Association between average daily television viewing time and the incidence of ovarian cancer: Findings from the Japan Collaborative Cohort Study

Shigekazu Ukawa PhD[1], Akiko Tamakoshi MD, PhD[1*], Mitsuru Mori MD, PhD[2], Satoyo Ikehara PhD[3,4], Toru Shirakawa MD[3], Hiroshi Yatsuya MD, PhD[5], Hiroyasu Iso MD, PhD[3], JACC study group[6]

[1]Department of Public Health, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Hokkaido, Japan

[2]Hokkaido Chitose College of Rehabilitation, Hokkaido, Japan.

[3]Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

[4]Department of Hygiene and Public Health, Osaka Medical College, Osaka, Japan

[5]Department of Public Health, Fujita Health University School of Medicine, Aichi, Japan

[6]The members of the JACC Study Group are detailed in the appendix.

*Corresponding author:

Akiko Tamakoshi, Department of Public Health, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7, Kita-ku, Sapporo 060-8638, Japan. Tel: +81 11 7065068; Fax: +81 11

7067805; E-mail: tamaa@med.hokudai.ac.jp

Abstract

PURPOSE: Seventy-five percent of epidemiological studies have reported that sedentary behavior is associated with ovarian cancer incidence. Although Japan has one of the most sedentary populations, with median sitting times of 7 hours/day, this association has not been investigated. This study aimed to elucidate the association between average daily television (TV) viewing time, which is a major sedentary behavior, and the incidence of ovarian cancer in a large-scale nationwide cohort study in Japan.

METHODS: A total of 34,758 female participants aged 40–79 years without a history of cancer at baseline were included in the study. The inverse probability weighted competing risk model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the incidence of ovarian cancer.

RESULTS: During a median follow-up of 19.4 years, 59 participants developed ovarian cancer (ICD-10: C56), 2,706 participants developed other types of cancer, and 4,318 participants died. Participants who watched TV for ≥5 hours/day were more likely to develop ovarian cancer than those who watched TV for <2 hours/day (HR 2.15; 95% CI 1.54-2.99).

CONCLUSION: Our findings suggest that reducing the amount of time spent sedentarily may be beneficial for preventing ovarian cancer.

Keywords: ovarian neoplasms, sedentary behavior, cohort study, risk assessment, epidemiology

Introduction

Ovarian cancer is the seventh most common type of cancer globally and the eighth most common cancer causing death in women (globally, 239,000 new cases resulting in 152,000 deaths were recorded in 2012)[1]. The incidence of ovarian cancer has been increasing in Japan with a cumulative incidence of 14.3 per 10,000 people in 2012[2]. This incidence was higher than in the United States (11.7 per 10,000 people)[3], and China (0.6 per 10,000 people)[4]. Early menarche or late menopause[5] and genetic associations such as a family history of ovarian, breast[6], or prostate[7] cancer or with a BRCA1 or BRCA2 mutation[8] have been demonstrated to be a likely risk factors for ovarian cancer.

Previously, the Ovarian Cancer Association Consortium reported that recreational physical inactivity, which is defined by the absence of moderate-vigorous physical activity, was positively associated with epithelial ovarian cancer[9]. Sedentary behavior, distinct from the absence of moderate-vigorous physical activity[10], was also reported to be a risk factor for ovarian cancer reported in the United states [11-13] and China [14]. However, consistent results were not obtained regarding this association. The length of sitting time among Japanese people has been reported to be approximately 7 hours/day, being the longest in the world [15]. The time spent watching television (TV) is a good indicator of leisure time associated sedentary and sitting time in developed countries, including Japan[16]. In 2015, the prevalence of TV watching for at least 5 hours was 25% in Japan[17]. However, whether TV watching is associated with the incidence of ovarian cancer among Japanese women remains unclear.

Therefore, we examined the association between daily TV viewing time and the incidence of ovarian cancer in Japanese women in a large-scale national cohort study.

Material and Methods

Study population and data collection

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in 1988-90 and has been described in detail in previous publications[18]. Briefly, 110,585 (46,395 men and 64,190 women) inhabitants aged 40 to 79 years from 45 areas throughout Japan were enrolled. Participants in this study were limited to 24 study areas where the incidence of cancer could be ascertained.

