

Lifestyle factors and the risk of kidney and bladder cancer in the Japanese population: A mini-review

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Abstract

The incidences of kidney cancer and bladder cancer are lower in Asian countries than in Western countries. However, the incidences and mortality rates of kidney cancer and bladder cancer have been increasing in Japan. In this paper, we would like to introduce findings from epidemiological studies about tobacco smoking, drinking alcohol and physical activity on the risk of kidney and bladder cancers in the Japanese population. Tobacco smoking is a risk factor both for kidney cancer and bladder cancer in the Japanese population. On the other hand, physical activity is suggested to reduce the risk of kidney cancer in the Japanese population. Regarding alcohol consumption, one study showed an increased risk of bladder cancer, while other studies showed no association between alcohol consumption and the risk of bladder cancer in the Japanese population. Further studies are needed to find an answer.

Introduction

The urinary system consists of the kidneys, ureters and bladder. In adults, renal cell carcinoma, which represents 80 to 90% of kidney cancer, arises from cells from the proximal convoluted renal tubules [1]. On the other hand, renal pelvic cancer, which represents the rest of the kidney cancer, arises from mucosa of the upper urinary tract [1] while bladder cancer arises from mucosa of the lower urinary tract [2]. Both upper urinary tract cancer and bladder cancer are urothelial cancer.

The incidences of kidney cancer [1,3] and bladder cancer [2,3] are lower in Asian countries than in Western countries. However, the incidences and mortality rates of kidney cancer and bladder cancer have been increasing in Japan. The crude and age-adjusted incidences of kidney cancer increased from 1.7/100,000 and 1.6/100,000 in 1975 to 17.9/100,000 and 7.1/100,000 in 2012 [4] while the crude and age-adjusted incidences of bladder cancer increased from 3.3/100,000 and 3.0/100,000 in 1975 to 16.1/100,000 and 4.9/100,000 in 2012 [4]. These findings suggest that lifestyle factors may play an important role in the development of these two cancers.

On the other hand, the crude and age-adjusted mortality of kidney cancer increased from 0.5/100,000 and 0.5/100,000 in 1958 to 7.3/100,000 and 1.9/100,000 in 2015 [5]. In contrast, age adjusted mortality of bladder cancer increased from 1.0/100,000 in 1958 to 1.6/100,000 in 1974 but decreased to 1.4/100,000 in 2015 although the crude mortality of bladder cancer increased from 1.0/100,000 in 1958 to 6.5/100,000 in 2015 [5].

Westernization of the life-style habits (e.g., westernization of eating habits, the spread of privately-owned cars and household electric appliances as well as agricultural mechanization) may increase the risk of kidney cancer and bladder cancer in Japan. Another plausible explanation is that the incidences and mortality rates of these two cancers increased because the proportion of the elderly has been

increasing in Japan. The proportion of elderly (i.e., 65 years or older) increased from 10.5% in 1985 to 26.7% in 2015 [6].

Smoking is a major risk factor for human cancer [3,7] and alcohol consumption has been suggested to increase the risk of human cancer as well [3,7]. However, it is controversial whether alcohol consumption influences the risk of kidney cancer and bladder cancer although smoking is an established risk factor for kidney cancer [1,3,7] and bladder cancer in western countries [2,3,7].

In this paper, we would like to introduce findings from epidemiological studies about life-style factors (e.g., tobacco smoking, alcohol drinking, physical activity) on the risk of kidney or bladder cancer in the Japanese population.

Tobacco

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 [8].

Kidney cancer

In western countries, McLaughlin *et al.* [9] reported that compared with nonsmokers, current smokers showed an increased risk of renal cell cancer (HR=1.47, 95%CI=1.20-1.80) and the risk of renal cell cancer (vs. nonsmoker) increased with the number of cigarettes per day (1-9 vs. 0: HR=1.31, 95%CI=0.93-1.83; 10-20 vs. 0: HR=1.37,

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Table 1. Life style factors and the risk of Kidney cancer and bladder cancer in a Japanese population

