Previously, we reported an increased risk of hypertension, diabetes mellitus, and weight gain among shift workers based on cohort studies of the same target population[15–17]. The increased risk of hypertension was only found in younger workers[15]. Workers who transferred from fixed day work to shift work and workers who had continued shift work had a greater weight gain during the follow-up period than other workers[17]. The present study showed that younger shift workers with midnight shifts had lower intakes of some micronutrients, while older shift workers had higher total intakes; these findings may be related to those of our previous cohort studies[15–17], but our conclusions are limited by the cross-sectional design of the present study.

To generalize the results from the present study, one needs to consider the characteristics of the subjects of this study, since the effects of shift work on nutrient intake and eating habits are modified by local circumstances, socioeconomic factors, and the shift schedule. The subjects of this study were manual workers who had permanent contracts in the main factory of a large company. Therefore, their socioeconomic status was considered to be relatively good. The shift schedule used in this factory is the usual system that is used in Japanese factories. The factory is located in a rural area where it is not convenient to eat out, but proper meals are served at lunch in the factory's cafeteria. Therefore, our results suggest that shift work, particularly when it includes midnight shifts, affects nutrient intake, even with better socioeconomic conditions.

To conclude, shift work, particularly when it includes midnight shift work, affects nutrient intakes. The type and extent of the effect of shift work on nutrient intakes depends on age and shift work history.

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Original article

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Influence of job strain on changes in body mass index and waist circumference—6-year longitudinal study

by Masao Ishizaki, PhD,[1] Hideaki Nakagawa, PhD,[2] Yuko Morikawa, PhD,[2] Ryumon Honda, PhD,[1] Yuichi Yamada, PhD,[1] Norito Kawakami, PhD,[3] The Japan Work Stress and Health Cohort Study Group[4]

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Objectives This study examined the effect of changes in psychosocial workplace characteristics on weight gain and abdominal obesity.

Methods Twice, at an interval of 6 years, the authors conducted examinations of job demand–control–support and measurements of body mass index and waist circumference among 2200 men and 1371 women aged 30–53 years and working in a factory. The scores of the psychosocial work characteristics in each examination were dichotomized at the median values for the men and women separately and then categorized into three groups as follows: group I: low score in both the first and second examinations, group II: low score in the first examination and high score in the second (or high at the first and low at the second), and group III: high in both the first and second examinations.

Results Although there was no statistically significant association between psychosocial work characteristics and the change in body mass index, for both genders, the change in waist circumference increased more in group III than in group I. Similarly, the odds ratios for the change in waist circumference above the 75th percentile for groups II and III increased more than in group I, being 1.13 [95% confidence interval (95% CI) 0.87–1.46 and 1.39 (95% CI 1.07–1.79) for the men in groups II and III, respectively, and 1.27 (95% CI 0.90–1.78) and 1.78 (95% CI 1.26–2.52) for the women in groups II and III, respectively.

Conclusions The results suggest that high job strain is a risk factor for increased abdominal obesity.

Key terms job control; job demand; waist circumference change.

Several studies have shown that psychosocial work stress, such as low job control and job strain combined with high job demand and low job control, which are considered to be work stressors in the job demand–control model proposed by Karasek, are related to the development of coronary heart disease (CHD) (1, 2). The pathophysiological mechanism underlying the relationship between work stress and CHD has been suggested to be increased ambulatory blood pressure (3, 4) and abnormalities of blood coagulation and fibrinolytic function (5).

On the other hand, although obesity is an important CHD risk factor, it is still unclear whether work stress is connected to weight gain. The metabolic syndrome, which is a pathophysiological state in which a cluster of factors such as abdominal obesity, atherogenic dyslipidemia, raised blood pressure, and glucose intolerance are believed to promote CHD, is attracting increasing attention (6). A cross-sectional analysis in the Whitehall II study suggested a biological explanation that socioeconomic inequality in CHD was partly attributable to the metabolic syndrome, because people with a lower

1 Social and Environmental Medicine, Kanazawa Medical University, Ishikawa, Japan.
2 Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, Japan.
3 Department of Mental Health, University of Tokyo Graduate School of Medicine, Tokyo, Japan.
4 The Japan Work Stress and Health Cohort Study Group: T Haratani (National Institute of Industrial Health, Kawasaki, Japan), F Kobayashi (Aichi Medical University, Nagakute, Japan), S Araki (National Institute of Industrial Health, Kawasaki, Japan).

Reprint requests to: Dr M Ishizaki, Social and Environmental Medicine, Kanazawa Medical University, 1–1 Daigaku, Uchinada, Ishikawa, Japan. [E-mail: hygiene@kanazawa-med.ac.jp]

socioeconomic status have a greater waist circumference (7). A recent Whitehall II study, with an average 14-year-follow-up, showed an association between chronic work stress and the metabolic syndrome, more exposure to a state of low support with job strain being associated with a greater risk of the metabolic syndrome even after adjustment for employment grade and health behavior (8).

Many epidemiologic investigations have used waist circumference or waist-to-hip ratio as an anthropometric measurement index of abdominal obesity, which is closely related to the metabolic syndrome. Rosmond et al (9) and Rosmond & Björntorp (10) reported that inferior work conditions, such as less satisfaction with work management, less influence on work situations, and a lack of attempts to alter work situations, were associated with an increased waist-to-hip ratio.

In our previous cross-sectional investigation on Japanese employees, we found no statistically significant correlation between job demand–control and body mass index (BMI) or waist-to-hip ratio (11). However, we believe that a follow-up study would better clarify the influence of job demand–control on anthropometric measures, waist circumference, or waist-to-hip ratio, since, for example, considerable time must elapse before any changes in anthropometric measurements become apparent after exposure to certain work conditions. In addition, in the past decade, many companies in industrial countries have been trying to dynamically outrun others in the global economy race by introducing various managerial innovations, such as just-in-time production and total quality management (12). As a result, we can expect a rapid change in the work stress perceived by employees.

Therefore, in this study, we compared the results of two psychosocial work characteristics of the same persons in investigations conducted at an interval of 6 years and examined how changes in job demand–control affected the workers' anthropometric measurements.

Study population and methods

In our study, nonmanual and manual employees working for an aluminum-products factory in a rural area of Japan were asked to reply to the Japanese version of the job content questionnaire (13), about the status of job demand–control–support as individual psychosocial work characteristics. The survey was conducted twice, first from April 1996 through March 1997 and then from April 2002 through March 2003. On both occasions, only the persons who had provided their written consent to participate were included in the investigation. The selected workers were aged 30 to 53 years at the time of the first examination so that they were under 60 years of age, namely, the retirement age of the factory, at the time of the second examination. The participation rate of the first examination was 91.4% of the registered workers, or 2821 men and 1701 women, excluding pregnant women, as of 1 May 1996. Altogether 121 men and 39 women out of this population missed the opportunities or refused to consent to having their waist circumference measured. Before the second examination, 186 men and 184 women had resigned and 185 men had been transferred, and consequently they were excluded from the follow-up. Furthermore, 72 men and 97 women who did not reply to the second job content questionnaire or failed to undergo the second waist circumference measurement were also excluded.

Altogether, we included 2200 men and 1371 women as eligible participants whose data from the questionnaire and anthropometric measurements at both examinations were available and who had given complete replies to the questions concerning the confounding factors, such as sedentary job, shift work, and other health behavior, at the first examination. Managers and professionals accounted for 14% of all the men, whereas only 2% of the women were managers or professionals.

