

RESEARCH ARTICLE

Quantitative Analyses of Esophageal Cancer Research in Pakistan

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Abstract

Background: Health-care research is a neglected discipline in Pakistan and research related to esophageal cancer (ranks 9th in Pakistani males and 5th in females) is no exception in this regard. Particularly, there are no data available to delineate the overall status of esophageal cancer epidemiological studies in Pakistan. This study describes the first ever effort to make a systematic quantification, in an attempt to provide a road-map to all stakeholders for designing appropriate epidemiological, diagnostic and therapeutic strategies. **Materials and Methods:** International (PubMed, ISI Web of Knowledge) and local (PakMedinet) scientific databases as well as Google search engine were searched using specified keywords to extract relevant publication. Well-defined inclusion criteria were implemented to select publications for final analyses. All data were recorded by at least 3 authors and consensus data were entered into and analyzed for descriptive statistics (such as frequencies, percentages and annual growth rates) using Microsoft Excel and SPSS software. **Results:** A total of 79 publications fulfilled the inclusion criteria including 20 publications for which full texts were not available. Of the 79 publications, 59 (74.6%) were original/research publications, 5 (6.3%) were case reports, 4 (5.1%) were research communications, 2 (2.5%) were review articles, 1 was (1.2%) correspondence and 8 (10.1%) were undefined categories. Only 13 (<20%) cities of Pakistan contributed towards the 79 publications. On average, only 1.9 relevant publications/year were published from 1976 (year of first publication) to the present. Alarming, a decline in the annual growth at -4.1% was recorded in the last six years. **Conclusions:** Esophageal cancer research is largely unfathomed in Pakistan. Urgent/dramatic steps are required by all concerned to address this common (and under reported) cancer of Pakistan.

Keywords: Esophageal cancer - research output - international literature - Pakistan

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Introduction

Esophageal cancer is the 8th most common cancer and 6th most common cause of cancer associated deaths across the globe. Approximately 80% of the esophageal cancer cases originate from the developing countries (Ferlay et al., 2015). Two high-risk regions commonly referred to as the “Asian belt” and the “African belt” have been identified. Global incidence of esophageal cancer is 3-fold higher in males compared to females. Major risk factors for esophageal cancer include gastroesophageal reflux disease (GERD), obesity and cigarette smoking (Napier et al., 2014; Rustgi et al., 2014). Moreover, several genes (including MRS1, ASCC1, CTHRC1, CDKN2A, SMAD4 and PIK3CA) have been associated with the pathogenesis of esophageal cancer (Rustgi et al., 2014).

Although national scale cancer registration does not exist in Pakistan (Qureshi et al., 2015), reports published

by the Punjab Cancer Registry (the only functional provincial scale population based cancer registry in Pakistan) listed esophageal cancer as the 4th most common cancer of adults in Pakistan in the year 2013 (Skmch & Rc, 2013). Previous data from the Karachi Cancer Registry (KCR-now non-functional since the demise of its founder Dr. Yasmeen Bhurgri) also listed esophageal cancer amongst the most common cancers in Karachi (Bhurgri et al., 2000; Bhurgri et al., 2004). In some parts of Pakistan, such as Balochistan, the incidence of esophageal cancer is even higher. For example, according to the Quetta cancer registry, esophageal cancer was the most common cancer in both genders (Bhurgri et al., 2002; Bhurgri et al., 2003). Another report from a cancer specialist hospital in Balochistan reported esophageal cancer to be 3rd most common diagnosed cancer at their practice (Roohulla et al., 2001; Roohulla et al., 2005). More recently, the Globocan 2012 reported that esophageal cancer is the

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9th most common cancer in males and 5th most common cancer in females in Pakistan (Globocan., 2012). Moreover, at the Pathology based cancer registry at our institute- the Dow University of Health Sciences, Karachi (the largest government based provincial level diagnostic and referral center), analyses of patients registered during 2010-2014 period showed that esophageal cancer is the 3rd most common cancer in females while 5th most common cancer in males (un-published data). These data suggest Pakistan as a country with a high esophageal cancer burden, notably in the absence of a national level cancer registration system, due to which a large number of esophageal cancers are being un-reported.

