RESEARCH COMMUNICATION

Patho-epidemiology of Cancer Cervix in Karachi South

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Abstract

Introduction: The present study was conducted with the objective of examining descriptive epidemiological and pathological characteristics of cancer cervix in Karachi South, an all urban district population of Karachi, Pakistan. Methodology: A total of 74 cases of cancer cervix, ICD-10 (International Classification of Diseases 10th Revision) category C53 were registered at the Karachi Cancer Registry, for Karachi South, during a 3 year period, 1st January, 1995 to 31st December 1997. Results: The age standardized incidence rate (ASR) world and crude incidence rate (CIR) per 100,000 were 6.81 (5.2, 8.43) and 3.22 (2.49 to 3.96). Cancer cervix accounted for approximately 3.6% of all cancers in females and was the sixth malignancy in hierarchy. The mean age of the cancer cases was 53.27 years [standard deviation (SD) 11.6; 95% confidence interval (CI) 50.58, 55.96; range (R) 32-85 years)]. The distribution by religion was Muslims (90.5%), Christians (8.1%) and Hindus (1.4%). There were no cases reported in Parsees. The frequency distribution by ethnicity was Urdu speaking Mohajirs (20.3%), Punjabis (17.6%), Gujrati speaking Mohajirs (4.1%), memon Mohajirs (8.1%), Sindhis (10.8%), Baluchs (8.1%), Pathans (5.4%) and Afghan migrants (2.7%). The ethnicity was not known in approximately a fourth (23.0%) of the cases.The socio-economic distribution was 27.0% financially deprived class, 24.4% lower middle class and 48.7% upper middle and affluent classes. The majority of the women were married (86.5%); a smaller number were unmarried (2.7%) or widows (10.8%). The age-specific curves showed a gradual increase in risk from the fourth up till the seventh decade, followed by an actual apparent decrease in risk after 64 years of age. The peak incidence was observed in the 60-64 year age group. The morphological categorization was squamous cell carcinoma (86.5%), adenocarcinoma (10.9%) and adenosquamous carcinoma (2.6%). The majority of cases presented with moderately differentiated or grade 2 lesions (45.9%). There were no in-situ cases. Approximately half the cancers (58.1%) had spread regionally and 8.1% to a distant site at the time of diagnosis. Odds ratios (OR) were calculated for socioeconomic residential categories, religion, ethnicity, age groups and education. The OR for socioeconomic residential categories ranged between 0.69 and 2.9 with a marginally higher risk in the lower [OR 2.09 (95% CI .97; 4.49)] and lower middle class [OR 2.08 (95%CI 0.95; 4.58)]. Hindus [OR 1.2 (95% CI 0.18; 2.2)] had a slightly higher risk then the Muslims [OR 0.14 (95% CI 0.17; 1.2)]. A higher risk was also observed for Christians [OR 7.76 (95% CI 1.74; 34.5)]. Conclusion: The incidence of cervical cancer in Karachi South (1995-97) reflects a low risk population with a late presentation and a high stage disease at presentation. It is suggested that cervical screening if implemented should focus on once a life time methodology involving 36-45 year old women. This should be combined with HPV vaccination for the young and public health education for all. A regular cervical screening program would require mobilization of considerable financial, structural and human resources along with training for personnel. This may burden the already stretched health resources of a developing country.

Key Words : Cervical cancer - Karachi - Pakistan

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Introduction

Cancer cervix ICD-10 category C53 (International Classification of Diseases 10th Revision), is one of the common neoplastic diseases affecting women. It represented nearly 10% of all cancers in women with a combined worldwide incidence of almost half a million new cases annually, second to breast cancer in the nineties (Parkin et al., 1993). In developing countries, cervical cancer was the most frequent neoplastic disease among women until the early 1990s, when breast cancer became the predominant cancer site (Parkin et al., 1999; Parkin,

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1994; Ferlay et al., 1998). Cancer cervix still occupies either the top rank or second among cancers in women in many developing countries. The truncated rate (TR) in the age group 35-64 years in Chennai, India (99.1/100,000; 1982-95), is probably the highest globally (Shanta et al., 2000). In the eighth volume of 'Cancer in the Five Continents' (CIV-VIII) the age-standardized incidence rates (ASRs) per 100,000 population for cervix cancer for the years 1993-97, all ages included, varied from the lowest (1.2) in China, Jiashan to the highest (55.0) in Zimbabwe, Harare (Parkin et al., 2002).