Job strain was calculated as a value of job demand divided by job control. The median value of each psychosocial work characteristic of the participants from the age of 30 to 53 years did not change between the two surveys. The median values of the job demand scores, the job control scores, and the scores for worksite support were 66, 32 and 23 for the men and 60, 32, and 22 for the women, respectively. But the median values of the job strain scores slightly changed, from 0.485 for the men and 0.533 for the women in the first examination to 0.500 for the men and 0.536 for the women, respectively, in the second examination. The scores for job control, job demand, worksite support, and job strain in each examination were dichotomized at the median value for the men and women separately and then categorized into three groups as follows: group I: low score in both the first and second examinations, group II: low score in the first examination and high score in the second (or high in the first and low in the second), and group III: high in both the first and second examinations (figure 1).

Anthropometric measurements

Anthropometric measurements were conducted within a month before or after the questionnaire survey on both occasions, the weight, height, and waist circumference of the participants being measured with them wearing light clothes. The BMI (kg/m^2) of the participants was calculated by dividing their weight by their height squared. The waist circumference (centimeters) was

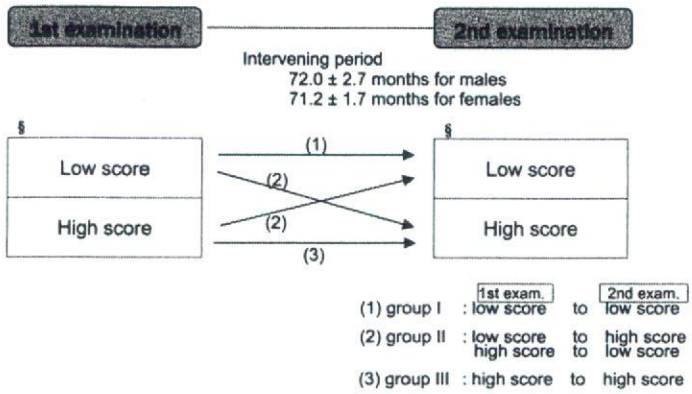

Figure 1. Categorization according to the change in psychosocial work characteristics. [§ = The scores for job control, job demands, worksite support, and job strain (demand and control) in each examination were dichotomized at the median value for 2200 men and 1371 women after those with no job content questionaire or anthropometric measurement data on either occation were excluded or who resigned or transferred after the 1st examination.]

measured at the umbilicus level by experienced nurses. Underwear worn to correct body shape was removed.

Sedentary job and shift work as other work characteristics

Sedentary job was categorized into three groups according to the average number of sedentary hours per workday in the previous year ("<1 hour", "≥1 and ≤4 hours", and "≥5 hours"). The three-shift workers who worked nights were categorized as a shift work group, as opposed to a nonshift work group. No female worker in the factory was engaged in three-shift work.

Other health behavior

Queries were made about several lifestyle factors. The workers were classified as "non- or ex-smokers" and "current smokers". Alcohol consumption was measured in terms of grams of ethanol consumed per week and was categorized into five groups for the men (ie, no drinking, 1–175 g/week, 176–350 g/week, 351–525 g/week, and ≥526 g/week). As only five women ingested more than 350 grams of alcohol per week, alcohol consumption was re-categorized into three groups as follows: non-drinker, 1–175 g/week, and ≥175 g/week. Exercise for the men was classified as "almost no exercise", "light exercise", "brisk and sweating exercise once or twice a week" and "brisk and sweating exercise more than three times a week". The degree of education for the men was determined by the total years of education and was classified as "<11 years", "11–12 years", "13–14 years", and "≥15 years" of education. Since relatively few women participated in brisk and sweating exercise more than three times a week or had more than 15 years of education, exercise and education were re-categorized into three groups for the women ("almost no exercise", "light exercise", and "brisk and sweating exercise" and "<11 years", "11–12 years", and "≥13 years", respectively). Marital status was divided into "married" and "previously or never married".

This study was approved by the Ethics Committee of the Kanazawa Medical University.

Statistical analyses

The data were analyzed separately for the men and women using an SAS program package (SAS Inc, Cary, NC, USA). Changes in BMI and waist circumference were expressed as (second examination value – first examination value) / first examination value. The BMI and waist circumference in the first examination, the change in BMI, and the change in waist circumference were compared among different groups using a general linear model. The data for sedentary job, shift work, smoking habits, alcohol consumption, exercise, education, and marital status (inquired about in the first examination) were adopted as potential confounding factors.

Logistic regression analyses were used to calculate the odds ratios of the change in BMI and the change in waist circumference above the 75th percentile according to changing job strain; they were 0.0458 and 0.0600 for the men and 0.0456 and 0.1080 for the women, respectively.

Results

The mean period from the first to the second examination of the job content questionnaire was 72.0 (SD 2.7) months for the men and 71.2 (SD 1.7) months for the women.

Table 1 shows the differences in the mean values for age, BMI, waist circumference, and psychosocial work characteristics in the first examination between the workers with complete data from the two surveys and those for whom only data from the first examination were available. For the men, those who participated in both examinations were younger and had lower job control than those who participated only in the first examination. For the women, the latter group was younger and had

Table 1. Mean levels and standard deviations (SD) of the body mass index (BMI), waist circumference, and psychosocial work characteristics at the first examination for those who participated in both the baseline and the follow-up examinations and those who participated only at the baseline.

	Men								Women							
	N	Particpation at baseline and in follow-up		N	Participation at baseline only		P-value		N	Particpation at baseline and in follow-up		N	Participation at baseline only		P-value
		Mean	SD		Mean	SD				Mean	SD		Mean	SD	
Age	2200	41.8	6.4	778	42.7	6.8	<0.01		1371	41.7	6.3	378	43.9	7.7	<0.01
BMI (kg/m²)		23.2	2.8	778	23.3	2.8	0.42			22.4	3.2	378	22.6	3.4	0.24
Waist (cm)		79.6	7.7	657	80.2	7.4	0.09			71.7	8.7	328	73.3	9.9	<0.01
Job control		65.2	10.0	751	66.3	10.4	0.02			58.6	10.0	348	58.1	10.4	0.35
Job demand		32.0	4.8	761	32.0	4.7	0.82			31.6	5.0	357	31.7	5.0	0.81
Worksite support		21.8	3.2	748	21.8	3.1	0.78			21.3	3.3	370	21.2	3.8	0.74
Job strain		0.504	0.118	740	0.495	0.119	0.06			0.557	0.141	329	0.567	0.174	0.33

Table 2. Body mass index (BMI) and waist circumference in the first examination according to the change in the psychosocial work characteristics. (group I = low score in both the first and second examinations, group II = low score in first examination and high score in second examination or high score in first examination but low score in second examination, group III = high score in both the first and second examinations)

	Men					Women				
	N	BMI (kg/m²)		Waist (cm)		N	BMI (kg/m²)		Waist (cm)	
		Unadjusted	Adjusted [a]	Unadjusted	Adjusted [b]		Unadjusted	Adjusted [a]	Unadjusted	Adjusted [b]
Job control										
Group I	863	23.0	23.5	79.1	80.6	569	22.4	23.2	71.7	72.0
Group II	635	23.1	23.6	79.1	80.4	442	22.4	23.1	71.5	71.8
Group III	702	23.5	23.8	80.8	81.5	360	22.4	23.3	72.2	72.4
P-value		<0.01	0.17	<0.01	0.05		0.98	0.86	0.50	0.62
Job demand										
Group I	591	23.3	23.8	80.3	81.6	371	22.3	23.1	72.1	72.6
Group II	731	23.0	23.5	78.8	80.2	509	22.4	23.2	71.1	71.6
Group III	878	23.3	23.8	79.9	81.1	491	22.5	23.2	72.1	72.5
P-value		0.03	0.04	<0.01	<0.01		0.66	0.89	0.12	0.17
Worksite support										
Group I	615	23.3	23.8	79.5	81.0	496	22.5	23.3	71.9	72.0
Group II	802	23.2	23.6	79.6	80.9	510	22.5	23.2	71.7	71.8
Group III	783	23.2	23.6	79.7	80.9	365	22.1	22.9	71.6	71.7
P-value		0.60	0.39	0.91	0.90		0.14	0.20	0.88	0.86
Job strain										
Group I	619	23.4	23.8	80.5	81.5	358	22.3	23.1	72.3	72.6
Group II	801	23.1	23.6	79.4	80.6	554	22.6	23.3	71.7	72.0
Group III	780	23.1	23.7	79.2	80.7	459	22.4	23.1	71.4	71.8
P-value		0.22	0.46	<0.01	0.07		0.36	0.58	0.35	0.46

