Renal cell cancer:
The role of physical activity and body size

by
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To the men and women who took part in these studies
Summary

The aim of this thesis was to explore how physical activity, obesity, weight change, and birth weight influence the risk of renal cell cancer.

The relation between occupational physical activity and risk of renal cell cancer was studied in a cohort of Swedish men and women identified in the nationwide censuses in 1960 and 1970, and followed for the occurrence of cancer by linkages to the Swedish Cancer Registry 1971-1989 (Paper I). We identified 2,704 male and 587 female cases with the same level of occupational physical activity in 1960 and 1970 (n=674,025 men and 253,336 women). In multivariate models, men with long-term sedentary jobs had a 25% increased risk compared to men with physically demanding occupations. In contrast, we found no clear evidence of an association between occupational physical activity and renal cell cancer risk among women.

The association between occupational and leisure time physical activity and renal cell cancer risk was further studied in a prospective cohort of 17,241 Swedish twins (Paper II). Exposure information was obtained through a mailed questionnaire. During follow-up from 1967 through 1997 we identified 102 renal cell cancer cases. We found no evidence of a significant association between either occupational or leisure time physical activity and risk of renal cell cancer in this cohort.

To evaluate the existing evidence that obesity increases the risk of renal cell cancer among both men and women, we conducted a quantitative summary analysis of published studies (Paper III). Fourteen studies on each sex assessed obesity as body mass index (BMI, kg/m²), or equivalent, and were included in our analysis. In contrast to previous qualitative reviews, our quantitative summary showed that increased BMI is equally strongly associated with renal cell cancer risk among both men and women. The risk increased by 7% per one unit of increase in BMI (1 kg/m², corresponding to about 3 kg body weight increase for a subject of average height).

The relation between body size and renal cell cancer was evaluated in more detail in a population-based case-control study with 877 patients with newly diagnosed renal cell cancer and 1,508 control subjects, frequency-matched by age (Paper IV). Exposure information was obtained through a mailed questionnaire. General and abdominal obesity (measured as BMI and waist-to-hip ratio, respectively) were independently associated with increased risk of renal cell cancer among both men and women. Furthermore, tall height was associated with an increased risk among both sexes. Weight gain and repeated weight changes in adult life were associated with an increased risk, especially among those with a high BMI already at age 20.

The relation between birth weight, a marker of fetal nutrition and growth, and renal cell cancer was evaluated in the case-control study described above (Paper V). A total of 648 cases and 900 control subjects reported their birth weight and were included in the analyses. An increased risk of renal cell cancer was suggested among men with a high (≥3500 g) birth weight, compared to men with a birth weight between 3000 and 3499 g. We found no clear association among men with a low (<3000 g) birth weight, or among women. Our study shows that conditions in utero, reflected by birth weight, might affect the risk of renal cell cancer in adulthood.
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1. List of original papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:


The contents of published and accepted material were reprinted with kind permission from John Wiley & Sons, Inc. (Papers I-II) and Kidney International (Volume 59, 3/01/2001, Blackwell Science Inc., Paper V).
2. Abbreviations

BMI  Body mass index, kg/m$^2$
CI   Confidence interval
RR   Relative risk
OR   Odds ratio
SIR  Standard incidence ratio
g    Grams
kg   Kilograms
m    Metres
cm   Centimetres
3. Introduction

Malignant tumours of the kidney account for about 2% of all new cancer cases world-wide, with 150,000 men and women affected in 1990. Renal cell cancer – the most common malignancy in the kidney – accounts for 80-90% of these cancers. There is a 10-fold variation in the incidence of renal cell cancer over the world, which implies that environmental factors might be important for the development of this disease. Although research on the aetiology of renal cell cancer has expanded substantially during the last few years, only a limited number of risk factors have been consistently observed. Furthermore, the understanding of how these factors may contribute to the development of renal cell cancer is still scarce.

The aim of this thesis was to explore how physical activity, obesity, weight change, and birth weight influence the risk of renal cell cancer.

4. Background

4.1 Terminology

The kidney is a complex organ composed of many different types of cells. The tumours, which arise from this complex organ, are themselves also diverse. In adults, cancer of the kidney encompasses two major histopathologic entities, namely renal cell (parenchymal) cancer and renal pelvis cancer. The latter arises in the transitional cell epithelium – in the same way as cancers of the ureter and urinary bladder. The epidemiology of renal pelvis cancer resembles that of bladder cancer more than renal cell cancer (McCredie, 1994). The majority of the renal cell tumours arise from renal epithelial cells of the proximal tubules. Renal cell cancer, however, compromise a heterogenous class of tumours arising form different cell types within the nephron. Recent advances in our understanding of the genetics underlying the pathogenesis of renal cell neoplasms have led to a histopathological classification of five subgroups: conventional (clear cell) renal cell carcinoma, also called “non-papillary” (75-80%), papillary (10-15%), chromophobe, collecting-duct and unclassified renal cell carcinoma (Kovacs et al., 1997). The description of etiologic factors in this thesis will be confined to renal cell cancer without having the possibility to distinguish between these sub-types.

In Sweden, 79% of the kidney cancers in 1998 were renal cell cancers, while 11% were renal pelvis cancers, and 10% were cancer at unspecified sub-sites (National Board of Health and Welfare, 2000). In the literature, especially in descriptive studies, renal cell and renal pelvis cancer are sometimes considered together, and the term kidney cancer has mostly been used.

Wilm’s tumour or nephroblastoma, a malignant tumour of embryonal origin, occurs primarily among children and is not reviewed in this thesis.
4.2 Incidence, mortality and survival

Kidney cancer accounts for about 2% of all new cancer cases worldwide, and it has been estimated that kidney cancer affected 150,000 individuals worldwide in 1990, making kidney cancer the fifteenth most common cancer in the world. The estimated numbers of new kidney cancers in North America was about 30,000 and in the European Union 35,000 (Ferlay et al., 1998). In Sweden, 1,029 kidney cancer cases occurred in 1998, of these, 808 were renal cell cancer (National Board of Health and Welfare, 2000).

Renal cell cancer is characterised by a lack of early warning signs, which results in a high proportion of patients with metastasis at the time of diagnosis (Motzer et al., 1997) and that some cases are not detected before death. Therefore, the true incidence of renal cell cancer is likely to be higher than the recorded (Hellsten et al., 1981).

The incidence of kidney cancer varies more than 10-fold over the world. The highest rates are found in North America and Western, Northern and Eastern Europe, whereas incidence rates are intermediate in Southern Europe and Japan, and low in Africa, Asia and the Pacific (Ferlay et al., 1998). Kidney cancer is more common in more developed than in less developed regions. Part of the geographic variations in incidence could be due to differences in diagnostic intensity, tumour classification, autopsy rates, and completeness of the cancer registers between different countries, but the geographical variation indicates that environmental factors may be important in renal cell carcinogenesis.

The incidence rate of renal cell cancer is higher in men than in women in most countries (McCredie, 1994). In Sweden, 453 (56%) men and 355 (44%) was affected in 1998 (National Board of Health and Welfare, 2000). The peak incidence is found between the sixth and seventh decades of life. Male to female ratios are generally between 1.5:1 and 2.5:1, being higher than 2:1 in France, Italy, Spain, Japan (Ferlay et al., 1998).

4.2.1 Time trends

An increasing trend in incidence has been observed in men and women from most areas in the world (Liu et al., 1997; Black et al., 1997; Chow et al., 1999). In the US, renal cell cancer incidence rates increased steadily between 1975 and 1995, and there was a greater annual increase among the black than among the white population (Chow et al., 1999). Analysis of time trends has suggested a continued rise in the incidence of renal cell cancer in the US (Katz et al., 1994). In Sweden, the incidence of renal cell cancer increased between 1960 and 1979 (National Board of Health and Welfare, 1982), but decreasing incidence rates has been observed the last 20 years (between 1979 and 1998) with 2.5% for men and 1.9% for women, this in contrast to many other areas of the world (National Board of Health and Welfare, 2000).

The overall increase in incidence may in part be explained by increased diagnostic intensity following introduction of new imaging methods such as ultrasound and computed tomography. A recent report from the United States showed that the rising incidence of renal cell cancer could partly, although not fully, be explained by an increased incidence of localised tumours (Chow et al., 1999). The trend of increased detection of renal cell cancer might be counteracted by decreased autopsy rates. Decreasing autopsy rates may partly explain the levelling off in incidence recognised in Sweden and some other countries (Vess and Alafuzoff, 1994).
4.2.2 Mortality

Trends in mortality from kidney cancer have accurately paralleled with trends in incidence, with rises in almost all countries (McCredie, 1994). The estimated worldwide mortality for 1990 was about 78,000 deaths due to kidney cancer, thereby accounting for 1.5% of all cancer deaths (Ferlay et al., 1998). As incidence, mortality from kidney cancer is 3 to 4 times more frequent in developed countries than in developing countries (Ferlay et al., 1998). In Sweden, 639 men and women died from renal cell cancer in 1997 (National Board of Health and Welfare, 2000).

4.2.3 Survival

Few population-based reports of survival rates and trends in survival are available for kidney cancer. In the United States, the 5-year relative survival rates for kidney cancer increased from 40% in the early 1960s to 50% during the period 1983-1988 (Boring et al., 1993). A recent report from the United States showed that the 5-year relative survival for renal cell cancer increased from about 50% to 60% in the white population, while there was only a small or no increase for the black population (Chow et al., 1999). In 17 European countries, the overall relative 5-year survival improved from 44% in 1978-1980 to 50% in 1987-1989, but large variations were observed between the countries (Damhuis and Kirkles, 1998).

Stage of the disease is the most important prognostic factor for patients with renal cell cancer (Van Popper et al., 2000). Since there has been no major improvement in treatment for the last decades, the observed increasing survival could in part be the result of increased incidental detection of asymptomatic, mostly small renal cell cancer with a more favourable prognosis (Chow et al., 1999).

4.3 Risk factors

Research on the aetiology of renal cell cancer has been expanded substantially during the last few years. Almost all information on risk factors for this disease has derived from case-control studies. These studies have been conducted in a number of countries, and have ranged in size from 64 cases and 197 controls (Kolonel et al., 1976) to 1,732 cases and 2,309 controls (McLaughlin et al., 1995a). The latter study, the largest and most comprehensive to date, was a multicentre investigation that took place in five countries (United States, Australia, Germany, Denmark, and Sweden) using a common protocol, questionnaire, and field procedures. Results from this international study will be presented throughout the review of risk factors for renal cell cancer.

4.3.1 Body size

Although obesity has been shown to increase the risk of renal cell cancer among women, the evidence for men has been considered weaker (Wolk et al., 1996a; McLaughlin and Lipworth, 2000). In the international multicentre study, high body mass index (BMI, kg/m^2) was found to be a risk factor among women and, to a lesser extent, among men (Mellemgaard et al., 1995). Furthermore, abdominal obesity, measured as waist-to-hip ratio, has been related to renal cell cancer risk among women (Prineas et al., 1997), while this association never has been investigated among men.
Tall height has been related to renal cell cancer in some (Lindblad et al., 1994; Mellemgaard et al., 1994; Tulinius et al., 1997) but not all (Chow et al., 1996; Chow et al., 2000) studies, and no association was observed in the international multicentre study (Mellemgaard et al., 1995).

### 4.3.2 Weight change

Weight change in adult life has been investigated in some studies. Adult weight gain was independently associated with renal cell cancer risk in two prospective studies, one among women (Prineas et al., 1997) and one among men (Chow et al., 2000), while a case-control study found an association among women, but not among men (McLaughlin et al., 1984). Weight loss in adult life was independently associated with increased risk of renal cell cancer in a prospective study among men, although with borderline statistical significance (Chow et al., 2000). A possible association with rate of weight change (estimated as weight change per annum in kilograms) was observed in the international study (Mellemgaard et al., 1995). In a separate analysis of data from one of the participating centres, weight fluctuation was associated with an increased risk of renal cell cancer (Lindblad et al., 1994), although it was not confirmed when all five participating centres were analysed together (Mellemgaard et al., 1995).

Pharmacologic treatment of obesity or use of “diet pills” containing amphetamine has been reported in seven studies (Yu et al., 1986; McCredie and Stewart, 1992; Lindblad et al., 1994; Mellemgaard et al., 1994; Mellemgaard et al., 1995; Chow et al., 1996; Yuan et al., 1998). Although regular use of amphetamines has been uncommon, all studies have suggested an association with renal cell cancer risk. In the international study, an almost 4-fold increased risk was shown among men, while a non-significant 80% increase was shown among women (Mellemgaard et al., 1995).

### 4.3.3 Physical activity

The association between physical activity and renal cell cancer is unclear. Although no clear relation was observed in the international multicentre study (Mellemgaard et al., 1995), when the Swedish centre was analysed separately, a decreased risk was observed among men with high occupational physical activity (Lindblad et al., 1994). However, separate analysis of the Danish centre revealed no association (Mellemgaard et al., 1994). Furthermore, no clear relation has been observed with leisure time physical activity (Goodman et al., 1986; Paffenbarger et al., 1987; Lindblad et al., 1994; Mellemgaard et al., 1994a; Mellemgaard et al., 1995; Prineas et al., 1997).

### 4.3.4 Tobacco

Cigarette smoking is the most established risk factor for renal cell cancer. Case-control studies show consistent evidence of an association between renal cell cancer and smoking. This is supported by cohort studies (McLaughlin et al., 1990; Coughlin et al., 1997; Heath et al., 1997).

The relation between tobacco smoking and renal cell cancer risk has especially been shown among men, but also among women. The relative risk observed was from 1.2-2.3 for ever smokers to 1.9-2.5 for heavy smokers (McLaughlin and Lipworth, 2000). In the international
multicentre study, current smokers had a 40% increased risk compared to never smokers, and the risk increased with intensity (number of cigarettes) and duration (years smoked). No association was observed between risk and use of cigars, pipes, or smokeless tobacco (McLaughlin et al., 1995a).

4.3.5 Medical conditions and medications

A number of medical conditions have been associated with renal cell cancer, although the evidence is consistent for only a few of them.

