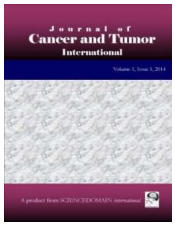

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Histo-Epidemiology of Kidney Cancer in Cameroon: About 110 Cases

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Authors' contributions

This work was carried out in collaboration between all authors. Author JPNE designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors YL, BDD, GS and AM participated in data collection supervision and analysis. Authors BS, CF and AE contributed in data collection and literature search. Authors AF, AH and JLOE reviewed the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: To describe the epidemiological and histopathological aspects of kidney cancer in Cameroon.
Materials and Methods: This was a descriptive retrospective study on malignant tumors of the kidney examined in the anatomical pathology laboratories of five regions (Center, Littoral, West, South-west and North-west), over a period of 12 years (2004-2015). The studied parameters were:

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frequency, age, sex, histological type.
Results: A total of 110 cases of kidney cancer were collected, representing 8.55% of malignant urogenital tumors. The mean age of patients was 28.72±24.79 years (extremes: 4 months - 76 years). Females are relatively more affected than males (56 cases, 50.91%), with female-to-male ratio of 1.04:1. A total of 58 (52.73%) cases of renal cell carcinomas (RCC), 46 (41.82%) cases of nephroblastomas (NB) and 3 (2.73%) of soft tissue tumors were identified.
Conclusion: Kidney cancer is the third urogenital cancer in Cameroon characterized by a relative female predominance with renal cell carcinoma as the predominant histological type.

Keywords: Cancer; kidney; epidemiology; histopathology; Cameroon.

1. INTRODUCTION

Kidney cancer is currently the ninth most common cancer in men and the 14th most common in women worldwide. The highest rates of kidney cancer incidence (338,000 new cases, 2.4% of the world total) are estimated in Northern America, Australia, New Zealand and Europe. Incidence rates are lowest in Africa and in the Pacific Islands [1,2]. Kidney cancer incidence and death rates are highest among AI/ANs, which may be due to high rates of obesity, smoking and hypertension [3]. Several histological types are known today including renal cell cancer (RCC), lymphoma, sarcoma and others [4]. Kidney cancer, predominantly renal cell carcinoma (RCC), is the most lethal genitourinary malignancy. The main treatment options for kidney cancer are as follows: Surgery, Radiation therapy, Immunotherapy, Molecular-targeted therapy [5]. The 5-year age-standardized relative survival for patients with kidney tumors diagnosed in Europe during 2000–2007 was 60% [6]. In the USA, the 5-year relative survival rates were 72.6% for white and 68.0% for black patients [7]. In Cameroon, some characteristics studies of renal cancer were made, including Sow et al. This pathology represented 15.12% of all urogenital cancers [8]. Another made by Engbang et al in the littoral region, found a percentage, twice lower (7.91%) [9]. This data shows us the necessity of national data and prompted us to conduct this study to give epidemiological and histopathological profile of kidney cancer in Cameroon.

2. MATERIALS AND METHODS

This was a retrospective and descriptive study of patients with kidney cancer confirmed histologically, diagnosed between January 2004 and December 2015. Data was obtained from histopathology, urology and oncology records of different health centers in five regions of Cameroon. Ethics Committee of all the concerned institutions approved the study protocol. The samples examined were mainly composed of biopsies and surgical specimens fixed in 10% formalin and processed according to the usual techniques of paraffin embedding, microtome cutting and staining with hematoxylin-eosin. Only patients for whom the diagnosis was confirmed by histology were included in the study. The information obtained included frequency, age, sex and histological type of the tumor. Data entry was done using computer based statistical Package for Social Sciences (SPSS) version 20. The descriptive statistics elements were used to calculate the frequencies and proportions.

3. RESULTS

3.1 Epidemiological Aspects

3.1.1 Frequency of urogenital cancers in Cameroon

We collected 1286 cases of malignant urogenital tumors, from 2004 to 2015. Kidney cancer (110 cases, 8.55%) was in the second position after the prostate, followed by the bladder (Fig. 1).

In Table 1, prostate cancer was in the first rank (1047 cases, 87.10%), followed by bladder cancer (60 cases, 4.99%) in males. In females, the kidney was the most affected urogenital organ (56 cases, 66.67%), followed by the bladder (21 cases, 25.00%).

3.1.2 Sex

Females are relatively more affected than males (56 cases, 50.91%), female-to-male ratio was 1.04:1.

3.1.3 Age

Age ranged from 4 months to 76 years with average of 28.72±24.79 years (33.90 years in men, 23.86 years in women)**.** As shown in Fig. 2, patients from 0 to 9 years are more affected, with a percentage of 39.47% (45 cases).

