Research Article **ISSN 2639-944X**

Journal of Medical - Clinical Research & Reviews

Epidemiological Characterization of Diseases of Abnormal Proliferation of Cells: the Bladder Cancer Situation

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Received: 15 Sep 2026; **Accepted:** 24 Oct 2026; **Published:** 03 Nov 2026

Citation: Ibama AS, Ogbonna C, Kakatei ID, et al. Epidemiological Characterization of Diseases of Abnormal Proliferation of Cells: the Bladder Cancer Situation. J Med - Clin Res & Rev. 2026; 10(11): 1-13.

ABSTRACT

Background: *Epidemiological principle of Person-Time-Place model in descriptive epidemiological studies has been very critical in establishing profiles of the population at risk of cancer of various sites. This review paper aimed at reporting the epidemiological characterization of cancer of the bladder in view of mapping of the important risk factors contributing to its development and highlight prevention and control measures.*

Methods: *The method used was scoping review of relevant literatures from open-access journals, cancer research centres, health institutes and google scholar data base, as well as research reports on variables of the subject across the globe.*

Results: *Findings showed that bladder cancer is diagnosed, globally in about 275,000 persons yearly, and about 108,000 dying from it, accounting for 2.5% of all cancer mortality. The survival rate for patients over 85 years of age is 40% against 83.4% for patients below 54 years of age. Its incidence, gave male-to-female ratio from 4.1 to 9:1 in developing countries compared to 3:1 to 4:1 in developed countries. The cancer is about six times more common in Caucasians than in Africans in incidence of transitional cell carcinoma. Widowed patients are shown to have significantly higher risk of bladder-cancer-specific mortality (P<.001). Occupational chemical of aromatic amines origin exposures are linked to about 25% of all bladder cancer cases. The disease has a long latency periods of 10 to 30 years requirement for accumulated damage to bladder tissue from carcinogens with a ratio 4:1 among smokers and non-smokers. Duration of catheterization directly correlates with an increased risk of developing squamous cell carcinoma. Early radiation therapy or specific chemotherapy are capable of increasing risk, leading to a median latency of about 10 years post-treatment. It has one of the highest recurrence rates of about 70% within 5years among malignancies. In Schistosoma endemic areas and countries, bladder cancer incidence male to female ratio ranges from 4:1 to 5.9:1 against 3:1 in areas/countries of non-endemicity. Religion and culture are considered as external influence on exposure to risk factors rather than direct differences in susceptibility to the disease.*

Conclusion/Recommendation: *Noting the enormous burden of cancer of the bladder and its public health implications based on the*

risk factors through epidemiological mapping, there is dire need to put in place public health intervention programme in line with the prevention and control measures as highlighted in this paper as well as need for studies on association between marital status and the occurrence of bladder cancer and the influence of treatment decision making, access, delay and racial discrimination in bladder cancer prognosis.

Keywords
Person-Time-Place epidemiological model, Bladder Cancer, Epidemiological characterization, Risk factors, Carcinogens, Transitional Cell Carcinoma, Squamous Cell Carcinoma, Prevention and Control.

Introduction

Diseases of abnormal proliferation of cells, otherwise called malignancy within the framework of cytopathology are described as cancers. Epidemiological principle of Person-Time-Place model in descriptive epidemiological studies, succinctly described by [1], has been useful in establishing profiles of the population at risk of cancer of various sites. It has also helped reasonably in making clearer the connected mechanisms of causation and thus contributing to the formulation of frameworks for effective control of cancer. In his argument, [2], stated that in the description of the characteristics of persons affected by cancer of various sites, demographic, socio-cultural, socio-economic, social-psychological variables are often employed in establishing factors that are associated with the risk of becoming a case of cancer.

He further stated that some of the more commonly used variables include age, sex, race, ethnicity, occupation, marital status, birth order, religious affiliation, level of education. All types of cancer show clustering with regard to a number of these variables. It is worthy of note that these variables alone without the necessary occupational and other implied exposures may not in themselves cause cancer, but their strong association with the occurrence of specific cancer are more often an indicator of more latent and subtle etiologic factors.

The bladder is a hollow, muscular organ that stores urine; which is located behind the pubis symphysis in the pelvis. Cancer of the bladder refers to any of several types of malignant growths of the urinary bladder (see Figure 1). It is a disease in which abnormal cells multiply without control in the bladder. These tumours spread within the walls of the bladder and may in rare cases, spread to other parts of the body [2]. Where the tumour occurs close to the opening of the ureter, the tube that carries urine from the kidney to the bladder, it can block the flow of urine and cause hydronephrosis (swelling of the kidney with urine). The most common type of bladder cancer begins in cells lining the inside of the bladder and is called transitional cell carcinoma (sometimes called urothelial cell carcinoma) [3].

Cancer of the bladder is clinically presented as blood in the urine or heamaturia, visible to the naked eye (gross heamaturia) or detectable only by microscope (microscopic heamaturia) as a key symptom. Other possible symptoms include burning sensation during urination, frequent urination (polyuria) or feeling the need to urinate without results or urinating small amount at frequent intervals [4]. However, it is important to note that these signs and symptoms are not specific to bladder cancer; they are also caused by non-cancerous conditions, including prostate infections and cystitis (inflammation of the bladder). Kidney cancer, can also cause heamaturia.

Under pathological classification, 90 percent of bladder cancers are Transitional cell carcinoma (derived from the transitional cells that line the bladder). The other 10% are squamous cell carcinoma (derived from squamous epithelium), adenocarcinoma (derived from glandular epithelium), Sarcoma – linked to connective tissue, including bone and cartilage, small cell carcinoma and secondary deposits from cancers elsewhere in the body [3]. For better understanding of the pathology of the cancer, five (5) stages are used to classify the location, size, and spread of the cancer, according to the TNM (tumor, lymph node, and metastasis) staging system:

- **Stage 0:** Cancer cells are found only on the inner lining of the bladder, usually treated successfully with surgery.
- **Stage I:** Cancer cells have proliferated to the layer beyond the inner lining of the urinary bladder but not to the muscles of the urinary bladder.
- **Stage II:** Cancer cells have proliferated to the muscles in the bladder wall but not to the fatty tissue that surrounds the urinary bladder.
- **Stage III:** Cancer cells have proliferated to the fatty tissue surrounding the urinary bladder and to the prostate gland, vagina, or uterus, but not to the lymph nodes or other organs.
- **Stage IV:** Cancer cells have proliferated to the lymph nodes, pelvic or abdominal wall, and/or other organs [5].

