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Prospective Cohort Study of the Risk of Prostate Cancer among Rotating-Shift Workers: Findings from the Japan Collaborative Cohort Study

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ABSTRACT

Shift workers have been reported to have an increased risk of some cancers. However, the risk of prostate cancer in shift workers is not known to have been examined previously. This study prospectively examined the association between shift work and risk of prostate cancer incidence among 14,052 working men in Japan enrolled in a large-scale prospective cohort. A baseline survey was conducted between 1988 and 1990. Subjects were asked to indicate the most regular work schedule they had undertaken previously: day work, rotating-shift work, or fixed-night work. During 111,974 person-years, 31 cases of prostate cancer were recorded. The Cox proportional hazards model was used to estimate the risk, with adjustments for age, family history of prostate cancer, study area surveyed, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status. Compared with day workers, rotating-shift workers were significantly at risk for prostate cancer (relative risk = 3.0, 95% confidence interval: 1.2, 7.7), whereas fixed-night work was associated with a small and nonsignificant increase in risk. This report is the first known to reveal a significant relation between

rotating-shift work and prostate cancer.

circadian rhythm; cohort studies; Japan; occupational exposure; prostatic neoplasms; work schedule tolerance

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Abbreviations: CI, confidence interval; JACC, Japan Collaborative Cohort; RR, relative risk

INTRODUCTION

Shift workers are known to be a high-risk population for sleep disturbances, gastrointestinal disturbances, obesity, hypercholesterolemia, hypertension, and also some cancers, including breast and colorectal (1–4). In the case of breast cancer, several observational studies have reported that female shift workers have a meaningful increase in the risk of cancer (2, 5–7). A systematic review and meta-analysis of the previous studies revealed a positive relation between night-shift work and breast cancer risk (relative risk (RR) = 1.51, 95 percent confidence interval (CI): 1.36, 1.68) (8). Changes in hormone secretion, caused by a disruption in circadian rhythm, was proposed as a factor contributing to the observed increase in risk (1, 9). Although breast cancer occurs predominantly in women and prostate cancer is restricted to men, the biology and epidemiology of these cancers share some similar features (10). For example, tumor progression in both breast and prostate cancers is strongly affected by sex hormones (11, 12). In addition, the levels of **melatonin**, a hormone closely linked to circadian rhythms, are reduced in some breast and prostate cancer patients (13, 14). Experimentally, **melatonin** has been shown to inhibit the proliferation of breast and prostate cancer cell lines (15, 16).

We addressed whether male shift workers, similar to female shift workers who have an elevated risk of breast cancer, have an elevated risk of prostate cancer. In this study, we examined the hypothesis that shift work is a risk factor for prostate cancer incidence among working men enrolled in the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), a nationwide, large-scale, prospective cohort. To the best of our knowledge, this report is the first to examine the possible association between shift work and the risk of prostate cancer.

MATERIALS AND METHODS

The sampling methods and protocols of the JACC Study have been described elsewhere (17, 18). Briefly, the JACC Study involved a total of 110,792 subjects (46,465 males and 64,327 females) who were 40–79 years of age at the time of recruitment and were enrolled in 45 study areas throughout Japan between 1988 and 1990. The 45 study areas are spread nationwide and include three in the Hokkaido district, five in the Tohoku district, five in the Kanto district, six in the Chubu district, 10 in the Kinki district, two in the Chugoku district, and 14 in the Kyusyu district; there was no study area in the Shikoku district (17). In 21 of the 45 areas, persons who had undertaken general health checkups periodically provided by the municipalities were invited to participate in the study. In 22 areas, all residents living in a given target area were regarded as study subjects. In two areas, the study subjects consisted of health examinees plus volunteers (18).