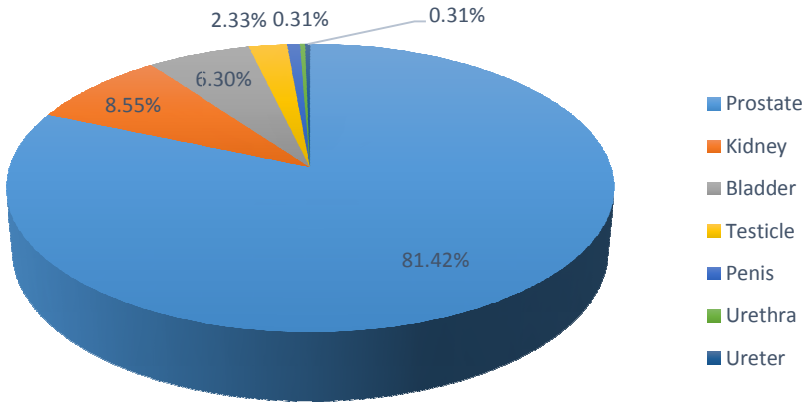

Fig. 1. Distribution of urogenital cancers by seat

Table 1. Distribution of urogenital cancers by seat and sex

Organ	Males		Females		Total	
	Eff	%	Eff	%	Eff	%
Prostate	1047	87.10	-	-	1047	81.42
Kidney	54	4.49	56	66.67	110	8.55
Bladder	60	4.99	21	25.00	81	6.30
Testicle	30	2.50	-	-	30	2.33
Penis	10	0.83	-	-	10	0.78
Urethra	-	-	4	4.76	4	0.31
Ureter	1	0.08	3	3.57	4	0.31
	1202	100.00	84	100.00	1286	100,00

Eff - Effective, % - Percentage
Kidney cancer represented 94.02% (110/117) of all kidneys tumors

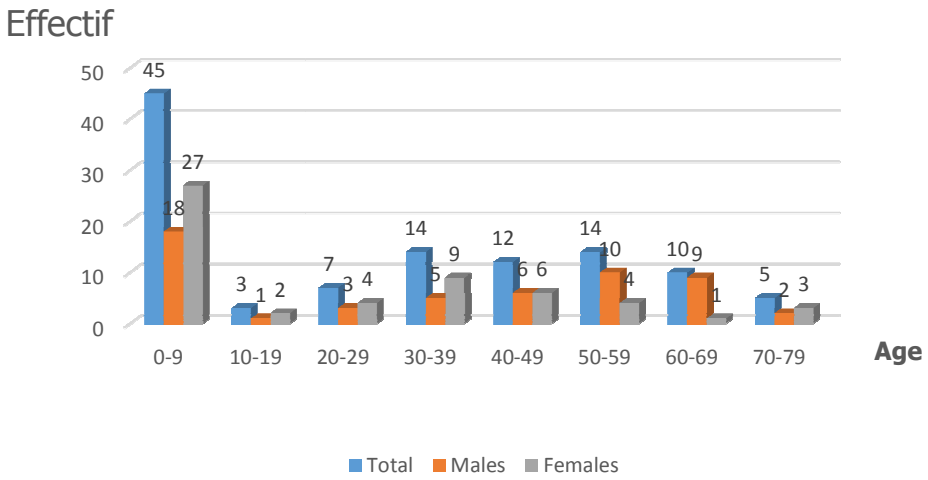

Fig. 2. Distribution according to age groups and sex

Table 2. Relationship between histological types and age

Age		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	Total	%	%
	ccRCC	-	1	3	10	9	4	2	1	30	27.27	
	pRCC	-	1	1	1	1	3	3	-	10	9.09	
A	chRCC	-	-	-	2	-	-	-	1	3	2.73	
	cdRCC	1	-	-	-	1	1	-	-	3	2.73	52.73
	mRCC	-	-	-	-	-	1	-	-	1	0.91	
	RCAN	1	-	-	-	-	-	-	-	1	0.91	
	ucRCC	-	-	2	1	1	2	3	1	10	9.09	
B	NB	43	1	1	-	-	-	-	1	46	41.82	41.82
	CCSK	-	-	-	-	-	1	-	-	1	0.91	
C	RAS	-	-	-	-	-	1	-	-	1	0.91	2.73
	RRMS	-	-	-	-	-	-	-	1	1	0.91	
D	RC	-	-	-	-	-	1	-	-	1	0.91	0.91
E	Lymphoma	-	-	-	-	-	-	2	-	2	1.82	1.82
Total		45	3	7	14	12	14	10	5	110	100.00	100.00

