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BLADDER CANCER IN EUROPE

Jerzy E. Tyczynski and D. Maxwell Parkin

Introduction

Bladder cancer is the 7th most common cancer worldwide, accounting for 3.2% of all cancers. There were an estimated 260,000 new cases in the 2000 in men and 76,000 in women (Ferlay et al., 2001).

The highest incidence rates of bladder cancer in both sexes are observed in Europe, North America and Australia. (Parkin et al., 2003).

In Europe, each year approximately 36,500 deaths due to bladder cancer occur in males and nearly 13,000 in females (Ferlay et al., 2001). It is 7th most common cancer in males in Europe and 14th in women.

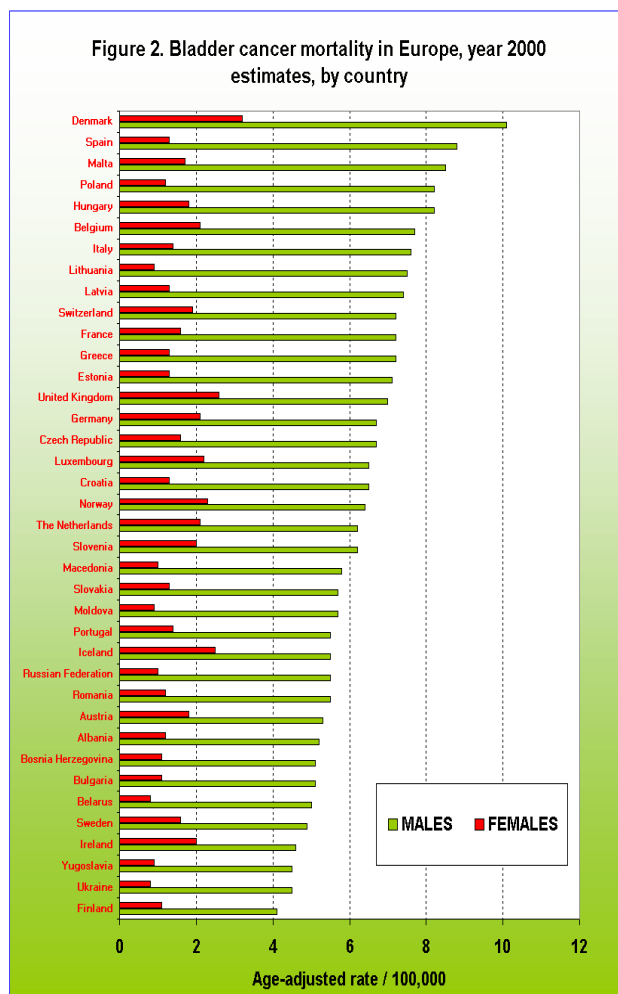
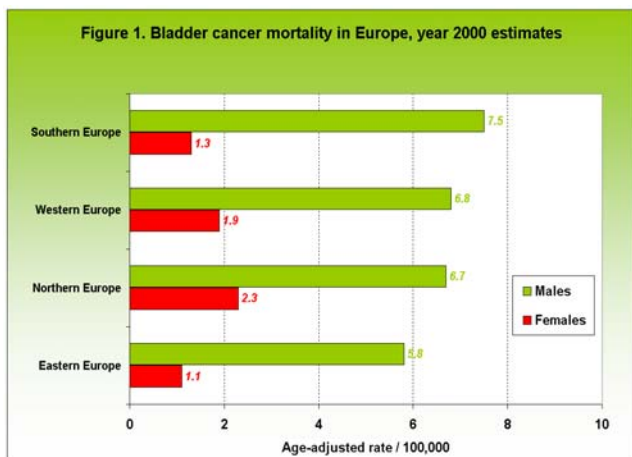
Tobacco smoking, some occupational exposures, infection by *Schistosoma haematobium*, diet, and volume of liquid intake are the major modifiers of bladder cancer risk.

Regional Differences in Bladder Cancer

There are some differences in the occurrence of bladder cancer across Europe. Figure 1 shows rates of mortality in four different areas of Europe. The highest mortality rates are observed in Southern and Western Europe in men and in Northern and Western Europe in women (Figure 1).

