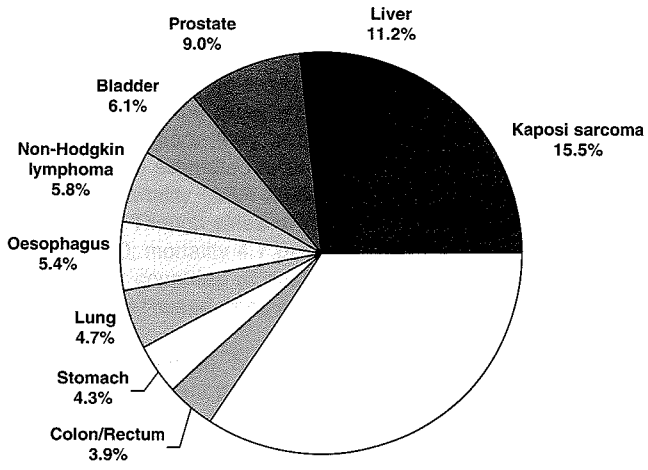
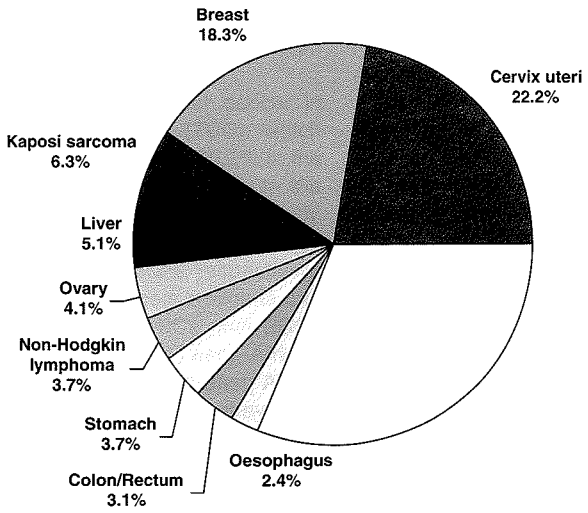
4. Cancer by site

MALES: 283,000 cases



FEMALES: 299,000 cases



Estimated incident cases in 2002
(GLOBOCAN 2002, in preparation)

4.1 Bladder cancer

Introduction

Worldwide, an estimated 336 000 cancers of the urinary bladder occur each year (about 3.3% of all new cancers). More than one third of these occur in the populations of Europe and North America. In Africa, there were an estimated 26 000 new cases in 2000 (4.1% of cancers), with a considerable predominance in men (20 000 cases, 6.7%) over women (6000 cases, 1.9%).

Descriptive epidemiology in Africa

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with data from Europe and North America for comparison. Table 2 shows incidence data from time periods in the 1960s and 1970s. The area of the world with the highest rates of bladder cancer mortality (in both sexes) and incidence (in men) is north Africa. Although the rates are relatively high in most countries of that region, they are particularly striking in Egypt, where, in men, the estimated rates of incidence (ASR 37.1 per 100 000) and mortality (ASR 20.8 per 100 000) are extremely high (Figure 1). Though rates are high in women too (incidence 8.6 per 100 000; mortality 4.7 per 100 000), they are similar to those in some countries of east Africa (Malawi, Zambia, Zimbabwe). Moderately raised rates are observed also in west Africa (Mali, Niger).

Comparability of statistics on the incidence of bladder cancer between populations is limited due to different practices concerning cystoscopy, biopsy of lesions, the extent of histological examination of biopsy material, and the classification of malignant, non-invasive tumours. These problems are likely to be less important in most of Africa, since an incident case almost always implies a frankly invasive, relatively advanced tumour.

In the United States, the incidence in the white population is higher than in blacks – about double among men and 50% greater among women (Table 1). It is unlikely that this is due to differences in exposure to environmental carcinogens, and explanations based upon differential susceptibility have been proposed (see Genetic Polymorphisms, below).

The most common histological type of bladder cancer in western countries is transitional cell carcinoma (TCC), which comprises 89.6% of cancers in England and Wales, 95.2% in the Netherlands and 94.6% in France (Parkin *et al.*, 2002). In the United States, the differences in histology by race are small, with, whites having 94.5% TCCs and 1.3% squamous cell carcinomas (SCCs), while the proportions are 87.8% and 3.2%, respectively, in blacks. In Africa, the majority of bladder cancers in Algeria and Tunisia (high-risk countries; see Table 1) are TCCs, with SCCs comprising less than 5% (Table 3). In some west African countries (Mali, Niger), and in east and south-east Africa (Zimbabwe, Malawi, Tanzania), SCCs predominate, as they do in Egypt (see Chapter 3.1.2). In South Africa, there are marked differences in histology between blacks (36% SCC, 41% TCC) and whites (2% SCC, 94% TCC). Similar findings with respect to black–white differences in proportions of the different histological types of bladder cancer have been reported from clinical series, for example in the Durban hospitals (Groeneveld *et al.*, 1996). These observations (as well as clinical features such as sex ratio, mean age at diagnosis and stage) relate to the prevalence of infection with *Schistosoma haematobium* (see below).

Migrants to France from Algeria and from west Africa (both areas of relatively high incidence of bladder cancer) appear to retain rates higher than the local-born population of France (Bouchardy *et al.*, 1995, 1996).

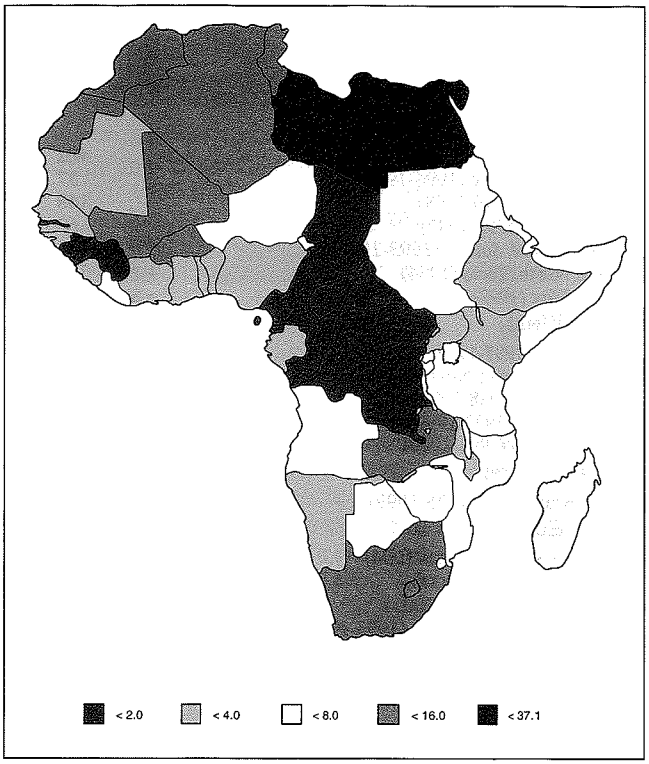


Figure 1. Incidence of bladder cancer: ASR (world) – Males

Thomas & Onyemenen (1995) reviewed cases of bladder cancer in Ibadan, Nigeria, over an 11-year period (1979–89) and noted an overall increase in the frequency of TCC (50%) relative to SCC of the bladder (although SCC remained the most common histological type under age 50 years). They speculated upon the roles of increasing urbanization, tobacco smoking and industrial exposures in the apparent increase in TCC.

Risk factors

Tobacco smoking

In 1986, IARC concluded, on the basis of many cohort and case–control studies, conducted in various parts of the world, that tobacco smoking (particularly of cigarettes) is an important cause of bladder cancer. The relationships of risk with duration and intensity of smoking are similar to those for lung cancer, although the risks are lower. Pipe and/or cigar smoking probably also increase the risk of bladder cancer, but at lower levels than the risk due to cigarette smoking. There have been relatively few studies in Africa, however.

Makhyoun (1974) studied 365 men with bladder cancer and age-matched hospital controls without cancer in Egypt (1966–71). 278 of the cases had previous urinary bilharziasis, and so the controls for these cases were matched for bilharziasis also. The odds ratio (OR) associated with cigarette smoking can be calculated as 3.3 (95% CI 1.2–9.3) for heavy smokers without bilharziasis, and 1.4 (95% CI 0.7–3.1) for those with bilharziasis.

In a study based upon data from the Bulawayo cancer registry (1963–72), Vizcaino *et al.* (1994) compared smoking history of 697 bladder cancer cases (71.2% of which were SCC) with cases of cancer not associated with tobacco smoking (i.e., excluding oesophagus, larynx and lung). A smoking history was available for 57% of cases, 55% controls. Adjusted for infection with *S. haematobium* (and other variables), there was only a

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Bladder (C67)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	402	7.3	**10.8**	0.61	86	1.6	**2.3**	0.12
Algeria, Constantine (1994-1997)	37	2.4	**4.6**	0.23	6	0.4	**0.7**	0.05
Algeria, Oran (1996-1998)	148	8.4	**13.6**	0.70	15	0.9	**1.3**	0.07
Algeria, Setif (1993-1997)	62	2.1	**4.0**	0.29	2	0.1	**0.1**	0.02
Tunisia, Centre, Sousse (1993-1997)	146	12.7	**17.4**	0.83	12	1.1	**1.4**	0.05
Tunisia, North, Tunis (1994)	204	9.4	**12.3**	0.64	15	0.7	**1.0**	0.05
Tunisia, Sfax (1997)	47	12.0	**14.9**	0.89	13	3.4	**4.6**	0.41
Africa, West								
The Gambia (1997-1998)	6	0.6	**1.2**	0.09	3	0.3	**0.5**	0.01
Guinea, Conakry (1996-1999)	12	0.5	**1.5**	0.10	13	0.6	**1.9**	0.13
Mali, Bamako (1988-1997)	160	4.1	**9.6**	0.57	61	1.7	**3.8**	0.31
Niger, Niamey (1993-1999)	30	1.6	**4.8**	0.35	25	1.4	**3.7**	0.23
Nigeria, Ibadan (1998-1999)	16	1.1	**2.3**	0.17	3	0.2	**0.3**	0.03
Africa, Central								
Congo, Brazzaville (1996-1999)	3	0.2	**0.4**	0.04	3	0.2	**0.3**	0.03
Africa, East								
France, La Reunion (1988-1994)	154	7.3	**10.2**	0.48	35	1.6	**1.7**	0.05
Kenya, Eldoret (1998-2000)	10	1.1	**2.9**	0.19	5	0.5	**1.4**	0.04
Malawi, Blantyre (2000-2001)	16	1.8	**3.4**	0.26	16	1.8	**4.1**	0.35
Uganda, Kyadondo County (1993-1997)	17	0.6	**2.9**	0.09	8	0.3	**1.1**	0.05
Zimbabwe, Harare: African (1990-1993)	95	4.0	**12.5**	0.53	54	2.5	**10.5**	0.62
Zimbabwe, Harare: African (1994-1997)	71	2.5	**7.1**	0.40	62	2.3	**8.5**	0.56
Zimbabwe, Harare: European (1990-1997)	74	48.4	**25.6**	1.06	32	19.0	**9.1**	0.45
Africa, South								
Namibia (1995-1998)	60	1.9	**3.4**	0.18	20	0.6	**0.9**	0.05
South Africa: Black (1989-1992)	545	1.0	**1.8**	0.10	509	0.9	**1.3**	0.10
South Africa: Indian (1989-1992)	88	4.5	**7.7**	0.44	37	1.9	**2.7**	0.18
South Africa: Mixed race (1989-1992)	245	3.8	**8.1**	0.37	69	1.0	**1.7**	0.10
South Africa: White (1989-1992)	2810	27.9	**25.8**	1.19	870	8.5	**6.5**	0.34
South Africa, Transkei, Umtata (1996-1998)	2	0.6	**0.9**	0.07	-	-	**-**	-
South Africa, Transkei, 4 districts (1996-1998)	2	0.3	**0.4**	-	1	0.1	**0.1**	0.02
Swaziland (1996-1999)	44	2.5	**5.7**	0.28	18	0.9	**1.5**	0.12
Europe/USA								
USA, SEER: White (1993-1997)	16059	33.0	**24.3**	1.01	5688	11.3	**6.7**	0.31
USA, SEER: Black (1993-1997)	683	10.2	**11.7**	0.50	377	5.1	**4.6**	0.17
France, 8 registries (1993-1997)	3638	26.5	**18.0**	0.78	792	5.5	**2.7**	0.09
The Netherlands (1993-1997)	8606	22.5	**15.8**	0.57	2500	6.4	**3.4**	0.14
UK, England (1993-1997)	39077	32.6	**19.8**	0.76	15519	12.1	**5.7**	0.22

In italics: histopathology-based registries

Table 2. Incidence of bladder cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	1.2	1.3	4
Mozambique, Lourenço Marques	1956–60	17.5	14.2	1
Nigeria, Ibadan	1960–69	3.9	2.0	3
SA, Cape Province: Bantu	1956–59	*8.6*	*2.0*	2
SA, Cape Province: Coloured	1956–59	6.5	2.6	2
SA, Cape Province: White	1956–59	9.6	3.0	2
SA, Johannesburg, Bantu	1953–55	19.2	*9.9*	1
SA, Natal province: African	1964–66	3.6	*2.6*	2
SA, Natal province: Indian	1964–66	7.3	*5.1*	2
Uganda, Kyadondo	1954–60	7.0	1.5	1
Uganda, Kyadondo	1960–71	5.6	*0.9*	5
Zimbabwe, Bulawayo	1963–72	17.9	9.5	6

Italics: Rate based on less than 10 cases

Table 3. Percentage distribution of microscopically verified cases by histological type
Bladder (C67) - Both sexes

	Carcinoma					Sarcoma	Other	Unspecified	Number of cases	
	Squamous	Transl.	Adeno	Other	Unspec.				MV	Total
Algeria, Algiers	2.9	64.8	17.6	-	14.2	0.2	-	0.2	**415**	488
Algeria, Batna	7.7	46.2	23.1	-	-	-	-	23.1	**13**	19
Algeria, Constantine	18.2	66.7	3.0	-	9.1	-	-	3.0	**33**	43
Algeria, Oran	1.3	86.6	0.7	-	10.1	-	-	1.3	**149**	163
Algeria, Setif	3.6	12.7	78.2	-	1.8	-	-	3.6	**55**	64
Burkina Faso, Ouagadougou	20.0	40.0	20.0	-	-	-	-	20.0	**5**	23
Congo, Brazzaville	-	-	-	-	100.0	-	-	-	**1**	6
France, La Reunion	2.7	87.2	3.7	-	5.3	-	-	1.1	**187**	189
The Gambia	33.3	-	-	-	66.7	-	-	-	**3**	9
Guinea, Conakry	41.7	58.3	-	-	-	-	-	-	**12**	25
Kenya, Eldoret	14.3	71.4	-	-	14.3	-	-	-	**7**	15
Malawi, Blantyre	71.4	14.3	7.1	-	7.1	-	-	-	**14**	32
Mali, Bamako	71.0	22.6	3.2	-	3.2	-	-	-	**31**	221
Namibia	6.3	73.4	10.1	1.3	2.5	3.8	-	2.5	**79**	80
Niger, Niamey	46.2	38.5	-	-	15.4	-	-	-	**13**	55
Nigeria, Ibadan	14.3	64.3	14.3	-	-	7.1	-	-	**14**	19
Rwanda, Butare	-	80.0	-	-	-	-	-	20.0	**5**	7
South Africa: Black	36.3	40.5	3.5	0.3	6.3	2.2	0.4	10.5	**1054**	1054
South Africa: White	2.0	93.6	1.2	0.0	2.3	0.4	0.2	0.2	**3680**	3680
South Africa: Indian	4.0	80.8	-	-	7.2	0.8	-	7.2	**125**	125
South Africa: Mixed race	7.3	83.8	1.3	0.6	5.1	1.6	0.3	-	**314**	314
South Africa, Elim	40.0	40.0	10.0	-	10.0	-	-	-	**10**	17
South Africa, Transkei, Umtata	-	-	-	-	-	-	-	-	**-**	2
South Africa, Transkei, 4 districts	-	100.0	-	-	-	-	-	-	**1**	3
Swaziland	11.1	77.8	11.1	-	-	-	-	-	**9**	62
Tanzania, Dar Es Salaam	45.3	28.3	3.8	-	9.4	5.7	-	7.5	**53**	53
Tanzania, Kilimanjaro	10.0	60.0	25.0	-	-	5.0	-	-	**20**	26
Tunisia, Centre, Sousse	3.2	93.6	1.3	-	1.9	-	-	-	**157**	158
Tunisia, North, Tunis	3.2	90.8	0.9	0.5	3.2	0.5	-	0.9	**217**	219
Tunisia, Sfax	3.4	96.6	-	-	-	-	-	-	**59**	60
Uganda, Mbarara	-	-	-	-	-	-	-	-	**-**	2
Uganda, Kyadondo County	27.3	45.5	-	-	27.3	-	-	-	**11**	25
Zimbabwe, Harare: African	47.4	28.6	8.4	-	12.3	1.3	1.3	0.6	**154**	282
Zimbabwe, Harare: European	6.7	86.7	3.3	1.1	-	-	2.2	-	**90**	106

weak association (OR in males smoking 15 g tobacco per day relative to never-smokers was 1.4 (95% CI 0.9–2.3). For transitional cell/adenocarcinomas, the OR for this smoking category was 2.0 (95% CI 0.8–.3).

Bedwani *et al.* (1997) compared 151 male bladder cancer cases hospitalized in Alexandria, Egypt (67% TCC) with 157 male controls (hospitalized for diseases not related to smoking). After adjustment for various confounders (including age), the risk of bladder cancer in current smokers (relative to non-smokers) was 6.6 (95% CI 3.1–13.9) and in ex-smokers 4.4 (95% CI 1.7–11.3). There was a significant trend in risk with intensity and duration of smoking. The risk was greater for TCC (9.1) than for other histologies (4.4). There was a significant interaction with a history of schistosomiasis (obtained by questionnaire), but it appeared that risk of tobacco smoking was *lower* in subjects with such a history.

Occupational exposures

Various occupational categories are associated with increased risk of bladder cancer. These include workers with dyestuffs, aromatic amine manufacturing, rubber workers, leather workers, and painters. There do not appear to have been any studies of such factors in Africa (other than of agricultural workers in relation to exposure to schistosomiasis; see below).

Genetic susceptibility

Genetic polymorphism of metabolic enzymes seems to influence the risk of bladder cancer. These enzymes are involved in bio-activation of carcinogens or in their detoxification and excretion.

N-Acetyltransferase (NAT) is involved in detoxification of some of the aromatic amines that are carcinogenic to the bladder. The NAT2 genotype is characterized by the rate of acetylation of certain marker drugs such as isoniazid or caffeine (the phenotypic distinction by acetylator status preceded identification of the genotype). Several studies have suggested a link between slow acetylator status (NAT2 slow polymorphisms) and bladder cancer (with a meta-analysis of 16 studies giving an overall OR of 1.4 (Vineis *et al.*, 1999)).It is possible that different prevalences of this polymorphism might explain some of the difference in bladder cancer risk between ethnic groups. In Los Angeles, (Yu *et al.*, 1994) noted that prevalence of tobacco smoking did not differ much between whites, Asians, and blacks, though bladder cancer incidence certainly does. The prevalence of the slow-acetylator phenotype followed the risk of bladder cancer. Similarly, the levels of haemoglobin adducts of 3-aminobiphenyl were higher in white, than black, than Asians, at all levels of smoking. This difference is a consequence of the different prevalence of slow acetylators.

Glutathione S-transferase 1 (GSTM1) is involved in conjugation of several reactive chemicals, including arylamines and nitrosamines. The null polymorphism has been associated with risk of bladder cancer in several studies. In Egypt, Anwar *et al.* (1996) compared 22 bladder cancer cases (19 with a history of schistosomiasis) and 21 control subjects, matched for age and smoking history. The OR associated with the null genotype of GSTM1 was 6.97 (95% CI 1.34–45.69). Lafuente *et al.* (1996) conducted a case–control study comparing 80 hospitalized cases of bladder SCC with 70 controls drawn from the hospital staff in Assiut, Egypt. Among the male subjects, they found a risk for the null genotype of GSTM1 of 4.80 (95% CI 1.06–21.77) among smokers, but not for all subjects (OR = 0.72; 95% CI 0.26–1.97). Abdel-Rahman *et al.* (1998) investigated the role of GSTM1 and GSTT1 as potential risk factors for bladder cancer among 37 Egyptian cases (26 TCC and 11 SCC), compared with 34 matched controls. Eighteen of the cases were infected with *Schistosoma*. The GSTM1 null genotype was associated with increased risk of bladder cancer (OR = 2.99; 95% CI 1.0–9.0). The GSTT1 polymorphism was also associated with risk of bladder cancer, and the risk for individuals with a null genotype for both GSTM1 and GSTT1 was 9.9 (95% CI 1.8–46.9), with a significantly higher risk for SCC (OR = 14.6) than TCC (OR = 8.5).

The IARC meta-analysis of 11 studies (Vineis *et al.*, 1999) gave an OR of 1.57. Yu *et al.* (1995) found that the null genotype of GSTM1 combined with the slow acetylator phenotype of NAT2 resulted in higher levels of 3- and 4-aminobiphenyl-haemoglobin adducts than did lower-risk profiles (rapid acelylator and/or at least one functional GSTM1 gene allele). The highest risk profile was seen in 27% of whites, 15% of blacks and 3% of Asians.

CYP2D6 polymorphism has been shown to be associated with bladder cancer in some studies, although the overall OR in the IARC meta-analysis (Vineis *et al.*, 1999) was 1.12 (95%CI 0.77–1.64). The case–control study of Anwar *et al.* (1996) in Egypt found an OR of 2.36 (95% CI 0.68–9.90) for extensive metabolizers (EM), relative to poor metabolizer (PM) genotypes. There was a significant interaction between CYP2D6 EM and GSTM1 null polymorphisms, with the OR for this combination (relative to PM/GSTM1+/+ genotypes) being 8.4 (95% CI 1.26–56.03).

Schistosomiasis and bladder cancer

Schistosomes are trematode worms that live in the bloodstream of human beings and animals. Three species (*Schistosoma haematobium*, *S. mansoni* and *S. japonicum*) account for the majority of human infections. People are infected by exposure to water containing the infective larvae (cercariae). The worms mature in the veins that drain the bladder (*S. haematobium*) or in the intestine (other species). The adults do not multiply in the body but live there for several years, producing eggs. Some eggs leave the body in the urine or faeces and hatch in water to liberate the miracidium larva, which infects certain types of freshwater snail. Within the snail, the parasites multiply asexually to produce free-swimming cercaria larvae, which infect people by skin penetration. Eggs remaining in the human body are trapped in the tissues, where they elicit hypersensitivity granulomas that cause disease in the urogenital system (*S. haematobium*) or in the liver and intestines (other species).

The diagnosis of infection with *S. haematobium* infection is based on a history of haematuria, observation of gross haematuria, detection of haematuria by chemical reagent strips or detection of eggs in urine by microscopy. Infections can be quantified by egg counts in urine.The available immunodiagnostic tests are useful for detecting light infections.

The geographical distribution of the schistosomiasis roughly corresponds to the distribution of susceptible snail hosts, which are present in many tropical and subtropical regions of Africa (Figure 2, Table 4).

Within endemic areas, transmission may be focal and can be localized to specific water sources. The intensity and frequency of exposure to contaminated fresh water determine the occurrence of the heavy infection that leads to disease. Prevalence and intensity of infection are usually correlated in endemic areas and especially among children. Sex differences in intensity of infection have been linked to differences in exposure.

Treatment with safe, effective antischistosomal drugs (i) results in a high rate of resolution of infection, (ii) prevents development of disease in people with heavy infection, (iii) arrests progression of existing severe disease and (iv) reverses some disease manifestations, particularly in children. Control of schistosomiasis has been achieved in some countries through combined approaches to intervention, including health education, improved water supplies and sanitation, environmental management, snail control and treatment.

The evidence linking infection with *S. haematobium* with bladder cancer has been extensively reviewed (Cheever, 1978; IARC, 1994; Mostafa *et al.*, 1999). There are essentially three lines of evidence:

- Clinical observations that the two diseases appear to frequently co-exist in the same individual, and that the bladder cancers tend to be of squamous cell origin, rather than transitional cell carcinomas.
- Descriptive studies showing a correlation between the two diseases in different populations.
- Case–control studies, comparing infection with *S. haematobium* in bladder cancer cases and control subjects.

Clinical series

The first suggestion of a link between schistosomiasis and cancer came from careful assessment of clinical and pathological observations (Goebel, 1905; Ferguson, 1911). Subsequent large series of cases of urinary bladder cancer in African countries have been reported in association with evidence of *S. haematobium* infection:

- Angola (da Silva Lopes, 1984)
- Egypt (Mohamed, 1954; Mustacchi & Shimkin, 1958; El-Gazayerli & Khalil, 1959; Hashem *et al.*, 1961; Aboul Nasr *et al.*, 1962; Makhyoun *et al.*, 1971; El-Bolkainy *et al.*, 1972; Khafagy *et al.*,1972; El-Sebai, 1980; El-Bolkainy *et al.*,1981; Christie *et al.*, 1986; Tawfik, 1988; Fukushima *et al.*,1989)
- Kenya (Anjarwalla, 1971; Bowry, 1975)
- Malawi (Lucas, 1982b)
- Mozambique (Prates & Gillman, 1959; Gillman & Prates, 1962; Ebert, 1987)
- Nigeria (Attah & Nkposong, 1976),
- Senegal (Quenum, 1967)
- South Africa (Transvaal) (Higginson & Oettlé, 1962; Hinder & Schmaman, 1969; Kisner, 1973); (Natal) (Cooppan *et al.* 1984; Groenveld *et al.* 1996)
- Sudan (Malik *et al.*, 1975; Sharfi *et al.*, 1992)
- Tanzania (Kitinya *et al.*, 1986)
- Uganda (Dodge, 1962)
- Zambia (Bhagwandeen, 1976; Elem & Purohit, 1983, Elem & Patil, 1991)
- Zimbabwe (Houston, 1964; Gelfand *et al.*, 1967; Thomas *et al.*, 1990)

The case descriptions have repeatedly emphasized the preponderance of squamous-cell urinary bladder tumours among cases with evidence of schistosomal infection, their rather different distribution within the bladder (notably the rarity of occurrence in the trigone) in comparison with bladder tumours in developed countries, and the prevalence of metaplastic changes in conjunction with evidence of infection (da Silva Lopes, 1984). Cases with evidence of a link to *S. haematobium* infection are consistently described as being younger than other cases.

Correlation studies

Some studies have attempted to correlated the presence or intensity of infection with *S. haematobium* with the geographical occurrence of bladder cancer, and squamous cell tumours in particular (Table 5).

The table also draws attention to other associations, for example, between the proportion of bladder cancers in the population that are squamous-cell tumours and the proportion of cancerous bladder specimens from that population which contain evidence of past schistosomal infection in the form of eggs or egg remnants (Lucas, 1982a). In the Nile delta, 99% of the bladder cancers occurring in high-risk male agricultural workers (*fellahin*) were associated with histological evidence of *S. haematobium* infection, whereas only 52% of the cases occurring in men with lower-risk occupations showed such evidence (Makhyoun *et al.*, 1971). Men do most of the agricultural work in the Nile Delta, and the ratio of male to female cases of urinary bladder cancer with histological evidence of past infection reached as high as 12:1 (Makhyoun *et al.*, 1971), while the sex ratio among those without such evidence approximated the 4:1 ratio seen in the United Kingdom (Prates & Gillman, 1959). In contrast, in Mozambique (Prates, 1963) and adjacent regions of the Transvaal in South Africa (Keen & Fripp, 1980), where women do most of the agricultural labour and are therefore more commonly infected, the sex ratios were reversed to 1:1.1 or even 1:2, even though ratios of 2:1 prevailed among cases referred from nearby areas. The sex ratio of bladder cancer cases has also been linked to the histologically measured intensity of infection in tumour specimens, and ranged from 8.7:1 in heavily infected people, to 4:1 in those who were lightly infected, to 2:1 in those without eggs in Egypt (Tawfik, 1988).

El-Bolkainy *et al.* (1982) described 10 cases of bladder cancer, detected during cytological screening of urinary bladder cancer conducted from 1976 to 1979 in the Nile Delta area, where *S. haematobium* infection is highly endemic. All the 10 cases of histologically confirmed bladder cancer appeared among the 4769 agricultural workers screened, who were presumed to have a higher prevalence of infection than the 1112 persons with other occupations.

In a community in Angola, where both males and females work in agriculture, the minimal age of infection with *S. haematobium* was 11 years. The mean age of patients with urinary bladder carcinomas associated with schistosomiasis was 44 years. The sex ratio was 1.6:1 for bladder carcinoma associated with schistosomiasis and 3.2:1 for bladder carcinoma not associated with schistosomal disease ($p \sim 0.05$) (da Silva Lopes, 1984).

It should be noted that in Uganda, although squamous-cell carcinomas of the urinary bladder are commoner than in Europe or North America, there is no evident association with prevalence of *S. haematobium* (Anthony, 1974).

Because of the lack of population-based cancer registration, the secular trends in incidence of SCC- or TCC of the urinary bladder have not been formally evaluated. In an area of the Nile Delta where the prevalence of *S. haematobium* infection was brought from a level of 60% in 1968 to 10% in 1988, no impact upon the rate of bladder cancer was clinically evident at the end of that period, although the mean age at diagnosis had increased (Tawfik, 1988). Some case series suggest that TCC has become more common relative to SCC in Egypt (Koraitim *et al.*, 1995) and elsewhere (Thomas & Onyemenen, 1995).

Case–control studies

Five case–control studies have been reported in which controls were properly matched to the cases with respect to age and sex. Table 6 summarizes these studies.

Mustacchi and Shimkin (1958) identified 48 male and 7 female hospitalized patients with urinary bladder cancer in the Egyptian Nile Delta city of Tanta among 1472 consecutive admissions to the hospital. All patients were evaluated for the presence of *S. haematobium* eggs in a urine sample taken at admission, and any subsequent evidence of *S. haematobium* infection. After adjustment for age, sex and urban or rural origin, ORs of 2.1 ($p = 0.04$) were seen for the finding of eggs at the time of admission and 2.2 ($p < 0.01$) for any subsequent evidence of schistosomal infection.

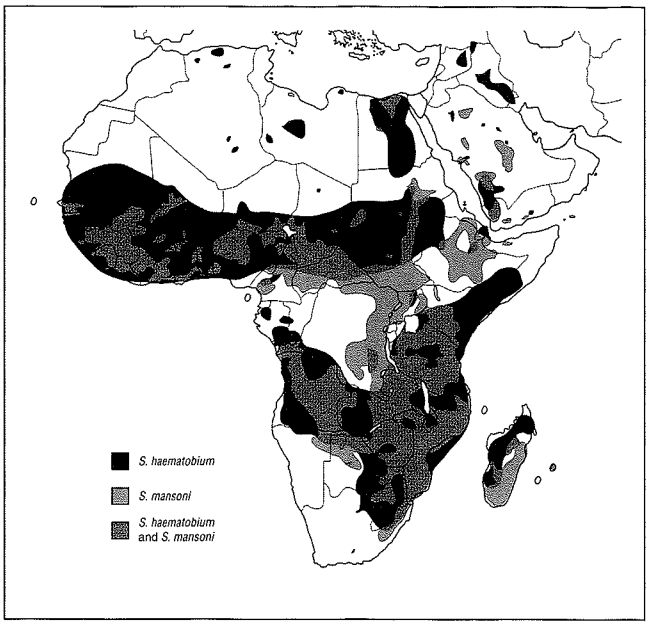


Figure 2. Geographical distribution of schistosomiasis in Africa

In Harare, Zimbabwe, Gelfand *et al.* (1967) compared 33 patients with urinary bladder cancer with other hospital patients who had been 'submitted to similar investigation' and were matched on age, sex and race. Comparisons were made on the basis of the results of pelvic X-rays (33 pairs) and rectal biopsies (31 pairs). Among the 16 pairs discordant for calcified eggs identified by X-ray, the case was positive in 15, giving an OR of 15 (95% CI 2.0–114); among the 15 pairs discordant for the results of rectal biopsy, the case was positive in 13, giving an OR of 6.5 (95% CI 1.5–29). The diagnoses of disease in the controls were not described, and no adjustment was made for differences in smoking habits or place of origin.

In Zambia, Elem and Purohit (1983) compared the bladders of 50 patients who had died of urinary bladder cancer with bladders from age- and sex-matched cadavers (mostly trauma victims matched on age and sex to the decedent) by means of X-ray examination and digestion of tissues away from the eggs they contained. The bladders of the cases were 3.8 (95% CI 1.4–10) times as likely to show schistosomiasis by X-ray and 14 (95% CI 4.6–43) times as likely to contain *S. haematobium* eggs.

In the Bulawayo region of Zimbabwe, the cancer registrar interviewed cancer cases between 1963 and 1977, obtaining information on past history of clinical schistosomiasis ('bilharzia' or 'blood in the urine'), as well as other exposures (Vizcaino *et al.*, 1994). Some difference in the availability of information about past schistosomiasis is evident between cases of urinary bladder cancer (61%) and cases of cancer of other types (50%). The exposures of 412 patients with bladder cancer were compared with those of 4483 other cancer patients, excluding those with cancers known to be linked to smoking. The occurrence of bladder cancer was associated with place of origin and a lower level of education. For a history of schistosomiasis in men, the OR (relative to no such history and adjusted for age, tobacco use, province of origin, education and occupation) was 3.9 (95% CI 2.9–5.2), and 5.7 (95% CI 3.7–8.7) in women. The association was rather stronger for squamous-cell carcinomas than transitional-cell/adenocarcinomas, especially in women.

Table 4. Geographical distribution of schistosomiasis by species

Country	*S. haematobium*	*S. mansoni*	*S. intercalatum*
Algeria	+		
Angola	+	+	
Benin	+	+	
Botswana	+	+	
Burkina Faso	+	+	
Burundi		+	
Cameroon	+	+	+
Central African Republic	+	+	+ [a]
Chad	+	+	+ [a]
Congo	+	+	+ [a]
Côte d'Ivoire	+	+	
Equatorial Guinea			+
Ethiopia	+	+	
Gabon	+	+	+
Gambia	+	+	
Ghana	+	+	
Guinea	+	+	
Guinea-Bissau	+	+	
Kenya	+	+	
Liberia	+	+	
Madagascar	+	+	
Malawi	+	+	
Mali	+	+	+ [a]
Mauritania	+		
Mauritius	+		
Mozambique	+	+	
Namibia	+	+	
Niger	+	+	
Nigeria	+	+	+ [a]
Rwanda	+		
Sao Tome and Principe	+ [a]		+
Senegal	+	+	
Sierra Leone	+	+	
South Africa	+	+	
Swaziland	+	+	
Togo	+	+	
Uganda	+	+	
United Republic of Tanzania	+	+	
Zaire	+	+	+
Zambia	+	+	
Zimbabwe	+	+	

Source: IARC (1994)

[a] Confirmation required

Table 5. Descriptive studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Outcome index	Exposure index	Geographical correlations	Secular or occupational correlations	Correlated sex ratios or age distributions
Anjarwalla (1971)	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Patients from coastal area, where schistosomiasis is common	–	–
Makhyoun *et al.* (1971)[a]	Egypt, Nile Delta University hospital	Proportional frequencies	Common knowledge	–	Cases in male fellahin: 99% histologically *S. haematobium* egg-positive Cases in men in other occupations: 52% positive	Exceptionally higher sex ratio for bilharzial cases (11.8:1) than for non-bilharzial cases (4.8:1).
Anthony (1974)	Uganda, referral hospital -	Proportional frequencies	Frequency of schistosomiasis diagnoses	Bladder cancer, including squamous-cell cancers, unrelated to small foci of schistosomiasis	–	–
Bowry (1975)[a]	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Cancer foci on coast and near Lake Victoria. both known foci of schistosomiasis	–	–
Malik *et al.* (1975)[a]	Sudan, referral hospital	Proportional frequencies	Ministry of Health records of 'highest endemicity'	Correspondence between frequency of bladder cancer and endemicity by province	–	–
Keen & Fripp (1980)[a]	South Africa (Transvaal)	Frequencies identified in regional surveys	None explicit	–	–	Wide variations in sex ratio (from 2:1 to 1:2) according to region and tribe
Lucas (1982a)[a]	Africa	Proportional frequencies	Histological identification of *et al.* eggs in bladder specimens	Geographical distribution of percentage of histologically *S. haematobium* egg-positive tumours correlated directly with percentage of all bladder cancers that are squamous-cell and inversely with the percentage that are transitional-cell tumours		
Kitinya *et al.* (1986)a	Tanzania referral hospital	Proportional frequencies	Known distribution - of snail vectors in relation to altitude	Low proportion of squamous-cell tumours and low prevalence of *S. haematobium* at high elevations near Mt Kilimanjaro	–	
Tawfik (1988)a	Egypt, referral hospital	Proportional frequencies	Histological identification of *et al.* eggs n bladder ispecimens; records of control programme	–	High bladder cancer proportional frequency despite 20 years of successful control efforts (prevalence reduced from 60 to 10% in one province)	High sex ratio correlated with documented intensity of infection. As period of successful control efforts lengthens, mean age of bladder cancer cases increases.
Thomas *et al.* (1990)	Zimbabwe, referral hospital	Proportional frequencies	National prevalence surveys among schoolchildren	Estimated bladder cancer incidence correlated with prevalence of *S. haematobium* infection ($r = 0.87$; $p < 0.01$). Ratio of squamous-cell to transitional-cell tumours linked to *S. haematobium* prevalence: 12:1 where prevalence was 67%, 2:1 where prevalence was 17%	–	Sex ratio for squamous-cell tumours, 1.0; for transitional-cell tumours, 2.9:1.

[a] Correlation not formally tested

Bedwani *et al.* (1998) reported on a case–control study in Alexandria, Egypt, of 190 bladder cancer cases and 186 hospitalized controls (with non-neoplastic, non-urinary tract conditions). Information on infection (and other exposures) was obtained by questionnaire. The OR, adjusted for age and sex, associated with a history of schistosomiasis was 1.8 (95% CI 1.2–2.9), or 1.7 (95% CI 1.0–2.9) after adjustment for other variables (including smoking and a history of other urinary infections). The OR increased with younger age at first infection, or with increasing time since first diagnosis. The paper gave no information on the histological type of bladder tumours included, although from another report of the same study (Bedwani *et al.*, 1997), only 18% of the 151 male cases were SCC.

Other comparative studies

Prates and Gillman (1959) compared 100 urinary bladder cancer cases in Maputo, Mozambique, with 185 "control" cases found at autopsy in people over 40 years of age (causes of death not described) with respect to the frequency of identification of *S. haematobium* eggs in relation to the histological type of bladder cancer. Eggs were found in 33 of the cases found at autopsy and in 61% of controls. Eggs were found in 56% of the 59 SCC patients but in none of the TCC patients. It is not possible to reconcile the figures of 61% infection rate in controls with the 0% (0/41) figure for non-SCC cases. In addition, the methods used to examine the biopsy and autopsy specimens were dissimilar.

Hinder and Schmaman (1969) compared the prevalence of histologically identified eggs in punch biopsy specimens from 79 patients with urinary bladder carcinoma in Johannesburg, South Africa, with the prevalence in two or more full-thickness biopsy specimens from 101 people over the age of 15 years who came to autopsy. Eggs were identified in 34.2% of the cases but in only 9.0% of the autopsied patients. The causes of death of the controls were not reported, and no adjustment was made for differences in specific age or place of origin. When cases were analysed by histological type, 19% of TCC and 68% of SCC contained eggs.

Mechanisms of carcinogenesis

Numerous explanations have been offered for the proposed association between schistosomiasis and human cancers.

Chronic irritation and inflammation with increased cell turnover provide opportunities for mutagenic events, genotoxic effects and activation of carcinogens through several mechanisms, including the production of nitric oxide by inflammatory cells (activated macrophages and neutrophils) (Rosin *et al.*, 1994a, b).

Alterered metabolism of mutagens may be responsible for genotoxic effects (Gentile, 1985, 1991; Gentile *et al.*, 1985). Quantitatively altered tryptophan metabolism in *S. haematobium*-infected patients results in higher concentrations of certain metabolites (e.g., indican, anthranilic acid glucuronide, 3-hydroxyanthranilic acid, L-kynurenine, 3-hydroxy-L-kynurenine and acetyl-L-kynurenine) in pooled urine (Abdel-Tawab *et al.*, 1966a, 1968b; Fripp & Keen, 1980). Some of these metabolites have been reported to be carcinogenic to the urinary bladder (Bryan, 1969).

Immunological changes have been suggested as playing a role (Raziuddin *et al.*, 1991, 1992, 1993; Gentile & Gentile, 1994).

Secondary bacterial infection may result in a variety of metabolic effects, and therefore may play an intermediary role in the genesis of squamous-cell carcinoma. Secondary bacterial infection of *Schistosoma*-infected bladders is a well documented event (Lehman et al, 1973; Laughlin *et al.*, 1978; Hill, 1979; El-Aaser *et al.*, 1982; Hicks *et al.*, 1982).

Nitrate, nitrite and N-nitroso compounds are detected in the urine of *S. haematobium*-infected patients (Hicks *et al.*, 1977, 1978, 1982; Tricker *et al.*, 1989, 1991; Abdel Mohsen *et al.*, 1999). Nitrosamines are formed by nitrosation of secondary amines with nitrites by bacterial catalysis (or via urinary phenol catalysis); they may be carcinogenic to bladder mucosa. Mostafa *et al.* (1994) also demonstrated the presence of nitrates and nitrites in the saliva and increased concentrations of *N*-nitroso compounds in the urine of *et al.*-infected people who were not on controlled diets. The high levels of urinary nitrosamines may also be explained by macrophage accumulation as a consequence of chronic inflammation, as noted above. The etiological significance of these findings is, however, unclear in the light of the finding that urine from schistosomiasis patients is not mutagenic (Everson *et al.*, 1983).

Nitrosamines have been detected in the urine of paraplegic patients with urinary tract infections due to urinary stasis (Hicks *et al.*, 1977, 1978). On follow-up of 6744 paraplegic patients in the United Kingdom, 25 urinary bladder cancers were identified (El Masri & Fellows, 1981). On the basis of information for an otherwise comparable population, 1.6% of these would have been expected to be of squamous origin, whereas 44% actually were (estimated relative risk = 49; 95% CI 20–119). In Uganda, squamous-cell bladder cancers are commonly seen in the absence of *S. haematobium* infection but in the presence of other urinary tract abnormalities (Anthony, 1974).

The findings with respect to enhanced risk in subjects with schistosomiasis-associated cancers and the null genotype of GSTM1 (see above) suggest that this enzyme may play a role either by preventing formation or in detoxication of *N*-nitroso compounds.

Viruses: Cooper *et al.* (1997) found no evidence of infection with human papillomavirus types 6, 11, 16, 18, 31 or 33 in specimens of 25 squamous-cell carcinomas associated with schistosomiasis in South Africa.

Elevated β-glucuronidase levels in schistosome-infected subjects could increase the release of carcinogenic metabolites from their glucuronides. No data are available at present to confirm this association, although schistosome-infected humans are known to have elevated β-glucuronidase activity in urine (Fripp, 1960; Abdul-Fadl & Metwalli, 1963; Fripp, 1965; Abdel-Tawab *et al.*, 1966b, 1968a; Norden & Gelfand, 1972; El-Sewedy *et al.*, 1978; El-Aaser *et al.*, 1979), for reasons that are unknown.

Genetic damage in the form of slightly increased sister chromatid exchange and micronucleus frequencies were seen in peripheral blood lymphocytes harvested from schistosomiasis patients (Shubber, 1987; Anwar, 1994), and micronuclei were more frequent in urothelial cells from chronic schistosomiasis patients than in controls (Rosin & Anwar, 1992). The mean frequency of micronuclei was reduced significantly after treatment with praziquantel, which may indicate that infection is involved in chromosomal breakage in epithelial cells (Anwar & Rosin, 1993). Some chromosomal abnormalities appear to be more frequent in SCCs associated with schistosomiasis than in TCCs; for example, loss of heterozygosity of 9p, in the region of the CDKN2 tumour-suppressor gene (Gonzalez-Zulueta *et al.*, 1995; Shaw *et al.*, 1999).

Several studies have investigated *H-ras* oncogene mutations in bladder cancers. Their frequency, and the expression of the corresponding protein, are similar for schistosomiasis-associated cancers and other cases (Badawi, 1996). However, Ramchurren *et al.* (1995) found point mutations in codon 13 of this gene in 2/21 schistosomiasis-related tumours. No mutation was detected at codon 12 of the *H-ras* oncogene in nine SCCs associated with schistosomiasis (Fujita *et al.*, 1987).

Mutations of the p53 tumour-suppressor gene are more frequent in schistosomiasis-associated tumours than in other cases. Habuchi *et al.* (1993) found p53 mutations in six of seven SCCs associated with *S. haematobium*; no specific pattern of mutation emerged, in contrast to the pattern seen in TCCs related

Table 6. Case–control studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Source of cases	Source of controls	Measure of exposure	No. of cases/ no. of controls	Cases/controls exposed (%)	Odds ratio	95% CI (or p)	Cases with squamous-cell tumours (%)
Mustacchi & Shimkin (1958)	Tanta, Nile Delta, Egypt	Hospital	Other admissions to hospital	Eggs in first urine sample	55/1417	14.5/7.6	2.1[a]	0.04	Not specified
				All clinical evidence, including history and cystoscopy	55/1417	49.0/23.3	2.2[a]	< 0.01	
Gelfand *et al.* (1967)	Harare, Zimbabwe	Hospital	Matched patients[b] of same age, sex, race, on different hospital ward	Pelvic X-ray Rectal biopsy	33/33 31/31	45.5/3.03 54.8/19.4 (discordant matched pairs) 1)15/1 2)13/2)	[15 [6.5	2.0–114] 1.5–29]	62 (62 with past exposure)
Elem & Purohit (1983)	Lusaka, Zambia	Autopsies	Cadavers without malignancy (mostly traumatic death)	Digestion and centri-fugation of bladder	50/50	94.0/40.0	[14	4.6–43]	72
				Pelvic X-ray	50/50	38/14	[3.8	1.4–10]	
Vizcaino *et al.* (1994)	Bulawayo, Zimbabwe	Cancer registry cases	Registry cases with other cancers	Self-reported history of bilharzia or blood in urine	300/2078 M 112/2405 F	33.7/12.6 M 34.8/4.7 F	3.9 [c] 5.7 [c]	2.9–5.2 3.7–8.7	71. No change when tobacco-related cancers excluded from controls
Bedwani *et al.* (1998)	Alexandria, Egypt	Hospital cases	Hospital without cancer or urinary tract disease	Self-reported history of schistosomiasis	190/187	45.3/36.9	1.7 [d]	1.0–2.9	18 [e]

[a] Adjusted for age, sex and urban or rural residence
[b] Who were 'submitted to same procedure'
[c] Adjusted for age, period, province, drinking and smoking
[d] Adjusted for age, sex, education, smoking, history of urinary infection, occupation
[e] For males, from Bedwani *et al.* (1997).

to tobacco smoking. p53 mutations limited to exons 7 and 8 were reported for 21 individuals with schistosomiasis-associated bladder cancer in South Africa (Ramchurren *et al.*, 1995). Warren *et al.* (1995) described p53 mutations in 90 bladder cancers from Egyptian patients with a history of schistosomiasis. Mutations in exons 5-8 were present in 17/53 SCCs and 8/23 TCCs, and molecular changes were consistent with nitric oxide production by inflammatory cells.

Tamimi *et al.* (1996) found deletion of the cyclin-dependent kinase inhibitor $p16^{INK4}$ in 23/47 samples from schistosomiasis-associated bladder cancer patients (more frequent than in other bladder tumours).

The Bcl-2 gene was found to be over-expressed in 32% schistosomiasis-associated bladder cancers, and this seemed to occur only in SCCs and adenocarcinomas, but not significantly in TCCs. Altered p53 expression was also found in the majority of tumours (Chaudhary *et al.*, 1997).

Methylation of DNA as shown by detection of O^6-methyldeoxyguanosine has been found in a high percentage of patients with schistosomiasis-associated cancers in Egypt (Badawi *et al.*, 1992, 1994).

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4.2 Breast cancer

Introduction

Worldwide, cancer of the breast is by far the most common cancer of women, with an estimated 1.05 million new cases in the year 2000, comprising 22% of all new cancers in women. In Africa, however, it is relatively less common, with an estimated 59 000 new cases (18% of cancers in women). There is a fair amount of regional variation, however, and in north Africa, breast cancer is considerably more common than cervical cancer, accounting for 27% of cancers, compared with 15.7% in sub-Saharan Africa.

Descriptive epidemiology in Africa

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with comparison data from Europe and North America. Table 2 shows incidence data from time periods in the 1960s and 1970s. Figure 1 shows estimated incidence rates by country, based on these data, and other information reported in this volume.

Incidence is highest in populations of north Africa and, in sub-Saharan Africa, in urban rather than rural settings. Thus, current incidence rates are highest in cities such as Abidjan (Côte d'Ivoire) and Harare (Zimbabwe). It also seems that incidence rates in the more recent registry series are higher than those reported in the past.

Robertson *et al.* (1971) calculated incidence rates of 3.7 per 100 000 (crude) and 4.5 (age-adjusted, African standard) in the rural low-veld area of South Africa for the period 1962–67. Rose and Fellingham (1981) reported a rate of 3.2 per 100 000 (age-adjusted, African standard) in women of rural Transkei in 1965–69. Isaacson *et al.* (1978) noted that rates in urban populations such as Soweto were higher than in rural populations, but that they were still low.

The incidence in white women living in Africa is much higher than in black Africans. This is clear in the old data in Table 2. Recent data (1993–95) from the National Cancer Registry of South Africa (Sitas *et al.*, 1998) indicate age-standardized rates of 70.2 per 100 000 in white females, and 11.3 per 10^5 in blacks (although some of this variation may represent differences in rates of treatment or biopsy, since the data are based on histologically diagnosed cases only). In Harare, Zimbabwe, in 1990–92, age-standardized incidence was 127.7 per 100 000 in white females and 20.4 per 100 000 in blacks. These large differences probably reflect the prevalence of risk factors (e.g., reproductive, body mass, etc.); in the United States, Brinton *et al.* (1997) found that the 20% difference in incidence between black and white women (at least at ages 40–54 years) was fully explicable in terms of difference in prevalence of reproductive variables (number of births, age at first birth, age at menarche) and lifestyle factors (oral contraceptive use, body mass, alcohol).

The risk of breast cancer increases with age, but the rate of increase slows down after the menopause, the lowering of risk coinciding with a decrease in circulating estrogens (Henderson *et al.*, 1988). In low-incidence countries, the slope of the age–incidence curve after the menopause may be very flat, or even negative. Almost certainly, this reflects increasing risks in successive generations of women, rather than a true decline in risk with age (Moolgavkar *et al.*, 1979). The young age structure of African populations, coupled with this rather flat age–incidence curve, means that the average age at diagnosis of cases in Africa is lower than in European and American populations. This is often remarked upon in clinical series from Africa (e.g., Ihekwaba, 1992; Muguti, 1993; Maalej *et al.*, 1999), but it has no etiological or prognostic significance.

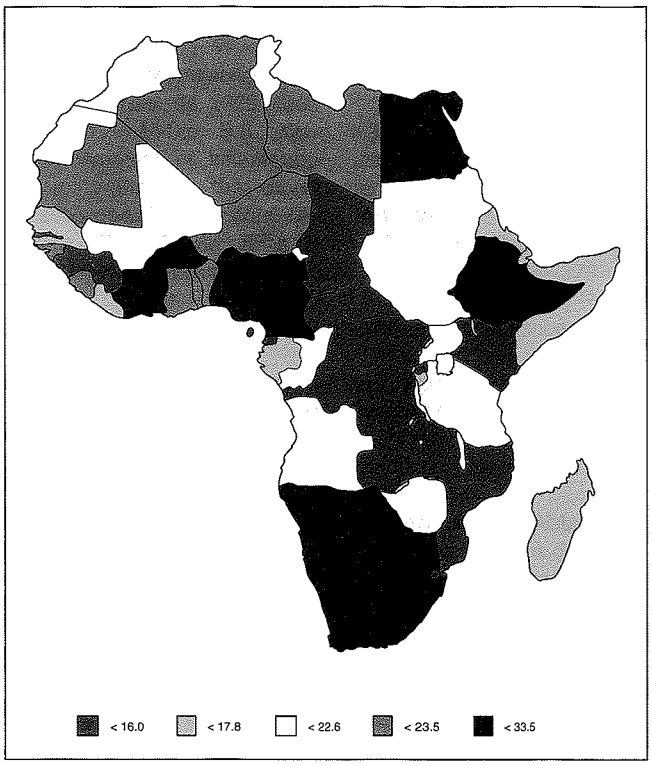

Figure 1. Incidence of breast cancer - ASR (world) females

Figure 2 shows age-specific incidence rates from four of the registry series in this volume (Oran, Algeria; Tunisia, Tunis; Kampala, Uganda; and Harare, Zimbabwe), in comparison with the black population covered by the SEER program of the United States.

Migrant studies suggest that migrants from north and east Africa to France retain their relatively low breast cancer mortality rates on migration to France (Bouchardy *et al.*, 1995, 1996), although African migrants to England and Wales do not have a significantly low mortality (Grulich *et al.*, 1992). Jewish migrants from North Africa to Israel also have low incidence rates (except for Jews born in Egypt (Steinitz *et al.*, 1989)).

Stage at presentation of tumours in African women is generally very advanced, with correspondingly poor prognosis (Walker *et al.*, 1984; Dansey *et al.*, 1988).

Time trends

In almost all developing countries with relatively low rates of incidence of breast cancer, the risk appears to be increasing (Parkin, 1994). There are very few data from Africa. As noted, rates appear to be rather higher in more recent data than in older series. In Ibadan, Nigeria, incidence in 1998–99 was 24.7 per 100 000, compared with 13.7 per 100 000 in 1960–69. In Kampala, Uganda, there has been a significant increase in incidence since the 1960s (Figure 3) (Wabinga *et al.*, 2000). Mortality rates in Mauritius have also been increasing since the 1960s (Figure 4).

Risk factors

The risk of breast cancer is clearly associated with socioeconomic status, with women of higher social class (as measured by education, income, housing, etc.) being at higher risk (Kogevinas *et al.*, 1997). In Bulawayo, women registered with breast cancer during 1963-1977 had a higher level of literacy than women with other types of cancer

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Breast (C50)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	26	0.5	**0.7**	0.05	906	16.6	**21.2**	1.73
Algeria, Constantine (1994-1997)	6	0.4	**0.7**	0.01	291	19.1	**28.3**	2.25
Algeria, Oran (1996-1998)	11	0.6	**0.9**	0.05	481	27.3	**34.5**	2.83
Algeria, Setif (1993-1997)	8	0.3	**0.5**	0.05	317	10.5	**17.0**	1.47
Tunisia, Centre, Sousse (1993-1997)	5	0.4	**0.6**	0.04	209	18.6	**22.7**	1.71
Tunisia, North, Tunis (1994)	6	0.3	**0.3**	0.02	409	19.4	**24.1**	1.85
Tunisia, Sfax (1997)	4	1.0	**1.2**	0.04	73	19.3	**22.7**	1.81
Africa, West								
The Gambia (1997-1998)	-	-	-	-	41	4.0	**7.0**	0.47
Guinea, Conakry (1996-1999)	-	-	-	-	188	8.5	**15.5**	1.33
Mali, Bamako (1988-1997)	10	0.3	**0.6**	0.04	249	6.9	**14.9**	1.23
Niger, Niamey (1993-1999)	7	0.4	**1.1**	0.13	175	9.7	**25.0**	2.05
Nigeria, Ibadan (1998-1999)	7	0.5	**1.3**	0.04	227	15.0	**25.3**	2.19
Africa, Central								
Congo, Brazzaville (1996-1999)	4	0.3	**0.5**	0.03	205	17.0	**22.5**	1.95
Africa, East								
France, La Reunion (1988-1994)	10	0.5	**0.6**	0.05	566	26.2	**29.2**	2.18
Kenya, Eldoret (1998-2000)	3	0.3	**0.8**	0.01	59	6.5	**14.3**	1.30
Malawi, Blantyre (2000-2001)	5	0.6	**1.7**	0.04	48	5.5	**12.0**	1.07
Uganda, Kyadondo County (1993-1997)	10	0.4	**1.1**	0.04	224	7.7	**21.0**	1.62
Zimbabwe, Harare: African (1990-1993)	5	0.2	**0.4**	0.04	171	8.0	**20.3**	1.55
Zimbabwe, Harare: African (1994-1997)	4	0.1	**0.5**	0.02	186	7.0	**19.8**	1.50
Zimbabwe, Harare: European (1990-1997)	2	1.3	**0.6**	-	347	205.7	**121.2**	8.55
Africa, South								
Namibia (1995-1998)	20	0.6	**1.1**	0.05	531	16.6	**25.6**	1.73
South Africa: Black (1989-1992)	299	0.5	**1.0**	0.07	5117	9.1	**13.6**	1.00
South Africa: Indian (1989-1992)	20	1.0	**1.6**	0.10	693	34.9	**42.5**	3.24
South Africa: Mixed race (1989-1992)	30	0.5	**1.0**	0.03	1285	19.2	**28.1**	2.07
South Africa: White (1989-1992)	206	2.0	**1.9**	0.12	7801	76.6	**62.8**	4.67
South Africa, Transkei, Umtata (1996-1998)	4	1.1	**1.6**	0.10	42	9.9	**14.9**	1.30
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.2**	-	36	4.0	**6.1**	0.48
Swaziland (1996-1999)	5	0.3	**0.7**	0.05	139	7.1	**12.9**	1.07
Europe/USA								
USA, SEER: White (1993-1997)	477	1.0	**0.8**	0.04	67272	134.1	**92.4**	6.51
USA, SEER: Black (1993-1997)	63	0.9	**1.1**	0.07	6527	87.9	**83.4**	5.98
France, 8 registries (1993-1997)	164	1.2	**0.8**	0.05	16870	116.8	**81.1**	6.20
The Netherlands (1993-1997)	268	0.7	**0.5**	0.02	49570	126.9	**85.9**	6.37
UK, England (1993-1997)	1036	0.9	**0.5**	0.03	150322	117.6	**75.6**	5.67

In italics: histopathology-based registries

Table 2. Incidence of breast cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	*0.7*	11.8	4
Mozambique, Lourenço Marques	1956–60	*0.0*	*3.2*	1
Nigeria, Ibadan	1960–69	*0.1*	15.3	3
SA, Cape Province: Bantu	1956–59	*0.4*	13.6	2
SA, Cape Province: Coloured	1956–59	*0.9*	25.9	2
SA, Cape Province: White	1956–59	*1.6*	57.2	2
SA, Johannesburg, Bantu	1953–55	*0.8*	15.3	1
SA, Natal Province: African	1964–66	*0.0*	11.9	2
SA, Natal Province: Indian	1964–66	*1.8*	19.9	2
Uganda, Kyadondo	1954–60	*0.3*	9.7	1
Uganda, Kyadondo	1960–71	*0.6*	10.8	5
Zimbabwe, Bulawayo	1963–72	*0.3*	13.4	6

Italics: Rate based on less than 10 cases

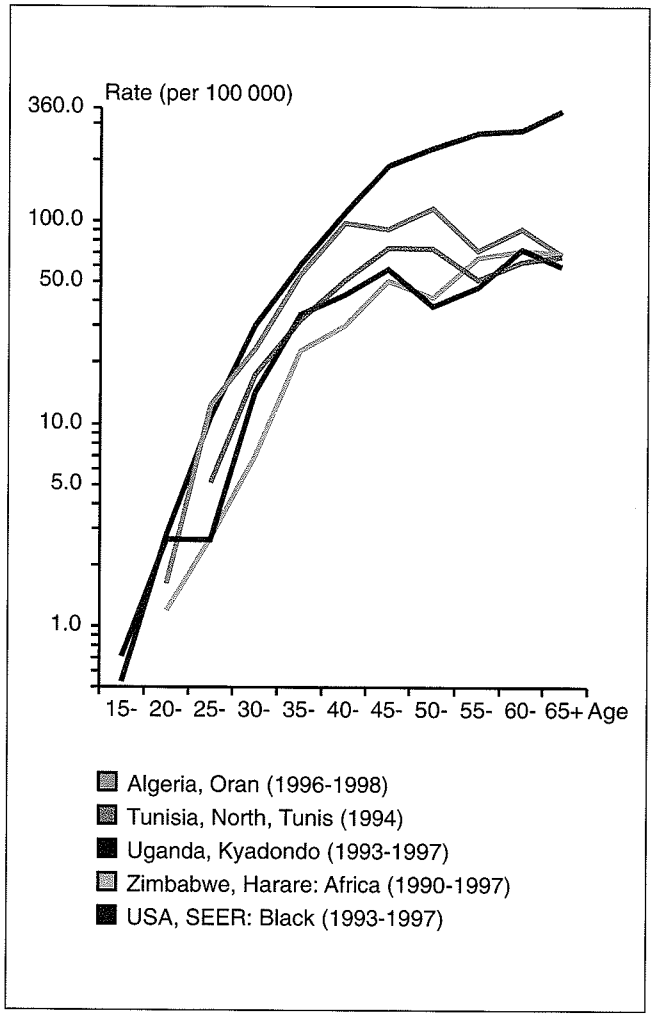

Figure 2. Age-specific incidence rates of breast cancer in Africa, and in black females in the United States

(Skinner *et al.*, 1993). Such differences may be due to the prevalence of risk factors between social classes (such as parity, age at menstruation and menopause, height, weight, alcohol consumption).

The most important risk factors for breast cancer are reproductive and hormonal factors. Thus, the risk is increased by early menarche, late menopause, late age at first birth, and low parity. All of these reflect a hormonal pattern of exposure to high levels of endogenous estrogens, in particular free estradiol (Henderson *et al.*, 1988).

In Kampala, Uganda, Ssali *et al.* (1995) compared 86 histologically diagnosed cases with 86 age-matched hospital controls. Most cases were pre-menopausal (median age 47.2 years); there was a clear association with age at first delivery (OR = 4.3 (95% CI 1.7–10.8) for age 22 years or more) and number of pregnancies (OR 0.21 (95% CI 0.09–0.49) for 4 or more vs 3 or less). There was an increased risk with *late* age at menarche, although this was not independent of the above associations. Adebamowo and Adekunle (1999), in a study of 250 breast cancer cases and age-matched hospital controls in Ibadan, Nigeria, also found a significantly older age at first pregnancy in cases than controls, but no difference in age at menarche. Using the cancer registry data from Bulawayo (1963–77), Parkin *et al.* (1994) found that late age at menarche and early age at menopause were associated with reduced risk of breast cancer, although the effects were small and not statistically significant. Parity and age at first pregnancy affected risk only in women aged 45 years or more at diagnosis. This observation may relate to the high parity of this African population, as similar observations have been made in other developing countries with high fertility and low age at first birth (e.g., Mirra *et al.*, 1971; Rosero-Bixby *et al.*, 1987). It probably relates to the increase in risk of breast cancer that follows each pregnancy, manifested as an increased risk in relation to age at last birth (Kelsey *et al.*, 1993); in young women with breast cancer, it is quite likely that with multiple pregnancies, the last one had occurred quite recently. This may explain the finding in the Ibadan study (Adebamowo & Adekunle, 1999) of fewer pregnancies (mean =4) in control subjects than in breast cancer patients (mean = 6), since the subjects were very young (mean age 43 years). A similar apparently anomalous finding in a case–control study in Tanzania (Amir *et al.*, 1998) of increasing risk with higher parity was a consequence of failure to adjust for the large age difference between case and control subjects.

In a large case–control study of 446 breast cancers in black and "coloured" women in Capetown, South Africa, Coogan et al (1999) found an association between risk of breast cancer and late age at first birth. Reporting on the same study, Shapiro *et al.* (2000) noted that there were associations between breast cancer risk and family history, low parity, and high socioeconomic status (as measured by medical insurance coverage), though no data were provided. Abdel-Rahman *et al.* (1993) compared 180 breast cancer cases from two hospitals in Egypt with 192 hospital controls (without malignancy). It seems that prevalent cancers were included, and, although the controls were stated to be age-matched, the age distribution of cases and control subjects was not very similar. Breast cancer was associated with the usual reproductive variables (nulliparity, age at first birth, age of menarche, and age of natural menopause), as well as a family history of breast cancer, height and weight (but not with body mass index). In a univariate analysis, there was no association with number of pregnancies (for >5 vs ≤ 5, OR = 1.4; 95% CI 0.9–2.4).

Since the report of Lane-Claypon over 70 years ago (1926), lactation has frequently been examined as being possibly protective against breast cancer, particularly in premenopausal women. The results are quite mixed. In the large case–control study in Capetown, Coogan *et al.* (1999) found no effect of lactation (age at onset, frequency, duration) on risk.

The possible effects of oral contraceptive hormones on risk of breast cancer has been the subject of much research. It seems that there is a small but detectable increase in risk in women taking oral contraceptives, but this diminishes when contraception ceases, and after 10 years, none of the excess risk remains (Reeves, 1996). In the large case–control study of 419 breast cancers in black and "coloured" women in Capetown, South Africa, Shapiro et al (2000) found a weak association in women taking combined estrogen/progesterone contraceptives (OR = 1.2), which was strongest in young women under 35 years of age (OR = 1.7), but no association with recency or duration of use. The same study investigated the risk associated with injectable progestogen contraceptives, especially depot medroxyprogesterone acetate (DMPA). Most studies have suggested that these pose only a small risk, if any, and that it is confined to young women (Skegg, 1996); there was no elevated risk in South African women, even in those aged under 35 years at diagnosis.

In a study of breast cancer cases and controls in Egypt and Britain, no differences in hormonal levels were found between cancer cases and controls (Anglo-Egyptian Health Agreement Collaborative Study, 1988). However, Egyptian women had a rather higher percentage of free estradiol than British women, and it was suggested that this might be associated with the claim that breast cancer presents in a more aggressive form in Egypt.

The role of diet in breast cancer has been controversial. Dietary fat appears as an important determinant of risk in inter-population studies (Prentice & Sheppard, 1990). However, in

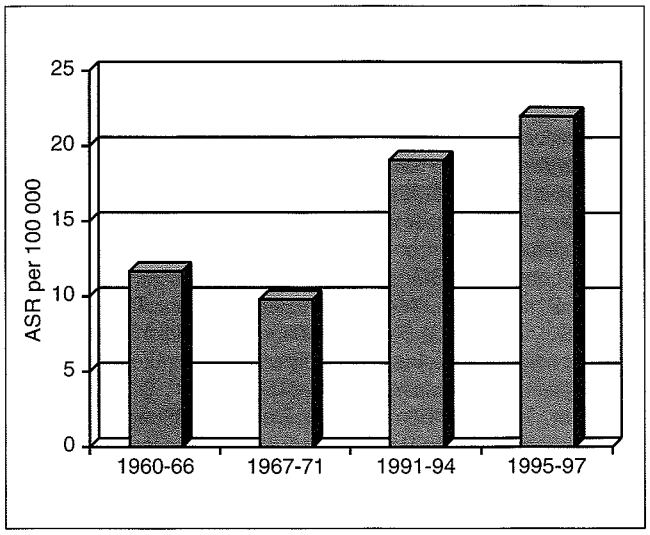

Figure 3. Trends in breast cancer incidence: Kampala, Uganda

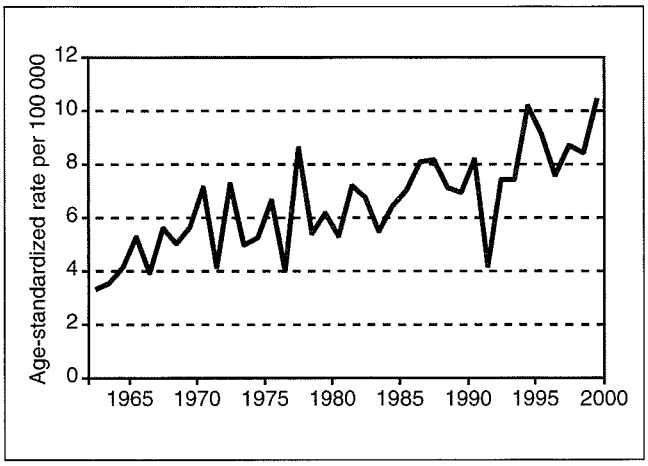

Figure 4. Mortality from breast cancer: Mauritius 1965–97

studies of individuals (case–control or cohort), this association has been difficult to confirm (Hunter *et al.*, 1996). Obesity in postmenopausal women is, however, important, increasing risk by some 2% per unit increase in body mass index (Bergström *et al.*, 2001). In a small hospital-based study in Johannesburg, Walker *et al.* (1989) observed higher nulliparity, obesity (body mass index ≥ 30) and a higher percentage of energy intake from dietary fat in breast cancer cases than in control patients. In their case–control study in Nigeria, Adebamowo and Adekunle (1999) found that breast cancer cases were significantly taller and heavier than (hospital) controls.

No studies of diet and breast cancer in African populations appear to have been reported. Traditional diets in Africa are low in animal products (especially fat) and high in fibre (Manning *et al.*, 1971; Labadarios *et al.*, 1996). This pattern is gradually being modified by urbanization and westernization of lifestyles. It is probable that average body weight in postmenopausal women in urban environments has increased (Steyn *et al.*, 1998). All these changes will tend to favour an increase in breast cancer incidence in African populations.

The role of genetic factors in breast cancer etiology has received much attention. At least part of the obvious family risk of the disease is mediated through the major susceptibility genes *BRCA1* and *BRCA2*. In European populations, around 2% of breast cancers are likely to be due to *BRCA1* mutations, but the proportion is much higher in younger breast cancer cases, for example 10% below the age of 40 years (Ford *et al.*, 1995). Nothing is known of the prevalence of mutations in *BRCA1* and *BRCA2* in African populations.