Of the 38,613 original female cohort participants, 705 were excluded because they had a history of cancer. A further 2,057 participants in two areas were also excluded because the questionnaire used did not include an item on average daily TV viewing hours. Finally, 1,093 participants with missing data on average daily TV viewing hours were excluded. Consequently, 34,758 participants were evaluated in the present study.

The data was collected using a self-administered questionnaire, and a response rate of 83% was obtained. Information on the average daily number of hours spent watching TV was obtained in the baseline questionnaire using the following question, “On average, how many hours a day do you spend

watching TV?". We sequentially created five categories for TV viewing time (<2, 2-2.9, 3-3.9, 4-4.9, ≥5 hours/day) and set <2 hours/day as a reference category based on previously identified associations with ovarian cancer risk[14].

Follow-up

The incidence of cancer could be ascertained in 24 study areas where population-based cancer registries or local major hospital records were available for review and coded according to the tenth revision of the International Classification of Disease (ICD-10). The primary outcome of interest in the present study was the incidence of ovarian cancer (ICD-10: C56). The date and cause of death were confirmed by death certificates. Participants who moved away from the study area during the study period were treated as censored cases. Those records were followed up until the end of 2009, with the exception of participants in 4 areas who were followed up until 2003. Participants in one area were another exception as they were followed up until 2002. The study design was approved by the Ethical Board of Nagoya University School of Medicine.

Statistical analysis

Multivariate hazard ratios (HR) and confidence intervals (CI) for the incidence of ovarian cancer were calculated using an inverse probability weighted (IPW) [19,20] competing risk model[21] in which we

treated incidence of cancer other than ovarian cancer and death as a competing events[22]. To develop the generalized propensity score, we conducted a multinomial logistic regression analysis using variables for all demographic information[23], including age (a continuous variable), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2, or missing), educational level (school up to age 15, 15–18, or ≥19 years, or missing), smoking status (never, former, or current smoker, or missing), alcohol drinking status (never, former, or current alcohol drinker, or missing), average daily sleeping time (<6.5, 6.5-8.4, or ≥8.5 hours/day, or missing), average daily walking time (<1, ≥1 hours/day, or missing), age at menarche (<13, 13-15, or ≥16 years, or missing), age at menopause (<44, 44-48, 49-52, or ≥52 years, or having periods/missing), parity (none, 1-2, ≥3 times, or missing), use of hormone therapy ever (never, user, or missing), family history of breast, ovarian, or prostate cancer (yes or no/missing) [24]. To assess the covariate balance, we showed the propensity score overlap using kernel density plots. An alpha level of 0.05 was considered to be a statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The graphs were drawn using JMP 12.2 (SAS Institute Inc., Cary, NC, USA)

Results

Table 1 shows the baseline characteristics of participants based on TV viewing hours. The mean age of participants ± standard deviation (SD) at baseline was 58.1 ± 10.1 years. Approximately 14.8% of

participants watched TV for longer than 5 hours daily. Compared to participants who viewed TV for less than 2 hours, participants who viewed TV for more than 5 hours tended to be older, more likely to be overweight/obese, current smokers, current alcohol drinkers, longer sleepers, older at menarche, and post-menopausal, and less likely to daily walkers, and parity. The distributions of propensity scores among the five categories of TV viewing were well balanced after weighting (Figure 1 and eTable 1).

During a median follow-up of 19.4 years, 59 participants developed ovarian cancer, 2,706 participants developed other types of cancer, and 4,318 participants died. Table 2 shows the HRs for the incidence of ovarian cancer based on the average daily TV viewing hours using a competing risk model. Participants that watched TV for ≥5 hours/day were more likely to develop ovarian cancer than those that watched TV for <2 hours/day (HR 2.15, 95% CI 1.54-2.99).

