



Review Article

Cancer scenario in North-East India & need for an appropriate research agenda

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Background & objectives: The North-Eastern (NE) region has the highest incidence of cancer in India, and is also burdened by higher prevalence of risk factors and inadequate cancer treatment facilities. The aim of this study was to describe the cancer profile of the NE region, focussing on the cancer sites that have high incidence and to identify research priorities.

Methods: Incidence data from population-based cancer registries (PBCRs) in the North-East region (8 States) were utilized and relevant literature was reviewed to identify risk factors.

Results: Aizawl district in Mizoram had the highest incidence of cancer in men [age-adjusted rate (AAR) of 269.4 per 100,000]. Among women, Papumpare district of Arunachal Pradesh had the highest incidence (AAR of 219.8) in India. East Khasi Hills district in Meghalaya had the highest incidence of oesophageal cancer (AAR of 75.4 in men and 33.6 in women). Aizawl district in Mizoram had the highest incidence of stomach (AAR–44.2 in men) and Papumpare district had highest incidence of stomach (AAR 27.1 in women), liver (AAR– 35.2 in men and 14.4 in women) and cervical cancers (AAR– 27.7). Lung cancer (AAR– 38.8 in men and 37.9 in women) and gall bladder cancer incidence (AAR– 7.9 in men and 16.2 in women) were highest in Aizawl and Assam (Kamrup urban) PBCRs, respectively. Nagaland had the highest incidence of nasopharyngeal cancer (AAR of 14.4 in men and 6.5 in women), a relatively rare cancer in other regions of India. Four States (Arunachal Pradesh, Manipur, Sikkim and Tripura) in NE had only one cancer treating facility.

Interpretation & conclusions: Further research on specific aetiological factors in the region and multi-disciplinary research for development of tools, techniques and guidelines for cancer control are the need of the hour.

Key words Cancer - cancer facilities - cancer incidence - cancer research needs - North-East India - research agenda

Cancer is one of the leading causes of death globally. In lower middle-income countries such as India, the impact of cancer is high, due to low awareness, lack of access to affordable care and poor prognosis^{1,2}. Due to diversity in ancestries, socio-economic and cultural attributes, eating habits

and lifestyles, geographical variations exist in genetic determinants, environmental exposures and patterns of cancers between regions^{3,4}. Hence, programmes conducting systematic data collection and reporting high-quality data on cancer from both urban and rural areas are essential to strengthen cancer epidemiology in

the country. The National Cancer Registry Programme (NCRP) initiated by the Indian Council of Medical Research (ICMR) in 1981 has developed a network of cancer registries, to collect and collate reliable cancer data from various parts of India⁵. The NCRP functions through population-based and hospital-based cancer registries (HBCRs) across different centres in India. Currently, under the NCRP, 38 population-based cancer registries (PBCRs) provide data on the types of cancer prevalent in particular regions and the geo-pathological variations between regions in India. In addition, 253 HBCRs are providing data on the treatment pattern and the survival (<https://www.ncdirindia.org/>).

Incidence rates of all sites of cancer have consistently been the highest in the north-eastern (NE) States of India since establishment of the earliest cancer registries in this region in 2003⁶⁻¹¹. In addition, this region also has a unique cancer profile with higher incidence of cancers of the upper digestive tract such as oesophagus, stomach and hypopharynx compared to other regions. A pooled analysis of the HBCR data from the North-East has also indicated low survival, lower detection of localized cases and different cancer patterns as compared to other regions of India¹¹.

There is an urgent need to comprehend the distinctive cancer patterns of this region, develop appropriate programmes and identify priorities for targeted research. Although there have been several publications addressing various aspects of the cancer burden in the region with either a focus on specific cancer types¹²⁻¹⁴ or reviews outlining the cancer profile¹⁵, but a comprehensive analysis of all relevant cancers, associated aetiological factors and possible public health measures is lacking. This study was aimed to provide an analysis of the cancer profile in the NE States of India based on the latest data published in 2020 (covering year 2012-2016) from the 11 PBCRs in the region, enumerate possible risk factors and propose key research areas to prioritize for cancer control.