Recurrent: Cancer has recurred in the urinary bladder or in another nearby organ after having been treated [5]. Bladder cancer has the highest recurrence rate of any malignancy (70% within 5years). Even when most patients with bladder cancer can be treated initially with organ-sparing therapy, most experience either recurrence or progression [6].

The gold standard for diagnosing bladder cancer is biopsy obtained during cystoscopy. Sometimes it is an incidental finding during cystoscopy [8]. Urine cytology can be obtained in voided urine or at the time of the cystoscopy ("bladder washing") - a procedure in which a flexible tube bearing a camera and various instruments is introduced into the bladder through the urethra. Cytology is very specific (a positive result is highly indicative of bladder cancer) but suffers from low sensitivity (a negative result does not exclude the diagnosis of cancer) (see Figure 2). There are newer urine bound markers for the diagnosis of bladder cancer. These markers are not currently used routinely in clinical practice due to absence of clear professional guidelines, since they are still undergoing research. They are much more expensive as well [9]. However, it is quite

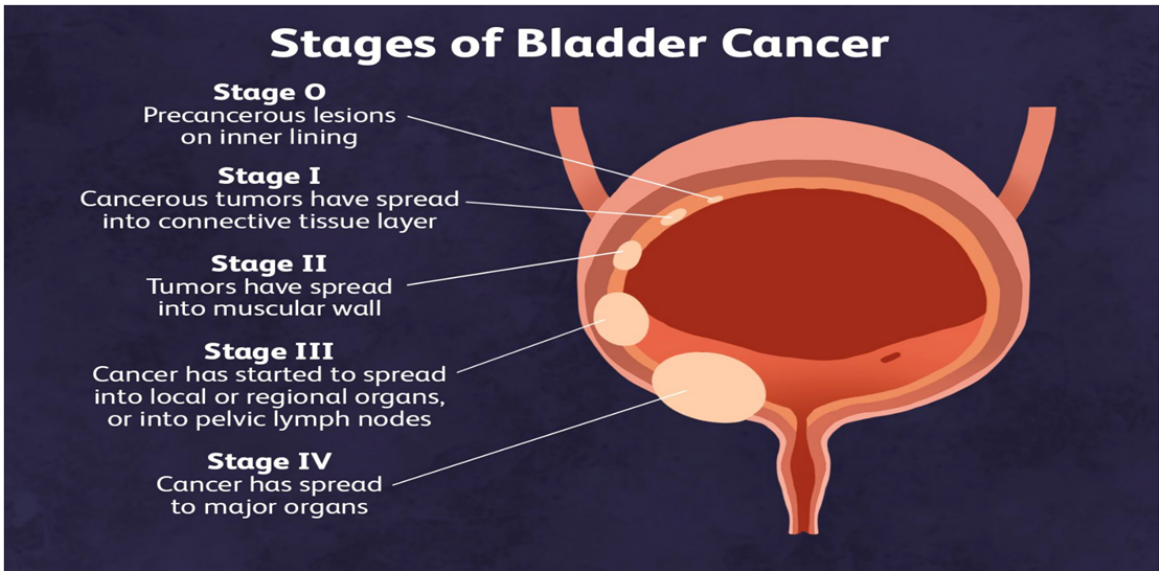


Figure 1: Stages of Cancer of the Bladder.
Source: [7]

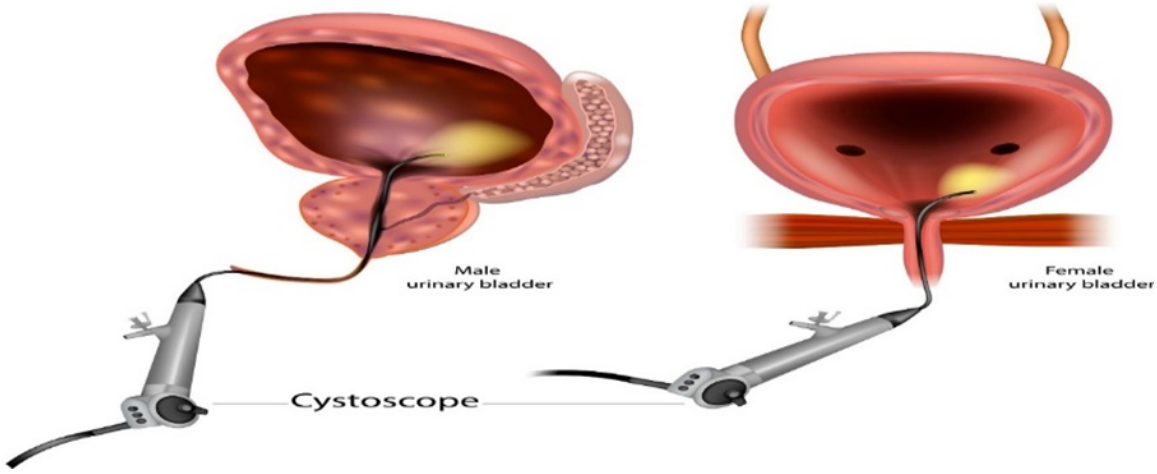


Figure 2: Cystoscopy procedure for Bladder & Urethra Diagnosis.
Source: [9].

intrusive to mention them to move with the dynamism of medical and clinical procedures around diagnosis of bladder cancer.