[a] Adjusted for age, sedentary job, shift work (only men), smoking, alcohol, exercise, education, and marital status in model 1.
[b] Adjusted for the factors listed for model 1 and also BMI in the first examination.

slenderer waists. The mean scores for job control, job demand, and worksite support among the workers who participated in both examinations were 65.2 (SD 10.0), 32.0 (SD 4.8), and 21.8 (SD 3.2), respectively, for the men and 58.6 (SD 10.0), 31.6 (SD 5.0), and 21.3 (SD 3.3), respectively, for the women. These scores did not differ very much from the scores of other large population studies of Japanese (14) and Belgians (15).

Regarding the association between psychosocial work characteristics and lifestyle at the first examination, there were no differences in smoking habits or alcohol consumption between the low and high psychosocial

Table 3. Change in body mass index (BMI) and waist circumference according to changes in job control, job demand, and worksite support. (group I = low score in both the first and second examinations, group II = low score in first examination and high score in second examination or high score in first examination but low score in second examination, group III = high score in both the first and second examinations)

	Men		Women	
	Change in BMI [a]	Change in waist circumference [b]	Change in BMI [a]	Change in waist circumference [b]
Job control				
Group I	0.009	0.018	0.021	0.061
Group II	0.013	0.022	0.020	0.057
Group III	0.011	0.016	0.017	0.050
P-value	0.36	0.16	0.56	0.32
Job demand				
Group I	0.009	0.016	0.019	0.049
Group II	0.010	0.017	0.018	0.057
Group III	0.012	0.021	0.019	0.055
P-value	0.39	0.18	0.92	0.50
Worksite support				
Group I	0.012	0.018	0.017	0.056
Group II	0.012	0.019	0.021	0.061
Group III	0.009	0.017	0.019	0.049
P-value	0.48	0.84	0.65	0.21

[a] Adjusted for age, sedentary job, shift work (only men), smoking, alcohol, exercise, education, and marital status in model 1.
[b] Adjusted for the factors listed for model 1 and also for BMI in the first examination.

work characteristic groups of either gender. More men in the high job-strain group had standing work, shift work, no regular exercise, and shorter education and were not married in comparison with the men in the low job-strain group. The women in the high job-strain group had more standing work, less regular exercise, and shorter education than those in the low job-strain group. The men in the low worksite-support group had more standing work and shorter education than those in the high worksite-support group. No difference between the low and the high worksite-support groups was found for the women (data not shown).

Table 2 on page 291 shows the mean BMI levels and waist circumference values according to the subgroups of job control, job demand, worksite support, and job strain in the first examination. For the men, both the BMI and waist circumference were larger in group III than in group I for job control and similarly larger in group I and III than in group II for job demand. As regards job strain, group I had the largest waist circumference among the three groups. For the women, there were no statistically significant differences in BMI or waist circumference among the subgroups of any of the psychosocial work characteristics. After adjustment for potential confounding factors, these differences did not change much for either gender.

The associations of the change in BMI and the change in waist circumference (after adjustment for the confounding factors) with job control, job demand, worksite support, and job strain are shown in table 3 and table 4. No significant difference was found in the change in BMI among the three different groups of the psychosocial work characteristics for either gender. The change in waist circumference was significantly higher in group III for job strain than in groups I and II among the men, and also a marginally significant similarity was found for the women. There was no significant interaction between job strain and the other work conditions (ie, sedentary work and shift work) with respect to the values of the change in BMI or the change in waist circumference. In the analyses of the relationship between job strain and the change in BMI and the change in waist circumference, BMI was categorized into slender, moderate, and overweight groups. Hereupon the moderate group denoted the mean value plus or minus one standard deviation of the BMI in the first examination. The ranges of the slender, moderate, and overweight groups were <20.38 kg/m^2, 20.38–26.02 kg/m^2, and ≥26.03 kg/m^2 for the men and <19.18 kg/m^2, 19.18–25.66 kg/m^2, and ≥25.67 kg/m^2 for the women, respectively. For the men, the proportions of people in the overweight group at the first examination who gained weight or had an increase in their waist circumference during the period between the two examinations were 53.1% (BMI) and 59.3% (waist). The rates were lower than those in the slender and moderate groups at the first examination. The change in BMI in the overweight group at the first examination was also smaller than that in the slender or moderate group for both genders.

On the other hand, the change in waist circumference increased in all of the BMI categories of slender, moderate, and overweight at the first examination. The change in waist circumference among the men was larger in group III than that in group I or group II. The change in waist circumference in group III was similarly larger than that in group I or group II for both the moderate and overweight women in the first examination.

For those who lost weight during the interval between the first and second examinations, no significant difference in the change in BMI or the change in waist circumference was found among the three job-strain groups (data not shown).

Table 5 shows the odds ratios of the change in BMI and the change in waist circumference above the 75th percentile according to the changes in job strain. Regarding the change in waist circumference for both genders, group III showed a significantly higher rate of change than group I. The odds ratios were 1.13 [95% confidence interval (95% CI) 0.87–1.46] in group II and 1.39 (95% CI 1.07–1.79) in group III for the men and 1.27 (95%

Table 4. Change in body mass index (BMI) and waist circumference in relation to job strain according to the BMI category in the first examination. (job-strain group I = low score in both the first and second examinations, job-strain group II = low score in first examination and high score in second examination or high score in first examination but low score in second examination, job-strain group III = high score in both the first and second examinations)

BMI in the first examination	Change in BMI					Change in waist circumference				
	Persons with weight gain (%)	Job-strain group I	Job-strain group II	Job-strain group III	P-value	Persons with waist increase (%)	Job-strain group I	Job-strain group II	Job-strain group III	P-value
Slender [a]										
Men (<20.38 kg/m²) (N=345) [b]	65.2 [c]	0.011	0.016	0.020	.	65.5 [c]	0.023	0.009	0.015	.
Women (<19.18 kg/m²) (N=170) [b]	62.9 [c]	0.012	0.019	0.022	.	60.6 [c]	0.040	0.064	0.059	.
Moderate [a]										
Men (20.38–26.02 kg/m²) (N=1523) [b]	62.4 [c]	0.012	0.016	0.015	.	66.6 [c]	0.031	0.033	0.032	.
Women (19.18–25.66 kg/m²) (N=1003) [b]	63.5 [c]	0.016	0.023	0.025	.	66.1 [c]	0.021	0.030	0.042	.
Overweight [a]										
Men (≥26.03 kg/m²) (N=332) [b]	53.1 [c]	–0.008	–0.009	0.008	.	59.3 [c]	–0.005	0.002	0.007	.
Women (≥25.67 kg/m²) (N=198) [b]	60.6 [c]	0.013	0.012	0.022	.	65.7 [c]	0.073	0.074	0.084	.
Total										
Men	.	0.008 [d]	0.010	0.013	0.26	.	0.013 [e]	0.019	0.022	0.03
Women	.	0.018 [d]	0.019	0.020	0.89	.	0.046 [e]	0.055	0.065	0.04

[a] BMI category: slender = <(mean–SD), moderate = (mean–SD) - (mean+SD), overweight = ≥(mean+SD).
[b] Number of persons in each BMI category.
[c] Percentage of persons in each BMI category with weight gain or waist increase during the period.
[d] Adjusted for age, sedentary job, shift work (only men), smoking, alcohol, exercise, education, and marital status in model 1.
[e] Adjusted for the factors listed for model 1 and also BMI in the first examination.