Early studies suggested that diuretic use was associated with increased risk of renal cell cancer (Yu et al., 1986; McLaughlin et al., 1988), but more recent studies, including the international case-control study, provided a less clear picture (McLaughlin and Lipworth, 2000). In the multinational study, adjustment for high blood pressure eliminated the excess risk associated with diuretic use (McLaughlin et al., 1995b). Since hypertension and antihypertensive medications are highly correlated, it is difficult to distinguish the effect of treatment from its indication, hypertension. However, the cumulative evidence suggests that of the two variables, hypertension itself rather than diuretics may have a role in the aetiology of renal cell cancer (McLaughlin and Lipworth, 2000). The mechanism by which high blood pressure may increase risk is unclear, but the development of hypertension due to undetected renal cell cancers is unlikely, since cohort studies with blood pressure readings taken long before cancer occurrence have also noted the relation (Raynor et al., 1981; Coughlin et al., 1997).

Diabetes mellitus has been associated with risk of renal cell cancer in some, but not all studies (Van Poppel et al., 2000). In the international multicentre study, a 40% excess risk was observed among subjects with diabetes (Schlehofer et al., 1996). This was supported by a recent Swedish prospective study, in which an increase in risk was observed among patients with diabetes mellitus (Lindblad et al., 1999).

The role of analgesics, e.g. phenacetin, aspirin or acetaminophen, in the development of renal cell cancer is unclear (McLaughlin and Lipworth, 2000). Phenacetin-containing analgesics have been inconsistently related to risk, although a number of studies have reported moderately elevated risks with regular or long-term use (Van Poppel et al., 2000). However, in the international case-control study, use of any type of analgesics was not consistently related to increase in risk (McCredie et al., 1995).

Among urological diseases, kidney stones and kidney infection, as well as urinary-tract infection in women, have been related to increased risk of renal cell cancer (Van Poppel et al., 2000), whereas one recent cohort study found no increased risk for kidney stones (Chow et al., 1997). Acquired cystic kidney disease, which occurs in end-stage renal disease, is strongly associated with the development of renal cell cancer (Van Poppel et al., 2000).
4.3.6 Dietary factors

Diet is believed to play an important role in the development of renal cell cancer, but contradictory results and methodological limitations have so far prevented definitive conclusions.

The hypotheses concerning diet and renal cell cancer have often been generated from ecologic studies of kidney cancer. In these early studies, positive correlations were observed for per capita consumption of milk, meat, fats and oils, coffee, and alcohol (Armstrong and Doll, 1975; Wynder et al., 1974; Shennan, 1973; Breslow and Engstrom, 1974; Hinds et al., 1980). On the nutrient level, total calories, total protein, and animal protein were correlated to renal cell cancer (Armstrong and Doll, 1975; Wynder et al., 1974), while protein from plant products was inversely correlated (Wynder et al., 1974).

Analytic epidemiologic studies – mostly case-control studies - have failed to give clear support for the ecologic results on coffee, alcohol, fat and protein (Wolk et al., 1996a). In fact, for alcohol intake there is, if anything, a suggestive inverse association in many case-control studies (Wolk et al., 1996a). In the international multicentre study, a significant inverse association was observed among women but not men (Wolk et al., 1996b). Moreover, a statistically significant association for total energy intake was observed in this study. After adjustment for energy, positive significant associations with some foods (milk, eggs, foods rich in animal protein, cereal/bread) were no longer significant. Therefore, the hypotheses that protein and fat are risk factors were not supported. Fried meat was associated with increased risk of renal cell cancer in the international study (Wolk et al., 1996b), but not in a recent Swedish study (Agustsson et al., 1999). The most consistent dietary finding has been a decreased risk with high intake of fruits and vegetables (Wolk et al., 1996a). In the international study, men and women in the highest quartile of fruit and vegetable intake had about a 20% reduced risk.

4.3.7 Reproductive and hormonal factors

Few analytic epidemiologic studies have focused on reproductive factors or exogenous hormones, but hormone-related factors might be associated with renal cell cancer (Van Poppel et al., 2000).

A significant trend in risk was observed for number of births in the international study, with an 80% excess risk for six or more births (Lindblad et al., 1995). An association with parity has also been suggested by other studies (Krieger et al., 1993; Chow et al., 1995), while some have found no association (McLaughlin et al., 1992).

Some studies have observed an increased risk for women having a hysterectomy, with or without oophorectomy, (Chow et al., 1995; Gago-Dominguez et al., 1999). In the international case-control study, women having had both a hysterectomy and an oophorectomy had about a 2-fold increase in risk (Lindblad et al., 1995).

Use of oral contraceptives or hormone replacement therapy has been related to renal cell cancer in some studies, but the results are conflicting. The multicentre case-control study found a significantly reduced risk of renal cell cancer following oral contraceptive use, with a suggestion of increased reduction with duration of use (Lindblad et al., 1995), although another recent study found no relationship (Gago-Dominguez et al., 1999). Weak increase in
risk has also been reported for oral contraceptives (McLaughlin et al., 1992) and for use of replacement estrogens in some (McLaughlin et al., 1992; Asal et al., 1988a), but not all (McLaughlin et al., 1984; Adami et al., 1989) studies.

4.3.8 Occupational factors

Renal cell cancer is not generally thought of as an occupationally induced malignancy, although a large number of studies of occupational exposures have been performed over the last 25 years (McLaughlin and Lipworth, 2000).

Asbestos has been linked to an increased risk in two cohort studies (Selikoff et al., 1979; Enterline et al., 1987), as well as in the international case-control study (Mandel et al., 1995). In the latter study, asbestos exposure was associated with a 40% increased risk of renal cell cancer. Other case-control studies have not observed any increased risk with asbestos exposure, but these studies have often included a low number of exposed workers (McLaughlin and Lipworth, 2000).

Coke oven workers exposed to high levels of polycyclic aromatic hydrocarbons have been reported to have an increased risk of renal cell cancer (McLaughlin and Lipworth, 2000). In the multinational case-control study, self-reported employment in the blast furnace/coke oven industry was associated with a 70% increased risk. There was, however, no duration-related effect of employment in this industry (Mandel et al., 1995).

Although numerous epidemiological studies have examined gasoline exposure in relation to renal cell cancer, there is no convincing evidence that gasoline is associated with an increased risk (McLaughlin and Lipworth, 2000). In the international case-control study, exposure to gasoline was associated with a 60% excess risk of renal cell cancer (Mandel et al., 1995). Oil refinery workers had no significant excess risk in this study (Mandel et al., 1995).

Much recent interest has focused on the solvent trichlorethylene, and the related solvent perchlorethylene. Despite the increased risk found in some epidemiological studies, a review of the available literature concluded that there is no clear evidence that these solvents pose a risk in humans (McLaughlin and Blott, 1997; McLaughlin and Lipworth, 2000).

A possible relation with renal cell cancer risk has also been suggested for other occupational exposures such as cadmium, but the results have been inconsistent (McLaughlin and Lipworth, 2000).

4.3.9 Familial and genetic factors

The majority of renal cell cancers occur in sporadic form. Familial history of the disease has been associated with an increase in risk, but the inherited forms account for a small proportion of the patients with renal cell cancer (Van Poppel et al., 2000). The majority of subjects in the international multicentre study reported no parents or siblings with a diagnosis of cancer of the kidney. However, having a first-degree relative with kidney cancer was associated with a 60% increased risk of renal cell cancer (Schlehofer et al., 1996).
Some genetic diseases are associated with renal cell cancer, including von Hippel-Lindau (VHL) syndrome and hereditary papillary renal carcinoma (Van Poppel et al., 2000). The genes underlying each of these conditions have been cloned and germline mutations in affected patients have been identified.

Von Hippel-Lindau syndrome is the best characterised form of hereditary renal cell cancer. Subjects affected by this rare autosomal dominantly inherited disorder are at risk of developing tumours at many sites including the kidney, CNS and pancreas. Renal cell cancer accounts for a high morbidity and many deaths among these subjects. Von Hippel-Lindau syndrome is associated with germline mutations of the tumour suppressor gene located on chromosome 3p. Moreover, chromosome 3p deletions are observed with high incidence in nonpapillary sporadic tumours of the kidneys, which suggests common genetic mechanisms for hereditary and sporadic forms of renal cell cancer (Van Poppel et al., 2000).

Hereditary papillary renal cell carcinoma is an autosomal dominant inherited syndrome characterised by for example multifocal, bilateral papillary renal cell cancer. This syndrome has been linked to germline mutation of the c-Met proto-oncogene on chromosome 7p. Somatic mutations of this gene have also been described in some sporadic cases with papillary tumours of the kidney (Van Poppel et al., 2000).

### 4.3.10 Other factors

Educational and socio-economic level has been associated with renal cell cancer in some, although not all studies (McLaughlin and Lipworth, 2000). In the multinational case-control study, there was an inverse association between education and renal cell cancer, with a 30 % reduced risk among subjects with college or university education compared to those with less than high school (Mandel et al., 1995). Furthermore, radiation has been related to risk of renal cell cancer (McLaughlin and Lipworth, 2000).
5. Aims

The overall objective of this thesis was to understand the relation between physical activity, body size, and renal cell cancer. The specific aims were:

- To investigate the relation between occupational and leisure time physical activity and risk of renal cell cancer (Papers I-II).
- To assess in detail the impact of body size, including general and abdominal obesity, and height, on renal cell cancer risk (Papers III-IV).
- To investigate the association between weight change and risk of renal cell cancer (Paper IV).
- To investigate the association between birth weight and risk of renal cell cancer (Paper V).
6. Material and methods

Three types of epidemiologic study designs are used in this thesis, namely the cohort study (Papers I-II), the meta-analysis (Paper III), and the case-control study (Papers IV-V). With exception of the meta-analysis based on published studies, all studies were conducted in Sweden where population-based registries and the possibility to link these through the national registration number, a unique identifier assigned to each inhabitant, provide an ideal setting for epidemiological studies.

In these studies we use the following of Sweden’s population-based registries:

The Population Registration System is the basic registry of the Swedish population. It provides current information on who lives in the country and where they live. The most important information in the Population Registry is name, national registration number, and residential address.

The Swedish Census of the Population and Housing has been obtained approximately every five years since 1960. A questionnaire covering demographic, occupational (including employment status, job title, industry and work address), and socio-economic factors for each household member during one October week, is mailed to every Swedish household (Official Statistics of Sweden, 1975). Since response to the census questionnaire was obligatory by law, and great efforts were made to recruit non-respondents, the censuses are almost 100% complete (Official Statistics of Sweden, 1965; Official Statistics of Sweden, 1974).

The Swedish Cancer Registry was established in 1958. Since the initiation of this nationwide registry, cancers have been coded according to the seventh edition of the International Classification of Diseases (ICD-7). Six regional cancer registries covering the whole country perform the registration of new cancer cases. Notification of newly diagnosed cancers is mandatory, and the registry covers more than 98% of all newly diagnosed cancers in Sweden (Mattson, 1977) and 98% of these are histologically verified (National Board of Health and Welfare, 2000). The proportion of morphologically verified kidney cancer was 93% in 1971 (National Board of Health and Welfare, 1975) and 94% in 1989 (National Board of Health and Welfare, 1992). The Cancer Registry is linked annually to the Swedish Cause of Death Registry to supply date and causes of death, and to the Population Registry to supply information on emigration. The national registration number is used as identifiers in these linkages.

The Swedish Cause of Death Registry records information on all diseased persons registered in the country at the time of death. The cause of death, including underlying and contributing causes, is generally determined from the medical death certificates, obligatory for physicians to complete within a week after death. All causes of death are coded in accordance with the ICD. The number of missing cases are few (0.4% of all deaths in 1997) (National Board of Health and Welfare, 2000).

The Cancer-Environment Registry III (CERIII), was established by linking the national population censuses from both 1960 and 1970 to the Cancer Registry data for 1971-1989 (EPC Rapport, 1994). The national registration numbers were used to ensure correct matching. The CERIII proper includes only cancer cases. To be included, cancer patients had to have resided in Sweden both in 1960 and 1970 and thus be recorded in both censuses. Missing data (individuals who were found in the Cancer Registry but not in the censuses despite verified residence in Sweden both 1960 and 1970 according to other independent sources) was estimated to be less than 0.9% (EPC Rapport, 1994).
A background registry, encompassing all individuals who took part in both the 1960 and 1970 censuses, was established as a reference. Except for the tumour data, the information in this background registry is virtually the same as in the CERIII proper, including dates (but not causes) of death among the deceased. After completion of the record linkages, the national registration numbers were removed from both the CERIII proper and the background registry to ensure confidentiality.

The Swedish Twin Registry includes data on all twins born from 1886 through 1958 (Pedersen et al., 1996). In the study presented in this thesis, we analysed Swedish twins born between 1886 and 1925 with both individuals alive in 1959-1961 when the registry was established (Cederlöf et al., 1977). In 1967, a 107-item questionnaire regarding life-style factors, such as occupational and leisure time physical activity, height, current weight, hypertension, diabetes, and tobacco smoking habits was mailed to the cohort participants. Those who did not return that questionnaire received an identical one in 1970.

6.1 Paper I

We conducted a nationwide cohort study within the Swedish Cancer-Environment Registry III and the background register described above (EPC Rapport, 1994), to assess risk for renal cell cancer in relation to occupational physical activity.

6.1.1 Classification of physical activity and covariates

Using a three-digit classification, the occupations reported in the census questionnaires were coded into 245 categories in the 1960 and 248 in the 1970 census, respectively (Official Statistics of Sweden, 1971). Proceeding from these codes, three experts in occupational medicine independently classified the occupations into jobs requiring very high, high, moderate, light, and sedentary activity.

In order to reduce misclassification of exposure we only considered occupations consistently classified by the three experts; we required absolute agreement between at least two of them while the third was allowed to diverge by no more than one category. A total of 202 occupations were thus unequivocally classified. Because few women were classified as having jobs with very high demands, the two categories of highest physical activity were subsequently merged to gain statistical power. The most frequent occupations for each estimated level of physical activity in the census 1970 are shown in Table 1.

