

Stability Over Time Of High Incidence Bladder Cancer In An Industrialized Area In North-Eastern Spain. A Longitudinal Study In A Region Of 400,000 Inhabitants.

José María Caballero (✉ jcaballero@mutuaterrassa.es)

Hospital Universitari MútuaTerrassa <https://orcid.org/0000-0001-6826-0966>

Meritxell Perez-Marquez

ConSORCI Sanitari de Terrassa

Jose M. Gili

Hospital Universitari MutuaTerrassa

Juan Camilo Pereira

Hospital Universitario MutuaTerrassa

Alba Gomáriz

Hospital Universitario MutuaTerrassa

Carlos Castillo

Hospital Universitari Mútua Terrassa

Montserrat Martin-Baranera

Autonomous University of Barcelona

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Abstract

Purpose: To study whether the incidence of bladder cancer in an industrialized area in North-Eastern Spain remains as high as in the nineties.

Methods: Patients diagnosed with histologically confirmed primary bladder cancer, during 2018-2019, in an area in North-Eastern Spain (430,883 inhabitants) were included. Crude incidence rates were estimated per 100,000 person-year based on the number of individuals getting their first diagnosis. Direct age-standardized incidence rates were calculated applying both the European and the World Standard Populations.

Results: 295 patients were included (mean age 72.5 ± 10.3 years; 89.8% men). The crude rate was 62.6 (95%CI:55.0-70.1) for men and 6.8 (95%CI:4.4-9.3) for women. The annual rate adjusted to the European Standard Population was 85.3 (95%CI:75.0-95.5) for men and 7.0 (95%CI:4.5-9.5) for women, and adjusted to the World Standard Population, 31.7 (95%CI:27.9-35.5) and 2.9 (95%CI:1.8-3.9) respectively.

Conclusion: The incidence of bladder cancer in this area in North-Eastern Spain is one of the highest in men and one of the lowest in women, both in Europe and Worldwide. The decrease in the industrial activity has not led to a decrease in bladder cancer incidence. The heterogeneity of bladder cancer registries in terms of definition and inclusion criteria makes it difficult to compare results.

Introduction

Bladder cancer (BC) is the most common of those affecting the urinary tract, and the tenth most common cancer in the World, accounting for 3% of all new annual cancer diagnoses. It is four times more frequent in men than in women. According to 2018 estimates, 549,393 new cases were diagnosed worldwide (424,082 men and 125,311 women) with a total mortality of 199,922 (148,270 men and 51,652 women) [1-4].

BC is typical of industrialized areas, being three times more frequent in wealthy areas than in emerging ones, although the highest mortality rates occur in developing countries [5,6]. The highest incidences of BC are observed in Southern Europe, Western Europe and North America [1-4]. In Spain, the 2018 incidence of BC per 100,000 person-year adjusted to the World Standard Population was 27.5 in men and 5.6 in women [5,7]. The estimated incidence may vary depending on the year, and whether the rate considered is raw or adjusted to either the World or the European Standard Populations. In Spain, the crude annual rate of new BC diagnoses is 41.8-65.0 per 100,000 men and 7.5-14.7 per 100,000 women; when adjusting by age, according to the European Standard Population, figures are 32.7-70.2 in men and 6.2-12.5 in women [7,8]. Certain areas of Spain, such as Murcia, the Balearic Islands or Tarragona [6], show even higher incidences, among the highest in Europe; in fact, in some industrialized areas, BC is the second most frequent cancer after lung cancer [8]. Previous studies in our area of the North-East of Spain demonstrated a high incidence of BC in men: data from 1992-1994 showed an annual crude rate for men and women of 44.1 and 6.2 cases per 100,000 person-year, respectively, and an annual incidence

adjusted for age to the European Standard Population of 52.2 and 5.4 cases, respectively, per 100,000 person-year [9,10]. Therefore, in men, the adjusted rate was very high, while it was intermediate in women when compared to other Spanish areas, and very low when compared to other European ones [10]. There is no recent study on the incidence of BC in this area, although indirect data suggest that it might be much higher [9,10]. The aim of this study is to estimate the current incidence of BC cases in an industrialized area of the North-East of Spain, and to describe the histological characteristics of the tumours.