The estimates for individual countries for the year 2000 show the highest mortality rates in males in Denmark

(10.1/10⁵), Spain (8.8/10⁵), Malta (8.5/10⁵), Hungary (8.2/10⁵), and Poland (8.2/10⁵). The lowest rates in males were observed in Finland (4.1/10⁵), Yugoslavia (4.5/10⁵), Ukraine (4.5/10⁵), Ireland (4.6/10⁵), and Sweden (4.9/10⁵). In females, the highest rates of mortality are noted in Denmark (3.2/10⁵), UK (2.6/10⁵), Iceland (2.5/10⁵), Norway (2.3/10⁵), and Luxembourg (2.2/10⁵). The lowest rates in females are observed in Ukraine (0.8/10⁵), Belarus (0.8/10⁵), Yugoslavia (0.9/10⁵), Lithuania (0.9/10⁵), and Moldova (0.9/10⁵) (Table 1, Figure 2-4).



Temporal Changes in Mortality from Bladder Cancer

Trends in rates of mortality are rather different in males and in females. In men, after an increase of mortality in the majority of European countries in the 1960s and 1970, there has been a decline in many countries in the 1980s and 1990s (e.g. Denmark, Italy, Finland, UK) (Figure 5). In some countries (Spain, Norway) no decline in mortality has been observed so far.

In women, the rates of mortality in the majority of European countries are low and relatively stable (Figure 5).

Biology of Bladder Cancer

The most common type of bladder cancer in developed countries is transitional cell carcinoma, derived from the uroepithelium, which constitutes more than 90% of bladder cancer cases in Europe (and in North America

Figure 3. Mortality from bladder cancer: ASR (World). Male (All ages). Europe 2000

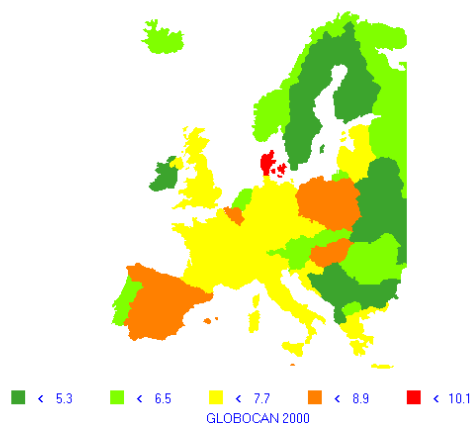
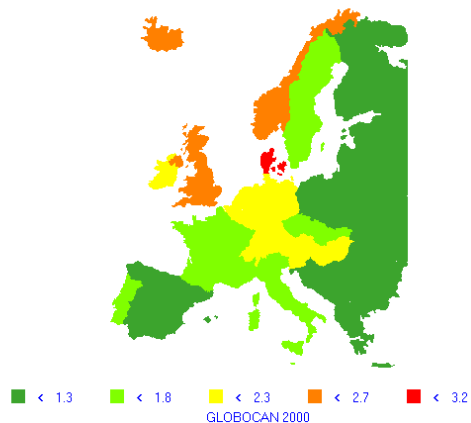


Figure 4. Mortality from bladder cancer: ASR (World). Female (All ages). Europe 2000



and Australia) (Figure 6 & 7). In other regions (South America, Africa, Asia) the relative frequency of transitional cell carcinoma of the bladder is lower. In general, among all registries included into the 8th volume of CI5, transitional cell carcinoma constitutes 84% of bladder cancer in males and 79% in females.

Other types of bladder cancer, i.e. squamous cell carcinoma and adenocarcinoma have much lower relative frequency. In all European registries present in 'Cancer Incidence in Five Continents' squamous cell carcinoma comprises 1.4% and 3.6% of all bladder cancers in men and women respectively. Adenocarcinoma of the bladder constitutes respectively 1.6% and 2.3% of all bladder tumours in Europe (Parkin et al., 2003). It is estimated that approximately 70-80% of patients with newly diagnosed bladder cancer present with superficial bladder tumours (i.e. stage Ta, Tis, or T1).

Aetiology of Bladder Cancer

There are several known and potential risk factors for bladder cancer, and cigarette smoking and occupational exposure to aromatic amines are the most important (Matanoski and Elliott, 1981; Silverman et al., 1996).

Tobacco smoking

Tobacco smoking is the major established risk factor of bladder cancer. It is estimated that the risk of bladder cancer attributed to tobacco smoking is 66% for men and 30% for women worldwide (with regard to ever smokers), and 32% and 18% for men and women respectively in current smokers (Brennan et al., 2000; Brennan et al., 2001; IARC, 2003).

