RESEARCH COMMUNICATION

Epidemiology of Ocular Malignancies in Karachi

Yasmin Bhurgri[1,2,3], Hadi Bhurgri[1], Ahmed Usman[4], Naveen Faridi[5], Jawaid Malik[5,6], Rehan Puri[1], Mehek Mirza[2], Asif Bhurgri[1,2], Rashida Ahmed[3], Suhail Muzaffar[3], Naila Kayani[3], Shahid Pervez[3], Sheema H Hasan[3], Akber Haider Soomro[2]

Abstract

The study was conducted with the objective of examining descriptive epidemiological characteristics of malignant ocular tumours in Karachi (1998-2002). The data for two hundred and forty two ocular malignancies registered at the Karachi Cancer Registry for Karachi Division during a 5-year period, from January 1st 1998 to December 31st 2002 were analysed. The age standardized incidence rate (ASIR) was 0.5/100,000 in males and 0.4/100,000 in females. The gender ratio (M:F) was 1.3. The mean age was 34.8 years (95% CI 30.1; 39.6) in males and 34.5 years (95% CI 28.0; 40.9) in females. A fourth of the malignancies were childhood tumours. The most common childhood malignancies were retinoblastomas and rhabdomyosarcomas, whereas the most common adult malignancies were conjunctival squamous cell carcinomas and melanomas. Approximately 97.0% of the tumours were histologically confirmed. The majority (62.5%) presented as low-grade (grade 1) lesions, and were localized to the eye (50%) at the time of diagnosis. The annual incidence rates remained stable during this period.

The crucial importance of ocular malignancies is the high 5-year survival rates, associated disability following unilateral or bilateral enucleation and the implications as preventable components of 'Cancer Control Programs'. This article provides demographic statistics, which could be useful for the foundation, establishment and monitoring of a component of an effective cancer control program, the risk factors of ocular malignancies being well established. It is recommended that public health education to prevent ultraviolet light related ocular malignancies, information on preventative sun protection behavior, legislation for occupation related ocular cancers and genetic counseling for familial retinoblastoma should be essential primary components of all National Cancer Control Programs even in apparently low risk countries. In the long-term perspective, these efforts should further reduce the incidence - meanwhile stabilization of incidence rates could be achieved. Early detection and standardized treatment will reduce the associated morbidity and mortality.

Key Words: Malignant tumours - eye - retinoblastoma - Karachi

Asian Pacific J Cancer Prev, **4**, 352-357

Introduction

The study was conducted with the objective of examining descriptive epidemiological characteristics of malignant ocular tumours in Karachi (1998-2002). This hot, humid city is located on the coast of Arabian Sea, latitude: 24 - 56'-00" and longitude: 67 -01'-00", the Tropic of Cancer passes just below it. The city of Karachi or Karachi Division is the catchment population of Karachi Cancer Registry (KCR). This registry provides population-based descriptive epidemiology data of cancer incidence by age, sex, race, and time period according to site and histologic characterization. The cancer profile in males is lung, oral cavity, larynx, urinary bladder and prostate whilst in females the commonest cancers are breast, oral cavity, gall bladder, cervix and ovary. Ocular malignancies do not rank amongst the ten most common malignancies in either gender.

In the global perspective, malignancies of the eye ICD-

[1]Karachi Cancer Registry, [2]Sindh Medical College, Karachi, [3]Aga Khan University Hospital, Karachi, [4]Jinnah Postgraduate Medical Centre, Karachi, [5]Liaquat National Hospital, Karachi, [6]Ziauddin Cancer Hospital, Karachi
Address all correspondence to: Dr. Yasmin Bhurgri, Karachi Cancer Registry, Department of Pathology, Sindh Medical College, Rafiqui Shaheed Road, Cantt, Adjacent Jinnah Postraduate Medical Centre, Karachi or Department of Pathology, Aga Khan University Hospital, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan. Fax: 92 21 493 4294; 92 21 493 2995. email bhurgri@cyber.net.pk

10 (International Classification of Diseases 10th Revision) category C69 do not affect a significant number of individuals, neither do they rank amongst the ten most common tumours overall for either gender. (WHO, 1992) The incidence rates remain low; only 12.4% and 2.4% of the 186 registries in CIV volume VIII cite an incidence above 1.0/100,000 in males and females respectively. The highest rates being observed in Uganda (ASIRs 2.9/100,000 males; 2.8/100,000 females) and Zimbabwe (ASIRs 2.2/100,000 males and 3.3/100,000 females). (Parkin et al, 2002).