A-Renal Cell Carcinoma, B-Nephroblastic Tumors, C-Soft Tissue Tumors, D-Neural/Neuroendocrine Tumors, E-Hematopoietic and Lymphoid Tumors. RCC-Renal Cell Carcinoma, ccRCC-Clear Cell, pRCC-papillary, cdRCC-Collecting conducts, mRCC-Medullary, RCAN-Renal Carcinoma Associated with Neuroblastoma, ucRCC-Unclassified, NB-Nephroblastoma, CCSK-Clear Cell Sarcoma of the Kidney, RAS-Renal Angiosarcoma, RRMS-Renal Rhabdomyosarcoma, RC-Renal Carcinoid

3.2 Histopathological Aspects

A total of 58 (52.73%) cases of Renal cell Carcinomas (RCC), 46 (41.82%) cases of nephroblastomas (NB) and 3 (2.73%) of soft tissue tumors have been identified (Table 2).

In Table 3, people with RCC were more likely to be male (31 cases, 53.45%), in that group a substantial higher proportion of ccRCC was female (20 cases, 66.67%). People with NB were significantly more likely to be female (28 cases, 61.87%).

4. DISCUSSION

Kidney cancers (8.55%) were in the second position after prostate. According to many authors, kidney cancers were in the third position among urogenital malignant tumors. For Darre et al. in Togo, although their percentage was lower than ours (8.11 %), this pathology came after bladder cancer [10]. Ouattara in Beninand Sow in Cameroon found respectively 8.5 and 15.12% [11,7]. This African data (Black) can be associated with that of the Unites States, where they observed an increase in incidence of renal cell cancer among blacks compared to whites. The RCC subtype distribution was different in black people from that of white, with a substantially higher proportion of patients with papillary RCC among blacks than white people [12,13]. Although so far the real reason is not yet found, some theories are trying to explain this phenomenon. The observed differences between blacks and whites in early stage of renal cell tumor distribution dating back to the 1970s is unlikely to be a result of long-term access to and utilization of imaging technologies by blacks [12]. Renal cell cancer may be a less aggressive tumor among blacks, as suggested by the favorable stage distribution and their higher survival, particularly for distant and unstaged cancer [14]. An estimated 2-4% of kidney cancers are caused by inherited factors [15]. Clear cell RCC is associated with cytogenetic loss of chromosome 3p; encompassing four of the most commonly mutated genes in this cancer: the closely linked Von Hippel–Lindau (VHL) tumor suppressor gene, which has been identified to be inactivated in about 92% of cases. 61% of renal cell carcinoma cases have Von Hippel Lindau mutations [16,17]. The VHL gene produces a protein that targets hypoxia inducible factors (HIFs) for ubiquitin-mediated degradation. Loss of function leads to accumulation of HIFs and subsequent upregulation of vascular endothelial growth factor and other factors that promote angiogenesis and tumor growth [18]. ccRCC is characterized by *VHL* mutations, but *VHL* inactivation alone is insufficient for tumor initiation. Both *BAP1* [BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)] and *PBRM1* (polybromo 1) are two-hit tumor suppressor genes and they are located on chromosome 3p. It is speculated that, in many instances, ccRCC development is initiated by a focal mutation in *VHL*, followed by a 3p deletion. 3p loss would leave cells without *VHL* gene function and with just one copy of *BAP1* and *PBRM1* [19]. Neither papillary nor chromophobe histology tumors have been associated with any of these genomic alterations.

Table 3. Relationship between histological types and sex

Histological type	Male		Female		Total	
	EFF	%	EFF	%	EFF	%
ccRCC	10	18.52	20	35.71	30	27.27
pRCC	8	14.81	2	3.57	10	9.09
chRCC	1	1.85	2	3.57	3	2.73
cdRCC	3	5.56	-	-	3	2.73
mRCC	1	1.85	-	-	1	0.91
RCAN	-	-	1	1.79	1	0.91
ucRCC	8	14.81	2	3.57	10	9.09
NB	18	33.33	28	50.00	46	41.82
CCSK	1	1.85	-	-	1	0.91
RAS	-	-	1	1.79	1	0.91
RRMS	1	1.85	-	-	1	0.91
RC	1	1.85	-	-	1	0.91
Lymphoma	2	3.70	-	-	2	1.82
	54	100.00	56	100.00	110	100.00

