RESEARCH ARTICLE

Cigarette Smoking and other Risk Factors for Kidney Cancer Death in a Japanese Population: Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study)

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Abstract

Background: Cigarette smoking is the largest single recognized cause of human cancers. In Western countries, many epidemiologists have reported risk factors for kidney cancer including smoking. However, little is known about the Japanese population. Materials and Methods: We evaluated the association of smoking with the risk of kidney cancer death in the Japan Collaborative Cohort (JACC) Study. Participants included 46,395 males and 64,190 females. The Cox proportional hazards model was used to determine age-and-sex adjusted relative risks. Results: A total of 62 males and 26 females died from kidney cancer during the follow-up of 707,136 and 1,025,703 person-years, respectively. Heavy smokers (Brinkman index >1200), fondness of fatty foods, hypertension, diabetes mellitus (DM), and obesity were suggested to increase the risk of renal cell carcinoma while walking was suggested to decrease the risk. Even after controlling for age, sex, alcohol drinking and DM, heavy smoking significantly increased the risk. Conclusions: The present study suggests that six factors including smoking may increase and/or reduce the risk of kidney cancer in the Japanese population. Because of the small number of outcomes, however, we did not evaluate these factors after adjusting for all possible confounding factors. Further studies may be needed to confirm the findings in this study.

Keywords: Renal cell carcinoma - smoking - obesity - diabetes mellitus - hypertension

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Introduction

In adults, 70-90% of cases of kidney cancer are renal cell carcinoma, which arises from cells of the proximal convoluted renal tubules (McLaughlin et al., 1996; Lindbland et al., 2002). Kidney cancer accounts for 2-3% of all malignancies in western countries (McLaughlin et al., 1996; Lindbland et al., 2002) and 2% in Japan (Toma, 2003). The incidence and mortality of kidney cancer have been increasing in recent years in the worldwide (McLaughlin et al., 1996; Lindbland et al., 2002). Also in Japan, the incidence of kidney cancer (persons per 100,000) increased from 7.1 for men and 3.1 for women in 1997 (Marumo et al., 2001) to 8.2 for men and 3.6 for women in 2002 (Marumo et al., 2007).

Although many epidemiologists have reported risk factors for kidney cancer such as smoking (Yu et al., 1986; McLaughlin et al., 1996; Chow et al., 2000; Lindbland et al., 2002; Vineis et al., 2004; Hu et al., 2005; Hunt et al., 2005), Obesity (Yuan et al., 1998; Chow et al., 2000), low physical activity (Menezes et al., 2003; Mahabir et al., 2004), diabetes mellitus (DM) (Wideroff et al., 1997; Lindblad et al., 1999), and hypertension (Yuan et al., 1998; Chow et al., 2000) in Western countries, there are a few information about risk factors for kidney cancer in Japanese population (Hirayama, 1990; Mikami, 1997; Washio et al., 2005; 2007; 2008; Sawada et al., 2010).

In these papers, the association was evaluated between the risk of kidney cancer and medical histories, body mass index and lifestyle factors in a Japanese population. However, there has been no report which clearly demonstrates that smoking is a risk factor for kidney cancer in a Japanese population.

Therefore, in the present study, we examined the

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influence of tobacco smoking and other risk factors on the risk of kidney cancer in a Japanese population, using data from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) until the end of 2009 (Tamakoshi et al., 2013) with an additional 10 year follow-up on the previous studies (Washio et al., 2005; 2007; 2008).

Materials and Methods

The JACC Study is a nationwide collaborative prospective cohort study to evaluate the various risks and/or protective factors influencing cancer mortality and incidence (Ohno et al., 2001; Tamakoshi et al., 2005; 2013). Study methods and ethical issues have been described elsewhere (Ohno et al., 2001; Tamakoshi 2007; Tamakoshi et al., 2005; 2013). Briefly, a cohort was established from 1988 to 1990, with 110,585 residents (46,395 males and 64,190 females) ranging in age from 40 to 79 years old in 45 study areas across Japan. Most subjects were recruited from the general population or when undergoing routine health checks in the municipalities. The participants completed a self-administrated questionnaire containing questions on their medical history, height, weight and lifestyle factors such as smoking and drinking (Ohno et al., 2001; Tamakoshi et al., 2005; 2013).

