ORIGINAL CONTRIBUTION

A Matched Case-Control Study on Sudden Unexpected Death among Japanese Workers

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A matched case-control study on sudden unexpected death, defined as a natural death within 24 hours after the onset of acute symptoms occurring in apparently healthy workers, was carried out. The purpose of our study is to analyze the factors that precede sudden unexpected death among Japanese workers, controlling for differences in working conditions. 102 male cases and 202 age- and sex-matched coworker controls were studied, using questionnaires sent to fulltime occupational health physicians. Mean values of blood pressure, number of cigarettes smoked daily were significantly higher and that of HDL-cholesterol were significantly lower in the sudden death cases than in the controls. A larger number of workers with hypertension and electrocardiogram abnormality and a smaller number of managerial workers and individuals with higher education were found among the sudden death cases than among the controls. Conditional logistic regression analysis suggested that hypertension may be the most positive predictor of sudden unexpected death among Japanese workers (relative risk = 2.37, 95% confidence interval : 1.29-4.35). *J Epidemiol*, 1993; 3 : 29-34.

sudden unexpected death, worker, occupational health physician, hypertension, occupation

In recent years, serious occupational diseases and fatal accidents in workplaces have decreased because of improvements in occupational safety and health. Causation of worker's illness has changed from a single, direct cause to a multifactorial, nonspecific one. Under such circumstance, WHO proposed in 1976 the term of "work-related diseases" for a variety of disorders that were probably more prevalent than specific occupational diseases among working people. It is now being given special attention in the field of occupational health¹⁾.

In Japan, sudden unexpected death among workers has aroused social concern because it is regarded as one of the work-related diseases caused by excessive work such as working for long hours. In fact, a number of claims, though only a few percent of the total, for workers' compensation from the families of the victims have been recognized²⁾.

However, few epidemiological, analytical studies on

sudden unexpected death in Japan have been carried out on the working population although several descriptive studies have been conducted with general population cohorts³⁾, medical examiner's reports⁴⁾, and information from death certificates^{5,6)}. It is considered, in general, that cardiovascular disorders are the most important factor in sudden unexpected death⁷⁾. Thus, it should be clarified to what extent such death is attributable to coronary risk factors, prioritizing over the analyses of its relation with work-related factors.

The purpose of our study is to analyze by using methods of case-control study the factors that precede sudden unexpected death among Japanese workers, controlling for differences in working conditions.

SUBJECTS AND METHODS

A preliminary questionnaire was sent to 392 full-

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time occupational health physicians (OHPs) who were active members of the Japan Association of Industrial Health. This questionnaire included the following two questions: (1) whether or not they would agree to join and cooperate in this study, and (2) number of sudden unexpected deaths that occurred in their company from Jan. 1, 1986, through Dec. 31, 1990. We defined sudden unexpected death as a natural death occurring within 24 hours after the onset of acute symptoms in a person who had had no restrictions on his daily working activities prior to the onset of symptoms.

Of the 242 OHPs who answered the questionnaire (response rate: 61.5%), 124 agreed to join in our study. However, 53 of those 124 OHPs had experienced cases of sudden unexpected death in their companies. The 53 OHPs reported all cases which occurred in each of the companies during the period (approximately 330,000 workers, annually). Two matched control subjects for each of the cases were selected according to sex and age (equal or of minimal difference) from among the workers of the same workplace. The selection of each control was conducted under clear instructions, the process of which included the making of lists of random sampling candidates for controls, using a table of random sample numbers. The questionnaires were sent to the OHPs which requested for the following information: (1) information on sudden unexpected death cases (age at death, sex, date of birth, date of death, time of death, time of onset of acute symptoms that resulted in sudden unexpected death, cause of death, post-mortem information), (2) information on physical examination of both cases and controls (body weight, height, blood pressure, serum total-cholesterol, serum HDL-cholesterol, a 12-lead electrocardiogram (ECG)), (3) information on lifestyle of both cases and controls (marital status, education, weekly consumption of alcohol, daily consumption of cigarettes, physical exercise), and (4) information on the working conditions both of cases and controls (occupation, shift work). Basically, the data for (2) and (3) were collected from the records of the annual periodical physical examination prior to the time of death, and the information for (4) was collected from data on file in each company. As for control data for (2) and (3), the records just prior to time of death were used. The control data were collected from records corresponding to each case record. The conditions used for the analyses were defined as follows: hypertension: either systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg and/or currently being medically treated for high blood pressure; diabetes: currently being medically treated and/or managed for impaired glucose tolerance; ECG abnor-

mality: a finding of one or more of left ventricular hypertrophy, cardiac arrhythmia, specific ST-T variation, and/or infarction in ECG; drinking: currently drinking alcoholic beverages at least 14 'go' (a Japanese term of measurement indicating about 30 milliliters of ethyl alcohol in alcoholic beverages) per week; smoking: currently smoking cigarettes more than a package per day; physical exercise: sometimes or usually doing physical exercise; shift work; currently being a shift worker regardless of the amount of exposure to it.

