

The Epidemiology and Risk Factors for Renal Cancer

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Key Words

Epidemiology • Renal cancer • Risk factors

Abstract

Background: Renal cancer is a frequently occurring malignancy with over 270,000 new cases diagnosed and it being responsible for 110,000 deaths annually on a global basis. Incidence rates have gradually increased whilst mortality rates are starting to plateau. **Objective:** To review epidemiology and risk factors for renal cancer. **Methods:** The current data is based on a thorough review of available original and review articles on epidemiology and risk factors for renal cancer with a systemic literature search utilising Medline. **Results:** The prevalence of associated risk factors such as genetic susceptibility, smoking, hypertension and obesity are changing and could account for the changes in incidence whilst the role of diet and occupational exposure to carcinogens requires further investigation. **Conclusion:** Despite the evidence of various associated risk factors, further work is required from well designed studies to gain a greater understanding of the etiology of renal cancer.

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Incidence and Survival Rates in Renal Cancer

Worldwide, renal cancer is the 13th most common malignancy with over 270,000 new cases diagnosed in

2008 [1]. In the UK alone, approximately 9,000 new cases of renal cancer are diagnosed each year [2]. Incidence rates have increased in the UK with age standardised incidence rates more than doubling between 1975 and 1977 and from 2007 to 2009 [2]. Age standardised ratios for both incidence and mortality is observed to be 50% lower in women compared to men [2]. Renal cell carcinoma (RCC) accounts for nearly 90% of all renal malignancies. There has been much debate that the increased incidence rate is due to the vast improvement in imaging modalities such as magnetic resonance imaging and computed tomography as well as the increased use of this imaging. It has been reported that there has been an increased rate of detection of incidental tumors which are asymptomatic and localised [3–6] but there has also been an increase detection of more advanced tumors and that the increase in incidence is real and cannot be solely accounted by incidentally detected tumors [3, 7].

Globally, renal cancer was responsible for over 110,000 deaths in 2008 [1]. Nearly 4,000 patients died from renal cancer in 2008 accounting for 2% of all cancer deaths in the UK [2]. And 20–30% patients present with metastatic disease [8] with another 20% of patients undergoing nephrectomy developing metastases during subsequent follow-up [9]. This can account for the increasing mortality rates. Various factors are involved in survival after diagnosis such as tumor involvement as well as overall health but there is only a 50% chance of survival at 5 years following diagnosis [2].

Risk Factors

Approximately 75% of those diagnosed are over 60 years of age with the disease being rare in those under 50 [2] and reaching a plateau around 70–75 years of age [10]. Incidence rates have increased in all age groups but this increase is predominantly in those over 75 years of age [2]. In addition mortality rates have predominantly increased in those over 75 [2], confirming that renal cancer is predominantly a disease of the elderly.

Age standardised incidences suggest that men are at an increased risk of RCC [1] with it being the 6th most common cancer in men and the 9th most common in women in the UK [2]. The increase in overall incidence is replicated in the increase in incidences in both sexes with there being an obvious higher occurrence in males accounting for the overall increase suggesting that there is a higher predisposition of renal cancer in males than females. It has been reported that between 2007 and 2030 there will be a 27 and 18% increase in the incidence of renal cancer in males and females, respectively [11]. In 2009 the age standardised incidence risk per 100,000 was 15.5 in men compared to 8.2 in women in the UK [2].

Mortality rates are also higher in males than in females as maybe expected given the obvious difference in incidence rates in both sexes. In 2008 the age standardised mortality rate per 100,000 was 6 in men compared to 3.1 in women in the UK [2]. It has long been thought that incidence and mortality rates have been higher in males due to lifestyle factors such as cigarette smoking which has been historically higher in males and also exposure to industrial carcinogens due to differing occupational bias between the sexes.

Smoking is a well established risk factor for RCC with a meta-analysis reporting not only a difference in a smoker and a non-smoker but also a dose-dependant risk with the number of cigarettes smoked [12]. Compared to those whom never smoked, there was a 50% increase in the risk for males and a 20% increase risk for females [12]. This risk can be reduced after smoking cessation for more than 10 years [10, 12, 13]. It is thought that cigarette smoking increases the risk of RCC through chronic tissue hypoxia due carbon monoxide exposure [14] as well as evidence suggesting higher level of DNA damage in peripheral blood lymphocytes in those with RCC compared to controls [15].

