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Original Contribution

A Prospective Cohort Study of Shift Work and Risk of Ischemic Heart Disease in Japanese Male Workers

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This study prospectively examined the association between shift work and the risk of ischemic heart disease among Japanese male workers. A baseline survey, which involved 110,792 inhabitants (age range: 40–79 years) from 45 areas throughout Japan, was conducted between 1988 and 1990. The causes of death were identified from death certificates. The analysis was restricted to 17,649 men (age range: 40–59 years) who were employed at the time of the baseline survey. All subjects were asked to indicate the most regular shift work that they had undertaken previously: day work, rotating-shift work, or fixed-night work. The Cox proportional hazards model was used to estimate the risks of shift work for ischemic heart disease. During the 233,869 person-years of follow-up, a total of 1,363 deaths were recorded, 86 of which were due to ischemic heart disease. Compared with the day workers, the rotating-shift workers had a significantly higher risk of death due to ischemic heart disease (relative risk = 2.32, 95% confidence interval: 1.37, 3.95; $p = 0.002$), whereas fixed-night work was not associated with ischemic heart disease (relative risk = 1.23, 95% confidence interval: 0.49, 3.10; $p = 0.658$). In addition, subjects with coronary risk factors, such as hypertension, overweight, habitual alcohol consumption, and smoking, were highly susceptible to the effect of rotating-shift work on the risk of death due to ischemic heart disease.

cardiovascular diseases; circadian rhythm; cohort studies; Japan; myocardial ischemia

Abbreviations: CI, confidence interval; ICD-10, *International Classification of Diseases*, Tenth Revision; JACC Study, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk.

There is growing concern over the possible increased risk of ischemic heart disease among shift workers (1–4). However, many of the earlier studies have reported null findings, which may partially have been related to small sample sizes, and they have been cross-sectional or used a case-referent design (5). To our knowledge, a total of six prospective studies (6–11) have examined this relation, and all except two (6, 11) reported a possible correlation between shift

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work and an increased risk of ischemic heart disease. However, some of these reports involved relatively small study groups (7, 9), and others failed to consider potential confounding factors (6, 10). More recently, Kawachi et al. (8) conducted a large-scale prospective cohort study (the Nurses' Health Study) and found an association between shift work and an increased risk of ischemic heart disease among female workers.

As the profiles of coronary risk factors and shift-work practices may differ between the sexes, the association between shift work and the risk of ischemic heart disease among male workers remains unresolved. In addition, there is no prospective evidence on the risk of shift work among non-White populations. Therefore, the present large cohort study examined the association between shift work and the risk of ischemic heart disease among Japanese male workers. Furthermore, if our a priori hypothesis that shift work is associated with an increased risk of ischemic heart disease is true, it will be important to determine which types of worker might be more susceptible to the adverse effect of shift work, because shift work is inevitable in modern industries and various areas of business. Therefore, we examined the modifying effects of coronary risk factors, such as hypertension, overweight, alcohol consumption, and smoking, on the risk of ischemic heart disease.

MATERIALS AND METHODS

The Japanese Collaborative Cohort Study for the Evaluation of Cancer Risk

The details of the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC Study), which was sponsored by the Ministry of Education, Science, Sports, and Culture of Japan, have been described previously (12, 13). Briefly, a baseline survey was conducted through 45 areas of Japan from 1988 to 1990 among 110,792 inhabitants (46,465 men and 64,327 women) who ranged in age from 40 to 79 years at recruitment. In 22 of 45 areas, all residents living in a given target area were regarded as study subjects. In 20 areas, those who had undertaken a basic health examination conducted under the Health and Medical Service Law for the Aged were invited to participate in the study. In two areas, the study subjects consisted of health examinees plus volunteers. In one area, subjects were defined on the basis of the health check-up for atomic bomb survivors. Response rates were obtainable from 17 of 22 areas, which included all living residents as the subjects; the average response rate was 83 percent. The vital status of each participant was checked annually by use of data held at regional research centers, with permission from the Ministry of Public Management, Home Affairs, Post, and Telecommunications of Japan to review the population registration sheets. The cause of death was coded according to the *International Classification of Diseases*, Tenth Revision (ICD-10). The present analysis also included follow-up data collected until the end of 2003. The informed consent procedures were approved by the ethics committees of Nagoya University and the University of Tsukuba, Japan.