The risk of bladder cancer in smokers is 2-6 fold that of non-smokers (Brennan et al., 2000; Negri and La Vecchia, 2001; Castela et al., 2001). The risk increases with increasing duration of smoking, and for those with the longest history of smoking (60 years or more) reaches approximately 6 in men and 5 in women (Brennan et al., 2000). The excess risk is observed also with increasing intensity of smoking (number of cigarettes per day), reaching maximum of about 3 for those smoking 40 or more cigarettes per day (Brennan et al., 2000). The increase of risk with increasing duration and intensity of smoking is similar in both sexes (IARC, 2003), however some studies indicate higher risk in women than in men at the equivalent level of exposure (Castela et al., 2001).

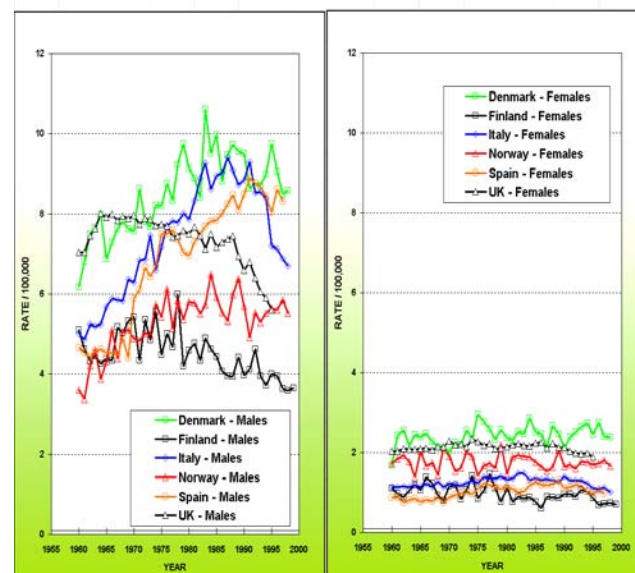
The risk of bladder cancer goes down after stopping smoking, and after 15 years after cessation tends to be approximately that of non-smokers (IARC, 2003). The decrease of risk after cessation is similar in both sexes (Castela et al., 2001).

Occupational exposure

Several occupations, such workers employed in aromatic amine manufacture, dyestuff manufacture and use, rubber manufacture, painting, aluminium industry, and leather industry, have been associated with an increased risk of bladder cancer (Negri and La Vecchia, 2001).

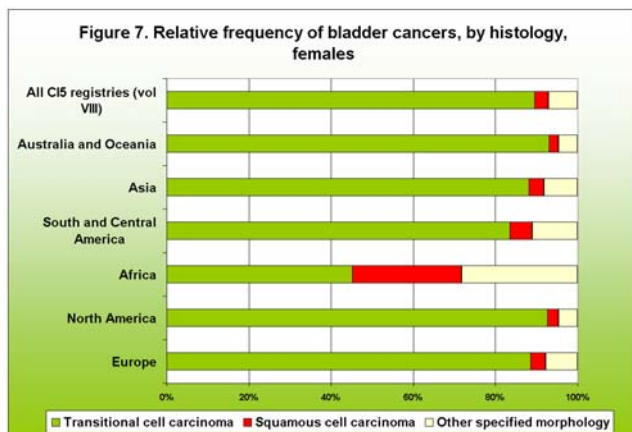
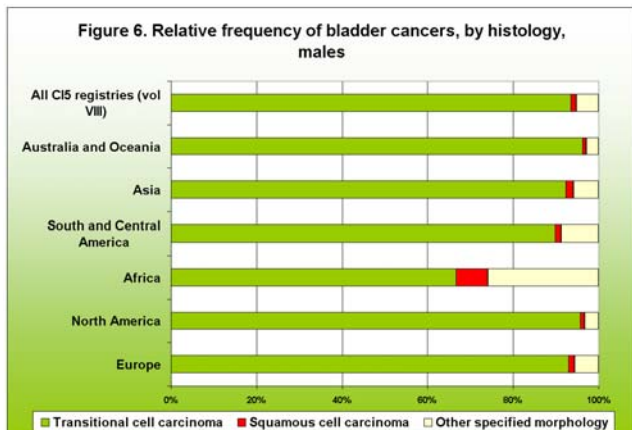
The most important occupational risk factor is exposure to aromatic amines, and particularly 2-naphtylamine and benzidine (IARC, 1987). It has been estimated that contact with occupational carcinogens causes about 25% of all bladder tumours.

