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ORIGINAL ARTICLE

Association between working hours and cancer risk in Japan: The Japan public health center-based prospective study

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Abstract

Objectives: In this study, we evaluated the association between working hours and cancer risk in the Japanese population, which has not been evaluated.

Methods: Using a cohort database from a Japan Public Health Center-based Prospective Study, we evaluated 26 738 participants (16 351 men and 10 387 women), who responded to a questionnaire about working hours and followed these participants from 1993–1994 to 2013. Participants were divided into four groups according to working hours (≤6, 7–8, 9–10, ≥11 h/day). The hazard ratio (HR) and 95% confidence interval (CI) of each cancer incidence were calculated using a multivariable-adjusted Cox proportional hazard model.

Results: During 488 383 person-years of follow-up, 481 patients with newly diagnosed cancers were identified. There was no clear association between long working hours and overall cancer, lung cancer, and stomach cancer risks. Long working hours tended to increase prostate cancer risk in men and breast cancer risk in women, although the difference was not statistically significant. Increased liver cancer risk with short working hours (HR [95% CI]; 3.15 [1.44–6.88] in the ≤6 h/day group vs. 7–8 h/day) was observed. Colorectal cancer also tended to increase risk in short working hours, however, there were not statistically significance.

Conclusions: In this population, long working hours were not associated with cancer risk with statistically significance. The association between short working hours and liver cancer risk was observed, probably due to the reverse causation of liver cancer.

KEYWORDS

breast cancer, cohort study, liver cancer, overall cancer, working hours

1 | BACKGROUND

Long working hours have received considerable attention in Japan. The Japanese worked for an extremely long time compared to other countries in the 1980s. However, from the end of the 1980s to the 1990s, the working hours of Japanese laborers have decreased. In recent years, Japanese working hours have been almost the same as those in the United States (US) and the United Kingdom (UK); however, they are still longer than those in other countries such as France, Germany, and Scandinavian nations.[1] Due to long working hours, work-life balance has collapsed in Japan, and there are some reports that long working hours lead to diseases such as type 2 diabetes, depression, coronary heart disease, and acute myocardial infarction.[2–6] The relationship between long working hours and diseases has been reported worldwide. The meta-analysis data suggested an increased coronary heart disease risk (1.12-fold) and stroke risk (1.21-fold) in ≥55 h/week working group.[7] Another report also suggested an association between ≥55 h/week of working hours and a higher coronary heart stroke risk.[8] Long working hours not only induce physical damage but also cause psychological effects. The previous study showed significant relationship between ≥60 h/week of working hours and psychological stress response.[9] Other reports showed perceived stress, as an indicator of psychological stress, contributes to the overall cancer incidence.[10,11] A multicohort study was conducted to examine the association between long working hours and cancer risk in Europe.[12] This study demonstrated that there was no relationship between ≥55 h/week of working hours and overall cancer, lung cancer, colorectal cancer, or prostate cancer risks. However, there was a tendency for long working hours to be associated with an increased breast cancer risk in women. Long working hours sometimes lead to short sleeping time.[13] Previous studies showed short sleeping time was associated with increased risk of cancer including breast cancer.[14–16] In addition, some occupation such as sedentary workers might relate to shorter physical activity. The shorter physical activity also related to increase of cancer risk.[17] Indeed, some occupation associated with cancer risk.[18,19] If the sedentary workers worked long hours, the cancer risk would increase. However, the association between working hours and cancer risk has not been evaluated in Japan even though the retirement age has been increasing. Therefore, it is important to evaluate cancer risk in the occupational population.

To clarify the effects of working hours on cancer risk, we evaluated the association between working hours and the overall cancer risk, as well as lung cancer, stomach cancer, liver cancer, colorectal cancer, prostate cancer, and breast cancer in women, using a large-scale prospective cohort database from the Japan Public Health Center (JPHC)-based prospective study.