The incidence and mortality of cervical cancer had declined in North America and Europe during the last 50 years as an outcome of cervical screening. However during the last few years the below 50 years cohort in both the regions show an increasing trend. This cohort effect has also been reported in Australia, New Zealand (non-Maori), Japan (Osaka) and among Chinese women in Singapore. This re-emergence of cervical cancer could reflect the use of new diagnostic techniques, such as human papillomavirus (HPV) testing and cervicography. Another factor potentially affecting incidence trends is the increase in rates of adenocarcinomas and adenosquamous carcinomas (Vizcaino AP et al.,1998; Franco EL et al, 2003).

In Pakistan, cancer cervix was reported as the second most common malignancy by Jafarey and Zaidi in 1976. Since then it has not been reported amongst the three most important malignancies in women from any region in Pakistan, though it features amongst the first ten most common malignancies (Jamal et al., 2006; Bhurgri et al., 2006; Bhurgri et al., 2005; Bhurgri et al., 2002). The hierarchy of malignancies in Karachi (age standardized incidencerate per 100,000) for the years 1995-97 was breast cancer ICD-10 category C50 (53.8), oral cavity C00-08 (15.5), ovary C56 (10.9), uterus C54-C55 (7.2), esophagus C15 (6.9), cervix C53 (6.8), colo-rectum C18-20 (5.5), gall bladder C23 (5.3), skin C44 (4.9), lymphoma C81-85; C96 (4.4) and thyroid C73 (4.2) (Parkin et al., 2002).

The present study was conducted with the objective of examining descriptive epidemiological and pathological characteristics of cancer cervix in Karachi South, an all urban southern-most district of Karachi, Pakistan.

Methods

Epidemiological data of incident cancer cervix cases, ICD-10 category C53 registered at KCR for Karachi South, during 1st January 1995 to 31st December 1997 were reviewed. The study included clinically diagnosed and microscopically verified cancer cervix cases. All surgical specimens were initially evaluated on Hematoxylin and Eosin (H&E) stained sections. Special stains were selectively used, whenever required.

The reported epidemiological cancer data were rechecked, and residency status re-ascertained. People residing in the specified geographical regions for more than six months were considered residents. The cases were categorized by tumor site, age and sex of the patient. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging (TNM). The data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-4 software. This software includes facilities for the detection of duplicate registrations and for performing internal checks on the validity of the entered data. Manual and computerized validity check for the cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR) (Parkin et al., 1994).

Crude, age-standardized, and age-specific incidence rates (CIR, ASR, ASIR) were calculated for cancer cervix. The person-years of female population at risk by 5-year age-groups were estimated with the mid 1996 population, estimates based on the 1998 census, copy obtained from the Sindh Bureau of Statistics, total population of 1,724,915; females 795,521, assuming an annual growth rate of 1.94%. The growth rates were based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution (Segi, 1960). 'The standardized rate is the incidence rate that, theoretically, would have been observed if the population had a standard age distribution. The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population averaged over the number of years for which data are presented'. Incidence tables were based on ICD-10 (WHO, 1992).

To determine the socioeconomic profile, the district was divided into 3 subcategories based on the income of approximately 70% of the resident population. The categories ranged from 1 to 3 in an ascending income strata (table 1). Category I was composed of the predominantly financially deprived class with an annual income of less than $2000, and a low literacy level. Residents of category II had an annual income range of $2001-$20,000 with a moderately high literacy. Category III was largely made up of educated professionals, with an annual income of more than $20,000. A sample survey was conducted to categorize the financial status of the population.

Odds ratio for age-groups, ethnicity, religion, and subdivision by socio-economic categories were calculated by considering malignancies of the stomach, small intestine, colon and rectum in females as the control group. The exclusion criteria for controls were ICD-O3 morphological categories less than and excluding M-8070, breast, reproductive system and oral cavity malignancies for the same period (1st January 1995 to 1st December 1997) as cases. The data were analyzed using SPSS 15.0.