In most areas, follow-ups on mortalities and causes of death were completed at the end of 2009 (Tamakoshi et al., 2013). Death from kidney cancer was defined as code 'C64' (i.e., renal cell carcinoma) in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) (Ohno et al., 2001; Tamakoshi et al., 2005; 2013). Eligible subjects included 46,395 males and 64,190 females with 707,136 and 1,025,703 person-year follow-ups, respectively, for the current analysis (Tamakoshi et al., 2013). A total of 88 participants (62 males and 26 females) died from kidney cancer during the follow-up period (Tamakoshi et al., 2013).

Smoking status at baseline was classified into three categories: never smokers, former smokers, and current smokers. Intensity of smoking was classified by the duration of smoking (0 years, 1-24 years, 25-39 years, and 40+ years) and by the Brinkman index (BI) (BI=0, BI=1-399, BI=400-799, BI=800-1199 and BI=1200+). The BI was determined as the number of cigarettes per day multiplied by the number of years of smoking (Brinkmann, et al., 1963). Drinking status at baseline was also classified into three categories: never drinkers, former drinkers, and current drinkers. The intensity was classified into three categories by the amount of drinking: never, less than 2 gou/drinking occasion, and 2 gou or more/drinking occasion. The gou is a traditional scale for the Japanese rice wine, sake (1 gou=180 ml of sake containing 22.8 g of ethanol). Preference of foods at baseline was classified into three categories according to fondness of salty foods and fatty foods: no, neutral, and yes. Sports activity at baseline was classified into three categories: less than 1 hour/week, 1-2 hours/week, and 3 hours or more/week. They were also classified by daily walking time at baseline into three groups: less than 30min/day, 30-60 min/day, and 60 min or more /day.

The body mass index (BMI) was calculated as the reported weight divided by the square of the reported height (kg/m^2). Obesity was defined as a high BMI (BMI> 25.0). 'DM subjects' were defined as the subjects who had a history of DM while 'non-DM subjects' were defined as those who had no history of DM. In addition, 'normal subjects' were defined as those without a history of DM or obesity, and 'obese subjects without DM' was defined as 'non-DM subjects' with obesity.

All statistical analyses were conducted using the Statistical Analysis System (SAS) package (SAS Institute Inc. Cary, North Carolina, USA). The hazard ratios (HRs) of kidney cancer death and 95% confidence intervals (95% CIs) were estimated with Cox's proportional hazard model. In the case of the analysis of the question item where some participants did not answer, these patients were excluded from each analysis. Age was treated as a continuous variable while indicator variables were used for other factors. The dose-dependent trend was tested by evaluating the regression coefficient when the categories were treated as equally spaced numerical variables in Cox's model. All probability values for statistical tests were 2-tailed and a P value of less than 0.05 was considered to indicate statistical significance. This investigation was approved by the Ethical Boards of Nagoya University School of Medicine and Kyoto Prefectural University of Medicine.

Results

Table 1 shows the relative risk of the age- and sex-adjusted relative risk of kidney cancer death in relation to smoking and drinking habits. Compared with never smokers, current smokers showed a non-significant increased risk (HR=1.79, 95%CI: 0.92-3.48) and heavy smokers (BI≥1200) had a greater and significant risk (HR=2.95, 95%CI: 1.21-7.21). The trend of the risk tended to increase with the duration of smoking (p for trend=0.071).

Former drinkers showed a high risk of kidney cancer death compared with never drinkers (HR=2.90, 95%CI: 1.21-6.97) while current drinkers failed to show a significant association with the risk compared with never drinkers (HR=1.57, 95%CI: 0.86-2.86). There was no significant association between the amount of alcohol consumption and the risk (p for trend =0.123).

Table 2 shows HRs for kidney cancer death in relation to a preference of foods. Compared with those who did not like eating fatty foods, those who liked eating them had a high HR (1.96, 95%CI: 1.00-3.85) and the trend was significant (p for trend =0.043). Fondness of salty foods showed no significant association with the risk of kidney cancer death.