Site of cancer	Factor	Association	Study design	Reference
Kidney	Tobacco	No association	Case control study	[11]
		No association	Cohort study	[14]
		Positive	Cohort study	[15]
		Positive	Cross sectional study	[17]
Upper urinary tract	Tobacco	Positive	Cohort study	[22]
		Positive	Meta-analysis	[20]
		Positive	Cohort study	[22]
		Positive	Cohort study	[23]
		Positive	Case control study	[24]
		Positive	Case control study	[21]
Bladder	Tobacco	Positive	Cohort study	[36]
		No association	Case control study	[11]
		No association	Cohort study	[15]
		No association	Case control study	[24]
Bladder	Alcohol	No association	Case control study	[21]
		No association	Cohort study	[22]
		Positive	Case control study	[30]
		Positive	Case control study	[21]
Kidney	Physical activity	Inverse	Cohort study	[15]

95%CI=1.08-1.73; 21-39 vs. 0: HR=1.60, 95%CI=1.23-2.09; 40 or more vs. 0: HR=2.06, 95%CI=1.28-3.33, p for trend<0.001). Hunt *et al.* [10] estimated an overall combined risk of development of renal cell cancer (ever smokers vs. never smokers: RR=1.38, 95%CI=1.27-1.50). Thus, cigarette smoking is an established risk factor for kidney cancer kidney cancer [1,3,7,9,10].

However, in Japan, Mikami [11] failed to demonstrate that smoking is a risk factor of kidney cancer in his case-control study, which may be partly explained by the fact that, in Japan, most men were smokers while most women were non-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) [12]. Another explanation may be some biases in his hospital-based case-control study because patients hospitalized with other diseases at the same hospitals may not have the same exposure distribution (i.e., smoking status) as the general population [13]. In addition, Washio *et al.* [14] reported that current smoking showed no meaningful association with the development of renal cell cancer a large scale population-based cohort study of 110,585 residents in Japan, which took place between 1988 and 1990 (the JACC study). However, only the subjects who lived in study areas where cancer registries were available were used for analysis [14]. In this study [14], only 40 incident cases of kidney cancer were detected among 62,869 participants during the follow-up periods (7.6 ± 1.9 years). The small number of kidney cancer cases may partly explain the failure to detect the effect of smoking on the development of kidney cancer. In this study, we could not evaluate the risk after adjusting for factors other than age and sex. On the other hand, recently, the JACC study demonstrated that smoking may increase the risk of kidney cancer death after the follow-up was completed at the end of 2009 [15], when 38.2% of men and 10.9% of women had smoking habits in Japan [16]. In this study [15], compared with never smokers, current smokers showed an increased (but not significant) risk, and heavy smokers (Brinkman index > 1200) had a significantly increased risk of kidney cancer death. Compared with never smokers, the risk of heavy smokers (HR=2.66, 95%CI: 1.05-6.74, p=0.04) was still significant after adjusting for age, sex, alcohol drinking and a self-reported history of diabetes mellitus. Also, the risk of kidney cancer death tended to increase with the duration of smoking (p for trend=0.071). Furthermore, Nobata *et al.* [17] reported that the proportion of current and former smokers was greater in those with

a history of kidney cancer (37 out of 54, 68.5%) than those without a history of kidney cancer (14,584 out of 39335, 37.1%) among those who received medical check-up in their cross sectional study (p=0.0027).

Bladder cancer

In western countries, Baris *et al.* [18] demonstrated that both current and former smoking showed an increased risk of bladder cancer in their population-based case-control study with 1170 urothelial carcinoma patients and 1413 control subjects (current smokers vs. never-smokers: OR=5.2, 95%CI: 4.0-6.6, former smokers vs. never-smokers: OR=2.3, 95%CI=1.9-2.8). Al-Zalabani *et al.* [19] reported that current cigarette smoking, former cigarette smoking, pipe smoking, and cigar smoking were found to increase the risk of bladder cancer in their systemic review of meta-analyses.