The baseline survey on lifestyle factors was conducted by using a self-administered questionnaire. Questions regarding occupational health were posed in 36 study areas. The response rates were obtainable from 17 of 22 areas, which included all living residents as the subjects. The average response rate was 83 percent (18). Subjects who died or moved out of the study areas were identified by using population registries, with permission from each municipality. For those who died, their causes of death were confirmed from death certificates, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications. Incidence of cancer was determined by linkage with cancer registries in 24 of the 45 study areas. Diagnosis of cancer of the prostate was defined by code C61 according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (19). All follow-up incidence surveys were conducted until the end of 1997. In one area, however, the follow-up survey was halted in 1994 because of incidental operational problems of regional investigators. Our cohort was not established by random sampling, although it seemed to be similar to the general Japanese population with respect to several demographic and lifestyle features (17). The mortality of the cohort appeared the same or slightly reduced compared with the general population (20).

Data retrieval for analysis

To isolate the appropriate data for our analysis, the objective group was initially restricted to 35,658 male subjects whose baseline age ranged from 40 to 65 years. We then selected those 17,389 men from 21 study areas in which questions regarding occupational health had been asked and cancer registries had been held. Of these men, 14,647 were working at the time of the baseline survey, and 14,053 provided information on the most regular work schedule they had undertaken previously. Consequently, after we excluded one subject who had a history of prostate cancer, the subjects in this study were 14,052 male workers. During the 111,974 person-years of follow-up (mean follow-up period, 8.0 years (standard deviation, 1.7)), 31 cases of prostate cancer were recorded by the cancer registries. Among these 31 cases, only one was certificated for death without a prostate cancer incidence report.

Exposure data

At baseline, participants were asked, Which form of work schedule have you engaged in the longest before now: daytime work, fixed-night work, or alternate night and day work (which is referred to as rotating-shift work)?

From the self-administered questionnaire, we acquired information on the following factors: age, height, weight, past medical history, family history of prostate cancer, smoking (current smoker, former smoker, nonsmoker), alcohol drinking (habitual drinker, former habitual drinker, nondrinker), job type (office work, manual work, other), physical activity at work (sitting, alternate sitting and standing, standing with/without moving), workplace (indoor, outdoor, both), degree of perceived stress (frequent, occasional/very occasional/never), educational level, and marriage status (married, single/divorced/separation by death).

Statistical analysis

The Cox proportional hazards model was used to estimate the relative risks of prostate cancer for rotating-shift workers and fixed-night workers compared with day workers (21). In the analysis, relative risks were adjusted for age only and for age, study area, and family history of prostate

cancer. Relative risks were further adjusted for the lifestyle-related factors and the occupational and psychosocial factors listed in table 1. Missing values for adjusting variables were treated as an additional category. The assumptions for the Cox proportional hazards model were checked by using the goodness-of-fit testing approach and were found to be valid. Calculations were performed with Stata version 8.0 (Stata Corporation, College Station, Texas) and SPSS version 12.0 (SPSS, Inc., Chicago, Illinois) statistical software.

TABLE 1. Baseline characteristics of 14,052 male workers according to type of work schedule, Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 1988–1990

Characteristic	Work schedule			*p* value
	Daytime	Fixed night	Rotating shift	
No. of subjects	11,269 (80.2%)	982 (7.0%)	1,801 (12.8%)	
No. of person-years	89,179	8,272	14,523	
No. of prostate cancer cases	21	3	7	
Mean age in years (standard deviation)	52.3 (7.3)	52.4 (7.3)	51.0 (7.3)	<0.001*
Family history of prostate cancer (%)	0.3	0.2	0.8	0.004†
Lifestyle-related factors (%)				
Body mass index‡				<0.001†
<21.6	33.4	26.7	29.9	
21.6–23.9	32.6	34.2	32.2	
>23.9	30.8	35.6	34.4	
Missing	3.2	3.5	3.6	
Smoking				<0.001†
Current smoker	53.8	53.5	55.4	
Former smoker	22.7	21.5	22.8	
Nonsmoker	21.0	17.4	17.9	
Missing	2.6	7.6	3.9	
Alcohol drinking				<0.001†
Current drinker	78.0	71.9	75.6	
Former drinker	3.7	3.1	3.8	
Nondrinker	15.5	14.2	15.2	
Missing	2.8	10.9	5.5	
Occupational and psychosocial factors (%)				
Job type				<0.001†
Office work	22.7	5.9	14.3	
Manual work	52.1	67.1	53.3	

