An Optimal Cutoff Point of Expired-Air Carbon Monoxide Levels for Detecting Current Smoking: in the Case of a Japanese Male Population whose Smoking Prevalence was Sixty Percent

Takeo Nakayama 1, Akio Yamamoto 1,2, Takayoshi Ichimura 1, Nobuo Yoshiike 3, Tetsuji Yokoyama 1, Edward K. Fujimoto 4, and Heizo Tanaka 1

An optimal cutoff point of expired-air carbon monoxide (Ex-CO) for detecting smokers should be determined in terms of its sensitivity and specificity and the prevalence of smoking in the target population. The purpose of this study is to determine the optimal cutoff point of Ex-CO for detecting smoking males in a Japanese community whose smoking prevalence was over 50%. Among free-living residents in a rural population, “true smokers” determined by presence of cotinine in serum were 61% (n=94). When Ex-CO at 7 ppm or over differentiated “smokers” from “non-smokers”, sensitivity and specificity for detecting smokers was 0.93 and 0.95, respectively, which comprised the best Youden’s index. This setting also produced the minimum percentage of misclassified cases. In conclusion, 7 ppm of Ex-CO, which is exceptionally low value relative to the western standard, appears to be the most optimal cutoff point for a survey in a population with such high smoking prevalence. J Epidemiol, 1998; 8:140-145.

cigarette, carbon monoxide, cutoff point, sensitivity, specificity, predictive value

To validate self-reported data on smoking, use of biochemical markers has been encouraged. Among some examined markers, cotinine is considered to be very good because of its high sensitivity and specificity to tobacco smoke exposure 14). However, it has not been widely used in usual medical practice or population surveys due to its high cost and the necessity of venepuncture. While using saliva or urine samples is much less invasive than using serum samples 3,4), the problem of cost would still be unresolved. In the 1970s, measuring expired-air carbon monoxide (Ex-CO) was shown to be valid as an alternative marker of current smoking 6,7). During this decade, a handy and inexpensive instrument to measure Ex-CO 8 was developed and gradually popularized. This is equipped with a sealed electrochemical sensor and provides an immediate display of subjects’ Ex-CO levels, which are proportional to carboxyhemoglobin levels in blood. Using this instrument, 8 - 11 ppm cutoff points were often used to discriminate smokers from non-smokers 6,8-14). However, selection of the cutoff points was almost arbitrary. An optimal cutoff point of Ex-CO for detecting current smokers should be determined in terms of its sensitivity and specificity and the prevalence of smoking in the target population 15). Ideally the optimal cutoff point should be set for each target group and for each specific purpose.

Compared with other developed countries, the Japanese male population is generally characterized as having an extremely high prevalence of smoking, approximately 60% by self report 16,17). Studies of the reliability of biochemical markers such as Ex-CO and serum cotinine and the setting of an optimal cutoff point for Ex-CO to detect current smoking in such a field setting have been rare.

We compared self-reported smoking status with the levels of serum cotinine and Ex-CO in free-living male residents in a Japanese rural community, and examined the reliability of Ex-CO for detecting current smoking by setting various cutoff points.

Received December 24, 1997; accepted March 23, 1998.

1 Department of Epidemiology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan.
2 Department of Epidemiological Information, Hyogo Prefectural Institute of Health, Kobe, Japan.
3 Division of Adult Health Science, National Institute of Health and Nutrition, Tokyo, Japan.
4 Division of Health Education, Tokyo Adventist Hospital, Tokyo, Japan.
5 Address for correspondence: Takeo Nakayama, Department of Epidemiology, Medical Research Institute, Tokyo Medical and Dental University 2-3-10, Kanda-Surugadai, Chiyoda-Ku, Tokyo 101-0062, Japan.
MATERIALS AND METHODS