Methods

West Vallès Occidental is a highly industrialized and urbanized healthcare area of the Catalonia (North-Eastern Spain) with 430,883 inhabitants (211,784 men and 219,099 women) [11], public healthcare services relying on two centres, the Hospital Universitari Mútua de Terrassa and the Consorci Sanitari de Terrassa.

From January 1st, 2018 to December 31st, 2019, all patients attended in these two hospitals, diagnosed with a primary urothelial BC, with histological confirmation, were included in the study. Exclusion criteria were applied for those cases with non-urothelial BC, with a recurrence of a previously diagnosed BC, and for those who were not residents of the study area. Demographic data (Age and gender) and histological data (TNM, 1973 WHO, and 2004-2016 WHO tumour classifications) were recorded. This study was approved by the Ethics and Research Committee of the Hospital Universitari Mútua de Terrassa and conformed to the principles of the declaration of Helsinki.

Statistical analysis was carried out using the SPSS package for Mac, version 21. Analysis of demographic data and histological variables according to gender and age was carried out with the Chi-square test for qualitative factors; Student's t tests, or Mann-Whitney test whenever required, were applied to compare quantitative variables between groups. The annual crude incidence was estimated based on the number of cases registered during the years 2018-2019 at both participating hospitals. For age and gender groups, specific incidence rates were calculated using the 2019 municipal data from IDESCAT as denominators [11]. The direct method was applied to adjust rates for age and gender, using as references the European Standard Population of 2013 [12] and the World Standard Population [13].

Results

A total number of 295 patients with primary BC were registered during years 2018 and 2019: 155 cases (52.5%) at the Hospital Universitari Mútua de Terrassa and 140 cases (47.4%) at the Consorci Sanitari de Terrassa. The annual global incidence per 100,000 person-year was 34.2 cases (95%CI: 30.3 - 38.1); 62.6 cases (95%CI: 55.0-70.1) in men and 6.8 cases (95%CI: 4.4-9.3) in women. The annual rate adjusted to the European Standard Population was 41.2 (95%CI: 36.5, 45.9), and to the World Standard Population, 15.9 (95%CI: 13.0-17.8). When analysed by gender, the annual incidence adjusted to the European Standard Population was 85.3 (95%CI: 75.0- 95.5) in men and 7.0 cases (95%CI: 4.5-9.5) in women, and

31.7 (95%CI: 27.9- 35.5) and 2.9 (95%CI: 1.8- 3.9) respectively when adjusted to the World Standard Population.

The number of BC cases in 2018 and their crude and adjusted rates in our area under study compared to several European countries are presented in table 1 [5,7]. The crude annual incidence in our area was very high in men (62.6), this indicator being similar to the one in Spain (65.0), but becoming higher when adjusted to the European Standard Population (85.3 vs 70.2) or to the World Standard Population (31.7 vs 27.5) [5,7].

The incidence rate in men adjusted to the World Standard Population in our area under study was much higher than in other areas of the World (Fig. 1), and ranked third, after Greece and Lebanon when compared to the countries with the highest BC incidence rates in men (Fig. 2) [4]. On the other hand, in women, in 2018, the incidence rate adjusted to the World Standard Population was the lowest when compared to the countries with the highest incidences in men (Fig. 2) [4]. In our area of the North-East of Spain, the incidence of BC in men, adjusted to the European Standard Population, ranks second after Greece among the European countries, with a much lower incidence in women (table 1) [5,7].

Table 1. Number of cases and estimated incidence of bladder cancer, crude and age-adjusted to the European Standard Population and to the World Standard Population, in European countries in 2018, compared to study area.