Figure 5. Bladder cancer mortality time trends in selected European countries, 1960-1999



Type and source of fluids

It has been suggested that high intake of fluids dilutes metabolites in the urine and increases the frequency of urination (which reduce contact of carcinogens with the bladder epithelium), and thus, decreases risk of bladder cancer (Michaud et al., 1999).



Some studies showed that use of drinking water containing chlorination by-products or contaminated by arsenic may increase risk of bladder cancer (Cantor et al., 1998; Smith et al., 1998; Hopenhaym-Rich et al., 1996).

There was a hypothesis that caffeine and its metabolites may play some role in bladder carcinogenesis. Although there is no clear evidence of carcinogenic effect of coffee or caffeine in experimental animals (IARC, 1991), several epidemiological studies in humans showed moderately elevated risk in coffee drinkers as compared with non-drinkers (Tavani & La Vecchia, 2000). The magnitude of this excess, estimated by Hartge et al. is approximately 40% (1983). Several studies showed an increased risk of bladder cancer caused by coffee drinking in never smokers (compared with ever smokers) (Clavel & Cordier, 1991; Escolar Pujolar et al., 1993; Vena et al., 1993; Momas et al., 1994; Woolcott et al., 2002).

Diet

Many dietary compounds play a role in the aetiology of bladder cancer. The best recognised is the role of fruit and vegetable consumption in diminishing cancer risk. Steinmaus and colleagues, based on meta-analysis of 38 studies, estimated that high fruit consumption may lower risk by approximately 30% and high intake of vegetables by about 20% (Steinmaus et al., 2000). The same study showed no significant association with meat consumption, or retinol and beta-carotene intake. There is no convincing evidence that artificial sweeteners (such as saccharin) play

a significant role in the aetiology of bladder cancer (IARC, 1999).

Other factors

- ✓ *Schistosoma haematobium*. There is an increased incidence of bladder cancer (especially squamous cell carcinoma) in areas with a high prevalence of infection with *Schistosoma haematobium*, and an association at individual level between bladder cancer and urinary schistosomiasis (IARC, 1994).
- ✓ Some authors suggest an association between bladder cancer and urinary tract infections and urinary tract stones. The underlying mechanism may be chronic irritation of the bladder epithelium, which may increase bladder cancer risk.
- ✓ High consumption of phenacetin - containing analgesics may be associated with an increased risk of bladder cancer.
- ✓ Offspring of bladder cancer patients have 70-80% higher risk of having bladder cancer than the general population (Hemminki and Li, 2003).

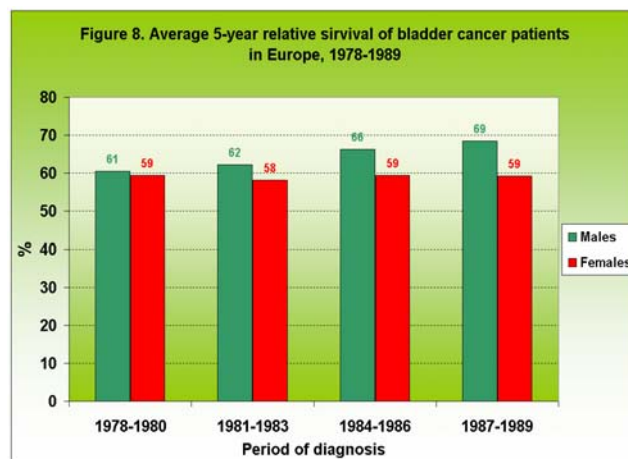
Bladder Cancer Prevention

The main way to prevent bladder cancer is smoking cessation. Other possibilities for bladder cancer prevention lie in reduction of the occupational exposure (mainly to aromatic amines) by appropriate regulations and education activities, reduction of infection by *Schistosoma haematobium* (in endemic areas), and promotion of consumption of fruits and vegetables.