2 | MATERIALS AND METHODS

2.1 | Study cohort

The JPHC-based prospective study consists of two cohorts, cohort I and cohort II, which started in 1990 and 1993, respectively. Cohort I included residents aged 40–59 years in five Japanese public health center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo), and cohort II included residents aged 40–69 years in six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). Details of the study design have been reported previously.[20] In the baseline survey, 140 420 individuals constituted the study population. Cohort II data were used in this study because working hours were collected only in Cohort II in the baseline questionnaire. Study participants were informed of the study's aims, and those who completed the survey questionnaire were regarded as consenting to participate. The study was approved by the Institutional Review Board of Osaka University (14020) and the National Cancer Center, Tokyo, Japan (13-021).

We used the information from the baseline questionnaire and followed the cancer incidence from 1993 to 1994 (in answering the baseline questionnaire) to 2013. In addition, we evaluated the answers about working hours and job changes at 5 and 10 years after the baseline survey. Figure 1 shows a flowchart of the selection of eligible participants for the analysis. In the present analysis, we excluded cohort I participants (n = 61 595). Ineligible individuals (non-Japanese nationality, late emigration report before follow-up, and duplicate registration) were also excluded (n = 577). Participants from two PHC areas (Katsushika in the Tokyo prefecture and Suita in the Osaka prefecture) were excluded (n = 9663) because the cancer incidence data were unavailable and the selection of participants differed from those in other PHCs. We also excluded participants who moved out of the study area or lost the end date of the observation before the baseline questionnaire survey (n = 125). In addition, participants who did not answer the baseline questionnaire (n = 12 233) and were diagnosed with cancer before the baseline questionnaire survey (n = 8799) were also excluded. Participants who did not answer the questionnaire about working hours at the baseline survey (n = 4557) were excluded. Participants who had an incorrect birthday (n = 2), were non-worker or housemaker (n = 12 951), and aged ≥65 years at the baseline survey (n = 3180) were also excluded. For the final analysis, the number of eligible participants were 26 738.

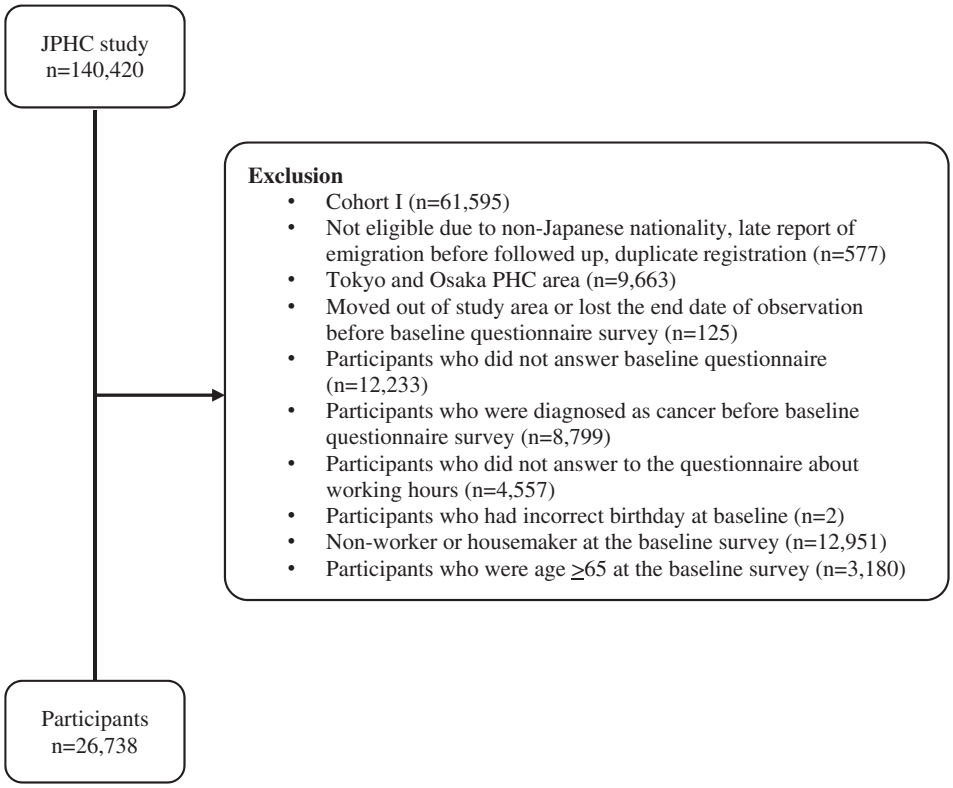

FIGURE 1 Patient flow chart. The flowchart summarizes the inclusion and exclusion criteria for participants selection. *n*, number; JPHC, Japan Public Health Center-based Prospective Study; PHC, Public Health Center.