The crucial importance of ocular malignancies is the high 5-year survival rates, associated disability following unilateral or bilateral enucleation and the implication as preventable components of 'Cancer Control Programs'. The 5-year relative survival rates given by the SEER even in the eighties (1983-1987) were high for ocular melanoma (79%) and retinoblastoma (96%). (Polednak and Flannery, 1995)

Methodology

Epidemiological data of incident ocular malignancies, diagnosed clinically or microscopically and registered at the Karachi Cancer Registry for Karachi Division during 1st January 1998 to 31st December 2002 were analysed. This included malignancies of the conjunctiva, retina, ciliary body, lacrimal gland, orbit and eye (not otherwise specified-nos) but excluded cancer of the eyelids. The data were rechecked, and residency status re-ascertained. People residing in the specified geographical regions for more than six months were considered residents. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging.

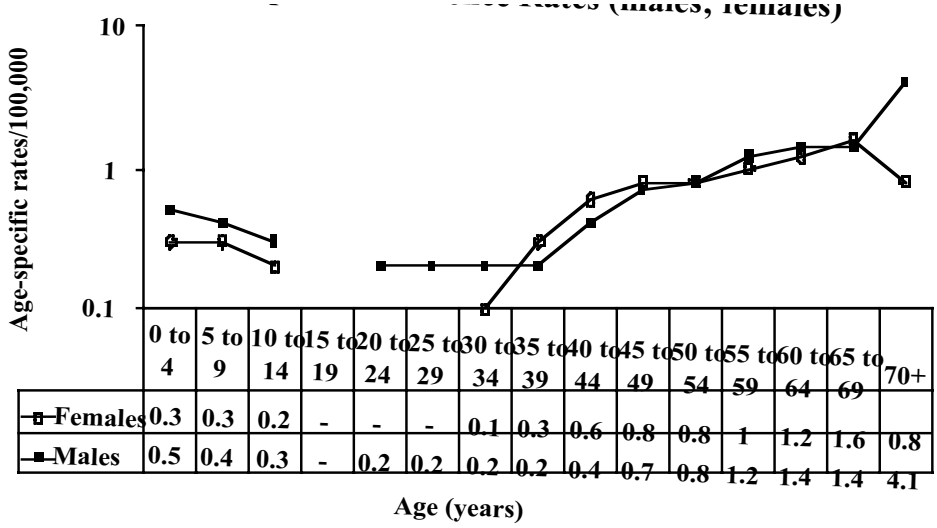
The data were classified using ICD-O2 (International Classification of Diseases-Oncology, 2nd edition) and computerized using a customized version of CANREG-3 software. (WHO, 1990) Manual and computerized validity checks for the cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR). This involved factors influencing comparability i.e. classification and coding. (Parkin et al, 1997; Parkin et al, 1994; Skeet, 1991).

The city of Karachi has a population of 9,802,134; males 5,261,712 and females 4,540,422 (Census 1998) Person-years of population at risk by sex and 5-year age groups were estimated based on the 1998 census, assuming an annual growth rate of 3.52%, as calculated by the Federal Bureau of Statistics. "Standardized incidence rate was calculated with an external reference population, the 'world' population. (Segi, 1960) The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented". (Parkin et al, 1997) The projection of incident ocular cancer cases for the years 2003-2027 is based on an assumed annual population growth rate of 3.52% for Karachi, and stable incidence rates for ocular malignancies. The population of Pakistan used for projections was 130,579,571. (census, 1998)

Results

A total of 242 malignant tumors of the eye were registered at the Karachi Cancer Registry for Karachi Division (KD) during a five-year period, 1998-2002. The age standardized incidence rate (ASIR) was 0.5/100,000 in males and 0.4/100,000 in females. The gender ratio (M:F) was 1.3. The mean age was 34.8 years (95% CI 30.1; 39.6) in males and 34.5 years (95% CI 28.0; 40.9) in females. Approximately a fourth of the malignancies were childhood tumours (26.4% males; 28.6% females). The ratio of adult to childhood tumours was 2.8 in males and 2.5 in females. Majority of the tumours (62.5%) presented as low-grade (grade 1) lesions, and were localized to the eye (50%) at the time of diagnosis.

