ORIGINAL ARTICLE

Cancer Epidemiology in Lahore, Pakistan – 2010-2015

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ABSTRACT

Objective: To study the cancer incidence rates in Lahore, which has an estimated annual population count of 10.3 million.
Study Design: Cross-sectional study.
Place and Duration of Study: Data on new cancer cases diagnosed between 2010 and 2015, among the residents of Lahore district, Pakistan, was reviewed retrospectively in 2015-2017.
Methodology: Nineteen collaborating centres of the population-based Punjab Cancer Registry (PCR), representing both the government and private sectors, reported their cases to the coordinating office located within the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC). The age-standardised incidence rates (ASIR) per 100,000 population, over a six-year period, were computed. Sixteen 5-year age groups were created beginning from 0-4 to 70-74 years, followed by 75+ years. Graphs on the five-year age-specific incidence rates by gender, were also generated.
Results: Between 2010 and 2015, 33,028 new malignancies were recorded in Lahore, with the crude average annual incidence rate being 53.1. In adults, the highest ASIRs were noted for cancers of the breast (77.3) among females and of prostate (11.4) in men. Age-specific incidence rates for female breast cancer showed an upward trend at the age of 20 years, reaching a figure of 160 at the age of 55 years. Among males, the rates for prostate cancer started to increase at the age of 55 years and reached a peak of 93 at 75 years.
Conclusion: These results warrant expanding cancer registration in the region and sharing statistics with policy-makers to establish hospitals accordingly to manage cancer, along with exploring various risk factors within the population.

Key Words: *Cancer incidence, Lahore, Malignancies, Population-based, Punjab Cancer Registry.*

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INTRODUCTION

Pakistan is categorised as a lower-middle-income country, with population estimated at 197 million in 2017 by the World Bank.[1] Although Pakistan is a populous country, there is a dearth of oncologists or dedicated facilities that deal specifically with cancer diagnosis or management.[2] This is compounded by the fact that cancer registration has never been taken seriously in the country in more than 70 years of existence, and enough efforts have not been made to establish population-based cancer registries in the region. Except for the population-based data from the Karachi Cancer Registry (KCR),[3] which was published by the International Agency for Research on Cancer (IARC) in 2007, the data reported from few other centres is institutional and does not represent the population of the region. Even the KCR data represented merely 1.7 million population of the Karachi South district, accounting for nearly 1% of the population of the country. The government's total expenditure on health is 2.6% of the GDP, and healthcare delivery is quite complex, with a large part of the population being served through a mixed health system *via* multiple health providers.[4]

The Punjab Cancer Registry was established in 2005 and the reporting of cancer cases was initiated under a mutual agreement between various centres.[5] During the early phase of the Registry, enough information could not be collected. Later, reports on its 3-year data (2010-2012) were published.[6,7] The current study is a comprehensive, retrospective study over an extended six-year period (2010-2015) reporting the cancer incidence rates within the population of Lahore.

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The objective was to determine the incidence rates for the cancers reported according to age group and present the age-specific incidence rates for cancers commonly diagnosed in the provincial metropolis.

METHODOLOGY

A population-based study was conducted in the district of Lahore, which is located in the northeast region of Pakistan. Its total land area is 1,772 square kilometres, with its average population density being 5,551 persons, per square kilometre.[8] The population of Lahore was taken as the population denominator for computing the incidence rates using cancer counts as the numerator. The average annual population estimate, determined using an average annual growth rate of 3.46% for Lahore,[9] over six years, was 10,364,878.

The 19 Punjab Cancer Registry (PCR) collaborating centres represent hospitals, laboratories, and collection centres, both in the government and private sectors, of the metropolis. Each centre is assigned a specific identification number within the Registry. The Registry also allocates a case record number, while retaining the specific number assigned to the case by the collaborating service. Data sources include the medical records from the clinical areas as the inpatient admissions, outpatient/emergency assessment visits, hospital death certificates, pathology/operative reports, chemotherapy/radiotherapy logs, radiology/nuclear medicine reports, and walk-in clinic logs (the initial assessment clinics where patients are triaged). In this way, information on patients, who are not registered through the walk-in clinics after undergoing initial assessment, is also captured into the database. Such patients go elsewhere for treatment, perhaps to another city, or opt for alternative forms of treatment. A check for duplicate registration is conducted using various combinations of name/age/gender/phone number/address/tumour morphology; and once it has been identified that a patient has been registered twice, they are included just once in the report.

Data are captured using both the active and passive methods of data collection and then entered into the system. Data collected by the data collectors of 19 centres within Lahore on the prescribed data collection form are reported to the coordinating office located within SKMCH&RC.[6] Both the paper-based forms and mobile data application, developed specifically for the Registry, are used. The variables on the form include; (1) demographic features: patient's name, age, birth date, gender, computerised national identity number, telephone number, address, and a question on whether the patient has come to Lahore for treatment only; (2) clinical features: the diagnosis date, primary tumour site, biopsy site, morphology, behaviour, grade, stage, metastasis, laterality, most valid basis of diagnosis, and procedure-related information (doctor's name and hospital); and (3) status at last follow-up, date and place of death.[5,6]

Data are saved in the PCR database, which is an integral part of the Oracle-based Hospital Information System developed in-house by the information technology staff of SKMCH&RC. This system also maintains the electronic health records of the patients.

Within the Registry, the incidence date is defined as the date of cytological/histological confirmation of a malignancy on a pathology report; the date of consultation at an outpatient clinic/walk-in clinic (without a clinical investigation or a tissue diagnosis); the date of clinical investigation(s) as imaging or tumour markers confirming the diagnosis; the date of admission to the hospital because of a malignancy; or the date of death, if no information is available other than the fact that the patient has died because of a malignancy. The proportion of cases microscopically verified (MV%) is determined by including both the histologically confirmed cases and cases diagnosed on the basis of exfoliative cytology of the specimens.