Socioeconomic status was categorised into four levels (unskilled blue collar, skilled blue collar, unskilled white collar, and skilled white-collar occupations) based on the occupational title, as described in detail elsewhere (Statistics Sweden, 1995). Place of residence was divided into six categories (Stockholm – capital; Gothenburg and Malmö – second and third largest cities in Sweden; Other large municipalities; Southern and central Sweden (except the cities and large municipalities); Northern densely populated areas; Northern sparsely populated areas), based on the residential municipality (Öberg and Springfeldt, 1991).
<table>
<thead>
<tr>
<th>Level of physical activity</th>
<th>Occupation</th>
<th>Men Freq. (%)</th>
<th>Occupation</th>
<th>Women Freq. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high/high</td>
<td>General farmers; specialized farmers; forestry workers</td>
<td>39</td>
<td>Nursing personnel not elsewhere classified</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Carpenters, joiners and parquetry workers</td>
<td>16</td>
<td>Cleaners and related workers</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Dockers and freight handlers</td>
<td>13</td>
<td>General farm workers; field crop and vegetable</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Loggers; forestry workers</td>
<td>10</td>
<td>farm workers; farm machinery operators;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>livestock workers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dockers and freight workers</td>
<td>4</td>
</tr>
<tr>
<td>Medium</td>
<td>Carpenters and related woodworkers</td>
<td>16</td>
<td>Maids and related housekeeping service workers</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Building caretakers</td>
<td>8</td>
<td>not elsewhere classified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Material handling equipment operators not elsewhere classified</td>
<td>8</td>
<td>Professional nurses</td>
<td>10</td>
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<tr>
<td></td>
<td>Stock clerks</td>
<td>7</td>
<td>Waiters, bartenders and related workers</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>Civil engineers, industrial engineers, civil engineering technicians and related workers</td>
<td>36</td>
<td>Elementary-school teachers</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Commercial travelers and manufactures agents; managers ( wholesale and retail trade); sale supervisors; buyers and related workers</td>
<td>10</td>
<td>Sewing-machine operators</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Working proprietors ( wholesale and retail trade)</td>
<td>4</td>
<td>Hairdressers, barbers, beauticians and related workers</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Compositors and type-setters; printing pressmen and related workers</td>
<td>4</td>
<td>Cashiers</td>
<td></td>
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<tr>
<td>Sedentary</td>
<td>Production managers, general managers and related workers</td>
<td>32</td>
<td>Secretaries</td>
<td>37</td>
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<tr>
<td></td>
<td>Bookkeepers</td>
<td>9</td>
<td>Bookkeepers</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Chemical engineers and related workers</td>
<td>8</td>
<td>Workers in telephone-answering services</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Personnel and occupational specialists; managers not elsewhere classified</td>
<td>6</td>
<td>Tellers</td>
<td>6</td>
</tr>
</tbody>
</table>

*Percentage of the most frequent occupations within each level of physical activity.
6.1.2 Study cohorts and follow-up

In 1960, a total of 1,348,971 men and 704,904 women in the background register reported employment in a job that had been unequivocally classified with regard to physical activity level. They constituted our cohort 1960. Cohort 1970, to a large extent overlapping with cohort 1960, included 1,377,629 men and 989,270 women whose occupation, as reported in the 1970 census, was also unequivocally classified according to physical activity level. Altogether 674,025 men and 253,336 women had jobs classified as representing the same physical activity level in both the 1960 and the 1970 censuses; these men and women with a stable long-term physical activity level constituted our study cohort 1960/70.

To ascertain renal cell cancer outcomes in these cohorts, we linked the background register with the CERIII proper, matching on all census variables and dates of death (Moradi et al., 1998). We analysed only first incident cancers. Cancers diagnosed first at autopsy were excluded from analyses. Person-years were calculated from 1 January 1971, until the diagnosis of any malignant tumour, death or end of follow-up (31 December 1989), whichever occurred first.

6.1.3 Statistical methods

Data was analysed in grouped form. Attained age (age at follow-up) was divided into eleven 5-year categories (<40, 40-44, …, 80-84, 85+ years). The nineteen calendar years of follow-up were divided into nine 2-year intervals and one 1-year interval (1 January 1971 – 31 December 1972, 1973-1974, …, 1 January 1989 – 31 December 1989).

We estimated risk of renal cell cancer in relation to occupational physical activity by performing internal comparisons between exposure groups within the cohorts. To compute the relative risk (RR) and 95% confidence intervals (CI), we fitted Poisson models, in which the log Poisson rate was linear in the factors, by the maximum-likelihood method. The baseline model was adjusted only for age at follow-up. The second model was additionally adjusted for socio-economic status, place of residence and calendar year of follow-up. The deviance in our models was of the same order as the degrees of freedom, thus no correction for over-dispersion was necessary.

6.2 Paper II

6.2.1 Study cohort and follow-up

We examined a cohort of 10,945 same-sex twin pairs included in the Swedish Twin Registry to assess the association between both occupational and leisure time physical activity and renal cell cancer. A total of 18,797 subjects returned either the 1967 or the 1970 questionnaire, that is 90% of those who received it. Usual occupational physical activity was assessed on a relative scale as “sedentary”, “active”, or “physically strenuous” and leisure time physical activity at ages 25-50 was assessed as “hardly any physical exercise”, “light exercise, e.g. regular walks, light gardening”, “regular exercise” or “hard physical training”.

Excluding 1,071 subjects who died prior to assessment and 485 subjects with prevalent cancer at baseline in 1967, our analysis includes 7,497 men and 9,744 women who responded to the questionnaire. Renal cell cancer incidence was ascertained by record linkage with the Swedish
Cancer Registry and death was ascertained by linkage to the Swedish Cause of Death Register. Subjects were followed from the exposure assessment in 1967 to one of three study endpoints: diagnosis of renal cell cancer, death, or the end of the study on December 31, 1997, whichever occurred first.

6.2.2 Statistical methods

Cox proportional hazards models were used to estimate hazard rate ratios (RR) with 95% confidence interval (CI). To ensure that confidence intervals were not erroneously narrowed, due to similarities within pairs, we performed proportional hazards analyses that adjusted variance estimates for correlated outcomes. We accomplished this through the use of a SAS (Statistical Analysis Software) macro that stems from the same theoretical background (White, 1982; Wei et al., 1989; Lin, 1994) and yields the same results as the published Fortran program of Lin (1993). In simple terms, variance estimates are increased in magnitude proportional to the degree of extra correlation within twin pairs. Adjusted confidence intervals are usually wider and are therefore more conservative than unadjusted. Relative risk estimates are not altered by this procedure. We analysed occupational and leisure time physical activity separately and combined. In those latter analyses, subjects with a sedentary occupation and with none or light leisure time physical activity were categorised as sedentary. Subjects with a sedentary occupation engaged in regular or hard exercise and subjects with an active or strenuous occupation with none or light leisure time activities were categorised as active, while persons with an active or strenuous occupation engaged in regular or hard exercise were categorised as strenuous. The effect of occupational, leisure time and total physical activity were explored in models including only age at entry to the study cohort (as a continuous variable) and sex, as well as in multivariate models additionally adjusted for tobacco smoking (categorised as current, former, or never), body mass index at start of follow-up (BMI=kg/m², divided into quartiles based on the distribution in the cohort), and hypertension (ever or never). The Swedish Twin Registry does not contain concordant pairs with respect to renal cell cancer and therefore the genetic component (heretability of liability) could not be computed.

6.3 Paper III

We performed a quantitative summary analysis, a so called meta-analysis, of published studies to evaluate the existing evidence of an association between obesity and renal cell cancer among both men and women.

6.3.1 Literature review

Original epidemiological studies investigating the relation between obesity and kidney cancer were identified through a MEDLINE search from 1966-1998. Additional studies were identified from systematical examinations of the list of references in the identified articles and previous reviews (Wolk et al., 1996a; McLaughlin and Lipworth, 2000).

6.3.2 Inclusion criteria

Studies on renal cell cancer or unspecified kidney cancer (i.e. studies unable to disentangle cancer of the renal parenchyma and cancer of the renal pelvis) were included in our review. We identified 28 such studies among men, and equally many among women. The individual studies are summarised in Table 2.
Each study-base was eligible only once. When multiple reports were available for the same study-base we chose the one analysing incident renal cell cancer as outcome, and/or defining obesity with body mass index (BMI, kg/m²) and in more detailed categories, and/or with more numerous cases. We excluded six studies among men (Whittemore et al., 1985; Mellemgaard et al., 1994; Moller et al., 1994; Lindblad et al., 1994; Muscat et al., 1995; Boeing et al., 1997) and equally many among women (Whittemore et al., 1985; Lindblad et al., 1994; Mellemgaard et al., 1994; Moller et al., 1994; Muscat et al., 1995; Boeing et al., 1997) due to overlapping reports. This left 22 studies on each sex.

Our quantitative summary analysis was limited to studies presenting category-limits of BMI and relative risk estimates with their 95% confidence interval (CI), or other results making it possible to compute these values. We excluded eight studies among men (Wynder et al., 1974; Lew and Garfinkel 1979; Whittemore et al., 1984; Yu et al., 1986; Kadamani et al., 1989; Maclure and Willett 1990; Partanen et al., 1991; Mellemgaard et al., 1991) and equally many among women (Wynder et al., 1974; Lew and Garfinkel 1979; Yu et al., 1986; Kadamani et al., 1989; Maclure and Willett 1990; Partanen et al., 1991; Mellemgaard et al., 1991; Finkle et al., 1993) since they did not assess obesity in a comparable way, or present their results in sufficient detail. Therefore, 14 studies on each sex were included in the qualitative analysis.

### 6.3.3 Data extraction and unification

From each published report we extracted the main characteristics of the study, the definition of exposure and the relative risk estimates (rate ratios, odds ratios, hereafter denoted as relative risk, RR), and their confidence intervals. All information was extracted separately for men and women. One study did not present results separately for men and women, but crude sex-specific relative risks were computed from the results presented in the article (Talamini et al., 1990).

If the risk of renal cell cancer was expressed in more than one way, the estimate reflecting greatest degree of controlling for confounders was used. We considered age and smoking to be the most important confounding factors in the relation between obesity and renal cell cancer. We therefore grouped studies as adjusted and unadjusted depending on if they had controlled for these two factors.

The studies were classified as cohort or case-control, and the latter were further divided into population-based and hospital-based. Nested case-control studies, where prospectively gathered information was analysed in a case-control design, were classified as cohort studies.

