Bladder Cancer in Lebanon: An Updated Epidemiological Comparison with Global Regions and a Comprehensive Review of Risk Factors

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Abstract

Objectives: This study aims to analyze urinary bladder cancer (UBC) incidence rates in Lebanon over a 12-year period (2005-2016) and compare them with rates in other countries. It also discusses UBC risk factors in Lebanon.

Introduction: Lebanon has one of the highest estimated age-standardized incidence rates (ASIRw) of UBC worldwide.

Methods: Data on UBC were obtained from the Lebanese national cancer registry for the years 2005-2016. The study calculated age-standardized incidence rates (ASIRw) and age-specific rates per 100 000 population. It also estimated the population attributable fractions of smoking, water pollution, and air pollution for UBC incidence in Lebanon in 2016. However, limited data precluded sensitivity analyses, potentially affecting the robustness of the estimates.

Results: During this period, UBC ranked as the third most common cancer in males (12.9% of all new cancer cases) and the eighth most common in females (2.8% of all new cancer cases), excluding non-melanoma skin cancer. The average ASIRw was 28.8 in men and 6.6 in women, placing Lebanon among the countries with the highest UBC incidence rates globally. UBC incidence rates increased with age. Estimates indicated that 46.4% of UBC cases in the Lebanese population were attributed to current smoking, 8.6% to water pollution with disinfection byproducts, and 6.0% to air pollution with PM2.5.

Conclusion: This study underscores the urgent need to mitigate UBC risk in Lebanon through tobacco control and by reducing exposure to preventable environmental and occupational risk factors, including tobacco smoking, water pollution, and air pollution.

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Background

Cancer is the second leading cause of death globally.[1] Urinary bladder cancer (UBC) is among the most prevalent and costly cancers due to its high recurrence and extensive diagnostic and treatment needs.[2-5] In 2020, UBC ranked 10th globally in cancer incidence (6th in males), with 573 000 new cases and 213 000 deaths.[5] Males are 3 to 4 times more likely to develop UBC, with global age-standardized incidence rates (ASIRw per 100 000 population, adjusted to the world population) of 9.5 for males and 2.4 for females in 2020.[5]

UBC is most prevalent in countries with very high Human Development Index, with the highest rates reported in Europe and North America (ASIRw: 19.4 per 100 000 males and 4.6 per 100 000 females).[5,6] South-central Asia, Central America, and sub-Saharan Africa have the lowest UBC incidence rates.[5,6]

Several risk factors contribute to UBC development.[5,7-12] Tobacco smoking is the leading contributor to geographic and sex disparities, as well as for temporal patterns in UBC incidence and mortality rates worldwide.[5,9-13] Cigarette smoking accounts for about 50% of all UBC cases, particularly urothelial cell carcinoma (UCC).[14-16] Occupational exposure to aromatic amines and other hazardous chemicals used in firefighting or in paint processing, dye, rubber, metal (e.g., aluminum), and petroleum products is the second most significant risk factor.[7,8,10,11] Environmental pollution, especially drinking water contaminated with arsenic or chlorine/ trihalomethanes and possibly ambient air pollution, also contributes to UBC risk.[7-11] Chronic inflammation of the urinary tract, particularly with *Schistosoma haematobium* (*S. haematobium*) in regions of northern and sub-Saharan Africa, further elevates the risk.[5,8-13] Genetic predispositions and mutations, particularly when combined with smoking, can also increase susceptibility.[8,10,11] To reduce UBC-specific morbidity and mortality, primary prevention is key, particularly through avoiding exposure to carcinogens such as tobacco smoke, the leading risk factor.[11-17] Despite advancements in diagnostics, there is no consensus on cost-effective screening methods for high-risk groups.[11,18-22]

The World Health Organization (WHO) projects that the Eastern Mediterranean region will experience the highest increase in cancer incidence among all regions over a 15-year period beginning in 2012.[23] In this region, lung and bladder cancers are the most prevalent among men, while breast and colorectal cancers are the most common among women.[23] Unfortunately, the majority of cancer patients in this region seek treatment at an advanced stage, which significantly reduces the effectiveness of even the best available treatments.[23]

This study analyzes the 12-year incidence rates and temporal trends of invasive UBC in Lebanon. It also compares the incidence rates of UBC in Lebanon to those in the Middle East and North Africa (MENA) region and other countries/regions worldwide. Furthermore, the study discusses the various factors contributing to the UBC age-standardized incidence rates in Lebanon and concludes with recommendations for effective UBC prevention and screening.

Materials & Methods

Lebanon

Lebanon, a developing country in the Middle East with a population of 6.3 million in 2016 (including about 1.6 million refugees, displaced persons, migrants, and refugees),[24] achieved a Human Development Index (HDI) of 0.757 in 2017 (the time corresponding to the data of this manuscript).[25] In 2015, life expectancy at birth in Lebanon was 76.0 years.[24]

The Lebanese National Cancer Registry (NCR)

In 2002, following years of conflict, Lebanon's Ministry of Public Health (MoPH) reinstated the national cancer registry (NCR). The NCR records for new cancer cases in Lebanon are almost complete (over 90%) but exclude in-situ lesions.[26] All sites involved in diagnosing and treating cancer report new cancer cases to the NCR through CanReg5. This WHO-recommended tool is an open-source software that facilitates the input, storage, validation, and analysis of cancer registry data. There are two ways that the MoPH constantly collects data: the capture system passively receives data from doctors' reports, and the recapture system actively collects data from histopathological and hematological laboratories to verify the capture system input.[26,27] Cancer incidence data, covering the years from 2005 to 2016, is available on the MoPH website.[27]

Twelve-Year Trend Analysis from 2005 until 2016

In this study, data encompass diagnoses of invasive UBC (C67) as classified by the International Classification of Diseases, 10th revision (ICD-10). This study examined the ranking of UBC among all cancers in males and females during the study period (2005-2016). The age-standardized incidence rate (ASIRw), adjusted to the world-standard population by Doll as a reference population[28] and the age-specific incidence rates[29] per 100 000 population were calculated using figures published by the Lebanese NCR on the MoPH website for the years 2005-2016.[27]

The Joinpoint Regression Program (JRP) version 4.7.0.0 was utilized to analyze trends in the observed cancer ASIRw.[30] Joinpoint regression applies a Monte Carlo permutation method to identify statistically significant changes in trends (joinpoints) and the rate of change (annual percent change) in each trend segment.[30] The JRP calculated the average annual percent change (APC) of UBC incidence rates among males and females over the years. Additionally, it computed the APC for age-specific UBC incidence rates. A *P*-value of less than 0.05 was deemed statistically significant.[30]

Comparison of UBC Incidence Rates in Lebanon to Other Countries

This study compares Lebanon's UBC ASIRw and age-specific rates with t regional and global estimated data from the Global Cancer Observatory (Cancer Over Time), published by the International Agency for Research on Cancer (IARC), which is affiliated with the WHO.[31] The Observatory reports age-standardized incidence rates (ASIRw), adjusted to the world-standard population using Doll's reference, based on high-quality, population-based cancer registries.[28]

Estimation of the Population Attributable Fraction (PAF) of Smoking, Water Pollution with Disinfection Byproducts, and Air Pollution with $PM_{2.5}$ on UBC Incidence in Lebanon, 2016

We conducted a retrospective data analysis to investigate the relationship between exposure to a specific risk factor and UBC incidence. We employed the population attributable fraction (PAF) to estimate the effect of trihalomethanes (THMs) on bladder cancer incidence in Lebanon.

The PAF indicates the proportion of disease cases that could be prevented if the population were not exposed to a particular risk factor. This measure accounts for both the prevalence of exposure and the increased risk it entails. Therefore, PAF estimates are useful for planning and prioritizing strategies to reduce the population's cancer burden.

To calculate the PAF of a risk factor's cancer burden, two key components are required: the prevalence of the population exposed to the risk (Pe) and the relative risk of cancer associated with that risk factor (RRe). Usually, cancers arising from exposure to a risk factor result from prolonged exposure over an extended period, with a 10-year latent period generally being adequate for most cancer risk factors.[32]

We used a standard formula: $PAF = Pe\,(RRe-1) / [1 + Pe\,(RRe-1)]$ if a risk factor is present at a single exposure level.[33]

We applied a modified version of the Levin formula: $PAF = Pe_1\,(RRe_1\text{-}1) + Pe_2\,(RRe_2\text{-}1) / 1 + [(Pe_1\,(RRe_1\text{-}1) + Pe_2\,(RRe_2\text{-}1)]$ in the case where the risk factor shows more than one exposure level (e.g., in tobacco smoking: former smokers, current smokers).[33]

Our analysis primarily relied on WHO estimates, population-based reports, and studies with representative samples of the Lebanese population. These sources identified the proportion of the population at risk approximately a decade ago, considering that the impact of the risk factor is not immediate and requires a 10-year lag to draw meaningful conclusions.[32] The study used the WHO's estimate of the prevalence of current tobacco smoking in Lebanon in 2005 (35.1% in males and females, 41.1% in males, and 28.7% in females), supplemented with the WHO's STEP estimate of former tobacco smoking prevalence in Lebanon in 2009 (6.9% in males and 3.3% in females), as there was no prior data on the prevalence of former smokers in Lebanon.[34,35,]

A study on THM contamination levels in drinking water revealed that 94.1% of the networks investigated in Lebanon exceeded the United States Environmental Protection Agency (USEPA) range of concern for increased carcinogenic risk from THM.[36] According to the Central Administration for Statistics (CAS), Lebanon's drinking water sources are either underground water or surface water.[37] Therefore, we can consider bottled water, originating from either ground or surface water, to be representative of both. Lebanon's ambient air pollution with particulate matter that is 2.5 microns or smaller in size ($PM_{2.5}$) exceeds WHO guidelines.[38-42] In this analysis, we considered that at least 90% of the population in Lebanon has long-term exposure to ambient air pollution with $PM_{2.5}$.