T-tests were performed first in order to evaluate differences in physical examination results and lifestyle between cases and controls. Second, the estimated relative risk of sudden unexpected death by using the Mantel-Haenszel method⁸⁾ and the 95% confidence intervals (CI) by Miettinen's method⁹⁾ were calculated. Third, conditional logistic regression analysis was performed in order to estimate the relative risk of sudden unexpected death after controlling for effects of confounding variables, using the SAS PHREG procedure.

RESULTS

Of the 143 cases of sudden unexpected deaths which the 53 OHPs reported, there were 141 males and 2 females. The analyses were restricted to males due to the small number of females. Of these 141 male cases, 39 were excluded because no data on physical examination was available. Thus, the 102 cases made sets of data for the analyses. Two of these sets, however, had only one control and they were excluded from the calculation of relative risk of sudden unexpected death by the Mantel-Haenszel method because the sets could not have been analyzed appropriately.

The characteristics of both cases and controls are presented in Table 1. A smaller number of managers and officials, and a larger number of individuals with lower education were found among the sudden death cases than among the controls.

Comparisons of mean values of physical examination data are shown in Table 2. Mean values of systolic blood pressure, diastolic blood pressure, number of cigarettes consumed per day were significantly higher in the cases than in the controls. That of HDL-cholesterol was significantly lower in the cases than in the controls. After excluding the values of those who had taken anti-hypertensive drugs, the mean systolic and diastolic blood pressures still remained significantly higher in the cases than in the controls. Mean values of total-cholesterol and alcohol consumption per week were relatively higher in the cases than in the controls, which were of borderline significance.

Table 1. Characteristics of the cases and the controls.

	Cases	Controls
Number	102 (100.0%)	202 (100.0%)
Age (years) ^a	46.6 ± 9.7	46.7 ± 9.7
Marital Status		
married	83 (81.4%)	135 (66.8%)
not married	10 (9.8%)	13 (6.9%)
divorced/others	2 (2.0%)	1 (0.5%)
unknown	7 (6.9%)	52 (25.7%)
Education		
high school graduate or higher	53 (52.0%)	113 (55.9%)
junior high school or lower	19 (18.6%)	17 (8.4%)
unknown	30 (29.4%)	72 (35.6%)
Occupation		
professional and technical workers	23 (22.5%)	46 (22.3%)
managers and officials	9 (8.8%)	42 (20.8%)
clerical and related workers	14 (13.7%)	17 (8.4%)
sales workers	4 (3.9%)	0 (0.0%)
workers in transport and communications occupations	0 (0.0%)	3 (1.5%)
craftsman and production process workers, labourers	49 (48.0%)	86 (42.6%)
productive service workers	2 (2.0%)	4 (2.0%)
not elsewhere classified	1 (1.0%)	0 (0.0%)
unknown	0 (0.0%)	4 (2.0%)

^a Mean age and standard deviation.

Table 2. Comparison of physical examination results and lifestyle of the cases and the controls.

	Cases		Controls		p-value
	mean ± SD ^a	(N)	mean ± SD	(N)	
Body mass index (kg/m ²)	23.4 ± 2.6	(97)	22.9 ± 3.1	(199)	NS ^c (0.125)
Systolic blood pressure (mmHg)	133.1 ± 17.6	(101)	126.9 ± 15.4	(200)	0.002
Diastolic blood pressure (mmHg)	81.4 ± 12.8	(101)	78.1 ± 12.1	(200)	0.028
Total-cholesterol (mg/100 ml)	198.2 ± 39.5	(89)	188.3 ± 41.1	(190)	NS ^c (0.086)
HDL-cholesterol (mg/100 ml)	44.6 ± 11.3	(89)	50.1 ± 11.4	(190)	0.009
Alcohol consumption per week (go ^b)	12.2 ± 5.4	(54)	10.4 ± 6.0	(103)	NS ^c (0.079)
Number of cigarettes per day	16.1 ± 14.2	(74)	12.4 ± 12.3	(166)	0.038

^a Standard deviation.

^b A Japanese term of measurement indicating about 30 ml of ethyl alcohol in alcoholic beverages.

^c Not statistically significant at the 5% level.

Estimated relative risk by the Mantel-Haenszel method and the 95% CI by Miettinen's method are shown in Table 3. Hypertension and ECG abnormality were associated with the elevated risks of sudden unexpected death. In addition, high educational level (high school graduate or higher) was also associated with the decreased risk of sudden unexpected death. Drinking was associated with the elevated risk at borderline significance, but history of cardiac heart disease or smoking were not associated with risk of

death. The risk of shift work was also not statistically significant.