Cancers are coded using the International Classification of Diseases, Clinical Modification, 10th revision, and the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3),[10,11] while multiple primaries are coded according to the multiple primary coding rules set by IARC.[12] All cancers with behaviour codes /2 and /3 of ICD-O-3, including skin and bladder cancers, and tumours of the Central Nervous System ((CNS), brain and spinal cord) with behaviour codes /0, /1, /2, and /3, were included. Data were submitted to the IARC-CHECK programme to examine the data based on the following edits: gender *versus* site, age *versus* the date of birth, site *versus* morphology, site/histology *versus* age, histology *versus* behaviour, and histology *versus* the basis of diagnosis. A check for multiple primaries was done using the IARCcrgTools package.[12] A check for duplicate records was done manually based on patient's name, telephone number, father's name, age, address, and primary site.

A retrospective review of the records within the PCR repository, for the period between 2010 and 2015, was carried out. The residents of Lahore diagnosed with cancer were selected. Annual ASIRs were computed using the Segi World Standard,[13] applying the direct method of age-standardisation, and presented per 100,000 population, over a 6-year period, by gender and tumour site/type. Sixteen 5-year age groups were created beginning from 0-4 to 70-74 years, followed by 75+, and age-specific incidence rates computed. Data were analysed using Microsoft Excel V.2016 and SPSS V.19.

The Institutional Review Board (IRB) of SKMCH&RC, registered with the OHRP as 'IRB00005898 - Shaukat Khanum Mem Cancer Hosp & Rsch Centre IRB #1 - SKMCH & RC', approved the study prior to its initiation (Reference No. 29-02-16-04).

RESULTS

Over a 6-year period (2010-2015), a total of 33,028 new malignancies were recorded in Lahore among 32,977 patients, attributed to multiple primaries seen in 51 patients. Females accounted for 57.1% of the total patients. There were 5.8% children (0-14 years), 2.2% young adults/adolescents (15-19 years), and 92% adults (20+ years). Approximately 43.6% of the patients were in

Table I: Annual age-specific incidence rates by 5-year age group and age-standardised incidence rates (ASIRs), per 100,000 females, Lahore, Pakistan, 2010-2015.