Table 5. Odds ratios (OR) and their 95% confidence intervals (95% CI) for the change in body mass index (BMI) and waist circumference above the 75th percentile according to job-strain change. (group I = low score in both the first and second examinations, group II = low score in first examination and high score in second examination or high score in first examination but low score in second examination, group III = high score in both the first and second examinations)

Job strain	Change in BMI [a]				Change in waist circumference [b]			
	Men		Women		Men		Women	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Group I	1	.	1	.	1	.	1	.
Group II	1.05	0.82–1.35	1.05	0.77–1.44	1.13	0.87–1.46	1.27	0.90–1.78
Group III	1.23	0.95–1.59	0.92	0.66–1.29	1.39	1.07–1.79	1.78	1.26–2.52

[a] Adjusted for age, sedentary job, shift work (only men), smoking, alcohol, exercise, education, and marital status in model 1.
[b] Adjusted for the factors listed for model 1 and also for BMI in the first examination.

CI 0.90–1.78) in group II and 1.78 (95% CI 1.26–2.52) in group III for the women.

Discussion

This 6-year follow-up study showed that the change in waist circumference in job-strain group III increased more than that in job-strain group I, even though no statistically significant association was noted between the psychosocial work characteristics and the change in BMI. Moreover, the prevalence rate of the change in waist circumference above the 75th percentile among both the men and women increased progressively in order from group I to group II to group III of job strain after adjustment for age, BMI, sedentary job, shift work, smoking, alcohol, exercise, education, and marital status. The results of this study showed that high job strain may contribute to abdominal obesity.

Although two previous cross-sectional investigations referred to the association between job strain and abdominal obesity among men (16, 17), one review noted that the association was not clear (18). Recently, Brunner et al (19) showed that job strain partly caused abdominal obesity, because a dose–response relationship between work stress and obesity was found in their 19-year follow-up study. With an increased number of cases classified as iso-strain (ie, the lowest tertile of worksite support combined with job strain, evaluated on four occasions during the follow-up), the incidences of a high BMI of ≥30 kg/m^2 for both genders and a large waist circumference of >102 cm among the men and >88 cm among the women increased.

Rosmond & Björntorp (20) and Rosmond (21) have suggested that, as one of the pathophysiological mechanisms underlying the association between job strain and waist circumference, psychosocial disadvantage pressure affects the activity of the hypothalamic–pituitary–adrenal axis and, as a result, increases the cortisol level. This increase in the cortisol level then causes abdominal fat to accumulate and therefore leads to an increased waist circumference.

The measurement of saliva cortisol has frequently been used to examine the neuroendocrine excretion status in field studies. Those who perceived high chronic work overload (22) and high social stress (23) showed increased cortisol levels on awakening in the morning. The mean cortisol level of workdays was higher in a low job-control group than in a high job-control group among the men, and, among the women with a low socioeconomic status, the mean cortisol level of the workdays was higher in a high job-demand group than in a low job-demand group (24). In addition, for men, a positive association was found between the waist-to-hip ratio and the cortisol response to waking (25), and, for women, the urinary cortisol level per 24 hours was increased (26).

It is well known that there is an inverse correlation between socioeconomic status and BMI among people in developed countries (27). Although people with a low socioeconomic status are expected to be under high work stress (ie, low job control), the influence of job demand–control on BMI is obscure. Job strain has not been found to be associated either with BMI in various large cross-sectional population studies among Japanese–Americans, working women, and Canadian white-collar workers (28–30), nor with weight gain in a 5-year prospective study on civil servants (31). High job demand or low job control was not associated with weight gain in the past year (32). On the other hand, according to the data collected from the 32 worksites in a cross-sectional study, the women in the high-strain group had a higher BMI than those in the other groups, but this trend was not found for the men (33). A study in France found a relationship between high job demand and overweight among women, but not among men (34). Kivimäki et al (31) pointed out the bidirectional effect of work stress on BMI as one reason for the inconsistent correlation between work stress and BMI, because work stress could not only lead to hyperphagia but also to hypophagia. The population of our study may have included some workers who lost weight due to work stress. However, no significant difference in the change in BMI or the change in waist circumference existed among the three job-strain groups for those who lost weight during the intervening period. It is possible that some of the workers who lost weight due to severe anorexia caused by work-stress-induced depression were not able to participate in the examinations because they were not working on the occasions and consequently were excluded from the participants.

Notably, in spite of focusing on the same target population, a 19-year follow-up study found work stress to be related to weight gain, while another 5-year follow-up study found no such relationship (19, 31). The former study noted the accumulated effect of work stress, and the observation lasted for a longer period in comparison with that of the latter study. In addition, another study pointed out that the evaluation of job strain at a single point in time possibly underestimated the association between job strain and CHD (35). Thus our previous cross-sectional study may similarly have underestimated the association between job strain and the waist-to-hip ratio.

No changes in the mean scores of job demand, job control, or worksite support were found between the first and second examinations in our study. Prior research showed stability for scores of the job content questionnaire on two occasions, before and after an average interval of 6.6 years among 2490 Europeans who remained in the same job (15). In addition, the scores of the work characteristics for the same persons did not change appreciably over a 5-year interval in Japan (36). However, the Japanese study also found that the scores were less stable when there was a position change even within the same company. Likewise, about one-third of the participants of our study showed some changes in the scores of the job content questionnaire during the 6-year period, shifting from the high group to the low group of psychosocial work characteristics and vice versa.

We categorized the persons with improved psychosocial work characteristics and those who showed deterioration in this respect together as group II, because they were likely to have experienced greater changes in other work conditions, such as workplace, shift work, and sedentary job than group I and group III did. In addition, it is difficult to know exactly when the particular change in psychosocial work characteristics started, as the effect of a change in an anthropometric measurement does not manifest itself immediately but, rather, takes time.

Adopting many factors as potential covariates may weaken the relationship between job strain and the change in BMI or the change in waist circumference.

For instance, many people in the high-strain group had less regular exercise in association with an increased BMI and waist circumference.

Incidentally, the job-strain scores of the women in this study were higher than those of the men. Furthermore, the women rarely changed their occupations and tended to remain in a relatively low employment job. These facts may have affected the results of this follow-up study, making the relationship clearer between job strain and the change in waist circumference.

Some investigations have also shown that work stress, when evaluated in a job demand–control model, was associated with glucose metabolism, blood coagulation, and fibrinolytic function as risk factors of cardiovascular disease in Japan, as well as in other developed countries (37). Obesity (BMI ≥30 kg/m^2) is certainly less common in Japan than in western Europe and the United States (38). However, the proportions of overweight (BMI ≥25 kg/m^2) Japanese men are 32.7% for those 40–49 years of age and 30.8% for those 50–59 years of age. The corresponding proportions for Japanese women are 17.9% and 24.1%, respectively. In addition, one in every two men and one in every five women are said to have suspected or potential metabolic syndrome (39). Therefore, the national government has begun to make a concerted effort to tackle the metabolic syndrome by making the measurement of waist circumference mandatory when people aged 40–74 years are screened in medical checkups (40).