	MEN				WOMEN			
COUNTRIES	N	CR	Ale	Alm	N	CR	Ale	Alm
Germany	27,812	68.6	66.6	26.4	7,926	19.0	15.1	6.3
Austria	984	22.9	25.1	9.9	370	8.3	7.3	3.0
Belgium	3,503	61.7	70.2	27.7	955	16.4	15.1	6.4
Bulgaria	1,448	42.3	44.5	20.8	438	12.1	10.3	4.9
Cyprus	121	20.3	30.2	12.4	43	7.2	9.0	3.9
Croatia	994	49.5	55.5	23.4	346	16.0	13.7	6.1
Denmark	1,954	68.3	74.4	29.3	570	19.7	18.6	7.7
Slovakia	842	31.8	45.7	18.5	324	11.6	12.0	5.2
Slovenia	388	37.5	42.1	16.9	137	13.1	11.3	5.0
Spain	14,793	65.0	70.2	27.5	3,475	14.7	12.5	5.6
Estonia	201	32.8	42.4	16.7	78	11.2	9.1	3.9
Finland	947	34.6	36.9	14.0	245	8.7	7.3	2.8
France	13,408	41.8	45.6	17.2	2,874	8.7	7.3	2.7
Greece	5,106	93.1	95.1	40.4	694	12.3	10.4	4.5
Hungary	2,334	50.6	60.9	26.9	1,057	20.8	18.7	9.1
Ireland	680	28.5	41.8	15.8	260	10.7	13.5	5.5
Iceland	69	40.7	53.6	22.1	17	10.1	11.9	5.3
Italy	20,695	71.6	66.2	27.4	5,213	17.2	13.3	6.0
Latvia	361	40.7	51.3	21.1	167	16.0	13.1	5.9
Lithuania	425	32.1	41.3	16.3	157	10.1	8.2	3.4
Luxembourg	89	30.0	44.6	15.3	21	7.2	8.3	2.7
Malta	106	48.8	54.3	21.6	27	12.6	11.6	4.6
Norway	1,182	43.7	55.1	20.9	371	14.0	14.8	5.9
Netherlands	5,087	59.8	66.1	25.8	1,628	19.0	18.0	7.9
Poland	8,197	44.5	56.8	23.7	2,686	13.6	12.9	5.8
Portugal	1,765	36.2	36.0	14.6	575	10.6	8.3	3.1
United Kingdom	8,826	26.9	30.6	10.8	3,392	10.1	9.6	3.6

Czech Republic	2,169	41.5	49.5	19.8	774	14.3	13.1	5.2
Rumania	3,051	32.2	38.5	16.9	873	8.6	8.0	3.3
Sweden	2,177	43.6	46.8	17.8	682	13.7	12.7	5.1
STUDY AREA	133	62.6	85.3	31.7	15	6.8	7.0	2.9
EU28	128,463	51.4	55.4	22.0	35,987	13.8	12.1	5.1
EU28+EFTA	131,751	51.3	55.4	22.0	36,951	13.8	12.1	5.1

N: number of cases. CR: Crude incidence rate. Alm: Incidence adjusted to the Word Standard Population. Ale: Incidence adjusted to the European Standard Population 2013 (EU 28+EFTA). All incidence estimations are expressed per 100,000 person-year.

Sources: ECIS and REDECAN [5,7].

Regarding demographic data, the mean age was 72.5 years (SD =10.4; range 30-91 years), and 89.8% were male, with no statistically significant differences in the mean age between genders. According to the age distribution, 77.3% of the patients were over 65 years (78.1% of men and 70.0% of women). BC was rare at younger ages, since only 6 patients (2.0%) were under 50 years. The highest crude annual incidence rate was observed in the 80-84 years' age group for the entire sample; in the 74-79 age group for men, and in the 84 to 89 age group for women.

The histological characteristics and the classification of bladder tumours are described in table 2. Most corresponded to grade 1 or grade 2 (35.6% and 31.5%, respectively). These percentages were similar either when considering gender or age (over/under 65 years) groups. About the TNM classification, most tumours were Ta (60.7%), N0 (97.6%), M0 (94.2%), and those proportions were also maintained when splitting by gender or by age groups.

Table 2. Distribution of the cases according to the histological type, for the entire sample and by gender and age groups.