Other	21.6	21.7	28.4	
Missing	3.5	5.3	4.0	
Physical activity at work				<0.001†
Sitting	28.1	77.2	48.4	
Alternate sitting and standing	18.0	5.6	16.7	
Standing with/without moving	52.6	15.3	34.1	
Missing	1.3	1.9	0.9	
Workplace				<0.001†
Indoor	38.6	46.1	44.5	
Outdoor	38.9	35.0	31.4	
Both	19.2	2.3	17.0	
Missing	3.2	16.5	7.2	
Perceived stress				0.020†
Frequent	13.2	13.7	15.3	
Occasional/very occasional/never	83.5	83.4	82.6	
Missing	3.3	2.9	2.2	
Educational level				<0.001†
<15 years	5.2	4.8	5.6	
15–17 years	37.2	42.1	36.6	
≥18 years	52.3	43.4	51.1	
Missing	5.3	9.8	6.7	
Marriage status				<0.001†
Married	90.7	86.8	89.3	
Separation by death/divorced/single	4.3	5.2	5.7	
Missing	5.1	8.0	4.9	

* Derived from analysis of variance.

† Derived from the chi-square test.

‡ Weight (kg)/height $(m)^2$.

Approval

This study was approved by the Ethics Committee for Medical Care and Research, University of Occupational and Environmental Health, Japan, and the Ethical Board of the Nagoya University School of Medicine, Japan.

RESULTS

Table 1 shows the baseline characteristics of the study subjects according to type of work schedule. Of the 14,052 men, 11,269 (80.2 percent) reported day work, 982 (7.0 percent) reported fixed-night work, and 1,801 (12.8 percent) reported rotating-shift work. Compared with those who had engaged in day work, men who had performed rotating-shift work reported a higher prevalence of high body mass index (>23.9 kg/m^2; 34.4 percent vs. 30.8 percent), sitting work (48.4 percent vs. 28.1

percent), and indoor work (44.5 percent vs. 38.6 percent) and a lower prevalence of office work (14.3 percent vs. 22.7 percent). The prevalences of family history of prostate cancer (0.8 percent vs. 0.3 percent), current smoking (55.4 percent vs. 53.8 percent), current alcohol drinking (75.6 percent vs. 78.0 percent), frequent stress (15.3 percent vs. 13.2 percent), higher educational level (higher than high school; 51.1 percent vs. 52.3 percent), and marriage (89.3 percent vs. 90.7 percent) revealed no differences in magnitude.

Table 2 shows the results of the Cox proportional hazards model analysis. Compared with that for the day workers, the age-adjusted relative risk for the rotating-shift workers revealed a significant increase (RR adjusted for age = 3.0, 95 percent CI: 1.2, 7.3). For the fixed-night workers, a slight increase was observed but was not significant (RR adjusted for age = 1.7, 95 percent CI: 0.5, 5.9). Adjustments for study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status did not significantly alter these results (rotating-shift work: RR adjusted for age, study area, and family history of prostate cancer = 2.5, 95 percent CI: 1.0, 6.2; RR adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status = 3.0, 95 percent CI: 1.2, 7.7 and fixed-night work: RR adjusted for age, study area, and family history of prostate cancer = 1.5, 95 percent CI: 0.4, 5.3; RR adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status = 2.3, 95 percent CI: 0.6, 9.2).

TABLE 2. Relative risk of prostate cancer associated with work schedule, Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 1988–1997

Work schedule	No. of person-years	No. of cases	Age adjusted			Multivariate adjusted					
			RR*	95% CI*	*p* value	RR†	95% CI	*p* value	RR‡	95% CI	*p* value
Daytime	89,179	21	1.0			1.0			1.0		
Fixed night	8,272	3	1.7	0.5, 5.9	0.387	1.5	0.4, 5.3	0.534	2.3	0.6, 9.2	0.231
Rotating shift	14,523	7	3.0	1.2, 7.3	0.016	2.5	1.0, 6.2	0.043	3.0	1.2, 7.7	0.020

* RR, relative risk; CI, confidence interval.