2.2 | Exposure definition

In this study, the main exposure variable was working hours. The working hours were determined from the baseline, 5-, and 10-year questionnaires by the answer to the question, "How long [number of hours] do you work per day?" Baseline questionnaires were distributed to all residents in 1993–1994. Using the answers of the baseline questionnaire, the working hours were categorized into four groups: ≤6 h/day, 7–8 hay, 9–10 h/day, and ≥11 h/day.

2.3 | Follow up and cancer incidence

All participants in this study were followed from the date of administering the baseline questionnaire until December 31, 2013. Cancer incidence was identified by active cancer patient notification through the major local hospitals in the study area and data linkage with population-based cancer registries. Cancer sites were coded according to the International Classification of Diseases for Oncology, Third Edition with overall cancer and lung, stomach, liver, prostate, and breast cancers being denoted as C00-99, C34, C16, C22, C61, and C50, respectively. Colorectal cancer was denoted as C18, C19, and C20. The first cancer diagnosis date was used in this analysis if multiple cancers had been diagnosed at different times.

2.4 | Statistical analyses

Among all eligible participants, we evaluated the association between working hours and cancer risk using hazard ratios (HRs) with 95% confidence intervals (CIs), derived from a Cox proportional hazards regression model. We set the 7–8 h/day group as a reference because the Labor Standards Law in Japan defines the maximum working time as 8 h/day.[21] In addition, person-years of follow-up were calculated for each participant from the starting point until the date of cancer diagnosis, date of migration from a study to a non-study area, date of death, or the end of follow-up, whichever occurred first.

Furthermore, all following variables were calculated as categorical variables in following classifications: age (by 5 years), body mass index (BMI) (<19.0, 19.0–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ≥30 kg/m^2), physical activity (metabolic equivalents of tasks [METS] [quantile]), smoking (non-smoker, current, former), alcohol consumption (<1 day per month, 1–3 days per month, 1–149 g/week, 150–299 g/week, 300–449 g/week, and ≥450 g/week), sleeping time (≤5 h, 6 h, 7 h,

8 h, 9 h, and ≥10 h), history of hepatitis (yes or no), occupation (agriculture, forestry and fishery worker, salaried employee, self-employee, professional worker, homemaker, and unemployed) in both sexes, and menstrual start age (≤13, 14, 15, and ≥16), delivery age (≤29 and ≥30), number of delivery (1, 2, 3, 4, 5, and ≥6), menopausal status (pre-menopause and post-menopausal age at ≤49, 50–54, and ≥55), and lactation [yes or no] in women.

Baseline characteristics, overall cancer, lung, stomach, liver, and colorectal cancer incidences were evaluated. Prostate cancer incidence was evaluated in men, and breast cancer incidence was evaluated in women. Basic models were adjusted for age (category). Multivariable models included related covariates such as age (category), BMI (category), alcohol consumption, smoking, sleeping time, and occupation for overall cancer, lung, stomach, and prostate cancers. For liver cancer, multivariate models included a history of hepatitis in addition to the above covariates. For colorectal cancer, multivariate models included physical activity (category as quartile), in addition to the above covariates. For breast cancer, we added menarche age (category), delivery age (category), number of deliveries (category), menopausal status (category), and breeding multivariate as covariates.

We calculated two-sided *P* values, and statistical significance was determined at $P < 0.05$. All statistical analyses were conducted using Stata/MP software (version 13.0; Stata Crop) and R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). As for missing data, we imputed missing data for covariates.

