Nagoya J. Med. Sci. **43.** 41 ~ 64, 1980

EPIDEMIOLOGY OF URINARY BLADDER CANCER: INTERNATIONAL VARIATION IN MORTALITY

YOSHIYUKI OHNO M.D., M.P.H. and KUNIO AOKI M.D.

Department of Preventive Medicine Nagoya University, School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466, Japan

ABSTRACT

To evaluate the epidemiological features and etiological backgrounds of bladder cancer, we examined the mortality statistics (1968/69–1974/75) for 26 populations in the world. Major findings are virtually unchanged age-adjusted mortality rates in the majority of countries, moderate male predominance over years and over countries, relatively younger deaths in Balkan States and Asian countries than in most European and Oceanian countries, very similar increase gradient of age specific death rates irrespective of the mortality levels, and almost identical risks for bladder cancer deaths in the birth cohorts born after around 1900. The countries with high mortality in both sexes are characterized by more aged population, manufacturing, recently moderate industrialization, high energy consumption, and less frequent deaths from infective and parasitic deseases; in contrast, the countries with low mortality in both sexes by less aged population, agriculture, recently remarkable industrialization, low energy consumption, and more frequent deaths from infective and parasitic diseases.

Possible determinants for the international variation in the mortality and universal male predominance in bladder cancer are discussed. Suggested by the present analysis are the etiological roles of both environmental factors and host predisposition, and the equilibrium of the host-environmental interactions in bladder cancer deaths.

INTRODUCTION

Bladder cancer is a world-wide disease, but is a relatively infrequent type of cancer in most countries; accounting for 1.6–4.5% of all cancer deaths in males and for 1.1–2.0% in females (1).

Risk factors incriminated for human bladder cancer are occupational exposures, use of tobacco, infection with Schistosoma haematobium, and possibly such variables as coffee drinking, use of artificial sweeteners, analgesics abuse and urine statis (2). Ingestion of bracken fern is considered potentially hazardous (3). Some of the endogenously produced metabolites of tryptophan-nicotinic acid pathway are also presumed to be resposible for some of human bladder cancers with no apparent industrial exposure to chemical carcinogens (4). Recent investigation on dietary factors (5) indicates the association of bladder cancer with lower level of vitamin A intake and with infrequent consumption of carrot, milk and cruciferous vegetables.

The range of worldwide variation in the cumulative incidence rate of bladder cancer is only four-fold and the smallest among 14 very common cancers; in contrast, the range being 300 times, 100 times, 70 times and 50 times in esophageal, lung, liver and stomach cancer, respectively (6). The range of variation in bladder cancer mortality among 21 countries is

大野良之・青木国雄
Received for Publication October 13, 1980

also 3.3 times in males and 2.5 times in females in 1966–1967 (1). This small variation in the morbidity and mortality is presumed to suggest the relative importance of host factors in bladder cancer carcinogenesis (7).

International mortality trends in bladder cancer have been shown by Segi and Kurihara (1) for the period of 1950–1967, and by Staszewski (8) for the period of 1968–1974.

This paper is prepared to illustrate the sociodemographic characteristics which are involved in internatinonal variation in bladder cancer mortality in 1970–1974, and to evaluate the etiological backgrounds in bladder cancer on an international basis.

MATERIALS AND METHODS

A cancer mortality data bank was established as a part of the WHO Dissemination of Statistical Information Services, and annual statistics on cancer mortality and population at risk, by age and sex, have been available on computer tapes for many countries since 1950.

The mortality statistics analysed here are those from the WHO data bank. Statistics provided are crude and age-adjusted mortality rates for 1960–1975, mostly for 1968–1974, with absolute numbers of the death and age specific death rates. ICD codes for bladder cancer are 181.0 and 188 in the 7th and 8th Revision, respectively. Age adjustment of the mortality is made by the direct method, using Segi-Doll's world population (9) as a standard.

Mortality statistics are provided for 34 countries in the world. Ten countries, however, are not included in the present analysis because of either incomplete serial mortality data or too small annual numbers of the death for 1968–1974. Such countries are the U.S.A., Urguay, Venezuela, Mexico, Israel, Czechoslovakia, Iceland, Poland, Thailand and Mauritius.

According to the mortality rates in 1970–1974, 23 countries and 3 districts of the United Kingdom are categorized into three mortality levels; high (6.0 and over per 100,000 for males and 1.6 and over for females), intermediate (4.00–5.99 for males and 1.00–1.58 for females) and low (less than 4.0 for males and less than 1.0 for females). The countries with high (intermediate or low) mortality level for both sexes will be denoted as concordantly high (intermediate or low) countries throughout the text, and the countries whose sex-specific mortality is not in the same category as discordant countries.

RESULTS

1. *International Variation of Age-adjusted Mortality Rate*

Figure 1 shows the variation in age-adjusted mortality rates from bladder cancer among 26 populations in 1970–1974. In males, Scotland demonstrated the highest mortality of 8.08 per 100,000 population, followed by Denmark, England and Wales, Belgium, Austria, Germany (FRG) and Netherlands. The difference between the highest and the lowest mortality rate was 3.5 times in males. In females, three highest mortality rates were observed in Scotland, Denmark, and England and Wales, likewise in males. Norway ranked fourth in females, but 16th in males. Hong Kong ranked next to Norway in females, but 21st in males. The difference between the highest and the lowest mortality rate was 3.1 times in females.

Concordantly high countries, where the mortality was 6.0 and over per 100,000 for males

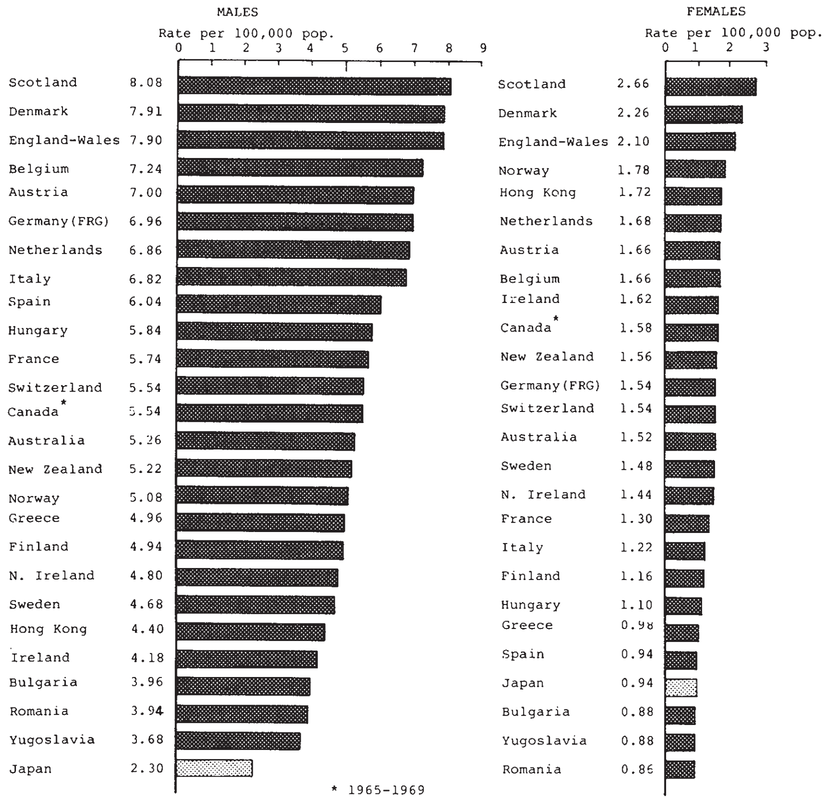

Fig. 1. Age-Adjusted Mortality Rates from Bladder Cancer in 1970–1974

and 1.6 and over for females, were Scotland, Denmark, England and Wales, Belgium, Austria and Netherlands. These countries seem to aggregate in North-Western part of Europe, and four of them are geographically adjacent to North Sea.

Concordantly low countries, where the mortality was less than 4.0 per 100,000 for males and less than 1.0 for females, were Japan and such Balkan States as Bulgaria, Romania and Yugoslavia.

Concordantly intermediate countries were Hungary, France, Switzerland, Canada, Australia, New Zealand, Finland, Northern Ireland and Sweden; discordant countries being Germany (FRG), Italy, Spain, Norway, Hong Kong, Ireland and Greece.

Sex ratio of age-adjusted mortality rate in 1970–1974 ranged from 3.0 to 4.4 in concordantly high countries and from 2.5 to 4.6 in concordantly low countries; being quite similar. The corresponding figure was 3.2–5.3 in concordantly intermediate countries, and 2.6–6.4 in discordant countries.