The study area was a rural community in the west central Japan, Yamasaki Town, Shiso County in Hyogo Prefecture. The subjects were adult males living in this area, who participated in an annual health checkup by the local administration in October, 1990. As habitual smoking is not so common for adult females living in rural areas in Japan, the subjects were limited to males only. Consecutive health checkup participants on a day were invited to be involved in our study. We asked them to report their smoking status and measured their Ex-CO using a CO-detector, “Micro-Smokerlizer” (Bedfont Technical Instrument Ltd., Sittingbourne, Kent., UK) that was calibrated with the standard gas by the company just before the examination. This measurement was done in the morning in a large room with good ventilation and no equipment producing excess CO. The subjects were requested to follow the standard protocol described in the manual: they were asked to exhale fully, then inhale deeply and hold breath for 15-20 seconds before exhaling into “Micro-Smokerlizer” through a disposable mouthpiece. Immediately after the subjects exhaled into the instrument, the maximum readings were noted as their Ex-CO levels. Throughout the study, Ex-CO levels were measured by one operator using the same instrument. On the same day, we took their fasting venous blood samples and after centrifugation, serum cotinine concentrations were measured by gas-chromatography. The lowest detectable limit of this method was 0.06 μM/L (10 ng/ml).

Before the principal examination, reproducibility of measuring Ex-CO levels by “Micro-Smokerlizer” was evaluated with selected subjects. They were tested twice (the interval was supposed to be within almost three minutes), and obtained values were used for simple regression and Pearson’s correlation analysis. The relationships of serum cotinine concentrations to Ex-CO levels and to self-reported numbers of cigarettes smoked before the test were examined by using Spearman’s rank correlation coefficient.

To evaluate the reliability of Ex-CO for detecting smoking status, sensitivity and specificity were assessed for the various cutoff points. Predictive values and the number of subjects misclassified were also obtained for each characteristic.

According to the lowest limit of the gas-chromatographic technique that we adopted and the cutoff point of serum cotinine previously established (0.084 μM/L) 2,3,15, we defined subjects whose serum cotinine was not detectable by this method as “non-smokers”. Subjects, other than these “non-smokers”, were classified as “smokers” in the present study. Namely, serum cotinine concentration was regarded as the gold standard in this research.

RESULTS

This study area was rural and most of the subjects were farmers or proprietors of small shops. All eligible subjects, total 100 males, consented to our requests for the study design. Among them, three smokers and three non-smokers who are confirmed by both self-report and serum cotinine concentrations were excluded because they failed to undergo Ex-CO measurement. Therefore, 94 subjects were analyzable for the present investigation. The mean age and standard deviation was 61.4 and 11.7 (range: 32-81), respectively. For examination of reproducibility, the following formula was obtained from the reported measurements of Ex-CO: second value = 0.99 × initial value + 0.13 (Pearson’s correlation coefficient was 0.99, p<0.01, n=57). This measurement was so reproducible that single measurements were adopted as a rule. In the subjects who took measurements twice, the initial value was used for analysis.

Table 1. shows the results of self-reported number of cigarettes smoked daily levels of Ex-CO and serum cotinine concentrations. As types of tobacco other than cigarettes are not common in Japan, types of tobacco were not specified in this study. According to the serum cotinine concentrations, 57 males were indicated to be “smokers”, each of which was in complete agreement with the smoking status by self-report. The percentage of “smokers” in this study was 61%, which was very similar to the Japanese national average 17). All “smokers” smoked regularly five or more cigarettes per day. Out of 37 self-reported non-smokers, 25 subjects were ex-smokers (mean period of time after quitting was 11.2 years) and 12 subjects were lifelong non-smokers.

Spearman’s rank correlation coefficients between serum cotinine concentrations and Ex-CO levels was 0.86 (p<0.01); between serum cotinine concentrations and self-reported number of cigarettes smoked was 0.76 (p<0.01), between self-reported number of cigarettes and Ex-CO levels was 0.84 (p<0.01), respectively.