It is therefore extremely important to include esophageal cancer research as a priority in Pakistani health care agenda. However, and unfortunately, there are no scientific data available to describe the status of esophageal cancer research in Pakistan - a possible cause of negligence towards esophageal cancer research in this country. In the research described herein, we quantitatively investigated the current status of esophageal research output from Pakistan. Main objectives of this study were (a) to investigate the total esophageal research output to date originating from Pakistan, (b) to investigate the types/categories and research foci of esophageal cancer research related publications published from Pakistan, and (c) to investigate major contributing universities/ research centers and cities towards esophageal cancer research output from Pakistan. We believe that the data provided herein would provide considerable information that can facilitate the process of designing appropriate epidemiological, diagnostic, screening, therapeutic and prognostic strategies for patients suffering from this common cancer of Pakistan.

Materials and Methods

The working algorithm

The study was conducted using a three-staged strategy:

(1) literature search, (2) screening of the extracted publications using strictly defined inclusion criteria, and (3) indexation and analyses of the selected publications for various parameters (figure 01). These steps are described as under

Literature search

In order to extract esophageal cancer related publications from Pakistan, international (PubMed, ISI Web of Knowledge) as well as local (PakMedinet) electronic scientific database were searched. In order to broaden the literature search, various combinations of key words were used including “esophageal cancer”, “esophageal carcinoma”, “esophageal malignancy”, “esophageal neoplasia”, “adenocarcinoma esophagus”, “squamous cell carcinoma esophagus”, “sarcomatoid carcinoma esophagus”, “adenosquamous carcinoma esophagus”, “small cell carcinoma esophagus”, “neuroendocrine carcinoma esophagus”, “lymphoepithelioma esophagus”, “cancer and esophagus”, “carcinoma and esophagus”, “malignancy and esophagus”, “neoplasia and esophagus” and “Pakistan”. In order to further broaden the literature

search, we did not implement any filters available at the databases. Data mining was further strengthened using the search engine “Google” as well as “Google Scholar” with a restriction to extract the webpages related to Pakistan only.

Screening of publications for eligibility

In order to identify publications of interest (to be included in final analyses), and after removal of all duplicate entries, a strict inclusion criteria were defined. Only those publications were included in the study where (a) esophageal carcinoma was the main focus of publication either directly, or in case of epidemiological studies, provided important information regarding esophageal carcinoma burden in Pakistan, (b) research was undertaken in Pakistan or was directly addressing esophageal carcinoma in Pakistan and/or, (c) at least the first (principle) author was affiliated to a Pakistani institution. All publications (with and without available full texts) fulfilling the aforementioned inclusion criteria were included in the final analyses.

Indexation and Analyses

Three of the authors (AQ, RK and BAK) electronically indexed the data in Microsoft Excel worksheets independent of each other. Each of the 79 selected publications were recorded for their PubMed ID (wherever applicable), title, name of the journal, year of publication, type of publication, affiliation of authors, major research focus and number of citations received. In order to identify the university/research institution affiliated with the publication, first author’s affiliation was used as previously described (Khan et al., 2015). Publications were labelled as indexed if they were indexed in PubMed (Medline), alternatively they were called as non-indexed publications.

Finally, data entered by all three authors were compared and any in-consistencies were investigated and sought to generate consensus indexation. Consensus data were then entered into SPSS for further descriptive analyses, such as calculation of frequencies and percentages. Annual growth rates of publications were calculated using the formula, Annual growth rate = $(Pe - Pi/Pi) \times 100/N$, where, Pe = number of publications at the end of a defined period, Pi = number of publications at the initiation of a defined period and N = total number of years in a defined period.

Results

Initially, a total of 302 publications were retrieved from the electronic databases using the specified key words. After removal of duplicate entries, a total of 123 publications were left. Of these, a total of 44 publications did not fulfil the inclusion criteria and therefore these were excluded from the study. Remaining 79 publications which fulfilled the inclusion criteria were included in the study for further analyses described as follows.

