Adolescent Obesity and Paternal Country of Origin Predict Renal Cell Carcinoma: A Cohort Study of 1.1 Million 16 to 19-Year-Old Males

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Purpose: The incidence of renal cell carcinoma has increased in recent decades, particularly among middle-aged adults. Early precursors of renal cancer remain unclear. We evaluated the association of body mass index and height determined in late adolescence, and paternal or grandpaternal country of origin with the risk of renal cell carcinoma.

Materials and Methods: Health related data on 1,110,835 males at ages 16 to 19 years who were examined for fitness for military service between 1967 and 2005 were linked to the Israel National Cancer Registry in this nationwide, population based cohort study. We used Cox proportional hazards modeling to estimate the HR of renal cell carcinoma associated with birth year, body mass index, height, father country of origin and socioeconomic indicators.

Results: During 19,576,635 person-years of followup renal cancer developed in 274 examinees. Substantial excess risk was conferred by a body mass index of greater than 27.5 kg/m^2 compared to less than 22.5 kg/m^2 (HR 2.43, 95% CI 1.54–3.83, p <0.0001). Asian or African origin was protective compared to European origin (African origin HR 0.67, 95% CI 0.49–0.92).

Conclusions: Overweight in late adolescence is a substantial risk factor for renal cell carcinoma. European origin is independently associated with excess risk and it persists among Israeli born males. Preventing childhood obesity may be a promising target for decreasing the burden of renal cancer.

Key Words: kidney; carcinoma, renal cell; obesity; ethnic groups; adolescent

Abbreviations and Acronyms

BMI = body mass index

RCC = renal cell carcinoma

VHL = von Hippel-Lindau

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THE incidence of RCC has increased in the last several decades, particularly among the younger middle-aged group. This increase cannot be attributed only to improved imaging and diagnosis since it apparently also reflects an increase in the prevalence of risk factors.[1,2] The determinants of RCC diagnosed in middle age remain unclear with respect to the effects of adolescent exposure.

Adult overweight is an established risk factor for RCC. A meta-analysis of 17 cohort studies showed that a 5 unit increase in BMI was associated with a 34% and 24% increased risk of RCC in women and men, respectively.[3] Other groups also reported an increased risk of RCC in obese women but much less so in obese men.[4,5]

The literature is equivocal regarding the relationship between age at

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obesity development and RCC risk.[6,7] A cohort study of 320,618 participants with a mean age of 63 years who recalled their height and weight at specific points in the past confirmed our knowledge of current adult BMI and RCC, and indicated a strong association with BMI recall at age 50 years.[8] However, the relationship was attenuated for BMI recalled at age 18 years. Researchers concluded that while BMI is clearly related to RCC, the main risk is derived from adult weight gain and adult weight, and not from overweight in childhood or adolescence.[8] This important issue should be addressed using measured rather than recalled anthropometric data.

Height, a complex variable determined by genetic, nutritional and health related factors, was related to RCC in a few studies, while others showed no such relation.[9]

The lowest worldwide incidence of RCC is in Asia, while the highest rates are in North America, Europe and Australia. It remains unresolved whether this geographic disparity is related to different genetic backgrounds, different environmental and lifestyle patterns or different access to health care and diagnostic modalities.[2]

To examine the role of obesity and height in late adolescence and of geographic origin in regard to generational effects we linked these variables, as measured at age 17 years in more than 1,100,000 young Israeli males, with the Israel National Cancer Registry to determine the incidence of RCC in early to mid adulthood.

MATERIALS AND METHODS

Israelis are called to military recruitment centers, predominantly at age 17 years, for an obligatory medical board examination to assess suitability for military service. This includes reviewing the medical file from the primary care physician, taking a medical history and performing physical examination. Included in this study were 1,110,835 Jewish males 16 to 19 years old (age 17 years in 84%) who were examined from 1967 to 2005. Excluded were males with a cancer diagnosis before the date of the medical examination. Baseline adolescent data included birth year, birth country, country of origin (paternal birthplace or grandpaternal birthplace if the father was Israeli born) grouped as Europe (including countries of emigration from Europe), Asia, Africa and Israel, socioeconomic status of the city/town/village/settlement of residence on a 1 to 10 scale (as defined by the Central Bureau of Statistics and grouped as 1 to 4, 5 to 7 and 8 to 10), school type (religious/secular) and years of schooling.

Height and weight were measured and recorded during the medical examination. BMI was calculated as weight in kg divided by height in m^2. BMI was analyzed in 2 modes, including initially by quintiles and then refined by 2.5 kg/m^2 increments (BMI less than 22.5, 22.5 to 25, 25 to 27.5 and greater than 27.5 kg/m^2). Height was analyzed according to quintiles.

The Israel National Cancer Registry, a population based registry in operation since 1960, meets internationally accepted requirements for the coding system (ICD-O-3) and completeness of data. Reporting has been mandatory since 1982 and it was excellent before this date. Coverage exceeds 95%. The cohort was followed a total of 19,576,635 person-years.

We included in analysis all malignant tumors of the renal parenchyma, of which most were hypernephroma and clear cell adenocarcinoma. We also included a few cases of kidney cancer with an uncertain histological classification or those not otherwise specified. We did not include nephroblastoma (Wilms tumor), liposarcoma or transitional cancer of the renal pelvis.

Statistical analyses were performed with SPSS®, version 17. Participant characteristics are presented as the arithmetic mean ± SD or a percent. Cox proportional hazards models were used to model associations between baseline adolescent characteristics and time to RCC diagnosis. Appearance of a first malignancy of any type during followup excluded further followup. Death and emigration from Israel were not censored since these data were only partially available. Variables were initially introduced individually. Multivariate analysis included variables showing a statistically significant association on univariate analysis at the $p < 0.05$ level, including birth year, BMI (quintiles or 2.5 kg/m^2 categories), height (quintiles) and paternal country of origin (Israel, Europe, Asia or North Africa). In an additional step education and socioeconomic grade were added. To analyze generational effects geographic origin was reclassified into 7 groups by the country of birth of the adolescent and the father or grandfather. Log minus log plots for each variable were inspected to verify the assumption of proportionality of hazards, which was confirmed for all variables studied.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of study participants. Mean age at examination was 17.3 ± 0.4 years and 82.6% of participants were Israeli born. Parents or grandparents of examinees originated mostly in Europe (41.5%) with 26.7% born in Asia and 26.3% born in North Africa. Of the examinees 53.7% had 12 or more years of education and 27% resided in a low grade socioeconomic area. BMI greater than 25 and 27.5 kg/m^2 or greater was noted in 12.1% and 5.2% of adolescents, respectively. Mean BMI increased during the years from 21.4 ± 2.7 in the first decade of followup to 21.8 ± 3.6 in the fourth decade. Mean height was 173.6 cm. There was an increase during the years from an average of 171.9 cm in the first decade to 174.1 in the most recent decade. Median followup was 15.9 years (IQR 8.3–26.1).