Material & Methods

Cancer incidence data were derived from 11 PBCRs, which provided data for the eight NE States (Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura) under the NCRP. For the process of cancer registration, records and information were obtained from hospitals, clinics and pathology laboratories on patient identification, socio-demographic variables, diagnostic and treatment details on a proforma. Death certificates were also

scrutinized from municipal corporation units to collect complete data on missed cancer cases. Coding of disease was done according to the International Classification of Diseases-10 (ICD-10)¹⁶ and International Classification of Disease for Oncology-3¹⁷. PBCR Data Management (PBCRDM) version 2.1 Software developed in-house was used to capture the patient's identifying, diagnostic and treatment information, followed by transmission of data to the coordinating unit [National Centre for Disease Informatics and Research (NCDIR)]. The data quality was maintained by individual registries through duplicate verification and matching with mortality records and thereafter by NCDIR. The data from individual registries undergo duplicates and quality checks at the NCDIR including range, consistency, unlikely and family checks as per the International Agency for Research on Cancer (IARC) norms^{18,19}. The checks are built into PBCRDM software and online PBCR data entry application and the cases with suspected errors are sent back to the individual registries for verification and corrections are updated in the cancer registry database.

The 11 PBCRs cover around 35 per cent of the population of the NE region. PBCRs in Manipur, Mizoram, Sikkim and Tripura have complete population coverage. PBCRs in Arunachal Pradesh and Meghalaya have 64.6 and 62.9 per cent population coverage, respectively. 32.7 per cent of the population in Nagaland and 13.7 per cent in Assam are covered by PBCRs¹¹. For this analysis, data on incidence of all and specific cancer types in this region were utilized. Cancer incidence rates are expressed as age-adjusted rates (standardized to world standard population) per 100,000 population.

A review of literature was conducted on PubMed and Google Scholar (2000 to 2020) to identify and enumerate aetiological factors for the cancers showing high incidence in North-East India. WHO-IARC monographs were also consulted to assess and enumerate aetiological factors for each of the selected cancer sites^{20,21}. In addition, data from national surveys such as the National Family Health Survey (NFHS-4), Global Adult Tobacco Survey (GATS-2) and NCRP publications were used to analyze and correlate prevalence of risk factors and high cancer incidence in the region^{22,23}.

Results

Data quality indicators for the North-Eastern population-based cancer registries for all sites

Table I. Data quality indicators of North-Eastern population-based cancer registries for all sites (ICD-10: C00-C97) for the period of 2012-2016

State	Registry	Per cent MV	Per cent DCO	Per cent O and U
Arunachal Pradesh	West Arunachal	94.1	0.1	2.6
	Papumpare district	95.5	0.0	2.3
	Pasighat	88.3	1.6	7.4
Assam	Cachar district	82.8	3.0	12.2
	Dibrugarh district	78.7	9.8	4.9
	Kamrup Urban	81.1	8.2	5.4
Manipur	Manipur State	93.2	0.6	4.2
	Imphal West district	94.2	0.5	4.4
Meghalaya	Meghalaya State	86.8	9.9	8.3
	East Khasi Hills district	89.7	7.0	6.3
Mizoram	Mizoram State	85.2	5.0	10.0
	Aizawl district	88.0	2.6	7.5
Nagaland	Nagaland	96.6	0.5	3.3
Sikkim	Sikkim State	88.1	4.8	8.3
Tripura	Tripura State	93.8	0.1	8.1

Source: Ref 6. Per cent MV, the proportion of microscopically verified cases; per cent DCO, proportion of death certificate 'only' cases; per cent O and U, relative proportion of cancers that fell into 'other and unspecified sites (O and U)' group as per ICD-10 (including codes C26, C39, C48, C75, C76, C77, C78, C79, C80, C97)

(ICD-10: C00-C97) for the period of 2012-2016 are shown in Table I. The microscopically verified (MV%) cases ranged from 78.7 (Dibrugarh district) to 96.6 per cent (Nagaland). Death Certificate Only (DCO) cases were below 10 per cent across all the 11 PBCRs. Only the Cachar district had higher (12.2%) Other and Unspecified (O&U) sites, while the other districts had less than 10 per cent⁶.

According to cancer incidence data for 2012-2016 from the 11 PBCRs, the highest incidence of cancer in India was in the NE region. In men, Aizawl district in Mizoram and in women, Papumpare district of Arunachal Pradesh, had the highest overall age-adjusted rates (AARs) of 269.4 and 219.8 per 100,000, respectively. The highest incidence of cancer outside the NE region was considerably lower [AAR of 147.0 per 100,000 in men (Delhi) and 146.8 per 100,000 in women (Bengaluru)]. Aizawl and Kamrup urban (Assam) had been leading in cancer incidence rates since 2003 in both men and women. However, as per the 2012-2016 NCRP data, Papumpare district had the highest incidence in women.

Cancers of the oesophagus, hypopharynx, stomach, lung, liver and cervix showed substantially higher AARs across the various districts of this region as compared to the other regions of India.

Some cancers had higher incidence in specific regions such as nasopharynx in Nagaland and thyroid in women in Papumpare. The key site-specific cancers that contributed to the high cancer burden in the NE region are summarized below.