There were several potential limitations in this study. First, we evaluated and classified psychosocial work characteristics for the same people using the job content questionnaire twice at an interval of 6 years, but we have no data on the fluctuation of the psychosocial work characteristics during this period. Similarly, although we used the scores of several confounding factors at the first examination, we did not record their subsequent changes. In addition, as about 25% of the men and about 20% of the women of all of the participants either retired, were transferred, did not fill out the questionnaire completely, or refused to participate in this examination, they were excluded from the follow-up survey. This exclusion may have conceivably affected the results, although a large population of both genders was available for continued follow-up. Second, the waist circumference was lower for group III in the first examination. This initial low score may possibly have contributed to the increase in waist circumference in the second examination. However, especially for the women, the difference in the change in waist circumference among the three job-strain groups was larger than the difference affected by the initial potential bias. Third, we did not make a dietary survey with respect to weight gain. However, a large-scale survey of 25 000 Japanese by Kawakami et al (41) did not reveal any evident connection between job strain and total energy intake, even after adjustment for age, educational background, and occupation. Fourth, since the participants of our study were all from a single company, whether our results can be generalized or not will have to be determined in further studies.

In conclusion, we examined psychosocial work characteristic twice for 2200 men and 1371 women with an interval of 6 years between the examinations. We admit that there was a bidirectional influence of work stress on BMI and waist circumference, and yet the results of our study showed that high job strain increased the change in waist circumference even when several potential confounding factors were taken into consideration. This result supports the finding of Brunner et al (19), who reported that chronic work stress may contribute to abdominal obesity. Hence it is important that we take measures to reduce the chronic work stress of workers in terms of preventing atherosclerotic and other diseases triggered by the metabolic syndrome.

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OBSERVATIONS

BMI May Be Better Than Waist Circumference for Defining Metabolic Syndrome in Japanese Women

We previously addressed sex differences in the associations between anthropometric indexes of obesity and blood pressure and showed that blood pressure was more strongly related to BMI than to waist circumference in Japanese women (1). As hypertension is a major component of metabolic syndrome in Japanese patients, a similar sex difference may exist in the association between anthropometric indexes and the metabolic components of metabolic syndrome. We investigated the possible sex differences of these associations.

Study subjects consisted of 2,935 men and 1,622 women between 35 and 59 years of age; 13% of the women were postmenopausal. Detailed information regarding this study population has been provided elsewhere (1). Metabolic abnormalities were determined using the Japanese criteria of metabolic syndrome (2). In a multiple linear regression analysis (supplemental Table 1*A*, available in an online appendix at http://dx.doi.org/10.2337/dc07-0309), both BMI and waist circumference were related independently to serum triglyceride and HDL cholesterol level. The relationship of anthropometric indexes to fasting plasma glucose (FPG) level was weaker than that to blood pressure (1) and to serum lipid levels. In multiple logistic regression analyses (supplemental Table 1*B*), waist circumference was more strongly associated with dyslipidemia (defined as having high triglycerides or low HDL cholesterol) and high FPG in men, whereas BMI was more strongly associated with dyslipidemia in women. Although high FPG was more strongly associated with waist circumference in women, the association was weaker than the relationship between BMI and hypertension (1) or dyslipidemia. The presence of two or more of three metabolic abnormalities (hypertension, dyslipidemia, and high FPG) was observed in 22.6% of men and 9.1% of women. The risk ratio of having accumulations of two or more metabolic abnormalities was higher for waist circumference than for BMI in men, whereas it was higher for BMI in women. When BMI and waist circumference were included simultaneously in a model, waist circumference showed a stronger association than BMI with the accumulation of metabolic abnormalities in men, and only BMI showed an independent association in women. The results were similar using the International Diabetes Federation definition (3) to determine the metabolic abnormalities.

In lean Asian women, for whom subcutaneous fat has a stronger influence on waist circumference(4), BMI may be a more appropriate index for total and abdominal fat. Thus, we should pay more attention to BMI in defining metabolic syndrome in Asian women.

Masaru Sakurai, MD, PHD[1,2]
Toshinari Takamura, MD, PHD[1]
Katsuyuki Miura, MD, PHD[2]
Shuichi Kaneko, MD, PHD[1]
Hideaki Nakagawa, MD, PHD[2]

From the [1]Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; and the [2]Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, Japan.

Address correspondence to Dr. Toshinari Takamura, Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan. E-mail: ttakamura@m-kanazawa.jp.

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Original Article

White Blood Cell Count, Especially Neutrophil Count, as a Predictor of Hypertension in a Japanese Population

Yoshimi TATSUKAWA[1)], Wan-Ling HSU[2)], Michiko YAMADA[1)], John B. COLOGNE[2)], Gen SUZUKI[3)], Hideya YAMAMOTO[4)], Kiminori YAMANE[4)], Masazumi AKAHOSHI[5)], Saeko FUJIWARA[1)], and Nobuoki KOHNO[4)]

Although several studies have shown that high WBC count is a risk factor for hypertension, the relationship between WBC count and the incidence of hypertension in Japanese is poorly understood, as are the effects of WBC components on that relationship. Our objective was to verify in a Japanese population whether WBC or differential WBC count predicts hypertension incidence. A total of 9,383 initially hypertension-free subjects (3,356 men and 6,027 women), whose WBC counts were within the normal range (3,000 to <10,000 cells/mm^3), were followed from 1965 to 2004. During this 40-year follow-up, 4,606 subjects developed hypertension. After adjusting for conventional risk factors, including smoking status, we found that elevated WBC count was associated with hypertension incidence in a Cox regression model with both fixed and time-varying covariates for women. For men, elevated WBC count was a significant risk factor for hypertension only in the time-varying Cox-regression covariate. We also observed a significant association between increased neutrophil count and hypertension incidence among women. In a fully adjusted model, the relative risks of hypertension incidence, from the lowest to the highest quartiles of neutrophil count, were 1.00, 1.18, 1.28, and 1.22 in women (*p* for trend <0.001). In conclusion, elevated WBC count predicted an increased incidence of hypertension in Japanese, especially among females. Moreover, neutrophils were the major WBC component contributing to the increased risk. (*Hypertens Res* 2008; 31: 1391–1397)

***Key Words*: hypertension, leukocyte, neutrophil, epidemiology, follow-up study**

Introduction

Numerous epidemiological studies have demonstrated an association between cardiovascular disease (CVD) and inflammatory markers, such as elevated levels of WBCs (*1–6*) or of C-reactive protein (CRP) (*6–8*). Several studies have also shown a positive association between hypertension and elevated WBC (*9–12*), CRP (*13, 14*), or interleukin (IL)-6 (*14*) levels. The subjects of those studies, however, were middle-aged or elderly, and the follow-up periods ranged from 4 to 20 years.

The activation of neutrophils, a major inflammatory WBC, leads to the release of reactive oxygen species (ROS), which

From the [1)]Department of Clinical Studies and [2)]Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan; [3)]Department of Environmental Health, National Institute of Public Health, Wako, Japan; [4)]Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; and [5)]Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan.
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Address for Reprints: Saeko Fujiwara, M.D., Ph.D., Department of Clinical Studies, Radiation Effects Research Foundation, 5–2 Hijiyama Park, Minami-ku, Hiroshima 732–0815, Japan. E-mail: fujiwara@rerf.or.jp
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contribute to oxidative stress (*15–17*). Oxidative stress has recently emerged as a factor in the pathogenesis of hypertension (*18–20*). In experimental models of hypertension, neutrophil counts rise prior to the development of hypertension (*21, 22*), but no epidemiological study has focused on the association between neutrophil count and hypertension incidence.

