

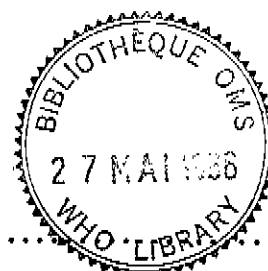


THE EPIDEMIOLOGICAL ASSOCIATION BETWEEN  
SCHISTOSOMA HAEMATOBIIUM INFECTION AND BLADDER CANCER<sup>a</sup>

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<sup>a</sup> This report was prepared in response to a request from the Cancer Unit (CAN), Division of Noncommunicable Diseases, and the Unit of Schistosomiasis and other Trematode Infections (SCH), Parasitic Diseases Programme, of the World Health Organization, Geneva, for: (1) a review of the evidence linking S. haematobium infection with bladder cancer; (2) suggestions for further study of the relationship, if such study is needed; and (3) assuming the relationship does hold, an analysis of the probable impact of a chemotherapy-based schistosomiasis control programme on bladder cancer rates. As part of this review process, the author visited CAN (Dr J. Stjernsward) and SCH (Dr K. E. Mott) in Geneva and also the Egyptian National Cancer Institute (Professor M. Sherif and Dr A. Ibrahim) in Cairo.

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## 1. INTRODUCTION

Urinary schistosomiasis caused by Schistosoma haematobium infection is now endemic in 52 African and Eastern Mediterranean countries. This disease is an occupational hazard affecting the poor agricultural rural populations in these countries. At least 180 million persons are at risk of infection and about 90 million persons are infected with S. haematobium.<sup>(14)</sup>

The highest prevalence of infection and the major proportion of heavy infections are observed in children of school age who by habit have the most extensive and frequent water contact. Among infected children the excretion of blood and protein in the urine is directly correlated with the number of S. haematobium eggs in the urine.<sup>(23)</sup> These clinical manifestations are related to severe focal lesions of the bladder which may develop into chronic disease including bladder cancer.<sup>(5)</sup>

## 2. REVIEW OF EVIDENCE LINKING S. HAEMATOBIMUM WITH BLADDER CANCER

The relationship between S. haematobium infection and bladder cancer has been the subject of a number of special reviews in recent years.<sup>(3,15,25)</sup> There are four lines of evidence suggesting that such infection can be a major cause of bladder cancer in a number of countries:

(1) Major differences in pathological classification of bladder cancers: squamous cell cases form a much higher percentage of all bladder cancer cases in areas endemic for S. haematobium than in most other areas of the world.

(2) Comparative case-control studies: in areas endemic for S. haematobium a higher rate of S. haematobium infection is generally found in bladder cancer cases than in controls, and a higher rate in squamous cell cases than in other histological types of bladder cancer.

(3) Primary site of bladder cancers: the trigone is rarely the primary site in cases associated with S. haematobium infection.

(4) Geographical correlation: there is a positive association of bladder cancer rates with S. haematobium infection rates in Africa.

Valid criticism can be made of much of this evidence, and consequently the association of S. haematobium and bladder cancer remains a matter open to debate.

### 2.1 Pathology of bladder cancer

Studies in many parts of Africa have consistently shown a much higher proportion of squamous cell bladder carcinomas than is seen in Europe or North America. Table 1 gives the results from most of the substantial studies carried out on the African continent. The proportion of squamous carcinomas varied from a low of 29% in South Africa to a high of 83% in Malawi. In North America squamous carcinomas comprise only some 7% of bladder carcinomas.<sup>(18)</sup> In England the figure is less than 10%.<sup>(24)</sup>

### 2.2 Evidence of S. haematobium in bladder cancer cases and controls

Data on evidence of a history of S. haematobium infection in bladder cancer cases and controls are given in Table 2. A number of points should be noted: (i) the association of S. haematobium with squamous cell carcinoma is considerably stronger than with transitional cell or the other histological types; (ii) four case-control comparison studies by Mustacchi & Shimkin,<sup>(19)</sup> Gelfand et al.,<sup>(11)</sup> Hinder & Schmamman,<sup>(12)</sup> and Elem & Purohit<sup>(10)</sup> showed strong positive associations of bladder cancer with S. haematobium infection, but the study of Prates & Gillman<sup>(21)</sup> in Mozambique did not; and (iii) in Uganda, although there is a high proportion of squamous tumours, S. haematobium infection was not noted by Anthony<sup>(1)</sup> in biopsies from any cases of carcinoma of the bladder - previously, however, Dodge<sup>(6)</sup> had found evidence of schistosomiasis in a number of squamous cell carcinoma cases.