Much more of upcoming and notable markers for bladder cancers are detectable in urine samples owing to their direct contact with the tumour, while ongoing research is focusing on blood-based liquid biopsy approaches, though few blood markers are used commonly in clinical practice for initial diagnosis compared to urine test and cystoscopy. In blood samples, are found some biomarkers including, Cancer-associated antigen (CAAg) and Cancer Cell Exosomes, Carcinoembryonic Antigen (CEA), Prostate-Specific Antigen (PSA), Tumour Markers, Cytokines, Antibodies and MicroRNAs (miRNAs) [10,11].

Among the markers, urinary exosomes are classified as emerging biomarkers in bladder cancer, where the nanoscale extracellular vesicles secreted by tumour cells have emerged as a rich source of bladder cancer biomarkers. Exosomes are carrier of proteins, DNA fragments, and RNA species like microRNAs (miRNAs) that reflect the molecular properties of the tumour [12].

This review therefore, is aimed at reporting the epidemiological characterization of cancer of the bladder with comparism whenever possible so as to enhance better understanding of the important risk factors which contribute to the development of the cancer and may help in drawing recommendation for prevention and control measures.

Materials and Methods

The materials and methods applied were scoping review of relevant literatures from open-access journals, cancer research centres, health institutes and google scholar data base, as well as research reports on variables of the subject across the globe.

Burden of Bladder Cancer

Epidemiological studies of urinary bladder cancer began in 1895 with a study of the excessive occurrence of bladder cancer among workers in the aniline dye industry [13]; this was confirmed by [14]. Quite reasonable epidemiological evidence over the years had shown increasing prevalence of cancer of the bladder reflecting associated risk factor(s).

Bladder cancer is the second most common genito-urinary neoplasm after prostate cancer. Eighty-four percent of cases occur on the lateral and posterior walls of the bladder, [2]. Ninety percent of bladder malignancies are transitional cell carcinomas (TCC), reflecting their origin from the transitional cells that line the bladder. Squamous cell carcinoma (SCC) comprises approximately 6-8 percent of bladder tumours, with only about 2 percent being adenocarcinoma. However, in Schistosoma endemic areas, SCC constitutes as high as 44-82 percent of bladder cancer [15,16]. Small cell carcinoma of the urinary bladder accounts for only 0.3-0.7% of all bladder tumors. High-grade urothelial carcinomas can also show divergent histologic differentiation, such as squamous, glandular, neuroendocrine, and sarcomatous features [6].

Clinical and pathologic data indicate that at least 3 different phenotypes, exist in urothelial carcinoma namely; low-grade proliferative lesions that develop into non–muscle-invasive tumors; these account for approximately 80% of bladder cancers, highly proliferative invasive tumors with a propensity to metastasize, Carcinoma In Situ (CIS), which can penetrate the lamina propria and eventually progress [17,18].

Globally, bladder cancer is diagnosed in about 275,000 persons yearly, and approximately 108,000 die of this disease. In industrialized countries, 90% of bladder cancers are urothelial carcinomas. In developing countries, particularly in the Middle East and Africa, the majority of bladder cancers are SCCs, and most of these cancers are secondary to *Schistosoma haematobium* infection. Urothelial carcinoma is reported to be the most common urologic cancer in China [6].

According to Abanobi [2] the disease accounts for 2.5 percent of all cancer deaths and has a male cause-specific mortality rate that is twice that of females. The incidence of bladder cancer continues to increase, with an estimated 53,000 new cases diagnosed in the United States in 1996, and 90 percent of which are transitional cell carcinomas [19]. However, the [20] estimates that 84,870 new cases of bladder cancer will be diagnosed in the United States in 2025 and that 17,420 people will die of the disease.

In Africa, the highest incidence of SCC has been seen in schistosomal endemic areas, notably Sudan and Egypt, where SCC ranges from 66-75 percent of all malignant tumors of the bladder. Since the turn of the century, a few studies from Egypt have shown a reversal of this trend due to the better control of schistosomiasis in the region, whereas in other parts of Africa the association is unchanged [21]. Increased smoking incidence is believed to have contributed to the shift in Egypt toward urothelial carcinoma, which has a stronger smoking association [6].

In Nigeria, bladder cancer ranks the second most common cancer after prostate cancer in males, though being less frequent, yet notable in females, with the burden characterized by a high proportion of SCC, linked to endemic infections e.g. schistosomiasis, where patients usually present with advanced disease, resulting to severe morbidity, high treatment costs and death, made worse by resource limitations in health care [22].

Epidemiological Mapping of Risk Factors of Bladder Cancer

Risk factors are factors either genetically or environmentally influenced, which presence is a more likely indicator of occurrence of a disease in an individual or population. Such factors may coexist and also interact with each other with greater consequences of disease occurrence. Therefore, in chronic disease epidemiology such as cancer of the bladder it is necessary to carry out an epidemiological mapping of risk factors with a view to understanding and showing the relative strength of such risk factors in the disease occurrence for the purpose of effective control measures of the disease condition.

It is important to reiterate that this review attempt to reporting the epidemiological characterization of the disease in terms of the more common variables associated with the risk of becoming a case of cancer of the bladder.

Age Relationships in Cancer of the Bladder

Generally, relationship between age and bladder cancer indicate significance, with older age principally linked to reduced survival rates [23]. According to [24], the median age of diagnosis of cancer of the bladder in America is 73 years, wherein the rate of new diagnosis has been decreasing in recent years, perhaps due to factors such as finding the diagnosis earlier, improvement in treatments, decline in smoking as well as increase in the awareness of the condition. In all of these, the survival rate for patients over 85 years of age is 40% whereas it is 83.4% for patients below 54 years of age [25].

Nevertheless, studies on cancer of the bladder have depicted marked variation in age of peak prevalence; principally between Transitional cell carcinoma and Squamous cell carcinoma. In the western society, most patients were over 50 years old with a peak prevalence among 60-70 years old [26]. The mean age of Transitional cell carcinomas (TCC) was 60.6 years, in Jordan [27].