Annual growth of publications

First publication addressing esophageal carcinoma from Pakistan was published in the year 1976 (Jafarey and Zaidi., 1976), whereas the most recent publication at the time of drafting this manuscript was published

in January 2016 (Sultan et al., 2016). Overall, a total of only 9 (11.3%) publications were published before the year 2000. During 2000-2005, a total of 28 publications (annual growth rate of 35.2%) were published while a total of 24 publications (annual growth rate of 1.5%) were published during 2006-2010. Since 2011 to date, a total

of 18 publications (annual growth rate of 4.1%) were published. Highest number of publications (n=10) were published in the year 2009. Alarming, average number of publications since first publication (1976) to date has been only 1.9 publications per year.

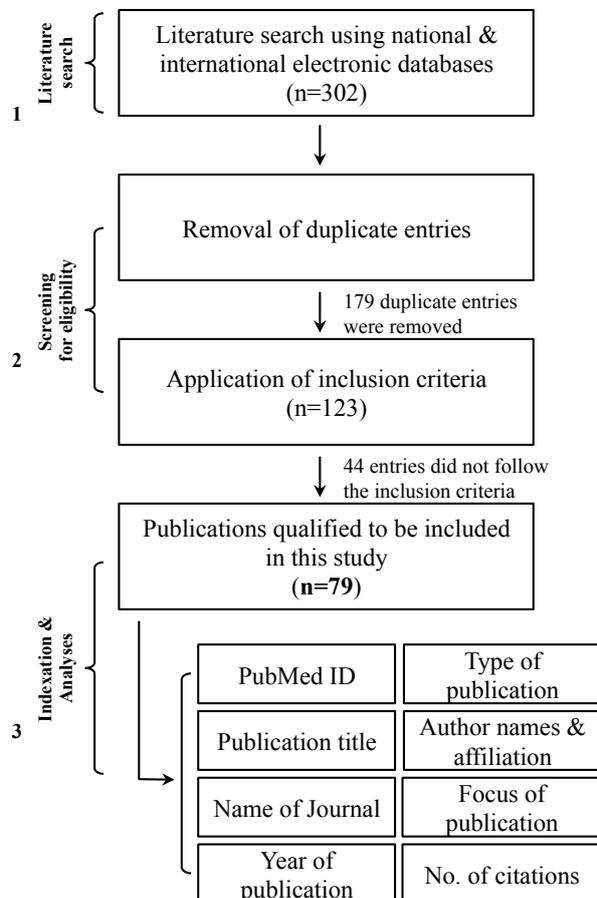


Figure 1. The Working Algorithm Utilized in this Study

Types and research foci of publications

Of the 79 publications that we investigated, a total of 43 (54.5%) publications were indexed in PubMed (Medline) while 36 (45.5%) were non-indexed publications. Main journals which published esophageal cancer research from Pakistan are represented in table 01 (journals with more than 1 publication are listed only). Of the 79 publications, a total of 59 (74.6%) were original/ research publications, 5 (6.3%) were case reports, 4 (5.1%)

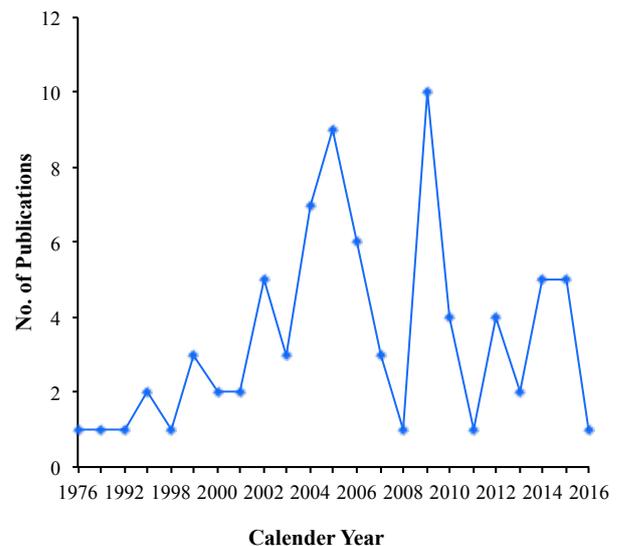


Figure 2. Annual Growth of Esophageal Cancer Related Publications from Pakistan During 1976 to Date