The category limits in studies assessing BMI as lb/ft² (McLaughlin et al., 1984; Asal et al., 1988b) or kg/cm² (Kreiger et al., 1993) were recalculated to kg/m². For studies assessing female obesity as kg/m¹.5 (McCredie and Stewart, 1992; Mellemgaard et al., 1995; Chow et al., 1996) we performed an approximate recalculation of these estimates to kg/m² by dividing the provided estimate with the square root of height. The height was set to 1.64 m, the mean height of women in recent cohort studies in Northern America, the Netherlands, and Sweden (Smith-Warner et al., submitted)
<table>
<thead>
<tr>
<th>First author, year of publication</th>
<th>Study base no.</th>
<th>Type of study†</th>
<th>Country</th>
<th>Number of cases‡</th>
<th>Exposure§</th>
<th>Categories</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wynder, 1974</td>
<td>1</td>
<td>CCH</td>
<td>USA</td>
<td>129 M</td>
<td>RBW¹</td>
<td>NA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73 F</td>
<td></td>
<td>P&lt;0.005 for RBW 125+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lew, 1979</td>
<td>2</td>
<td>Coh</td>
<td>USA</td>
<td>Unknown</td>
<td>RBW²</td>
<td>M: 130-139 vs 90-109</td>
<td>1.51</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F: 140+ vs &lt;80</td>
<td>2.03</td>
<td>–</td>
</tr>
<tr>
<td>McLaughlin, 1984</td>
<td>3</td>
<td>CCP</td>
<td>USA</td>
<td>313 M</td>
<td>BMI</td>
<td>&gt;28.0 vs ≤23.6</td>
<td>1.5</td>
<td>1.0-2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>182 F</td>
<td></td>
<td>&gt;26.2 vs ≤21.6</td>
<td>2.1</td>
<td>1.2-3.9</td>
</tr>
<tr>
<td>Whittemore, 1984</td>
<td>4</td>
<td>Coh</td>
<td>USA</td>
<td>77 M</td>
<td>Weight (lb)</td>
<td>180+ vs &lt;140</td>
<td>2.5</td>
<td>0.9-6.8</td>
</tr>
<tr>
<td>Whittemore, 1985</td>
<td>4</td>
<td>Coh</td>
<td>USA</td>
<td>74 M+F</td>
<td>Weight Units of 10 lbs</td>
<td>1.2</td>
<td>1.0-1.3</td>
<td></td>
</tr>
<tr>
<td>Goodman, 1986</td>
<td>5</td>
<td>CCH</td>
<td>USA</td>
<td>189 M</td>
<td>BMI</td>
<td>28+ vs &lt;24</td>
<td>2.67</td>
<td>1.49-5.94</td>
</tr>
<tr>
<td>Yu, 1986</td>
<td>6</td>
<td>CCP</td>
<td>USA</td>
<td>109 M</td>
<td>BMI</td>
<td>Highest vs lowest quartile</td>
<td>1.8</td>
<td>0.8-4.0</td>
</tr>
<tr>
<td>Asal, 1988b</td>
<td>7</td>
<td>CCP</td>
<td>USA</td>
<td>209 M</td>
<td>BMI</td>
<td>Highest vs lowest quartile</td>
<td>2.7</td>
<td>0.8-9.3</td>
</tr>
<tr>
<td>Kadamani, 1989¶</td>
<td>8</td>
<td>CCP</td>
<td>USA</td>
<td>142 M</td>
<td>% standard BMI</td>
<td>140+ vs &lt;120</td>
<td>3.8</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68 F</td>
<td></td>
<td>140+ vs &lt;120</td>
<td>3.0</td>
<td>–</td>
</tr>
<tr>
<td>Maclure, 1990a**</td>
<td>9</td>
<td>CCP</td>
<td>USA</td>
<td>135 M</td>
<td>BMI</td>
<td>&gt;28 vs ≤28</td>
<td>1.7</td>
<td>0.9-3.2</td>
</tr>
<tr>
<td>Talamini, 1990</td>
<td>10</td>
<td>CCH</td>
<td>Italy</td>
<td>150 M+90 F</td>
<td>BMI</td>
<td>&gt;27 vs &lt;24</td>
<td>0.74</td>
<td>0.51-1.07</td>
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<tr>
<td>Mellemgaard, 1991</td>
<td>12</td>
<td>Coh</td>
<td>Denmark</td>
<td>25 M</td>
<td>Obesity</td>
<td>1.52</td>
<td>0.05&gt;P&gt;0.001</td>
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</tr>
<tr>
<td>Partanen, 1991</td>
<td>11</td>
<td>CCP</td>
<td>Finland</td>
<td>338 M+F</td>
<td>Obesity</td>
<td>1.2</td>
<td>0.9-1.7</td>
<td></td>
</tr>
<tr>
<td>McCredie, 1992</td>
<td>13</td>
<td>CCP</td>
<td>Australia</td>
<td>310 M</td>
<td>BMI</td>
<td>&gt;25.34 vs &lt;23.05</td>
<td>1.6</td>
<td>1.1-2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>179 F</td>
<td>kg/m² ¹.⁵</td>
<td>&gt;30.79 vs &lt;27.21</td>
<td>1.3</td>
<td>0.8-2.1</td>
</tr>
<tr>
<td>McLaughlin, 1992††</td>
<td>14</td>
<td>CCP</td>
<td>China</td>
<td>90 M</td>
<td>BMI</td>
<td>&gt;23.3 vs ≤19.7</td>
<td>1.7</td>
<td>0.5-5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64 F</td>
<td></td>
<td>&gt;30.6 vs ≤24.4</td>
<td>3.3</td>
<td>0.7-15.1</td>
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<td>Benhamou, 1993</td>
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<td>CCH</td>
<td>France</td>
<td>138 M</td>
<td>BMI</td>
<td>≥27 vs ≤20</td>
<td>2.4</td>
<td>1.0-5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58 F</td>
<td></td>
<td>≥27 vs ≤20</td>
<td>3.5</td>
<td>1.0-11.8</td>
</tr>
<tr>
<td>Finkle, 1993</td>
<td>16</td>
<td>Coh</td>
<td>USA</td>
<td>191 F</td>
<td>kg/m² ¹.⁵</td>
<td>Highest vs lowest quartile</td>
<td>2.6</td>
<td>1.4-4.8</td>
</tr>
<tr>
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<td>17</td>
<td>CCP</td>
<td>Canada</td>
<td>282 M</td>
<td>BMI</td>
<td>&gt;25.1 vs ≤21.5</td>
<td>1.3</td>
<td>0.8-2.2</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>181 F</td>
<td></td>
<td>&gt;23.0 vs ≤19.7</td>
<td>2.5</td>
<td>1.4-4.6</td>
</tr>
<tr>
<td>First author, year of publication</td>
<td>Study base no.</td>
<td>Type of study†</td>
<td>Country</td>
<td>Number of cases‡</td>
<td>Exposure§</td>
<td>Categories</td>
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<td>----------------------------------</td>
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<td>-----------</td>
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</tr>
<tr>
<td>Hiatt, 1994</td>
<td>18</td>
<td>Coh</td>
<td>USA</td>
<td>167 M</td>
<td>BMI</td>
<td>≥28.3 vs &lt;24.6</td>
<td>1.4</td>
<td>0.7-3.1</td>
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<td>90 F</td>
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<td>≥27.8 vs &lt;21.8</td>
<td>1.2</td>
<td>0.4-4.3</td>
</tr>
<tr>
<td>Lindblad, 1994</td>
<td>19</td>
<td>CCP</td>
<td>Sweden</td>
<td>379 M</td>
<td>BMI</td>
<td>&gt;25.8 vs &lt;23.1</td>
<td>1.37</td>
<td>0.78-2.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>353 F</td>
<td></td>
<td>&gt;25.2 vs &lt;21.3</td>
<td>1.43</td>
<td>0.71-2.88</td>
</tr>
<tr>
<td>Mellemaagard, 1994</td>
<td>19</td>
<td>CCP</td>
<td>Denmark</td>
<td>225 M</td>
<td>BMI</td>
<td>&gt;26.4 vs ≤23.1</td>
<td>1.2</td>
<td>0.7-2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>141 F</td>
<td>kg/m²</td>
<td>&gt;31.7 vs ≤27.2</td>
<td>2.2</td>
<td>1.1-4.2</td>
</tr>
<tr>
<td>Moller, 1994</td>
<td>12</td>
<td>Coh</td>
<td>Denmark</td>
<td>21 M</td>
<td>Obesity</td>
<td></td>
<td>1.2</td>
<td>0.7-1.8</td>
</tr>
<tr>
<td></td>
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<td>58 F</td>
<td></td>
<td></td>
<td>2.0</td>
<td>1.5-2.6</td>
</tr>
<tr>
<td>Mellemaagard, 1995</td>
<td>19</td>
<td>CCP</td>
<td>International</td>
<td>1050 M</td>
<td>BMI</td>
<td>≥26.6 vs &lt;23.1</td>
<td>1.6</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>682 F</td>
<td>kg/m²</td>
<td>≥32.7 vs &lt;27.3</td>
<td>2.0</td>
<td>1.5-2.7</td>
</tr>
<tr>
<td>Muscat, 1995</td>
<td>7</td>
<td>CCH</td>
<td>USA</td>
<td>543 M</td>
<td>BMI</td>
<td>Highest vs lowest quartile</td>
<td>1.4</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>245 F</td>
<td></td>
<td>Highest vs lowest quartile</td>
<td>1.4</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>Chow, 1996</td>
<td>20</td>
<td>CCP</td>
<td>USA</td>
<td>274 M</td>
<td>BMI</td>
<td>≥29.75 vs ≤23.13</td>
<td>1.3</td>
<td>0.7-2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>163 F</td>
<td>kg/m²</td>
<td>≥36.57 vs ≤26.75</td>
<td>3.8</td>
<td>1.7-8.4</td>
</tr>
<tr>
<td>Gamble, 1996</td>
<td>21</td>
<td>Coh</td>
<td>USA</td>
<td>37 M</td>
<td>BMI</td>
<td>≤25 vs &lt;21</td>
<td>3.29</td>
<td>0.93-11.62</td>
</tr>
<tr>
<td>Boeing, 1997</td>
<td>19</td>
<td>CCP</td>
<td>Germany</td>
<td>277 M+F</td>
<td>BMI</td>
<td>&gt;27 vs &gt;25</td>
<td>2.22</td>
<td>1.29-3.81</td>
</tr>
<tr>
<td>Heath, 1997</td>
<td>22</td>
<td>Coh</td>
<td>USA</td>
<td>212 M</td>
<td>BMI</td>
<td>≥31.1 vs 20.7-24.6</td>
<td>1.6</td>
<td>0.9-2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>123 F</td>
<td></td>
<td>≥32.3 vs 19.1-21.9</td>
<td>3.1</td>
<td>1.5-6.4</td>
</tr>
<tr>
<td>Prineas, 1997</td>
<td>23</td>
<td>Coh</td>
<td>USA</td>
<td>62 F</td>
<td>BMI</td>
<td>≥28.3 vs &lt;24.3</td>
<td>2.77</td>
<td>1.34-5.70</td>
</tr>
<tr>
<td>Yuan, 1998</td>
<td>24</td>
<td>CCP</td>
<td>USA</td>
<td>781 M</td>
<td>BMI</td>
<td>≥30 vs &lt;22</td>
<td>4.6</td>
<td>2.9-7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>423 F</td>
<td></td>
<td>≥30 vs &lt;22</td>
<td>4.0</td>
<td>2.3-7.0</td>
</tr>
</tbody>
</table>

†Coh = cohort study; CCP = Population-based case-control study; CCH = hospital-based case-control study.
‡RBW¹, relative body weight = actual weight/ideal weight; RBW², relative body weight = actual weight/average weight; BMI, body mass index = kg/m².
§Relative risk (RR) and 95% confidence interval (CI) for highest category vs. reference category.
||Relative risk (RR) for men and women unexposed to hydrocarbon (21 cases).
**Both men and women as reference.
††Weight at age 50.
6.3.4 Statistical methods

We first estimated the relative risk associated with a unit increase in BMI (1 kg/m^2) for each individual study. The odds ratio was used as a measure of the relative risk for case-control studies, and the relative risk estimates were log-transformed. When results were reported in categories of BMI, these were transformed to an estimate per unit increase in BMI. To treat BMI as a continuous exposure variable, its value was set at the midpoint of each category. For open-ended categories the approximate midpoint was set at double the distance between the midpoint and upper bound of the closest category. The log relative risk, as well as the BMI, for the reference category was set to zero (corresponding to a relative risk of 1). We subtracted the midpoint BMI of this category from the midpoint BMI of all other categories. A weighted regression was then fit through the origin where the exposure was at the reference level with log relative risk zero. The regression was weighted by the inverse variance of the log relative risk for each category. The correlation between categories was estimated using the method of Greenland and Longnecker (Greenland and Longnecker 1992).

We used a mixed effects weighted regression model to combine estimates from BMI categories from the individual studies. Between-study variation was modeled as a random effect, and heterogeneity over studies was assessed by the significance of the between-study variance (Berkey et al., 1995; Takkouche et al., 1999). The within-study variance was taken to be the estimated variance of the log relative risks for each study, giving more precise estimates greater weights in the summary measure (Greenland, 1998). Since each study contributed more than one relative risk estimate (from different BMI categories), this was a covariance matrix of dimension equal to the number of categories minus the reference. For the summary measure, we thus estimated the effect of BMI under the random-effects model while accounting for within-study correlation. To examine whether the mean of the random coefficients for BMI was the same for different groups defined by study characteristics (e.g., males versus females, USA studies versus non-USA studies), models including interaction term(s) between BMI and the study characteristics were further fitted and the significance of the interaction term(s) tested. The PROC MIXED procedure in SAS was applied in our analysis (SAS Institute, 1996) with the parms option allowing the input of known within-study variances. To examine whether a curvilinear model fits the data better than the linear, we added a quadratic term for BMI to the model.

Potential influence that unpublished data could have on our summary analysis was examined using a distortion analysis (Rosenthal, 1979). It was assumed that some studies had data on BMI and renal cell cancer risk but that the results were not published because they were not significant. To be conservative, it was assumed that the association between BMI and renal cell carcinoma in these studies was inverse. An average relative risk of 0.85 (95% confidence interval 0.67-1.08) associated with each unit increase in BMI was used. Confidence intervals including 1.0 were chosen, assuming that reports with significant associations would probably have been published.
6.4 Papers IV-V

6.4.1 Study population

We conducted a population-based case-control study of men and women aged 20-79 years, without previously diagnosed renal cell cancer, born in Sweden or any other Nordic country and resident in any of 19 counties in Sweden between January 1, 1996 and June 30, 1998. We identified all incident cases of renal cell cancer in this population through five of Sweden’s six regional cancer registers (covering 79% of the population in Sweden). Patients were asked to participate through their physicians. A total of 1,275 eligible cases were detected from whom 877 (69%) participated in the study. Non-participation was due to death (12% of eligible cases), the patient being too ill or disabled (6%), or the patient refusing to participate (13%). The cancer patients were contacted at least one month after diagnosis and on average after 3 months.

Control subjects were randomly selected from the continuously updated nationwide Swedish Population Registry. They were frequency-matched to the case subjects by age (in 10-year strata) and sex. Of 2,046 selected control subjects, 1,508 (74%) agreed to participate in the study. Non-participation was mainly due to refusal to participate (24% of selected control subjects). The selection process of cases and controls is illustrated in Figure 1.

Figure 1. Selection of cases and controls in the population-based case-control study (Papers IV-V). The shadowed areas represent the 19 counties included in the study base, and the white areas represent the 2 excluded counties.
6.4.2 Data collection

Detailed information on personal and medical history, including height, weight at age 20, 30, 40, 50, 60, 70, usual adulthood weight, physical activity, reproductive history, smoking, hypertension, and diabetes was obtained through a mailed self-administered questionnaire, identical for case and control subjects. A tape measure and written instructions were enclosed so that circumferences of the waist and hip could be measured. The questionnaire also requested detailed information on weight gains of 5 kg or more (gained for a period of less than 2 years), weight losses of 5 kg or more, and diets resulting in a weight loss of 5 kg or more. Women were asked to disregard weight changes during pregnancies. The questionnaire inquired about birth weight in 5 predefined categories: <2500g, 2500-2999 g; 3000-3499 g, 3500-3999 g, and ≥4000 g, or “do not know”. If needed, case and control subjects were contacted by telephone to complete essential information missing in their responses. Among the controls, 284 failed to return the mailed questionnaire but agreed to a telephone interview that included most questions except weight at age 20, 30, 40, 50, 60, 70, waist and hip circumferences, birth weight, hypertension, and diabetes.

6.4.3 Statistical methods

Odds ratios and 95% confidence intervals estimated from unconditional logistic regression models were used as a measure of relative risk. Height was analysed as a categorical variable stratified into quintiles, and body mass index (BMI, kg/m²) and waist-to-hip ratio (waist circumference divided by hip circumference) were stratified into quartiles, based on the distributions among control men and women. We examined different aspects of weight change. Weight change between age 20 and 50, a measure of a continuous weight change in adult life, was grouped into 5 categories (<0 kg, 0-4 kg, 5-9 kg, 10-19 kg, ≥20 kg). The information on weight gains and/or weight losses of 5 kg or more in adult life up until 2 years before the interview were used as measures of weight fluctuation that might not be captured by the measure of continuous weight change throughout adult life. Subjects were stratified into four categories: those who had stable weight, those who only gained weight, those who only lost weight and those who both gained and lost weight. Reasons for weight loss were stratified into three categories: those who only lost weight due to dieting, those who never lost weight due to dieting, and a mixed group who lost weight both due to dieting and for unknown reasons. Birth weight was merged into 3 categories: <3000 g; 3000-3499 g, and ≥3500 g, since few persons reported a low (<2500 g) or high (≥4000 g) birth weight. The two categories of the lowest and the highest birth weight, respectively, were subsequently merged to increase statistical power.