TUMOR HISTOPATHOLOGY	TOTAL N =295	MEN N=265	WOMEN N=30	£ 65 years N=67	>65 years N=228
Tumour grade					
X	0	0	0	0	0
1	105 (35.6%)	96 (36.2%)	9 (30.0%)	24 (35.8%)	81 (35.5%)
2	93 (31.5%)	81 (30.6%)	12 (40.0%)	24 (35.8%)	69 (30.3%)
3	85 (28.8%)	77 (29.1%)	8 (26.7%)	18 (26.9%)	67 (29.4%)
CIS	34 (11.5%)	33 (12.5%)	1 (3.3%)	8 (11.9%)	26 (11.4%)
T classification					
Tx	0	0	0	0	0
Ta	179 (60.7%)	160 (60.4%)	19 (63.3%)	44 (65.7%)	135 (59.2%)
Tis	13 (4.4%)	12 (4.5%)	1 (3.3%)	1 (1.5%)	12 (5.3%)
T1	66 (22.4%)	61 (23.0%)	5 (16.7%)	13 (19.4%)	53 (23.2%)
T2a	15 (5.1%)	11 (4.1%)	4 (13.3%)	4 (6.0%)	11 (4.8%)
T2b	18 (6.1%)	17 (6.4%)	1 (3.3%)	4 (6.0%)	14 (6.1%)
T3a	1 (0.3%)	1 (0.4%)	0	0	1(0.4%)
T3b	0	0	0	0	0
T4a	2 (0.7%)	2 (0.8%)	0	1 (1.5%)	1 (0.4%)
T4b	1 (0.3%)	1 (0.4%)	0	0	1 (0.4%)
N classification					
Nx	0	0	0	0	0
N0	288 (97.6%)	258 (97.4%)	30	65 (97.0%)	223 (97.8%)

N1	1 (0.3%)	1 (0.4%)	0	0	1 (0.4%)
N2	5 (1.7%)	5 (1.9%)	0	2 (3.0%)	3 (1.3%)
N3	1 (0.3%)	1 (0.4%)	0	0	1 (0.4%)
M classification					
Mx	0	0	0	0	0
M0	278 (94.2%)	251 (94.7%)	27 (90.0%)	61 (91.0%)	217 (95.2%)
M1	2 (0.7%)	2 (0.8%)	0	1 (1.5%)	1 (0.4%)
ISUO/WHO (2004)					
Papillary urothelial neoplasm of low malignant potential	0	0	0	0	0
Low grade Ca	151 (51.2%)	136 (51.3%)	15 (50.0%)	36 (53.7%)	115 (50.4%)
High grade Ca	131 (44.4%)	117 (44.1%)	14 (46.7%)	30 (44.8%)	101 (44.3%)
CIS	34 (11.5%)	33 (12.5%)	1 (3.3%)	8 (11.9%)	26 (11.4%)

Discussion

The incidence of BC in our area of the North-East of Spain was very high in men, as reported in previous studies [9,10]. When considering the crude annual rate, such figure was similar to the one in Spain for the same period, but became higher when adjusting to the European or the World Standard Populations) [4,5,7]. When comparing with all European countries, in 2018 the incidence of BC in men, adjusted to the European Standard Population, ranked second after Greece [5,7], and third after Greece and Lebanon when adjusted to the World population [4]. Alternatively, the incidence in women was much lower, ranking the lowest of all European countries whether considering the crude or the adjusted rate (European Standard Population), and one of the lowest when considering the incidence adjusted to the World Standard Population [4,5,7].

According to the previously published incidence of BC in our area under study during the period 1992-1994 both the crude and the age-adjusted annual incidence have risen in both sexes, although the increase in men is notably higher [9,10]. In our area of North-Eastern Spain, the high incidence of BC in men could be related to a high prevalence in this area of well-known risk factors for BC, such as smoking, residence in industrialized areas and occupational exposures to certain carcinogenic products [10,14]. In 2015, 27.7% of the population of our area under study declared to be a smoker, a percentage above the average for Catalonia, which was 25.7% [15]. Although in our area data on the proportion of smokers by

gender were not available in 2018, in Catalonia such prevalence was higher in men (30.9%) than in women (20.5%), a percentage that increased up to 40.3% in the group of men from 35 to 44 years [16].

In relation to the occupational exposure, historically the high incidence of BC in this area was related to the existence of an important textile industry since the mid-19th century. The decline of textile industry began in the 1970s, becoming marginal at the end of the eighties. The 1992-1994 studies, where a high incidence was observed, only found some moderate occupational risk in relation to previous and prolonged exposures in the textile industry [10,14], as a significant percentage of the population had previously worked in this sector without the current security conditions. Our study shows that, more than three decades after the receding of the textile industry, the incidence of BC in men has not decreased, in fact it is higher than before. Currently most workers in the studied area belong to the service sector (58.6%), followed by the industrial sector (32.4%), construction (8.7%) and agriculture (0.2%) [17]. It is probable that factors, such as the textile industry, which favoured the high incidence of BC in the past, have been replaced by others related to pollution or dietary habits.