Table 1. Major Journals to Publish Esophageal Cancer Research from Pakistan

(journals with more than 1 publication were included in the list as "major journals")				
Name of Journal	number of publications, n(%)	PubMed indexed	Impact factor	H-Index
J Pak Med Assoc	15 (18.9%)	Yes	0.4	27
J Coll Physicians Surg Pak	8 (10.1%)	Yes	0.5	22
J Ayub Med Coll Abbottabad	8 (10.1%)	Yes	0.1	17
Annals of King Edward Medical College	5 (6.3%)	No	-	-
Asian Pac J Cancer Prev	6 (7.5%)	Yes	2.5	47
Gomal J Med Sci	3 (3.7%)	No	-	-
J Postgrad Med Inst	3 (3.7%)	No	-	-
Pak J Med Sci	3 (3.7%)	Yes	0.2	17
Pak J Surg	3 (3.7%)	No	-	-
Journal of Rawal Med College	2 (2.5%)	No	-	-

Table 2. Major Contributing Institutions to Esophageal Cancer Research in Pakistan

University/Research Institution	City	n/%
Aga Khan University Hospital (AKUH)	Karachi	11 (13.9%)
Lady Reading Hospital (LRH)	Peshawar	09 (11.3%)
Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC)	Lahore	08 (10.1%)
Jinnah Postgraduate Medical Centre (JPMC)	Karachi	06 (7.5%)
Karachi Cancer Registry (KCR)	Karachi	05 (6.3%)
Centre for Nuclear Medicine & Nuclear Medicine & Radiotherapy (CENAR)	Quetta	04 (5.1%)
Civil Hospital Karachi (CHK)	Karachi	03 (3.7%)

were research communications, 2 (2.5%) were review articles, 1 (1.2%) was correspondence to the journal and 8 (10.1%) were un-defined categories. Of the 59 original/research publications, a total of 29 (49.1%) focused on frequency and distribution of various subtypes of esophageal cancer (14 publications were hospital based, 10 were pathology based while only 5 were population based data), 19 (32.2%) publications focused on various treatment modalities and/or their outcomes, 8 (13.5%) publications focused on diagnostic strategies, 2 (3.3%) were laboratory experimental studies while 1 (1.7%) study focused on identifying factors associated with esophageal carcinoma. Of the five case reports, four reported uncommon esophageal cancer diagnosis or metastatic sites, while one reported motor neuropathy associated with esophageal carcinoma.

Of the four research communications, three focused on epidemiological data (2 Pathology based while 1 population based data) and one focused on the use of self-expandable stents at a tertiary care hospital. Both the review articles focused on diagnostics, therapeutics and guidelines associated with the disease. Indeed, one of the review publications largely focused on the guidelines associated with gastroesophageal reflux disease but in diagnostic context to adenocarcinoma of esophagus and was therefore included in our study. The only correspondence was focused on 5-fluorouracil induced vasculitic injury in patients suffering from esophageal carcinoma.

Author affiliations and contributing institutions

A total of 34 universities/research institutions participated in the publications that were investigated in this study. Of these, a total of 29 (85.2%) were public/government sector while 5 (14.7%) were private sector institutions. Interestingly, all the 34 contributing institutions belonged to only 13 cities of Pakistan leaving behind >80% of the cities with “zero” research output in the field of esophageal cancer research. Major contributing institutions towards the publications are listed in table 02.

Number of citations received

Of the 79 publications that were investigated, a total of 39 (49.5%) publications did not receive any citation to date. Of these, a total of 25 (64.1%) publications were published in non-indexed journals while 14 (35.8%) were published in indexed journals. The remaining 40 publications were cited at least once since they were published. Cumulatively, these 40 publications received a total of 459 citations. Of these, a total of 405 (88.2%) citations were received by publications related to epidemiology/frequency/distribution of esophageal cancers in various parts of Pakistan.

Discussion

Health care research, in general, is a neglected area in Pakistan as evident by the lack of defined research priorities in the National Health Plan 2010-2015 published by the government of Pakistan (Government of Pakistan., 2010). However, we (and others) have previously reported

that research output in various scientific disciplines in Pakistan has increased in the last decades, particularly in the post-2000 era (Mushtaq et al., 2012; Gupta., 2012). This growth may be attributed to the establishment of the Higher Education Commission of Pakistan in the year 2002. Nevertheless, it is extremely important to note that a national level policy document that delineates priority areas/guidelines for health-care research in Pakistan is non-existent and esophageal cancer research is no exception in this regard.