Site	Cases	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75+	Crude	%	ASIR	ICD-10 code
Lip	19	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.0	1.2	0.2	0.9	1.1	0.3	0.1	0.1	0.1	C00
Tongue	274	0.0	0.0	0.0	0.0	0.1	0.1	0.5	1.1	1.5	4.4	3.8	6.5	8.3	6.4	5.3	5.8	0.9	1.5	1.7	C01-C02
Mouth	290	0.0	0.0	0.0	0.1	0.2	0.2	0.3	1.2	2.3	2.6	6.2	5.2	5.2	9.1	9.0	5.5	1.0	1.5	1.7	C03-C06
Salivary glands	93	0.0	0.0	0.1	0.1	0.1	0.4	0.4	0.7	0.3	0.8	1.3	0.8	2.0	2.1	2.3	1.0	0.3	0.5	0.5	C07-C08
Tonsil	4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	C10
Nasopharynx	43	0.0	0.0	0.0	0.3	0.1	0.2	0.2	0.2	0.2	0.5	0.3	0.5	0.2	0.3	0.8	0.0	0.1	0.2	0.2	C11
Hypopharynx	68	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.5	0.4	0.8	0.6	1.5	2.0	1.5	1.5	0.7	0.2	0.4	0.4	C12-C13
Pharynx	9	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.2	0.0	0.0	0.4	0.7	0.0	0.0	0.0	C14
Oesophagus	213	0.0	0.0	0.0	0.0	0.1	0.3	0.7	1.1	1.2	3.8	2.2	2.8	5.5	5.8	4.9	4.8	0.7	1.1	1.3	C15
Stomach	217	0.0	0.0	0.0	0.0	0.2	0.2	0.9	1.1	1.9	3.2	2.9	4.3	3.3	7.3	2.3	3.4	0.7	1.2	1.2	C16
Small intestine	53	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.3	0.9	0.1	0.5	1.8	2.1	1.9	2.1	0.2	0.3	0.3	C17
Colon	328	0.0	0.0	0.1	0.3	0.3	0.8	1.0	1.5	2.0	3.3	3.6	6.8	5.5	8.8	7.9	8.9	1.1	1.7	1.9	C18
Rectum	290	0.0	0.0	0.1	0.4	0.9	0.9	1.0	1.3	1.7	2.7	2.7	3.5	5.7	7.3	6.4	5.8	1.0	1.5	1.6	C19-C20
Anus	54	0.0	0.0	0.0	0.0	0.2	0.1	0.3	0.1	0.7	0.5	0.5	0.3	0.9	1.2	1.5	0.7	0.2	0.3	0.3	C21
Liver	288	0.2	0.0	0.0	0.1	0.2	0.2	0.3	0.3	0.9	3.1	4.5	8.7	9.6	11.5	5.3	3.8	1.0	1.5	1.8	C22
Gall bladder, *etc.**	276	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.5	1.4	2.7	4.2	6.3	8.3	13.6	8.6	6.2	0.9	1.5	1.8	C23-C24
Pancreas	60	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.3	0.2	0.8	0.8	1.0	1.3	3.6	1.5	0.7	0.2	0.3	0.4	C25
Nose, sinuses	45	0.0	0.0	0.0	0.1	0.0	0.0	0.2	0.2	0.0	0.7	0.5	0.8	1.7	1.5	0.4	1.0	0.2	0.2	0.3	C30-C31
Larynx	50	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.4	0.4	1.0	1.5	0.9	0.9	0.8	2.4	0.2	0.3	0.3	C32
Trachea, bronchus, lung	225	0.0	0.0	0.1	0.1	0.1	0.1	0.7	0.8	1.2	1.2	3.4	6.2	5.7	7.6	6.8	4.5	0.8	1.2	1.4	C33-C34
Other thoracic organs	28	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.1	0.5	0.2	0.2	0.7	0.6	0.8	1.4	0.1	0.1	0.2	C37-C39
Bone	184	0.1	0.4	0.9	1.5	0.8	0.3	0.3	0.8	0.4	0.8	0.4	0.7	0.6	0.6	1.1	1.0	0.6	1.0	0.6	C40-C41
Melanoma of skin	38	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.1	0.3	0.2	0.5	0.0	0.6	0.4	0.3	0.1	0.1	0.2	C43
Other skin	402	0.1	0.0	0.1	0.1	0.2	0.3	0.6	1.5	2.6	2.7	4.9	6.5	11.4	14.6	18.0	19.3	1.4	2.2	2.6	C44
Mesothelioma	5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.4	0.0	0.4	0.0	0.0	0.0	0.0	C45
Connective and soft tissue	232	0.4	0.2	0.3	0.6	0.5	0.7	0.6	1.5	1.5	1.5	2.4	2.7	2.8	3.9	1.9	2.1	0.8	1.2	1.1	C47,C49
Breast	8340	0.0	0.0	0.1	0.1	2.8	14.2	29.8	56.3	81.1	119.8	120.7	161.0	152.9	162.0	117.8	99.4	28.3	44.3	46.4	C50
Vulva	34	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.2	0.4	0.7	1.3	1.2	0.8	1.7	0.1	0.2	0.2	C51
Vagina	38	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.3	0.2	0.7	0.6	0.8	0.6	0.6	0.8	1.0	0.1	0.2	0.2	C52
Cervix uteri	491	0.0	0.0	0.0	0.0	0.2	0.4	1.3	3.3	5.3	8.5	7.0	9.3	8.7	10.0	6.0	5.5	1.7	2.6	2.8	C53
Corpus uteri	636	0.0	0.0	0.0	0.0	0.0	0.3	0.5	1.5	2.1	6.9	10.6	20.0	21.2	22.4	21.8	8.3	2.2	3.4	4.1	C54
Uterus, unspecified	176	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.9	1.2	2.5	3.4	3.8	5.9	3.9	4.5	0.7	0.6	0.9	1.1	C55
Ovary	877	0.0	0.1	0.6	0.6	1.4	2.3	2.4	4.1	7.3	11.9	11.7	16.3	15.3	16.7	10.1	6.9	3.0	4.7	4.7	C56
Other female genital org	51	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.3	0.8	1.0	0.8	1.7	1.5	0.8	0.0	0.2	0.3	0.3	C57
Placenta	15	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	C58
Kidney	210	0.5	0.2	0.1	0.0	0.1	0.0	0.5	1.1	1.3	1.9	3.1	5.2	3.3	3.3	4.1	2.8	0.7	1.1	1.1	C64
Renal pelvis	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	C65
Ureter	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	C66
Bladder	226	0.1	0.0	0.0	0.1	0.1	0.2	0.2	1.0	1.0	1.8	2.4	4.8	5.2	8.8	9.0	10.0	0.8	1.2	1.4	C67
Other urinary organs	3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.2	0.0	0.0	0.4	0.0	0.0	0.0	0.0	C68
Eye	92	1.1	0.3	0.1	0.0	0.0	0.0	0.1	0.1	0.4	0.4	0.1	0.2	0.4	2.4	0.8	1.7	0.3	0.5	0.4	C69
Brain, nervous system	559	0.4	0.9	1.0	1.2	1.1	2.0	2.2	2.7	3.7	4.6	6.0	5.8	6.1	6.1	4.5	2.8	1.9	3.0	2.5	C70-C72
Thyroid	440	0.0	0.0	0.1	0.4	1.8	2.1	2.6	3.3	3.5	4.1	4.8	3.2	4.4	3.3	7.5	2.1	1.5	2.3	2.0	C73
Adrenal	9	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.4	0.3	0.0	0.0	0.0	0.0	0.0	C74
Other endocrine	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	C75
Hodgkin lymphoma	168	0.2	0.4	0.3	0.6	0.9	0.8	0.5	0.6	0.6	1.0	0.7	1.5	1.1	1.2	2.3	0.0	0.6	0.9	0.7	C81
Non-Hodgkin lymphoma	590	0.3	0.5	0.3	0.5	0.8	0.8	1.4	2.0	3.1	5.4	8.8	12.0	11.2	11.2	14.6	12.7	2.0	3.1	3.3	C82-C86, 88.4, C96
Multiple myeloma	76	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.5	1.1	1.3	1.2	2.9	3.0	2.6	0.7	0.3	0.4	0.5	C90
Lymphoid leukaemia	240	2.1	1.6	1.2	0.4	0.2	0.1	0.2	0.2	0.2	0.2	0.1	0.7	0.6	0.6	1.1	0.7	0.8	1.3	0.7	C91
Myeloid leukaemia	152	0.2	0.1	0.2	0.3	0.6	0.9	1.0	0.9	0.4	0.9	0.8	2.0	1.8	0.6	1.1	0.0	0.5	0.8	0.6	C92-94
Leukaemia unspecified	76	0.5	0.4	0.2	0.2	0.1	0.2	0.2	0.1	0.3	0.2	0.3	0.3	0.0	0.6	0.4	0.3	0.3	0.4	0.3	C95
Other and unspecified	1190	0.5	0.2	0.2	0.4	1.3	1.8	2.5	3.8	5.5	13.8	15.1	26.1	25.8	36.4	30.8	31.3	4.0	6.3	7.1	O&U Other benign
Benign CNS**	367	0.1	0.1	0.3	0.5	0.7	1.6	2.0	3.2	3.2	3.9	4.4	2.5	3.7	3.9	2.6	0.7	1.2	1.9	1.7	CNS
All sites	18847	6.9	5.7	6.3	9.0	16.7	33.6	57.0	101.5	142.7	229.0	250.6	347.5	358.3	412.2	335.4	271.8	64.0	100.0	103.9	C00-C96

**Gall bladder, etc = Includes the extrahepatic bile ducts; **CNS = Central Nervous System.*

the 45-64 year age group. The mean age at presentation was 48.7 ±18.4 years with median = 50 years, and mode = 60 years. Nearly 96.2% of the cancers were microscopically verified (histology of primary tumour in 83%, histology of a metastasis in 7.9%, and cytology in 5.3% of the cases), 2.6% were clinically diagnosed, 1.2% through clinical investigations, and none by death certificates only. The MV% was 88.3%-100% among females and 76.2%-100% in males, except for liver cancer in either gender where it was 50%.

The ASIR was 103.9 in females and 66.5 in males, per 100,000 population. The ASIR was higher in males than

Table II: Annual age-specific incidence rates by 5-year age group and age-standardised incidence rates (ASIRs), per 100,000 males, Lahore, Pakistan, 2010-2015.

