Original Article

Television Viewing Time and the Risk of Colorectal Cancer Mortality among Japanese Population: The JACC Study

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Purpose Sedentary behavior attributes to the increased risk of some cancers and all-cause mortality. The evidence is limited for the association between television (TV) viewing time, a major sedentary behavior, and risk of colorectal cancer death. We aimed to examine this association in Japanese population.

Materials and Methods A prospective cohort study encompassed of 90,834 men and women aged 40-79 years with no prior history of colorectal cancer who completed a self-administered food frequency questionnaire, and provided their TV viewing information. The participants were followed-up from 1988-1990 to the end of 2009. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by the Cox proportional hazard regression for risk of colorectal cancer mortality according to TV viewing time.

Results During the median 19.1-year follow-up period, we documented 749 (385 men and 364 women) colorectal cancer deaths. The multivariable-adjusted HRs for mortality from colorectal cancer were 1.11 (0.88-1.41) for 1.5 to < 3 hr/day, 1.14 (0.91-1.42) for 3 to < 4.5 hr/day and 1.33 (1.02-1.73) for ≥ 4.5 hr/day in comparison to < 1.5 hr/day TV watching; p-trend=0.038, and that for 1-hour increment in TV viewing time was 1.06 (1.01-1.11). Moreover, the multivariable-adjusted HR (95% CI) of colon cancer for 1-hour increment in TV viewing time was 1.07 (1.02-1.13). Age, body mass index, and level of leisure-physical activity did not show significant effect modifications on the observed associations.

Conclusion TV viewing time is associated with the increased risk of colorectal cancer mortality among Japanese population, more specifically colon rather than rectal cancer.

Key words Television viewing time, Sedentary behavior, Colorectal neoplasms, Cohort study, Japan

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database [1]. CRC mortality has been decreasing since the 1980s in several high-income, east Asian and east European countries, probably because of the improved early detection and treatments [2], but the rates in Japan is still increasing [3], probably due to adopting Westernized lifestyles characterized by higher meat and fat consumption and lower physical activity [4].

Sedentary behavior, such as television (TV) viewing, computer use and driving is known to be associated with poor health outcomes such as diabetes mellitus, cardiovascular disease, some cancers and all-cause mortality [5-7]. According to the Descriptive Epidemiology of Sitting study, the length of sitting time is approximately 7 hr/day among Japanese people, which is the longest in the world [8]. TV viewing time is a good indicator of leisure-time sedentary behavior in developed countries, including Japan [9].

Although a few previous studies [10,11] in non-Asian countries have examined the association between TV viewing time and the risk of CRC; however, the epidemiological data are limited, and no study has been conducted to investigate the association with the risk of CRC mortality in Asian populations. Therefore, our study aimed to evaluate the association of daily TV viewing time on risk of CRC mortality among Japanese population.

Materials and Methods

1. Study population

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks is a large prospective cohort study, the details of this study have been described in previously [12]. Briefly, the JACC study was established in 1988 to 1990 and covered a total of 110,585 individuals (46,395 men and 64,190 women) in 45 areas throughout Japan. Participants' eligibility was verified by investigators in each area to confirm the participant's residence in the study area, and that their age was 40-79 years at the baseline. The baseline information was collected by a self-administered questionnaire covering lifestyles and medical histories after obtaining informed consent from participants or local community leaders. Of the total 110,585 participants, we excluded 126 individuals with a medical history of CRC, 19,481 individuals with missing information for daily TV viewing time, and 144 individuals with inappropriate response to the daily TV viewing time ($\geq$ 12 hours) at the baseline survey. This left a total of 90,834 participants (38,130 men and 52,704 women) for the analyses.