Discussion

In this large cohort study, we found that a prolonged average daily TV viewing time at baseline was associated with an increased risk of ovarian cancer incidence among Japanese women. Our results are consistent with the findings from 75% of other studies, including a Chinese case-control study[14] and two American cohort studies[12,11]. There was an association between an interviewer-administered exposure to sitting duration while watching TV and epithelial ovarian cancer (adjusted odds ratio 3.39, 95% CI 1.00–11.50 for >4 vs. <2 h/day) among 906 Chinese women (cases n = 254, controls n = 652)

who were < 75 years old[14]. Additionally, there were two cohort studies investigating similar associations; one of which evaluated the association between self-reported sitting time and the incidence of ovarian cancer (adjusted HR 1.55, 95% CI 1.08-2.22 for ≥6 vs. <3 h/day) among 59,695 (a mean age of 62.7 years) United States (US.) women[12], and another which evaluated the association between self-reported leisure-time sitting and the incidence of ovarian cancer (adjusted HR for total ovarian cancer 1.44, 95% CI 1.12-1.85 for ≥6 vs. <3 h/day) among 63,972 postmenopausal US. women aged 50-74 years[11]. In contrast, a cohort study evaluated the association between sedentary behavior and the incidence of ovarian cancer among 148,892 US. women aged 50-71 years, but there were no statistically significant association between self-reported sedentary behavior and the incidence of ovarian cancer (adjusted relative risk 1.06, 95% CI 0.81-1.39 for ≥7 vs. <3 h/day overall sitting time; 1.02, 95% CI 0.67-1.55 for ≥7 vs. <3 h/day TV watching time)[13].

Although potential mechanisms are still unclear, metabolic dysfunction may be involved in the pathogenesis of ovarian cancer. Sedentary lifestyles are associated with obesity[25,26], elevated insulin resistance[27], and type 2 diabetes mellitus[28]. These conditions lead to hyperinsulinemia which increases the rate of androgen synthesis [29]. High serum androgens may stimulate ovarian epithelial proliferation and contribute to ovarian cancer risk [30]. In addition to the effects of hyperinsulinemia, excess adipose tissue found in overweight and obese individuals can increase levels of inflammatory factors such as free fatty acids, interleukin-6, tumor necrosis factor-alpha, and leptin [31]. Each of these

factors might play an etiologic role in regulating malignant transformation or cancer progression.

A previous study showed risk factors for ovarian cancer differed by histological types of ovarian cancer[32]. Although the exact biologic pathway is unclear, the association between sedentary behavior and ovarian cancer may differ by histological types of ovarian cancer as a prospective cohort study of 63,972 postmenopausal US. women showed a different association between self-reported leisure-time sitting and the incidence of ovarian cancer based on histological type (adjusted HR for serous ovarian cancer 1.52, 95% CI 1.06-2.16; adjusted HR for non-serous ovarian cancer 1.08, 95% CI 0.57-2.04 for ≥6 vs. <3 h/day) [11]. Approximately 70% of ovarian cancer cases in US are the serous type, whereas 31.4% of those cases in Japan are the serous type [33]. However, we were unable to obtain information on the histological types of ovarian cancer. Further epidemiological studies with information on histological types of ovarian cancer will be valuable to evaluate the histological-specific effect of sedentary behavior.

One major form of sedentary behavior in many industrialized countries such as Japan, the United Kingdom, and the US. is watching TV[34-36]. Thus, watching TV could be an indicator of leisure-time sedentary behavior[16]. However, data regarding the average TV viewing hours was obtained via self-report and was not validated in this study, thus there may have been misclassification of exposure to the average TV viewing hours[37]. Furthermore, Japanese women reportedly spend 4 to 5 hours/day on housework such as kitchen chores, vacuuming, laundry, ironing, and sewing and of those women spend

more than 1.3 hours/day on housework while watching TV[38]. Such cases might cause an overestimation of the sedentary time, and consequently, our results may be under-estimated. Using an objective measurement, such as an accelerometer, would ensure more robust results[39].

