EYE CANCER IN ADULTS IN UZBEKISTAN, 1978-1998

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ABSTRACT

Incidence rate, age-adjusted and standardized incidence and mortality of malignant eye tumours (METs) in Uzbekistan in 1978-1998 and professional, ethnic, environmental, and geographical factors which could influence it are analyzed. Before 1978, there was no information about patients with METs in Uzbekistan. We gathered 4872 primary new cases, of whom 79.7% (3882 patients) were treated in our department. All samples were statistically tested.
Age-adjusted MET incidence has a peak in the 60-69 age subgroup. The highest incidence was in ''non-local'' ethnic group. Eyelid tumours occurred most frequently, followed by conjunctival, intraocular and orbital tumours. Urban and rural females had higher incidence than urban and rural males. For 10 years, standardized incidence has increased 2,3 and mortality 6,0 times. The highest incidence and mortality were in Karakalpakstan and Khorezm Wiloyat.

RÉSUMÉ

Une analyse portant sur les taux d'incidence et de mortalité, par âge et standardisés de la tumeur maligne de l'oeil (TMO) ainsi que sur les facteurs professionnels, ethniques, environnementaux et géographiques pouvant exercer une influence sur cette affection a été effectuée en Ouzbékistan pour la période de 1978-1998. Avant 1978, l'on ne disposait d'aucune information sur les patients atteints de TMO en Ouzbékistan. Nous avons recueilli 4872 nouveaux cas primaires, dont 79.7% (3882 patients) ont été traités dans notre département. Tous les cas ont été testés statistiquement.
L'incidence par âge de la TMO a son pic dans le sous-groupe de 60-69 ans. L'incidence la plus élevée a été remarquée dans le groupe ethnique ''non-local''. Les tumeurs de la paupière sont les plus fréquentes. Après viennent les tumeurs conjonctivales, intra-oculaires et orbitaires. L'incidence parmi les femmes urbaines et rurales est supérieure à celle des hommes. Au cours de 10 ans l'incidence standardisée a augmenté 2.3 fois et la mortalité 6.0 fois. L'incidence la plus élevée a été remarquée dans les régions de Karakalpakstan et de Khorezm.

KEY WORDS

Incidence. Localization. Malignant eye tumours. Mortality. Pollution.

MOTS-CLÉS

Incidence. Localisation.Tumeurs malignes d'oeil. Mortalité. Pollution.

In cherished memory of Ikhtibor Yuldasheva

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INTRODUCTION

Epidemiological study of METs is very important in identifying the relationship between various external factors and incidence in order to determine methods of prevention and effective treatment. In doing so, the authors writing on the subject use standardized indices (10, 21), age-standardized incidence (2), mean age-adjusted incidence (26), average annual incidence (8), average annual age-adjusted incidence (11), average annual age standardized incidence (9), incidence (15), age-specific rates (22), and specific incidence (5). Most authors calculate incidence rates per 100,000 inhabitants but some calculate incidence per 1,000,000 inhabitants (9, 11, 26). In addition, types and localizations of studied METs differ greatly, e.g., "eye" (8, 10, 11), "eye, orbit, related adnexa" (2), "intraocular" (5, 10, 15), "intraocular, conjunctival, orbital" (9), "ocular malignant melanoma" (21), "uveal melanoma" (26), and "malignant melanomas of the choroid and ciliary body" (1). Nonetheless, the total incidence of intraocular METs is not more than 1.0 per 100,000 inhabitants (5, 10, 15). Moravcova et al (15) found that incidence of intraocular tumours in the Slovak Republic was 8.2 per 100,000 inhabitants in 1968-1985. In the same period and country (5), a specific incidence of intraocular tumours for males was 1.0 and for females 0.8 per 100,000 inhabitants, i.e. more than ten times less. MET incidence is not more than 1.0 per 100,000 inhabitants (5, 8, 10) in 1966-1986. Incidence of malignant melanoma of the choroid and the ciliary body is also less than 1.0 (0.72 per 100,000 inhabitants) (1). Concerning ethnic groups of patients with METs, most authors argue that basal cell carcinoma is the most common malignant eyelid tumour in whites (4), that eye cancer occurs more frequently in whites than in blacks (8), that primary eyelid tumours of any type are rare in blacks (13), that age-adjusted rates were higher for whites than for blacks and declined from 1973-1977 to 1983-1987 in whites (22), that most cases (97.8%) of uveal melanomas occurred in the white population (26), that the incidence rate was approximately fivefold higher among white males (27), and that in white men the incidence rate increased by 295% within 27 years (35).