The mean age of BC diagnosis was similar to the one reported in other series [8,9,18], without differences between both genders. As in the previous study [9], the incidence of this cancer in our healthcare area is ten times higher in men than in women, while in the World Population it is only four times higher. The discrepancy in incidence between genders in different countries has been attributed to differences in the prevalence of tobacco use. Thus, countries like Lebanon, where smoking is culturally prevalent among women, have the highest incidence of BC [1-3]. Other factors that may reduce women's predisposition to BC would be those related to hormonal and genetic factors and lower occupational exposure to carcinogenic products in agriculture, textile, chemical or construction industries [19-21]. Finally, certain dietary habits such as the consumption of coffee and alcohol, low consumption of fruits and vegetables, and diets rich in red meat and animal proteins, are factors possibly implicated in the higher incidence in men than in women [21-24].

The histological characteristics of the tumours are similar to other series [8,18], with predominance of grade 1 and 2 low-grade tumours (51.2%), and those limited to the Ta (60.7%) and T1 mucosa (22.4%), muscle invasive tumours being rare (12.2%) and metastatic spread exceptional (2.3%). Unlike the previous study in our area, we have not found that grade 3 tumours were more frequent in those over 65 years, nor that Ta tumours were significantly more frequent in patients under 65 years of age [9,10]. Neither did we observe a relationship between the degree of infiltration and gender, so that the percentage of invasive tumours was not significantly higher in women in the present study [9,18].

The possibility that residents in our healthcare area were diagnosed and treated for BC in centres other than the referral hospitals might have led to a certain underestimation of the incidence of BC. However, according to the 2017 health survey of the National Institute of Statistics (INE), in Spain, 83.4% of the population uses the public health system exclusively, 15.4% attends both public and private centres, and only 0.9% is an exclusive user of the private health system [25]. Another limitation, shared with other epidemiological studies on BC, is related to the difficulty of comparing different series. First, the national

and international BC registries are not homogeneous because there are differences in definition and inclusion criteria [26-27]. Despite the use of systematic classifications of tumours such as the TNM classification, some specific characteristics of bladder cancer lead to great heterogeneity when labelling the tumour. Some registries include non-invasive tumours (Tis and Ta) while others only include invasive ones (T1 or higher). Furthermore, the nomenclature is prone to confusion, since the term "invasive" does not have a clear definition; it may be applied either to describe tumours that invade the *lamina propria* (T1) or to refer, depending on clinicians, to those that invade the bladder muscle layer (T2 or higher). In parallel, given that Ta tumours may account for up to 50% of BC, their inclusion or exclusion has an important effect when assessing incidence, survival or mortality [27]. In addition, bladder carcinoma in situ has clinical, diagnostic, and therapeutic implications that do not correspond to the ones of carcinoma in situ of other organs; in many cancer registries, often with no participation of urologists, those cancers are not included. Secondly, it is difficult to make comparisons between adjusted rates, and it has already been suggested that incidences adjusted to the European Standard Population of 2013 are not comparable with those adjusted to the previous European population of 1976 that many registries have used. Finally, another epidemiologically relevant factor is the high rate of relapses of superficial BC delayed in time, which can be mistakenly considered as new onset cases.

Conclusions

The incidence of BC in an industrialized area of North-Eastern Spain is one of the highest in men and one of the lowest in women, both in Europe and in the World. The decline in the industrial activity has not led to a decrease in BC annual rates; therefore, a case-control study would be valuable to identify the risk factors specifically related to the high incidence in this area. The histological characteristics of BC are like those of other regions, except for a greater prevalence of low-grade Ta carcinoma, regardless of gender and age. Lastly, the epidemiological analysis of BC would benefit from more standardized and homogeneous registries to strengthen comparisons and draw clinical conclusions.

Declarations

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Conflicts of interest

The authors declared no conflicts of interest.

Availability of data and material

Data is not publicly available. Data can be requested through e-mail to corresponding author.

Authors' contribution

JMC and MMB contributed to the study conception and design. JMC and MPM contributed to data collection. JMC and MMB were responsible for data analysis and data interpretation. JMC and MMB were responsible for manuscript writing. All authors were responsible for the approval of the manuscript.