Alarming, and to the best of our knowledge, there are no scientific data available to describe the status of esophageal cancer research in Pakistan. This is the first effort that systematically collected all relevant publications from Pakistan and investigated them quantitatively for various parameters. Since the first publication in 1976, only a total of 79 publications related to esophageal cancer were published from Pakistan. These publications do not follow a regular pattern with sporadic ups and down spread all over the years. Importantly, the decrease of annual growth rate in the recent years is an alarming signature, indicating a rapid decline for esophageal cancer research as a priority. In addition to several reasons that are responsible for overall decreased research output from Pakistan, there could be at least two obvious reasons as to why esophageal cancer research is largely un-addressed and indeed decreased in the recent years. Firstly, lack of any national research guidelines in itself is sufficient to render Pakistani researchers blind to the national needs (such as esophageal cancer research) in the area of health-care research. Secondly, the fact that there are no data available to demonstrate the paucity in the field of esophageal cancer research in Pakistan may have further contributed towards the negligence towards conducting esophageal cancer research. This study therefore holds tremendous potential in establishing the current status so that Pakistani researchers can focus on design appropriate experiments related to esophageal cancer in Pakistan. Moreover, the government agencies in Pakistan may also benefit from our findings in designing appropriate strategies.

Of the 79 publications that we investigated, 32 publications (29 research publications and 3 research communications) focused on frequency, distribution and patterns of esophageal malignancies in various parts of Pakistan. Of these, only 6 were based on population data while all the others described regional data from hospital based or diagnostic (pathology) based experiences. A major area of concern is the fact that of the 6 population based studies, only 1 was published (in 2005) by the Shaikat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC) and five were published by the KCR which is currently non-functional after the demise of its founder, Dr. Yasmin Bhurgri and thus no more contributory towards cancer statistics of Pakistan. Another alarming fact is the complete absence of esophageal cancer frequency/distribution data from >80% cities of Pakistan. This is particularly more distressing for those cities of Khyber Pakhtunkhwa (KPK) and Baluchistan where only Peshawar (from KPK) and Quetta (from Baluchistan) were the contributors. KPK share a long (2,250 km), and

extremely busy for cross-border-population-movement, border with Afghanistan - a country of high incidence and prevalence for esophageal cancer (Hamrah et al., 2014; Globocan., 2012). Since approximately half of the cross border travelers have family and/or friends in both countries (UNHCR., 2009), there are high chances that such families (and daily cross-border movement) would make an impact on the statistics of esophageal cancer in Pakistan.

According to the Globocan 2012 report, esophageal cancer is the 9th most common cancer in males and 5th most common cancer in females in Pakistan (Globocan., 2012). However, we have previously emphasized that the Pakistani statistics utilized by the Globocan 2012 are regional (defined as category E data by the Globocan 2012) and therefore not exact representative of the national level disease burden (Qureshi et al., 2015). It is therefore difficult to accurately estimate esophageal cancer incidence, prevalence and mortality rates in Pakistan. However, there are some data available to support the fact that esophageal cancer is amongst the most common cancers in Pakistan. For example, according to the SKMCH&RC, esophageal cancer was the 4th most common cancer in Pakistani adults in the year 2013 (SKMCH&RC., 2013). At our pathology based cancer registry, retrospective analyses of 2010-2015 data analyses show that esophageal cancer is 3rd most common cancer in females and 5th most common cancer in males. In some parts of Pakistan, particularly Quetta, the situation is even worse where esophageal cancer has been reported to be the most common cancer in males and females (Bhurgri et al., 2002; Bhurgri et al., 2003; Bhurgri et al., 2004). Notably, due to absence of national level cancer registration system in Pakistan, it is plausible to state that the possibility of a large number of esophageal cancers being un-registered is very high. Therefore, it is possible that the available regional statistics represent only tip of the ice berg and the real esophageal cancer burden in Pakistan may be very high compared to what is being reported at the moment. Nevertheless, it is extremely important that researchers from all over Pakistan report their regional statistics more frequently in order to obtain a more representative statistical picture.