In the present study, we investigated the relationship between WBC count, including differential WBC count, and the incidence of hypertension over a 40-year period in 9,383 subjects (3,356 men and 6,027 women) who did not have hypertension at baseline.

Methods

Study Population

Approximately 20,000 subjects were invited to participate in biennial health examinations conducted by clinical physicians of the Atomic Bomb Casualty Commission (and later succeeded by the Radiation Effects Research Foundation) beginning in July 1958 in Hiroshima and Nagasaki. A detailed description of the examinations is available elsewhere (*23*). We obtained informed consent from all participants, and the study was approved by the Radiation Effects Research Foundation institutional ethics committee and the Human Investigation Committee.

A total of 12,870 subjects underwent a health examination in Hiroshima and Nagasaki at baseline (1965–1967). This study excluded 2,718 subjects who had a history of hypertension, 295 subjects whose smoking habits were unknown, and 409 subjects who did not return for the next follow-up examination. We also excluded an additional 65 subjects whose WBC count at baseline was outside the normal range (3,000 to <10,000 cells/mm³) on the assumption that they might have had an infection or acute illness. The remaining 9,383 subjects, with ages ranging from 19 to 85 years old at baseline, were analyzed in the present study. Although follow-up was stopped in 1974 for the quartile of all subjects who were not in the cities at the time of the bombing, a high participation rate (75–90%) was maintained for the rest of the subjects (*24*).

Measurements

Blood pressure (BP) was measured at least twice by an experienced nurse with a mercury column sphygmomanometer and a cuff of appropriate size applied to the sitting subject's left arm at heart level after a sufficient sedentary period. Systolic and diastolic BP was determined by Korotkoff phases I and V, respectively. Standing height and body weight were measured without shoes or outer clothing. Body mass index (BMI) was calculated as body weight divided by the square of the standing height (kg/m²). Until 1967 in Hiroshima and 1976 in Nagasaki, WBC count was measured by the Melangeur method after venous blood was diluted with 3% acetic acid, and Wright staining was used for differential WBC counts. After that, hematological autoanalyzers were used. WBC counts by each autoanalyzer were compared by the Melangeur method, and a good correlation was confirmed. WBC values were coded at the 100-unit level. Total serum cholesterol level was also measured by an automated method. The examinations were performed separately in Hiroshima and Nagasaki Laboratories, depending on where the subject lived. The machines in both laboratories were calibrated every month with control blood samples to maintain reproducibility and consistency. Values were standardized based on the machine used in 1986. Diabetes was diagnosed according to 1985 WHO criteria (*25*).

We obtained information about cigarette smoking, alcohol consumption, physical activity, and menopause status from a mail survey and a self-administered lifestyle questionnaire. The subject was categorized as a "never smoker," "former smoker," or "current smoker" and as a "drinker" or "non-drinker." Physical activity level was converted into an oxygen consumption index as defined in the Framingham cohort study (*26*). The most sedentary physical activity was represented by a physical activity index score ≤28.

Table 1. Baseline Clinical Characteristics of Study Subjects

Characteristics	Men	Women
Number of subjects	3,356	6,027
Age at baseline (years)	45.0±14.1	44.4±12.5
White blood cell (10³/mm³)	6.7±1.7	6.0±1.6
Neutrophil (10³/mm³)	3.8±1.3	3.5±1.3
Lymphocyte (10³/mm³)	2.1±0.7	1.9±0.6
Monocyte (10³/mm³)	0.5±0.2	0.4±0.2
Body mass index (kg/m²)	20.7±2.9	21.5±3.7
Systolic blood pressure (mmHg)	120±15	116±16
Diastolic blood pressure (mmHg)	76±10	73±10
Total cholesterol (mmol/L)	4.3±1.6	4.3±1.9
Diabetes (%)	5.3	2.3
Most sedentary physically active* (%)	72.3	82.3
Current smoker (%)	76.0	13.6
Former smoker (%)	9.9	1.6
Alcohol drinking (%)	70.0	14.3
Menopause (%)		29.8

Each continuous variable is expressed as mean±SD. *Physical activity index score ≤28.

Assessment of Hypertension Incidence

Incident cases of hypertension were defined when subjects were newly diagnosed or newly started on antihypertensive medication between follow-up exams and the diagnosis was confirmed by an AHS examining physician. Subjects with secondary hypertension were excluded from incident cases. In our data, most hypertension cases had a diagnosis of hyper-

Table 2. Relative Risk of Hypertension by WBC Count Quartile for Men and Women

Men	Quartile of WBC count (× 10³/mm³)				*p* for trend
	≤5.4	>5.4–6.4	>6.4–7.7	>7.7	
Number of observation	904	786	830	836	
Number of cases	429	377	411	437	
Rate per 1,000 person-years	33.5	31.6	32.8	35.4	
Age-adjusted RR (95% CI)	1.00	1.02 (0.88–1.17)	1.08 (0.94–1.24)	1.22 (1.07–1.40)	0.003
Multivariate-adjusted RR* (95% CI)	1.00	0.92 (0.80–1.17)	0.90 (0.78–1.03)	1.02 (0.89–1.17)	0.88
Women	Quartile of WBC count (× 10³/mm³)				*p* for trend
	≤4.9	>4.9–5.8	>5.8–6.9	>6.9	
Number of observation	1,586	1,599	1,354	1,488	
Number of cases	740	753	693	766	
Rate per 1,000 person-years	26.9	28.3	31.5	31.1	
Age-adjusted RR (95% CI)	1.00	1.15 (1.04–1.27)	1.30 (1.17–1.44)	1.40 (1.27–1.55)	<0.001
Multivariate-adjusted RR* (95% CI)	1.00	1.08 (0.97–1.19)	1.14 (1.03–1.27)	1.21 (1.09–1.35)	<0.001

RR, relative risk; CI, confidence interval. *Adjusted for age at baseline, city, radiation exposure, body mass index, smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, menopause status was additionally adjusted.

Table 3. Risk of Hypertension by Continuous WBC Count in Time-Varying and Fixed Covariate Cox Regression Models

Cox regression model	RR* (95% CI) of hypertension with increasing WBC count (per 10³/mm³)	*p*
Men		
Fixed covariate	1.02 (0.99–1.05)	0.22
Time-varying covariate†	1.10 (1.07–1.13)	<0.001
Women		
Fixed covariate	1.04 (1.01–1.06)	0.002
Time-varying covariate†	1.05 (1.03–1.07)	<0.001

RR, relative risk; CI, confidence interval. *Adjusted for age at baseline, city, radiation exposure, body mass index (BMI), smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, menopause status was additionally adjusted. †In the time-varying Cox regression model, WBC, BMI, and total cholesterol were the time-varying covariates.

tension at least twice in different examination cycles. We assumed the date of onset of hypertension to be the midpoint between the exam date when hypertension was first noted and the previous exam date. All participants were followed from the baseline examination to the date of incident hypertension or, for those with no hypertension, the last examination date through 2004.

Statistical Analysis

For each sex, we categorized the baseline WBC count into quartiles. The Cox proportional hazards model was used to evaluate the independent effect of WBC count on the risk of hypertension incidence. We assessed the proportionality assumption of the Cox model by plotting the Kaplan-Meier curves for all categorical predictors and by performing the proportionality test for continuous predictors. Based on the plots and test results, we estimated the final Cox models for each sex in order to examine the independent effect of WBC count on hypertension incidence.