Estimated relative risk and the 95% CI by conditional logistic regression analysis are presented in Table 4. Hypertension was associated with the elevated risk of sudden unexpected death after controlling for other variables. In contrast, none of the other variables, i.e., total-cholesterol, ECG abnormality, drinking, and educational level, showed significant risks.

Table 3. Relative risk by the Mantel-Haenszel method and the 95% CI by Miettinen's method.

Risk factor	Sets ^a	Relative risk (95% CI)
Diabetes ^b	87	1.50 (0.26 — 8.75)
Hypertension ^b	94	4.20 (1.46 — 6.64)
History of cardiac heart disease	87	4.00 (0.56 — 28.68)
ECG abnormality ^b	55	2.50 (1.00 — 6.27)
Drinking ^b	77	2.05 (0.96 — 4.38)
Smoking ^b	77	1.42 (0.79 — 2.56)
Physical exercise ^b	46	0.58 (0.17 — 1.94)
Married	73	0.91 (0.29 — 2.85)
Educational level ^c	53	0.20 (0.05 — 0.88)
Shift work ^b	77	1.50 (0.68 — 3.29)

^a Number of analyzed data sets which include 1 case and 2 controls.

^b See text, for definition of diabetes, hypertension, ECG abnormality, drinking, smoking, physical exercise and shift work.

^c High school graduate or higher.

Table 4. Relative risk by conditional logistic regression analysis.

Risk factor	Parameter estimate	Standard error	Relative risk (95% CI)
Hypertension ^a	0.86	0.31	2.37 (1.29 — 4.35)
ECG abnormality ^a	0.55	0.32	1.74 (0.92 — 3.28)
Total-cholesterol ^b	0.59	0.40	1.80 (0.82 — 3.95)
Drinking ^a	0.43	0.36	1.54 (0.76 — 3.14)
Educational level ^c	0.02	0.29	1.02 (0.58 — 1.79)

^a Dichotomous variable coded as 0=absent, 1=present.

^b Dichotomous variable coded as 0=total-cholesterol 240 or less (mg/100 ml), 1=total-cholesterol more than 240 (mg/100 ml).

^c Dichotomous variable coded as 0=junior high school graduate or less, 1=high school graduate or higher.

DISCUSSION

To our knowledge, this is the first epidemiological study to be carried out on sudden unexpected death among Japanese workers¹⁰⁾. In this study, we matched the workplace of the case and the controls because the working condition is regarded as a confounding factor in the occurrence of sudden unexpected death. Thus, the co-worker matching made it possible to adjust for the differences of the work style and work environment. For comparison of working condition, we analyzed the data of the working time in the four weeks prior to each death for a subset of cases and controls (Table 5). No difference in mean working hours was found between cases and controls. In addition, the relative risk of exposure to shift work showed no significant difference. Therefore, it is assumed that there was no recognizable difference in

the working condition at least just prior to the case's death compared to the controls.

The relative risks calculated by the Mantel-Haenszel method were statistically elevated for hypertension and ECG abnormality. These results may be confounded by factors not used for matching in this study⁸⁾. We performed conditional logistic regression analysis to control for the effect of confounding variables. The independent variables in the analysis included those five variables which have shown statistically significant or borderline differences in the univariate analyses in this study. Total-cholesterol was included because its dichotomous variable (≥ 240 , $240 >$ (mg/100 ml)) showed significantly increased risks by the Mantel-Haenszel method (data not shown). HDL-cholesterol and blood pressure were excluded since they were correlated with hypertension. Smoking was also excluded because of no significant risk by the Mantel-Haenszel method. The results of the conditional

Table 5. Comparison of a subset of cases and controls with available information on working conditions.

	Cases	Controls	
Number	46	86	
Total working hours ^a			
< 120	5	4	
120 — < 180	28	48	
180 — < 220	9	27	
220 —	4	7	
mean $\pm$ SD ^b	170.2 $\pm$ 34.7	174.1 $\pm$ 36.4	NS ^c
Extra working hours ^a			
< 20	29	51	
20 — < 35	6	7	
35 — < 50	4	15	
50 —	7	13	
mean $\pm$ SD	21.3 $\pm$ 21.4	24.4 $\pm$ 22.9	NS
Working days ^a			
— 15	6	3	
16 — 20	19	45	
21 — 25	20	36	
26 —	1	2	
mean $\pm$ SD	19.9 $\pm$ 3.1	20.2 $\pm$ 3.2	NS

^a During 4 weeks prior to each death.^b Standard deviation.^c Not significantly different at the 5% level.

logistic regression analysis suggested that hypertension is the most positive predictor of sudden unexpected death.

