MINI-REVIEW

Risk Factors for Renal Cell Carcinoma in a Japanese Population

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Abstract

The incidence of renal cell carcinoma (RCC) is high in Western and Northern Europe and North America, and low in Asia. Although the incidence of RCC in Japan is lower than the rates in the other industrialized countries, there is no doubt that it is increasing. In this paper, we would like to introduce the summary of findings of JACC study, which evaluate the risk factors for RCC in a Japanese population. JACC study suggests nine risk factors (i.e., smoking, obesity, low physical activity, hypertension, diabetes mellitus, kidney diseases, beef, fondness for fatty food and black tea) and one preventive factor (i.e., starchy roots such as taro, sweet potato and potato) in a Japanese population. In Japan, however, drinking black tea may be a surrogate for westernized dietary habits while eating starchy roots may be a surrogate for traditional Japanese dietary habits. Further studies may be needed to evaluate risk factors for RCC because the number of cases is small in our studies.

Keywords: Renal cell carcinoma - risk factor - Japan

Introduction

Renal cell carcinoma (RCC), which arises from cells of the proximal convoluted renal tubules (McLaughlin et al., 1996; Lindblad et al., 2002; WHO, 2003), accounts for 2-3% of all malignancies in western countries (Brosman, 1989; Lindblad et al., 2002; McLaughlin et al., 1996; Parkin, 2002) and 1-2% in Japan (Parkin, 2002; Toma, 2003). However, the incidence of RCC is higher in Japanese Americans than in native Japanese (Parkin, 2002). These findings suggest that the environmental factors such as life-style factors may play a role in the development of RCC. The incidence and mortality of RCC have been increasing in recent years in Japan (Toma, 2003). The incidence rates (persons per 100,000) were 7.1 for men and 3.1 for women in 1997 (Marumo et al., 2001) while they were 8.2 for men and 3.6 for women in 2002 (Marumo et al. 2007). Westernization of the lifestyle (e.g., westernization of eating habits, the spread of privately-owned cars and household electric appliances as well as agricultural mechanization) may increase the incidence of RCC. According to the westernization of dietary habits, it decreased to eat traditional Japanese foods (i.e., eating a lot of rice with salty food such as salty grilled fish, salty pickles and miso soup, and drinking green tea), and it increased to take westernized foods (i.e., eating animal protein and fat such as breaded pork cutlet and beefsteak, and drinking coffee or black tea). High-fat and high-protein diet is reported to increase the risk of RCC (Handa et al., 2002). Low physical activity is also reported to play a role in the development of RCC (Mahabir et al. 2004; Menezes et al., 2003). Many epidemiologists have reported risk factors for RCC in western countries (Lindblad et al., 2002). Even in textbooks of RCC written in Japanese (Toma, 2003), however, we have to get knowledge about the risk factors for RCC from studies in western countries (McLaughlin et al., 1996; Lindblad et al., 2002; WHO, 2003). Therefore, we evaluated the risk factors for RCC in a large population-based cohort study in Japan (JACC study) (Washio et al., 2005; 2007; 2008; 2013), which has followed up for more than 1 million-person years (Ohno et al. 2001, Tamakoshi et al. 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

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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., 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., RCC) in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) (Ohno et al., 2001; Tamakoshi et al., 2013).

In this paper, we would like to introduce the summary of findings from JACC study on risk factors for both incidence and mortality RCC (Washio et al., 2005; 2007; 2008; 2013), and to discuss on the risk factors for RCC in a Japanese population.

Risk Factors

Old age and male sex

Men have a higher risk of RCC than women (age-adjusted hazard ratio=4.52, 95% confidence interval: 2.28 to 8.96) and the risk increases with age (sex-adjusted HR=1.08 per 10-year increment, 95%CI: 1.05 to 1.11) in a Japanese population (Washio et al., 2008).

Medical conditions and obesity

a. Hypertension: Hypertension as well as anti-hypertensive medication has been reported to be a risk factor for RCC in Western countries (Lindblad et al., 2002; McLaughlin et al., 1996; Mellemgaard et al., 1994; WHO, 2003; Yuan et al., 1998). In a Japanese population, there is a positive association between hypertension and the incidence of RCC (age- and sex-adjusted HR=4.27, 95%CI: 2.07 to 8.79) (Washio et al., 2008). In addition, hypertension increases the risk of RCC death as well (age- and sex-adjusted HR=1.98, 95%CI: 1.06 to 3.70) in the JACC study (Washio et al., 2005).