It was recently suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may play some protective role in chemoprevention of bladder cancers (Castelao et al., 2000). No association between bladder cancer and intake of beta-carotene was found in male smokers in the ATBC cohort study (Virtamo et al., 2000; Michaud et al., 2002). Some studies suggest a protective role of long-duration vitamin E supplementation (Michaud et al., 2000; Jacobs et al., 2002).

Survival of Bladder Cancer Patients

The average 5-year survival of patients diagnosed with bladder cancer in Europe throughout the period 1978-1989 increased in males from 61% to 69%, while in women survival remained stable at a value of 59% (Berrino et al., 1999) (Figure 8).



There are substantial differences in survival among European countries. The EURO CARE II study has showed that the highest 5-year survivals among patients diagnosed in 1987-1989 were in Sweden (72%), Germany (72%) and Spain (69%). The lowest survival was observed in Poland

(37%), Slovenia (40%), and Denmark (49%) (Berrino et al., 1999) (Figure 9).

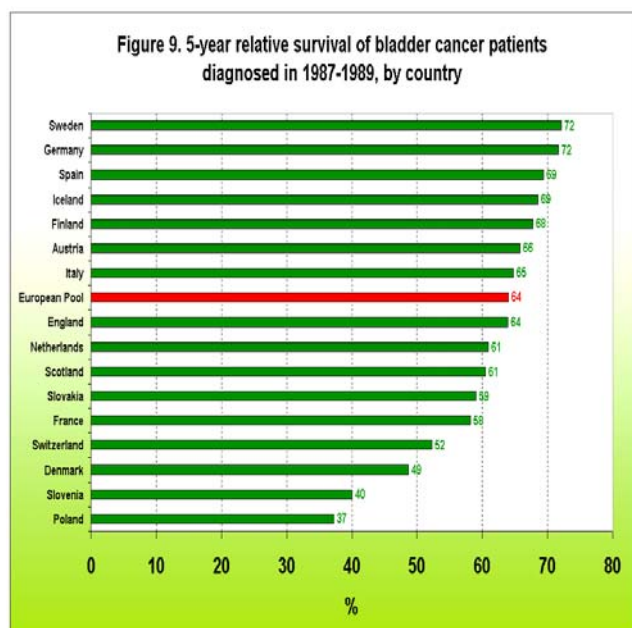


Table 1. Estimates of bladder cancer mortality in Europe in 2000

Country (region)	Males		Females	
	Deaths	ASR (World)	Deaths	ASR (World)
Eastern Europe	10,843	5.8	3,333	1.1
Belarus	310	5.0	88	0.8
Bulgaria	347	5.1	93	1.1
Czech Republic	493	6.7	171	1.6
Hungary	610	8.2	208	1.8
Moldova	126	5.7	30	0.9
Poland	1,932	8.2	441	1.2
Romania	883	5.5	257	1.2
Russian Federation	4,473	5.5	1,513	1.0
Slovakia	182	5.7	64	1.3
Ukraine	1,486	4.5	465	0.8
Northern Europe	5,459	6.7	2,545	2.3
Denmark	456	10.1	190	3.2
Estonia	64	7.1	23	1.3
Finland	166	4.1	70	1.1
Iceland	11	5.5	5	2.5
Ireland	116	4.6	62	2.0
Latvia	108	7.4	38	1.3
Lithuania	171	7.5	41	0.9
Norway	249	6.4	121	2.3
Sweden	432	4.9	194	1.6
United Kingdom	3,670	7.0	1,795	2.6
Southern Europe	9,653	7.5	2,379	1.3
Albania	65	5.2	18	1.2
Bosnia Herzegovina	117	5.1	32	1.1
Croatia	226	6.5	67	1.3
Greece	796	7.2	179	1.3
Italy	4,272	7.6	1,078	1.4
Macedonia	73	5.8	15	1.0
Malta	23	8.5	6	1.7
Portugal	455	5.5	166	1.4
Slovenia	88	6.2	47	2.0
Spain	3,175	8.8	672	1.3
Yugoslavia	355	4.5	95	0.9
Western Europe	10,591	6.8	4,414	1.9
Austria	336	5.3	174	1.8
Belgium	694	7.7	278	2.1
France	3,568	7.2	1,173	1.6
Germany	4,772	6.7	2,277	2.1
Luxembourg	22	6.5	10	2.2
The Netherlands	761	6.2	342	2.1
Switzerland	435	7.2	158	1.9

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