We used multiple adjusted UBC relative risks (RRe) from meta-analyses of epidemiological studies for each risk factor: current smoking (3.47 in males and females, 3.44 in males and 3.56 in females), former smoking (1.92 in males and 2.04 in females), THM pollution in water (1.1), and $PM_{2.5}$ pollution in the ambient air (1.07), to estimate the corresponding PAF.[15,16,43,44]
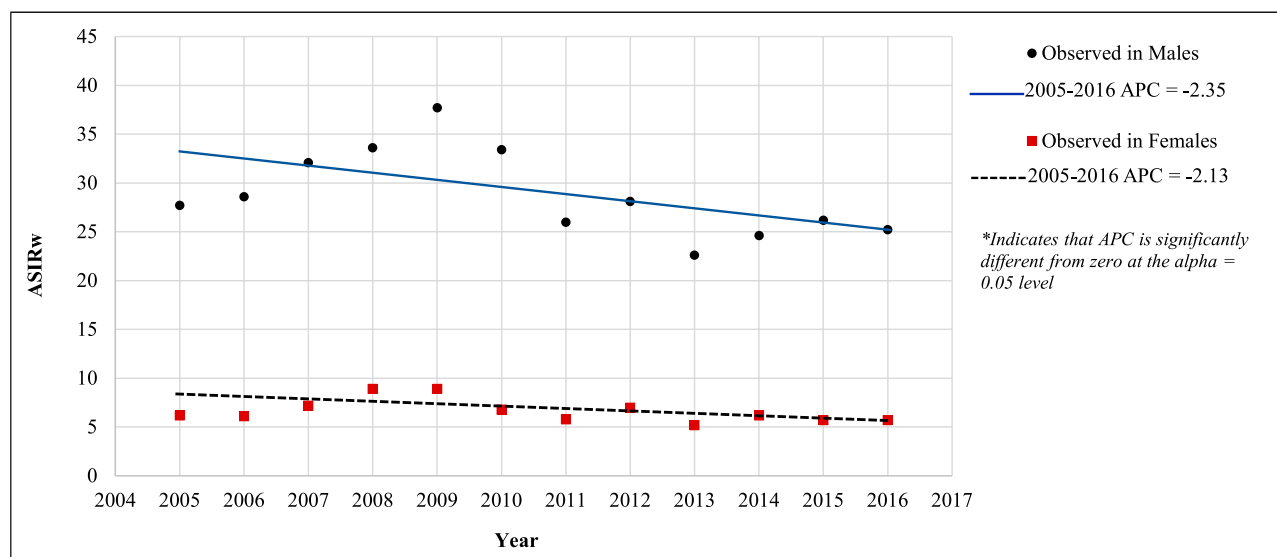
Results

Twelve-Year Trend Analysis (2005-2016)

Over the study period (2005-2016), excluding non-melanoma skin cancer, UBC was the third most common cancer in males (12.85% of all new cancer cases) and the eighth most common cancer in females (2.82% of all new cancer cases).

We computed the APC for all study participants to reflect trends in the ASIRw of UBC among males and females throughout the 12-year study period. With a 0 Joinpoint model, the UBC ASIRw among both males and females decreased non-significantly from 2005 to 2016 (APC: −2.35 and −2.13, respectively, *P*-value > .05) (Figure 1). However, the best Joinpoint model identified three trends in the Lebanese ASIRw of UBC in males and two trends in females. In males, there was a significant increase in the period 2005-2009 (APC: 7.60, *P*-value < .05) with a peak in 2009 (37.7), followed by a significant decrease in the period 2009-2013 (APC: −10.68, *P*-value < .05), and then a non-significant increase in the period 2013-2016 (APC: 3.85, *P*-value > .05), reaching 25.2 in 2016 (Figure 2). In females, there was a significant increase during the period 2005-2008 (APC: 11.48, *P*-value < .05), with a peak in 2008 and 2009 (8.9), followed by a non-significant decrease in the period 2008-2016 (APC: −5.32, *P*-value > .05), reaching 5.70 in 2016 (Figure 2).

UBC incidence rates increase with age. Figure 3 illustrates the increasing UBC incidence rates in Lebanon with age in the years 2005-2016.

In males, UBC incidence decreased in all age groups over 35 during the study period, but this decrease was statistically significant only in the 45-49 age group (Table 1). In females, UBC incidence increased non-significantly in the age groups 55-59 and 60-64 and decreased non-significantly in the other age groups over 35 years during the study period (Table 1).
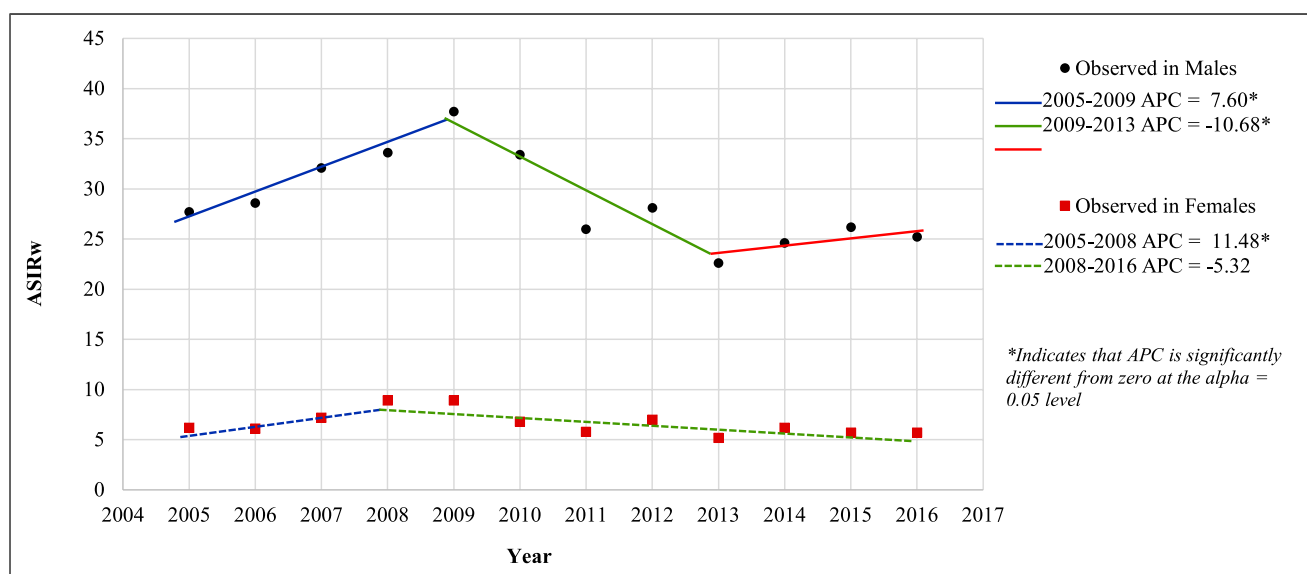
Figure 1. Age-Standardized Incidence Rates (World Population) per 100,000 Population for Bladder Cancer (ICD10: C67) in Lebanon for the Years 2005-2016. (Model: 0 JoinPoint).

Results from Global Cancer Observatory, Cancer Overtime Statistics (2012-2016)

The Global Cancer Observatory's Cancer Overtime Statistics website provides data for the UBC ASIRw in various countries from 2012 to 2016 (5 years), but it does not include Lebanon.,[31] This allows for a comparison with Lebanon's national registry data, which also uses ASIRw. Figure 4 reveals that Lebanon's UBC ASIRw is among the highest worldwide, ranking sixth for men and 10th for women compared to other reported countries and territories.

Estimation of the Population Attributable Fraction (PAF) of Smoking, Water Pollution with Disinfection Byproducts, and Air Pollution with PM$_{2.5}$ for UBC Incidence in Lebanon, 2016

Smoking. We estimated that 51.6% of UBC cases among Lebanese males and 43.5% of UBC cases among Lebanese females in 2016 were attributed to smoking across all age groups. However, these fractions do not account for the relative risks of UBC associated with second-hand (passive)