Female-to-male ratio in our series was 1.04:1. Fall and al in Senegal revealed also the female domination (51.3%) [20]. In Togo, 56.36% female subjects were affected [10]. A study from Nigeria published a report showing a clear worldwide female predominance (a male to female ratio of 1:2.1) [21]. This is in contrast with Ouattara et al. who found the predominance of male with a sex ratio (male to female) of 11/3 [11]. Honde also observed that 63% of males were affected (sex ratio 1.7) [22]. Cigarette smoking can play a great role in the evolution of RCC. An estimated 29% of kidney cancers in men, and 15% in women, in the United Kingdom are caused by smoking [23]. Hunt et al. reported statistically significant relative risks of 1.5 and 1.2 for male and female smokers, respectively. In that study, there was firstly a strong dose-dependent increase in risk, up to 2- and 1.6-fold (21 or more cigarettes per day)among heavy men and women smokers, respectively; secondly a significant decline in risk in both sexes with years of cessation (10 to 15 years after quitting), with a 15 to 30% risk reduction [24]. Kidney cancer risk is 52-54% higher in current smokers compared to never-smokers; it is 58-103% higher in those who smoke more than 20 cigarettes per day, compared to never-smokers. It is also important to know that the risk among ex-smokers who quit more than 10 years ago is comparable to that of never-smokers [25]. Cigarette smoking is not implicated only to renal cell carcinogenesis, but also may promote cancer progression that may translate into more advanced disease [26]. Several mechanisms have been suggested to explain how smoking can induce renal damage, including the tubulotoxic effects, hemodynamic changes, endothelial cell dysfunction and oxidative stress [27,28]. These toxic effects may increase cell turnover and induce DNA damage, which are potentially involved in carcinogenesis and cancer progression. We know also that tobacco smoking is associated with a myriad of genetic and epigenetic abnormalities such as gene mutations, deletions, and DNA methylation. For instance, polycyclic aromatic hydrocarbons present in tobacco smoke can induce mutations in the p53 gene, which can potentially lead to accelerated cancer progression [29]. Smoking has also been demonstrated to have an effect on the immune system, promoting inflammation and suppressing the immune function by reducing T-cell and natural killer cell activation [30]. Both pathways (inflammation and immune suppression) could facilitate neoplastic growth. Furthermore, nicotine contained in tobacco smoke has been associated with alteration of the vascular endothelial growth factor signaling pathway [31].

The median age of our patients was 28.72±24.79 years (33.90 years in men, 23.86 years in women), with extremes ranging from 4 months to 76 years. The most affected group were patients from 0 to 9 years, with a percentage of 39.47% (45 cases). Darre in Togo revealed a mean age of 35.9 years with extremes from 11 to 83 [10]. Ouattara in Benin found 53.21 ± 15.55 years, Honde in Ivory Coast – 40.9 years (15-67 years) [11,22]. The mean age at diagnosis was 54.7 years, 50 years and 56.9 years in men and 51.9 years, 41.5 years and 57.6 years in women in the United Arab Emirates (UAE), Algeria and Jordan respectively [32]. In Morocco the median age at diagnosis was 57 years in men and 53 years in women [32]. Some other factors such as obesity, diabetes and hypertension can be considered as risks factors. Wilms tumor risk is higher in children with a higher birth-weight [33]. Kidney cancer risk among men is 22% higher in those who are overweight (body mass index [BMI] 25-30) and 63% higher in those who are obese (BMI 30+) [34]. Kidney cancer risk among women is 38% higher in those who are overweight and 95% higher in those who are obese [34]. Obesity might be associated with increased risk of kidney cancer through several hormonal mechanisms. A potential mechanism by which obesity may increase kidney cancer risk involves increased levels of insulin-like growth factor (IGF) or lipid peroxidation increasing BMI is associated with elevated levels of fasting serum and free IGF-I among men and women, which contributes to the stimulation of renal cell proliferation and inhibition of apoptosis, which could have a profound impact on tumor growth [35,36]. Obesity also affects the hormonal milieu by increasing levels of free endogenous oestrogen, which may in turn influence renal cell proliferation and growth by direct endocrine receptor-mediated effects, via regulation of receptor concentrations or through paracrine growth factors [37]. Obesity may also induce chronic low-grade inflammation resulting in an alteration of local and systemic levels of cytokines (e.g., interleukin-6, C-reactive protein) and adipokines (e.g., leptin, adiponectin), which may play a role in bladder carcinogenesis to bladder cancer mortality [38,39]. People with high BMI have been reported to have higher glomerular filtration rate and renal plasma flow, which may increase the risk of kidney damage, and thereby render the kidney more susceptible to carcinogen [40]. Analyses have determined a

