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Research Article

Kidney Cancer Research: Sex-Inclusive but Sex-Unspecific

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ABSTRACT

Background: Preclinical and clinical research is largely inclusive of both the female and the male population, but the lack of specific separation of data according to patient sex prevents the detection of the impact of sex on cancer biology and response to medications and treatment. This study aimed to examine the consideration of sex as a biological variable in preclinical and clinical studies in kidney cancer.

Methods: Preclinical and clinical studies pertaining to kidney cancer published in three leading urology journals over a two-year period were reviewed for the reporting of cells, animal or patient sex, and the inclusion of sex as a biological variable in both study design and data analysis.

Results: 171 clinical studies and 5 preclinical studies were included. While the sex of the participants was disclosed in all but 10 of the 171 clinical studies reviewed, the patient populations were largely male-dominated (male to female ratio > 1.5). Only 5 studies contained more female than male patients. Sex-specific reporting was performed in 3% of studies, and only 37% included sex as part of the statistical analysis. 26% of these identified a statistically significant difference in measured outcomes between male and female participants.

Conclusion: Kidney cancer research is sex-inclusive, but the female patient population remains underrepresented. The consideration of sex in data analysis is low and could prevent the identification of key sex-specific optimization opportunities for the improved management of the disease.

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Introduction

Renal cell carcinoma has a 1.5: 1 male predominance [1]. Sex is a fundamental biological variable whose impact on the efficacy of medications and treatments for urological malignancies is being increasingly raised [2, 3]. Yet, the explicit recognition that the disease could affect male and female cancer patients differently could be provided by our study design and data analysis practices. The National Institute of Health published the Sex as a Biological Variable (SABV) policy in 2014 in an attempt to enhance reproducibility and increase the

number of women being enrolled in clinical trials [4, 5]. The application of these guidelines is increasingly identifying associations between sex and the regulation of miRNAs and mRNA, the microbiome, genetic polymorphism in antibody responses, and the functions of both the innate and adaptive immune systems [6-10].

Analyses of the literature have reported unequal representation between male and female participants, and a lack of sex-specific data analysis. With regards to basic and translational research in surgical biomedicine, it was estimated that sex was either not specified (76% of cell lines

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studies reviewed) or male-dominated (79% of those that did only included male cell lines). Sex-based results reporting was only identified in 1% of the studies included [11]. Similar data exist in otolaryngology and orthopaedic research [12, 13]. This study aimed to establish the prevalence of sex-specific reporting and the consideration of sex as a statistically controlled variable in preclinical and clinical research studies on renal cancer. Our analysis identifies that the kidney cancer patient research population is female depleted, and the pooling of male and female data is common practice.

Materials and Methods

I Data Collection

A PubMed search was carried out for manuscripts published in European Urology, Urology and the British Journal of Urology from January 2017 to August 2019 using the MeSH search terms kidney, cancer, renal and neoplasm. All studies pertaining to kidney cancer were reviewed for inclusion in this study. Systematic reviews, meta-analysis, case reports, letters to editor, review articles and papers relating to benign renal neoplasms were excluded.

II Variables Extracted

The following data were extracted from each article: 1) the type of study – studies were categorised as clinical if the data was collected from patients; studies were categorised as preclinical if the data was collected from animals and/or cells (primary or cell lines), 2) the first author name, 3) the title of the manuscript, 4) the institutional affiliation of the first author, 5) the disease site or normal tissue studied, 6) the disclosure of the sex of the patients studied, 7) the number of each male and female patients included, 8) the disclosure of the sex of each animal used, 9) the sex of each animal used, 10) the disclosure of sex of the cell line used, 11) the name of cell line used, and 12) the presence of sex-based reporting. Sex-based reporting was defined as presenting the results for both males and females separately. 13) the inclusion of sex as a variable

in data analysis. Manuscripts that reported the sex of the patients used but did not include the results stratified by sex were classified as not including sex-specific reporting. Manuscripts that included sex as a variable in univariate and/or multivariate analysis of outcome data were classified as sex-inclusive studies.

III Data Analysis

The total number of male and female participants across all included studies was calculated. Articles were grouped according to their male to female ratio (<1, >1, >1.5, >3, >5), reported as frequency and percentages. The mean, median and standard deviation of male to female ratios were calculated. The distribution of articles according to location, study type and sex disclosure were reported as frequency and percentages. Presence of sex-specific reporting and sex inclusive analysis were reported as percentages. The sex of the cell line used was searched by reviewing the product sheet provided by the American Type Culture Collection or the ExPaSy portal. A p-value < 0.05 was deemed statistically significant.