Figure 2. Age-Standardized Incidence Rates (World Population) per 100,000 Population for Bladder Cancer (ICD10: C67) in Lebanon for the Years 2005-2016. (Final Selected Models: 2 Joinpoints in Males, and 1 JoinPoint in Females).
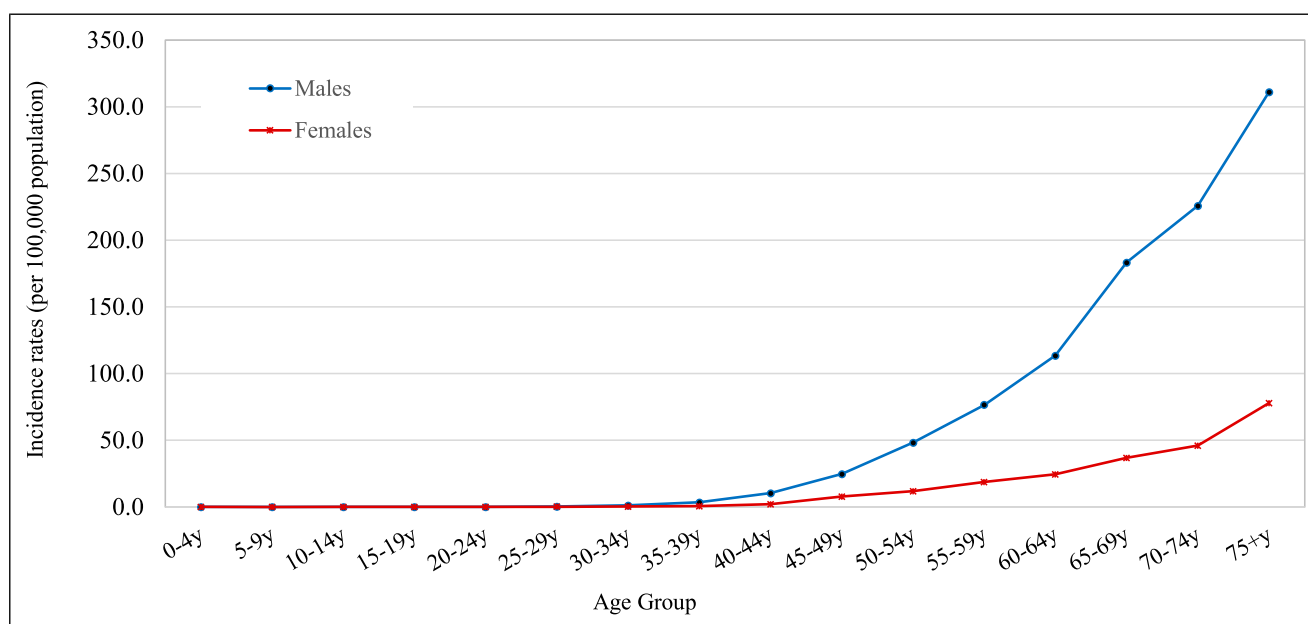
Figure 3. Age-Specific Incidence Rates (per 100 000 Population) for Bladder Cancer (ICD10: C67), Lebanon 2005-2016.

smoking. Additionally, we estimated that current smoking contributed to 46.4% of UBC cases in the Lebanese population (Table 2).

Water pollution with disinfection byproducts (DBPs) from chlorination, specifically trihalomethanes (THMs): We estimated that 8.6% of UBC cases in Lebanon in 2016 were attributed to water pollution with THMs across all age groups and both genders.

Ambient Air Pollution with PM2.5. We estimated that 6.0% of UBC cases in Lebanon in 2016 were attributed to air pollution with PM2.5 across all age groups and both genders.

Discussion

The Global Cancer Observatory (Cancer Over Time) does not report cancer incidence rates for Lebanon.[31] Using the MoPH's NCR and world standard population, Lebanon had one of the highest UBC incidence rates (ASIRw) globally. The Global Burden of Disease (GBD) 2019 report, using a different standardized population, ranked Monaco (31.9) and Lebanon (30.2) as having the highest global UBC ASIRs per 100 000.[45] UBC also imposes a significant economic burden in Lebanon.[46,47]

A 2020 study by Teoh et al. examined international UBC trends over a decade, noting declining incidence and mortality in Oceania and the Americas, rising incidence but declining mortality in Europe, and decreasing incidence but increasing mortality in Asia.[13] In this study, tobacco use correlated positively with UBC incidence ($r = 0.20$ in men and $r = 0.67$ in women) and mortality rates ($r = 0.38$ in men and $r = 0.22$ in women).[13] Lebanon saw a slight decline in UBC ASIRs

between 2005 and 2016, aligning with mildly reduced tobacco use, though mortality data remain unavailable.[48-51]

Geographic variations in UBC incidence are linked to tobacco use, environmental and occupational risks, as well as healthcare disparities.[52] In Africa, late-stage presentations limit treatment options.[52] While UBC diagnoses are expected to increase with global population growth and aging, the overall risk may not necessarily rise. Globally, life expectancy increased from 66.8 years in 2000 to 73.3 years in 2019, and in Lebanon, from 74.6 to 76.4 years.[53] The United Nations (UN) projects a global population of 9.7 billion by 2050, with the 60-plus population more than doubling, thereby increasing the burden of late-onset diseases like UBC, particularly in Africa, where the population is expected to nearly double between 2017 and 2025.[54]

Prevention is key: primary prevention targets risk behaviors like tobacco use, secondary prevention focuses on early detection in high-risk groups, and tertiary prevention aims to prevent complications. UBC is rising in various MENA countries (Figure 5), largely due to tobacco smoking.[55] The following discussion highlights primary prevention efforts in Lebanon, while also recognizing the complex etiology of UBC.

Primary Prevention of UBC

Understanding modifiable risk factors is key for cancer prevention. While age and male gender are non-modifiable, factors such as tobacco use, exposure to carcinogens, and chronic urinary inflammations (e.g., *S. haematobium*) are preventable. Although Genome-Wide Association Studies
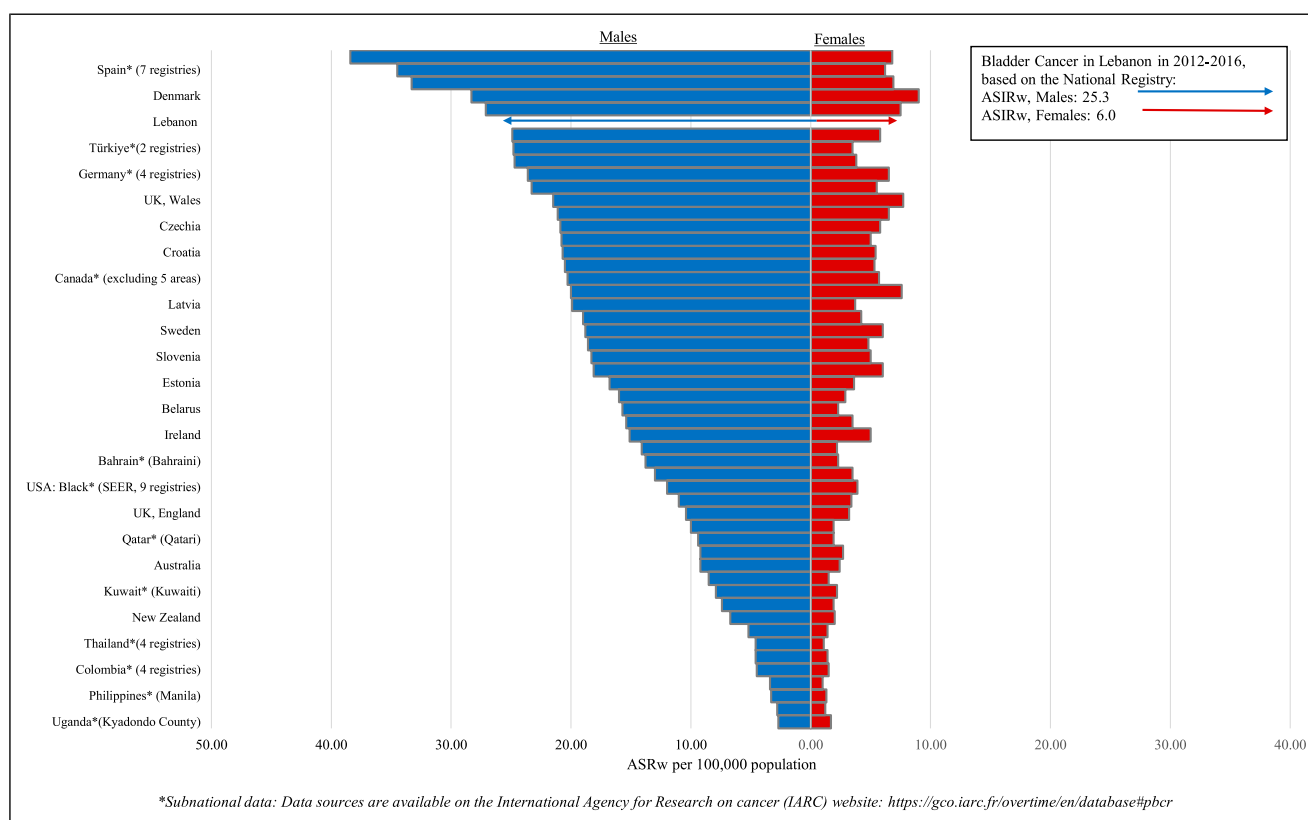
Table 1. Bladder Cancer (ICD10: C67) Age-Standardized Incidence Rate (World Population) and Age-specific Incidence Rates in Lebanon in the Years 2005-2016.