In the prospective study of all patients admitted to the University of Maiduguri Teaching Hospital (UMTH), North-East Nigeria, with a provisional diagnosis of carcinoma of the urinary bladder in a six year period between January, 2001 and December, 2006, showed that the peak age for Squamous cell carcinoma (SCC) was 31 to 50 years. The age of patients seen in the study ranged from 21 to 70years, with a peak age incidence between 51 and 60 years [26].

Also, in a study on Trends in Carcinoma of the Bladder in the Young in Northern Nigeria, revealed that persons below 40 years

of age accounted for 19.8% of all bladder carcinomas diagnosed, with a mean age of 54.3 years and having predominant histological subtype of Transitional cell carcinomas at 59.8% [28].

While in the study on Cancer of the Bladder in South-East Nigeria, published in year 2021, showed that majority of the cases of Squamous cell carcinoma were seen in patients below 30 years of age (66.7%) whereas majority for Transitional cell carcinomas were above 50 years (91.7%) [29].

This pattern of occurrence of bladder cancer in relation to age may most probably due to the insidious and protracted nature of the incubation period from exposure to carcinogens and the time of diagnosis of the disease which is more often than not influenced by ignorance, misconception and misdiagnosis, thereby making the disease associated with older age. In the case of Squamous cell carcinoma, the explanation may be as a result of intensity of exposure to carcinogens due to endogenous initiation from bacterial infection as a complication of *Schistosoma haematobium* infection which is endemic and therefore a significant factor in the etiology of bladder cancer.

It is important to note that this variation in the epidemiology of bladder cancer is significant, in that SCC mediated by Schistosomiasis affects the younger, able bodied workforce of the society and bread winners of the homes. The economic impact on the society at large is tremendous and cannot easily be assessed.

Sex Differences in Cancer of the Bladder

Differences in gender (sex) in the occurrence of cancer of the bladder as indicated by several studies showed an increasing trend toward the males. This is mainly attributable to exposure factors and biological determinants (hormonal factor).

In the United States, bladder cancer is the fourth most common type of cancer among men and the ninth most common cancer among women. More than 50,000 men and 16,000 women are diagnosed with bladder cancer each year. One reason for its higher incidence in men is that the androgen receptor, which is much more active in men than in women, plays a major part in the development of the cancer [30]. This gives a male to female ratio of 3:1. Exposure potential to carcinogens may also be one of the reasons for the higher incidence in men noting the gender differences in employment/occupational patterns.

In Jordan, Middle East (a developing country), the overall age-standardized annual incidence rates of bladder cancer are 25.7 and 6.2 per 100,000 population in males and females, respectively [31]. Its incidence, increased by 36 percent between 1984 and 1993 [32]. In a clinicopathological studies on urinary bladder cancer at a major University Hospital in northern Jordan for over seven years, [27] reported a male-to-female ratio of 9:1, which is much higher than that described in the USA, where it ranges from 3:1 to 4:1 [32]. Since cigarette smoking is one of the main etiological factors related to the development of TCC that is prevalent in Jordan [33], this high male to female ratio may be related to a lower number of Jordanian women who smoke and to the very low percentage of women who work in Jordan.

In the prospective study of all patients admitted to the University of Maiduguri Teaching Hospital (UMTH), North-East Nigeria, with a provisional diagnosis of carcinoma of the urinary bladder in a six year period between January, 2001 and December, 2006, showed that all but 13 of the 65 cases seen were males giving a male to female ratio of 4:1. The male preponderance agrees with other reports. It may be that males are generally more exposed to the environmental or occupational hazards associated with bladder cancer [26]. Whereas in the study on Trends in Carcinoma of the Bladder among Young persons in Northern Nigeria, reported a male to female ratio of 7:1 [28]. This may equally be founded on similar exposure potential to environmental or occupational hazards implicated in cancer of the bladder, being an active population group. However, the study on Cancer of bladder in South-East, Nigeria in 2021, reflects a general male-to-female ratio of 2:1, but 3:1 for Transitional Cell Carcinoma with majority of the patients being petty traders [29]. Such lower proportion or ratio is a shift from the situation in the northern region and characterizing regional peculiarity in exposure factors of low resource areas implicated in cancer of the bladder.

Ethnic Differences in Cancer of the Bladder

Epidemiological evidence has revealed remarkable differences in the occurrence of cancer of the bladder between the Caucasians (white people of European descent) and the Blacks (indigenous Africans). It is more common in the industrialized communities and in Caucasians than in Blacks [26]. This trend as a global comparism is still on track for a decade, as the White people having the highest number of new cases of bladder cancer, followed by black people. Latinos and Asian and Pacific Islanders having the lowest number of new cases [34].

In a study of the incidence of different histological types of bladder cancer in various racial groups living within the same geographical region which included 615 new patients with bladder cancer seen at three Provincial Hospitals in Durban, South Africa from January 1980 to January 1990. The patients were classified as Caucasians, Africans (indigenous black people), Asians (people originating from the Indian subcontinent) or Coloured (people of mixed race). The study revealed that transitional cell carcinoma constituted 95 percent of the cancers in Caucasians, compared with only 30 percent in Africans, whereas squamous cell carcinoma occurred in 53 percent of the African patients, but in only 2 percent of the Caucasians. In Asian patients, 75 percent of the tumours were transitional cell and 18 percent were squamous cell carcinoma, whereas in Coloured patients, 82 percent were transitional cell and 9 percent squamous cell carcinoma. Undifferentiated carcinoma occurred in 8 percent of Africans and only 1 percent of Caucasian patients, whereas adenocarcinoma, mixed tumours and sarcoma occurred in 9 percent of African patients and only 2 percent of Caucasian patients. Ova of *Schistosoma haematobium* were seen in microscopic sections of the bladder tumour in 85 percent of the patients with squamous cell carcinoma, in 50 percent of those with

undifferentiated tumours and adenocarcinoma, in 17 percent of those with mixed tumours or sarcoma, and in only 10 percent of the patients with transitional cell carcinoma [35].