Results

I A Female and Male Data Gap Exists in Kidney Cancer Research

A total of 171 articles collectively involving 479,092 consenting patients with kidney cancer were reviewed, 4 (2%) were clinical trials, 167 were clinical studies (98%) (Figure 1). 108 studies (62.1%) were from institutions based in North America, 42 (24.9%) were based in Europe, and 21 (12.4%) were based in Asia/Australia. One study was based in South America. Of these, 162 (95%) disclosed the sex of the patients: 301,258 men and 177,834 women in total. The mean and median male to female ratio were 2.3 and 1.8 respectively (range 0.3-42). 156 studies (96%) had a male to female ratio of greater than 1. 22 studies (14%) had a male to female ratio of greater than 3.0. Only five studies (3%) contained more female than male participants.

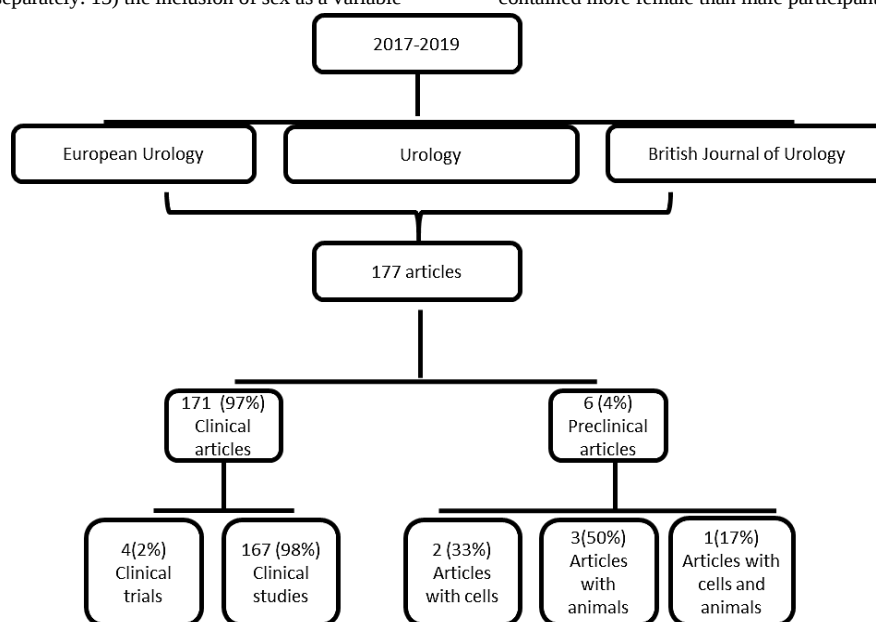


Figure 1: Box diagram of the number and types of manuscripts identified among the three urology journals reviewed.

II The Use of Sex as a Controlled Variable in Statistical Analysis is Limited

Sex-specific reporting of study outcomes was present in only 6 (4%) of the 162 studies reporting the sex of the patients (Figure 2). Sixty-six studies (37%) included sex as a controlled variable as part of the statistical analysis, usually in the form of univariate analysis. Of these,

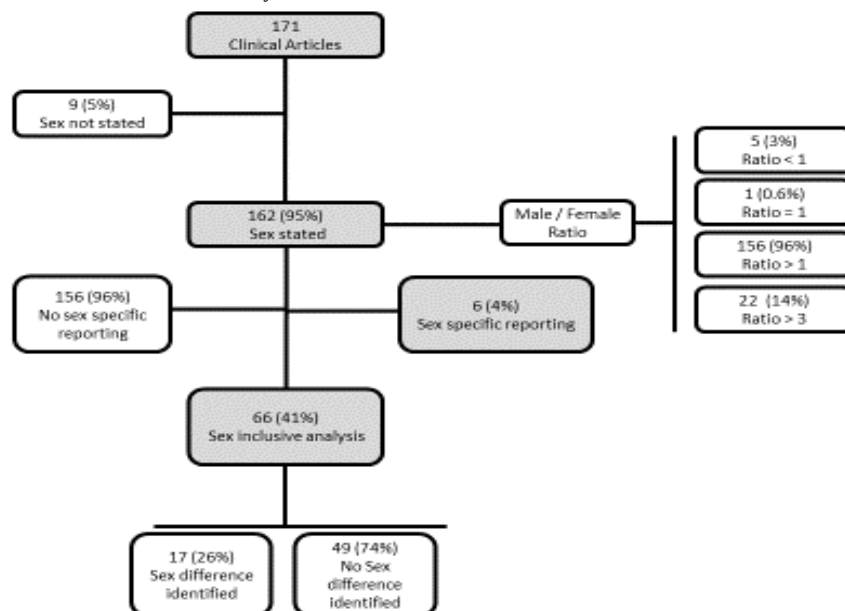


Figure 2: Box diagram of the number of clinical manuscript reporting data from human participants.