Age-specific rates

	Year	ASRw	0-4 y	5-9 y	10-14 y	15-19 y	20-24 y	25-29 y	30-34 y	35-39 y	40-44 y	45-49 y	50-54 y	55-59 y	60-64 y	65-69 y	70-74 y	75+ y
Males	2005	27.7	0	0.5	0.5	0	0	0.7	0	6.4	13.3	26.4	46.3	83.8	116.5	162.4	174.0	308.7
	2006	28.6	0	0	0	0.5	0	1.3	1.4	2.4	13.9	18.0	43.4	71.4	110.2	196.0	204.1	345
	2007	32.1	0	0	0.0	0.5	0	0	2.8	4.2	10.2	33.6	66.3	102.1	151.4	178.2	220.9	285
	2008	33.6	0	0	0	0	0.5	0.6	2.6	5.7	16.6	40.4	62.4	65.0	117.8	228.1	277.1	333.8
	2009	37.7	0	0	0	0	0.5	0.6	3.2	4.8	13.4	30.4	81.4	97.8	134.6	230.7	329.8	378.5
	2010	33.4	0	0	0	0	0	0.6	1.9	4.7	13.2	35.6	60.3	78.8	137.9	194.6	272.5	351.7
	2011	26.0	0	0	0	0	0.5	0.6	1.2	2.3	6.5	28.2	27.8	69.6	93.7	180.9	193.2	320.8
	2012	28.1	0.5	0	0.4	0	0	0	0	2.3	3.6	23.3	41.6	72.3	109.9	181.9	268.1	306.3
	2013	22.6	0.4	0	0	0.4	0	0	1	0.7	7.3	13.9	34.9	64.6	77.6	149.1	193.7	268.9
	2014	24.6	0	0.3	1	0.7	0.8	1.3	1.4	4.7	6.6	16.4	40.6	61.9	114.3	153.9	185.3	250.8
	2015	26.2	0	0	0	0	0	0.4	0	2.8	12.0	17.5	39.4	84.5	115.3	165.8	175.5	288.7
	2016	25.2	0	0	0	0	0	0	0.9	1.8	9.4	14.5	37.1	68.2	82.8	180.1	215.2	297.3
	Average	28.8	0.1	0.1	0.2	0.2	0.2	0.5	1.4	3.6	10.5	24.9	48.5	76.7	113.5	183.5	225.8	311.3
	APC	-	-	-	-	-	-	-	-	-8.43	-5.75	-6.18*	-4.25	-1.84	-2.89	-1.49	-1.05	-1.64
Females	2005	6.2	0	0	0	0	0	0.6	1.3	1.3	4.7	8.3	13.6	17	20.7	24.9	40.7	72.5
	2006	6.1	0	0	0	0	0	0	0.7	0.0	1.3	5.4	12.2	12.9	23.1	27.8	51.2	87.8
	2007	7.2	0	0	0	0	0	0	0.7	3.4	3.6	9.3	21.3	17.7	22.8	34.2	50.9	73.7
	2008	8.9	0.6	0	0	0	0	0.5	0	0	2.6	11.1	14.9	24.7	33.1	70.0	51.3	88.8
	2009	8.9	0	0	0	0	0	0.5	0.6	0	5.2	18.6	15.9	21.7	21.2	72.7	57.6	79.4
	2010	6.8	0	0	0	0	0.5	0	0	0	1.7	9.7	15.6	21.4	25.0	32.8	47.1	78.0
	2011	5.8	0	0	0	0	0	0.5	1.1	0	0	5.3	8.3	17.3	23.2	26.6	55.7	71.0
	2012	7.0	0	0	0.4	0	0	0	0	0.7	0	12.5	13.9	14.6	24.2	26.1	47.8	109.3
	2013	5.2	0	0	0	0	0	0	0	0	2.2	0.9	2.1	25.8	22.6	26.4	28.0	76.6
	2014	6.2	0	0	0	0.7	0	0.8	1.2	1.1	2.7	3.4	7.7	20.8	22.4	35.1	45.0	71.0
	2015	5.7	0.3	0	0	0	0.4	0.4	0	1	2	4.9	10.4	15.3	25.5	31.2	28.1	71.3
	2016	5.7	0	0	0	0	0	0	0.5	0.7	2.2	4.2	5.8	16.6	31.7	36.4	48.5	56.9
	Average	6.6	0.1	0.0	0.0	0.1	0.1	0.3	0.5	0.7	2.2	7.8	11.8	18.8	24.6	37.0	46.0	78.0
	APC	-	-	-	-	-	-	-	-	-	-	-9.89	-9.57	0.43	1.36	-0.96	-2.67	-1.62

Abbreviations: ASRw, Age-Standardized Incidence Rate (World Population); APC, Annual Percent Change.
*Indicates that APC is significantly different from zero at the alpha = 0.05 level.

Figure 4. GLOBOCAN Estimates for Bladder Cancer (ICD10: C67) Age-Standardized Incidence Rate (World) per 100 000, Males and Females, [2012-2016].

(GWAS) highlight genetic susceptibility, its role in public health remains unclear.

Tobacco Smoke. Tobacco smoke from cigarettes, waterpipes (shisha), cigars, or pipes contains carcinogens that damage the Deoxyribonucleic Acid (DNA), significantly increasing UBC risk.[7-16] Smoking remains the leading global UBC risk factor,[12-16] with secondhand smoke contributing to a lesser extent.[15,16,56] Similar to our study, tobacco smoking has a PAF of around 50% for UBC in the United States of America (USA) (50-65% in men and 20-30% in women), reflecting its significant impact on UBC incidence.[14,57,58]

Despite a global decline, tobacco is rising in North Africa and the Middle East, including Lebanon, where smoking rates in 2025 are projected to be among the highest worldwide: 55.4% (men) and 37.7% (women).[48,49] Weak anti-smoking

Table 2. Percentage Attributable Fraction (PAF) of Smoking, THM, and Air Pollution With PM2.5 on Bladder Cancer (UBC) Cases in Lebanon.

Risk factor	Lebanese Population at risk		References	Relative Risk or Odd Ratio		References	PAF on UBC		Applied Formula
Smoking	Males	Females		Males	Females		Males	Females	
Former smokers	6.9%	3.3%	[35]	1.92	2.04	[15]	51.6%	43.5%	Formula 1
Current smokers	41.1%	28.7%	[34]	3.44	3.56	[15]			
Current smokers (Pooled risk)		35.1%	[34]		3.47	[16]		46.4%	Formula 2
Trihalomethanes (Mid-Term exposure, i.e., during Winter)		94.1%	[36]		1.1	[43]		8.6%	Formula 2
Air Pollution with a 5 μg/m3 increase in PM2.5		90.0%	[38-42]		1.07	[44]		6.0%	Formula 2

Formula 1: PAF = Pe1 (RRe1−1) + Pe2 (RRe2−1) / 1 + [(Pe1 (RRe1−1) + Pe2 (RRe2−1)].
Formula 2: PAF = Pe (RRe−1) / [1 + Pe (RRe−1)].
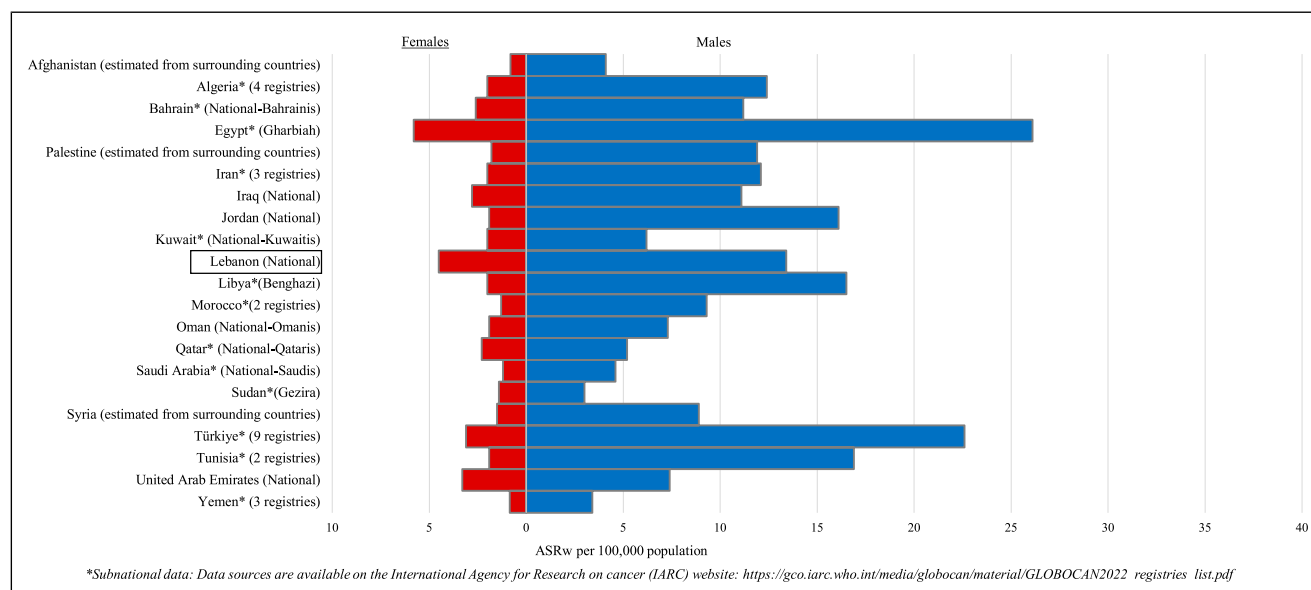
Figure 5. Globocan Estimates for Bladder Cancer Incidence Rates (ASRw) for the Year 2022 in the MENA Countries.

policies and industry interference hinder control efforts, necessitating stronger enforcement to mitigate cancer risks.[59-61]

Water and Vegetables Chemical Pollution. Arsenic in drinking water is a known risk factor for UBC.[7-11,62-68] Most high-income countries adhere to WHO guidelines, limiting arsenic levels to 10 μg/L.[62] Chronic exposure to arsenic, even at low concentrations (10 μg/L), increases cancer risk and other health issues.[62,64] Exposure to 10 μg/L of arsenic in drinking water can double the UBC risk or increase it by approximately 40%.[64] Cadmium, primarily sourced from food in non-smokers, is a probable UBC risk factor.[69] Prolonged exposure to chlorinated domestic water, through disinfection by-products (DBPs) like trihalomethanes (THMs), also increases UBC risk.[7-11,70-75] Exposure to THM levels above 25 μg/L causes a 35% or higher risk for men.[74] DBPs account for 10% of UBC cases in the USA and 23.2% in Europe, with an average of 4.9%, despite laws and monitoring.[72,73]