In the study group, it appears that bladder cancer is about six times more common in Caucasians than in Africans in incidence of transitional cell carcinoma, this may not be unconnected with the associated industrialization and urbanization influenced life pattern/style. In African patients, endemic Schistosomiasis appears to be related to a high incidence of not only squamous cell carcinoma, but also undifferentiated tumours and adenocarcinoma of the bladder due mainly to occupational exposures.

In 2005, there were an estimated 63,210 new cases of bladder cancer and 13,180 related deaths in the US. African Americans reportedly had a lower incidence of bladder cancer, but a higher mortality [36].The reason being that African Americans were diagnosed with more aggressive and more advanced tumors, which may be due to factors such as treatment decision making, access, delay and potential bias in the black community which of course need to be subjected to further study.

Religion and Cultural Differences in Cancer of the Bladder

The influence of religion and culture in the incidence and mortality of cancer is still poorly understood in the epidemiological point of view. However, religion is seen as a socio-cultural factor and since cultural background and religious belief are strongly correlated, it may influence late presentation among persons with problems associated with bladder cancer in some environment. This is because based on belief or misconception, most patients first seek native, unorthodox treatment for their problems and waste vital time when the disease can be diagnosed and treated at an early stage.

For instance, the belief by some villagers in schistosomiasis endemic areas that one of the overt schistosomiasis symptoms, haematuria among the infected boys is a male version of menstruation signifying the outset of puberty is misleading and therefore hinders any modern control measures [37]. This may also be the perception of ancient Egyptian society which led to the use of a metal cap be it gold, silver, copper or lead (depending on the economic status of the wearer) to cover the tip of the penis as a preventive measure against the disease [38]. Similarly, religious practices, such as ablution and wadu (ritual washing), are required of male Muslims several times a day. Wadu is performed only by males and entails washing three times all exposed parts of the body. According to [39] while working in Yemen, southwest Arabia reported that ablution pools of some Mosques have at times become contaminated with schistosomiasis snail vectors and may serve as sites for the disease transmission. Schistosomiasis has been shown to be a significant risk factor in the causation of cancer of the bladder particularly squamous cell carcinoma. In this perspective therefore, religion and culture is seen as exerting influence on exposure to risk factors rather than direct differences in susceptibility to cancer of the bladder.

Marital Status in the Epidemiology of Cancer of the Bladder

Although, there is paucity of documented literature on marital status in the epidemiology of bladder cancer as a critical factor in the difference in causation of the disease, but the available literature at our disposal did indicates epidemiological evidence of marital status as a critical factor in the difference in prognostic survival of the disease.

The implication of marital status in the epidemiology of cancer of the bladder is recognized as a significant independent factor of prognosis for survival and to a lesser extent, the diagnosis of stages of the disease, having that married persons experience better outcomes than their single, divorced or widowed counterparts.

To identify the extent to which difference in marital status is implicated in survival of patients with bladder urothelial carcinoma, a Surveillance, Epidemiology, and End Results population-based data, involving 133,846 patients diagnosed with bladder urothelial carcinoma between 1988 and 2009 was used. Kaplan–Meier methods and multivariable Cox regression models were employed for survival analyses and evaluation of the association between marital status and survival, after controlling for gender, age, race, primary site, tumor (topography), lymph node, metastasis stage, pathological grading, and surgery. Findings indicated that patients in the married group had a higher proportion of men within group comparisons, more often white, older, earlier clinical stage at diagnosis, surgical treatment, all of which were statistically significant (P<.001). Widowed patients had the worst bladder urothelial carcinoma cause-specific survival compared with married, single, and so on groups classified by stage and grade. The 5-year Cause-specific survival of widowed patients compared with that of married patients was, respectively, all (P<.001), 89.8% versus 95.8% at non-invasive papillary carcinoma stage, 84.1% versus 91.6% at occur in situ stage, 74.3% versus 86.1% at stage I, 41.2% versus 61.6% at stage II, 39.2 versus 52.5% at stage III, and 8.8% versus 17.0% at stage IV. Widowed patients tend to have a significantly higher risk of bladder-cancer-specific mortality. This is a clear reflection that marital status was relevant to improved Cause-specific survival in patients with bladder urothelial carcinoma [40].

Also, in a review paper involving 204,862 cases of transitional cell carcinoma (TCC), of which 64.26%, 10.64%, 1.01%, 7.31%, and 16.78% were married, single, separated, divorced, and widowed, respectively. Wherein married patients had the highest overall survival (median 123 months), followed by single patients (median 111 months), divorced (median 102 months), separated (median 60 months), and widowed (median 43 months). The findings on bladder cancer-specific survival, equally revealed relatively similar trends with married patients having significantly better survival when compared to other groups. After adjustment for age, sex, race, stage, grade, and undergoing cancer-targeted surgery, married patients still had better survival outcomes when compared to single patients (HR = 1.322, p-value < 0.001), separated patients (HR = 1.409, p-value < 0.001), divorced patients (HR = 1.358, p-value < 0.001), and widowed patients (HR = 1.242, p-value <

0.001). The study concluded with demonstration of clear survival advantage in cases of transitional cell carcinoma of the bladder with married individuals having the highest overall and cancer-specific median survival. Furthermore, the results shed the light on the lifestyle and the psychosocial factors, not leaving out the social support that married patients may have compared to unmarried patients, and their effect on the disease prognosis and survival. Meaning, a better understanding on the social and psychological factors associated with the observed differences may strengthen management plans for affected patients [41]. This is equally our considered view in the epidemiological characterization of marital status in the risk of occurrence of bladder cancer.

Occupational Differences in Cancer of the Bladder

Differential occurrence in the cancer of the bladder is attributable to occupational exposure to carcinogens, wherein occupational chemical (containing aromatic amines) exposures have been linked to about 25% of all bladder cancer cases [42,43]. They further stated that, occupations at higher risk of exposure include; mining, rubber workers, leather and textiles, trucking and railroad, hairdressers and barbers, machinists, painters, printers, mechanics. Table 1, indicates examples of agents (carcinogens) linked to higher-risk and differential occupations with potential risk for exposure.