The age specific incidence rates (ASIRs) for ocular malignancies in both genders showed a bimodal age



	0 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70+
Females	0.3	0.3	0.2	-	-	-	0.1	0.3	0.6	0.8	0.8	1	1.2	1.6	0.8
Males	0.5	0.4	0.3	-	0.2	0.2	0.2	0.2	0.4	0.7	0.8	1.2	1.4	1.4	4.1

Figure 1. Ocular Malignancies Age Specific Incidences Rates

distribution with peaks occuring during early childhood and again during adulthood. The ASIRs showed a peak rise in infancy (0-4 years of age) with a gradual fall till the 10-14 year age group. Retinoblastoma was the most common ocular malignancy in children, followed by embryonal rhabdomyosarcoma. In males the ASIRs showed a second rise from the 20-24 year age group, increasing gradually uptil the 65-69 year age group. Subsequently a sharp rise was observed in the 8th decade, which could reflect an actual increase in incidence in the older men. In females a second gradual rise was observed in the 30-34 year age group, rising to a maximum in the 7th decade followed by an actual apparent decrease in the risk in the 70+ age group.

Approximately 97.0% of the tumours were histologically confirmed. The rest (3.0%) were clinically diagnosed advanced malignancies. The most common childhood malignancies were retinoblastoma and rhabdomyosarcoma, the most common adult malignancies were conjunctival squamous cell carcinoma and melanoma. The topographic frequency distribution of ocular cancers in males was the conjunctiva (29.7%) followed by the orbit (26.4%), retina (23.1%), ciliary body (7.7%), lacrimal gland (4.4%) and eye, nos (8.8%). Eqvivalent sites in females were conjunctiva (36.7%) followed by the orbit (22.4%), retina (22.4%), ciliary body (8.2%), lacrimal gland (2.0%) and eye, nos (8.2%).

The histological characterization of ocular malignancies in males was squamous cell carcinoma (29.7%), retinoblastoma (23.1%), lymphoma (13.2%), rhabdomyosarcoma (9.9%), melanoma (8.8%), and adenocarcinoma (4.4%). In females the histological characterization was squamous cell carcinoma (36.8%), retinoblastoma (22.4%), rhabdomyosarcoma (12.0%), melanoma (8.2%), adenocarcinoma (8.2%) and lymphoma (6.1%).

Sixty percent of the retinoblastoma presented in the 0-4 year age group, however 37.5% presented later as neglected, advanced, usually bilateral malignancies in the 5-9 year age group and the rest in the 10-14 year age group. Rhabdomyosarcoma presented with a trimodal pattern. The first peak of rhabdomyosarcoma (embryonal variant) was observed in the 0-4 year age group, a second sharp rise was seen in young adults (15-24 year age group), and a third rise in older adults, (35-54 year age group). Primary ocular lymphoma first presented in the early twenties, the numbers gradually increasing till the 55-64 year age group. A diffuse B-cell pattern was predominantly observed. Conjunctival squamous cell carcinoma (SCC) was first observed in the 15-24 year age group, with a subsequent gradual rise to a peak in the 55-64 year group, tapering off in the 75+ group. A plateau rise of melanoma was observed between 25 to 64 years of age.