### 2.3 Site of origin

The trigone is rarely the site of origin for bladder cancers in Egypt; Nasr et al.<sup>(20)</sup> reported this site in 2.8% of their series of 324 cases. The comparable figure in US series varies from 20% upwards. Of more importance, at least 38% of the bladder cancers in Uganda arose in the trigone.<sup>(1)</sup>

(Note: In discussions with the author, Professor Sherif, Egyptian National Cancer Institute, Cairo, Egypt, said that S. haematobium calcifications also spare the trigone: this most interesting observation suggests that calcifications constitute the correct measure of S. haematobium damage as far as bladder cancer risk is concerned. No reference on this has been found as yet to confirm or refute the claim. In a personal communication, Professor J. H. Smith, Professor of Pathology, University of Texas Medical School at Galveston, Texas, United States of America, has suggested that the trigone may be spared in cases of bladder cancer since its involvement would cause obstructive uropathy and early death before bladder cancer arises. This hypothesis fits current observations.)

### 2.4 Correlations of geographical distribution of S. haematobium and bladder cancer rates in central and southern Africa

Cook-Mozaffari & Burkitt<sup>(4)</sup> have conducted long-term surveys of cancer occurrence in many hospitals in central and southern Africa. On the basis of these surveys they estimated bladder cancer rates in the different areas and correlated these with estimates of the local intensity of S. haematobium infection. Although noting that there was a moderately high rate of bladder cancer but apparently no schistosomiasis in this area in the north and west of Lake Victoria in Uganda and Tanzania, they concluded:

"Grouping the data for the whole of Africa, a degree of geographical association seems to exist between the occurrence of bladder cancer and the level of schistosomiasis infestation ... The estimations of the level of schistosomiasis in each region ... have been taken largely from a compendium of different studies ... As with almost any data from Africa, the standard of the evidence is variable ... In support of an association, all regions with bladder cancer rates over 12 per 100 000, in men or women or both, are found in areas with moderate or high schistosomiasis rates. Also there are a dozen or so regions with zero or very low rates which occur in areas which are said to be free from schistosomiasis. There are no regions with zero or very low rates in the areas of high schistosomiasis prevalence and ... those areas where the incidence is higher in women than in men offer further support that schistosomiasis infection does play a part in the development of cancer of the bladder. The majority of such areas are those where a high proportion of men go away to work in distant mines or cities. Under these circumstances the women are left to work the fields and thus incur a greater risk of infection."

There can be no doubt that the distribution of bladder cancer by histological type is different in Africa compared to the rest of the world. It has been suggested that the high proportion of squamous cell carcinomas in Africa merely reflects the advanced stage at which most of these bladder cancer cases present. The fact that within hospital series squamous cell carcinomas are more frequently involved with S. haematobium than are other cell types offers some evidence against this, however; and, for the present, it is more reasonable to conclude that the causes of bladder cancer in Africa differ from those in the developed countries. Bladder cancers in the United Kingdom, the USA and other industrial societies are associated with exposure to certain industrial chemicals, cigarette smoking, and a number of additional substances which have all been uncommon in Africa. The data of Anthony<sup>(1)</sup> and certain other data<sup>(4)</sup> show, however, that squamous cell carcinomas can make up a high proportion of all bladder cancer cases in an area without S. haematobium being involved. The data shown in Table 1, therefore, provide of themselves, little or no evidence for a role of S. haematobium in bladder cancer aetiology in Africa.

The results of Cook-Mozaffari & Burkitt,<sup>(4)</sup> however, offer reasonably convincing evidence that S. haematobium infection does increase the risk of bladder cancer. Three of the four positive case-control comparisons shown in Table 2 provide much stronger evidence. In these studies conducted in three different countries, Egypt,<sup>(19)</sup> Zimbabwe<sup>(11)</sup> and Zambia,<sup>(10)</sup> the cases and controls were matched for sex and age, and appear to have been investigated in a very similar manner.