We used two models in our analysis: an age-adjusted model and a multivariate-adjusted model. The latter adjusted for age at baseline, city (Hiroshima or Nagasaki), smoking status (never smoker, former smoker, or current smoker), BMI, radiation exposure, total cholesterol level, alcohol consumption status (drinker or nondrinker), systolic BP, menopausal status for women (yes or no), diabetes (present or absent), and physical activity level (≤28 or >28). Quartiles and continuous WBC count were both analyzed. Furthermore, since WBC and covariates such as BMI and total cholesterol level change over time, we also conducted a time-varying Cox regression model. We used Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, USA) for all statistical procedures.

Results

The average age at baseline was 45.0 years in men and 44.4 years in women (Table 1). The average WBC count was slightly higher for men than for women. More than 70% of men were current smokers and drinkers, respectively. Most women were never smokers and did not drink.

During the 40-year follow-up, 1,654 men and 2,952 women developed hypertension. The median follow-up period of the incident cases was 9.0 years. Table 2 shows the relative risk

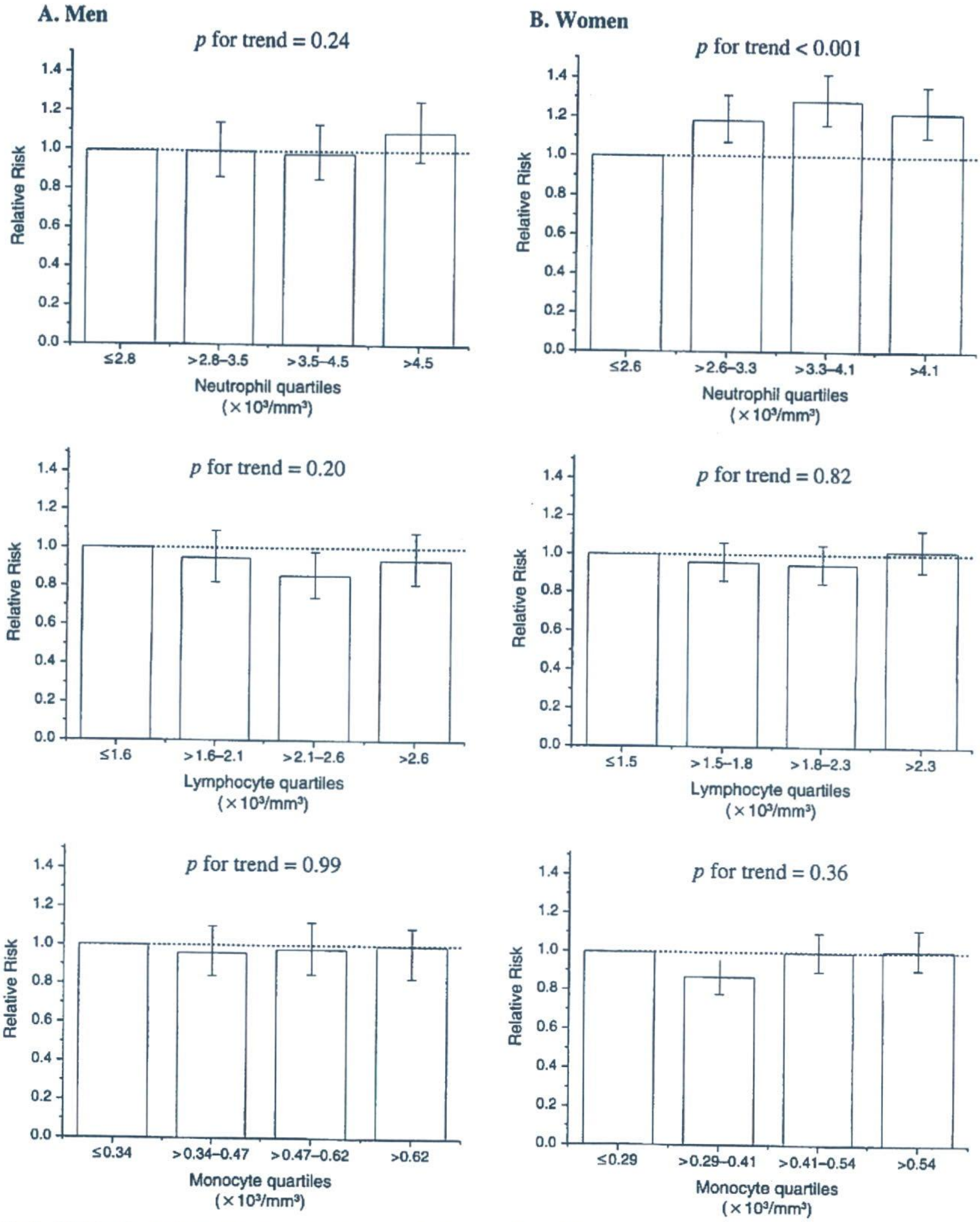

Fig. 1. *Multivariate-adjusted relative risk of hypertension by quartile of differential WBC count in men (A) and women (B). The relative risks were adjusted for age at baseline, city, radiation exposure, body mass index, smoking status, total cholesterol, diabetes mellitus, physical activity, alcohol drinking, and systolic blood pressure. For females, the risk was adjusted also for menopause status. The error bars represent 95% confidence intervals.*

(RR) of hypertension incidence by WBC quartiles for each sex. In the age-adjusted model, the highest WBC count quartile for men and the top three quartiles for women were significantly associated with the incidence of hypertension, and the RR of hypertension incidence increased from the lowest (referent) to the highest WBC count in both men (p for trend 0.003) and women (p for trend <0.001). In the multivariate-adjusted model, the significance of WBC's effect on hypertension incidence in men was diminished (p for trend 0.88). On the other hand, for women, the RR was attenuated but still positively associated with hypertension incidence, with elevated risk from the lowest to the highest quartiles of WBC count. Current smoker, higher BMI, and higher systolic BP were associated with an increased risk of hypertension for both men and women, while drinking was a statistically significant risk factor only for men (data not shown).

The relationship between continuous WBC count and the incidence of hypertension in the fixed and time-varying multivariate Cox regression models is shown in Table 3. Although the RRs for the fixed multivariate Cox regression models were almost the same as those for women in the time-varying multivariate Cox regression model, WBC count was also significantly associated with the incidence of hypertension in men.

The RRs of hypertension incidence in the multivariate-adjusted model by quartiles of differential WBC count are shown by sex in Fig. 1. Similar to the result for WBC count, no significant association was observed in any differential WBC counts for men. For women, only the neutrophil count quartiles, and not the monocyte or lymphocyte count quartiles, were significantly associated with hypertension incidence (p for trend <0.001).

Discussion

This cohort study covered a large number of subjects with a wide range of ages (19 to 85 years) for a long follow-up period (about 40 years). To our knowledge, this is the first demonstration that neutrophil count is, like total WBC count, significantly associated with the incidence of hypertension. The analysis was adjusted for conventional cardiovascular risk factors, and all subjects had normal WBC counts at baseline.

Many studies have suggested that elevated levels of inflammatory markers (WBC count, CRP, or IL-6) are associated with increased risks of hypertension (*9–14*) and CVD (*1–8*), and recent epidemiologic studies have shown a positive association between neutrophil count and CVD (*4, 5, 27*). Although we have not seen any epidemiologic study indicating an association between neutrophil count and hypertension, elevated WBC and neutrophil counts have been shown to precede the development of hypertension in animal models (*21, 22*). Our results support those studies and further suggest that neutrophils may be the major component of WBCs responsible for an increased risk of hypertension.