Discussion

The descriptive epidemiological data for ocular malignancies from KD are supported by the data of Karachi South (KS), the southern-most district of Karachi, along the seacoast. (Bhurgri et al, 2001) The ASIRs were identical for KD and KS, 0.5/100,000 in males and 0.4/100,000 in females. In Quetta, another city of Pakistan, the incidence was higher in males (ASIR 0.7/100,000) but lower in females (ASIR 0.2/100,000). (Bhurgri et al, 2002) This city located at a higher latitude (latitude 30-25'-00"; longitude 67-00'-00") than Karachi, has a lighter-skinned and lighter eyed population. The vast majority of the female population of Quetta observes purdah or the use of veil; this tradition is not so popular in the relatively westernized culture of Karachi. A geographical variation of incidence is often observed within countries as risk factors vary. In US the average annual age-adjusted incidence of ocular cancer varies from 0.6 to 0.9 per 100,000 for the male population and from 0.5 to 0.8 per 100,000 for the female population. (Marshall, 1993; Swanson and Cloud 1991)

Retinoblastoma is the most common ocular malignancy in children worldwide, this held true in Karachi. Uveal melanoma and conjunctival SCC are the most common ocular malignancies in adults globally; the reverse is true for Karachi. (Lee et al, 2000; Marshall, 1993; Swanson and Cloud 1991)

Conjunctival SCC, was the most common adult ocular malignancy (both genders) in Karachi, the male female ratio being 0.8. In Quetta the frequency of conjunctival SCC in males was twice that of their contempories in the predominantly urban Karachi, probably a result of higher sun exposure in the former. Quetta has a large rural population where outdoor work is more prevalent. In Quetta conjunctival SCC was four times more common in the older men than in the women. The women in Quetta generally observe purdah. The lower incidence in the dark-eyed population of Karachi may also suggest a lower sensitivity

Table 1. Distribution of Ocular Malignancies According to Morphology and Topography

	Males (N=143)	Females (N=99)	ICD-10 codes
Morphology	%	%	
Retinoblastoma	23.1	22.4	951
Squamous cell carcinoma	29.7	36.8	807
Rhabdomyosarcoma	9.9	12.0	890-892
Lymphoma	13.2	6.1	959-970
Adenocarcinoma	4.4	8.2	814 -
Melanoma	8.8	8.2	872-879
Unspecified morphology	11.0	6.1	800-802
Topography	%	%	
Conjunctiva	29.7	36.7	690
Retina	23.1	22.4	692
Ciliary body	7.7	8.2	694
Lacrimal gland	4.4	2.0	695
Orbit	26.4	22.4	696
Eye, NOS	8.8	8.2	699

Table 2. Distribution of Ocular Malignancies by Age and Morphology

Age-groups (years)	Retinoblastoma %	Rhabdomyosarcoma %	Lymphoma %	Squamous cell Carcinoma %	Melanoma %
0-4	59.4	25.0	-	-	-
5-9	37.5	-	-	-	-
10-14	3.1	-	-	-	-
15-24	-	50.0	6.7	6.9	-
25-34	-	-	6.7	11.5	18.2
35-44	-	16.7	13.4	13.6	27.3
45-54	-	8.3	20.0	18.2	45.5
55-64	-	-	53.4	38.6	9.1
65-74	-	-	-	9.1	-
75+	-	-	-	2.3	-
Mean ages	3.1			50.1	

to solar radiation. Poor hygienic conditions, epidemics of viral conjunctivitis, solar UV and latitude gradient may play an important pathogenic role. (Osterlind, 1993) An increased risk of conjunctival cancer is observed in HIV infected individuals. The role of other oncogenic viral infections is unclear. (Newton et al, 2002) Certain occupations are considered high risk for this malignancy. Precise risk association data for occupational ocular cancers is not available for any population in Pakistan. No eye protection measures are used by high-risk occupations viz. electricians, welders' etc. during work, neither is it compulsory by legislation. Public health education in this context is also recomended.

The pathogenesis of uveal melanoma is linked to a genetic-environmental interaction. Mutational inactivation of two tumor suppressor genes is considered oncogenic for uveal melanoma. (Tschentscher et al, 2000) The genetic effect on pigment determines to a large extent the degree to which the eye is susceptible to some carcinogenic agent. The ultraviolet light component of sunlight is the most plausible carcinogenic agent that affects the eye. An increasing amount of pigment lessens both susceptibility and the probability of lesion development, but whether lesions develop in the absence of pigment depends to a large extent on the amount of ultraviolet light to which the eye is exposed. Hormonal effects (oral contraceptives) may also play a limited role in causing ocular melanoma. (Hartge et al, 1989)