It has been suggested that the different incidence rates observed between males and females maybe due to exposure to potential occupational carcinogens. The most extensively studied is the solvent trichloroethylene which

is widely used as a metal degreaser and has been considered a human carcinogen by the International Agency for Research on Cancer as well as a common environmental contaminant [16]. A case controlled series in Europe reported an increased risk following exposure to trichloroethylene [17] with one review reporting increased risk of various malignancies including renal following exposure [18] and a meta-analysis suggesting a weak association with exposure to trichloroethylene [19] whilst others have reported that given the complexities of trichloroethylene pharmacokinetics and limitation of studies this prevents a definitive relationship [16, 18, 20]. Various other compounds have been investigated with one study reporting an association with lead which requires further investigation whilst associations have been reported for glass and wool fibres as well as brick dust [21, 22]. Exposure to industrial agents such as cadmium and uranium has shown no relationship to RCC risk [10, 23, 24] and neither have arsenic, nitrate and radon in drinking water [10]. Interestingly an association between agricultural workers and RCC was reported [25] and an inverse relationship between exposure of ultraviolet light in men and RCC risk was observed [22].

Excess body weight has been established as a risk factor for RCC with it accounting for 30% of cases in Europe [26]. Various prospective studies conducted worldwide have reported that overweight and obese individuals were found to have an elevated subsequent risk of RCC [27–30] with a meta-analysis of this work also suggesting that an association between body mass index and risk of RCC exists [31]. Some have suggested that body fat distribution is associated with an increased risk of RCC [28, 30] but evidence is limited suggesting that abdominal obesity is independent of body mass index with the association with RCC. Two factors closely related to each other and obesity is diet and physical activity. The majority of studies have demonstrated an inverse relationship between physical activity and RCC risk [32–40] with some authors reporting a dose response with further reduction of risk with increasing levels of activity [35, 37, 38]. Assessing dietary intake has reported mixed results with association with RCC. The role of vitamins that are abundant in fruit and vegetables has produced variable results with the risk of RCC with some reporting an association with RCC [41] whilst others have reported no correlation [42–44] whilst analysis of cohort studies has reported that diets rich in fruits and vegetables are inversely related to RCC [45]. High consumption of fat and protein has not been shown to be associated with an increased risk of RCC [46–48]. The consumption of

alcohol has also been demonstrated to have a negative relationship with risk of RCC in a dose response manner [49] whilst in contrast no correlation was demonstrated with total fluid intake from any fluids or from individual types of fluids [50, 51] suggesting that it is not duration of contact with any potential carcinogens which prevents RCC risk with alcohol consumption.

Of all RCC 2–3% are familial [52, 53] with a 2-fold increase in a first degree relative [54]. Of the various subtypes of RCC, each has a corresponding hereditary component caused by a distinct genetic alteration [55]. The most common familial syndrome for RCC is von Hippel-Lindau (VHL) syndrome which can also cause patients to develop pheochromocytomas, retinal angiomas and hemangioblastomas of the central nervous system with only 40% suffering from RCC with VHL. The VHL gene is responsible for the degradation of hypoxia inducible factors without which leads to up-regulation of factors which promote angiogenesis and tumour growth such as vascular endothelial growth factor. In those with VHL syndrome, RCC is the most common cause of death.

Various medical conditions have been demonstrated to have an association with an increased risk of RCC. Types of renal tumors have been shown to cause hypertension [56]. Interestingly however, several studies have reported an association with long-term hypertension and risk of RCC [32, 33, 40, 57] as well as some reporting a dose response relationship [32] with the risk of RCC increasing with further elevation of blood pressure and decreasing with a reduction in blood pressure [57]. There have been reports that usage of anti-hypertensive treatment is also associated with an elevated risk of RCC but it is thought that it is hypertension causing this increased risk and not the actual treatment [32, 35, 36, 39, 58]. Obesity as a risk factor has already been mentioned but it has been reported that despite the relationship between obesity and hypertension, both are independent with their association with RCC and risk is higher in amongst those suffering from both conditions than those with only one [32, 36, 39, 57].

Diabetes mellitus is known to be associated with an increased risk of several cancers. Its relationship in RCC has not been demonstrated to be an independent factor but was closely associated with obesity and hypertension [35, 36, 40, 58–63].

It has been demonstrated that acquired renal cystic disease develops in those with end stage renal disease and in those on hemodialysis [64]. The incidence of RCC is higher in those with cystic disease [65, 66] but the evidence suggesting that these cysts undergo malignant

change is not conclusive [66, 67]. Those who are undergoing hemodialysis are at a higher risk of RCC [67–69] as well as there being an increased risk of RCC after renal transplantation [69–71].

There has some been controversy surrounding an association between urinary tract infections and RCC, one study suggests that a history of a urinary tract infection increases the risk of RCC and this risk is further exacerbated with a history of smoking [72] whilst another report has demonstrated that no relationship between these parameters is present [73].

Conclusion

The incidence and mortality rates of renal cancer are starting to stabilise. Despite increasing usage of imaging, many tumors present at advanced stages. The rise in hypertension and obesity which are well established factors for RCC are likely to have contributed to the upward trend in recent years. The impact of smoking on RCC will decrease in Western countries but may grow in developing countries. Despite the evidence of various genetic, iatrogenic and lifestyle risk factors associated with RCC further work is required from well designed epidemiological studies incorporating these various factors to gain further understanding of the etiology of renal cancer.

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