The purpose of this paper is to analyze incidence rate, age-adjusted and standardized incidence and mortality of METs in Uzbekistan in 1978-1998 and to study professional, ethnic, environmental, and geographical factors which could influence MET incidence and mortality.

PATIENTS AND METHOD

Before 1978, there was no information about the number of patients with METs in Uzbekistan. Since 1978, the Institute of Oncology and Radiology (IOR) of Uzbekistan's Academy of Sciences has been collecting the information about primary new cases of all malignant tumours after histopathologic confirmation, including METs of adults and children. In joint collaboration with the IOR's Resource Department, we have gathered MET related information from 1978 to 1998. The information includes patient's name, age, ethnic background, address, profession, diagnosis, method of treatment, results of treatment and, where applicable, date and cause of death. During that period, 4872 patients have been registered - 2377 males (48.8%) and 2495 females (51.2%). 79.7% (3883 patients) were treated in the IOR's Department of Ophthalmology. The rest 20.2% (983 patients) were treated in regional cancer dispensaries, less than 0.1% (5 patients) in Russia (Moscow and St. Petersburg), Ukraine (Odessa) and one patient was treated in Israel. Histopathologic confirmation has been done in the IOR's Department of Histopathology or in regional cancer dispensaries.

For statistical purposes, the patients were divided into 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79,80-84, 85-89, and 90 and more age subgroups. We have calculated incidence rate, age-adjusted and standardized incidence. Incidence rate is defined as ''a number of new cancers of a specific site/type occurring in a specified population during a year, usually expressed as a number of cancers per 100,000 population'' (18). Age-adjusted incidence is ''a weighted average of the age-specific rates, where the weights are the proportion of persons in the corresponding age groups of a standard population'' (18). The standardized incidence is calculated first by estimating

the age-specific rates and then applying these rates to the reference population, which is the standard world population (34). To calculate incidence rate, age-adjusted and standardized incidence, similar number of population divided by the same age subgroups was used. Incidence in different ethnic groups was compared to the number of the same ethnic groups in Uzbekistan. Population data were obtained from Uzbekistan's Statistics State Committee. Confidence intervals were calculated using the log rank test to determine differences among the groups of interest. All rates were statistically tested and considered statistically significant if intersecting the 95% confidence interval (CI 95%, $P \leqslant 0{,}05$). To analyze MET incidence, the International Classification IX, 1984, was used: eyelid skin (172.1, 173.1), conjunctiva (190.3), retina (190.5), uveal tract (190.6), orbit except for bones (190.1), and orbital bones (170.0). Other malignant tumours of eyelid as well as malignant tumours of lacrimal gland and malignant Meibomian tumours were included in the sections 190.1 and 173.1 respectively. For statistical purposes, all METs were divided into four subgroups: eyelid, conjunctiva, intraocular and orbit. For mortality rates, only those cases were considered where death has been caused by a MET.

Climatic and geographic characteristics of MET incidence have been studied by plotting incidence and climatic zone data presented in single scale on Uzbekistan's maps. Climatic maps and maps of water and soil pollution were obtained from the Central Asian Regional Research Hydrometeorological Institute. Air pollution data were provided by the State Committee of Nature Protection of Uzbekistan. Computer application for statistical data manipulation was developed by the Central Asian Regional Computing Centre and the Institute of Nuclear Physics.