This international comparison clearly indicates the epidemiological characteristics of bladder cancer deaths: the intercountry difference in mortality, though not so large, and moderate male predominance over countries with quite similar range of sex ratio between concordantly high and low countries.

Table 1 Mean Age at Death from Bladder Cancer by Sex in 1970–1974.

Mean age at death for females in parenthesis

Males \ Females	High AAMR* ≥ 1.6	Intermediate 1.6 > AAMR ≥ 1.0	Low AAMR < 1.0
High AAMR* ≥ 6.0	Scotland 69.9 (70.6) Denmark 70.5 (70.8) Eng.Wales 70.3 (72.5) Belgium 70.7 (73.0) Austria 71.6 (72.7) Netherlands 71.5 (73.7)	Germany (FRG) 71.0 (72.4) Italy 69.0 (71.9)	Spain 70.0 (71.9)
Intermediate 6.0 > AAMR ≥ 4.0	Norway 71.5 (73.7) Hong Kong 63.8 (68.3) Ireland 71.3 (72.6)	Hungary 70.3 (71.9) France 70.6 (73.7) Switzerland 70.3 (72.4) Canada + 71.9 (72.7) Australia 70.6 (72.3) New Zealand 71.0 (74.2) Finland 70.2 (72.2) N. Ireland 72.0 (73.0) Sweden 71.6 (73.6)	Greece 70.2 (71.4)
Low AAMR < 4.0			Bulgaria 67.3 (69.2) Romania 67.1 (67.5) Yugoslavia 68.6 (69.2) Japan 69.6 (70.3)

*: Age-adjusted Mortality Rate, +: 1965–1969

2. *Mean Age at Death and Proportion of Deaths Aged Less than 60 Years in All Bladder Cancer Deaths*

Table 1 summarizes the mean age at death from bladder cancer in 1970–1974. The mean age at death ranged from 69.6 to 71.6 years in males and from 70.6 to 73.7 years in females in concordantly high countries, whereas from 67.1 to 69.6 years in males and from 67.5 to 70.3 years in females in concordantly low countries; indicating no overlap of the mean age at death between two groups of countries. In concordantly intermediate countries, it ranged from 70.2 to 72.0 years in males and from 71.9 to 74.2 years in females; the range being almost identical with that in concordantly high countries for both sexes. The mean age at death in discordant countries was not substantially different from that in concordantly high or intermediate countries, except Hong Kong, where it was fairly close to the mean age at death in concordantly low countries.

Female predominance in the mean age at death was universal. Females predominated males in the mean age at death by 0.3–2.3 years, 0.4–1.9 years, 0.8–3.2 years, and 1.2–4.5 years in concordantly high, low and intermediate, and discordant countries, respectively.

The deaths at less than 60 years of age accounted for 7.7–14.7% in males and for 8.6–15.4% in females in concordantly high countries, whereas for 15.1–20.7% in males and for 13.7–21.0% in females in concordantly low countries. Corresponding proportions ranged from 10.8 to 13.8% in males and from 5.9 to 13.6% in females in concordantly intermediate countries, and from 9.6 to 23.8% in males and from 7.9 to 21.2% in females in discordant countries. Proportions in Hong Kong (28.3% in males and 21.2% in females) were rather similar to those in concordantly low countries.

These findings indicate that bladder cancer deaths in Balkan and Asian countries are

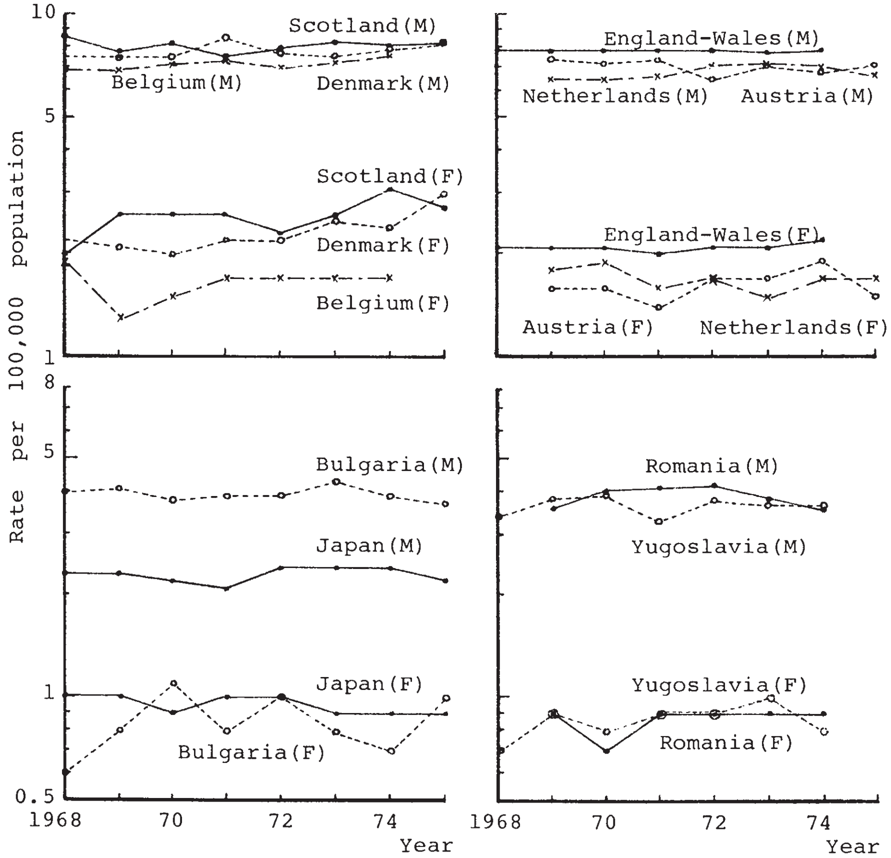

Fig. 2. Trends in Age-adjusted Mortality Rates from Baldder Cancer (Rates per 100,000 population)

relatively younger than those in most European and Oceanian countries.

3. *Trends in Age-adjusted Mortality and Sex Ratio*

For the period of 1960–1967, age-adjusted mortality rates from bladder cancer were available only for seven among 26 populations. In males, for the period of 1960–1967, age-adjusted mortality rate increased slightly in Japan, France, Italy and Sweden, but unaltered in Canada, Finland and Scotland. In females, for the corresponding period, the mortality was virtually unchanged in all seven populations.

Figure 2 illustrates the mortality trends for 1968/69–1974/75 in concordantly high and low countries. The mortality trends for males were fairly stable in concordantly low countries as well as in concordantly high countries; those for females also stable with minor random fluctuations. The mortality seemed to increase from 1970 onwards in females in Denmark.

Table 2 summarizes the mortality trends for 26 populations. An arrow of upright direction denotes a significantly increasing trend, in which the lower 95% confidence limit of the slope of regression line is positive. An arrow of transverse direction indicates a vir-

Table 2 Summary of Mortality Trends for Bladder Cancer by Sex, for the Available Period Between 1968 and 1975.

Trends for females in parenthesis

Males \ Females	High AAMR* $\geq$ 1.6	Intermediate $1.6 > \text{AAMR} \geq 1.0$	Low AAMR < 1.0
High AAMR* $\geq$ 6.0	Scotland → (→) Denmark → (↑) Eng. Wales → (→) Belgium → (→) Austria → (→) Netherlands → (→)	Germany (FRG) → (→) Italy → (→)	Spain ↑ (↑)
Intermediate $6.0 > \text{AAMR} \geq 4.0$	Norway → (→) Hong Kong ↑ (→) Ireland → (→)	Hungary ↑ (→) France → (→) Switzerland → (→) Canada → (→) Australia → (→) New Zealand → (→) Finland → (→) N. Ireland → (→) Sweden → (→)	Greece → (→)
Low AAMR < 4.0			Bulgaria → (→) Romania → (→) Yugoslavia → (→) Japan → (→)

*: Age-adjusted Mortality Rate

tually unchanged mortality trend, in which the slope has the negative lower and positive upper 95% confidence limits. Among 52 mortality trends, only five mortality trends were significantly upward; those for males in Hungary, Hong Kong and Spain, and those for females in Denmark and Spain, though the mortality for females in Spain was unchanged for 1972–1974.

Of particular interest in this summary table is that a virtually unchanged mortality trend is observed in the majority of countries, irrespective of mortality levels, and even in concordantly low countries.

Table 3 details the trends in sex ratio of age-adjusted moatality rate for five consecutive periods of three years en bloc. Male predominance in bladder cancer deaths was universal over years and over countries. The ranges of sex ratio were almost identical for the first three consecutive periods: 2.1–4.8, 2.3–4.7 and 2.3–4.9, respectively. For the subsequent two periods, they were 2.3–6.4 and 2.4–6.4, respectively; being also identical, but slightly wider than those for the first three periods. The smallest sex ratio was observed in Japan for the first four periods and in Ireland for the last period. The largest sex ratio was found in Finland in 1960–62, Italy in 1963–65, and 1966–68, and Spain in 1969–71 and 1972–74. For the last four periods, the largest sex ratio was observed in two of discordant countries; Italy and Spain.