Data retrieval for analysis

To isolate the appropriate data for our analysis, the study group was initially restricted to male workers whose baseline age ranged from 40 to 59 years ($n = 25{,}822$), since the most common retirement age is 60 years in Japan. We then selected only those subjects who were working as full-time employees or who were self-employed at the time of the baseline survey ($n = 20{,}368$). Of these workers, 17,937 provided information on the most regular shift pattern that they had worked previously. We then further limited this group to subjects free ($n = 17{,}649$) from a previous history of myocardial infarction ($n = 198$) or cerebrovascular disease ($n = 98$).

Of the 1,363 deaths that occurred during the 233,869 person-years of follow-up, 304 deaths were attributed to circulatory system disease (according to ICD-10 codes I00–I99), 86 deaths were attributed to ischemic heart disease (ICD-10 codes I20–I25), and 132 deaths were attributed to cerebrovascular disease (ICD-10 codes I60–I69).

Exposure data

All subjects completed a self-administered questionnaire at baseline. This included the following question regarding patterns of shift work: "During your working life, until the present, what shift (time of day) did you work most: mainly daytime, mainly night (i.e., fixed-night shift), or alternate night and daytime (that is, rotating-shift work)?"

The self-administered questionnaire also inquired about other baseline characteristics that could potentially be related to mortality. These included the following: smoking status (never, former, or current smoker); alcohol intake (nonhabitual drinker, former habitual drinker, or habitual drinker of ethanol at 1–22, 23–45, and $\geq$46 g per day); past medical history (hypertension or diabetes); educational level (school attendance beyond the 18th birthday, until the age of 16–17 years, or until the age of $\leq$15 years); degree of perceived stress in daily life (frequent, occasional, very occasional, or never); hours of walking ($<$0.5, 0.5, 0.6–0.9, and $\geq$1.0 hour per day); hours of exercise ($<$1, 1–2, 3–4, and $\geq$5 hours per week); and type of job (office worker, manual worker, or other).

Statistical analysis

The Cox proportional-hazards model was used to estimate the relative risks of rotating-shift work and night work for each cause of death: total death, circulatory system disease, ischemic heart disease, and cerebrovascular disease (14). Day workers were used as a referent group after adjustment for the potential confounding factors listed above. The model included age divided into 5-year groups and body mass index divided into four groups ($<$22, 22–23.9, 24–25.9, $\geq$26). In order to assess the modifying effects of the factors, we estimated multivariate relative risks of rotating-shift work for ischemic heart disease for separate strata of selected coronary risk factors, including hypertension, overweight, alcohol consumption, and smoking. The assumptions of the proportional-hazards model were checked by including the interaction terms of the predictors

and a function of survival time (15). All calculations were performed using the SAS statistical software package (16).

RESULTS

Of the 17,649 men, 14,774 (83.7 percent) reported that they had most regularly performed day work, 864 (4.9 percent) reported that they had most regularly engaged in fixed-night work, and 2,011 (11.4 percent) reported that they had most regularly undertaken rotating-shift work (table 1). Compared with those who had engaged in day work, men who had performed rotating-shift work reported a lower prevalence of hypertension (12.5 vs. 10.8 percent), a higher prevalence of current smoking (55.4 vs. 59.3 percent), and higher perceived levels of frequent and occasional stress (25.8 vs. 32.1 percent). In addition, shift workers were less likely to engage in office work.

No significant difference in the risk of total death was observed among the three groups (day workers, fixed-night workers, and rotating-shift workers) (table 2). Overall, fixed-night work shows no significant association with any cause of death. However, rotating-shift work was associated with a 1.6-fold increase in the risk of circulatory system diseases compared with day work. This was due mainly to an increased risk of ischemic heart disease. Compared with the day workers, the rotating-shift workers had a significantly higher risk of death due to ischemic heart disease (relative risk = 2.32, 95 percent confidence interval (CI): 1.37, 3.95; $p = 0.002$), whereas fixed-night work was not associated with ischemic heart disease (relative risk = 1.23, 95 percent CI: 0.49, 3.10; $p = 0.658$). In the multivariate model for ischemic heart disease, the relative risk of hypertension was 1.81 (95 percent CI: 1.07, 3.06; $p = 0.027$), the relative risk of diabetes was 2.53 (95 percent CI: 1.29, 4.97; $p = 0.007$), that of current smokers was 4.76 (95 percent CI: 2.05, 11.02; $p < 0.001$), that of ethanol intake of 1–22 g per day was 0.66 (95 percent CI: 0.36, 1.22; $p = 0.187$), that of ethanol intake of 23–45 g per day was 0.61 (95 percent CI: 0.33, 1.13; $p = 0.115$), that of ethanol intake of 46 g per day or over was 1.00 (95 percent CI: 0.52, 1.95; $p = 0.997$), and that of body mass index of 26 and over was 2.07 (95 percent CI: 1.15, 3.73; $p = 0.015$). The risk of death due to cerebrovascular disease did not differ significantly among the three types of workers. Adjustment for multiple potential risk factors did not significantly alter these results.