When we analyzed the relationship between differential WBC counts and hypertension incidence, we found that an elevated neutrophil count was a significant risk factor, though only for women. Lee *et al.* (*4*) showed that CVD incidence and mortality were independently associated with elevated granulocyte counts and to a lesser degree with elevated monocyte counts. However, there has been no report of a significant relationship between monocyte count and the incidence of CVD (*5, 27*). The effect of monocytes on CVD seems to be still unclear.

In women, we detected a significant association between WBC count and the incidence of hypertension. In men, a significant relation between WBC count and the incidence of hypertension was observed only in the time-varying Cox regression model. This sex difference may be attributable to several factors. In this cohort, most of the women were nonsmokers, but the majority of men were current smokers at baseline. For men, the prevalence of smoking has changed dramatically during the study period, whereas the change in the prevalence of smoking among women was small, as it was in the rest of the Japanese population (*28*). Since WBC count tends to increase with the number of cigarettes smoked (*2, 29*), the true association between WBC count and the incidence of hypertension might be detected only when the WBC count is treated as a time-varying covariate. BMI might have had a similar effect, since the average BMI change from 1976 to 1995 has been greater in men than in women in Japan (*30*). WBC count increased with increased BMI (*31*). Since the cohort in the present study has had a very long follow up, using the baseline measurement in the time-invariant Cox model may not fully capture the association between WBC and hypertension incidence. Thus, the time-varying Cox model seems to be the most suitable method for detecting any such relationship.

Although we did not measure pro-inflammatory cytokines or CRP, the effect of neutrophils on the development of hypertension may follow from their role in inflammation. Accumulating evidence suggests that the inflammatory process, in part, mediates the development and progression of atherosclerosis (*32, 33*). Pro-inflammatory cytokines, especially IL-6 and IL-8, are associated with obesity (*34, 35*), diabetes mellitus (*36*), and cardiovascular disease (*37*). IL-8 is also the major cytokine responsible for neutrophil recruitment and activation (*38, 39*). Activated neutrophils have an increased tendency to adhere to vascular endothelium, which may result in capillary leukocytosis and increased vascular resistance (*40*). In addition, activated neutrophils release ROS, which contribute to oxidative stress (*15–17*), which in turn is involved in the pathogenesis of hypertension through impairment of endothelium-dependent vasorelaxation (*18–20*). In animal hypertension models, elevated neutrophil and ROS levels preceded the development of hypertension (*21, 22*).

Our study had some limitations. First, the criteria for hypertension have changed during the long follow-up (from BP

≥160/95 mmHg to ≥140/90 mmHg) (*41*, *42*), but the bias resulting from the change in criteria would be small because most of the incident cases were diagnosed before the criteria were changed, and subjects with grade 2 or 3 hypertension by the WHO criteria had already been assessed. Also, the frequency of hypertension did not change in the general Japanese population (*43*). Furthermore, we confirmed that the result did not include a major change when we analyzed the models using 1992 as the last follow-up year, which is the year before the criteria changed. Second, some bias may have resulted from the end of follow-up in 1974 for the quartile of all subjects who were not in the cities at the time of the bombing. However, our study results (not shown here) also confirmed that no major change resulted from that exclusion. Another limitation is the lack of smoking information over time. As is well known, smoking is a significant risk factor for elevated WBC count (*2*, *29*). In the time-varying Cox regression model, however, we updated only WBC count, BMI, and total cholesterol during the follow-up. Finally, dietary intake of sodium and potassium is also a major determinant of BP (*44*, *45*). However, we had no dietary information, and we thus did not use such data as adjustment factors in the present study.

In conclusion, elevated WBC count, especially neutrophil count, was significantly associated with an increased risk of developing hypertension among Japanese men and women, although the relative risks were modest. This study provides evidence that inflammation may play a role in the development of hypertension, and that neutrophils may be involved in that role. This finding may be useful for clarifying the mechanism underlying the development of hypertension.

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SHORT COMMUNICATION

Follicle-stimulating hormone and oestradiol levels during perimenopause in a cohort of Japanese women

M. Yamada,[1] M. Soda,[2] S. Fujiwara[1]

SUMMARY

Context: There had been a lack of longitudinal studies regarding follicle-stimulating hormone (FSH) and oestradiol (E2) during perimenopause for non-Caucasian populations. **Objective:** To investigate FSH and E2 levels during perimenopause in a Japanese cohort. **Design and setting:** The Adult Health Study is a longitudinal population-based study. Perimenopausal women from this study cohort were followed between 1993 and 2003. **Participants and main outcome measures:** Non-menopausal women, aged 47–54 years, were measured in terms of FSH and E2 levels every 6 months. For 89 women whose FSH and E2 levels were measured within 3 months from their final menstrual period (FMP), trends of FSH and E2 within 21 months of FMP were investigated at 6-month intervals. **Results:** Follicle-stimulating hormone and E2 levels within 3 months from FMP showed wide ranges. Neither FSH nor E2 levels differed by age, weight or duration of amenorrhoea. Although FSH increased and E2 decreased during perimenopause, FSH and E2 levels at a single time point were found to not be a reliable marker of biological menopause, as hormone levels in and between the subjects showed wide variation and any trend in one individual was not necessarily one directional. **Conclusions:** Among Japanese women who had natural menopause around the age of 50, hormone levels in and between individuals showed wide variation throughout perimenopause with a converged biochemical menopausal pattern characterised by high FSH and low E2 at about 2 years after FMP.

What's known

- That, among Caucasian populations, increased FSH and decreased E2 levels were major changes during perimenopause, and that variations of hormone levels between individuals were large.
- That changes in hormone levels (decreased E2 and increased FSH) occurred within one to two years on each side of the final menstrual period.

What's new

- Longitudinal changes in FSH and E2 during perimenopause were investigated among Japanese living in Japan.
- Individual trends of the combination of FSH and E2 were observed.

[1]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan
[2]Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan

Correspondence to:
Michiko Yamada,
Department of Clinical Studies, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan
Tel.: + 81 82 261 3131
Fax: + 81 82 263 7279
Email: yamada@rerf.or.jp

Disclosures
None.

Introduction

Although knowledge about changes in follicle-stimulating hormone (FSH) and oestradiol (E2) during perimenopause has been accumulated over the years, not many longitudinal studies have been conducted, especially for non-Caucasian populations. Observations on continuous menstrual cycles among a limited number of perimenopausal women showed marked fluctuation of individual hormone levels (1,2). The Melbourne Women's Midlife Health Project, based on a cross-sectional survey of a randomly selected large population, showed that increased FSH and decreased E2 were major changes during the menopausal transition and that variations of hormone level between individuals were large (3). They also reported, based on a longitudinal study, that decreased E2 and increased FSH occurred within 1–2 years on each side of the final menstrual period (FMP) (4). Based on self-reporting, the Massachusetts Women's Health Study estimated the length of perimenopausal transition to be nearly 4 years (5).

The Study of Women's Health Across the Nation (SWAN) reported effects of ethnicity and age on the menopausal transition (6). Although Japanese women living in the US had lower E2 but similar FSH compared with Caucasian women (6), the longitudinal changes in FSH and E2 during perimenopause among Japanese living in Japan was unknown.

The aim of this study was to observe FSH and E2 levels in Japanese in relation to FMP. For this purpose, frequent hormone measurements among a relatively large number of subjects were required, as FMP was determined retrospectively after 12 months of amenorrhoea (7).

Materials and methods

The study subjects belong to the Radiation Effects Research Foundation (RERF)'s Adult Health Study (AHS), which is described elsewhere (8). In the