Ethical approval

This study was approved by the Ethics and Research Committee of the Hospital Universitari Mútua de Terrassa. All procedures performed in the study involving human participants were in accordance with the ethical standards of the Trust and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all participants.

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Figures

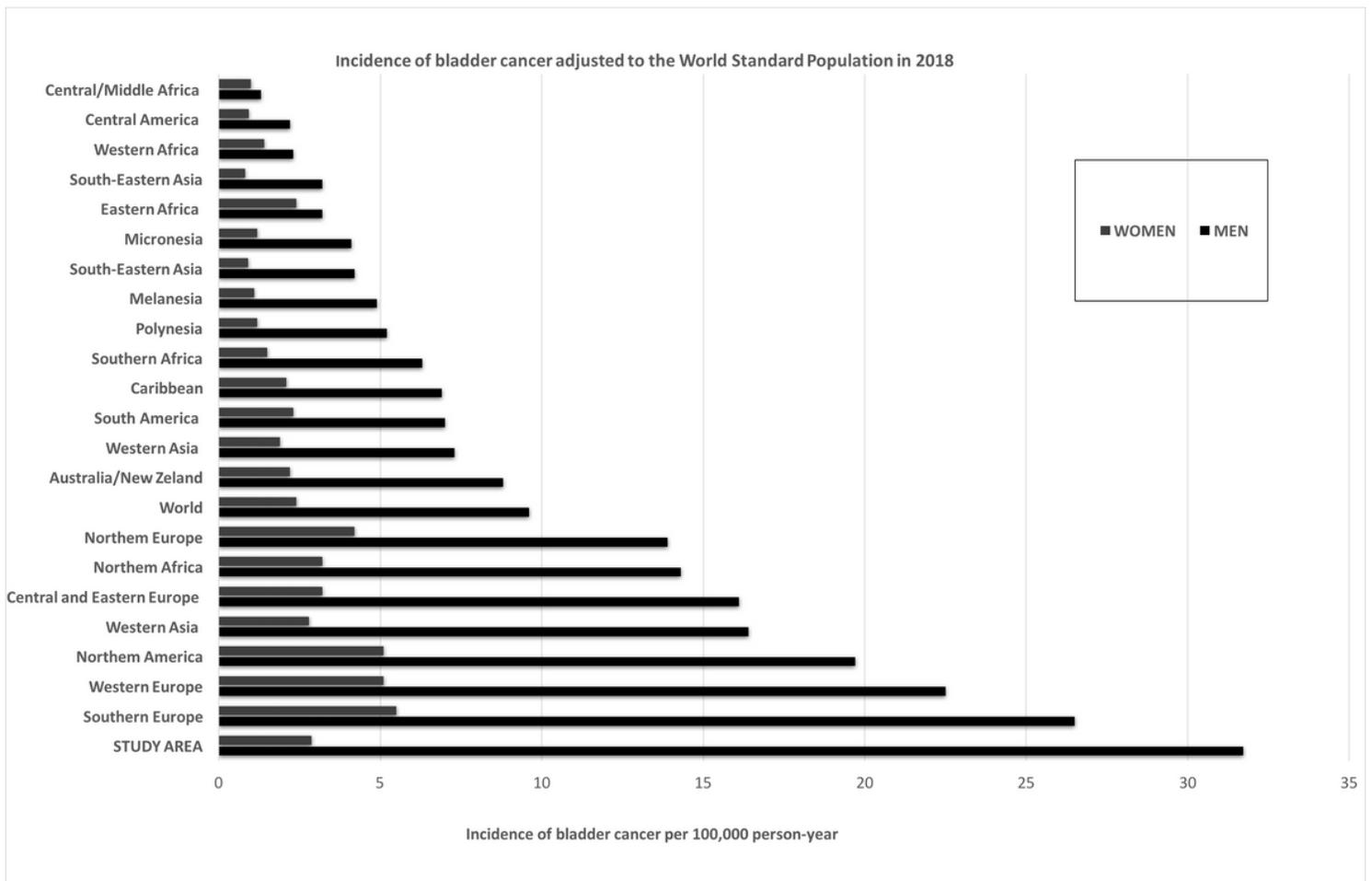


Figure 1

Incidence of bladder cancer adjusted to the World Standard Population in 2018, worldwide and in the study area. Source: GLOBOCAN 2018 [4].