The strengths of the present study include its prospective cohort design, the long follow-up period, and the inclusion of participants from throughout Japan. However, the present study also includes some limitations that warrant consideration. First, several meta-analyses reported that sedentary behavior is a risk factor for all-cause mortality, and mortality due to cardiovascular disease and cancer[22,40]. Therefore, since sedentary behavior is a risk factor of mortality from cardiovascular disease and cancer, it leads to an underestimation of the incidence of ovarian cancer. However, to reduce this bias, we conducted a competing risk analysis. Second, the information on the average TV viewing hours was only collected at baseline and was not updated during the study period. The average TV viewing hours is gradually decreasing in Japan[41], thus, some non-differential reporting bias such as misclassification might have been affected our results. Third, although the incidence of ovarian cancer in this study was 0.1 per 1,000 person-years, there are many potential confounders to adjust in the statistical model. Since Cox models should be used with a minimum of 10 outcome events per covariate [42], we used an IPW method based on generalized propensity scores. This approach is not only useful for reducing the number of covariates but it also offers a statistical alternative to implementing propensity score matching to balance for confounders in non-randomized studies[19]. However, the weights may be inaccurate or unstable for

participants with a very low probability due to the nature of the logistic regression [43]. Fourth, we could not obtain information on the use of oral contraceptives. The baseline surveys of this cohort were performed in 1988-90. The first oral contraceptive was introduced in 1999; therefore, the lack of data on oral contraceptives might not have affected our data. Fifth, although we adjusted age at menopause as a potential confounder, the proportion of participants with premenopausal data missing was the largest category. However, we could not distinguish between participants with premenopausal and with data missing because we do not have any further information. Therefore, some misclassification might be included in our results. Sixth, the number of ovarian cancer cases was very small (n = 56); therefore, our findings may be premature to claim that the associations are evident. Further larger-scale epidemiologic studies or a larger meta-analysis are warranted to help verify our findings.

Conclusion

This nationwide cohort study provides evidence that Japanese women, aged between 40–79 years, who watched TV ≥5 hours/day were more likely to develop ovarian cancer than those who watched TV <2 hours/day. Thus, reducing exposure to the hours spent watching TV may help to prevent ovarian cancer incidence among Japanese women.

Acknowledgments

We express our sincere thanks to Drs. Kunio Aoki and Yoshiyuki Ohno, Professors Emeritus of the Nagoya University School of Medicine and former chairpersons of the JACC Study. For their encouragement and support during this study, we are also greatly indebted to Dr. Haruo Sugano, former Director of the Cancer Institute, Tokyo, who contributed greatly to the initiation of the JACC Study; to Dr. Tomoyuki Kitagawa, Director Emeritus of the Cancer Institute of the Japanese Foundation for Cancer Research and former project leader of the Grant-in-Aid for Scientific Research on Priority Area 'Cancer'; and to Dr. Kazao Tajima, Aichi Cancer Center, who was the previous project leader of the Grant-in-Aid for Scientific Research on Priority Area of Cancer Epidemiology.

Source of support

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) (Monbusho); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; and Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT (MonbuKagaku-sho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, and 20390156). This work was also supported by Grant–in–Aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, Japan (Research on Health Services: H17–Kenkou–007; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H18–

Junkankitou[Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H19–Junkankitou [Seishuu]–Ippan–012; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H20–Junkankitou [Seishuu]–Ippan–013; Comprehensive Research on Cardiovascular and Life–Style Related Diseases: H23–Junkankitou [Seishuu]–Ippan–005), and an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H26-Junkankitou [Seisaku]-Ippan-001.

Appendix

Writing Committee Members for the JACC Study Group: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Drs. Mitsuru Mori and Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yoshikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and

Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Faculty of Nutrition, University of Kochi; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, School of Human Science and Environment, University of Hyogo; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Drs. Takesumi Yoshimura and Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Moriyama Municipal Hospital.

Conflicts of interest

The authors declare that they have no conflict of interest with respect to this research study and paper.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN

2012. Int J Cancer 136 (5):E359-386. doi:10.1002/ijc.29210

2. Ministry of Health, Labour and Welfare. Vital Statistics, 2014. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei14/index.html Accessed July 30, 2017.