Data was explored in models including only age (categorised as <40, 40-49, 50-59, 60-69, 70-79) and sex (when men and women were analysed together) as well as models with age and the following covariates: education (<10, 10-12, >12 years), smoking (ever/never), hypertension (ever/never), diabetes (yes/no), BMI (stratified as defined above), and height (stratified into quartiles). The latter adjustment was only made in the analyses of birth weight (Paper V). When the analyses of obesity and weight change (Paper IV) were further adjusted for total physical activity (categorised as low or high) and parity (categorised as 0, 1-2, 3-4, ≥5), this did not alter the risk estimates and were therefore not included in the multivariate model.
Changes in body weight were further analysed using an approach described by Lissner and co-workers (1991). A regression model with the assumption of a linear relation between age and BMI was applied to each subject’s BMI values at age 20, 30, 40, 50, 60, and 70 (or for the available ages). Three separate features of weight change were estimated from this regression model: the coefficient of variation, the average level of BMI, and the change in BMI per year (the slope of the regression line). The first, hereafter referred to as variability in weight, was calculated as the standard deviation of each subject’s BMI values divided by the average level of BMI for that subject (i.e. the coefficient of variation). A high degree of variability in weight indicates many changes in weight or large changes, whereas a low value indicates stability of the body weight values. Variability in weight was explored in models including only age in addition to multivariate models with age, sex, education, smoking, hypertension, diabetes, the level of BMI, and the slope of BMI. Including the slope of BMI over time as an independent variable made it possible to distinguish the effects of systematic change in body weight from the effects of random or periodic fluctuation. This distinction was necessary because the variability in weight and the slope of BMI regression line are correlated. Similarly, correcting for the level of BMI enabled us to separate any direct effects of obesity from the effects of variability in weight.

Subjects with low BMI at age 20 are more likely to gain weight with age, while subjects with high BMI at age 20 might be more likely to lose weight with age (a concept known as regression to the mean (Bland and Altman, 1994a,b)). To study if weight change affects subjects with low or high weight at young age differently, we performed all weight change analyses (i.e. the analyses of weight change in adult life, weight fluctuation, reason for weight change, and variability in weight) both for all subjects together, and stratified by BMI at age 20 (lowest three tertiles, <23.30 kg/m² vs. highest tertile >23.30 kg/m²). For example, to study the effect of weight fluctuation, the model included an interaction term between BMI at age 20 (2 levels) and weight fluctuation (4 levels). The reference category for all OR estimates was subjects with a BMI <23.30 kg/m² at age 20 and stable weight.
7. Results

7.1 Physical activity and risk of renal cell cancer (Papers I-II)

7.1.1 Occupational physical activity

We evaluated the association between occupational physical activity and renal cell cancer risk in a large, nationwide cohort study in Sweden (Paper I). In all three study cohorts fewer women than men had jobs classified as heavy or very heavy, and more women than men had jobs classified as sedentary. During nineteen years of follow-up we observed 5,066 male and 1,519 female cases of renal cell cancer in the cohort 1960. In the cohort 1970 we observed 4,257 male and 1,698 female cases. In the cohort 1960/70 2,704 male and 587 female cases were observed.

The association between level of occupational physical activity and renal cell cancer based on comparisons within the cohorts is presented in Table 3. After adjustment for age we found an inverse association among men in all the three cohorts. The association showed a clear trend of increasing risk with decreasing level of physical activity (p for trend <0.001 in all three cohorts). This trend remained largely unaltered after further adjustments for socioeconomic status, place of residence, and calendar year of follow-up, which only negligibly attenuated the risk estimates. In the multivariate model, men with long-term sedentary jobs, that is both in 1960 and 1970 (the cohort 1960/70), had 25% higher risk of renal cell cancer compared to men with occupations with very high or high physical activity both in 1960 and 1970. For women, the age-adjusted analyses suggested that sedentary jobs were associated with a decreased risk of renal cell cancer. However, the dose-risk trend was not significant in women with the same long-term level of physical activity. Further adjustment for socioeconomic status, place of residence and calendar year of follow-up attenuated the risk estimates and made the dose-risk trend even weaker (p for trend >0.50).

The relation between occupational physical activity and renal cell cancer was further investigated in a cohort of Swedish twins (Paper II). In this cohort, as in paper I, more men than women reported occupations classified as active or physically strenuous, but in contrast an equal amount of men and women reported having a sedentary occupation. Among men, 96% reported their occupational physical activity, while 51% of the women did. Housewives did not report occupational exposure. Women who did not report occupational physical activity were slightly older at enrollment (57.0 vs. 56.2 years), were more likely to be non-smokers (83% vs. 77%), and had slightly higher BMI (29% vs. 25% in the highest BMI quartile) compared to women who did report occupational physical activity. No differences were seen for prevalence of hypertension or diabetes. When the cohort was followed-up for the occurrence of cancer, we identified 50 male and 52 female incident cases of renal cell cancer.

Since we observed no major difference in the risk estimates between men and women, we present the results for both sexes together. Both age-adjusted and multivariate models revealed a non-significant 20% decreased risk of renal cell cancer among men and women with an active or sedentary occupation compared to those with a physically strenuous occupation (RR=0.8, 95% CI 0.5-1.3 for subjects with an active occupation, and RR=0.8, 95% 0.4-1.6 for sedentary occupation). Further adjustments for leisure time physical activity or parity among women did not affect this association (data not shown). Since only one case had diabetes, adjusting for diabetes was not possible. Housewives did not report occupational
exposure, and only 70% of the cohort was therefore included in the analysis of occupational physical activity. We assumed that women with missing occupational activity had been housewives, with a daily physical activity equivalent to an "active" occupation. When the value for “active” occupation was imputed into the analyses, this did not affect the obtained relative risk (data not shown).

Table 3. Relative risk (RR) with 95 percent confidence interval (CI) for renal cell cancer by occupational physical activity level in 1960, 1970 and for men and women with the same level in 1960 and 1970. Results obtained by Poisson regression.

<table>
<thead>
<tr>
<th>Study cohorts</th>
<th>Physical activity</th>
<th>Men RR*</th>
<th>95% CI</th>
<th>Women RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>Very high/high</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1.06</td>
<td>0.98-1.16</td>
<td>0.99</td>
<td>0.86-1.15</td>
</tr>
<tr>
<td></td>
<td>Light</td>
<td>1.18</td>
<td>1.07-1.31</td>
<td>0.98</td>
<td>0.82-1.16</td>
</tr>
<tr>
<td></td>
<td>Sedentary</td>
<td>1.25</td>
<td>1.10-1.42</td>
<td>0.90</td>
<td>0.72-1.14</td>
</tr>
<tr>
<td></td>
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<td>0.49</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>Very high/high</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
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<tr>
<td></td>
<td>Medium</td>
<td>1.07</td>
<td>0.98-1.18</td>
<td>1.01</td>
<td>0.89-1.14</td>
</tr>
<tr>
<td></td>
<td>Light</td>
<td>1.05</td>
<td>0.94-1.17</td>
<td>0.94</td>
<td>0.80-1.10</td>
</tr>
<tr>
<td></td>
<td>Sedentary</td>
<td>1.15</td>
<td>1.00-1.32</td>
<td>0.75</td>
<td>0.59-0.95</td>
</tr>
<tr>
<td></td>
<td>P-value for trend</td>
<td>0.06</td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>1960/70</td>
<td>Very high/high</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1.11</td>
<td>0.97-1.27</td>
<td>0.99</td>
<td>0.77-1.29</td>
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<tr>
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<td>1.16</td>
<td>0.99-1.36</td>
<td>1.01</td>
<td>0.76-1.35</td>
</tr>
<tr>
<td></td>
<td>Sedentary</td>
<td>1.25</td>
<td>1.02-1.53</td>
<td>0.80</td>
<td>0.51-1.27</td>
</tr>
<tr>
<td></td>
<td>P-value for trend</td>
<td>0.03</td>
<td></td>
<td>&gt;0.50</td>
<td></td>
</tr>
</tbody>
</table>

*Relative risk adjusted for age at follow-up in 5-year intervals, socioeconomic status, place of residence, and calender year of follow-up.

7.1.2 Leisure time physical activity

The relation between leisure time physical activity and renal cell cancer was investigated in a cohort of Swedish twins (Paper II). More men than women reported regular or hard leisure time physical activity, while more women reported light or no activity during leisure time. All men and women in the cohort reported their leisure time physical activity.

We observed no major difference in the risk estimates between men and women, and therefore present the results for both sexes together. We observed a 40% non-significant decreased risk of renal cell cancer among men and women who reported regular, light or no exercise compared to those who had had hard exercise. This association was observed in models adjusting for age and sex, as well as in models also adjusting for smoking, BMI, and hypertension (RR=0.6, 95% CI 0.2-1.4 for regular activity, RR=0.6, 95% CI 0.3-0.9 for light activity, RR=0.6, 95% CI 0.3-1.2 for no exercise). Further adjustments for occupational physical activity or parity among women did not change the association (data not shown).
7.2 Body size and risk of renal cell cancer (Papers III-IV)

7.2.1 General obesity
The existing evidence of an association between body mass index and renal cell cancer risk was evaluated through a quantitative summary analysis on the published literature (Paper III). The quantitative summary analysis was based of 14 studies on each sex. The relative risks and their 95% confidence intervals for BMI as a continuous variable in studies on men are shown in Figure 2, together with the summary estimate based on a random effects model. Of the 14 studies included in the summary analysis, all but one (Talamini et al., 1990) indicated a positive association with obesity, significant in all but four studies (McLaughlin et al., 1992; Kreiger et al., 1993; Hiatt et al., 1994; Chow et al., 1996). The summary relative risk for all male studies combined with a random effect model was 1.07 (95% CI 1.04-1.09) per unit of increase in BMI (1 kg/m²). There was some heterogeneity across studies (p-value for between-study variance = 0.08). The point estimates and their 95% confidence intervals for BMI as a continuous variable in studies on women are shown in Figure 3. Only one of the 14 studies included in the summary analysis showed no association between BMI and risk of renal cell cancer (Talamini et al., 1990), while all the other indicated an increased risk among obese women. This positive association was significant in half of the studies (McLaughlin et al., 1984; Kreiger et al., 1993; Mellemgaard et al., 1995; Chow et al., 1996; Heath et al., 1997; Prineas et al., 1997; Yuan et al., 1998). When all studies on women were combined, the summary estimate from a random effect model was 1.07 (95% CI 1.05-1.09) per unit of increase in BMI. There was no significant between-study variance (p=0.24). The summary relative risk for men and women together was 1.07 (95% CI 1.05-1.09) per unit of increase in BMI. One unit of increase in BMI corresponds to 3.1 kg for a man of average height (1.77 m) and to 2.7 kg for a woman (1.64 m). When combining all studies among men and women the test for heterogeneity became statistically significant (p=0.03).

We hypothesised that different study characteristics might explain why the results varied between studies. However, positive associations of comparable strengths were present in all subsets of studies, regardless of study design, study size, study location (studies from the US vs. studies from other countries) or degree of adjustment for confounding (studies not adjusted for smoking vs. studies adjusted for smoking). For most subsets of studies, the stratum-specific between-study variance became non-significant, indicating no significant heterogeneity between the studies in these subgroups. Significant heterogeneity between studies was found only for studies with incident cases (p=0.03). However, some between-study variance was found for studies on men (p=0.08) and studies not adjusted for smoking (p=0.06). Furthermore, we found no effect modification between BMI and sex (p=0.77), study location (p=0.24), study design (p=0.16) or study size (p=0.14), respectively.

The potential influence that unpublished data could have on our summary analysis was examined. The distortion ("file drawer") analysis (Rosenthal, 1979) showed that if we could find 47 or more unpublished studies showing an inverse association between BMI and renal cell carcinoma, the hypothetical pooled estimate of the relative risk would no longer be significant. This indicates that our summary risk estimate is robust, and is not sensitive to potential publication bias.
**Figure 2.** Results of the reanalyses and summary analyses of published studies on the association between body mass index (BMI) and risk of renal cell cancer among men. Relative risk per unit of increase in BMI (kg/m²) and 95% confidence intervals (CI).

**Figure 3.** Results of the reanalyses and summary analyses of published studies on the association between body mass index (BMI) and risk of renal cell cancer among women. Relative risk per unit of increase in BMI (kg/m²) and 95% confidence intervals (CI).
The relation between BMI and renal cell cancer risk was evaluated in more detail in our population-based case-control study (Paper IV). The mean BMI increased with increasing age among both cases and controls, and at all the investigated ages cases were somewhat heavier than controls. Multivariate analyses confirmed that high BMI was associated with an increased risk of renal cell cancer for all ages, although high BMI at age 70 was associated with an increased risk only among women. The odds ratios for BMI at age 20, 70 and usual adulthood BMI are shown in Table 4. For usual adulthood BMI, we observed a trend of increasing risk with increasing BMI among women, while the trend was less apparent among men. When BMI was analysed as a continuous variable, the relative risk estimate in the multivariate model was 1.07 (95% CI 1.02-1.13) among men and 1.10 (95% CI 1.05-1.16) among women per unit increase in BMI. We found no evidence of interaction between sex and usual adult BMI (p=0.4).

General obesity is associated with hypertension and non-insulin-dependent diabetes (Ashwell, 1994), both established risk factors for renal cell cancer (McLaughlin et al., 1995; Schlehofer et al., 1996; Yuan et al., 1998; Lindblad et al., 1999). Therefore, we evaluated the associations between BMI and renal cell cancer risk in a subset of the study population without hypertension and/or diabetes. Also in this sub-sample, containing 506 cases (293 men and 213 women) and 879 controls (541 men and 338 women), we observed an association between general obesity and renal cell cancer risk. In a multivariate model adjusting for age, education, smoking, and number of times of weight loss having a BMI in the highest quartile was associated with an odds ratio of 1.7 (95% CI 1.2-2.6) among men and of 1.9 (95% CI 1.1-3.2) among women. This corresponded to 9% (OR=1.09, 95% CI 1.02-1.16) increase among men and 9% (OR=1.09, 95% CI 1.02-1.16) increase among women when BMI was analysed as continuous variable.