Lebanon's aging water infrastructure, cross-contamination, and industrial pollution cause fecal coliforms, excessive heavy metals (e.g., arsenic and cadmium) levels, and pesticides.[36,37,76,77] Population growth, the Syrian refugee crisis, economic instability, and climate change worsen water shortages and contamination,[78] increasing UBC risks. Arsenic and cadmium contamination of coastal water, agricultural soil, and cops in Lebanon further compound the public health risks.[78]

Environmental Risk Factors for UBC - Ambient Air Pollution. Ambient air pollution from industry, power generation, transportation, and domestic burning can cause systemic inflammation, oxidative stress, and DNA damage, potentially increasing UBC risk.[44,79-83] While strongly associated with lung cancer, long-term $PM_{2.5}$ exposure is probably associated with

UBC.[44,79-86] A 5 μg/m^3 increase in $PM_{2.5}$ raises UBC risk by 7%, and a 10 μg/m^3 increase in NO_2 raises it by 4%.[44] The role of polycyclic aromatic hydrocarbons (PAHs) in ambient air as a UBC risk factor remains unresolved.[44] Air pollution and tobacco smoking may have a synergistic effect on UBC rates.

Ambient air pollution is a major issue in Lebanon.[87-93] Lebanon had the highest per capita air pollution rate in the Middle East, along with Egypt, with 2700 premature deaths in 2018 costing $1.4 billion (2% of GDP), according to a 2020 Greenpeace research study.[92] From 1990 to 2019, Lebanon's mean annual exposure to PM2.5 air pollution surpassed 18.0 μg/m^3, above the earlier WHO guideline of 10 μg/m^3, which was lowered to 5 μg/m^3 in 2021 to reduce health hazards and save millions of lives, according to the GBD 2019.[38,93,94] Greater Beirut studies reveal PM_{10}, $PM_{2.5}$, and NO_2 exceed earlier WHO guidelines.[38-42] Unregulated private diesel-fueled generators and heavy traffic, especially in Greater Beirut, pollute Lebanon.[90,93] Small enterprises and uncontrolled power plants also contribute to pollution. The 2020 Beirut blast and diesel generators ongoing operation owing to power grid failures further worsened air quality, resulting in around 24.2 μg/m^3 $PM_{2.5}$ annual mean levels in Lebanon.[93] Despite Lebanon's 2018 WHO-based air quality law, the country has taken little action to mitigate the growing air pollution. In 2013, Lebanon's Ministry of Environment launched the national air quality monitoring network (AQMN), which expanded in 2017. AQMN reports over the past decade reveal that NO_2, PMs, and volatile organic compounds (VOCs) levels consistently exceed WHO annual limits.[92]

Occupational Exposure to Pollutants. Workplace exposure to carcinogenic chemicals, such as aromatic amines (e.g.,

2-naphthylamine, 4-aminobiphenyl, benzidine) and 4,4-methylenebis (2-chloroaniline), accounts for 20%-27% of UBC cases in industrialized countries.[7,8,17,95,96] These hazardous exposures are common in dye, paint, fungicide, rubber, plastics, metals (e.g., aluminum), and petroleum industries.[7,8,17,95,96]

Lebanon has thousands of small- to medium-sized industries, most of which operate without proper safety measures.[97] Many businesses produce agrifood products, construction materials, chemicals (pharmaceuticals, plastics, paints and derivatives, soaps, and detergents), printed materials, furniture, wood products, and natural stones.[98] Additionally, occupational exposure to diesel or fuel combustion emissions in Lebanon's cities is an independent UBC risk factor.[99] Recent large epidemiologic studies back up the IARC's finding that diesel exhaust exposure raises UBC risk.[80,100] Although regulatory measures exist, weak enforcement underscores the need for stronger public health interventions.[101]

Infection with Schistosoma Haematobium. Schistosoma haematobium causes most UBC squamous cell carcinoma (SCC). SCC dominated UBC in schistosomiasis-endemic countries like Egypt for years, but not anymore because of successful schistosomiasis control.[102] In Egypt, SCC cases dropped from 78% in 1980 to 27% in 2005, while transitional cell carcinoma (TCC) rose from 22% to 73%.[103] Public health measures and the Aswan High Dam's construction replaced *S. haematobium* with *S. mansoni*, reducing infection rates, except in Minya.[104,105]

Lebanon has eradicated schistosomiasis with no new cases reported in recent years.[106] In fact, the majority of UBC cases are non-SCC.[26,99]

Genetic Susceptibility. Inherited mutations such as BRCA and Lynch syndrome, along with acquired genetic variations discovered in genome-wide association studies (GWAS), influence UBC.[11,107] Family history of UBC increases risk, suggesting a genetic predisposition beyond environmental influences.[107] DNA mismatch repair genes (e.g., MSH2, MSH6, MLH1) in Lynch syndrome are the only established hereditary UBC risk factors. GWAS have identified many acquired genetic mutations (28 susceptibility loci) associated with UBC risk.[17-19,108] These include NAT2 and GSTM1 gene modifications that repair and detoxify DNA. These changes can increase cancer risk, especially along with tobacco smoking, environmental pollution, and certain occupational hazards.[17-19,108] The MENA region is understudied because most GWAS studies have focused on populations in Europe, the USA, and Asia.[17-19,108] Novel evidence suggests that bladder carcinogen THMs interact with specific genotypes (e.g., rs907611).[109]

In Lebanese patients, a case-control study found no associations between UBC and known genetic variants, like NAT1 rs4986782.[110] Previous studies found that Lebanese UBC patients had higher NAT1*14A concentrations than controls, which is in line with findings from Michigan Lebanese communities.[111,112] To identify preventive targets, these findings suggest integrating genetic data with tobacco smoking, environmental pollution, and occupational toxins.

Early Detection of UBC in High-Risk Populations

Most medical organizations do not recommend UBC screening for asymptomatic, average-risk adults.[18-21] The European Society for Medical Oncology and the United States National Cancer Institute advise prompt attention to bladder symptoms as the best early detection method.[18,19] While early detection is crucial, hematuria dipstick testing has low predictive value.[113] Some urinary biomarkers could be used for early UBC diagnosis,[114] but more research is necessary to evaluate their cost-effectiveness in screening asymptomatic high-risk groups.[11] The IARC's uTERTpm urine biomarker assay shows promise in early UBC detection, particularly for high-risk groups like smokers.[115] It detects TERT gene promoter mutations non-invasively by testing two separate urine samples.[115]

Raising Public Awareness

Public awareness is also crucial in reducing UBC incidence and mortality. Studies in Lebanon have shown significant gaps in public knowledge about the disease, its symptoms, and its link to tobacco use, underscoring the need for targeted awareness campaigns.[116]

Improving Access to Timely Diagnosis and Care

Timely access to imaging (e.g., CT urography), cystoscopy, and biopsy, is crucial for accurate diagnosis and treatment, especially in underprivileged patients. Up-to-date care and genetic profiling help tailor treatment options and identify potential therapeutic targets.

Improving Cancer Data and Monitoring

Lebanon, like many countries in the MENA region, lacks comprehensive cancer registries and electronic medical record systems that hinder effective cancer surveillance and control.[117] Population-based cancer registries are essential for tracking new cases, deaths, and survivals to evaluate cancer control strategies.[118] However, inconsistencies in cancer registration and coding practices complicate incidence and mortality comparisons. Accurate coding plays a crucial role in differentiating between invasive and non-invasive (in situ) UBC, which makes up 75% of cases and has a favorable prognosis but also carries a high risk of recurrence.[5,9,119] Outcomes research is also crucial to evaluate and improve intervention strategies.

Limitations of the Study

This study estimated the PAFs for UBC associated with smoking, water pollution with THMs, and air pollution with PM$_{2.5}$ as potential risk factors. However, limited data prevented sensitivity analyses for these calculations, potentially affecting the robustness of the estimates due to variations in the underlying assumptions and data inputs. Additionally, limited data excluded other UBC risk factors (e.g., second-hand smoke, water and vegetable contamination, other air pollutants, occupational exposure to other carcinogens, family history of UBC) and covariates (e.g., dietary habits, body mass index, socioeconomic status) from the analysis, which may have introduced bias. Cancer data from Lebanon's MoPH website, though improved between 2014 and 2016, remains incomplete, lacking information on precancerous and in situ conditions, as well as mortality and survival rates. Notably, the MoPH has not published any cancer-related data since 2016, posing a risk to the progress of the NCR.

Conclusion

Lebanon has one of the highest UBC rates globally, primarily driven by tobacco smoking and, to a lesser extent, by water and air contamination. Strengthening tobacco control, investing in cessation programs, and raising awareness are crucial. Improving water and air quality must also be a priority, with clear goals for long-term progress. These measures are essential for reducing UBC rates and protecting public health.