Table 3 illustrates the relative risk of kidney cancer death in relation to physical activity. Those who walked 60 minutes or longer a day showed a lower HR than the unity compared with those who walked less than 30 min a day (HR=0.57, 95%CI: 0.32-1.00, p=0.051) and the risk was negatively associated with daily walking time

Table 1. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Kidney Cancer Death in Relation to Smoking and Drinking Habits

Smoking and drinking habits	Person-years	No. of kidney cancer death	Age-and sex-adjusted HR (95% CI)	p value
Smoking status				
Never smokers	1,005,828	26	1.00(reference)	
Former smokers	191,111	14	1.09(0.49-2.39)	0.835
Current smokers	416,760	37	1.79(0.92-3.48)	0.085
Smoking index				
0 (Never smokers)	1,005,828	26	1.00(reference)	
1-399	195,804	13	1.46(0.67-3.18)	0.344
400-799	252,540	19	1.46(0.69-3.10)	0.321
800-1199	114,966	10	1.24(0.52-2.95)	0.628
1200+	43,182	9	2.95(1.21-7.21)	0.017
			p for trend =0.391	
Duration of smoking				
0 (Never smokers)	1,005,828	26	1.00(reference)	
1-24 years	196,751	6	0.98(0.36-2.65)	0.965
25-39 years	252,960	19	1.58(0.74-3.36)	0.240
40+ years	132,068	23	1.87(0.88-3.99)	0.104
			p for trend =0.071	
Alcohol drinking status				
Never drinkers	830,472	21	1.00(reference)	
Former drinkers	50,141	8	2.90(1.21-6.97)	0.017
Current drinkers	773,263	48	1.57(0.86-2.87)	0.143
Amount of alcohol drinking				
Never	830,472	21	1.00(reference)	
-1.9 gou*/drink occasion	322,783	19	1.10(0.58-2.09)	0.765
2 gou+/drink occasion	222,636	18	1.47(0.74-2.93)	0.275
			p for trend =0.123	

*gou: traditional scale measuring sake (Japanese rice wine). I gou (= 180ml) of sake continning 22.8 g of ethanol

Table 2. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Kidney Cancer Death in Relation to Preference of Food

Preference of foods	Person-years	No. of kidney cancer death	Age-and sex-adjusted HR (95% CI)	p value
Fond of salty foods				
No	223,747	11	1.00(reference)	
Neutral	731,037	31	0.85(0.43-1.70)	0.649
Yes	467,697	27	1.10(0.54-2.24)	0.748
			p for trend =0.593	
Fond of fatty foods				
No	401,335	14	1.00(reference)	
Neutral	729,023	32	1.21(0.64-2.28)	0.553
Yes	303,658	24	1.96(1.00-3.85)	0.051
			p for trend =0.043	

(p for trend=0.039). In contrast, there was no meaningful association between sports activity and the risk of kidney cancer death.

As shown in Table 4, history of hypertension showed an HR higher than the unity, (HR=1.40, 95%CI: 0.85-2.30), but failed to show statistical significance. The risk tended to increase with systolic blood pressure (p for trend=0.065). Compared with 129 mmHg or less, HRs were 3.84 (95%CI: 1.63-9.08) for 130-139 mmHg and 2.64 (95%CI: 1.12-6.20) for 140 mmHg or over. On the other hand, there was no meaningful association between the risk of kidney cancer death and level of diastolic blood pressure. Compared with 79 mmHg or less, HRs were 2.29 (95%CI: 1.15-1.99) for 80-84 mmHg and 0.95 (95%CI: 0.45-2.00) for 90 mmHg or over.

Table 5 shows the relative risk of kidney cancer death in relation to DM and obesity. Having a history of DM showed a significantly increased risk compared with no history of DM (HR=2.00, 95%CI: 0.99-4.03). In addition, compared with 'normal subjects,' 'DM subjects' showed a significantly increased risk (HR=2.19, 95%CI: 1.03-4.68) and 'obese subjects without DM' showed an increased, but not significant, risk (HR=1.69, 95%CI: 0.96-2.98). The trend of the increased risk with BMI was significant (p for trend=0.027).

Table 3. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Kidney Cancer Death in Relation to Physical Activity

Physical activity	Person-years	No. of kidney cancer death	Age-and sex-adjusted HR (95% CI)	p value
Sports activity				
≤1 hour /week	1,039,215	48	1.00(reference)	
1-2 hours/week	214,066	9	0.81(0.40-1.65)	0.558
≥3 hours /week	163,449	8	0.64(0.30-1.37)	0.255
			p for trend =0.226	
Walking				
≤30min/day	384,066	23	1.00(reference)	
30-60 min/day	265,070	18	1.07(0.58-1.84)	0.830
≥60 min/day	690,647	25	0.57(0.32-1.00)	0.051
			p for trend =0.039	

Table 4. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Kidney Cancer Death in Relation to Hypertension