† Adjusted for age, study area, and family history of prostate cancer.

‡ Adjusted for age, study area, family history of prostate cancer, body mass index, smoking, alcohol

drinking, job type, physical activity at work, workplace, perceived stress, educational level, and marriage status.

Table 3 shows the characteristics of the prostate cancer cases according to type of work schedule. Between day workers and rotating-shift workers, there were no differences in mean age at baseline (58.5 years vs. 59.3 years), mean number of years of follow-up (6.7 vs. 6.3), mean age at endpoint (65.2 years vs. 65.6 years), family history of prostate cancer (one case for each work schedule), and mean body mass index at baseline (22.8 kg/m^2 vs. 21.6 kg/m^2).

TABLE 3. Characteristics of prostate cancer cases according to type of work schedule, Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 1988–1997

Characteristic	Work schedule			*p* value
	Daytime	Fixed night	Rotating shift	
No. of cases	21	3	7	
Death certificate only	1	0	0	
Mean age in years at baseline (standard deviation)	58.5 (6.4)	53.7 (4.0)	59.3 (5.4)	0.39*
Mean no. of years of follow-up (standard deviation)	6.7 (3.0)	5.6 (2.6)	6.3 (2.5)	0.82*
Mean age in years at endpoint (standard deviation)	65.2 (6.6)	59.3 (1.8)	65.6 (4.8)	0.27*
No. of cases with a family history of prostate cancer	1	0	1	0.60†
Mean body mass index‡ at baseline (standard deviation)	22.8 (2.0)	21.9 (0.9)	21.6 (2.0)	0.33*

* Derived from analysis of variance.

† Derived from the chi-square test.

‡ Weight (kg)/height (m)^2.

DISCUSSION

We found a significant increase in prostate cancer risk among rotating-shift workers. This result supports the hypothesis that shift work is a risk factor for prostate cancer. To our knowledge, this is the first report to reveal the association of rotating-shift work with prostate cancer.

The **melatonin** pathway, which is closely linked to circadian rhythms, is most frequently implicated

in the observed increase in tumor incidence among shift workers. Secretion of the hormone is low during daytime, increases soon after the onset of darkness, peaks in the middle of the night, and gradually falls until morning. The hormone has been reported to affect circadian rhythms and exhibit both hypnotic and antineoplastic effects (9). Several possible mechanisms have been proposed regarding tumor growth inhibition by **melatonin**. **Melatonin** may suppress tumor growth by down-regulating transcription, secretion, or activity of growth factors; it may stimulate the immune system through increased production of interleukin-2 and interleukin-4 by T-helper cells; lastly, it may protect DNA against oxidative damage by scavenging free radicals (9). Among shift workers, it has been proposed that an elevated risk of cancer may be due to a phase shift and reduced secretion of **melatonin**, resulting from a disruption in circadian rhythms (22–24). In terms of prostate cancer, previous studies showed that **melatonin** could directly inhibit proliferation of cultured prostate cancer cells (25). The **melatonin** pathway may therefore be relevant to prostate cancer incidence among shift workers.

The effect of sex hormones may be secondary to **melatonin**. **Melatonin** suppression is believed to increase the level of sex hormones (9, 24). Among female shift workers, increased levels of estradiol and low levels of **melatonin** have been reported (22). An interrelation between **melatonin** and **testosterone** has also been suggested for males (26), so high levels of **testosterone** due to low levels of **melatonin** could also be hypothesized in male shift workers. The growth and differentiation of the prostate is under androgen control (12); therefore, this pathway should attract attention as a relevant mechanism.