In the study by Hinder & Schmamman<sup>(12)</sup> the 35% infection rate refers to cases of both sexes (85% male, 15% females). The 16% infection rate for controls refers only to males and the controls appear to have been examined more thoroughly (95% of the cases had only a biopsy specimen for examination); both of these factors imply that the true difference between cases and controls will tend to be larger than that observed. Unfortunately, the cases and controls were not age matched and the results were not given in a form in which an age adjustment could be made: without this information it is impossible to determine whether the observed difference could be explained by a difference in the age distribution of cases and controls.

The contrary results of Prates & Gillman<sup>(21)</sup> are difficult to interpret. It is not possible to reconcile the 61% infection rate in controls with the 0% (0/41) figure for non-squamous carcinoma cases. Since it is likely that the classification of the cases did not depend on their precise histology, it is probably the control figure that is out of line. This negative case-control study and the positive case-control study of Hinder & Schmamman<sup>(12)</sup> should, due to their limitations, both be discounted in a general evaluation of available data.

The substantial positive evidence from the case-control comparisons of Mustacchi & Shimkin,<sup>(19)</sup> Gelfand et al.,<sup>(11)</sup> and Elem & Purohit<sup>(10)</sup> is further strengthened by the data (Table 2) showing that the association is much stronger with squamous cell carcinoma. It is also strengthened by the observation that the trigone is spared as a primary site of bladder cancer in areas of Africa endemic for S. haematobium, but not in the Uganda cases which have been associated with damage from gonorrhoea.<sup>(1)</sup>

The totality of evidence associating S. haematobium infection with bladder cancer is now more than sufficiently strong to assume its validity and to base on this assumption a prevention programme.

### 3. SUGGESTIONS FOR FURTHER STUDY OF THE RELATIONSHIP BETWEEN S. HAEMATOBIIUM INFECTION AND BLADDER CANCER

#### 3.1 Need for case-control studies

As discussed above, three case-control studies<sup>(10,11,19)</sup> provide the most convincing evidence for a causal association between S. haematobium infection and bladder cancer. In the first two studies detailed data on the cases and the controls are lacking, and consequently the possibility exists that the bladder cancer cases simply came from areas of endemic schistosomiasis while the controls did not; if this is so, then information on calcification or other evidence of S. haematobium infection is no more significant than information on area of residence alone, and some other factor associated with rural living (and exposure to S. haematobium) could be responsible for the apparent association with S. haematobium infection. Additional case-control studies which directly address this question are therefore feasible and necessary.

#### 3.2 A proposed case-control study

In a clinical centre of an endemic country where a large number of bladder cancer cases are seen each year, it should be possible to conduct a substantial case-control study successfully.

##### 3.2.1 Objectives

The objectives of a proposed study would be to:

(i) Establish criteria for the positive identification of S. haematobium calcifications by a non-invasive technique.

(ii) Compare the prevalence of bladder calcifications in bladder cancer cases and age-sex matched controls. Each case would be matched to: (a) a first control group chosen at random from non-bladder patients admitted to the hospital the day before the procedure is carried out; (b) a second control group chosen as above with the added condition that this person must come from the same general area as the case; and (c) a third neighbour control group specially invited to participate. A study of 200 cases

(with uniform pathological review and a detailed questionnaire on known bladder cancer risk factors, and a residential, occupational and medical history) should be more than adequate.

(iii) Establish the status of S. haematobium infection in both cases and controls using a quantitative urine filtration technique.

### 3.2.2 Rationale

#### Step 1

An essential element of a valid case-control study is the equivalence of the investigation of cases and controls. A method of objectively identifying prior infection with S. haematobium, that can be equally applied to cases and controls, would substantially strengthen the evidence obtainable by any case-control study. Mustacchi & Shimkin<sup>(19)</sup> relied on a simple urine specimen; this is unsatisfactory mainly because it shows only current infection. The method of Elem & Purohit<sup>(10)</sup> required bladder specimens from controls, thereby severely restricting the controls that can be used and making indefinable biases probably inevitable: Elem & Purohit<sup>(10)</sup> used autopsy material with its well-known potential for creating biased comparisons. The method of Gelfand et al.,<sup>(11)</sup> i.e. bladder calcifications detected by X-ray as evidence of chronic S. haematobium infection, appears at first sight to avoid both these problems. Taking X-ray films of the bladders of controls may however be considered unethical. It is therefore proposed that a study should first be undertaken to identify a non-invasive technique of detecting calcifications which could be applied without constraints equally to cases and controls. The use of ultrasound to detect bladder calcifications due to S. haematobium is controversial. Opinions should be canvassed from physicians knowledgeable in this field as experience accumulates.