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is characterized by inflammatory symptoms (erythema, skin oedema or '*peau d'orange*' and ridging of the skin) and invasion of breast dermal lymphatic ducts with tumour emboli (Jaiyesimi *et al.*, 1992). A special code is allocated in ICD-O (8530/3), although the condition does not have specific histological characteristics. It is the most lethal and fulminant form of breast cancer, with rapid growth, short doubling times and rapid systemic dissemination. Inflammatory breast cancer represents 1–6% of breast cancers in the United States, affects younger women disproportionately, and is characterized by extremely poor survival (between 0 and 28% at five years, with a median of 18 months) (Chang *et al.*, 1998a).

In the United States, IBC incidence doubled between 1975–77 and 1990–92, increasing among whites from 0.3 to 0.7 per 100 000 and among blacks from 0.6 to 1.1 per 100 000; this increase was considerably greater than for other forms of breast cancer (Chang *et al.*, 1998a).

Little is known about the causes of inflammatory breast cancer; no studies have investigated the risk factors, thus it is not known whether they differ from those for breast carcinoma in general (Chang *et al.*, 1998a). High body mass index has been found to be significantly associated with increased risk of IBC. This association did not vary by menopausal status, although IBC patients were more likely to be of pre-menopausal status (Chang *et al.*, 1998b).

This form of breast cancer, also known as '*poussée evolutive*' (PEV) has been reported to be particularly frequent in Tunisia, comprising as many as 55% of breast cancer cases in clinical series (Mourali *et al.*, 1980), although some authors are more sceptical of these high figures (Maalej *et al.*, 1999). Breast tumours with inflammatory signs were larger and had more frequent metastases (Tabbane *et al.*, 1989). IBC is particularly frequent among younger patients (under 30 years), though this may be due, in part at least, to the frequent association with pregnancy or lactation; nearly all the cases of breast cancer associated with pregnancy or lactation were rapidly growing inflammatory cancer (Tabbane *et al.*, 1985). There appears to be associations with rural residence and with blood group A (Mourali *et al.*, 1980); although this suggests a genetic predisposition, there was no association with any particular HLA antigen (Levine *et al.*, 1981), and cellular immunity appears to be normal in these patients.

Male breast cancer

Male breast cancer is a rare tumour in all parts of the world. About 1% of all breast cancers occur in men, but the male/female ratio is higher among black than among white populations. The male/female ratio is also relatively high in case series and registry data from Africa, including north Africa (Nectoux & Parkin, 1992; Sasco *et al.*, 1993). It is not clear, however, that this represents a higher incidence in men in these populations; rather it is the result of relatively low rates of breast cancer in women in Africa. Nevertheless, incidence rates in the black population of the United States are significantly higher (about 60%) than those among whites (Parkin *et al.*, 1997). As in females, there appears to be higher risk in Jewish subjects (Sasco *et al.*, 1993). A study in Egypt (El-Gazayerli & Abdel-Aziz, 1963) found that cases of male breast cancer (and of gynaecomastia) frequently had associated bilharziasis, raising the possibility of an etiological link.

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4.3 Cervix cancer

Introduction

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 468 000 new cases and 233 000 deaths in the year 2000. Almost 80% of the cases occur in developing countries, where, in many regions, this is the most common cancer among women.

Descriptive epidemiology in Africa

The incidence is high in sub-Saharan Africa, with an estimated 57 000 cases in 2000, comprising 22% of all cancers in women, equivalent to an age-standardized incidence of 31 per 100 000. In north Africa, the incidence is rather lower. Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with comparison data from Europe and North America. Table 2 shows incidence data from time periods in the 1960s and 1970s.

Figure 1 shows estimated incidence rates by country, based on these data and other information reported in this volume. The scale has been chosen to be equivalent to quintiles of incidence rates on a global basis, to show the moderate–high incidence throughout the continent, except for the relatively low-incidence rates estimated for Tunisia (based on the data from Table 1) and Egypt (see Chapter 3.1.2). The latter observation is supported by a low prevalence of cervical intraepithelial neoplasia (0.36%) found on cytological evaluation of women attending a gynaecology clinic in Cairo (Mohga *et al.*, 1987).

On the basis of frequency of different cancers in hospital case series, Cook-Mozaffari (1982) hypothesized the existence of a 'belt' of low incidence of cervix cancer along the line of the western Rift Valley in Uganda, Rwanda, Burundi and Zaire. This observation seems not to be confirmed.

The relationship of cervix cancer risk with age is unusual for an epithelial cancer. In most countries, risk rises to a maximum at about age 50 years, and then somewhat declines; the age of maximum incidence may, however, be rather later in African populations – 50–65 years (Gustafsson *et al.*, 1997). The young age structure of African populations, coupled with this rather flat age–incidence curve, means that the average age at diagnosis of cases in Africa is lower than in European and American populations. This is often noted in clinical series from Africa (e.g., Rogo *et al.*, 1990), but has no etiological or prognostic significance.

Figure 2 shows age-specific incidence rates from five of the registry series in this volume (Algiers, Algeria; Bamako, Mali; Conakry, Guinea; Kampala, Uganda; and Harare, Zimbabwe). All show the rapid rise in incidence in young women, and a peak or plateau in older women. However, in several populations (Algeria, Mali, Zimbabwe), the peak incidence appears to occur relatively late.

Migrant studies suggest that migrants to France from north Africa (Algeria, Tunisia) have relatively low mortality rates compared with the local-born population (Bouchardy *et al.*, 1996), although migrants from sub-Saharan Africa to France (Bouchardy *et al.*, 1995) and to England and Wales (Grulich *et al.*, 1992) do not have significantly higher rates than the local populations. On the other hand, Jewish migrants from north Africa to Israel have significantly higher incidence rates, although these are no longer present in the daughters of migrants (Parkin & Iscovich, 1997).

In all large case series, squamous cell carcinomas comprise the large majority of tumours, with adenocarcinomas accounting for 4% (Schonland & Bradshaw, 1969; Rogo *et al.*, 1990) to 7% (Oettlé, 1961).

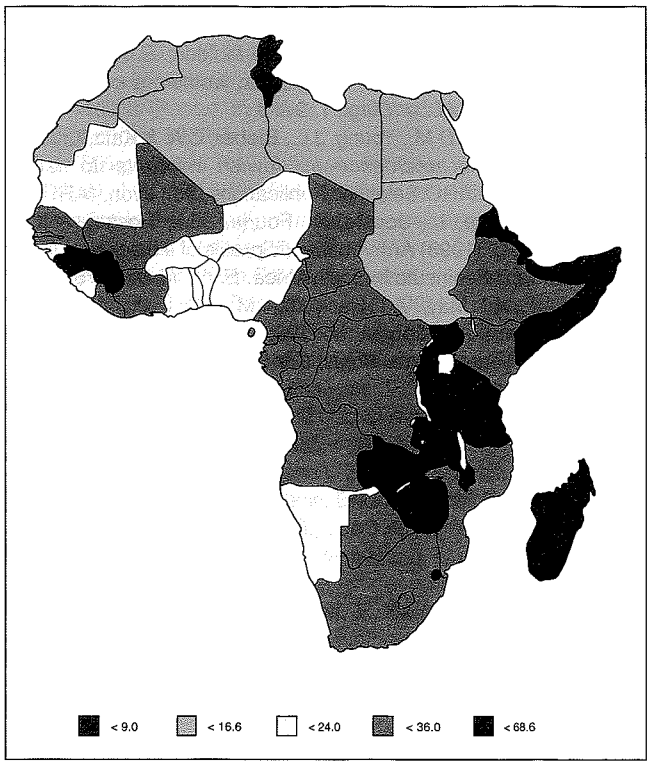

Figure 1. Age-standardized incidence of cervix cancer in Africa

Stage at presentation of tumours in African women is generally very advanced (Schonland & Bradshaw,1969; Lomalisa *et al.*, 2000), with correspondingly poor prognosis (Rogo *et al.*, 1990).

Time trends

In many developed countries, declining incidence of invasive cervix cancer has been observed, as a consequence of the introduction of screening programmes. There are very few data from Africa. In Bulawayo, Zimbabwe, the frequency of cervix cancer increased significantly during the period 1963–77 (Skinner *et al.*, 1993). Mortality data from South Africa suggested some increase in rates for the 'coloured' population between 1949 and 1979, but little change in the black population from 1964 to 1977 (Bradshaw & Harington, 1985). Updating this study, Bailie *et al.* (1996) observed that, after about 1980, the mortality in the 'coloured' population remained more or less constant, while in the white population, mortality had declined since the mid 1960s. The difference was ascribed to the availability of screening services, particularly for older women.

In some registry series, the more recent rates appear to be higher than the older ones. In Kampala, Uganda, for example, there has been a significant increase in incidence since the 1960s (Figure 3) (Wabinga *et al.*, 2000). On the other hand, there seems to have been little change in the recorded rate in Nigeria; it was 21.6 in 1960–69 (Table 2) and 19.4 in 1998–99 (Table 1).

Risk factors

Early observers noted the very marked differences in risk of cervix cancer according to such classical demographic variables as social status, religion, occupation, marital status and ethnicity. Later, epidemiological studies (mainly case–control studies) showed a consistent association between risk and early age at

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Cervix uteri (C53)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	-	-	-	-	506	9.3	**12.6**	1.07
Algeria, Constantine (1994-1997)	-	-	-	-	113	7.4	**12.1**	0.89
Algeria, Oran (1996-1998)	-	-	-	-	324	18.4	**24.9**	2.14
Algeria, Setif (1993-1997)	-	-	-	-	203	6.7	**11.5**	0.96
Tunisia, Centre, Sousse (1993-1997)	-	-	-	-	70	6.2	**7.9**	0.61
Tunisia, North, Tunis (1994)	-	-	-	-	103	4.9	**6.1**	0.51
Tunisia, Sfax (1997)	-	-	-	-	10	2.6	**3.4**	0.32
Africa, West								
The Gambia (1997-1998)	-	-	-	-	170	16.6	**29.6**	2.53
Guinea, Conakry (1996-1999)	-	-	-	-	659	29.7	**49.6**	4.03
Mali, Bamako (1988-1997)	-	-	-	-	516	14.3	**30.8**	2.50
Niger, Niamey (1993-1999)	-	-	-	-	167	9.3	**19.6**	1.60
Nigeria, Ibadan (1998-1999)	-	-	-	-	157	10.4	**19.9**	1.53
Africa, Central								
Congo, Brazzaville (1996-1999)	-	-	-	-	279	23.1	**31.7**	2.67
Africa, East								
France, La Reunion (1988-1994)	-	-	-	-	447	20.7	**22.3**	1.74
Kenya, Eldoret (1998-2000)	-	-	-	-	93	10.2	**25.9**	2.22
Malawi, Blantyre (2000-2001)	-	-	-	-	222	25.6	**53.1**	4.47
Uganda, Kyadondo County (1993-1997)	-	-	-	-	465	16.1	**40.7**	3.26
Zimbabwe, Harare: African (1990-1993)	-	-	-	-	410	19.2	**62.6**	4.30
Zimbabwe, Harare: African (1994-1997)	-	-	-	-	510	19.3	**53.1**	3.73
Zimbabwe, Harare: European (1990-1997)	-	-	-	-	32	19.0	**12.7**	0.91
Africa, South								
Namibia (1995-1998)	-	-	-	-	468	14.6	**22.2**	1.60
South Africa: Black (1989-1992)	-	-	-	-	15450	27.4	**40.3**	3.15
South Africa: Indian (1989-1992)	-	-	-	-	330	16.6	**20.2**	1.45
South Africa: Mixed race (1989-1992)	-	-	-	-	1541	23.0	**31.6**	2.50
South Africa: White (1989-1992)	-	-	-	-	1465	14.4	**11.9**	0.91
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	75	17.7	**26.3**	2.35
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	134	14.9	**21.7**	1.83
Swaziland (1996-1999)	-	-	-	-	655	33.4	**59.3**	4.96
Europe/USA								
USA, SEER: White (1993-1997)	-	-	-	-	4372	8.7	**6.7**	0.53
USA, SEER: Black (1993-1997)	-	-	-	-	853	11.5	**10.3**	0.75
France, 8 registries (1993-1997)	-	-	-	-	1771	12.3	**8.9**	0.67
The Netherlands (1993-1997)	-	-	-	-	3594	9.2	**6.6**	0.50
UK, England (1993-1997)	-	-	-	-	14294	11.2	**8.2**	0.62

In italics: histopathology-based registries

Table 2. Incidence of cervix cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74		17.2	4
Mozambique, Lourenço Marques	1956–60		28.5	1
Nigeria, Ibadan	1960–69		21.6	3
SA, Cape Province: Bantu	1956–59		24.9*	2
SA, Cape Province: Coloured	1956–59		34.4*	2
SA, Cape Province: White	1956–59		22.7*	2
SA, Johannesburg, Bantu	1953–55		52.0	1
SA, Natal Province: African	1964–66		49.4	2
SA, Natal Province: Indian	1964–66		19.9	2
Uganda, Kyadondo	1954–60		22.2	1
Uganda, Kyadondo	1960–71		19.4	5
Zimbabwe, Bulawayo	1963–72		32.0	6

Italics: Rate based on less than 10 cases

* Includes carcinoma *in situ*

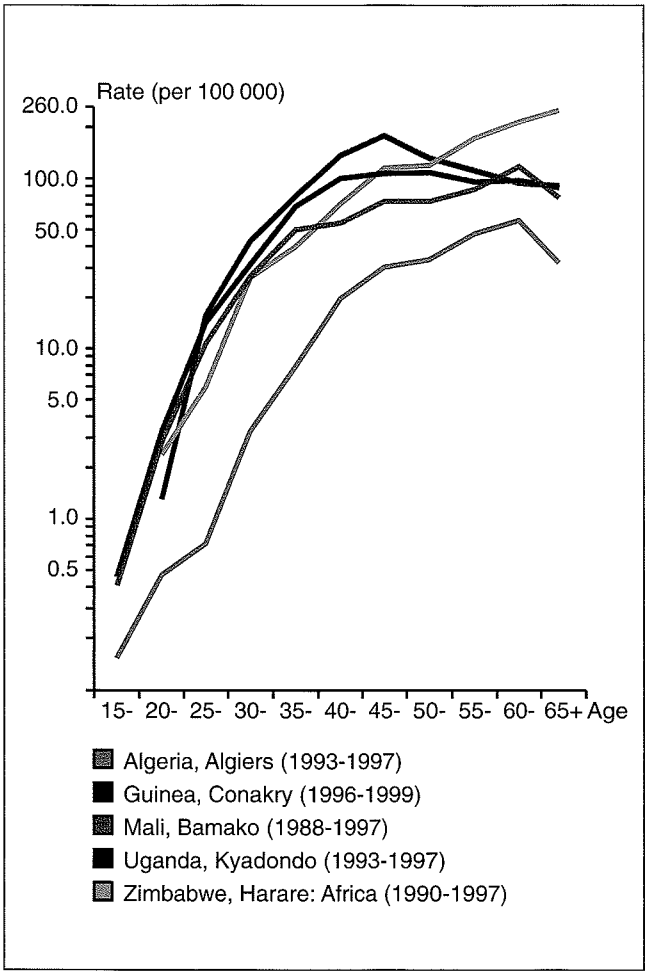

Figure 2. Age-specific incidence of cancer of cervix

initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners, and other indicators of sexual behaviour. These findings were strongly suggestive of a causative role for a sexually transmitted agent. Additional factors included an increasing number of pregnancies, smoking, possibly exposure to oral contraceptives, and specific dietary patterns. Within the last 20 years, it has become established that certain sexually transmitted types of human papillomavirus (HPV), notably types 16, 18, 31 and 45, are responsible for the initiation of the disease in the vast majority of cases. The virus is found in almost all cancers and a much smaller proportion of controls, with relative risks reaching several hundreds for certain viral types in the most recent studies. Studies of the natural history of HPV suggest that infection is very common in young women after the onset of sexual activity, but that the prevalence of infection declines with time (or age), possibly reflecting elimination of the virus by immunological mechanisms. Women who remain infected at later ages (30–50 years) are at risk of developing the epithelial abnormalities recognized as precursors of cancer.

Since 1993, cervix cancer has been considered to be an 'AIDS-defining' condition, meaning that if it occurs in someone who is positive for human immunodeficiency virus (HIV), that person is deemed to have AIDS. However, it was only some year later that studies in the United States, Italy, and France, linking cohorts of subjects with HIV/AIDS to cancer registries, demonstrated the increased risk of invasive cancer of the cervix (Goedert *et al.*, 1998; Franceschi *et al.*, 1998; Serraino *et al.*, 1999; Frisch *et al.*, 2000). A similar study in Australia was negative (Grulich *et al.*, 1999). Estimates of the risk in these studies are between 5 and 15. It is not clear how much of the excess risk is due to the confounding effect of HPV infection, which is known to be associated with HIV infection, because of their common mode of transmission. The prevalence of cervical intraepithelial neoplasia (CIN) is clearly higher in HIV-infected women, although most of the early studies failed to adjust for infection by HPV. Careful adjustment for such confounding suggests that there is an independent effect of HIV on risk of CIN, although it is not very large, and that there is an interaction between the effects of HIV and HPV, as might be expected if the role of HIV was indirect, through creation of immune dysfunction (Mandelblatt *et al.*, 1999).

The roles of other infectious agents, especially herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis*, independent of HPV infection, in the etiology of cervix cancer remain much less clear.

Social class

An association between lower social status (as measured by literacy) and cervix cancer risk was observed in Bulawayo (Skinner *et al.*, 1993) and a case–control study by Chaouki *et al.* (1998) in Morocco (see section on HPV below) found a very strong negative association with social status, family income and educational attainment.

Ethnicity

Data on hospital admissions in Moshi, northern Tanzania, indicated a higher incidence of cervix cancer in the Pare tribe, compared to the Chaggas, although, on the grounds of proximity to the hospital, the opposite might have been expected (Kitinya *et al.*, 1988). The difference was ascribed to sexual lifestyles, with multiple partners reportedly more common among the Pare.

Sexual and reproductive variables

Several studies in Africa have investigated effects of sexual and reproductive variables on risk. In an early study of Johannesburg residents, Oettlé (1961) compared cervix cancer cases with other cancers (excluding breast and female genital sites) as controls (age-matched). There was almost no difference between the two groups in age at menarche or in parity (slightly fewer pregnancies or births to cervix cancer cases), but age at marriage and age at birth of first child were lower for cervix cancer cases (though not significantly). In a later study in Africans in Durban, South Africa (Schonland & Bradshaw, 1969), cervix cancer cases had a significantly earlier age at first intercourse (18.2 years), age at first pregnancy and higher parity than controls. There was no difference in age at menarche. Freedman *et al.* (1974) compared 48 cervix cancers patients from Baragwanath Hospital (Johannesburg) with age-matched (± 10 years) controls from the same hospital. Although the results are not clearly presented, there appears to be no significant difference between cases and controls in education level, mean age at first coitus (16.2 years in both groups), average number of sexual partners (2.4 in cases; 2.8 in controls) or age at menarche. There was a suggestion of higher parity in the cases than the controls. In a study in Kampala, Uganda, comparing 62 cases of cervix cancer with a group of age-matched controls, Adam *et al.* (1972) noted earlier age at first intercourse (and of marriage and first pregnancy) in cases versus controls, but no difference with respect to parity or history of venereal disease. Adelusi (1977) compared cervix cancer patients and healthy women attending a family planning clinic in Ibadan, Nigeria; although the latter were considerably younger, they reported a significantly later age at first intercourse than the cervix cancer patients

In a registry-based case–control study in Bulawayo (Parkin *et al.*, 1994), age at first intercourse had little effect on risk, although the range of ages given was narrow, with half of the cases reporting age 17 or 18 years. The median age (18.3 years) was relatively high, as in the earlier studies summarized above. The number of

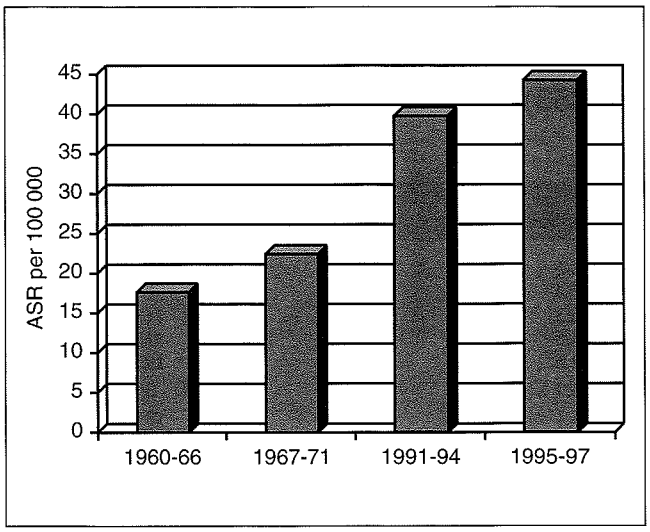

Figure 3. Trends in incidence of cervix cancer, Kampala, Uganda (Wabinga *et al.* 2000)

sexual partners was not investigated, but high parity appeared to confer an increased risk, with ORs of 1.3 (95% CI 1.0–1.7) for 3–6 full-term pregnancies, and 1.8 (95% CI 1.3–2.3) for more than six pregnancies, relative to less than three.

The results of a hospital-based case–control study in Nairobi, Kenya, with 112 cases and 749 controls, conducted as part of the WHO collaborative study on neoplasia and steroid contraceptives, were reported by Williams *et al.* (1994). Age at first intercourse, number of lifetime sexual partners, parity and a history of abnormal vaginal discharge were independently significantly associated with risk.

In a study in Bamako, Mali, Bayo *et al.* (2002) compared 82 cases of cervix cancer with 92 hospital controls. There were almost no differences between the two groups with respect to age at first intercourse (or marriage) and number of sexual partners (one quarter of cases and controls reported at least one casual partner). Having a husband with more than one wife was associated with an increase in risk (OR = 2.2, 95% CI 1.0–5.0). There was a clearly increased risk with increasing parity (OR for >10 versus <5 children = 4.8, 95% CI 1.5–4.7).

It has been suggested that trauma to the cervix through multiple childbearing, particularly at young ages, in some way increases the risk of neoplastic change, or that hormonal or nutritional influences of pregnancy are responsible. If so, high fertility may provide part of the explanation for the elevated incidence of cervix cancer in sub-Saharan Africa.

Male circumcision

Because of the previously observed high rates of penile cancer in Uganda and the geographical correlations in the frequency of penile and cervical cancer, the importance of non-circumcision of the male partners has been raised (Dodge *et al.*, 1973). However, the evidence that circumcision status really plays a role in the etiology of cervix cancer is weak, and probably is related simply to the degree of penile hygiene (Schmauz & Owor, 1984).

Smoking

The prevalence of smoking in women in Bulawayo was very low, and there was no apparent excess risk for cervix cancer in smokers (Parkin *et al.*, 1994).

Alcohol

Alcohol drinking has rarely been reported as an independent risk factor for cervix cancer. In a survey in Johannesburg residents with cancer, undertaken in 1953–55, Oettlé (1961) found a higher proportion of cervix cancer cases reporting a history of local beer drinking; compared with age-matched other cancers (excluding breast and genital sites), the relative risk was 3.0. In a study in Lesotho (Martin & Hill, 1984), comparing 257 cervix cancer cases with controls (matched for age, parity and residence), there was a significantly increased risk (RR = 3.2) for consumption of indigenous alcohol (frequent versus never) and European alcohols (RR = 1.9) (each adjusted for the other, and for tobacco consumption). In the case–control study using data from the Bulawayo cancer registry (Parkin *et al.*, 1994), an excess risk (OR = 1.6, 95% CI 1.3–1.9) was observed for frequent alcohol drinkers, relative to abstainers.

Oral contraceptives

Long-term use of oral contraceptives was found to be associated with risk of cervix cancer in HPV-positive women in the case–control study of Chaouki *et al.* (1998) in Rabat, Morocco (see section on HPV below). In the case–control study in Nairobi, Kenya, which was part of the WHO collaborative study on neoplasia and steroid contraceptives (Williams *et al.*, 1994), the association with use of oral contraceptives was weak and non-significant.

Genital hygiene

The case–control study of Bayo *et al.* (2002) in Bamako, Mali, found that vaginal douching decreased the risk of cervical cancer [OR ever versus never = 0.06 (95% CI 0.01–0.24)] while use of home-made sanitary napkins and re-use of such napkins were strong predictors of risk. The study in Morocco by Chaouki *et al.* (1998) had made similar observations: a decreased risk (adjusted for age, income and HPV status) associated with washing the genital area during menstruation (OR ever versus never = 0.26, 95% CI 0.10–0.72), and use of commercial (rather than home-made) sanitary pads (OR = 0.36, 95% CI 0.13–0.95).

HPV

The evidence for the causative role of certain types of human papilloma virus, especially HPV16 and HPV 18 in cervical cancer etiology is now accepted (Walboomers *et al.*, 1999). In east Africa HPV 18 infection may be particularly important (Schmauz *et al.*, 1989; Ter Meulen *et al.*, 1992).

Chaouki *et al.* (1998) carried out a case–control study, with 214 cases of invasive cancer and 203 control subjects recruited in the National Cancer Institute, Rabat, Morocco as part of an IARC-coordinated multinational study. Testing for 30 HPV types was carried out by PCR using cellular material from biopsies (cases) or scrapes (controls). The OR for any HPV was 61.6 (95% CI 29.2–130), with HPV 16 the most common type (present in 68% of cases), followed by HPV 18. In addition to the strong effect of HPV, low socioeconomic status, multiple partners before age 20 years, use of oral contraceptives, and parity emerged as independent risk factors.

La Ruche *et al.* (1998b) compared 13 cases of cervix cancer, from among gynaecology outpatients in Abidjan, Côte d'Ivoire, with 65 age-matched controls with normal cytology; HPV infection, present in 10 cases, was strongly associated with risk (OR = 13.3; 95% CI 3.2–55.5).

In the case–control study in Bamako, Mali (Bayo *et al.*, 2002), HPV infection in cases and controls was evaluated by the presence of antibodies to HPV virus-like particles (VLPs). At an optical density cut-off point of 0.4, antibodies to HPV 16, 18 and 31 were detected in 60.4% of cases and 45.4% of controls (OR = 1.8, 95% CI 1.0–2.2). HPV DNA was present in 63/65 (96.9%) of the tumours tested. As described above, high parity, a polygamous husband and poor genital hygiene were independent risk factors.

Several studies in Africa have examined the association between HPV infection and precursor lesions (CIN and squamous intra-epithelial lesions (SIL)), the latter usually diagnosed on the basis of cytology (Table 3). In a study of 198 prostitutes in Nairobi,

Table 3. Percentage distribution of microscopically verified cases by histological type
Cervix uteri (C53)

	Carcinoma				Sarcoma	Other	Unspecified	Number of cases	
	Squamous	Adeno	Other	Unspecified				MV	Total
Algeria, Algiers	69.3	11.6	-	18.5	0.6	-	-	**475**	506
Algeria, Batna	90.3	5.6	-	1.4	1.4	1.4	-	**72**	72
Algeria, Constantine	86.6	5.4	-	6.3	-	-	1.8	**112**	113
Algeria, Oran	75.2	4.4	0.3	3.5	0.3	-	16.4	**318**	324
Algeria, Setif	94.9	2.1	-	2.6	0.5	-	-	**195**	203
Burkina Faso, Ouagadougou	36.7	20.0	13.3	16.7	3.3	6.7	3.3	**30**	41
Congo, Brazzaville	71.3	1.3	0.6	26.1	-	-	0.6	**157**	279
France, La Reunion	86.7	5.4	2.7	4.7	-	0.5	-	**444**	447
The Gambia	78.3	4.3	-	6.5	-	-	10.9	**46**	170
Guinea, Conakry	81.1	3.1	-	15.6	-	-	0.3	**359**	659
Kenya, Eldoret	81.8	4.5	-	10.6	1.5	1.5	-	**66**	93
Malawi, Blantyre	86.9	5.6	-	5.6	-	-	1.9	**107**	222
Mali, Bamako	90.6	3.0	0.6	4.5	0.3	-	0.9	**330**	516
Namibia	87.2	10.2	0.2	2.0	-	0.2	0.2	**460**	468
Niger, Niamey	82.1	7.7	-	6.4	-	1.3	2.6	**78**	167
Nigeria, Ibadan	87.2	7.7	0.9	3.4	0.9	-	-	**117**	157
Rwanda, Butare	15.2	2.2	-	-	-	-	82.6	**46**	46
South Africa: Black	72.5	8.1	0.5	4.1	0.3	0.3	14.2	**15450**	15450
South Africa: White	79.5	13.9	0.5	4.5	0.5	0.3	0.8	**1465**	1465
South Africa: Indian	67.6	10.3	0.6	4.8	1.2	0.6	14.8	**330**	330
South Africa: Mixed race	86.0	11.0	0.5	1.9	0.1	0.1	0.4	**1541**	1541
South Africa, Elim	78.6	12.5	-	8.9	-	-	-	**112**	127
South Africa, Transkei, Umtata	86.4	1.7	-	6.8	-	-	5.1	**59**	75
South Africa, Transkei, 4 districts	90.5	1.9	-	7.6	-	-	-	**105**	134
Swaziland	94.5	4.6	-	0.9	-	-	-	**219**	655
Tanzania, Dar Es Salaam	90.4	7.0	-	2.1	0.4	0.2	-	**530**	530
Tanzania, Kilimanjaro	72.0	10.0	-	17.3	-	0.7	-	**150**	168
Tunisia, Centre, Sousse	94.3	4.3	-	-	1.4	-	-	**70**	70
Tunisia, North, Tunis	88.2	7.8	-	1.0	1.0	1.0	1.0	**102**	103
Tunisia, Sfax	80.0	10.0	10.0	-	-	-	-	**10**	10
Uganda, Mbarara	91.5	3.4	-	5.1	-	-	-	**59**	143
Uganda, Kyadondo County	82.2	8.4	0.3	7.7	-	-	1.3	**297**	465
Zimbabwe, Harare: African	83.3	6.5	0.1	9.7	0.1	0.1	-	**672**	920
Zimbabwe, Harare: European	62.1	17.2	-	13.8	6.9	-	-	**29**	32

Kreiss *et al.* (1992) found HPV in 81% of Pap smears showing CIN, compared with 28% without (adjusted OR = 7.2, 95% CI 1.6–32.1). HPV was present in 19/25 cases of SIL and 59/204 normal smears (OR = 7.4, $p < 0.001$) from post-partum women in Malawi (Miotti *et al.*, 1996). Among attenders at a family planning clinic in Nairobi, HSIL was strongly associated with presence of HPV (OR = 14.9, 95% CI 6.8–32.8) (Temmerman *et al.*, 1999). In the study of La Ruche *et al.* (1998b), comparison of HPV prevalence in 60 cases of high-grade SIL (HSIL) (half of them defined by colposcopy or biopsy) and controls, gave an OR of 14.3 (6.6–30.9) and in 151 cases of cytologically diagnosed low-grade SIL (LSIL) and 151 controls, an OR of 4.4 (2.6–7.4). These ORs were adjusted for HIV status (see below). A strong association with a cytological diagnosis of SIL and presence of DNA from high-risk HPV types was also observed in a study of two groups of women in Abidjan, Côte d'Ivoire (Vernon *et al.*, 1999). The ORs (adjusted for age, HIV, and various variables related to sexual behaviour) were 5.4 (95% CI 1.5–19.8) in a group of 258 women participating in a study of mother–child HIV transmission, and 23.7 (95% CI 4.4–126.0) among 278 prostitutes. In a study of 612 women attending an antenatal clinic in Mwanza, Tanzania (Mayaud *et al.*, 2001), SIL was significantly more prevalent among HPV-positive women (14% vs 4%, OR = 3.7, 95% CI 1.9–7.0, especially among women with high-risk HPV (17%, OR =4.8, 95% CI 2.3–9.8).

The prevalence of HPV in the general population has not been carefully studied in Africa, most investigations being of women attending screening or other clinics, and with the information on prevalence not stratified by age. In Chitungwiza (a satellite of Harare), Zimbabwe, 2206 women aged 25–55 years attending primary care clinics were recruited and cervical cells, obtained by cytobrush, were tested for HPV by hybrid capture II test (HC II) (Womack *et al.*, 2000a). In this population at high risk for cervix cancer, HPV prevalence was very high (42.7%) but declined with age: 48.5% at 25–34, 34.9% at 35–44, 25.6% at 45–55 years. HSIL lesions (biopsy-proved) were five times more common in HPV-positive women than in those who were HPV-negative. In a random sample of 960 women aged 15–59 years in rural Uganda, HPV prevalence (evaluated by hybrid capture II assay) in self-collected vaginal swabs, was 16.7% overall (Serwadda *et al.*, 1999). Prevalence was strongly associated with infection with HIV (age-adjusted OR = 5.4, 95% CI 3.8–7.5). In HIV-negative women, prevalence was highest in the 15–19 years age group (23.7%), and was only 4% over 30 years of age. In pregnant women in Mwanza, Tanzania, HPV prevalence was much higher (34%), with little difference by age (Mayaud *et al.*, 2001).

The prevalence of HPV infection, in relation to other genital infections, and lifestyle variables, has been studied in several different African populations, as in a myriad of similar investigations elsewhere.

Table 4. Case–control studies of CIN in relation to infection with HPV in Africa

Reference	Area, subjects	Cases, controls	HPV test	HPV prevalence (%)	Odds ratios (95% CI)	Comments/adjustments
Kreiss *et al.*, 1992	Nairobi, Kenya Prostitutes	16 CIN 47 normal cytology	Dot filter Southern transfer hybridization	Cases: 81.3 Controls: 27.7	7.2 (1.6–32.1)	OR adjusted for age and duration of prostitution HPV types 6, 11, 16, 18, 31, 33, 35
Miotti *et al.*, 1996	Malawi Post-natal clinic	28 SIL 268 normal cytology	PCR. L1 primer	Cases: 76.0 Controls: 28.9	7.4 ($p<0.001$)	High-grade SIL was associated with HPV only in HIV-seronegative subjects
Langley *et al.*, 1996	Dakar, Senegal Prostitutes	48 SIL 485 normal cytology	PCR	Cases: Any HPV: 66.7 HPV 16,18,45: 12.5 Controls: Any HPV: 39.0 HPV 16,18,45: 8.3	3.6 (1.8–7.3) any HPV 4.8(1.8–12.7) HPV 16, 18, 45 LSIL: 4.4 (2.6–7.4) HSIL:14.3 (6.6–30.9)	 ORs adjusted for HIV status
La Ruche *et al.*, 1998b	Abidjan, Côte d'Ivoire Gynaecology clinic	151 LSIL; 60 HSIL 151 and 240 age-matched subjects, normal cytology	PCR. L1 primer GP 5/6 primers	Cases: LSIL all HPV : 68.2 HPV 16/18: 16.8 HSIL all HPV: 81.7 HPV 16/18: 28.6 Controls: LSIL all HPV : 30.5 HPV 16/18: 2.3 HSIL all HPV :20.4 HPV 16/18: 3.7		
Temmerman *et al.*, 1999	Nairobi, Kenya Family planning clinics	28 HSIL +5 cancers 28 LSIL + 583 normal cytology	PCR. GP 5/6 primers	Cases (HSIL/Ca) 69.7 Control (LSIL/normal) 16.9	14.9 (6.8–32.8) 10.9 (5.4–30.1)[1]	[1]Adjusted for HIV status
Mayaud *et al.*, 2001	Mwanza, Tanzania Antenatal clinics	43 SIL (16 HSIL, 27 LSIL) 564 normal cytology	PCR (L1 primer) Reverse blot typing	Cases: Any HPV: 61.9 HR HPV: 42.0 Controls: Any HPV: 0.7 HR HPV: 18.9	3.7 (1.8–7.4) 3.3 (1.4–6.6)[1]	[1]Adjusted for HIV status

Infection has been shown to be linked to sexual behaviour (e.g., number of recent partners) or presence of other sexually transmitted diseases (Mayaud *et al.*, 2001; Temmerman *et al.*, 1999).

HIV

None of the case–control studies of HIV and cancer conducted in Africa have shown an excess risk of invasive cervix cancer and HIV. There is, however, evidence that the risk of pre-invasive disease (CIN) is increased in the presence of HIV infection, and that this is confined to women who are infected with HPV. The evidence is reviewed in Chapter 6.

Other infections

In a hospital-based study in Kampala, Uganda, Adam *et al.* (1972) investigated prevalence of antibodies to HSV-2 in cases of cervix cancer and in control subjects (matched for age and cervix cancer risk factors). Prevalence of infection in this population was high, with rather little difference between the cases and controls. Schmauz *et al.* (1989) investigated the prevalence of infection with HPV types 16 and 18, HSV-1 and -2, cytomegalovirus, Epstein–Barr virus and *C. trachomatis* in 34 cases of cervix cancer and 23 controls seen in Mulago hospital, Kampala. They found that the risk of cervix cancer increased with the number of concurrent infections, suggesting that chronic cervico-vaginal inflammation might increase the oncogenicity of HPV infection.

There is no evidence that the risk of cervix cancer is augmented by infection of the cervix with *Schistosoma* (Edington, 1970; Freedman *et al.*, 1974; Szela *et al.*, 1993).

Prevention

Control of cervix cancer has traditionally been through programmes of detection and treatment of precursor lesions (dysplasia/carcinoma *in situ*, CIN, SIL) by cytology. Organized screening programmes in many European countries have been successful in reducing incidence and mortality rates from levels which, before they were introduced, were not so different from those seen today in much of Africa. That the traditional Pap smear can give significant protection against development of invasive cancer has been demonstrated in many case–control studies (Parkin, 1997), including one in Morocco (Chaouki *et al.*, 1998). In this study, about one third of control women reported having had a Pap smear at some past time, and this was associated with a significantly reduced risk of invasive cancer (OR = 0.31, 95% CI 0.18–0.55).

However, screening programmes in Africa have been very limited in scope, and all have been 'opportunistic', centred on hospital or family planning clinics, rather than population-based. Reports on limited screening projects from various countries have been published: South Africa (Leiman,1987; Baile *et al.*, 1995; Heystek *et al.*, 1995; Lancaster *et al.*, 1999), Lesotho (Schneider & Meinhardt, 1984), Kenya (Mati *et al.*, 1984; Engels *et al.*, 1992), Nigeria (Ayangade & Akinyeme,1989) and Egypt (Mohga *et al.*, 1987). However, population coverage remains very low. In a survey of cytology laboratories in four countries (Côte d'Ivoire, Guinea, Mali, Senegal) in about 1995, Woto-Gaye *et al.* (1996) estimated that less than 1% of women aged at least 15 years had received a smear test that year. The results of these programmes, in terms of the yield of abnormal smears requiring follow-up or treatment, are difficult to compare, because of the selected nature of the clientèle in many 'screening' projects. However, in previously unscreened populations with a high incidence of cervix cancer, prevalence of lesions may be very high indeed. In the University of Zimbabwe/JHPIEGO Cervix Cancer Project (1999), among 10 934 women aged 25–55 years examined at 15 primary care clinics in Chitungwiza, Zimbabwe, 11% were found to have SIL, about equal numbers having LSIL and HSIL, and there were 20 prevalent cancers (1.8 per 1000).

The difficulties in implementing community programmes of screening in developing countries using the Pap smear have become increasingly obvious in recent years. The reasons lie in the logistics of organization, for all phases of the programme (screening, diagnosis and follow-up) and in the problems of maintaining good-quality cytology laboratories (Sankaranarayanan & Pisani, 1997). For this reason, there has been increasing interest in alternative screening strategies which may be easier to apply. In particular, much attention has focused on the value of screening with visual inspection following acetic acid impregnation of the cervix (VIA). One of the earliest studies to suggest that this technique might be as effective as cytology in detecting SIL was carried out in Cape Town, South Africa (Megevand *et al.*, 1996). The experience has been repeated in studies elsewhere, notably in the University of Zimbabwe/JHPIEGO Cervical Cancer Project (1999). In the second phase of this study, 2203 women underwent a Pap smear test, VIA and HPV testing, and all received diagnostic colposcopy, as well as biopsy when indicated. VIA was more sensitive (76.7%) than cytology (44.3%) in detecting HSIL or worse lesions, but specificity was lower (64.1% versus 90.6%). The relatively large number of false positives in this study may have been related to the high prevalence of sexually transmitted diseases in this particular population. Nevertheless, the high negative predictive value of VIA (96.3%) means that few significant lesions will be missed, and, if simple diagnostic triage and/or treatment can be immediately available to women who test positive, the technique holds considerable promise as a means of reducing the toll of cervix cancer in low-resource countries.

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4.4 Colorectal cancer

Introduction

Large bowel cancer is predominant in affluent societies and most frequent in North America, western Europe, Australia/New Zealand and the southern part of South America. In 2000, colorectal cancer was estimated to be the fourth most common cancer in the world in both sexes, and the second in developed countries, with an estimated 943 000 new cases (9.4% of the total). In Africa, colorectal cancers account for just 2.5% of all cancers. Almost all colorectal cancers are adenocarcinomas.

Descriptive epidemiology in Africa

Incidence is very low in Africa, except in white populations. Rates are a little higher in North Africa than in sub-Saharan Africa. The higher rates seen in the French department of La Réunion may be due to the influence of European lifestyle factors and the ethnically diverse population. Table 1 presents age-standardized incidence from cancer registries reported in this volume, with comparison data from Europe and North America. Table 2 shows incidence data from registries for the 1950s to 1970s.

Figure 1 illustrates estimated incidence rates by country, based on the incidence data available. The high incidence in the south is due to the high rates in the white populations of South Africa.

Early data from Africa show that large bowel cancers were rare. A review of published data and four hospital series obtained from doctors in up-country hospitals in Africa summarized the frequency of cancer of the colon and rectum in the 1950s and 1960s (Burkitt, 1971) (Table 3).

Davies *et al.* (1965) compared the very low rate of intestinal cancer in Kyadondo County, Uganda for the period 1954–60 with US and Norwegian rates. In Uganda, the ASR per 100 000 for colon cancer was 0.2 in males and 0.6 in females, and for rectal cancer 0.6 and 1.8, compared with 12.4 and 14.0 (colon) and 10.6 and 7.8 (rectum) in US whites. It was suggested that the paucity of gastrointestinal cancer in Ugandan Africans, particularly in the older age groups, could be attributed to lack of death certification, as 22% of the US cases were based on death certificate diagnoses. This does not suffice to explain the difference, however, since the US rates remain much higher even if the cases based on a death certificate alone are excluded.

Cancer of the rectum is more common than cancer of the colon in Africa, as in other low-risk populations, such as those in India and China (Parkin *et al.*, 2001). This is the reverse of the pattern in high-incidence populations, notably the very high incidence of colon cancer in US blacks. This difference may be influenced by easier diagnosis of rectal cancer.

Time trends

The few long data series available for Africa show an increasing trend in incidence and mortality. Rates in the long series from Kampala, Uganda (Wabinga *et al.*, 2000) rose from ASR 3.0 (1960–66) to 6.8 (1995–97) in males and from 2.7 to 6.6 in females.

Colorectal cancer is one of the leading cancers in South African whites, but 10 times rarer in the black population than in the white (2.3 and 22 per 100 000 respectively). In South Africa, changes in exposure to environmental factors have resulted in the African population overtaking the whites in prevalence of obesity in women, hypertension and diabetes (Walker, 1996). However chronic bowel diseases, and occurrence of appendicitis, diverticular disease and colon cancer have risen only slightly (Walker & Segal, 1997).

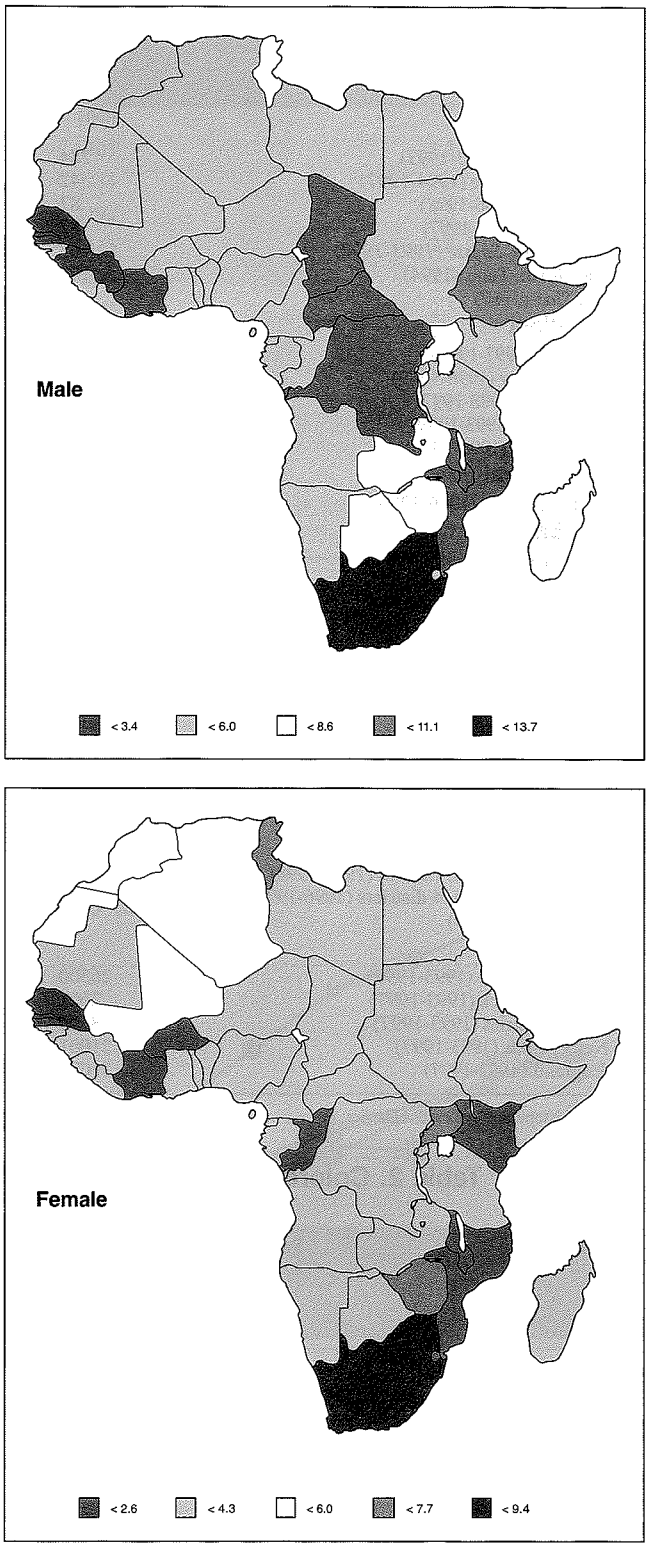

Figure 1. Age-standardized incidence of colorectal cancer in Africa

Migrant studies

Low mortality from colorectal cancer has been found among North African migrants in France (Bouchardy *et al.*, 1996) and Egyptian migrants to Australia (McCredie & Coates, 1989; Khlat *et al.*, 1993).

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Colon, rectum and anus (C18-21)

	MALE				FEMALE			
	Cases	CRUDE	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	284	5.2	**7.1**	0.41	248	4.6	**6.1**	0.42
Algeria, Constantine (1994-1997)	42	2.7	**4.1**	0.28	43	2.8	**4.2**	0.24
Algeria, Oran (1996-1998)	87	4.9	**7.2**	0.51	83	4.7	**6.1**	0.39
Algeria, Setif (1993-1997)	82	2.7	**4.6**	0.36	89	3.0	**4.3**	0.32
Tunisia, Centre, Sousse (1993-1997)	65	5.6	**7.7**	0.45	77	6.8	**8.8**	0.58
Tunisia, North, Tunis (1994)	109	5.0	**6.2**	0.41	113	5.4	**7.0**	0.37
Tunisia, Sfax (1997)	28	7.1	**8.9**	0.38	31	8.2	**9.6**	0.54
Africa, West								
The Gambia (1997-1998)	8	0.8	**1.5**	0.10	14	1.4	**2.5**	0.16
Guinea, Conakry (1996-1999)	35	1.5	**3.2**	0.23	30	1.4	**3.2**	0.16
Mali, Bamako (1988-1997)	97	2.5	**5.0**	0.34	59	1.6	**3.5**	0.27
Niger, Niamey (1993-1999)	37	2.0	**4.8**	0.35	24	1.3	**3.6**	0.23
Nigeria, Ibadan (1998-1999)	29	2.0	**3.8**	0.35	24	1.6	**2.8**	0.22
Africa, Central								
Congo, Brazzaville (1996-1999)	34	2.8	**4.4**	0.25	25	2.1	**2.8**	0.23
Africa, East								
France, La Reunion (1988-1994)	199	9.5	**12.6**	0.65	199	9.2	**10.0**	0.58
Kenya, Eldoret (1998-2000)	24	2.6	**6.3**	0.45	10	1.1	**2.2**	0.09
Malawi, Blantyre (2000-2001)	11	1.2	**2.7**	0.12	13	1.5	**2.7**	0.12
Uganda, Kyadondo County (1993-1997)	68	2.4	**8.0**	0.39	61	2.1	**7.0**	0.47
Zimbabwe, Harare: African (1990-1993)	84	3.5	**8.5**	0.47	47	2.2	**7.1**	0.53
Zimbabwe, Harare: African (1994-1997)	82	2.9	**7.4**	0.34	52	2.0	**6.7**	0.42
Zimbabwe, Harare: European (1990-1997)	133	87.0	**49.8**	2.48	118	70.0	**35.5**	1.90
Africa, South								
Namibia (1995-1998)	85	2.7	**4.4**	0.30	67	2.1	**3.3**	0.21
South Africa: Black (1989-1992)	981	1.7	**3.0**	0.18	870	1.5	**2.3**	0.15
South Africa: Indian (1989-1992)	161	8.3	**14.2**	0.66	132	6.7	**9.4**	0.56
South Africa: Mixed race (1989-1992)	252	3.9	**7.5**	0.46	280	4.2	**6.4**	0.33
South Africa: White (1989-1992)	2414	24.0	**22.2**	1.06	2295	22.5	**17.1**	0.91
South Africa, Transkei, Umtata (1996-1998)	10	2.8	**4.9**	0.37	5	1.2	**1.5**	0.05
South Africa, Transkei, 4 districts (1996-1998)	6	0.8	**1.6**	0.14	6	0.7	**0.9**	0.03
Swaziland (1996-1999)	39	2.2	**4.2**	0.22	26	1.3	**2.4**	0.20
Europe/USA								
USA, SEER: White (1993-1997)	26300	54.0	**40.0**	1.79	26334	52.5	**30.3**	1.31
USA, SEER: Black (1993-1997)	2601	38.9	**45.0**	2.40	2844	38.3	**35.7**	1.84
France, 8 registries (1993-1997)	8500	61.8	**42.2**	1.91	7215	50.0	**27.0**	1.29
The Netherlands (1993-1997)	21001	55.0	**39.3**	1.76	20703	53.0	**29.9**	1.41
UK, England (1993-1997)	71079	59.2	**36.8**	1.62	65948	51.6	**25.0**	1.09

In italics: histopathology-based registries

Table 2. Colorectal cancer pre-1980. Age-standardized incidence (all ages)

Registry	Period	ASR (per 100 000)				Source
		Colon		Rectum/anus		
		Male	Female	Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	*0.6*	0.7	1.5	1.0	4
Mozambique, Lourenço Marques	1956–60	*1.9*	*1.9*	*0.0*	*0.0*	1
Nigeria, Ibadan	1960–69	1.3	1.2	1.2	2.0	3
SA, Cape Province: Bantu	1956–59	*2.3*	*4.6*	*4.6*	*4.2*	2
SA, Cape Province: Coloured	1956–59	4.4	7.7	3.5	3.5	2
SA, Cape Province: White	1956–59	13.8	16.9	4.5	5.4	2
SA, Johannesburg, Bantu	1953–55	*1.8*	*4.1*	*2.0*	*2.2*	1
SA, Natal Province: African	1964–66	*2.0*	*2.1*	*1.1*	*3.9*	2
SA, Natal Province: Indian	1964–66	*2.7*	*7.6*	*3.5*	*10.3*	2
Uganda, Kyadondo	1954–60	*0.3*	*0.6*	*1.1*	*2.5*	1
Uganda, Kyadondo	1960–71	1.7	1.3	2.2	3.3	5
Zimbabwe, Bulawayo	1963–72	4.8	*4.1*	1.2	0.0	6

Italics: Rate based on less than 10 cases

Table 3. Proportion of cancer of the colon and rectum among total cancer in different parts of Africa

Place	Period	Total cases	Colorectal as % of total
Johannesburg (S. Africa)	1952-54	1076	2.6
Johannesburg (S. Africa)	1962-64	2407	2.4
Durban (S. Africa)	1964-66	1040	2.1
Lourenço Marques (Mozambique)	1956-60	603	1.3
Sudan	1954-61	2234	2.8
Accra (Ghana)	1942-55	1192	1.8
Kampala (Uganda)	1954-60	615	2.8
Nairobi (Kenya)	1957-63	4206	2.5
Dakar (Senegal)	1955-64	1838	2.5
Salisbury (Rhodesia)	1963-65	1415	1.6
Ilesha (Nigeria)	1954-67	465	5.8
Stanleyville (Congo Kinshasa)	1939-55	2536	1.1
Kenya (5 hospitals)	Questionnaire survey	934	1.5
Uganda (7 hospitals)	Questionnaire survey	613	2.1
Tanzania (23 hospitals)	Questionnaire survey	1743	2.3
Malawi (22 hospitals)	Questionnaire survey	827	1.7

Source: Burkitt (1971)

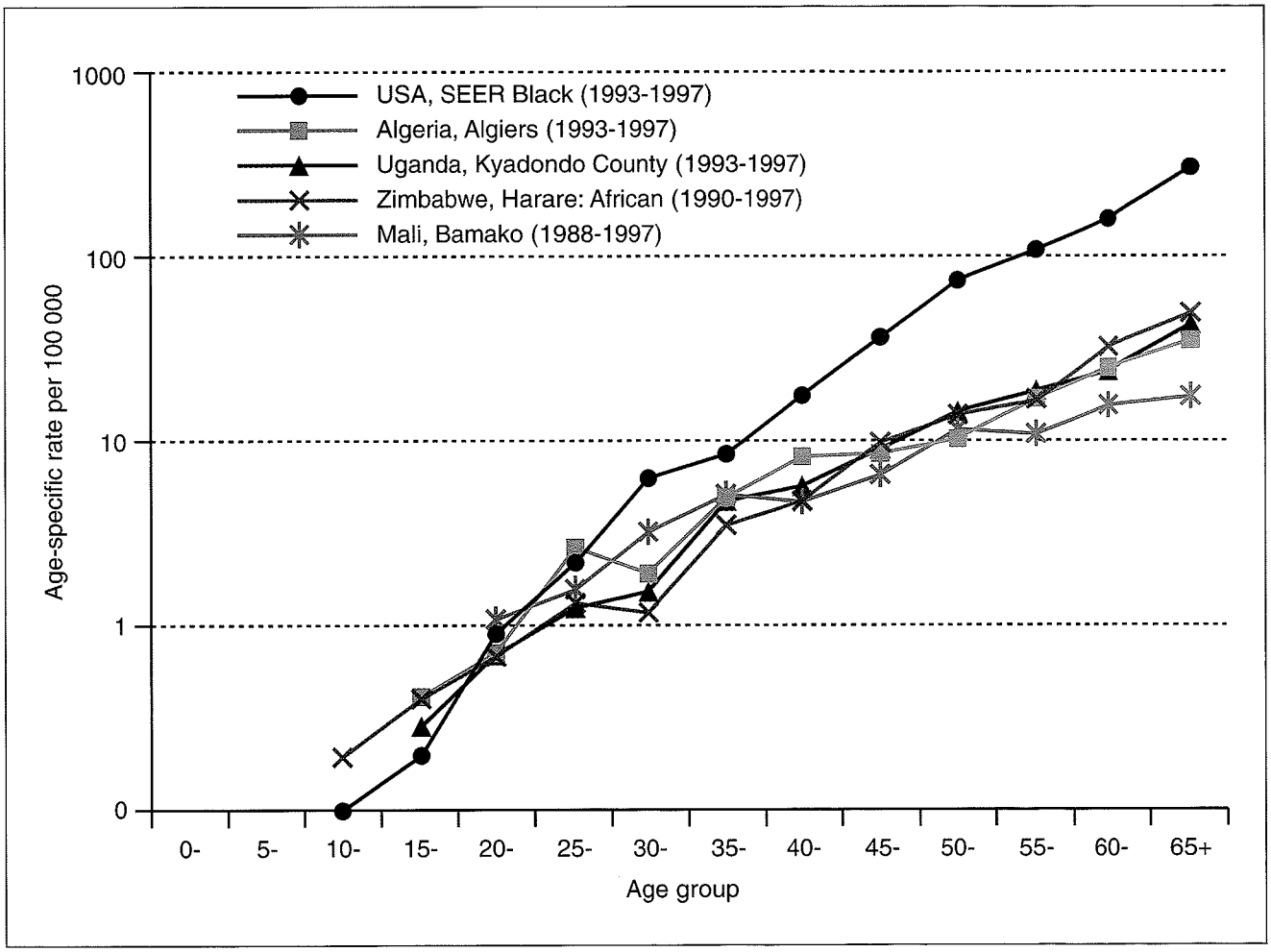

Figure 2. Age-specific incidence of colorectal cancer in four African registries and the United States

North African Arab immigrants have maintained their traditional diet, rich in cereals, legumes, green vegetables and fruit and poor in animal fats and grilled meat. The incidence in migrants from North Africa to Israel is half that of European migrants (Steinitz *et al.*, 1989).

Age-specific incidence

In many case series from Africa, e.g. in Uganda (Hutt *et al.*, 1967), Zaire (Kenda, 1976), Sudan (Elmasri & Boulos, 1975), Nigeria (Ojo *et al.*, 1991; Iliyasu *et al.*, 1996) and Egypt (Soliman *et al.*, 1999), the average age of patients with large bowel cancer was lower than in western countries. In the Egyptian study, 30.6% of cancers occurring in patients under the age of 40 years were mucin-producing tumours, compared with 13.7% in patients over the age of 40.

These differences may simply reflect the young age structure of African populations. However, age-specific incidence rates from this volume (Figure 2) do suggest that the increase of incidence wth age is much slower in African populations than in western countries (the data for the black population of the United States are shown). This may represent a cohort effect, due to increasing risk in successive generations of Africans. In South Africa, there is an eight-fold difference in incidence between the older black and white populations (e.g., males 55–64 years: 276.3 vs 33 per 100 000), but no difference in the younger age groups (e.g., 15–24 years: 1.6 vs 1.6 per 100 000), which suggests that the same lifestyle factors affecting the younger white generation may be affecting the younger black generation.

Location of lesions

The distribution of cancers within the large bowel shows marked differences according to geographical region. Evidence on the location of colorectal tumours in Africans is confusing. The distribution of carcinomas of the large intestine among the Bantu in the 1960s was reported to resemble that in westernized populations, over two thirds occurring on the left side, with the rectum as most common site followed by the caecum (Oettlé, 1964). Similarly, a report of 76 cases in Benin described 92% of malignancies occurring in the left side of the colon, 86.8% of which were in the sigmoid colon and rectum (Osime *et al.*, 1988) and in a ten-year pathology review of cases in Ile-Ife, Nigeria, the site distribution was 57.3% recto-sigmoid, 23.2% descending colon, 12.2% caecum and 3.7% for both ascending and transverse colon (Ojo *et al.*, 1991).

On the other hand, in a 20-year hospital series of 526 histologically confirmed colorectal cancers from Ibadan, Nigeria between 1971 and 1990, Iliyasu *et al.* (1996) found that neoplasms were predominantly right-sided (34.3% caecal). Colorectal cancer accounted for 3.7% of all neoplasms recorded during the period. An excess of cancer of caecum and ascending colon and a 'marked deficiency' in the sigmoid and rectosigmoid were observed by Davies (1959) in Ugandan Africans. Templeton (1973) observed that epithelial tumours were considerably more frequent in the right colon than in the left in Uganda. Muir Grieve (1967) reported a similar finding in the Cape Division of South Africa. A report on cases of colorectal cancer recorded in the Kampala Cancer Registry for the period 1964–76 described 36 (20%) of cancers of the colon as mucoid carcinomas, of which 19 were in the caecum, 7 in the ascending colon, 3 in the transverse, 2 in the descending and 5 in the sigmoid (Owor, 1983).

Risk factors

Diet

The increases in incidence in migrant populations point to an environmental causation, probably due to dietary factors, with a possible link to exercise. The roles of fat, fibre and protein and the protective effect of vegetables have been extensively examined. Protein and fat, notably from meat, are related consistently to risk of colon cancer, but inverse associations have been reported with physical activity and with intake of fish and shellfish (Potter, 1996; Hill, 1999; Kato *et al.*, 1997). There may be an association with alcohol consumption, and processed meat may confer more risk than red meat. The risk factors for cancers of both colon and rectum do not appear to be very different, but physical activity does not appear to play a role in rectal cancer.

The low incidence of cancer of the colon and rectum in Africans has frequently been related to the characteristics of the African diet, with high cereal and low animal protein consumption. Davies *et al.* (1965) described the population of Kyadondo, with its low rates, as 'peasant agriculturalists, minimally exposed to urbanization and industrialization, living on high-carbohydrate, low-protein, low-fat diets of largely unprocessed foodstuffs'. A variety of plantains remains the major source of carbohydrate in the area (Wabinga *et al.*, 2000).

Burkitt proposed a mechanism whereby fibre might protect against colorectal cancer, after measuring intestinal transit time in African villagers, boys on a semi-European diet and boys in an English boarding school and finding a clear correlation between transit time, stool bulk and the fibre content of food (Burkitt, 1971). A further factor suggested as capable of enhancing bowel motility was frequent use of emetics, laxatives and enemas (Oettlé, 1964). This was investigated in a survey among 584 residents in Lourenço Marques in the period 1956–61, which found that 9.7% of this population used emetics, 31.7% used laxatives and 3.8% enemas (Prates & Torres, 1965).

However, Walker and Segal (1997) noted that stool frequency in Africans in urban areas now averages about one motion daily, much the same as in the white population, and transit times are similar between the two populations. Mean levels of all components of faecal short-chain fatty acids (FSCH) with the exception of butyrate are significantly higher in Africans than in whites and FSCH are associated with a reduction in pH. Faecal pH values remain significantly lower in African adults and children than in the white population, which may be a protective factor (Segal, 1998).

It has been postulated that, although the dietary fibre content of the typical diet has fallen, the proportion of 'resistant' starch remains high and that this, allied with colonic microflora which seem to be more effective in fermenting fibre in Africans, may provide continuing protection (Segal *et al.*, 2000).

A dietary survey in South Africa compared nutrients in fishermen with a westernized white control group. While total fat intake in the two groups was similar, the fishermen (at low risk of colorectal cancer) had markedly higher polyunsaturated fat intake, notably of the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, and it was postulated that these fatty acids might be protective (Schloss *et al.*, 1997).

Intestinal bacteria

Burkitt (1971) reported that the stools of developing country populations were bulky, soft and non-odorous compared to those of populations in western countries, perhaps indicating a lower rate of bacterial decomposition. Individuals seem to maintain their own distinctive flora compositions, so there may be a genetic element to this factor.

Faecal specimens were examined in an ecological study of individuals (non-randomized) from four populations at different risk of colon cancer. *Bacteroides vulgatus*, *Bacteroides stercoris*, *Bifidobacterium longum* and *Bifidobacterium angulatum* were found to be significantly associated with high risk of colon cancer, *Lactobacillus S06* and *Eubacterium aerofaciens* with low risk, and total lactobacilli were inversely related to risk (Moore & Moore, 1995). Diet and output of methane (from fermented complex carbohydrate) have been studied in adult white and black South Africans (O'Keefe *et al.*, 1999). Both fasting and food-induced

breath methane production was two to three times higher in blacks, and it was concluded that differences in colonic bacterial fermentation might influence the cancer risk.

Adenomatous polyps

Adenomatous polyps and villous papillomas are strongly correlated with bowel cancer. It is probable that genetic and environmental factors interact in the formation and transformation of polyps. The hereditary cancer syndromes hereditary nonpolyposis colon cancer (HNPCC), involving a familial pattern of early onset, and the rare condition familial adenomatous polyposis coli (FAP), associated with multiple polyps in the large intestine which show a high frequency of malignant transformation, have been well characterized. It seems probable that most tumours occur in a section of the population with increased genetic susceptibility, a fact that complicates the interpretation of epidemiological studies of diet.

It has been repeatedly reported that premalignant diseases such as polyposis coli, ulcerative colitis, villous papilloma and adenoma are rare in Africans. No evidence of polyps was found in a series of 76 cases of colorectal cancer cases reported from a hospital series in Benin (Osime *et al.*, 1988). A search for polyps in the colon and rectum was made in a series of 343 post mortems of Africans over age 25 years in Uganda and no adenomatous polyps, villous papillomas or hyperplastic polyps were found (Hutt & Templeton, 1971). Owor (1983) found 18 cases of adenomatous polyps in biopsy material, and one at autopsy, in 180 cases of carcinoma of colon and 238 of rectum recorded in the Kampala Cancer Registry for the years 1964–76. In addition he noted six cases of carcinoma in the rectum and two in the colon which appeared to arise from pre-existing polyps.

In a comparison of colorectal polyps in surgical biopsies from American blacks and Nigerians in the 1960s, only 7.5% of the polyps in Nigerians were neoplastic, compared with 87% in the Americans. However, the average age of the two case series was very different, most of the Nigerian patients being under 20 years of age, and juvenile polyps accounted for about 60% of the total compared with only 9% in Americans (Williams *et al.*, 1975). In a Nigerian hospital series of 526 colorectal neoplasms, two isolated cases of familial polyposis were observed, at ages 22 and 36 years (Iliyasu *et al.*, 1996). Reports of this condition in Africans are very rare.

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4.5 Cancers of the eye and orbit

Introduction

The ICD-10 code C69 includes several anatomically distinct structures, (conjunctiva, cornea, retina, choroid, ciliary body, lacrimal gland, and orbit). The skin of the eyelid (C44.1) and the optic nerve (C72.3) are excluded, as well as lymphomas and leukaemias occurring in the orbit. Table 1 shows the incidence rates of tumours of the eye in the population-based series in this volume, and Table 2 the results from older series.

Particularly in the more recent data, the incidence rates for all eye cancers combined are rather higher in many of the sub-Saharan populations than in Europe or the United States. Table 3 shows the histological subtypes for the data-sets published in this volume, indicating that there is a relatively high percentage of squamous-cell carcinomas, which occur almost entirely on the conjunctiva. The predominance of retinoblastoma and squamous-cell conjunctival cancers in African case series has been noted many times before, as has the rarity of uveal melanomas in African populations. Case series are generally concerned with the percentages of different histological types of eye and orbital tumours, but comparison between them is complicated by lack of information on the age distribution of the series (those containing many children will include more retinoblastomas), the inclusion of tumours of surrounding structures, and lymphomas (particularly Burkitt lymphomas). Involvement of the orbit is frequently seen in Burkitt lymphoma, but involvement of the globe itself is very infrequent.

Templeton (1973) reported a series of 314 invasive tumours of the eye and adnexae in Uganda, comprising 59 cases of Burkitt lymphoma of the orbit, 53 squamous-cell carcinomas of the conjunctiva and 57 retinoblastomas. Three melanomas (one uveal) and four Kaposi sarcomas (one of eyelid) were noted in this series. No rhabdomyosarcomas were reported. Klauss and Chana (1983) reported on 470 cases of orbital disease, including 187 malignant tumours, in Kenya. The histological profile was similar to that in the Uganda series (39% retinoblastomas, 23% Burkitt lymphomas and 6.4% squamous cell carcinomas).

Retinoblastomas are found mainly in children (see Chapter 5), and are very rare after the age of 5 years.

Melanoma of the eye

As noted earlier, melanomas of the eye are rare in black African populations. For example, in the South African series, in whites, melanomas of the eye comprised 19% of all eye cancers, while only 1.9% of eye cancers in blacks were melanomas. Similar results were found in other series, reviewed by Klauss and Chana (1983): melanoma of the eye comprised 0.7% of 1487 eye cancer cases seen in Kenya (Awan & Shah, 1980), 0.3% of 312 cases in Uganda (Templeton, 1967), 1.6% of 191 cases in Nigeria (Olurin & Williams, 1972) and 0.7% of 279 cases seen in Sudan (Malik & Sheikh, 1979).

Northern European ancestry, presence of naevi and intense sun exposure and UV radiation appear to be risk factors for uveal melanoma (Seddon *et al.*, 1990; Holly *et al.*, 1990); this could explain the 10-fold higher relative frequency among white South Africans than among blacks. In the United States, the incidence of melanoma of the eye is at least ten times higher in whites (adults) than blacks (Parkin *et al.*, 1997). Reasons for the variations among Africans are unclear, and are more likely to relate to the unsystematic nature of data collection than to any real trend. Nevertheless, in the Sudan all six cases of intra-ocular melanoma occurred in the Arab population, and none in Africans (Malik & Sheikh, 1979). No geographical association was found between ultraviolet radiation and melanoma incidence in cancer registries from the United States (Sun *et al.*, 1997).

Squamous-cell carcinoma of the conjunctiva

This tumour appears to be common in many parts of Africa. Klauss and Chana (1983) reported relative frequencies of squamous-cell conjunctival cancers, which appeared to vary from place to place. Conjunctival cancers comprised 21.8% of eye cancers in Kenya (Awan & Shah, 1980), 16.0% in Uganda (Templeton, 1967), 6.2% in Nigeria (Olurin & Williams, 1972) and 50% in Sudan (Malik & Shah, 1979). The tumours occur close to the limbus, usually on the nasal aspect. They are preceded by a spectrum of lesions, showing progression from slight acanthosis and hyperkeratosis (pterygium), through progressive degrees of epithelial dysplasia and intra-epithelial carcinoma, to frank invasion (Clear *et al.*, 1979). It has long been suspected that increased exposure to ultraviolet light is responsible, although roles for other factors, such as dust, dry air, wind, trachoma and vernal catarrh have been suggested (Klauss & Chana, 1983).