RESULTS

In the subgroups between 15-19 and 30-34 years (Figure 1), the age-adjusted incidence did not change significantly but beginning from the 35-39 to 60-64 age subgroups the age-adjusted incidence increased and then declined in both sexes in the 65-69 to 90 and more age subgroups.

Of all 125 ethnic groups in Uzbekistan in 1978-1987, the highest MET incidence rate was in Jews, Germans and Russians, followed by Ukrainians, Tartars, Armenians, Turkmens, Azeris, Koreans, Uzbeks, Karakalpaks, Kazakhs, Tajiks, and Kyrgyz. If dividing patients into "local"

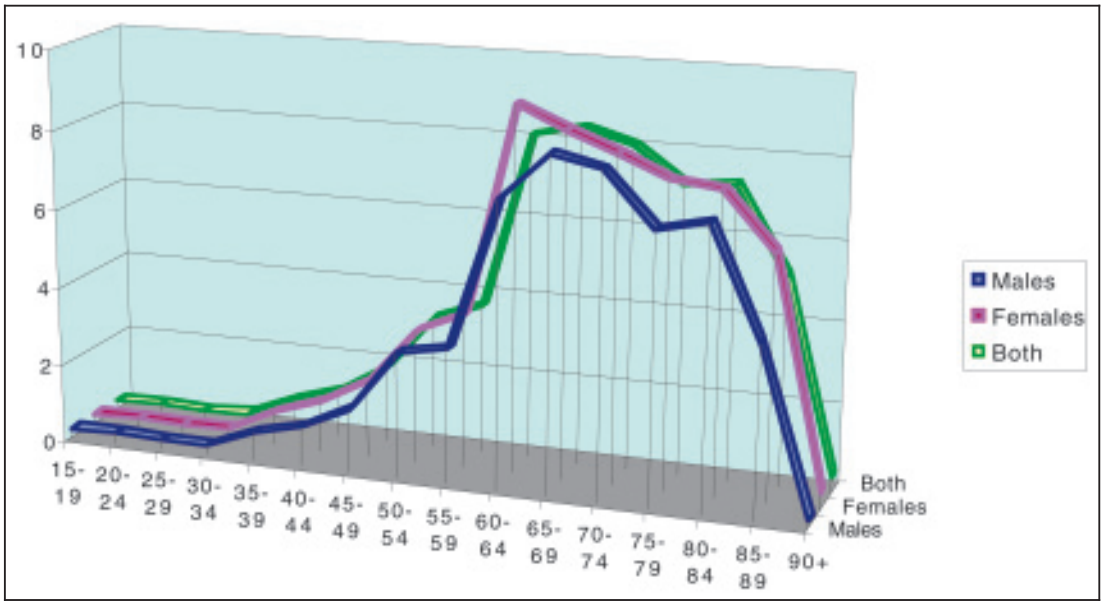

Fig 1. Sex and age-adjusted MET incidence per 100,000 in 1978-1998.