The frequency of retinoblastoma (22.0% males; 22.4% females) in Karachi was lower then the figures (69.7% and 53.6%) cited by the Bombay Cancer Registry (1986-1998) and the Singapore Cancer registry (1968-1995). (Yeole and Advani, 2002; Lee et al, 2000) This may suggest an underregistration of childhood tumours or a relatively higher incidence of other ocular malignancies. The invariant feature of retinoblastoma is the mutational inactivation of the retinoblastoma gene (RB), a prototype of a class of genes, called tumor suppressor genes, for which loss-of-function mutations are oncogenic. (Bookstein and Lee, 1991; Chen et al, 1992)

"Projections usually involve the assumption that past trends in rates of incidence or mortality will be maintained, and will apply to projected changes in the population". (NCCP, 2002) The ASIRs for ocular malignancies have remained stable at KD for 5 years, and in KS for 8 years (1995-2002), yet the public health impact should not be underestimated. In Karachi, and in a larger context in Pakistan, with an increasing population despite a stable incidence, the total number of ocular malignancies will increase, thus adding to the cancer burden of the country. For ocular malignancies in Karachi, there is at present only a marginal deviation from past trends, as observed from the difference in observed and expected number of registered cases (Table 3). The cumulative effect over the next two decades however will manifest as a financial burden to a health sector, which lacks future planning, unless provisions are made to minimize this impact by intervention. We should expect approximately 2000 incident cases of ocular malignancies for Karachi over the next 25 years and 30,000 for Pakistan. The psychological and economic problems of the individual and the family are uncomprehensible. The associated disability and morbidity have a negative cumulative effect on the economy of the country. Long-term health care policies should take these factors into consideration.

Conclusion

This article provides demographic statistics, which are essential for the foundation, establishment and monitoring of cost-effective cancer control programs. Solar radiation is a well-documented risk factor for conjunctival squamous cell carcinoma and melanoma eye. It is recommended that public health education to prevent ultraviolet light related ocular malignancies, information on preventative sun protection behaviors viz. the selection of optimal eye protective measures, legislation for occupation related ocular cancers and genetic counseling for familial retinoblastoma should be essential primary components of all National Cancer Control Programs even in apparently low risk

Table 3. Cancer Burden of Ocular Tumours – projection of Incident Cases, (1998-27)

Year	Male Population	Expected Cases	Female Population	Expected Cases	Total Cases	Expected Cases 1998-2002	Observed Cases 1998-2002
1998	5261712	26	4540422	18	44		
1999	5446924	27	4700245	19	46		
2000	5638656	28	4865694	19	47		
2001	5837137	29	5036966	20	49		
2002	6042604	30	5214267	21	51	237	242
2003	6255304	31	5397809	22	53		
2004	6475490	32	5587812	22	55		
2005	6703428	34	5784503	23	57		
2006	6939388	35	5988118	24	59		
2007	7183655	36	6198899	25	61		
2008	7436519	37	6417101	26	63		
2009	7698285	38	6642983	27	65		
2010	7969264	40	6876816	28	67		
2011	8249783	41	7118880	29	70		
2012	8540175	43	7369464	30	72		
2013	8840789	44	7628869	31	75		
2014	9151985	46	7897405	32	77		
2015	9474135	47	8175394	33	80		
2016	9807624	49	8463168	34	83		
2017	10152853	51	8761072	35	86		
2018	10510233	53	9069461	36	89		
2019	10880193	54	9388706	38	92		
2020	11263176	56	9719189	39	95		
2021	11659640	58	10061304	40	99		
2022	12070059	60	10415462	42	102		
2023	12494925	63	10782086	43	106		
2024	12934746	65	11161616	45	109		
2025	13390050	67	11554505	46	113		
2026	13861379	69	11961223	48	117		
2027	14349300	72	12382258	50	121		
Total		1361		945	2303		

countries like Pakistan. In long-term perspective these efforts will further reduce the incidence, meanwhile stabilization of the incidence rates could be achieved. Early detection and standardized treatment will reduce the associated morbidity and mortality.

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