Human papillomavirus (HPV) has been measured in a variety of ways in a number of small studies and types 6, 16, 11 and 18 were found in lesions of dysplasia and conjunctival cancer (Newton, 1996; IARC, 1995), but the results are inconsistent. Bovine papillomaviruses infect the conjunctiva of cattle (Ford *et al.*, 1982) and it is plausible that certain HPV types may infect the conjunctiva and cause cancer. However, in a case–control study in Uganda, comparing 60 conjunctival neoplasms (60% with histological confirmation) with 1214 controls (subjects with a variety of proved or suspected cancers, excluding those known to be associated with HIV, HPV or human herpes virus 8 (HHV-8)), Newton *et al.* (2002) found no association with presence of antibody to HPV-16 (OR 1.5, 95% CI 0.5–4.3). There was no association either with antibody to HPV 18 and 45, although seroprevalence to these two types was low, so that the confidence intervals were wide.

Ecological studies have shown that there is a significant association between cloud-adjusted UV-B ultraviolet B radiation and incidence of squamous-cell conjunctival cancers internationally (Newton *et al.*, 1996) and in the United States (Sun *et al.*, 1997). Newton *et al.* (1996) estimated that the incidence of squamous-cell conjunctival cancer declines by 49% for each 10° increase in latitude, falling from about 12 cases per million in Uganda (0.3°N) to less than 0.2 cases per million in the northern European countries. In the case–control study described above (Newton *et al.*, 2002), risk was increased in individuals who spent a lot of time cultivating; this perhaps indicates higher exposures to UV radiation.

The incidence of squamous-cell carcinoma of the conjunctiva has been greatly increased by the epidemic of HIV/AIDS. This topic has been reviewed by Newton (1996) and IARC (1996), and is described in Chapter 6. Incidence rates of conjunctival carcinoma in the registry series in this volume are shown in Table 4.

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Table 1. Age-standardized (world) and cumulative (0-64) incidence
Eye (C69)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	20	0.4	**0.5**	0.02	22	0.4	**0.5**	0.03
Algeria, Constantine (1994-1997)	2	0.1	**0.2**	0.01	2	0.1	**0.2**	0.03
Algeria, Oran (1996-1998)	18	1.0	**1.2**	0.04	8	0.5	**0.6**	0.02
Algeria, Setif (1993-1997)	4	0.1	**0.2**	0.02	5	0.2	**0.2**	0.00
Tunisia, Centre, Sousse (1993-1997)	5	0.4	**0.5**	0.04	5	0.4	**0.5**	0.02
Tunisia, North, Tunis (1994)	9	0.4	**0.5**	0.03	6	0.3	**0.4**	0.02
Tunisia, Sfax (1997)	2	0.5	**0.5**	0.03	1	0.3	**0.2**	0.02
Africa, West								
The Gambia (1997-1998)	6	0.6	**1.0**	0.06	5	0.5	**0.6**	0.05
Guinea, Conakry (1996-1999)	31	1.4	**1.7**	0.11	10	0.5	**0.4**	0.02
Mali, Bamako (1988-1997)	28	0.7	**0.9**	0.05	25	0.7	**1.1**	0.05
Niger, Niamey (1993-1999)	15	0.8	**1.1**	0.11	7	0.4	**0.6**	0.03
Nigeria, Ibadan (1998-1999)	15	1.0	**1.3**	0.03	7	0.5	**0.5**	0.03
Africa, Central								
Congo, Brazzaville (1996-1999)	6	0.5	**0.6**	0.02	9	0.7	**0.7**	0.04
Africa, East								
France, La Reunion (1988-1994)	7	0.3	**0.4**	0.01	7	0.3	**0.4**	0.03
Kenya, Eldoret (1998-2000)	9	1.0	**0.9**	0.07	5	0.5	**0.6**	0.04
Malawi, Blantyre (2000-2001)	18	2.0	**2.5**	0.10	25	2.9	**4.2**	0.34
Uganda, Kyadondo County (1993-1997)	76	2.7	**2.9**	0.22	64	2.2	**2.8**	0.23
Zimbabwe, Harare: African (1990-1993)	17	0.7	**1.0**	0.05	17	0.8	**0.9**	0.07
Zimbabwe, Harare: African (1994-1997)	67	2.4	**2.6**	0.16	73	2.8	**3.6**	0.27
Zimbabwe, Harare: European (1990-1997)	6	3.9	**2.7**	0.15	-	-	**-**	-
Africa, South								
Namibia (1995-1998)	45	1.4	**1.8**	0.14	42	1.3	**1.6**	0.13
South Africa: Black (1989-1992)	271	0.5	**0.6**	0.04	206	0.4	**0.4**	0.02
South Africa: Indian (1989-1992)	7	0.4	**0.5**	0.02	3	0.2	**0.2**	0.01
South Africa: Mixed race (1989-1992)	12	0.2	**0.2**	0.01	23	0.3	**0.4**	0.02
South Africa: White (1989-1992)	102	1.0	**1.0**	0.05	77	0.8	**0.7**	0.04
South Africa, Transkei, Umtata (1996-1998)	-	-	**-**	-	-	-	**-**	-
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.1**	0.00	4	0.4	**0.5**	0.02
Swaziland (1996-1999)	16	0.9	**1.4**	0.11	13	0.7	**0.9**	0.06
Europe/USA								
USA, SEER: White (1993-1997)	459	0.9	**0.8**	0.04	372	0.7	**0.6**	0.04
USA, SEER: Black (1993-1997)	13	0.2	**0.2**	0.01	15	0.2	**0.3**	0.01
France, 8 registries (1993-1997)	141	1.0	**0.9**	0.05	108	0.7	**0.5**	0.03
The Netherlands (1993-1997)	353	0.9	**0.8**	0.05	336	0.9	**0.7**	0.04
UK, England (1993-1997)	1025	0.9	**0.7**	0.04	969	0.8	**0.6**	0.03

In italics: histopathology-based registries

Table 2. Incidence of cancer of the eye in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	1.5	0.9	4
Mozambique, Lourenço Marques	1956–60	*2.4*	*0.6*	1
Nigeria, Ibadan	1960–69	*0.3*	0.5	3
SA, Cape Province: Bantu	1956–59	0.0	*1.5*	2
SA, Cape Province: Coloured	1956–59	*0.2*	*0.6*	2
SA, Cape Province: White	1956–59	*1.5*	*0.6*	2
SA, Johannesburg, Bantu	1953–55	*0.7*	*0.3*	1
SA, Natal Province: African	1964–66	*0.6*	*1.0*	2
SA, Natal Province: Indian	1964–66	*1.3*	*0.0*	2
Uganda, Kyadondo	1954–60	1.0	1.6	1
Uganda, Kyadondo	1960–71	0.8	*0.3*	5
Zimbabwe, Bulawayo	1963–72	*0.7*	*0.4*	6

Italics: Rate based on less than 10 cases

Table 3. Percentage distribution of microscopically verified cases by histological type

Eye (C69) - Both sexes

	Retino-blastoma	Melanoma	Carcinoma Squamous	Carcinoma Other	Carcinoma Unspec.	Sarcoma	Other	Unspecified	Number of cases MV	Number of cases Total
Algeria, Algiers	59.5	5.4	13.5	2.7	13.5	5.4	-	-	**37**	42
Algeria, Batna	50.0	50.0	-	-	-	-	-	-	**2**	3
Algeria, Constantine	25.0	25.0	25.0	25.0	-	-	-	-	**4**	4
Algeria, Oran	65.4	3.8	19.2	-	7.7	-	-	3.8	**26**	26
Algeria, Setif	44.4	-	55.6	-	-	-	-	-	**9**	9
Burkina Faso, Ouagadougou	28.6	-	28.6	28.6	-	14.3	-	-	**7**	16
Congo, Brazzaville	50.0	-	16.7	16.7	-	-	-	16.7	**6**	15
France, La Reunion	30.8	23.1	30.8	-	7.7	7.7	-	-	**13**	14
The Gambia	16.7	-	50.0	-	-	33.3	-	-	**6**	11
Guinea, Conakry	-	-	75.0	-	25.0	-	-	-	**4**	41
Kenya, Eldoret	21.4	14.3	50.0	-	-	14.3	-	-	**14**	14
Malawi, Blantyre	8.3	2.8	80.6	-	2.8	2.8	-	2.8	**36**	43
Mali, Bamako	67.7	-	19.4	-	3.2	9.7	-	-	**31**	53
Namibia	12.9	1.2	80.0	-	-	3.5	-	2.4	**85**	87
Niger, Niamey	25.0	16.7	41.7	-	16.7	-	-	-	**12**	22
Nigeria, Ibadan	71.4	-	28.6	-	-	-	-	-	**14**	22
Rwanda, Butare	8.3	8.3	16.7	-	-	8.3	-	58.3	**12**	14
South Africa: Black	33.1	1.9	45.9	2.1	0.4	3.6	0.2	12.8	**477**	477
South Africa: White	20.7	19.0	52.5	1.1	2.8	2.2	0.6	1.1	**179**	179
South Africa: Indian	60.0	-	10.0	-	10.0	-	-	20.0	**10**	10
South Africa: Mixed race	48.6	14.3	31.4	2.9	-	2.9	-	-	**35**	35
South Africa, Elim	36.8	5.3	52.6	-	5.3	-	-	-	**19**	21
South Africa, Transkei, Umtata	-	-	-	-	-	-	-	-	**-**	-
South Africa, Transkei, 4 districts	40.0	-	40.0	-	-	-	-	20.0	**5**	5
Swaziland	7.7	3.8	84.6	3.8	-	-	-	-	**26**	29
Tanzania, Dar Es Salaam	23.5	-	58.8	5.9	2.9	4.4	2.9	1.5	**68**	68
Tanzania, Kilimanjaro	14.1	-	78.1	1.6	6.3	-	-	-	**64**	66
Tunisia, Centre, Sousse	40.0	10.0	50.0	-	-	-	-	-	**10**	10
Tunisia, North, Tunis	15.4	23.1	61.5	-	-	-	-	-	**13**	15
Tunisia, Sfax	-	-	-	66.7	-	-	33.3	-	**3**	3
Uganda, Mbarara	45.0	5.0	40.0	10.0	-	-	-	-	**20**	22
Uganda, Kyadondo County	14.0	2.2	78.5	1.1	2.2	-	-	2.2	**93**	140
Zimbabwe, Harare: African	20.9	-	73.4	1.3	1.9	1.9	0.6	-	**158**	174
Zimbabwe, Harare: European	-	16.7	66.7	-	-	-	16.7	-	**6**	6

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Table 4. Age-standardized (world) and cumulative (0-64) incidence
Conjunctiva: squamous cell carcinoma*

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	1	0.0	**0.0**	-	2	0.0	**0.0**	0.00
Algeria, Constantine (1994-1997)	-	-	-	-	-	-	-	-
Algeria, Oran (1996-1998)	2	0.1	**0.2**	-	2	0.1	**0.1**	0.00
Algeria, Setif (1993-1997)	1	0.0	**0.0**	0.00	2	0.1	**0.1**	0.00
Tunisia, Centre, Sousse (1993-1997)	1	0.1	**0.1**	0.02	-	-	-	-
Tunisia, North, Tunis (1994)	1	0.0	**0.1**	0.01	-	-	-	-
Tunisia, Sfax (1997)	-	-	-	-	-	-	-	-
Africa, West								
The Gambia (1997-1998)	2	0.2	**0.4**	0.03	2	0.2	**0.2**	0.01
Guinea, Conakry (1996-1999)	13	0.6	**0.9**	0.08	3	0.1	**0.1**	0.01
Mali, Bamako (1988-1997)	5	0.1	**0.2**	0.01	1	0.0	**0.1**	-
Niger, Niamey (1993-1999)	1	0.1	**0.2**	0.02	1	0.1	**0.3**	-
Nigeria, Ibadan (1998-1999)	3	0.2	**0.4**	0.00	-	-	-	-
Africa, Central								
Congo, Brazzaville (1996-1999)	1	0.1	**0.1**	0.01	-	-	-	-
Africa, East								
France, La Reunion (1988-1994)	2	0.1	**0.1**	0.00	-	-	-	-
Kenya, Eldoret (1998-2000)	4	0.4	**0.5**	0.04	3	0.3	**0.4**	0.03
Malawi, Blantyre (2000-2001)	13	1.4	**2.0**	0.07	17	2.0	**2.6**	0.23
Uganda, Kyadondo County (1993-1997)	57	2.0	**2.3**	0.20	47	1.6	**2.0**	0.16
Zimbabwe, Harare: African (1990-1993)	5	0.2	**0.3**	0.02	5	0.2	**0.2**	0.02
Zimbabwe, Harare: African (1994-1997)	43	1.5	**1.5**	0.12	56	2.1	**2.5**	0.17
Zimbabwe, Harare: European (1990-1997)	2	1.3	**0.7**	0.05	-	-	-	-
Africa, South								
Namibia (1995-1998)	35	1.1	**1.5**	0.12	33	1.0	**1.3**	0.11
South Africa: Black (1989-1992)	84	0.1	**0.2**	0.01	63	0.1	**0.1**	0.01
South Africa: Indian (1989-1992)	1	0.1	**0.1**	-	-	-	-	-
South Africa: Mixed race (1989-1992)	2	0.0	**0.1**	-	8	0.1	**0.1**	0.01
South Africa: White (1989-1992)	57	0.6	**0.5**	0.03	20	0.2	**0.2**	0.01
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	2	0.2	**0.3**	0.01
Swaziland (1996-1999)	14	0.8	**1.2**	0.11	9	0.5	**0.6**	0.06
Europe/USA								
USA, SEER: White (1993-1997)	40	0.1	**0.1**	0.00	9	0.0	**0.0**	0.00
USA, SEER: Black (1993-1997)	-	-	-	-	-	-	-	-
France, 8 registries (1993-1997)	9	0.1	**0.0**	0.00	4	0.0	**0.0**	-
The Netherlands (1993-1997)	6	0.0	**0.0**	0.00	1	0.0	**0.0**	0.00
UK, England (1993-1997)	23	0.0	**0.0**	0.00	10	0.0	**0.0**	0.00

* Includes conjunctival neoplasm (C69.0) with unspecified histology or carcinoma NOS (M8000-8034), and squamous cell carcinoma (M8070) of eye, NOS (C69.9)
In italics: histopathology-based registries

4.6 Kaposi sarcoma

Introduction

Kaposi sarcoma is a tumour arising from a pluripotential angioformative cell, or angioblast. The cells of the tumour show features of venous endothelial, fibroblastic, smooth muscle and peripheral cell differentiation. The early patch-stage macular lesions contain abnormally shaped, dilated vessels surrounded by a mononuclear-cell infiltrate containing plasma cells; nuclear atypia and mitoses are rarely seen. In the plaque-stage lesions, there is proliferation of spindle-shaped cells in the superficial-to-deep dermis, with rare proliferation of spindle-shaped cells, nuclear atypia and mitoses. Spindle cells, which often surround slit-like vascular spaces, are characteristic of more advanced nodular lesions.

Epidemiologically, Kaposi sarcoma has been classified into sporadic (classic), endemic (African), epidemic (AIDS-related) and immunosuppression-associated (usually in transplant recipients) types; however, the histopathology of all of these types is identical (Templeton, 1981).

The earliest reports from Africa describe the presence of Kaposi sarcoma (KS) histopathology slides in South Africa as early as 1912 (Oettlé, 1962) and in the Cameroon in 1914 (Gigase, 1984). Since about 1950, it was noted that this tumour had an unusual worldwide distribution, with the highest incidence in central Africa. Although rarer, KS was also found in southern and northern Africa and countries around the Mediterranean littoral and the Middle East. It was almost non-existent elsewhere, except in immigrants from these endemic countries (Biggar *et al.*, 1984, Grulich *et al.*, 1992, Hjalgrim *et al.*, 1996) and a few isolated clusters elsewhere.

In developed countries, KS was one of the most common cancers occurring among recipients of organ transplants (Penn, 1995; Margolius, 1995), especially if the recipients were of Mediterranean or Middle Eastern origin. Immune suppression caused by cancer chemotherapeutic drugs was found to be a risk factor for KS, and these observations led to suspicion that KS was caused by an infection (e.g., Kinlen, 1982). The appearance of an aggressive form of KS in 1981 in the United States among homosexual men heralded the onset of the HIV/AIDS epidemic (Centers for Disease Control, 1981) and it was suggested that KS was caused by a combination of a sexually transmitted agent and immune suppression (Peterman *et al.*, 1993). In the meanwhile, as the HIV epidemic spread in East and then Southern Africa, KS became increasingly common. For example, in Kampala in 1989–92, KS was the most common cancer in males and the second most common cancer in females (Wabinga *et al.*, 1993) and it is now the commonest cancer in males in Harare, Malawi, Rwanda, Zambia and possibly other central, eastern and southern African countries where cancer registration is non-existent. In 1996, a new virus of the herpes virus family (human herpesvirus 8 (HHV-8)) was found to be present in almost all tissues of KS (Chang *et al.*, 1994) and this virus is now thought to be the cause of KS (Chang *et al.*, 1994; Whitby *et al.*, 1995). The close association between KS and immune suppression (post-transplant, cancer chemotherapy or HIV-induced) suggests that KS is under tight immunological control (Boshoff & Moore, 1998).

Distribution in Africa before the advent of HIV: endemic KS

'Classic' or endemic Kaposi sarcoma affects predominantly the skin of the lower limbs; internal organs are rarely involved, Figure 1. The disease typically follows an indolent course, patients surviving for an average of 10–15 years (Templeton & Bhana, 1975). Young children tend to have more severe disease than adults, with a corresponding poorer prognosis. The sex distribution is more equal than in adults and the lesions often affect the lymphatic system and internal organs rather than the skin (Oettlé, 1962; Slavin *et al.*, 1970; Olweny *et al.*, 1976; Ziegler & Katongole-Mbidde, 1996).

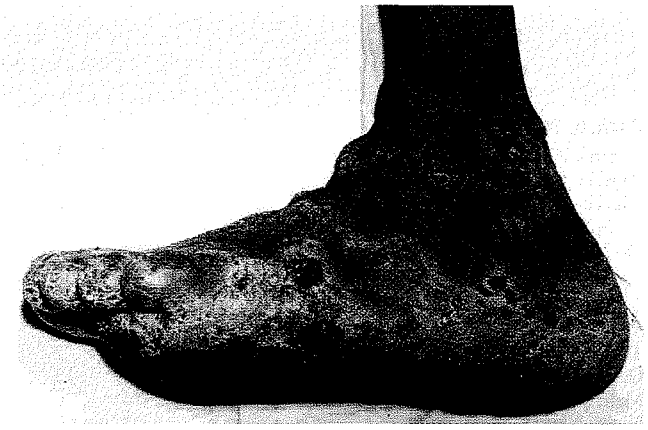

Figure 1. Kaposi sarcoma.

A number of reviews described the striking distribution of KS in Africa before the advent of HIV, defined here for practical reasons as before 1980 (Oettlé, 1962; Templeton, 1981; Hutt, 1981, 1984; Gigase, 1984; Cook-Mozzaffari *et al.*, 1998). Figure 2 draws together results of these early studies, in terms of relative frequency of KS in clinical series from different regions.

KS appeared to have an 'epicentre' around the West Nile district in Uganda and the north-west of the Democratic Republic of the Congo (former Zaire), with relative frequencies ranging between 5% and 18% of all cancers (Oettlé, 1962; Templeton, 1981; Hutt & Burkitt, 1965; Hutt 1981; Oates *et al.*, 1984) stretching to the west

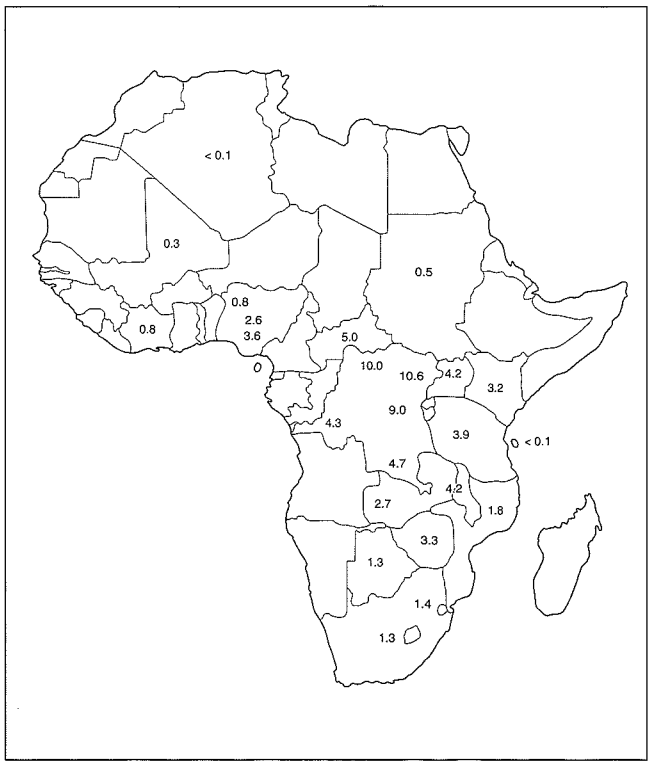

Figure 2. Map showing percentage frequency of Kaposi sarcoma (both sexes combined) (from Hutt, 1984)

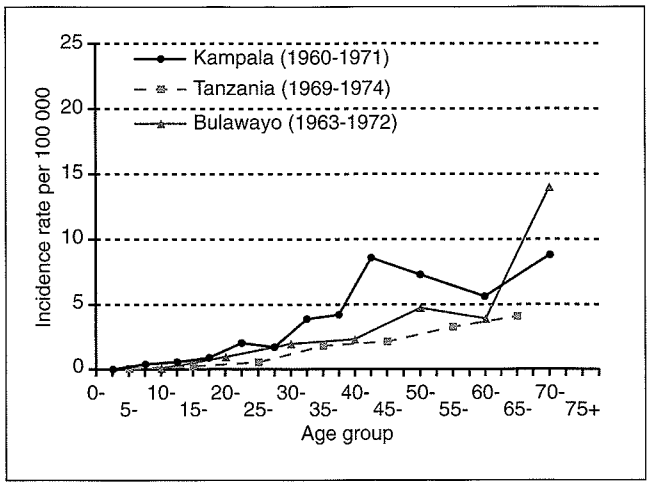

Figure 3. Kaposi sarcoma: estimated incidence in males
Sources: Wabinga *et al.*, 2000; Bland *et al.*, 1977; Skinner *et al.*, 1993

coast of the Cameroon (Jensen *et al.*, 1978) and to the south along the rift valley to southern Africa (Oettlé, 1962). The cumulative incidence rate of KS around the West Nile district was estimated to be about 6–15 per 1000, i.e. similar to the incidence of colon cancer in certain developed countries (Cook-Mozzaffari *et al.*, 1998). Cook-Mozzaffari *et al.* (1998) speculate that the distribution of KS shows an original focus in the high altitudes of north-eastern Zaire spreading via trade or migration routes to North Africa, Mecca and the Mediterranean littoral, and to the mines of southern Africa.

KS was rare (comprising about 1% of all cancers or less) in western, northern and southern Africa, although even in these places the estimated cumulative incidence of about 1 per 1000 was much greater than that seen in countries such as the United Kingdom, United States, Norway and Sweden, where the cumulative incidence of KS was typically around 0.005 per thousand or less, comprising about 0.3% of male and 0.1% or less of female cancers (Hjalgrim *et al.*, 1996; Grulich *et al.*, 1992; Gigase, 1984).

Age and sex

Endemic KS in Africa was primarily a disease of the elderly, with incidence rates rising progressively after the age of 30–35 years. In older age groups, KS was about 10 times more common in men than women (Oettlé, 1962; Hutt, 1981). Figure 3 shows estimated incidence in men in Kampala Uganda in 1960–71 (Wabinga *et al.*, 2000), in Tanzania in 1972–74 (Bland *et al.*, 1977) and in Bulawayo, Zimbabwe in 1963–72 (Skinner *et al.*, 1993).

The sex ratio (M:F) of sporadic KS in developed countries varies from about 3:1 in the United States and Sweden to 1:1 in the United Kingdom (Grulich *et al.*, 1992). Hormonal factors have been postulated as the reason for the male:female differences but possible mechanisms underlying these findings remain unclear.

Within-country contrasts

Striking within-country distributions of KS were documented within Uganda and the Democratic Republic of the Congo, with populations around the West Nile district and the areas bordering Lake Kivu showing the greatest relative frequencies in Africa and worldwide. In Kenya and Tanzania, KS comprised about 3–5% of all cancers, whereas on the island of Zanzibar, 0.1% of all cancers (Hutt, 1984; Oettlé, 1962). In the early reviews, KS was reported to be common in southern Sudan, but absent in the north (Malik *et al.*, 1974).

Geographical and/or ethnic differences in frequency of KS have been described in Uganda (Hutt & Burkitt, 1965; Cook & Burkitt, 1971; Taylor *et al.*, 1972; Owor & Hutt, 1977), Tanzania (Bland *et al.*, 1977) and Kenya (Rogoff, 1968). Hutt (1981), however, suggested that geographical rather than ethnic or sociocultural factors appeared more important. It is unclear whether these and the within-country differences suggest some lifestyle, genetic or geographical difference in environmental exposure. In South Africa, pre-AIDS KS was rarer in whites, coloureds and Indians than in blacks, suggesting that some sociodemographic factors may play an important role in certain places.

Migrant studies

Pre-AIDS reports from developed countries suggested that KS was a disease of men of Italian or Jewish origin (Rothman, 1962). Nevertheless, in the United Kingdom, immigrants from central and west Africa, the Middle East and the Caribbean had greater relative risks of developing KS (about 8- to 50-fold) compared with, e.g., Irish immigrants (RR = 1.1; Grulich *et al.*, 1992). No cases of KS were found in the American negro population of Washington, DC in 1965–69 (Kovi & Heshmat, 1972). Similarly in Haiti, inhabited by black populations originating from the West African coast, no cases of KS were recorded before 1979; however, between 1979 and 1984, KS comprised 4.3% of all male and 1.3% of all female cancers (Mitacek *et al.*, 1986). Reasons for the absence of KS among migrants of African origin in France, Haiti and the United States before the advent of AIDS are unclear, but it is possible that these populations originated from places where the pre-AIDS incidence of KS was low.

Environmental and genetic determinants of risk

On the basis of the geographical distribution of KS, high rainfall (Gigase, 1984), humidity or proximity to water (Ziegler *et al.*, 1997), high rural density and altitudes over 600 m (Cook-Mozzaffari *et al.*, 1998) and residence on volcanic soils (Ziegler, 1993) have been suggested as risk factors for development of KS, but confounding by other factors associated with these exposures cannot be ruled out. In rural Africa, many of these features are closely correlated (Cook-Mozzaffari *et al.*, 1998), as they are found in the most fertile and therefore the most populated places.

There have been disappointingly few individual-based studies of potential risk factors for endemic KS. Early studies in Europe and the United States suggested that markers of infection by cytomegalovirus (CMV) were more frequent in cases of KS than in control subjects (Giraldo *et al.*, 1984). However, in Africa, although subjects with KS also had high titres of antibody to CMV, they were not significantly different from those in the age–sex-matched control subjects (Giraldo *et al.*, 1981). The tiny case–control study of McHardy *et al.* (1984) in the West Nile district of Uganda (19 cases, 19 controls) had insufficient power to detect all but the grossest risks. Cases were more prone to drink water from rivers or to have received bites from various types of insect, though neither was close to statistical significance. Kestens *et al.* (1985) studied 27 cases of clinically endemic KS (histologically confirmed) and 41 age-, sex- and tribe-matched controls from Katana in eastern Zaire (Congo). All were HIV (HTLV III)-negative and the authors found no association with immune status (as judged by immunoglobulin levels, counts of different lymphocyte subsets, skin test reactivity, etc.) and antibody titres to various viruses (Epstein–Barr, CMV, hepatitis B) were similar in cases and controls. In a later report on 23 of these KS cases and 23 matched controls, Melbye *et al.* (1987) found no difference with respect to HLA antigens, notably DR5 and DR3. These had been suspected as being linked to KS (sporadic and AIDS-related) susceptibility in earlier studies in the United States and Europe.

KS after HIV: epidemic KS

In the 'epidemic' form of KS, the lesions are usually multiple, progress rapidly and may affect any area of the skin as well as internal organs. The tumours frequently begin as dusky red or violet macules, progressing over weeks or months to plaques and raised, usually painless, firm nodules and plaques. Although the tumour may affect

the legs, as seen with 'classic' KS, lesions of the trunk, arms, genitalia and face are also common. Lymph nodes and the oral cavity, most notably the palate, may be extensively involved. Oral KS is often associated with involvement elsewhere in the gastrointestinal tract (Levine, 1993). Pulmonary KS generally presents with shortness of breath and cough and is clinically difficult to distinguish from other pulmonary complications of AIDS (Levine, 1993).

Although the incidence of KS has increased a thousand-fold or more in populations at high risk of HIV in, for example, the United States (Biggar *et al.*, 1984; Rabkin *et al.*, 1991), in the rest of the population the tumour still remains relatively rare (Rabkin *et al.*, 1991; Grulich *et al.*, 1992). In Africa, an increase in the frequency of KS cases, with the clinical features described above, was noted first in Zambia in the early 1980s (Bayley, 1984). In the following 10–15 years, in areas with a high prevalence of HIV infection and where KS was relatively common before the era of AIDS, the incidence of KS has increased about 20-fold, for example in Malawi, Swaziland, Uganda and Zimbabwe, and it is now the most common cancer in men and the second most common in women (Wabinga *et al.*, 1993; Bassett *et al.*, 1995; Banda *et al.*, 2001; Wabinga *et al.*, 2000).

The incidence of KS (age-standardized incidence per 100 000 person years) from the series presented in this volume is shown in Table 1. Age-standardized incidence of KS is highest in Kyadondo county in Uganda (M = 37.7, F = 20.5), Blantyre, Malawi (M = 49.9, F = 31.7), Harare, Zimbabwe (African) (M = 50.9, F = 21.6) and Swaziland (M = 17.2, F = 9.5). In the black population in South Africa, the incidence of KS (until 1992) was low (males = 0.7, females = 0.2, Sitas *et al.*, 1997), but about a three-fold increase occurred between 1993 and 1995 (Sitas *et al.*, 1998), in keeping with the increases seen in Uganda and other central African countries at the beginning of the HIV epidemic. In West Africa the incidence of KS is low—less than 2/100 000 in males and 1 per 100 000 in females. In both South and West Africa, however, HIV was introduced later than in the countries of East and Central Africa. Overall, there does appear to be a geographical association between the median prevalence of HIV in different countries (see Chapter 6, Table 1) and the incidence of KS.

Age-specific incidence

Since the early 1990s, the age-specific incidence rates in countries of East and Central Africa have been markedly influenced by the prevalence of infection with HIV. Thus, incidence shows a pattern reminiscent of the prevalence of HIV infection, with a modest peak for children aged zero to four years, a decline until age 15 years and then a progressive increase to a peak at age 35–39 years in men and 25–29 years in women (Figure 4).

KS in children

A few reports have described the incidence of KS in children in Africa. Bland *et al.* (1977) reported an incidence of KS in children (0–9 years) in Tanzania between 1969 and 1974 of 1.1 per million in boys and 0.6 per million in girls, whereas in Nigeria it appeared to be rare (< 0.1% of childhood cancers; see Chapter 3.2.13, Table 6). The incidence of KS in children In Zambia has increased since the HIV epidemic (Chintu *et al.*, 1995) and in the rest of Africa, KS in childhood comprises about 10% of all childhood cancers and has increased to about 10 per million (see tables).

Risk factors

HIV

Four case–control studies in Africa have assessed the relationship between HIV and KS. All found elevated relative risks between HIV and KS: 35 in Rwanda (Newton *et al.*, 1995), 62 in Johannesburg (Sitas *et al.*, 1997), 95 in children from Uganda (Newton *et al.*, 2001) and 22 in a later study in Johannesburg (Sitas *et al.*, 2000). The relative risks found in the African studies are much lower than those found among HIV-infected people in developed countries, which are usually 300 or more (Goedert *et al.*, 1998). Complex pathology and rapid mortality may hide some of the cancers that occur in association with HIV in Africa. However, as the pre-AIDS incidence of KS in Africa was much greater than elsewhere, it is not surprising that the relative risks in Africa in association with HIV and the magnitude of the increase over time are much lower in Africa. In the Gambia, Ariyoshi *et al.* (1998) observed 15 cases of KS among 609 HIV-1-positive subjects diagnosed in 1986–96 in two hospitals, compared with one case among 636 persons found to be positive for HIV-2. This corresponds to an OR (adjusted for sex and CD4%) of 12.4 (95% CI 1.5–100.6) for KS in HIV-1 infection, relative to HIV-2.

Human herpes virus 8 (HHV-8)/Kaposi sarcoma herpes virus

Occurrence: Human herpesvirus-8 (HHV-8), a recently discovered human herpesvirus (Chang *et al.*, 1994), has been consistently associated with KS and is now considered to be the principal cause of the disease (Whitby *et al.*, 1995; Boshoff, 1999). Hayward (1999) suggests that HHV-8 is an ancient human virus and its distribution using nucleotide sequence analysis of the ORF K1 subtype reflects the migration of human populations 35 000–60 000 years ago.

A number of assays have been developed to measure the presence of antibodies to HHV-8 in human sera for diagnostic and epidemiological purposes. There is variation in both the sensitivity and the specificity of these assays (Engels *et al.*, 2000a), but in general, HHV-8 seroprevalence in 'normal' populations (i.e., blood donors, patients without KS and population samples) appears to be highest in Africa (prevalence varying from 10 to 100%, depending on the assay), intermediate in the Middle East and Mediterranean littoral and lowest in northern Europe (Chatlynne & Ablashi, 1999). In Uganda, for example, the prevalences of HHV-8 infection were between 53% and 77% (Gao *et al.*, 1996b; Lennette *et al.*, 1996; Simpson *et al.*, 1996). Testing sera obtained from a variety of different patient groups in the West Nile district of Uganda in 1972–75, de The *et al.* (1999) found a seroprevalence of 84% in adults. In the high-incidence areas of eastern Congo (Zaire), prevalence of HHV-8 was 82% in 1984 (Engels *et al.*, 2000b).

In all reported series, there has been no difference in seroprevalence between men and women.

Epidemiology: HHV-8 appears to be transmitted by sexual contact in developed countries (Martin *et al.*, 1998). Men who develop KS tend to be more sexually active and to have more sexual partners from epicentres of the AIDS epidemic. In conjunction with the much higher risk for KS among homosexual men than among other HIV transmission groups, these data indicate that an infectious sexually transmitted agent (independent of HIV) is associated with KS. Transmission of such an agent via the blood is apparently less common, since KS occurs in only 3% of people who acquire HIV through a blood transfusion (IARC, 1996). Several serological studies have suggested that, irrespective of the type of antigen used, HHV-8 infection is more common among people attending sexually transmitted disease clinics than among blood donors (Kedes *et al.*, 1996; Lennette *et al.*, 1996; Simpson *et al.*, 1996). Among Danish homosexual men, variables such as promiscuity and receptive anal intercourse increased the risk for HHV-8 infection, while, in the United States in the early 1980s, contact with homosexual men markedly enhanced the likelihood of having or acquiring antibodies to HHV8 (Melbye *et al.*, 1998).

In Africa, sexual transmission is probably important in adolescents and young adults. In Uganda, increased risk for KS was seen in HIV-seropositive adults of each sex who had a history of sexually transmitted diseases, and especially those who were relatively affluent, well educated, and had travelled (Ziegler *et al.*, 1997). In Cameroon, Rezza *et al.* (2000) found that a history of sexually transmitted diseases was an independent determinant of HHV-8 infection (adjusted odds ratio 2.47; 95% CI 1.09–4.91) and seroprevalence was higher in prostitutes than in pregnant women at

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Kaposi sarcoma (C46)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	16	0.3	**0.4**	0.02	3	0.1	**0.1**	0.01
Algeria, Constantine (1994-1997)	2	0.1	**0.3**	-	2	0.1	**0.3**	0.02
Algeria, Oran (1996-1998)	3	0.2	**0.2**	0.02	1	0.1	**0.1**	0.01
Algeria, Setif (1993-1997)	-	-	**-**	-	1	0.0	**0.1**	-
Tunisia, Centre, Sousse (1993-1997)	11	1.0	**1.2**	0.05	3	0.3	**0.3**	0.00
Tunisia, North, Tunis (1994)	2	0.1	**0.1**	-	2	0.1	**0.1**	0.01
Tunisia, Sfax (1997)	1	0.3	**0.3**	-	1	0.3	**0.3**	0.04
Africa, West								
The Gambia (1997-1998)	4	0.4	**0.6**	0.04	4	0.4	**0.4**	0.03
Guinea, Conakry (1996-1999)	2	0.1	**0.2**	0.02	1	0.0	**0.0**	0.00
Mali, Bamako (1988-1997)	46	1.2	**1.8**	0.10	16	0.4	**0.7**	0.06
Niger, Niamey (1993-1999)	5	0.3	**0.3**	0.03	4	0.2	**0.2**	0.02
Nigeria, Ibadan (1998-1999)	3	0.2	**0.2**	0.02	1	0.1	**0.1**	0.00
Africa, Central								
Congo, Brazzaville (1996-1999)	37	3.1	**4.3**	0.34	14	1.2	**1.4**	0.11
Africa, East								
France, La Reunion (1988-1994)	9	0.4	**0.4**	0.03	-	-	**-**	-
Kenya, Eldoret (1998-2000)	35	3.7	**5.8**	0.51	15	1.6	**2.4**	0.21
Malawi, Blantyre (2000-2001)	385	42.8	**49.9**	4.15	234	27.0	**31.7**	2.58
Uganda, Kyadondo County (1993-1997)	843	30.0	**37.7**	2.94	533	18.4	**20.5**	1.49
Zimbabwe, Harare: African (1990-1993)	679	28.6	**31.3**	2.45	185	8.7	**9.4**	0.75
Zimbabwe, Harare: African (1994-1997)	1278	45.8	**50.9**	4.15	482	18.3	**21.6**	1.70
Zimbabwe, Harare: European (1990-1997)	2	1.3	**1.3**	0.09	-	-	**-**	-
Africa, South								
Namibia (1995-1998)	158	5.0	**6.8**	0.53	54	1.7	**1.9**	0.13
South Africa: Black (1989-1992)	232	0.4	**0.7**	0.04	69	0.1	**0.2**	0.01
South Africa: Indian (1989-1992)	2	0.1	**0.2**	0.00	2	0.1	**0.1**	0.00
South Africa: Mixed race (1989-1992)	23	0.4	**0.6**	0.03	5	0.1	**0.1**	0.00
South Africa: White (1989-1992)	68	0.7	**0.6**	0.03	17	0.2	**0.1**	0.01
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.3**	0.02	-	-	**-**	-
South Africa, Transkei, 4 districts (1996-1998)	2	0.3	**0.7**	0.07	1	0.1	**0.1**	0.01
Swaziland (1996-1999)	209	11.9	**17.2**	1.37	164	8.4	**9.5**	0.70
Europe/USA								
USA, SEER: White (1993-1997)	2788	5.7	**4.4**	0.36	70	0.1	**0.1**	0.00
USA, SEER: Black (1993-1997)	560	8.4	**6.8**	0.55	32	0.4	**0.3**	0.02
France, 8 registries (1993-1997)	204	1.5	**1.2**	0.09	26	0.2	**0.1**	0.01
The Netherlands (1993-1997)	425	1.1	**0.8**	0.07	25	0.1	**0.0**	0.00
UK, England (1993-1997)	672	0.6	**0.5**	0.04	68	0.1	**0.0**	0.00

In italics: histopathology-based registries

an antenatal clinic (Bestetti *et al.*, 1998). In South Africa, Sitas *et al.* (1999a) found an association with number of lifetime sexual partners. Ariyoshi *et al.* (1998) did not, however, find any association between infection with HHV-8 and serological evidence (treponema pallidum antibody; TPA) of syphilis in Gambia.

Other risk factors for HHV-8 include lower standard of education (Olsen *et al.*, 1998; Sitas *et al.*, 1999a), birth in a rural area (Sitas *et al.*, 1999a) and having an HHV-8-positive mother (Bourboulia *et al.*, 1998), especially if the mother has high antibody titres against HHV-8 (Sitas *et al.*, 1999b).

Antibody to HHV-8 is transmitted transplacentally, so that most children born to seropositive mothers have antibody present at birth, although titres fall rapidly thereafter (Gessain *et al.*, 1999; Mantina *et al.*, 2001). However, prevalence of antibody to HHV-8 is higher in older children whose mothers are HHV-8-positive, suggesting that transmission of HHV-8 from mother to child is possible. A study of South African mothers and their children revealed that about 30% of the children (under 10 years) of HHV-8-seropositive mothers were themselves HHV-8-seropositive, whereas none of the children of HHV-8-seronegative mothers were HHV-8-seropositive (Bourboulia *et al.*, 1998) Furthermore, the proportion of children who were seropositive for HHV-8 increased in relation to their mothers' HHV-8 antibody titre; the data suggested that HHV-8 seropositive mothers with high titer may be about twice as likely to have HHV-8-seropositive children as mothers with a low titre (Sitas *et al.*, 1999b). In a study of 89 HHV-8-seropositive mothers and their children in Lusaka, Zambia, Mantina *et al.* (2001) observed 13 mothers (14.6%) with HHV-8 DNA detectable in peripheral blood mononuclear cells. 83% of the neonates (< 24 hours old) were seropositive and two also had HHV-8 DNA detectable in peripheral blood mononuclear cells. This suggests that vertical mother-to-child transmission does occur, but that it is rather rare.

On the other hand, the steady increase in the prevalence of HHV-8 infection throughout childhood suggests that transmission of the virus from person to person, via non-sexual routes, may be more important (Wilkinson *et al.*, 1999; Mayama *et al.*, 1998; Olsen *et al.*, 1998; de Thé *et al.*, 1999; Sitas *et al.*, 1999a). The presence of HHV-8 DNA sequences in mucosal secretions (oral, vaginal) of women with KS lesions in Zimbabwe suggests possible routes of transmission (Lampinen *et al.*, 2000).

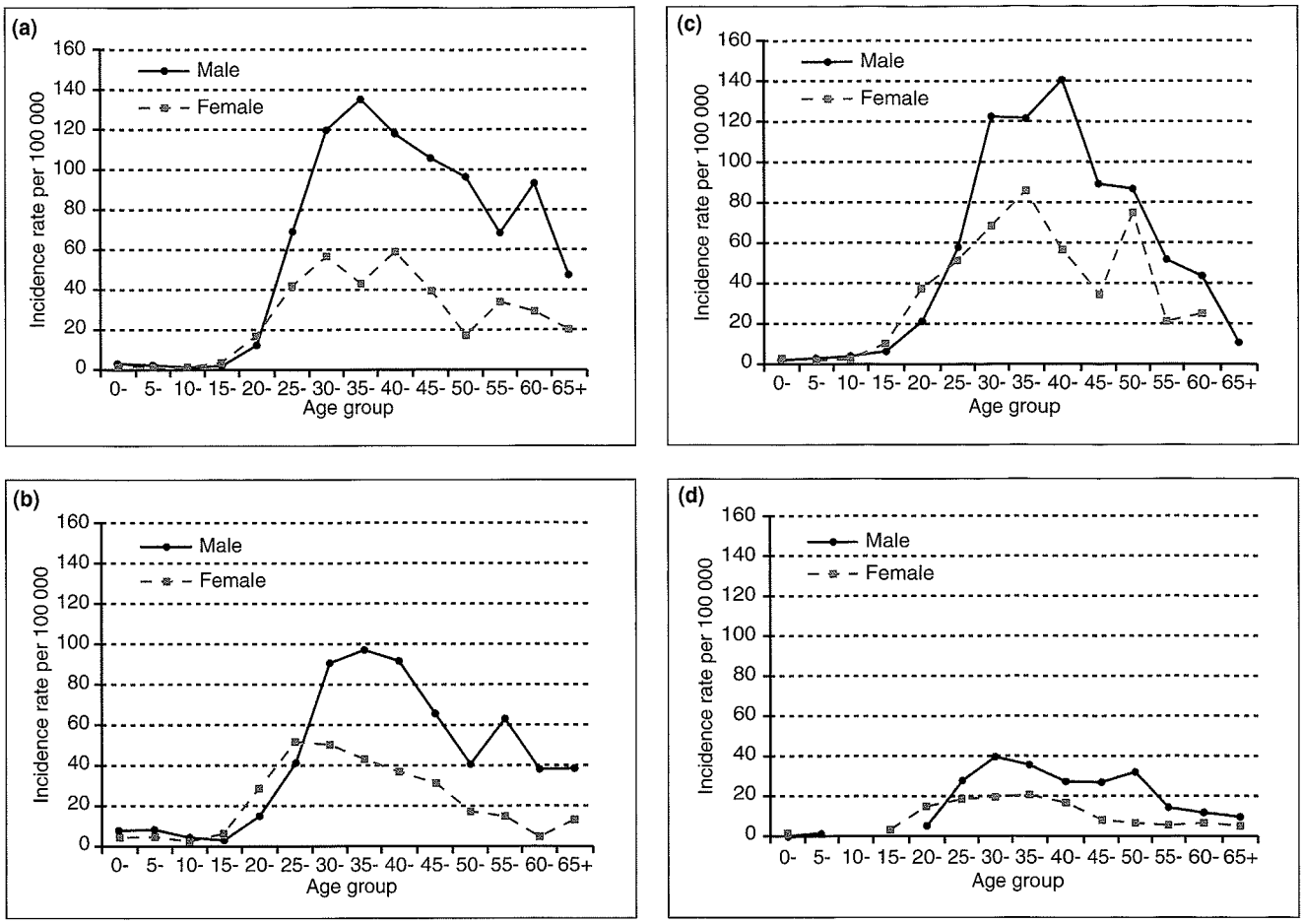

Figure 4. Incidence of Kaposi sarcoma in (a) Zimbabwe, (b) Uganda, (c) Malawi and (d) Swaziland

A recent study in Uganda showed that HHV-8-seropositivity in children was strongly correlated with the presence of antibodies to hepatitis B core antigen (Mayama *et al.*, 1998) Hepatitis B virus is known to be transmitted from person to person and this finding may suggest a similar route for HHV-8 (Abdool Karim *et al.*, 1988). The linear increase of HHV-8 infection with age of child suggests a causal horizontal pattern of infection, similar to that of other herpes viruses, between mothers and possibly other family members before puberty (Gessain *et al.*, 1999; Lyall *et al.*, 1999; Mayama *et al.*, 1998). In Egypt, young children (1–3 years) had higher titres of anti-lytic antibodies, suggesting the time of greatest risk of HHV-8 acquisition and/or viral activity in this group (Andreoni *et al.*, 1999)

In South Africa, the lower seroprevalence of HHV-8 in whites compared with blacks, and the decrease in seroprevalence with increasing education (Sitas *et al.*, 1999a) suggests that factors associated with poverty contribute to transmission of the virus. In contrast to this association between poverty and acquisition of HHV-8, in Uganda the development of KS, irrespective of HIV status, appears to be associated with markers of higher social class, such as better education and wealth (Ziegler *et al.*, 1997, 1998).

If high social status protects an individual from early infection with HHV-8, it could imply that the age at which infection occurs (or even the route of infection) could affect the subsequent risk of KS. This hypothesis is reminiscent of the effect of late infection with Epstein-Barr virus (a closely related gamma herpesvirus) in relation to the risk of infectious mononucleosis (Sitas *et al.*, 1999a).

Pathology: Kaposi sarcoma: DNA analysis has consistently demonstrated the presence of HHV-8 at high (>90%) rates in KS lesions (whether or not the patients are HIV-infected) and at a generally low rate in neoplastic and non-neoplastic tissues from control patients (Boshoff & Weiss, 2001). The load of viral DNA is higher in tissue from KS than in unaffected tissues from the same patients. When mononuclear cells from KS patients and controls are examined using a polymerase chain reaction (PCR) method, HHV-8 is detected in significantly more cases (up to 50%) than controls (IARC, 1997). Detection of HHV-8 in peripheral blood correlates with, and in asymptomatic HIV-infected individuals predicts the development of, KS (Whitby *et al.*, 1995; Moore *et al.*, 1996), and sero-conversion (acquisition of anti-HHV-8 antibody) during HIV infection is predictive of development of KS (Renwick *et al.*, 1998).

Despite the differences in the antigens examined by the different serological tests for HHV-8, and in the sensitivity and specificity of these tests, all studies are consistent in showing high rates of antibody-positivity in KS patients and lower rates of seropositivity among various controls. A case–control study of black cancer patients in South Africa found that the presence of antibodies against HHV-8 was strongly associated with KS, but not with any other major cancer site or type, including prostate cancer and multiple myeloma (Sitas *et al.*, 1999a). In addition, the risk of KS increased with increasing antibody titre (as measured by the intensity of the fluorescent signal) to HHV-8, but, for a given titre, the risk was much greater in HIV-seropositive than in HIV-seronegative subjects. The highest fluorescent signal intensity for HHV-8, corresponding to an antibody titre of 1:204 800, was associated with a 12-fold increase in risk of KS among HIV-seronegative subjects, but with a more than 1600-fold increase in risk among HIV-seropositive subjects

No data on the relationship between HHV-8 antibody titre and viral load are available, but it can be presumed that a high anti-HHV-8 antibody titre reflects a high viral load and that it is this, rather than antibody titre, that primarily determines the risk of KS. Nevertheless,

the relationship between high antibody titre and disease is reminiscent of the association between the related Epstein–Barr virus and African Burkitt lymphoma (de Thé *et al.*, 1978a) and nasopharyngeal cancer (de Thé *et al.*, 1978b), where individuals with high titres appear to be at highest risk of developing these cancers.

Nevertheless, it is clear that HHV-8 is not the only determinant of KS. Prevalence of infection is much the same in both sexes, despite the male excess of KS, especially the endemic form, in most of sub-Saharan Africa, but KS was rare in women before the AIDS epidemic (Serraino *et al.*, 2001). Furthermore, as far as one can tell from the data available, there does not seem to have been a close geographical correlation between prevalence of antibody to HHV-8 and the incidence of KS in the pre-AIDS era. Serraino *et al.* (2001) compared prevalence of lytic and latent antigens to HHV-8 in sera from subjects in northern Cameroon, northern Uganda, and Alexandia, Egypt. Prevalence of lytic antibody in adolescents (aged 13–19 years) was highest in Egypt (56.2% positive), an area where KS is rare, but prevalence of latent antibody was lower (8.3%) than in Cameroon and Uganda (19–26%). In adults, sero-prevalence was higher in Cameroon than in northern Uganda, although endemic KS is almost certainly more common in the latter. Ablashi *et al.* (1999) found no difference in prevalence of IgG antibody to HHV-8 (38–42%) between healthy adult subjects from Uganda, Zambia (areas of moderate to high risk of endemic KS) and Ghana (a low-risk area). A high prevalence of HHV-8 has been found in Gambia (Ariyoshi *et al.*, 1998) and Botswana (Engels *et al.*, 2000b), countries where KS was not a common cancer (see Chapters 3.2.5 and 3.5.1 and Figure 1).

Mechanisms: HHV-8 has numerous genes capable of deregulating mitosis, interrupting apoptosis (programmed cell death), increasing angiogenesis and blocking presentation of antigenic epitopes. It is conjectured that the virus may establish a persistent infection which (as with EBV) is normally controlled by the immune system. When immune control declines (e.g., due to AIDS), the number of HHV-8-infected cells increases, with subsequent unchecked proliferation and tumour development (Boshoff & Weiss, 2001).

Joint effects of HIV and HHV-8

It seems clear from the studies cited above that the risk of KS is increased both by infection with HIV and with HHV-8. However, most studies in Africa suggest that the association between infection with the two viruses is either weakly positive or inconsistent (Gao *et al.*, 1996a, b; Simpson *et al.*, 1996; Bestetti *et al.*, 1998; He *et al.*, 1998). In Gambia, Ariyoshi *et al.* (1998) found very little difference in prevalence of HHV-8 infection (by serology, or PCR to detect HHV-8 genome in peripheral blood mononuclear cells) between pregnant women who were HIV-1-positive (73% seropositive for HHV-8), HIV-2-positive (83% seropositive) or HIV-negative (79% seropositive). In South Africa, prevalence of antibody to HHV-8 was 30% in HIV-seropositive subjects and 33% in seronegative (Sitas *et al.*, 1999a). The latter study suggests that the effect of the two viruses on risk is independent (and more or less multiplicative). The effect of HIV is probably through immunosuppression, for example by allowing HHV-8 to escape control and increase viral load. In cohort studies in the United States and Europe, the risk of developing KS in HIV-positive subjects is related to the degree of immunosuppression, as measured by CD4+ lymphocyte counts (Goedert *et al.*, 1987; Hermans *et al.*, 1996; Rezza *et al.*, 1999).

The possible role of immunodeficiency in the etiology of endemic KS is clearly of interest, given the supposed role of immune surveillance in the control of latent infection with HHV-8. Early studies in Uganda (Master *et al.*, 1970; Taylor & Ziegler, 1974) suggested some impairment in skin reactivity to dinitrochlorobenzene. However, in their study in East Kivu (Congo) in 1984, Kestens *et al.* (1985), comparing 27 cases of endemic KS with 41 age–sex–tribe-matched control subjects (all HIV-negative), did not find any significant difference in terms of skin reactivity to a variety of recall antigens, and serum levels of immunoglobulin and complement factors. White blood cell counts and lymphocyte counts, as well as the absolute counts of CD4+ cells and CD8+ cells were slightly higher in cases than in controls, but there was no difference in the CD4/CD8 ratios. Conversely, a study of sporadic KS in Greece (Touloumi *et al.*, 1999) showed slightly lower white cell and lymphocyte counts in the KS cases, with a significantly low CD4+ lymphocyte count (mean 812 cells per µl compared with 1009 per µl in controls) that was not explained by overall lymphopenia. There were also significantly increased levels of neopterin and ß2-microglobulin, which are interferon-induced products suggesting immune activation.

A study in Tanzania (Urassa *et al.*, 1998) reported on lymphocyte counts in 39 endemic KS patients, 93 AIDS–KS patients and 82 unmatched controls. The HIV status of the cases was not reported. The main finding was a low CD4-T lymphocyte count in endemic KS, who also had a CD8-T lymphocyte count higher than the controls. However, the results are sometimes inconsistent and the very low CD4 count (mean 104 cells/µl) in endemic KS—significantly lower than in the AIDS–KS cases (mean 340 per µl)—suggests that some of the former group may have been HIV-positive.

The effect of HIV may also occur through different mechanisms. In vitro studies suggest that HIV-1 Tat may have angiogenic properties (Ensoli *et al.*, 1994), and that it may be responsible for activating HHV-8 (Harrington *et al.*, 1997). Nevertheless, the reasons for the dramatic increase in risk of developing KS among HHV-8-infected individuals who are HIV-seropositive remain unclear.

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4.7 Leukaemia

The features of childhood leukaemia in Africa have been discussed in the chapter on childhood cancer.

In adults, there seem to be few features of note in the epidemiology of these cancers in Africa. Overall incidence rates are lower than those recorded in western countries (Tables 1a–c). Most descriptions of leukaemia in Africa are based upon clinical series. It is difficult to know how much the age structure of the population, selective factors influencing access to hospital and diagnostic facilities influence the pattern by age, sex and cell type. The literature up to 1985 was summarized by Fleming (1986).Older data on incidence in Africa are presented in Table 2.

In many series, chronic leukaemias apparently outnumber acute leukaemias; this possibly reflects the deficit of childhood acute lymphocytic leukaemia (ALL) and possibly the poor prognosis or misdiagnosis of acute leukaemias, especially in earlier data.

In some African series (mainly from east Africa), chronic myeloid leukaemia (CML) appears to be more frequent than chronic lymphocytic leukaemia (CLL) (Edington & Hendrickse, 1973; Williams, 1984). CML occurs with peak frequency in the third and fourth decades of life in most case series, although this presumably relates to the age structures of the populations, rather than to any special feature of age-specific incidence rates. These seem to be similar to the rates in the United States (Figure 1).

It is difficult to be certain of the reality of the descriptive features of CLL reported from Africa, because of the arbitrary distinction from the common B-cell lymphomas. Fleming (1985) considered that there are two forms of CLL in tropical Africa. About half the patients described are aged less than 45 years, and in this age group, the male to female ratio is 1:2, and CLL is reported more commonly in west than in east Africa. Over the age of 45 years, most cases are in men (ratio 2:1), as in European populations. Williams (1985) found that CLL cases in Ibadan, Nigeria, were of lower social status than subjects with other forms of leukaemia or than the general population.

In north Africa, the pattern seems to be much the same as in European populations (Bellabes *et al.*, 1983; El Bolkainy *et al.*, 1984)

The epidemiology of acute T-cell leukaemia-lymphoma (ATLL) in Africa is described in the chapter on lymphomas.

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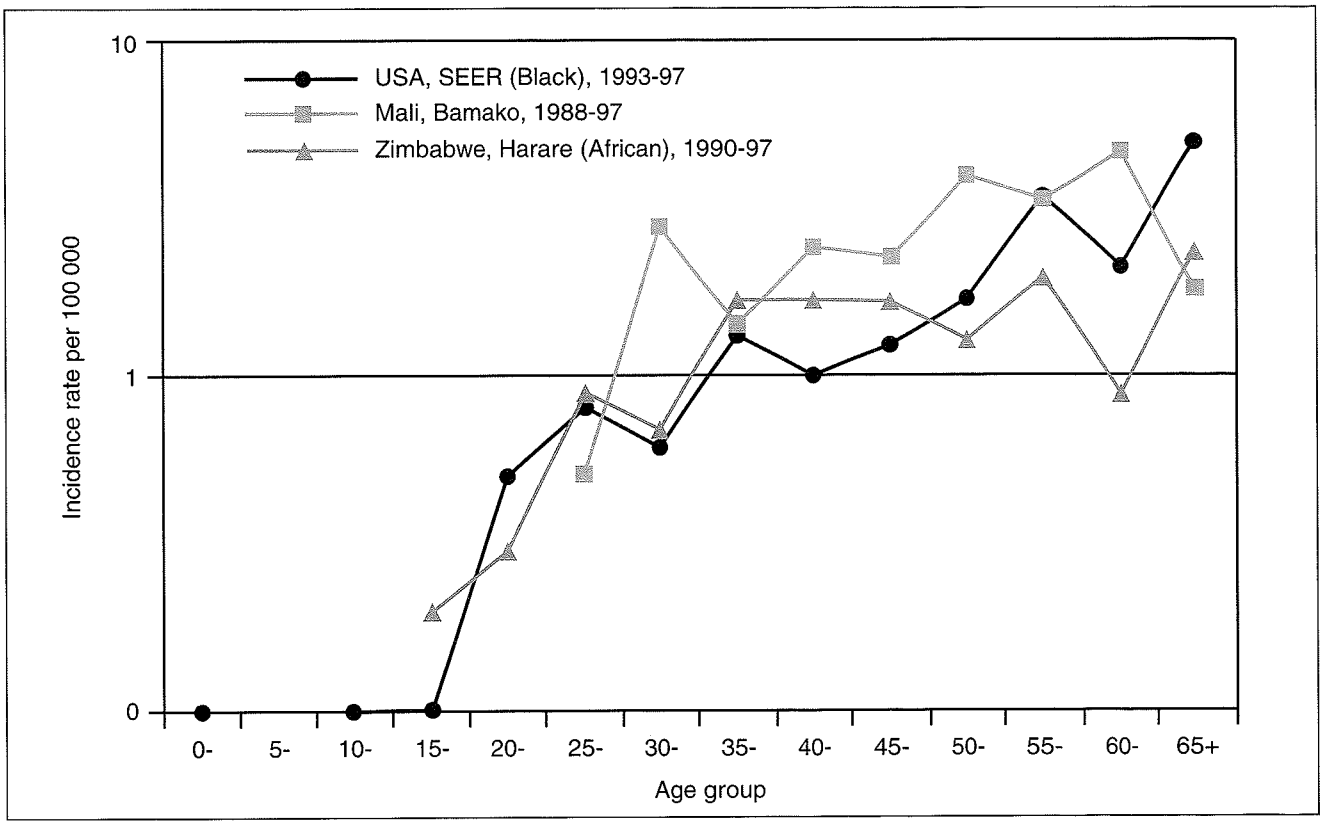

Figure 1. Age-specific incidence of chronic myeloid leukaemia in Bamako (Mali), Harare (Zimbabwe) and the black population of the USA (SEER data)

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Table 1a. Age-standardized (world) and cumulative (0-64) incidence
Lymphoid leukaemia (C91)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	56	1.0	**1.2**	0.07	29	0.5	**0.7**	0.03
Algeria, Constantine (1994-1997)	29	1.9	**2.7**	0.15	13	0.9	**1.1**	0.05
Algeria, Oran (1996-1998)	25	1.4	**1.5**	0.09	12	0.7	**0.8**	0.03
Algeria, Setif (1993-1997)	43	1.4	**1.5**	0.08	22	0.7	**0.7**	0.03
Tunisia, Centre, Sousse (1993-1997)	25	2.2	**2.5**	0.14	13	1.2	**1.3**	0.07
Tunisia, North, Tunis (1994)	42	1.9	**2.2**	0.12	32	1.5	**1.7**	0.13
Tunisia, Sfax (1997)	19	4.8	**5.3**	0.19	11	2.9	**3.2**	0.15
Africa, West								
The Gambia (1997-1998)	1	0.1	**0.1**	0.01	-	-	-	-
Guinea, Conakry (1996-1999)	12	0.5	**0.6**	0.05	10	0.5	**1.0**	0.03
Mali, Bamako (1988-1997)	1	0.0	**0.0**	0.00	2	0.1	**0.1**	0.00
Niger, Niamey (1993-1999)	18	1.0	**1.6**	0.11	16	0.9	**2.1**	0.15
Nigeria, Ibadan (1998-1999)	2	0.1	**0.1**	0.01	2	0.1	**0.2**	0.03
Africa, Central								
Congo, Brazzaville (1996-1999)	18	1.5	**1.8**	0.13	19	1.6	**2.2**	0.17
Africa, East								
France, La Reunion (1988-1994)	32	1.5	**1.8**	0.11	29	1.3	**1.5**	0.08
Kenya, Eldoret (1998-2000)	21	2.2	**4.1**	0.24	5	0.5	**1.2**	0.12
Malawi, Blantyre (2000-2001)	-	-	-	-	2	0.2	**0.4**	0.04
Uganda, Kyadondo County (1993-1997)	6	0.2	**0.2**	0.01	7	0.2	**0.5**	0.05
Zimbabwe, Harare: African (1990-1993)	26	1.1	**2.2**	0.08	16	0.7	**1.7**	0.14
Zimbabwe, Harare: African (1994-1997)	25	0.9	**1.2**	0.06	15	0.6	**1.3**	0.06
Zimbabwe, Harare: European (1990-1997)	11	7.2	**5.4**	0.27	5	3.0	**2.2**	0.05
Africa, South								
Namibia (1995-1998)	20	0.6	**1.0**	0.06	9	0.3	**0.4**	0.03
South Africa: Black (1989-1992)	449	0.8	**1.2**	0.07	302	0.5	**0.7**	0.04
South Africa: Indian (1989-1992)	37	1.9	**2.2**	0.13	21	1.1	**1.1**	0.06
South Africa: Mixed race (1989-1992)	70	1.1	**1.3**	0.07	39	0.6	**0.7**	0.04
South Africa: White (1989-1992)	347	3.4	**3.6**	0.19	225	2.2	**2.2**	0.12
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.2**	0.01	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	-	-	-	-
Swaziland (1996-1999)	5	0.3	**0.2**	0.02	2	0.1	**0.1**	0.00
Europe/USA								
USA, SEER: White (1993-1997)	3361	6.9	**5.9**	0.29	2326	4.6	**3.5**	0.16
USA, SEER: Black (1993-1997)	252	3.8	**4.3**	0.21	162	2.2	**2.1**	0.09
France, 8 registries (1993-1997)	890	6.5	**5.3**	0.29	633	4.4	**3.2**	0.17
The Netherlands (1993-1997)	2100	5.5	**4.8**	0.24	1287	3.3	**2.6**	0.12
UK, England (1993-1997)	7370	6.1	**4.7**	0.22	5259	4.1	**2.8**	0.12

In italics: histopathology-based registries

Table 1b. Age-standardized (world) and cumulative (0-64) incidence
Myeloid leukaemia (C92-94)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	37	0.7	**0.8**	0.05	26	0.5	**0.5**	0.04
Algeria, Constantine (1994-1997)	25	1.6	**2.4**	0.13	24	1.6	**2.0**	0.16
Algeria, Oran (1996-1998)	13	0.7	**0.9**	0.05	10	0.6	**0.6**	0.06
Algeria, Setif (1993-1997)	22	0.7	**1.0**	0.06	34	1.1	**1.6**	0.12
Tunisia, Centre, Sousse (1993-1997)	21	1.8	**2.1**	0.11	12	1.1	**1.3**	0.08
Tunisia, North, Tunis (1994)	37	1.7	**1.9**	0.10	47	2.2	**2.6**	0.21
Tunisia, Sfax (1997)	13	3.3	**3.8**	0.17	4	1.1	**1.2**	0.06
Africa, West								
The Gambia (1997-1998)	-	-	**-**	-	-	-	**-**	-
Guinea, Conakry (1996-1999)	14	0.6	**0.9**	0.06	11	0.5	**0.6**	0.05
Mali, Bamako (1988-1997)	30	0.8	**1.0**	0.08	24	0.7	**1.5**	0.14
Niger, Niamey (1993-1999)	10	0.5	**0.8**	0.07	15	0.8	**1.4**	0.09
Nigeria, Ibadan (1998-1999)	9	0.6	**0.7**	0.04	3	0.2	**0.3**	0.01
Africa, Central								
Congo, Brazzaville (1996-1999)	9	0.7	**0.9**	0.06	6	0.5	**0.7**	0.07
Africa, East								
France, La Reunion (1988-1994)	59	2.8	**3.4**	0.18	51	2.4	**2.5**	0.14
Kenya, Eldoret (1998-2000)	16	1.7	**2.2**	0.19	19	2.1	**3.9**	0.35
Malawi, Blantyre (2000-2001)	2	0.2	**0.2**	0.01	-	-	**-**	-
Uganda, Kyadondo County (1993-1997)	8	0.3	**0.2**	0.02	7	0.2	**0.6**	0.06
Zimbabwe, Harare: African (1990-1993)	38	1.6	**1.9**	0.13	26	1.2	**2.4**	0.12
Zimbabwe, Harare: African (1994-1997)	35	1.3	**1.4**	0.09	35	1.3	**1.6**	0.10
Zimbabwe, Harare: European (1990-1997)	14	9.2	**5.3**	0.31	7	4.1	**2.3**	0.13
Africa, South								
Namibia (1995-1998)	21	0.7	**0.9**	0.06	19	0.6	**0.8**	0.07
South Africa: Black (1989-1992)	504	0.9	**1.1**	0.07	388	0.7	**0.8**	0.06
South Africa: Indian (1989-1992)	28	1.4	**1.4**	0.09	21	1.1	**1.2**	0.07
South Africa: Mixed race (1989-1992)	86	1.3	**1.8**	0.11	71	1.1	**1.3**	0.09
South Africa: White (1989-1992)	329	3.3	**3.1**	0.18	275	2.7	**2.3**	0.16
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.3**	-	1	0.2	**0.3**	-
South Africa, Transkei, 4 districts (1996-1998)	-	-	**-**	-	2	0.2	**0.3**	0.03
Swaziland (1996-1999)	-	-	**-**	-	4	0.2	**0.3**	0.02
Europe/USA								
USA, SEER: White (1993-1997)	3095	6.4	**4.9**	0.24	2550	5.1	**3.4**	0.19
USA, SEER: Black (1993-1997)	258	3.9	**4.1**	0.21	249	3.4	**3.1**	0.17
France, 8 registries (1993-1997)	735	5.3	**4.0**	0.21	610	4.2	**2.8**	0.16
The Netherlands (1993-1997)	1935	5.1	**3.9**	0.20	1494	3.8	**2.5**	0.14
UK, England (1993-1997)	6616	5.5	**3.8**	0.19	5877	4.6	**2.7**	0.15

In italics: histopathology-based registries

Table 1c. Age-standardized (world) and cumulative (0-64) incidence
Leukaemia, unspecified

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	18	0.3	**0.4**	0.02	14	0.3	**0.3**	0.02
Algeria, Constantine (1994-1997)	2	0.1	**0.2**	0.01	-	-	**-**	-
Algeria, Oran (1996-1998)	5	0.3	**0.3**	0.01	-	-	**-**	-
Algeria, Setif (1993-1997)	9	0.3	**0.4**	0.03	11	0.4	**0.5**	0.03
Tunisia, Centre, Sousse (1993-1997)	1	0.1	**0.1**	0.01	1	0.1	**0.1**	-
Tunisia, North, Tunis (1994)	3	0.1	**0.2**	0.00	3	0.1	**0.1**	0.01
Tunisia, Sfax (1997)	1	0.3	**0.3**	-	2	0.5	**0.5**	0.01
Africa, West								
The Gambia (1997-1998)	3	0.3	**0.2**	0.01	3	0.3	**0.4**	0.04
Guinea, Conakry (1996-1999)	2	0.1	**0.1**	0.01	3	0.1	**0.3**	0.04
Mali, Bamako (1988-1997)	9	0.2	**0.3**	0.02	11	0.3	**0.4**	0.03
Niger, Niamey (1993-1999)	-	-	**-**	-	3	0.2	**0.1**	0.01
Nigeria, Ibadan (1998-1999)	3	0.2	**0.3**	0.03	2	0.1	**0.1**	0.01
Africa, Central								
Congo, Brazzaville (1996-1999)	9	0.7	**0.9**	0.06	7	0.6	**0.6**	0.05
Africa, East								
France, La Reunion (1988-1994)	7	0.3	**0.4**	0.01	3	0.1	**0.1**	0.00
Kenya, Eldoret (1998-2000)	4	0.4	**0.5**	0.03	2	0.2	**0.2**	0.01
Malawi, Blantyre (2000-2001)	3	0.3	**0.8**	0.08	3	0.3	**0.2**	0.01
Uganda, Kyadondo County (1993-1997)	9	0.3	**0.4**	0.04	10	0.3	**0.5**	0.02
Zimbabwe, Harare: African (1990-1993)	2	0.1	**0.4**	0.01	-	-	**-**	-
Zimbabwe, Harare: African (1994-1997)	6	0.2	**0.5**	0.01	5	0.2	**0.4**	0.03
Zimbabwe, Harare: European (1990-1997)	5	3.3	**1.7**	0.10	-	-	**-**	-
Africa, South								
Namibia (1995-1998)	1	0.0	**0.0**	0.00	1	0.0	**0.1**	-
South Africa: Black (1989-1992)	319	0.6	**0.8**	0.05	263	0.5	**0.6**	0.04
South Africa: Indian (1989-1992)	30	1.5	**1.6**	0.11	23	1.2	**1.2**	0.08
South Africa: Mixed race (1989-1992)	12	0.2	**0.2**	0.01	10	0.1	**0.2**	0.01
South Africa: White (1989-1992)	126	1.3	**1.2**	0.07	124	1.2	**1.2**	0.08
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.3**	-	1	0.2	**0.3**	-
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.4**	0.04	-	-	**-**	-
Swaziland (1996-1999)	19	1.1	**1.6**	0.05	15	0.8	**1.1**	0.07
Europe/USA								
USA, SEER: White (1993-1997)	451	0.9	**0.7**	0.02	431	0.9	**0.5**	0.01
USA, SEER: Black (1993-1997)	31	0.5	**0.5**	0.02	23	0.3	**0.3**	0.01
France, 8 registries (1993-1997)	47	0.3	**0.2**	0.01	35	0.2	**0.2**	0.01
The Netherlands (1993-1997)	103	0.3	**0.2**	0.01	94	0.2	**0.1**	0.00
UK, England (1993-1997)	572	0.5	**0.3**	0.01	545	0.4	**0.2**	0.01

In italics: histopathology-based registries

Table 2. Incidence of leukaemia in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	*0.7*	*0.2*	4
Mozambique, Lourenço Marques	1956–60	*3.8*	*2.3*	1
Nigeria, Ibadan	1960–69	4.0	3.9	3
SA, Cape Province: Bantu	1956–59	*7.9*	*0.7*	2
SA, Cape Province: Coloured	1956–59	5.4	3.4	2
SA, Cape Province: White	1956–59	6.5	5.2	2
SA, Johannesburg, Bantu	1953–55	2.7	3.8	1
SA, Natal Province: African	1964–66	2.4	9.2	2
SA, Natal Province: Indian	1964–66	4.7	*3.6*	2
Uganda, Kyadondo	1954–60	2.4	3.2	1
Uganda, Kyadondo	1960–71	2.7	2.4	5
Zimbabwe, Bulawayo	1963–72	5.5	8.2	6

Italics: Rate based on less than 10 cases

4.8 Liver cancer

Introduction

Liver cancer is estimated to be the fifth most common cancer worldwide, responsible for around 564 000 new cases (398 000 in men and 166 000 in women) in the year 2000 (Ferlay *et al.*, 2001). Because it has a very poor prognosis, the number of deaths (549 000) is not far short of the number of new cases, and it represents the third most common cause of death from cancer. The geographical distribution of liver cancer is very uneven; 81% of cases occur in the developing countries. The highest incidence rates are in West and central Africa (where it accounts for almost one fifth of cancer in men), eastern and south-eastern Asia, and Melanesia. China alone accounts for 54% of the total cases in the world. With the exception of Japan, the incidence rates are low in developed countries, with the highest incidence found in southern Europe, especially in Greece.