3 | RESULTS

The characteristics of the participants at the start of follow-up are shown in Tables 1 and 2. Participants with long working hours (≥11 h/day) were younger than those with shorter working hours, and the number of women with long working hours was much higher than that of men. Sleeping time in the participants with long working hours was shorter compared to the participants in the short working hours group in both sexes. In men, participants in the short working hours group (≤6 h/day) had a slightly higher history of hepatitis compared to other working groups; in contrast, the same tendency was not observed in women. In women, working hours did not affect delivery age and number of deliveries. In this study, we also evaluated smoking status and alcohol consumption; however, there were no apparent associations with working hours. As for occupation, approximately half of the agriculture, forestry, or fishery workers were in the short working hours group (≤6 h/day) in both sexes.

During 488 383 person-years of follow-up, 481 patients with newly diagnosed cancers (397 men and 84 women) were identified. Table 3 shows the age-adjusted and multiple variable-adjusted HRs and 95% CIs of overall cancer and lung, stomach, liver, and colorectal cancers in both sexes according to working hours. Liver cancer risk increased clearly in short working hours (≤6 h/day) compared to 7–8 h/day working hours (multiple variables-adjusted HR [95% CI]; 3.15 [1.44–6.88] in ≤6 h/day group). In addition, colorectal cancer risk tended to increase in the short working hours group (≤6 h/day) compared to the 7–8 h/day group (multiple variables-adjusted HR [95% CI]; 1.72 [0.83–3.59] in ≤6 h/day group). On the other hand, there were no associations between working hours and overall cancer and lung and stomach cancer risks in both sexes.

Table 4 shows the age-adjusted and multiple variables-adjusted HRs and 95% CIs of prostate cancer in men and breast cancer in women according to working hours. The tendency of increased prostate cancer risk was found in the short and long working hours groups (≤6 h/day and ≥11 h/day) compared to the 7–8 h/day group; multiple variables-adjusted HR (95% CI): 1.85 (0.62–5.48) in the ≤6 h/day groups, and 1.54 (0.60–3.95) in the ≥11 h/day groups, respectively. We also found the tendency of increased multiple variables-adjusted HRs (95% CI) in women with breast cancer depending on longer working hours as follows: 1.30 (0.33–5.19) in the 9–10 h/day group and 1.74 (0.46–6.64) in the ≥11 h/day group. There were no participants with breast cancer in the short working group (≤6 h/day).

4 | DISCUSSION

This study evaluated the association between cancer risk and working hours in the Japanese population. We found no clear association between long working hours and cancers. However, a statistically significant association between short working hours and liver cancer risk was observed. To the best of our knowledge, our report is the first to evaluate the association between working hours and any site of cancer risk using a large-scale prospective cohort database.

The tendency of increased breast cancer risk in women according to the long working hours was observed in this study, whereas there was no clear association between long working hours and overall cancer, lung and stomach cancer risks. The possibility of an association between long working hours and breast cancer risk in women was suggested in a previous study.[12] In general, women who work long hours have fewer children and show aging at their first birth[22] because women who work longer hours

TABLE 1 Characteristics of men according to working hours at the baseline

	Working hours (h)/day			
	≤6	7–8	9–10	≥11
Participants				
n, (%)	1055 (6.5)	7002 (42.8)	6234 (38.1)	2060 (12.6)
Age				
Mean (SD)	55.4 (6.0)	48.2 (6.0)	47 (5.5)	45.9 (4.7)
BMI				
Mean (SD)	23.8 (3.0)	23.7 (2.9)	23.6 (2.8)	23.6 (2.6)
Physical activity, METS hour/day				
Mean (SD)	34.3 (6.1)	33.9 (5.8)	34.4 (5.7)	34.6 (5.7)
Sleeping time %				
≤5 h	4.9	2.8	2.9	9.6
6 h	14.8	13.5	15.8	26.0
7 h	22.8	32.1	35.5	33.3
8 h	38.5	39.1	35.7	25.1
9 h	7.7	7.4	6.9	3.8
≥10 h	7.4	3.3	2.5	1.4
Missing	3.9	1.8	0.7	0.8
Smoking status %				
Non-smoker	28.2	25.4	26.2	24.5
Former smoker	24.4	20.9	21.1	22.1
Current smoker	46.5	53.1	52.3	53.0
Missing	1.0	0.6	0.3	0.4
Alcohol consumption %				
<1 day per month	27.8	20.0	18.1	21.2
1–3 days per month	6.9	8.8	8.2	10.3
1–149 g/week	19.8	25.8	28.8	26.6
150–299 g/week	16.4	20.8	22.1	18.9
300–449 g/week	12.6	11.7	11.5	11.1
≥450 g/week	12.0	9.5	8.2	9.6
Missing	4.5	3.4	3.1	2.3
History of hepatitis %				
Yes	3.7	2.3	2.0	2.6
No	47.4	39.2	39.8	39.1
Missing	48.9	58.5	58.3	58.4
Occupation %				
Agriculture, forestry or fishery worker	44.4	16.3	16.8	18.1
Salaried employee	23.6	62.7	59.3	50.2
Self-employee	25.0	15.9	19.8	28.3
Professional worker	2.8	3.8	3.2	2.5
Missing	4.2	1.3	1.0	1.0