Each stratum of the selected coronary risk factors confirmed that subjects with coronary risk factors, such as hypertension, overweight, habitual high alcohol consumption, and current smoking habits, were highly susceptible to the effect of rotating-shift work on the risk of death due to ischemic heart disease (table 3). Compared with those of day work, the relative risks of rotating-shift work for ischemic heart disease were as follows: 3.40 ($p = 0.031$) among subjects with hypertension; 2.12 ($p = 0.018$) among subjects without hypertension; 5.68 ($p < 0.001$) among subjects with body mass index of 26 or more; 1.71 ($p = 0.291$) among subjects with body mass index of less than 22; 2.50 ($p = 0.002$) among current smokers; 6.56 ($p = 0.001$) among the subjects with ethanol intake of 46 g or more per day; and 0.52 ($p = 0.538$) among nonhabitual drinkers. None of the interaction terms (i.e., hypertension × rotating-shift work) when included in the model showed significance ($p = 0.974$ for hypertension, $p = 0.980$ for smoking, $p = 0.243$ for alcohol consumption, $p = 0.457$ for body mass index).

DISCUSSION

The present study showed that rotating-shift work was associated with increased risk of death due to ischemic heart disease. This association was robust even after adjustment for several possible confounding factors. In addition, this association was emphasized among the subjects with unfavorable coronary risk factors, although the interaction effects of hypertension, overweight, alcohol consumption, and smoking were not statistically significant.

Tenkanen et al. (7) conducted a prospective cohort study involving 1,806 industrial workers in Finland. They reported that, when all shift workers were compared with all day workers, the relative risk for ischemic heart disease was 1.4 (95 percent CI: 1.0, 1.9) after adjustment for lifestyle factors, blood pressure, and serum lipid levels. The Nurses' Health Study (8), which was a large cohort study involving 79,109 female nurses from the United States, reported that the multivariate adjusted relative risks of shift work for ischemic heart disease were 1.21 (95 percent CI: 0.92, 1.59) among women reporting less than 6 years of rotating night shifts and 1.51 (95 percent CI: 1.12, 2.03) among women reporting 6 or more years of rotating night shifts, compared with women who had never done shift work. A similar relation was reported by Knutsson et al. (9). These findings are consistent with those of the present study, although we obtained a much higher relative risk of ischemic heart disease. However, these results should be interpreted with caution, as the epidemiologic studies used different definitions of cardiovascular diseases (5): The present study examined the risk of mortality due to ischemic heart disease, whereas some previous studies examined morbidity. In addition, differences in type of shift work, duration of shift work, and work hours per week might explain differences from the results of previous studies.

Several possible underlying pathways for the association between shift work and an increased risk of ischemic heart disease warrant discussion. The first potential mechanism involves differences in levels of coronary risk factors among groups of workers. Several studies have shown that unfavorable coronary risk factor profiles are more prevalent among shift workers than among day workers (17–25). However, the present study, as well as three previous cohort studies (7–9), showed a significant association between shift work and ischemic heart disease, even after adjustment for these potential confounding factors.

Second, shift work has an influence on the circadian rhythms and physiologic functions of the human body—particularly those associated with the circulatory system, such as blood pressure, heart rate, and the secretion and excretion of hormones including catecholamines (20, 26–31). This may partly explain the fact that rotating-shift work increased the risk of ischemic heart disease, while fixed-night

TABLE 1. Selected baseline characteristics according to forms of shift work, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, 1988–1990