Liver cancer comprises a variety of different cancers, which show different epidemiological features (see Table 3). The most frequent subtype in most areas is hepatocellular carcinoma, and much of the geographical variation worldwide is linked to this cancer. Cholangiocarcinoma, a tumour of the epithelium of the intrahepatic bile ducts, is generally less frequent, comprising around 10–25% of liver cancers in men in Europe and North America, but a rather higher proportion in women, because although the incidence rates of cholangiocarcinoma are rather similar in males and females, the rates of hepatocellular carcinoma are some 2–3 times higher in males in low-incidence areas (Europe, North America) and up to fivefold higher in the high-risk populations of Asia and sub-Saharan Africa. The incidence of cholangiocarcinoma shows rather little variation worldwide, with rates in males between 0.5 and 2.0 per 100 000 and somewhat lower in females (Parkin *et al.*, 1993), although incidence in some local areas of Asia (e.g., north-east Thailand) is high.

Other types of liver cancer are much less common. Hepatoblastoma is a tumour of young children, with overall 82% of cases occurring in the first five years of life. There is very little geographical variation in incidence. Malignant vascular tumours (haemangiosarcomas) are even rarer and affect principally adults.

Descriptive epidemiology in Africa

The high frequency of liver cancer in sub-Saharan Africa has been clear for as long as records have been kept (Oettlé, 1964; Cook & Burkitt, 1971). Reports from cancer registries in the 1980s and 1990s have helped to establish the contemporary pattern (Figure 1).

In West Africa, the data from the Gambia, Mali and Guinea, and previous publications from these registries (Bah *et al.*, 1990; Bayo *et al.*, 1990; Koulibaly *et al.*, 1997) have shown liver cancer to be the most common tumour in males. Incidence rates, standardized to the world standard population (ASR), range from 38 to 49 in males and 12 to 18 per 100 000 in females (Table 1). In Abidjan (Côte d'Ivoire) and Niamey (Niger), the recorded rates are lower, probably due to some under-registration, but liver cancer comprises 15% and 24% of cancers in men. These observations confirm early reports from the region, indicating a high incidence of the disease in men (Edington, 1978; Fakunle *et al.*, 1977).

Data from East Africa suggest that incidence rates are not as high as in West Africa. The long time series from Kampala, Uganda, from 1960 to 1997 (Wabinga *et al.*, 2000), suggests a rather fluctuating incidence, with the rates in men between 6 and 12 per 100 000, and in women between 2 and 6 per 100 000. This is consistent with the low incidence reported from Malawi: 4.6 in men and 2.2 in women per 100 000 in 1994–98 (Banda *et al.*, 2001).

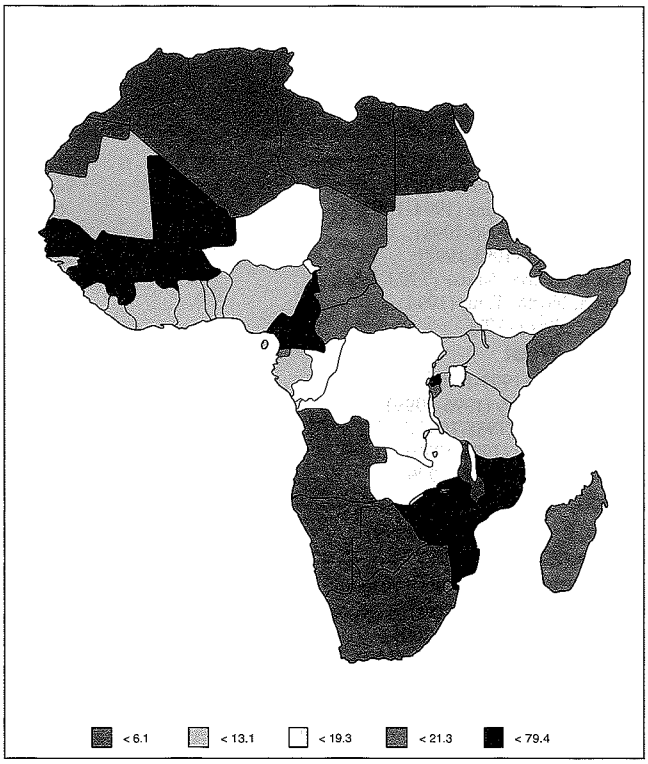

Figure 1. Incidence of liver cancer: ASR (world)-male (all ages)

In central Africa, the actual incidence is uncertain, but liver cancer is the commonest tumour of men in Butare (Rwanda) and in Brazzaville (Congo), where the recorded incidence was 17.2 per 100 000 in men and 8.4 in women. Kocheleff *et al.* (1984) estimated the crude incidence rate of liver cancer in Burundi to be 8.8 per 100 000.

In southern Africa, there are marked differences in the incidence of liver cancer between the different races. Populations of European origin living in Zimbabwe for the past 30 years show lower incidence rates than the native African populations (albeit with a much higher rate than their European counterparts living in Europe or North America (Bassett *et al.*, 1995a, b)). A similar phenomenon has been observed for the Asian population, largely of Indian origin, living in Natal, South Africa (Akoojee *et al.*, 1990). The native black African population in Zimbabwe exhibits high rates of 30.7 and 17.1 per 100 000 for males and females, respectively, in 1993–97.

Older data confirm the high rates in the region (Table 2). The highest recorded rate was 100.8 per 100 000 in males in Maputo (then Lourenço Marques), Mozambique, in 1956–60. In Bulawayo, Zimbabwe, the incidence was 52.1 in men and 20.6 in women per 100 000 in 1963–72 (Parkin *et al.*, 1994).

In North Africa, the incidence of liver cancer is low. Age-standardized rates in Algeria are around 1 per 100 000 and range from 1 to 3 in males in Tunisia (Table 1).

Notwithstanding the tendency for deep-seated tumours to be under-diagnosed, and some methodological differences that exist between cancer registries (Burkitt, 1969; Parkin, 1986), the picture of high incidence and a 3–5-fold male excess in most of sub-Saharan Africa is clear.

In addition to the variation by region, age group, sex and race, some reports have suggested differences in occurrence between specific tribal groups. A study of Mozambican

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Liver (C22)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	34	0.6	**0.9**	0.04	34	0.6	**0.9**	0.03
Algeria, Constantine (1994-1997)	6	0.4	**0.6**	0.05	6	0.4	**0.6**	0.04
Algeria, Oran (1996-1998)	2	0.1	**0.2**	0.01	10	0.6	**0.9**	0.08
Algeria, Setif (1993-1997)	23	0.8	**1.4**	0.09	32	1.1	**1.9**	0.15
Tunisia, Centre, Sousse (1993-1997)	11	1.0	**1.3**	0.10	6	0.5	**0.7**	0.04
Tunisia, North, Tunis (1994)	49	2.3	**2.9**	0.13	29	1.4	**1.8**	0.10
Tunisia, Sfax (1997)	5	1.3	**1.4**	0.02	1	0.3	**0.3**	0.01
Africa, West								
The Gambia (1997-1998)	257	26.0	**48.9**	3.92	91	8.9	**17.6**	1.45
Guinea, Conakry (1996-1999)	453	19.8	**37.6**	3.02	144	6.5	**12.1**	1.02
Mali, Bamako (1988-1997)	752	19.4	**38.2**	2.85	283	7.8	**17.8**	1.26
Niger, Niamey (1993-1999)	135	7.3	**16.9**	1.30	65	3.6	**9.3**	0.67
Nigeria, Ibadan (1998-1999)	56	3.8	**7.7**	0.43	19	1.3	**2.1**	0.13
Africa, Central								
Congo, Brazzaville (1996-1999)	150	12.4	**17.2**	1.23	76	6.3	**8.4**	0.61
Africa, East								
France, La Reunion (1988-1994)	47	2.2	**2.9**	0.19	32	1.5	**1.6**	0.11
Kenya, Eldoret (1998-2000)	44	4.7	**10.0**	0.75	29	3.2	**7.3**	0.60
Malawi, Blantyre (2000-2001)	28	3.1	**5.1**	0.35	2	0.2	**0.6**	-
Uganda, Kyadondo County (1993-1997)	74	2.6	**6.5**	0.48	59	2.0	**5.5**	0.46
Zimbabwe, Harare: African (1990-1993)	289	12.2	**30.7**	1.51	93	4.4	**17.1**	1.39
Zimbabwe, Harare: African (1994-1997)	281	10.1	**26.0**	1.22	84	3.2	**10.6**	0.51
Zimbabwe, Harare: European (1990-1997)	23	15.1	**8.4**	0.48	15	8.9	**4.1**	0.18
Africa, South								
Namibia (1995-1998)	59	1.9	**3.2**	0.21	37	1.2	**1.8**	0.11
South Africa: Black (1989-1992)	1863	3.3	**5.6**	0.38	736	1.3	**1.9**	0.13
South Africa: Indian (1989-1992)	47	2.4	**3.8**	0.20	16	0.8	**1.2**	0.07
South Africa: Mixed race (1989-1992)	124	1.9	**3.5**	0.24	52	0.8	**1.1**	0.07
South Africa: White (1989-1992)	353	3.5	**3.2**	0.22	210	2.1	**1.6**	0.10
South Africa, Transkei, Umtata (1996-1998)	35	9.8	**16.0**	1.16	15	3.5	**4.5**	0.35
South Africa, Transkei, 4 districts (1996-1998)	19	2.6	**5.5**	0.42	7	0.8	**1.2**	0.09
Swaziland (1996-1999)	193	11.0	**22.0**	1.65	63	3.2	**5.2**	0.37
Europe/USA								
USA, SEER: White (1993-1997)	2505	5.1	**3.9**	0.19	1301	2.6	**1.5**	0.07
USA, SEER: Black (1993-1997)	412	6.2	**7.1**	0.49	177	2.4	**2.2**	0.10
France, 8 registries (1993-1997)	1810	13.2	**9.1**	0.46	425	2.9	**1.6**	0.08
The Netherlands (1993-1997)	853	2.2	**1.6**	0.08	476	1.2	**0.7**	0.04
UK, England (1993-1997)	4676	3.9	**2.5**	0.12	3176	2.5	**1.3**	0.05

In italics: histopathology-based registries

Shangaans has shown primary hepatocellular carcinoma to occur at a significantly younger age (mean 33.4 years) than among non-Shangaans (mean 40.0 years) (Kew *et al.*, 1977). In Uganda, a significantly higher frequency of liver cancer has long been noted among the largely immigrant Bantu tribes from Rwanda and Burundi and the Nilohamitic tribes of the north-west of the country than in neighbouring and racially related tribes (Alpert *et al.*, 1968; Templeton & Hutt, 1973). Kew *et al.* (1983) drew attention to the markedly younger age at incidence among rural versus urban populations in southern African blacks (and inferred a higher incidence in the former, too). There was no apparent difference, however, with respect to age-specific prevalence of markers of infection with hepatitis B virus (see below).

Age-specific incidence

Although one must be careful in interpreting age-specific cancer incidence rates, because of differential diagnosis and reporting of liver cancer with age, as well as the uncertainty of many older persons concerning their actual age, it is clear that, in countries with a high incidence, the risk of liver cancer begins to rise quite early in life. Figure 2 shows data from the Gambia (where special attention has been paid to identification of cases), which suggest an increase in incidence in young adults, reaching a peak about age 50 years. A similar pattern of a sharp rise in young males is observed in Conakry and Bamako (although in Bamako the peak is at a much later age, 60–74 years). In contrast, in Kampala, Uganda, an area of low risk for PHC, there is a less dramatic rise in age-specific incidence, with a plateau at ages above 55 years (see chapter on Uganda).

Migrants

Studies of cancer mortality in migrants to France have shown a high death rate from liver cancer among migrants from West and Central Africa (Bouchardy *et al.*, 1995). A similar observation was made for migrants to England and Wales from West Africa, but not for East Africans, who were largely of Asian ethnicity (Grulich *et al.*, 1992).

Table 2. Incidence of liver cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	25.6	9.0	4
Mozambique, Lourenço Marques	1956–60	100.8	30.8	1
Nigeria, Ibadan	1960–69	10.4	3.9	3
SA, Cape Province: Bantu	1956–59	26.3	8.4	2
SA, Cape Province: Coloured	1956–59	1.5	0.7	2
SA, Cape Province: White	1956–59	1.2	0.6	2
SA, Johannesburg, Bantu	1953–55	19.2	9.9	1
SA, Natal Province: African	1964–66	28.4	6.9	2
SA, Natal Province: Indian	1964–66	9.5	3.8	2
Uganda, Kyadondo	1954–60	-	-	1
Uganda, Kyadondo	1960–71	8.9	3.1	5
Zimbabwe, Bulawayo	1963–72	52.1	20.6	6

Italics: Rate based on less than 10 cases

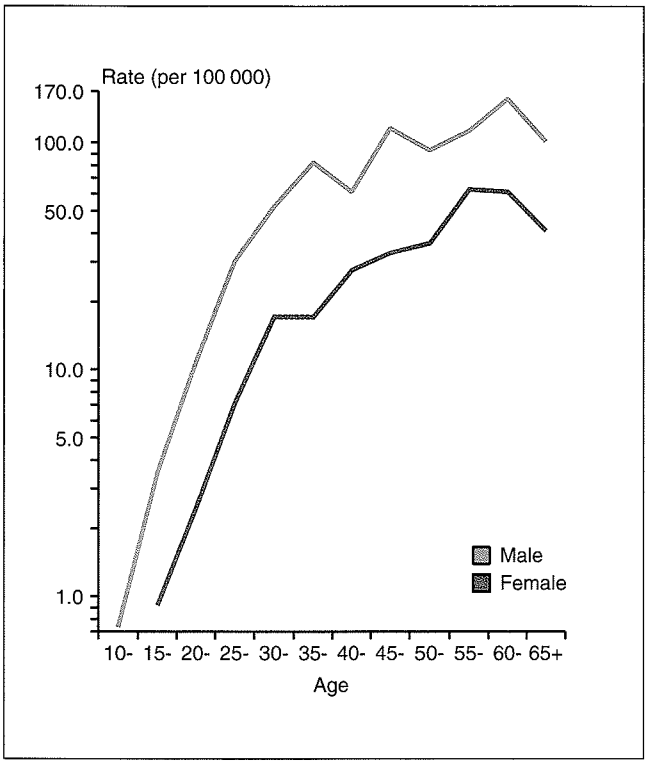

Figure 2.. Age-specific incidence rates per 100 000 of liver cancer, by sex (Gambia, 1988–97) (Bah *et al.*, 2001)

Time trends

There are very few long time series of data from Africa. Comparing the incidence rates in Ibadan, Nigeria, in 1960–69 (Table 2) with those reported for 1998–99 (Table 1) suggests almost no change in the intervening 30 years, although the rates are very low. The long series from Kampala, Uganda (Wabinga *et al.*, 2000) suggests that, in the most recent period (1995–97), there has been a small decline in recorded incidence in men, but not in women. In the 15-year observation period in Bulawayo from 1963 to 1977 (Skinner *et al.*, 1993), there was little to suggest any marked change in incidence.

In the studies of incidence rates of cancer among black gold miners in South Africa (Bradshaw *et al.*, 1982; Harington *et al.*, 1983), quite marked declines in incidence of liver cancer were observed, especially among miners from Mozambique. The crude incidence fell from 80.4 per 100 000 in 1964–71 to 40.8 per 100 000 in 1972–79 and 29.9 per 100 000 in 1981.

Risk factors

The major risk factors implicated in the very high incidence of liver cancer in sub-Saharan Africa are infection with the hepatitis viruses, especially hepatitis B, and exposure to aflatoxins. Other known risk factors probably play more minor roles.

Hepatitis B virus infection

Chronic carriage of the hepatitis B virus (HBV), as shown by seropositivity for HBV surface antigen (HBsAg), is associated with a large increase in risk of liver cancer, specifically of hepatocellular carcinoma. The earliest reports were case series that noted the rather higher prevalence of HBsAg in liver cancer cases than in the general population (Szmuness, 1978). Since then, many case–control studies have confirmed the relationship; the IARC (1994a) review summarized more than 20 studies in Africa alone, between the study of Prince *et al.* (1970) in Uganda and 1992 (Table 4). In most, the odds ratio associated with the carrier state was between 6 and 20. Since then, at least three more case–control studies have been published from South Africa (Kew *et al.*, 1997), from Nigeria (Olubuyide *et al.*, 1997), and from Egypt (Badawi and Michael 1999), with similar findings (Table 4).

In general, cohort studies yield rather greater relative risks than case–control studies. This is partly because the cases occurring during follow-up of apparently healthy individuals tend to be those detected at young ages, and hence are more likely to be related to HBV carrier status. It is also the result of misclassification of HBV infection status – there is a tendency for HBsAg titre to decline with age, becoming undetectable in some subjects, so that there will be misclassification in case–control studies, where HBsAg status is assessed only at the time of diagnosis.

Only one cohort study has been reported from Africa (London *et al.*, 1995; Evans *et al.*, 1998). The paucity of studies reflects the difficulties in identifying suitable population cohorts, and in conducting prospective follow-up, in the African situation. In Senegal, 13 036 soldiers aged 20–55 years were screened for HBsAg. The only published results are the age-standardized incidence rate of liver cancer in the 2611 men who were HBsAg-positive (68.3 per 100 000 person years). The rate in non-carriers was not reported, but, if we assume that these men (mean

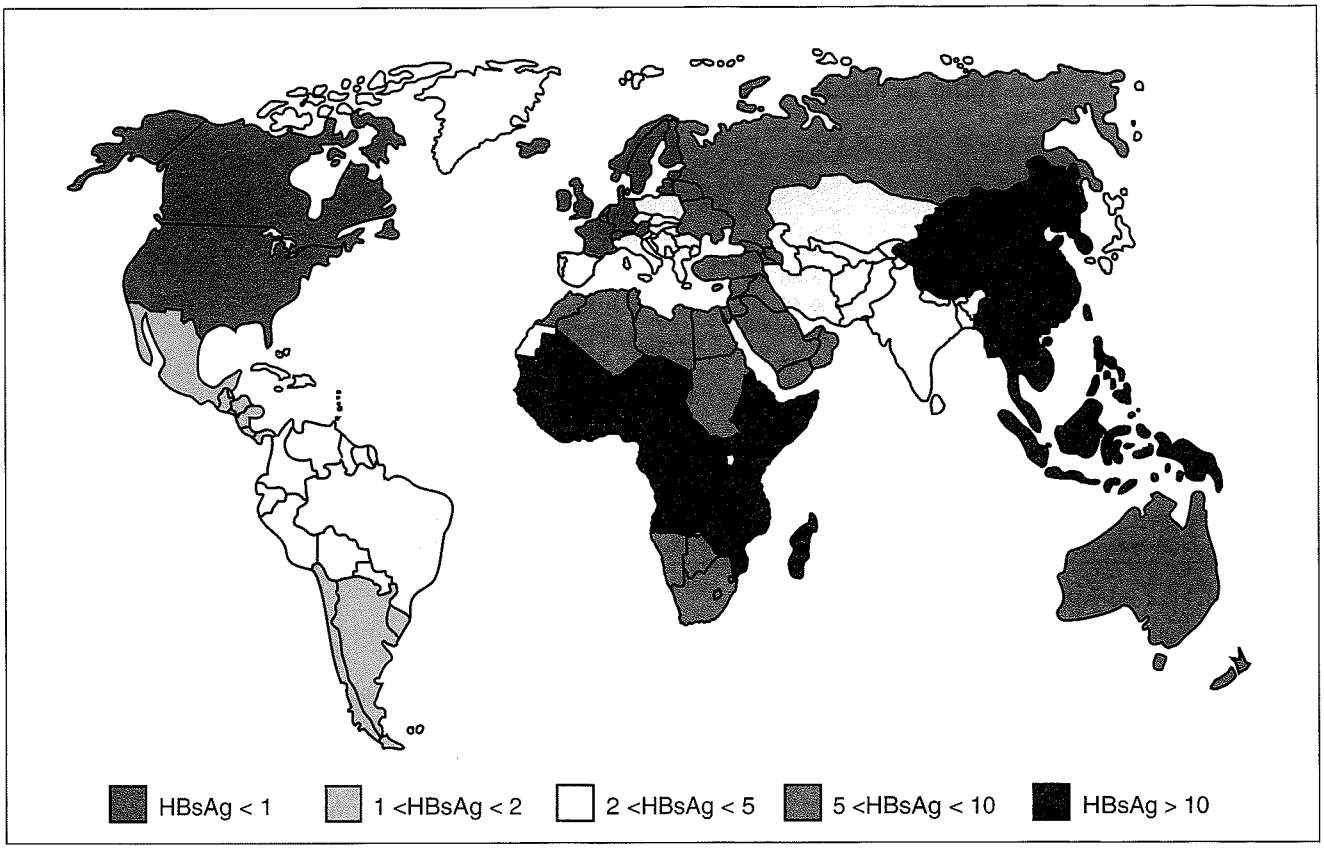

Figure 3. Prevalence of HBsAg carriers worldwide (%)

age 30 years) had the same incidence of liver cancer as men aged 25–34 in Dakar in 1969–74 (Waterhouse *et al.*, 1982)—26.0 per 100 000—then, with an HBsAg prevalence of 0.20, we may estimate the rate in non-carriers as [26.0 – (0.2 x 68.3)]/0.8 or 12.3, and the relative risk about 5–6. Evans *et al.* (1998) drew attention to the very much lower risk (one tenth) of liver cancer in the Senegal cohort than in carriers in China (or in Asian Americans). The Senegalese carriers have a much lower prevalence of serum HBV DNA than Chinese (mainly due to a more rapid decline with age); serum HBV DNA is associated with serum glutathione *S*-transferase titres, a marker of liver damage.

Figure 3 shows prevalence of HBsAg carriers among adults in different countries around 1993 (data supplied by WHO). Prevalence of chronic infection with hepatitis B virus is high in sub-Saharan Africa (average for all countries in the region is 11.6%), but lower in the north (average 5.4%). Because of this, the proportion of liver cancer cases attributable to hepatitis B infection can be estimated to vary from 50% in North Africa to 70% in West Africa, with a continent-wide average of 66% (28 000 cases per year).

Chronic carriage of HBV implies the persistence of replication of the virus, as reflected by the continued presence of HBsAg in the blood, although the titres of serum HBsAg in infected individuals decline with age (Evans *et al.*, 1998). The most important factor influencing this persistence is age at infection, with the likelihood of becoming a chronic carrier decreasing with age (Edmunds *et al.*, 1993). The high prevalence of HBV chronic carriage in Africa is a reflection of the high rates of infection in the first decade of life (Kew *et al.*, 1982). Perinatal infection seems to be rather uncommon, accounting for only 5–10% of carriers. It is possible that age at infection also determines the intensity of viraemia in chronic carriers—as noted above, Chinese subjects, infected perinatally, have higher and more persistent levels of serum HBV DNA than Senegalese. However, unlike in adults, in whom parenteral and sexual transmission are the most common, the modes of transmission in children are not clear (IARC, 1994a). In rural Africa, risk of infection in childhood is associated with the number of siblings in a household (Whittle *et al.*, 1990). Late birth order has also been shown to influence the risk of becoming a carrier of

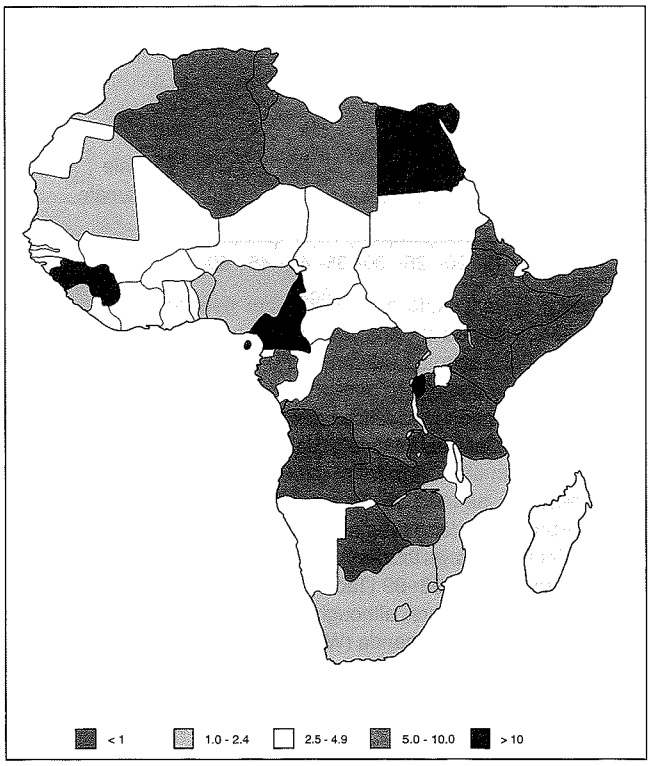

Figure 4. Prevalence of hepatitis C (source: WHO, 1999)

Table 3. Percentage distribution of microscopically verified cases by histological type
Liver (C22) - Both sexes

	Carcinoma				Hepato-	Sarcoma		Other	Unspec.	Number of cases	
	Hepato	Cholangio	Other	Unspec.	blastoma	Haemangio	Other			MV	Total
Algeria, Algiers	57.1	20.4	-	12.2	8.2	-	2.0	-	-	**49**	68
Algeria, Batna	33.3	50.0	-	-	-	-	-	-	16.7	**6**	33
Algeria, Constantine	11.1	22.2	-	44.4	11.1	-	-	-	11.1	**9**	12
Algeria, Oran	40.0	30.0	10.0	10.0	-	-	-	-	10.0	**10**	12
Algeria, Setif	5.0	60.0	-	5.0	-	-	5.0	-	25.0	**20**	55
Burkina Faso, Ouagadougou	100.0	-	-	-	-	-	-	-	-	**9**	66
Congo, Brazzaville	75.9	16.5	1.3	6.3	-	-	-	-	-	**79**	226
France, La Reunion	54.8	19.4	3.2	12.9	-	-	-	-	9.7	**62**	79
The Gambia	100.0	-	-	-	-	-	-	-	-	**11**	348
Guinea, Conakry	94.4	2.2	1.1	-	2.2	-	-	-	-	**89**	597
Kenya, Eldoret	92.6	7.4	-	-	-	-	-	-	-	**27**	73
Malawi, Blantyre	63.2	10.5	10.5	5.3	-	-	-	-	10.5	**19**	29
Mali, Bamako	90.9	-	-	6.1	-	-	-	-	3.0	**33**	1035
Namibia	65.1	22.9	1.2	4.8	-	-	4.8	-	1.2	**83**	96
Niger, Niamey	85.7	7.1	-	7.1	-	-	-	-	-	**14**	200
Nigeria, Ibadan	87.5	4.2	-	8.3	-	-	-	-	-	**24**	75
Rwanda, Butare	43.8	3.1	-	-	-	-	-	-	53.1	**32**	53
South Africa: Black	65.0	13.6	3.6	5.7	0.5	0.0	0.9	0.3	10.3	**2599**	2599
South Africa: White	32.0	43.7	7.3	11.5	0.7	0.5	1.2	0.9	2.1	**563**	563
South Africa: Indian	54.0	20.6	3.2	11.1	-	-	-	1.6	9.5	**63**	63
South Africa: Mixed race	60.2	21.6	4.5	7.4	2.3	-	0.6	1.1	2.3	**176**	176
South Africa, Elim	93.6	2.1	-	4.3	-	-	-	-	-	**47**	48
South Africa, Transkei, Umtata	84.6	7.7	-	-	-	-	-	-	7.7	**13**	50
South Africa, Transkei, 4 districts	93.8	-	-	-	-	-	6.3	-	-	**16**	26
Swaziland	70.6	23.5	-	-	5.9	-	-	-	-	**17**	256
Tanzania, Dar Es Salaam	87.5	6.3	-	6.3	-	-	-	-	-	**16**	16
Tanzania, Kilimanjaro	90.0	6.7	-	3.3	-	-	-	-	-	**30**	77
Tunisia, Centre, Sousse	76.5	5.9	-	5.9	5.9	5.9	-	-	-	**17**	17
Tunisia, North, Tunis	78.0	10.0	2.0	2.0	4.0	-	2.0	-	2.0	**50**	78
Tunisia, Sfax	83.3	-	-	-	-	-	-	16.7	-	**6**	6
Uganda, Mbarara	50.0	-	-	50.0	-	-	-	-	-	**2**	41
Uganda, Kyadondo County	78.0	14.0	4.0	2.0	-	-	-	-	2.0	**50**	133
Zimbabwe, Harare: African	96.0	1.3	-	-	1.3	-	1.3	-	-	**150**	747
Zimbabwe, Harare: European	100.0	-	-	-	-	-	-	-	-	**11**	38

HBsAg (Ryder *et al.*, 1992). This presumably reflects the fact that children with many older siblings are likely to be exposed to infection at a very young age. The possibility that biting insects (specifically bed bugs) play a role was tested in a randomized study in the Gambia, but the result was negative (Vall-Mayans *et al.*, 1994). Moreover, low socioeconomic status plays a major role in the perpetuation of HBV endemicity in Africa. This factor was shown to be important elsewhere in both developed (Szmuness, 1978) and developing countries (Toukan, 1987).

HBV sub-type *ad* is associated with long-term carriage of HBsAg while *ay* is associated with short-term carriage (Rioche, 1986) and a significant relationship exists between sub-types and ethnic group in Africa. Reports from West Africa, where incidence of PHC is highest, show a high preponderance of *ayw*, which is also known to be common among non-Bantu West Africans in Uganda (Lwanga *et al.*, 1977). To what extent these sub-types determine the incidence of PHC in Africa is worth further investigation (Wild & Hall, 1997).

The mechanism of carcinogenesis of HBV remains uncertain. The virus is not integrated into any specific part of the genome of the host, and some hepatocellular carcinomas in HBV carriers do not contain integrated HBV DNA (Matsubara & Tokino, 1990). One possibility is that cell proliferation associated with chronic hepatitis and cirrhosis is the important factor, the increased rate of cell turnover favouring accumulation of genetic alterations in liver cells. In Africa, liver cancer is practically always preceded by cirrhosis, and it seems likely that the main role of HBV (as for HCV; see below) is in inducing cirrhosis, although there is evidence for an effect independent of this (Wild & Hall, 2000).

Hepatitis C virus infection

The recognition of the hepatitis C virus (HCV) and its role in hepatocarcinogenesis is much more recent than for HBV (IARC, 1994a). Presence of infection can be recognized by detecting antibody to the virus, or, more sensitively, by testing for viral RNA. The early tests for antibody (first-generation tests) were rather non-specific, so there is some doubt about the true prevalence of infection in studies that used them. Now, a large number of case–control studies (using second-generation tests) have been carried out in many countries. Overall, they suggest that the presence of antibody to HCV is associated with a relative risk of about 25. The results of seven studies in Africa are shown in Table 5. In a further study in Somalia (Bile *et al.*, 1993), the cases were subjects with chronic liver disease and, although most were liver cancers, results were not reported separately. Several cohort studies have also been reported, but none from Africa. The prevalence of antibody-positive subjects in the population is rather lower than for HBsAg (see below); worldwide, prevalence seems to be highest in Japan, Egypt and parts of sub-Saharan Africa. Thus, although the relative risk associated with HCV infection is high, the proportion of cases of

Table 4. Summary of results of case–control studies of hepatocellular carcinoma and presence versus absence of hepatitis B surface antigen (HBsAg)

Reference and location	Subjects	Seroprevalence of HBsAg				OR	95% CI	Comments*
		Cases		Controls				
		No.	%	No.	%			
Prince *et al.* (1970); Uganda	Sex unspecified	4	12	6	2	[6.8]	[1.8–25]	Blood donor controls
Vogel *et al.* (1972); Uganda	Women and men	90	40	224	3	[19]	17.6–451	Adjusted for age and sex; testing by CF, CEP and PHA
Kew *et al.* (1974); South Africa	Men	75	40	18377	7	[8.7]	[5.3–14]	Mineworkers; testing by CEP and CF
Michon *et al.* (1975); Prince *et al.* (1975); Senegal	Women and men	165	61	154	12	[11]	[5.8–19]	Adjusted for age
	Controls with other cancer							
	Controls without cancer	165	61	328	11	[14]	[8.7–24]	
Larouzé *et al.* (1976); Senegal	Women and men	28	79	28	57	[2.8]	[0.74–10]	
Tsega *et al.* (1976); Tsega (1977); Ethiopia	Women and men	46	50	90	7	[14]	[4.6–44]	
Tabor *et al.* (1977)	Women and men							
Uganda		47	47	50	6	[14]	[3.8–51]	
Zambia		19	63	40	8	[21]	[4.7–96]	
USA		27	30	6726	0.02	[134]	[53–337]	
Reys *et al.* (1977); Mozambique	Women and men	32	60	231	9	[15]	[5.9–37]	Male controls; solid-phase RIA + CEP
Van Den Heever *et al.* (1978); South Africa	Women and men	92	34	92	9	[5.3]	12.2–14]	Blacks
Kew *et al.* (1979); South Africa	Women and men	289	62	213	11	[13]	[7.6–21]	Blacks; solid-phase RIA
Bowry and Shah (1980); Kenya	Women	76	51	33	6	[16]	[3.4–106]	Testing by PHA
Coursaget *et al.* (1981); Senegal	Women and men							
	Blood donor controls	134	63	100	12	[12]	[5.9–26]	
	Rural controls	134	63	833	14	[11]	[6.9–16]	
	Leprosy patient controls	134	63	560	25	[5.0]	[3.3–7.5]	
Gombe (1984); Congo	Women and men							
	Blood donor controls	65	74	120	9	[32]	[11–87]	Adjusted for sex; testing by RIA or PHA
	Other cancer controls	65	74	71	3	[55]	[12–256]	
Sebti (1984); Morocco		46	17	379	5	[4.2]	[1.6–11]	Adjusted for sex
Kew *et al.* (1986a); South Africa	Women and men	62	40	62	3	[20]	[4.3–132]	Blacks
Otu (1987); Nigeria	Women and men	200	49	400	7.5	[12]	[7.3–19]	
Gashau & Mohammed (1991); Nigeria	Women and men	65	65	69	36	[3.2]	[1.5–7.0]	Testing by ELISA and reverse PHA
Mohamed *et al.* (1992); South Africa	Men	77	35	77	5	7.5	2.2–25	Adjusted for alcohol intake and smoking; blacks
	Women	24	25	24	4	12	1.0–154	
Tswana & Moyo (1992); Zimbabwe	Women and men	182	56	100	11	[10]	[5.0–22]	Testing by ELISA
Ryder *et al.* (1992); Gambia	Women and men	70	63	70	21	6.9		Adjusted for age; $p < 0.01$; 64 cases, 67 controls tested
Kashala *et al.* (1992); Zaire	Women and men	40	57.6	68	7.4	[17]	[5.7–51]	Testing by immunoperoxidase
Kew *et al.* (1997); South Africa	Women and men	231	53.3	231	8.2	21.8	8.9–53.4	Matched for age ± 2 years
Olubuyide *et al.* (1997); Nigeria	Men and women	64	59	64	50	1.0	0.5–8.0	Adjusted for age
Badawi & Michael, (1999); Egypt	Women and men	102	91	96	7	12.5	6.1–25.6	Adjusted for "confounders". Testing by ELISA

OR, odds ratio
CI, confidence interval
HCV, hepatitis C virus
NR, not reported
NS not significant
[ ], calculated values, unadjusted unless otherwise indicated in the comments
*, serological testing for HBV markers by radioimmunoassay unless otherwise specified:
ID, immunodiffusion,; CF complement fixation; CEP countercurrent immunoelectrophoresis; PHA passive haemagglutination; ELISA enzyme-linked immunoabsorbent assay

Table 5. Summary of results of case-control studies of hepatocellular carcinoma and the prevalence of antibody to HCV

Reference and location	Subjects	Seroprevalence of antibodies to HCV				OR[a]	95% CI	Comments*
		Cases		Controls				
		No.	%	No.	%			
Coursaget *et al.* (1990); Senegal	NR	80	37.5	136	3	[20]	[6.9–57]*	1982–86; stringent cut-off used for assay*
Kew *et al.* (1990); South Africa	Men and women	380	29	152	0.7	[62]	[11–353]*	Unmatched hospital controls
Dazza *et al.* (1993); Mozambique	NR	178	6	194	2	1.1	0.4–3.1	Blood donor controls; adjusted for age; mean age of cases, 40.8 years; controls, 31.3 years
Coursaget *et al.* (1992); Senegal	NR	49	4	134	1	[5.7]	[0.5–69]	General population controls
Kew *et al.* (1997); South Africa	Men and women	231	20.7	231	5.2	6.1	2.8–13.7	Age-matched hospital controls
Olubuyide *et al.* (1997); Nigeria	Men and women	64	19	64	11	1.1	0.4–7.8	Adjusted for age
Yates *et al.* (1999); Egypt	Men and women	31	67	26	30	[4.7]	[1.4–17.2]	Hospital cases, healthy controls. Confined to ages 42–52 for age-matching

[a]Cornfield limits
* As measured by first-generation assays

Table 6. Separate effects of HBV and HCV on risk for hepatocellular carcinoma

Reference and location	HBsAg seronegative HCV Ab seronegative		HBsAg seronegative HCV Ab seropositive			HBsAg seropositive HCV Ab seronegative			HBsAg seropositive HCV Ab seropositive		
	Cases	Controls	Cases	Controls	OR	Cases	Controls	OR	Cases	Controls	OR
Coursaget *et al.* (1992); Senegal	23	82	4	0	[•]	20	50	[1.4]	2	2	[3.6]
Dazza *et al.* (1993); Mozambique	52	163	8	4	1.4	115	27	[13]	3	0	[•]
Kew *et al.* (1997); South Africa	69	197	39	15	6.6	103	18	23.3	20	1	82.5
Olubuyide *et al.* (1997) Nigeria	21	29	5	3	[2.3]	31	28	[1.5]	7	4	[2.4]

liver cancer due to the virus is rather less than for HBV—perhaps 20–25% worldwide. Hepatitis C virus is transmitted mainly by blood and blood products, and most infection worldwide seems to be a consequence of blood transfusion or injections with unsterilized equipment. HCV is an RNA virus, and is not, therefore, integrated into the host cell DNA. Several different genotypes exist, which differ in their geographic distribution and, reportedly, in the severity of the hepatitis they cause. It seems that HCV causes liver cancer by causing chronic hepatitis and cirrhosis, both known to act as precursors of liver cancer through the intense hepatocyte regeneration occurring in these conditions.

The epidemiology of HCV infection on the African continent is not clearly described, and must be deduced from rather non-systematic small-scale studies of seroprevalence and surveys of blood donors and pregnant women. The available data (from WHO, 1999) are summarized in Figure 4.

One striking finding is the extraordinarily high prevalence of infection in Egypt. The average seroprevalence is about 15%, but there is considerable regional variation within the country, with the highest seroprevalence in the governorates (provinces) in the Nile delta (20–40%) and along the Nile valley (Arthur, 1996; Arthur *et al.*, 1997). This is now recognized to be a result of campaigns of eradication of schistosomiasis, with inadequate sterilization of the syringes and needles used for injection of antimonal compounds (Tartar emetic) between 1950 and 1982, when oral praziquantel became available (Attia, 1998). Seroprevalence increases with age, reaching a plateau around age 40 years (Hibbs *et al.*, 1993; Yates *et al.*, 1999). Frank *et al.* (2000) have shown that the birth-cohort-specific prevalence of HCV can be well explained by exposure to parenteral anti-schistosomal therapy in the 1960s and 1970s. For individuals in two large surveys of HCV prevalence, a regression model adjusting for region and age showed that there is a significant association between seroprevalence, and an index of exposure to such therapy. The high prevalence of infection in the general population—(35–55% at age 40–50 years in the non-metropolitan areas of the Nile valley) implies that continuing transmission may be maintained through blood transfusion and other, ill-defined, parenteral means.

The effects of *combined* infection with HBV and HCV are not very clear. Although joint infection occurs more often than would be expected by chance, it is still relatively rare in the general population, so that stable estimates of associated odds ratios are difficult to obtain. Four studies from Africa are summarized in Table 6. A further case–control study in Khartoum, Sudan (Omer *et al.*, 2001) compared 115 hospital cases of liver cancer (probably mainly histologically confirmed) with 199 unmatched community controls

with respect to positivity for HBsAg and/or anti-HCV. The crude OR was 12.9 (95% CI 6.9–24.2), although results for the two viruses separately, or together, were not given. A meta-analysis of case–control studies suggests that the combined effect lies somewhere between additive and multiplicative effects (Donato *et al.*, 1998), and the results of a cohort study (Wang *et al.*, 1996) are also compatible with this conclusion.

Aflatoxin B_1

Aflatoxins are produced by moulds of the *Aspergillus* species, which infect stored grains and nuts, and one of these, aflatoxin B_1, long known to cause liver tumours in animals, has been classified by IARC as a human carcinogen (IARC, 1993, 2002).

In Africa, high levels of contamination have been found particularly in groundnuts and maize. Human exposure to aflatoxin B1 in tropical Africa is in the range 3–200 ng/kg bw per day (Hall & Wild, 1994). Aflatoxins and their metabolites can be detected in various human tissues and body fluids. Thus, their presence in urine samples from Zimbabwe (Nyathi *et al.*, 1987), Gambia (Wild *et al.*, 1988), Kenya (Autrup *et al.*, 1987) has been described. In the Gambia, urinary excretion was shown to correlate with dietary intake over the previous 24–48 hours (Groopman *et al.*, 1992). Aflatoxins have been detected in blood samples in Nigeria (Denning *et al.*, 1988), Sudan (Hendrickse *et al.*, 1982) and Nigeria and Ghana (Lamplugh *et al.*, 1988). The levels of covalently bound aflatoxin–albumin adducts in serum from subjects in the Gambia, Senegal and Kenya were much higher than those found in Europe or south-east Asia (Wild *et al.*, 1990). Exposure levels did not vary with age and sex in the Gambia, but there were strong seasonal effects and higher levels in rural than urban dwellers (Allen *et al.*, 1992; Wild *et al.*, 2000). Aflatoxins can also be detected in human milk, as observed in Sudan (Coulter *et al.*, 1984), Zimbabwe (Wild *et al.*, 1987) and the Gambia (Zarba *et al.*, 1992).

The first evidence for a carcinogenic effect in humans came from ecological studies that compared aflatoxin levels in foodstuffs with liver cancer incidence rates in different geographical locations. There are inherent problems in deducing probable effects in individuals from observations at the ecological level. In addition, the studies in Africa suffer from problems of estimating exposure (usually from some measures in foodstuffs) and outcome (data on liver cancer incidence are often very imprecise) and in taking into account such other important factors as exposure to HBV. Table 7 summarizes eight ecological studies carried out in Africa. They include studies comparing different population groups within Uganda (Alpert *et al.*, 1971), Kenya (Peers & Linsell, 1973; Autrup *et al.*, 1987), Swaziland (Peers *et al.*, 1976, 1987), Mozambique (van Rensburg *et al.*, 1985), South Africa (van Rensburg *et al.*, 1990) and Sudan (Omer *et al.*, 1998). For example, in Swaziland, aflatoxin intake was estimated from dietary samples and crop surveys; it varied more than five-fold between the four topographic regions of the country. Liver cancer incidence in 10 sub-regions was more closely related to mean estimated aflatoxin intake than to mean HBsAg prevalence (Peers *et al.*, 1987).

Measurement of aflatoxins in body fluids and tissues has provided a more accurate measure of dietary exposure. In the Gambia, the levels of aflatoxin–albumin adducts in blood correlated well with dietary intake in the preceding seven days (Wild *et al.*, 1992). In Kenya, Autrup *et al.* (1987) observed a significant correlation between liver cancer "incidence" (as estimated from attendance at a liver clinic in Kenyatta Hospital, Nairobi) and aflatoxin levels in the urine of patients attending outpatient departments in nine different district hospitals.

The ability to measure aflatoxin bound to cellular macromolecules, including DNA and proteins in urine and serum, has sharpened the measure of exposure, providing a biomarker that does reflect individual intake of aflatoxin (Hall & Wild, 1994). These measures have been used in cohort studies to study the association between aflatoxin exposure and liver cancer risk. Thus, using urinary aflatoxin N7-guanine as a marker in a cohort study carried out in Shanghai, China, an increased risk of liver cancer was observed in individuals positive for the marker at enrolment compared with those who were negative (Qian *et al.*, 1994). Furthermore, there appeared to be a multiplicative interaction with chronic HBV infection (also a clear risk factor in this study), suggesting a different mechanism of action from the virus. The effect of aflatoxin alone, in the absence of HBV, was rather weak. One mechanism for the interaction may be the diminished activity of aflatoxin-metabolizing enzymes in the presence of chronic infection by HBV. Thus, some studies in West Africa have suggest that there are higher levels of aflatoxin–albumin adducts in serum of HBsAg-positive subjects than in HBsAg-negative subjects, especially in children (Wild & Hall, 1997).

Recent work has focused on the role of polymorphisms of the genes responsible for aflatoxin metabolism in modifying risk due to aflatoxin exposure. Chen *et al.* (1996) observed that, among HBsAg carriers, the risk of liver cancer was related to serum aflatoxin B–albumin levels, but only in individuals with the null genotype for the enzymes glutathione *S*-transferase (GST) M1 and GST T1, possibly responsible for conjugation and detoxification of aflatoxin. Wild *et al.* (2000) found that blood levels of aflatoxin–albumin adducts in Gambian subjects were higher in those with GSTM1 null genotype in the absence of HBV infection. In a case–control study in China (McGlynn *et al.*, 1995), a mutation in one or both alleles of the gene coding for epoxide hydrolase—another detoxifying enzyme—had a stronger association with hepatocellular carcinoma (OR = 3.3) than did the null genotype of GSTM1 (OR = 1.9).

Three case–control studies have been conducted in Africa to compare intake of aflatoxin in liver cancer patients with that in control subjects (Table 7). Case–control studies are much less satisfactory that the cohort studies mentioned earlier, since it is highly probable that dietary habits are profoundly altered in patients suffering from liver cancer. Even when serum or urine levels of aflatoxin adducts are used to measure exposure, only relatively recent intake (days or weeks) of aflatoxin is being evaluated. This may not reflect exposures during the etiologically relevant period (years earlier). Moreover, the presence of liver disease may modify the levels of aflatoxin found in serum or urine, biasing comparisons between cases and controls.

In small studies in Nigeria (Olubuyide *et al.*, 1993a,b), cases were 22 patients at a university hospital in Ibadan in 1988 and controls were 22 patients from the gastroenterology ward of the same hospital with acid peptic disease, matched to cases on sex and age. Blood samples were collected and analysed for HBsAg and a variety of aflatoxins (B_1, B_2, M_1, M_2, G_1, G_2 and aflatoxicol). HBsAg was detected in 16 cases and 8 controls. Elevated levels of aflatoxins were detected in five (23%) cases and one (5%) control, the difference being significantly different ($p < 0.05$).

Mandishona *et al.* (1998) carried out a small case–control study in South Africa aiming primarily to determine the role of dietary iron overload in the etiology of hepatocellular carcinoma (see below), which included information on exposure to aflatoxin B_1. Cases were 24 consecutive patients with HCC in two hospitals of one province of South Africa. There were two sets of controls: a matched (sex, age, race) series of 48 (two controls per case) selected from patients hospitalized with trauma or infection, and 75 relatives of the cases. Analyses of blood samples yielded measures of serum aflatoxin B_1–albumin adducts, iron overload, HBsAg, HCV and other biochemical parameters. The median level of aflatoxin B_1–albumin adducts was lower among cases (7.3; range 2.4–91.2) than among hospital controls (21.7; range 0–45.6) and family controls (8.7; range 0.7–82.1). The use of median values to compare the groups may have obscured differences in the distribution of values between them.

Table 7. Summary of principal ecological and cross-sectional studies on liver cancer and aflatoxins in Africa

Reference	Area	Units of observation/ number of units	Exposure measure(s)	Outcome measure(s)	Covariate	Results	Comments
Alpert *et al.* (1971)	Uganda	Main tribes and districts of Uganda; 7	Aflatoxin contamination of nearly 500 food samples taken from randomly selected native homes and markets; 1966–67	Hepatoma incidence identified from hospital records; 1963–66	Nil	The highest incidence of hepatoma occured in areas with highest levels of aflatoxin contamination.	
Peers & Linsell (1973)	Kenya	Areas of Murang'a district; 3	Aflatoxin extracted from food samples, repeated sampling over 21 months	Incident hepatocellular cancers ascertained from local hospital; 1967–70	Nil	Using 6 data points (3 areas, both sexes), correlation ($r = 0.87$) between aflatoxin intake and liver cancer	Questionable completeness of liver cancer registration. Small number of units of observation
Peers *et al.* (1976)	Swaziland	Altitude areas; 4	Aflatoxin from food and beer samples: every 2 months for period 1 year, over 1000 samples analysed; 1972–73	Primary liver cancer (PLC) incidence rates, from national cancer registry, 1964-68	Nil	Correlation ($r = 0.99$) between aflatoxin and PLC rates	Exposure post-dated cancer data
Van Rensberg *et al.* (1985)	Southern Africa	7 regions in Mozambique and 1 in South Africa	Mean aflatoxin contamination of food samples, over 2500 samples analysed; 1969–74	Incidence rates of hepatocellular carcinoma (HCC); 1968–75. A variety of sources including local hospitals and South African mines	Nil	Rank correlations between HCC and mean total aflatoxin 0.64 ($p < 0.05$) in men and 0.71 ($p < 0.01$) in women	
Autrup *et al.* (1987)	Kenya	Districts of Kenya; 9	Prevalence of urinary AFB-Gual adducts as ascertained in surveys of local clinic patients in the various districts (total sample, 983); 1981–84	Primary hepatocellular carcinoma (PHC) incidence diagnosed at one large hospital in Nairobi; 1978–82	HBV measured by HBsAg in same sample as used for AFB	Spearman rank correlation showed moderate association ($r = 0.75$) between rate of AFB exposure and incidence of PHC. Using the same type of analysis, no correlation between HBV and PHC ($r = 0.19$). No interaction detected between AFB and HBV	Possible confounding by ethnic characteristics
Peers *et al.* (1987)	Swaziland	Administrative regions; 10	Aflatoxin measured in food samples from households and crop samples from the fields over 1200 samples analysed; 1982–83.	Incidence rates of PLC; 1979–83	Serum samples from the Swaziland blood bank HBsAg	Significant correlation between mean aflatoxin contamination and PLC; little effect of HBsAg on PLC.	
Van Rensberg *et al.* (1990)	South Africa	Natives of districts of the Transkei, working as goldminers; 4	Aflatoxin contamination of local food samples, based on over 600 samples; 1976-77	PLC incidence	Nil	Rank order correlations between aflatoxin intake and PLC incidence in goldminers from the Transkei were significant at $p < 0.05$.	
Omer *et al.* (1998)	Sudan	Two areas, one high risk, one low risk	Peanut butter samples collected in markets and analysed for AFB1. Type of storage assessed	Clinical experience and Khartoum hospital records	Nil	Aflatoxin consumption levels were much higher in the presumed high risk area than in the presumed low risk area	Only two areas compared. Unreliable measures of liver cancer incidence

Table 8. Summary of case-control studies on liver cancer and aflatoxins in Africa

Reference	Area	Study base	Cases	Controls	Exposure measures	Covariate	Results				Comments
Olubidye *et al.* (1993)	Nigeria	Hospital in Ibadan	Primary hepatocellular cancer diagnosed in 1988; $n = 22$	Matched patients from gastro-enterology ward; $n = 22$	Serum levels of aflatoxin	HBsAg was measured but not included in analysis of aflatoxins	High aflatoxin levels were detected in 5 cases and 1 control ($p < 0.05$)				
Mandishona *et al.* (1998)	South Africa	Two hospitals in one province of South Africa	Suspected cases of HCC; $n = 24$	Two control series: one hospital-based (trauma or infection patients), $n = 48$; family-based (including related and unrelated family members), $n = 75$	Measured AFB_1–albumin adducts	Several measured, but not used in analysis of aflatoxin	Levels of AFB_1–albumin adducts were lower among cases than among both sets of controls				High risks of HCC found for subjects with HBV, alcohol, and iron overload. Questionable comparability of hospital control series, and possible overmatching with family control series
Omer *et al.* (2001)	Sudan	Residents of two regions of Sudan	Cases of hepatocellular cancer diagnosed in 5 hospitals in Khartoum; $n = 150$	Community-based, selected from lists in 'sugar shops' in same localities as cases; $n = 205$	Questionnaire on peanut butter consumption and on storage of peanuts	HBsAg, HCV, smoking alcohol, $GSTM_1$ genotype		OR	95% CI	No.	Questionable comparability of cases and controls
							High peanut butter intake	3.0	1.6–5.5	63	
							High peanut butter intake +$GSTM_1$ null genotype	16.7	2.7–104	–	

Omer *et al.* (2001) conducted a case–control study in Sudan to assess the association between peanut butter intake as a source of aflatoxin and the $GSTM_1$ genotype in the etiology of HCC. Cases were 150 patients with HCC who were diagnosed in one of the six major hospitals of Khartoum and whose place of residence was in one of two regions: West Sudan which is about 650 km from Khartoum and Central Sudan which is about 500 km from Khartoum. Controls were 205 residents of the two study areas, selected by a two-stage process, the second stage of which involved random selection from local village 'sugar shops'. Consumption of peanut butter (and some other factors) was obtained by interview by the principal investigator and transformed into a quantitative cumulative index. Usable blood samples were collected from 110 cases and 189 controls, and were analysed for HBsAg and genotyped for GSTM. In West Sudan, the cases consumed more peanut butter than controls, and there was a dose–response relationship between cumulative consumption and risk for HCC. In the highest quartile of consumption, the odds ratio was 8.7. However, peanut butter consumption conferred no increased risk in Central Sudan. $GSTM_1$ was not a risk factor for HCC, but it was a strong effect modifier; the excess risk due to peanut butter consumption was restricted to subjects with the $GSTM_1$ null genotype; the odds ratio in the high peanut butter exposure group among GSTM1 null genotype subjects was 16.7 (95% CI 2.7–105). There was no interaction between "hepatitis infection" (positivity for HBsAg or anti-HCV) and estimated consumption of peanut butter.

Some liver tumours have a highly specific point mutation involving a GC to TA transversion in codon 249 of the *TP53* tumour-suppressor gene (Greenblatt *et al.*, 1994; Montesano *et al.*, 1997). This mutation appears to be more frequent in populations where aflatoxin intake is thought to be high, for example, in Senegal (Coursaget *et al.*, 1993) and Mozambique and South Africa (Bressac *et al.*, 1991). In addition, the same base pair has been shown to be a hot-spot for mutation by aflatoxin in hepatocytes in vitro (Aguilar *et al.*, 1993) and to be more frequently mutated in non-tumorous liver tissue of patients originating from regions of supposed high aflatoxin exposure than those from low-exposure regions (Aguilar *et al.*, 1994). Kirk *et al.* (2000) observed the same mutation in DNA extracted from plasma of 36% patients with hepatocellular carcinoma in Gambia (but not in European patients), as well as in patients with cirrhosis (15%) and apparently normal subjects (6%). To date, no positive correlation has been made at the individual level between aflatoxin exposure and *TP53* mutation.

Iron overload

The role of iron overload as a cause of hepatocellular carcinoma has been of particular interest on the African continent. The observation that cases of liver cancer are often associated with elevated levels of serum ferritin, the principal iron storage protein (Kew *et al.*, 1978; Ola *et al.*, 1995), does not clarify whether this is a cause or an effect of the liver damage. However, prospective observation of subjects with haemochromatosis, a common inherited disorder of increased intestinal iron absorption and progressive parenchymal iron overload, shows that they have a high risk of developing cirrhosis and hepatocellular carcinoma (Niederau *et al.*, 1985).

Iron overload appears to be relatively frequent in some populations of sub-Saharan Africa, especially in South Africa (Bothwell *et al.*, 1964; Friedman *et al.*, 1990) and Zimbabwe (Gordeuk *et al.*, 1986), but has been reported also from Uganda (Owor, 1974) and Tanzania (Haddock, 1965) in East Africa, and Ghana (Dodu *et al.*, 1958) and Nigeria (Isak *et al.*, 1985) in West Africa. It is ascribed to excessive intake of iron derived from preparation of food and drink in iron vessels. Traditional beer has been particularly implicated (Walker & Segal, 1999). However, it has been suggested that, in addition to the quantity of iron consumed, there is also a familial predisposition, presumably implicating a genetic mechanism, though the responsible gene does not appear to be linked to HLA (as is the haemochromatosis gene) (Gordeuk *et al.*, 1992; Moyo *et al.*, 1998a).

Most of the evidence relating hepatocellular carcinoma to iron overload derives from autopsy studies in southern Africa. The initial observation by Strachan (1929) that hepatic iron concentrations were higher in subjects dying with hepatocellular carcinoma than in those with other causes of death has been confirmed in later studies (Friedman *et al.*, 1990; Jaskiewicz *et al.*, 1991; Gordeuk *et al.*, 1996). Moyo *et al.* (1998b) measured hepatocellular iron in a series of 215 liver biopsies in Harare, Zimbabwe; the odds of hepatocellular carcinoma (36 cases) were 3.1 times (95% CI 1.05–9.4) higher in the presence of iron overload. Mandishona *et al.* (1998), in a case–control study in Mpumulanga Province of South Africa, compared 24 biopsy-proved liver cancer cases with 48 hospital controls and 75 family members of the cases. Iron overload (defined as markedly raised serum transferrin saturation combined with an elevated serum ferritin concentration) was present in five cases and three controls, corresponding to an odds ratio of 10.6 (95% CI 1.5–76.8) after adjustment for alcohol consumption, infection with HBV and HCV, and exposure to aflatoxin B. Compared with the 75 family members, the risk conferred by iron overload was 4.1 (95% CI 0.5–32.2).

There have been no prospective studies in Africa. In a nested case–control study within a cohort of male government employees in Taiwan, the risk of developing liver cancer was increased 1.4-fold (95% CI 1.0–2.0) in subjects with elevated serum ferritin at entry (Stevens *et al.*, 1986). However, HBV carriers have higher mean iron levels than the general population (Israel *et al.*, 1989) and no adjustment was made for HBV infection status, possibly because almost all of the liver cancer cases were HBsAg carriers. In a prospective study of subjects with chronic liver disease in Korea, Hann *et al.* (1989) observed an odds ratio of 4.4 (95% CI 1.3–14.5) of developing liver cancer eight months or more after entry among 93 chronic carriers of HBsAg with the highest tertile of serum ferritin at entry, compared with those having lower levels.

Mechanisms by which a high level of serum or tissue iron may predispose to liver cancer are not yet clear; it may act by promoting tissue damage and cirrhosis, by enhancing chronic carriage of HBV and/or HCV, or by a direct mutagenic effect of iron (Gangaidzo & Gordeuk, 1995).

Other risk factors

Excessive alcohol consumption is an important cause of hepatocellular carcinoma in western countries; in an evaluation in 1988, IARC (1988) considered four cohort studies and six case–control studies, and concluded that the evidence was sufficient to indicate a causative association. Since that time, other work has suggested that the effects of alcohol on HBsAg-positivity are independent and have a multiplicative effect (Chen *et al.*, 1991), and that the same may be true for alcohol and infection with HCV (Yu *et al.*, 1991). In South Africa, habitual drinking of more than 80g of ethanol daily in the presence of HBV infection was associated with increased risk in urban men aged over 40 years (Mohammed *et al.*, 1992). Alcohol is believed to operate through its action as a hepatotoxin, promoting liver cirrhosis and regeneration with rapid cell division, favouring oncogenic mutations.

Because of the close association between alcohol consumption and tobacco smoking, it has been difficult to establish whether tobacco smoking plays an independent role in the etiology of liver cancer. In general, the evidence suggests a weak association, independent of alcohol and hepatitis B infection (Doll, 1996), with only a two- to three-fold increase in risk. In South Africa, Kew *et al.* (1985) did not find any association between smoking and risk of hepatocellular carcinoma, and no significant association was observed for cigarette smoking or alcohol consumption in a study in Nigeria (Olubuyide & Bamgboye, 1990).

Use of oral contraceptives is well known to increase the risk of hepatic adenomas. The evidence is less convincing for hepatocellular carcinoma, although several studies suggest that there is an increased risk (Kew *et al.*, 1990) that is higher with more prolonged use (Schlesselman, 1995). A WHO multicentre study, which included countries in which hepatitis B is endemic, found no association, although adjustment for HBV status was not done or was inadequate (WHO, 1989).

Evidence linking schistosomal infection with liver cancer has come mainly from observations in China and Japan, where *S. japonicum* is involved. The studies are not convincing (IARC, 1994b). In a hospital-based case–control study in Cairo, Egypt, Badawi and Michael (1999) found infection with *S. mansoni* to be more common in liver cancer cases (59%) than in control subjects (11%), corresponding to an odds ratio of 5.2. The estimate may have been adjusted for HBV infection, but there was no adjustment for HCV infection, common in this population and known to be associated with schistosomal infection (Darwish *et al.*, 1993).

Several studies have suggested that ingestion of inorganic arsenic is a risk factor for hepatocellular carcinoma.

There is also evidence that membranous obstruction of inferior vena cava (MOIVC) has a minor causal association with primary hepatocellular carcinoma in Africa, in a manner similar to that thought to occur with cirrhosis elsewhere (Kew *et al.*, 1989).

Prevention

Prevention of chronic carriage of HBV became a reality with the development of vaccines in the early 1970s (Krugman *et al.*, 1970, 1971). Early trials suggested that vaccination could prevent approximately 70–75% transmission of hepatitis B virus infection from carrier mother to infant. If hepatitis B immune globin (HBIG) was given with vaccine in the neonatal period, 90–95% of transmission was prevented (Beasley *et al.*, 1983; Wong *et al.*, 1984).

Two randomized studies were set up in Qidong county, China (Sun *et al.*, 1991) and in the Gambia, West Africa (GHIS, 1987), to formally establish the effectiveness of vaccination against hepatitis B in preventing liver cancer later in life. It will be many years before results are available. However, follow-up of the vaccinated children does demonstrate that there is a much lower rate of natural infection and a greatly reduced prevalence of chronic HBsAg carriers (Viviani *et al.*, 1999). In Taiwan, mass vaccination against hepatitis B was introduced in the 1980s, first to neonates born of HBsAg-positive mothers, then, in 1984, for all new-borns. By 1994, it was possible to compare liver cancer incidence in children aged 6–9 years born before vaccination was introduced with those born after. There was a fourfold difference in incidence (Chang *et al.*, 1997). These results suggest that vaccination will, indeed, be as successful as hoped.

Wild and Hall (2000) have reviewed measures to prevent aflatoxin-induced liver disease. They distinguish individual-level and community-level preventive measures, with the latter category subdivided into pre- and post-harvest actions. Pre-harvest measures include reducing crop vulnerability to fungal infection (using irrigation, insecticides and fungicides), introduction of non-aflatoxigenic strains of *A. flavus* to compete with aflatoxin-producing strains (biocontrol) and use of genetically modified crops (*Aspergillus*-resistant).

Post-harvest, the objective is to minimize aflatoxin accumulation due to food storage in hot and humid conditions, with rodent or insect damage. Improved drying and storage are key elements, along with use of pesticides and biological pest control.

At the individual level, consumers can be educated to avoid obviously mouldy grains, and to consume a more varied diet, with less reliance on staple crops (especially maize and peanuts) that are heavily contaminated with aflatoxin. Chemoprevention is a different approach to prevention of aflatoxin toxicity; the aim is to enhance detoxification of ingested aflatoxin by modulating expression of enzymes such as glutathione S-transferases. Oltipraz is a drug which induces these enzymes in animals (rats) and results in enhanced excretion of aflatoxin–glutathione conjugates in bile, lowered formation of aflatoxin–DNA adducts in liver and inhibition of aflatoxin B_1-mediated hepatocarcinogenesis. In a small-scale trial in China (Wang *et al.*, 1999), a relatively large dose of oltipraz was observed to reduce the level of albumin–aflatoxin adducts in humans and to increase excretion of glutathione conjugates. However, it is doubtful whether this type of chemoprevention will have a practical application in the control of liver cancer.

Screening for liver cancer among high-risk subjects (HBsAg carriers, patients with chronic liver disease) using serum alpha-fetoprotein (AFP) and/or abdominal ultrasound has been tried in a number of settings, but there is no evidence of benefit from a properly conducted randomized trial (Brown & Scharschmitt, 1999). A small study in Cameroon (Biwole-Sida *et al.*, 1992) using both ultrasound and AFP (cut-off > 1000 ng/ml) found a high prevalence of liver cancer in subjects with clinical cirrhosis (20/48) and chronic hepatitis (9/45), but no cases in 70 otherwise healthy carriers of HBsAg.

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4.9 Lung cancer

Introduction

Lung cancer is now the leading cancer worldwide, with an estimated 1.24 million new cases (12.3% of all cancers) occurring in the year 2000 (Ferlay *et al.*, 2001). However, only a small proportion of this burden (19 500 cases; 1.9% of the world total) is estimated to occur in Africa.

Descriptive epidemiology in Africa

A summary of the age-standardized incidence rates from the registries reporting results in this volume is presented in Table 1 and old data from the 1950s and 60s are given in Table 2.

Incidence rates in women are very low (except among the populations of European origin in Zimbabwe and South Africa) and are indeed considerably lower than the rates among non-smoking women in the United States (4.8 per 100 000; Parkin *et al.*, 1994). In men, the rates are, in general, rather higher in North Africa (Algeria and Tunisia) than in sub-Saharan Africa. In West Africa, incidence rates are low, ranging from 0.7 per 100 000 in Ibadan, Nigeria to 8.2 in Conakry, Guinea. In southern Africa, the rates are higher. In Zimbabwe, the incidence rates recorded in Bulawayo in the 1960s were very high, but in Harare, the incidence among the African population in 1993–97 is very much lower (12.1 per 100 000) and only about half that reported in the first results from this cancer registry (24.6 per 100 000) (Bassett *et al.*, 1995). In an early study of 'Bantu' gold miners in Gwanda (Zimbabwe), Osburn (1957) noted that lung cancers comprised more than 40% of malignancies found at autopsy, and estimated incidence as 18 per 100 000. In South Africa, the incidence rates recorded in Cape Province and Natal in the 1950s and 1960s (Table 2) were very high by African standards. In the recent data (1989–92) from the histopathology-based National Cancer Register (Table 1), the incidence is higher in the white, mixed-race and Indian populations than in the black population. In a study by Bradshaw *et al.* (1983), age-standardized mortality rates (per 100 000) from lung cancer were 42.8 in whites, 45.3 in mixed race and 13.2 in populations of 'Asian/Indian' origin. Among females, rates were 9.5 in whites, 6.3 in mixed-race populations and 6.8 in populations of Asian/Indian origin.