Site	Total	0-	5-	10-	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75+	Crude	%	ASIR	ICD-10 code
Lip	33	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.1	0.4	0.5	0.9	0.7	0.6	1.1	0.1	0.2	0.2	C00
Tongue	355	0.0	0.0	0.0	0.0	0.2	0.4	0.5	1.6	3.0	3.9	3.9	5.0	6.4	6.1	9.0	4.1	1.1	2.5	1.7	C01-C02
Mouth	481	0.0	0.0	0.0	0.0	0.1	0.3	1.1	1.7	3.5	6.2	5.8	9.6	9.4	8.6	7.0	4.1	1.5	3.4	2.3	C03-C06
Salivary glands	117	0.0	0.0	0.0	0.1	0.1	0.3	0.3	0.5	0.9	0.7	1.2	1.5	2.1	1.5	2.3	2.7	0.4	0.8	0.5	C07-C08
Tonsil	6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.3	0.1	0.0	0.3	0.0	0.0	0.0	0.0	C10
Nasopharynx	57	0.0	0.0	0.1	0.2	0.1	0.0	0.2	0.3	0.3	0.5	0.5	0.9	0.6	0.5	0.3	0.3	0.2	0.4	0.2	C11
Hypopharynx	48	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.4	0.2	0.5	0.4	1.2	1.0	1.1	1.6	0.1	0.3	0.2	C12-C13
Pharynx	14	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.2	0.3	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.1	C14
Oesophagus	295	0.0	0.0	0.0	0.1	0.1	0.3	0.4	0.7	1.0	2.5	3.0	5.4	5.8	9.1	8.7	7.9	0.9	2.1	1.5	C15
Stomach	332	0.0	0.0	0.0	0.0	0.1	0.6	0.8	1.2	1.5	4.1	3.2	6.1	5.2	9.3	5.9	5.2	1.0	2.3	1.6	C16
Small intestine	62	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.2	0.2	0.4	0.7	1.1	0.7	1.0	2.8	1.9	0.2	0.4	0.3	C17
Colon	486	0.0	0.0	0.1	0.2	0.6	0.6	1.1	1.8	2.5	4.7	5.2	6.2	9.7	12.8	9.8	6.5	1.5	3.4	2.3	C18
Rectum	396	0.0	0.0	0.0	0.4	0.6	0.8	1.4	1.4	1.2	2.9	3.6	4.6	7.8	11.3	6.8	7.3	1.2	2.8	1.9	C19-C20
Anus	78	0.0	0.0	0.0	0.1	0.1	0.1	0.4	0.1	0.4	0.7	0.8	0.8	1.5	2.5	0.8	1.1	0.2	0.6	0.4	C21
Liver	557	0.3	0.0	0.0	0.0	0.1	0.1	0.1	0.7	1.8	3.7	7.3	12.4	12.5	22.1	13.8	12.0	1.7	3.9	3.0	C22
Gall bladder, *etc*.*	182	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	1.1	0.9	2.2	3.8	4.5	6.1	3.7	4.9	0.6	1.3	1.0	C23-C24
Pancreas	101	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.5	0.8	1.0	2.0	2.7	3.9	3.7	1.6	0.3	0.7	0.5	C25
Nose, sinuses	71	0.0	0.0	0.0	0.1	0.1	0.2	0.2	0.3	0.4	0.4	0.3	0.9	1.5	0.7	3.1	0.8	0.2	0.5	0.3	C30-C31
Larynx	408	0.0	0.0	0.0	0.0	0.2	0.0	0.3	0.7	1.4	3.6	4.9	8.6	10.9	11.5	12.1	8.4	1.2	2.9	2.2	C32
Trachea, bronchus, lung	844	0.0	0.0	0.0	0.0	0.1	0.1	0.5	1.4	1.8	4.7	7.3	13.7	19.9	35.1	36.0	33.1	2.6	6.0	4.7	C33-C34
Other thoracic organs	70	0.0	0.0	0.1	0.1	0.0	0.1	0.3	0.1	0.5	0.4	1.2	0.1	1.3	0.2	1.1	2.2	0.2	0.5	0.3	C37-C39
Bone	286	0.2	0.4	1.1	2.3	1.4	0.5	0.7	0.4	0.7	0.7	0.5	0.5	1.9	0.5	0.8	0.5	0.9	2.0	0.8	C40-C41
Melanoma of skin	44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.2	0.7	0.7	0.2	0.0	1.1	0.1	0.2	0.2	C43
Other skin	589	0.1	0.1	0.1	0.1	0.3	0.6	1.5	1.8	2.1	3.1	5.4	9.4	11.0	17.7	15.8	25.5	1.9	4.3	3.0	C44
Mesothelioma	6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.5	0.0	0.0	0.0	C45
Connective and soft tissue	276	0.5	0.4	0.2	0.6	0.8	0.8	0.7	0.9	0.7	2.0	1.1	3.2	2.7	4.4	2.8	1.9	0.8	1.9	1.1	C47,C49
Breast	166	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.4	0.9	2.3	1.3	2.9	3.1	6.4	4.5	2.2	0.5	1.2	0.9	C50
Penis	6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	C60
Prostate	1174	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.2	1.5	4.5	13.3	28.5	53.0	68.9	93.4	3.6	8.3	6.8	C61
Testis	196	0.3	0.0	0.0	0.5	1.0	1.5	1.3	1.3	0.7	0.6	0.4	0.4	0.3	1.0	0.6	0.5	0.6	1.4	0.6	C62
Other male genital org	5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.3	0.0	0.0	0.0	0.0	C63
Kidney	352	0.8	0.2	0.0	0.1	0.1	0.2	0.6	0.9	2.2	2.6	3.2	4.2	7.0	9.1	7.6	4.9	1.1	2.5	1.7	C64
Renal pelvis	4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.3	0.0	0.0	0.0	0.3	0.0	0.0	0.0	C65
Ureter	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	C66
Bladder	957	0.0	0.0	0.0	0.0	0.1	0.3	0.6	1.6	2.3	5.7	7.5	17.4	25.8	30.9	35.2	40.7	2.9	6.7	5.2	C67
Other urinary organs	3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.3	0.0	0.0	0.0	C68
Eye	132	1.2	0.4	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.6	0.5	0.3	1.8	2.0	1.4	1.4	0.4	0.9	0.5	C69
Brain, nervous system	952	0.7	1.2	0.9	1.6	1.9	3.2	4.1	3.8	4.2	6.9	7.3	9.9	10.8	10.8	6.8	4.1	2.9	6.7	3.7	C70-C72
Thyroid	181	0.0	0.0	0.0	0.2	0.3	0.7	0.9	0.8	0.9	1.6	2.1	2.2	1.2	2.5	2.5	1.1	0.6	1.3	0.7	C73
Adrenal	10	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.2	0.3	0.0	0.0	0.1	0.0	C74
Other endocrine	5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	C75
Hodgkin lymphoma	394	0.7	1.5	0.8	1.0	1.1	1.3	1.1	1.2	1.3	2.0	1.5	2.4	1.5	2.9	2.8	0.8	1.2	2.8	1.3	C81
Non-Hodgkin lymphoma	1047	0.5	1.2	1.1	1.4	1.6	1.8	2.1	3.2	4.3	6.2	9.3	12.9	18.1	17.4	17.7	16.8	3.2	7.4	4.6	C82-C86,C88, C96
Immunoproliferative dis.	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	C88
Multiple myeloma	97	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	1.0	1.3	2.5	2.4	1.2	2.3	2.7	0.3	0.7	0.5	C90
Lymphoid leukaemia	418	3.0	2.4	2.0	0.7	0.4	0.3	0.3	0.1	0.5	0.9	1.0	1.3	0.7	1.7	1.4	1.1	1.3	2.9	1.2	C91
Myeloid leukaemia	230	0.3	0.3	0.4	0.4	0.6	0.8	1.0	1.2	1.4	1.4	0.8	2.2	2.1	1.7	0.3	0.5	0.7	1.6	0.8	C92-94
Leukaemia unspecified	118	0.7	0.5	0.7	0.1	0.3	0.1	0.1	0.2	0.2	0.2	0.1	0.4	0.3	0.0	0.3	0.0	0.4	0.8	0.3	C95
Myelodysplastic synd.	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	MDS
Myeloproliferative dis.	4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.3	0.0	0.0	0.0	MPD
Other and unspecified	1158	0.4	0.2	0.4	0.9	0.6	1.7	2.1	2.9	4.3	6.9	11.4	18.0	22.8	29.9	29.0	32.3	3.5	8.2	5.7	O&U
Benign CNS**	375	0.2	0.3	0.2	0.5	0.7	1.6	1.5	2.6	2.4	3.6	2.9	2.4	3.0	1.7	3.4	0.8	1.1	2.6	1.4	Other benign CNS
All sites	14181	9.9	9.5	8.6	12.0	14.2	19.9	27.1	37.3	53.0	91.8	115.9	191.9	251.0	339.9	333.8	340.6	43.3	100.0	66.5	Total