The precise mechanisms how hypertension may affect the risk of RCC has not been clarified. However, hypertension-induced renal injury may play a role in the development of RCC, and metabolic or functional changes within the renal tubules, caused by hypertension, may increase susceptibility to carcinogens (McLaughlin, 2006). Another explanation is that insulin-resistance seen among hypertensive subjects regardless of obesity (Kaplan, 2002), may increases the risk of RCC because insulin resistance contributes a risk factor for numerous malignancies (Levine et al., 2006).

b. Obesity and diabetes mellitus: Obesity is an established risk factor for RCC in Western countries (Yu et al., 1986; McLaughlin et al., 1996; Yuan et al., 1998; Chow et al., 2000; Lindblad et al., 2002; WHO, 2003). Yuan et al. (1998) reported that compared with those with BMI of 21 or smaller, those with BMI of 24-25 and 26-27 were 1.5-fold and 1.7-fold more likely to develop RCC, respectively. Insulin resistance, which is common in obesity and leads to elevated levels of insulin-like growth factor type 1 (Levine et al, 2006), increases the risk of cancer (Hirata, 1991; Levine et al., 2006). In a

Japanese population, the JACC study reported that BMI was positively associated with the risk of RCC death(p for trend=0.027) (Washio et al.,2013). On the other hand, Sawada et al. (2010) found that a U-shape association between BMI and RCC in another population-based large cohort study, and reported that high BMI as well as low BMI increased the risk of RCC.

Diabetes mellitus increases the risk of RCC in some cohort studies in Northern Europe (Lindblad et al., 1999; Wideroff et al., 1997), but it is not an established risk factor in Western countries (McLaughlin et al., 1996; Lindblad et al., 2002; WHO, 2003). In a Japanese population, diabetes mellitus (age- and sex-adjusted HR=1.72, 95%CI: 0.51 to 5.79) fails to be a significant risk factor for the development of RCC (Washio et al., 2008) while diabetes mellitus (age- and sex-adjusted HR=2.22, 95%CI: 1.04 to 4.70) shows an increased risk of RCC death in the same study (Washio et al., 2007). In addition, after excluding obese subjects without diabetes mellitus, diabetes mellitus (age- and sex-adjusted HR=2.59, 95%CI: 1.19 to 5.64) shows a higher risk of RCC death in the JACC study (Washio et al., 2007). Furthermore, a significantly increased risk was observed according to the stages of DM (i.e, normal [those without either obesity or DM], pre-DM [obesity without DM], and DM; p for trend=0.02) (Washio et al., 2007). These findings may be partly explained by the possibility that patients with diabetes mellitus are not necessarily obese in Japan as Japanese patients with diabetes mellitus may have reduce their weight after consulting with doctors for this disease as described in a Japanese textbook on diabetes mellitus (Hirata, 1991).

The mechanisms of how obesity and diabetes mellitus increase the risk of RCC may be explained by the following way. Although the precise mechanism of how obesity contributes to insulin resistance and diabetes mellitus has not yet been identified, both obesity and diabetes mellitus are associated with hyperinsulinemia (Landsberg, 2005; Maratos-Fleier, 2004). Insulin stimulates cell growth, either directly through the insulin receptor, or through its ability to cross-react with insulin-like growth factors I receptor, and it is generally held that growth factor are likely to play an important role in carcinogenesis. Cerhan et al. (1997) suggested that DM is preceded by a long period of insulin resistance, which may increase the risk of cancer through leading to elevated levels of insulin-like growth factor type 1 (Levine et al., 2006).