The sex ratio of age-adjusted mortality rate from bladder cancer appeared unaltered over years in most countries irrespective of mortality levels, but apparently increased in two of discordant countries; Italy and Greece.

4. *Mortality by Age and Sex*

Age specific death rate increased noticeably with advancing ages in both sexes, particu-

Table 3 Trend in Sex Ratio (M/F) of Age-adjusted Mortality Rate from Bladder Cancer by Mortality Level and Country

Mortality Level and Country	1960–62	1963–65	1966–68	1969–71	1972–74
Concordantly High					
Scotland	3.2	2.9	3.4	3.0	3.0
Denmark	-	-	-	3.7	3.3
England and Wales	-	-	-	3.8	3.7
Belgium	-	-	-	4.8	4.3
Austria	-	-	-	4.8	3,9
Netherlands	-	-	-	3.7	4.3
Concordantly Low					
Bulgaria	-	-	-	4.5	5.0
Romania	-	-	-	4.8	4.3
Yugoslavia	-	-	-	4.3	4.2
Japan	2.1	2.3	2.3	2.3	2.6
Concordantly Intermediate					
Hungary	-	-	-	5.4[a]	5.3
France	3.7	3.9	4.2	4.2	4.6
Switzerland	-	-	-	3.8	3.6[b]
Canada	3.1	2.8	3.2	3.5	3.6[b]
Australia	-	-	-	3.3	3.4
New Zealand	-	-	3.9	3.2	3.5
Finland	4.8	4.0	4.4	4.9	4.6
N. Ireland	2.2	-	-	3.3	3.2
Sweden	2.5	3.3	2.9[c]	3.2	3.3
Discordant Countries					
Germany (FRG)	-	-	-	4.6[a]	4.5
Italy	4.5	4.7	4.9	5.6	5.7
Spain	-	-	-	6.4	6.4
Norway	-	-	-	2.8	2.8
Hong Kong	-	-	-	2.2	3.0
Ireland	-	-	-	2.7	2.4
Greece	-	-	4.0	4.5	5.3

a: excluding 1969, b: excluding 1974, c: excluding 1967

larly after the age group of 40–44 years.

Figures 3 and 4 graphically present the age curve of age specific death rate by sex in concordantly high and low countries, respectively.

In concordantly high countries (Fig. 3), the range of age specific death rates became gradually narrower after the age group of 50–54 years in males and after that of 65–69 years in females. The range was wider in males and narrower in females in concordantly low countries (Fig. 4), compared to that in concordantly high countries.

As the increase gradients of age specific death rates were rather similar each other in both concordantly high and low countries, they were evaluated as the slope of regression line on the semi-logarithmic graph papers, excluding the countries with annual number of deaths less than one hundred.

The slope calculated ranged from 1.84 to 2.08 for males and from 1.52 to 1.78 for females in concordantly high countries; from 1.55 to 1.83 for males and from 1.57 to 1.74 for females in concordantly low countries. The corresponding ranges were 1.76–2.08 for males and 1.64–1.83 for females in concordantly intermediate countries; 1.63–2.15 for males and 1.63–1.89 for females in discordant countries. In males, the increase gradients of age specific death rates seemed slightly more moderate in concordantly low

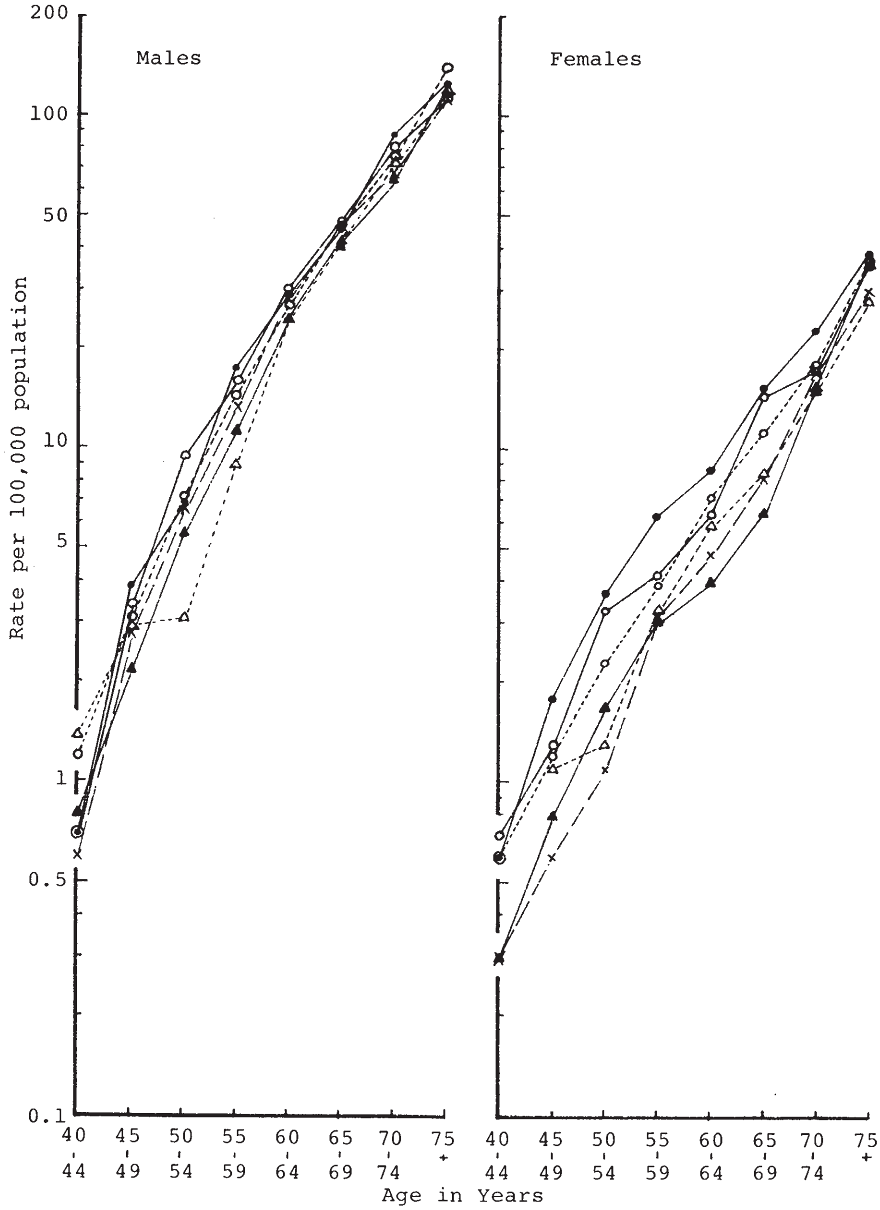

Fig. 3. Distribution of Age Specific Death Rates from Bladder Cancer in 1970–1974
Scotland ●——●, Denmark ○——○, England-Wales ○---------○,
Belgium x— — —x, Austria Δ---------Δ, Netherlands ▲——▲