#### Step 2 (see also section 3.2.1(ii))

The first control group (hospital control) will make it possible to compare the results of this study with those of previous studies: by collecting detailed occupational, residential and medical histories, it will also be possible to investigate the relationships between these variables and the presence (and extent) of calcifications. The second and third control groups will provide a basis for showing the strength of the relationship between S. haematobium and bladder cancer since the controls would match the cases even more closely as regards residential particulars and probably also occupational history. If comparison with the second control group, and even more with the third control group, shows that bladder cancer cases have a higher proportion of S. haematobium-related calcifications, then a causal relationship between S. haematobium infection and bladder cancer will have been firmly established.

### 4. PROBABLE IMPACT OF A CHEMOTHERAPY-BASED URINARY SCHISTOSOMIASIS CONTROL PROGRAMME ON BLADDER CANCER RATES

The increasing large-scale use of the existing safe, effective, oral antischistosomal drugs can be expected to reduce the risk of development of morbidity, including bladder cancer, related to schistosomiasis. The study of Gelfand et al.<sup>(11)</sup> in Zimbabwe, suggests that the relative risk for bladder cancer associated with calcifications is  $(16 \times 31) / (17 \times 2) = 14.6$  and the prevalence of calcifications in the controls is  $(2/33) = 6.1\%$ ; on the basis of these figures the bladder cancer rate in Zimbabwe would have been cut by 45% (from  $(0.939 + 0.061 \times 14.6) = 1.830$  to 1) if S. haematobium calcifications were eliminated. Similarly, a study in Zambia<sup>(10)</sup> suggests a relative risk of  $(21 \times 46) / (29 \times 4) = 8.3$ , a prevalence of  $(4/50) = 8.0\%$ , and a reduction of 37%. These results clearly show that eliminating S. haematobium calcifications should have a major impact on bladder cancer rates in many countries in Africa.

Bladder cancer, even in Egypt and other countries with major S. haematobium infection rates, shows an increased incidence with age and few cases are seen in persons under 40 years old. Treatment of children with S. haematobium infections should, as has been seen, make a marked impact on their subsequent risk of bladder cancer; but it must be understood that the effect is unlikely to be noted before some 25 years or more. Treatment of adults with active S. haematobium infections would seem to be much less apt to be effective in preventing bladder cancer unless it could significantly reduce the prevalence of sequelae

(calcifications?) of chronic infection. Effective treatment of all adults for the sequelae of chronic infection (even if they do not show active infection) offers perhaps the only possibility of reducing bladder cancer rates in the short term. The potential for actually reversing established sequelae, such as calcifications, by treatment has not yet been investigated with the current antischistosomal drugs.

The monitoring of changes in bladder cancer rates by national cancer registries of endemic countries with control programmes and widespread use of antischistosomal drugs will be a long-term effort.

#### 5. FURTHER ASSESSMENT OF BLADDER CANCER SCREENING BY URINE CYTOLOGY

Bladder cancer mortality rates may, in the short term, also be reduced by a screening programme for early diagnosis of bladder cancer cases. The Dakahliya Cytology Project<sup>(8)</sup> showed the feasibility of screening for bladder cancer by urine cytology in an Egyptian setting, and further work on cytology screening is recommended. Preliminary results from the Dakahliya Cytology Project are encouraging. The methodology may be much more cost-effective by restricting screening to a high-risk group (male farmers over age 40, say) and, perhaps even more important, by restricting repeated screening to persons showing cytological abnormalities at a first screening.

Between 1976 and 1979 in 15 villages of the Dakahliya Governorate situated at about 115 km from Cairo, a study was undertaken to evaluate urine cytology as a screening method for early detection of bladder cancer.<sup>(8,9)</sup> The Dakahliya Governorate is located in the Nile Delta, an area of intensive agriculture with endemic schistosomiasis.

Special surveys of the area revealed a population over 5 years of age of approximately 30 000. The organizers of the study argued that, since bladder cancer is rare in very young people and is a sequela of intense *S. haematobium* infection, screening should be concentrated on adult "farmers". The populations involved, the screening plan, the screening rate and the number of bladder cancer cases detected are given in Table 3. Of the 10 bladder cancers detected, eight were in men and nine were in persons over 45 years of age. Detection rates for farmers by age and sex were estimated using published data (Table 4).