3. National Cancer Institute. Cancer of the Ovary. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed Dec 2, 2017.

4. Wang B, Liu SZ, Zheng RS, Zhang F, Chen WQ, Sun XB (2014) Time trends of ovarian cancer incidence in China. Asian Pac J Cancer Prev 15 (1):191-193. doi: 10.7314/APJCP.2014.15.1.191

5. Gong TT, Wu QJ, Vogtmann E, Lin B, Wang YL (2013) Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. Int J Cancer 132 (12):2894-2900. doi:10.1002/ijc.27952

6. Bergfeldt K, Rydh B, Granath F, Gronberg H, Thalib L, Adami HO, Hall P (2002) Risk of ovarian cancer in breast-cancer patients with a family history of breast or ovarian cancer: a population-based cohort study. Lancet 360 (9337):891-894. doi:10.1016/s0140-6736(02)11023-3

7. Hemminki K, Sundquist J, Brandt A (2011) Incidence and mortality in epithelial ovarian cancer by family history of any cancer. Cancer 117:3972-3980. doi:10.1002/cncr.26016

8. Schrader KA, Hurlburt J, Kalloger SE, Hansford S, Young S, Huntsman DG, Gilks CB, McAlpine JN (2012) Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy. Obstet Gynecol 120:235-240. doi:10.1097/AOG.0b013e31825f3576

9. Cannioto R, LaMonte MJ, Risch HA, Hong CC, Sucheston-Campbell LE, Eng KH, Brian Szender J,

Chang-Claude J, Schmalfeldt B, Klapdor R, Gower E, et al. (2016) Chronic Recreational Physical Inactivity and Epithelial Ovarian Cancer Risk: Evidence from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 25:1114-1124. doi:10.1158/1055-9965.epi-15-1330

10. Owen N (2012) Sedentary behavior: understanding and influencing adults' prolonged sitting time. Prev Med 55:535-539. doi:10.1016/j.ypmed.2012.08.024

11. Hildebrand JS, Gapstur SM, Gaudet MM, Campbell PT, Patel AV (2015) Moderate-to-vigorous physical activity and leisure-time sitting in relation to ovarian cancer risk in a large prospective US cohort. Cancer Causes Control 26:1691-1697. doi:10.1007/s10552-015-0656-7

12. Patel AV, Rodriguez C, Pavluck AL, Thun MJ, Calle EE (2006) Recreational physical activity and sedentary behavior in relation to ovarian cancer risk in a large cohort of US women. Am J Epidemiol 163:709-716. doi:10.1093/aje/kwj098

13. Xiao Q, Yang HP, Wentzensen N, Hollenbeck A, Matthews CE (2013) Physical activity in different periods of life, sedentary behavior, and the risk of ovarian cancer in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 22:2000-2008. doi:10.1158/1055-9965.epi-13-0154

14. Zhang M, Xie X, Lee AH, Binns CW (2004) Sedentary behaviours and epithelial ovarian cancer risk. Cancer Causes Control 15:83-89. doi:10.1023/B:CACO.0000016633.47025.2a

15. Bauman A, Ainsworth BE, Sallis JF, Hagstromer M, Craig CL, Bull FC, Pratt M, Venugopal K, Chau J, Sjostrom M (2011) The descriptive epidemiology of sitting. A 20-country comparison using the

International Physical Activity Questionnaire (IPAQ). Am J Prev Med 41:228-235. doi:10.1016/j.amepre.2011.05.003

16. Sugiyama T, Healy GN, Dunstan DW, Salmon J, Owen N (2008) Is television viewing time a marker of a broader pattern of sedentary behavior? Ann Behav Med 35:245-250. doi:10.1007/s12160-008-9017-z

17. NHK Research Institute. Japanese and Television 2015. 2015. https://www.nhk.or.jp/bunken/summary/yoron/broadcast/pdf/150707.pdf. Accessed June 30, 2017.

18. Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, Kikuchi S, Iso H, Sakauchi F, Motohashi Y, Tsuji I, et al. (2013) Cohort profile of the Japan Collaborative Cohort Study at final follow-up. J Epidemiol 23:227-232 doi:10.2188/jea.JE20120161

19. Robins JM, Hernan MA, Brumback B (2000) Marginal structural models and causal inference in epidemiology. Epidemiology 11:550-560

20. Sugihara M (2010) Survival analysis using inverse probability of treatment weighted methods based on the generalized propensity score. Pharm Stat 9:21-34. doi:10.1002/pst.365

21. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509. doi:10.2307/2670170

22. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA (2015) Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 162 :123-132. doi:10.7326/m14-1651

23. Imbens G (2008) The role of the propensity score in estimating dose-response functions. Biometrika 87:706-710

24. Pettapiece-Phillips R, Kotlyar M, Chehade R, Salmena L, Narod SA, Akbari M, Jurisica I, Kotsopoulos J (2016) Uninterrupted Sedentary Behavior Downregulates BRCA1 Gene Expression. Cancer Prev Res (Phila) 9:83-88. doi:10.1158/1940-6207.capr-15-0291

25. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB (2001) Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 161:1542-1548

26. Tucker LA, Bagwell M (1991) Television viewing and obesity in adult females. Am J Public Health 81:908-911

27. Helmerhorst HJ, Wijndaele K, Brage S, Wareham NJ, Ekelund U (2009) Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. Diabetes 58:1776-1779. doi:10.2337/db08-1773

28. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE (2003) Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA 289:1785-1791. doi:10.1001/jama.289.14.1785

29. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D (2010) Diabetes and cancer: a consensus report. Diabetes Care 33:1674-1685.

doi:10.2337/dc10-0666

30. Risch HA (1998) Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 90:1774-1786

31. van Kruijsdijk RC, van der Wall E, Visseren FL (2009) Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 18:2569-2578. doi:10.1158/1055-9965.epi-09-0372

32. Yang HP, Trabert B, Murphy MA, Sherman ME, Sampson JN, Brinton LA, Hartge P, Hollenbeck A, Park Y, Wentzensen N (2012) Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. Int J Cancer 131:938-948. doi:10.1002/ijc.26469

33. Marugame T, Sobue T (2003) Mortality trend of ovarian cancer in Japan: 1960-2000. Jpn J Clin Oncol 33:595-596

34. Japan Broadcasting Culture Research Institute. National Lifetime Study 2010. Available at: http://www.nhk.or.jp/bunken/summary/yoron/lifetime/pdf/110223.pdf. Accessed September 6, 2017.

35. Office for National Statistics. The Time Use Survey, 2005. Available at: http://www.ons.gov.uk/ons/rel/lifestyles/time-use/2005-edition/time-use-survey-2005--how-we-spend-our-time.pdf. Accessed September 6, 2017.

36. United States Department of Labor. American Time Use Survey: 2007 results. Available at: http://www.bls.gov/tus/. Accessed September 6, 2017.

37. Harvey JA, Chastin SF, Skelton DA (2015) How Sedentary are Older People? A Systematic Review of

the Amount of Sedentary Behavior. Journal of aging and physical activity 23:471-487. doi:10.1123/japa.2014-0164

38. Office for National Statistics. The Time Use Survey, 2011. Available at: http://www.stat.go.jp/data/shakai/2011/index.htm Accessed September 28, 2016.

39. Chen T, Narazaki K, Honda T, Chen S, Haeuchi Y, Nofuji YY, Matsuo E, Kumagai S (2015) Tri-Axial Accelerometer-Determined Daily Physical Activity and Sedentary Behavior of Suburban Community-Dwelling Older Japanese Adults. J Sports Sci Med 14:507-514

40. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, Yong CM (2016) Sedentary Behavior and Cardiovascular Morbidity and Mortality: A Science Advisory From the American Heart Association. Circulation 134:e262-279. doi:10.1161/cir.0000000000000440

41. Office for National Statistics. The Time Use Survey, 2015. Available at: https://www.nhk.or.jp/bunken/summary/yoron/broadcast/pdf/150707.pdf. Accessed September 6, 2017.