Table 2. shows the reliability of Ex-CO levels for detecting “true smokers” in terms of sensitivity and specificity with various cutoff points. In the cases that the subjects whose Ex-CO levels were 8 ppm or over were classified as current “smokers” (8 ppm cutoff point), sensitivity was 0.86 and specificity was 1.00. That is, the false positive rate of detecting “smokers” in this case was 0. If 7 ppm cutoff point was adopted, sensitivity improved up to 0.93 but specificity decreased to 0.95. In the case of 11 ppm cutoff point, as Bedfont suggests that Ex-CO levels were 1-10 ppm indicating “non-smoker”, sensitivity and specificity was 0.70 and 1.00, respectively. Youden’s index (sensitivity+specificity-1) 18,19 was the highest at 7 ppm cutoff point (0.88), which was followed by 8 ppm cutoff point (0.86). In terms of the number of subjects misclassified, 7 ppm cutoff point produced the minimum cases, six cases out of those
### Table 1. Results of the three methods of evaluating smoking status.

|                              | mean  | SD   | median | range |
|------------------------------|-------|------|--------|-------|
| Self-reported number of      |       |      |        |       |
| cigarettes smoked daily      |       |      |        |       |
| all subjects, n=94           | 12.6  | 12.5 | 15     | 0-60  |
| smokers only, n=57           | 20.9  | 9.1  | 20     | 5-60  |
| Ex-CO levels (ppm)           |       |      |        |       |
| all subjects, n=94           | 10.9  | 7.5  | 8      | 3-39  |
| smokers only, n=57           | 14.9  | 7.3  | 13     | 3-39  |
| Serum cotinine concentrations (uM/L) |   |     |       |       |
| all subjects, n=94           | 1.04  | 1.15 | 0.80   | 0-4.67|
| smokers only, n=57           | 1.74  | 1.00 | 1.72   | 0.12-4.67|

all subjects, n=94; smokers only, n=57.
SD, standard deviation; Ex-CO, Expired-air carbon monoxide.

### Table 2. Reliability of expired-air carbon monoxide levels for detecting “true smokers” with various cutoff points in Yamasaki Town, Shisho County, Hyogo Prefecture, Japan.

| Ex-CO cutoff point (ppm) | “true smoker” | SS | SP | PPV | NPV | Y  | FP | FN | total |
|--------------------------|---------------|----|----|-----|-----|----|----|----|-------|
|                          | -             | 28 | 1  | 29  |     |    |    |    |       |
|                          | +             | 9  | 56 | 65  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 6                        | -             | 35 | 4  | 39  |     |    |    |    |       |
|                          | +             | 2  | 53 | 55  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 7                        | -             | 37 | 8  | 45  |     |    |    |    |       |
|                          | +             | 0  | 49 | 49  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 8                        | -             | 37 | 12 | 49  |     |    |    |    |       |
|                          | +             | 0  | 45 | 45  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 9                        | -             | 37 | 17 | 54  |     |    |    |    |       |
|                          | +             | 0  | 40 | 40  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 10                       | -             | 37 | 17 | 54  |     |    |    |    |       |
|                          | +             | 0  | 40 | 40  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 11                       | -             | 37 | 17 | 54  |     |    |    |    |       |
|                          | +             | 0  | 40 | 40  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |
| 12                       | -             | 37 | 21 | 58  |     |    |    |    |       |
|                          | +             | 0  | 36 | 36  |     |    |    |    |       |
|                          | total         | 37 | 57 | 94  |     |    |    |    |       |

“True smokers” were determined by presence of cotinine in serum.
Ex-CO, expired-air carbon monoxide; SS, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; Y, Youden’s Index; FP, false positive; FN, false negative.
If a cutoff point is 6 ppm, the subjects whose Ex-CO levels are 6 ppm or over are classified as smokers.
examined (6%) , while 17 cases (18%) resulted if 10 or 11 ppm cutoff point was used.

**DISCUSSION**

We regarded the utility of measuring Ex-CO in clinical setting or health education as the following. (i) As an objective marker of smoking, to detect true current smokers either in cessation program or field survey. (ii) For smokers, as a determinant how much they have been exposed to CO. (iii) As a tool of motivation for smokers to quit in the real-time and self-feedback nature of measurement. (iv) As information for subjects to verify the ability of Ex-CO measurements to facilitate them to make true answer about their smoking status (pipeline procedure) 28. The purpose of the present analysis is mainly concerned with Ex-CO as a marker in a field setting (i).