**Gall bladder, etc = Includes the extrahepatic bile ducts; **CNS = Central Nervous System.*

Table III: Global comparison of the age-standardised incidence rates, per 100,000 population, by cancer site/type and gender.

	Pakistan[1] Lahore 2010-2015	India[2] Ahmedabad 2008-2011	Iran Golestan 2008-2011	Saudi Arabia Riyadh 2008-2012	Israel Israel 2008-2012	USA SEER, White 2008-2012
Count (N)	33,028	2,029	4,312	7,080	64,181	289,223
Oral cavity and salivary glands-C00-C08						
Female	4.0	5.0	1.5	1.5	2.2	3.3
Male	4.7	21.3	1.4	1.3	3.7	7.5
Pharynx-C09-C14						
Female	0.6	1.8	1.0	1.2	0.5	1.0
Male	0.5	8.5	1.2	2.5	1.4	4.4
Oesophagus-C15						
Female	1.3	1.9	16.2	1.0	0.8	1.1
Male	1.5	4.1	22.3	1.2	1.7	5.4
Stomach-C16						
Female	1.2	0.7	12.3	2.1	5.3	2.5
Male	1.6	0.9	25.5	3.5	9.6	5.4
Small intestine-C17						
Female	0.3	0.1	0.8	0.4	0.7	1.3
Male	0.3	0.2	1.5	0.7	1.0	1.8
Colo-rectum-C18-C21						
Female	3.8	1.5	12.5	11.9	27.9	22.6
Male	4.6	3.0	16.0	12.9	36.1	28.7
Liver-C22						
Female	1.8	0.2	2.5	4.8	1.5	2.3
Male	3.0	1.9	3.9	9.2	3.5	7.5
Gall bladder-C23-C24						
Female	1.8	0.8	1.3	2.2	1.5	1.5
Male	1.0	0.6	1.0	1.1	1.5	1.7
Pancreas-C25						
Female	0.4	0.2	2.2	2.0	6.6	6.4
Male	0.5	0.6	3.2	2.4	9.1	8.6
Nose & sinuses-C30-C31						
Female	0.3	0.4	0.2	0.1	0.3	0.3
Male	0.3	0.8	0.1	0.2	0.5	0.6
Larynx-C32						
Female	0.3	0.3	1.0	0.1	0.6	0.8
Male	2.2	3.2	5.3	0.9	4.3	3.6
Trachea, bronchus, and lung-C33-C34						
Female	1.4	1.1	6.5	2.4	14.4	31.2
Male	4.7	9.4	15.1	5.8	32.0	38.6
Other thoracic organs-C37-C38						
Female	0.2	0.1	0.5	0.1	0.3	0.3
Male	0.3	0.2	0.7	0.2	0.7	0.4
Bone-C40-C41						
Female	0.6	0.5	1.5	0.7	0.8	0.9
Male	0.8	0.4	1.4	1.0	1.3	1.3
Melanoma of skin-C43						
Female	0.2	0.1	0.5	0.4	9.5	17.1
Male	0.2	0.2	0.4	0.2	11.7	21.8
Skin-C44						
Female	2.6	0.6	6.1	2.8	0.8	1.1
Male	3.0	0.5	11.5	3.4	1.4	1.5
Mesothelioma-C45						
Female	0.0[8]	0.1	0.0	0.1	0.2	0.3
Male	0.0	0.0	0.2	0.2	0.7	1.0
Kaposi sarcoma-C46						
Female	-	0.0	0.1	0.1	0.5	0.0
Male	-	0.0	0.6	0.4	1.5	0.7
Connective and soft tissue-C47, C49						
Female	1.1	0.2	1.4	0.9	2.1	2.2
Male	1.1	0.5	1.5	0.9	2.8	3.1
Breast-C50						
Female	46.4	11.6	30.5	24.5	84.6	89.9
Male	0.9	0.4	0.6	0.4	1.0	0.8
Cervix uteri-C53						
Female	2.8	9.5	5.2	1.9	5.5	5.3
Corpus uteri, uterus, and placenta-C54-C55, C58						
Female	5.3	0.8	3.3	6.2	15.1	20.7
Ovary-C56						
Female	4.7	2.9	6.0	3.3	7.8	9.4
Other female genital organs-C51-C52, C57						
Female	0.7	1.4	0.4	0.4	3.1	2.9
Penis and other male genital organs-C60, C63						
Male	0.0	0.7	0.2	0.0	0.3	0.7
Prostate-C61						
Male	6.8	1.9	11.8	6.8	59.2	95.6
Testis-C62						
Male	0.6	0.5	1.7	1.1	4.0	6.6
Kidney, *etc.*[4] -C64, C65, C66, C68						
Female	1.1	0.6	2.2	2.7	6.2	7.6
Male	1.7	0.9	3.0	4.2	12.9	14.7
Bladder-C67						
Female	1.4	0.2	2.9	1.2	4.9	5.6
Male	5.2	1.2	9.9	4.7	26.5	21.5