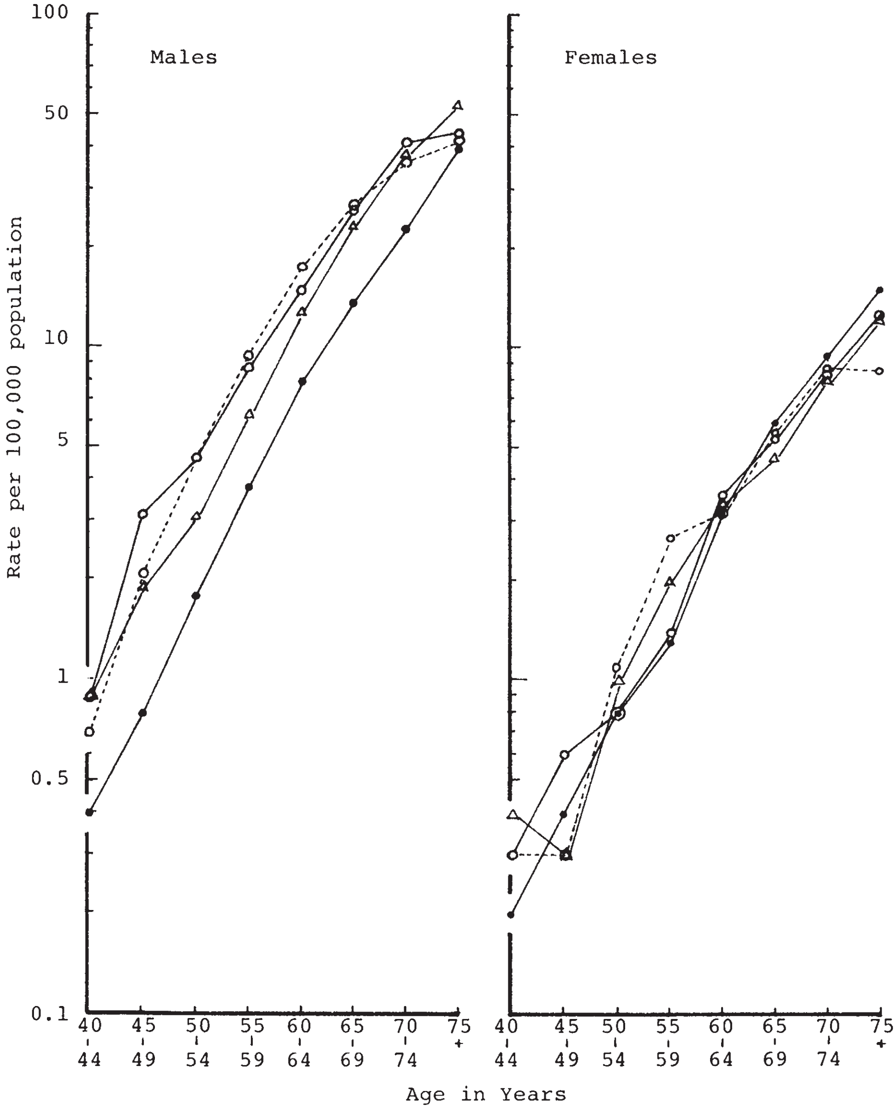

Fig. 4. Distribution of Age Specific Death Rates from Bladder Cancer in 1970–1974
Japan ●——●, Bulgaria ○——○, Romania ○---------○, Yugoslavia Δ——Δ

countries than in concordantly high or the other countries, but were presumed not to be different substantially, because the increase gradient was rather small only for Bulgaria (1.55), but almost identical for Japan (1.83), Romania (1.83) and Yugoslavia (1.74).

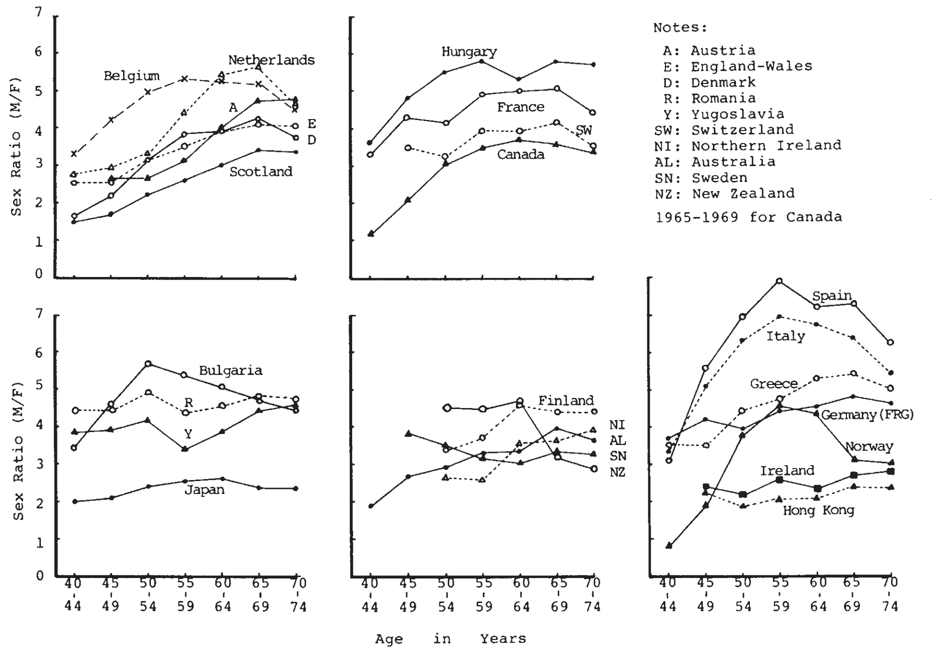

Fig. 5. Sex Ratio of Age Specific Death Rates from Bladder Cancer in 1970–1974

In general, therefore, the increase gradients of age specific death rates for bladder cancer are considered to be similar each other, irrespctive of mortality levels; being around 1.8 for males and around 1.6 for females.

Figure 5 illustrates the sex ratio (male to female) of age specific death rates from bladder cancer in 1970–1974 after three point moving average. Apparently increasing sex ratio with advancing ages with or without a drop in the age group of 70–74 years, i.e. an increasing pattern, was observed in 14 populations; Netherlands, Austria, England and Wales, Denmark, Scotland, Hungary, France, Switzerland, Canada, Finland, Northern Ireland, Australia, Greece and Germany (FRG). A convex pattern, increasing and then decreasing sex ratio with advancing ages, was found in Belgium, and also in Spain, Italy and Norway with much exaggerated convexity. The curve in Bulgaria might also be a convex pattern. The age curves of sex ratio in Romania and Yugoslavia were quite similar each other, with a dip at the age group of 55–59 years. The curves in Romania, Yugoslavia and Japan might be regarded as a neither increasing nor decreasing pattern, to which the curves in Ireland and Hong Kong might also be categorized. The age curves of sex ratio in Sweden and New Zealand were quite different from those in the other countries. The sex ratio was decreasing in 45–64 years of age and slightly increasing thereafter in Sweden. It was unaltered in 50–64 years of age and apparently dropped thereafter in New Zealand, where the annual numbers of deaths were fairly small in both sexes.

In short, the curve of sex ratio of age specific death rates is an increasing or convex pattern in most countries of concordnatly high or intermediate countries. The sex ratio seems neither increase nor decrease apparetly with advancing ages in concordantly low countries, except Bulgaria.

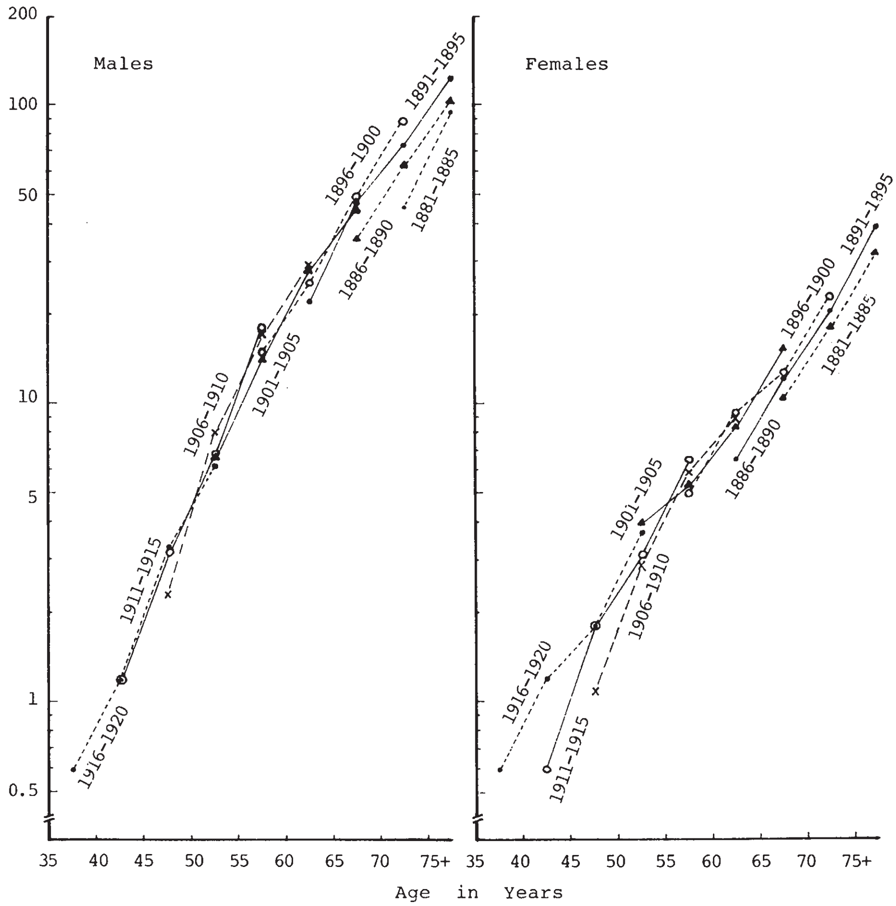

Fig. 6. Death Rates from Bladder Cancer by Birth Cohort in Scotland, UK (Rate per 100,000 population)

5. *Birth Cohort Analysis*

Mortality statistics provided from WHO data bank permitted the birth cohort analysis of bladder cancer deaths for four populations; Scotland, Japan, France and Italy.

