

DOI: 10.21767/2472-5056.100034

Obesity, Diabetes Mellitus, Hypertension and other Risk Factors for Renal Cell Carcinoma in Japan: A Mini-Review

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Received date: May 16, 2017; **Accepted date:** May 22, 2017; **Published date:** May 30, 2017**Citation:** Washio M, Mori M (2017) Obesity, Diabetes Mellitus, Hypertension and other Risk Factors for Renal Cell Carcinoma in Japan: A Mini-Review. *J Clin Exp Nephrol* 1: 34. doi: 10.21767/2472-5056.100034**Copyright:** © 2017 Washio M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: The incidence of kidney cancer is high in Western Europe, Northern Europe and North America, while it is low in Asia. Although the incidence of kidney cancer 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 result of epidemiological studies, which evaluate the non-genetic risk factors for kidney cancer in the Japanese population.

Methods: Relevant studies were identified in the PubMed database using the combination of "Japan", "kidney cancer", "renal cell cancer" and "risk", and the ICHUSHI database (Japanese database) using a combination of "kidney cancer /renal cell cancer", and "risk factor". In addition, we selected one cohort study from the references of these reports.

Results and Discussion: Several studies were identified in the database. In these studies, obesity, diabetes mellitus, hypertension, kidney diseases, chronic renal disease with dialysis, tobacco smoke, fondness for fatty food, milk, and black tea are associated with an increased risk of kidney cancer. On the other hand, an inverse association with the kidney cancer risk is found for an intake of starchy roots (i.e., taro, sweet potato and potato), physical activity and educational level. In Japan, however, drinking black tea and milk may be surrogates for a westernized dietary habit while eating starchy roots may be a surrogate for a traditional Japanese dietary habit. Additional studies are needed to confirm the risk factors for kidney cancer in the Japanese population.

Keywords: Renal cell carcinoma; Risk factor; Obesity; Diabetes mellitus; Hypertension

Introduction

Renal cell cancer, which arises from the cells of the proximal convoluted renal tubules [1,2], accounts for 2-3% of all malignancies in western countries [2,3] and 1-2% in Japan [3,4]. We use the term "kidney cancer" for renal cell carcinoma in this paper, although it covers both cancer of the renal parenchyma (i.e., renal cell carcinoma) and cancer of the pelvis (i.e., transitional cell cancer). The incidence of kidney cancer is high in Western Europe, Northern Europe, and North America while it is low in Asia [1,2]. However, the incidence of kidney cancer is higher in Japanese Americans than in native Japanese [3]. These findings suggest that environmental factors (i.e., non-genetic risk factors) may play an important role in the development of kidney cancer.

Therefore, we identified relevant studies [4-13] in the PubMed database using a combination of the search terms "Japan", "kidney cancer", "renal cell carcinoma" and "risk". In the ICHUSHI database (the Japanese database) we used a combination of the search terms "kidney cancer /renal cell carcinoma", and "risk factor" (the last search update on May 2017). In addition, we selected one cohort study [14] from the references of these reports.

In this paper, we would like to introduce the result of these studies on the risk factors for kidney cancer in the Japanese population [4-14].

Among them, seven reports [5-10,14] were the findings from three large population based cohort studies in Japan [13-15]. The first study is the Hirayama cohort study [14]. The Hirayama cohort study is a large scale census based cohort study in Japan, which started in 1965. In this study, 122,261 men and 142,857 women were followed up until 1982. A total of 14,740 deaths from cancer including 92 kidney cancer deaths occurred during the 17 years follow up, out of 3,849, 637 person-years of observation. The second study is the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk sponsored by Japanese Ministry of Education, Culture, Sports, Science and Technology (the JACC Study) [15]. The JACC Study, a large population-based cohort study in Japan, is a large-scale prospective study involving