2. Follow-up

The follow-up survey for cancer mortality was available in the 45 study areas. The follow-up ended at the end of 1999 in four areas, 2003 in four areas, 2008 in two areas and at the end of 2009 in 35 areas. For data analysis, we obtained a prior approval from the Director-General of the Prime Minister's Office and/or the Ministry of Health, Labor and Welfare, Japan. As part of death monitoring in each community, investigators conducted a systematic review of the death certificates. The date and cause of death were confirmed and documented once a year or once every 2 years. Participants who moved from their areas during the study period were also verified by the investigator in each area every year or every half a year via reviewing the population-register sheets of the cohort participants. Death from CRC was determined by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems. Tumors with International Classification of Diseases, 10th revision (ICD-10) codes C18, C19, and C20 were classified as CRC. C18 was classified as colon cancer (C18.0-C18.3 for right colon cancer, C18.4 for transverse colon cancer, and C18.5-C18.9 for left | colon cancer), and C19-C20 were classified as rectal cancer as described in a previous study [13].

3. Statistical analysis

This study's statistical analyses were based on the mortality rates from CRC during the follow-up period from 1988-1990 to the end of 2009. The person-years of follow-up were calculated for all participants from the time of the initial enrollment to the death from CRC or any other cause, the time of moving out from the study area or the end of follow-up, whichever came first. Mean values (standard deviations) and proportions of the baseline characteristics were calculated, and the age-adjusted p-values of trend were calculated using the linear and logistic regressions, respectively. The hazard ratios (HRs) and confidence intervals (CIs) for CRC mortality were calculated using the Cox proportional regression analysis. Information on lifestyle factors and the average daily TV viewing time were obtained in the baseline questionnaire. We classified the daily TV viewing time into four categories: < 1.5 hours, 1.5 to < 3 hours, 3 hours to < 4.5 hours, or $\geq$ 4.5 hours. Potential confounding factors for adjustment were the baseline's age (continuous), sex, and residential area in the first model. Additionally, factors associated with the risk of CRC, not only in our data, but also from previous studies, were adjusted in the second model: the family history of CRC in parents or siblings (yes or no), frequency of bowel movement (daily, every 2-3 days, every 4-5 days and every 6 days or less), education level (primary school, junior high school, high school or college and higher), alcohol consumption (never drinkers, ex-drinkers or current drinkers), smoking habits (never smokers, ex-smokers, current smoker of at least 1 cigarette/day but no more than 20 cigarettes/day, or current smoker of more than 20 cigarettes/day), and frequency consumption of beef and pork (almost never, 1-2 times a month, 1-2 times a week, 3-4 times a week, almost every day) were adjusted in the second model. In the fully-adjusted model, we further adjusted for the other proxy variables of the level of physical activity: the body mass index (BMI quartiles), weekly sport hours (seldom or never, 1-2, 3-4, and $\geq$ 5 hours), and daily walking time in minutes (seldom or never, < 30 minutes, 30-59 minutes, or $\geq$ 60 minutes). Missing values for these covariates were treated as additional missing categories and their dummy variable indicators were included into the model. p-value for trend across the TV viewing time categories was calculated by adding the median value of TV viewing time into each category in the model. In sensitivity analyses, we stratified by the median age, BMI (< or $\geq$ 25 kg/m²), and levels of leisure-time physical activity (low or high, where persons with high level of leisure-time physical activity included those who walk for 1 hour or more per day and/or practice sports for 5 hours or more per week, while those with low level of leisure-time physical activity included persons who walk for less than 1 hour per day and practice sports for less than 5 hours per week). We also examined the associations after removing the first 3-year of follow-up for all study participants to confirm whether TV viewing time was associated with the later onset of CRC with avoiding immortal bias time [14]. We used the SAS ver. 9.4 software (SAS Institute Inc, Cary, NC) in all

Table 1. Baseline characteristics of participants according to television viewing time