Abbreviations: BMI, body mass index; h, hours; METS, metabolic equivalent of task; *n*, number; SD, standard deviation.

have difficulty to take time for childcare as long as they do not have much childcare cost to delegate childcare to some vendors.[12] However, there were no effects on the number of deliveries and delivery age by long working hours in this study. It was reported that menopausal status and hormone replacement therapy is also associated with breast cancer

TABLE 2 Characteristics of women according to working hours at the baseline

	Working hours (h)/day			
	≤6	**7–8**	**9–10**	**≥11**
Participants				
n, (%)	984 (9.5)	2373 (22.9)	3201 (30.8)	3829 (36.9)
Age				
Mean (SD)	55.0 (7.4)	51.8 (7.3)	51.0 (6.9)	49.2 (6.4)
BMI				
Mean (SD)	23.9 (3.3)	23.4 (3.2)	23.3 (3.1)	23.1 (3.0)
Physical activity, METS-hour/day				
Mean (SD)	33.8 (5.9)	33.9 (5.7)	34.0 (5.6)	34.0 (5.4)
Sleeping time %				
≤5 h	4.7	4.1	4.2	6.6
6 h	16.6	18.3	20.5	27.6
7 h	29.4	34.9	37.7	42.2
8 h	33.4	33.6	30.6	20.7
9 h	6.6	4.4	4.1	2.0
≥10 h	2.5	1.4	1.7	0.5
Missing	6.8	3.2	1.2	0.5
Smoking status %				
Non-smoker	90.8	89.3	91.7	91.6
Former smoker	1.4	1.6	1.3	1.2
Current smoker	7.6	8.5	6.5	6.8
Missing	0.2	0.7	0.5	0.5
Alcohol consumption %				
<1 day per month	80.0	74.1	71.5	70.3
1–3 days per month	6.6	10.3	11.0	12.7
1–149 g/week	8.0	10.5	13.2	12.8
150–299 g/week	1.8	2.0	1.6	1.9
300–449 g/week	0.8	0.8	0.6	0.7
≥450 g/week	1.4	0.9	0.4	0.5
Missing	1.3	1.4	1.8	1.2
History of hepatitis %				
Yes	0.9	0.5	0.8	1.0
No	35.1	28.3	29.5	28.2
Missing	64.0	71.2	69.8	70.8
Occupation %				
Agriculture, forestry or fishery worker	51.9	27.7	23.7	14.4
Salaried employee	22.2	47.2	49.0	51.5
Self-employee	19.6	17.9	19.7	24.2
Professional worker	1.9	4.5	6.0	8.8
Missing	4.4	2.7	1.7	1.2
Menstral start age %				
≤13	17.8	24.3	29.8	35.9
14	18.2	22.6	24.8	26.7
15	19.4	20.8	19.3	19.7

TABLE 2 (Continued)