Continues...

Table III continues....

	Pakistan[6] Lahore 2010-2015	India[7] Ahmedabad 2008-2011	Iran Golestan 2008-2011	Saudi Arabia Riyadh 2008-2012	Israel Israel 2008-2012	USA SEER, White 2008-2012
Count (N)	33,028	2,029	4,312	7,080	64,181	289,223
Eye-C69						
Female	0.4	0.0	0.0	0.5	0.7	0.7
Male	0.5	0.1	0.3	0.5	0.8	0.8
Brain, CNS[5] -C70-C72						
Female	2.5	0.8	5.3	1.9	4.8	5.3
Male	3.7	1.3	6.6	3.0	6.3	6.9
Thyroid-C73						
Female	2.0	0.9	2.8	10.3	16.8	18.7
Male	0.7	0.3	1.3	2.6	5.7	6.0
Adrenal and other endocrine-C74-C75						
Female	0.0	0.0	0.7	0.1	0.5	0.4
Male	0.0	0.0	0.4	0.4	0.5	0.5
Hodgkin lymphoma-C81						
Female	0.7	0.3	1.2	2.1	3.2	2.5
Male	1.3	0.7	1.2	2.9	3.3	3.0
NHL-C82-C86, C96						
Female	3.3	0.9	3.2	6.3	12.3	10.5
Male	4.6	1.9	6.6	6.9	16.7	15.6
Multiple myeloma-C88, C90						
Female	0.5	0.4	2.2	1.5	4.3	3.8
Male	0.5	0.5	2.8	1.3	5.9	5.6
Leukaemia-C91-C95						
Female	1.6	2.9	7.0	4.0	6.4	7.4
Male	2.3	3.6	9.8	5.8	10.4	11.8
Myeloproliferative disorders and myelodysplastic syndromes						
Female	0.0	0.0	0.5	0.6	2.3	3.9
Male	0.0	0.0	0.3	0.8	3.5	5.6
Other and unspecified-O&U						
Female	7.1	2.6	5.5	3.1	6.1	4.5
Male	5.7	6.9	6.1	2.7	7.0	4.9
All sites-C00-C96						
Female	103.9	51.4	146.4	105.4	260.3	295.3
Male	66.5	77.3	175.5	92.0	288.8	344.2

[1]Results for the Lahore district, Pakistan, include C44 skin tumours.
[2]Results for India, Iran, Saudi Arabia, Israel, and USA were obtained from IARC's publication, CI5XI. It includes all sites including C44 skin tumours.
[3]A figure of 0.0 within the table means rates were under 0.1 and - means no statistic was available.
[4]Kidney, etc. includes renal pelvis, ureter, and other & unspecified urinary organs.
[5]Benign tumors of the brain are not included in the table. However, a total of 103.9 and 66.5 includes an ASIR of 1.7 for females and 1.4 for males, respectively, for benign tumors of the brain.

in females representing children (9.4 *vs*. 6.3, respectively) and adolescents (12.0 *vs*. 9.0, respectively), but low in adult males (104.1) *versus* females (168.5).

The ASIRs by cancer site/type are given in Tables I and II. Figure 1 shows high ASIRs for leukaemia among children and for bone and brain/nervous system tumours in adolescents and, the ASIRs for cancers diagnosed in adults, by gender.

The age-specific incidence rates computed for common cancers in females showed that breast cancer peaked markedly (160 per 100,000) between 55- and 65-years of age, whereas, the incidence rates for cancers of lip/oral cavity, corpus uteri/uterus/placenta, brain/nervous system tumours, and ovary increased slightly with increasing age (Figure 1). Among males, the age-specific incidence rates for prostate cancer continued to rise in the 55+ age group and peaked at 75 (95 per 100,000) without showing any decline, whereas, the incidence rates for colo-rectum/anal cancers peaked at 65-years, but those for lip/oral cavity, brain/nervous system tumours, and lymphoma did not show any significant increase as age increased (Figure 1).

DISCUSSION

The information related to the vast majority of cancer patients was captured in the Registry as the main hospitals and laboratories of Lahore dealing with patient diagnosis/management are reporting their cases to the Registry. The data are comparable to the data presented by the developed regions of the world in terms of the systems used for classifying/coding the neoplasms, the definition of incidence date applied, and the rules for assessing multiple primaries. However, since no centralised system exists for gathering mortality data in the region, it contributed to the failure to capture the 'death certificate only' cases.