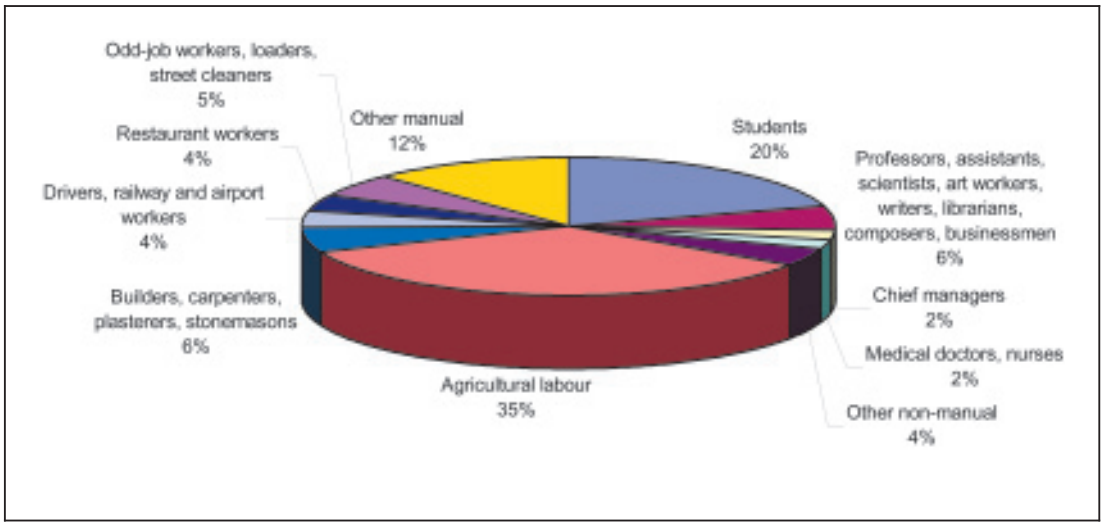

Fig 2. Percentage of METs by patients' professional activities.

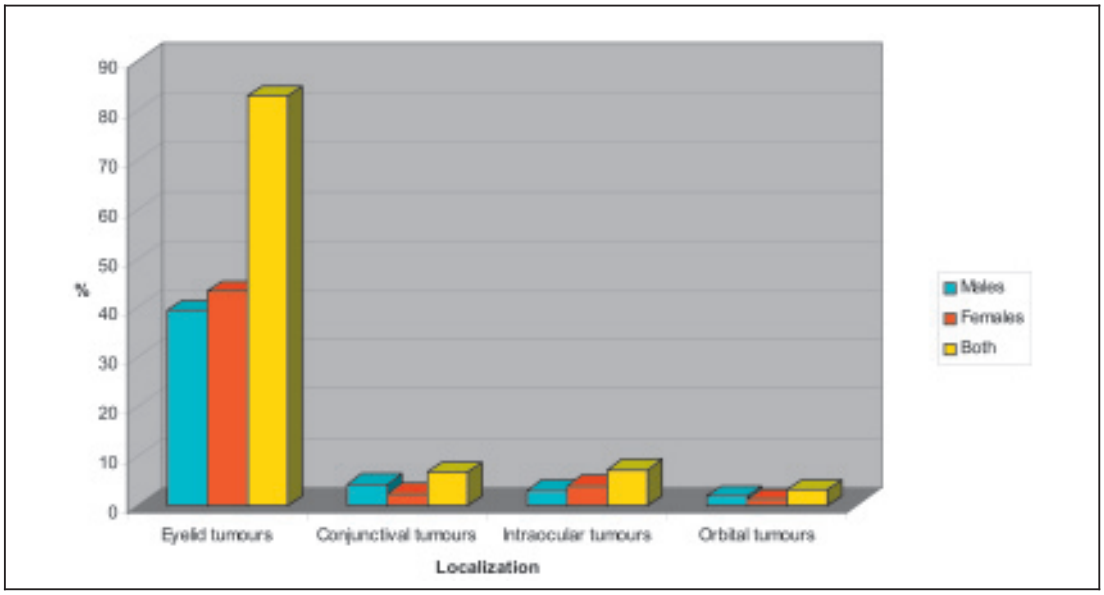

Fig 3. Percentage of malignant eye tumours by localization

(Uzbeks, Karakalpaks, Kazakhs, Tajiks, Kyrgyz, and Turkmens) and "non-local" (Russians, Ukrainians, Germans, Jews, Koreans, Azeris, and Armenians) ethnic groups, it is evident that the MET incidence of "non-local" ethnic subgroup has increased 3.5 times compared to "local" ethnic subgroup. From 1988 to 1998, "non-local" subgroup has decreased in number but MET incidence in "non-local" subgroup continued to be 1,8 times than the one in "local" subgroup.

We have studied the patients' professional activities to find out which profession or group of professions had the majority of eye cancer cases (Figure 2). Percentage of METs among manual workers was 1,9 times higher (65.6%) than that among non-manual workers (34.4%) (CI 95%). Interestingly enough, this figure for medical doctors and nurses was 2%.

