



# INCIDENCE, MORTALITY AND RISK FACTORS OF KIDNEY CANCER IN THE WORLD

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**Abstract – Background:** *Kidney cancer is the ninth and fourteenth common cancer cases in men and women, respectively. Also, it is the sixteenth cause of death from cancer in the world, and is known as the most deadly cancer of the urinary tract. Given the importance of information about the incidence, mortality and risk factors in prevention programs, the aim of this review was to investigate the incidence, mortality, and risk factors for kidney cancer in the world.*

**Materials and Methods:** *This review study was conducted on published English research by January 2017 with the search in PubMed, Scopus and Web of Science databases. The search strategy included the key words “kidney cancer”, “epidemiology”, “incidence”, “mortality” and “risk factors”. Studies related to incidence, mortality, and causes of kidney cancer risk were studied and included.*

**Results:** *Five countries with the highest incidence of kidney cancer in the world included China, the United States, Russia, Germany and Japan, respectively. The standardized incidence of kidney cancer in the world was 4.4 per 100,000 (6 per 100,000 in men and 3 per 100,000 in women). The five countries with the highest mortality rates were China, the United States, Russia, Japan and Germany, respectively. In 2012, the standardized age-related mortality rate for kidney cancer was 1.8 per 100,000 (2.5 per 100,000 in men and 1.2 per 100,000 in women). The most important risk factors for kidney cancer were smoking, occupational exposure, cystic disease, heredity, obesity and high blood pressure.*

**Conclusions:** *The findings of this study showed that the incidence of kidney cancer varies considerably according to the geographical area. Considering preventable risk factors and the effective time of diagnosis, disease prevention, training programs, good life promotion policies, timely diagnosis and treatment are appropriate for reducing this cancer.*

**KEYWORDS:** *Kidney cancer, Incidence, Mortality, Risk factors, World.*

## BACKGROUND

Cancer is one of the major causes of mortality in the world<sup>1,2</sup>. Cancer is currently the second leading cause of death in the developed world economically, and is the third leading cause of death in developing countries<sup>3,4</sup>. Among the types of cancers, kidney cancer with an annual incidence of 338,000 new cases and 144,000 deaths worldwide is considered the most deadly cancer of the urinary tract<sup>5-7</sup>. It is responsible for about 3% of

malignancies in adults. There are several different types of cancers in the kidney, like other organs. The most common type of cancer is renal cell carcinoma (RCC), which affects more than 30,000 people annually and 40% of them die due to complications from this cancer<sup>8</sup>. Kidney cancer is the ninth and fourteenth common cancer cases in men and women, respectively. On the other hand, it is the sixteenth cause of death from cancer in the world<sup>6,9</sup>. The age standardized incidence rate (ASIR) of the cancer was 4.4, mortality rate of 1.8



and 5-year prevalence of 17.5 in 2013 worldwide<sup>10</sup>. The incidence of the cancer is higher in men than in women and it increases with age<sup>5</sup>. The cancer is one of the ten dangerous diseases that occurs between the ages of 50-70 years and includes nearly 2% of all deaths<sup>11-15</sup>. There is a great difference in the incidence of kidney cancer in the world. A difference of 15 units was observed between regions with the highest and lowest incidence<sup>16</sup>. Most studies in this area focus more on clinical challenges and therapeutic approaches to manage kidney cancer. Given the importance of information about the incidence, mortality, and risk factors in prevention programs, the aim of this review was to investigate the incidence, mortality, and risk factors for kidney cancer in the world.

## MATERIALS AND METHODS

This review study was conducted on published English research by January 2017 with the search in PubMed, Scopus and Web of Science databases. The search strategy included the key words “kidney cancer”, “epidemiology”, “incidence”, “mortality”, “risk factors”, and “world”. Studies related to incidence, mortality, and causes of kidney cancer risk, were studied and included in this review.