As regards risk factors implicated in the etiology of the disease, tobacco-related cancers have been classified as those of the trachea, bronchus, lung, oral cavity, larynx, pharynx, oesophagus, kidney, bladder, cervix, liver, pancreas, stomach, colon/rectum, and acute myeloid leukaemia.[14] These cancers together accounted for nearly one-fifth of the cases in females and two-fifths in males in our study (Tables I and II). Based on the World Health Organization's (WHO) 2013 standardised

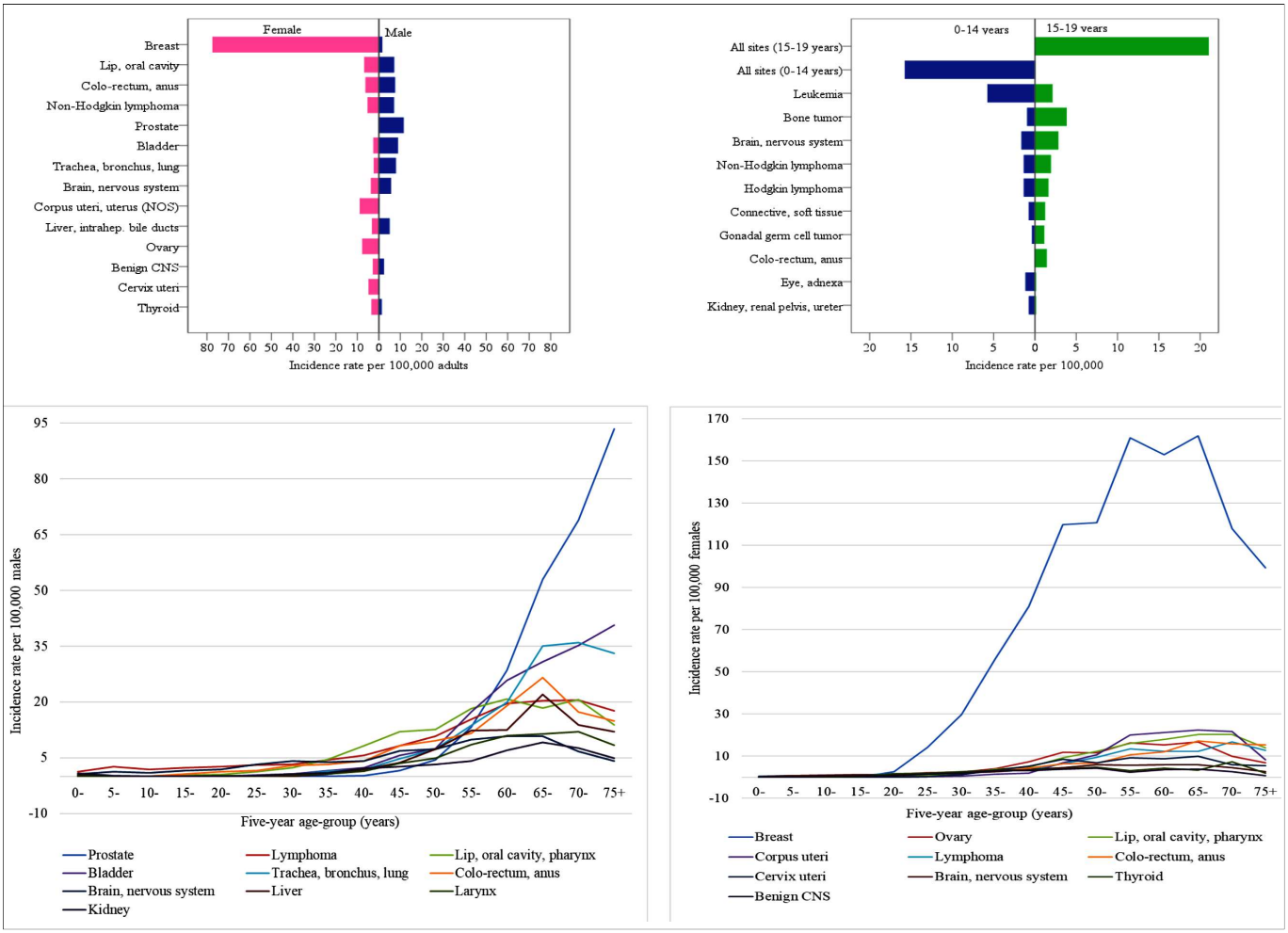

Figure 1: Age-standardised incidence rates per 100,000 population, in children and adolescents, for both sexes combined, among adults, by sex, and age-specific incidence rates, per 100,000 population, for commonly diagnosed cancers among females and males, Lahore, Pakistan, 2010-2015.

estimate of smoking prevalence, 31.8% of men, 5.8% of women, and 19.1% of Pakistan's adult population currently use tobacco in one form or another, thus partially explaining the occurrence of tobacco-related cancers in our population, especially in males.[15] According to the WHO, Pakistan is one of the 15 countries worldwide with a heavy burden of tobacco-related conditions. Therefore, it would be worth accelerating different measures to control the manufacture, import, and sale of various tobacco-related products in the country.[14] However, in our study, the incidence rates for tobacco-related cancers were not very high, thus suggesting that such cases could have been under-reported by the collaborating centres.

Cancer of the stomach did not contribute substantially to the burden in either gender (<3%), thus questioning the prevalence of *Helicobacter pylori* that might increase the risk of stomach cancer. HPV associated cancers as those of the cervix, vagina, and vulva accounted for nearly 3% of the cancers; of the oral cavity and throat, nearly 4% in females and nearly 7% in males; and anal and penile cancers less than 1% of all cancers (Tables I and II). It has been reported that within Pakistan, almost 12 million people are suffering from hepatitis B or C, and each year, almost 150,000 new cases are being diagnosed.[16] In the present study, Hepatocellular Carcinoma (HCC) accounted for nearly 1.5% of the cases in females and 4% in males. Since the role of Hepatitis C Virus (HCV) as a risk factor for HCC is well established, and as HCV is a commonly diagnosed infection in Pakistan contributing significantly to the HCV burden globally, the likely role of HCV in the etiology of HCC should be highlighted along with treatment and preventive measures to slow liver damage, and to reduce cancer risk within the population.[17] Concerning other infections as the Epstein-Barr Virus implicated in the etiology of Hodgkin disease and the Human Immunodeficiency Virus in NHL, extensive studies are needed to elaborate on them as risk factors within our population.