Table 1: *Incidence rate (IR) and standardized (SI) MET incidence by localization per 100,000 urban and rural inhabitants*

Localization	IR & SI	Urban population			Rural population			Total		
		Males	Females	Both	Males	Females	Both	Males	Females	Both
Eyelids	IR	4.3	5.1	4.9	4.1	4.9	4.6	4.3	5.2	5.1
	SI	7.2	10.1	8.7	7.0	9.6	8.4	7.1	9.9	8.6
Conjunctiva	IR	1.5	1.8	1.7	1.2	1.7	1.8	1.6	1.8	1.9
	SI	2.9	3.8	3.7	2.5	3.2	3.1	2.5	3.3	3.4
Intraocular	IR	2.0	2.6	2.5	1.9	2.3	2.0	2.1	2.4	2.3
	SI	2.9	5.3	3.8	3.0	3.9	3.9	3.1	4.7	3.8
Orbit	IR	0.5	0.9	0.8	0.4	0.7	0.6	0.5	0.8	0.7
	SI	1.2	1.9	1.7	0.9	1.6	1.2	1.1	1.7	1.5
Total	IR	1.2	2.0	1.9	1.9	1.7	1.8	1.0	1.5	1.6
	SI	3.2	5.1	4.3	2.7	4.5	3.4	3.0	4.9	3.8

Of all MET cases (Figure 3), the highest is the percentage of eyelid tumours (males 39.5%, females 43.4%, both 82.9%), followed by conjunctival tumours (males 3.1%, females 4.1%, both 7.2%), intraocular tumours (males 4.3%, females 2.4%, both 6.7%) and orbital tumours (males 1.9%, females 1.3%, both 3.2%).

Incidence rate and standardized incidence (Table 1) of eyelid and conjunctival tumours has no statistically significant difference between gender and between urban and rural population.

Standardized intraocular tumour incidence for urban females is higher than that for urban males (CI 95%). Total incidence of female intraocular tumours (4,7) is higher than the one of males' (3,1). Incidence rate (0,9) and standardized incidence (1,9) of female orbital tumours in both urban and rural areas (0,7 and 1,6 respectively) is higher than that for urban and rural males. Total incidence rate (2.0) and standardized incidence (5.1) for urban females is higher than total incidence rate (1.2) and standardized incidence (3.2) for urban males. Total standardized incidence for rural females (4.5) is higher than for rural males (2.7). Urban and rural females have METs more frequently than males but there is no difference between incidence rate (1.9) and standardized incidence (4.3) of METs for both sexes of urban and rural population.

Annual standardized incidence (Figure 4) was at maximum in 1982 and in 1986. For 20 years, the incidence rate has varied, yet in total annual standardized incidence increased from 0.09 to 2.1 per 100,000 inhabitants, i.e. 2.3 times. Annual incidence rate of METs followed the same pattern and increased from 0.2 in 1978 to 0.8 in 1998, i.e. fourfold.

Annual mortality incidence between 1978 and 1987 exceeded not more than 0.2 and from 1988 to 1998 it increased from 0.1 to 0.6 per 100,000 inhabitants, i.e. sixfold.

MET incidence rate in various regions of Uzbekistan (Figures 5 and 6) was the highest in the Karakalpak Autonomous Republic (KKAR) (5.9) and in Khorezm Wiloyat (4.8). MET mortality rates per 100,000 inhabitants were the highest in the KKAR (2.2), followed by Khorezm Wiloyat (1.6). The KKAR is situated in the estuary of the Amu Darya river and on the shore of the Aral Sea, the site of the world's worst environmental disaster for the past 20 years. Khorezm Wiloyat is the only Uzbekistan region which is situated along both banks of the Amu Darya river. Intensive agriculture and abundant irrigation have resulted in land degradation and salinisation and contamination of water with salt and agricultural chemicals (27). The Amu Darya, especially its estuary, is still polluted with organo-chlorine pesticides and a total of 84 tons of salt is discharged into the river annually. Huge amounts of salt, fertiliser, herbicides and pesticides found their way to the rivers as a return flow from the cotton fields (27, 32). In the 80s-90s, pesticide pollution load per 1 ha exceeded the USSR's average limits by 15 times and per capita permissible pollution load by 3.5 times (16), though for the past 10 years the contamination of soil with pesticides tends to decrease in Uzbekistan.