	Daytime worker ($n = 14,774$)	Fixed-night worker ($n = 864$)	Rotating-shift worker ($n = 2,011$)
Mean age, years (SD*)	49.6 (5.9)	49.6 (5.8)	48.5 (5.9)
Mean body mass index, kg/m^2 (SD)	23.0 (3.9)	23.3 (2.8)	23.2 (2.7)
Past history of hypertension (%)	12.5	11.7	10.8
Past history of diabetes (%)	4.4	3.2	3.9
Educational levels (%)			
<15 years	23.6	28.5	23.8
15–17 years	13.5	16.2	14.1
≥18 years	48.0	42.4	50.0
Unreported	14.9	13.0	12.0
Smoking (%)			
Current smoker	55.4	56.7	59.3
Former smoker	19.7	20.5	19.5
Never smoker	22.3	16.8	17.9
Unreported	2.7	6.0	3.3
Alcohol drinking (%)			
Nonhabitual drinker	15.5	14.2	15.4
Former drinker	3.0	3.0	3.3
Habitual drinker	79.0	73.5	77.2
Ethanol at 1–22 g per day	30.4	23.6	28.0
Ethanol at 23–45 g per day	28.7	28.1	28.1
Ethanol at ≥46 g per day	12.7	13.4	13.5
Unreported	2.6	9.3	4.1
Perceived stress (%)			
Frequent	12.2	14.2	15.2
Occasional	13.6	11.9	16.9
Very occasional	47.6	51.0	47.7
Never	9.5	12.0	8.7
Unreported	17.2	10.8	11.5
Job type (%)			
Office work	21.6	6.6	14.1
Manual work	52.8	67.7	50.7
Other	22.6	21.4	31.5
Hours of walking per day (%)			
<0.5	13.1	13.0	13.7
0.5	18.2	17.0	18.6
0.6–0.9	18.2	17.0	18.6
≥1.0	46.9	49.8	45.9
Unreported	3.6	3.2	3.2
Hours of exercise per week (%)			
<1	68.8	70.4	67.8
1–2	18.0	17.3	18.5
3–4	6.0	5.1	6.7
≥5	4.5	4.2	4.3
Unreported	2.8	3.1	2.7

* SD, standard deviation.

TABLE 2. Relative risks of shift work associated with cause-specific mortality, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, 1988–2003

	Age adjusted					Multivariate*		
	Person-years (no.)	Deaths (no.)	Relative risk	95% confidence interval	*p* value	Relative risk	95% confidence interval	*p* value
Total deaths								
Daytime worker	195,280	1,138	Referent			Referent		
Fixed-night worker	11,751	81	1.13	0.90, 1.42	0.290	1.06	0.85, 1.34	0.593
Rotating-shift worker	26,838	144	1.00	0.84, 1.19	0.973	0.98	0.82, 1.17	0.835
Circulatory system diseases								
Daytime worker	195,280	235	Referent			Referent		
Fixed-night worker	11,751	21	1.41	0.90, 2.21	0.131	1.29	0.82, 2.03	0.270
Rotating-shift worker	26,838	48	1.62	1.19, 2.21	0.002	1.59	1.16, 2.18	0.004
Ischemic heart disease								
Daytime worker	195,280	63	Referent			Referent		
Fixed-night worker	11,751	5	1.28	0.51, 3.17	0.601	1.23	0.49, 3.10	0.658
Rotating-shift worker	26,838	18	2.27	1.34, 3.84	0.002	2.32	1.37, 3.95	0.002
Cerebrovascular disease								
Daytime worker	195,280	109	Referent			Referent		
Fixed-night worker	11,751	7	1.00	0.47, 2.15	0.997	0.88	0.41, 1.91	0.748
Rotating-shift worker	26,838	16	1.17	0.69, 1.97	0.564	1.12	0.66, 1.91	0.672

* Multivariate model included age, smoking, alcohol consumption, educational level, perceived stress, past medical history, body mass index, hours of walking, hours of exercise, and job type.

work did not in the present study, because adaptation of circadian rhythm by fixed-night workers can be achieved better than by rotating-shift workers (32, 33). In addition, Tenkanen et al. (34) suggested that coronary risk factors, such as smoking and obesity, accelerate the physiologic and metabolic disturbances resulting from disruption of circadian rhythm due to shift work. Smoking and obesity, for example, decrease fibrinolysis and increase fibrinogen levels and the ability of platelets to aggregate, while shift work decreases fibrinolytic activity. This is backed up by the present findings, which confirmed that subjects with coronary risk factors were more likely to be affected by shift work.