loss of activity in the VHL tumor suppressor gene causes an increase in the expression of the very low-density lipoprotein receptor (VLDL-R) on RCC cells, resulting to an increase in cholesterol ester uptake from the systemic circulation, with subsequent growth of adipose deposits inside the renal tubular epithelium [41]. Hyperplasia and hypertrophy induced by increased cholesterol uptake in kidney cells increases the metabolic rate in the individual capillary beds feeding this tissue, which subsequently leads to a relative tissue hypoxia. In response to this oxygen deficit, the tissues up-regulate production of hypoxia-inducible factor-1-α (HIF -1α) [42]. HIF-1α suppresses cellular apoptosis and up-regulates expression of vascular endothelial growth factor (VEGF) [42]. Suppression of cellular apoptotic mechanism permits abnormal cells to proliferate and VEGF promotes local blood vessel proliferation (neoangiogenesis), both of which are characteristic of RCC tumor growth.

Concerning diabetics and hypertension, we can say that diabetes was associated with the increased risk of bladder cancer [43]. Type 2 diabetes is associated with insulin resistance, compensatory hyper-insulinemia, and up-regulated level of IGF-1. IGF-1 could stimulate cell proliferation and inhibit apoptosis, which could have a profound impact on tumour growth [35,36]. Diabetes is also associated with an increased risk of urinary tract infection and urinary tract calculi, which have been related to various histologic types of bladder cancer, including transitional cell carcinoma, the predominant type [44,45,46]. The accumulation of oxidative DNA damage, which was increased through the hyperactivation of Akt/tuberin/mTOR pathway in kidney cancer patients with diabetes, may play an important role in initiating kidney tumorigenesis [47]. Kidney cancer risk is 62% higher in people with a history of hypertension; this may relate to hypertension treatment but evidence is unclear [48]. Several biologic mechanisms for the association between high blood pressure and renal cell cancer risk have been proposed, including hypertension-induced renal injury, metabolic or functional changes within the renal tubule induced by hypertension, increasing susceptibility to carcinogens. It has also been speculated that elevated levels of insulin-like growth factor-I (IGFI) or lipid peroxidation associated with hypertension, as well as up-regulation of hypoxia-inducible factors, could contribute to the development of renal cell cancer [12].

We found 58 (52.73%) cases of renal cell carcinomas (RCC), 46 (41.82%) cases of nephroblastomas (NB) and 3 (2.73%) of soft tissue tumors. Ghosn et al revealed a predominance of clear cell carcinoma: 79% in UAE and 68% in Morocco [32]. In Togo, Darre described 50.90% of nephroblastoma, 23.63 % of ccRCC and 7.27% of Lymphoma [10]. In Ivory Coast, RCC – 85.2% (78.3% of ccRCC) and 14.8% of NB [22]. Sow et al in Cameroon found 74.10% of NB [49]. In our studies, people with RCC were more likely to be male (31 cases, 53.45%), in that group a substantial higher proportion of ccRCC was female (20 cases, 66.67%). People with NB were significantly more likely to be female (28 cases, 61.87%). In the literature, the most frequent histological subtypes of RCC include clear cell renal cell carcinomas (ccRCC), papillary renal cell carcinomas (pRCC), and chromophobe renal cell carcinomas (crRCC). These three subtypes together represent more than 90% of all RCCs [49]. CcRCC is the most common variant, representing between 70% and 75% of all RCCs. Most clear cell carcinomas (95%) are sporadic, and the remaining 5% are associated with hereditary syndromes (von Hippel-Lindau disease, tuberous sclerosis) [50]. Lipworth in USA revealed a substantially higher proportion of patients with papillary RCC among black people than white; compared with clear-cell RCC, people with papillary RCC were significantly more likely to be black and less likely to be female. People with chromophobe RCC were significantly more likely to be female [13]. Primary angiosarcoma of the kidney is extremely rare in the literature. The disease arises significantly more frequently in men than women. Median age of patients was 59.9 ± 12.6 years, range mainly from 50 to 69 years old [51]. Renal RMS in adults is also extremely uncommon. Histologically, the primary renal RMS is a high-grade tumor that needs to be differentiated from other malignant lesions, such as sarcomatoid renal cell carcinoma, metastatic carcinoma or melanoma, and rhabdoid tumor [52].

5. CONCLUSION

Kidney cancer is the third urogenital cancer in Cameroon characterized by a relative female predominance with renal cell cancer as the predominant histological type. The fight against smoking, the prevention of diseases such as hypertension and diabetes are among the key elements that can help for the decrease in the

prevalence of this pathology. It should be noted that the effective initiation of cancer registries is still essential to master the epidemiological data, foundation for a better coordination and prevention of the anti-cancer fight.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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