Medical history of hypertension and blood pressure level	Person-years	No. of kidney cancer death	Age-and sex-adjusted HR (95% CI)	p value
Medical history				
Hypertension				
(-)	1,275,447	50	1.00(reference)	
(+)	332,186	24	1.40(0.85-2.30)	0.189
Systolic blood pressure (mmHg)				
≥129	479,369	7	1.00(reference)	
130-139	268,662	21	3.84(1.63-9.08)	0.002
≥140	385,991	25	2.64(1.12-6.20)	0.026
			p for trend =0.065	
Diastolic blood pressure (mmHg)				
≤80	511,546	15	1.00(reference)	
80-84	294,192	16	1.49(0.74-3.01)	0.269
≥85+	319,484	20	1.68(0.86-3.29)	0.129
			p for trend =0.715	

Table 5. Hazard Ratio (HR) and 95% Confidence Interval (CI) for Kidney Cancer Death in Relation to Physical Activity

Medical history of diabetes mellitus and obesity	Person-years	No. of kidney cancer death	Age-and sex-adjusted HR (95% CI)	p value
Diabetes mellitus				
(-)	1,498,298	66	1.00(reference)	
(+)	71,125	9	2.00(0.99-4.03)	0.053
Normal subjects**	1,121,681	43	1.00(reference)	
Obesity without diabetes mellitus	305,964	17	1.69(0.96-2.98)	0.068
Diabetes mellitus	67,476	8	2.19(1.03-4.68)	0.043
			p for trend =0.013	
Body mass index(Kg/m^2)				
≤19.9	257,281	9	1.00(reference)	
20.0-23.9	879,137	37	1.25(0.62-2.53)	0.532
≥24.0	548,354	31	1.94(0.95-3.99)	0.070
			p for trend =0.027	

*Obesity: body mass index >25.0 Kg/m^2; **Normal subjects: those without either diabetes mellitus or obesity

Discussion

Cigarette smoking is associated with an increased risk of malignancies of both organs in direct contact with smoke such as the esophagus and lung, and organs not in direct contact with smoke, such as the bladder, urinary tract and kidney (Gajalakshmi et al., 2000). Cigarette smoking is hypothesized to increase kidney cancer risk through tissue hypoxia due to carbon monoxide exposure and smoking related conditions such as chronic pulmonary diseases (Chow et al., 2010). In addition, kidney cancer patients show a higher level of DNA damage in their peripheral blood lymphocytes cells induced by tobacco-specific N-nitrosoamines compared to the control subjects (Chow et al., 2010).

In Western countries, many epidemiologists have reported that cigarette smoking is a risk factor of kidney cancer (Yu et al., 1986; McLaughlin et al., 1996; Lindbland et al., 2002; Vineis et al., 2004). However, in Japan, Mikami (1997) failed to demonstrate that smoking is a risk factor of kidney cancer in his case control study. In his study, 105 of 136 cases and 105 of 136 controls were smokers or ex-smokers in men while 13 of 64 cases and 11 of 64 controls were smokers in women. The result may be explained by the fact that, in Japan, most men had smoking experiences while most women were not smokers in those days (between 1975 and 1995: smoking rate: between 58.8% and 76.2% for men, between 13.7% and 15.2% for women) (Health and Welfare Statistics Association, 2007). Some large scale population-based cohort studies in Japan including the Hirayama cohort study (Hirayama, 1990) and the JACC study (Washio et al., 2005; 2007; 2008) also failed to show a significantly increased risk of kidney cancer with smoking. These findings may be explained by the small number of kidney cancer in these studies because of the low incidence of kidney cancer in Japanese population (Toma, 2003; Marumo et al., 2001; 2007).

In the present study, compared with never smokers, current smokers showed an increased (but not significant) risk, and heavy smokers (BI>1200) had a significantly increased risk. Compared with never smokers, the risk of heavy smokers (HR=2.66, 95%CI: 1.05-6.74, p=0.04, not shown in the table) was still significant after adjusting for age, sex, alcohol drinking and history of DM. Also the trend of the risk tended to increase with the duration of smoking (p for trend=0.071).

These findings suggested that smoking is a risk factor of kidney cancer death in the Japanese population as well as in Western populations. An increased number of kidney cancer deaths with additional 10-year follow up in the JACC study is thought to enhance the fact that smoking is a risk factor of this cancer, compared with the previous studies (Washio et al., 2005; 2007; 2008).