Third, several potential selection biases have been highlighted (8). For example, sources of bias might be the hiring procedure of the workplace or the worker's estimate of his or her own ability to tolerate irregular working hours. A second source of selection bias might be workers' giving up shift work because of health problems. However, both of these biases would tend to attenuate any association between shift work and ischemic heart disease; therefore, the actual risk might be greater than that reported in the present study. In addition, the shift work was not associated with the risk of total death in the present study, suggesting that there was no difference in the general health conditions of day workers and shift workers.

Some important limitations of our study should be discussed. First, the questionnaire did not ascertain whether workers were engaged in shift work at baseline, although some previous studies have found the highest risk of ischemic heart disease in former shift workers (10, 35). Instead, we determined the most regular type of shift work in which individuals had been engaged up until the time of the baseline survey. We believe that this information was more useful than information on current shift-working patterns for evaluating our hypothesis in terms of the long lifetime effects of shift work. Second, the definition of shift work remains ambiguous. Although substantial variety in the form of shift work exists, common forms of shift work in Japan refer to rotating-shift work (i.e., when workers alternate among three 8-hour shifts in a 24-hour cycle) or fixed-night work. Fixed-night work means working mainly at night at about the same time every day. In fixed-night work situations, workers are scheduled to work either for a certain period (e.g., monthly or seasonally) or permanently. Third, the present study failed to obtain information regarding several important possible confounding factors, such as occupational exposures, job stress, job function (i.e., service workers, industrial workers, or experts), and particularly serum cholesterol levels. Some previous studies have shown that workers with shift work or irregular working hours had higher levels of serum cholesterol and low-density lipoprotein cholesterol and lower levels of high-density lipoprotein cholesterol (19, 20). However, Kawachi et al. (8) suggested that, if the mechanism for the increased risk of ischemic heart disease is elevated serum cholesterol, then adjustment for that mechanism may lead to statistical overadjustment. Finally, inherent work tasks and practices might differ between day- and nightshift workers, even if their job descriptions are similar and they are employed in the same occupational environments (such as factories, offices, or

TABLE 3. Multivariate relative risks of rotating-shift work for ischemic heart disease in separate strata of selected risk factors, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, 1988–2003

Strata	Daytime worker		Rotating-shift worker				
	Person-years (no.)	Cases (no.)	Person-years (no.)	Cases (no.)	Relative risk*	95% confidence interval	*p* value
Hypertension							
No	171,618	48	24,003	13	2.12	1.14, 3.94	0.018
Yes	23,662	15	2,835	5	3.40	1.12, 10.29	0.031
Smoking							
Never	44,154	6	4,867	0			
Former	38,306	7	5,298	2	2.93	0.55, 15.61	0.207
Current	107,628	49	15,798	15	2.50	1.39, 4.51	0.002
Alcohol drinking							
Nonhabitual drinker	30,027	14	4,152	1	0.52	0.07, 4.14	0.538
Former habitual drinker	5,539	4	814	2	4.90	0.24, 101.00	0.303
Habitual drinker	154,590	43	20,735	15	2.94	1.62, 5.32	<0.001
Ethanol at 1–22 g per day	59,637	14	7,616	4	2.30	0.74, 7.10	0.149
Ethanol at 23–45 g per day	56,085	16	7,557	3	1.56	0.45, 5.46	0.484
Ethanol at ≥46 g per day	24,322	8	3,463	7	6.56	2.09, 20.56	0.001
Body mass index, kg/m^2							
<22	70,630	23	9,203	5	1.71	0.63, 4.65	0.291
22–23.9	56,255	15	7,301	3	1.33	0.37, 4.81	0.667
24–25.9	39,482	12	5,650	2	1.67	0.35, 7.89	0.516
≥26	22,912	11	3,762	7	5.68	2.08, 15.50	<0.001
Age, years							
40–49	96,281	19	15,431	5	1.66	0.61, 4.52	0.318
50–59	99,000	44	11,407	13	2.77	1.48, 5.18	0.001

* Multivariate model included age, smoking, alcohol consumption, educational level, perceived stress, past medical history, body mass index, hours of walking, hours of exercise, and job type.

hospitals); these differences might influence the risk of ischemic heart disease to some degree.

In conclusion, this large prospective cohort study demonstrated a significant association between rotating-shift work and ischemic heart disease among Japanese male workers, which supports the previous findings. In addition, this association was emphasized among the subjects with coronary risk factors, such as hypertension, overweight, heavy drinking, and smoking, which may draw attention for occupational health policy. The interaction effects, however, were not statistically significant, and further studies are needed to clarify the modifying effects of coronary risk factors on the risk of ischemic heart disease.

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