The island populations of Reunion, Mauritius and the Seychelles all have high lung cancer incidence and mortality rates. For example, in the Seychelles, age-standardized mortality rates of 45.7 in males and 14.0 per 100 000 in females have been reported for the period 1985–87 (WHO, 1988).

Based on these incidence/mortality data, and frequencies in various clinical series, estimated incidence and mortality by country have been prepared (Figure 1).

Within-country/regional variation

Oettlé (1964) described increased mortality ratios from lung cancer in the South African asbestos districts of the Northern Cape in white and mixed-race populations. McGlashan & Harington (1985) used death certification data from South Africa, excluding the 'homeland' areas, to describe the geographical distribution of lung cancer. While the representativity of these findings is unclear (only blacks resident on white farms or in townships and urban areas were included), a higher standardized mortality ratio (SMR) compared with the national rate was observed in urban areas (SMR = 1.80) and in the predominantly rural northwestern Cape (SMR = 1.84), an area rich in asbestos. McGlashan and Harington (1985) also found inter-ethnic differences, with the Xhosa having higher SMR (1.48) than the Zulu (0.79), Tswana (0.77), South Sotho (0.57) North Sotho (0.16) and the Swazi (0.88) groups.

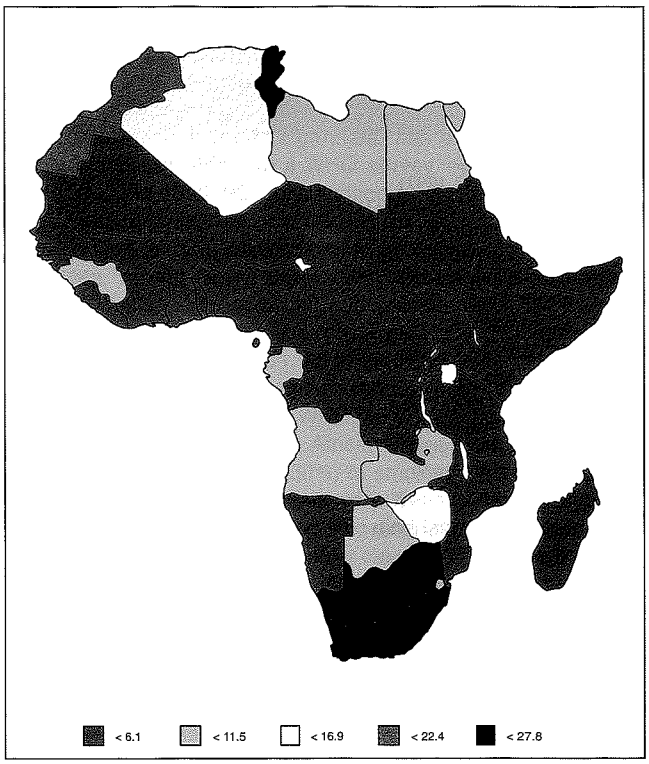

Figure 1. Incidence of lung cancer: ASR (world)- male (all ages)

Bradshaw *et al.* (1982) described cancer patterns among African gold miners from southern Africa. In this group, 'respiratory' cancer (including primary and secondary cancer of the larynx, bronchus, trachea and antrum) comprised 11.2% of all cancers (up from 5.4% of all cancers in an earlier survey; Harington *et al.*, 1975). The crude incidence was higher among miners recruited from the former Natal, Transvaal and the Cape, and lower in those from Botswana, Lesotho, Malawi, 'Northern Territories' (mainly Namibia, Angola, Zimbabwe and Zambia) and Mozambique. Using the same data, McGlashan *et al.* (1982) found a close geographic correlation between the occurrence of respiratory and oesophageal cancers (r = 0.66), suggesting that the two cancers share some etiological factors. Bradshaw *et al.* (1982) examined the geographical variation of lung (and stomach) cancers in white and mixed-race (coloured) populations in South Africa. No reliable mortality data were available for Africans. No striking geographical differences were found except for urban/rural contrasts. However, in a study by Botha *et al.* (1986), elevated standardized mortality ratios were again observed in districts in the Northern Cape where crocidolite asbestos was mined. (SMR white males = 1.75, coloured males =1.28, and in white and coloured females 1.87 and 2.47, respectively).

Trends over time

In South Africa, there have been marked increases in lung cancer mortality rates among males of all ethnic groups, with the rates among whites increasing almost three-fold between 1949 and 1979, and the increase in coloured males is even more dramatic (see Figure 1 in South Africa chapter). Some much smaller increases are also seen among females.

Data from Kampala, Uganda show an increase in age-standardized lung cancer rates over time, from 0.8 in 1960–66 to

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Trachea, bronchus and lung (C33-34)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	635	11.5	**17.2**	1.08	73	1.3	**1.9**	0.12
Algeria, Constantine (1994-1997)	108	7.0	**13.1**	0.96	20	1.3	**2.2**	0.12
Algeria, Oran (1996-1998)	263	14.8	**23.7**	1.48	30	1.7	**2.4**	0.18
Algeria, Setif (1993-1997)	246	8.2	**15.5**	1.04	31	1.0	**1.7**	0.07
Tunisia, Centre, Sousse (1993-1997)	255	22.1	**30.6**	1.70	16	1.4	**1.8**	0.08
Tunisia, North, Tunis (1994)	437	20.2	**26.6**	1.78	37	1.8	**2.3**	0.16
Tunisia, Sfax (1997)	76	19.3	**24.2**	1.32	7	1.9	**2.2**	0.15
Africa, West								
The Gambia (1997-1998)	22	2.2	**5.1**	0.25	3	0.3	**0.5**	0.04
Guinea, Conakry (1996-1999)	101	4.4	**8.2**	0.61	20	0.9	**1.7**	0.14
Mali, Bamako (1988-1997)	60	1.5	**3.7**	0.27	14	0.4	**0.9**	0.09
Niger, Niamey (1993-1999)	23	1.2	**4.9**	0.22	2	0.1	**0.4**	0.05
Nigeria, Ibadan (1998-1999)	5	0.3	**0.7**	0.05	2	0.1	**0.3**	0.04
Africa, Central								
Congo, Brazzaville (1996-1999)	28	2.3	**3.9**	0.29	4	0.3	**0.5**	0.03
Africa, East								
France, La Reunion (1988-1994)	522	24.9	**34.4**	1.80	64	3.0	**3.3**	0.17
Kenya, Eldoret (1998-2000)	15	1.6	**4.0**	0.28	10	1.1	**3.0**	0.24
Malawi, Blantyre (2000-2001)	9	1.0	**2.5**	0.13	1	0.1	**0.5**	0.06
Uganda, Kyadondo County (1993-1997)	33	1.2	**3.6**	0.28	23	0.8	**2.3**	0.20
Zimbabwe, Harare: African (1990-1993)	156	6.6	**20.9**	1.03	32	1.5	**7.2**	0.29
Zimbabwe, Harare: African (1994-1997)	120	4.3	**12.1**	0.66	40	1.5	**5.9**	0.25
Zimbabwe, Harare: European (1990-1997)	112	73.3	**38.4**	1.70	86	51.0	**24.5**	1.24
Africa, South								
Namibia (1995-1998)	104	3.3	**6.1**	0.40	45	1.4	**2.3**	0.19
South Africa: Black (1989-1992)	3347	5.9	**11.2**	0.79	841	1.5	**2.3**	0.16
South Africa: Indian (1989-1992)	288	14.8	**22.5**	1.69	50	2.5	**3.3**	0.24
South Africa: Mixed race (1989-1992)	627	9.8	**19.2**	1.43	220	3.3	**5.1**	0.40
South Africa: White (1989-1992)	2187	21.7	**20.3**	1.23	1120	11.0	**8.8**	0.60
South Africa, Transkei, Umtata (1996-1998)	33	9.2	**15.7**	1.03	10	2.4	**3.6**	0.30
South Africa, Transkei, 4 districts (1996-1998)	15	2.1	**4.9**	0.46	4	0.4	**0.7**	0.06
Swaziland (1996-1999)	81	4.6	**10.1**	0.68	15	0.8	**1.4**	0.10
Europe/USA								
USA, SEER: White (1993-1997)	36165	74.3	**55.6**	2.58	28036	55.9	**34.5**	1.89
USA, SEER: Black (1993-1997)	4879	72.9	**86.5**	4.95	2789	37.6	**36.4**	2.26
France, 8 registries (1993-1997)	10080	73.3	**52.8**	3.21	1681	11.6	**7.2**	0.46
The Netherlands (1993-1997)	35244	92.2	**66.0**	3.01	9501	24.3	**15.8**	1.13
UK, England (1993-1997)	104901	87.4	**53.1**	2.08	57382	44.9	**22.1**	1.04

In italics: histopathology-based registries

Table 2. Incidence of lung cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	1.1	*0.1*	4
Mozambique, Lourenço Marques	1956–60	*4.1*	*1.6*	1
Nigeria, Ibadan	1960–69	0.8	0.8	3
SA, Cape Province: Bantu	1956–59	26.9	*0.0*	2
SA, Cape Province: Coloured	1956–59	42.8	0.7	2
SA, Cape Province: White	1956–59	44.7	0.5	2
SA, Johannesburg, Bantu	1953–55	7.4	*3.1*	1
SA, Natal Province: African	1964–66	41.2	10.2	2
SA, Natal Province: Indian	1964–66	20.0	*3.3*	2
Uganda, Kyadondo	1954–60	*0.9*	*0.0*	1
Uganda, Kyadondo	1960–71	1.5	*1.0*	5
Zimbabwe, Bulawayo	1963–72	48.4	*3.0*	6

Italics: Rate based on less than 10 cases

3.2 per 100 000 in 1995–97 among males and from 0.6 in 1960–66 to 3.2 in 1995–1997 among females.

Migrant studies

Dean (1959) found that the mortality rate due to lung cancer among whites in South Africa was higher among British immigrants than in persons of local descent, and was higher in populations of urban rather than rural origin. Given that the current tobacco consumption of these groups was similar, Dean concluded that air pollution in urban centres was responsible, at least in part, for the excess lung cancers. (At the time, the effect of duration of smoking had not been investigated). However, noting that white females in highly polluted urban areas did not have excess lung cancer mortality rates and that British-born whites had rates intermediate between those in the United Kingdom and South Africa, Oettlé (1964) argued that pollution was not an important cause of lung cancer in these populations.

Risk factors

Tobacco smoking

Tobacco smoking is by far the most important cause of lung cancer (IARC, 1986; US DHHS, 1989). It has been estimated that in 1985 about 76% of all lung cancer worldwide (84% of cases in men and 46% in women) could be attributed to tobacco smoking (Parkin *et al.*, 1994). However in Africa, because smoking is a relatively recently acquired habit in most areas, the proportion of tobacco-attributed lung cancers is still low. Only where the habit has been established in a significant percentage of the population for a long time is there a high proportion of tobacco-attributable cancers – 85% of cases in males in southern Africa and 68% in North Africa, for example.

Because of the small proportion of lung cancers estimated to occur in Africa (and the low prevalence of tobacco consumption in most places in Africa), there is a widespread misconception that the hazards of tobacco are relevant only in developed countries. The increase in consumption of tobacco, and particularly of manufactured cigarettes, has occurred relatively recently in most of Africa. In a WHO survey, over two decades from 1970–72 to 1990–92, consumption of cigarettes increased in 15 African countries, decreased in six, and remained unchanged in five (data were unavailable for the rest of Africa). In comparison, among 'more developed' countries, 12 increased their consumption, 18 decreased and one remained the same, and the bulk of the increase in developed countries occurred decades earlier (WHO, 1997). Adult smoking rates also varied significantly, prevalence among men ranging from 10 to 50% and among women from 1 to 10% (WHO, 1997). An exception is the mixed-race population of South Africa, where there has been a high prevalence (currently 40–50%) of smoking among women.

In a continuation of his previous work, Dean (1961) interviewed the next-of-kin of (white) individuals who died from lung cancer, and a group of controls who died from other causes, about their smoking habits. Among South African-born men, compared with those who

Table 3. Percentage distribution of microscopically verified cases by histological type

Bronchus and lung (C34) - Both sexes

	Carcinoma						Sarcoma	Other	Unspec.	Number of cases	
	Squamous	Adeno	Small cell	Large cell	Other	Unspec.				MV	Total
Algeria, Algiers	32.7	20.9	4.9	4.3	2.6	34.4	-	0.2	-	**575**	707
Algeria, Batna	70.0	6.7	3.3	8.3	-	8.3	-	-	3.3	**60**	75
Algeria, Constantine	43.3	12.4	1.0	5.2	1.0	22.7	-	-	14.4	**97**	128
Algeria, Oran	49.6	5.9	2.9	18.5	0.4	18.1	0.4	-	4.2	**238**	265
Algeria, Setif	70.2	6.3	-	2.7	-	11.0	-	-	9.8	**255**	277
Burkina Faso, Ouagadougou	50.0	25.0	-	-	-	25.0	-	-	-	**12**	12
Congo, Brazzaville	-	50.0	20.0	-	-	20.0	-	-	10.0	**10**	32
France, La Reunion	46.7	21.5	6.4	11.6	2.7	9.1	0.5	-	1.5	**550**	579
The Gambia	50.0	-	50.0	-	-	-	-	-	-	**2**	24
Guinea, Conakry	16.1	12.9	-	-	-	71.0	-	-	-	**31**	121
Kenya, Eldoret	7.1	35.7	14.3	14.3	7.1	14.3	-	-	7.1	**14**	25
Malawi, Blantyre	75.0	25.0	-	-	-	-	-	-	-	**4**	10
Mali, Bamako	56.3	6.3	-	6.3	-	31.3	-	-	-	**16**	73
Namibia	36.2	33.1	11.5	12.3	0.8	3.1	0.8	-	2.3	**130**	146
Niger, Niamey	50.0	-	-	50.0	-	-	-	-	-	**4**	25
Nigeria, Ibadan	50.0	25.0	-	-	-	-	25.0	-	-	**4**	6
Rwanda, Butare	-	-	-	-	-	-	-	-	-	**-**	1
South Africa: Black	38.9	18.6	8.1	6.5	4.9	7.0	0.3	0.3	15.5	**4122**	4122
South Africa: White	32.5	28.8	14.5	8.8	4.1	8.5	0.5	0.6	1.6	**3275**	3275
South Africa: Indian	33.8	19.3	12.1	10.0	5.7	7.3	0.6	0.3	10.9	**331**	331
South Africa: Mixed race	37.9	27.3	11.5	8.5	3.6	9.1	0.2	-	1.9	**836**	836
South Africa, Elim	21.4	14.3	21.4	28.6	-	7.1	-	-	7.1	**14**	17
South Africa, Transkei, Umtata	66.7	5.6	-	-	-	5.6	-	-	22.2	**18**	43
South Africa, Transkei, 4 districts	55.6	22.2	11.1	-	-	11.1	-	-	-	**9**	19
Swaziland	54.5	9.1	18.2	-	-	9.1	-	9.1	-	**11**	94
Tanzania, Dar Es Salaam	25.0	25.0	12.5	25.0	-	12.5	-	-	-	**8**	8
Tanzania, Kilimanjaro	50.0	50.0	-	-	-	-	-	-	-	**2**	6
Tunisia, Centre, Sousse	41.9	24.7	18.0	6.4	1.5	7.1	0.4	-	-	**267**	269
Tunisia, North, Tunis	51.2	15.8	13.3	2.4	1.2	12.1	-	-	3.9	**412**	474
Tunisia, Sfax	44.2	35.1	10.4	2.6	-	6.5	1.3	-	-	**77**	83
Uganda, Mbarara	-	-	-	-	-	-	-	-	-	**-**	1
Uganda, Kyadondo County	17.1	17.1	11.4	-	-	40.0	-	-	14.3	**35**	56
Zimbabwe, Harare: African	44.2	27.5	10.1	5.1	-	10.9	2.2	-	-	**138**	348
Zimbabwe, Harare: European	40.6	28.1	20.8	6.3	-	3.1	1.0	-	-	**96**	197

Table 4. Summary of case–control studies on lung cancer in Africa
Odds ratio vs. non exposed (with 95% CI)

Exposure		Parkin *et al.*, 1994	Mzileni *et al.*, 1999	Pacella-Norman *et al.*, 2002
Ex-smoker	M	3.4 (1.9–5.8)	2.6 (1.0–4.6)	6.8 (2.9–16.0)
	F		5.8 (1.3–25.8)	7.1 (2.6–19.4)
Current smoker	M		10.7 (6.6–17.3)	9.7 (4.3–22.2)
	F		5.5 (2.6–11.3)	13.7 (5.7–32.8)
Current smoker,	M	3.9 (3.0–5.0)	9.4 (5.9–16.4)	6.2 (2.6–14.9)
0–14 g/day	F		–	10.7 (4.2–27.6)
Current smoker,	M	5.2 (3.5–7.7)	12.0 (6.5–22.3)	24.2 (9.6–61.0)
15+ g/day	F		–	50.8 (12.7–203.4)
Wood, coal	M		1.9 (0.9–3.3)	1.6 (0.7–3.8)
	F		1.4 (0.6–3.2)	0.7 (0.2–1.8)
Dusty occupation	M	1.2 (0.9–1.4)*	3.2 (1.8–5.8)	2.8 (1.1–7.6)
	F		0.5 (0.3–1.1)	5.8 (0.7–45.6)
Asbestos residence	M		2.1 to 2.8	–
	F		1.1 to 5.4	–
Asbestos birth	M		2.9 (1.2–6.7)	–
	F		3.1 (0.4–21.4)	–
Asbestos mine	M	0.7 (0.5–1.0)		–
Gold mine	M	1.5 (0.9–2.3)		–
Other mines	M	Nickel (2.6; 1.6–4.2), Copper (1.5; 1.0–2.2)		–

*Mining

had never smoked, the odds ratio of lung cancer associated with smoking was 1.8 in those whose family reported consumption of 1–20 cigarettes per day, 6.6 in those who smoked 25–45 per day and 11.8 in those who smoked 50 cigarettes or more. The corresponding odds ratios for British-born immigrants of 2.1, 6.3 and 9.0 were similar. Individuals dying from lung cancer were not employed in occupations with likely air pollution more frequently than the controls. However, the differences in lung cancer rates between British- and South African-born males was still poorly understood at that time and it was still thought that aside from tobacco consumption, environmental pollution played an important role.

In a cancer registration survey in Lourenço Marques (now Maputo) in Mozambique covering 1956–61, Prates and Torres (1964) found that three out of four male lung cancer cases were smokers compared with 206 out of 757 non-cancerous subjects (OR = 8); in females the single case of lung cancer was reported to be a smoker, compared with 7 out of 328 non-cancer controls (O/E = 46).

In studies among Rhodesian (Zimbabwean) Africans, Gelfand *et al.* (1968) found that 28/32 males with lung cancer admitted to Harare Hospital were regular smokers, compared with 7/32 age- and sex-matched controls (OR with respect to non-smokers = 32.6, 95% CI 5.3–324). Osburn (1968) noted that the majority of lung cancer patients in Gwanda, near Bulawayo were also miners (although no comparison group was used).

Three case–control studies of lung cancer in relation to smoking in Africa have been conducted (Table 4). In a study based on interview of cancer cases (or their relatives) recorded in the Bulawayo cancer registry between 1963 and 1977, Parkin *et al.* (1994) compared 877 lung cancers with 4434 other cancers (excluding those cancers related to smoking). After adjustment for confounding factors, the odds ratios for lung cancer in relation to smoking were 3.4 in ex-smokers, 3.9 in those smoking less than 15 g tobacco per day, and 5.2 in those smoking 15 g per day or more. Prevalence of smoking in men in the control group was 41%, but consumption was not high: 86% of smokers were smoking less than 15 cigarettes daily.

In a case–control study of 288 males and 60 females with lung cancer and 183 male and 197 female controls in the Northern Province of South Africa, Mzileni *et al.* (1999) found that although tobacco smoking is the most important risk factor for the development of lung cancer, environmental exposure to asbestos, a 'dusty' occupation in men, and indoor pollution may also contribute to the development of lung cancer in this province. In males, compared with non-smokers, the risks associated with lung cancer were 9.4 in smokers of 0–14 g cigarettes daily and 12.0 in men who smoked 15 g or more. In females, the risk in current smokers was 5.5.

In a South African case–control study of 105 cases of lung cancer in males and 816 controls, and 41 females and 1383 controls, Pacella-Norman *et al.* (2002) found that in males, the risks for lung cancer relative to non-smokers were 6.8 in ex-smokers, 6.2 in current light smokers and 24.2 in current heavy smokers, while among females, the corresponding figures were 7.1, 10.7 and 50.8. The mean daily cigarette consumption by current smokers in this study was 9.7 ± 7.2 in the male control group and 8.1 ± 7.6 in the female control group. This is rather higher than was previously reported among the control groups in a study of oesophagus cancer in Soweto in 1988: 4.73 ± 0.4 in males and 1.1 ± 0.3 in females (Segal *et al.*, 1988).

Occupational exposures

Other factors known to increase risk of lung cancer are occupational exposures to asbestos, some metals (e.g., nickel, arsenic and cadmium), radon (particularly among miners) and ionizing radiation. Some of these have been addressed in African studies.

In one of the South African case–control studies, lung cancer was associated with birth or residence in areas where asbestos was mined (Mzileni *et al.*, 1999). In the study by Parkin *et al.* (1994), however, no association between lung cancer and occupation in asbestos mines was found, perhaps because in Zimbabwe mainly chrysotile is mined, whereas in South Africa, the asbestos is crocidolite and amosite (which pose a much higher risk of lung cancer) as well as chrysotile. Indeed, South African incidence rates of mesothelioma are high and similar to rates in other asbestos-rich countries (Zwi *et al.*, 1989) and excess lung cancer risks related to asbestos exposure have been found in white miners (SMR 1.4 for amosite and 2.0 for crocidolite) (Sluis-Cremer *et al.*, 1992).

Gold miners in South Africa have been observed to be at increased risk of lung cancer. In a cohort of 3971 white middle-aged miners, followed up over nine years, a standardized mortality ratio of 1.61 (95% CI 1.15–2.20) was reported (Wyndham *et al.*, 1986). When follow-up was extended to 20 years, the SMR was 1.39 (95% CI 1.18–1.65) and the relative risk of exposure to dust was estimated as 1.08 (95% CI 0.94–1.20) per 10 000 particle-years (Reid & Sluis-Cremer, 1996). A second study, in which a cohort of 2209 white miners aged 45–54 years was followed up for 16 years, found a statistically significant association with cumulative dust exposure (RR 1.02, 95% CI 1.00–1.04) per 1000 particle-years (Hnizdo *et al.*, 1991). Two case–control studies of deceased white gold miners did not show any association between lung cancer and exposure to dust, radiological silicosis or silicosis identified at necropsy; most of the excess risk in the miners was due to smoking (Hessel *et al.*, 1986, 1990). Hnizdo *et al.* (1997) compared 78 lung cancer cases identified in their cohort of 45–54-year-old miners, with 386 matched controls. An increased risk of lung cancer was found in patients with prior silicosis (RR = 2.45, 95% CI 1.2–5.2, after adjustment for smoking) (Hnidzo *et al.*, 1997), but not with uranium production.

In the study based on records from the Bulawayo cancer registry in 1963–77, Parkin *et al.* (1994) found an increased risk of lung cancer (after adjustment for smoking) in subjects who reported having worked in mines extracting nickel (OR = 2.6; 95% CI 1.6–4.2) or copper (OR = 1.5; 95% CI 1.0–2.2), but not gold (OR 1.5; 95% CI 0.9–2.3), chrome (OR 1.1) or coal (OR 1.1). The copper/nickel ores mined in Matabeleland (served by the hospital in Bulawayo) contain varying amounts of arsenic; the ores are converted locally to matte form in furnaces before transport elsewhere for refining and this process has been associated with an increased incidence of lung cancer in studies elsewhere (IARC, 1990). In a mortality study among South African white iron moulders, a significantly increased proportional mortality ratio (1.71) was found for lung cancer in those dying after the age of 65 (Sitas *et al.*, 1989).

Exposure to smoke from wood or coal appears to be important in certain settings. In the Northern Province of South Africa, where 80% of the population use it as a primary source of energy for heating and cooking, Mzileni *et al.* (1999) found a significant association between lung cancer and indoor pollution (RR 2.0, 95% c.i., 1.1-3.6) for both sexes combined. The study of Pacella Norman *et al.* (2002) in Soweto found no association, which may be due to low-levels of exposure, in an area where heating is rarely required in winter.

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4.10 Lymphomas

Introduction

Advances in molecular biology, genetics and immunology have led to profound changes in the classification of neoplasms of lymphoid cells over the last 20 years. Previously, a sharp distinction was made between lymphomas (solid tumours) and leukaemias (involving bone marrow and peripheral blood), although it was recognized that some lymphomas developed into a 'leukaemic phase'. Now, in the Revised European-American Lymphoma (REAL) classification system (Harris *et al.*, 1994) and its successor, the WHO classification (Jaffe *et al.*, 2001), the unity of lymphoid neoplasms is stressed, and three broad categories are recognized: Hodgkin disease (in which the malignant cell is the Reed–Sternberg cells of lymph nodes) and T-cell and B-cell non-Hodgkin lymphomas. The lymphocytic leukaemias fall within the B-cell non-Hodgkin lymphoma group.

Hodgkin disease comprises about 18% of malignant lymphomas worldwide (about 62 000 annual cases). There is a strong male predominance (sex ratio 1.6:1). Two disease entities are recognized: nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma. Within the latter, four subtypes have been distinguished: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted (Jaffe *et al.*, 2001). In developing countries, Hodgkin disease occurs mainly in children (most cases are the mixed cellularity subtype) and in the elderly, while in developed countries there is a peak in young adults, of the nodular sclerosing subtype. In Africa, there were an estimated 7200 new cases in the year 2000, representing 1.2% of all new cancer cases, compared with the frequency worldwide of 0.6%.

Non-Hodgkin lymphomas are a very heterogeneous group of neoplasms. The types which generally manifest as leukaemias (precursor lymphoblastic leukaemia/lymphoma, and B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma) are considered in the chapter on leukaemias. The remaining non-Hodgkin lymphomas comprise around 290 000 cases worldwide per year (2.9% of all cancers), rather more in males than females. Geographically, non-Hodgkin lymphomas are most common in developed countries (51% of the world total of cases), although in Africa, the frequency is above the world average: 5400 new cases in North Africa (3.9% of cancers) and 24 800 in sub-Saharan Africa (5.1% of new cancers). In part, this arises from the high incidence rates of Burkitt lymphoma (BL) in the tropical zone of Africa, where the incidence rates of this tumour in childhood may be very high.

In this chapter we describe the epidemiology of the lymphomas in Africa, and review also what is known about multiple myeloma on the continent. Myeloma is a multifocal neoplasm of plasma cells, responsible for about 74 000 new cases worldwide (0.75% of new cancers).

Hodgkin disease

Geographical distribution

In general, incidence rates in Africa appear to be rather low in comparison with those in developed countries. The rates in North Africa appear to be higher than in sub-Saharan African populations (Table 1(a)). Males are predominantly affected.

Table 2(a) shows rates from older series.

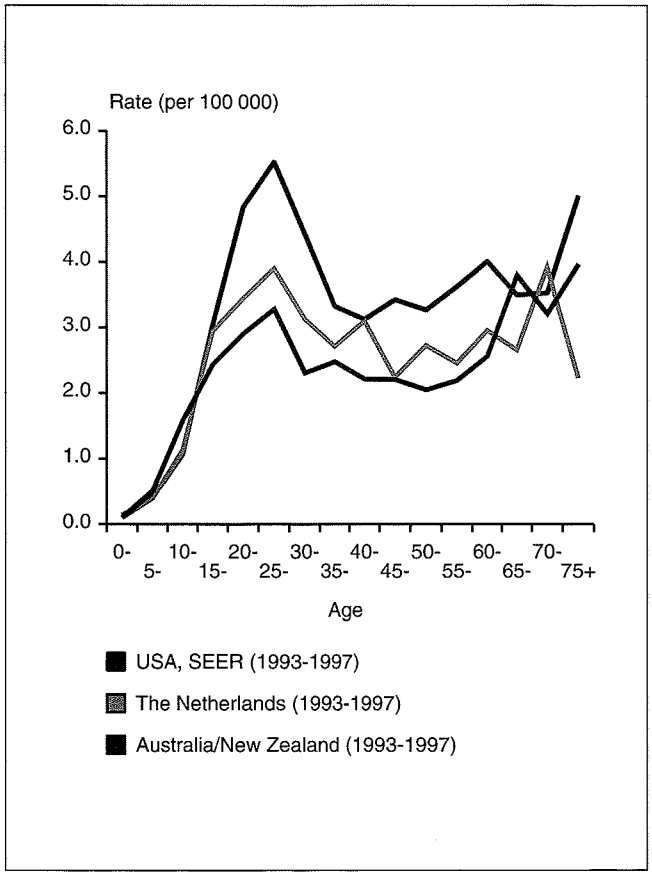

Figure 1. Hodgkin disease in male Caucasian populations

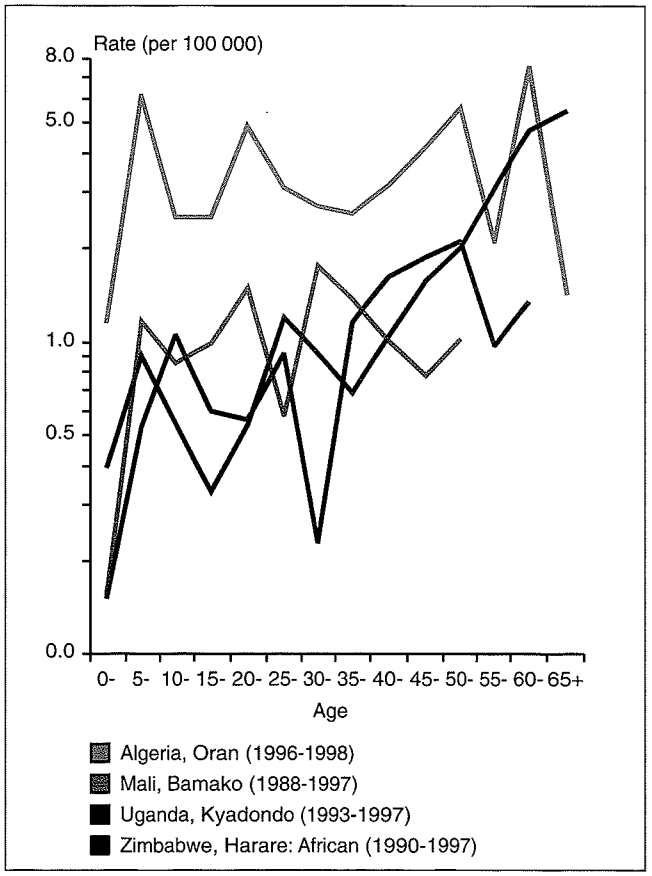

Figure 2.. Hodgkin disease in male African populations

Table 1a. Age-standardized (world) and cumulative (0-64) incidence
Hodgkin disease (C81)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	33	0.6	**0.5**	0.04	27	0.5	**0.5**	0.03
Algeria, Constantine (1994-1997)	19	1.2	**1.5**	0.10	16	1.1	**1.1**	0.08
Algeria, Oran (1996-1998)	56	3.2	**3.1**	0.22	20	1.1	**1.3**	0.08
Algeria, Setif (1993-1997)	55	1.8	**2.3**	0.16	29	1.0	**1.1**	0.09
Tunisia, Centre, Sousse (1993-1997)	20	1.7	**2.2**	0.16	15	1.3	**1.2**	0.07
Tunisia, North, Tunis (1994)	33	1.5	**1.6**	0.13	18	0.9	**0.9**	0.06
Tunisia, Sfax (1997)	10	2.5	**2.8**	0.23	4	1.1	**1.0**	0.03
Africa, West								
The Gambia (1997-1998)	6	0.6	**0.5**	0.03	3	0.3	**0.4**	0.00
Guinea, Conakry (1996-1999)	27	1.2	**1.6**	0.09	10	0.5	**0.4**	0.03
Mali, Bamako (1988-1997)	33	0.9	**0.8**	0.05	16	0.4	**0.7**	0.05
Niger, Niamey (1993-1999)	10	0.5	**0.6**	0.04	1	0.1	**0.1**	0.01
Nigeria, Ibadan (1998-1999)	7	0.5	**0.6**	0.06	1	0.1	**0.1**	0.01
Africa, Central								
Congo, Brazzaville (1996-1999)	2	0.2	**0.3**	0.02	2	0.2	**0.2**	0.02
Africa, East								
France, La Reunion (1988-1994)	21	1.0	**1.0**	0.07	12	0.6	**0.5**	0.03
Kenya, Eldoret (1998-2000)	15	1.6	**2.4**	0.17	8	0.9	**1.4**	0.12
Malawi, Blantyre (2000-2001)	5	0.6	**0.6**	0.06	3	0.3	**0.2**	0.01
Uganda, Kyadondo County (1993-1997)	18	0.6	**1.1**	0.06	20	0.7	**0.7**	0.05
Zimbabwe, Harare: African (1990-1993)	18	0.8	**0.9**	0.08	6	0.3	**0.4**	0.04
Zimbabwe, Harare: African (1994-1997)	18	0.6	**0.6**	0.04	15	0.6	**0.6**	0.04
Zimbabwe, Harare: European (1990-1997)	2	1.3	**2.0**	0.11	5	3.0	**2.8**	0.18
Africa, South								
Namibia (1995-1998)	15	0.5	**0.6**	0.04	9	0.3	**0.4**	0.03
South Africa: Black (1989-1992)	390	0.7	**0.8**	0.05	213	0.4	**0.4**	0.03
South Africa: Indian (1989-1992)	22	1.1	**1.1**	0.08	9	0.5	**0.4**	0.04
South Africa: Mixed race (1989-1992)	74	1.2	**1.2**	0.09	38	0.6	**0.7**	0.05
South Africa: White (1989-1992)	215	2.1	**2.0**	0.14	181	1.8	**1.6**	0.10
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.2**	0.01	1	0.2	**0.2**	0.01
South Africa, Transkei, 4 districts (1996-1998)	-	-	**-**	-	-	-	**-**	-
Swaziland (1996-1999)	8	0.5	**0.4**	0.03	8	0.4	**0.5**	0.03
Europe/USA								
USA, SEER: White (1993-1997)	1661	3.4	**3.1**	0.22	1408	2.8	**2.6**	0.17
USA, SEER: Black (1993-1997)	187	2.8	**2.7**	0.20	162	2.2	**2.0**	0.14
France, 8 registries (1993-1997)	412	3.0	**2.7**	0.18	293	2.0	**1.8**	0.12
The Netherlands (1993-1997)	955	2.5	**2.2**	0.16	730	1.9	**1.7**	0.12
UK, England (1993-1997)	3084	2.6	**2.3**	0.16	2323	1.8	**1.7**	0.11

In italics: histopathology-based registries

Table 2(a). Incidence of Hodgkin disease in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	2.2	1.5	4
Mozambique, Lourenço Marques	1956–60	*0.0*	*0.0*	1
Nigeria, Ibadan	1960–69	3.8	2.0	3
SA, Cape Province: Bantu	1956–59	2.6	*1.2*	2
SA, Cape Province: Coloured	1956–59	2.8	*0.8*	2
SA, Cape Province: White	1956–59	*0.9*	*0.0*	2
SA, Johannesburg, Bantu	1953–55	1.1	*1.4*	1
SA, Natal Province: African	1964–66	3.0	*0.4*	2
SA, Natal Province: Indian	1964–66	*0.7*	*0.5*	2
Uganda, Kyadondo	1954–60	1.7	*0.7*	1
Uganda, Kyadondo	1960–71	1.7	*0.7*	5
Zimbabwe, Bulawayo	1963–72	2.0	*0.1*	6

Italics: Rate based on less than 10 cases

Table 3. Percentage distribution of microscopically verified cases by histological type
Hodgkin disease (C81) - Both sexes

	Lymphocytic predominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	Unspecified	Number of cases MV	Number of cases Total
Algeria, Algiers	3.3	10.0	10.0	-	76.7	**60**	60
Algeria, Batna	5.6	5.6	50.0	-	38.9	**18**	21
Algeria, Constantine	-	-	2.9	-	97.1	**35**	35
Algeria, Oran	1.3	3.9	1.3	1.3	92.1	**76**	76
Algeria, Setif	13.1	7.1	20.2	10.7	48.8	**84**	84
Burkina Faso, Ouagadougou	-	-	-	-	100.0	**3**	3
Congo, Brazzaville	-	25.0	-	-	75.0	**4**	4
France, La Reunion	12.1	48.5	21.2	-	18.2	**33**	33
The Gambia	14.3	-	57.1	-	28.6	**7**	9
Guinea, Conakry	2.7	2.7	5.4	-	89.2	**37**	37
Kenya, Eldoret	-	-	27.3	-	72.7	**22**	23
Malawi, Blantyre	-	20.0	-	-	80.0	**5**	8
Mali, Bamako	17.4	4.3	26.1	17.4	34.8	**46**	49
Namibia	-	16.7	37.5	29.2	16.7	**24**	24
Niger, Niamey	37.5	37.5	-	12.5	12.5	**8**	11
Nigeria, Ibadan	-	-	20.0	-	80.0	**5**	8
Rwanda, Butare	20.0	20.0	40.0	20.0	-	**5**	5
South Africa: Black	3.5	19.7	18.6	5.1	53.1	**603**	603
South Africa: White	3.8	21.0	12.4	3.0	59.8	**396**	396
South Africa: Indian	3.2	9.7	19.4	3.2	64.5	**31**	31
South Africa: Mixed race	1.8	20.5	14.3	6.3	57.1	**112**	112
South Africa, Elim	-	-	40.0	20.0	40.0	**5**	5
South Africa, Transkei, Umtata	-	50.0	-	-	50.0	**2**	2
South Africa, Transkei, 4 districts	-	-	-	-	-	**-**	-
Swaziland	-	8.3	-	-	91.7	**12**	16
Tanzania, Dar Es Salaam	-	-	-	-	100.0	**13**	13
Tanzania, Kilimanjaro	-	-	-	14.3	85.7	**7**	7
Tunisia, Centre, Sousse	2.9	85.7	11.4	-	-	**35**	35
Tunisia, North, Tunis	-	45.1	37.3	3.9	13.7	**51**	51
Tunisia, Sfax	-	7.1	-	-	92.9	**14**	14
Uganda, Mbarara	-	-	-	50.0	50.0	**2**	2
Uganda, Kyadondo County	-	11.4	-	5.7	82.9	**35**	38
Zimbabwe, Harare: African	-	14.8	22.2	7.4	55.6	**54**	57
Zimbabwe, Harare: European	-	42.9	14.3	-	42.9	**7**	7

In Caucasian populations, there is a clear bimodal pattern of incidence, with very few cases in childhood, a rising incidence to a 'young adult' peak at about age 25 years, a subsequent decrease, and then a further increase in old age. This pattern is observed in Europe, North America and Australia/New Zealand (Figure 1). Correa and O'Conor (1971) first observed that the pattern in developing countries is rather different, with an initial peak in childhood (especially in boys), no young adult peak, and then a rise in incidence to old age. They also described an 'intermediate' pattern, and a shift from the 'developing' to 'intermediate' patterns with economic development has been noted by others (Hartge *et al.*, 1994).

Current patterns in African populations mainly conform to the 'developing' pattern (Figure 2), so that, in case series, a relatively high percentage of cases occur in children. Cohen and Hamilton (1980) noted that the age–incidence pattern among blacks in Johannesburg, South Africa was 'developing-intermediate' while that among whites was 'intermediate-developed'.

In Europe and North America, there is an association between risk of Hodgkin disease and socioeconomic status, but this is confined to cases in young adults, and to the nodular sclerosis subtype (Cozen *et al.*, 1992). This is consistent with Mueller's (1996) observations that cases of Hodgkin disease in developing countries are predominantly of mixed cellularity and lymphocytic depletion subtypes, while the young adult peak of developed countries involves mainly the nodular sclerosing type (Figure 3).

The early data from Africa have been reviewed by Glaser (1990). Wright (1973), reviewing cases recorded by the Uganda Cancer Registry in 1964–68, noted the deficit of lymphocyte predominance (and nodular sclerosis) subtypes and an excess of mixed cellularity and lymphocyte-depleted groups, compared with series from the United States and the United Kingdom. Similar profiles have been observed in Ibadan, Nigeria (Edington *et al.*, 1973; Okpala *et al.*, 1991), Zimbabwe (Levy, 1988), Sudan (Abu El Hassan *et al.*, 1993) and Egypt (El Bolkainy *et al.*, 1984) and in black and 'coloured' children in South Africa (Vianna *et al.*, 1977; Cohen & Hamilton, 1980; Hesseling *et al.*, 1997).

Table 3 shows the distribution by cell type in the series presented in this volume. A large proportion of the cases in most centres are without specification of subtype. However, among the remainder, mixed cellularity is the predominant type of Hodgkin disease in most series.

Etiology

The epidemiological features of Hodgkin disease have given rise to hypotheses concerning an infectious etiology. Thus it has been suggested that early infection (associated with crowding and lower socioeconomic status) is associated with childhood Hodgkin disease, while delayed infection would explain the association of young adult Hodgkin disease (age 15–40 years) with higher socioeconomic status, small families, less crowding and low birth order.

Table 1b. Age-standardized (world) and cumulative incidence
Burkitt lymphoma (age 0-14)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	-	-	-	-	-	-	-	-
Algeria, Constantine (1994-1997)	-	-	-	-	-	-	-	-
Algeria, Oran (1996-1998)	-	-	-	-	-	-	-	-
Algeria, Setif (1993-1997)	2	0.1	**0.1**	0.00	1	0.0	**0.1**	0.00
Tunisia, Centre, Sousse (1993-1997)	1	0.1	**0.2**	0.00	-	-	-	-
Tunisia, North, Tunis (1994)	2	0.1	**0.3**	0.00	3	0.1	**0.5**	0.01
Tunisia, Sfax (1997)	-	-	-	-	-	-	-	-
Africa, West								
The Gambia (1997-1998)	4	0.4	**0.8**	0.01	6	0.6	**1.2**	0.02
Guinea, Conakry (1996-1999)	12	0.5	**1.3**	0.02	12	0.5	**1.3**	0.02
Mali, Bamako (1988-1997)	2	0.1	**0.1**	0.00	1	0.0	**0.1**	0.00
Niger, Niamey (1993-1999)	6	0.3	**0.7**	0.01	5	0.3	**0.6**	0.01
Nigeria, Ibadan (1998-1999)	12	0.8	**1.8**	0.03	2	0.1	**0.3**	0.00
Africa, Central								
Congo, Brazzaville (1996-1999)	5	0.4	**1.0**	0.01	6	0.5	**1.2**	0.02
Africa, East								
France, La Reunion (1988-1994)	6	0.3	**1.0**	0.01	-	-	-	-
Kenya, Eldoret (1998-2000)	3	0.3	**0.7**	0.01	5	0.5	**1.3**	0.02
Malawi, Blantyre (2000-2001)	10	1.1	**2.8**	0.05	2	0.2	**0.6**	0.01
Uganda, Kyadondo County (1993-1997)	53	1.9	**4.7**	0.07	37	1.3	**3.0**	0.05
Zimbabwe, Harare: African (1990-1993)	3	0.1	**0.4**	0.01	1	0.0	**0.1**	0.00
Zimbabwe, Harare: African (1994-1997)	-	-	-	-	2	0.1	**0.2**	0.00
Zimbabwe, Harare: European (1990-1997)	-	-	-	-	-	-	-	-
Africa, South								
Namibia (1995-1998)	2	0.1	**0.1**	0.00	1	0.0	**0.1**	0.00
South Africa: Black (1989-1992)	18	0.0	**0.1**	0.00	11	0.0	**0.1**	0.00
South Africa: Indian (1989-1992)	-	-	-	-	-	-	-	-
South Africa: Mixed race (1989-1992)	5	0.1	**0.3**	0.00	1	0.0	**0.1**	0.00
South Africa: White (1989-1992)	8	0.1	**0.3**	0.01	2	0.0	**0.1**	0.00
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	-	-	-	-
Swaziland (1996-1999)	6	0.3	**0.8**	0.01	6	0.3	**0.7**	0.01
Europe/USA								
USA, SEER: White (1993-1997)	35	0.1	**0.3**	0.01	9	0.0	**0.1**	0.00
USA, SEER: Black (1993-1997)	7	0.1	**0.4**	0.01	1	0.0	**0.1**	0.00
France, 8 registries (1993-1997)	24	0.2	**0.8**	0.01	5	0.0	**0.2**	0.00
The Netherlands (1993-1997)	51	0.1	**0.7**	0.01	10	0.0	**0.1**	0.00
UK, England (1993-1997)	41	0.0	**0.2**	0.00	4	0.0	**0.0**	0.00

In italics: histopathology-based registries

Table 2(b). Incidence of BL in children aged 0–14 years (rates per million)

		Rate	Source
Uganda: Kampala	1960–71	9.5* (12 boys, 7 girls)	
	1992–95	36.0* (49 boys, 29 girls)	Wabinga *et al.*, 2000
Lango District	1963–68	42.9* (65 boys, 26 girls)	
Acholi District	1963–68	31.8* (36 boys, 28 girls)	Morrow *et al.*, 1977
Nigeria: Ibadan 1960–66		83.6* (113.9 boys, 58.5 girls)	Edington & Hendrikse 1973
	1985–92	18.0* (24 boys, 12 girls)	Parkin *et al.*, 1998
North Mara, Tanzania	1964–70	57 (62 boys, 51 girls)	Brubaker *et al.*, 1973
Harare, Zimbabwe	1991–95	2.4*	Parkin *et al.*, 1998
Algeria, Setif	1986–95	1.3*	Parkin *et al.*, 1998
Mali, Bamako	1987–95	1.7*	Parkin *et al.*, 1998
Namibia	1983–92	1.9*	Parkin *et al.*, 1998
USA (SEER)	1983–92		Parkin *et al.*, 1998
White		2.5 (4.1 boys, 0.7 girls)*	
Black		0.6*	

* Age-standardized rate

Much evidence points to an association between Hodgkin disease and Epstein–Barr virus (EBV) (IARC, 1997). A history of infectious mononucleosis (indicating adolescent infection with EBV) is associated with increased risk of Hodgkin disease. Many case–control studies have shown that Hodgkin disease subjects have higher prevalence and a higher titre of antibody to EBV than control subjects. In a large cohort study, Mueller *et al.* (1989) showed that elevated titres of antibodies to EBV were predictive of later development of Hodgkin disease.

Markers of EBV infection or EBV DNA can be detected in tumour tissue from a proportion of subjects. The virus appears to be located within the Reed–Sternberg cells or their variants, in up to 50% of patients. It has been difficult to distinguish patterns of EBV infection in relation to other features (geography, age, etc.), since most clinical series have been rather small. However, in a large multi-centre study including more than 1500 cases of Hodgkin disease, Glaser *et al.* (1997) concluded that the important determinants of presence of EBV, independently associated, were:

- Mixed cellularity versus nodular sclerosing or lymphocyte-predominant subtypes
- Age (lowest in young adults, higher in childhood and the elderly)
- Sex (higher in male than in female and in young adults)
- Socioeconomic development (higher in populations of lower socioeconomic status).

Data from clinical series in Africa are largely consistent with these observations. There is a higher prevalence of EBV in Hodgkin disease cases from Kenya than in European countries (Leoncini *et al.*, 1996; Weinreb *et al.*, 1996; Lazzi *et al.*, 1998) and Japan (Kusuda *et al.*, 1998), with almost all of the paediatric cases from Kenya being EBV-positive.

Burkitt lymphoma

Burkitt lymphoma (BL) was first described by Sir Albert Cook, who established the first mission hospital in Uganda in 1897. In the 1950s, various clinicians and pathologists working in Africa described facial 'sarcomas' and lymphomas occurring at high frequency in African children. Comprehensive clinical and pathological descriptions of "African lymphoma" were made by Denis Burkitt and his colleagues (Burkitt, 1958; O'Conor & Davies, 1960, Burkitt & O'Conor, 1961; O'Conor, 1961).

Soon after these reports, it was observed that the pathological features of 'African lymphoma' were present in certain childhood lymphomas in North America and Europe (O'Conor *et al.*, 1965; Wright & Roberts, 1966). Comparative studies of the incidence or frequency of BL have been difficult because of the lack of a clear and consistent definition. For example, BL can be regarded as a clinical syndrome or as a pathological entity (the two will not exactly coincide) and the presence or absence of evidence of EBV infection has sometimes been taken into account in making the 'diagnosis'. In fact, comparative studies must still rely upon the entity as defined by histology.

Clinical features

The jaw is the most frequently involved site and the commonest presenting feature in patients with BL in sub-Saharan Africa (Burkitt, 1958, 1970) (Figure 3). Jaw involvement is age-dependent, occurring much more frequently in young children, and the tumour arises in close proximity to the developing molar tooth buds. In series of cases of Burkitt lymphoma in Uganda, 70% of children under five years of age and 25% of patients over 14 had jaw involvement (Burkitt, 1970). Very young children who do not have overt jaw tumours often have orbital involvement (Olurin & Williams, 1972). Jaw involvement appears to be more frequent in regions of higher incidence, and a decline in the incidence of BL may result in proportionately fewer jaw tumours in clinical series (Biggar *et al.*, 1981). Patients from highland regions, where incidence rates are relatively low (see below), are also of higher median age, and this probably accounts for the lower frequency of jaw tumours (Burkitt & Wright, 1966; Kitinya & Lauren, 1982). It has been suggested that the frequency of jaw tumours is decreasing in some regions of equatorial Africa, with a corresponding increase in the fraction of abdominal tumours but with no clear change in the age-related incidence (Nkrumah, 1984).

Abdominal involvement, often with ascites, is found in a little over half of equatorial African patients at presentation (Magrath, 1991; Williams, 1975). Bone-marrow involvement is seen in some 7–8% of cases in Uganda (Magrath & Ziegler, 1980). Central nervous system involvement, with cranial nerve palsy and paraplegia due to paraspinal disease, is relatively common in Africa, being found in about one third of patients at presentation (Ziegler *et al.*, 1970).

Pathology

BL is characterized by a monomorphic cytoarchitecture composed of medium-sized cells with a high nucleus to cytoplasm ratio, a round or oval nucleus with a coarse or 'open' chromatin pattern and usually two to five readily discernible nucleoli. Histological sections often show the presence of tingible body macrophages scattered among the tumour cells, giving rise to a 'starry sky' appearance. This appearance is not pathognomonic of BL and may be seen in other lymphomas (O'Conor, 1961). BL is invariably of B-cell origin, the presence of surface immunoglobulin having first been shown by Klein *et al.* (1967). The surface immunoglobulin is usually IgM, but IgG and IgA are occasionally present and kappa or lambda immunoglobulin light chains are nearly always detected.

Cytogenetic studies have permitted the characterization of BL in terms of chromosomal translocation. These invariably involve the part of chromosome 8 (the q24 region) in which is located c-*myc*, an oncogene important in controlling cell proliferation. However, the breakpoint does not always concern the c-*myc* gene itself, although c-*myc* is moved adjacent to a region on a different chromosome concerned with production of part of the immunoglobulin molecules. These chromosomal breakpoint locations are quite different in BL cases in Africa and in America (Magrath, 1990); in the United States, for example, only 9% of tumours have a breakpoint outside c-myc, compared with 75% in Africa. This suggests that there are different subtypes of BL within the histopathological entity, in different parts of the world.

Incidence and geographical occurrence

Burkitt and O'Conor (1961) noted the age distribution (maximum occurrence in children age 5–9 years), predominance of boys over girls, and limited geographical extent. Table 1(b) shows incidence rates of BL in children reported from population-based cancer registries in this volume, and Table 2(b) data from other series published in the last 30–40 years. BL cases do occur in Africa after the childhood age range, but the rates are very much lower.

BL accounts for between one quarter and one half of all paediatric cancers in tropical East, Central and West Africa, but appears much less frequently in northern and southern Africa and in series from Europe and North America. Nevertheless, even in the latter areas, it may comprise 20–30% of non-Hodgkin lymphoma (NHL) in the childhood age range.

The geography of BL in Africa has been the subject of many reviews. The early work of Burkitt relied upon collecting information on the relative frequency of cancers in clinical series from hospitals in Africa. Crude and simple though this method may appear, it allowed detection of the striking geographical patterns seen for BL, for which incidence rates vary at least 100-fold. Thus, Burkitt delimited a zone 15° north and south of the equator (with a prolongation southward into Mozambique to the east) as the high-incidence area (Wright, 1967). Even within this area, however, BL

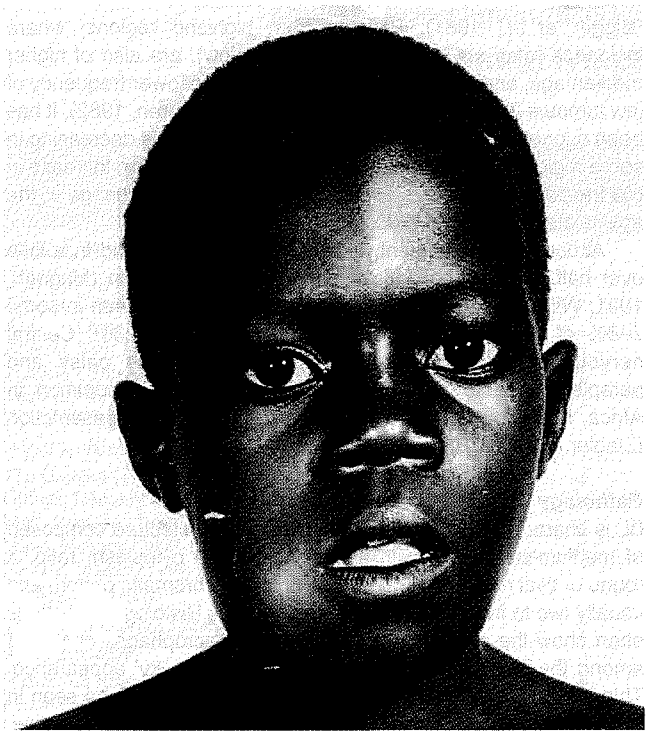

Figure 3. Typical presentation of Burkitt lymphoma

is infrequent in high-altitude regions, such as Rwanda and Burundi, the Kenya Highlands and the plateaux of Zambia and Zimbabwe. These limits are related to climate; areas of high BL incidence have been associated with an annual rainfall above 50 cm and an average temperature in the coolest month above 15.6°C (Haddow, 1963). It was initially thought that this might indicate the importance of an arthropod-borne virus (and the specific vector), but Burkitt (1969) and O'Conor (1970) drew attention to the close relationship to endemicity of malaria and malaria parasitaemia.

The interesting distribution in relation to climatic factors persists when the focus is on smaller geographical areas in Africa. The most detailed studies have been undertaken in Uganda (Wright, 1973), where there are marked differences in the incidence of BL between different districts. The highest rates are seen in the lowland areas around the Nile in the north-west (West Nile, Madi, Acholi and Lango), while mountainous districts in the south-west show low rates. This pattern closely reflects the endemicity of malaria (Kafuko & Burkitt, 1970); it cannot be explained by quality of communications and medical facilities, since the distribution of other lymphomas approximates to that expected on the basis of population density (Wright & Roberts, 1966). Within the West Nile district itself, the same phenomenon is seen, with an almost total absence of cases from the highlands in the south of the district (Williams, 1968).

In Kenya, the lowest incidence of BL was in the Kalenjin tribe, living in highland areas above 1500 m altitude, with higher incidence in tribes from lower-lying lakeshore or coastal areas (Dalldorf *et al.*, 1964). This pattern coincided with prevalence of malaria (and associated splenomegaly).

In northern Tanzania, Kitinya and Lauren (1982) found a low frequency (2.2% of tumours) of BL around Mount Kilimanjaro, and most of the cases occurred at lower altitudes (under 1000 m). In this low-incidence area, the average age of patients was higher (16.4% over 20 years of age) and the frequency of jaw tumours lower (22%) than in the high-incidence areas of Uganda.

The link between BL and climate is supported by studies of migrant populations. Populations migrating from low- to high-incidence areas have a higher average age of onset of BL than those born in endemic areas (Burkitt & Wright, 1966; Morrow *et al.*, 1976, 1977). This, together with the lower rates observed in urban than rural populations in Ghana (Biggar & Nkrumah, 1979), has lent support to the concept of the etiological role of malaria (see below).

Space–time clustering

Pike *et al.* (1967) drew attention to space–time clustering of BL cases (pairs of cases occurring closer in space/time than would be expected by chance) in the West Nile District of Uganda in the period 1961–65. Morrow *et al.* (1971) also reported a remarkable outbreak of seven cases of BL in Bwamba County of Toro District in western Uganda. These observations provoked great interest, since clustering was thought to imply that infectious agents, spread from person to person, were somehow involved in etiology. Seasonal variation in presentation of BL cases, consistent from year to year (Williams *et al.*, 1974; Morrow *et al.*, 1976), also favours such a hypothesis, although seasonality was not seen in other studies (Morrow *et al.*, 1977). The putative infectious agent was not supposed to be the ubiquitous EBV (see below), but it was thought that maybe the waxing and waning in intensity of malaria infection might be responsible. In fact, the latent period for an effect would have to be very short to generate clustering, if it were not to be masked by variation in latent period.

Williams *et al.* (1978) reviewed the observations in West Nile District from a 15-year period (1961–75), during which time an attempt was made to identify all new diagnosed cases in local hospitals and from the referral centres and pathology laboratory in Kampala. 202 cases were found (81% with histology) and there was no trend in incidence over time. As had been reported by Pike *et al.* (1967), marked clustering was evident in the first quinquennium, but not in the next 10 years (except for the two-year period 1972–73). The incidence of BL varied within the different subdivisions (counties of West Nile) between the three quinquennia, suggesting that the intensity of the precipitating factor varied over relatively wide areas with time.

Elsewhere in Uganda there has been no evidence of space–time clustering, either in the relatively low-incidence Mengo District in the south (Morrow *et al.*, 1976) or in the high-risk districts of Acholi and Lango in the centre north (Morrow *et al.*, 1977). Nor was any clustering observed in the high-incidence area of North Mara District, Tanzania (Siemiatycki *et al.*, 1980). Biggar and Nkrumah (1979) did not observe any space–time clustering among 236 cases seen in the main teaching hospital of Ghana in 1970–75.

On the other hand, van den Bosch *et al.* (1993a) found limited evidence, based on interviews of 146 cases referred to Kamuzu Central Hospital in Lilongwe, Malawi, of space–time clustering (more pairs of cases <2.5 km distant and <60 days apart than expected by chance). The clustering was more marked when the analysis was confined to cases aged 8 years or more.

The significance and any biological explanation of the clustering found in West Nile and Malawi remain speculative; the possibility of biased case ascertainment and pure chance cannot be excluded.

Etiology

Role of EBV

EBV was first identified in an attempt to confirm the hypothesis that African BL is caused by a vectored virus. Evidence that EBV was associated with BL was based initially on serological evidence of the presence of viral antibodies (Henle & Henle, 1966). This test was later shown to reflect the level of viral capsid antigen (VCA) in the cells; cells that gave positive results in immunofluorescence assays were shown to contain viral particles by electron microscopy (Henle & Henle, 1967; Epstein & Achong, 1968). Later, EBV DNA was detected in tumour cells using a nucleic acid hybridization technique (zur Hausen & Schulte-Holthausen, 1970). Viral DNA is present in cells in which late viral antigens or viral particles cannot be detected, indicating that the virus can latently infect cells, i.e. remain within the cell without replicating viral particles.

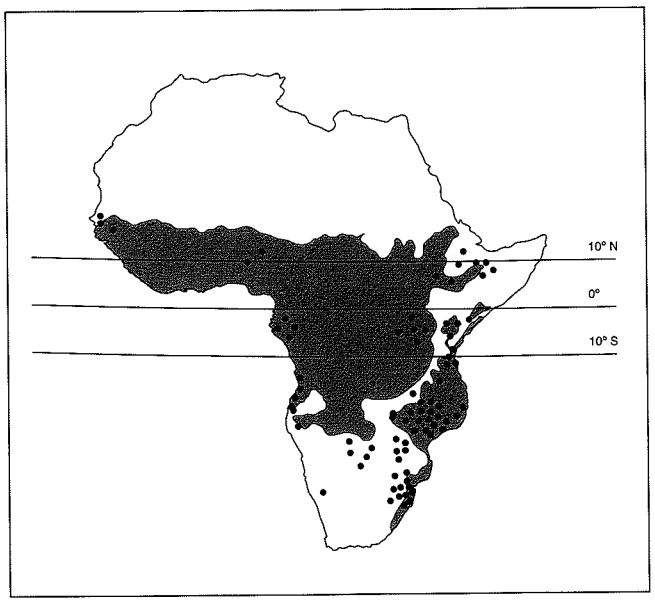

Figure 4. Distribution of Burkitt lymphoma in Africa (from Haddow, 1963)
The shaded area represents the area in which, on climatological grounds, Burkitt lymphoma might be expected to occur. The black points show the distribution of the series of cases compiled by D. Burkitt. The method used was to fill in any degree-square in which the condition had been recorded, irrespective of the number of cases

Differences in the frequency of the association of BL with EBV, as determined by the presence of EBV DNA (or RNA) or EBV antigens, are found in different regions of the world. Case series from Africa have been reviewed by IARC (1997). In Africa, some 95% of BL are associated with EBV, as demonstrated by the presence of either EBV nuclear antigen (EBNA) or EBV DNA in the tumour cells, and such patients have higher geometric mean titres (GMT) of antibodies against EBV-associated antigens. In North Africa, around three quarters of BL is associated with EBV, compared with 15–20% in Europe and North America (Ladjadj *et al.*, 1984, Anwar *et al.*, 1995).

A number of case–control studies compared the prevalence of antibodies to EBV in cases of BL and in control subjects, but adjustment for the age of subjects being compared, necessary because the prevalence of antibodies to EBV changes with age, appears to have rarely been made (IARC, 1997). In all of these studies, the antibody was more often detected in cases than in controls, and antibody titres of cases were higher (Henle & Henle, 1967; Henle *et al.*, 1969; Klein *et al.*, 1970; Henle *et al.*, 1971; Hirshaut *et al.*, 1973; Nkrumah *et al.*, 1976). Case–control studies cannot resolve whether the antibodies to EBV in BL cases represent a response to infection or re-activation of latent EBV following tumour onset (an effect rather than cause of disease).

In a large cohort study in West Nile District of Uganda, sera were obtained from 42 000 children aged 4–8 years, who were then followed up for up to seven years. In the initial analysis (de The *et al.*, 1978), each of the 14 cases of BL detected in the cohort was matched for age, sex and locality with five control subjects. The cases had significantly higher prediagnostic anti-VCA titres than control subjects (GMT, 425.5 versus 125.8), but no difference was observed between cases and controls in the titres of anti-early antigen (EA) and anti-EBNA. Two additional EBV-associated, histologically confirmed cases of BL were detected up to 1979, both of which had high anti-VCA titres before the onset of BL (Geser *et al.*, 1982). This study showed that anti-VCA titres can be elevated as long as six years before the onset of BL and as early as three months after birth. The relative risk for developing BL increased multiplicatively by a factor of 5.1 for each two-fold dilution in anti-VCA titre for all cases of BL and by a factor of 9.2 when the analysis was confined to cases in which EBV DNA was present in the tumour.

Role of malaria

The evidence linking risk of BL to malaria infection, derived from ecological comparisons, has been reviewed by Morrow (1985):

- The incidence of BL correlates within and between countries with the incidence of malaria and with parasitaemia rates.
- The age at which peak levels of antimalarial antibodies are acquired (5–8 years) corresponds to the age of peak incidence of BL.
- Individuals who live in urban areas where malarial transmission rates are lower also have a lower incidence of BL.
- In regions where death rates due to malaria have declined, BL incidence has also declined.
- The age at onset of BL in immigrants from malaria-free areas to malarious areas is higher than that of the original inhabitants.
- There is an inverse relationship between the age at onset of BL and the intensity of infection with Plasmodium falciparum.
- There is an apparently reduced incidence (though not statistically significant) of BL in individuals with sickle-cell trait, which also protects against malaria.
- There is some evidence for seasonal variation in the onset of BL and for time-space clustering.

Dalldorf (1962) appears to have been the first to suggest that malaria is relevant to the development of BL. In his ecological study in Kenya (Dalldorf *et al.*, 1964), the highest incidence of BL occurred in areas where malaria was holoendemic, namely in the coastal and lakeside regions. Kafuko and Burkitt (1970) summarized the early geographical studies linking malaria infection to risk of BL, noting that the disease was not common in any area where malaria transmission occurs for less than six months in the year. In Ghana, a significant difference in malaria parasitaemia (*P. falciparum*) rates between urban (1.4%) and rural populations (22%) was accompanied by similar differences in antimalarial antibody titres (Biggar *et al.*, 1981). Persons who had taken chloroquine for treatment of suspected malaria had a lower antibody frequency and lower titres than those who did not use chloroquine. This difference correlated with the distribution of BL in Ghana (Biggar & Nkrumah, 1979). Morrow (1985) reported a significant correlation between malaria parasitaemia (*P. falciparum*) rates and the incidence of BL in various districts in Uganda. Parasitaemia rates ranged from 7.9% (in Ankole) to 75.2% (in Madi), and the incidence of BL in children aged 0–14 years from 0.1 (in Ankole) to 6.0 (in Lango) per 100 000. In holoendemic areas, the peak age of prevalence and of the density of falciparum parasitaemia is two to three years, whereas the maximal level of antimalarial and non-antimalarial immunoglobulin occurs two to five years later, coinciding with the peak age of incidence of BL in these regions. Also in Uganda, immigrants into Mengo District (around Kampala) from highland regions with low malarial prevalence who developed BL were significantly older (median, 12 years) at the onset of BL than patients from meso-endemic Mengo (median, 8 years; $p < 0.008$), while patients from Mengo were significantly older than patients from hyper- or holoendemic regions at lower altitude (median, 6 years; $p < 0.04$) (Morrow *et al.*, 1976; Morrow, 1985).

Despite these ecological observations, an association between risk of BL and malaria infection, or its intensity, has never been demonstrated at the individual level. No differences have been reported in the levels of malarial antibodies between BL patients and controls (Morrow, 1985).

Conclusive evidence exists regarding the role of haemoglobin S (HbS; beta6Glu → Val) heterozygosity in protecting against severe malaria. Furthermore, in a large case–control study in Burkina

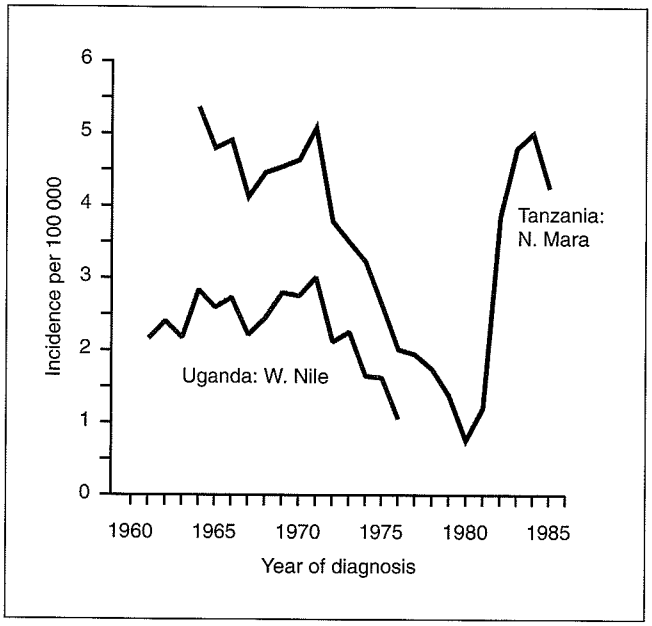

Figure 5. Trends in the incidence rate (three-year moving average) of Burkitt lymphoma in East Africa (data from Geser *et al.*, 1989)

Faso, Modiano *et al.* (2001) showed that HbC is associated with a 29% reduction in risk of clinical malaria in HbAC heterozygotes, and of 93% in HbCC homozygotes. If BL is associated with malaria, these haemoglobinopathies should, therefore, be associated with a decreased risk of BL. Williams (1966) compared the haemoglobin electrophoretic patterns of 100 Yoruba children (Nigeria) with BL with those of 331 children of the same ages from the same hospital. There was an significant excess of AA haemoglobin in BL cases (78%) compared with control children, 32% of whom were homo- or heterozygous for HbS or HbC. An earlier study (Gilles, 1963) had found no difference. The study has been criticized for using hospital controls, which could have introduced a selective bias in favour of children with AS haemoglobin. In Uganda, a case–control study by Pike *et al.* (1970), matching 36 cases of BL and controls by age, sex, tribe and place of residence, found that in children with AA haemoglobin, the risk of BL was about twice that of those with AS, but (due to the small study size), this increase was not significant (p = 0.16, one-sided). In Ghana, Nkrumah and Perkins (1976) compared 112 patients with BL with nearest neighbour controls of the same age, sex, and tribe, and with sibling controls. There was no significant protective advantage for sickle cell trait (HbAS) against BL. Haemoglobin C trait appeared to offer a slight protective advantage ($p < 0.1$).

The observational data are supported by the results of an intervention study in North Mara District, Tanzania (Geser *et al.*, 1989), during which, for a period of five years, chloroquine tablets were regularly distributed to a cohort of children below the age of 10 years. In the pre-trial period (1964–76), malarial parasitaemia was high in the lowlands (near Lake Victoria) where BL cases were occurring, and low in the high plateau (over 1500 m) bordering Kenya, where BL was rare. The prevalence of malarial parasitaemia, titres of antimalarial fluorescent antibody, and incidence of BL fell during the period of chloroquine administration (1977–82), the latter to the lowest level ever recorded in the region: 0.5 per 100 000 in 1980 and 1981 in comparison with 2.6–6.9 per 100 000 before the trial (Figure 5). When chloroquine distribution ceased, prevalence of malaria rapidly rose again to pre-trial levels, followed some two years later by an increase in incidence of BL, to reach a high of 7.1 in 1984 (Figure 5). There was no decline in the prevalence of malarial parasitaemia or incidence of BL in the neighbouring South Mara District during the period of the trial.