Somewhat less risks for bladder cancer deaths were noted in the birth cohorts born before 1891 for males and before 1896 for females in Scotland (Fig. 6), and in those born before 1896 for males and before 1891 for females in Japan (Fig. 7). In France (concordantly intermediate country), the birth cohorts born before 1896 seemed to be at less risk of bladder cancer deaths in both sexes (Fig. 8). In Italy (discordant country), similar less risks for bladder cancer deaths were likely to be observed in the birth cohorts born before 1901 in both sexes (Fig. 9).

The year which delineated the risk for bladder cancer deaths seems to be around 1900

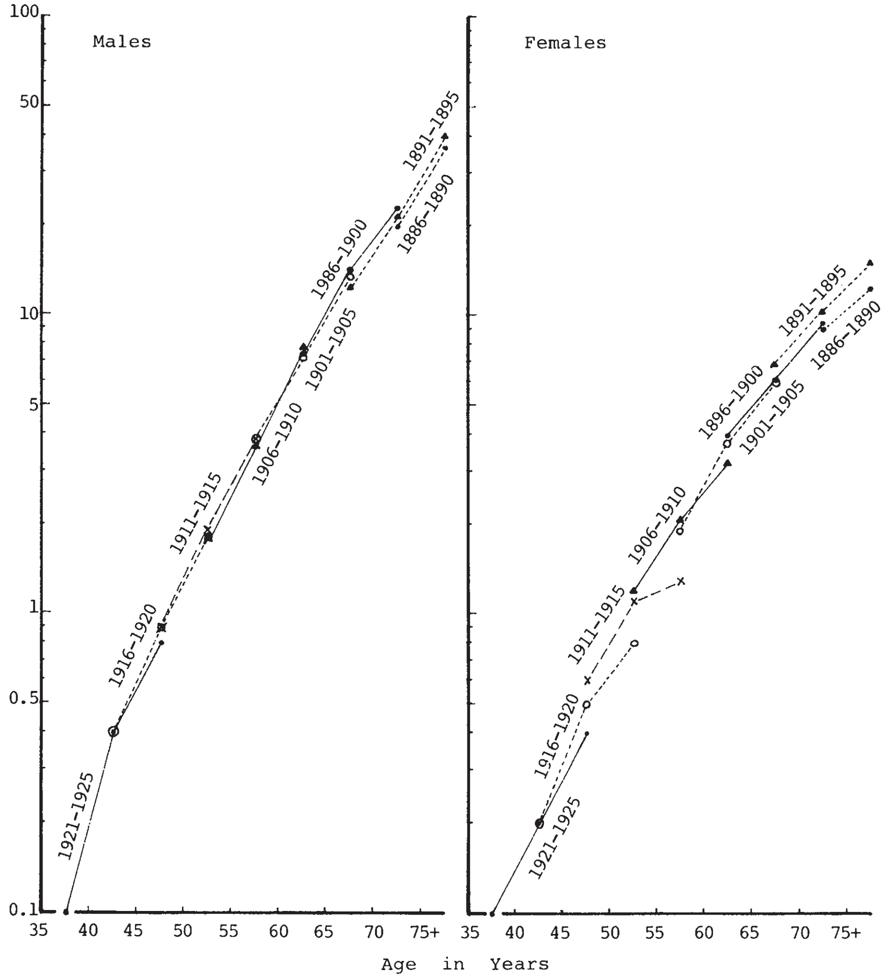

Fig. 7. Death Rates from Bladder Cancer by Birth Cohort in Japan (Rate per 100,000 population)

for both sexes, and the birth cohorts born after this year are at almost identical risks in these four popoulations, irrespective of the mortality levels.

6. *Comparison of Sociodemographic Features*

Some of sociodemographic variables are compared among countries to examine the epidemiological backgrounds of bladder cancer deaths.

Table 4 summarizes the proportions of inhabitants aged 60 years and over around 1973 (10). The proportions in females are expressed in parenthesis.

In concordantly high countries, the proportion of inhabitants aged 60 years or more ranged from 13.2 to 18.3% in males and from 16.8 to 24.0% in females, while in concordantly low countries from 10.4 to 12.7% in males and from 13.0 to 15.7% in females. In

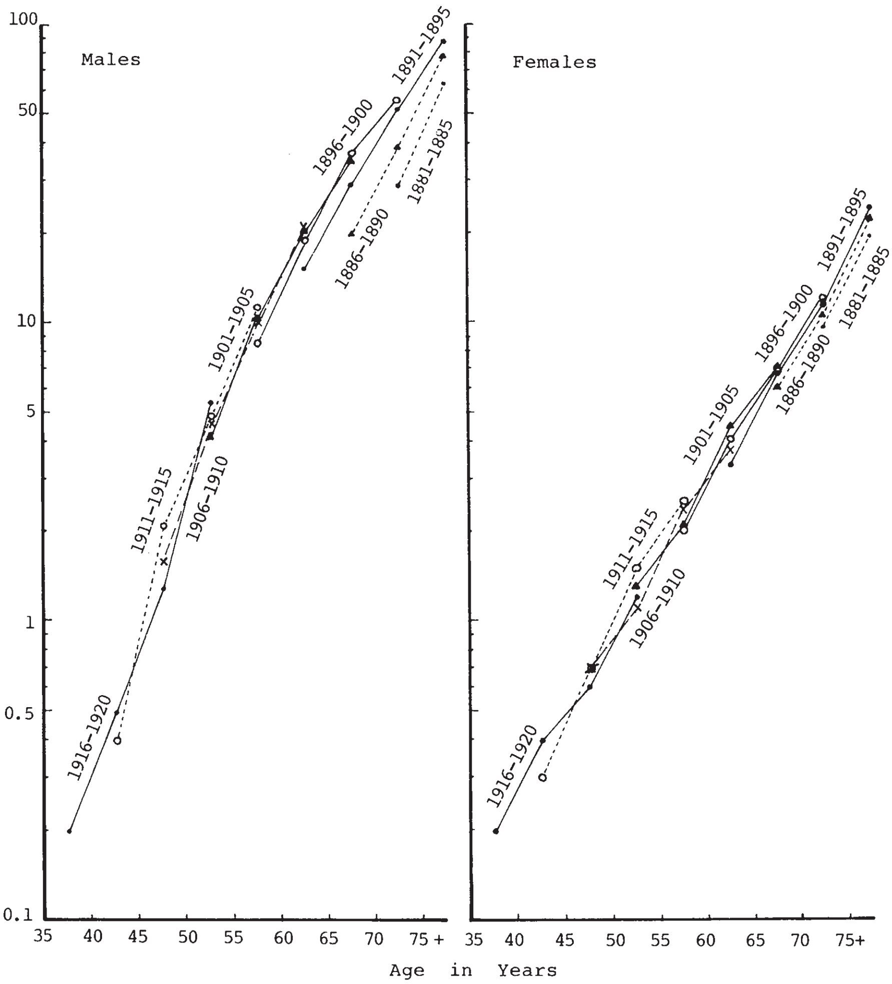

Fig. 8. Death Rates from Bladder Cancer by Birth Cohort in France (Rate per 100,000 population)

concordantly intermediate countries, it was 10.9–19.0% in males and 13.3–22.6% in females. In discordant countries, the corresponding proportions in Germany and Norway were similar to those in concordantly high countries, and those in Ireland and Italy to those in concordantly intermediate countries. The proportion in Spain was almost identical with that in Romania in concordantly low countries.

This comparison clearly indicates the contrast of more aged inhabitants in concordantly high countries and less aged inhabitants in concordantly low countries.