Smoking is a risk factor for bladder cancer in the Japanese population as well (ever smokers vs. never smokers: RR=2.14, 95%CI: 1.87-2.44) [20], (ever smokers vs. never smokers: OR=2.40, 95%CI=1.42-4.04) [21], (current smokers vs. non-smokers: RR=1.98, 95%CI: 1.37-2.84) [22]. Kurahashi *et al.* [23] reported that both current and former smoking showed an increased risk of bladder cancer in both men and women (current smokers vs. never-smokers: RR=1.69, 95%CI: 1.09-2.63 for men, HR=5.45, 95%CI=2.56-11.61 for women) while Wakai *et al.* [24] demonstrated that cumulative consumption of cigarettes(pack-years) was positively associated with the risk of bladder cancer in their case control study with 124 cancer patients and 620 hospital controls(1-19 vs. 0: OR=1.30, 95%CI=0.65-2.59, 20-39 vs. 0: OR=1.58, 95%CI=0.82-3.05, 40-49 vs. 0: OR=2.90, 95%CI=1.55-5.42, 60+ vs. 0: OR=2.42, 95%CI=1.21-4.78, p for trend=0.0009).

Alcohol

Although drinking alcohol has been demonstrated to increase the risk of several sites of cancers (e.g., oral cavity, pharynx, larynx, esophagus, colorectum, liver, breast), ethanol has been suggested to play no role in the development of kidney and bladder cancer [25,26].

Kidney cancer

In western countries, alcohol consumption has been suggested to reduce the risk of kidney cancer in some studies [27-29]. Karami *et al.* [29] demonstrated that increasing alcohol consumption reduced the risk of renal cell cancer in the US population even after adjusting for smoking and other risk factors (9.75 grams/day or more vs. non-drinkers: HR=0.67, 95%CI: 0.50-0.89, p trend=0.002). In their cohort study, 408 renal cell cancer cases were identified among 107,998 men and women during the 1,236, 486.5 person-years follow-ups.

However, Japanese epidemiologists failed to show any meaningful association between alcohol consumption and the risk of kidney cancer in the Japanese population [11,15].

These findings may be partly explained by the following way. Japanese often smoke when they drink alcohol beverages. In these studies [11,15], however, smoking was not controlled when evaluating the risk of kidney cancer. Mikami [11] did not adjusted smoking because smoking showed no meaningful association with the risk of kidney cancer while Washio *et al.* [15] could not do so because of small number of kidney cancer death in spite of a large scale of cohort study (i.e., 88 kidney cancer death among 110,585 participants with 1,025,703 person-year follow-ups).

Bladder cancer

It has not been suggested that alcohol consumption may play some role on the development of bladder cancer in western countries [2,3,7].

In Japan, either Nakata *et al.* [21] or Wakai *et al.* [24] reported no meaningful association between alcohol drinking and the risk of bladder cancer in their case control studies after adjusting for smoking status and other factors. In addition, Washio *et al.* [22] found no association between drinking alcohol and the risk of bladder cancer death after controlling for age, sex, and smoking status in a large scale cohort study, either. In contrast, Zaitzu *et al.* [30] reported that current and former alcohol drinking increased the risk of bladder cancer (ever vs. never: OR=1.33, 95%CI: 1.06-1.66) in their case control study. Japanese adolescents start smoking tobacco after drinking alcohol [31,32], and more than half of them smoke with friends at tea rooms, public houses(saloon), or in friends rooms [31]. In addition, parental smoking is positively associated with adolescents' smoking [32]. Furthermore, Japanese men often smoke at pubs, bars or public houses (saloon) when they drink alcohol beverages. Therefore, Japanese drinkers are often exposed to environmental tobacco smoke regardless of their smoking status. Since the environmental tobacco smoke increases the risk of bladder cancer [33], we cannot deny the possibility that Zaitzu *et al.* [30] could not adjust the effect of environmental tobacco smoke on the risk of bladder cancer although they controlled the effect of active smoking to evaluate the association between alcohol drinking and the risk of bladder cancer. Another possibility is that alcohol consumption enhanced the risk of cancer caused by tobacco smoke because ethanol facilitates uptake of carcinogen from tobacco smoke [26]. Inoue *et al.* [34] reported that the positive association between alcohol consumption and cancer risk was more striking among current smokers in their large scale population-based cohort study in Japan. Last explanation may be some biases in his hospital-based case-control study because patients hospitalized with other diseases at the same hospitals may not have the same exposure distribution (i.e., smoking status) as the general population [13]. Furthermore, they compared never drinkers with ever drinkers. A part of former drinkers may have quit alcohol because of their diseases (e.g. diabetes mellitus, liver diseases).