In the present subjects, classification of “smokers” or “non-smokers” by serum cotinine concentrations completely agreed with that by self-reported smoking status. There was a small discrepancy between the lowest detectable limit of the present method (0.060 µM/L) and the cutoff point set according to the previous reports (0.084 µM/L) 2, 3, 15. However, the lowest value actually measured among 57 smokers with detectable serum cotinine was 0.12 µM/L and none showed the border zone value. Therefore, the complete agreement of the self-reported with the cotinine-determined smokers would be acceptable as is. This meant that none of the subjects misrepresented their current smoking status, even if some underreporting was possible 24, 12, 21.

Shown by Youden’s index, the most optimal cutoff point for effective detection of “smokers” in this population was 7 ppm, followed by 8 ppm. Sensitivity and specificity obtained in the present study was intermediate among the values reported in the previous reports that set each best cutoff point in terms of sensitivity and specificity 2, 3, 15.

The prevalence of smoking in the population tested can alter the predictive values of the diagnostic test and consequently change the number of subjects misclassified 20. Cummings 15 advocated that higher cutoff points than the value that had been used in the previous studies should be adopted in groups in which smoking percentage was low. Otherwise, considerable number of false positive cases may be produced. The percentage of smokers in the present study population was 61 %, which was almost twice as high as those in most western male populations. Adopting a higher cutoff point that would be appropriate for most western male populations would produce more misclassified cases, particularly false negative cases in the population under study. So, a lower cutoff point would be better in this population to decrease the subjects misclassified. Adopting 7 ppm cutoff point produced the minimum misclassified cases, 6% of cases, while 18% were misclassified if 10 or 11 ppm was taken in the present study. Percentage of misclassified subjects could be calculated as prevalence of smoking × (false negative rate - false positive rate) + false positive rate 19. Figure 1. shows the difference in percentage of misclassified subjects for three levels of smoking percentages in the population for various values of cutoff point. In this figure, each percentage of misclassified subjects was calculated using the formula as mentioned above and false positive and negative rates shown in Table 2. To estimate the smoking percentage in a population using this instrument, the best cutoff points were the values that produced an equal number of false negative and false positive cases 19. The case of 7 ppm cutoff point showed the number of false positive and false negative of two and four, respectively, being the most balanced among all combinations. Therefore from this standpoint also, 7 ppm was the best cutoff point in the population such as the present one.

The subjects were asked to participate in the study on the day of examination and were not informed previously that their serum cotinine and Ex-CO would be measured. Therefore, few smoking subjects would have been able to change their habitual smoking in advance. However, seven subjects who reported to take their first cigarettes usually within 30 minutes after waking up did not smoke in the morning of the day just for the routine health checkup. If more smokers abstained from smoking just before the examination, the relationship between levels of Ex-CO and serum cotinine may have been changed due to difference in their biological half-life (Ex-CO, 1-5 hours; serum cotinine, 20 hours). However, most smoking subjects would not be expected to change their habitual smoking. So the relationships observed would be largely valid. Irregular smokers who sometimes smoke may show somewhat different pattern from regular smokers 2, however, such type of smokers were not found in the present subjects. There are several other factors that may influence Ex-CO levels: subjects' clumsiness in using this instrument, the period of time after last smoking, the depth of inhaling smoke, the pattern of puffing, the butt length of cigarettes smoked and so on, which need further studies. When the subjects under environments such as air-polluted urban area and the crowded office where passive smoking is inevitable are examined, these living conditions may potentially influence the subjects' Ex-CO levels. To study this possibility, further researches are to be done.

In conclusion, 7 ppm of Ex-CO is proposed as the most optimal cutoff point for appropriate detection in a population whose percentage of smoking was up to 60% such as in the present one. The optimal cutoff points of Ex-CO would vary according to population and purpose of examination concerned. If true smokers are misclassified false-negatively into non-smokers due to inappropriate cutoff points, their motivation to quit smoking may be weakened and this undesirable behavior may be reinforced by the absence of adequate feedback. Determination of optimal cutoff points of Ex-CO is important and needs considerations on sensitivity, specificity...
Figure 1. Percentage of misclassified cases of smoking (both false positive and false negative) according to various cutoff points of expired-air carbon monoxide levels and populations with different smoking prevalence. Each percentage of misclassified case is calculated by the following formula: 
(prevalence of smoking of each population) × (false negative rate - false positive rate) + (false positive rate), where false negative and positive rates are drawn from Table 2).