Kidney infection, kidney stone and kidney cyst are reported to be risk factors for RCC (McLaughlin et al., 1996; Lindblad et al., 2002; WHO, 2003). Very recently, Lowrance et al. (2014) reported that lower kidney function increased the risk of RCC in a dose-responsive manner. In our studies, kidney disease (age- and sex-adjusted HR=4.42, 95%CI: 1.68 to 11.63) shows an increased risk of the development of RCC (Washio et al., 2008), but fails to be a significant risk factor for dying from RCC (age- and sex-adjusted HR=2.35, 95%CI: 0.83 to 6.64) (Washio et al., 2005). These findings may be partly explained in the following way. Japanese Ministry of Health, Labour and Welfare (2013) has required employers and municipalities to supply the health checkup examination for employees and citizens aged 40 years and more in order to find early

Table 1. Factors Related to the Development of Renal Cell Carcinoma and the Death from Renal Cell Carcinoma in JACC Study

Factors	Incidence/Mortality		HR(95%CI)	Reference
Sex and age				
Male sex	Incidence	Women	1.00(reference)	Washio et al. 2008
		Men	4.52 (2.28-8.96)	
Old age	Incidence	Per 10 years increment	1.08(1.05 - 1.11)	Washio et al. 2008
Hypertension				
Medical history of hypertension	Incidence	Hypertension (-)	1.00(reference)	Washio et al. 2008
		Hypertension (+)	4.27(2.07-8.79)	
Medical history of hypertension	Death	Hypertension (-)	1.00(reference)	Washio et al. 2005
		Hypertension (+)	1.98(1.06-3.70)	
Blood pressure level	Incidence	Systolic blood pressure		Washio et al. 2008
		139 mmHg or less	1.00(reference)	
		140-149mmHg	1.64(0.57-4.72)	
		150mmHg or over	4.34(1.75-10.74)	
			p for trend<0.01	
Blood pressure level	Incidence	Diastolic blood pressure		Washio et al. 2008
		84mmHg or less	1.00(reference)	
		85-89mmHg	2.00(0.55-7.22)	
		90mmHg or over	4.82(2.13-10.93)	
			p for trend<0.01	
Blood pressure level	Death	Systolic blood pressure		Washio et al. 2013
		129 mmHg or less	1.00(reference)	
		130-139mmHg	3.84(1.63-9.08)	
		140mmHg or over	2.97(1.42-6.20)	
			p for trend=0.01	
Blood pressure level	Death	Diastolic blood pressure		Washio et al. 2013
		89mmHg or less	1.00(reference)	
		80-84mmHg	1.49(0.74-3.01)	
		85mmHg or over	1.68(0.86-3.29)	
			p for trend=0.72	
Obesity and diabetes mellitus				
Medical history of Diabetes Mellitus	Death	Diabetes mellitus (-)	1.00(reference)	Washio et al. 2007
		Diabetes mellitus (+)	2.22(1.04-4.70)	
Diabetes mellitus and obesity	Death	Normal subjects	1.00(reference)	Washio et al. 2013
		Obesity without Diabetes mellitus	1.69(0.96-2.98)	
		Diabetes mellitus	2.19(1.03-4.68)	
			p for trend=0.01	
Body mass index	Death	Body mass index(kg/m2)		Washio et al. 2013
		19.9 or less	1.00(reference)	
		20.0-23.9	1.25(0.62-2.53)	
		24.0 or over	1.94(0.95-3.99)	
			p for trend=0.03	
Kidney disease				
Medical history of kidney disease	Incidence	Kidney disease(-)	1.00(reference)	Washio et al. 2008
		Kidney disease(+)	4.42(1.68-11.63)	
	Death	Kidney disease(-)	1.00(reference)	Washio et al. 2005
		Kidney disease(+)	2.35(0.83-6.64)	
Smoking				
Smoking status	Death	Never smokers	1.00(reference)	Washio et al. 2005
		Former smokers	1.36(0.48-3.82)	
		Current smokers	2.13(0.87-5.24)	
			p for trend=0.07	
Cumulative dose of smoking in one's life	Death	Brinkman Index		Washio et al. 2013
		0 (Never smokers)	1.00 (reference)	
		1-399	1.46(0.67-3.18)	
		400-799	1.46(0.69-3.10)	
		800-1199	1.24(0.52-2.95)	
		1200 or over	2.95(1.21-7.21)	
Duration of smoking	Death	Years		Washio et al. 2013
		0 (Never smokers)	1.00(reference)	
		1-24	0.98(0.36-2.65)	
		25-39	1.58(0.74-3.36)	
		40 or over	1.87(0.88-3.99)	
			p for trend=0.07	
Physical activity				
Walking	Death	Minutes/day		Washio et al. 2013
		29 or less	1.00(reference)	
		30-59	1.07(0.58-1.84)	
		60 or over	0.57(0.32-1.00)	
			p for trend=0.04	
Dietary habits				
Fatty food	Death	Fond of fatty food		Washio et al. 2005