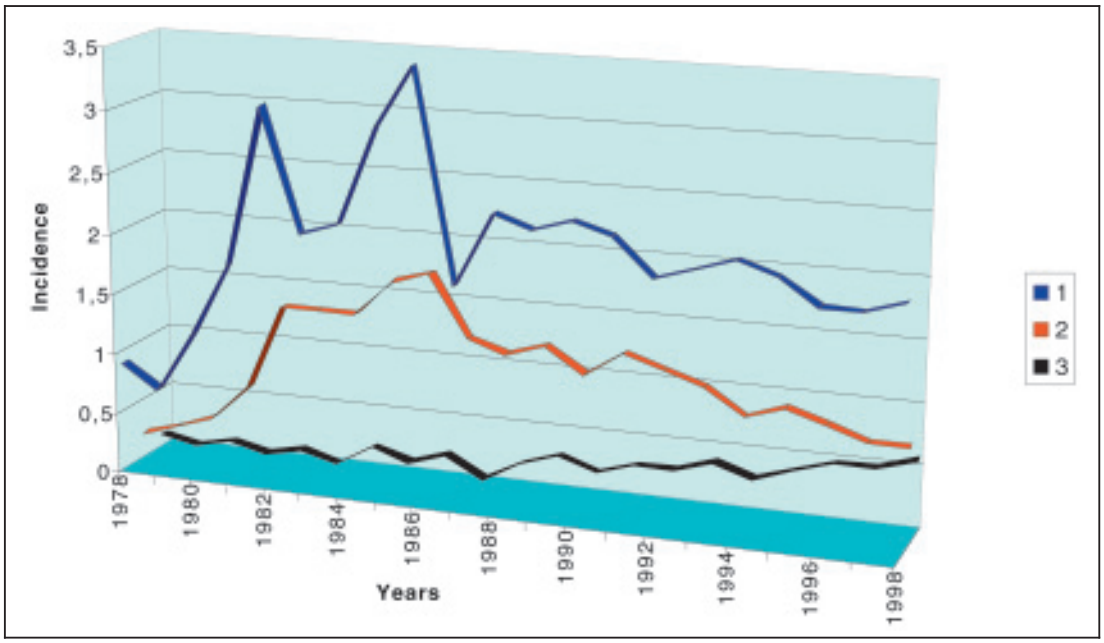

Fig 4. Annual incidence rate (1) and standardized incidence (2) and mortality (3) for patients of both sexes with METs per 100,000 inhabitants in 1978-1998

Of 28 cities having statistically significant higher MET incidence rate compared to respective wiloyat's urban incidence in 1978-1987, 11 (39.3%) cities are situated on the rivers with the highest level of pesticide pollution (Muynak, Chimbay, Khodjeyli, Bustan, Beruni, Karmana, Shakhrisyabz, Sherabad, Baysun, Shurgi and Akkurgan) and 14 cities (50%) are situated on the DDT polluted soils (Kagan, Aktash, Nurabad, Chelek, Djuma, Krasnogvardeysk, Yangier, Shirin, Almalyk, Yangiabad, Chirchik, Chinaz, Kokand and Leninsk).

We analyzed air pollution with dust, sulphur dioxide, carbon oxide and nitrogen oxide. The content of these pollutants in the air varied from 1.3 to 4.8 (dust), 1.3 to 15.9 (sulphur dioxide), 0.3 to 5.2 (carbon oxide) and 0.5 to 2.3 (nitrogen oxide) of maximum tolerance dose units. However, no relationship between air pollution and MET incidence was found.

Comparing MET incidence rate to Uzbekistan's climate in various areas, we found that the highest incidence rate was in the southern Surkhandarya Wiloyat, where the highest annual average soil temperature (over 12°C) and air temperature (over 18°C) and the longest sunshine duration (more than 3000 hours per annum) have been registered.