III Sex is Poorly Considered in Preclinical Studies

Six studies were based on cell or animal participants. Three of these contained animals only, one study contained cell and animals, one study contained cell and humans and one study contained cells only. None of the cell/animal-based studies performed sex-based reporting or included sex as part of the statistical analysis. Each of the four studies which contained animals disclosed the sex of those animals. Two studies contained male animals only, one contained female only and one contained both male and female animals. The total number of animal participants across the studies included 52 male and 46 female animals. Five different cell lines were used in the cell-based studies (Caki-1, Caki-2, A-498, 786-O and MZ1774). Three of these cell lines were male, one female and one unspecified.

Discussion

This study, to our knowledge, is the first examining the presence of sex as a biological variable in kidney cancer research. Our analysis of a selection of articles involving patients with kidney cancer identifies that the research population is inclusive of women but dominated by male patients. This may reflect the known higher incidence of kidney cancer in men [14]. However, while the sex of the consented patients was disclosed in most of the studies reviewed, less than 3% segregated the male and female cohorts, and less than 40% of the studies included sex as a variable in their statistical analysis.

17 (26%) identified a statistically significant difference in the measured outcomes between male and female participants. These included differences in cancer-specific mortality, all-cause mortality, poor surgical outcomes and complications. Sex-inclusive analysis was performed in 39.1% of studies from North America, 36.4% of studies from Europe and 27.3% of studies from Asia/Australia.

Early policies advised that women of childbearing potential should be excluded from drug trials. These guidelines, while likely wrongly assuming the applicability of male data to the female patient population, generated data possibly more robust than that published today. The accepted practice of combining data into one large dataset, known as data “pooling”, in order to increase the precision of the value of a characteristic, could increase the risk for an effect being lost or claimed [15]. With regards to sex, conclusions may be applicable to neither the male nor the female population. Publication of outcomes by sex was identified as key to the reproducibility of preclinical biomedical research and minimizes the risk of implementing unsafe practices [5].

An impact of sex on the presentation and prognosis of renal carcinoma is documented. Renal cell carcinoma in men is associated with higher tumor stages and more frequent metastasis at diagnosis along with inferior tumor-specific survival [16]. Patients with papillary renal cell carcinoma were significantly less likely to be female [17]. The efficacy of adjuvant Sunitinib for unfavorable renal cancer was also decreased among older women with renal cell carcinoma [18]. Improved prognosis was also reported in patients with clear-cell renal cell carcinoma undergoing curative surgery [19].

Differences between the sexes can have an impact on the efficacy of medications and treatments [20-22]. For example, aspirin does not provide the same cardiovascular protective effect between men and women [23]. A growing number of studies are drawing attention to the impact of sex on human biology, including cancer biology [10, 24-29]. Cell death programs appear differentially regulated in males and

females, with males possibly prone to PARP-1 necrosis and females to caspase-dependent apoptosis in a process is likely mediated by Poly-(ADP-Ribose) Polymerase-1 (PARP-1) and oestrogens [30, 31]. Sex differences were reported in relation to response to oxidative stress, basal redox state, sensitivity to both apoptosis and autophagy [32-34]. The segregation of the gene expression patterns generated from a series of male and female lung tumor samples revealed distinct cluster groups [29]. Both the innate and adaptive immune systems display major differences between males and females, which may be explained by a number of sex-specific genetic, hormonal and environmental factors [8-10, 35].

Although limited to a relatively small sample of articles, the results of our analysis are consistent with reports from other fields [13, 36]. In particular, the lack of consideration of sex in preclinical, cells and animal studies are omnipresent. The analysis of the orthopaedics research literature identified failure to report the sex of animals or cells in 35% of the articles reviewed. Where the sex was disclosed, both sexes were used in 33% of studies, with only 13% reporting data according to sex [13]. Overrepresentation of male animals and a lack of sex-specific reporting was also highlighted in biomedical research [36].

Conclusion

This study highlights that the female kidney cancer patient population is understudied in the literature. The application of the Sex as a Biological Variable guidelines should be more readily encouraged. The assessment of study endpoints such as pain, inflammation, blood counts and even imaging parameters may need to be adjusted in this patient population [37-41]. The systematic report of study outcomes in both the male and the female patient population could identify a need for sex-specific management of kidney cancer patients.

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