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References

1. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2022;400(10352):563-591. doi:10.1016/S0140-6736(22)01438-6

2. Mossanen M, Gore JL. The burden of bladder cancer care: direct and indirect costs. *Curr Opin Urol.* 2014;24(5):487-491. doi:10.1097/MOU.0000000000000078

3. Leal J, Luengo-Fernandez R, Sullivan R, Witjes JA. Economic burden of bladder cancer across the European union. *Eur Urol.* 2016;69(3):438-447. doi:10.1016/j.eururo.2015.10.024

4. Sloan FA, Yashkin AP, Akushevich I, Inman BA. The cost to medicare of bladder cancer care. *Eur Urol Oncol.* 2020;3(4):515-522. doi:10.1016/j.euo.2019.01.015

5. Sung H, Ferlay J, Siegel RL, et al. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-249. doi:10.3322/caac.21660

6. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893-2917. doi:10.1002/ijc.25516

7. International Agency for Research on Cancer. List of classifications by cancer sites with sufficient or limited evidence in humans. IARC monographs volumes 1–132. July 1, 2022. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

8. U.S. Department of Health and Human Services; National Cancer Institute. Bladder cancer causes and risk factors. Updated: February 16, 2023. https://www.cancer.gov/types/bladder/causes-risk-factors. Accessed 08 Aug 2024.

9. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. *Eur Urol.* 2017;71(1):96-108. doi:10.1016/j.eururo.2016.06.010

10. Cumberbatch MGK, Jubber I, Black PC, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. *Eur Urol.* 2018;74(6):784-795. doi:10.1016/j.eururo.2018.09.001

11. Lobo N, Afferi L, Moschini M, et al. Epidemiology, screening, and prevention of bladder cancer. *Eur Urol Oncol.* 2022;5(6):628-639. doi:10.1016/j.euo.2022.10.003

12. Silverman DT, Koutros S, Figueroa JD, Prokunina-Olsson L, Rothman N. Bladder cancer. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. *Cancer Epidemiology and Prevention.* 4th ed. Oxford: Oxford University Press; 2018:977-996.

13. Teoh JY, Huang J, Ko WY, et al. Global trends of bladder cancer incidence and mortality, and their associations with tobacco use and gross domestic product per capita. *Eur Urol.* 2020;78(6):893-906. doi:10.1016/j.eururo.2020.09.006

14. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA.* 2011;306(7):737-745. doi:10.1001/jama.2011.1142

15. van Osch FH, Jochems SH, van Schooten FJ, Bryan RT, Zeegers MP. Quantified relations between exposure to tobacco

smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol*. 2016;45(3):857-870. doi:10.1093/ije/dyw044

16. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *Eur Urol*. 2016;70(3):458-466. doi:10.1016/j.eururo.2015.06.042

17. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013;63(2):234-241. doi:10.1016/j.eururo.2012.07.033

18. Figueroa JD, Koutros S, Colt JS, et al. Modification of occupational exposures on bladder cancer risk by common genetic polymorphisms. *J Natl Cancer Inst*. 2015;107(11):djv223. doi:10.1093/jnci/djv223

19. Powles T, Bellmunt J, Comperat E, et al. Electronic address: clinicalguidelines@esmo.org. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(3):244-258. doi:10.1016/j.annonc.2021.11.012

20. U.S. Department of Health and Human Services; National Cancer Institute. Bladder cancer screening. Updated: April 27, 2023. https://www.cancer.gov/types/bladder/screening. Accessed 08 Aug 2024.

21. Final Update Summary. Bladder cancer in adults: screening. Rockville, MD: US preventive Services task force web site. 2011. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/bladder-cancer-in-adults-screening. Accessed 08 Aug 2024.

22. Zlotta AR, Roumeguere T, Kuk C, et al. Select screening in a specific high-risk population of patients suggests a stage migration toward detection of non-muscle-invasive bladder cancer. *Eur Urol*. 2011;59(6):1026-1031. doi:10.1016/j.eururo.2011.03.027

23. World Health Organization (WHO). Eastern Mediterranean regional office (EMRO). What is the regional burden? ©2023 WHO. https://www.emro.who.int/fr/right-teasers/cancer-info/what-is-the-regional-burden.html. Accessed 23 Feb 2023.

24. World Health Organization (WHO). Lebanon. https://data.who.int/countries/422. Accessed 08 Aug 2024.

25. United Nations Development Programme. Human development reports. Human development indices and indicators. 2018 Statistical Update. https://hdr.undp.org/en/content/human-development-indices-indicators-2018-statistical-update. Accessed 23 Feb 2021.

26. Adib S, Daniel J. *Cancer in Lebanon 2004 with an Update of Cancer 2003. Beirut, Lebanon: Ministry of Public Health*. National Cancer Registry; 2008. https://www.moph.gov.lb/DynamicPages/download_file/571. Accessed 23 Feb 2021.

27. National Cancer Registry. Lebanon. Ministry of public health, republic of Lebanon. 2020. https://www.moph.gov.lb/en/Pages/2/7164/national-cancer-registry#/en/Pages/2/193/esu. Accessed 23 Feb 2023.

28. Bray F, Ferlay J. Age standardization (chapter 7) In: Bray F, Colombet M, Mery L, et al., eds. *Cancer Incidence in Five Continents*. Lyon, France: International Agency for Research on Cancer (IARC), Vol. XI (electronic version); 2017. https://ci5.iarc.fr/CI5-XI/Pages/Chapter7.aspx. Accessed 23 Feb 2021.

29. United States Cancer Statistics (USCS). Centers for Disease Control and Prevention (CDC) Website. https://www.cdc.gov/cancer/npcr/uscs/technical_notes/stat_methods/rates.htm. Updated August 20, 2014. Accessed 23 Feb 2021.

30. *Joinpoint Help System 4.7.0.0 (Online)- Surveillance Research Program*. National Cancer Institute (NCI), Division of cancer control and population sciences, USA. https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab [accessed 23 Feb 2021].

31. Ervik M, Lam F, Laversanne M, Ferlay J, Bray F. *Global Cancer Observatory: Cancer over Time*. Lyon, France: International Agency for Research on Cancer; 2021. Available from: https://gco.iarc.fr/overtime. Accessed 23 Feb 2023.

32. Parkin DM, Boyd L, Walker LC. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer*. 2011;105(Suppl 2):S77-81. doi:10.1038/bjc.2011.489

33. Hanley JA. A heuristic approach to the formulas for population attributable fraction. *J Epidemiol Community Health*. 2001;55(7):508-514. doi:10.1136/jech.55.7.508

34. Sibai A, Hwala N. *WHO Steps Chronic Disease Risk Factor Surveillance: Data Book for Lebanon*. Ministry of Public Health; 2009. https://www.moph.gov.lb/DynamicPages/download_file/559. Accessed 12 Jan 2023.

35. World Health Organization. The Global Health Observatory. Estimate of current tobacco use prevalence (%). https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-tobacco-control-monitor-current-tobaccouse-tobaccosmoking-cigarrettesmoking-nonagestd-tobnonagestdcurr. Accessed 12 Jan 2023.

36. Semerjian L, Dennis J. Multipathway risk assessment of trihalomethane exposure in drinking water of Lebanon. *J Water Health*. 2007;5(4):511-522. doi:10.2166/wh.2007.046

37. Ministry of Environment/LEDO. Lebanon state of the environment report. Caper 8: water. Available from. https://www.unep.org/dewa/westasia/Assessments/national_SOEs/west_asia/Lebanon/Chap8Water.pdf. Accessed 27 09 2016.

38. Global Burden of Disease Collaborative Network. *Global Burden of Disease Study 2019 (GBD 2019) Air Pollution Exposure Estimates 1990-2019*. Seattle, USA: Institute for Health Metrics and Evaluation (IHME); 2021. doi:10.6069/70JS-NC54

39. Saliba NA, Kouyoumdjian H, Roumie M. Effect of local and long-range transport emissions on the elemental composition of PM10-2.5 and PM2.5 in Beirut. *Atmos Environ*. 2007;41(31):6497-6509. doi:10.1016/j.atmosenv.2007.04.032

40. Saliba NA, El Jam F, El Tayar G, Obeid W, Roumie M. Origin and variability of particulate matter (PM10 and PM2.5) mass concentrations over an eastern Mediterranean city. *Atmos Res*. 2010;97(1–2):106-114. doi:10.1016/j.atmosres.2010.03.011

41. Massoud R, Shihadeh AL, Roumie M, et al. Intraurban variability of PM10 and PM2.5 in an eastern mediterranean city. *Atmos Res*. 2011;101:893-901. doi:10.1016/j.atmosres.2011.05.019

42. Office of Communications, American University of Beirut News. Beirut shrouded in polluted air. https://www.aub.edu.lb/news/Pages/115861.aspx. Published online on 02 Aug 2011, Accessed 17 May 2021.

43. Villanueva CM, Fernández F, Malats N, Grimalt JO, Kogevinas M. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. *J Epidemiol Community Health*. 2003;57(3):166-173. doi:10.1136/jech.57.3.166

44. Li J, Deng Z, Soerensen SJC, et al. Ambient air pollution and urological cancer risk: a systematic review and meta-analysis of epidemiological evidence. *Nat Commun*. 2024;15(1):5116. doi:10.1038/s41467-024-48857-2

45. Safiri S, Kolahi AA, Naghavi M. Global Burden of Disease Bladder Cancer Collaborators. Global, regional and national burden of bladder cancer and its attributable risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease study 2019. *BMJ Glob Health*. 2021;6(11):e004128. doi:10.1136/bmjgh-2020-004128

46. Raad E, Helou S, Hage K, Daou M, El Helou E. Cost of bladder cancer in Lebanon before and after the economic collapse: a probabilistic modeling study. *Int J Equity Health*. 2023;22(1):77. doi:10.1186/s12939-023-01885-8

47. Mesmar A, Sabbagh R, Maskineh C, Hashem GE, Becker RV. PCN87 Real-world costs of bladder cancer treatment in Lebanon using a private payer dataset. *Value Health*. 2019;22:S72. doi:10.1016/j.jval.2019.04.211

48. The World Bank. Prevalence of current tobacco use (% of adults). Prevalence of current tobacco use, males (% of male adults). https://data.worldbank.org/indicator/SH.PRV.SMOK.MA. Accessed 09/Aug/2024. Prevalence of current tobacco use, females (% of female adults).https://data.worldbank.org/indicator/SH.PRV.SMOK.FE. Accessed 09 Aug 2024.