Results

A total of 74 cases of cancer cervix, ICD-10 (International Classification of Diseases 10th Revision) category C53 were registered at the Karachi Cancer Registry, for Karachi South, during a 3 year period, 1st

Table 1. Frequency and Odds Ratio for Cancer Cervix Cases on the Basis of Age-Group, Socio-Economic Categories, Religion, Ethnicity and Education

	N=74	Frequency %	Odds Ratio	Confidence interval
Age groups				
30-34	2	2.7	4.0	0.33-48.7
35-39	2	2.7	0.6	0.66-5.45
40-44	10	13.5	0.6	0.72-5.28
45-49	13	17.6	0.7	0.08-5.64
50-54	16	21.6	1.1	0.13-10.4
55-59	7	9.5	0.7	0.77-5.75
60-64	12	16.2	2.3	0.23-22.1
65-69	4	5.4	0.8	0.06-8.83
70-74	4	5.4	0.0	0.00-0.00
75-79	1	1.4	3.0	0.24-37.7
80+	3	4.1	1.0	
Socio-economic categories				
Unknown	1	1.4	1.0	
Category I	20	27.0	2.09	0.97-4.5
Category II	17	23.0	2.08	0.95-4.6
Category III	36	48.6	0.69	0.70-1.7
Religion				
Muslim	67	90.5	0.14	0.17-1.2
Non-muslim	7	9.5	1.20	0.18-2.2
Ethnicity				
Unknown	17	23.0	1.00	
Sindhi	8	10.8	1.4	0.29-6.90
Punjabi	13	17.6	2.0	0.27-14.8
Pathan	4	5.4	4.6	0.90-23.1
Baluch	6	8.1	1.7	0.37-7.95
Mohajir (u)	15	20.3	2.0	0.27-14.8
Mohajir (g)	3	4.1	3.6	0.65-19.4
Mohajir (m)	6	8.1	0.0	0.00-0.0
Goanese	2	2.7	7.8	1.74-34.7
Education				
Illiterate	35	47.3	-	-
Literate	7	9.5	-	-
Graduation	6	8.1	-	-
Unknown	26	16.8	-	-

January, 1995 to 31st December 1997. The age standardized incidence rate (ASR) world and crude incidence rate (CIR) per 100,000 were 6.81 (5.2, 8.43) and 3.22 (2.49 to 3.96). The ASR world and CIR per 100,000 were 5.68 (4.22 to 7.14) and 2.75 (2.07 to 3.42) for squamous cell carcinoma cervix and 1.08 (0.40 to 1.77) and 0.44 (0.17 to 0.71) for adenocarcinoma. Cancer cervix accounted for approximately 3.6% of all cancers in females and was the sixth malignancy in hierarchy.

The mean age of the cancer cases was 53.27 years (SD 11.6; 95% CI 50.58, 55.96; R 32-85 years). The mean age of squamous cell carcinoma cases was 53.05 years (SD 12.24; 95% CI 49.99, 56.11, R 32-85 years) and adenocarcinoma was 54.7 years (SD 6.29; 95% CI 50.2, 59.19; R 45-65 years).

The distribution by religion was Muslims (67 cases; 90.5%), Christians (6 cases; 8.1%) and Hindus (1 case; 1.4%). There were no cases reported in Parsees. The frequency distribution by ethnicity was Urdu speaking Mohajirs (15 cases; 20.3%), Punjabis (13 cases; 17.6%), Gujrati speaking Mohajirs (3 cases; 4.1%), memon Mohajirs (6 cases; 8.1%), Sindhis (8 cases; 10.8%), Baluchs (6 cases; 8.1%), Pathans (4 cases; 5.4%) and Afghan migrants (2 cases; 2.7%). The ethnicity was not known in 17 cases (23.0%). The socio-economic distribution was 20 cases (27.0%) in category I the financially deprived class, 18 cases (24.4%) in category II the middle class and 37 cases (48.7%) in category III, the upper middle and affluent class. There were 64 (86.5%) married women, 2 (2.7%) unmarried women and 8 (10.8%) widows (table 1). Housewives and unskilled household workers formed the bulk of the cases (72 cases, 97.2%), whereas there were only 2 (2.8%) professionally working women. The professions followed were office work and teaching (1 case, 1.4%) each. A fifth of the females were (14 cases; 19%) college graduates. Completely illiterate females composed 55.4% of the cases. The level of education was not known in 12.2% of the cases.