110,585 healthy subjects (46,395 men and 64,190 women) aged 40 to 79 years from 45 areas in 19 prefectures across Japan, which started in 1988-90. Most study subjects were followed up for mortality until the end of 2009. However, the incident of cancer was ascertained in only 24 out of 45 study areas in which cancer registries were available, where the mortality-incident rate deviated from 0.31 to 0.61 in men and from 0.15 to 0.53 in women [16]. The third study is the Japanese Public Health Center-Based Prospected Study (JPHC Study) [17]. The JPHC Study is a population-based prospective cohort study involving 140,420 residents, which was launched in 1990 for cohort I (inhabitants were aged 40 to 59 years in 5 prefectural public health center areas) and in 1993 for cohort II (inhabitants ranged from the ages of 40 to 69 years in 6 prefectural public health center areas). The average follow-up period was over 10 years. In the JPHC Study, however, Inoue et al. [9] evaluated the risk of kidney cancer including not only renal cell carcinoma but also renal pelvis/ureter cancer in a Japanese population. On the other hand, Sawada et al. [10] investigated the association between body mass index and the risk of renal cell carcinoma in the JPHC Study.

Next is a case control study. Mikami [4] carried out a case control study (200 pairs of cases and controls) in order to evaluate classical risk factors for renal cell carcinoma.

The others are studies regarding the risk of renal cancer among dialysis patients compared with the general population. Satoh et al. [11] conducted a retrospective cohort study of 6,201 chronic dialysis patients between 1990 and 2003, while Kojima et al. [12] carried out a prospective cohort study of the 2,624 dialysis patients between 1993 and 2004 [12]. The final study is the summary of annual nation-wide questionnaire studies from 1982 to 2004 conducted by the Japanese Society for Dialysis Therapy [13].

Risk Factors

Medical conditions

Obesity and Diabetes mellitus: Obesity is an established risk factor for kidney cancer in Western countries [1,2,18-20]. Insulin resistance, which is common in obesity [21,22], contributes a risk factor for numerous cancers [21,22]. In Japan, Mikami [4] found that the body mass index (BMI) showed a positive association with the risk of kidney cancer (BMI 22-25 vs. BMI<22, odds ratio=2.0, 95%CI: 1.1 to 3.4, BMI>25 vs. BMI<22, OR=1.2, 95%CI: 0.6 to 2.4, $p<0.05$) in his case control study. In addition, Washio et al. [7] found a positive association between BMI and the risk of kidney cancer (20.0-23.9 vs. 19.9 or less: HR=1.25, 95%CI=0.62-2.53; 24.0 or more vs. 19.9 or less: HR=1.94, 95%CI=0.95-3.99, p for trend=0.027) in the JACC study. Furthermore, Sawada et al. [10] found that highest BMI showed a significantly increased risk of kidney cancer for men (BMI>27 vs. BMI=21-22.9: age and sex adjusted HR=2.35, 95%CI=1.27 to 4.36) and a non-significantly increased risk of kidney cancer for women (BMI>25 vs. BMI=21-22.9: age and sex adjusted HR=1.64, 95%CI=0.81 to 3.33) in the JPHC study.

Diabetes mellitus increases the risk of kidney cancer in some cohort studies in Northern Europe [23,24] and North America [25], but it is not an established risk factor in Western countries [1,2]. In Southern Europe, Zucchetto et al. [26] found a positive association between diabetes mellitus and the risk of kidney cancer in the Italian population in their case-control study, but the risk failed to show the statistical significance.

In the East Asian countries other than Japan, two studies demonstrated a positive association between diabetes mellitus and the risk of kidney cancer in the Taiwanese population [27,28] while no association was detected between diabetes mellitus and the risk of kidney cancer in the Taiwanese population in another study [29]. On the other hand, Choi et al. [30] reported no association between diabetes mellitus and the risk of kidney cancer in the Korean population.

In Japan, diabetes mellitus (age- and sex-adjusted HR=2.22, 95% CI: 1.04 to 4.70) increased the risk of kidney cancer death in the JACC study [6]. Inoue et al. [9] reported the findings from the JPHC study, which evaluated the risk of kidney cancer (renal cell cancer and renal pelvis/ureter cancer). In their study, diabetes mellitus increases the risk of kidney cancer (renal cell cancer and renal pelvis/ureter cancer) for males (age-adjusted HR=2.02, 95% CI: 1.13 to 3.64) but fails to do so for females (age-adjusted HR=1.62, 95% CI: 0.39 to 6.82) [9].