	Working hours (h)/day			
	≤6	7–8	9–10	≥11
≥16	42.7	29.9	24.3	16.7
Missing	1.9	2.4	1.8	1.0
Delivery age %				
≤29	77.5	82.8	88.1	90.0
≥30	5.2	6.2	6.0	7.0
Missing	17.3	11.1	5.9	3.1
Number of delivery %				
1	6.5	9.1	7.3	6.2
2	6.2	5.9	7.4	6.5
3	23.7	31.1	36.5	38.9
4	20.0	23.5	25.0	29.7
5	12.1	9.7	10.4	9.9
≥6	15.9	10.7	8.4	5.8
Missing	15.7	9.9	4.9	3.1
Lactation %				
Yes	70.1	71.0	78.4	79.8
No	10.7	13.1	11.7	12.8
Missing	19.2	15.9	9.9	7.4
Menopausal status %				
Pre-menopause	25.7	41.1	43.7	54.1
Post-menopause age				
≤49	35.4	27.8	27.3	23.0
50–54	32.6	25.4	24.1	19.3
≥55	3.3	2.3	2.0	1.5
Missing	3.1	3.5	2.8	2.1

Abbreviations: BMI, body mass index; h, hours; METS, metabolic equivalent of task; *n*, number; SD, standard deviation.

risk,[23] and these factors did not affect breast cancer risk in this study. It is suggested that shorter sleeping time is associated with breast cancer risk.[16,24,25] In this study, shorter sleeping time was observed in the long working hours group (≥11 h/day). The previous report suggested high job demands for the workers with long working hours lead to sleep disturbance,[26] while the detailed mechanism of relationship between long working hours and shorter sleeping time was not clear. To date, the association between breast cancer risk and night shift work has been well investigated. There are reports that suggest relationships between breast cancer risk and night shift work,[27] in contrast, some reports denied this relationships.[28–31] However, in our study, night shift work was not evaluated as a confounder. We also observed increased colorectal cancer and prostate cancer risks in participants with short working hours (≤6 h/day). As for prostate cancer, we observed a tendency of increased risk in the long working hours group (≥11 h/day). In colorectal cancer, sporadic colorectal cancer risk factors such as older age, smoking, high alcohol intake, and short duration of exercise have been reported.[32] However, apart from occupation, the characteristics of participants in the short working hours group, including physical activity in the short working hours group, did not differ compared to other groups; around 50% of participants in the short working hours group worked as an agriculturist, forestry and fishery workers. In a previous study, slightly elevated prostate cancer risk was observed in men who worked 49–54 h/week.[12] Some reports indicate that night shift work induces an increase in prostate cancer risk.[33,34] In contrast, a report suggested no association between night shift work and prostate cancer risk.[35] Therefore, the mechanisms underlying the increased prostate cancer risk due to short and long working hours are unclear. Further investigation is needed to clarify the association between working hours and prostate cancer risk.

In this study, we observed an increased liver cancer risk in participants with short working hours (≤6 h/day). We

TABLE 3 Age, area- and multiple variables-adjusted hazards ratio (HRs), and 95% confidence interval (CIs) of cancer risk according to working hours (overall cancer, lung cancer, stomach cancer, liver cancer, and colorectal cancer)

	Working hours (h)/day			
	≤6	7–8	9–10	≥11
Participants	2039	9375	9435	5889
Person-years	36 857.5	168 902.9	172 648.2	109 974.6
Overall cancer				
No. of cases	54	177	170	80
Crude rate	146.51	104.79	98.47	72.74
Age, area-adjusted HR (95% CI)	1.00 (0.73–1.36)	1.00	0.87 (0.70–1.07)	0.63 (0.48–0.83)
Multiple variables-adjusted[#1] HR (95% CI)	1.26 (0.91–1.74)	1.00	0.95 (0.76–1.19)	0.91 (0.68–1.21)
Lung				
No. of cases	7	25	21	6
Crude rate	18.99	14.80	12.16	5.46
Age, area-adjusted HR (95% CI)	0.82 (0.35–1.91)	1.00	0.76 (0.42–1.36)	0.35 (0.14–0.87)
Multiple variables-adjusted[#1] HR (95% CI)	1.12 (0.47–2.71)	1.00	0.90 (0.49–1.67)	0.54 (0.21–1.39)
Stomach				
No. of cases	8	30	35	11
Crude rate	21.71	17.76	20.27	10.00
Age, area-adjusted HR (95% CI)	0.89 (0.40–1.96)	1.00	1.08 (0.66–1.76)	0.53 (0.26–1.07)
Multiple variables-adjusted[#1] HR (95% CI)	1.18 (0.52–2.65)	1.00	1.28 (0.77–2.13)	1.04 (0.50–2.15)
Liver				
No. of cases	12	18	15	9
Crude rate	32.56	10.66	8.69	8.18
Age, area-adjusted HR (95% CI)	2.31 (1.09–4.87)	1.00	0.79 (0.40–1.57)	0.72 (0.32–1.61)
Multiple variables-adjusted[#2] HR (95% CI)	3.15 (1.44–6.88)	1.00	0.97 (0.48–1.98)	1.07 (0.43–2.62)
Colorectal				
No. of cases	12	31	22	11
Crude rate	32.56	18.35	12.74	10.00
Age, area-adjusted HR (95% CI)	1.28 (0.65–2.52)	1.00	0.63 (0.36–1.09)	0.49 (0.24–0.98)
Multiple variables-adjusted[#3] HR (95% CI)	1.72 (0.83–3.59)	1.00	0.74 (0.42–1.32)	0.78 (0.36–1.67)