Since Al-Zalabani *et al.* [19] reported no statistically significant association between alcohol consumption and the risk of bladder cancer in their systemic review of meta-analyses and hospital controls may not have the same exposure distribution (i.e., alcohol consumption) as the general population [13], further studies are needed to confirm the association between alcohol consumption and the risk of bladder cancer in the Japanese population.

Physical activity

Obesity is a convincing/probable risk factor for various cancers (i.e., esophagus, colon and rectum, pancreas, liver, gall bladder, kidney, breast, endometrium, ovary, prostate, Hodgkin and non-Hodgkin lymphoma, leukemia, multiple myeloma) [25] while physical activity is a convincing/probable preventive factors for several cancers (i.e., colon and rectum, breast, endometrium, lung) [25].

Kidney cancer

Physical activity may prevent kidney cancer by improving obesity, insulin resistance and hypertension [35]. Behrens *et al.* [35] reported an inverse relationship between physical activity and the risk of kidney cancer in their systemic review and meta-analysis. In addition, Williams [36] found that the risk of kidney cancer reduced by running or walking even after adjusting for body mass index(BMI), hypertension, diabetes mellitus, and smoking(i.e., pack-years of cigarette use).

Washio *et al.* [15] 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 a large scale cohort study, and reported that walking reduced the risk of kidney cancer (60min/day or more vs. 30min/day or less: HR=0.57 95%CI: 0.32-1.00) in the Japanese population.

Bladder cancer

Physical activity showed a small preventive effect against bladder cancer in a systemic review of meta-analyses by Al-Zalabani *et al.* [19]. On the other hand, Latino-Martel *et al.* [24] reported that either obesity or physical activity showed no meaningful association with the risk of bladder cancer in their review.

Since there is no meaningful association between obesity and the risk of bladder cancer in either a cohort study in a Japanese population (vs. normal: HR=0.92, 95%CI: 0.59-1.44) [21] or a hospital based-case-control study in Japan (OR=1.00, 95%CI: 0.83-1.22) [30], low physical activity seems to play little role in the development of bladder cancer in the Japanese population.

Discussion

Since both renal pelvic cancer and bladder cancer are urothelial cancer and incidence of renal pelvic cancer is very low, Sakauchi *et al.* [37] investigated the risk factors for the development of urothelial cancer in a large scale cohort study (i.e., the JACC study). In this study [37], the risk of urothelial cancer incidence increased according to the cumulative consumption of cigarettes (p for trend=0.002). Compared with never smokers, those with 799 cigarette-year or less showed 2 times increased risk (HR=2.16, 95%CI=1.21-3.86) and those with 800 cigarette-year or more showed 3 times increased risk (HR=2.75, 95%CI=1.49-5.08). As primary localization, 12 renal pelvic cancer cases, 7 ureter cancer cases and 104 bladder cancer cases were detected among 64,539 participants in this study [37]. Although Washio *et al.* [22] investigated risk factors for upper and lower urinary tract cancer using the data-set of the JACC study, the end point was death cases because cancer registries were available only a part of participants. In this study [22], 61 participants died from upper urinary tract cancer while 166 participants died from bladder cancer among 110585 participants. Current smokers showed an increased risk of upper urinary tract cancer death (vs. nonsmokers: HR=2.32, 95%CI=1.22-4.40), which is consistent with findings in the case control study in the United States [38].

On the other hand, current drinkers showed a non-significantly increased risk (vs. nondrinkers: HR=1.86, 95%CI=0.95-3.71). Even after controlling for age, sex and smoking status, current drinkers showed an HR greater than the unity (HR=1.64, 95%CI=0.82-3.28), which may be consistent with the result of the case control study of bladder cancer by Zaitzu *et al.* [30]. On the other hand, there was no association between obesity and the risk of upper urinary tract cancer death. In Japan, not a small number of case control studies of bladder cancer are case control studies of urothelial cancer [20].

Conclusion

Tobacco smoking is a risk factor both for kidney cancer and bladder cancer in the Japanese population. On the other hand, physical activity is suggested to reduce the risk of kidney cancer in the Japanese population. Regarding alcohol consumption, one study showed an increased risk of bladder cancer while other studies showed no association between alcohol consumption and the risk of bladder cancer in the Japanese population. Further studies are needed to find an answer.

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