7.2.2 Abdominal obesity

In our population-based case-control study (Paper IV), larger waist-to-hip ratio – a measure of abdominal obesity – was associated with a significantly increased risk of renal cell cancer among both men and women in age-adjusted and multivariate models. In the multivariate model not including BMI, being in the highest quartile of waist-to-hip ratio was associated with a 80% (OR=1.8, 95% CI 1.3-2.6) increase in risk among men and a 2-fold (OR=2.1, 95% CI 1.4-3.3) increase in risk among women. Further adjustment in the multivariate model for BMI, as shown in Table 5, somewhat attenuated the association among women, but not among men. When waist-to-hip ratio was analysed as a continuous variable, we observed a 3% (OR=1.03, 95% CI 1.01-1.05) increase in risk per 0.01 unit of increase (e.g. changing from 0.96 to 0.97) in waist-to-hip ratio for men and a 4% (OR=1.04, 95% CI 1.02-1.06) increase for women in the multivariate model not including BMI. In a multivariate model simultaneously adjusting for BMI, the risk estimate was 1.03 (95% CI 1.01-1.05) among men and 1.03 (95% CI 1.01-1.06) among women. The risk estimate for usual adulthood BMI in this model was also slightly attenuated (OR=1.3, 95% CI 0.9-1.9 among men and OR=1.7, 95% CI 1.1-2.7 among women in the highest quartile). We found no evidence of interaction between sex and waist-to-hip ratio (p=0.3).
<table>
<thead>
<tr>
<th>Age 20 years</th>
<th>No of cases/controls</th>
<th>OR*</th>
<th>95% CI</th>
<th>Age 70 years</th>
<th>No of cases/controls</th>
<th>OR*</th>
<th>95% CI</th>
<th>Usual adulthood</th>
<th>No of cases/controls</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>&lt;20.78</td>
<td>98/155</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>20.78-22.30</td>
<td>114/164</td>
<td>1.1</td>
<td>0.8-1.6</td>
<td></td>
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<tr>
<td></td>
<td>22.31-23.59</td>
<td>93/156</td>
<td>1.0</td>
<td>0.7-1.4</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>≥23.60</td>
<td>133/160</td>
<td>1.2</td>
<td>0.9-1.7</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>&lt;19.37</td>
<td>63/103</td>
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<td>Referent</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>19.37-20.75</td>
<td>58/108</td>
<td>0.9</td>
<td>0.6-1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>20.76-22.22</td>
<td>58/102</td>
<td>1.0</td>
<td>0.6-1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥22.23</td>
<td>111/104</td>
<td>1.7</td>
<td>1.1-2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;23.67</td>
<td>46/61</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>23.67-25.26</td>
<td>40/66</td>
<td>0.8</td>
<td>0.4-1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.27-27.30</td>
<td>38/64</td>
<td>0.7</td>
<td>0.4-1.3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>≥27.31</td>
<td>48/63</td>
<td>0.9</td>
<td>0.5-1.6</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Women</td>
<td>&lt;23.15</td>
<td>34/42</td>
<td>1.0</td>
<td>Referent</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>23.15-24.97</td>
<td>19/43</td>
<td>0.6</td>
<td>0.3-1.3</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>24.98-27.40</td>
<td>32/41</td>
<td>1.0</td>
<td>0.5-2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>≥27.41</td>
<td>50/41</td>
<td>1.6</td>
<td>0.8-3.2</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;22.72</td>
<td>113/213</td>
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<td>Referent</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.72-24.08</td>
<td>115/220</td>
<td>0.9</td>
<td>0.7-1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.09-25.34</td>
<td>101/215</td>
<td>0.8</td>
<td>0.5-1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥25.35</td>
<td>173/220</td>
<td>1.5</td>
<td>1.1-2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>&lt;21.26</td>
<td>61/147</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.26-22.84</td>
<td>74/140</td>
<td>1.3</td>
<td>0.8-2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.85-24.60</td>
<td>90/144</td>
<td>1.7</td>
<td>1.0-2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥24.61</td>
<td>117/143</td>
<td>2.1</td>
<td>1.3-3.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, education, smoking, hypertension, and diabetes.

Since abdominal obesity is associated with hypertension and non-insulin-dependent diabetes (Ashwell, 1994), established risk factors for renal cell cancer we investigated the association between waist-to-hip ratio and renal cell cancer risk in a subset of the study population without hypertension and/or diabetes. Having a high waist-to-hip ratio (the highest quartile as compared to the lowest) was associated with an 80% increased risk (OR=1.8, 95% CI 1.2-2.7) among men, and a 50% increase in risk (OR=1.5, 95% CI 0.9-2.6) among women in a multivariate model not including BMI. Corresponding risk estimates for waist-to-hip ratio analysed as a continuous variable were OR=1.04 (95% CI 1.01-1.07) among men and OR=1.03 (95% CI 1.00-1.06) among women. Further adjustment for BMI had little effect on the risk estimates.
Table 5. Odds ratio (OR) and 95% confidence intervals (CI) of renal cell cancer in relation to waist-to-hip ratio.

<table>
<thead>
<tr>
<th>Men</th>
<th>No of cases/controls</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.92</td>
<td>85/180</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>0.92-0.94</td>
<td>118/180</td>
<td>1.3</td>
<td>0.9-1.9</td>
</tr>
<tr>
<td>0.95-0.97</td>
<td>123/183</td>
<td>1.4</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>&gt;0.98</td>
<td>173/180</td>
<td>1.8</td>
<td>1.2-2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>No of cases/controls</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.78</td>
<td>51/119</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>0.78-0.82</td>
<td>76/118</td>
<td>1.4</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>0.83-0.87</td>
<td>93/119</td>
<td>1.7</td>
<td>1.1-2.7</td>
</tr>
<tr>
<td>&gt;0.88</td>
<td>129/118</td>
<td>1.9</td>
<td>1.2-2.9</td>
</tr>
</tbody>
</table>

*Adjusted for age, education, smoking, hypertension, diabetes, and usual adulthood BMI.

7.2.3 Height

When the relation between height and renal cell cancer risk was evaluated in our population-based case-control study, we observed an increased risk among the tallest men both in the univariate and multivariate model. In the multivariate model, men 182 cm and taller had a 70% increased risk compared to men shorter than 172 cm (Table 6). Among women there was no apparent relation in the age-adjusted model, but further adjustment for potential confounders revealed a non-significant increase in risk among women 159 cm and taller in comparison to those shorter than 159 cm (Table 6). When height was analysed in the multivariate model as a continuous variable we observed a 14% increased risk among men (OR=1.14, 95% CI 1.04-1.26) and a 5% (OR=1.05, 95% CI 0.92-1.20) increased risk among women per 5 cm increase in height. We found no evidence of interaction between sex and height (p=0.7).

Table 6. Odds ratio (OR) and 95% confidence intervals (CI) of renal cell cancer in relation to height (cm).

<table>
<thead>
<tr>
<th>Men</th>
<th>No of cases/controls</th>
<th>Model 1* OR</th>
<th>95% CI</th>
<th>Model 2† OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;172</td>
<td>89/180</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>172-174</td>
<td>87/183</td>
<td>0.9</td>
<td>0.7-1.4</td>
<td>0.9</td>
<td>0.6-1.4</td>
</tr>
<tr>
<td>175-177</td>
<td>87/162</td>
<td>1.1</td>
<td>0.7-1.5</td>
<td>1.0</td>
<td>0.7-1.6</td>
</tr>
<tr>
<td>178-181</td>
<td>103/191</td>
<td>1.1</td>
<td>0.8-1.5</td>
<td>1.1</td>
<td>0.8-1.7</td>
</tr>
<tr>
<td>≥182</td>
<td>145/187</td>
<td>1.5</td>
<td>1.1-2.1</td>
<td>1.7</td>
<td>1.1-2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>No of cases/controls</th>
<th>Model 1* OR</th>
<th>95% CI</th>
<th>Model 2† OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;159</td>
<td>70/123</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>159-162</td>
<td>86/122</td>
<td>1.2</td>
<td>0.8-1.9</td>
<td>1.2</td>
<td>0.7-1.9</td>
</tr>
<tr>
<td>163-165</td>
<td>70/126</td>
<td>1.0</td>
<td>0.6-1.5</td>
<td>1.2</td>
<td>0.7-1.8</td>
</tr>
<tr>
<td>166-168</td>
<td>67/108</td>
<td>1.1</td>
<td>0.7-1.7</td>
<td>1.2</td>
<td>0.8-2.0</td>
</tr>
<tr>
<td>&gt;169</td>
<td>69/119</td>
<td>1.0</td>
<td>0.7-1.5</td>
<td>1.3</td>
<td>0.8-2.1</td>
</tr>
</tbody>
</table>

*Adjusted for age.
†Adjusted for age, education, smoking, hypertension, diabetes, usual adulthood BMI.

36
7.4 Weight change in adult life and risk of renal cell cancer (Paper IV)

We evaluated the risk of renal cell cancer in relation to different aspects of weight change. Since we observed no major difference in the risk estimates between men and women, nor observed any significant interactions between sex and weight change in adult life (p=0.54), weight fluctuations (p=0.39), reason for weight loss (p=0.62), or variability in weight (p=0.30), we present the results for both sexes together. However, the observed association of weight changes with risk of renal cell cancer depended on BMI at age 20 (p-values for interaction with BMI at age 20 were 0.05 for weight change in adult life, 0.02 for weight fluctuations, 0.04 for reason for weight loss, and 0.02 for variability in weight) and we therefore present our results stratified by BMI at age 20.

Firstly, we evaluated risk of renal cell cancer in relation to weight change in adult life (Figure 4). Subjects with a low BMI at age 20 and with a stable adult weight (gaining 0-4 kg between age 20 and 50) were used as the reference. Subjects with a high BMI at age 20 had higher risk for future development of renal cell cancer than the reference category regardless of future weight development (multivariate OR=1.7, 95% CI 1.1-2.7 among subjects with stable weight, and OR=2.9, 95% CI 1.4-6.0 among subjects gaining 20 kg or more). Weight gain was associated with an increased risk also among those with low BMI at age 20. Furthermore, weight loss was associated with increased risk, especially among subjects with a low BMI at age 20 (OR=2.6, 95% CI 1.4-4.7).

Figure 4. Risk of renal cell cancer in relation to weight change between age 20 and 50 among subjects with low (<23.30 kg/m$^2$) or high (>23.30 kg/m$^2$) BMI at age 20. Adjusted for age, education, smoking, hypertension, and diabetes. The error bars represent 95% confidence intervals for the odds ratio. The reference group is indicated Ref.
Table 7. Odds ratio (OR) and 95% confidence intervals (CI) of renal cell cancer in relation to weight fluctuations stratified by BMI at age 20, with one common reference category.

<table>
<thead>
<tr>
<th>Weight fluctuations</th>
<th>BMI at age 20 &lt;23.30 kg/m²</th>
<th></th>
<th></th>
<th>BMI at age 20 ≥23.30 kg/m²</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases/controls</td>
<td>Mean no of times of weight change</td>
<td>OR*</td>
<td>95% CI</td>
<td>No of cases/controls</td>
<td>Mean no of times of weight change</td>
<td>OR*</td>
</tr>
<tr>
<td>Stable weight</td>
<td>231/594</td>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>52/117</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain only</td>
<td>58/105</td>
<td>1.6</td>
<td>1.1</td>
<td>0.7-1.7</td>
<td>19/16</td>
<td>1.9</td>
</tr>
<tr>
<td>Weight loss only</td>
<td>86/164</td>
<td>1.6</td>
<td>1.5</td>
<td>1.0-2.2</td>
<td>37/44</td>
<td>1.6</td>
</tr>
<tr>
<td>Weight gain and weight loss</td>
<td>119/202</td>
<td>4.9</td>
<td>1.2</td>
<td>0.8-1.6</td>
<td>72/50</td>
<td>6.3</td>
</tr>
<tr>
<td>Reason for weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable weight</td>
<td>231/594</td>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>52/114</td>
<td>0</td>
</tr>
<tr>
<td>Never dieted</td>
<td>114/233</td>
<td>1.5</td>
<td>1.2</td>
<td>0.9-1.7</td>
<td>59/42</td>
<td>1.6</td>
</tr>
<tr>
<td>Only dieted</td>
<td>76/124</td>
<td>2.5</td>
<td>1.3</td>
<td>0.8-1.7</td>
<td>32/36</td>
<td>3.3</td>
</tr>
<tr>
<td>Dieted and lost weight for unknown reasons</td>
<td>20/22</td>
<td>4.0</td>
<td>2.0</td>
<td>0.9-4.5</td>
<td>9/6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education, smoking, hypertension, diabetes, and usual adulthood BMI
Secondly, we evaluated the effect of weight fluctuations. Subjects with a high BMI at age 20 who had both gained and lost weight, had 90% increased risk of renal cell cancer, while a weak and non-significant increase was found among those with low BMI at age 20 (Table 7). The number of times of weight loss differed between the categories, and subjects who had both gained and lost weight had changed weight more than the other categories.

Subjects who reported ever losing weight were stratified into three categories: those who only lost weight due to dieting, those who never lost weight due to dieting, and an intermediate group who lost weight both due to dieting and for unknown reasons (Table 7). Subjects who only lost weight due to dieting had a weak and non-significant increased risk of renal cell cancer in the multivariate model, regardless of BMI at age 20. Those with high BMI at age 20 who lost weight, but never due to dieting, had a two-fold increase in risk, while those with low BMI at age 20 had a weak and non-significant increased risk. Subjects who lost weight both due to dieting and for unknown reasons had an increased risk regardless of their BMI at age 20. The number of times of weight loss differed between the categories, and subjects who had lost weight both due to dieting and for unknown reasons had the highest number of weight changes.

Thirdly, changes in body weight throughout adult life were also explored as variability in weight derived from the weight change regression model. Variability in weight was only associated with renal cell cancer risk among subjects with high BMI at age 20. Multivariate adjustment attenuated this association, but a 60%, non-significant, increased risk persisted among subjects in the highest quartile (OR=1.6, 95% CI 0.8-3.0).