Note: Multiple variables-adjusted[#1]: age, area, sex, BMI, alcohol, smoking, sleeping time, and occupation.

Multiple variables-adjusted[#2]: age, area, sex, BMI, alcohol, smoking, sleeping time, occupation, and history of hepatitis.

Multiple variables-adjusted[#3]: age, area, sex, BMI, alcohol, smoking, sleeping time, occupation, and physical activity.

Abbreviations: BMI, body mass index; CI, confidence interval; h, hours; HR, hazard ratio.

also calculated HR of liver cancer by excluding 2-year follow-up period from the start of follow-up. However, there were still statistically significant increase of HR in liver cancer in short working hours (data not shown), and we considered the reverse causation was occurred in the long term. In addition, we calculated HR of liver cancer by inverse probability of treatment weighting (IPTW) method as a sensitivity analysis, and the HR of liver cancer was same tendency as the result by an analysis using Cox proportional hazards regression model (HR by IPTW method

TABLE 4 Age, area- and multiple variables-adjusted hazards ratio (HRs), and 95% confidence interval (Cis) of cancer risk according to working hours (prostate cancer and breast cancer)

	Working hours (h)/day			
	≤6	7–8	9–10	≥11
Male				
Participants	1055	7002	6234	2060
Person-years	18 322.0	123 770.4	111 885.4	36 710.6
Prostate				
No. of cases	5	13	18	8
Crude rate	27.29	10.50	16.09	21.79
Age, area-adjusted HR (95% CI)	1.73 (0.61–4.94)	1.00	1.18 (0.57–2.43)	1.41 (0.58–3.44)
Multiple variables-adjusted[#1] HR (95% CI)	1.85 (0.62–5.48)	1.00	1.06 (0.50–2.28)	1.54 (0.60–3.95)
Female				
Participants	984	2373	3201	3829
Person-years	18 535.4	45 132.5	60 762.9	73 264.0
Breast				
No. of cases	0	3	8	11
Crude rate	0	6.65	13.17	15.01
Age, area-adjusted HR (95% CI)	–	1.00	1.63 (0.43–6.19)	1.72 (0.47–6.23)
Multiple variables-adjusted[#2] HR (95% CI)	–	1.00	1.30 (0.33–5.19)	1.74 (0.46–6.64)

Note: Multiple variables-adjusted[#1]: age, area, sex, BMI, alcohol, smoking, sleeping time, and occupation.

Multiple variables-adjusted[#2]: age, area, sex, BMI, alcohol, smoking, sleeping time, occupation, menstrual start age, delivery age, number of deliveries, breeding, and menopausal status.

Abbreviations: BMI, body mass index; CI, confidence interval; h, hours; HR, hazard ratio.