Characteristic	Television viewing time (hr/day)				
	< 1.5	1.5 to < 3	3 to < 4.5	≥ 4.5	p for trend
No. at risk	15,386	27,430	35,977	12,041	
Age, mean±SD (yr)	56±10	56±10	58±10	62±9	< 0.001
Men (%)	41.5	45.0	42.9	33.2	< 0.001
BMI, mean±SD (kg/m²)	22.6±2.9	22.7±2.9	22.9±3.0	23.0±3.3	< 0.001
BMI ≥ 25 kg/m² (%)	17.3	18.4	20.8	22.6	< 0.001
BMI ≥ 30 kg/m² (%)	1.3	1.3	1.7	2.6	< 0.001
Family history of colorectal cancer (%)	2.3	2.3	2.2	2.0	0.13
Exercise ≥ 3 hr/wk (%)	10.9	12.2	12.1	12.6	< 0.001
Walking ≥ 30 min/day (%)	70.9	71.9	71.2	65.2	< 0.001
College or higher education (%)	14.5	12.0	9.7	7.9	< 0.001
Current smokers (%)	23.3	26.9	27.7	25.2	< 0.001
Current drinkers (%)	45.7	48.3	45.1	37.6	< 0.001
Consumption of beef ≥ 3 times/wk (%)	10.4	9.4	9.3	9.1	< 0.001
Consumption of pork ≥ 3 times/wk (%)	21.7	21.5	20.6	17.3	< 0.001

p for trend was adjusted for age. BMI, body mass index; SD, standard deviation.

statistical analyses. Two-tailed p-values of < 0.05 were considered statistically significant.

Results

Table 1 shows the baseline characteristics of the participants according to TV viewing time. The proportion of participants spent 4.5 hours or longer daily on TV watching was 13.3%. Compared with participants with TV viewing time < 1.5 hr/day, participants in longer TV viewing time categories tended to be older, with higher BMI and less educated, and consumed less beef and pork.

Among the 90,834 participants (38,130 men and 52,704 women) aged 40-79 years at the baseline examination and within the median 19.1-year follow-up period, we identified 749 CRC deaths (385 in men and 364 in women). Table 2 shows the HRs for mortality from the total CRC and anatomical sub-sites of CRC according to TV viewing time categories as well as for 1-hour increment of TV viewing time in minimal-and fully-adjusted models. The multivariable HRs (95% CIs) of mortality from CRC were 1.11 (0.88-1.41) for 1.5 to < 3 hours, 1.14 (0.91-1.42) for 3 to < 4.5 hours, and 1.33 (1.02-1.73) for $≥ 4.5$ hours of daily TV viewing; p-trend=0.038, and 1-hour increment of TV viewing time was associated with a HR 1.06 (1.01-1.11). In addition, the multivariable HR (95% CI) of colon cancer mortality in highest compared with the lowest category of TV viewing time was 1.43 (1.04-1.96); p for trend=0.049. The multivariable HRs (95% CIs) in highest compared with the lowest category of TV viewing time were 1.42 (0.98-2.07, p-trend=0.131) for left colon cancer, 3.55

(0.72-17.46, p-trend=0.182) for transverse colon cancer, and 1.16 (0.60-2.24, p-trend=0.465) for right colon cancer. Further adjustment for the perceived mental stress, sleep hours, history of diabetes, and intakes of vegetables and fruit into the model did not change the associations (data not shown). Sex-specific results were similar and no significant interaction by sex could be detected ($p > 0.1$); the HRs of CRC mortality per 1-hour increment in TV viewing time were 1.07 (1.00-1.15) in men and 1.06 (1.00-1.13) in women (data not shown).

Table 3 shows the stratification analyses by the median age, BMI cutoff level of overweight, and level of leisure-time physical activity. The p-values for interactions between TV viewing time and all the stratifying variables were > 0.1 for all cancers, and the increased risk of CRC mortality with longer TV viewing time did not largely differ for the younger and older participants. However, the positive association between longer TV viewing time and risk of CRC mortality was more robust for persons with BMI < 25 kg/m², and for persons with high level of leisure-time physical activity; HRs per 1-hour increment in TV viewing time were 1.07 (1.02-1.13), and 1.07 (1.00-1.15), respectively than for those with BMI $≥ 25$ kg/m² and for persons with low level of leisure-time physical activity; the respective HRs were 1.02 (0.92-1.21), and 1.04 (0.97-1.10).