A possible mechanism for the link between BL and malaria is loss of cytotoxic T cell control of EBV in B cells following infection with *P. falciparum*, possibly due to the destruction or dysfunction of a subset of CD4 cells responsible for the induction of suppressor/cytotoxic CD8 cells. This could result in activation and proliferation of foci of B cells containing EBV. The expanded pool of B cells and their rapid turnover would increase the chance of genetic alterations involving the c-*myc* gene leading to malignant transformation (Whittle *et al.*, 1990; Pagano, 1992).

Other factors

Socioeconomic factors have been claimed to be important in BL. Williams (1988) noted an association with low socioeconomic status in Nigeria and suggested a reduced incidence following the economic boom in the country. Morrow *et al.* (1974) compared 56 BL cases with neighbourhood controls in Uganda. The BL cases lived in poorer houses, had more siblings (and sibling deaths) and shared their rooms with more people than the control children. However, Wood *et al.* (1988) found no association in southern Africa.

Family aggregation in siblings was described by Brubaker *et al.* (1980) in the North Mara District of Tanzania. The possibility of a genetic basis for familial cases is raised by the association with certain HLA phenotypes (Jones *et al.*, 1985).

Environmental exposure to the plant *Euphorbia tirucalli*, and other medicinal plants containing phorbol esters, has been suggested as a risk factor for BL. Osato *et al.* (1987, 1990) found *E. tirucalli* around almost all houses, fields and reservoirs in villages near Lake Victoria and in other high-incidence regions in Kenya and Tanzania. The plant was reported to be uncommon in areas of these countries where BL is rare. In Malawi, van den Bosch *et al.* (1993b) reported that *E. tirucalli* was found significantly more often near to the homes of cases of BL than to those of control subjects. Phorbol esters present in this plant have been reported to increase the ability of EBV to transform B lymphocytes and to increase the likelihood that a chromosomal translocation will develop in transformed cells.

The observation that the pattern of space–time clustering of BL cases in Malawi (see above) coincided with an epidemic of Chikungunya fever prompted van den Bosch and Lloyd (2000) to carry out a sero-epidemiological study of the association of the responsible arbovirus with BL. 108 BL cases (12 clinically diagnosed) were compared with two age-sex matched hospital controls and two neighbourhood (same village) controls per case. Comparing the BL cases with hospital controls, there was no difference in the presence of antibody at time of admission, but when antibody at the time of discharge was considered, the odds ratio was 2.36 (95% CI 1.28–4.56). For neighbourhood controls, recruited some 8–16 weeks after the case was first admitted, antibody presence was compared with BL cases at their third admission to hospital; the odds ratio was similar (2.28, 95% CI 1.14–5.07).

Burkitt lymphoma in relation to AIDS

In the United States and Europe, NHLs are the most common malignancy in children with AIDS and about one-third are BL (Mueller, 1998). AIDS-related BL resembles the form of the disease (sporadic; sBL) that comprised up to a third of NHL cases in childhood before the advent of the AIDS epidemic (Parkin *et al.*, 1985). It occurs with a peak at 10–19 years of age (Beral *et al.*, 1991) and frequently involves lymph nodes and the bone marrow (Knowles, 1996). The EBV genome is present in around 30% of cases, which is similar to the proportion in sBL cases (Hamilton-Dutoit *et al.*, 1993a; IARC, 1996). Molecular analyses of translocation breakpoints in the chromosomes of tumour cells suggest that the pattern in most cases of AIDS-related BL resembles that observed in sBL in Europe and America, and is quite different from that in endemic, EBV-related, African BL (Roithmann & Andrieu, 1992).

The effect of the AIDS epidemic on lymphoma in childhood is described in the chapter on AIDS and cancer in sub-Saharan Africa.

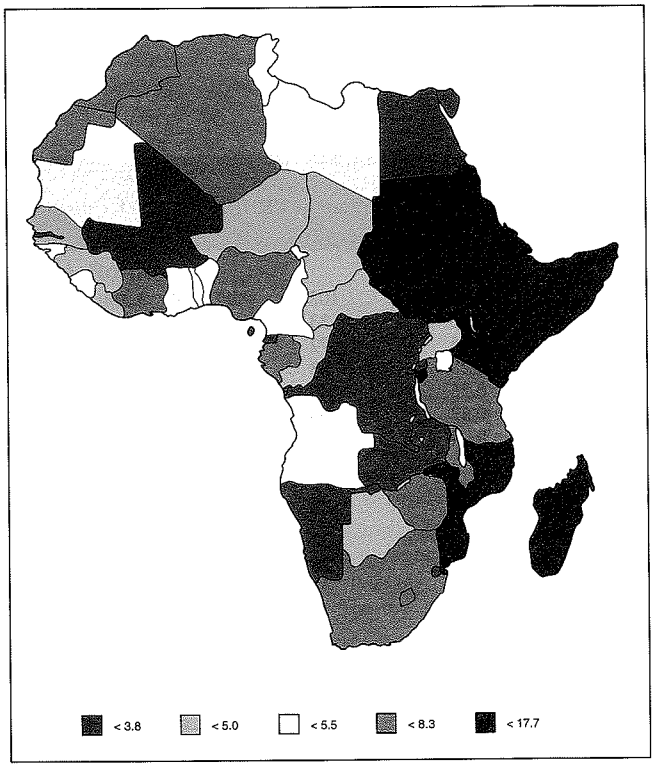

Figure 6. Incidence of non-Hodgkin lymphoma: ASR (world) - males, age 15–65+

Non-Hodgkin lymphomas

Pathology

The greatest problem in the study of NHLs has always been that these do not by any means constitute a single diagnostic entity. The very title indicates that it is a diagnosis of exclusion. Many attempts at classification of this group of neoplasms have been made, but the most usual criteria chosen, such as morphological pattern, immunological origin, histological grade and prognosis may have little or no relevance to etiology, the usual concern of epidemiologists. The most recent WHO classification attempts to incorporate morphological, immunophenotypic and molecular information to produce groupings with more relevance to cause (Jaffe *et al.*, 2001).

Unfortunately, most studies, descriptive and analytic, use older terminologies that are impossible to translate into equivalents in more modern schemas. It is generally necessary, therefore, to group together all 'non-Hodgkin lymphomas', accepting that this will be grossly unsatisfactory for elucidating meaningful patterns.

Geography

Overall rates of NHL seem to be highest in the more developed areas of the world. Nevertheless, estimated rates of incidence (Ferlay *et al.*, 2001) suggest that West and East Africa have relatively high incidence. Most studies of the relationship of NHL to socioeconomic status have been non-conclusive (Faggiano *et al.*, 1997). Studies in the United States (e.g., Cantor & Fraumeni, 1980) have suggested that geographical distribution is associated with relative affluence of the population, but this has not been clearly shown in individual-based studies (La Vecchia *et al.*, 1992).

Adult NHL in Africa

It is not clear whether or not there is significant variation in the incidence of NHL as an entity in Africa as a whole.

Figure 6 shows estimated incidence rates for adult NHL (excluding children) for males, by country. These estimates are derived largely from a knowledge of the contemporary incidence rates shown in Table 1(c).

Comparison of these rates with those observed in Europe and North America suggests that, in general, the incidence of NHL is relatively low in adults in African populations. Wright (1973) suggested, on the basis of data from Kyadondo county and Ibadan, that incidence in African populations was similar to that in Europe (at least up to age 50 years). In fact, this observation was only partly correct, as incidence in Ibadan at that time (1960–62), based on just 52 adult cases, was unusually high, and incidence rates in European populations were lower than in more recent years.

There seems to have been rather little change in incidence of NHL in African adults over time, as judged from a comparison of older (Table 2(c)) and the more recent series.

Therefore, it seems that, although lymphomas appear to be frequent in clinical or histopathology series, the actual incidence rates are not particularly high.

Clinical series show an excess of high-grade lymphomas in series from Africa, and a deficit of nodular lymphomas (El Bolkainy *et al.*, 1984; Fleming, 1985; Okpala *et al.*, 1991; Ngendahayo & Schmauz, 1992; Cool & Bitter, 1997). Few systematic studies have classified African lymphomas using modern techniques. In general, B-cell lymphomas predominate in both East Africa (Cool & Bitter, 1997), South Africa (Jacobs, 1985), North Africa (El Bolkainy *et al.*, 1984) and Nigeria (Thomas *et al.*, 1991).

The so-called Mediterranean lymphoma reported from countries of the Middle East (Rappaport *et al.*, 1972) appears to be uncommon in North Africa, although the small intestine was noted to be the most common location for gastrointestinal lymphomas in Eqypt (El Bolkainy *et al.*, 1984).

A relatively high prevalence of antibodies to HTLV-I has been reported from various parts of Africa (Saxinger *et al.*, 1984; Delaporte *et al.*, 1989), with particularly high prevalence in Gabon. It is estimated that sub-Saharan Africa constitutes the largest reservoir of the virus in the world—possibly as many as 10 million carriers (Hunsmann *et al.*, 1984). Despite this, T-cell lymphomas in general, and acute T-cell leukaemia-lymphoma (ATLL) in particular, are not commonly observed. Williams *et al.* (1993) described four cases of ATLL from Nigeria, all positive for HTLV-I, and Fouchard *et al.* (1998) three HTLV-I positive cases (among 14 cutaneous T-cell lymphomas) from Bamako, Mali.

Etiology

Wright and Roberts (1966) and Schmauz *et al.* (1990) investigated whether BL and other NHLs had similar geographical distributions in Uganda (implying etiological similarities). Their conclusions were different (negative and positive, respectively). However, regional incidence rates were based upon dispatch of biopsy material to a central pathology laboratory, and must be subject to a number of unknown biases, as well as being considerable underestimates of the true incidence.

The role of EBV in NHL (other than BL) in immunocompetent subjects is unclear. Although viral DNA is found in a proportion of tumours, the evidence that reactivation of the virus precedes tumour development is sparse and the evaluation by IARC (1997) found no clear evidence for an etiological role.

Certain chemical exposures—particularly to pesticides/herbicides and petrol products have been implicated in several studies (reviewed by Cartwright & McNally, 1994). There have been reports of various drugs increasing risk (Bernstein & Ross, 1992).

Since 1992, there has been interest in a possible association between NHL and hepatitis C virus (HCV), mainly based upon observations from case–control studies (Silvestri *et al.*, 2000). We are not aware of any such studies in Africa.

Table 1c. Age-standardized (world) and cumulative (15-64) incidence
Adult non-Hodgkin lymphoma (age 15+)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	138	3.6	**4.7**	0.26	102	2.7	**3.3**	0.15
Algeria, Constantine (1994-1997)	50	5.4	**7.3**	0.30	33	3.5	**4.3**	0.23
Algeria, Oran (1996-1998)	91	7.6	**9.2**	0.45	72	6.0	**7.6**	0.40
Algeria, Setif (1993-1997)	58	3.4	**4.4**	0.23	38	2.1	**2.6**	0.14
Tunisia, Centre, Sousse (1993-1997)	73	9.6	**11.5**	0.56	46	6.1	**7.3**	0.35
Tunisia, North, Tunis (1994)	88	6.0	**7.3**	0.32	53	3.7	**4.5**	0.15
Tunisia, Sfax (1997)	15	5.7	**6.4**	0.24	11	4.3	**5.3**	0.26
Africa, West								
The Gambia (1997-1998)	9	1.9	**2.6**	0.13	5	0.9	**1.2**	0.02
Guinea, Conakry (1996-1999)	44	3.4	**4.9**	0.26	27	2.2	**2.6**	0.14
Mali, Bamako (1988-1997)	40	1.8	**2.4**	0.10	32	1.7	**2.1**	0.12
Niger, Niamey (1993-1999)	29	2.9	**4.4**	0.23	26	2.8	**4.2**	0.22
Nigeria, Ibadan (1998-1999)	35	4.1	**6.1**	0.32	23	2.5	**3.7**	0.21
Africa, Central								
Congo, Brazzaville (1996-1999)	31	4.5	**5.2**	0.30	16	2.2	**2.3**	0.13
Africa, East								
France, La Reunion (1988-1994)	83	5.7	**7.2**	0.32	69	4.5	**4.7**	0.12
Kenya, Eldoret (1998-2000)	39	7.4	**10.1**	0.40	20	3.9	**6.1**	0.35
Malawi, Blantyre (2000-2001)	30	5.4	**7.2**	0.41	23	4.6	**6.8**	0.40
Uganda, Kyadondo County (1993-1997)	57	3.4	**4.9**	0.22	49	3.0	**3.7**	0.17
Zimbabwe, Harare: African (1990-1993)	58	3.6	**5.3**	0.28	35	2.6	**6.1**	0.22
Zimbabwe, Harare: African (1994-1997)	111	5.9	**8.5**	0.44	69	4.2	**7.1**	0.33
Zimbabwe, Harare: European (1990-1997)	15	11.8	**8.9**	0.46	19	13.3	**8.3**	0.32
Africa, South								
Namibia (1995-1998)	47	2.6	**3.2**	0.16	35	1.9	**2.4**	0.09
South Africa: Black (1989-1992)	865	2.5	**3.5**	0.16	569	1.6	**2.1**	0.10
South Africa: Indian (1989-1992)	99	7.4	**10.3**	0.43	61	4.4	**6.0**	0.30
South Africa: Mixed race (1989-1992)	168	4.0	**5.5**	0.26	150	3.3	**4.7**	0.22
South Africa: White (1989-1992)	1094	14.1	**14.4**	0.61	995	12.5	**11.3**	0.52
South Africa, Transkei, Umtata (1996-1998)	5	2.5	**2.6**	0.08	4	1.5	**1.6**	0.08
South Africa, Transkei, 4 districts (1996-1998)	1	0.3	**0.4**	0.03	2	0.4	**0.5**	0.02
Swaziland (1996-1999)	32	3.4	**4.4**	0.24	21	1.9	**2.0**	0.09
Europe/USA								
USA, SEER: White (1993-1997)	10643	27.9	**24.4**	0.99	8639	21.5	**15.7**	0.59
USA, SEER: Black (1993-1997)	1002	20.7	**21.9**	1.08	590	10.5	**10.6**	0.47
France, 8 registries (1993-1997)	2107	19.3	**16.4**	0.67	1784	15.2	**10.8**	0.44
The Netherlands (1993-1997)	5407	17.5	**15.3**	0.62	4562	14.2	**10.3**	0.40
UK, England (1993-1997)	17200	17.9	**14.2**	0.59	15120	14.5	**9.6**	0.39

In italics: histopathology-based registries

Table 2(c). Incidence of non-Hodgkin lymphoma in Africa (adults), 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	4.4	1.3	4
Mozambique, Lourenço Marques	1956–60	5.7	*2.9*	1
Nigeria, Ibadan	1960–69	9.0	8.8	3
SA, Cape Province: Bantu	1956–59	3.8	*0.0*	2
SA, Cape Province: Coloured	1956–59	2.4	2.3	2
SA, Cape Province: White	1956–59	6.4	4.0	2
SA, Johannesburg, Bantu	1953–55	*1.7*	*2.4*	1
SA, Natal Province: African	1964–66	4.0	*2.7*	2
SA, Natal Province: Indian	1964–66	*2.4*	*1.0*	2
Uganda, Kyadondo	1954–60	3.5	2.8	1
Uganda, Kyadondo	1960–71	3.8	2.6	5
Zimbabwe, Bulawayo	1963–72	2.9	*0.6*	6

Italics: Rate based on less than 10 cases

Table 1d. Age-standardized (world) and cumulative (0-64) incidence
Multiple myeloma (C90)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	24	0.4	**0.7**	0.04	23	0.4	**0.6**	0.03
Algeria, Constantine (1994-1997)	13	0.8	**1.2**	0.08	7	0.5	**0.8**	0.01
Algeria, Oran (1996-1998)	13	0.7	**1.2**	0.11	16	0.9	**1.2**	0.08
Algeria, Setif (1993-1997)	6	0.2	**0.3**	0.01	3	0.1	**0.2**	0.02
Tunisia, Centre, Sousse (1993-1997)	4	0.3	**0.6**	0.04	10	0.9	**1.2**	0.09
Tunisia, North, Tunis (1994)	30	1.4	**1.8**	0.13	25	1.2	**1.6**	0.11
Tunisia, Sfax (1997)	3	0.8	**0.8**	0.01	3	0.8	**1.0**	0.07
Africa, West								
The Gambia (1997-1998)	-	-	-	-	-	-	-	-
Guinea, Conakry (1996-1999)	-	-	-	-	-	-	-	-
Mali, Bamako (1988-1997)	-	-	-	-	-	-	-	-
Niger, Niamey (1993-1999)	3	0.2	**0.2**	0.02	1	0.1	**0.1**	0.01
Nigeria, Ibadan (1998-1999)	1	0.1	**0.2**	-	5	0.3	**0.6**	0.05
Africa, Central								
Congo, Brazzaville (1996-1999)	9	0.7	**1.2**	0.08	12	1.0	**1.4**	0.12
Africa, East								
France, La Reunion (1988-1994)	52	2.5	**3.4**	0.18	64	3.0	**3.1**	0.12
Kenya, Eldoret (1998-2000)	8	0.9	**2.2**	0.17	3	0.3	**0.6**	0.00
Malawi, Blantyre (2000-2001)	2	0.2	**0.4**	0.05	1	0.1	**0.5**	0.06
Uganda, Kyadondo County (1993-1997)	2	0.1	**0.1**	0.01	9	0.3	**1.2**	0.08
Zimbabwe, Harare: African (1990-1993)	27	1.1	**2.6**	0.18	18	0.8	**4.1**	0.29
Zimbabwe, Harare: African (1994-1997)	27	1.0	**2.9**	0.15	25	0.9	**3.7**	0.25
Zimbabwe, Harare: European (1990-1997)	12	7.9	**3.9**	0.10	8	4.7	**2.0**	0.05
Africa, South								
Namibia (1995-1998)	12	0.4	**0.7**	0.03	16	0.5	**0.8**	0.05
South Africa: Black (1989-1992)	450	0.8	**1.5**	0.10	418	0.7	**1.2**	0.09
South Africa: Indian (1989-1992)	22	1.1	**1.9**	0.09	19	1.0	**1.2**	0.11
South Africa: Mixed race (1989-1992)	53	0.8	**1.7**	0.10	44	0.7	**1.1**	0.07
South Africa: White (1989-1992)	146	1.5	**1.3**	0.08	103	1.0	**0.8**	0.04
South Africa, Transkei, Umtata (1996-1998)	5	1.4	**3.1**	0.28	3	0.7	**0.9**	0.02
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.4**	0.03	1	0.1	**0.1**	-
Swaziland (1996-1999)	3	0.2	**0.4**	0.05	-	-	-	-
Europe/USA								
USA, SEER: White (1993-1997)	2648	5.4	**4.0**	0.19	2329	4.6	**2.7**	0.12
USA, SEER: Black (1993-1997)	517	7.7	**9.0**	0.46	552	7.4	**7.0**	0.37
France, 8 registries (1993-1997)	627	4.6	**3.2**	0.16	591	4.1	**2.2**	0.11
The Netherlands (1993-1997)	1978	5.2	**3.7**	0.17	1824	4.7	**2.6**	0.12
UK, England (1993-1997)	6832	5.7	**3.5**	0.16	6523	5.1	**2.5**	0.11

In italics: histopathology-based registries

Table 2(d). Incidence of myeloma in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	0.2	0.2	4
Mozambique, Lourenço Marques	1956–60	*0.0*	*0.0*	1
Nigeria, Ibadan	1960–69	0.9	*0.8*	3
SA, Cape Province: Bantu	1956–59	*3.1*	*2.2*	2
SA, Cape Province: Coloured	1956–59	*1.7*	*0.4*	2
SA, Cape Province: White	1956–59	2.2	*0.3*	2
SA, Johannesburg, Bantu	1953–55	7.4	*3.1*	1
SA, Natal Province: African	1964–66	2.3	*4.3*	2
SA, Natal Province: Indian	1964–66	*1.2*	*1.4*	2
Uganda, Kyadondo	1954–60	*0.5*	*0.0*	1
Uganda, Kyadondo	1960–71	1.4	*0.6*	5
Zimbabwe, Bulawayo	1963–72	*2.5*	*2.8*	6

Italics: Rate based on less than 10 cases

Non-Hodgkin lymphoma and AIDS

In 1985, the United States Centers for Disease Control (CDC) revised the case definition for AIDS surveillance to include NHL of B-cell or indeterminate phenotype (Centers for Disease Control, 1985). In the USA and Europe, approximately 5–10% of HIV-infected persons will develop a lymphoma, and NHL is the AIDS-defining illness in about 3% of HIV-infected patients (Remick, 1995).

The epidemiology of AIDS-related lymphomas is summarized in the chapter on AIDS-related cancers in Africa, together with a review of the current status of research in this field in Africa.

Myeloma

Myeloma is more common in the black population of the United States than in whites. Incidence in the SEER registries in 1988–92 was 8.6 (males) and 6.1 (females) per 100 000 in blacks and 3.9 (males) and 2.3 (females) per 100 000 in whites. It used to be considered that the disease was rare in Africa, but Blattner *et al.* (1979) reported rates of 7.5 (males) and 5.1 (females) in the black population of South Africa.

Table 1(d) shows the rates from the population-based series in this volume and Table 2(d) presents data from the older series.

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4.11 Malignant melanoma of skin

Introduction

Malignant melanoma is a tumour of melanocytes, which are pigment-producing cells of the epidermis. There are similar densities of melanocytes in different races, and differences in skin colour reflect differences in melanocyte activity in transferring melanin granules organized into melanosomes to surrounding keratinocytes (Crombie, 1979).

Descriptive epidemiology in Africa

Malignant melanoma of skin accounts for about 1.3% of new cancer cases in Africa. The incidence is much higher in white populations of European origin than in black populations of African descent. In the United States, the incidence rate in white males is 15 times that of black males. Reports from both population-based and histology-based cancer registries in southern Africa where populations of European origin have lived for more than three generations show significant differences in the incidence of melanoma between blacks and whites (Sitas & Pacella, 1994; Bassett *et al.*, 1995).

There are also clear ethnic differences in the site distribution of melanomas. In Africans, 60% or more are reported to occur on the sole of the foot (Figure 1), compared with 6–12% in whites (Oettlé, 1966; Lewis, 1967; Giraud *et al.*, 1975; Isaacson 1978) and a similar distribution is observed in blacks and whites in the United States (Feibleman & Maize 1981). However, the difference in the actual *incidence* of plantar melanoma between black and white populations is small (Feibleman & Maize, 1981; Stevens *et al.*, 1990).

Examination of recent data from Africa confirms the low incidence rates in most populations. In southern Africa, there is an approximately 15-fold difference in incidence between black and white populations of South Africa and Zimbabwe (although the difference is much smaller for females in Zimbabwe, because of the relatively high incidence rate in black females (Table 1).

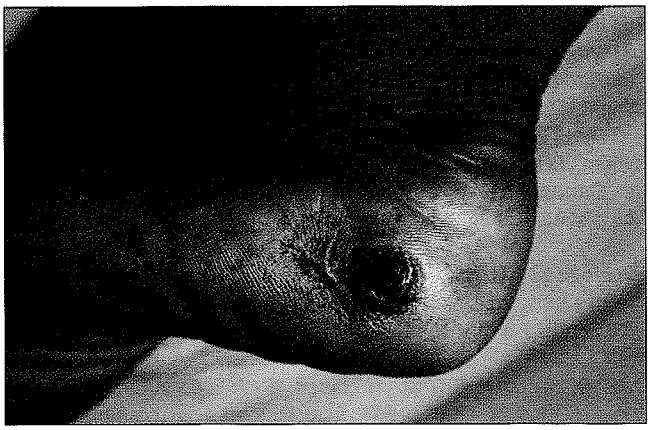

Figure 1. Plantar melanoma

Table 2 shows incidence data from time periods in the 1960s and 1970s.

In white populations, the incidence of malignant melanoma increases rapidly with age, so that it is already a relatively common cancer by the age of 20–29 years. The incidence is higher in young females (under age 45 years) and in older males (Figure 2) In contrast, the increase with age is more gradual in blacks in the

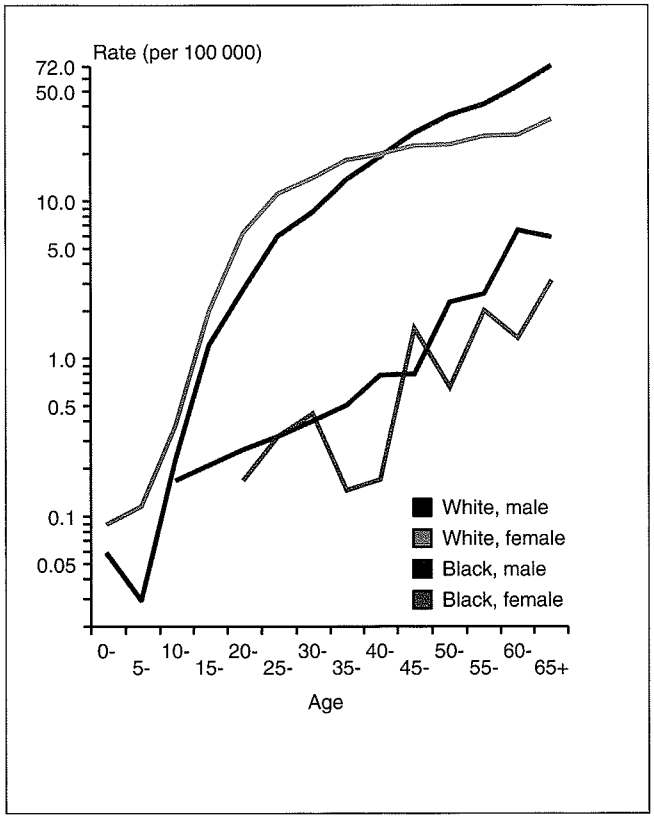

Figure 2. Age-specific incidence of melanoma of skin. USA, SEER, 1993–97

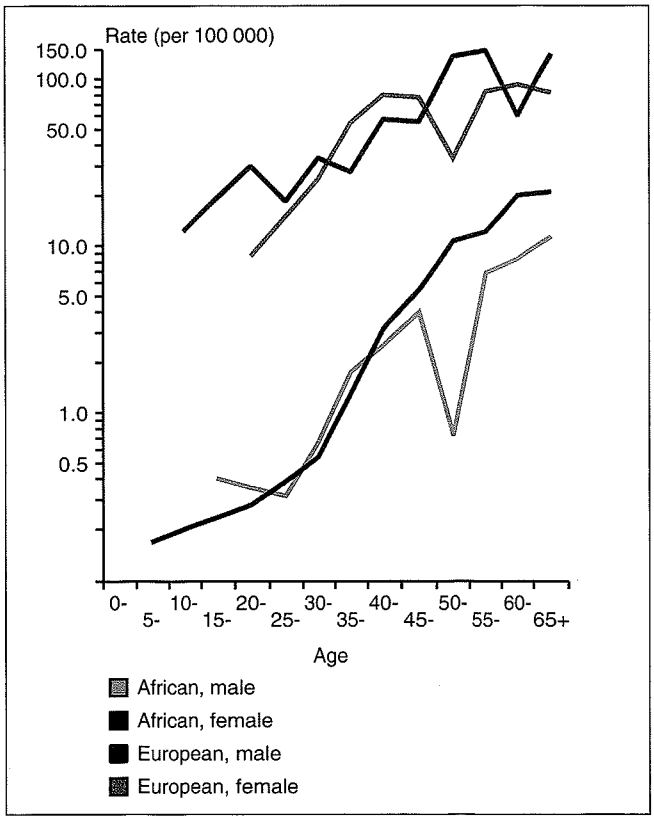

Figure 3. Age-specific incidence of melanoma of skin. Harare, Zimbabwe, 1990–97

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Melanoma of skin (C43)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	22	0.4	**0.6**	0.03	19	0.3	**0.4**	0.03
Algeria, Constantine (1994-1997)	3	0.2	**0.3**	0.02	3	0.2	**0.4**	0.02
Algeria, Oran (1996-1998)	9	0.5	**0.6**	0.05	15	0.9	**1.2**	0.08
Algeria, Setif (1993-1997)	-	-	-	-	1	0.0	**0.1**	-
Tunisia, Centre, Sousse (1993-1997)	4	0.3	**0.5**	0.03	9	0.8	**1.0**	0.03
Tunisia, North, Tunis (1994)	8	0.4	**0.5**	0.02	12	0.6	**0.7**	0.04
Tunisia, Sfax (1997)	2	0.5	**0.6**	0.02	1	0.3	**0.2**	0.01
Africa, West								
The Gambia (1997-1998)	2	0.2	**0.3**	0.02	1	0.1	**0.1**	0.01
Guinea, Conakry (1996-1999)	18	0.8	**1.6**	0.16	14	0.6	**1.5**	0.09
Mali, Bamako (1988-1997)	9	0.2	**0.4**	0.04	16	0.4	**1.2**	0.12
Niger, Niamey (1993-1999)	3	0.2	**0.7**	0.01	4	0.2	**0.8**	0.09
Nigeria, Ibadan (1998-1999)	5	0.3	**0.7**	0.03	4	0.3	**0.4**	0.04
Africa, Central								
Congo, Brazzaville (1996-1999)	8	0.7	**1.1**	0.09	9	0.7	**1.1**	0.04
Africa, East								
France, La Reunion (1988-1994)	28	1.3	**1.6**	0.13	40	1.8	**1.8**	0.12
Kenya, Eldoret (1998-2000)	2	0.2	**0.4**	0.00	14	1.5	**3.2**	0.18
Malawi, Blantyre (2000-2001)	3	0.3	**0.6**	0.05	4	0.5	**1.4**	0.13
Uganda, Kyadondo County (1993-1997)	11	0.4	**1.3**	0.06	13	0.4	**2.0**	0.12
Zimbabwe, Harare: African (1990-1993)	18	0.8	**1.7**	0.10	17	0.8	**3.5**	0.22
Zimbabwe, Harare: African (1994-1997)	24	0.9	**2.0**	0.12	34	1.3	**4.4**	0.31
Zimbabwe, Harare: European (1990-1997)	91	59.5	**40.5**	2.91	78	46.2	**30.2**	2.34
Africa, South								
Namibia (1995-1998)	65	2.0	**3.5**	0.24	53	1.7	**2.4**	0.17
South Africa: Black (1989-1992)	349	0.6	**1.2**	0.07	475	0.8	**1.4**	0.08
South Africa: Indian (1989-1992)	13	0.7	**0.7**	0.07	13	0.7	**0.9**	0.06
South Africa: Mixed race (1989-1992)	27	0.4	**0.8**	0.05	45	0.7	**1.1**	0.07
South Africa: White (1989-1992)	1718	17.1	**15.3**	1.05	1762	17.3	**14.2**	0.99
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	3	0.4	**0.9**	0.08	1	0.1	**0.2**	0.02
Swaziland (1996-1999)	6	0.3	**0.6**	0.04	10	0.5	**0.9**	0.07
Europe/USA								
USA, SEER: White (1993-1997)	9558	19.6	**15.5**	1.05	7772	15.5	**11.6**	0.85
USA, SEER: Black (1993-1997)	59	0.9	**1.0**	0.07	45	0.6	**0.6**	0.03
France, 8 registries (1993-1997)	1157	8.4	**6.5**	0.43	1543	10.7	**7.9**	0.58
The Netherlands (1993-1997)	3985	10.4	**8.0**	0.58	5710	14.6	**10.9**	0.82
UK, England (1993-1997)	9624	8.0	**5.8**	0.40	13791	10.8	**7.5**	0.54

In italics: histopathology-based registries

Table 2. Incidence of malignant melanoma of skin in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	1.2	1.3	4
Mozambique, Lourenço Marques	1956–60	–	–	1
Nigeria, Ibadan	1960–69	0.9	2.2	3
SA, Cape Province: Bantu	1956–59	*0.7*	*3.3*	2
SA, Cape Province: Coloured	1956–59	0.2	*1.0*	2
SA, Cape Province: White	1956–59	3.1	5.2	2
SA, Johannesburg, Bantu	1953–55	*1.2*	*2.0*	1
SA, Natal Province: African	1964–66	*0.8*	*2.4*	2
SA, Natal Province: Indian	1964–66	*0.9*	*0.0*	2
Uganda, Kyadondo	1954–60	*1.4*	*0.0*	1
Uganda, Kyadondo	1960–71	*0.6*	2.2	5
Zimbabwe, Bulawayo	1963–72	*0.1*	*0.3*	6

Italics: Rate based on less than 10 cases

United States, and rates remain higher in men at all ages. In Zimbabwe, the pattern is somewhat similar, with the difference between whites and blacks narrowing with age (Figure 3).

In clinical series from hospitals in Johannesburg, South Africa, Rippey and Rippey (1984) noted a much later stage at presentation for black patients (half of the lesions 5 cm or more, compared with 6% in whites) and their poorer survival: a crude three-year survival of 28% in blacks versus 56% in whites.

Etiology

Solar and artificial ultraviolet radiation

Sun exposure accounts for more than 60% of melanomas worldwide, especially in white populations (IARC, 1992; Armstrong & Kricker, 1995). In addition, there is evidence that exposure to artificial sources of ultraviolet (UV) radiation, in particular sunlamps and sun beds, can increase the risk of melanoma (Armstrong *et al.*, 1995). These two sources of exposure to UV irradiation and their relationship with melanoma of skin have been extensively reviewed by the International Agency for Research on Cancer (see IARC, 1992). Intermittent intense exposure to UV radiation from sunlight is associated with increased risk. Although there is a consistent and strong association between melanoma and a history of sunburn, the relationships with occupation and with total or chronic sun exposure are inconsistent (Elwood, 1996; Osterlind, 1992), which is an indication of the complexity of the relationship. Benign pigmented naevi, especially the so-called dysplastic naevi, of pale skin, are an indicator of risk. Their development is associated with sun exposure in childhood, and it seems that exposures early in life are critically important in determining lifetime risk in white populations. Thus, studies of migrants to Australia have shown that arrival in the sunny environment in childhood determines the increase in risk of melanoma later in life (Khlat *et al.*, 1992). Other factors of possible relevance to etiology are hereditary (familial dysplastic naevi syndrome), and hormonal (as shown by associations with fertility in women), as well as diet, alcohol, medications, hair dyes, fluorescent light, petroleum and hydrocarbons (reviewed by Armstrong & Holman, 1987).

The rapid increase in the incidence of melanoma in the last 20–30 years in many Caucasian populations suggests that there has been increasing sun exposure (Coleman *et al.*, 1993; Gallagher *et al.*, 1989). Evidence from analytical studies implicates intermittent recreational sun exposure as responsible for these increases, which are evident in successive birth cohorts in many European countries (Osterlind, 1992). It is also possible that some of the increase is the result of increased awareness and early diagnosis of thin lesions (Armstrong, 1988); however this is not a major factor in the increasing rates (van der Esch *et al.*, 1991). A 43% increase in mortality from melanoma of skin over a period of 10 years (1962–71) has been reported for whites living in South Africa (Rippey & Rippey, 1984). Similar increases in incidence in white populations over the past three decades have also been demonstrated in Queensland, Australia. However, no corresponding increases were observed in black populations living in these geographical areas (see Rippey & Rippey, 1984; Armstrong, 1988).

Melanin pigmentation of the skin protects against UV radiation and presumably accounts for the low risk of melanoma on the sun-exposed parts of the body in black populations. The low risk persists in migrant populations, and, in African migrants to Israel, in their offspring (Parkin & Iscovich, 1997).

Plantar melanoma

Exposure to UV radiation seems unlikely to play a major role in plantar melanoma, and etiological hypotheses have focused on other environmental and constitutional factors.

Pigmented patches and frank naevi (areas of dark pigmentation with clear-cut margins) appear to be relatively frequent in some African populations (Gordon & Henry, 1971). Lewis (1967) noted a correlation between the prevalence of such pigmented spots in different tribes of Uganda and the histological diagnosis rate of melanoma of the foot, and suggested that such ectopic, unstable collections of melanocytes may be important precursors of invasive disease. Some clinical studies have suggested that a relatively high proportion of plantar melanomas may arise from pre-existing naevi (Allen & Spitz, 1953; Lewis, 1967; Clark *et al.*, 1978). A history of naevi preceding the occurrence of malignant melanoma was reported by 7.5% of black patients in the United States (Muelling, 1948), but Feibleman *et al.* (1980) found no evidence of antecedent naevi in any of a series of retrospectively examined melanoma specimens among 49 cases of plantar melanoma occurring in white patients during a 50-year period.

Trauma has often been suggested as a risk factor, in part because walking barefoot is common in populations in which plantar melanoma appears to be frequent (McDonald, 1959; Oettlé, 1966). A high proportion of melanomas are found in weight-bearing areas of the sole (Camain *et al.*, 1972; Feibleman *et al.*, 1980), and there are numerous clinical reports of the development of melanoma being related to trauma (e.g., arising in burn scars). According to Higginson and Oettlé (1960), the incidence decreased with urbanization (and habitual shoe-wearing) in South Africa, but others found no difference between urban and rural residents (Giraud *et al.*, 1975; Isaacson *et al.*, 1978). In a study of 150 rickshaw boys in Durban, whose bare feet were habitually exposed to the grossest degree of trauma, no evidence of "traumatic melanoma" was found (Bentley-Phillips & Bayles, 1972). The sole of the foot remains the most common site of melanoma for shoe-wearers in Africa and in the United States, with virtually no sex differences in incidence (Lewis, 1967; McGovern,1977).

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4.12 Nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) has been recognized for many years, and traces of the disease can be found in Egyptian mummies dating from 5000 years ago (Smith *et al.*, 1924). NPC is an epithelial neoplasm arising in the squamous epithelium overlying the nasopharyngeal lymphoid tissue. Most of the tumours are undifferentiated or poorly differentiated, comprising small cells with heavy lymphoid infiltration.

Nasopharyngeal carcinoma is a rare malignancy in most parts of the world; age-standardized incidence rates for people of either sex are generally less than 1 per 100 000 per year (Parkin *et al.*, 1997), so that NPC comprises only about 0.6% of new cancer cases. However, in several regions, rates are very much higher. The overall incidence is elevated in the southern provinces of China (Guangdong, Guanxi, Hunan and Fujian) (Li *et al.*, 1979) and in Inuit (Eskimo) populations of Alaska and northern Canada (Nielsen *et al.*, 1996). NPC occurs with moderately raised incidence in populations from south-east Asia (Parkin *et al.*, 1997).

Descriptive epidemiology in Africa

In Africa, there are about 5500 new cases of NPC annually (0.9% of new cancers), but almost half of this total is from north Africa, where NPC comprises 2.1% of new cancer cases. Incidence rates in north Africa (Algeria and Tunisia) are in the low to moderate range (3–7.5 per 100 000 in men and 1.5–2.5 per 100 000 in women) (Table 1). Reviews of hospital series indicate that the frequency of nasopharyngeal carcinoma is relatively high in the mainly Arab populations of Tunisia, Morocco, Sudan and Saudi Arabia (Muir, 1971; Cammoun *et al.*, 1974; Hidayatalla *et al.*, 1983; Al-Idrissi, 1990).

Table 2 shows incidence data from time periods in the 1960s and 1970s.

A peak in incidence is observed in adolescents of each sex in a number of populations at low to moderate risk for nasopharyngeal carcinoma, including Tunisia (Ellouz *et al.*, 1978) (Figure 2). As a result, up to a quarter of NPC cases occur before the age of 25 years in these populations. In the United States, a minor peak in the age group 10–19 years is seen in blacks (Burt *et al.*, 1992; Parkin *et al.*, 1997).

Sub-Saharan Africa is a relatively low-risk area for nasopharyngeal carcinoma, and undifferentiated nasopharyngeal carcinoma is also the predominant histopathological type (Cammoun *et al.*, 1974). In general, incidence rates are low (Table 1), with somewhat higher values in Kampala, Uganda, and especially in Eldoret, in western Kenya. The data on frequency of NPC in early case series from Africa were reviewed by Clifford (1970a). The percentage of NPC among different series from Kenya was 2–9%, but there were higher rates (of hospitalization) estimated for the inland, highland areas of the country than on the coast, irrespective of ethnic group (Clifford, 1965, 1967). The highest (crude) incidence recorded was among men of the Nandi tribe (2.8 per 100 000) (Clifford 1965). Varying rates have also been reported within Uganda (Schmauz & Templeton, 1972) and Sudan (Hidayatalla *et al.*, 1983).

Migrant studies

The risk of NPC in Chinese living in the United States is high, and, although the risk in Chinese born in the United States is about half that of migrants born in China, it remains at least ten times higher than in the white population of the United States (Buell, 1974). In Singapore, the different Chinese dialect groups preserve the ratio of risks observed in southern China, with the highest risk in Cantonese

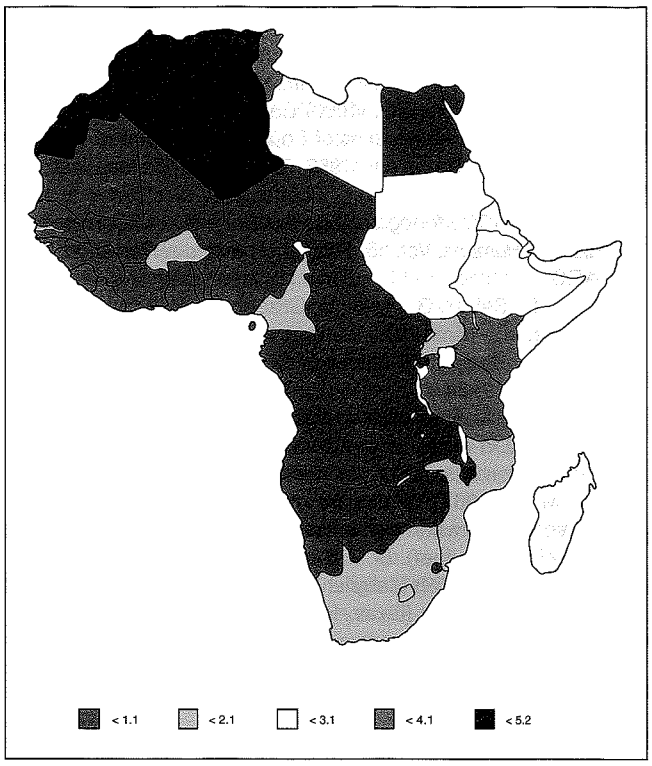

Figure 1. Incidence of nasopharyngeal cancer: ASR (world) - males

(double that in other dialect groups), and little change in incidence between the locally born and migrants from China (Lee *et al.*, 1988). Migrants to France from North African countries (Morocco, Algeria and Tunisia) have higher rates of mortality from NPC than the locally born population, and among such migrants, there is a small peak in age-specific mortality rates at ages 15–24 years (Bouchardy *et al.*, 1996). There also is a significantly higher than expected mortality from NPC among migrants to Australia from Egypt (Khlat *et al.*, 1993). Migrants to Israel from North Africa also have higher risks of NPC than the local population, and furthermore the offspring of such migrants retain their elevated risk relative to individuals with locally born parents (Parkin & Iscovich, 1997).

These findings, as for those of migrants of southern Chinese origin, suggest a strong genetic component to the increased risk in these populations. However, Jeannel *et al.* (1993) found that men of French origin who were born in North Africa also had a significantly higher rate of nasopharyngeal carcinoma than French men born in France.

Etiology

Environmental risk factors

Environmental risk factors for NPC have been extensively studied. The Epstein–Barr virus (EBV) is now generally accepted to be important in carcinogenesis at this site. The initial evidence came from serological studies, showing higher titres of antibodies to various EBV antigens in NPC cases (particularly undifferentiated NPCs) than control subjects. Klein *et al.* (1970) found higher reactivity in three assays of anti-EBV activity in sera of 26 cases of NPC (23 of them Africans) than in control subjects. Patients with advanced nasopharyngeal carcinoma, whether Cantonese Chinese in Hong Kong, Maghrebian Tunisians or Caucasians in France, had higher

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Nasopharynx (C11)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	128	2.3	**2.7**	0.22	61	1.1	**1.2**	0.09
Algeria, Constantine (1994-1997)	51	3.3	**5.3**	0.38	26	1.7	**2.5**	0.22
Algeria, Oran (1996-1998)	103	5.8	**6.6**	0.50	50	2.8	**3.3**	0.28
Algeria, Setif (1993-1997)	134	4.5	**6.3**	0.52	51	1.7	**2.2**	0.17
Tunisia, Centre, Sousse (1993-1997)	46	4.0	**4.9**	0.36	16	1.4	**1.5**	0.12
Tunisia, North, Tunis (1994)	67	3.1	**3.7**	0.34	33	1.6	**1.8**	0.15
Tunisia, Sfax (1997)	12	3.1	**3.7**	0.27	3	0.8	**0.9**	0.05
Africa, West								
The Gambia (1997-1998)	1	0.1	-	-	-	-	-	-
Guinea, Conakry (1996-1999)	5	0.2	**0.5**	0.05	1	0.0	**0.1**	0.00
Mali, Bamako (1988-1997)	1	0.0	**0.1**	0.01	1	0.0	**0.0**	0.00
Niger, Niamey (1993-1999)	1	0.1	**0.3**	-	-	-	-	-
Nigeria, Ibadan (1998-1999)	12	0.8	**1.1**	0.10	6	0.4	**0.6**	0.04
Africa, Central								
Congo, Brazzaville (1996-1999)	3	0.2	**0.4**	0.04	2	0.2	**0.2**	0.01
Africa, East								
France, La Reunion (1988-1994)	11	0.5	**0.6**	0.05	4	0.2	**0.2**	0.01
Kenya, Eldoret (1998-2000)	20	2.1	**3.9**	0.32	13	1.4	**2.9**	0.24
Malawi, Blantyre (2000-2001)	1	0.1	**0.1**	0.01	1	0.1	**0.4**	0.05
Uganda, Kyadondo County (1993-1997)	33	1.2	**1.8**	0.18	30	1.0	**1.4**	0.12
Zimbabwe, Harare: African (1990-1993)	14	0.6	**1.4**	0.04	7	0.3	**0.7**	0.04
Zimbabwe, Harare: African (1994-1997)	12	0.4	**0.6**	0.05	7	0.3	**0.6**	0.04
Zimbabwe, Harare: European (1990-1997)	-	-	-	-	2	1.2	**1.2**	0.09
Africa, South								
Namibia (1995-1998)	22	0.7	**1.1**	0.06	14	0.4	**0.5**	0.03
South Africa: Black (1989-1992)	445	0.8	**1.4**	0.10	111	0.2	**0.3**	0.02
South Africa: Indian (1989-1992)	7	0.4	**0.6**	0.02	6	0.3	**0.4**	0.02
South Africa: Mixed race (1989-1992)	97	1.5	**2.5**	0.18	24	0.4	**0.5**	0.04
South Africa: White (1989-1992)	123	1.2	**1.1**	0.08	42	0.4	**0.3**	0.02
South Africa, Transkei, Umtata (1996-1998)	4	1.1	**2.1**	0.20	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.3**	0.04	1	0.1	**0.1**	-
Swaziland (1996-1999)	2	0.1	**0.2**	0.02	-	-	-	-
Europe/USA								
USA, SEER: White (1993-1997)	271	0.6	**0.5**	0.03	145	0.3	**0.2**	0.01
USA, SEER: Black (1993-1997)	57	0.9	**0.9**	0.06	23	0.3	**0.3**	0.03
France, 8 registries (1993-1997)	107	0.8	**0.6**	0.05	37	0.3	**0.2**	0.01
The Netherlands (1993-1997)	222	0.6	**0.5**	0.03	82	0.2	**0.2**	0.01
UK, England (1993-1997)	637	0.5	**0.4**	0.03	304	0.2	**0.2**	0.01

In italics: histopathology-based registries

Table 2. Incidence of nasopharyngeal carcinoma in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	*0.3*	*0.3*	4
Mozambique, Lourenço Marques	1956–60	*2.2*	*0.0*	1
Nigeria, Ibadan	1960–69	2.5	1.8	3
SA, Cape Province: Bantu	1956–59	*0.0*	*0.0*	2
SA, Cape Province: Coloured	1956–59	*0.6*	*0.1*	2
SA, Cape Province: White	1956–59	*0.4*	*0.4*	2
SA, Johannesburg, Bantu	1953–55	*0.9*	*1.2*	1
SA, Natal Province: African	1964–66	*1.1*	*0.7*	2
SA, Natal Province: Indian	1964–66	*0.8*	*0.2*	2
Uganda, Kyadondo	1954–60	*0.0*	*0.0*	1
Uganda, Kyadondo	1960–71	*1.0*	*0.5*	5
Zimbabwe, Bulawayo	1963–72	*0.1*	*0.8*	6

Italics: Rate based on less than 10 cases

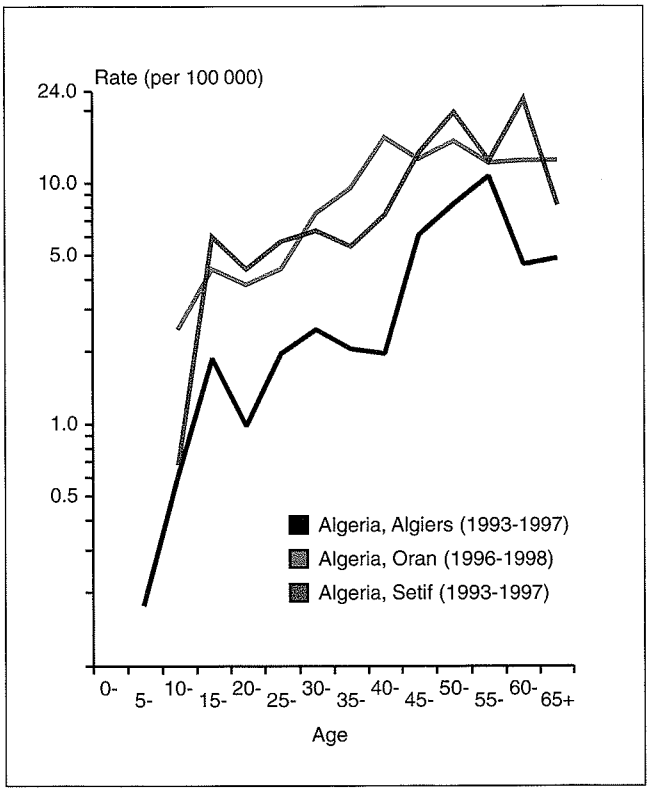

Figure 2. Age-specific incidence rates of NPC in three Algerian registries (males)

IgG and IgA titres to VCA and EA than patients with other tumours or than normal subjects (de Thé *et al.*, 1978). The viral genome is present in all NPCs, and in monoclonal form, implying that its presence antedates the tumour; it is never found in normal epithelial cells in the nasopharynx (IARC, 1997). But human infection with EBV is ubiquitous, so that it can by no means explain the striking geographical and ethnic patterns, and other agents must be involved.

Several studies strongly support the hypothesis that Cantonese-style salted fish is a nasopharyngeal carcinogen in humans. The studies suggest that age at exposure is an important co-determinant of risk, earlier age at exposure being associated with a higher risk for disease. There are also experimental data to support the carcinogenicity of Cantonese-style salted fish (IARC, 1997; Hildesheim & Levine, 1993). Jeannel *et al.* (1990) conducted a case–control study among Tunisians, who are at intermediate risk for nasopharyngeal carcinoma. Eighty histologically confirmed incident cases identified at the only cancer hospital in Tunisia and 160 population controls individually matched to the cases by age, sex and neighbourhood of residence were interviewed about dietary habits in the year preceding the cancer diagnosis and during childhood. The intake of several preserved food products during childhood and/or adulthood was significantly associated with the risk for nasopharyngeal carcinoma after adjustment for socioeconomic status. These foods were *touklia* (a stewing mixture of red and black peppers, paprika, caraway seed and/or coriander seed, salt and olive or soya-bean oil), *quaddid* (dried mutton preserved in olive oil), pickled vegetables, pickled olives and *harissa* (a mixture of red pepper, garlic, caraway seed, salt and olive oil). After adjustment for each other and for other potential confounders, only childhood exposure to *touklia*, *quaddid* and *harissa* were significant risk factors for nasopharyngeal carcinoma in Tunisia. The odds ratio for childhood consumption of *touklia* was 8.6 (95% CI 1.7–44), that for consumption of *quaddid* more than once a month was 1.9 (95% CI 1.0–3.7) and that for consumption of *harissa* more than once a month was 4.2 (95% CI 1.1–17).

Low levels of several volatile nitrosamines and directly acting genotoxic substances have been detected in Tunisian *touklia, quaddid* and *harissa* (Poirier *et al.*, 1987, 1989). In addition, samples of *harissa* and *quaddid* were shown to contain EBV-activating substances (Poirier *et al.*, 1989).

A variety of other possible etiological factors have been studied in case–control studies. Few have shown a strong or consistent association with risk (Hildesheim & Levine, 1993).

Clifford (1965) noted the presence of wood fires in chimneyless houses among tribal groups in Kenya with moderately elevated rates of nasopharyngeal carcinoma, and suggested a role for wood smoke. The same author (1972) measured serum carotene levels in 17 male African patients with nasopharyngeal carcinoma and 53 male controls and reported a significantly lower level in the cases.

Two case–control studies in US populations suggest an association with tobacco smoking (Mabuchi *et al.*, 1985; Nam *et al.*, 1992), while one was negative (Henderson *et al.*, 1976). In the US veterans cohort (Dorn, 1959), 46 deaths from NPC had occurred after 26 years; the odds ratio for smoking (ever/never) was 3.2.

Snuff has been suggested as an etiological factor; based upon chemical analysis of Zulu and Venda snuff, it appears that benzo[a]pyrene (for which a role has been proposed in China and Tunisia) is present in a considerable amount together with other carcinogenic hydrocarbons (Hubert & de Thé, 1982; Hubert *et al.*, 1993).

The results of analyses for trace quantities of six elements in maize leaf samples (iron, manganese, zinc copper, boron, molybdenum, nickel and lead) suggested that there was no association with incidence of nasopharyngeal carcinoma in Kenya (Robinson, 1967; Robinson & Clifford, 1968).

A comparison of the microflora of the nasopharyngeal area in subjects from Algeria and France suggested that the count of nitrate-reducing bacteria was higher in the former. This was suggested as a possible link to the higher risk of NPC, via the formation of nitrosamines (Charrière *et al.*, 1991).

Host factors

Observations of squamous metaplasia of the nasal mucosa following prolonged administration of estrogenic hormones appears to have stimulated several studies of sex hormone profiles in cases of NPC and controls in east Africa (Clifford & Bulbrook, 1966; Wang *et al.*, 1968). They showed a ratio of urinary estrogen to 11-deoxy-17-oxosteroids higher in NPC cases than in controls, while serum levels of dehydroepiandrosterone sulfate were lower, and no difference was observed in levels of androsterone sulfate. The significance, if any, of these observations is not clear.

Clifford (1970b) compared the ABO blood group profile of 233 patients with NPC from six Kenyan tribes with the normal distribution of blood groups in the same tribes; he observed that blood group A individuals appeared to be at reduced risk of NPC.

Several studies within populations of southern Chinese origin have identified associations between HLA locus A and B antigens and NPC risk (Chan *et al.*, 1983). It is not clear how much of the difference between populations could be attributed to HLA profiles, though Simons *et al.* (1976) did note that the frequency of the A2-B46 phenotype, associated with a relative risk of about 2, was twice as common in Cantonese relative to the Chiu Chau/Fujianese dialect groups, in parallel with the two-fold difference in NPC incidence.

A significant link with the HLA groups B5 and B17 has been observed in Algerian NPC patients (Tursz *et al.*, 1982). An investigation of HLA profiles among NPC cases and controls from Tunisia showed that at the second HLA locus, the results were similar to those found in Singapore, but the effect was less marked and did not reach statistical significance. At the first HLA locus, no association between A2 and NPC was found, in contrast to the Singapore results (Betuel *et al.*, 1975). Herait *et al.* (1983),

comparing 76 cases of NPC from Algeria with a control population (with renal failure) did not observe any statistically significant difference in frequency of HLA-A and HLA-B antigens. On the other hand, Hall *et al.* (1982) in a study of 141 cases in Kenya found an elevated risk with HLA-A29 and a factor of resistance associated with Bw44 for both NPC and Burkitt lymphoma. In addition to HLA, Chaabani & Ellouz (1986) found a relationship between NPC and certain immunoglobulin allotypes (Gm (1,17; 11,15,21) and Gm (1,3; 5,11), and the Km (1) antigen), but these findings were not confirmed in a study in Malaysia (Tarone *et al.*, 1990).

A linkage study based on affected sib pairs among southern Chinese in China, Hong Kong, Singapore and Malaysia suggests that a gene (or genes) closely linked to the HLA locus is associated with a 20-fold increased risk of NPC (Lu *et al.*, 1990). Some cancers show deletions at specific regions of chromosome 9 (Lo *et al.*, 1995). However, the genetic basis of susceptibility to NPC remains largely an enigma.

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4.13 Cancer of the oesophagus

Introduction

Oesophageal cancer ranks eighth in frequency of occurrence worldwide, with about 391 000 new cases each year, and 355 000 deaths. The geographical variation in risk is very large—more than for almost any other cancer. The highest-risk areas of the world are in the Asian 'oesophageal cancer belt' (stretching from northern Iran through the central Asian republics to north-central China), with incidence rates as high as 200 per 100 000 (and, in some areas, a female predominance), East and south-eastern Africa (Uganda, Zimbabwe, Natal, Transkei), eastern South America (southern Brazil, Uruguay, Paraguay, northern Argentina) and certain parts of western Europe (especially France and Switzerland). Oesophageal cancer is more common in males in most areas—for example, the sex ratio is 6.5:1 in France (Ferlay *et al.*, 2001), although in the high-risk areas of Asia, the sex ratio is much closer to unity, e.g. 1.5 in Linxian County, Henan, China (Lu *et al.*, 1985).

Descriptive epidemiology in Africa

Table 1 shows the incidence rates in the population-based data-sets in this volume. The incidence is low in North, West, and Central Africa (ASR less than 2 per 100 000 in men and 1 per 100 000 in women). However, in the African populations of eastern and southern Africa, the incidence is high (rates in white populations are similar to those in Europe and United States). Generally, the sex ratio is not very wide, 2–3:1; the exception is Reunion, which resembles metropolitan France in the large excess in men. The results from the older data in the 1950s and 60s are not dissimilar (Table 2), although the sex ratios in southern Africa seem to be rather wider in some centres (e.g., Johannesburg 10:1, Bulawayo, 7:1, Natal 3.3:1, Cape Province 2.6:1).

Cancer incidence among the Bantu of the Transkei, South Africa, has been reported in a number of surveys covering the period 1955–84 (Rose, 1967, 1973; Rose & Fellingham, 1981; Jaskiewicz *et al.*, 1987a). Age-standardized incidence (African standard) for all cancer sites combined (1965–69) was 60 and 42 per 100 000 per year for men and women, respectively (Rose & Fellingham, 1981); oesophageal cancer accounted for approximately half of the cases (35 and 17–19 per 100 000) in 1955–69, based on 5095 cases (Rose, 1973). More recently, in what was formerly Transkei, an incidence rate for males of 46.7 per 100 000 was recorded (Makaula *et al.*, 1996) and the data from the cancer registry in Umtata, Transkei, from 1996–98 (Table 1) confirm the persistence of these high rates.

In South Africa and Zimbabwe, the incidence of oesophageal cancer is higher in the black population than among whites; persons of mixed or Asian/Indian background in South Africa have rates that are intermediate between those of blacks and whites.

These various data from registries and relative frequencies from case series have been used to estimate national incidence rates (Figure 1). The estimates of age-standardized incidence in males range from less than 1 in many countries of West and Central Africa, to more than 10 per 100 000 in East and South Africa.

Transkei, South Africa

Within the Transkei, areas of high, moderate and low risk of oesophageal cancer were identified by Oettlé (1963) and Burrell (1957, 1962), with the high-risk districts being in the western part of the Transkei and the low risk ones in the eastern part.

Transkei subsequently became the focus of cancer registration and study (Rose, 1973). Between 1964 and 1969, all hospitals in the Transkei, three major referral hospitals in Natal (now KwaZulu-Natal) Province, and the major radiotherapy centre just outside the

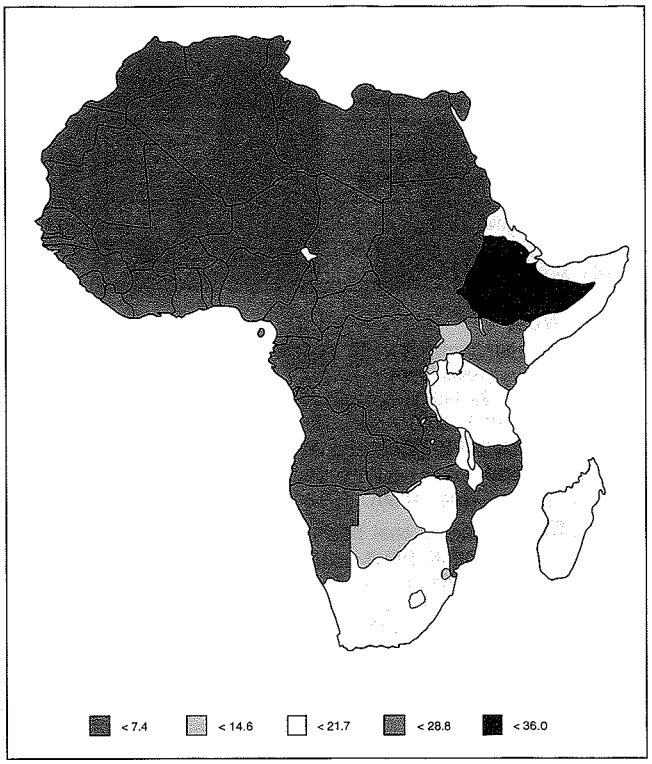

Figure 1. Incidence of oesophagus cancer: ASR (world) - males

Transkei in the Eastern Cape (East London), provided data on a total of 4247 cases of cancer (Rose & McGlashan 1975; Rose & Fellingham 1981). Overall, the age-standardized incidence rate for oesophageal cancer per 100 000 in males was 102.6 in the high-risk districts, 59.5 in the moderate-risk districts and 22.4 in the low-risk districts (Table 3). Incidence in the moderate-risk districts was similar to that observed in Durban in 1964–66 (40.7; Schonland & Bradshaw, 1968) and in Cape Town (37.5; Muir Grieve, 1967, 1970). Rates for oesophageal cancer in Johannesburg black males were lower, (12.8) (Table 2).

Cancer registration was continued by the Medical Research Council in the Transkei in two low-risk (Bizana and Lusikisiki) and two high-risk districts (Butterworth and Kentani). Data for 1981–84 (Jaskiewicz *et al.*, 1987 a) and 1985–90 (Makaula *et al.*, 1996) suggest that the incidence of oesophageal cancer has been declining in the high-risk districts and increasing in the low-risk districts. The reasons for this 'equalization' of the oesophageal cancer rates in the Transkei are unclear, but it is possible, given the high rates of migration in these areas and the large contrasts in access to diagnostic facilities, that some of the past differences in risk between the different regions may have been exaggerated.

Kenya

On the basis of hospital records, marked local variation in risk of oesophageal cancer among people of similar ethnic origin around Lake Victoria was suggested by Ahmed (1966) and Ahmed and Cook (1969), who noted that about 30% of cancers seen at the Kisumu hospital in western Kenya were oesophageal, whereas in Shirati hospital nearby in Tanzania, cancer of the oesophagus comprised only 2% of all cases, and in Uganda 1.8% of all cases. There was some evidence of variation within Nyanza province but this was inconclusive, partly because of the selective admission of

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Oesophagus (C15)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	34	0.6	**0.9**	0.06	19	0.3	**0.5**	0.02
Algeria, Constantine (1994-1997)	3	0.2	**0.4**	0.01	1	0.1	**0.1**	0.02
Algeria, Oran (1996-1998)	17	1.0	**1.5**	0.08	8	0.5	**0.6**	0.02
Algeria, Setif (1993-1997)	9	0.3	**0.5**	0.02	5	0.2	**0.3**	0.02
Tunisia, Centre, Sousse (1993-1997)	3	0.3	**0.4**	0.01	3	0.3	**0.4**	0.03
Tunisia, North, Tunis (1994)	19	0.9	**1.2**	0.09	16	0.8	**1.0**	0.06
Tunisia, Sfax (1997)	2	0.5	**0.6**	-	2	0.5	**0.7**	0.04
Africa, West								
The Gambia (1997-1998)	7	0.7	**1.4**	0.10	5	0.5	**1.1**	0.05
Guinea, Conakry (1996-1999)	13	0.6	**0.9**	0.08	5	0.2	**0.5**	0.05
Mali, Bamako (1988-1997)	34	0.9	**2.0**	0.18	17	0.5	**0.9**	0.07
Niger, Niamey (1993-1999)	7	0.4	**1.0**	0.12	7	0.4	**1.3**	0.11
Nigeria, Ibadan (1998-1999)	7	0.5	**1.1**	0.03	2	0.1	**0.3**	0.03
Africa, Central								
Congo, Brazzaville (1996-1999)	4	0.3	**0.5**	0.04	1	0.1	**0.1**	-
Africa, East								
France, La Reunion (1988-1994)	362	17.3	**22.8**	1.76	36	1.7	**1.9**	0.11
Kenya, Eldoret (1998-2000)	89	9.5	**24.5**	1.66	51	5.6	**15.5**	1.36
Malawi, Blantyre (2000-2001)	72	8.0	**17.4**	1.28	38	4.4	**10.7**	0.79
Uganda, Kyadondo County (1993-1997)	106	3.8	**13.3**	0.82	91	3.1	**12.1**	0.68
Zimbabwe, Harare: African (1990-1993)	212	8.9	**27.9**	1.38	36	1.7	**8.6**	0.48
Zimbabwe, Harare: African (1994-1997)	169	6.1	**17.2**	0.89	51	1.9	**8.4**	0.37
Zimbabwe, Harare: European (1990-1997)	18	11.8	**6.3**	0.19	8	4.7	**2.3**	0.14
Africa, South								
Namibia (1995-1998)	107	3.4	**6.3**	0.36	33	1.0	**1.7**	0.07
South Africa: Black (1989-1992)	7009	12.3	**23.1**	1.61	3220	5.7	**9.1**	0.68
South Africa: Indian (1989-1992)	179	9.2	**13.1**	1.04	102	5.1	**7.3**	0.46
South Africa: Mixed race (1989-1992)	520	8.1	**16.0**	1.13	178	2.7	**4.2**	0.31
South Africa: White (1989-1992)	597	5.9	**5.5**	0.35	208	2.0	**1.6**	0.09
South Africa, Transkei, Umtata (1996-1998)	117	32.7	**62.5**	5.30	97	22.9	**34.5**	2.57
South Africa, Transkei, 4 districts (1996-1998)	134	18.5	**37.5**	2.83	173	19.2	**26.5**	2.01
Swaziland (1996-1999)	113	6.4	**14.0**	1.01	41	2.1	**4.1**	0.32
Europe/USA								
USA, SEER: White (1993-1997)	3025	6.2	**4.8**	0.26	1125	2.2	**1.3**	0.06
USA, SEER: Black (1993-1997)	593	8.9	**10.6**	0.74	252	3.4	**3.4**	0.24
France, 8 registries (1993-1997)	2045	14.9	**11.0**	0.75	346	2.4	**1.4**	0.08
The Netherlands (1993-1997)	3297	8.6	**6.3**	0.35	1640	4.2	**2.4**	0.12
UK, England (1993-1997)	16669	13.9	**8.7**	0.41	11059	8.7	**4.0**	0.14

In italics: histopathology-based registries

Table 2. Incidence of oesophageal cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	*0.2*	*0.2*	4
Mozambique, Lourenço Marques	1956–60	*4.4*	*0.0*	1
Nigeria, Ibadan	1960–69	1.5	*1.1*	3
SA, Cape Province: Bantu	1956–59	37.5	*14.3*	2
SA, Cape Province: Coloured	1956–59	10.1	*0.0*	2
SA, Cape Province: White	1956–59	6.4	1.0	2
SA, Johannesburg, Bantu	1953–55	12.8	*1.2*	1
SA, Natal Province: African	1964–66	40.9	12.3	2
SA, Natal Province: Indian	1964–66	22.1	30.0	2
Uganda, Kyadondo	1954–60	*1.8*	*1.1*	1
Uganda, Kyadondo	1960–71	3.3	5.3	5
Zimbabwe, Bulawayo	1963–72	58.6	8.1	6

Italics: Rate based on less than 10 cases

Table 3. Oesophageal cancer incidence (age-standardized incidence, world standard) in Transkei, 1965–69 (calculated from Rose & McGlashan, 1975)

	Males	Females	MV (%)
High-risk districts	102.6	56.4	77%
Moderate-risk districts	59.5	29.9	75%
Low-risk districts	22.4	6.3	85%

cancer patients from around the main hospital (Ahmed & Cook, 1969). Using data from the histopathology register at Kenyatta National Hospital, Nairobi, Gatei *et al.* (1978) noted that 80% of oesphageal cancer cases occurred in individuals from just three tribes: the Kikuyu, Luo and Luhya. Since the first group lives in central Kenya (around Nairobi), a relative over-representation is perhaps not surprising, but the large number of cases among the Luo and Luhya, who come from western Kenya (around Lake Victoria) was considered a significant finding. Interestingly, there were few cases (< 1%) among the Kalenjin, who come from the Rift Valley region, around Eldoret, yet the most recent registry data from Eldoret, presented in this volume, show a fairly high incidence, suggesting that the area of high risk is considerably greater than implied in these publications.