The age-specific curves showed a gradual increase in risk from the fourth up till the seventh decade, followed by an actual apparent decrease in risk after 64 years of age (Figure 1). The peak incidence was observed in the 60-64 year age group. Microscopic confirmation of malignancies was 100%, though 1 (1.4%) case was confirmed by cytology and subsequently lost to follow-up.

The morphological categorization was squamous cell carcinoma - SCC (64cases; 86.5%), adenocarcinoma (7 cases; 9.5%), papillary adenocarcinoma (1 case; 1.4%) and adenosquamous carcinoma (2 cases; 2.7%). Thusadenocarcinoma was observed in 8 (10.9%) cases. Majority of the cases presented as moderately differentiated or grade 2 lesions (34 cases; 45.9%), whereas well differentiated (grade 1) and poorly differentiated (grade 3) malignancies formed 14 (18.9%) and 7 (9.5%) of the cases respectively. The tumor grade was not known for 6 (9.5%) cases. Localized malignancy was observed in a fourth of the cancers (19 cases; 25.7%) however there were no in-situ cases. Approximately half the cancers (43 cases; 58.1%) had spread regionally and 6 cases (8.1%) to a distant site at the time of diagnosis. Six (8.1%) cases could not be staged due to a lack of clinical and pathological information.

The odds ratio (OR) for 74 cases was calculated with 80 gender matched controls. The odds ratios were calculated for socioeconomic residential categories, religion, ethnicity, age groups and education. The OR for socioeconomic residential categories ranged between 0.69 and 2.9 with a marginally higher risk in the lower [OR 2.09 (95% CI 0.97; 4.49)] and lower middle class [OR 2.08 (95% CI 0.95; 4.58)] socio-economic categories. Hindus [OR 1.2 (95% CI 0.18; 2.2)] had a slightly higher risk then the Muslims [OR 0.14 (95% CI 0.17; 1.2)]. A higher risk was also observed for Goanes Christians [OR 7.76 (95% CI 1.74; 34.5)]. The risk of developing cancer cervix was three to four fold in the gujrati Mohajirs OR 3.56 (95% CI 0.65; 17.4) females in both of Muslim and Hindus (Table 1). The highest risk of breast cancer was observed in the 60-64 year age group [OR 2.3 (95% CI 0.23; 22.1)].