We compared the participants' characteristics for those included in the study and those who were excluded due to missing answers of TV viewing time in the S1 Table. There were no differences in the mean age, BMI, or sleep duration, nor in the frequency of bowel movement or sports activity habits. However, the excluded participants were less likely to have a family history of CRC, less likely to walk for $≥ 30$

Table 2. Hazard ratios (95% confidence intervals) of colorectal cancer mortality according to television viewing time

	Television viewing time (hr/day)				p for trend	1-Hour increment television viewing time
	< 1.5	1.5 to < 3	3 to < 4.5	≥ 4.5		
Person-years	256,146	454,237	577,700	172,018		
Colorectal cancer						
No. of cases	102	212	308	127		
Model 1	1.00	1.12 (0.88-1.41)	1.15 (0.92-1.44)	1.36 (1.04-1.77)	0.022	1.07 (1.02-1.11)
Model 2	1.00	1.12 (0.88-1.41)	1.15 (0.91-1.43)	1.34 (1.03-1.74)	0.031	1.06 (1.02-1.11)
Model 3	1.00	1.11 (0.88-1.41)	1.14 (0.91-1.42)	1.33 (1.02-1.73)	0.038	1.06 (1.01-1.11)
Colon cancer						
No. of cases	67	152	216	96		
Model 1	1.00	1.22 (0.92-1.63)	1.21 (0.92-1.60)	1.47 (1.07-2.01)	0.026	1.08 (1.02-1.13)
Model 2	1.00	1.24 (0.93-1.65)	1.22 (0.93-1.61)	1.45 (1.06-2.00)	0.035	1.07 (1.02-1.13)
Model 3	1.00	1.22 (0.92-1.63)	1.20 (0.91-1.58)	1.43 (1.04-1.96)	0.049	1.07 (1.02-1.13)
Right colon cancer						
No. of cases	18	35	63	19		
Model 1	1.00	1.05 (0.60-1.85)	1.33 (0.79-2.26)	1.12 (0.58-2.14)	0.554	1.06 (0.96-1.18)
Model 2	1.00	1.07 (0.60-1.88)	1.39 (0.82-2.35)	1.19 (0.62-2.28)	0.422	1.08 (0.97-1.20)
Model 3	1.00	1.05 (0.60-1.86)	1.36 (0.81-2.31)	1.16 (0.60-2.24)	0.465	1.08 (0.97-1.20)
Transverse colon cancer						
No. of cases	2	10	14	7		
Model 1	1.00	2.72 (0.60-12.40)	2.67 (0.61-11.74)	3.59 (0.74-17.46)	0.164	1.17 (0.97-1.42)
Model 2	1.00	2.78 (0.61-12.71)	2.69 (0.61-11.90)	3.60 (0.74-17.65)	0.174	1.18 (0.97-1.43)
Model 3	1.00	2.74 (0.60-12.56)	2.67 (0.60-11.80)	3.55 (0.72-17.46)	0.182	1.19 (0.97-1.44)
Left colon cancer						
No. of cases	47	107	139	70		
Model 1	1.00	1.22 (0.87-1.72)	1.11 (0.79-1.54)	1.51 (1.04-2.19)	0.057	1.07 (1.01-1.14)
Model 2	1.00	1.23 (0.87-1.74)	1.10 (0.79-1.53)	1.45 (1.00-2.11)	0.102	1.06 (1.00-1.13)
Model 3	1.00	1.23 (0.87-1.73)	1.09 (0.78-1.52)	1.42 (0.98-2.07)	0.131	1.06 (0.99-1.13)
Rectal cancer						
No. of cases	35	60	92	31		
Model 1	1.00	0.91 (0.60-1.39)	1.04 (0.70-1.53)	1.13 (0.69-1.84)	0.451	1.03 (0.94-1.13)
Model 2	1.00	0.89 (0.59-1.35)	1.01 (0.68-1.49)	1.11 (0.68-1.81)	0.492	1.03 (0.94-1.13)
Model 3	1.00	0.90 (0.59-1.36)	1.01 (0.69-1.50)	1.13 (0.69-1.85)	0.450	1.03 (0.94-1.13)