7.3 Birth weight and risk of renal cell cancer (Paper V)
A total of 648 cases of renal cell cancer and 900 control subjects in our population-based case-control study reported their birth weight and were included in the analyses.

Case subjects with missing or unknown birth weight (n=229) tended to be older than case subjects who reported their birth weight, while there was no difference in sex distribution. After adjustment for age and sex, they had lower education, were shorter, and suffered more often from hypertension. No difference was seen in the prevalence of smoking, BMI, or diabetes. Similarly, control subjects with missing or unknown birth weight (n=608) were older than control subjects who reported their birth weight, but there was no difference in sex distribution. After adjustments for age and sex, they were less educated, smoked less, were shorter, and had higher BMI. No difference was seen in the prevalence of hypertension or diabetes.

In age-adjusted models as well as in multivariate models further adjusting for education, smoking, usual adult BMI and height, an increased risk was observed among men with a birth weight of 3500 g and over compared to those with a birth weight between 3000 g and 3499 g (multivariate OR=1.3, 95% CI 1.0-1.8). Men with a birth weight below 3000 g had a weak and non-significant increased risk of renal cell cancer (OR=1.2, 95% CI 0.8-1.8). We found no clear relation between birth weight risk of renal cell cancer among women (OR=0.9, 95% CI 0.6-1.3 for high, and OR=1.0, 95% CI 0.6-1.5 for low birth weight).
Low birth weight is associated with hypertension (Barker et al., 1990; Barker et al., 1993) and non-insulin-dependent diabetes (Barker et al., 1993; Hales et al., 1991), both associated with an increased risk of renal cell cancer (McLaughlin et al., 1995; Schlehofer et al., 1996; Yuan et al., 1998; Lindblad et al., 1999). Therefore, we investigated the association between birth weight and renal cell cancer in a subset of the study population without hypertension or diabetes. Also in this sub-sample, containing 380 case subjects (217 men and 163 women) and 657 control subjects (394 men and 263 women), men with a birth weight of 3500 g or more had a significantly increased risk of renal cell cancer multivariate OR=1.8, 95% CI 1.2-2.6, while women did not (OR=0.8, 95% CI 0.5-1.3). Furthermore, we observed a non-significant increased risk of renal cell cancer among both men and women with birth weight below 3000 g (OR=1.6, 95% CI 0.9-2.8 and OR=1.3, 95% CI 0.8-2.3, respectively). Due to the limited numbers, separate analyses on men and women with hypertension or diabetes were not meaningful.
8. General discussion

8.1 Methodological considerations

8.1.1 Study design
Two of the studies in this thesis were cohort studies (Papers I-II), based on prospectively collected data. In cohort studies, exposure information is collected before the occurrence of the outcome event and any misclassification of exposure will therefore be non-differential. A disadvantage of a cohort study design is that large number of participants and a long follow-up time is needed to study a rare disease like renal cell cancer. Therefore there are few cohort studies of renal cell cancer published and they often include relatively few case subjects. Both our cohorts used in this thesis are large compared to previous reports on physical activity and renal cell cancer risk. Lack of information of possible confounding factors is a weakness in most register based cohort studies, and also in our study from the Swedish Cancer-Environment Registry. However, we were able to control for potential confounding factors in our study based on the Swedish Twin Registry, and found no evidence of major confounding.

A meta-analysis of the published literature on obesity and renal cell cancer risk is included in this thesis (Paper III). Meta-analysis is a systematic approach to identify, appraise, synthesise, and combine the results of relevant studies to arrive at conclusions about a body of research. The strengths of our meta-analysis of the published literature on obesity and renal cell cancer risk include the large number of included studies and, more importantly, the quantitative summary analysis comparing the relative risk of renal cell cancer is based on the same increase in BMI for both sexes.

The case-control study design is well suited for studying a rare disease like renal cell cancer with a long latency period from exposure to disease development. Furthermore, it provides an opportunity to evaluate the risk of developing a particular disease in relation to a wide range of exposures and is usually more cost-effective compared to a cohort study. The population-based design used in this thesis (Papers IV-V) should further give a high external validity, provided that the internal validity is satisfactory.

The accuracy of the studies in this thesis – as with any epidemiological study – depends on the absence of error in estimation. Such errors can be either random or systematic. Precision corresponds to the reduction of random error, while validity corresponds to the reduction of systematic error.

8.1.2 Precision
The precision depends mainly on the sample size, exposure prevalence and the extent of exposure misclassification. We used 95% confidence intervals to provide information about the precision of our studies. A statistically significant result does not mean that chance cannot have accounted for the findings, only that such explanation is unlikely. The sample size of our case-control study was based on power-calculations indicating that we would be able to detect a relative risk of 2 with 90% power if 10% of the individuals were exposed and the significance level was 0.05.
Given the observed dose-response, chance alone is an unlikely explanation of the observed inverse association between physical activity (Paper I) and renal cell cancer, or of the increased risk observed among subjects with abdominal obesity (Paper IV). Given the consistency between studies, it is unlikely that chance alone accounts for the observed association with general obesity (Paper III-VI). However, the findings of weak and non-significant association with physical activity (Paper II) and birth weight (Paper V) with renal cell cancer must be interpreted with caution. Random error may be of more concern in subgroup analysis but – even though the stratified analysis of weight change (Paper IV) could be hampered by low statistical power – the consistency between the results from the different measurements of weight change makes chance alone an unlikely explanation for these findings.

8.1.3 Validity

Selection bias

Selection bias – error due to systematic differences in characteristics between those who are selected for study and those who are not – is a potential pitfall of epidemiological studies. In cohort studies, the selection of study participants does not give rise to selection bias, but the non-response which occurs if all individuals cannot be followed-up will introduce this systematic error. Complete case identification is therefore a major challenge in epidemiologic studies. In our studies, cases were ascertained using the more than 98% complete Swedish Cancer Register, which should minimise the selection bias in our cohort studies (Papers I-II).

Despite this, we cannot exclude the possibility that some cases of renal cell cancer may be undetected (Hellsten et al., 1981), and that control subjects could have subclinical disease. However, this misclassification is not a large problem since renal cell cancer is a relatively rare disease in the population. Moreover, such misclassification would only underestimate the obtained risk estimates. Misclassification among cases in our case-control study is improbable as all were confirmed by histopathology or cytology.

Selection bias is a main limitation in meta-analyses. The term “publication bias” is often used to describe the possibility that the studies included in a meta-analysis are a biased selection of studies in general, since some studies may remain unpublished. A further limitation of a meta-analysis is that not all published studies can be included in the summary analysis, since they may not present required information. However, it is not likely that any of these biased our observation (Paper III) since we found similar relative risks in all strata when our analysis was stratified by different study characteristics. Moreover, the distortion analysis, used to evaluate the sensitivity of our estimates to the publication bias, indicated that a large number of non-significant unpublished studies would be necessary to nullify the summary results.

The selection of controls in a case-control study might be a potential source of selection bias. In our case-control study (Papers IV-V), controls were randomly selected from the entire study base, which means that they adequately represent the study base that generated the cases and that selection bias is avoided. However, non-participation may introduce selection-bias, and obtaining high participation rates is therefore a primary goal of any case-control study. We managed to obtain a reasonably high participation (69% of the eligible cases and 74% of the selected controls) in our study. Non-participants did not differ from participants with regards to sex or residency, but were slightly older. Although a substantial number of cancer patients (12%) died before they could be included in the study or were too ill to participate
(6%), this would influence our results only if any of the investigated exposures is associated with short-term prognosis of renal cell cancer. Likewise, refusing to participate in the study, which was more common among the controls, would affect our results only if refusal was associated with any of the investigated exposures. When selection bias was evaluated in an earlier case-control study of renal cell cancer, no association between participation and obesity was found among male cases or control subjects or among female controls, with the exception that participating case women were slightly more obese than non-participating (Maclure and Hankinson, 1990b). Phone interviews were used in 14% of the control subjects as only 60% of them completed the mailed questionnaire. The interview covered most items in the questionnaire with the exceptions of weight at age 20, 30, 40, 50, 60, 70, waist and hip circumferences, birth weight, hypertension, and diabetes. Thus, a proportion of controls had to be excluded from analyses of these exposures, possibly introducing bias. Yet, as controls participating through the interview did not differ essentially from other controls with regard to most important renal cell cancer risk factors, we judge our data unlikely to be flawed by selection bias.

**Information bias**

Misclassification of exposure information in our data is likely. Yet, self-reported information on weight, height, and even birth weight is known to be quite accurate (Kuskowska-Wolk et al., 1989; Curhan et al., 1996; Troy et al., 1996; Sanderson et al., 1998). Furthermore, in the cohort studies (Papers I-II), any misclassification of the exposure should be non-differential, and thus only lead to underestimation of the true association (Rothman and Greenland, 1998). In the case-control study (Papers IV-V), on the other hand, differential misclassification of the exposure can not be excluded, for example obese subjects in general underreport their weight more than non-obese subjects, and underweight subjects overestimate their body size (Kuskowska-Wolk et al., 1989). Furthermore, we can not exclude that differential misclassification affected our results on weight changes, although we disregarded recent weight and weight changes during the last two years before interview, that might be affected by the renal cell cancer among the case subjects. Moreover, our finding that a high waist-to-hip ratio is associated with an increased risk of renal cell cancer must be interpreted with caution, since we used self-reported information on waist- and hip circumference taken after diagnosis, and most often also after surgery, for the case subjects. Although self-reported waist- and hip circumference have been found to be reasonably valid (Rimm et al., 1990), waist- and hip circumference might be affected by the disease, or the treatment. However, our finding that a high waist-to-hip ratio is associated with increased renal cell cancer risk is in agreement with a prospective study where exposure information was collected before diagnosis (Prineas et al., 1997).

**Confounding**

Confounding – the distortion of a measured association between main exposure and disease introduced by another factor related to both this exposure and the disease – is another principal validity issue in observational studies. Lack of information of possible confounding factors is a weakness in most register-based cohort studies, and also in our study within the Swedish Cancer-Environment Register (Paper I). However, we were able to control for potential confounding factors in our study within the Swedish Twin Register (Paper II), and found no evidence of major confounding. In our case-control study (Papers IV-V) we had detailed information on most established and suggested risk factors for renal cell cancer, and were thus able to adjust for them.
External validity

The study participants in all studies, with exception of the meta-analysis, were selected from the general population. The Cancer-Environment Register study (Paper I) included virtually all Swedish men and women, and the results from this study should therefore be generalizable to men and women in Sweden. The Twin Registry study (Paper II) should at least be generalizable to Swedish twins, but there is no obvious reason why physical activity would affect twins differently than other men and women. In the case-control study (Papers IV-V), both cases and controls were selected from 19 counties in Sweden (covering most of the country). The participation-rate in this study was relatively high and, given internal validity, it is therefore likely that the results would be applicable to the target population.

8.2 Interpretations and implications

8.2.1 Physical activity and risk of renal cell cancer (Papers I-II)

In our large cohort study based on the Swedish Cancer-Environment Register (Paper I), we observed an inverse association between estimated occupational physical activity and renal cell cancer risk among men. The risk increased monotonically with decreasing level of physical activity, and men with long-term sedentary jobs had a statistically significant 25% excess risk compared with those who had very high or high levels of physical activity at work. In contrast, we found no evidence of an inverse association between either occupation or leisure time physical activity among men in our prospective cohort of Swedish twins (Paper II). Furthermore, we found no evidence of an inverse association for either occupational or leisure time activity among women, from either of these studies. The results from our two studies are summarized in Figure 5.

Figure 5. Multivariate risk ratio (RR) and 95% confidence intervals (CI) for renal cell cancer

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>RR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational, men (CER III)*</td>
<td></td>
</tr>
<tr>
<td>Occupational, women (CER III)*</td>
<td></td>
</tr>
<tr>
<td>Occupational, men and women (Twins)†</td>
<td></td>
</tr>
<tr>
<td>Leisure time, men and women (Twins)‡</td>
<td></td>
</tr>
</tbody>
</table>

*Sedentary vs. very high/high occupational physical activity.
†Sedentary vs. physically strenuous occupation.
‡None vs. hard leisure time physical activity.
There is no obvious reason for the inconsistency of the risk estimates from our two studies. In the study based on the Swedish Cancer-Environment Register, we observed an inverse association among men, but not among women. If the effect of physical activity is dose-dependent, as indicated by the results on men, women might not reach the levels necessary to obtain a protective effect. Further, occupational physical activity might represent a larger part of the total physical activity for men than for women.

There is also a lack of consistency for the results on occupational physical activity based on the Swedish Cancer-Environment Register and the Swedish Twin Registry. This might be explained by the different assessment of physical activity used in these two studies. However, when our physical activity matrix, used to assess physical activity through job titles in Paper I, was validated against self-reported level of occupational physical activity in the Swedish Twin Registry (i.e. the measurement of exposure in Paper II), good agreement was found between the self-scoring and the experts’ scoring (Moradi et al., 1998). Despite this, the three predefined categories of occupational physical activity used in the Swedish Twin Registry might be insufficient to assess the range of exposure needed to detect a possible association. In the Swedish Cancer-Environment Register the subjects were classified into four categories.

Confounding by known risk factors for renal cell cancer is not likely to explain the significant association detected in the study from the Swedish Cancer-Environment Register, since we found no evidence of strong confounding in our study from the Swedish Twin Register, where we adjusted for most of the established risk factors.

However, it should be noted that despite the significant association observed for occupational physical activity among men in the Swedish Cancer-Environment Register, the confidence intervals for all our findings in Paper I and Paper II are overlapping. Thus, there is no significant difference between our findings.

Our finding of an inverse association between occupational physical activity and renal cell cancer among men is consistent with a previous Swedish case-control study showing an inverse association among men and no clear association among women (Lindblad et al., 1994). Three other case-control studies found no apparent association with occupational physical activity for either sex (Goodman et al., 1986; Mellemgaard et al., 1994; Mellemgaard et al., 1995). In contrast to our study within the Swedish Cancer-Environment register, all these studies used retrospective self-reported estimations of occupational physical activity level. Our finding of no clear association for leisure-time physical activity is in agreement with all previous studies (Goodman et al., 1986; Paffenbarger et al., 1987; Lindblad et al., 1994; Mellemgaard et al., 1994; Mellemgaard et al., 1995; Prineas et al., 1997).