Since 1977, of all 4872 patients (2377 males, or 48.8%, and 2495 females, or 51.2%) with METs in Uzbekistan, 3883 patients (79.7%) have been treated in the Department of Ophthalmology at the IOR which is the only medical institution in Uzbekistan where all conditions for early diagnosis and treatment of eye cancer are met. To diagnose eye cancer, all ophthalmologic methods together with x-rays, ultrasonography, computerized tomography, magnetic resonance imaging (in collaboration with Tashkent State Medical Institute), and cytological and histological analysis of biopsy and operative material are used. For eye cancer treatment, surgical and non-surgical methods are used. Surgical methods include micro- and macrosurgery with or without sparing of the eyeball, plastic surgery if necessary, laser surgery and cryosurgery. Among non-surgical methods are radiotherapy and chemotherapy. In most cases (70-75%), different combinations of these methods are used. There is a lack of qualified specialists and equipment to treat patients with METs in the remote provincial health institutions and the patients have to visit Uzbekistan's

Fig 5. Administrative map of Uzbekistan

capital, Tashkent, for treatment. Lots of patients have not enough money to make such a long way and in many cases the treatment starts inadmissibly late. Hence, 68% of patients in Uzbekistan are being registered in the late stage of tumour growth. Even patients with eyelid and conjunctival cancers were in 59.9% registered and began treatment in the late stage of the neoplastic process. In 1978-1998, only 7 patients with intraocular choroidal melanoma at the early stage were reported, and all patients with malignant orbital tumours have begun their treatment later than those with other localizations.

Although there are obviously successful cases, late diagnosis and delayed treatment are still the most important causes of growing MET mortality in Uzbekistan.

DISCUSSION

We found that the age-adjusted MET incidence has a peak in the 60-69 age subgroup. Sunderraj (29), Ud-Din et al (31) and Osterlind (21) came to the same conclusion but in their findings the peak was between 40 and 60 years (21), above 50 years (31), and in the 80-84 age subgroup (6). Distribution of eye cancer risk by age is bimodal with the peaks occurring during early childhood and again during adulthood (14). We had similar results regarding two peaks of incidence in children (17) and in adults.

Manual workers have been reported to have METs more frequently than others. Swerdlow (30) found that proportional registration ratios were generally higher for non-manual than for manual social classes and notably high for electrical and electronics workers.

There are different opinions about frequency of ocular cancer. For example, Marshall (14) be-