Model 1: Adjusted for age, sex and areas; Model 2: Further adjusted for smoking, drinking, family history of colorectal cancer, education level, frequency of bowel movement, frequency consumption of beef and pork; Model 3: Further adjusted for hours of sport, minutes of waking and body mass index.

minutes per day, less likely to be educated to a college or higher levels, but more likely to smoke and to drink alcohol and consumed more beef and pork than those included in our analyses.

After excluding the first 3-year of the follow-up, during which there were 42 CRC deaths (42 colon cancer and 0 rectal cancer), the associations between the TV viewing time and risk of mortality from CRC and colon cancer did not change materially in both the categorical and continuous analyses. Actually, it was slightly augmented, especially for the asso-

ciation with colon cancer mortality (S2 Table).

Discussion

In this large prospective study of Japanese men and women, we found that the longer average daily TV viewing time was associated with the increased risk of CRC mortality. The 1-hour increment of TV viewing time was associated with almost similar ~6% higher risk of CRC mortality and ~7%

Table 3. Multivariable hazard ratios (95% confidence intervals)[a)] of colorectal cancer mortality, stratified by median age, BMI and level of physical activity according to television viewing time

	Television viewing time (hr/day)				p for trend	1-Hour increment television viewing time
	< 1.5	1.5 to < 3	3 to < 4.5	≥ 4.5		
Age < 58 yr						
Person-years	158,912	266,818	293,830	59,339		
Colorectal cancer						
No. of cases	31	63	85	21		
HR (95% CI)	1.00	1.13 (0.73-1.73)	1.32 (0.87-2.00)	1.61 (0.92-2.83)	0.057	1.08 (0.98-1.20)
Colon cancer						
No. of cases	16	42	54	13		
HR (95% CI)	1.00	1.48 (0.83-2.64)	1.67 (0.95-2.93)	1.87 (0.89-3.94)	0.070	1.11 (0.98-1.26)
Rectal cancer						
No. of cases	15	21	31	8		
HR (95% CI)	1.00	0.74 (0.38-1.44)	0.95 (0.51-1.78)	1.35 (0.56-3.24)	0.402	1.03 (0.86-1.24)
Age ≥ 58 yr						
Person-years	97,234	187,419	283,870	112,679		
Colorectal cancer						
No. of cases	71	149	223	106		
HR (95% CI)	1.00	1.10 (0.83-1.46)	1.06 (0.81-1.39)	1.24 (0.91-1.68)	0.204	1.05 (1.00-1.11)
Colon cancer						
No. of cases	51	110	162	83		
HR (95% CI)	1.00	1.14 (0.82-1.59)	1.08 (0.78-1.48)	1.30 (0.92-1.86)	0.180	1.06 (1.01-1.13)
Rectal cancer						
No. of cases	20	39	61	23		
HR (95% CI)	1.00	0.99 (0.58-1.70)	1.03(0.62-1.71)	1.06 (0.58-1.70)	0.801	1.03 (0.93-1.14)
$p_{interaction}$					> 0.1	
BMI < 25 kg/m²						
Person-years	197,109	349,028	426,867	119,891		
Colorectal cancer						
No. of cases	73	155	227	89		
HR (95% CI)	1.00	1.12 (0.84-1.47)	1.18 (0.91-1.54)	1.39 (1.01-1.90)	0.034	1.07 (1.02-1.13)
Colon cancer						
No. of cases	49	108	159	65		
HR (95% CI)	1.00	1.16 (0.83-1.63)	1.21 (0.88-1.67)	1.39 (0.96-2.03)	0.090	1.08 (1.02-1.15)
Rectal cancer						
No. of cases	24	47	68	24		
HR (95% CI)	1.00	1.03 (0.63-1.69)	1.13 (0.71-1.81)	1.40 (0.78-2.49)	0.206	1.05 (0.95-1.17)
BMI ≥ 25 kg/m²						
Person-years	45,035	85,783	123,662	41,900		
Colorectal cancer						
No. of cases	18	42	62	28		
HR (95% CI)	1.00	1.15 (0.66-2.00)	1.09 (0.64-1.85)	1.16 (0.63-2.12)	0.751	1.02 (0.92-1.21)
Colon cancer						
No. of cases	10	33	43	22		
HR (95% CI)	1.00	1.67 (0.82-3.39)	1.38 (0.69-2.76)	1.62 (0.76-3.47)	0.475	1.03 (0.92-1.16)
Rectal cancer						
No. of cases	8	9	19	6		
HR (95% CI)	1.00	0.52 (0.20-1.35)	0.72 (0.31-1.65)	0.56 (0.19-1.65)	0.520	0.95 (0.78-1.17)
$p_{interaction}$					> 0.1	