## RESULTS

### Incidence

In 2012, there were 337,860 kidney cancers in the world, of which 213,924 were men and 123,936 women. Five countries with the highest incidence of kidney cancer in the world were China, the United States, Russia, Germany and Japan. The standardized incidence rate of kidney cancer in the world was 4.4 per 100,000 people (in men, 6 per 100,000 people and 3 per 100,000 in women)<sup>5</sup>. The incidence of kidney cancer varies considerably according to the geographical area. Five countries with the highest incidence of kidney cancer in men were China with 62.1 per 100 000 people<sup>17</sup>, the United States with 39,650 cases<sup>18</sup>, Germany with 11,353 cases, Russia with 10,921 cases, and Italy with 7,681 cases<sup>5</sup>, respectively. Five countries with the highest incidence of kidney cancer in women were China with 23.6 per 100 000 people<sup>17</sup>, the United States with 23,050 cases<sup>18</sup>, Russia with 8,392 cases, Germany with 7,262 cases, and Japan with 5,689 cases<sup>5</sup>, respectively. Various factors affect the incidence and mortality of this cancer among different ethnic and geographical areas around the world. They are screening, timely diagnosis, environmental and genetic risk factors,

socioeconomic status and reporting of data<sup>19-22</sup>. The standardized incidence rate for kidney cancer is 12.6 and 3.4 per 100,000 per year in men in developed and non-developed regions, respectively. The standardized incidence rate for kidney cancer is 6.2 and 1.8 per 100,000 per year in women in developed and non-developed regions, respectively<sup>23</sup>. The standardized incidence rates of kidney cancer for both genders increased for about 23% (3.82-4.7) between 1990 and 2013. These rates were lower in developed countries than in developed countries, but these indicated relative increases in both regions. In developing countries, it was observed an increase of 34% (1.69-2.27) while in developed countries, it was of 36% (7.15-9.71)<sup>24</sup>.

### Mortality

Overall, there were 143,406 deaths from kidney cancer (90,802 in men and 52,604 in women) in 2012 worldwide<sup>5</sup>. The five countries with the highest number of deaths were China, the United States, Russia, Japan and Germany, respectively. In 2012, the standardized age-related mortality rate for kidney cancer was 1.8 per 100,000 (2.5 in men and 1.2 in women per 100,000)<sup>5</sup>. Five countries with the highest mortality rates in men were China 15.2 per 100,000<sup>17</sup>, the United States 9,240 cases<sup>18</sup>, Russia 5,601 cases, Japan 5,177 cases and Germany 4,713 cases, respectively<sup>5</sup>. Five countries with the highest mortality rates in women were China 8.2 per 100,000<sup>17</sup>, the United States 5,000 cases<sup>18</sup>, Russia 3,424 cases, Japan 2,947 cases and Germany 2,872 cases, respectively(5). The standardized mortality rate for all kidney cancers was 4.2 and 1.7 per 100,000 per year in men, and 1.7 and 0.9 per 100,000 per year in women in developed and non-developed regions, respectively<sup>23</sup>. In developed countries, standardized age-related incidence and death rates have been higher and 52% of deaths from the disease occurred in developed countries<sup>6,10</sup>. Although an increase was observed in the incidence of kidney cancer in developed countries, it was associated with fewer deaths because of the increased frequency and quality of cross-image imaging in diagnosis<sup>25</sup>. This leads to the discovery of smaller masses in the early stages of cancer than advanced stages, which ultimately lead to a reduction or persistence of mortality in these countries<sup>26-28</sup>. In developed and underdeveloped countries, the prevalence of risk factors, such as high blood pressure and diabetes increased, may have an important role in increasing the incidence of this cancer<sup>29</sup>. In the United States, risk factors such as smoking, obesity, high blood pressure, and African-American race, are associated with an increase in the incidence of kidney cancer. However, factors

such as the stage of cancer diagnosis, rural status, urologist numbers and socioeconomic status (SES) are associated with an increase in mortality<sup>30-34</sup>. According to a study conducted in the United States, an increase in the incidence and costs associated with kidney cancer has been revealed for more than 10 years. On the other hand, with increasing age of the population and the prevalence of risk factors such as obesity and high blood pressure, the incidence of this cancer is significantly increased. Due to the advances in disease registration, such as surveillance, epidemiology and the final outcome of disease and treatment, the cost and effectiveness of treatment can be improved<sup>22</sup>. It should be noted that the mortality rate of kidney cancer peaked in the European Union (EU) in the early 1900s (4.8 per 100,000 in men and 2.1 per 100,000 in women)<sup>35</sup>. Thereafter, a declining trend was observed in several countries in Western and Central Europe, including France, Germany, Italy, Austria and the Netherlands. This downward trend can be due to improvements in the diagnosis, treatment and reduction of tobacco use<sup>36</sup>. The lowest rates of incidence and mortality were in Asia and Africa<sup>37,38</sup>. An increased risk of kidney cancer has been observed in many Asian countries, such as Korea, China, Hong Kong, Singapore and Japan<sup>39</sup>. These significant increases in incidence and mortality in Asian countries represent an important role of lifestyle, especially diet, in the progression of kidney cancer. The reason for these different trends is not understood, but it is assumed that different trends are associated with early diagnosis, improved access to health care and sophisticated diagnostic imaging or the availability of treatment<sup>40-42</sup>.

