 g/day (787 mg as sodium) or more between the intervention and control groups after 1 year, with a 5% alpha error (two-sided) and 20% beta error. A previous study reported a mean dietary sodium intake in a nearby area of 5940 mg/day (standard deviation  $\pm 2594$ ) for men and 6013 mg/day ( $\pm 2622$ ) for women [9]. We estimated that a minimum of 352 participants would be needed for the trial, 176 allocated to each of the intervention and control groups. To allow for non-completion of the intervention study we aimed to recruit 470 participants. Five hundred and fifty volunteers (202 men and 348 women, aged 40–69 years) participated. All participants were informed of the study protocol, and written informed consent was obtained. They were assigned randomly into two groups and received tailored dietary education in either the first year (intervention group,  $n = 274$ ) or the second year (control group,  $n = 276$ ) by the same researcher. The random number of 0 (allocated to the first intervention group) or 1 (second intervention group) was generated for each subject using a function of Microsoft Excel. Subjects within one family were assigned to the same group. This procedure was repeated until the subject number in the two groups was the same.

Dietary goals at the group level were to reduce salt intake to less than 8 and 10 g/day in women and men, respectively, to increase carotene intake to more than

5000  $\mu\text{g}/\text{day}$ , and to increase vitamin C intake to more than 200 mg/day. Our intervention consisted of individual 15-min dietary counseling sessions (two), a group lecture, and newsletters (two). First, dietary counseling was provided after the subject's annual health check-up. Individualized education schemes were prepared based on the results of the dietary survey and health check-up. About 5 months later, a second dietary assessment was performed and the same individual dietary counseling was provided to each subject. During the intervention period, a total of two newsletters about recommended diet were mailed to the participants to maintain motivation throughout the trial. The group lecture was performed at the mid-point of the intervention period.

To increase carotene and vitamin C intake, subjects were advised to increase their intake of fruit and vegetables. To decrease sodium intake, they were primarily instructed to decrease their intake of salted foods, such as miso (fermented and salted soybean paste), salted vegetable pickles, salted fish, and seasonings.

### Data collection

A validated, self-administered diet history questionnaire (DHQ) was completed by all subjects three times, just before the annual health check-up conducted between April and August in 1998, 1999 and 2000. The DHQ surveyed dietary habits for the previous 1 month. The structure and validity of the DHQ have been described in detail elsewhere [10–12].

Forty-eight-hour urine samples were collected just after the annual health check-up. The subjects were requested to record the times at which they started and finished the urine collection. Urinary volume was measured, and a part of each sample was stored at  $-20^{\circ}\text{C}$  until measurement. Whenever urine collection was missed, the estimated volume was reported by the subject and added to that of the collected urine to estimate the total urinary volume. The urinary concentrations of sodium and potassium were analyzed by flame photometry and creatinine by Jaffe's procedure using an autoanalyzer (Hitachi Clinical Analyzer 7070; Tokyo, Japan). The expected intakes were computed using observed urinary excretion, as reported in a carefully designed balance study, namely 0.86 for sodium and 0.77 for potassium [13].

BP was measured at the annual health check-up by trained nurses, using a sphygmomanometer OKOSE-300 model (Matsuyoshi & Co., Tokyo, Japan) according to a common protocol. A single measurement was performed in this trial. All measurements at each point were conducted by one nurse who was engaged in the health check-ups, and not by study staff. The nurse was blinded to the intervention assignment and was requested by the study staff not to inquire about the subject's allocation at BP measurement.