(Continued to the next page)

Table 3. Continued

	Television viewing time (hr/day)					
	< 1.5	1.5 to < 3	3 to < 4.5	≥ 4.5	p for trend	1-Hour increment television viewing time
High leisure-time physical activity						
Person-years	126,529	224,779	276,834	71,163		
Colorectal cancer						
No. of cases	50	110	148	57		
HR (95% CI)	1.00	1.19 (0.85-1.66)	1.17 (0.85-1.62)	1.53 (1.04-2.24)	0.045	1.07 (1.00-1.15)
Colon cancer						
No. of cases	31	81	104	42		
HR (95% CI)	1.00	1.44 (0.95-2.17)	1.33 (0.89-1.99)	1.72 (1.08-2.76)	0.059	1.09 (1.01-1.18)
Rectal cancer						
No. of cases	19	29	44	15		
HR (95% CI)	1.00	0.79 (0.44-1.40)	0.91 (0.53-1.57)	1.20 (0.60-2.39)	0.456	1.03 (0.90-1.18)
Low leisure-time physical activity						
Person-years	122,794	221,136	289,445	96,141		
Colorectal cancer						
No. of cases	49	96	153	64		
HR (95% CI)	1.00	1.00 (0.71-1.41)	1.08 (0.78-1.49)	1.10 (0.75-1.61)	0.515	1.04 (0.97-1.10)
Colon cancer						
No. of cases	34	69	105	49		
HR (95% CI)	1.00	1.04 (0.69-1.57)	1.05 (0.71-1.55)	1.13 (0.72-1.77)	0.575	1.04 (0.97-1.12)
Rectal cancer						
No. of cases	15	27	48	15		
HR (95% CI)	1.00	0.91 (0.48-1.71)	1.15 (0.64-2.06)	1.02 (0.49-2.11)	0.727	1.03 (0.91-1.16)
$p_{interaction}$					> 0.1	

p for interaction with age, BMI and level of physical activity were > 0.1 for all cancers in Table 3. BMI, body mass index; CI, confidence interval; HR, hazard ratio. [a)]Multivariable adjustments are the same as shown in Model 3 of Table 2, except for the stratifying variable.

higher risk of colon cancer deaths. The exclusion of the initial 3 years of follow-up did not alter the observed associations. No significant effect modifications by age, BMI, or level of leisure-time physical activity could be detected; however, the findings suggested robust decline in the risk of CRC mortality by reducing the TV watching time among lean participants with BMI < 25 kg/m^2 and persons who frequently walk and/or practice sports.