42. Peduzzi P, Concato J, Feinstein AR, Holford TR (1995) Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 48:1503-1510

43. Austin PC (2011) An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 46:399-424.

doi:10.1080/00273171.2011.568786

Table 1. Baseline characteristics based on average daily television viewing hours

Characteristic	Category	Average daily television viewing hours (h/day)				
		<2 (n = 6,341)	2-2.9 (n = 9,525)	3-3.9 (n = 9,081)	4-4.9 (n = 4,468)	≥5 (n = 5,343)
Age, years		55.2 ± 10.4	56.6 ± 10.0	58.2 ± 9.7	59.5 ± 9.5	62.5 ± 9.3
Body mass index, kg/m^2	<18.5	6.9	5.6	6.3	5.4	6.0
	18.5–24.9	69.4	69.8	65.6	65.5	60.7
	≥25.0	18.6	20.0	23.3	23.3	26.0
	Missing	5.1	4.7	4.9	5.8	7.3
College education	Yes	0.2	0.1	0.1	0.1	0.0
	No	88.8	87.3	85.5	84.8	82.2
	Missing	10.9	12.7	14.4	15.2	17.8
Smoking status	Current	3.0	4.0	4.3	5.9	7.6
	Former	1.0	1.0	1.4	1.6	2.7
	Never	88.1	85.6	84.0	81.7	75.4
	Missing	8.0	9.4	10.4	10.8	14.2
Alcohol consumption	Current	20.8	22.1	22.0	22.9	23.8
	Former	1.2	1.4	1.6	1.7	3.4
	Never	73.1	70.2	69.7	68.5	64.7
	Missing	4.9	6.3	6.7	7.0	8.2
Daily sleeping time, h/day	<6.5	29.4	26.3	24.9	24.5	25.8
	6.5-8.4	61.4	64.5	64.1	63.7	59.4
	≥8.5	4.7	5.2	6.2	6.4	7.8
	Missing	4.5	4.0	4.8	5.5	7.1
Daily walking time, h/day	<1	42.7	42.4	42.9	46.1	50.0
	≥1	47.5	46.4	45.0	41.3	36.9
	Missing	9.8	11.2	12.1	12.6	13.1
Age at menarche, years	<13	8.1	7.0	5.6	5.9	5.6
	13-15	57.7	56.5	56.1	54.9	51.2
	≥16	28.0	30.8	31.9	32.1	34.1
	Missing	6.1	5.7	6.5	7.1	9.1
Age at menopausal, years	<44	6.6	7.5	7.8	8.5	9.3
	44-48	9.8	11.1	11.5	11.6	12.6
	49-52	24.7	27.6	30.6	32.1	33.6
	≥52	15.2	17.1	18.4	19.9	21.8
	Having periods/missing	43.7	36.7	31.8	27.8	22.7
Parity, times	None	4.1	3.5	3.9	4.8	6.1
	1-2	40.9	42.0	42.0	41.8	37.5
	≥3	49.1	47.8	46.4	45.1	45.1
	Missing	5.9	6.8	7.8	8.3	11.2
Hormone therapy	Nonuser	85.8	85.5	84.8	84.0	81.8
	User	4.5	4.4	4.2	4.7	5.0
	Missing	9.8	10.0	11.0	11.4	13.2
Family history of breast, ovarian, or prostate cancer	No	97.8	98.1	98.1	97.6	98.2
	Yes	2.2	1.9	1.9	2.4	1.8

Values are expressed as mean ± standard deviation or %.

Table 2. Hazard ratios for the incidence of ovarian cancer based on average daily television viewing hours using a competing risk model

	Average daily television viewing time (h/day)				
Category	<2	2-2.9	3-3.9	4-4.9	≥5
Person-years	107,045	159,744	147,551	70,195	75,367
Number of cases	10	14	16	6	13
HR (95% CI)[a]	ref	0.97(0.43, 2.17)	1.21(0.54, 2.71)	0.98(0.36, 2.69)	2.00(0.83, 4.83)
HR (95% CI)[b]	ref	0.98(0.44, 2.18)	1.17(0.53, 2.60)	0.90(0.33, 2.44)	1.81(0.75, 4.39)
HR (95% CI)[c]	ref	1.03(0.70, 1.50)	1.18(0.82, 1.70)	0.81(0.54, 1.21)	2.15(1.54, 2.99)*