[95% CI]; 2.01 [0.88–4.61] in the ≤6 h/day group vs. 7–8 h/day). To analyze possible mechanism of increased risk of liver cancer in short working hours, we also calculated HR by excluding each confounder one by one from multi variables adjusted model (Table S4). When we exclude hepatitis and sleeping time, respectively, the HR decreased compared to full multi variables adjusted model. One of the liver cancer risk factors,[36] hepatitis as a surrogate covariant factor of hepatitis virus, was evaluated in this study, and the percentage of hepatitis in the shorter working hours group (≤6 h/day) was found to be slightly higher than that of participants in other working hours groups. The sleeping time in the short working hours group was tendency of longer compared to other working groups in this study. In general, patients with liver diseases such as hepatitis, non-alcoholic fatty liver disease, and chronic liver disease experience fatigue.[37–39] Furthermore, it is known that fatigue caused by liver disease is one of the causes of work productivity loss.[40] Therefore, we considered the symptoms of liver disease such as fatigue as one of the causes of short working hours and longer sleeping time, and the possibility that the participants with short working hours who have liver disease would lead to liver cancer incidence. In other words, short working hours were not a direct cause of liver cancer, but a consequence of liver disease, and short working hours might be considered to be the reverse causation of liver cancer.

4.1 | Limitations

Some limitations may have affected the results of this study. First, the working hours and other variables evaluated in this study were collected as self-reported questionnaires in the JPHC database. Therefore, we cannot rule out the possibility that our results were affected by the exposure misclassification. Second, we could not evaluate the possible confounding factors such as night shift work and socioeconomic inequalities, while the previous reports showed that night shift work and socioeconomic inequalities associated with cancer incidence,[27,41,42] respectively, and other previous reports suggested the night shift worker and economic vulnerable workers work longer hours.[43,44] Third, there is the possibility that long working hours have

interactions with variables such as sleeping hours, physical activity, occupation. However, we could not evaluate interactions between these factors because the number of cancer incidence was small and interaction term analysis was not converged. Forth, some participants might have retired or changed their type of work and changed the working hours. We evaluated the distribution of job changes in the survey conducted at 5 and 10 years after the baseline survey (Tables S1 and S2) and transition of working hours (Table S3). Regarding to the transition of working hours, working hours were collected in 3 categories, <5 h, 5–9 h or >9 h, in 5-year survey. Thus, we recategorized working hours of baseline survey and 10-year survey to 3 categories. Distributions of participants who did not change job were not apparently different between working hours group. The transition of working hours showed that the proportion of participants who worked ≥9 h at baseline survey and still worked ≥9 h at the 5- or 10-year surveys were lower compared to the groups in which participants did not change the working hours between baseline survey and 5-year/10-year survey in <5 h and 5–9 h. From this result, most of the long hours worker did not continue to work long hours in the long term. In addition, the number of each cancer incidence in these 3 categorized working hours was small, and we could not calculate meaningful HR. If the long hours worker continued to work with long hours in longer period, we might make clear the cancer risk by long working hours. As for occupational change, we evaluated the cancer risk of workers who worked same job at 5- and 10 years survey especially in overall, colorectal, liver cancers in both sexes, prostate cancer in men and breast cancer in women (data not shown). However, the number of cancer incidence was small, and detailed interpretation was difficult. In contrast, the strength of the present study was that we used the largest prospective study dataset in Japan.

5 | CONCLUSIONS

Long working hours were not associated with cancer risk in this population. However, the association between short working hours and liver cancer risk was observed in total, probably due to the reverse causation of liver cancer.

AUTHOR CONTRIBUTIONS

Kana Hattori, Tomotaka Sobue and Ling Zha designed the work that led to the submission. Norie Sawada and Tomotaka Sobue acquired the data. All authors participated in the interpretation of data. Kana Hattori carried out the statistical analyses and drafted the manuscript. Tomotaka Sobue, Ling Zha, Tetsuhisa Kitamura, Norie Sawada, Motoki Iwasaki, Manami Inoue, Taiki Yamaji and Shoichiro Tsugane critically revised the manuscript. Shoichiro Tsugane is the principal investigator of the JPHC Study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA AVAILABILITY STATEMENT

For information on how to gain access to the JPHC data, follow the instructions at https://epi.ncc.go.jp/en/jphc/805/8155.html

DISCLOSURE

Ethical approval: The study was approved by the Institutional Review Board of Osaka University and the National Cancer Center, Tokyo, Japan. *Informed consent*: Study participants were informed of the study's aims, and those who completed the survey questionnaire were regarded as consenting to participate. *Conflict of interest*: The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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