		No	1.00(reference)	
		Yes	2.64(1.03-6.78)	
Fatty food	Death	Fond of fatty food		Washio et al. 2013
		No	1.00(reference)	
		Neutral	1.21(0.64-2.28)	
		Yes	1.96(1.00-3.85)	
			p for trend=0.04	
Black tea	Death	Cups/day		Washio et al. 2005
		None	1.00(reference)	
		2 or less	2.15(0.67-2.33)	
		3 or more	13.60(1.83-101.30)	
			p for trend <0.01	
Coffee	Death	Cups/day		Washio et al. 2005
		None	1.00(reference)	
		2 or less	1.25(0.67-2.33)	
		3 or more	2.69(0.89-8.10)	
			p for trend=0.08	
Beef	Death	Seldom	1.00(reference)	Washio et al. 2005
		1-2/month	0.59(0.20-1.76)	
		1-2/week or more	1.73(0.74-4.08)	
			p for trend=0.08	
Taro, sweet potato, and potato	Death	1-2/month or less	1.00(reference)	Washio et al. 2005
		1-2/week	0.67(0.31-1.41)	
		3-4/week or more	0.44(0.21-0.94)	
			p for trend=0.03	

HR: age and sex adjusted hazard ratio, 95% CI: 95% confidence intervals; Body mass index: weight(kg) divided by the square of height(m); Obesity: body mass index>25.0; Brinkman index: the number of cigarettes per day multiplied by the number of years of smoking.

stage of cancer as well as to prevent life-style related chronic diseases such as metabolic syndrome. Therefore, in Japan, may cases of RCC may be incidentally detected with imaging techniques such as ultrasonography (Toma, 2003).

Acquired cystic kidney, which occurs in 7% to 22% of patients with end-stage renal disease prior to dialysis and increases to 90% after dialysis, is strongly associated with the development of RCC (Lindblad et al., 2002). Although we did not evaluated the risk of RCC among the patients with end-stage renal diseases, Kojima et al. (2006) performed annual screening for renal cell carcinoma using abdominal ultrasonography (US) and computed tomography(CT) in 2,624 dialysis patients between 1993 and 2004. During the follow-up periods, 44 of dialysis patients (1.68%) were pathologically diagnosed renal cell carcinoma. The incidence rate is much higher than those in a general population in Japan, whose incidence rates (persons per 100,000) were 8.2 for men and 3.6 for women in 2002 (Marumo et al., 2007).

Smoking, drinking and other life-style habits
a. Tobacco: Tobacco is the largest single recognized cause of human cancer in Western countries (Thun et al., 2006), and tobacco smoking is associated with an increased risk of malignancies of both organs in direct contact with smoke and organs not in direct contact with smoke (Gajalakshmi et al., 2000). Tobacco smoke contains numerous carcinogens generated by the combustion of tobacco, including many polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines as well as formaldehyde, phenolic compounds, and a variety of free radicals (Thun et al., 2006), and most of constituents in tobacco smoke are metabolized or excreted through the urinary tract (Lindblad et al., 2002). In Western countries, tobacco smoking (Chow et al., 2000; Yu et al., 1986) has been reported to increase the risk of RCC. In a Japanese population, tobacco smoking (current smokers *vs*

never smokers: age- and sex-adjusted HR=2.13, 95%CI: 0.87 to 5.24) shows a marginally increased risk of dying from RCC (Washio et al., 2005). In the JACC study (Washio et al., 2013), 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) compared with never smokers. The trend of the risk tended to increase with the duration of smoking (p for trend=0.071) (Washio et al., 2013).

b. Alcohol: In Western countries, drinking alcohol (Lindblad et al., 2002) has been suggested to reduce the risk of RCC. Lew and coworkers (2011) found an inverse association between alcohol consumption and the risk of RCC 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 RCC. Alcohol drinking reduces the risk of RCC by enhancing insulin sensitivity because alcohol intake improves insulin sensitivity (Davies et al., 2002). In the JACC study, however, there was no significant association between alcohol consumption and the risk of RCC death (Washio et al., 2013).