Table 5 compares the proportions of inhabitants engaged in agriculture (including forestry and fishery) (11) and in manufacturing (12) among economically active population (age: 15 year and over) around 1962. The proportions of economically active populations engaged in manufacturing are presented in parenthesis. Agricultural population accounted

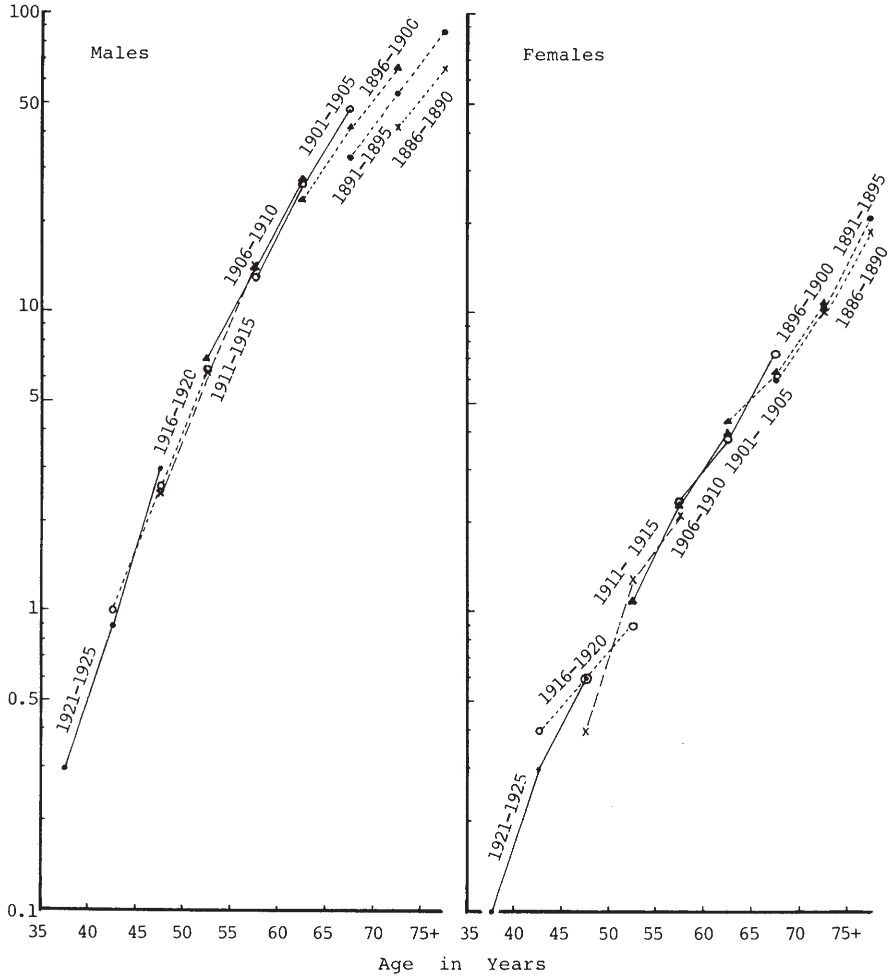

Fig. 9. Death Rates from Bladder Cancer by Birth Cohort in Italy (Rate per 100,000 population)

for 5–23%, 11–38%, 27–70% and 7–54%, in concordantly high, intermediate and low, and discordant countries, respectively. Economically active populations engaged in manufacturing were 29–37%, 22–40%, 17–24% and 13–38%, correspondingly.

These proportions show that concordantly high countries are industrial countires, whereas concordantly low countries are agricultural countries.

The magnitudes of change in industrial production are compared among countries in the past two decades; between 1955 and 1964 and between 1965 and 1974. Table 6 presents the index numbers of industrial productions in 1964 (13) and 1974 (14). Industrial production covers the productions in mining, manufacturing, electricity and gas. The index numbers in 1964 and 1974 are shown as percentage changes, taking the productions in 1955 and 1965 as 100, respectively. The index numbers in 1974 are presented in parenthesis.

Table 4 Proportions of inhabitants aged 60 years and more in total population around 1973.
Unit : percentage

Proportions for females in parenthesis

Males \ Females	High AAMR* ≥ 1.6		Intermediate 1.6 > AAMR ≥ 1.0		Low AAMR < 1.0	
High AAMR* ≥ 6.0	Scotland+	16.6 (22.7)	Germany (FRG)	16.1 (23.1)	Spain	12.3 (15.8)
	Denmark	16.5 (20.1)	Italy	15.3 (19.0)		
	Eng.Wales	- -				
	Belgium	16.6 (21.7)				
	Austria	18.3 (24.0)				
	Netherlands	13.2 (16.8)				
Intermediate 6.0 > AAMR ≥ 4.0	Norway	17.0 (21.0)	Hungary	16.1 (20.4)	Greece	15.9 (18.4)
	Hong Kong	- -	France	15.5 (21.7)		
	Ireland	14.7 (16.6)	Switzerland	14.9 (19.5)		
			Canada	11.1 (13.3)		
			Australia	10.9 (14.0)		
			New Zealand	11.3 (14.1)		
			Finland	12.2 (18.0)		
			N. Ireland	- -		
			Sweden	19.0 (22.6)		
Low AAMR < 4.0					Bulgaria	- -
					Romania	12.7 (15.7)
					Yugoslavia	11.3 (13.9)
					Japan	10.4 (13.0)

*: Age-adjusted Mortality Rate, +: Includes England and Wales.

The index numbers of industrial production in 1964 ranged from 129 to 166, from 146 to 199, from 284 to 359 and from 156 to 200 in concordantly high, intermediate and low, and discordant countries, respectively. Corresponding figures in 1974 were 118–183, 142–190, 189–293 and 152–251, respectively. In 1974, the index numbers in Spain and Greece were rather close to those in concordantly low countries.

It is clear from this comparison that the remarkable industrialization has been in progress in concordantly low countries and moderate industrialization in concordantly high countries in the past two decades.

When comparing the index numbers of manufacturing production alone in 1964 (13) and 1974 (14), in the same fashion, remarkable increases in manufacturing production in concordantly low countries and moderate increases in concordantly high countries were similarly observed.

Table 7 presents the energy consumption per capita in tons of coal equivalent in 1964 (15) and 1974 (16). Energy consumption in 1974 is presented parenthesis. Energy consumption was quite in contrast between concordantly high and low countries; 2.5–5.1 tons vs. 1.1–2.4 tons in 1964, and 3.8–6.6 tons vs. 1.9–3.8 tons in 1974. Corresponding figures were 2.2–7.1 tons in 1964 and 3.4–9.8 tons in 1974 in concordantly intermediate countries; those in discordant countries being 0.6–4.2 tons and 2.0–5.6 tons in 1964 and 1974, respectively. Energy consumption in Hong Kong, Spain and Greece of discordant countries was rather close to that in concordantly low countries.

This comparison indicates that economical and industrial activities are quite high in concordantly high countries, but still not high in concordantly low countries, despite recent remarkable industrialization.

Table 5 Proportions of Agricultural and Manufacturing Population among Economically Active Population around 1962 : Units; percentage.

Proportion of Manufacturing Population in parenthesis

Males \ Females	High AAMR* ≥ 1.6	Intermediate 1.6 > AAMR ≥ 1.0	Low AAMR < 1.0
High AAMR* ≥ 6.0	Scotland 7 (37)+ Denmark 17 (29) Eng.Wales 5 - Belgium 6 (34) Austria 23 (29) Netherlands 11 (30)	Germany (FRG) 11 (38) Italy 25 (28)	Spain 35 (25)
Intermediate 6.0 > AAMR ≥ 4.0	Norway 19 (26) Hong Kong 7 - Ireland - -	Hungary 38 (27) France 20 (27) Switzerland 11 (40) Canada 11 (23) Australia 11 (27) New Zealand 14 (25) Finland 35 (22) N. Ireland - - Sweden 14 (34)	Greece 54 (13)
Low AAMR < 4.0			Bulgaria 64 - Romania 70 (14) Yugoslavia 57 (17) Japan 27 (24)

*: Age-adjusted Mortality Rate, +: Includes England and Wales.

Table 6 Index Numbers of Industrial Production in 1964 and 1974.
Unit : percentage when 1955=100 for 1964 and 1965=100 for 1974

Percentage in 1974 in parenthesis

Males \ Females	High AAMR* ≥ 1.6	Intermediate 1.6 > AAMR ≥ 1.0	Low AAMR < 1.0
High AAMR* ≥ 6.0	Scotland+ 129 (118) Denmark 159 - Eng. Wales - - Belgium 145 (148) Austria 160 (173) Netherlands 166 (183)	Germany (FRG) 175 (148) Italy 200 (169)	Spain 171 (251)
Intermediate 6.0 > AAMR ≥ 4.0	Norway 156 (152) Hong Kong - - Ireland - (171)	Hungary 199 (171) France 166 (171) Switzerland 148 (146) Canada 158 (162) Australia 146 (142) New zealand - (168) Finland 164 (190) N. Ireland - ¬ Sweden 158 (149)	Greece - (232)
Low AAMR < 4.0			Bulgaria 337 - Romania 284 (293) Yugoslavia 287 (189) Japan 359 (264)

*: Age-adjusted Mortality Rate, +: Includes England and Wales.

Table 7 Energy Consumption per Capita in 1964 and 1974.
Unit : in tons of coal equivalent.

Values in 1974 in parenthesis.