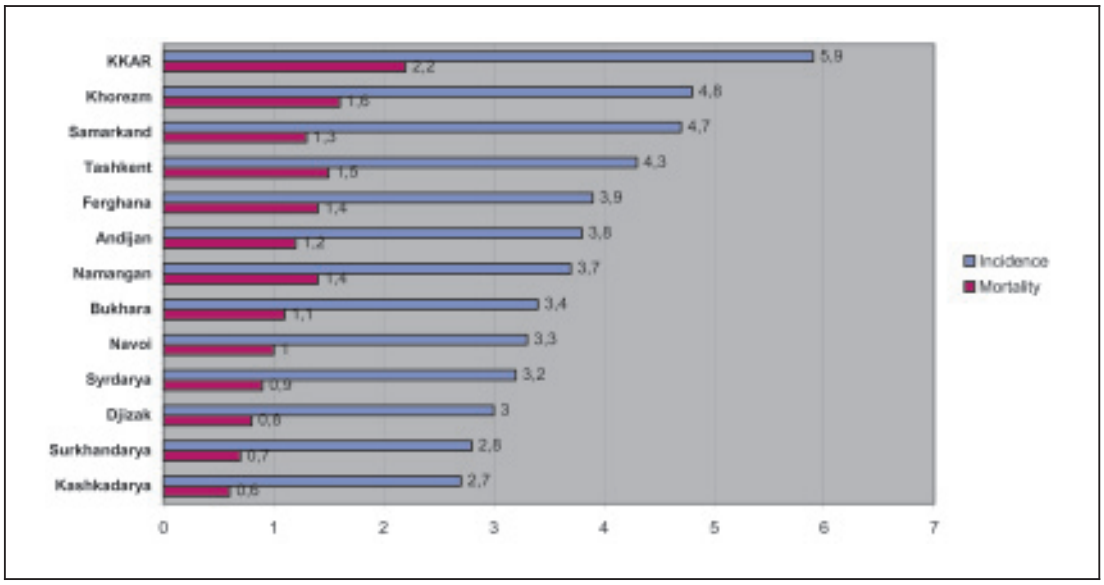

Fig 6. Geographical distribution of MET incidence rate and mortality by Uzbekistan's regions (wiloyats)

lieves that the most frequent anatomical site of ocular cancer is the eye, followed by the orbit, the conjunctiva and the lacrimal gland. Scat et al (25) found that of 1705 malignant tumours of the eye and the adnexa, 1305 tumours were localized ''endo-ocularly'', 398 in the lids, 119 in the conjunctiva, and 90 in the orbit. Malik et al (12) found that of 279 primary METs studied, conjunctival squamous carcinoma was the commonest (50.4%). According to Poso et al (24), epibulbar (35%) and intraocular (33%) tumours were the most frequent, followed by orbital tumours (20%).

In our practice, annual mortality incidence in 1978-1998 was 0.03 to 0.6 per 100,000 inhabitants while Furdova (5) found the mortality rate to be over 0.3 per 100,000 inhabitants. Wang et al (33) found that for all eyelid malignancies the mortality rates at 5 years were 7.3% (1.1% between 5-9 years according to our results).

Estimated Cancer Deaths for eye ranged from 125 male patients and 125 female patients in 1994 (3) to 100 male patients and 100 female patients in 2003 (7).

The causes of eye cancer development are disputable. Some authors found ultraviolet light to be an important risk factor for the development of squamous cell carcinoma of the eye (19) and of conjunctival melanoma (35), but others argue that conjunctival cancers were associated with human papilloma viral infection (22) or that ''the epidemic appears to be related to HIV infection, on a background of ultraviolet light exposure'' (23).

Geographic and racial factors play an important role in determining the frequency and pattern of eye neoplasms (12). We believe that adult incidence rate of METs, as well as MET mortality to the large extent depend on ethnic, economic, environmental and even political factors.

Ethnic factors include hygiene, marriages between family members, and literacy level and cultural level of an ethnic group. Economic factors influence literacy, culture, level of staffing with qualified experts and hospital facilities and, most importantly, early diagnosis of METs.

The environmental situation in Uzbekistan continues to be alarming. Substantial dioxin residues were found in mothers' milk, especially in the KKAR (28). According to Uzbekistan's Academy of Sciences, only 8% of Uzbekistan's rivers are ''clean'', around 15% of river water is of ''satisfactory'' quality, and 41% is ''bad''. In 1996, over 10 million people (about 50% of the population) resided in the river basins that fell into the latter category. Around 36% of river water is considered ''dangerous'' or ''extremely dangerous'', particularly in the KKAR

and in the lower delta of the Zeravshan river, where 24% of the Uzbek population lives. In many cases, rural dwellers are forced to drink irrigation water, being the only water available, with all health risks involved (28). Chemical water pollution coupled with a long-term ultraviolet light exposure is likely to play significant role in the development of skin cancer in Uzbekistan, in particular eyelid skin cancer. However, further research is required to prove this hypothesis.

Political situation as a result of the collapse of the former Soviet Union has brought in a dramatic impoverishment. For people living in the rural area, this means lack of opportunity to find money to buy necessary and often very expensive medicines, e.g. chemotherapeutic drugs, and to visit a central hospital, while there are no conditions for diagnosing and treating patients with METs in rural hospitals.

Taken in total, these factors have led to the increase in MET incidence in Uzbekistan. This view is supported also by the fact that for the last 10 years the MET mortality has grown sixfold in Uzbekistan.

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