Hinkle reported that in a prospective cohort study with follow-up of 1,152 actively employed men, ECG abnormality was associated with increasing the risk of sudden coronary, unexpected death in middle-aged men¹¹. He also reported that most of these cases had a history of cardiac heart disease or chronic lung disease, with abnormal metabolism such as hyperlipidemia, impaired glucose tolerance, elevated serum uric acid, obesity, and alcoholism¹¹. A large proportion of sudden deaths, in general, have been attributed to coronary heart disease⁷. Since autopsies were performed only in four cases from the present case series, the cause of death depended on that stated on death certificates. Of the 102 cases, 77 were suggestive of cardiovascular origin, 20 were cerebrovascular, 3 were gastrointestinal, and 2 were unknown. Ideally, in a study of sudden death, information on cause of death should be obtained from autopsy data. For reference, we compared the frequency of cause of

deaths with that of the other Japanese studies on sudden unexpected death based on information from death certificates^{4,5}. Both these studies and ours showed that nearly 70% of deaths were due to heart diseases. Although death certificate information provide only indirect evidence for cause of death, our data suggested that the majority of cases may actually have died of cardiovascular disease when combined with the fact that hypertension was the most positive predictor of sudden unexpected death.

Descriptive epidemiological characteristics of the 141 male case series are given elsewhere and need only to be briefly mentioned¹². The onset of sudden unexpected deaths took place most frequently at home (77 cases, or 54.6%), and most often during sleep (37 cases, or 26.2%). A small peak of onset was found in the morning (4:00AM-9:00AM), although this was not statistically significant. They tended to occur on Monday, Thursday, Friday, and Saturday (not statistically significant), and more deaths occurred in April, November, and December (statistically significant).

With regard to educational level, significant difference was found between cases and controls in spite of some missing data. Education was related to occupation, especially when a separate correlational analysis was done for the two variables after dichotomization (results not shown). Myers et al. reported that from a retrospective study of 100 sudden coronary deaths using coroner's postmortems, the most significant relationship with sudden unexpected death was acute psychological stress prior to time of death¹³. Robinson et al. reported that from a retrospective study using coroner's records of 212 deaths that occurred at work among employed white males, men employed in service occupations had the highest age-adjusted sudden natural death rate at work (27.0 per 100,000), which was 2.5 times the overall county rate¹⁴. As noted above, it is also suggested that sudden unexpected death among Japanese workers might in some degree be attributable to occupational factors such as being under more stress at the busy periods of the workplace.

The study population of this project is mostly composed of workers of large-scale enterprises, with 1,000 or more employees. It does not represent an overall picture of Japanese workers because large-scale enterprises of this size occupy only 0.17% (1986) of all enterprises in Japan¹⁵. It should be noted that all the workers of this study received occupational health services from fulltime OHPs and other health staffs and thus can be assumed that the quality of health information on the workers was better than had it been otherwise. The researchers were able to obtain information on health condition and lifestyle from annual periodical physical examination records without much

difficulty. However, it is possible that information on the sudden death case's health condition may be biased in the direction of overestimation. After a worker's death, the cause of death may be investigated extensively from the standpoint of whether or not it was related to his work. If this happened, more information such as a history of disease would be collected for the cases than for the controls, and might influence the estimated risk of sudden unexpected death to increase.

Another limitation of the present study is self-participation, that is, each OHP himself decided whether or not to participate in our study. This may have caused selection bias, but not to the extent to affect internal validity. In addition, such bias may be minimal if it can be assumed that the OHPs who experienced sudden death were more likely to join in the study than those who did not experience sudden death.

We had to exclude several data sets due to lack of information from our analyses. Breslow and Day described this as a waste of important information and introduced one approach to the analysis of matched sets containing a variable number of controls⁹). Using this method, 2 to 13 data sets with the case and one control were restored and reanalyzed in our study. As a result, the relative risk for hypertension and ECG abnormality were similarly elevated (relative risk = 2.93, 95% CI: 1.45-5.96; relative risk = 3.21, 95% CI: 1.28-6.73, respectively). The relative risk for high educational level was similarly decreased (relative risk = 0.14, 95% CI: 0.03-0.82). Other relative risks did not show significant increase or decrease. These results are consistent with those of Table 3 and is thus unlikely that missing data occurred in a systematic manner.

In addition, for the clarification of causal relationship between sudden unexpected death and working conditions, the investigators should seek information as follows. Information on the working conditions should be collected for as long a period as possible, and be analyzed as causal factors, which in this study could be focused on for short periods and as confounding variables.

In conclusion, hypertension and ECG abnormality were significantly associated with elevated risks and high educational level with decreased risk of sudden unexpected death. Conditional logistic regression analysis suggested that hypertension may be the most positive predictor of sudden unexpected death among Japanese workers.

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