Physical activity could affect the risk of renal cell cancer either directly or indirectly, by affecting some other factors associated with renal cell cancer. Possible direct actions of physical activity include effects on plasma levels of insulin and insulin-like growth factors (IGFs). A sedentary life might lead to higher levels of these hormones (Mayer-Davis et al., 1998, Eliakim et al., 1996, 1998), which both could contribute to the growth, proliferation, and/or metabolism of renal cell cancer (Kellerer et al., 1995). Epidemiological studies indicate that subjects with diabetes, which is associated with higher plasma insulin levels, have an increased risk of renal cell cancer (Schlehofer et al., 1996; Lindblad et al., 1999). Furthermore, physical activity might affect other aspects of the hormonal milieu for example by decreasing plasma levels of some estrogens (Cauley et al., 1989, Mendoza et al., 1991).
Potent estrogens have been shown to induce renal tumours in animal models (Stadler and Vogelzang, 1993), but there is little epidemiological evidence supporting an association of exogenous estrogens in humans (McLaughlin and Lipworth, 2000). Moreover, the immune system, which is involved in regulating the susceptibility to both the initiation and promotion of tumours, can be suppressed or enhanced by physical activity, depending on the intensity, duration, and frequency of activity (Shephard and Shek, 1995). In general, a moderate dose of endurance exercise has a beneficial effect on immune response. Physical activity might also be associated with renal cell cancer risk via obesity or hypertension, both established risk factors for this disease (McLaughlin and Lipworth, 2000).

8.2.2 Body size and risk of renal cell cancer (Papers III-IV)

Our quantitative summary analysis (Paper III) showed that the association between general obesity, measured as increasing BMI, and risk of renal cell cancer was equally strong among men and women. Our population-based case-control study (Paper IV) added further evidence to the existing results on general obesity, and moreover, revealed an independent association with abdominal obesity, measured as increasing waist-to-hip ratio. This study also indicates that tall men and women might have an increased risk of renal cell cancer.

The discrepancy between the results from our quantitative summary analysis and previous qualitative reviews, reporting stronger association between general obesity and renal cell cancer risk among women than among men, could be explained by the differences in distribution of BMI among men and women. Although an equal amount of men and women is of excess weight, women tend to be more obese. In the US, where a majority of the published studies was conducted, 59% of the men and 50% of the women have a BMI of 25 kg/m² or more, but 20% of the men and 25% of the women are obese (BMI>30 kg/m²) (Flegal et al., 1998). Therefore, the highest BMI quartile for women usually consists of individuals with higher mean BMI than the highest quartile for men, resulting in a higher observed relative risk. The results from our population-based case-control study were in agreement with the results from our meta-analysis. Although the odds ratios were somewhat higher for women than for men, the confidence intervals were overlapping. The relation between abdominal obesity and renal cell cancer has, to our knowledge, previously only been investigated among women, with results similar to ours (Prineas et al., 1997). Our finding that tall height might be associated with increased risk of renal cell cancer is in contrast to three previous studies (Mellemgaard et al., 1995; Chow et al., 1996; Chow et al., 2000), but being in the highest tertile or quartile of height was associated with a weak and non-significant association among women, but not among men, in two earlier studies (Lindblad et al., 1994; Mellemgaard et al., 1994). Furthermore, height was significantly associated with increased risk in an Icelandic cohort study (Tulinius et al., 1997). Also in our study, the association with height was limited to the tallest men and women.

General and abdominal obesity and height might be associated with increased risk of renal cell cancer through hormonal mechanisms. Increasing BMI and a high waist-to-hip ratio is accompanied by elevated levels of fasting serum insulin and free insulin-like growth factor-I (IGF-I) among both men and women (Kissebah, 1991; Frystyk et al., 1995). Furthermore, previous studies have shown that height is positively associated with circulating IGF-I levels (Landin-Wilhelmsen et al., 1994; Signorello et al., 2000). As for physical activity, general and abdominal obesity and height might affect the risk of renal cell cancer through insulin and/or IGF-I. General and abdominal obesity might also be associated with renal cell cancer risk via hypertension or diabetes, both established risk factors for this disease (McLaughlin et
al., 1995; Schlehofer et al., 1996; Yuan et al., 1998; Lindblad et al., 1999). It is therefore plausible that the increase in risk of renal cell cancer among obese individuals could be mediated via hypertension and/or diabetes. However, in our study, this increased risk persisted also among a sub-sample without hypertension or diabetes, indicating that there might also be some other mechanism involved. Both general and abdominal obesity might affect other aspects of the hormonal milieu by increasing levels of free endogenous estrogen (Zumoff, 1988; Kirschner & Samojlik, 1991). Although potent estrogens have been shown to induce renal tumours in animal models (Stadler and Vogelzang, 1993), there is little epidemiological evidence supporting an association of exogenous estrogens in humans (McLaughlin and Lipworth, 2000). Obese individuals have been reported to have a higher glomerular filtration rate and renal plasma flow independent of hypertension, which may increase risk of kidney damage (Hall, 1994; Ribstein et al., 1995). Conceivably, such damage could result in increased cell proliferation to replace damaged cells and therefore make the kidney more susceptible to carcinogens.

8.2.3 Weight change and risk of renal cell cancer (Paper IV)

We evaluated the risk of renal cell cancer in relation to different aspects of weight change (Paper IV). Weight gain in adulthood was associated with an increased risk of renal cell cancer, especially among subjects with high BMI in young adulthood. Adult weight loss was also associated with an increased risk, especially among those with low BMI at age 20. Having both gained and lost weight, or having a high variability in weight, was associated with increased risk primarily among those with high BMI in young adulthood. However, the findings on weight loss and weight variability must be interpreted with caution since we can not exclude the possibility that differential misclassification affected these results. Furthermore, weight loss due to dieting was not associated with a clear increase in risk, in our study. On the other hand, weight loss might have different effects depending on its reason.

Our findings that weight gain in adult life is an independent predictor of renal cell cancer risk is in agreement with two prospective studies, one among women (Prineas et al., 1997), and one among men (Chow et al., 2000), while a previous case-control study found an association only among women (McLaughlin et al., 1984). Our results indicating that further weight gain in adult life among those who are obese already at age 20 is associated with the highest risk, are in agreement with one previous case-control study (Asal et al., 1988b). We observed a relation between weight loss in adult life and risk of renal cell cancer. A similar association was observed in a prospective study among Swedish men, although with borderline statistical significance (Chow et al., 2000). Weight fluctuation was associated with an increased risk in one previous study (Lindblad et al., 1994), although only among women, not among men, and not in two other studies (Mellemgaard et al., 1995, Chow et al., 1996). In our study, the positive association of weight fluctuation and variability was confined only to subjects with high BMI at age 20. This may explain the lack of consistency with previous studies not taking into account weight in early adulthood.

Weight gain might increase the risk of renal cell cancer simply by increasing the total obesity. It is also possible that diabetes is an intermediate step in an association between weight gain and renal cell cancer, since adult weight gain has been shown to be a risk factor for diabetes (Colditz et al., 1995). It is less clear how weight loss could affect the risk of renal cell cancer.
8.2.4 Birth weight and risk of renal cell cancer (Paper V)

Our study suggests that birth weight, a marker for fetal nutrition and growth, might be associated with the risk of renal cell cancer many years later. To our knowledge, this has not previously been studied. In our data, both high and low birth weight was related to increased renal cell cancer risk among men, while the results on women were less clear. The reason for this discrepancy in findings between men and women is not clear. However, low birth weight was associated with an increased risk among both sexes in a subset of men and women without hypertension or diabetes.

An association between birth weight and renal cell cancer is biologically plausible. The total number of nephrons, the structural and functional unit of the kidney, is defined at birth, after which no new nephrons are formed (Mackenzie and Brenner, 1995). Birth weight is linearly correlated with the number of nephrons (Merlet-Benichou et al., 1999), and subjects with high birth weight therefore have a larger number of nephrons, and thereby more cells at risk of malignant transformation. On the other hand, fetal growth retardation, marked by low birth weight, leads to small kidneys with deficiency in nephron number (Mackenzie and Brenner, 1995; Merlet-Benichou et al., 1999). Recent evidence supports the view that deficits in nephron number indeed predispose to renal disease (Brenner and Mackenzie, 1995; Barker et al., 1993). A compensatory glomerular hypertrophy and hyperfiltration could result in glomerulosclerosis, which makes the nephrons more vulnerable for exposure to carcinogens. Furthermore, low birth weight is associated with hypertension (Barker et al., 1990; Barker et al., 1993) and non-insulin-dependent diabetes (Barker et al., 1993; Hales et al., 1991). Both these diseases are associated with an increased risk of renal cell cancer (McLaughlin et al., 1995; Schlehofer et al., 1996; Yuan et al., 1998; Lindblad et al., 1999) and could therefore be intermediate steps in an association between low birth weight and renal cell cancer. In our study, however, low birth weight was suggested to increase the risk of renal cell cancer among a sub-sample of men and women without hypertension or diabetes, indicating that there may also be some other mechanism involved.

8.2.5 Preventive measures

Morbidity and mortality of renal cell cancer might be decreased by prevention. Since localised tumours have a better prognosis, earlier detection of the tumours could decrease the mortality of renal cell cancer. Incidental detection of renal cell cancer is rising, partly because of increased use of imagine procedures, such as ultrasound and computed tomography, but mass screening for renal cell has not been recommended for the general population. Therefore, primary prevention emerges as an attractive strategy for decreasing both morbidity and mortality (Chow et al., 1999; Van Poppel et al., 2000).

Never starting to smoke, or quitting smoking, is probably the most effective way to prevent renal cell cancer. The decreasing prevalence of tobacco smoking might reduce the incidence of renal cell cancer. A recent international study showed that 16% of the renal cell cancer cases could be attributed to smoking (McLaughlin et al., 1995a). Moreover, this will also prevent against most chronic diseases.

The close relation between obesity and renal cell cancer indicates that recommendations of maintaining a healthy weight in adulthood might reduce the incidence of this disease. Overall excess body mass (BMI>25 kg/m²) have been estimated to account for 25% of the kidney cancers in Europe (Bergström et al., 2001). A key question for prevention is whether or not
we should advice overweight individuals to lose weight, given the potential health risks associated with weight loss. Our study indicates that weight loss might be associated with increased risk of renal cell cancer, but we found no significant excess risk among subjects who only lost weight due to dieting, compared to subjects with stable weight. Moreover, weight loss and repeated weight changes might have other adverse health effects, such as increasing over-all and cardiovascular mortality (Lissner et al., 1991). The literature about weight loss, weight variability and subsequent health effects is conflicting, but a review a few years ago led to the conclusion that the available evidence that weight loss would have an adverse effect was not sufficiently compelling to override the potential benefits of a moderate weight loss in obese individuals (National Task Force on the Prevention and Treatment of Obesity, 1994).

8.2.6 Future studies of physical activity, body size, and birth weight in relation to renal cell cancer risk

The results of this thesis give rise to questions that need to be disentangled in future research.

The potential association between physical activity and renal cell cancer merits further attention. To date, the results are inconsistent. Accurate measurement of type, intensity and duration of physical activity is critical in future studies. Long-term physical activity, i.e. in different periods of life, should also be assessed in future studies.

The association between abdominal obesity and risk of renal cell cancer needs to be investigated in prospectively collected data. To date, this has only been done among women (Prineas et al., 1997). Although our study shows an independent effect among both sexes, we cannot exclude the possibility that our information on waist- and hip circumference, measured after diagnosis and most often also after surgery for the cases, introduced differential misclassification between cases and controls.

To better understand the mechanisms underlying the observed associations between physical activity, general and abdominal obesity, and height, a direct study of insulin-like growth factor-I (IGF-I) and renal cell cancer risk is needed. Physical activity and body size might influence the risk of renal cell cancer through IGF-I, which has been shown to be associated with other hormone dependent cancers like prostate cancer (Chan et al., 1998; Wolk et al., 1998), premenopausal breast cancer (Hankinson et al., 1998), colon cancer (Ma et al., 1999; Giovannucci et al., 2000), but was never studied in relation to renal cell cancer.

Future exploration of our finding that weight change through adult life is associated with an increased risk of renal cell cancer is warranted. Accurate measurement of the direction and reason for the weight change is essential in these studies. Since the possibility of differential misclassification between cases and controls is a major weakness of our study, especially for the information on weight loss, being able to from weight changes caused by the renal cell cancer is essential in future studies. This is ideally assessed in prospectively collected data.

Our observation that obesity already in young adulthood was associated with an increased risk of renal cell cancer indicates the need for studies on body size in childhood and adolescence in relation to renal cell cancer risk in adult life. To our knowledge, there are no published reports on childhood and adolescence weight, height and growth and the risk of adult renal cell cancer.
The relation between birth weight and risk of renal cell cancer needs to be clarified in further studies. To exclude the effect of non-differential misclassification on observed results, these studies should be based on actual birth weight, obtained from birth records. Furthermore, these studies should also take into account other pre- and perinatal factors.

Today, it is largely unknown if and how environmental and life-style factors affect prognosis of renal cell cancer. The cases in our case-control study (Papers IV-V) provide an ideal setting for a prognostic study. This study would also take into account clinical and tumour associated variables.
9. Conclusions

• There is a potential inverse association between physical activity and risk of renal cell cancer. High occupational physical activity was associated with a decreased risk among men, while we found no evidence for this among women. Furthermore, we found no evidence of a protective effect of leisure time physical activity.

• Body size is related to renal cell cancer risk.
  – General obesity, reflected by a high body mass index, is associated with an increased risk among both men and women.
  – Abdominal obesity, reflected by a high waist-to-hip ratio, might be associated with an increased risk independently of general obesity.
  – Tall height might be associated with an increased risk of renal cell cancer.

• Weight gain and repeated weight changes throughout adult life might increase the risk, especially among those who have a high body mass index already in young adulthood.

• Factors operating in utero, reflected by a high or low birth weight, might affect the risk of renal cell cancer in adulthood.
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