Breast cancer contributed substantially to the cancers recorded in the district (Table I). Studies have shown that the vast majority of cases are sporadic in nature but most of the findings regarding risk factors do not appear to be consistent with one another.[7] However, young age at menarche, single marital status, nulliparity, late first

full-term pregnancy, use of oral contraceptives, late menopause, a high body mass index, obesity, and a family history of breast cancer are implicated with an increased risk of this disease.[7]

Further discussion of various risk factors including exposure to ultraviolet radiation and certain chemicals (as asbestos), genetic disorders, and a family history of cancer especially relating to skin cancer and leukaemia, is very extensive and is beyond the scope of this manuscript.

The literature was reviewed to obtain similar reports published on populations adjacent to or close to Lahore or, anywhere else in the country. Other than the KCR's reports on the Karachi South district (1998-2002) published several years ago,[3] the authors were not able to find any reports from Pakistan for the most recent years. However, a comparison of the Lahore district incidence rates was made with the Globocan rates for Pakistan and also the incidence rates reported in CI-5, Volume XI publication, for selected regions of the world (Table III).[18,19] The cancer estimates for Pakistan based on the Globocan 2012 and Globocan 2018 reports have shown that the estimated age-standardised incidence rates are not remarkably different from one another during these two years under consideration. However, the number of incident cases has increased by about 17%, which also means that the cancer burden has gone up considerably over the years.

From the CI-5 publication, Ahmedabad (India), Golestan (Iran), Riyadh (Saudi Arabia), Israel, and the SEER program were selected. The results for 9-SEER cancer registries studying White population of the US in the 2008-2012 period have shown very high ASIRs as compared to the Lahore district results particularly for cancers of the colo-rectum, trachea/bronchus/lung, breast, prostate, and skin melanoma. This could perhaps be attributed to the regulation requiring case reporting from all facilities/practitioners to state cancer registries, access by the statewide cancer registries to medical records of persons with cancer, and screening and detection practices prevalent in the US apart from differences in the dietary habits, lifestyle factors, and exposure to tobacco. Further comparisons have shown that the ASIRs for Lahore, for all cancers combined were considerably low compared to those for Israel and Golestan, comparable to those for Riyadh; but high compared to the Ahmedabad data. The ASIRs for the Israeli population were, in general, higher than those for Lahore notably for cancers of the GI system, pancreas, lower respiratory tract, female breast, prostate, bladder, brain, thyroid, NHL, multiple myeloma, leukaemia, and skin melanoma. The ASIRs for the Ahmedabad population, compared to the ASIRs for Lahore, were high for cancers of the lip/oral cavity, lower respiratory tract, cervix uteri and leukaemia, low for GI system, prostate, urinary tract, brain, thyroid, Hodgkin lymphoma, and NHL, and comparable with the rest of cancers. The ASIRs for the population of Golestan compared to those for Lahore were considerably high for cancers of the Gastrointestinal (GI) system, pancreas, larynx, lower respiratory tract, prostate, bladder, cervix uteri/other female genital organs, multiple myeloma, and leukaemia, somewhat high for tumours of the ovary, brain/nervous system, thyroid, and NHL, but low for cancers of the oral cavity/salivary glands and female breast cancer. In case of the population of Riyadh, compared to Lahore, the ASIRs for cancers of the GI system, pancreas, lower respiratory tract, corpus uteri, ovary, thyroid, Hodgkin lymphoma, NHL, multiple myeloma, and leukaemia were relatively high, but low for the oral cavity/salivary glands, breast, and cervix uteri. It is worth mentioning here that geographically, Pakistan is located in South Asia and its neighbouring countries include India (South Asia) and Iran (West Asia); Saudi Arabia is in the Middle East, and Israel, also in the Middle East, is located at the eastern end of the Mediterranean Sea. It has been observed that the dietary habits of the inhabitants of Lahore, Golestan, Riyadh, and Israel are alike as a very large majority of the people living in the first three cities are Muslims and consume both meat and a vegetarian diet, while in Israel, Jews consume Kosher food and a Mediterranean diet, but their dietary habits would be different from the people of Ahmedabad, a populous city of India where Hindus constitute nearly 80% of the population and primarily consume a vegetarian diet.[20] Given that the ASIRs of cancers of the GI system, respiratory tract, and leukaemia were considerably high in Golestan, those of the cervix were high in Ahmedabad, and breast cancer in Lahore and Israel, it would be worth conducting extensive population-based studies to evaluate risk factors implicated in the etiology of the disease, to account for the geographic variations in the epidemiology of cancer.

Finally, as shown in Figure 1, the peaks in the age-specific incidence rates for breast and prostate cancer are similar to what is seen globally.

This is the first time that an extensive 6-year incidence report on cancer has been generated for any district of Pakistan. Pakistan has 150 districts as its administrative units, while the district of Lahore is one of the 36 districts in the province of Punjab.[8] Further, according to the World Bank[1] and Punjab Growth Strategy,[21] the Lahore district represents nearly 1/20th of the population of the country and 1/10th of the population of Punjab. Therefore, the generalisability of the results is debatable. However, once reports representing other districts are presented, a comparison can be made to assess the generalisability of the results. Regardless, Lahore is a heavily populated region of Pakistan and the significance of the results cannot be denied. Accordingly, the collection of these statistics is noteworthy as a continuum of care in the region.

CONCLUSION

These results warrant expanding cancer registration in the region and sharing statistics with policy-makers to establish hospitals accordingly to manage cancer, along with exploring various risk factors within the population.

DISCLOSURE:
The PCR is registered under the Societies Registration Act of Pakistan and is also a member of the International Association of Cancer Registries, France. The Registry is being sponsored by the Shaukat Khanum Memorial Trust.

ETHICAL APPROVAL:
The Institutional Review Board of SKMCH&RC approved this study.

PATIENTS' CONSENT:
Individual patient consent was not obtained for this study as a retrospective review of the records was conducted, results were collated and anonymised data presented in the manuscript.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTIONS:
FB: Conceived the idea of the study, designed it, supervised the statistical analysis, did literature search, interpreted the results, drafted the manuscript and finalised it.
SM: Did the case finding, indexing and coding of cases, computed the incidence rates and created figures and tables.
MTM, MM, IT, ORC, SN, AA: Contributed to the acquisition of data and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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