Morphology

Worldwide, most oesophageal cancers are squamous-cell carcinomas, arising in the middle and lower third of the oesophagus. Recently, in developed countries an increase has been observed in relative and absolute numbers of adenocarcinomas of the lower third of the oesophagus, associated with Barrett's oesophagus (Vizcaino *et al.*, 2002). The profiles of genetic changes (mutations) are different in these two histological subtypes, implying different etiology. In Africa, oesophageal cancer is predominantly of squamous-cell origin. Adenocarcinoma of the oesophagus comprises less than 15% of oesophageal cancers in sub-Saharan African populations. In the Caucasian populations of South Africa and in North African countries, adenocarcinoma of the oesophagus comprises about a third of all cases (see Table 4).

Sex ratio

As noted earlier, the sex ratio of oesophageal cancer is quite variable, with a strong male predominance in some high-risk areas in Europe (where tobacco and alcohol are the main risk factors—see below) to near equality, or even a female predominance, in the high-risk areas of central Asia and China. In Africa, the male:female ratio is usually about 2 (Table 1), although earlier ratios of 11.8 in Kenya and 4.2 in Johannesburg were recorded (Cook Mozzaffari, 1989), while in the former Transvaal, South Africa, a ratio of 75 was reported by Oettlé (1967).

Time trends

Several pieces of evidence suggest that the high incidence of oesophageal cancer in South and East Africa is a relatively recent phenomenon. Oesophageal cancer was rare in the 1930s in South Africa (Berman, 1935), but it is now the leading cancer in black males (Higginson & Oettlé, 1962; Sitas *et al.*, 1998). Increases in the relative frequency have been noted in the rural Transvaal (now Northern Province) (Higginson & Oettlé, 1962; Sitas *et al.*, 1998) (see Chapter 3.5.4). Records from Umtata hospital (Transkei) also show a dramatic increase in the frequency of oesophageal cancer relative to all other major cancer types (liver, cervix and breast): in

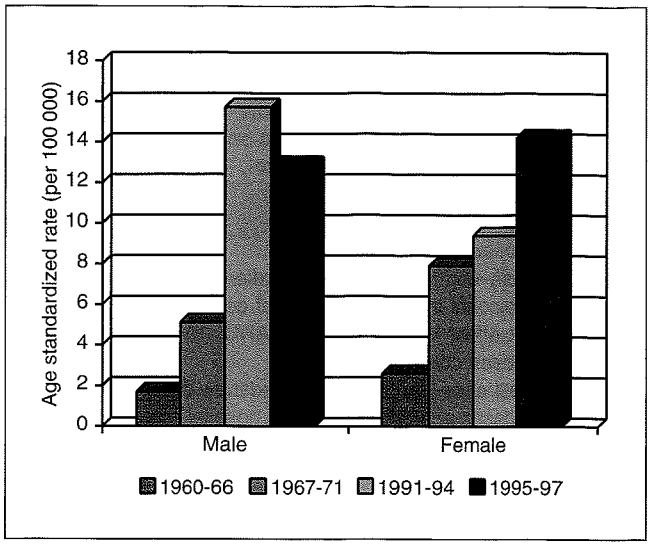

Figure 2. Trends in incidence of oesophageal cancer, Kyadondo County, Uganda, 1960–1997 (Wabinga *et al.* 2000)

1925 oesophageal cancer comprised less than 10% of all these cancers, but by 1969 this proportion had increased to just under 60% (Rose & Fellingham, 1981).

In their analysis of incidence rates of cancer among black gold miners in South Africa, Bradshaw *et al.* (1982) observed a small decrease in crude incidence rates over the period 1964–79.

Increases in the frequency of oesophageal cancer have also been noted in Kenya (0.1% in 1930 vs. 16% in the 1960s (Vint, 1935; Cook & Burkitt, 1975), in Swaziland (Keen & Martin, 1971) and in Botswana (Macrae & Cooke, 1975).

In Kampala, Uganda, the incidence of oesophageal cancer has increased progressively in both sexes over the last 30–40 years (Figure 2).

Survival

Survival of oesophageal cancer patients is poor and is strongly related to stage at presentation. In a study in South Africa, 21% of 265 patients with oesophageal cancer presented with the disease confined to the oesophagus, and only 30% of these survived over three years after oesophagotomy (Kneebone & Mannell, 1985).

Risk factors

Studies of squamous-cell carcinoma in developed countries have consistently shown the etiological importance of tobacco and alcohol, particularly in combination. However, the geographical patterns in Africa (and elsewhere) strongly imply that other factors play an important role. In general, the populations at highest risk are poorer, have limited or restricted diets, and consume certain forms of alcohol and tobacco (smoked or chewed) (Rose, 1981). McGlashan (1969a), reviewing geographical variation in oesophageal cancer in East and southern-central Africa, noted that there seemed to be a correlation between relative frequency in hospital case series and consumption of certain spirits brewed from maize husks. Polarographic analysis of these drinks suggested the presence of nitrosamines (McGlashan *et al.*, 1968; McGlashan, 1969b). However, Collis *et al.* (1971), analysing alcoholic drinks from areas near hospitals in Kenya and Uganda with different frequencies of oesophageal cancers, found no association between the suspected constituents, as indicated by polarography, and presence of nitrosamine as evaluated by gas chromatography and mass spectrometry. The nitrosamine levels were not related to the local frequency of oesophageal cancer. Cook (1971) and later van Rensburg (1981) showed a geographical correlation between incidence of oesophageal

cancer and consumption of maize-based staple diets and beer brewed from maize (replacing the traditional sorghum or millet). Several studies of the carcinogenicity of these maize-based beers (for example, nitrites, fermentation products or fungal contaminants such as fumonisins) have been conducted but none has shown, at the individual level, an association with oesophageal cancer.

Alcohol and tobacco

Numerous case–control and cohort studies have shown that both tobacco and alcohol increase the risk of oesophageal cancer, and that their joint effect is multiplicative (IARC, 1986, 1988). Several studies have been conducted in Africa.

The earliest case–control study (Bradshaw & Schonland, 1969) examined 98 cases and 341 unmatched hospital controls in Durban, South Africa. This study was re-analysed, together with a later one of 196 male cases and 1064 age-matched controls in Baragwanath Hospital, Johannesburg (Bradshaw & Schonland, 1974). In both, oesophageal cancer was strongly associated with tobacco use, particularly with the use of pipe tobacco in cigarettes (OR in Durban 5.4, in Johannesburg 7.8, relative to non-smokers). Stratified by level of tobacco consumption, there was no significant effect of alcohol (traditional beer, western type liquors, or 'concoctions') on risk.

In a subsequent hospital-based case–control study in Durban, South Africa, in 1978–81 (van Rensburg *et al.*, 1985), 211 hospital cases (Zulu males) were compared with controls matched on age and residence (urban/rural). In a multivariate model, an association was again found with smoking of commercial cigarettes (OR = 2.6 for current smokers, 1.6 for past smokers) and pipe smoking (OR = 2.1), but data for alcohol consumption were not shown.

In a case–control analysis based on data collected in the cancer registry of Bulawayo, Zimbabwe, in 1963–77 (Vizcaino *et al.*, 1995), 881 cases of oesophageal cancer were compared with 5238 controls (patients with cancers not related to tobacco or alcohol). In men, a dose–response relationship was found for tobacco consumption, with an OR of 3.5 for those smoking 1–14 cigarettes per day and 5.7 for those smoking over 15 g of total tobacco per day (cigarettes usually weigh about a gram). Among women who had ever smoked tobacco, the OR was 4.0 compared with those who had never smoked. No effect in relation to alcohol drinking was found (OR = 0.9) for daily consumption of either local beer or total alcohol.

In the Transkei, populations with 'high', 'medium' and 'low' incidence of oesophageal cancer were compared with respect to prevalence of tobacco smoking (particularly pipes) and consumption of different alcoholic beverages (McGlashan *et al.*, 1982). The correlation was stronger for tobacco than for alcohol.

Also in the Transkei, a hospital-based case–control study (130 cases, controls matched by age and level of education) (Sammon, 1992) found a positive association with smoking (OR = 2.6; 95% CI 1.5–5.0), but no relationship with drinking of 'traditional' beer (OR = 1.6; 95% CI 0.9–3.0).

In contrast, a hospital-based case–control study in Soweto (Segal *et al.*, 1988) found that both alcohol and tobacco had an independent and multiplicative effect on the risk of developing oesophageal cancer. For example, in the heaviest drinkers and smokers (more than 40 g tobacco and 91 g ethanol per day) an OR of 39 was observed. For tobacco alone (adjusted for alcohol), the OR was 3.0 for those smoking 20–39 g per day and 2.2 for those smoking over 40 g per day. By contrast, the relative risks in relation to alcohol consumption (adjusted for tobacco) were 5.4 in those consuming 31–60 g ethanol per day, 10.5 in those consuming 61–90 g and 18.3 for the highest daily consumption of ethanol (> 90 g per day).

In a study by Pacella-Norman *et al.* (2002), among the black population of Johannesburg and Soweto, the odds ratio associated with heavy smoking in males (15+ g of tobacco per day) was 6.0 (95% CI 3.2–11.0) for developing oesophageal cancer and in females, 6.2 (95% CI 1.9–20.2). Daily alcohol consumption was a risk factor for the development of oesophageal cancer in males (OR = 1.8, 95% CI 1.2–2.8) and females (OR = 1.7; 95% CI 1.0–2.9). For alcohol consumption in combination with smoking, males and females were at increased risk of developing oesophageal cancer (OR = 4.7; 95% CI 2.8–7.9, and 4.8; 95% CI 3.0–7.8, respectively) compared with lifelong non-smokers and non-drinkers. Increased risks of developing oesophageal cancer were noted in both males and females who reported having lived in the former Transkei for over 34 years (OR males = 3.1; 95% CI 0.9–10.8; OR females = 14.7; 95% CI 4.7–46.0).

The reason for the rather discrepant results between earlier studies and more recent ones based on urban populations, with respect to the effect of alcohol on risk, may lie in the actual amounts of alcohol consumed. In Soweto, consumption (in grams of alcohol per day) was far greater than that reported in the studies from Bulawayo and rural South Africa, where the principal alcoholic beverage was maize beer, with a low alcohol content (2–4%). In Bulawayo, for example, it was estimated that individuals in the heaviest drinking categories were consuming only about 20–40 g of alcohol per day, a quantity that is associated with only about a doubling of risk of oesophageal cancer in studies elsewhere. It is therefore possible that the early southern African studies could not detect such low relative risks.

Chewing/ingestion of tobacco

In the Transkei, swallowing of dottle from the pipe stem (i.e., tobacco pyrolysis products) was thought to be associated with increased oesophageal cancer risk (Rose, 1978). A bacterial mutagenicity assay demonstrated significant mutagenic activity in this material (Hewer *et al.*, 1978;). However, only 2–5% of the population claimed to do this (Bradshaw *et al.*, 1983).

Nutritional deficiencies

Many of the 'clusters' of high oesophageal cancer risk appear to occur in populations who are poor and consume restricted diets. Oesophageal cancer has been found to be associated with low social class in developed countries (e.g., USA; Brown *et al.*, 1994) and China (Cheng *et al.*, 1992) and with poor nutritional status. Thus in the United States, those with diets poor in nutrients and low in fruits and vegetables (particularly those rich in vitamin C) are at increased risk of developing oesophageal cancer (Brown *et al.*, 1998). In many African populations, a restricted diet could be a major background factor associated with oesophageal cancer (Cook Mozzaffari, 1989); Burrell (1957) noted that the Transkei was an infertile area where plants had a number of mineral deficiencies. In a comparison of areas of moderate and high risk of oesophageal cancer, persons living in areas of high risk had lower levels of vitamins A and C, magnesium and riboflavin (van Rensburg *et al.*, 1983). In the Transkei, populations with high oesophageal cancer rates appeared to eat maize as a staple, which has low levels of niacin, riboflavin, vitamin C, zinc, calcium and magnesium. Pellagra is associated with high intake of maize and acute oesophagitis is associated with this disease.

In the hospital-based case–control study of Sammon (1992) in Umtata (Transkei), cases reported more frequent use of traditional dietary staples than controls. In the case–control study in Durban, Natal (van Rensburg *et al.*, 1985), consumption of maize meal was a risk factor for oesophageal cancer (OR for daily consumers 5.7, weekly consumers 2.4, compared with those who consumed it less often). It has been suggested that chronic oesophagitis is a precursor of oesophageal cancer, but it is unclear under what circumstances acute oesophagitis develops into chronic oesophagitis.

Table 4. Percentage distribution of microscopically verified cases by histological type
Oesophagus (C15) - Both sexes

	Carcinoma				Sarcoma	Other	Unspecified	Number of cases	
	Squamous	Adeno	Other	Unspecified				MV	Total
Algeria, Algiers	46.2	33.3	-	20.5	-	-	-	**39**	53
Algeria, Batna	92.3	7.7	-	-	-	-	-	**13**	14
Algeria, Constantine	50.0	50.0	-	-	-	-	-	**2**	4
Algeria, Oran	55.0	35.0	-	10.0	-	-	-	**20**	25
Algeria, Setif	41.7	41.7	-	16.7	-	-	-	**12**	14
Burkina Faso, Ouagadougou	-	80.0	-	20.0	-	-	-	**5**	9
Congo, Brazzaville	25.0	25.0	-	50.0	-	-	-	**4**	5
France, La Reunion	93.9	4.1	0.5	1.0	-	0.3	0.3	**392**	398
The Gambia	100.0	-	-	-	-	-	-	**1**	12
Guinea, Conakry	50.0	20.0	-	30.0	-	-	-	**10**	18
Kenya, Eldoret	75.9	1.9	-	16.7	-	-	5.6	**54**	140
Malawi, Blantyre	83.3	16.7	-	-	-	-	-	**24**	110
Mali, Bamako	85.7	10.7	-	3.6	-	-	-	**28**	51
Namibia	89.9	4.3	-	5.1	0.7	-	-	**138**	140
Niger, Niamey	77.8	22.2	-	-	-	-	-	**9**	14
Nigeria, Ibadan	100.0	-	-	-	-	-	-	**2**	9
Rwanda, Butare	-	-	-	-	-	-	-	**-**	1
South Africa: Black	88.9	1.8	0.3	2.2	0.1	0.1	6.8	**10229**	10229
South Africa: White	64.5	28.1	1.2	5.2	0.2	-	0.7	**805**	805
South Africa: Indian	79.0	6.8	-	5.3	-	-	8.9	**281**	281
South Africa: Mixed race	90.1	5.6	0.6	3.4	-	-	0.3	**698**	698
South Africa, Elim	85.7	2.4	-	11.9	-	-	-	**42**	57
South Africa, Transkei, Umtata	87.5	-	-	6.3	-	-	6.3	**64**	214
South Africa, Transkei, 4 districts	100.0	-	-	-	-	-	-	**24**	307
Swaziland	100.0	-	-	-	-	-	-	**14**	154
Tanzania, Dar Es Salaam	92.0	4.6	-	3.4	-	-	-	**87**	87
Tanzania, Kilimanjaro	65.2	13.0	-	21.7	-	-	-	**23**	100
Tunisia, Centre, Sousse	100.0	-	-	-	-	-	-	**6**	6
Tunisia, North, Tunis	65.6	31.3	-	3.1	-	-	-	**32**	35
Tunisia, Sfax	100.0	-	-	-	-	-	-	**3**	4
Uganda, Mbarara	50.0	8.3	-	41.7	-	-	-	**12**	52
Uganda, Kyadondo County	86.3	8.8	-	2.5	-	-	2.5	**80**	197
Zimbabwe, Harare: African	89.1	3.6	-	7.3	-	-	-	**220**	468
Zimbabwe, Harare: European	54.5	36.4	-	9.1	-	-	-	**11**	26

Contaminants in the diet

In a case–control study in the Transkei, 'usual consumption' of the plant *Solanum nigrum* in the previous ten years was found to be associated with oesophageal cancer. *S. nigrum* has an irritating effect on the oesophageal mucosal lining (Sammon, 1992). *Candida albicans* infection of the oesophagus (common in China; Hsia *et al.*, 1988) is thought to promote the production of nitrosamines, which are thought to be carcinogenic. This may be of particular relevance to southern Africa, especially against a background of tobacco smoking and alcohol consumption (Silber, 1985).

Mycotoxins

Fumonisin B_1, fumonisin B_2 and fusarin C are mycotoxins produced by *Fusarium* species that occur primarily on maize. These toxins occur particularly when maize is grown under warm, dry conditions. Exposure occurs through dietary consumption of contaminated maize. Populations that eat milled or ground maize as a dietary staple can be exposed to significant amounts of fumonisins and to lesser amounts of fusarin C.

An IARC (1993) working group concluded that there was sufficient evidence for the carcinogenicity to experimental animals of cultures of F. moniliforme that contain significant amounts of fumonisins, and limited evidence for the carcinogenicity of fumonisin B_1 and fusarin C.

A number of ecological studies have addressed the relationship between exposure to *Fusarium* toxins and oesophageal cancer. Most of the studies refer to mixtures of many toxins from many species of fungi on maize.

Marasas *et al.* (1979) examined the amounts of deoxynivalenol and zearalenone in samples of mouldy maize from randomly selected areas in the high-risk and low-risk oesophageal cancer regions of the Transkei, where maize is the main dietary staple. The level of contamination of maize kernels with each of these two *Fusarium* mycotoxins was apparently higher in the pooled samples from the high-risk than the low-risk region. In an extension of this study, Marasas *et al.* (1981) included an area of the Transkei with an intermediate rate of oesophageal cancer and collected visibly healthy maize samples at random from each of the three study areas. The proportion of kernels in both mouldy and healthy maize samples infected by *F. graminearum* (which was responsible for contamination of the crops with deoxynivalenol and zearalenone), was not correlated with oesophageal cancer rates.

Marasas *et al.* (1988) studied the prevalence of three *Fusarium* species and other fungi in home-grown maize harvested in 1985 by 12 households situated in a district of high incidence of oesophageal cancer in the Transkei (Kentani) and by 12 households in a low-incidence district (Bizana). Households in the high-incidence area were identified during a preliminary cytological screening for oesophageal

cancer as having one or more adult occupants who showed mild to severe oesophageal abnormalities; households in the other study area were chosen at random. The ears of maize were sorted by the housewife at each domicile into 'good' ears intended for making porridge and 'mouldy' ears intended for brewing beer. No correlation was found between the occurrence of *F. graminearum* in healthy maize and risk for oesophageal cancer, but an inverse correlation was seen with the occurrence of this fungus in mouldy maize. However, the mean proportions of maize kernels infected with *F. moniliforme* in both healthy and mouldy maize samples from households in the area of high oesophageal cancer incidence were significantly higher (42% in healthy and 68% in mouldy maize) than those in the low-incidence area (8% and 35%, respectively). The same authors conducted a similar survey one year later, with the same criteria for high and low incidence but adding 24 households from a study area with an intermediate incidence of oesophageal cancer (Butterworth). Although the proportion of kernels infected with *F. moniliforme* in healthy maize from the latter area lay between those from the high- and low-incidence areas, further subdivision of households in the intermediate-incidence area into 12 situated in a low-risk zone and 12 in a high-risk zone (with an estimated six-fold difference in oesophageal cancer rates) did not reveal a difference in the proportion of infected kernels in the corresponding samples (26 and 24%, respectively). Furthermore, there was no difference in the prevalence of cytological abnormalities of the oesophagus in adult occupants of the low- and high-risk zones of the intermediate-incidence area and the sampling strategy differed between the high- and low-risk areas.

Sydenham *et al.* (1990a) found high concentrations of various *Fusarium* mycotoxins in the same samples of mouldy home-grown maize collected during 1985 and examined by Marasas *et al.* (1988). The mean levels of nivalenol and zearalenone, produced by *F graminearum*, were significantly higher in mouldy maize samples from the low-risk area than in those from the high-risk area (Sydenham *et al.*, 1990b). Significantly higher mean numbers of kernels infected with *F. moniliforme* and correspondingly higher levels of the mycotoxins fumonisin B_1 and fumonisin B_2 were found in mouldy maize samples in the high-risk oesophageal cancer area than in the low-risk area ($p < 0.01$). Fumonisin B_1 and B_2 levels in healthy maize samples from the low-risk area were approximately 20 times lower than those in healthy samples from the high-risk area, and only three out of 12 samples in the low-risk areas contained these toxins versus 12/12 in the high-risk areas, but again the sampling strategy differed between the high- and low-risk areas.

Because of the methodological difficulties encountered in these studies, the IARC (1993) working group concluded that there was inadequate evidence in humans for the carcinogenicity of toxins derived from *F. moniliforme* and that toxins derived from *F. moniliforme* were possibly carcinogenic to humans.

Human papillomaviruses

Dillner *et al.* (1994), in a study in Sweden based on serology (anti-HPV antibody), found an association between the HPV 16 subtype and oesophageal cancer (OR = 14.6); however, in a subsequent study (Lagergren *et al.*, 1999), no association was found with high serum antibody levels for either the HPV 16 (OR = 0.9) or the 18 subtypes (OR = 0.3). In South Africa, Hale *et al.* (1989) found HPV in 13/20 oesophageal cancer biopsies; no control specimens were tested. However in another South African study, no virally-induced koilocytosis was found in 513 oesophageal cancer autopsies in the western Cape and the Transkei (Jaskiewicz *et al.*, 1992). It is possible that HPV is merely an indirect measure of poorer environmental conditions, known to be risk factors for the development of oesophageal cancer.

Other exposures

In a small case–control study in Ethiopia, Astini *et al.* (1990) found that subjects with oesophageal cancer drank less water during meals (2/26) than controls (37/52) (OR = 0.06; 95% CI 0.02–0.19). No association with intake of hot food was found.

Genetic factors

Knowledge about the molecular and genetic basis of oesophageal cancer development has increased significantly and the mechanisms of carcinogenesis have been reviewed (see, for example, Montesano *et al.*, 1996; Stemmerman *et al.*, 1994). One area of interest, largely unexplored in Africa, has been the epidemiology of aldehyde dehydrogenase 2 (ALDH2) and its mutant allele ALDH*2. ALDH2 is a key enzyme that eliminates acetaldehyde formed from alcohol. Acetaldehyde is thought to be a carcinogen and may be responsible for alcohol-related cancers in humans (Blot *et al.*, 1991). The mutation in ALDH*2 leads to inactivity of the enzyme and accumulation of acetaldehyde; this allele is common in far-eastern populations and is responsible for the 'flushing syndrome'. Increased risks for oesophageal and upper digestive tract cancers have been found in relation to the presence of the ALDH*2 mutant in Japan (Yokoyama *et al.*, 1998). The relevance of ALDH2 metabolism in the epidemiology of oesophageal cancer in Africa is, however, unclear and the distribution of these mutants in African populations is unknown.

Conclusion

While the importance of both alcohol and tobacco in the development of oesophageal cancer in Africa (and other parts of the world) is clear, much needs to be done to measure the relative importance of different alcoholic drinks in different settings. Defining the content of these drinks is notoriously difficult and it is often unclear whether they should be defined according to their alcoholic content or to a range of potential contaminants. In addition, the 'recipes' for many of the alcoholic drinks vary from place to place, seasonally and over time, often depending upon which fruits or vegetables are available. This makes any precise measurement of exposure very problematic.

Smoking data appear to be reasonably well collected retrospectively, but data on diet and alcohol, especially usual quantities consumed in the past have not been uniformly collected, especially in Africa. In addition it is also often difficult to identify a role for dietary factors in studies that are based within populations that are typically poor and consuming a relatively homogeneous diet.

The Transkei has been consistently associated with high oesophageal incidence rates, and the risks appear to increase with increasing period of residence there, even after adjustment for smoking and alcohol consumption (albeit incomplete). This suggests the influence of an environmental factor, but it remains unclear which factors are responsible (low nutritional status, exposure to mycotoxins).

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4.14 Oral cavity and pharynx

Introduction

This chapter considers cancers of the oral cavity (ICD-10 codes C00–C06, including lip, tongue and mouth cancers), cancers of the pharynx, excluding nasopharynx (ICD-10 codes C09–C10 and C12–C14) and tumours of the salivary glands (ICD-10 codes C07–C08).

Cancers of this group were responsible for an estimated 390 000 new cases worldwide in 2000 (3.9% of the total). They are more common in men (70% of cases), in whom they account for 5.1% of new cancer cases, being the seventh most common form of cancer.

Cancers of the oral cavity, and those of the pharynx, are mainly squamous-cell carcinomas arising in the mucosa of the mouth (including cheek, lips and palate), gums, tongue and the oropharynx (including tonsil) and hypopharynx (including the pyriform fossa). There is a great deal of geographical variation in their incidence. High incidence rates are seen particularly in the Indian subcontinent and in Papua New Guinea (related to chewing of tobacco/betel, as described below). Rates are also high in some parts of western (France and Switzerland) and eastern (Hungary, Slovakia) Europe, where the important factors are tobacco and alcohol. The distributions of sites within the oral cavity and pharynx also differ considerably. Lip cancers are generally uncommon, except in white populations exposed to high levels of ultraviolet radiation, as in Australia; the lower lip is involved in some 80% of cases. In France, pharyngeal cancers predominate, while in most series from India, most cancers occur in the mouth (gum or floor of mouth).

Carcinomas of the salivary glands are relatively rare. They comprise less than 10% of cancers of the oral cavity and pharynx, and are mainly adenocarcinomas.

Precancerous lesions

Oral leukoplakia is defined as a white patch or plaque occurring on the oral mucosal surface that cannot be characterized clinically or pathologically as any other disease (WHO, 1978). Leukoplakias are considered to be precancerous lesions, since a proportion will progress to dysplasia, carcinoma *in situ* and invasive cancer. The overall risk of malignancy is some 1–5%, but varies with clinical subtype, with non-homogeneous leukoplakias, particularly nodular, being more prone to progression than homogeneous lesions. Oral erythroplakia refers to red patches on the mucosa, indicating epithelial atrophy and inflammation; these lesions are much rarer than leukoplakia, but have a much higher probability of malignant transformation (tenfold in some series). Oral submucous fibrosis has been more recently characterized and appears to be specifically linked to areca nut use. It manifests as mucosal rigidity and fibrous bands, with restricted mouth opening and tongue mobility; malignant transformation is common.

Descriptive epidemiology in Africa

In Africa, the frequency of cancers of the oral cavity and pharynx is rather lower than their worldwide frequency. The estimated 19 500 new cases in 2000 represent 3.1% of new cancers (3.9% in men, 2.4% in women). Worldwide, cancers of the pharynx (excluding nasopharynx) represent less than one third of such cancers, but they are apparently more rare in Africa, where they make up only 17% of the total.

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with data from Europe, North America and India for comparison. Table 2 shows incidence data from time periods in the 1960s and 1970s.

The incidence rates in Africa are generally lower than in the European and US populations in Table 1. For cancers of the oral cavity, the highest recorded incidence is in white males from Harare, Zimbabwe. Only 5 of the 19 cases upon which this rate is based were cancers of the lip. A high incidence is observed also in South African white males. In Reunion, only 2 of the 142 cancers in men were lip cancers, the remainder being equally divided between the oral cavity and pharynx, with the most common sites being mouth (30%), pyriform sinus (19%), tongue (17%) and tonsil (13%).

The data from the 1960s suggest that rates of oral cancer were lower in the Indian population of Natal province than in India, with a small excess in females (Table 2). The incidence of histologically diagnosed cancers from the South African National Registry (Table 1) suggests that the rates have remained moderate, and that the female predominance remains. Schonland and Bradshaw (1968) provided a commentary on the three South African series in Table 2. They noted that a relatively high proportion of oral–pharyngeal cancers in the white population of Cape Town were lip cancers (52.6% of male cases, 21.6% of female cases). There was a relatively high incidence of mouth cancers among Indian females in Durban. Altini and Kola (1985) estimated incidence rates of oral squamous cell cancers from pathology laboratory data in the Witwatersrand of South Africa for the period 1970–80. The age-standardized rates were 5.1 in men and 0.9 in women, with the most common sites involved being the tongue (51.4% cases) and floor of the mouth (32.7%).

Relative frequency data from pathology-based series frequently give the impression that oral cancers, in particular, are more common than the incidence data in Tables 1 and 2 suggest. Thus, the frequency of oral cancers in men in the series from Gabon was 10.5%, from Namibia 10.3% and from Swaziland 9.8%. These high frequencies probably relate, at least in part, to ease of biopsy. The same phenomenon can be observed in the frequency data in published series reported elsewhere in this volume. Nevertheless, the high frequency of oral cancers consistently reported in series from Sudan (see Chapter 3.1.5; Idris *et al.*, 1995a) is particularly noteworthy, in view of what is known of the prevalence of risk factors in the Sudanese population.

Most published data from Africa comprise descriptions of case series, from various clinical settings, such as those from Kenya (Onyango *et al.*, 1995 a, b) and Nigeria (Ogunbodede & Ugboko, 1997).

Migrant studies

Templeton and Viegas (1970) noted that oral cancer comprised a greater proportion of cancers in the population of Indian origin in Uganda, and recorded by the Kampala Cancer Registry (mainly histology-based) in 1959–68 (5.7%) than among the black (1.4%) or European (0.8%) populations, and ascribed this to chewing of betel nut. They noted, however, that the habit was much less frequent in this population than in India. Chopra *et al.* (1975) made equivalent observations in Kenya, where cancers of the tongue and mouth comprised 7% of cancers in Asian males and 2.4% in females, compared with 0.9% in African males and 1.7% in females. They noted that these frequencies were far below those in Indian data (from Baroda) and that chewing and bidi smoking are relatively uncommon in Kenyan Asians (perhaps due to their relatively high social status). Some data on Indian populations resident in South Africa are described below.

Risk factors

Tobacco is a major risk factor for cancers of the tongue, mouth and pharynx, whether smoked (IARC, 1986) or chewed (IARC, 1985).

Table 1a. Age-standardized (world) and cumulative (0-64) incidence
Mouth (C00-06)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	49	0.9	**1.3**	0.08	29	0.5	**0.7**	0.05
Algeria, Constantine (1994-1997)	21	1.4	**2.5**	0.16	9	0.6	**1.0**	0.04
Algeria, Oran (1996-1998)	26	1.5	**2.3**	0.14	10	0.6	**0.9**	0.07
Algeria, Setif (1993-1997)	46	1.5	**2.8**	0.14	16	0.5	**0.9**	0.05
Tunisia, Centre, Sousse (1993-1997)	31	2.7	**3.7**	0.19	8	0.7	**1.0**	0.08
Tunisia, North, Tunis (1994)	48	2.2	**2.8**	0.23	16	0.8	**1.0**	0.05
Tunisia, Sfax (1997)	13	3.3	**4.2**	0.26	2	0.5	**0.6**	0.06
Africa, West								
The Gambia (1997-1998)	4	0.4	**0.9**	0.07	7	0.7	**1.2**	0.07
Guinea, Conakry (1996-1999)	33	1.4	**2.9**	0.21	14	0.6	**1.3**	0.10
Mali, Bamako (1988-1997)	14	0.4	**0.8**	0.07	11	0.3	**0.6**	0.02
Niger, Niamey (1993-1999)	10	0.5	**1.8**	0.09	9	0.5	**0.8**	0.07
Nigeria, Ibadan (1998-1999)	9	0.6	**1.1**	0.05	2	0.1	**0.3**	0.02
Africa, Central								
Congo, Brazzaville (1996-1999)	9	0.7	**1.2**	0.10	13	1.1	**1.6**	0.12
Africa, East								
France, La Reunion (1988-1994)	205	9.8	**12.5**	1.00	17	0.8	**0.9**	0.06
Kenya, Eldoret (1998-2000)	16	1.7	**3.7**	0.31	5	0.5	**1.4**	0.11
Malawi, Blantyre (2000-2001)	4	0.4	**0.8**	0.08	7	0.8	**1.3**	0.13
Uganda, Kyadondo County (1993-1997)	23	0.8	**2.1**	0.14	16	0.6	**1.8**	0.11
Zimbabwe, Harare: African (1990-1993)	17	0.7	**1.7**	0.10	5	0.2	**1.0**	0.03
Zimbabwe, Harare: African (1994-1997)	23	0.8	**1.9**	0.10	10	0.4	**1.2**	0.03
Zimbabwe, Harare: European (1990-1997)	24	15.7	**9.4**	0.58	17	10.1	**5.4**	0.38
Africa, South								
Namibia (1995-1998)	265	8.3	**15.4**	0.97	130	4.1	**6.5**	0.42
South Africa: Black (1989-1992)	2545	4.5	**8.7**	0.58	598	1.1	**1.7**	0.11
South Africa: Indian (1989-1992)	65	3.3	**4.8**	0.38	83	4.2	**5.5**	0.45
South Africa: Mixed race (1989-1992)	449	7.0	**13.5**	0.87	143	2.1	**3.3**	0.22
South Africa: White (1989-1992)	1294	12.9	**11.8**	0.77	559	5.5	**4.3**	0.26
South Africa, Transkei, Umtata (1996-1998)	14	3.9	**7.9**	0.64	2	0.5	**0.6**	-
South Africa, Transkei, 4 districts (1996-1998)	11	1.5	**2.9**	0.25	2	0.2	**0.3**	0.02
Swaziland (1996-1999)	18	1.0	**2.2**	0.15	12	0.6	**1.2**	0.07
Europe/USA								
USA, SEER: White (1993-1997)	4309	8.9	**6.9**	0.43	2298	4.6	**2.9**	0.18
USA, SEER: Black (1993-1997)	476	7.1	**8.4**	0.67	206	2.8	**2.8**	0.20
France, 8 registries (1993-1997)	2348	17.1	**13.1**	1.01	468	3.2	**2.1**	0.14
The Netherlands (1993-1997)	2738	7.2	**5.3**	0.35	1518	3.9	**2.5**	0.17
UK, England (1993-1997)	5845	4.9	**3.4**	0.22	3550	2.8	**1.6**	0.09
India								
Ahmedabad (1993-1997)	1075	10.8	**15.9**	1.16	268	3.0	**4.6**	0.33
Mumbai (Bombay) (1993-1997)	2248	7.6	**11.7**	0.76	1048	4.3	**6.9**	0.45

In italics: histopathology-based registries

The association has been demonstrated in case–control and cohort studies in a variety of populations. Alcohol drinking is also an important risk factor (IARC, 1988), and acts multiplicatively with smoking with respect to cancers of both the oral cavity and pharynx. Differences in the prevalence and use of tobacco and alcohol are thought to explain the differences in incidence between men and women, and between blacks and whites in the USA (Day *et al.*, 1993). Diet may also be important in etiology, and diets low in fruit and vegetables have been found to increase risk, possibly due to low intake of micronutrients, especially vitamin C (WCRF, 1997). More recently, the role of human papillomaviruses has received attention, following detection of HPV DNA in tumour tissue (IARC, 1995).

Tobacco smoking/alcohol drinking

In a case–control study based upon cancer patients admitted to two hospitals in Johannesburg and Soweto, Pacella-Norman *et al.* (2002) compared 124 cases of oral cancer (87 men, 37 women) with control subjects (2174) with cancers not associated with tobacco or alcohol consumption. The odds ratio associated with heavy smoking in males (15+ g of tobacco per day) was 12.5 (95% CI 4.6–33.5) and in females, 6.2 (95% CI 0.9–44.2). Daily alcohol consumption, adjusted for smoking, was a not risk factor for the development of oral cancer in either sex.

Tobacco/betel chewing

The relatively high incidence of oral cancer, especially cancers of the tongue and mouth, among Indian females in Durban, Natal, has been noted above. Schonland and Bradshaw (1969) investigated chewing habits in a special survey of 500 households in Durban. They noted that the habit was more frequent in females (30.7%) than in males (5.5%), increased in prevalence with age, and decreased with level of educational attainment. The quid used in Durban rarely contained tobacco (7.8% male chewers, 2.8% females), comprising betel nut and/or leaf, usually with lime and flavouring. The authors considered that the habit was slowly dying out in this community.

Table 1b. Age-standardized (world) and cumulative (0-64) incidence
Salivary gland (C07-08)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	18	0.3	**0.4**	0.03	9	0.2	**0.2**	0.01
Algeria, Constantine (1994-1997)	2	0.1	**0.2**	0.02	2	0.1	**0.2**	0.00
Algeria, Oran (1996-1998)	3	0.2	**0.3**	-	5	0.3	**0.3**	0.02
Algeria, Setif (1993-1997)	7	0.2	**0.4**	0.01	8	0.3	**0.4**	0.04
Tunisia, Centre, Sousse (1993-1997)	3	0.3	**0.3**	0.01	4	0.4	**0.4**	0.01
Tunisia, North, Tunis (1994)	3	0.1	**0.2**	0.01	5	0.2	**0.3**	0.02
Tunisia, Sfax (1997)	1	0.3	**0.3**	0.02	-	-	-	-
Africa, West								
The Gambia (1997-1998)	2	0.2	**0.1**	0.01	2	0.2	-	-
Guinea, Conakry (1996-1999)	3	0.1	**0.2**	0.01	4	0.2	**0.3**	0.02
Mali, Bamako (1988-1997)	-	-	-	-	3	0.1	**0.2**	0.01
Niger, Niamey (1993-1999)	5	0.3	**0.7**	0.04	3	0.2	**0.3**	0.02
Nigeria, Ibadan (1998-1999)	5	0.3	**0.6**	0.06	4	0.3	**0.4**	0.04
Africa, Central								
Congo, Brazzaville (1996-1999)	5	0.4	**0.5**	0.05	5	0.4	**0.5**	0.04
Africa, East								
France, La Reunion (1988-1994)	8	0.4	**0.4**	0.03	5	0.2	**0.2**	0.03
Kenya, Eldoret (1998-2000)	3	0.3	**0.4**	0.03	3	0.3	**0.7**	0.04
Malawi, Blantyre (2000-2001)	2	0.2	**0.9**	0.11	-	-	-	-
Uganda, Kyadondo County (1993-1997)	4	0.1	**0.3**	0.01	9	0.3	**0.8**	0.07
Zimbabwe, Harare: African (1990-1993)	7	0.3	**0.7**	0.02	6	0.3	**0.5**	0.01
Zimbabwe, Harare: African (1994-1997)	13	0.5	**1.0**	0.07	14	0.5	**0.7**	0.04
Zimbabwe, Harare: European (1990-1997)	2	1.3	**0.7**	0.05	2	1.2	**0.8**	0.09
Africa, South								
Namibia (1995-1998)	18	0.6	**0.9**	0.07	16	0.5	**0.8**	0.06
South Africa: Black (1989-1992)	149	0.3	**0.4**	0.03	124	0.2	**0.3**	0.02
South Africa: Indian (1989-1992)	10	0.5	**0.8**	0.05	8	0.4	**0.5**	0.05
South Africa: Mixed race (1989-1992)	19	0.3	**0.5**	0.02	12	0.2	**0.3**	0.02
South Africa: White (1989-1992)	132	1.3	**1.2**	0.07	60	0.6	**0.5**	0.03
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	1	0.1	**0.3**	0.04	-	-	-	-
Swaziland (1996-1999)	2	0.1	**0.3**	0.03	4	0.2	**0.3**	0.02
Europe/USA								
USA, SEER: White (1993-1997)	679	1.4	**1.1**	0.06	538	1.1	**0.8**	0.05
USA, SEER: Black (1993-1997)	60	0.9	**1.0**	0.06	51	0.7	**0.6**	0.05
France, 8 registries (1993-1997)	138	1.0	**0.7**	0.04	112	0.8	**0.5**	0.03
The Netherlands (1993-1997)	294	0.8	**0.6**	0.03	231	0.6	**0.4**	0.03
UK, England (1993-1997)	1061	0.9	**0.6**	0.03	883	0.7	**0.4**	0.03
India								
Ahmedabad (1993-1997)	38	0.4	**0.6**	0.04	24	0.3	**0.4**	0.03
Mumbai (Bombay) (1993-1997)	100	0.3	**0.5**	0.03	59	0.2	**0.3**	0.02

In italics: histopathology-based registries

In a later study in Durban, Seedat and van Wyk (1988) investigated betel-nut chewing habits and the intake of chillies in the diet in 178 chewers and 124 hospital patients suffering from submucous fibrosis (SF). In the survey of chewers, 63 subjects were found to have features of impending or established SF. Those suffering from SF had practised the habit for a significantly *shorter* period than chewers without SF, and were significantly younger. A significantly larger proportion of this group preferred the boiled nut by itself and not as part of a betel quid (pan). No relationship was established between SF and the use of tobacco, lime or chillies.

van Wyk *et al.* (1993) studied 143 cases of oral squamous-cell carcinoma diagnosed in Indian patients in Natal in 1983–89. Information on smoking and chewing habits was obtained by interview of the patients (52%) or their relatives (29%) or from hospital records (18%). There were 89 women and 54 men. Squamous-cell carcinomas of the cheek (buccal mucosa, alveolar sulcus and gingiva) occurred most frequently, especially in women (64%), while in men tongue cancer predominated (41%). 93% of women (83/89) and 17% of men (9/54) habitually chewed the areca nut. Most female chewers used only the areca nut (53%), with 13% using betel quids, and 34% both. In contrast, most of the male cases (87%) were smokers, while only 7% of female cases smoked. The cases were compared with a group of "controls": Indian-origin subjects who had been interviewed during a community survey in 1983. From the data on distribution of female cases and "controls" by age stratum and areca nut chewing habit, one can estimate age-stratified (Mantel–Haenszel) odds ratios of 38.7 (95% CI 15.8–104.1) for areca nut alone, and 52.9 (95% CI 11.1–56.8) for areca nut with tobacco, versus no use.

Toombak

The sparse information on the cancer profile in Sudan suggests a relatively high frequency of oral cancer in data from the pathology-based Sudan Cancer Registry (SCR), and from the hospital-based registry in the Radiation and Isotope Centre, Khartoum (RICK) (see Chapter 3.1.5). Idris *et al.* (1995a) confirmed that the frequencies of oral neoplasms in 1970–85 were 12.6% from SCR

Table 1c. Age-standardized (world) and cumulative (0-64) incidence
Pharynx (excl. nasopharynx) (C09-10,C12-14)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	31	0.6	**0.8**	0.05	10	0.2	**0.2**	0.02
Algeria, Constantine (1994-1997)	7	0.5	**0.8**	0.06	1	0.1	**0.1**	0.02
Algeria, Oran (1996-1998)	15	0.8	**1.3**	0.10	6	0.3	**0.5**	0.04
Algeria, Setif (1993-1997)	58	1.9	**3.8**	0.30	9	0.3	**0.5**	0.04
Tunisia, Centre, Sousse (1993-1997)	6	0.5	**0.8**	0.06	2	0.2	**0.2**	0.02
Tunisia, North, Tunis (1994)	16	0.7	**0.9**	0.09	6	0.3	**0.3**	0.03
Tunisia, Sfax (1997)	4	1.0	**1.3**	0.09	4	1.1	**1.4**	0.06
Africa, West								
The Gambia (1997-1998)	-	-	-	-	-	-	-	-
Guinea, Conakry (1996-1999)	18	0.8	**1.6**	0.11	5	0.2	**0.3**	0.02
Mali, Bamako (1988-1997)	10	0.3	**0.5**	0.02	2	0.1	**0.1**	0.01
Niger, Niamey (1993-1999)	7	0.4	**0.9**	0.05	2	0.1	**0.2**	0.02
Nigeria, Ibadan (1998-1999)	3	0.2	**0.4**	0.05	1	0.1	**0.1**	-
Africa, Central								
Congo, Brazzaville (1996-1999)	13	1.1	**1.7**	0.13	5	0.4	**0.5**	0.04
Africa, East								
France, La Reunion (1988-1994)	228	10.9	**13.9**	1.16	16	0.7	**0.8**	0.08
Kenya, Eldoret (1998-2000)	5	0.5	**0.9**	0.05	-	-	-	-
Malawi, Blantyre (2000-2001)	-	-	-	-	-	-	-	-
Uganda, Kyadondo County (1993-1997)	17	0.6	**1.8**	0.16	6	0.2	**0.7**	0.08
Zimbabwe, Harare: African (1990-1993)	6	0.3	**0.8**	0.03	4	0.2	**0.9**	0.06
Zimbabwe, Harare: African (1994-1997)	15	0.5	**1.3**	0.11	2	0.1	**0.1**	0.01
Zimbabwe, Harare: European (1990-1997)	5	3.3	**1.8**	0.10	5	3.0	**1.6**	0.09
Africa, South								
Namibia (1995-1998)	74	2.3	**4.4**	0.28	26	0.8	**1.3**	0.10
South Africa: Black (1989-1992)	361	0.6	**1.2**	0.09	64	0.1	**0.2**	0.01
South Africa: Indian (1989-1992)	14	0.7	**1.2**	0.06	7	0.4	**0.4**	0.02
South Africa: Mixed race (1989-1992)	64	1.0	**1.8**	0.13	18	0.3	**0.4**	0.04
South Africa: White (1989-1992)	84	0.8	**0.8**	0.05	26	0.3	**0.2**	0.01
South Africa, Transkei, Umtata (1996-1998)	10	2.8	**4.6**	0.36	5	1.2	**1.8**	0.14
South Africa, Transkei, 4 districts (1996-1998)	2	0.3	**0.5**	0.04	-	-	-	-
Swaziland (1996-1999)	24	1.4	**3.0**	0.26	5	0.3	**0.4**	0.03
Europe/USA								
USA, SEER: White (1993-1997)	1982	4.1	**3.3**	0.23	715	1.4	**0.9**	0.06
USA, SEER: Black (1993-1997)	417	6.2	**7.4**	0.62	115	1.5	**1.6**	0.14
France, 8 registries (1993-1997)	4438	32.3	**24.4**	1.78	564	3.9	**2.5**	0.17
The Netherlands (1993-1997)	9549	25.0	**18.1**	0.92	2326	6.0	**3.7**	0.24
UK, England (1993-1997)	8499	7.1	**4.7**	0.27	3234	2.5	**1.4**	0.08
India								
Ahmedabad (1993-1997)	736	7.4	**12.1**	0.79	132	1.5	**2.1**	0.14
Mumbai (Bombay) (1993-1997)	1660	5.6	**9.7**	0.56	379	1.6	**2.5**	0.15

In italics: histopathology-based registries

Table 2. Incidence of cancer of the oral cavity in Africa, 1953–74

Registry	Period	Oral cavity		Salivary gland		Pharynx*		Source
		Male	Female	Male	Female	Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	2.1	2.0	*0.5*	*0.0*	*0.6*	0.0	4
Mozambique, Lourenço Marques	1956–60	*3.0*	*3.1*	*0.0*	*3.8*	*2.2*	*0.0*	1
Nigeria, Ibadan	1960–69	2.2	1.6	1.9	1.4	0.8	*0.4*	3
SA, Cape Province: Bantu	1956–59	*13.7*	–			*6.8*	*1.3*	2
SA, Cape Province: Coloured	1956–59	8.0	*0.9*			5.4	*0.2*	2
SA, Cape Province: White	1956–59	28.5	3.4			13.6	*0.8*	2
SA, Johannesburg, Bantu	1953–55	5.5	*1.1*	*0.3*	*0.8*	*0.1*	*0.0*	1
SA, Natal Province: African	1964–66	5.8	*1.5*	*0.8*	*0.8*	4.0	*0.2*	2
SA, Natal Province: Indian	1964–66	*6.7*	11.7	*0.7*	*0.4*	*1.0*	*2.1*	2
Uganda, Kyadondo	1954–60	–	*1.0*	*0.2*	*0.9*	*0.4*	*0.5*	1
Uganda, Kyadondo	1960–71	1.0	1.2	*0.1*	*0.1*	*0.6*	*0.4*	5
Zimbabwe, Bulawayo	1963–72	2.2	–	*0.6*	*0.2*	*1.3*	–	6

Italics: Rate based on less than 10 cases

* Excluding nasopharynx

and 8.1% from RICK. In the SCR series, squamous-cell carcinoma was the most common malignancy (66.5%), followed by tumours of the salivary gland (14.7%), neoplasms of non-epithelial origin (9.6%) and odontogenic neoplasms (8.6%). Men had a higher frequency than women. A large proportion of cases of squamous-cell carcinoma were among patients from northern Sudan. It was noted that 58% of subjects with squamous-cell cancers of the lip and mouth were users of 'toombak', compared with 11% of subjects with salivary or non-epithelial cancers. Toombak is a form of snuff prepared locally in pats of north, central and eastern Sudan from *Nicotiana rustica*, an indigenous tobacco species with high levels of nicotine and nornicotine. The finely ground tobacco leaves are mixed with sodium bicarbonate, water is added, and a paste is made. The resulting 'saffa' is placed in the oral vestibule where it remains for up to several hours. In general, a saffa is replaced 10–30 times per day. In a survey in Nile province, northern Sudan (Idris *et al.*, 1994), the toombak habit was found to be especially prevalent (> 45%) among males aged 40 years or older. Among women, toombak use is popular only in the older age groups, where up to 10% engage in the habit, while cigarette smoking is uncommon (< 1.5%).

Chemical analytical studies have shown that toombak contains at least 100-fold higher concentrations of tobacco-specific *N*-nitrosamines than Swedish commercial snuff and a US brand. These nitrosamines are by far the most powerful and most abundant carcinogens in snuff (Idris *et al.*, 1991). Mucosal lesions characterized by parakeratosis, pale surface staining of the epithelium and basal-cell hyperplasia, similar to those observed in Swedish snuff-dippers, are observed in long-term users, although epithelial dysplasia seems to be infrequent (Idris *et al.*, 1996).

Early studies suggested a link between use of toombak and oral cancers, and noted that the majority of tumours were at the site of contact with the tobacco or in adjacent areas (Elbeshir *et al.*, 1989). In a curious case–control study, Idris *et al.* (1995b) compared 375 cases with cancers of the lip and mouth with a group of 204 controls from the same hospital with non-epithelial oral and head and neck cancers, and salivary neoplasms, and 2840 "population controls" attending health education programmes in various parts of the country. Subjects were interviewed about their smoking habits and use of toombak. The groups were very different with respect to every variable measured—age, sex, tribe, region of residence, so an adjustment was made to the estimated odds ratios. Toombak use was associated with a significant increase in risk (OR ever/never 7.3; 95% CI 4.3–12.4) for hospital controls, 3.9 (95% CI 2.9–5.3) for population controls). The effect was entirely confined to long-term (> 10 years) users. Cigarette smoking did not increase risk of these cancers. When a different group of oral cancers (tongue, palate, maxillary sinus) was compared with the two control groups, there was no significant effect of either toombak or of cigarette smoking. The authors ascribed this to these sites not being in direct contact with the toombak quid during its use.

The squamous-cell tumours from toombak users appear to have a rather different profile of mutations in the p53 gene from those in non-users (Ibrahim *et al.*, 1999).

Oral leukoplakia, tobacco and alcohol

Macigo *et al.* (1995a) carried out a population survey for oral mucosal lesions in a rural population in Meru district, north-central Kenya. 48.6% of the population aged 15 years or more had some type of lesion; the prevalence of oral leukoplakia was 10.6%. This was significantly more frequent in males; 80/85 were homogeneous lesions and 67/85 were noted to be associated with tobacco use. Tobacco use in this population is predominantly a male habit, and takes the form of smoking of cigarettes or of kiraiku (hand-rolled traditionally processed tobacco). These observations prompted a case–control comparison of the 85 leukoplakia cases, who were matched with 141 controls form the same survey (by sex, age ± 3 years and neighbourhood) without oral lesions; both groups were interviewed about tobacco and alcohol habits. The OR associated with cigarette smoking (never/current) was 8.4 (95% CI 4.1–17.4) and with kiraiku smoking (never/current) was 10.0 (95% CI 2.9–43.4). The OR associated with smoking cigarettes alone was 4.5 (95% CI 1.9–10.8), smoking of both products (OR = 15.2) suggested probable synergy or additive effects. Commercial beer, wines and spirits were relatively weak, but statistically significant, risk factors. The independent effects of these various risk factors were not evaluated (Macigo *et al.*, 1995b). A further analysis (Macigo *et al.*, 1996) suggested a dose-dependent association between oral leukoplakia and the use of tobacco and alcohol, in which the number of cigarettes smoked, the quantity of beer consumed and the frequency of consumption were more important than the duration of use of these products.

Viruses

Van Rensburg *et al.* (1996) examined 146 fixed tissue blocks from South African cases of oral squamous-cell carcinoma for four types of human papillomavirus (HPV) (6,11,16,18) using a polymerase chain reaction (PCR)-based method. Only two cases were positive (one for HPV 11, one for HPV 16). In a different study (van Rensburg *et al.*, 1995), using the same materials, DNA of Epstein–Barr virus was found in 26% of tumours and in 42% of blocks from non-malignant, non-viral-associated lesions.

Other factors

Badawi *et al.* (1998) found higher levels of salivary nitrate, nitrite and the enzyme nitrate reductase in oral cancer patients than in healthy individuals in Egypt; this could simply reflect the presence of the tumour rather than an antecedent risk pattern.

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4.15 Cancer of the penis

Introduction

On a global basis, cancer of the penis is a rare cancer, accounting for less than 1% of cancers in men. In western countries, the age-standardized incidence is less than 1 per 100 000. Incidence rates greater than 1.5 per 100 000 are observed in cancer registries in India, south-east Asia (Thailand and Viet Nam), Latin America (Paraguay, Puerto Rico, Peru, Brazil) and the Caribbean (Martinique), as well as in sub-Saharan Africa. In India, the incidence in non-Muslims (Hindus, Buddhists) is significantly higher than reported in Muslims and Parsis (Muir & Nectoux, 1979). Incidence in Jewish populations is particularly low – 0.05 per 100 000 in the Jewish population of Israel in 1988–92, for example (Parkin *et al.*, 1997).

Descriptive epidemiology in Africa

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with comparison data from Europe and North America.

Table 2 shows incidence data from time periods in the 1960s and 1970s.

The incidence of cancer of the penis in Africa is generally not very high compared with that of liver, Kaposi sarcoma and cervical carcinoma, but there is considerable variation between countries. From Tables 1 and 2, it is clear that the incidence is low in northern and western Africa and considerably higher in eastern and southern Africa. Frequency data in this volume show relatively high percentages of penile cancers in Swaziland (4.4% of all male cancers, 1990–95) and Rwanda (2.9% of male cancers in 1991–93). The highest recently recorded incidence is in Uganda with an estimated rate from Kampala Cancer Registry for Kyadondo county of 4.1 per 100 000. The incidence reported by this registry in the 1990s is lower than that in the 1960s (Figure 1).

In addition to the international variation of incidence, there is considerable variation within countries, regionally, and by ethnic group. This has been widely discussed within the context of the etiological importance of circumcision (see below).

Risk factors

The importance of circumcision in determining the risk of penile cancer has been evident for many years on the basis of the clinical observation that it occurs very rarely in men who have been circumcised at birth. The observation has been confirmed in case–control studies in the United States, which suggest that the risk is reduced about threefold (Maden *et al.*, 1993; Tseng *et al.*, 2001). Phimosis is also clearly an important risk factor; a large proportion of cases (in western countries) are preceded by a history of phimosis, and the association has been confirmed in several case–control studies (Widerhoff & Schottenfeld, 1996).

The mechanisms underlying these findings have been a subject of much debate. Originally, it was thought that exposure to chemical carcinogens in smegma were important, and that the adverse consequences of possession of a foreskin, and of phimosis, could be countered by penile hygiene. More recently, it has been suggested that the prepuce could predispose to sexually transmitted infections, by permitting accumulation of infected vaginal secretions, or by simply providing an increased surface of non-keratinized epithelium. Studies in Kenya have shown that lack of circumcision predisposes to infection with HIV (Cameron *et al.*, 1989). The role of infectious agents has been suspected for many years, based upon the frequent history of sexually transmitted diseases, including genital warts, in cases of penile cancer. The concordance of cancer of cervix and cancer of the penis in married couples suggested a possible common etiology. This link has since been refined by detection of HPV DNA in about 40–50% of all penile cancers and by cross-sectional and prospective serological studies that have confirmed the role of, especially, HPV 16 and 18 (Dillner *et al.*, 2000).

Studies in Africa

The clinical observations with respect to the protective effect of circumcision resulted in many ecological studies comparing risk of penis cancer and prevalence of circumcision in different populations. Africa was a particularly fruitful location for this type of study.

Dodge *et al.* (1973), in an analysis of histopathology data for the whole of Uganda for the period 1964–68, found penile cancer to be the commonest tumour in males, accounting for 12% of the total. However the frequency of penile cancer as a percentage of all cancers in the series varied in different ethnic groups. As already reported by Schmauz and Jain (1971), the frequency was highest among the Banyoro, Toro and Iteso, while lowest rates were reported among the Gishu, Bakonjo Lugbara and Kiga. Similar observations had been made by Hutt and Burkitt (1965), who showed that cancer of the penis accounted for 17% and 20% of all malignant tumours in Teso and Bunyoro, respectively, whereas in Lango and West Nile/Madi the figures were only 1.4% and 0.0%, respectively.

The low frequency of penile cancer among the Gishu and Bakonjo has been ascribed to the circumcision carried out on young adults as a cultural practice (Dodge & Kaviti, 1965). However, there was clearly some variability in frequency between tribes which do not practice circumcision (Schmauz & Jain, 1971). Kyalwazi (1966) had earlier reported that genital cleansing may be responsible for the variation of frequency of this tumour among those ethnic groups which do not practice circumcision.

A recent study of cancer patterns in Mbarara, western Uganda, found that penile cancer accounted for 17% of male cancer and this was thought to be due to the rural setting with perhaps lack of hygiene; circumcision is not practiced by the majority of males in this area (Wabinga, 2002).

Dodge and Linsell (1963) examined the records of the Medical Research Laboratory, Nairobi, for the period 1957–61. There were 27 penile cancers diagnosed, 1.9% of cancers in men. The Kikuyu, the largest tribal group, who practise circumcision, contributed only one case, but the frequency was much higher among the Luo and Turkan ethnic groups, who do not practice circumcision (Dodge & Kaviti 1965). In the recent results from the new population-based cancer registry in Eldoret, western Kenya, there was no case of penile cancer in a series of 254 cancer cases (see Chapter 3.4.6).

In Tanzania also, the prevalence of penile cancer is very low in ethnic groups which culturally practice circumcision—mainly the Masai in the north-eastern part of Tanzania and those in the coastal area, with a cultural influence from the Arabs (Dodge & Kaviti, 1965). Zanzibar and Pemba Islands, which were predominantly Islamic, recorded a low frequency of penile cancer. In northern Tanzania, records from Shirati Hospital indicate that penile cancer was more common in the Luo ethnic group and low in the Bantu ethnic groups in that region; all the Bantu ethnic groups in this region practise circumcision, unlike the Luo (Eshleman, 1960).

Prates and Torres (1965) reported a low frequency of penile cancer in their survey in Lourenço Marques, Mozambique; it accounted for only 0.8% of all tumours in this population. They also observed that the

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Penis (C60)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	-	-	-	-	-	-	-	-
Algeria, Constantine (1994-1997)	-	-	-	-	-	-	-	-
Algeria, Oran (1996-1998)	-	-	-	-	-	-	-	-
Algeria, Setif (1993-1997)	1	0.0	**0.1**	-	-	-	-	-
Tunisia, Centre, Sousse (1993-1997)	1	0.1	**0.1**	-	-	-	-	-
Tunisia, North, Tunis (1994)	1	0.0	**0.1**	0.01	-	-	-	-
Tunisia, Sfax (1997)	-	-	-	-	-	-	-	-
Africa, West								
The Gambia (1997-1998)	4	0.4	**0.7**	0.04	-	-	-	-
Guinea, Conakry (1996-1999)	-	-	-	-	-	-	-	-
Mali, Bamako (1988-1997)	3	0.1	**0.2**	0.01	-	-	-	-
Niger, Niamey (1993-1999)	-	-	-	-	-	-	-	-
Nigeria, Ibadan (1998-1999)	-	-	-	-	-	-	-	-
Africa, Central								
Congo, Brazzaville (1996-1999)	-	-	-	-	-	-	-	-
Africa, East								
France, La Reunion (1988-1994)	14	0.7	**0.9**	0.05	-	-	-	-
Kenya, Eldoret (1998-2000)	2	0.2	**0.7**	0.05	-	-	-	-
Malawi, Blantyre (2000-2001)	4	0.4	**0.3**	0.02	-	-	-	-
Uganda, Kyadondo County (1993-1997)	34	1.2	**4.1**	0.12	-	-	-	-
Zimbabwe, Harare: African (1990-1993)	17	0.7	**2.3**	0.10	-	-	-	-
Zimbabwe, Harare: African (1994-1997)	17	0.6	**1.6**	0.07	-	-	-	-
Zimbabwe, Harare: European (1990-1997)	1	0.7	**0.3**	-	-	-	-	-
Africa, South								
Namibia (1995-1998)	14	0.4	**0.8**	0.06	-	-	-	-
South Africa: Black (1989-1992)	404	0.7	**1.3**	0.08	-	-	-	-
South Africa: Indian (1989-1992)	23	1.2	**2.1**	0.09	-	-	-	-
South Africa: Mixed race (1989-1992)	43	0.7	**1.2**	0.07	-	-	-	-
South Africa: White (1989-1992)	75	0.7	**0.7**	0.04	-	-	-	-
South Africa, Transkei, Umtata (1996-1998)	1	0.3	**0.7**	0.07	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	-	-	-	-
Swaziland (1996-1999)	31	1.8	**3.2**	0.22	-	-	-	-
Europe/USA								
USA, SEER: White (1993-1997)	307	0.6	**0.5**	0.02	-	-	-	-
USA, SEER: Black (1993-1997)	39	0.6	**0.6**	0.03	-	-	-	-
France, 8 registries (1993-1997)	145	1.1	**0.7**	0.03	-	-	-	-
The Netherlands (1993-1997)	378	1.0	**0.7**	0.03	-	-	-	-
UK, England (1993-1997)	1487	1.2	**0.8**	0.05	-	-	-	-

In italics: histopathology-based registries

Table 2. Incidence of penis cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)	Source
		Male	(see Chap. 1)
Senegal, Dakar	1969–74	*0.4*	4
Mozambique, Lourenço Marques	1956–60	2.7	1
Nigeria, Ibadan	1960–69	*0.2*	3
SA, Cape Province: Bantu	1956–59	4.6	2
SA, Cape Province: Coloured	1956–59	2.5	2
SA, Cape Province: White	1956–59	0.8	2
SA, Johannesburg, Bantu	1953–55	1.5	1
SA, Natal Province: African	1964–66	6.9	2
SA, Natal Province: Indian	1964–66	*2.8*	2
Uganda, Kyadondo	1954–60	–	1
Uganda, Kyadondo	1967–71	5.9	5
Zimbabwe, Bulawayo	1963–72	5.9	6

Italics: Rate based on less than 10 cases

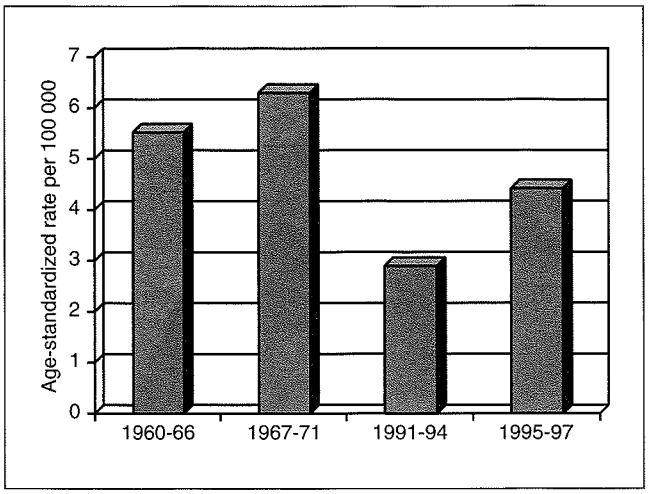

Figure 1. Trends in incidence of penile cancer, Kampala Uganda (Wabinga *et al*, 2000)

frequency of circumcision in their penile cancer cases (20%) was the same as in patents with cancer at other sites (26%), and noted that the lack of effect may be ascribed to circumcision being performed relatively late, generally in adulthood.

In South Africa, penile cancer is less prevalent in the Zulu community, who also practice circumcision (Krige, 1936), than in the Bantu of Natal province who do not circumcise, and in whom the frequency of penile cancer is relatively high (8%) (Wainwright & Roach, 1957).

As noted above, penile cancer is rare in West Africa. Edington and MacLean (1965) reported only one cases in a period of three years among residents of Ibadan, western Nigeria (0.3%) and Gueye *et al.* (1992) found it to comprise less than 1% of cancers in men in their series from Senegal. In these areas, circumcision is routinely practised.

The association of penile cancer with an infective agent was supported by the observations of Schmauz and Owor (1984), who demonstrated a relationship between cervical cancer and penile cancer in the 18 districts of Uganda, and also between condylomata acuminata and penile cancer. HPV DNA has been isolated from a high proportion of specimens of penile cancers from Uganda (Durst *et al.*, 1983; Tornesello *et al.*, 1992), and a HPV variant (Af1-u) has been particularly implicated (Buonaguro *et al.*, 2000).

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4.16 Prostate cancer

Introduction

On a global basis, prostate cancer is the third most common cancer of men, with an estimated 543 000 new cases diagnosed each year (about 10.2% of all new cancers in men). More than 74% of these occur in the populations in Europe and North America. In Africa, there were an estimated 27 400 new cases in 2000 (9.1% of cancers in men).

Incidence rates are now influenced by the diagnosis of latent cancers both by screening of asymptomatic individuals and by detection of latent cancer in tissue removed during prostatectomy operations or at autopsy. Thus, especially where screening examinations are prevalent, recorded 'incidence' may be very high (in the United States, for example, where this is now by far the most commonly diagnosed cancer in men). The distribution of mortality rates is less affected by the effects of early diagnosis of asymptomatic cancers.

More than any other, this is a cancer of the elderly. About three quarters of cases worldwide occur in men aged 65 years or more.

Descriptive epidemiology in Africa

Comparability of statistics on the incidence of prostate cancer between populations is hampered by different practices concerning biopsy of lesions, the extent of histological examination of biopsy material and the use of prostate-specific antigen (PSA) testing for diagnosis. The problems introduced in the use of incidence data when latent cancers discovered through PSA screening are included in cancer registry data are likely to be rather minimal in most of Africa, where an incident case almost always implies a clinically evident, frankly invasive, relatively advanced tumour.

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with data from Europe and North America for comparison. Table 2 shows incidence data from time periods in the 1960s and 1970s.

Figure 1 shows estimated incidence rates by country, based on these data and other information reported in this volume.

It is clear that incidence is moderately high in many of the countries of sub-Saharan Africa, and it is difficult to be sure whether the regional variations seen in Table 1 and Figure 1 are real or simply reflect awareness of the disease and diagnostic capabilities. Rates appear to be higher in urban populations than in rural settings. Thus, current incidence rates are highest in cities such as Abidjan (Côte d'Ivoire) and Harare (Zimbabwe). It also seems that incidence rates in the more recent registry series are higher than those reported in the past. In contrast, incidence rates appear to be low in all of the countries of North Africa.

Dodge *et al.* (1973) noted that there was little evidence for any significant difference in incidence of prostate cancer between the different tribal groups in Uganda, with frequency of recording paralleling the frequency of cancer diagnoses overall.

The relatively high incidence (and mortality) recorded in African populations is reflected in populations of African descent elsewhere. Thus, within the United States, the black population has the highest incidence (and mortality) rates, some 72% higher than in whites (Table 1), who in turn have rates considerably higher than populations of Asian origin (e.g., Chinese, Japanese and Korean males). In the islands of the Caribbean, largely populated by descendants of persons from West Africa, mortality rates are some of the highest in the world (ASR 55.3 per 100 000 in Barbados, 33.3 in the Bahamas, and 32.3 in Trinidad, for example). In São Paulo, Brazil, the risk of prostate cancer in black males was 1.8 (95% CI 1.4–2.3) times that of white men, with an intermediate risk (1.4) among men of mixed race ('mulatto') (Bouchardy *et al.*, 1991).

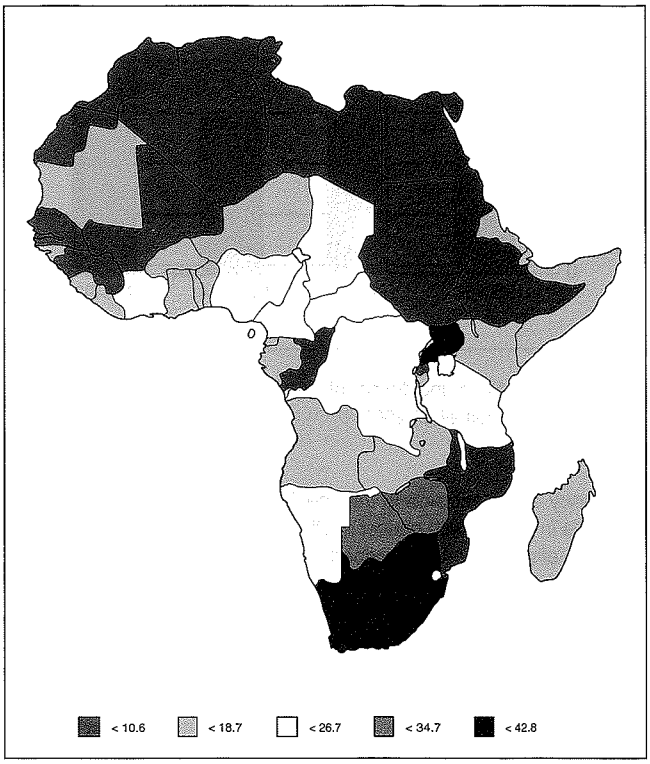

Figure 1. Incidence of prostate cancer: ASR (world)

In the recent African series reported in Table 1, incidence rates were higher in white populations than in black. This probably represents their more ready access to modern diagnostic and treatment methods, as well as testing for PSA (Bassett *et al.*, 1995). It is notable that in the old data (1956–59) from the registry in Cape Province, South Africa, the incidence in blacks was double that in whites (Table 2).