This project showed that screening for bladder cancer is feasible in a rural Egyptian context. As many of the cases were detected at an early stage, it is implied that the screening may be effective in reducing mortality. This aspect however was not part of the original research plan and was not proved. Furthermore, the sample size was too small to have had any chance of detecting even a 50% reduction in mortality.

The urine samples were classified into five categories according to degree of "atypia" found: none, mild, moderate, marked or positive for carcinoma. All cases classified as moderate or marked atypia or positive for carcinoma underwent complete urological evaluation. Of all the urine samples examined, 1.4% were classified as moderate or marked atypia; thus approximately 125 patients were investigated to identify the 10 bladder cancers. Mild atypia was found in 9.0% of the screened subjects, i.e. approximately 790 people.

Some three years later 64 males and 36 females with moderate or marked atypia at first examination were rescreened: two of the men were diagnosed with carcinoma. At the same time, 1243 other male and female farmers over 20 years of age were also screened: no further cases of bladder carcinoma were found (unpublished Egyptian-NCI data).

As a continuation of the above studies, the following study is suggested for further assessment of bladder cancer screening by urine cytology.

##### Proposed study

- (i) Identification of all bladder cancer cases that have occurred in the Dakahliya Cytology Project population since the original study.
- (ii) Screening of the 8744 persons originally screened (see Table 3): i.e. all persons with previously recorded stypia of any degree, all farmers over 40 years of age, and 50% of the other remaining persons.

### Rationale

(i) This proposed study will make it possible to calculate the true incidence of bladder cancer in the Dakahliya Cytology Project population classified by age, sex, occupation and urine cytology result.

The published results from the Dakahliya Cytology Project give no breakdown of the degree of atypia according to age or to sex and occupation (jointly), and such data are essential as background information for the above proposed study. These data will also provide valuable further information on urine cytology, and should be published. The results given in Tables 3 and 4 suggest that atypia of all degrees will be found most commonly in male farmers probably in the older age-groups.

If atypia is found to progress in individuals, then bladder cancers should be found to occur in those individuals with previous atypia and the risk should increase progressively with increasing degrees of atypia. If the relationship is sufficiently strong, then repeated screening could be restricted to those individuals with some degree of atypia at first examination. This would represent a major saving in costs.

(ii) Repeated screening of a sample of the previously screened population will make it possible to evaluate the nature of the progression and regression of atypia in an Egyptian rural population. This information will be most valuable in interpreting the results of part (i) of the above proposed study; in particular, it will allow an estimation of the need for multiple "initial" screens to establish bladder cancer risk categories.

The Dakahliya Cytology Project provides background information to assist in the designing of any new prospective studies in other endemic areas. Studies aimed at assessing mortality due to bladder cancer will ideally require a much larger screened population; in Dakahliya Cytology Project the screened population of 8744 is at the lower limit necessary to assess the risk of development of bladder cancer. Since bladder cancer rates due to S. haematobium may vary from one endemic country to another the available data may aid in determining an adequate sample size.

### 6. CONCLUSIONS

From the available data it may be concluded that the totality of evidence associating S. haematobium infection with bladder cancer is now more than sufficiently strong to assume its validity and to base a prevention programme on this assumption.

Future case-control and population-based studies which take into account the limitations of past studies are feasible and should be encouraged.

While chemotherapy-based schistosomiasis control programmes can be expected to have an impact on bladder cancer rates, information concerning these rates will probably have to be derived from long-term analysis of national cancer registry data.

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TABLE 1. HISTOLOGY OF BLADDER CARCINOMAS IN SURVEYS  
 CARRIED OUT ON THE AFRICAN CONTINENT

Reference	Country	Histology			Total
		Squamous	Transitional	Other	
El-Bolkainy et al. (7)	Egypt	68% (152)	24% (54)	8% (19)	225
Nasr et al. (20)	Egypt	62% (185)	33% (100)	5% (14)	299
Lucas (16)	Malawi	83% (297)	6% (23)	11% (40)	360
Prates & Gillman (21)	Mozambique	59% (59)	21% (21)	20% (20)	100
Prates & Torres (22)	Mozambique	67% (65)	1% (1)	32% (31)	97
Hinder & Schmaman (12)	South Africa	29% (22)	56% (43)	16% (12)	77
Houston (13)	Zimbabwe	63% (27)	12% (5)	26% (11)	43
Gelfand et al. (11)	Zimbabwe	70% (23)	18% (6)	12% (4)	33
Malik et al. (17)	Sudan	40% (101)	48% (122)	13% (32)	255
Anthony (1)	Uganda	54% (75)	14% (19)	32% (44)	138
Dodge (6)	Uganda	38% (26)	45% (31)	17% (12)	69
Bhagwandeem (2)	Zambia	75% (163)	10% (21)	15% (33)	217
Elem & Purohit (10)	Zambia	72% (36)	18% (9)	10% (5)	50