It is important to note that a total of 46 (58.2%) publications were generated alone by only 7 institutions suggesting that these were the major contributors in the field of esophageal cancer research. City wise, there is only 1 dominating city from each of the 4 provinces in Pakistan to generate all (or most) of the esophageal cancer research publications. For example, in the province of Baluchistan, all 4 publications were generated from the city of Quetta alone. In the province of KPK, the city of Peshawar was the main contributor while Lahore and Karachi were the major contributors from the provinces of Punjab and Sindh respectively. Importantly, no esophageal cancer research data was available from majority of the cities in Pakistan. This could be attributed to an overall lack of health care facilities in Pakistan where most of the tertiary care health institutions are located only in the major cities (WHO., 2011). Additionally, Pakistan also faces a plethora of challenges such as high population density, illiteracy,

political instability and corruption. All these factors affect the health care system in general and this is also reflected by the lack of esophageal cancer research from most (>80%) of the Pakistani cities.

Of note is the negligible performance of cancer specialist hospitals in Pakistan suggesting their low priority for esophageal cancer research. This includes the SKMCH&RC and the Pakistan Atomic Energy Commission. It is important to mention here that the SKMCH&RC is a major contributor to the only functional provincial population based cancer registry, the Punjab cancer registry. Although the SKMCH&RC appears to be a major contributor in terms of overall number of publications, its responsibility as a cancer specialist research center increases and thus a total of 8 publications since its inception cannot be considered as a considerable contribution. This is true particularly with reference to incidence, prevalence and mortality data for esophageal cancer published by the SKMCH&RC which was published only once in the year 2005. Although, SKMCH&RC publishes annual reports stating cancer burden within Punjab at their institutional website, these population-based data, at least in case of esophageal cancer, are not regularly published in scientific journals. Therefore, the statistics are not reachable by a majority of readers including major stakeholders such as planning division of the government of Pakistan.

Visibility and readability of publications is undoubtedly associated to a great extent with indexation of journals with international databases (Vines TH et al., 2013; Akhigbe., 2012). In our study, only 43 (54.5%) of the esophageal cancer research from Pakistan was indexed in international databases. Moreover, full text articles for a total of 20 publications were not available even at the parent journal's website. Therefore, such publications are not easily visible to the readers as well as to the policy makers.

At present, we did not find a single publication from Pakistan that addresses esophageal cancer biology in terms of genetic, epigenetic, social and/or environmental factors responsible for/associated with the pathogenesis of esophageal cancer. It is a well-established fact that tumour behavior is a complex phenomenon that depends on a range of genetic and environmental factors, specific for distinct geographical areas of the world. In breast cancer for example, American females with African background tend to develop poor prognosis basal type breast cancers compared to white females with breast cancer (DeMore KN., 2005). Pakistan accommodates a genetically distinct population with unique environmental and social risk factors. Moreover, risk factors can also be heavily influenced by influx of immigrants from neighboring countries. For example, a famous drink in Afghanistan is a hot tea beverage (known as "kahwa") - a common risk factor for esophageal cancer (Islami et al., 2009; Lin et al., 2011), is also utilized by a lot of Afghani families living in Pakistan. It is therefore important to investigate esophageal cancer for genetic, epigenetic, social and environmental associations in Pakistan.

Taken together, the data presented herein suggest that esophageal cancer research in Pakistan is alarmingly

scarce and largely unfathomed. We believe that our findings will provide a considerable platform for health care policy makers as well as researchers in Pakistan to devise appropriate strategies to address this common cancer of Pakistan. We also emphasize that researchers working in the field of esophageal cancer research in Pakistan should publish their research in indexed journals so that it is broadly visible to all concerned. While institutions in all cities in Pakistan should focus to increase their research output, well established and cancer specialist centers should take a lead in prioritizing esophageal cancer research. Finally, we strongly recommend the policy makers to devise appropriate strategies on urgent basis so that esophageal cancer research in Pakistan can be prioritized and appropriately addressed.

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