Migrants from West Africa to England & Wales have mortality rates 3.5 times (95% CI 2.4–5.1) those of the local-born population, and mortality is significantly higher also among migrants from the Caribbean (RR 1.7; 95% CI 1.5–2.0); in contrast, mortality among migrants from East Africa, of predominantly Asian (Indian) ethnicity, are not high (Grulich *et al.*, 1992). The risk of prostate cancer mortality among migrants from sub-Saharan Africa to France was not, however, significantly different from that of the local-born population (Bouchardy *et al.*, 1995). Migrants to France from North Africa (Morocco, Algeria, Tunisia) had significantly lower mortality rates (OR 0.7–0.8), in keeping with the low rates of prostate cancer in their countries of origin (Bouchardy *et al.*, 1996).

Many elderly men are found to harbour latent cancers in their prostate, the prevalence of which greatly exceeds the cumulative incidence in the same population. Two international studies have looked at prevalence of latent prostate cancer at autopsy in different populations. Breslow *et al.* (1977) studied seven populations, two of them (Uganda and Jamaica) black. Prevalence of latent cancer increased steeply with age; allowing for this factor, it was highest in Sweden, Jamaica and Germany (28–32%), with Uganda in the middle of the range (20%), significantly above the Asian populations of Hong Kong and Singapore (13–16%). Drury and Owor (1981) reported separately on the 150 Ugandan cases in this study; prevalence increased from 12% at ages 45–54 years to 36% at ages 65 years and over. Yatani *et al.* (1982) found the highest

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Prostate (C61)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	194	3.5	**5.4**	0.18	-	-	-	-
Algeria, Constantine (1994-1997)	46	3.0	**5.8**	0.15	-	-	-	-
Algeria, Oran (1996-1998)	74	4.2	**7.2**	0.20	-	-	-	-
Algeria, Setif (1993-1997)	71	2.4	**4.3**	0.16	-	-	-	-
Tunisia, Centre, Sousse (1993-1997)	79	6.8	**9.3**	0.11	-	-	-	-
Tunisia, North, Tunis (1994)	132	6.1	**7.9**	0.18	-	-	-	-
Tunisia, Sfax (1997)	41	10.4	**12.4**	0.22	-	-	-	-
Africa, West								
The Gambia (1997-1998)	20	2.0	**4.7**	0.10	-	-	-	-
Guinea, Conakry (1996-1999)	62	2.7	**9.7**	0.46	-	-	-	-
Mali, Bamako (1988-1997)	73	1.9	**5.7**	0.22	-	-	-	-
Niger, Niamey (1993-1999)	41	2.2	**10.8**	0.33	-	-	-	-
Nigeria, Ibadan (1998-1999)	115	7.7	**19.8**	0.84	-	-	-	-
Africa, Central								
Congo, Brazzaville (1996-1999)	45	3.7	**6.4**	0.36	-	-	-	-
Africa, East								
France, La Reunion (1988-1994)	353	16.8	**24.5**	0.50	-	-	-	-
Kenya, Eldoret (1998-2000)	54	5.8	**16.8**	0.77	-	-	-	-
Malawi, Blantyre (2000-2001)	30	3.3	**10.7**	0.57	-	-	-	-
Uganda, Kyadondo County (1993-1997)	215	7.6	**38.6**	1.19	-	-	-	-
Zimbabwe, Harare: African (1990-1993)	161	6.8	**26.9**	0.88	-	-	-	-
Zimbabwe, Harare: African (1994-1997)	209	7.5	**28.5**	0.78	-	-	-	-
Zimbabwe, Harare: European (1990-1997)	210	137.4	**70.1**	1.99	-	-	-	-
Africa, South								
Namibia (1995-1998)	352	11.1	**21.8**	0.87	-	-	-	-
South Africa: Black (1989-1992)	3432	6.0	**14.3**	0.44	-	-	-	-
South Africa: Indian (1989-1992)	121	6.2	**13.0**	0.31	-	-	-	-
South Africa: Mixed race (1989-1992)	681	10.6	**25.4**	0.67	-	-	-	-
South Africa: White (1989-1992)	4455	44.3	**41.1**	1.33	-	-	-	-
South Africa, Transkei, Umtata (1996-1998)	11	3.1	**3.7**	-	-	-	-	-
South Africa, Transkei, 4 districts (1996-1998)	12	1.7	**2.9**	0.15	-	-	-	-
Swaziland (1996-1999)	153	8.7	**21.5**	1.07	-	-	-	-
Europe/USA								
USA, SEER: White (1993-1997)	71146	146.1	**108.7**	4.74	-	-	-	-
USA, SEER: Black (1993-1997)	10337	154.4	**185.7**	9.12	-	-	-	-
France, 8 registries (1993-1997)	12274	89.3	**57.6**	1.61	-	-	-	-
The Netherlands (1993-1997)	31479	82.4	**56.6**	1.48	-	-	-	-
UK, England (1993-1997)	89532	74.6	**42.8**	0.99	-	-	-	-

In italics: histopathology-based registries

Table 2. Incidence of prostate cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)	Source
		Male	(see Chap. 1)
Senegal, Dakar	1969–74	4.3	4
Mozambique, Lourenço Marques	1956–60	9.2	1
Nigeria, Ibadan	1960–69	9.7	3
SA, Cape Province: Bantu	1956–59	20.2	2
SA, Cape Province: Coloured	1956–59	18.5	2
SA, Cape Province: White	1956–59	10.9	2
SA, Johannesburg, Bantu	1953–55	9.4	1
SA, Natal Province: African	1964–66	23.2	2
SA, Natal Province: Indian	1964–66	9.4	2
Uganda, Kyadondo	1954–60	4.4	1
Uganda, Kyadondo	1960–71	4.5	5
Zimbabwe, Bulawayo	1963–72	21.9	6

Italics: Rate based on less than 10 cases

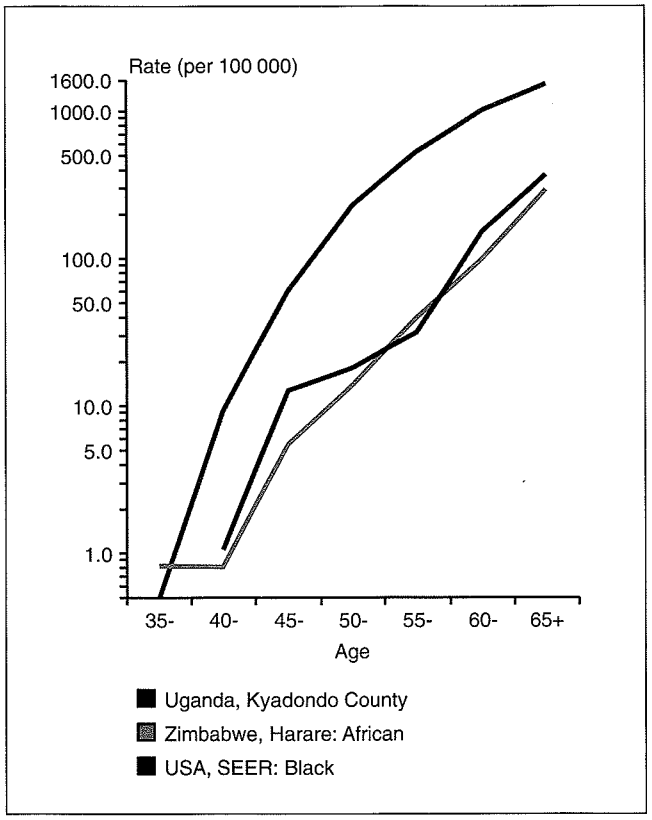

Figure 2. Age-specific incidence of prostate cancer

prevalence in US blacks (23.5%), and the differences between populations (US whites, Colombia, Japanese) were largely due to variations in prevalence of the infiltrative type of latent cancer.

The risk of prostate cancer increases very steeply with age, at approximately the 9th–10th power of age, compared with the 5th–6th power for other epithelial cancers (Cook *et al.*, 1969). The young age structure of African populations means that the average age at diagnosis of cases in Africa is lower than in European and American populations. This is often remarked upon in clinical series from Africa (e.g., Jackson et al, 1977; Udeh, 1981), although the curves of incidence versus age are very similar to those observed elsewhere. Figure 2 shows age-specific incidence rates from two of the registry series in this volume (Kampala, Uganda, and Harare, Zimbabwe) in comparison with the black population covered by the SEER program of the United States.

Stage at presentation of tumours in Africa is generally very advanced (Jackson *et al.*, 1977; Kehinde, 1995), with correspondingly poor prognosis.

Time trends

In almost all developing countries with relatively low rates of prostate cancer incidence, the risk appears to be increasing (Hsing *et al.*, 2000). There are very few data from Africa. In South Africa, Bradshaw and Harington (1985) observed that mortality rates in the white population were not rising very rapidly in the period 1949–79, although the rates the 'coloured' population approximately doubled during the period, so that, by the mid-1970s, mortality was similar to that in whites; the rates in the black population were, of course, considerably underestimated. In cancer registry data, rates appear to be rather higher in more recent data than in older series. In Ibadan, Nigeria, incidence in 1998–99 was 19.8 per 100 000, compared with 9.7 per 100 000 in 1960–69 (Table 2), and Ogunbiyi and Shittu (1999) noted the increase in frequency of prostate cancer in the same registry, where it increased from 4.5% cancers in men (aged > 17 years) in the 1960s to become, with 11% of the total, the most common cancer of men in the 1990s. In Kampala, Uganda, there has been a significant increase in incidence since the 1960s (Figure 3) (Wabinga *et al.*, 2000). This observed increase is certainly not due to screening but may be due to increased awareness and greater readiness to perform prostatectomy for urinary symptoms in elderly men.

Mortality rates in Mauritius have also been increasing since the 1960s (Figure 4).

Risk factors

Despite extensive research, the environmental risk factors for prostate cancer are not well understood, although the fact that they do play a role is shown by the changes of risk observed in many migrant populations and their offspring. Evidence from ecological, case–control and cohort studies implicates dietary fat in the etiology of prostate cancer, although few studies have adjusted the results for caloric intake, and no particular fat component has been consistently implicated. There is a strong positive association with intake of animal products, especially red meat. The evidence from these studies for a protective effect of fruits and vegetables on prostate cancer is, unlike many other cancer sites, not convincing. There is little evidence for anthropometric associations with prostate cancer, or for a link with obesity (Kolonel, 1996; WCRF, 1997).

Walker *et al.* (1992) studied 166 cases of mainly advanced prostate cancer and 166 neighbourhood controls from Soweto, South Africa, using a questionnaire that included a 24-hour dietary recall. They observed a positive association of risk with high fat consumption (≥ 25% energy) and high intake of meat and eggs (≥ 5 times per week), and a reduced risk in high consumers of vegetables (carrots). These were noted to be features of a western-style diet, consumed by persons taking regular meals away from home, in canteens, or while in domestic service, so that this variable (outside meals > 10 years) emerged as the strongest risk factor (OR 3.2, 95% CI 2.0–5.1). No association was seen with anthropometry, education, social class, smoking or alcohol drinking.

Platz *et al.* (2000), in a cohort study of health professionals in the United States, found that differences in the distribution of possible dietary and lifestyle risk factors did not explain the higher risk (RR 1.81) of prostate cancer in blacks versus whites. Genetic factors appear therefore to play a major role in explaining the observed racial differences, and findings of elevated risk in men with a family history of the disease support this. Steinberg *et al.* (1990) demonstrated a 5–11-fold increased risk among men with two or more affected first-degree relatives. A similar study involving a population-based case–control study of prostate cancer among blacks, whites and Asians in the United States and Canada found the prevalence of positive family histories somewhat lower among the Asian Americans than among blacks or whites (Whittemore *et al.*, 1995).

It is clear that male sex hormones play an important role in the development and growth of prostate cancers. Testosterone diffuses into the gland, where it is converted by the enzyme steroid 5-alpha reductase type II (SRD5A2) to the more metabolically active form dihydrotestosterone (DHT). DHT and testosterone bind to the androgen receptor (AR), and the receptor/ligand complex translocates to the nucleus for DNA binding and transactivation of genes which have androgen-responsive elements, including those controlling cell division. Much research has concentrated on the role of polymorphisms of the genes regulating this process and how inter-ethnic variations in such polymorphisms might explain the higher risk of prostate cancer in men of African descent (Ross *et al.*, 1998). Polymorphisms in the *SRD5A2* genes may provide at least part of the explanation (Shibata & Whittemore, 1997), but more interest is focused on the *AR* gene, located on the long arm of chromosome X. The *AR* gene contains a highly polymorphic region of CAG repeats in exon 1, the normal range being 6–39 repeats. Several studies suggest that men with a lower number of AR CAG repeat lengths are at higher risk of prostate cancer (Chan *et al.*,

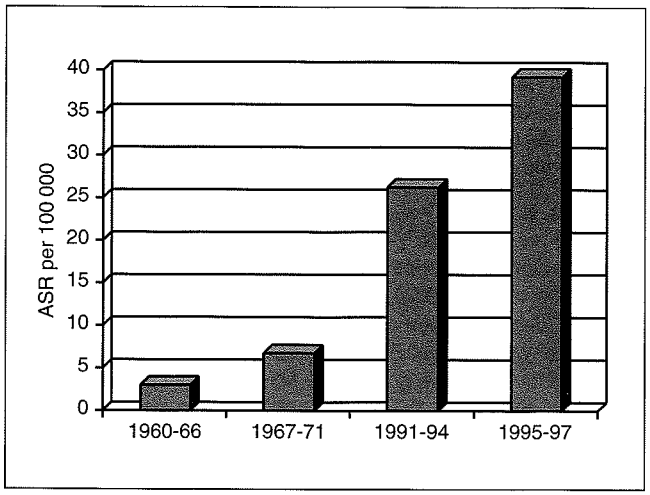

Figure 3. Trends in incidence of prostate cancer, Kampala, Uganda (Wabinga *et al.*, 2000)

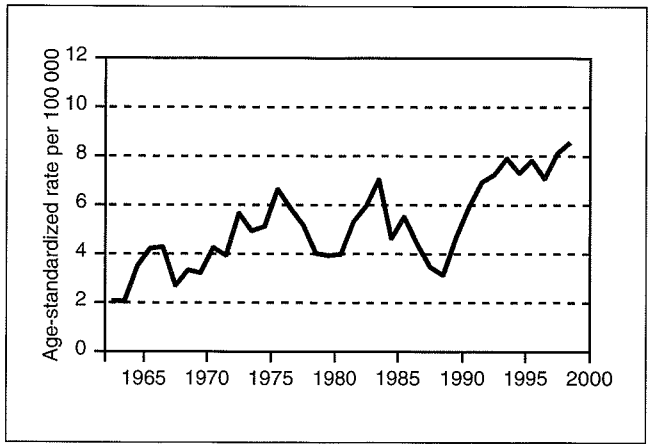

Figure 4. Mauritius: Prostate cancer mortality 1964–1998 (3-year moving average)

1998). Blacks in the United States have fewer CAG repeats than whites, which has been postulated to partly explain their susceptibility to prostate cancer (Ross *et al.*, 1998; Platz *et al.*, 2000). Other genetic mechanisms possibly related to prostate cancer risk are polymorphisms in the vitamin D receptor gene (Ingles *et al.*, 1997, 1998) or in the insulin-like growth factor (IGF) signalling pathway (Chan *et al.*, 1998b), but there is no evidence for significant inter-ethnic differences in these systems.

There have been no studies of these aspects of prostate cancer etiology in African populations.

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4.17 Skin cancer (non-melanoma)

Introduction

The incidence of non-melanoma skin cancer (NMSC) is difficult to assess. These cancers are very common but rarely fatal, and completeness of registration varies widely depending on access to out-patient records and general practitioners. Some cancer registries record basal-cell carcinomas (BCC) only, others register squamous-cell (SCC) only, and many do not collect data on either form. It has been estimated that 2.75 million new cases are diagnosed annually worldwide (Armstrong & Kricker, 1995). Some 75% are of basal-cell origin and around 25% squamous-cell (Strom & Yamamura, 1997). Other skin cancers are rare.

BCCs are generally found on the head and neck, and although they grow slowly and metastasize very rarely, can result in large (maignant-type) ulcers if neglected. SCCs can occur on any part of the body and are more frequent on the back of the hand and on the legs (particularly in Africa). In a large case series from the Sudan, 73.0% of BCC occurred on the head and neck, compared with 40% of SCC (Malik *et al.*, 1974).

NMSC increases in frequency with increasing proximity to the equator (IARC, 1992), and white-skinned populations exposed to UV radiation are particularly at risk. Susceptibility to skin cancer is inversely related to degree of melanin pigmentation. The highest rates ever reported are those from the European population of Harare, Zimbabwe, in this volume, with a standardized incidence per 100 000 of 635.3 in males and 363.3 in females (Figure 1). The lowest incidence is found in China and India, where standardized rates are generally less than 2.

Descriptive epidemiology in Africa

In Africa, incidence rates are low, except in white populations and in areas where there is a high proportion of non-black residents. Incidence is higher in lighter-skinned North Africans than in sub-Saharan Africa. Table 1 presents the incidence data from registries in this volume, with European data for comparison. Earlier data are presented in Table 2.

Histological type

While worldwide, the frequency of BCC is much higher than that of SCC, the majority of malignant epithelial tumours in the black populations of sub-Saharan Africa are SCC (Hutt, 1991), an observation confirmed in numerous studies. The distribution of NMSC by histological type in the series from cancer registries reported in this volume is shown in Table 3. BCC is generally elevated in North Africa and in sub-Saharan populations where there are a high proportion of whites. Elsewhere SCC is predominant.

A pathology series of 24 900 specimens in Mashonaland (then in Southern Rhodesia, now Zimbabwe) yielded 4124 malignant tumours in Africans for the ten-year period from October 1955. 75.9% of skin tumours were SCC, 5.5% BCC, 0.4% sebaceous epithelioma, 0.1% sweat gland carcinoma and 17.9% melanoma. In the European population, 34.4% of skin cancers were SCC and 56.7% BCC, a ratio very different to that of the African population (Ross, 1967).

Between 1969 and 1978, SCC accounted for 59% of NMSC diagnoses reported to the pathology-based Tanzanian Cancer Registry, while only 5% were BCC. The corresponding percentages in US Blacks were 39% and 35%. In the period 1978–88, SCC still accounted for 59% of total skin malignancies (including Kaposi sarcoma and melanoma) (Amir *et al.*, 1992a).

Munyao and Othieno-Abinya (1999), using data collected in 1968–97 by the pathology-based Kenya Cancer Registry, estimated that the incidence of BCC in Africans was almost one hundred times less than that in Caucasians.

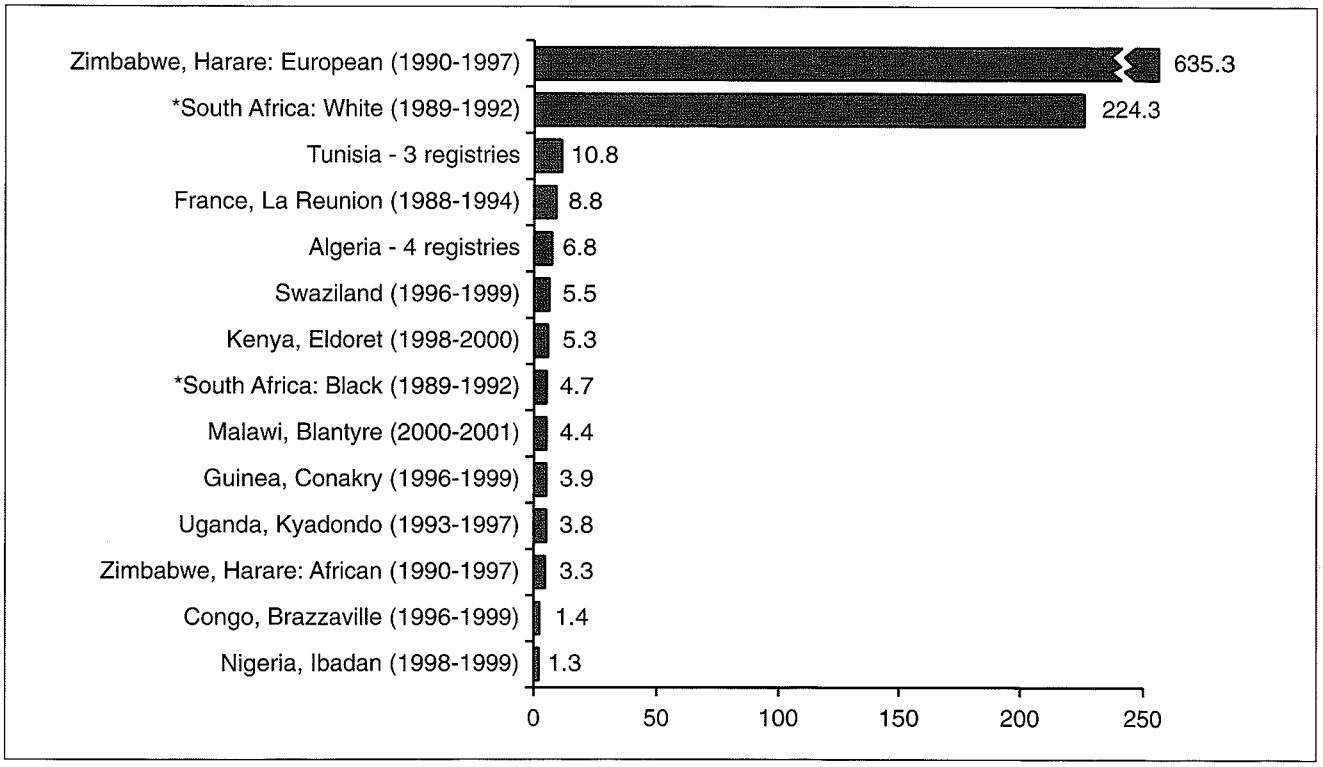

Figure 1. Age-standardized incidence rates (per 100 000) of non-melanoma skin cancer in Africa, male (all ages)

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Other skin (C44)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	292	5.3	**7.8**	0.44	142	2.6	**3.5**	0.17
Algeria, Constantine (1994-1997)	27	1.7	**3.2**	0.15	15	1.0	**1.5**	0.10
Algeria, Oran (1996-1998)	130	7.3	**11.7**	0.53	89	5.1	**7.1**	0.41
Algeria, Setif (1993-1997)	55	1.8	**3.0**	0.17	24	0.8	**1.3**	0.07
Tunisia, Centre, Sousse (1993-1997)	109	9.4	**12.4**	0.70	82	7.3	**8.9**	0.32
Tunisia, North, Tunis (1994)	138	6.4	**8.1**	0.44	91	4.3	**5.7**	0.30
Tunisia, Sfax (1997)	65	16.5	**20.2**	0.95	38	10.1	**12.0**	0.66
Africa, West								
The Gambia (1997-1998)	6	0.6	**1.0**	0.05	12	1.2	**2.4**	0.14
Guinea, Conakry (1996-1999)	40	1.7	**3.8**	0.30	33	1.5	**3.2**	0.26
Mali, Bamako (1988-1997)	63	1.6	**3.3**	0.27	42	1.2	**2.7**	0.20
Niger, Niamey (1993-1999)	30	1.6	**4.4**	0.38	24	1.3	**4.4**	0.42
Nigeria, Ibadan (1998-1999)	12	0.8	**1.3**	0.10	9	0.6	**1.1**	0.07
Africa, Central								
Congo, Brazzaville (1996-1999)	12	1.0	**1.4**	0.12	17	1.4	**1.8**	0.10
Africa, East								
France, La Reunion (1988-1994)	136	6.5	**8.8**	0.48	127	5.9	**6.3**	0.29
Kenya, Eldoret (1998-2000)	19	2.0	**5.3**	0.36	8	0.9	**1.6**	0.13
Malawi, Blantyre (2000-2001)	16	1.8	**4.4**	0.29	17	2.0	**4.9**	0.46
Uganda, Kyadondo County (1993-1997)	32	1.1	**3.8**	0.19	12	0.4	**1.0**	0.07
Zimbabwe, Harare: African (1990-1993)	28	1.2	**3.4**	0.11	21	1.0	**4.4**	0.16
Zimbabwe, Harare: African (1994-1997)	50	1.8	**3.3**	0.20	33	1.3	**2.5**	0.22
Zimbabwe, Harare: European (1990-1997)	1584	1036.5	**635.3**	42.34	1036	614.2	**363.3**	25.68
Africa, South								
Namibia (1995-1998)	588	18.5	**32.5**	2.05	438	13.7	**21.1**	1.27
South Africa: Black (1989-1992)	1446	2.5	**4.7**	0.25	1174	2.1	**3.2**	0.20
South Africa: Indian (1989-1992)	65	3.3	**5.4**	0.25	60	3.0	**4.2**	0.19
South Africa: Mixed race (1989-1992)	227	3.5	**6.8**	0.34	256	3.8	**5.9**	0.31
South Africa: White (1989-1992)	24620	244.6	**224.3**	12.58	16448	161.6	**125.1**	7.27
South Africa, Transkei, Umtata (1996-1998)	4	1.1	**1.9**	0.16	3	0.7	**1.0**	0.08
South Africa, Transkei, 4 districts (1996-1998)	3	0.4	**1.0**	0.10	1	0.1	**0.1**	-
Swaziland (1996-1999)	46	2.6	**5.5**	0.39	37	1.9	**3.2**	0.27
Europe/USA								
France, 8 registries (1993-1997)	6431	46.8	**31.6**	1.29	5552	38.4	**21.0**	0.97
The Netherlands (1993-1997)	8985	23.5	**16.3**	0.52	5739	14.7	**7.8**	0.29
UK, England (1993-1997)	93990	78.3	**48.9**	2.16	84431	66.1	**33.9**	1.67

In italics: histopathology-based registries

Table 2. Non-melanoma skin cancer 1953–74. Age-standardized incidence (all ages)

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	10.3	7.9	4
Mozambique, Lourenço Marques	1956–60	7.9	*7.7*	1
Nigeria, Ibadan	1960–69	1.2	1.6	3
SA, Cape Province: Bantu	1956–59	*0.9*	*0.8*	2
SA, Cape Province: Coloured	1956–59	4.2	2.8	2
SA, Cape Province: White	1956–59	133.0	72.2	2
SA, Johannesburg, Bantu	1953–55	1.4	2.8	1
SA, Natal Province: African	1964–66	3.0	*1.3*	2
SA, Natal Province: Indian	1964–66	*2.5*	*3.4*	2
Uganda, Kyadondo	1954–60	6.6	3.0	1
Uganda, Kyadondo	1960–71	3.9	3.2	5
Zimbabwe, Bulawayo	1963–72	6.5	*2.5*	6

Italics: Rate based on less than 10 cases

Table 3. Percentage distribution of microscopically verified cases by histological type
Skin (C43+C44) - Both sexes

	Carcinoma		Melanoma	Other	Unspecified	Number of cases	
	Basal cell	Squamous cell				MV	Total
Algeria, Algiers	51.5	28.2	9.0	6.3	5.0	**458**	475
Algeria, Batna	53.9	33.0	1.9	9.7	1.5	**206**	223
Algeria, Constantine	8.5	53.2	12.8	19.1	6.4	**47**	48
Algeria, Oran	51.5	23.0	10.0	0.8	14.6	**239**	243
Algeria, Setif	3.8	78.8	1.3	11.3	5.0	**80**	80
Burkina Faso, Ouagadougou	40.0	-	20.0	20.0	20.0	**5**	12
Congo, Brazzaville	3.8	15.4	57.7	3.8	19.2	**26**	46
France, La Reunion	-	73.0	20.6	3.6	2.7	**330**	331
The Gambia	23.5	58.8	5.9	-	11.8	**17**	21
Guinea, Conakry	2.6	22.1	41.6	13.0	20.8	**77**	105
Kenya, Eldoret	11.1	41.7	41.7	5.6	-	**36**	43
Malawi, Blantyre	30.8	41.0	17.9	5.1	5.1	**39**	40
Mali, Bamako	7.6	61.9	21.2	0.8	8.5	**118**	130
Namibia	51.0	37.2	10.3	1.3	0.3	**1141**	1144
Niger, Niamey	11.6	37.2	16.3	23.3	11.6	**43**	61
Nigeria, Ibadan	11.1	33.3	25.9	22.2	7.4	**27**	30
Rwanda, Butare	3.1	37.5	18.8	15.6	25.0	**32**	32
South Africa: Black	16.9	43.0	23.9	10.1	6.0	**3444**	3444
South Africa: White	70.8	20.1	7.8	0.8	0.5	**44548**	44548
South Africa: Indian	37.1	25.8	17.2	12.6	7.3	**151**	151
South Africa: Mixed race	41.8	36.2	13.0	6.5	2.5	**555**	555
South Africa, Elim	23.3	26.7	43.3	3.3	3.3	**30**	30
South Africa, Transkei, Umtata	80.0	20.0	-	-	-	**5**	7
South Africa, Transkei, 4 districts	-	40.0	60.0	-	-	**5**	8
Swaziland	44.4	31.7	15.9	7.9	-	**63**	99
Tanzania, Dar Es Salaam	9.8	68.8	9.8	8.9	2.7	**112**	113
Tanzania, Kilimanjaro	14.3	48.6	25.7	11.4	-	**35**	35
Tunisia, Centre, Sousse	68.6	17.2	6.4	7.8	-	**204**	204
Tunisia, North, Tunis	69.5	18.5	8.0	4.0	-	**249**	249
Tunisia, Sfax	68.9	25.5	2.8	2.8	-	**106**	106
Uganda, Mbarara	-	38.9	16.7	22.2	22.2	**18**	22
Uganda, Kyadondo County	18.9	39.6	34.0	-	7.5	**53**	68
Zimbabwe, Harare: African	10.7	34.0	38.6	10.7	6.1	**197**	225
Zimbabwe, Harare: European	68.5	24.9	5.9	0.5	0.3	**2773**	2789

Table 4. Site distribution of SCCs in the Gold Coast (Ghana), 1942–55
From Edington (1956)

Site	Number
Lower leg and foot	24
Orbital area	16
Penis	16
Mouth and tongue	13
Vulva	10
Scrotum	6
Hand and forearm	6
Face	5
Neck	4
Arms	3
Other	6

Skin cancer was the most common site in a ten-year biopsy series in Yirga Alem Hospital, Ethiopia (1986–95), 46.6% of them SCC and 34.8% melanomas. Most of the cancers were located on the lower limbs and, as in other East African countries, were often associated with old tropical ulcers and scars (Ashine & Lemma, 1999).

Site distribution

Biopsy specimens for the years 1942–55 in the Gold Coast were analysed by Edington (1956). The site distribution recorded for 109 SCCs (57 were of unknown site) is shown in Table 4.

A review of SCC of skin in non-Albino black Tanzanians found that the most affected site was the lower limb, with 40% of diagnoses, followed by head and neck. The penis in males and the vulva in females were the third most affected sites (Amir *et al.*, 1992a). 30% of BCC cases arose on the face. The scalp, ear, nose and eyelid each had 9–11% of the BCC cases, and site was not specified for 17% of cases (Amir *et al.*, 1992b).

In 524 cases of SCC seen in a hospital series in Zaria, Nigeria, 54% were on the lower limb, followed by the head and neck region. Chronic leg ulcer was the most common predisposing factor (Yakubu & Mabogunje, 1995).

Risk factors

Burkitt (1973) described scar epithelioma as 'ubiquitous' throughout Uganda, Kenya, Tanzania and Malawi in the 1970. This epithelioma usually arose from a chronic ulcer, was more common in men and was usually located on the lower limb. Some cases had had an ulcer for 35–40 years. It was suggested that women might be protected by their long dresses (Davies, 1957).

Tropical ulcers were found to be frequent in East Africa and much of West Africa, but rare among the Bantu of South Africa. The tumours (mostly SCC) normally arise many years after the initial ulcer develops and often after complete healing, in the depigmented scar tissue (Cook & Burkitt, 1971). SCC was the commonest diagnosis in a biopsy series from north-eastern Zaire during the period 1971–83 and 43% of these tumours arose in a chronic (tropical) ulcer or the site of previous trauma (Oates *et al.*, 1984).

Skin cancer reported in Ugandan Africans from the Kampala cancer registry for 1964–68 arose almost entirely in association with scars, often as a result of a tropical ulcer, and at least 80% occurred in the lower leg. The majority were well differentiated SCC and the underlying connective tissue never showed evidence of solar damage, even under depigmented scars. The picture in the Kampala Europeans was very different, with most skin tumours seen on the face and ears. Albino Africans showed a similar pattern to Europeans, but incidence was higher and the cancer occurred at an earlier age (Templeton & Viegas, 1970).

Hutt (1991) agreed that the great majority of SCCs of the skin arise in areas of damaged skin, particularly at the site of old tropical ulcers on the lower leg, and – less commonly – because of burn scars and chronic sinuses. He noted that the highest frequency of skin cancers was generally found in very poor areas with few health facilities, and occurrence could be reduced by better management of tropical ulcers and other chronic skin lesions. A report from Tanzania noted that SCC following leg ulcers had become less common because of improved treatment of tropical ulcers and better nutrition (Samitz, 1980).

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4.18 Stomach cancer

Introduction

In 1980, stomach cancer was still reckoned to be the most common cancer in the world (Parkin *et al.*, 1988). However, at least in developed countries with reliable data, incidence and mortality have progressively declined – a phenomenon referred to as 'an unplanned triumph' (Howson *et al.*, 1986). Stomach cancer now ranks only fourth in frequency, accounting for some 876 000 new cases (8.7% of all cancers) worldwide in the year 2000 (Ferlay *et al.*, 2001). Internationally, the world age-standardized incidence (ASR) of stomach cancer in males varies from a high of about 80 cases per 100 000 in Japan to less than 10 per 100 000 in places in India, Thailand and Africa.

Overall, stomach cancer is less common in Africa: it accounted for an estimated 28 000 new cancers in 2000, some 4.5% of the total. However, there was certainly until recently considerable underreporting because of the rapid fatality rate and lack of diagnostic facilities. This was noted in Tanzania by Burkitt *et al.* (1968); in a gastric cancer series of about 250 cases, only 25% were histologically verified. Stomach cancer diagnoses were reviewed in a rural hospital in Chogoria, Kenya, between 1960 and 1986 (MacFarlane *et al.*, 2001a). The age-standardized 'incidence' of stomach cancer increased from a low of about 3 per 100 000 before 1983 to 14 per 100 000 in 1986 (similar to rates observed in eastern Europe) after an endoscope was purchased in 1984.

Descriptive epidemiology in Africa

Table 1 shows the incidence rates of stomach cancer in Africa from cancer registries reported in this volume. The geographical patterns are not obvious; there are moderately high rates in both West Africa (Bamako, Mali – ASR 18.5 per 100 000 in men and 15.0 per 100 000 in women) and in the island of Reunion (25.3 per 100 000 for males and 9.1 per 100 000 for females). Rates are also moderately high in East Africa (Eldoret, Kenya – ASR 11.3 and 7.6 per 100 000; Harare, Zimbabwe – 13.0 and 11.5 per 100 000 for males and females, respectively). In contrast, Abidjan (Côte d'Ivoire), Niamey (Niger), Ibadan (Nigeria) and the Gambia all reported stomach cancer incidence rates less than ~3 per 100 000. In South Africa, the ASR (derived from the pathology-only National Cancer Registry) was 3.6 for males and 1.9 for females.

Data from cancer registries between the 1950s and 1970s showed marked variation in stomach cancer incidence in Africans, ranging from 2.3 per 100 000 in Kyadondo (Uganda) to a high of 37.5 per 100 000 in Cape Province, South Africa (Table 2). Corresponding rates in females were 0.9 in Uganda and 18.4 per 100 000 in Cape Province. The South African coloured (mixed race) population showed even higher rates (53.4 in males and 25.5 per 100 000 in females) in the 1950s. This high rate in the western Cape coloured population of South Africa persisted until at least the 1970s (mortality rate in 1968–72 of 49.9 per 100 000; Bradshaw *et al.*, 1983). In 1989 (the last year for which mortality statistics were available by ethnic group in South Africa), national age-standardized stomach cancer mortality rates in coloured males increased to 98 per 100 000 in males and 49 per 100 000 in females.

High stomach cancer rates were recorded between 1956 and 1960 in the Kivu province of the Democratic Republic of the Congo (former Zaire), with age-standardized rates of 9.3 per 100 000 person years among males and 15.1 per 100 000 among females (Clemmesen *et al.*, 1962). In the 'zone de santé' of Katana hospital in Kivu province during the period 1983–86, stomach cancer was the third most common cancer among males, accounting for 14.7% of all cancers, and the leading cancer in females, accounting for 17.8% of all cancers (Bourdeaux, 1988). By contrast, Oates *et al.* (1984) analysed pathological data from north-east of the country and found that between 1971 and 1983, among 794 cancers, cancer of the stomach comprised only 3%. However, in areas lacking endoscopic biopsy facilities, stomach cancers are likely to be under-reported. In Rwanda, which neighbours Kivu province of the Democratic Republic of the Congo, the age-standardized incidence rate of stomach cancer was 13 per 100 000 in males and 15 per 100 000 in females; the stomach was the third commonest tumour site in males and second commonest in females in the prefecture of Butare, southern Rwanda (Newton *et al.*, 1996). Burundi also seems to have a moderately high incidence of stomach cancer, particularly in males (8 and 5 per 100 000 in males and females, respectively) (Hamber & von Bergen, 1971).

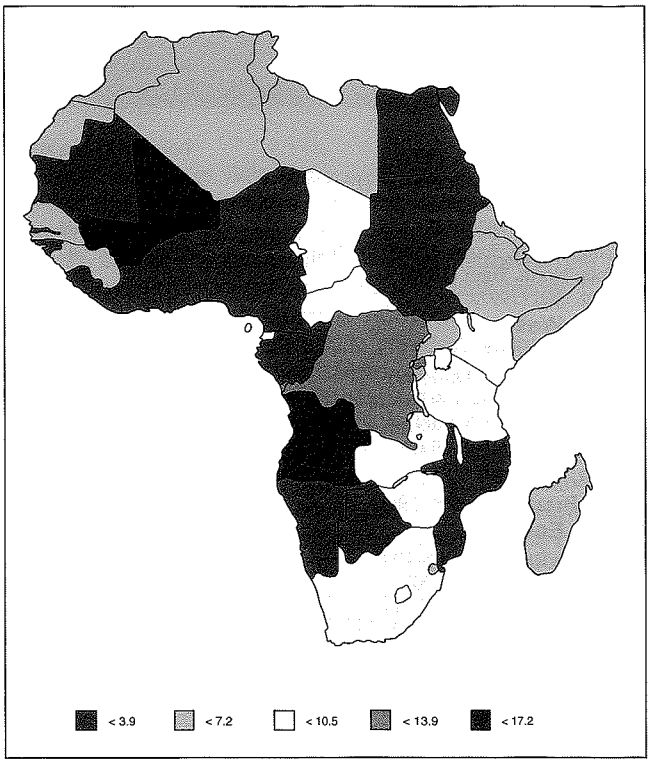

Figure 1. Incidence of stomach cancer: ASR (world) - males (all ages)

The relative frequency of stomach cancer appears to decrease as one moves away from the province of Kivu eastward into Uganda. Hutt *et al.* (1965) reported the incidence of stomach cancer in Kampala Cancer Registry (Uganda) to be highest among the Ankole ethnic group and Rwandan immigrants, compared with other Ugandan tribes. Both groups inhabit an area to the south-west of Kampala which borders the Democratic Republic of the Congo's Kivu province.

Burkitt *et al.* (1969) reported data from hospitals in western Kenya and north-west Tanzania; stomach cancer accounted for 15% of all malignancies in Ndolage Hospital, which is near the border with Rwanda, but only 4.3% at Shirati Hospital on the eastern shore of Lake Victoria.

Further south, in Swaziland, stomach cancer rates of 1.8 per 100 000 in males and 0.2 in females have been reported (Peers & Keen, 1986).

Most of the stomach cancer data reported by Parkin (1986) were derived from either pathology-based cancer registries, which

Table 1. Age-standardized (world) and cumulative (0-64) incidence
Stomach (C16)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	211	3.8	**5.6**	0.35	155	2.8	**3.7**	0.25
Algeria, Constantine (1994-1997)	32	2.1	**3.6**	0.20	21	1.4	**2.2**	0.16
Algeria, Oran (1996-1998)	91	5.1	**7.6**	0.42	52	3.0	**4.0**	0.24
Algeria, Setif (1993-1997)	131	4.4	**7.8**	0.51	56	1.9	**3.1**	0.26
Tunisia, Centre, Sousse (1993-1997)	42	3.6	**5.0**	0.26	24	2.1	**2.7**	0.15
Tunisia, North, Tunis (1994)	102	4.7	**6.1**	0.37	61	2.9	**3.5**	0.25
Tunisia, Sfax (1997)	10	2.5	**3.1**	0.18	9	2.4	**2.9**	0.19
Africa, West								
The Gambia (1997-1998)	11	1.1	**2.5**	0.12	8	0.8	**2.1**	0.19
Guinea, Conakry (1996-1999)	59	2.6	**6.1**	0.38	34	1.5	**3.6**	0.26
Mali, Bamako (1988-1997)	290	7.5	**17.3**	1.25	216	6.0	**14.6**	1.16
Niger, Niamey (1993-1999)	13	0.7	**2.7**	0.28	15	0.8	**3.3**	0.34
Nigeria, Ibadan (1998-1999)	9	0.6	**1.2**	0.09	11	0.7	**1.4**	0.13
Africa, Central								
Congo, Brazzaville (1996-1999)	15	1.2	**2.0**	0.15	11	0.9	**1.3**	0.10
Africa, East								
France, La Reunion (1988-1994)	340	16.2	**21.8**	1.21	158	7.3	**7.8**	0.36
Kenya, Eldoret (1998-2000)	36	3.8	**10.4**	0.58	26	2.8	**7.8**	0.59
Malawi, Blantyre (2000-2001)	9	1.0	**2.3**	0.12	3	0.3	**0.9**	0.10
Uganda, Kyadondo County (1993-1997)	57	2.0	**7.2**	0.39	47	1.6	**5.6**	0.51
Zimbabwe, Harare: African (1990-1993)	90	3.8	**12.6**	0.44	67	3.1	**15.1**	0.58
Zimbabwe, Harare: African (1994-1997)	105	3.8	**10.6**	0.57	70	2.7	**10.3**	0.61
Zimbabwe, Harare: European (1990-1997)	41	26.8	**15.8**	1.06	18	10.7	**5.0**	0.23
Africa, South								
Namibia (1995-1998)	49	1.5	**2.7**	0.15	37	1.2	**1.8**	0.08
South Africa: Black (1989-1992)	1085	1.9	**3.6**	0.22	702	1.2	**2.0**	0.13
South Africa: Indian (1989-1992)	140	7.2	**11.7**	0.68	91	4.6	**6.4**	0.31
South Africa: Mixed race (1989-1992)	534	8.3	**16.1**	0.95	281	4.2	**6.4**	0.40
South Africa: White (1989-1992)	1110	11.0	**10.1**	0.53	638	6.3	**4.8**	0.26
South Africa, Transkei, Umtata (1996-1998)	5	1.4	**2.0**	0.05	4	0.9	**1.3**	0.05
South Africa, Transkei, 4 districts (1996-1998)	7	1.0	**1.8**	0.13	2	0.2	**0.3**	0.01
Swaziland (1996-1999)	36	2.0	**4.5**	0.29	24	1.2	**2.2**	0.19
Europe/USA								
USA, SEER: White (1993-1997)	4546	9.3	**6.9**	0.31	2618	5.2	**3.0**	0.12
USA, SEER: Black (1993-1997)	792	11.8	**13.6**	0.66	482	6.5	**5.8**	0.26
France, 8 registries (1993-1997)	2228	16.2	**11.1**	0.50	1339	9.3	**4.7**	0.17
The Netherlands (1993-1997)	7324	19.2	**13.6**	0.56	4165	10.7	**5.8**	0.23
UK, England (1993-1997)	27209	22.7	**13.8**	0.52	16159	12.6	**5.7**	0.19

In italics: histopathology-based registries

Table 2. Incidence of stomach cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source (see Chap. 1)
		Male	Female	
Senegal, Dakar	1969–74	3.7	2.0	4
Mozambique, Lourenço Marques	1956–60	*3.0*	*2.4*	1
Nigeria, Ibadan	1960–69	7.2	6.4	3
SA, Cape Province: Bantu	1956–59	37.5	18.4	2
SA, Cape Province: Coloured	1956–59	53.4	25.5	2
SA, Cape Province: White	1956–59	32.4	13.8	2
SA, Johannesburg, Bantu	1953–55	10.2	6.2	1
SA, Natal Province: African	1964–66	12.1	8.3	2
SA, Natal Province: Indian	1964–66	22.1	30.0	2
Uganda, Kyadondo	1954–60	2.3	0.9	1
Uganda, Kyadondo	1960–71	3.7	2.0	5
Zimbabwe, Bulawayo	1963–72	10.6	7.3	6

Italics: Rate based on less than 10 cases

are likely to under-report the relative frequency of deep-seated tumours such as stomach cancer, or hospital-based registries that may distort rates depending on specialist interest in different conditions. In most of these registries, the male to female ratio was around 2:1 (Table 3).

These various data from registries and relative frequencies from case series have been used to estimate national incidence rates (Figure 1). The estimates of age-standardized incidence in males range from less than 3 per 100 000 in Burkina Faso, Gambia, Republic of the Congo (Brazzaville), Niger, Gabon and Tanzania, to over 15 per 100 000 in Angola, Democratic Republic of Congo, Mali and Reunion.

Gastric cancer morphology

In areas of high gastric cancer incidence, there appear to be higher proportions of the intestinal type of gastric cancer versus the diffuse type. Oettlé (1967), reviewing South African histological material from 1949–53, reported a proportion of intestinal-type gastric cancers in Africans of 54%, compared with 73% in whites. Isaacson *et al.* (1978) found 45% of gastric cancers among urban Africans to be of the intestinal type, whereas in Zimbabwe (Nkanza, 1988) the corresponding proportion was 77%. Kitinya *et al.* (1988) reported 82% intestinal-type gastric cancers in the Mount Kilimanjaro area of Tanzania, whereas the proportion in other regions of the country was 70%. In contrast, Templeton (1973) found that in Uganda 55% of gastric cancers were of the intestinal type. The reasons for these variations in the distribution of morphological types of gastric cancer are poorly understood.

Time trends

In the cancer registry of Uganda (Kyadondo), the age-standardized incidence of gastric cancer in males increased from 2.7 per 100 000 in 1960–66 to 7.6 per 100 000 in 1995–97 (Table 4); however the trend was not statistically significant (Wabinga *et al.*, 2000).

In 1949, stomach cancer was the most common cause of cancer death among whites, coloured and Asians of both sexes in South Africa. By 1969, the mortality rates had dropped for whites and Asians but not for the coloured population, who still maintained the fourth highest rate in the world (Bradshaw & Harington, 1982). However, mortality rates have subsequently fallen in all ethnic groups (see Figure 2 of Chapter 3.5.4). In a review of records at Baragwanath hospital (near Soweto, South Africa), covering 17 years (1948–64), Robertson (1969) found that stomach cancer comprised about 2.2% of all cancers in males and 1.1% in females and Isaacson *et al.* (1978) reported similar figures for the same hospital between 1966 and 1975. In the National Cancer Registry's national pathology data, stomach cancer comprised 2.8% of male and 1.7% of female cancers in 1989–92 (see Table 10 of Chapter 3.5.4).

Risk factors

Diet, tobacco, alcohol

There is convincing evidence that diets high in vegetables and fruit protect against stomach cancer. Diets high in salt probably increase risk. There is good evidence that refrigeration of food also protects against this cancer by facilitating year-round consumption of fruit and vegetables and probably by reducing the need for salt as a preservative. Vitamin C, contained in vegetables, fruits and other foods of plant origin, is probably protective, and so too are diets high in whole-grain cereals, carotenoids and also green tea (World Cancer Research Fund, 1997). Many studies suggest a small increase in risk (about two-fold) in smokers (Tredaniel *et al.*, 1997), but alcohol does not affect risk except at the gastric cardia.

In Africa, there have been no studies on the relation of diet, salt or pickled foods on the risk of developing stomach cancer. A geographical study in western Uganda suggested that most of the ethnic groups with high risk of developing stomach cancer are cattle-keepers who consume plenty of milk (Cook & Kajubi, 1966). No studies have been conducted to measure the association between alcohol consumption or other environmental risk factors and gastric cancer. However Kitinya *et al.* (1988) noted that in the Mount Kilimanjaro area, with high frequency of stomach cancer, the alcohol commonly consumed is brewed from bananas, whereas in low-risk areas, the alcohol is made from grains. Similarly, people of western Uganda and the Gishu also brew alcohol from bananas, while the rest of the country consumes alcohol made from millet.

Helicobacter pylori

H. pylori, isolated in 1984 (Marshall & Warren, 1984), has been shown to be associated with a number of gastroduodenal diseases, including duodenal and gastric ulcers (Blaser, 1990), chronic active gastritis, chronic atrophic gastritis, intestinal metaplasia (the latter two lesions being important precursors of stomach cancer; Correa, 1988) and finally stomach cancer (IARC, 1994).

H. pylori infection is particularly prevalent among third-world populations, and in western countries, those of a lower socio-economic status have higher infection rates (Sitas *et al.*, 1991). Crowding at a young age seems to be a risk factor (Sitas *et al.*, 1992). In Africa, prevalence of infection with *H. pylori* is about 50% in children under 15 years of age (Sitas, 1990; Sathar *et al.*, 1994) and reaches over 70% in most adult populations studied (Table 5). However, in South African whites, adult infection rates resemble those in western countries (40%) (Sathar *et al.*, 1994). In Africa, *H. pylori* infection is associated with markers of hepatitis A infection (Sathar *et al.*, 1994), premastication of food in Burkina Faso (Albengue *et al.*, 1990), race (Sathar *et al.*, 1994), social class and educational standard in South Africa, but not with number of persons sharing current accommodation (Louw *et al.*, 1993). However, other population studies of seroprevalence in South Africa found no association with any index of social class (Sitas *et al.*, 1997). Virtually no studies have looked at the distribution of intestinal metaplasia in the stomach in Africa. In a follow-up endoscopic series of 51 *H. pylori*-positive patients in Kenya by McFarlane *et al.* (2001b), 61% had atrophic gastritis and 24% both atrophic gastritis and intestinal metaplasia. After a year's follow-up, the proportion of those with atrophic gastritis increased to 70% but the proportion of those with intestinal metaplasia remained the same (22%). The progression from moderate to severe atrophy was 1.8%, as in other regions of the world. Given the slow progression from atrophic gastritis to gastric cancer, the authors speculated that other factors may modulate this process. CagA-positive strains of *H. pylori* predominate in Africa (Ally *et al.*, 1998) but their role in modulating the progression of gastritis to gastric cancer remains speculative (Kuipers & Meijer, 2000).

In a number of endoscopic studies, *H. pylori* was observed microscopically or was cultured from gastric biopsies more frequently in patients diagnosed with gastritis (of varying forms). For example, Rouvroy (1987) found *H. pylori* to be present in 33% of biopsies with normal gastric mucosa, in 83% of those with gastric atrophy and in 43% with gastric cancer.

It appears that, even in a continent where the prevalence of *H. pylori* infection is high, differences in prevalence exist between those who have a 'normal' gastric mucosa (0–40%) and those with gastritis (80–100%) (Table 6). Very few data exist on the prevalence of gastritis in asymptomatic populations. In a group of 40 hospital volunteers in Kenya, 23 (58%) were found to have mild or moderate atrophic gastritis, but none had severe gastritis or intestinal metaplasia. In this group the seroprevalence of *H. pylori* was 95%, but 70% had organisms detected microscopically. This may indicate that while most adults have been infected with the organism sometime during their lives, and show elevated antibody levels, active colonization may be associated with gastritis.

Only one study in Africa has found a positive association between *H. pylori* and gastric cancer. In a series of 176 patients, the prevalence of *H. pylori* detected by microscopy was 34% in those with a normal mucosa, 79% in those with superficial

Table 3. Stomach cancer in various cases series (from Parkin, 1986)

Country	Place	Dates	%		ASR	
			male	female	male	female
Algeria	Algiers, Oran, Constantine (pathology)	1966–75	4.4	1.7	3.6	1.4
Angola	Luanda: Pathology Dept	1977–80	9.8	4.7	–	–
Egypt	Cairo	1978–79	7.3	5.5		
Gabon	Libreville: Pathogy Dept	1978–84	1.1	1.8		
Kenya	National Cancer Registry (Pathology)	1968–78	4.3	2.4		
	Coast General Hospital, Mombasa	1981	3.6	2.8		
Liberia	Cancer registry	1976–80	3.5	1.3		
Madagascar	Pathology series	1979–81	1.3	0.5		
Malawi	Pathology	1976–80	2.1	0.4		
Nigeria	Ibadan	1970–76	6.0	2.2	7.1	4.0
	Zaria (Pathology)	1976–78	1.5	1.1		
Rwanda	Pathology series	1982–84	9.9	6.5		
Sudan	Hospital (Radiotherapy) Cancer Registry	1978	2.7	1.5		
Swaziland	Cancer Registry	1979–83	2.3	0.3	1.8	0.2
Tanzania	Tanzania Cancer Registry (Pathology)	1980–81	1.7	1.5		
	Mwanza Hospital	1980–81	1.6	0.9		
	Kilimanjaro Hospital	1975–79	8.6	9.9	5.6	4.6
Tunisia	Hospital Registry	1976–80	2.1	1.5		
Uganda	Kuluva Hospital W. Nile	1961–78	0.5	–		
Zambia	Zambian Cancer Registry	1981–83	5.0	4.9		
	Ndola (Pathology)	1976–79	2.8	1.4		
Zimbabwe	Bulawayo Cancer Registry	1973–77	4.5	2.6		
	Harare (Pathology)	1973–77	4.6	2.7		

Table 4. Trends in gastric cancer incidence, Kyadondo Cancer Registry, 1960–97 (Wabinga et al., 2000)

Time period	ASR (per 100 000)	
	Males	Females
1960–66	2.7	0.8
1967–71	4.7	3.4
1991–94	4.7	3.2
1995–97	7.6	5.6

Table 5. Population seroprevalence of *H. pylori* antibodies in African adults

Population	Prevalence	Reference
Algeria	79%	Megraud *et al.*, 1989
Côte d'Ivoire	71%	Megraud *et al.*, 1989
Dem. Rep. Congo (Zaire)	79%	Glupczynski *et al.*, 1992
Nigeria	85%	Holcombe *et al.*, 1992
South Africa	86%	Sitas *et al.*, 1997
South Africa		Sathar *et al.*, 1994
Africans	93%	
Indians	83%	
Mixed race	81%	
Whites	42%	

gastritis, 89% in those with chronic atrophic gastritis and 100% (6/6) in those with stomach cancer (Jaskiewicz *et al.*, 1989). In this study, *H. pylori* status in those with stomach cancer was assessed microscopically in tissue from the adjoining gastric mucosa, rather than the cancer itself (Rouvroy *et al.*, 1987). In a review of all African studies on *H. pylori* and gastroduodenal pathology, the prevalence of *H. pylori* was 78% in six studies in relation to gastric atrophy, 78% in six studies that recorded intestinal metaplasia and 69% in studies recording stomach cancer (Kidd *et al.*, 1999b). Wabinga (1996) studied gastric endoscopic biopsies of patients with upper gastrointestinal symptoms and demonstrated a high frequency of colonization by *H. pylori* in populations with high risk of stomach cancer development. Using a commercial kit to detect anti-HP IgG antibody in a small case–control study in South Africa (48 gastric cancer cases, 48 controls), Louw *et al.* (2001) found a high prevalence of infection in the control subjects with non-ulcer dyspepsia (79%), but a non-significant association with cancer (OR estimated from authors' data 1.5, 95% CI 0.5–4.9).

H. pylori strain differences may be important in the development of gastric cancer. For example, the vacA s1 genotype to be more common in patients with gastric cancer (Kidd *et al.*, 1999a; Louw *et al.*, 2001).

Volcanic soils

The relative frequency of gastric cancer in highland areas of East and Central Africa has led to a hypothesis of an association with exposure to volcanic soils. High relative frequencies have been recorded in the Gishu ethnic group on the slopes of Mount Elgon in eastern Uganda and among residents of the slopes of Mount Kenya (Templeton, 1973). Kitinya (1988) reported high proportions of stomach cancer in persons living on the slopes of Mount Kilimanjaro. All these mountain areas are volcanic. Ethiopia, another particularly volcanic country, has reported relatively high incidence rates of gastric cancer (Madebo *et al.*, 1994). However, some populations living in volcanic areas have low occurrence. The

Table 6. Presence of *H. pylori* in biopsy specimens of gastric mucosa

Place	Normal	Gastritis	Atrophic gastritis	Intestinal metaplasia	Gastric cancer	Reference
Ghana		100				Wyatt *et al.*, 1987
Nigeria	33 (1/3)	87			0/1	Holcombe *et al.*, 1990
Kenya	10	80				Lachlan *et al.*, 1988
Uganda	–	100				Weir *et al.*, 1988
Zimbabwe		96				Weir *et al.*, 1988
Tunisia	24	86				Fendri *et al.*, 1988
Rwanda	33	46–96	83		43%	Rouvroy *et al.*, 1987
South Africa	38		52		100 (6/6)	Jaskiewicz *et al.*, 1989
Kenya	0 (0/9)		82			Sitas, 1990
Malawi		90–100*				Harries *et al.*, 1992

*Gastritis 'score >2'

Kiga tribe, for example, lives on slopes of the volcanic Mount Muhavura, but has low incidence rates (Templeton, 1973). Therefore, volcanic soil is unlikely to be the only factor responsible for high incidence of stomach cancer; no known carcinogens have been found in these soils (Ilnilsky *et al.*, 1976).

Blood group A

The risk of developing gastric cancer has been reported to be higher in those of blood group A (Correa, 1988). However in Africa, areas with high incidence of stomach cancer appear to have the lowest frequency of blood group A (Ssebabi, 1975).

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4.19 Thyroid cancer

Introduction

Cancer of the thyroid is not particularly common; worldwide, the estimated 123 000 new cases annually comprise 1.2% of all cancers (0.6% of cases in men and 1.9% in women). In Africa, it is proportionately a little more common, with 6300 new cases accounting for 1.4% of new cancers (0.8% in men and 2.0% in women). The large majority of cases are carcinomas, which are classified as papillary, follicular, medullary and undifferentiated (anaplastic). In most series, papillary carcinoma is the most common, with follicular carcinomas representing about one quarter, and medullary/anaplastic tumours some 5–15% (Ron, 1996). The sex ratio is about 3:1 (except for medullary carcinomas, which occur equally in the two sexes).

It is known that diagnostic practices (for example, with respect to histological examination of resected goitres, or at autopsy) can influence apparent rates of incidence. This may account for the particularly high rates observed in the US white population. In the United States, the higher incidence of thyroid cancer among whites is confined to papillary carcinomas (Correa & Chen, 1995).

Descriptive epidemiology in Africa

Table 1 shows age-standardized incidence rates from different centres, as reported in this volume, with data from Europe and North America for comparison. Table 2 shows incidence data from time periods in the 1960s and 1970s.

In Africa, it appears that the incidence rates are similar to those elsewhere in the world (except in North American white populations). In most series, papillary carcinomas are the predominant histological subtype (Table 3). Templeton (1973) described 82 cases from the pathology department in Kampala, Uganda. Follicular tumours were more numerous than papillary (as appears to be the case today – Table 3), all types having a female excess (F:M ratio 2:1). Incidence of papillary tumours was highest in the fourth decade and declined thereafter, with the risk of follicular cancers continuing to increase with age. There did not seem to be any increased frequency in ethnic groups from goitrous areas, or regions with volcanic soils.

McGill (1978) described 63 thyroid cancers in Kenyans; papillary carcinoma predominated in lowland tribal groups, follicular carcinoma in highland groups, and a possible link between follicular carcinoma and endemic goitre was postulated. In Khartoum, Sudan (Omran & Ahmed, 1993), in a series of 112 cases, follicular carcinoma predominated (42%), followed by papillary (22.3%) and anaplastic tumours (21.4%). In Ibadan, Nigeria (Thomas & Ogunbiyi, 1995), papillary and follicular tumours occurred in equal numbers, with a sex ratio of about 2:1; medullary carcinoma comprised 5%. Kalk *et al.* (1997) studied data from the histopathology register of South Africa and noted an excess of follicular carcinomas in black women. Follicular morphology predominated in blacks resident in rural areas of the former Transvaal (58%), while papillary histology predominated in urban areas, irrespective of race. The authors attributed these patterns to regional differences in iodine deficiency.

Etiology

Risk factors for thyroid cancer include radiation and possibly diet, with cruciferous vegetables being protective and seafood a possible risk factor. Areas of endemic goitre (deficiency in dietary iodine) appear to be associated with elevated risk of follicular (and perhaps anaplastic) thyroid cancer, whereas iodine rich-areas have been associated with enhanced risk of papillary carcinoma (Ron, 1996). Attention has also been drawn to the frequency of thyroid cancer in areas with volcanic activity (Hawaii and Iceland) (Kung *et al.*, 1981).

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Table 1. Age-standardized (world) and cumulative (0-64) incidence
Thyroid (C73)

	MALE				FEMALE			
	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)	Cases	CRUDE (per 100,000)	ASR(W) (per 100,000)	Cumulative (%)
Africa, North								
Algeria, Algiers (1993-1997)	52	0.9	**1.2**	0.08	192	3.5	**4.2**	0.33
Algeria, Constantine (1994-1997)	11	0.7	**1.1**	0.07	31	2.0	**2.8**	0.20
Algeria, Oran (1996-1998)	7	0.4	**0.4**	0.04	62	3.5	**4.0**	0.28
Algeria, Setif (1993-1997)	7	0.2	**0.3**	0.02	36	1.2	**1.7**	0.12
Tunisia, Centre, Sousse (1993-1997)	7	0.6	**0.8**	0.04	27	2.4	**2.5**	0.16
Tunisia, North, Tunis (1994)	12	0.6	**0.6**	0.05	55	2.6	**2.9**	0.18
Tunisia, Sfax (1997)	1	0.3	**0.3**	0.02	7	1.9	**2.1**	0.11
Africa, West								
The Gambia (1997-1998)	-	-	-	-	4	0.4	**1.0**	0.12
Guinea, Conakry (1996-1999)	6	0.3	**0.5**	0.02	17	0.8	**1.3**	0.13
Mali, Bamako (1988-1997)	4	0.1	**0.1**	0.01	28	0.8	**1.5**	0.10
Niger, Niamey (1993-1999)	3	0.2	**0.3**	0.03	13	0.7	**1.4**	0.10
Nigeria, Ibadan (1998-1999)	6	0.4	**0.8**	0.04	9	0.6	**1.0**	0.04
Africa, Central								
Congo, Brazzaville (1996-1999)	2	0.2	**0.2**	0.02	5	0.4	**0.5**	0.04
Africa, East								
France, La Reunion (1988-1994)	12	0.6	**0.7**	0.05	33	1.5	**1.6**	0.12
Kenya, Eldoret (1998-2000)	2	0.2	**0.6**	0.07	7	0.8	**1.5**	0.05
Malawi, Blantyre (2000-2001)	1	0.1	**0.2**	0.02	6	0.7	**1.5**	0.12
Uganda, Kyadondo County (1993-1997)	6	0.2	**0.6**	0.06	47	1.6	**4.5**	0.41
Zimbabwe, Harare: African (1990-1993)	11	0.5	**1.2**	0.08	31	1.5	**5.4**	0.35
Zimbabwe, Harare: African (1994-1997)	12	0.4	**0.8**	0.04	21	0.8	**3.2**	0.11
Zimbabwe, Harare: European (1990-1997)	1	0.7	**0.9**	0.05	7	4.1	**2.5**	0.13
Africa, South								
Namibia (1995-1998)	9	0.3	**0.4**	0.02	37	1.2	**1.7**	0.10
South Africa: Black (1989-1992)	171	0.3	**0.5**	0.03	476	0.8	**1.2**	0.10
South Africa: Indian (1989-1992)	21	1.1	**1.5**	0.10	53	2.7	**2.9**	0.22
South Africa: Mixed race (1989-1992)	19	0.3	**0.5**	0.03	38	0.6	**0.7**	0.05
South Africa: White (1989-1992)	177	1.8	**1.6**	0.10	560	5.5	**4.7**	0.35
South Africa, Transkei, Umtata (1996-1998)	-	-	-	-	2	0.5	**0.8**	0.10
South Africa, Transkei, 4 districts (1996-1998)	-	-	-	-	3	0.3	**0.5**	0.04
Swaziland (1996-1999)	9	0.5	**0.9**	0.09	17	0.9	**1.3**	0.07
Europe/USA								
USA, SEER: White (1993-1997)	1664	3.4	**2.8**	0.21	4658	9.3	**7.7**	0.59
USA, SEER: Black (1993-1997)	86	1.3	**1.4**	0.09	323	4.4	**4.0**	0.31
France, 8 registries (1993-1997)	322	2.3	**1.9**	0.15	1115	7.7	**6.3**	0.51
The Netherlands (1993-1997)	499	1.3	**1.0**	0.07	1137	2.9	**2.2**	0.16
UK, England (1993-1997)	1262	1.1	**0.8**	0.05	3383	2.6	**2.0**	0.14

In italics: histopathology-based registries

Table 2. Incidence of thyroid cancer in Africa, 1953–74

Registry	Period	ASR (per 100 000)		Source
		Male	Female	(see Chap. 1)
Senegal, Dakar	1969–74	*0.6*	1.1	4
Mozambique, Lourenço Marques	1956–60	*1.8*	*2.3*	1
Nigeria, Ibadan	1960–69	0.8	*1.7*	3
SA, Cape Province: Bantu	1956–59	*0.0*	*2.7*	2
SA, Cape Province: Coloured	1956–59	*0.6*	*1.1*	2
SA, Cape Province: White	1956–59	*1.2*	3.0	2
SA, Johannesburg, Bantu	1953–55	*0.1*	*1.7*	1
SA, Natal Province: African	1964–66	*0.2*	*3.3*	2
SA, Natal Province: Indian	1964–66	*1.0*	*3.0*	2
Uganda, Kyadondo	1954–60	*0.1*	2.6	1
Uganda, Kyadondo	1960–71	*0.4*	2.1	5
Zimbabwe, Bulawayo	1963–72	*2.0*	*1.8*	6

Italics: Rate based on less than 10 cases

Table 3. Percentage distribution of microscopically verified cases by histological type
Thyroid (C73) - Both sexes

	Carcinoma						Sarcoma	Other	Unspec.	Number of cases	
	Follic.	Papil.	Medul.	Anapl.	Other	Unspec.				MV	Total
Algeria, Algiers	25.6	46.3	5.3	0.9	5.3	16.7	-	-	-	**227**	244
Algeria, Batna	21.4	60.7	-	7.1	7.1	3.6	-	-	-	**28**	31
Algeria, Constantine	34.1	17.1	12.2	-	14.6	12.2	-	-	9.8	**41**	42
Algeria, Oran	10.6	24.2	-	1.5	13.6	45.5	1.5	-	3.0	**66**	69
Algeria, Setif	32.5	45.0	-	-	15.0	5.0	2.5	-	-	**40**	43
Burkina Faso, Ouagadougou	100.0	-	-	-	-	-	-	-	-	**1**	1
Congo, Brazzaville	20.0	40.0	-	-	20.0	20.0	-	-	-	**5**	7
France, La Reunion	22.2	51.1	6.7	2.2	13.3	-	-	-	4.4	**45**	45
The Gambia	50.0	50.0	-	-	-	-	-	-	-	**2**	4
Guinea, Conakry	16.7	66.7	-	-	8.3	8.3	-	-	-	**12**	23
Kenya, Eldoret	60.0	-	-	-	-	-	-	-	40.0	**5**	9
Malawi, Blantyre	75.0	25.0	-	-	-	-	-	-	-	**4**	7
Mali, Bamako	9.5	14.3	-	-	42.9	33.3	-	-	-	**21**	32
Namibia	31.8	38.6	9.1	2.3	6.8	6.8	2.3	-	2.3	**44**	46
Niger, Niamey	20.0	70.0	-	10.0	-	-	-	-	-	**10**	16
Nigeria, Ibadan	38.5	53.8	-	-	-	7.7	-	-	-	**13**	15
Rwanda, Butare	100.0	-	-	-	-	-	-	-	-	**2**	3
South Africa: Black	34.8	26.1	3.4	4.9	8.7	6.2	0.5	0.3	15.1	**647**	647
South Africa: White	18.7	59.3	3.7	2.4	9.4	4.6	0.3	0.1	1.5	**737**	737
South Africa: Indian	13.5	40.5	2.7	5.4	9.5	8.1	1.4	-	18.9	**74**	74
South Africa: Mixed race	40.4	45.6	3.5	5.3	1.8	3.5	-	-	-	**57**	57
South Africa, Elim	-	-	-	-	-	-	-	-	-	**-**	-
South Africa, Transkei, Umtata	50.0	50.0	-	-	-	-	-	-	-	**2**	2
South Africa, Transkei, 4 districts	-	33.3	-	-	33.3	33.3	-	-	-	**3**	3
Swaziland	61.5	15.4	15.4	-	7.7	-	-	-	-	**13**	26
Tanzania, Dar Es Salaam	28.6	14.3	-	14.3	14.3	28.6	-	-	-	**7**	7
Tanzania, Kilimanjaro	7.7	53.8	-	-	23.1	7.7	-	-	7.7	**13**	15
Tunisia, Centre, Sousse	11.8	76.5	-	8.8	2.9	-	-	-	-	**34**	34
Tunisia, North, Tunis	11.9	79.1	1.5	1.5	1.5	4.5	-	-	-	**67**	67
Tunisia, Sfax	12.5	75.0	-	-	-	-	-	-	12.5	**8**	8
Uganda, Mbarara	50.0	50.0	-	-	-	-	-	-	-	**2**	3
Uganda, Kyadondo County	56.8	9.1	2.3	-	9.1	18.2	-	-	4.5	**44**	53
Zimbabwe, Harare: African	58.3	16.7	-	8.3	8.3	6.3	-	-	2.1	**48**	75
Zimbabwe, Harare: European	16.7	66.7	-	-	-	16.7	-	-	-	**6**	8