49. World Health Organization. The Global Health Observatory. Prevalence of smoking any tobacco product among persons aged >= 15 years. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-smoking-any-tobacco-product-among-persons-aged-=-15-years. Accessed 08 Aug 2024.

50. Mansour Z, Said R, Dbaibo H, et al. Non-communicable diseases in Lebanon: results from world health organization STEPS survey 2017. *Public Health*. 2020;187:120-126. doi:10.1016/j.puhe.2020.08.014

51. Baddoura R, Wehbeh-Chidiac C. Prevalence of tobacco use among the adult Lebanese population. *East Mediterr Health J*. 2001;7(4-5):819-828.

52. Cassell A, Yunusa B, Jalloh M, et al. Non-Muscle invasive bladder cancer: a review of the current trend in Africa. *World J Oncol*. 2019;10(3):123-131. doi:10.14740/wjon1210

53. World Health Organization. The global health observatory. Life expectancy at birth. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/life-expectancy-at-birth-(years). Accessed 08/Aug/2024.

54. DESA UN. World population prospects, the 2017 revision, volume I: comprehensive tables. New York United Nations department of economic & social affairs. 2017. https://population.un.org/wpp/Publications/Files/WPP2017_KeyFindings.pdf. Accessed 08 Aug 2024.

55. Mansour R, Al-Ani A, Al-Hussaini M, Abdel-Razeq H, Al-Ibraheem A, Mansour AH. Modifiable risk factors for cancer in the middle East and North Africa: a scoping review. *BMC Public Health*. 2024;24(1):223. doi:10.1186/s12889-024-17787-5

56. Yan H, Ying Y, Xie H, et al. Secondhand smoking increases bladder cancer risk in nonsmoking population: a meta-analysis. *Cancer Manag Res*. 2018;10:3781-3791. doi:10.2147/CMAR.S175062

57. Cumberbatch MG, Cox A, Teare D, Catto JW. Contemporary occupational carcinogen exposure and bladder cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2015;1(9):1282-1290. doi:10.1001/jamaoncol.2015.3209. Erratum in: JAMA Oncol. 2015 Dec;1(9):1224.

58. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018;68(1):31-54. doi:10.3322/caac.21440

59. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. *World J Urol*. 2020;38(8):1895-1904. doi:10.1007/s00345-019-02984-4

60. Nakkash R, Khader Y, Chalak A, et al. Prevalence of cigarette and waterpipe tobacco smoking among adults in three Eastern Mediterranean countries: a cross-sectional household survey. *BMJ Open*. 2022;12(3):e055201. doi:10.1136/bmjopen-2021-055201

61. Heydari G, Zaatari G, Al-Lawati JA, El-Awa F, Fouad H. MPOWER, needs and challenges: trends in the implementation of the WHO FCTC in the Eastern Mediterranean Region. *East Mediterr Health J*. 2018;24(1):63-71.

62. Frisbie SH, Mitchell EJ. Arsenic in drinking water: an analysis of global drinking water regulations and recommendations for updates to protect public health. *PLoS One*. 2022;17(4):e0263505. doi:10.1371/journal.pone.0263505

63. Boffetta P, Borron C. Low-level exposure to arsenic in drinking water and risk of lung and bladder cancer: a systematic review and dose-response meta-analysis. *Dose Response*. 2019;17(3):1559325819863634. doi:10.1177/1559325819863634

64. Saint-Jacques N, Parker L, Brown P, Dummer TJ. Arsenic in drinking water and urinary tract cancers: a systematic review of 30 years of epidemiological evidence. *Environ Health*. 2014;13:44. doi:10.1186/1476-069X-13-44

65. Mendez WMJ, Eftim S, Cohen J, et al. Relationships between arsenic concentrations in drinking water and lung and bladder cancer incidence in U.S. counties. *J Expo Sci Environ Epidemiol*. 2017;27(3):235-243. doi:10.1038/jes.2016.58

66. Baris D, Waddell R, Beane Freeman LE, et al. Elevated bladder cancer in northern new England: the role of drinking water and arsenic. *J Natl Cancer Inst*. 2016;108(9):djw099. doi:10.1093/jnci/djw099

67. Begum M, Horowitz J, Hossain MI. Low-dose risk assessment for arsenic: a meta-analysis approach. *Asia Pac J Public Health*. 2015;27(2):NP20-35. doi:10.1177/1010539512466568

68. Fernández MI, López JF, Vivaldi B, Coz F. Long-term impact of arsenic in drinking water on bladder cancer health care and mortality rates 20 years after end of exposure. *J Urol*. 2012; 187(3):856-861. doi:10.1016/j.juro.2011.10.157

69. Feki-Tounsi M, Hamza-Chaffai A. Cadmium as a possible cause of bladder cancer: a review of accumulated evidence. *Environ Sci Pollut Res Int*. 2014;21(18):10561-10573. doi:10. 1007/s11356-014-2970-0

70. International Agency for Research on Cancer (IARC), World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans. 2012; volume 101. Some chemicals present in industrial and consumer products, food and drinking-water. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono101.pdf. Accessed 01 Mar 2021.

71. Helte E, Säve-Söderbergh M, Ugge H, Fall K, Larsson SC, Åkesson A. Chlorination by-products in drinking water and risk of bladder cancer – a population-based cohort study. *Water Res*. 2022;214:118202. doi:10.1016/j.watres.2022.118202

72. Weisman RJ, Heinrich A, Letkiewicz F, et al. Estimating national exposures and potential bladder cancer cases associated with chlorination DBPs in U.S. Drinking water. *Environ Health Perspect*. 2022;130(8):87002. doi:10.1289/EHP9985

73. Evlampidou I, Font-Ribera L, Rojas-Rueda D, et al. Trihalomethanes in drinking water and bladder cancer burden in the European Union. *Environ Health Perspect*. 2020;128(1): 017001. doi:10.1289/EHP4495

74. Beane FLE, Cantor KP, Baris D, et al. Bladder cancer and water disinfection by-product exposures through multiple routes: a population-based case-control study (new England, USA). *Environ Health Perspect*. 2017;125(6):067010. doi:10.1289/EHP89

75. Costet N, Villanueva CM, Jaakkola JJ, et al. Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case-control studies. *Occup Environ Med*. 2011;68(5):379-385. doi:10. 1136/oem.2010.062703

76. World Health Organization, United Nations Children's Fund. *Lebanon Water Quality Survey 2016*. WHO/UNICEF. https://washdata.org/report/lebanon-water-quality-survey-2016. Accessed 14 Aug 2022.

77. Halwani DA, Jurdi M, Salem FKA, et al. Cadmium health risk assessment and anthropogenic sources of pollution in mount-Lebanon springs. *Exposure and Health*. 2020;12:163-178. doi: 10.1007/s12403-019-00301-3

78. Ministry of Environment/LEDO. Republic of Lebanon. Lebanon state of the environment and future outlook: turning the crises into opportunities. 2021. https://www.undp.org/lebanon/publications/lebanon-state-environment-and-future-outlook-turning-crises-opportunities. Accessed 14 Aug 2022.

79. Schraufnagel DE, Balmes JR, Cowl CT, et al. Air pollution and noncommunicable diseases: a review by the forum of international respiratory societies' environmental committee, Part 2: air pollution and organ systems. *Chest*. 2019;155(2): 417-426. doi:10.1016/j.chest.2018.10.041

80. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013;14(13): 1262-1263. doi:10.1016/s1470-2045(13)70487-x

81. Coleman NC, Burnett RT, Higbee JD, et al. Cancer mortality risk, fine particulate air pollution, and smoking in a large, representative cohort of US adults. *Cancer Causes Control*. 2020;31(8):767-776. doi:10.1007/s10552-020-01317-w

82. Turner MC, Andersen ZJ, Baccarelli A, et al. Outdoor air pollution and cancer: an overview of the current evidence and public health recommendations. *CA Cancer J Clin*. 2020;25: 10.3322/caac.21632. doi:10.3322/caac.21632

83. Turner MC, Krewski D, Diver WR, et al. Ambient air pollution and cancer mortality in the cancer prevention study II. *Environ Health Perspect*. 2017;125(8):087013. doi:10.1289/EHP1249

84. Chen J, Rodopoulou S, Strak M, et al. Long-term exposure to ambient air pollution and bladder cancer incidence in a pooled European cohort: the ELAPSE project. *Br J Cancer*. 2022; 126(10):1499-1507. doi:10.1038/s41416-022-01735-4

85. Zhang HW, Tsai ZR, Kok VC, et al. Long-term ambient hydrocarbon exposure and incidence of urinary bladder cancer. *Sci Rep*. 2022;12:20799. doi:10.1038/s41598-022-25425-6

86. Zare Sakhvidi MJ, Lequy E, Goldberg M, Jacquemin B. Air pollution exposure and bladder, kidney and urinary tract cancer risk: a systematic review. *Environ Pollut*. 2020;267:115328. doi:10.1016/j.envpol.2020.115328

87. World Health Organization. Regional office for the eastern Mediterranean. Addressing the impact of air pollution on health in the eastern Mediterranean region. 2014. https://www.emro.who.int/about-who/rc61/impact-air-pollution.html. Accessed 13 Sep 2021.