TABLE 2. EVIDENCE OF HISTORY OF *S. HAEMATOBIIUM* INFECTION IN BLADDER CARCINOMA CASES AND CONTROLS

Reference	Country	Bladder carcinoma cases				Controls	Evidence of infection <sup>a</sup>	Controls
		Total	Squamous	Transitional	Other			
Mustacchi & Shimkin (19)	Egypt	17% (8/48)	---	---	---	10% (96/940)	Eggs in first urine sample	Age, sex, rural-urban adjusted hospital patients
Lucas (16)	Malawi	68% (246/360)	70% (208/297)	39% (9/23)	73% (29/40)	---	Eggs in hist. sections	---
Prates & Gillman (21)	Mozambique	33% (33/100)	56% (33/59)	0% (0/21)	0% (0/20)	61% (113/185)	Eggs in hist. sections	Autopsies aged 40+ years
Hinder & Schuman (12)	South Africa	35% (27/77)	68% (15/22)	19% (8/43)	33% (4/12)	16% (9/57)	Eggs in hist. sections	Male autopsies aged 15+ years
Houston (13)	Zimbabwe	35% (15/43)	30% (8/27)	60% (3/5)	36% (4/11)	---	Eggs in hist. sections	---
Gelfand et al. (11)	Zimbabwe	48% (16/33)	52% (12/23)	33% (2/6)	50% (2/4)	6% (2/33)	Calcifications (X-ray)	Age, sex matched hospital patients
Malik et al. (17)	Sudan	20% (51/255)	44% (44/101)	3% (4/122)	9% (3/32)	---	Eggs in hist. sections	---
Anthony (1)	Uganda	0% (0/138)	0% (0/75)	0% (0/19)	0% (0/44)	---	Eggs in hist. sections	---
Dodge (6)	Uganda	7% (5/69)	19% (5/26)	0% (0/31)	0% (0/12)	---	Eggs in hist. sections	---
Bhagwandeem (2)	Zambia	65% (141/217)	71% (116/163)	52% (11/21)	42% (14/33)	---	Eggs in hist. sections	---
Blum & Purohit (10)	Zambia	94% (47/50)	---	---	---	40% (20/50)	Eggs in (digested) bladder	Age, sex matched autopsies
		42% (21/50)	---	---	---	8% (4/50)	Calcifications (X-ray) by 'calculation'	- many accident victims

<sup>a</sup> hist. = histological.

TABLE 3. DISTRIBUTION OF RISK GROUPS AMONG THE STUDY, ELIGIBLE AND SCREENED POPULATION IN THE DAKAHLIYA CYTOLOGY PROJECT, EGYPT<sup>a</sup>

	Total No. individuals	Low risk		High risk
		(A) Persons 5-20 years old	(B) Nonfarmers 21+ years old	Farmers 21+ years old
Study population	30 614	15 699	9 113	5 802
Population eligible for screening	10 508	1 274	3 432	5 802
Population actually screened	8 744	1 112	2 863	4 769
Bladder cancer cases detected (rate/1000)	10 (1.1)	0 (0.0)	0 (0.0)	10 (2.1)

<sup>a</sup> Data from El-Bolkainy & Chu. (8)

TABLE 4. ESTIMATED DISTRIBUTION OF FARMERS BY AGE AND SEX, AND ESTIMATED BLADDER CANCER DETECTION RATES IN THE DAKAHLIYA CYTOLOGY PROJECT, EGYPT<sup>a</sup>

Age (in years)	Males			Females			Total		
	P	C	R	P	C	R	P	C	R
	20-44	1 200	1	0.8	1 596	0	0.0	2 796	1
45+	1 098	7	6.4	875	2	2.3	1 973	9	4.6
20+	2 298	8	3.5	2 471	2	0.8	4 769	10	2.1

P = population

C = bladder cancer cases

R = bladder cancer cases per 1000 population

<sup>a</sup> Data from El-Bolkainy & Chu. (8)