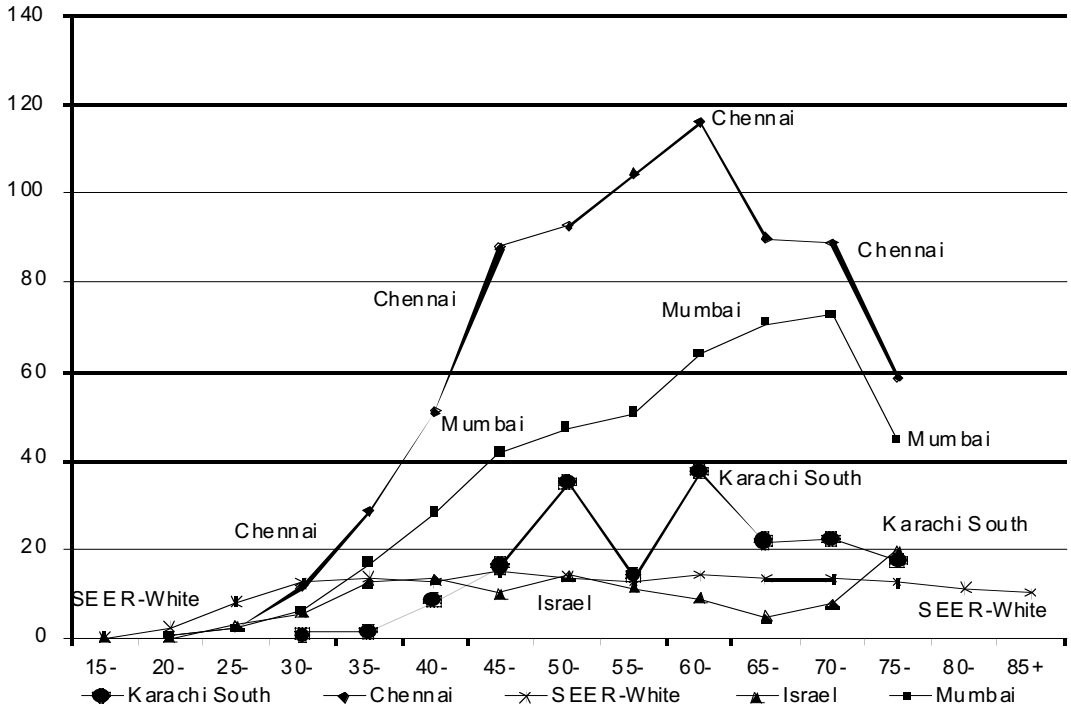

Figure 1. Highlights the ASIRs in Karachi South(KS) in Comparison to Contemporary Asian Registries and SEER Whites. Uptil the age of 40 years the ASIRs in KS are lower than in Israel and US SEER, beyond 45 years in the KS ASIRs are higher. The KS ASIRs remain below the rates of Chennai and Bombay for all age groups.

Discussion

The incidence of cervical cancer in Karachi (ASR 6.81 per 100,000) reflects a low risk population. The demographic profile of the cervical cancer patients in KS was middle aged women with little to no education, a lower socio-economic status, predominantly housewives or unskilled household workers. The malignancy was predominantly a moderately differentiated squamous cell carcinoma (SCC), with late presentation. There was a higher component of adenocarcinoma then otherwise reported in literature.

Globocan grades the world region into 5 categories, on a rising scale of 1 to 5 on the basis of the age standardized incidence rates of the country or the estimates of the same prepared by IARC (Ferlay et al., 2002). In the first category (grade1) are included countries with a cervical cancer incidence (ASR) below 9.4 per 100,000. The other categories are grade 2 (ASR <16.8 per 100,000), grade 3 (ASR <25.8 per 100,000), grade 4 (ASR <33.4 per 100,000) and grade 5 (ASR <87.3 per 100,000). Based on this scheme Pakistan and other Muslim counties are included into category 1 the least risk zone. The incidence of cancer cervix in Karachi substantiates this categorization. The low incidence of cervical cancer in Karachi meanwhile is supported by the overall lower (0.5%) prevalence of abnormal smears in this population (Wasti et al., 2004). Other populations from Pakistan have also reported a lower incidence (ASR per 100,000) viz. Larkana (2.2), Hyderabad (3.6) and Quetta (2.7) (Bhurgri et al., 2006; Bhurgri et al., 2005, Bhurgri et al., 2002).

Earlier studies from Karachi conducted at the Department of Radiotherapy, Jinnah Postgraduate Medical Centre, Karachi (1960 to 1972) reported a higher frequency of cancer cervix, as the third most common tumor after oral cavity and breast (Jafarey and Zaidi, 1976). The probable reason was a selection bias associated with data representing patients being treated at a radiotherapy centre.

The findings of our study are compatible with reports of a low cervical cancer incidence in Muslim countries (Ferlay et al., 2002). This low risk for Muslim women has also been observed in countries like India which have a large Muslim population, the country otherwise has been considered one of the high risk regions for cancer cervix (Jussawalla et al., 1985; Yeole et al., 2006). In fact a lower incidence has been documented for Muslim women in the entire Asian region though squamous cell carcinoma of the cervix has been reported as a major problem in this region (Moore and Tajima , 2004). The hierarchy of cancer cervix (ASR/100,000) in Asian registries for the 1993-97 period as reported in CIV volume VIII was Chennai, India (30.1) Delhi, India (25.8), Chiang Mai, Thailand, (25.3), Taiwan, China (24.9) and Lampang, Thailand (24.2). Comparative contemporary (1993-97) rates in the US for SEER white were 6.8/100,000 (Parkin et al., 2002).

Figure 1 highlights the age specific incidence rates in Karachi South in comparison to some Asian registries and SEER white (Parkin et al., 2002). Uptil the age of 40 years the ASIRs in KS are lower than observed for Jews in Israel and US SEER white, beyond 45 years the KS ASIRs are higher then both populations. The KS ASIRs remain below the rates reported for two Indian registries, Chennai and Bombay for all age groups.