Table 1: Carcinogens linked to bladder Cancer.

Examples of agents linked to higher-risk of bladder cancer	Examples of occupations with potential risk for exposure
Aromatic amines (i.e. 4-aminobipheyl, benzidine, 2-naphthylamine, ortho-toluidine)	Dyes and pigment manufacture, painters, metal plastic textile and rubber industries, pesticide and cleaning product users, possibly hairdressers and barbers.
Coal tars and pitches	Production of refined products, aluminium industry, road paving and construction.
Polyaromatic hydrocarbons (i.e. benzo[a]pyrene)	Working in close contact with burning matter- i.e. foundries, steel working, fire-fighters, and mechanics.
Diesel engine exhaust	Professional drivers, mechanics.
Mineral oils	Lubricants, printing industry, cosmetics, pharmaceutical industries.
Solvents	Rubber industry, leather working industries.
Leather dust	Leather working industries.

Source: [42].

Case-control studies revealed that about 19 and 6 percent of bladder cancers in males and females, respectively, were related to occupational exposure to industrial carcinogens that are specifically implicated in the induction of bladder cancer, such as α- and ß-naphthylamine, 4-aminobiphenyl, methylene dianiline, 4-chloro-*o*-toluidine and toluidine [44-47].

Squamous Cell Carcinoma (SCC) of the bladder is regarded as an occupational hazard of farming particularly those involved in irrigation supported farming in Schistosomiasis endemic regions of developing countries such as Middle East and parts of Africa. Nevertheless, differences in occupation in cases of bladder cancer survival is rarely documented. Several studies of the Western world suggested that bladder cancer patients from blue-collar job backgrounds such as manufacturing and mining had a worse prognosis compared with white-collar counterparts such as professionals and managerial workers [48-50].

In the purview of clinical and pathological features such as pathology, stage, and treatment of bladder cancer, besides smoking behaviour and environmental factors, are considered as the underlying factor of the monotonic pattern of occupational gradient in survival: depicting, higher occupational class workers enjoy more favorable bladder cancer survival [48-51]. From all indications, it is still difficult to declare studies that have evaluated occupational disparities in bladder cancer survival in the non-Western context. However, in Japan, the picture is that, working in managerial and professional positions, the highest occupational class background, may not ensure the best health outcome in all-cause and cancer-specific mortality and cardiovascular risks [52-54]. This is a deviation from the monotonic occupational gradient widely seen in the Western context.

Temporal Factors in Cancer of the Bladder

Temporal factors in the occurrence of cancer of the bladder is instructive of how timing, duration, latency, and age are intersected with the development of the disease, with the most prominent factors, as age and cumulative exposure time to carcinogens such as tobacco smoke for over decades. Such variables define who is affected and when [55].

However, it is succinctly stated that, time line, as an epidemiological measure of risk of chronic disease condition such as cancer of the bladder is posed with serious challenges due to the insidious nature of the onset of the disease and its protracted pre-pathogenesis period. Perhaps the most important contribution of time consideration in the epidemiology of cancer is in the analysis and interpretation of trends [2]. In this regards, secular trends became more relevant than short-term associated with annual or seasonal cyclicity in the disease occurrence. Factors under consideration in secular trends of occurrence of cancer include; changes in disease classification criteria or case-fatality rates; changes in population characteristics; gradual improvement in clinical diagnosis, concepts and terminology; frequent contacts with specific carcinogens; possible increase in dose of carcinogens; effect of any preventive intervention including screening and early detection and modifications in lifestyle-related risk factors [2]. These specific variables, characterizing temporality in bladder cancer occurrence, shall be considered to unravel the extent of intersections in trend.

Age and Latency: According to [55], the risk of bladder cancer increases sharply with age, reflecting most cases being diagnosed in individuals over 55 years of life. This indicates the long latency periods (10 to 30 years) required for accumulated damage to bladder tissue from carcinogens.

Duration of Smoking: Smoking is noted as the leading risk factor for cancer of the bladder. Both the intensity of smoking and the

duration of the habit are directly linked to the risk; those who have smoked for 20 to 40 years face exponentially higher relative risks compared to those with shorter smoking histories, with a ratio 4:1 among smokers and non-smokers [56]. Nevertheless, it is worth noting that, as long-term smoking increases risk, quitting helps in reversing the trend. The relative risk of bladder cancer drops significantly over time after an individual quits smoking with risk reduction of 30-40% in 5 years, and more over time [57,58].

More so, [2], stated that the main, natural changes in secular trends of cancer of the lung, cervix, uterus, among others, have been found to be due to epidemiological factors of exposure to risk factors. In cancer of the bladder, cigarette smoking has been implicated as a major causal factor. In industrialized countries, cigarette smoking is the most important. There is a linear relationship between smoking and risk of bladder cancer, and quitting smoking reduces the risk [59].

In a clinicopathological studies on urinary bladder cancer at a major University Hospital in northern Jordan for over seven years, [27], reported a male-to-female ratio of 9 to 1, which is much higher than that described in the USA, where it ranges from 3:1 to 4:1 [32]. Since cigarette smoking is one of the main aetiological factors related to the development of TCC, which is prevalent in Jordan [33], this high male: female ratio may be related to a lower number of Jordanian women who smoke and to the very low percentage of women who work in Jordan.

Age at First Exposure: In occupational settings associated with exposure to aromatic amines and industrial dyes, the age at first exposure matters. Younger persons with first exposure before age of 25years had a longer window for bladder cancer to manifest compared to those exposed later in life. The following hypothetical situations helped in illustrating how various time-related factors are intersected. “For illustration, the exposure of interest is referred to as "the agent".

Two persons were born in 1945. Both were exposed continuously to the agent for 10 years. One person began exposure at age 20 continuously to age 30, the other began at age 30 continuously to age 40. In 1995, at age 50, the first person has 30 years since first exposure, whereas the second has only 20 years. Thus, the age at first exposure and the time since first exposure, for a given duration of exposure, are linked. One person began exposure to the agent in 1970; a second starts in 1975. They are the same age at first exposure and exposure continues until 1985. When evaluated in 1995, the first person has both a longer duration of exposure (15 years versus 10 years) and a longer time since first exposure (25 years versus 20 years), which illustrates the link between these two factors for a given age at first exposure.