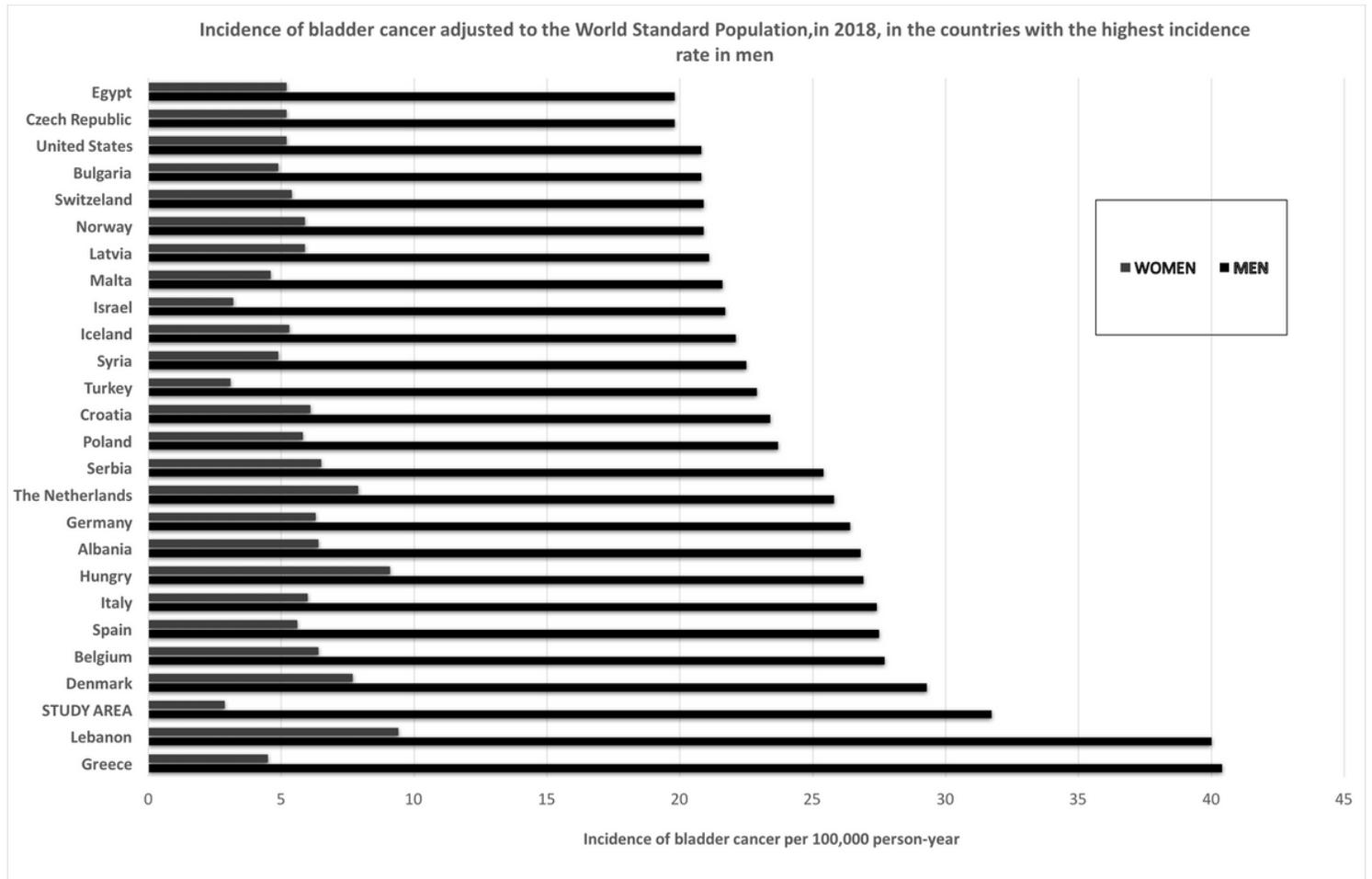


Figure 2

Incidence of bladder cancer in 2018, adjusted to the World Standard Population, in the countries with the highest incidence rate in men, compared to that of the study area. Source: GLOBOCAN 2018 [4].