ACKNOWLEDGEMENTS

This work was supported by the Grant-in-Aid for Cancer Research (1-47) from the Ministry of Health and Welfare. We would like to thank the subjects, the staff members of Yamasaki Town Health Center, Dr. Takashi Yamamoto, Dr. Manami Inoue and Dr. Yoshio Matsuda.

REFERENCES

1. Perez-Stable E, Benowitz N, Marin G. Is serum cotinine a better measure of cigarette smoking than self-report? Prev Med 1995;24:171-179.
2. Wagenknecht L, Burke G, Perkins L, Haley N, Friedman G. Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. Am J Public Health 1992;82:33-36.
3. Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. Am J Public Health 1987;77:1435-1438.
4. Muranaka H, Higashi E, Itani S, Shimizu Y. Evaluation of nicotine, cotinine, thiocyanate, carboxyhemoglobin, and expired carbon monoxide as biochemical tobacco smoke uptake parameters. Int Arch Occup Environ Health 1988;60:37-41.
5. Abrams D, Follick M, Biener L, Carey K, Hitti J. Saliva cotinine as a measure of smoking status in field settings. Am J Public Health 1987;77:846-848.
6. Vogt T, Selvin S, Widdowson G, Halley SB. Expired air carbon monoxide and serum thiocyanate as objective measures of cigarette exposure. Am J Public Health 1977;67:545-549.
7. Jarvis M, Russell M, Saloojee Y. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. Br Med J 1980;281:484-485.
8. Bedfont Technical Instruments Ltd. Operator's manual for mini and “new” microsmokerlyzers: breath testing CO monitors for smoking education and cessation applications. Sittingbourne, England

9. Cohen J, Bartsch G. A comparison between carboxyhemoglobin and serum thiocyanate determinations as indicators of cigarette smoking. Am J Public Health. 1980;70:284-286.

10. Pettiti D, Friedman G, Kahn W. Accuracy of information on smoking habits provided on self-administered research questionnaires. Am J Public Health 1981;71:308-311.

11. Pojer R, Whitfield J, Poulos V. Carboxyhemoglobin, cotinine and thiocyanate assay compared for distinguishing smokers from non-smokers. Clin Chem 1984;30:1377-1380.

12. Fortman S, Rogers T, Vranizan K, Haskell W, Solomon D, Farquhar J. Indirect measures of cigarette use: expired-air carbon monoxide versus plasma thiocyanate. Prev Med 1984;13:127-135.

13. Ruth KJ, Neaton JD. Evaluation of two biological markers of tobacco exposure. MRFIT Research Group. Prev Med 1991;20:574-89.

14. Waage H, Silsand T, Urdal P, Langard S. Discrimination of smoking status by thiocyanate and cotinine in serum, and carbon monoxide in expired air. Int J Epidemiol. 1992;21:488-493.

15. Cummings S, Richard R. Optimum cutoff points for biochemical validation of smoking status. Am J Public Health 1988;78:574-575.

16. Pierce J. International comparisons of trends in cigarette smoking prevalence. World Smoking and Health 1989;14:3-6.

17. Ministry of health and welfare of Japan, Statistical Bureau. Smoking and Health. Hoken Dojin Sha, Tokyo. 1993 (in Japanese).

18. Youden W. Index for rating diagnostic tests. Lancet 1950;3:32-35.

19. Last J, A dictionary of epidemiology (3rd ed). Oxford University Press, New York. 1995:176.

20. Murray D, O'Connell C, Schmid L, Perry C. The validity of smoking self-reports by adolescents: a re-examination of the bogus pipeline procedure. Addict Behav. 1987;12:225-233.

21. Sillett R, Wilson M, Malcolm R, Ball K. Deception among smokers. Br Med J 1978;2:1185-1186.

22. Sox H. Probability theory in the use of diagnostic tests: an introduction to the critical study of the literature. Ann Intern Med 1986;104:60-66.