Decreased exposure to daylight is known to be a risk factor for prostate cancer (27, 28). This link was explained by decreased production of vitamin D due to reduced exposure to ultraviolet rays. The biologically active form of vitamin D, 1α,25-dihydroxyvitamin D_3, has been reported to inhibit proliferation of prostate cancer cells (29, 30). In shift work, daylight exposure is shortened, so elevated risk could be explained through this pathway. In our studies, however, rotating-shift workers, whose exposure to daylight is longer, had a higher risk compared with fixed-night workers, whose exposure is relatively shorter. Effects on circadian rhythms were suggested to be more serious for rotating-shift workers compared with fixed-night workers (31). Disrupting the circadian rhythm in rotating-shift workers may therefore have a greater effect on tumorigenesis than shortening exposure to daylight.

The scientific field of chronotoxicology examines the biologic cycle of susceptibility to chemical toxicity (32). The toxicity of many chemical agents was reported to vary with circadian change, and the possibility was suggested that susceptibility to chemical agents may increase at night in humans (4, 32). Occupational exposure to chemical agents such as cadmium and manganese is suspected to increase the risk of prostate cancer (33, 34), so these agents may have a stronger influence among shift workers. Exposure to these chemicals is considered rare, however. Thus, the relevance of chemical toxicity to this study is questionable.

Diet is also known to play a role in prostate cancer. A Western diet, which is relatively high in fat and meat, may contribute to higher prostate cancer risk (12). We examined confounding dietary factors, including meat, vegetables, fried foods, milk, and butter, but adjustment for these covariates

did not alter the results (data not shown).

An association between prostate cancer and obesity has not been established in spite of repeated studies. However, obesity has been hypothesized to be a risk factor for prostate cancer because of the connections between body size and **testosterone** (35). Shift workers are known to be a high-risk group for obesity (4). In the current study population, rotating-shift workers showed a higher distribution of the highest body mass index compared with daytime workers (table 1). High body mass index among shift workers might confound the result. However, there was no significant difference in baseline body mass index between the prostate cancer cases in day work and in rotating-shift work (table 3). In addition, the significant association between rotating-shift work and prostate cancer was still observed after we adjusted for body mass index. Therefore, the effect of obesity, or at least body mass index at the time of the baseline survey, on the current study appears limited.

Limitations of our study

Important limitations of our study should be discussed. First, in terms of ascertaining the risk of prostate cancer, the follow-up time was short and the cohort was relatively small. Although this study had enough power to show the effect for rotating-shift workers, it involved 10 years of follow-up and only 31 cases of prostate cancer, so the result needs to be interpreted with caution. To maximize statistical stability, we performed the same analysis on data for an additional 15,906 working men aged 40–79 years. Fifty-five cases of prostate cancer were included in the analysis, but the result remained the same.

Second, the validity of our questionnaire assessing participants' work schedule experiences is uncertain. The questionnaire ascertained the type of schedule in which workers' engaged the longest. A previous report revealed a length-dependent effect of rotating-shift work on tumor incidence (2). We therefore assumed that the longest type of work schedule experienced was more preferable than the current schedule in terms of life-course effects. Unfortunately, information regarding duration of employment was not obtained, so the length-dependent effect of work schedule on tumor incidence could not be evaluated in this study.

Third, access to medical consultation during the follow-up period or information regarding tumor-node-metastasis (TNM) classification of the cancer patients was not obtained. We therefore could not evaluate the effect of early cancer detection. Previous studies have reported a high prevalence of gastrointestinal disturbances, hypertension, sleep disturbances, obesity, and hypercholesterolemia among shift workers (4). More frequent access to medical care may result in relatively early detection of prostate cancer, in which case risk would be overestimated. However, there were no differences in mean age at baseline, mean follow-up period, and mean age at endpoint between the cases engaged in day work and rotating-shift work. This result may indicate that there is no difference in the quality of the survey assessing cancer incidence associated with the various types of work schedule. To account for frequency of medical consultation, we also adjusted for a covariate "existence of illness under treatment at the time of the baseline" in the model, but the result remained the same.

Conclusion

This prospective cohort study revealed a significant association between rotating-shift work and

prostate cancer incidence among Japanese male workers. Because this is the first time that this risk factor has been known to be identified, the association needs to be replicated and confirmed in other settings.

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