With respect to alcohol drinking, most case control studies and cohort studies showed no association between alcohol drinking and the risk of kidney cancer while a few case control studies indicated some inverse association between them (McLaughlin et al., 1996; Lindbland et al., 2002). However, Lew and coworkers (2011) recently found an inverse association between alcohol consumption and the risk of kidney cancer in a dose-responsive manner based on an observation of 1,814 cases during a follow-up with 4,476,544 person-years. A very recent meta-analysis (Bellocco et al., 2012) also demonstrated an inverse association between alcohol consumption and the risk of kidney cancer. Alcohol drinking is considered to reduce the risk of kidney cancer by enhancing insulin sensitivity because alcohol intake reduces fasting insulin concentration and improve insulin sensitivity (Davies et al., 2002). However, the present study failed to show any meaningful association between the drinking status or drinking amount in current drinkers and the risk of kidney cancer death. These findings may be partly explained by the small number of the outcomes (88 deaths) and the possibly weaker association with drinking than that with smoking.

Although it has been suggested that alcohol drinking decreased the risk of kidney cancer (Lew et al., 2011; Bellocco et al., 2012), former drinkers showed a high risk of kidney cancer death in the present study. This finding is thought to be explained by the following possibilities. First, former drinkers were thought to quit drinking because they acquired bad health conditions such as DM, chronic liver disease, and other diseases. Ogimoto et al (2004) reported that former drinkers but not current drinkers were thought to have a risk of death from hepatocellular carcinoma in the JACC study. They considered that former drinkers had a large cumulative alcohol intake before they quit drinking since a large cumulative alcohol intake was reported to be associated with increased risk of hepatocellular carcinoma. In the present study, DM was more common in former drinkers than never drinkers (13.6% *vs* 4.6%, p<0.01). Some former drinkers may have quit drinking because they had secondary DM due to liver diseases and subsequently former drinkers were thought to have an increased risk of kidney cancer. Second, if former drinkers stopped drinking because of their illness, they may have smoked a lot before in their life since it was observed in Japanese youth that alcohol drinking was positively associated with the initiation of smoking and negatively associated with smoking cessation (Ozawa et al., 2008). In the present study, the prevalence of heavy smokers with high BI (≥1200) was greater in former drinkers than in never-drinkers (7.6% *vs* 1.3%, p<0.01). After adjusting for age, sex, BI and history of DM, the risk of former drinkers failed to show statistical significance (HR=2.49, 95%CI: 0.86-7.20, p=0.09, not shown in the table) although the risk of heavy smokers with high BI was still significant. These findings suggest that former drinking itself may not increase the risk of kidney cancer. Further studies are recommended because there may be some other unknown confounding factors to alter the results.

The incidence and mortality of kidney cancer have been increasing in recent years in Japan (Toma, 2003). Westernization of Japanese lifestyle (e.g. Westernization of eating habits, the spread of privately-owned cars and household electric appliances as well as agricultural mechanization) is thought to be one of the reasons. Westernization of dietary habits indicates a decrease in eating traditional Japanese foods (i.e. eating a lot of rice with salty food such as salty grilled fish, salty pickles and soybean paste soup), and an increase in consuming Westernized foods (i.e. eating animal protein and fat such as breaded pork cutlet and beefsteak). In the present study, fondness of fatty foods was positively associated with an

increased risk of kidney cancer but fondness of salty foods showed no meaningful relation to the risk. These findings are consistent with the results of studies which suggested that a high intake of meat (McLaughlin et al., 1984), and beef (Maclure et al., 1990) increased the risk of kidney cancer.

Low physical activity was reported as a risk factor of kidney cancer in Western countries (Lindbland et al., 2002; Menezes et al., 2003; Mahabir et al., 2004). Since energy expenditure is an important determinant of obesity, it is unclear whether the improvement of obesity by the exercise or physical activity itself reduces the risk of kidney cancer (Lindbland et al., 2002). In the present study, walking for a long time each day significantly decreased the risk of kidney cancer death with a dose-responsive relationship. In contrast, there was no meaningful association between sports activity and the amount of risk. These findings were thought be explained by the following possibilities. The first possibility is that those who walked for a short time each day might have had more driving experience than those who walked for a long time each day. Mikami (1997) reported that driving experience increased the risk of kidney cancer by three times in the Japanese population. He explained that driving experience increased the risk by the exposure to petroleum or its exhaust gases (Mikami, 1997). The second possibility is that those who walked for a short time each day lived in urban areas with Westernized lifestyles while those who walked for a long time each day lived in rural areas with traditional Japanese lifestyles, because those who lived in rural areas may have to walk due to the lack of efficient public transportation. The incidence of kidney cancer is high in Europe and North America whereas it is low in Asia (McLaughlin et al., 1996; Lindbland et al., 2002). However, the incidence of kidney cancer is higher in Japanese-Americans than in native Japanese (Parkin et al., 2002), suggesting that Japanese suffer from kidney cancer at a higher rate when exposed to a Western culture. The last possibility is that the number of kidney cancer death among participants with high sports activity was too small to detect the risk in the present study. In this study, only 8 kidney cancer deaths were observed among 10,556 participants with more than 3 hours a week sports activity while 25 outcomes were observed among 42,243 participants who walked more than 60 minutes a day.