## RISK FACTORS FOR KIDNEY CANCER

Table 1 shows risk factors of kidney cancer.

**TABLE 1.** Factors related to the kidney cancer.

<b>Modifiable and environmental risk factors</b>	<b>Genetic or non-modifiable risk factors</b>
Smoking, Occupational exposure to Chemical carcinogens, Radiation, Viruses, Diuretics, Analgesics Estrogens (diethylstilbestrol), Acquired cystic disease/ chronic dialysis, Obesity, Coffee, alcohol, and other beverages, low Physical activity, Hypertension and Type 2 diabetes	Age, sex, race, and socioeconomic status, Inheritance

## SMOKING

Many studies have mentioned smoking as a proven risk factor for kidney cancer<sup>21,43,44</sup>. Also, in studies conducted by McLaughlin and Lipworth<sup>45</sup> and Lipworth et al<sup>46</sup>, smoking is known as a major risk factor for 20% of kidney cancer. Smoking is not only an important factor in the development of kidney cancer, but also in the development of prognostic monogram<sup>47</sup>. In addition to carcinogenic compounds, it may increase the risk of kidney cancer through hypoxia and chronic lipid peroxidation<sup>21</sup>. About 24-32% of kidney cancer cells in men and about 9-16% of these cells in women result from smoking. The risk of kidney cancer increases with the number of cigarettes a day, so the risk of cancer in people who consume 20 cigarettes a day would increase by 60-100% than non-smokers<sup>48</sup>. A number of studies have shown the possible relationship between passive smoking, exposure to cigarette smoke among non-smokers, and kidney cancer<sup>49,50</sup>.

## OCCUPATIONAL EXPOSURE TO CHEMICAL CARCINOGENS

Some radiological transformers are associated with an increased incidence of kidney cancer<sup>(51)</sup>. Although Cycasin (a date-derived fruit that grows on Guam Island) causes kidney cancer in animals, the increase in the incidence of kidney cancer was not observed in people from this island. The effect of cadmium on the progression of the disease has also been proven in smokers<sup>52,53</sup>.

### *Asbestos (Occupational exposure to Chemical carcinogens)*

A significant increase in kidney cancer deaths has been reported in two cohort studies. These studies have been carried out on those who manufacture asbestos and work with asbestos<sup>54,55</sup>. Autopsy and studies on animals revealed the storage of asbestos fibers in the kidney tissue<sup>44</sup>.

### *Organic solvents (Occupational exposure to Chemical carcinogens)*

Pesticides, copper sulphate, benzidine, benzene herbicides and vinyl chloride are known to be risk factors for long-term kidney cancer. The dose-dependent effect was observed only for pesticides and copper sulphate<sup>56,57</sup>. Cohort studies demonstrated poor evidence of an increased risk of kidney cancer among people exposed to gasoline and oil-derived products<sup>58,59</sup>.



## **Polycyclic aromatic hydrocarbons (Occupational exposure to Chemical carcinogens)**

An increased risk for kidney cancer in workers exposed to high levels of polycyclic hydrocarbons in workers who work in furnace coal, fire and bitumen have been reported<sup>44</sup>.

## **RADIATION**

It seems that irradiated radiation increases the risk of kidney cancer, especially in patients treated with ankylosing spondylitis, and cervical cancer<sup>60</sup>. There is also an increased risk of kidney cancer in patients receiving radium 224 for the treatment of bone tuberculosis and ankylosing spondylitis<sup>61</sup>.

## **VIRUSES**

The immune-inducing status of HIV infection can increase the prevalence of kidney cancer in the infected population about 8.5 times higher than who do not have this infection. The effect of polyomavirus SV40 and adenovirus 7 has been investigated in empirical studies. There is a clear relationship between the types of herpes virus and kidney tumors in toad. These findings have led to a better search for evidence of the herpes virus protein in human tumors<sup>44</sup>. The herpes simplex protein was found only in one study. These findings should be confirmed through further research<sup>62,63</sup>.