Oesophageal cancer: The highest incidence of oesophageal cancer for both men and women was found in East Khasi Hills district in Meghalaya (Table II). The AAR in East Khasi Hills district (AAR– 75.4) was 10 times higher compared to the rate in Delhi (AAR– 6.5) and Bengaluru (AAR– 7.0) in men. In women, the incidence (AAR– 33.6) was 7 to 9 times that of Bengaluru (AAR– 5.2) and Delhi (AAR– 3.8) registries. Meghalaya (AAR– 54.6 in men and 23.0 in women) and Mizoram (AAR– 30.2 in men and 7.0 in women) were the States with the highest incidence. Manipur with AAR of 3.5 per 100,000 in men and 1.1 per 100,000 in women had the lowest incidence of oesophageal cancer among the NE States⁶.

The major risk factors for oesophageal cancer was found to be betel nut chewing in a study conducted in Assam²⁴. Fruit consumption was low in these States ranging from 39.1 per cent in Nagaland to 64.5 per cent in Meghalaya in women, and 36.6 per cent in Mizoram to 70 per cent in Meghalaya in men²⁵. Consumption of

Table II. Ranking of north-eastern population-based cancer registries (PBCRs) with highest site-specific age-adjusted rate (AAR) in men and women for 2012-2016

Site	Rank 1		Rank 2		Rank 3		Rank 1	
	PBCr area	AAR	PBCr area	AAR	PBCr area	AAR	Outside NE region*	AAR
Oesophagus								
Men	East Khasi Hills district	75.4	Meghalaya State	54.6	Aizawl district	46.7	Patiala	11.5
Women	East Khasi Hills district	33.6	Meghalaya State	23.0	Kamrup urban	17.9	Patiala	8.2
Stomach								
Men	Aizawl district	44.2	Papumpare district	40.3	Mizoram State	39.1	Chennai	10.5
Women	Papumpare district	27.1	Aizawl district	21.7	Mizoram state	18.8	Chennai	5.1
Lung								
Men	Aizawl district	38.8	Mizoram State	32.1	Papumpare district	20.1	Kollam	23.1
Women	Aizawl district	37.9	Mizoram State	27.6	Imphal west district	16.6	Hyderabad district	6.0
Liver								
Men	Papumpare district	35.2	West Arunachal	21.5	Aizawl district	12.2	Mumbai	6.6
Women	Papumpare district	14.4	West Arunachal	8.0	Mizoram State	5.9	Mumbai	3.3
Gall bladder								
Men	Kamrup urban	7.9	Cachar district	5.6	Dibrugarh district	4.4	Delhi	5.4
Women	Kamrup urban	16.2	Cachar district	11.9	Papumpare district	10.7	Delhi	11.6
Nasopharynx								
Men	Nagaland	14.4	Papumpare district	9.3	Mizoram state	5.2	Thiruvananthapuram	0.6
Women	Nagaland	6.5	Papumpare district	3.9	Aizawl district	2.8	Chennai	0.3
Breast								
Women	Aizawl district	30.7	Papumpare district	29.6	Kamrup urban	27.1	Hyderabad district	48.0
Cervix								
Women	Papumpare district	27.7	Aizawl district	27.4	Mizoram State	23.2	Bengaluru	17.7

Source: Ref 6

very spicy food and hot beverages was also high in this region²⁶.

Stomach cancer: The highest AARs for men and women are in Aizawl district and Papumpare district (AAR of 44.2 and 27.1, respectively) (Table II). Arunachal Pradesh and Mizoram had the highest incidence of stomach cancer⁶. A high incidence of stomach cancer in Mizoram was linked to the peculiar dietary habits followed by the locals in this region, such as the consumption of sa-um (fermented pork fat) (odds ratio [OR]– 3.4), smoked dried salted meat (OR – 2.8) and fish (OR – 2.5) and use of Soda (alkali) (OR – 2.9) as a food additive²⁶. The prevalence of *Helicobacter pylori* infection which may act as a co-carcinogen was high in this region, as shown by studies done in Sikkim^{27,28}.

Lung: Mizoram State, particularly Aizawl district, had the highest AARs for lung cancer in both men and women (Table II). Tobacco smoking was identified as the primary risk factor established for cancers causation. IARC also established a causal association between exposure to second-hand smoke and lung cancer risk²⁰. Apart from direct exposure through cigarette smoke, inhalation of second-hand smoke was found to be high in this region, the highest being in households in Mizoram (83.2%), followed by Meghalaya (73.6%), Manipur (65.9%) and Tripura (65.2%)²².