Our findings were consistent with previous studies [15,16]; the UK Biobank cohort study of 430,584 men and women with a median follow-up time of 5.6 years showed that TV viewing time was associated with increased risk of CRC; the multivariable HR (95% CIs) was 1.26 (1.04-1.53) for > 5 hr/day versus ≤ 1 hr/day, p-trend=0.01 [15]. In a meta-analysis [16] of 47,84,339 participants from 28 cohort studies with a total of 46,071 incident cases of CRC, the summary relative risk (RR) of CRC per 2 hours increment of TV viewing time was 1.07 (95% CI, 1.05 to 1.10; p < 0.001). The TV viewing time was not only positively associated with the risk of develop-

ing CRC, but also was inversely associated with the survival among CRC patients in two American cohorts [17,18]. However, one study showed the association with survival was confined to pre-diagnostic (HR, 2.13 [1.31-3.45] for 21 hr/wk vs. 7 hr/wk) but not post-diagnostic TV viewing hours (HR, 1.45 [0.73-2.87] for 21 hr/wk vs. 7 hr/wk] [17], and the other showed the opposite; RRs were 1.33 (0.96-1.84) for ≥ 6 hr/day compared to < 3 hr/day pre-diagnosis leisure sitting time, and 1.62 (1.07-2.44) for ≥ 6 hr/day compared to < 3 hr/day post-diagnosis leisure sitting time [18].

As for the anatomical site of CRC, TV viewing time was associated more strongly with risk of mortality from colon cancer rather than rectal cancer, which was consistent with a finding from the previous studies [11,15] where sedentary behaviors were associated with higher risk of colon cancer but not rectal cancer. For example, in 430,584 participants of the UK Biobank study, TV viewing time was associated with higher risk of colon cancer but not rectal cancer; HRs for ≥ 5 hr/day versus ≤ 1 hr/day were 1.32 (1.04-1.68) and

1.13 (0.79-1.61), respectively [15]. However, another possible explanation for the non-significant association between TV viewing time and risk of mortality from rectal cancer in our study may be due to the low statistical power to detect the association. TV viewing time tended to be positively associated with risk of mortality from left colon cancer and transverse colon cancer, but we could not find an association with risk of mortality from right colon cancer. This also could be attributed to the low power to detect the association. However, the histopathologic, epidemiologic, molecular, and genetic perspectives of right and left colon cancers were shown to vary greatly [19]; therefore, further studies to explore the possible differential associations between sedentary behaviors and risk of right, transverse and left colon cancers, and to propose biological mechanisms are needed.

It has been indicated that age, obesity besides to the physical activity are important factors in the pathogeneses of CRC [4,20]. We not only controlled for these factors in our model, but in order to test the independent association of TV viewing time with risk of CRC mortality, we also stratified our analyses by the median age of our participants (58 years), by the BMI cut off level of obesity (25 kg/m^2), and by the level of leisure-time physical activity indicated by hours of sports and walking activities. We found no significant effect modifications of these factors, and the positive association between TV viewing time and risk of CRC mortality was evident in both younger and older persons.

The level of leisure-time physical activity was suggested as an important factor in the pathogenies of CRC [18], and obesity could be an intermediate outcome between sedentary lifestyles such as long TV watching time and the risk of CRC mortality [4].

However, the stratified analyses by leisure-physical activity and BMI in our study suggested that the longer TV viewing duration was associated with risks of CRC and colon cancer mortality in persons with high level of leisure-physical activity and those with BMI < 25 kg/m^2 rather than persons with low level of leisure-physical activity and those with higher BMI. Accordingly, reducing the time in front of TV could be associated with the lower risk of CRC mortality in lean and more physically active, but not overweight and less physically active Japanese men and women. For the overweight and less physically active persons, reducing the TV watching time seems not enough to counteract the increased risk of CRC, or in another expression, longer TV viewing time added no more significant risk of CRC to those who are less physically active or overweight.