The incidence of cervical cancer in Karachi South and

the late stage at presentation, reflect the absence of cervical screening in the population. With the initiation of screening the incidence in KS would show an initial sharp rise, down-staging and higher frequency of in-situ disease at presentation. Until the early 1970s, approximately 75% to 80% of cervical cancer in the United States (US) was invasive at the time of diagnosis. With the initiation of cervical screening about 78% of the cervical cancer cases are diagnosed at the in situ stage (Miller et al., 1996). Only a fourth of the cases in the present study presented as localized malignancy (25.7%) and there were no in-situ cases reported. With a country-wise screening, the same would be reflected in Lahore which has reported a high staged disease albeit with marginal differences from the statistics for Karachi. Lahore reports 0.5% stage 0 or in-situ, 11.7% stage I, 33.4% stage II, 21.5% stage III and 12.4% stage IV (Badar et al., 2007). Both studies report a low to no in situ cases, reflecting the lack awareness or availability of cervical screening in Pakistan.

The determination of the age trends at presentation for cancer cervix are important as this helps in the identification of the target age group for the implementation of cervical screening by a single smear in the life time methodology (Gupta et al., 2007). The mean age of cancer cervix cases was 53.3 years in KS, which is higher than the mean age of breast cancer (47.5 years) in KS. It is also higher then the mean age for cancer cervix reported from Lahore (Badar et al., 2007), North-eastern Nigeria (Kyari et al., 2004). Greece (Papanikolaou et al., 2006). The older mean age at presentation in the present study indicates a later exposure to risk factors or reflects the late presentation and the lack of screening. The lower mean age in Lahore supports the theory of a later exposure to risk factor/s as the other two factors (later presentation and lack of screening) are common to both populations within the country. This is further supported by the observation that the youngest case in Karachi was 32 years old and in Lahore below 18 years. The oldest cases from both populations were 85 years of age, thus indicating a wide variation of risk factors and exposures within Pakistan, which should be kept in perspective whilst identifying the risk group for cervical screening.

Keeping the KS data in perspective the once a life time methodology of cervical cancer screening should be applied to the 36-45 year age group. In KS no case was diagnosed below 30 years of age, two thirds of the cancers were observed in women above 50 years of age and 18% were diagnosed above 64 years of age. In the US more than half (58%), in Mumbai 45% and in Chennai 43% of the cases were seen in women below 50 years (Parkin et al., 2002).

The morphological categorization of cancer cervix is also important for management of cancer cervix. In Karachi South the morphological categorization was SCC (86.5%), adenocarcinoma (10.9%) and mucoepidermoid carcinoma (2.6%), the later 2 forming a composite of 13.5%. The component of adenocarcinoma and adenosquamous carcinoma is slightly higher than reported from elsewhere and requires due consideration as hormonal factors may also be important in the carcinogenesis. Lahore has an adenocarcinoma component of 7.9% and adenosquamous carcinoma of 0.7% (Badar et al., 2007). Western populations have recently documented a morphological shift with a rising adenocarcinoma component of cancer cervix; adenocarcinomas and adenosquamous carcinomas at present account for about 10% of all cervical cancers (Franco et al., 2003).

Vallikad in 2006 recently drew an appropriate profile of the cancer cervix patient, reporting that the majority of women belong to the lower socioeconomic status, are rural, aged between 35 and 64 years and highly non-compliant to treatment. This holds true for the KS cases with a single difference, it is an all urban population. Unskilled workers and less well educated women were more frequently affected as they remain susceptible to other high risk factors viz. worse socio-economic and marital conditions. This has also been observed by other researchers in the region (Kurkure and Yeole, 2006). Muslims formed the majority (90%) of the cervical cancer cases, this being 97% Muslim population, however a higher relative risk was observed for the non-Muslims, both Hindus and Christians. There was no case reported in the Parsee population; an observation also reported from Bombay which has a larger population of Parsees (Yeole et al., 2001).

The predominant risk factor is infection with a high risk 'oncogenic' type of human papilloma virus (HPV), multiple partners, other sexually transmitted diseases and smoking. A strong relationship between HPV type 16 infection and cervical cancer has been reported in Karachi (Khan et al., 2007), though this study has not addressed protective factors like consumption of vegetables or modifying factors which may influence carcinogenesis. The etiogenesis needs further investigation.

Conclusion

The incidence of cervical cancer in Karachi South (1995-97) reflects a low risk population with a late presentation and a high stage disease at presentation. It is suggested that cervical screening if implemented should focus on once a life time methodology involving 36-45 year old women. This should be combined with HPV vaccination for the young and public health education for all. A regular cervical screening program would require mobilization of considerable financial, structural and human resources along with training for personnel. This may burden the already stretched health resources of a developing country.

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