Males \ Females	High AAMR*≥ 1.6	Intermediate 1.6 > AAMR ≥ 1.0	Low AAMR < 1.0
High AAMR*≥ 6.0	Scotland+ 5.1 (5.5) Denmark 4.0 (5.1) Eng. Wales - - Belgium 4.6 (6.6) Austria 2.6 (3.8) Netherlands 3.3 (6.2)	Germany (FRG) 4.2 (5.6) Italy 1.7 (3.2)	Spain 1.0 (2.1)
Intermediate 6.0 > AAMR ≥ 4.0	Norway 3.5 (4.9) Hong Kong 0.6 - Ireland 2.3 (3.5)	Hungary 2.8 (3.6) France 2.9 (4.3) Switzerland 2.5 (3.6) Canada 7.1 (9.8) Australia 4.5 (6.0) New Zealand 2.2 (3.4) Finland 2.4 (4.5) N. Ireland - - Sweden 4.3 (5.8)	Greece 0.6 (2.0)
Low AAMR < 4.0			Bulgaria 2.4 - Romania 1.8 (3.5) Yugoslavia 1.1 (1.9) Japan 1.7 (3.8)

*: Age-adjusted Mortality Rate, +: Includes England and Wales.

Table 8 Proportion of Deaths from Infective and Parasitic Diseases in Total Deaths in 1973.
Unit : per 1000

Proportion for females in parenthesis

Males \ Females	High AAMR*≥ 1.6	Intermediate 1.6 > AAMR ≥ 1.0	Low AAMR < 1.0
High AAMR*≥ 6.0	Scotland 7.9 (6.3) Denmark 5.8 (6.1) Eng. Wales 6.4 (4.4) Belgium+ 11.7 (7.4) Austria 13.5 (6.5) Netherlands 6.3 (7.5)	Germany (FRG) 11.9 (7.3) Italy 16.3 (10.9)	Spain 26.6 (17.6)
Intermediate 6.0 > AAMR ≥ 4.0	Norway 7.4 (8.1) Hong Kong 89.6 (33.9) Ireland+ 11.0 (8.5)	Hungary 23.5 (13.1) France 16.5 (13.0) Switzerland 13.4 (11.1) Canada 6.8 (7.6) Australia 7.3 (6.9) New Zealand+ 10.8 (10.8) Finland 11.3 (9.4) N. Ireland 9.4 (7.5) Sweden 7.9 (6.2)	Greece 22.2 (14.9)
Low AAMR < 4.0			Bulgaria 18.2 (11.2) Romania 26.8 (14.7) Yugoslavia 32.7 (22.9) Japan 31.8 (22.2)

*: Age-adjusted Mortality Rate, +: 1972

Table 8 shows the proportion of deaths from infective and parasitic diseases (ICD. A1-A44) in total deaths in 1973 (17). Proportions are expressed in unit of per 1,000 with those for females in parenthesis. Infective and parasitic diseases accounted for 5.8–13.5‰ of total deaths in males and for 4.4–7.5‰ in females in concordantly high countries, whereas for 18.2–32.7‰ in males and for 11.2–22.9‰ in females in concordantly low countries. Corresponding proportions were 6.8–23.5‰ in males and 6.2–13.1‰ in females in concordantly intermediate countries. Proportions in Germany (FRG) and Norway were similar to those in concordatnly high countries, and those in Italy and Ireland to those in concordantly intermediate countries. Proportions in Spain and Greece were rather close to those in concordantly low countries. Proportions in Hong Kong were exceptionally high, and higher than those in concordantly low countries.

Noteworthy in this comparison is that the proportions of deaths from infective and parasitic diseases are quite in contrast between concordantly high and low countries.

In summarly concordantly high countries are characterized by more aged population, munufacturing, moderate industrialization, high energy consumption and less frequent deaths from infective and parasitic diseases; in contrast, concordantly low countries by less aged population, agriculture, remarkable industrialization, low energy consumption and more frequent deaths from infective and parasitic diseases.

DISCUSSION

International comparison of age-adjusted mortality rates from bladder cancer revealed that Scotland, Denmark and England and Wales experienced the three highest mortalities in both sexes in 1970–1974. These populations were followed by Belgium, Austria, Germany (FRG) and Netherlands in males, and by Norway, Hong Kong, Netherlands, Austria and Belgium in females. Bulgaria, Romania, Yugoslavia and Japan were the countries with four lowest mortalities in both sexes. The differences between the highest and the lowest mortality rate was 3.5 times in males and 3.1 times in females.

Can these intercountry differences in the rates, though not so large compared to the mortality of cancers of other sites, safely be assumed to reflect the real differences in the mortality and/or incidence of the disease? The differences in the mortality, in general, could be due to two possible components; real and artifactual.

Artifactual components may arise from the errors in the denominator and the numerator. The erroneous numeration or estimaiton of populations by age and sex is the sole cause of errors in the denominator. The errors in the numerator may be ascribable, at least, to the differences in diagnosis or recognition of the disease, the differences in stating the causes of death on the death certificate, the differences in coding causes of death and the differences in case fatality or survivorship.

Disease specific magnitude of these errors could neither readily be assessed for an individual country, nor be compared among countries. Nevertheless, since the majority of countries in Figure 1 have already established satisfactory systems for population census, death registration and classification of causes of death, and since bladder cancer has been diagnosed with relative ease by cytoscopic examination with cytological confirmation, most of these artifactual components are believed not to be involved seriously enough to distort the real figures of bladder cancer deaths.

Rank order of the mortality in 1970–1974 is almost identical with that in 1958–1959 and 1966–1967 (1). Similar phenomenon of concordance and discordance of the mortality level by sex is also observed in 1958–1959 and 1966–1967 (1). International variation in the mortality is in almost same magnitude from 1960 onwards (1). These particular findings may possibly indicates that the artifactual components in the international mortality statistics of bladder cancer, if any, are unaltered over years in the developed countries, and therefore endorse the possibility of no serious distortion of real figures by artifactual components.

Contribution of the different survivorship to international mortality statistics of bladder cancer could not readily be assessed for 1970–1974. Some limited data on cancer survival statistics (18), however, show that five-year survival rates of bladder cancer are comparatively similar among countries: 35% (males) and 21% (females) in Osaka, Japan in 1965–68, 42% (males) and 34% (females) in Scotland in 1959–61, 39% (males) and 35% (females) in England and Wales in 1963, 24% (males) and unavailable percent (females) in France in 1965–68, and 36% (males) and 27% (females) in Norway in 1963–67. This limited statistics for bladder cancer survival rate may seemingly suggest the minor and similar contribution of survivorship to the mortality among countries.

Differences in age construction of the denominator also contribute to the mortality variation, but they are eliminated by age adjustment of the mortality.

The mortaliy rate is believed to be well in parallel with the morbidity rate (19,20), despite a variable prognosis in bladder cancer.

Among the age-adjusted incidence rates of bladder cancer (21) for the countries in Figure 1, the highest incidence rate in males is 22.2 per 100,000 in Scotland (Aryshire), followed by Denmark (16.1), Canada (15.9, mean of seven rates). Switzerland (15.3, Geneva), and England and Wales (15.1, Liverpool). In females, six highest incidence rates are observed in Scotland (5.0, Aryshire), Denmark (4.2), New Zealand (3.9, mean of two rates), Sweden (3.8), Canada (3.8, mean of seven rates), and England and wales (3.7, Liverpool). The incidence rates for Romania (Timis), Yugoslavia (Slovania) and Japan (Miyagi, Okayama and Osaka) are 8.1, 7.0, and 4.8 (mean of three rates) in males, and 1.3, 1.4, and 1.3 (mean of three rates) in females, respectively. This particular observation may probably prove the parallelism of the mortality rate with the incidence rate, and therefore, more importantly, may indicate that the observed differences in the mortality rate in 1970–1974 are quite likely to be the real reflection of the incidence of the disease, and that the incidence of the disease may roughly be estimated as 2–3 times more frequent in males and 1.5–2.5 times more frequent in females than the deaths.

Then, though the range of international varation in the mortality is not so wide as that for cancers of other sites, what are the possible determinants for the mortality variation?

Since bladder cancer is one of the few malignant neoplasms in which the role of environmental agents has been clearly shown to be important, international variation in some known environmental factors should be examined.

Population-attributable risk percent of smoking for bladder cancer is reported to be 56% for males and 29% for females (22). Smoking should accordingly be incriminated as a responsible environmental agent for bladder cancer. However, smoking is believed not to be a definitive determinant for international difference in the mortality level, since consumption of cigarettes per adult (23) somewhat varies from country to country, but international variation in consumption of cigarettes did not coincide with international variation in the mortality.