Again, two persons were born in 1945. One began exposure at age 20; the other, at age 30. Exposure stops for both at age 40. The first person has a younger age at first exposure, a longer duration of exposure, and a longer time since first exposure, showing that all three factors may potentially be linked. The two persons were exposed to the same concentration of the agent. The person with the longer duration of exposure will, by definition, have a higher cumulative exposure. Although it is possible to construct counter examples to the above, these are fairly typical examples of what happens in many occupational settings. They are presented primarily to illustrate that examining the effects of one time-related factor may be difficult without information about the others [60].

Case-control studies revealed that about 19 and 6 percent of bladder cancers in males and females, respectively, were related to occupational exposure to industrial carcinogens that are specifically implicated in the induction of bladder cancer, such as α- and ß-naphthylamine, 4-aminobiphenyl, methylene dianiline, 4-chloro-*o*-toluidine and toluidine [44-47].

Time on Indwelling Catheters: Prolonged use of urinary catheters causes repeated urinary tract infections as well as chronic bladder inflammation. The duration of catheterization directly correlates with an increased risk of developing squamous cell carcinoma [61].

Cancer Treatment Timelines: Earlier radiation therapy to the pelvis or specific chemotherapy drugs (like cyclophosphamide) are known to increase risk, often presenting with a median latency of about 10 years post-treatment [62].

High Recurrence Rates: Upon diagnosis and treatment, bladder cancer has one of the highest recurrence rates of any malignancy (up to 70% within 5 years). This necessitates lifelong, scheduled cystoscopy surveillance [63].

Locational Factor in Cancer of the Bladder

The occurrence of bladder cancer has been reported to be heavily influenced by exposure to industrial chemicals and parasitic infections endemic to specific geographical locations, and contaminated drinking water sources (deep wells that contain naturally high levels of arsenic) in such locations as the primary local and regional triggers for the disease, noting the case of bladder infection caused by *Schistosoma haematobium*, a leading cause of squamous cell bladder cancer, which is common in Africa and the Middle East but rare in the United States [64]. However, reported regional prevalence, showed that, the highest incidence rates of cancer of the bladder are generally observed in North America and Southern and Western Europe, being typically attributed to higher concentrations of industrialization and higher rates of tobacco use [65].

According to [2], in the epidemiological description of the occurrence of cancer diseases, a lot of insights can be gained by looking at variability in risk levels as a function of geographical location. The variability in the risk of occurrence of cancer of the bladder as shown by studies is influenced by endemic infections/ infestations of the urinary system of regions/locations and urbanization/industrialized community lifestyle.

In schistosome-free countries throughout the world, the peak incidence of bladder cancer is in the sixth or seventh decade of

life [66] and is maximal between the ages of 65 and 75 years [67]; only 12 percent of bladder cancer cases occur in people younger than 50 years [68].

By contrast, in Egypt, Sudan, Iraq, Zambia, Malawi, and Zimbabwe, the mean age of the highest incidence of bilharzial bladder cancer is between 40 and 49 years [69-73], which clearly contrasts with the findings for non-schistosomal locations.

In developing countries, especially in the Middle East and parts of Africa, infections with species of the genus *Schistosoma* are responsible for a high incidence of bladder cancer. While in *Schistosoma* endemic areas, SCC constitutes as high as 44-82 percent of bladder cancer [74,75]. Whereas in *Schistosoma haematobium* infestation, the parasite supplies the proliferative stimulus (i.e. promotional factor) necessary to accelerate the development of detectable tumours from latent foci produced by exposure to bladder carcinogen [76-79].

The ratio of bladder cancer incidence (males to females) in countries with endemic infection was reported to be 5:1 [80,81] but may vary within the range of 4:1 to 5.9:1 [75]. These relatively higher gender ratio in the countries with endemic infection in contrast to 3:1 in countries of non-endemicity has been suggested that in rural areas the main route of infection is through contact with infected waters during agricultural activities, which are normally done by men rather than women [82].

Public Health Significance of Bladder Cancer

The age variation in the epidemiological characterization of bladder cancer is significant, in that SCC mediated by Schistosomiasis affects the younger, able bodied workforce of the population and bread winners of the households. The economic impact on the society at large is enormous and cannot easily be assessed. Cancer of the bladder can damage a large portion of bladder tissue and if metastasis does occur, present with poor prognosis (the prospects of successful treatment are not good). This has an attendant psychological and economic burden on the family, community and society at large.

Prevention and Control of Bladder Cancer

Disease control in public health point of view conceptualized prevention to occur at primordial, primary, secondary, tertiary and quaternary levels. This is applicable in the prevention and control of cancers, bladder cancer inclusive.

Primordial Prevention of Bladder Cancer

This aims to elicit strategies that alter societal structures toward inhibition of associated underlying determinants of diseases that are basically social, economic, behavioural and environmental in nature, known for occurrence of cancer diseases in the population. It seeks to address the determinants of bladder cancer at the systemic level, rather than modification of personal risk factors, including; public health policies, community level actions to prevent tobacco use, reduction in industrial chemical exposures as well as availability of safe drinking water. These are encapsulated under the following;

- **Policies on Tobacco Control:** Enforcement measures through the invocation of the police powers of the State or Government to force compliance to the laws, such as laws and prescribed legislations regarding smoking of cigarette in public places, high tobacco taxes, as well as plain packaging laws to stop young persons from starting smoking. For instance, Nigeria National Agency for Food and Drug Administration and Control [NAFDAC] ensuring through certification that only cigarette with required levels of carcinogen content are marketed as a typical environmental modification through engineering measures in the context of the encounter between persons at risk of bladder cancer and the cancer-inducing agents.
- **Standards in Occupational Safety:** Strict workplace regulation implementation in industries involved in the use of rubber, leather, textiles, dyes, and paint to reduce worker exposure to carcinogenic aromatic amines.
- **Water Quality Control:** Monitoring to ensure reduction in arsenic and industrial pollutant levels in municipal and well water supplies.
- Public health education aimed at controlling snail intermediate host, and access to sanitation and safe water.