Hypertension: Hypertension [1,2,17,31] has been reported to be a risk factor for kidney cancer in Western countries [1,2,17,24,26] as well as in East Asian countries (e.g., Japan [5,8], Taiwan [29], Korea [30]). In the JACC study, there is a positive association between hypertension and the development of kidney cancer (age- and sex-adjusted HR=4.27, 95% CI: 2.07 to 8.79) in the population of Japan [8]. In addition, hypertension is a risk factor for kidney cancer death (age- and sex-adjusted HR=1.98, 95% CI: 1.06 to 3.70) in Japan as well [5].

Kidney diseases: Kidney infection, kidney stone, kidney cyst and end-stage renal disease are reported to be risk factors for kidney cancer [1,2]. Recently, Lowrance et al. [32] found a positive association between demonstrated that chronic kidney disease increased the risk of kidney cancer in the American population while Lai et al. [29] found a positive association between chronic kidney disease and the risk of kidney cancer in the Taiwanese population.

In the JACC study, kidney disease shows an increased risk for the development of kidney cancer (age- and sex-adjusted HR=4.42, 95% CI: 1.68 to 11.63) [8] and non-significantly increased risk for kidney cancer death (age- and sex-adjusted HR=2.35, 95% CI: 0.83 to 6.64) in the Japanese population [5].

Regarding end-stage renal failure with dialysis, Bulter et al. [33] reported that dialysis patients showed an increased risk of kidney cancer including renal pelvic cancer compared to general population in the United States. In East Asia, Cheung et al. [34] reported that chronic dialysis patients showed a significantly higher incidence and mortality of kidney cancer than general population in Hong Kong while Chien et al. [35] found that dialysis patients increased the risk of dying from kidney cancer compared to the general population in Taiwan. In Japan, Satoh et al. [11] reported that 38 (0.6%) out of 6201 dialysis patients

developed renal cell carcinoma between 1990 and 2003, while Kojima et al. [12] reported that 44 patients (1.7%) were pathologically diagnosed with renal cell carcinoma in 2,624 dialysis patients between 1993 and 2004. These incidences of kidney cancer among dialysis patients appear higher than the incidence of general population (i.e., 7.1/100,000 for males and 3.1/100,000 [36]). On the other hand, the annual nation-wide questionnaire studies between 1982 and 2004 conducted by the Japanese Society for Dialysis Therapy revealed that hemodialysis patients had a significantly higher risk of renal cell cancer than the general population ($p < 0.05$) [13]. Standardized incidence ratios of renal cell carcinoma were 8.9-18.2 for males and 8.3-17.1 for females in their surveys [13].

Lifestyle factors

Tobacco: In Western countries, tobacco smoking [19,20] has been reported to increase the risk of kidney cancer. In Japan, smoking (current smokers vs. never smokers: age- and sex-adjusted HR=2.13, 95% CI: 0.87 to 5.24) marginally increased the risk of kidney cancer death in the JACC study [5]. Recently, with additional follow-ups, the JACC study demonstrated that heavy smokers (Brinkman index=1200 or greater vs. never smokers) had a significantly increased risk of kidney cancer death (age- and sex adjusted HR=2.95, 95%CI: 1.21 to 7.21) (Table 1) [7].

Table 1. Risk factors for renal cell carcinoma in Japan.

Factors	Association	Comments
Medical Conditions		
Hypertension	Positive	
Obesity	Positive	
Diabetes mellitus	Positive	Most are type 2 diabetes
Kidney disease	Positive	
Chronic renal failure with Dialysis	Positive	
Lifestyle factors		
Tobacco smoking	Positive	
Physical activity	Inverse	Non-occupational physical activity
Dietary habits		
Milk	Positive	Westernized dietary habits
Black tea	Positive	Westernized dietary habits
Fondness for fatty food	Positive	Westernized dietary habits
Taro, sweet potato, potato	Inverse	Traditional Japanese dietary habits
Other		
Education level	Inverse	

Physical activity: Because physical activity induces changes in body fat with changes in insulin and insulin sensitivity [37], physical inactivity and low physical fitness are associated with an

increased risk of several cancers [37]. In Western countries, low physical activity [2,38,39] has been suggested to increase the risk of kidney cancer. In the JACC Study, Washio et al. [7] found that walking reduced the risk of kidney cancer (60 min/day or more vs. 30 min/day or less: HR=0.57 95%CI: 0.32-1.00) in the Japanese population. In addition, Mikami [4] reported that men who drove cars showed an increased risk of kidney cancer (OR=2.9, 95%CI: 1.6 to 5.7). Since those who have cars need not walk a long distance, they may walk a shorter time each day than their counterparts. These findings suggest that low physical activity may increase the risk of kidney cancer in the Japanese population.