It is worth pointing here to the low prevalence of obesity in Japanese (3.9%) [21]; persons with BMI ≥ 30 kg/m^2 in our study composed only 1.6% of the total study participants. Another hypothesis could explain the association between longer TV viewing time and CRC mortality, especially in lean persons is that sedentary behavior may also be associated enhanced systematic inflammation independent of obesity [22]. C-reactive protein, a marker of inflammation, was positively associated with sedentary time [22] and risk of CRC mortality [23]. An 8-year follow-up study [23] of 368 CRC patients showed that the plasma levels of C-reactive protein was positively associated with the risk of CRC mortality; the multivariable HRs (95% CIs) of CRC mortality was 1.80 (1.07-3.04) for highest versus lowest quintiles of C-reactive protein. On the other hand, previous studies suggested that obesity may promote cancer progression through a number of pathways including the increased levels of insulin-like growth factors (IGFs) and cortisol and the reduced immune function [24]. In the metabolic syndrome, diabetes-related visceral obesity is characterized by high serum levels of IGFs that may affect tumor aggressiveness [25,26] by promoting tumor cell proliferation and angiogenesis [27]. Moreover, IGFs binding protein levels were inversely associated with the risk of CRC mortality in American experimental [28] and cohort studies [29]. Last, leisure-time sedentary behavior such as watching TV are usually associated with unhealthy dietary behaviors [30], such as heavily burnt meat intake, higher consumption of sugar sweetened beverages, and less consumption of vegetables, which were related to the development and progression of CRC [31]. We adjusted for these potential confounders in the multivariable model and found no material change in the results.

The strengths of this study were its community-based prospective design and the large cohort sample size with high response rate and perfect follow-up [12]. Errors of recall should have been non-differential between the CRC cases and non-cases because we assessed TV viewing time before the diagnosis of CRC, and we also excluded the first 5 years of follow-up. Moreover, the information on potential confounding factors of CRC was collected at baseline and adjusted for as much as possible.

Our study also has several limitations. First, the information on average TV viewing time was collected only at baseline and was not updated during the study period. Misclassifications might have been included in the results if the participants had changed their lifestyle. However, such error would have occurred at random that might have reduced the estimated HRs toward the null. Second, the average TV viewing time was self-reported which may have led to some misclassifications. However, a previous review [32] reported that the reliability of the self-reported time spent on TV watching was consistently moderate to high (r=0.69-0.83, p < 0.001). Third, residual confounding cannot be eliminated; for example, we do not have data on CRC screening or the time or the stage of cancer at diagnosis in our cohort study

which are important factors associated with CRC mortality [20,33]. Last, although the age and BMI of the studied participants did not differ than those of the excluded ones; however, those excluded due to missing data on the TV viewing time carried more risky profile such as less walking activity, higher prevalence of smokers and alcohol drinkers which could infer some sort of unavoidable selection bias.

In conclusion, our findings provide further evidence that TV viewing time associate with increased risk of CRC mortality, more specifically mortality from colon cancer, among Japanese men and women.

Electronic Supplementary Material
Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement
This cohort study was sponsored by the Ministry of Education, Sport, and Science and approved by the ethical Review Board of Hokkaido University and Osaka University, with the approval number 14285-6.

Author Contributions
Conceived and designed the analysis: Li Y, Iso H.
Collected the data: JACC Study Group.
Contributed data or analysis tools: Tamakoshi A, Iso H, Cui R.
Performed the analysis: Li Y, Eshak ES.
Wrote the paper: Li Y.
Revised paper: Iso H, Eshak ES, Cui R, Shirai K, Liu K, Ikehara S, Tamakoshi A, Ukawa S.

Conflicts of Interest
Conflicts of interest relevant to this article was not reported.

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