Many studies demonstrated that hypertension was associated with an increased risk of kidney cancer in Western countries (McLaughlin et al., 1996; Yuan et al., 1998; Chow et al., 2000; Lindbland et al., 2002). In the present study, a history of hypertension tended to increase the risk. The risk tended to increase with systolic blood pressure. Compared with 129 mmHg or less, a significantly increased risk was detected for 130-139 mmHg and for 140 mmHg or over. On the other hand, there was no meaningful association between the risk of kidney cancer death and level of diastolic blood pressure and the increased risk was detected only for 80-84 mmHg compared with 79 mmHg or less. These findings suggest that systolic blood pressure may be more important in the risk of kidney cancer death than diastolic blood pressure. In our previous study, however, both systolic and diastolic blood pressure was positively associated with the risk of development of kidney cancer (Washio et al., 2008). Further studies are needed to confirm this hypothesis.

DM increased the risk of renal cell carcinoma in some cohort studies (Wideroff et al., 1997; Lindblad et al., 1999), but it is not an established risk factor (McLaughlin et al., 1996; Lindbland et al., 2002). In the present study, the subjects with DM showed an increased risk of kidney cancer death compared with non-DM subjects and the subjects without either DM or obesity. These findings were consistent with the result of our previous study (Washio et al., 2007).

Obesity is a risk factor for kidney cancer in Western countries (McLaughlin et al., 1996; Yuan et al., 1998; Chow et al., 2000; Lindbland et al., 2002). Insulin resistance, which is common in obesity (Kaplan, 2002), contributes for numerous cancers (Levine et al., 2006). In our previous studies, however, obesity failed to show any meaningful association with kidney cancer death (Washio et al., 2005) although obesity showed a marginal increased risk of dying from kidney cancer after excluding those with a history of diabetes mellitus (Washio et al., 2007). On the other hand, Sawada et al. (2010) found that a U-shape association between BMI and kidney cancer in another population-based large cohort study, and reported that high BMI as well as low BMI increased the risk of kidney cancer. In the present study, the trend of the increased risk with BMI was significant (p for trend=0.027). In addition, obese subjects showed a marginally increased risk of kidney cancer death compared with those without either of DM or obesity. The findings in our studies are consistent with the findings in the Western countries (McLaughlin et al., 1996; Yuan et al., 1998; Chow et al., 2000; Lindbland et al., 2002). Further studies should be recommended because the number of kidney cancer was small in Japanese cohort studies in spite of a large population based cohort studies (Sawada et al., 2010; Tamakoshi et al., 2013).

This study has several strengths and limitations. The strength of this study is a large-scale prospective cohort study among the Japanese population. However, there are some limitations. First, despite its large size (i.e., 46,395 males and 64,190 females), we had small numbers of kidney cancer deaths (i.e., 62 males and 26 females) to evaluate the risk of kidney cancer because of its rarity. Therefore, this study had limited potential to evaluate the risk. Second, the outcome of the present study was not an incidence of kidney cancer but a death from kidney cancer. Since many cases of kidney cancer have been detected with renal imaging techniques such as ultrasonography in Japan (Toma, 2003), this study might have missed an important risk factor for kidney cancer in Japan because of non-fatal cases that were not identified in death certificates.

In summary, it was suggested that current and former smoking, fondness of fatty foods, hypertension, history of diabetes mellitus, and obesity all increased the risk of kidney cancer death while walking decreased the risk in this study. Even after controlling age, sex, alcohol drinking and history of DM, current and former heavy smokers with high BI (≥1200) significantly increased the risk of death from kidney cancer. However, these findings should be interpreted with caution, because the number of outcomes was so small that we could not evaluate these factors after adjusting for all possible confounding factors. Further studies may be needed to confirm the findings in this study.

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