## **DIURETICS**

These types of drugs help to absorb water in the tubular kidney cells. It seems to be responsible for the high prevalence of kidney cancer in patients with long-term diuretics<sup>64,65</sup>. Hydrochlorothiazide and furosemide (both effective at the level of tubular kidney cells) cause tubular cell adenomas and adenocarcinomas of the kidneys in rats<sup>66</sup>. Yuan et al<sup>67</sup> showed that a proper use of diuretics to treat high blood pressure eliminates the risk associated with these drugs. He also found the effect of high blood pressure as a risk factor for kidney cancer compared to diuretics.

## **ANALGESICS**

Several studies have reported increased incidence of kidney cancer in long-term consumer patients with analgesics such as paracetamol, salicylates, or

phenacetin<sup>68,69</sup>. In other studies, association with kidney cancer has not been approved for either the duration of use or the dose of these drugs<sup>70</sup>. Although the high use of phenacetin-containing drugs increases the risk of renal pelvic cancer, its association with kidney cancer is much weaker. On the other hand, there is an increased risk of kidney cancer in aspirin or acetaminophen users<sup>71</sup>. Others argue that neither acetaminophen nor any of the analgesics are definitively related to kidney cancer<sup>46</sup>.

## **ESTROGENS (DIETHYLSTILBESTROL)**

Estrogens can cause kidney cancer in the animal model. There is little evidence that estrogen is associated with kidney cancer in humans<sup>72</sup> and only a weak relationship has been reported with postmenopausal estrogen and oral contraceptive pills<sup>73</sup>.

## **INHERITANCE**

The genetic background of kidney cancer has been shown to be related to a family history<sup>74-76</sup>. Having a sister and a brother with kidney cancer increases the risk for kidney cancer from 4 to 7 times<sup>48</sup>. Most cases of kidney cancer are sporadic; however, there are some types of kidney cancer defined by a hereditary pattern<sup>77,66</sup>. Von Hippel-Lindau VHL is inherited through the dominant autosomal feature. This syndrome is caused by germinal mutations of the VHL tumor suppressor located on the chromosome 3p25-26; these mutations can virtually always be detected<sup>78,79</sup>. 40-60% of patients with VHL have kidney cancer. Although they usually have low tumor levels, their progress in metastasis is about 30%<sup>80</sup>.

## **ACQUIRED CYSTIC DISEASE/ CHRONIC DIALYSIS**

Approximately 35-47% of dialysis patients, especially those who have long dialysis, are cystic. Papillary hyperplasia in the epithelium of the cysts grows in some patients<sup>81,82</sup>. The risk of kidney cancer increases by 7 times in those who receive dialysis for 10 years of dialysis<sup>48</sup>. About 5-9 % of patients suffering from cystic have kidney cancer<sup>48,83</sup>.

## **DIET AND OBESITY**

High-calorie diet and obesity are associated with an increased risk for kidney cancer. Obesity has been reported in 30% cases of kidney cancers<sup>79,84</sup>.

In some studies, high prevalence of kidney cancer is associated with a high body mass index (BMI). The relative risk is 3.3% for men and 2.3% for women<sup>85,86</sup>. The risk of kidney cancer increases by 7% with an increase in the BMI<sup>48</sup>. The weak evidence suggested abdominal obesity, independent of BMI or body weight, as a risk factor for kidney cancer. Limited information indicates the increased risk of kidney cancer with weight gain or weight fluctuations<sup>87-89</sup>. Low levels of vitamin D, which are commonly seen in obese people, may be prone to kidney cancer. This vitamin is known to act as an inhibitor of kidney cancer cells<sup>90,91</sup>.

Geographic variations in the incidence and mortality of this cancer confirmed a role of environmental and dietary factors in the cause of kidney cancer. Western lifestyle habits are suggested as a potential risk factor for kidney cancer. In a meta-analysis of case-control studies, consumption of red meat or processed meat was associated with an increased risk of kidney cancer<sup>46,92</sup>. According to Lipworth's report<sup>46</sup> and several other studies<sup>93</sup>, the consumption of fruits and vegetables are protective factors.