c. Physical activity
Low physical activity is reported as a risk factor for RCC in the Western countries (Menezes et al., 2003, Mahabir et al., 2004). Although it is unclear whether low physical activity is an independent risk factor for RCC or not, favorable changes in adiposity may be one of the major pathways through which high physical activity reduces the risk of RCC because obesity increases the risk of RCC (Yu et al., 1986; McLaughlin et al., 1996; Yuan et al., 1998; Chow et al., 2000; Lindblad et al., 2002; WHO, 2003). In the JACC study (Washio et al., 2013), 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 (p for trend=0.039) in the JACC study (Washio et al., 2013). These findings suggest that low physical activity may increase the risk of RCC in a Japanese population as well.

Dietary habits

In the JACC study (Washio et al., 2005), those who drink black tea (3+cups/day *vs* none: age- and sex-adjusted HR=13.60, 95%CI: 1.83 to 101.30) have an increased risk of RCC death even after adjusting for other factors. In addition, those who drink coffee (3+cups/day *vs* none: age- and sex-adjusted HR=2.69, 95%CI: 0.89 to 8.10) have a marginally increased risk (Washio et al., 2005). However, there has been no convincing evidence linking RCC and consumption of black tea or coffee despite numerous studies in western countries (Lindblad et al., 2002). In Japan, drinking black tea or coffee may be a surrogate for westernized dietary habits and thus it may be the latter rather than the former that is actually responsible for RCC. Further studies are needed to ascertain whether there is any truth to this hypothesis. Handa et al. (2002) reported that both a 'dessert' diet factor and a 'beef' diet factor were associated with an increased risk of RCC, suggesting that high-fat and high-protein diets as well as sugar- and fat-rich confectioneries might be risk factors for RCC. In the JACC study (Washio et al., 2005), a fondness for fatty food (yes *vs* no: age- and sex-adjusted HR=2.64, 95%CI: 1.03 to 6.78) is associated with an increased risk, even after adjusting for other factors, and a frequent intake of beef (1-2 times /day or more *vs* seldom: age- and sex-adjusted HR=1.73, 95%CI: 0.74 to 4.08, p=0.08) have a marginally increased risk. Since the incidence of RCC is higher in Japanese Americans than in native Japanese (Parkin et al., 2002) and it is increasing in Japan now (Toma, 2003), we cannot deny that westernization of dietary habits may play some role in the increased incidence of RCC in Japan. Chow et al. (1994) also reported that an intake of staple food (i.e., bread, cereals, potatoes, rice, and spaghetti) was associated with an increased risk of RCC. On the other hand, Mucci et al. (2003) reported that none of potato, bread and cereal was a risk factor for RCC. In the JACC study, an intake of starchy roots (i.e., taro, sweet potato and potato) was associated with a decreased risk of RCC death while an intake of rice showed no meaningful relation (Washio et al., 2005). Taro (Kim et al.,1998; Kim et al., 2002) and sweet potato (Pandey et al., 2002), a part of the traditional Japanese diet, are reported to have cancer preventive potential, suggesting that these traditional diets may partly be the reasons for the lower incidence of RCC death in Japan compared with the other developed countries.

Conclusion

The increasing incidence and mortality of kidney cancer in a Japanese population may be partly due to westernization of the lifestyle. The JACC study (Washio et al., 2005; 2007; 2008; 2013) suggests nine risk factors (i.e., smoking, obesity, low physical activity, hypertension, diabetes mellitus, kidney diseases, beef, fondness for fatty food and black tea) and one preventive factor (i.e., starchy roots such as taro, sweet potato and potato) in a Japanese population. However, these findings should be interpreted with caution, because the number of outcomes was very small. Despite its large size (i.e., more than 110,000 participants), we had small numbers of incidence and mortality of RCC (i.e., less than 100) to evaluate the risk of RCC because of its rarity (Washio et al., 2005; 2007; 2008; 2013). Therefore, we could not evaluate risk factors on the incidence and mortality of RCC after adjusting for all possible confounding factors. Further studies may be needed to confirm the risk factors for RCC in a Japanese population.

Acknowledgements

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