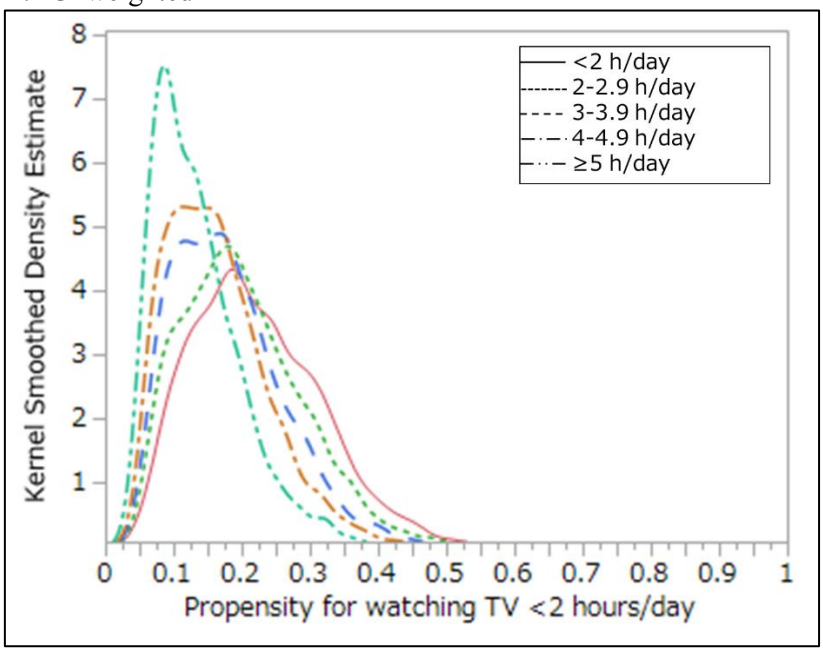
HR: hazard ratio, CI: confidence interval; ref, reference. *P<0.05

[a]adjusted for age.

[b]adjusted for all variables indicated in Table 1.

[c]inverse propensity weighted competing risk model.

A. Unweighted



B. Weighted

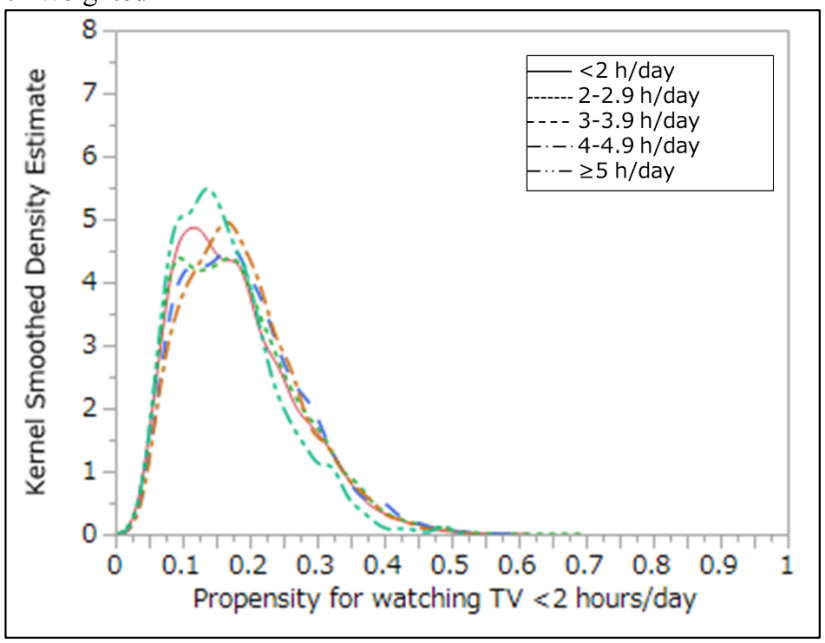


Figure 1. Kernel smoothed density estimate of propensity for watching television <2 h/day
Kernel smoothed density estimates show improved overlap of propensity for watching television <2 h/day after inverse probability weighting.