The present analysis clearly revealed that concordantly high countries are characterized by manufacturing, recent moderate industrialization and hgih energy consumption; in contrast concordantly low countries by agriculture, recent remarkable industrialization and low energy consumption. In Japan, the cities with high bladder cancer mortality, but with average lung cancer mortality in males, are much more inhabited by the workers in risk industries incriminated for bladder cancer (24). Similar pattern of industrial employment is reported for the high risk counties in the U.S.A. (25). Accordingly, occupational exposures are undoubtedly important in bladder cancer carcinogenesis, and these findings may also indicate the contribution of potential occupational agents with industrialization to both international and regional differences in bladder cancer mortality level. The contribution is, however, presumed to be partial, since occupational bladder cancer is reported to be 10–20% (26) or 18% (27) of all bladder cancer cases, and this extent of proportion is considered not to be sufficiently large enough to determine total variation in the mortality. To examine the magnitude of occupational contribution to bladder cancer, the careful observations of future changes in the mortality in concordantly low countries may be helpful, since remarkable industrialization has recently been in progress there.

Coffee drinking has been reported to increase the risk of bladder cancer, but the association is inconsistent as to sex (28–31). Recent investigation for ten countries (32) concluded that the relationship between per capita coffee imports and bladder cancer incidence is neither strong nor consistent in direction and therefore provides little support for an association of coffee drinking with the development of bladder cancer. Artificial sweeteners, particuarly saccharin, have been incriminated as one of hazardous agents to bladder, but are seemingly regarded as non-carcinogenic to humans in recent years (33–35). Accordingly, neither coffee drinking nor use of artificial sweeteners is presumed to be the determinants for the international variation in the mortality.

Less dietary intake of vitamin A is recently reported to increase the risk of bladder cancer (5). A single vitamin nutrient could hardly determine the mortality level of bladder cancer, but further studies are undoubtedly required on the dietary and nutritional factors in bladder cancer.

Concordantly high countries seem to cluster in North-Western part of Europe and England, and concordantly low countries in Balkan States and Japan. In Japan, high bladder cancer mortality was clustered in rural districts, without statistical significance (24) (36). These geographic contrast may, however, be suggestive of the possible existence of environmental, socioeconomic or demographic variables relevant to each country or region. It is hard to believe that meteorological variables such as temperature, humidity or rainfall could determine the geographic contrast and international variation in the mortality.

A determinant presumed to be most probable at moment seems to be the proportion of the aged populations, since bladder cnacer is a disease of the advanced ages. This concept is endorsed by the facts that concordantly high countries are much more inhabited by the aged persons of 60 years or more and that the mean age at death is much higher in concordantly high countries than in concordantly low countries.The proportion of deaths from infective and parasitic diseases among total deaths is much higher in concordantly low countries than in concordantly high or intermediate countires. This may essentially endorse the above concept by the possibility that a certain segment of population succumbs before attaining the ages sufficiently old enough to develop bladder cancer.

In respect of the aging of population and smoking, the suggestion (37) is of quite interest that the age curve for bladder cancer morbidity is placed about ten years later in life than the curve for lung cancer morbidity, and the age curves for these two neoplasms are approximately identical. The statement (38) is also relevant in this respect that when bladder cancer is thought to be related to smoking, the latent period is consideredly longer than in bronchus cancer so that death from bronchial disease may occur before a bladder tumor developed.

In summary, among various explanatory variables for the international variation in bladder cancer mortality, the proportion of the aged population and potential occupational exposures with the past industrialization seem to be the most and more probable variables than smoking, coffee drinking, use of artificial sweetners or dietary deficiency of vitamin A. Further investigations are, however, undoubtedly required to conclude this.

Male predominance in bladder cancer is universal over year and over countries. Then, what are the determinants for male predominance?

Population-attributable risk percent of occupational exposures is estimated as 35% in males and only 1% in females (21). Occupational exposures are accordingly believed to be one of major contributes to male predominance in bladder cancer.

Smoking may also partly contribute to the sex discrepancy, but is presumed not to be a major factor, since the range of sex ratio for bladder cancer mortality, (2.4–6.4 in 1972–1974) should have been much wider as the ranges for lung or larynx cancer mortalities; being 2.7–16.5 for lung cancer and 2.3–31.3 for larynx cancer in 1966–1967 (1). To examine the magnitude of contribution of smoking to the sex discrepancy, the effect of the recent increase of smokers in females should carefully be investigated in futurue.

Even if the degrees of coffee drinking, use of artificial sweeteners and dietary intake of vitamin A could be different by sex, they are not believed to be the major explanatory factors for the sex discrepancy in bladder cancer.

The different proportions of the aged population by sex do not also explain the sex discrepancy, because the proportions of the aged population are much larger in females than in males, and yet the mortality is much lower in females than in males.

When the increase gradients of age specific death rates are compared by sex, they are much more moderate in females than in males; being around 1.6 for females and around 1.8 for males. This finding may seemingly suggest the less susceptibility to bladder cancer in females. The sex differences in such physiological conditions as endocrine or metabolism would possibly be related in this respect.

Sex ratio of age specific death rates shows three major patterns of distribution by age; increasing, convex and no apparently increasing patterns. The peak of sex ratio of age specific death rates varies from country to country; the peak being at 50–54 years of age in Bulgaria, and at 50–59 years of age in Belgium, Spain, Italy and Norway. This finding may fundamentally suggest the changing effects of the determinants by age and sex, and the determinants are supposed to be environmental in nature.

In summary, male predominance in bladder cancer is presumed to be determined by environmental factors such as occupational exposures and smoking, and possibly by some host factors such as endocrine or metabolism. In canine bladder cancer, an excessive risk for female dogs is reported (39). This sex predisposition is ascribed to the result of female dogs urinating less frequently as compared to male dogs (1:3 ratio) (40), therefore, more prolonged contact of bladder epithelium with urine-borne agents in female dogs than in male dogs (39). Such a sex difference in the opposite direction, if any, may possibly be relevant to the male predominance in human bladder cancer, though no apparent sex difference is found in the frequency of urination per day in the preliminary analysis of the data obtained by a case-control study of human bladder cancer in Metropolitan Nagoya (41).

Among 52 trends in age-adjusted mortality rates from bladder cancer for the period of 1968/69–1974/75, only five trends are significantly upward; males in Hungary, Hong Kong and Spain, and females in Denmark and Spain, though the mortality for females in Spain is unchanged for 1972–1974. These countries are not substantially different from other countries with a similar mortality level in terms of the mean age at death and the proportion of the aged population. Males in Hungary, Hong Kong and Spain are, however, quite similar to males in the countries with low mortality in terms of the proportion of deaths from infective and parasitic diseases (cf. Table 13). The upward trends in these five populations are unexplainable, and should be evaluated with the mortality trends in subsequent 10 to 15 years.

The remaining 47 mortality trends are stable and virtually unchanged over years. The virtually unchanged trends may possibly suggest that bladder cancer mortality attained or is going to attain its maximum level of mortality under the present enviornmental conditions in each country; indicating the epidemiological phenomenon of equilibrium in host-environmental interactions in bladder cancer carcinogenesis or deaths. The phenomenon of equilibrium may be epidemiologically interpreted as the reflection of possibly unaltered envrionmental effects, at least, for the recent one or two decades, even in the countries with low mortality, and/or the possible existence of a certain segment of population predisposed to succumb to bladder cancer in each country. The evidence for the possible existence of the predisposed to bladder cancer has not sufficiently been documented. The concept of the predisposition to bladder cancer, however, seems to emerge materially from the epidemiological findings obtained by the present analysis; not only the virtually unchanged mortality trends and the almost identical risks for the birth cohorts born after around 1900, but also the unchanged magnitudes of international variations in the mortality and its sex ratio, the unaltered order of mortality ranking over years, and the quite similar increase gradients of age specific death rate over countries. Since there is little evidence for the role of inheritance in human bladder cancer (42–44), the predisposition is presumed to be metabolic or nutritional as suggested (45, 46).

To evaluate the relative importance of host predispositions or environmental factors in bladder cancer carcinogenesis, the future trends in the incidence and deaths should carefully be investigated in the subsequent one or two decades, particularly in such countries with low mortality as Bulgaria, Romania, Yugoslavia and Japan, where industrialization has recently been quite remarkable.

In conclusion, the present evaluation of bladder cancer mortality statistics in the countries of the world, in terms of mortality variation and trends, age distribution, sex ratios, some sociodemographic variables and birth cohort analysis, suggests the etiological roles of both environmental factors and host predispositions and the equilibrium in host-enviornmental interactions for bladder cancer deaths or carcinogenesis.

ACKNOWLEGEMENT

The authors thank Dr. H. Hansluwka, chief statistician, Dissemination of Statistical Information, WHO, for his providing us the valuable mortality statistics of bladder cancer in the world.

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