### **COFFEE, ALCOHOL, AND OTHER BEVERAGES**

Case-control studies have not confirmed the relationship between kidney cancer and coffee consumption with adjusting cigarette smoking. Another study showed a positive relationship between the doubling of the increased risk of kidney cancer in both sexes with decaffeinated coffee consumption<sup>95-99</sup>. In another study, the risk of kidney cancer has been rising steadily among women who use regular coffee. The relationship between alcohol and mortality of kidney cancer has not been clearly shown in studies<sup>94</sup>. Recent studies have reported a significant reciprocal relationship between alcohol consumption and the risk of kidney cancer. Of course, not for those who are over-drinking<sup>95-99</sup>.

### **PHYSICAL ACTIVITY**

A moderate recreational activity reduces the risk of kidney cancer in men and women. Its mechanism is not clear. There is no doubt that it is related to obesity (a major risk factor for kidney cancer)<sup>44</sup>.

### **HYPERTENSION**

In several prospective large cohort studies, high blood pressure or its treatment has been reported as a risk factor for kidney cancer<sup>89,100-103</sup>. However, the

use of antihypertensive drugs, including diuretics, is not likely to be a risk factor for kidney cancer<sup>100,102-104</sup>.

### **TYPE 2 DIABETES**

The role of type 2 diabetes as a risk factor for kidney cancer is controversial<sup>105,106</sup>. Diabetes may increase the risk of kidney cancer in men and women<sup>107</sup>. Diabetes mellitus, after controlling obesity and the risk of high blood pressure, may not be a cause of kidney cancer<sup>99</sup>.

### **ALTERATIONS IN DEVELOPMENT OF THE KIDNEY**

In horseshoe kidneys, there is an empty area, which is susceptible to tumor progression due to the indirect migration of cells to this area<sup>108</sup>. The most common tumor progression in this abnormality is kidney cancer. However, the incidence of these changes remains the same as the general population without any difference in evolution or prognosis<sup>109</sup>.

### **AGE, SEX, RACE, AND SOCIOECONOMIC STATUS**

Age, sex and race are important factors in the progression of kidney cancer. The incidence of kidney cancer is related to age. The highest prevalence is in the sixth and seventh decades. About 80% of kidney cancer patients are between 40 and 69 years of age<sup>110</sup>. Age is one of the most important risk factors for this cancer. According to the Globocan 2015, kidney cancer increased between 1990 and 2013. ASIR in both sexes increased by 23% (3.82 to 4.7), with an increase of 34% in developing countries (1.96 to 2.27) and 36% in developed countries<sup>24</sup>.

The incidence of this cancer is higher in men than in women and it increases with ageing<sup>111</sup>. The incidence of all kidney cancers in the United States is increasing; it is higher in blacks compared to whites, while the survival rate is lower at all stages of diagnosis both in blacks and whites<sup>22</sup>. The incidence of kidney cancer in countries with higher economic incomes is higher than in countries with lower economic status. This may be due to the increased incidence of tumor detection, higher prevalence of obesity and high blood pressure in high-income countries, such as the United States, compared to lower-income countries, including Brazil and China, as well as urban areas than rural areas<sup>112,113</sup>.



## CONCLUSIONS

The purpose of this review was to determine the incidence and mortality rate of kidney cancer in the world and the relationship between environmental risk factors and the incidence of kidney cancer. The findings of the study showed that the standardized incidence of kidney cancer in the world was 4.4 per 100,000 and the standardized mortality rate for kidney cancer was 1.8 per 100,000. There is a great difference in the incidence of kidney cancer in the world; a 15-fold difference was observed between the regions with the highest and lowest incidence. The most important risk factors for kidney cancer were smoking, occupational exposure, cystic disease and inheritance. The consumption of fruits and vegetables is known to be the protective agent of this cancer. In particular, diet, obesity and dietary habits related to Western lifestyles have been suggested as potential risk factors for kidney cancer. Diuretics, analgesics, type 2 diabetes, no physical activity, blood pressure and viruses need to be further investigated, to understand their mechanisms in causing kidney cancer.

Most studies in this area focus more on clinical challenges and therapeutic approaches to managing kidney cancer. Considering preventable risk factors and the effective time of diagnosis, disease prevention, training programs, good life promotion policies, timely diagnosis and treatment, is appropriate for reducing this cancer.

## CONFLICT OF INTERESTS:

The Authors declare they have no conflict of interest.

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