Dietary habits

Westernized dietary habits: In Japan, daily milk consumption increased the risk of kidney cancer death (daily consumers vs. non-daily consumers: age- and sex-adjusted HR=2.11, 95%CI: 1.47 to 3.04) in the Hirayama cohort study [14] while Mikami [4] found that regular milk consumption from the age of 15 years increased the risk of kidney cancer among males in his case control study. On the other hand, in the JACC study [5], the high consumption of black tea (3+cups/day vs. none: age- and sex-adjusted HR=13.60, 95% CI: 1.83 to 101.30) increased the risk of kidney cancer death, while the high consumption of coffee (3+cups/day vs. none: age- and sex-adjusted HR=2.69, 95% CI: 0.89 to 8.10) showed a marginally increased risk. However, there has been no convincing evidence linking kidney cancer and the consumption of black tea or coffee despite numerous studies in western countries [2]. Therefore, drinking milk, black tea or coffee may be surrogates for westernized dietary habits in the Japanese population.

Handa et al. [40] reported that both a 'dessert' diet factor and a 'beef' diet factor were associated with an increased risk of renal cell cancer, suggesting that high-fat and high-protein diets as well as sugar- and fat-rich confectionaries might increase the risk of renal cell cancer. In the JACC study [5], a fondness for fatty food (yes vs. no: age- and sex-adjusted HR=2.64, 95%CI: 1.03 to 6.78) was associated with an increased risk of kidney cancer death and a frequent intake of beef showed a non-significantly increased risk of kidney cancer death (1-2 times/day or more vs. seldom: age- and sex-adjusted HR=1.73, 95%CI: 0.74 to 4.08, $p=0.08$) in the Japanese population.

Traditional Japanese dietary habits: In Western countries, Chow et al. [41] reported that an intake of staple foods (i.e., bread, cereals, potatoes, rice, and spaghetti) was associated with an increased risk of kidney cancer. In Japan, however, Washio et al. [6] reported that the consumption of starchy roots (i.e., taro, sweet potato and potato) decreased the risk of kidney cancer death (3-4+/week vs. 1-2/month or less: age- and sex-adjusted HR=0.44, 95% CI: 0.21 to 0.94). Taro [42,43] and sweet potato [44] are reported to have a cancer preventive potential, these traditional diets may partly explain the reasons for the lower incidence of kidney cancer in Japan compared to other developed countries.

Other risk factors

Education level has sometimes been inversely associated with kidney cancer [2]. Mikami [4] showed that a low educational level increased the risk of kidney cancer among Japanese males (high school vs. college, OR=2.2, 95%CI: 1.1 to 4.4, junior high school vs. college, OR=2.5, 95%CI: 1.2 to 5.0) but not among Japanese females (high school vs. college, OR=0.8, 95%CI: 0.2 to 3.9, junior high school vs. college, OR=0.7, 95%CI: 0.2 to 3.2). Further studies are needed to ascertain an inverse association between educational level and the risk of kidney cancer in the Japanese population.

Conclusion

We introduced six studies which evaluated the risk of kidney cancer for the Japanese population. In these studies, obesity, diabetes mellitus, hypertension, kidney diseases, end-stage renal disease with dialysis, tobacco smoke, fondness for fatty food, milk, and black tea are associated with an increased risk of kidney cancer. On the other hand, an inverse association with the kidney cancer risk is found with the intake of starchy roots (i.e., taro, sweet potato and potato), physical activity and an education level. In Japan, however, drinking black tea and milk may be a surrogate for westernized dietary habits while eating starchy roots may be a surrogate for traditional Japanese dietary habits. Additional studies are needed to confirm the risk factors for kidney cancer in the Japanese population.

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