88. Daher N, Saliba NA, Shihadeh AL, et al. Oxidative potential and chemical speciation of size-resolved particulate matter (PM) at near-freeway and urban background sites in the greater Beirut area. *Sci Total Environ*. 2014;470-471:417-426. doi:10. 1016/j.scitotenv.2013.09.104

89. Farah W, Nakhlé MM, Abboud M, et al. Time series analysis of air pollutants in Beirut, Lebanon. *Environ Monit Assess*. 2014; 186(12):8203-8213. doi:10.1007/s10661-014-3998-9

90. Nakhle MM, Farah W, Ziade N, Abboud M, Coussa-Koniski ML, Annesi-Maesano I. Beirut air pollution and health effects-BAPHE study protocol and objectives. *Multidiscip Respir Med*. 2015;10(1):21. doi:10.1186/s40248-015-0016-1

91. Farah W, Nakhle MM, Abboud M, et al. Analysis of the continuous measurements of pm10 and pm2.5 concentrations in beirut, Lebanon. *Environ Eng Manag J*. 2018;17(7): 1693-1700. https://eemj.eu/index.php/EEMJ/article/view/3632

92. Cherry D. Greenpeace: Lebanon's death rate and economic cost due to air pollution among the highest in the MENA region. https://www.greenpeace.org/mena/en/appr/. Published online on 24/Jun/2020, Accessed 13 Sep 2021.

93. Faour A, Abboud M, Germanos G, Farah W. Assessment of the exposure to $PM_{2.5}$ in different Lebanese microenvironments at different temporal scales. *Environ Monit Assess*. 2022;195(1): 21. doi:10.1007/s10661-022-10607-6

94. WHO global air quality guidelines. *Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240034228. Accessed 19 Oct 2024.

95. Cumberbatch MG, Cox A, Teare D, Catto JW. Contemporary occupational carcinogen exposure and bladder cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2015;1(9):1282-1290. doi:10.1001/jamaoncol.2015.3209. Erratum in: JAMA Oncol. 2015 Dec;1(9):1224.

96. Hashim D, Boffetta P. Occupational and environmental exposures and cancers in developing countries. *Ann Glob Health*. 2014;80(5):393-411. doi:10.1016/j.aogh.2014.10.002

97. International Rescue Committee. Market overview of small and medium enterprises in beirut and mount Lebanon. A report by building markets for the international rescue committee (IRC). 2016. https://www.rescue.org/sites/default/files/document/656/ircandbuildingmarketssmemarketoverviewlebanonrelease.pdf. Accessed 14 Aug 2024.

98. IDAL Invest in Lebanon. Sectors in focus. https://investinlebanon.gov.lb/en/sectors_in_focus. Accessed 14 Aug 2024.

99. Kobeissi LH, Yassine IA, Jabbour ME, Moussa MA, Dhaini HR. Urinary bladder cancer risk factors: a Lebanese case-control study. *Asian Pac J Cancer Prev*. 2013;14(5):3205-3211. doi:10.7314/apjcp.2013.14.5.3205

100. Koutros S, Kogevinas M, Friesen MC, et al. Diesel exhaust and bladder cancer risk by pathologic stage and grade subtypes. *Environ Int*. 2020;135:105346. doi:10.1016/j.envint.2019.105346

101. UNDP. Lebanon. Support to the Lebanon environmental pollution abatement project (LEPAP) @2024. https://www.undp.org/lebanon/projects/support-lebanon-environmental-pollution-abatement-project-lepap. Accessed 14 Aug 2024.

102. Crow P, Ritchie AW. National and international variation in the registration of bladder cancer. *BJU Int*. 2003;92(6):563-566. doi:10.1046/j.1464-410X.2003.04421.x

103. Felix AS, Soliman AS, Khaled H, et al. The changing patterns of bladder cancer in Egypt over the past 26 years. *Cancer Causes Control*. 2008;19(4):421-429. doi:10.1007/s10552-007-9104-7

104. Kyritsi F, Loffredo CA, Zheng YL, Philips G, Amr S. Urinary bladder cancer in Egypt: are there gender differences in its histopathological presentation? *Adv Urol*. 2018;2018:3453808. doi:10.1155/2018/3453808

105. Ibrahim AH, Shash E. General Oncology care in Egypt. In: Al-Shamsi HO, Abu-Gheida IH, Iqbal F, Al-Awadhi A, eds. *Cancer in the Arab World*. Singapore: Springer; 2022. doi:10.1007/978-981-16-7945-2_4. https://link.springer.com/chapter/10.1007/978-981-16-7945-2_4#Sec7. Accessed 25 Apr 2023.

106. World Health Organization. The global health observatory. Schistosomiasis. Status of schistosomiasis endemic countries; 2022. https://www.who.int/data/gho/data/themes/topics/schistosomiasis. Accessed 14 Aug 2024.

107. Pemov A, Wegman-Ostrosky T, Kim J, et al. Identification of genetic risk factors for familial urinary bladder cancer: an exome sequencing study. *JCO Precis Oncol*. 2021;5:1830-1839. doi:10.1200/PO.21.00115

108. de Maturana EL, Rava M, Anumudu C, Sáez O, Alonso D, Malats N. Bladder cancer genetic susceptibility. A systematic review. *Bladder Cancer*. 2018;4(2):215-226. doi:10.3233/BLC-170159

109. Beane Freeman LE, Kogevinas M, Cantor KP, et al. Disinfection by-products in drinking water and bladder cancer: evaluation of risk modification by common genetic polymorphisms in two case-control studies. *Environ Health Perspect*. 2022;130(5):57006. doi:10.1289/EHP9895

110. Kourie HR, Succar B, Chouery E, et al. Genetic susceptibility of bladder cancer in the Lebanese population. *BMC Med Genomics*. 2022;15(1):217. doi:10.1186/s12920-022-01372-z

111. Yassine IA, Kobeissi L, Jabbour ME, Dhaini HR. N-acetyltransferase 1 (NAT1) genotype: a risk factor for urinary bladder cancer in a Lebanese population. *J Oncol*. 2012;2012:512976. doi:10.1155/2012/512976

112. Dhaini HR, Levy GN. Arylamine N-acetyltransferase 1 (NAT1) genotypes in a Lebanese population. *Pharmacogenetics*. 2000;10(1):79-83. doi:10.1097/00008571-200002000-00010

113. Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. *J Urol*. 1992;148(3):788-790. doi:10.1016/s0022-5347(17)36720-4

114. Woldu SL, Souter L, Boorjian SA, Barocas DA, Lotan Y. Urinary-based tumor markers enhance microhematuria risk stratification according to baseline bladder cancer prevalence. *Urol Oncol*. 2021;39(11):787.e1-787.e7. doi:10.1016/j.urolonc.2021.03.022

115. International Agency for Research on Cancer (IARC), World Health Organization. Promising urine test could improve early detection and clinical management of bladder cancer: IARC Evidence Summary Brief No. 3. press release no. 314. Lyon, France, 2022. https://www.iarc.who.int/featured-news/improving-early-detection-and-clinical-management-of-bladder-cancer/. Accessed 01 Mar 2023.

116. Souaid T, Hindy JR, Eid R, Kourie HR, Kattan J. Bladder cancer knowledge in the Lebanese population: when ignorance could be harmful. *Bull Cancer*. 2018;105(10):857-861. doi:10.1016/j.bulcan.2018.08.004

117. Abdul-Sater Z, Mukherji D, Adib SM, et al. Cancer registration in the Middle East, North Africa, and Turkiye (MENAT) region: a tale of conflict, challenges, and opportunities. *Front Oncol*. 2022;12:1050168. doi:10.3389/fonc.2022.1050168

118. Parkin DM. The role of cancer registries in cancer control. *Int J Clin Oncol*. 2008;13(2):102-111. doi:10.1007/s10147-008-0762-6

119. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol*. 2013;64(4):639-653. doi:10.1016/j.eururo.2013.06.003

Appendix

List of Abbreviations

Abbreviation	Description
APC	Average Annual Percent Change
AQMN	Air Quality Monitoring Network

ASIRw	Age-Standardized Incidence adjusted to the world population	PM	Particulate Matter
DBP	Disinfection Byproducts	PM_{10}	Particulate Matter 10 microns or less in diameter
DNA	Deoxyribonucleic Acid	$PM_{2.5}$	Particulate Matter 2.5 microns or less in diameter
HDI	Human Development Index		
IARC	International Agency for Research on Cancer	S. haematobium	Schistosoma haematobium
		THMs	Trihalomethanes
ICD10	International Classification of Diseases, 10th revision	UBC	Urinary Bladder Cancer
		USA	United States of America
JRP	Joinpoint Regression Program	USPSTF	United States Preventive Services Taskforce
MENA	Middle East and North Africa		
MoPH	Ministry of Public Health	VOCs	Volatile Organic Compounds
NCR	National Cancer Registry	WHO	World Health Organization
NO_2	Nitric Dioxide	WHO STEP	WHO STEPwise Approach For Non-Communicable Diseases Risk Factor Surveillance
PAHs	Polycyclic Aromatic Hydrocarbons		
PAF or PAR	Population Attributable Fraction or Ratio		