Primary Prevention of Bladder Cancer

This refers to strategies and techniques designed to offset the onset of the cancer, usually directed at the pre-pathogenesis (before clinically detectable manifestations onset) stage of the natural history of the cancer. These include:

- Behaviour (lifestyle) change modification measures aimed at eliciting non-exposure to carcinogens implicated in the induction of bladder cancer as in cigarette smoking and risk factors associated with the occurrence of the cancer, such as cultural and religious practices (ablution and wadu) among the Muslim society that are linked to exposure and transmission of schistosomiasis, a significant etiologic factor in bladder cancer. Also very important healthful attitudes that may reduce or prevent the incidence of bladder cancer is the intake of lots of water daily which may help wash away carcinogens that may be excreted in urine. In a 10-year prospective study involving almost 48,000 men, researchers found that men having high intake of water (over 2.5 litres daily) correlated with 24% reduced risk of bladder cancer when compared with men who drank less than 240mL (around 1 cup) per day [83]. Also, a 2008 study concluded "specific fruit and vegetables may act to reduce the risk of bladder cancer" [84].
- Use of Specific Personal Protective Equipment at work to limiting or ensuring non-exposure in occupations involving carcinogens capable of inducing bladder cancer as earlier highlighted in this paper.

Secondary Prevention of Bladder Cancer

Secondary prevention methods are applied in the prevention and control of cancers whenever primary prevention strategies are insufficient or ineffective. These methods which are applied at the early stages of development of the cancer, including the

symptomatic or sub-clinical stage is to limit or forestall the progression of the cancer and prevent sequelae conditions such as metastasis and clinical complications. These secondary prevention strategies of bladder cancer include;

- Early detection of cases and prompt follow-up treatment, probably when the cancer is at stage 0 (Cancer cells are found only on the inner lining of the bladder). Superficial tumors (those not entering the muscle layer) can be "shaved off" using an electrocautery device attached to a cystoscope. Immunotherapy in the form of BCG instillation is also used to treat and prevent the recurrence of superficial tumors [85]. BCG immunotherapy is effective in up to 2/3 of the cases at this stage. Also included here is health education to improve health seeking behavior of the populace and treatment of the population at risk via mass chemotherapy.
- Untreated, superficial tumors may gradually begin to infiltrate the muscular wall of the bladder. Tumors that infiltrate the bladder require more radical surgery where part or the entire bladder is removed (a cystectomy) and the urinary stream is diverted.
- Substantial secondary prevention of most cancers can be achieved through recommended checkups for purposes of early detection and control of cancers. In this regards most professionals recommend a routine cancer-related check up every three years for symptoms-free people 20 to 40 years for age and more thorough cancer-related checkup annually for symptom-free people 40-years old and over [20,86]. This should be applicable in cancer of the bladder.
- Mass screening of high risk population groups using presumptive procedures (haematuria) to identify persons who apparently have cancer of the bladder or are sick with cancer related illness as to determine whether enough evidence exists to warrant further diagnosis to establish cancer of the bladder.

Tertiary Prevention of Bladder Cancer

Tertiary prevention of cancers refer to strategies applied late in the prognosis of the disease after resultant disability has been observed, with a view to achieving successful rehabilitation of disabled persons so that as much functional capacity as possible is regained. These strategies in cancer of the bladder include;

- Psychotherapy to enable affected individual and family to cope with extent of disability and to perform possible functional capacity.
- Also applicable here is more radical surgery (a cystectomy) where the tumors infiltrate the bladder thereby requiring removal of its part or entirely and the urinary stream diverted. However, in some cases, skilled surgeons can create a substitute bladder (a neobladder) from a segment of intestinal tissue, but this largely depends upon patient preference, age of patient, renal function, and the site of the disease [87].

Quaternary Prevention of Bladder Cancer

This new paradigm in disease prevention focuses on measures targeted at persons at risk of excessive medicalization with a view to protecting them from further unnecessary interventions, thereby avoiding iatrogenic damages. For cancer of the bladder, the concern is avoidance of unnecessary invasive diagnostic tests for harmless symptoms to reduce harms of overtreatment during surveillance, through;

- Application of rationalization technique in haematuria workup towards avoidance of aggressive or repetitive invasive cystoscopies and CT scans for isolated, transient, and low-risk microhaematuria in young, asymptomatic patients devoid of real risk factors.
- Application of conservative framing technique to ensure non-conduct of overly frequent, burdensome routine scopes or imaging tests for patients with low-risk, non-muscle-invasive cancer of the bladder with a very low empirical stance of dangerous progression.
- Management of incidental findings to avoid engaging in unnecessary biopsies for benign, incidental bladder wall changes or minor inflammatory spots seen during unrelated imaging of the pelvis.
- Reduction in medical harm on patients from cumulative physical trauma, urinary tract infections as well as psychological distress following excessive repeated transurethral resections or surveillance instrumentation.
- Real-time engagement with patients in realistic discussions on real benefits in midst of discomfort associated with intense follow-up schedules, to prevent the cascade of diagnostic creep.

Conclusion

Having noted the enormous burden of cancer of the bladder and its public health implications from the analysis and interpretation of risk factors through epidemiological mapping and characterization for better understanding of these risk factors and their relative strength in the causation of the disease condition using most common descriptive epidemiological variables, there is the dire need to put in place public health intervention programme in line with the prevention and control measures as highlighted in this paper as much as possible to reduce the burden of cancer of the bladder and its attendant morbidity and mortality. However, there is also the need to carry out studies on association between marital status and the occurrence of bladder cancer as well as the influence of treatment decision making, access, delay and racial discrimination in bladder cancer prognosis.

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