Liver: The incidence of liver cancer in men was highest in the State of Arunachal Pradesh. Papumpare district had the highest incidence in men (AAR– 35.2) as well as in women (AAR– 14.4) (Table II). Alcohol consumption is an established cause of liver cancer²¹. As per the NFHS-4 data, alcohol use was the highest in the country in Arunachal Pradesh in both men (59.0%) and women (26.3%)²². There is a significant interaction between heavy smoking and heavy drinking in causing liver cancer²⁹, both of which were prevalent in North-East India²². Other preventable risk factors such as chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV)³⁰ showed a high seroprevalence in certain isolated tribes of Arunachal Pradesh³¹ and intravenous drug users in Manipur³².

Gall bladder: Gall bladder cancer incidence was found to be highest in Assam for both men and women (Table II). Kamrup urban district had the highest incidence (AAR of 7.9 in men and 16.2 in women) followed by Cachar district (AAR of 5.6 in men and 11.9 in women). Gall bladder cancer was observed to be higher in women as compared to men

in the North-East. A number of risk factors could be associated with gall bladder carcinoma in this region such as presence of pesticides, aromatic hydrocarbons³³, nitrosamines, nitrates, nitrites and heavy metals (iron, lead and cadmium)^{34,35} in Brahmaputra, Ganga and Pachin rivers and groundwater in some parts, and possible presence of adulterants in edible mustard oil used for cooking in eastern and NE parts of the country³⁶. Chronic inflammation and bile acid degradation due to bacterial infection is one of the causes of gall bladder cancer. These risk factors correlated well with *Salmonella typhi* infection which is highly prevalent in some parts of the region^{37,38}.

Nasopharynx: The NE region showed among the highest AARs in cancer of the nasopharynx. In both men and women, Nagaland had the highest AAR, which was approximately 21 and 34 times that of Delhi in men and women, respectively (Table II). Thiruvananthapuram (AAR in men of 0.6) and Chennai (AAR in women of 0.3) had the highest incidence of nasopharyngeal cancer outside of the NE region in men and women, respectively. Nasopharyngeal carcinoma known to be associated with the consumption of smoked meat³⁹ which was high in the NE region of India. Smoked and smokeless tobacco use was also higher in this region as compared to the rest of the country, which are risk factors in causation of head and neck cancers^{40,41}. Infection with Epstein–Barr virus (EBV) has been found to be associated with nasopharyngeal carcinoma in several studies, particularly in North-East India⁴²⁻⁴⁴. Other risk factors included living in poorly ventilated houses, consumption of nitrosamine-containing food items and lack of fruit intake, as shown by a study in Manipur⁴⁵.

Breast (women): Aizawl district in Mizoram had the highest incidence (AAR– 30.7) among all the NE PBCRs (Table II). The incidence of breast cancer was relatively lower in the NE region compared to Hyderabad district (AAR–48.0), Chennai (AAR–42.2), Bengaluru (AAR–40.5), Delhi (AAR–38.6) and Patiala District (AAR–38.6)⁶. However, Aizawl (AAR–30.7) and Papumpare (AAR–29.6) districts, despite having a lower urban (54.9 and 78.6%) population, showed higher incidence of breast cancer compared to Ahmedabad urban (AAR–23.6), and Kolkata (AAR–21.6) both of which have completely urban populations.

Known risk factors for breast cancer include BRCA1 and 2 sequence alterations⁴⁶, older age at first childbirth⁴⁷, breastfeeding duration⁴⁸, high body mass

Table III. Cancer-related health facilities in north-eastern States

State	Population	Cancer-treating facilities	Radiotherapy facilities	Cancer patient welfare schemes	Palliative care centres
Arunachal Pradesh	1,383,727	1	1	0	0
Assam	31,205,576	6	6	9	8
Manipur	2,855,794	1	0	0	1
Meghalaya	2,966,889	7	1	0	1
Mizoram	1,097,206	5	1	3	2
Nagaland	1,978,502	6	1	0	1
Sikkim	610,577	1	0	0	1
Tripura	3,673,917	1	1	0	1

Source: Refs 55,57

index and obesity⁴⁹ and rural–urban differences due to lifestyle changes such as alcohol consumption or socio-economic differences⁵⁰. The high incidence of breast cancer in the predominantly rural NE region was a conundrum⁵¹. This indicated contribution of lesser known risk factors in disease causation in this region. A retrospective cohort study in Assam has shown 32 per cent of breast cancer cases from NE States to be the triple-negative subtype⁵², a highly aggressive phenotype that presents at an early age, is associated with high-grade large tumours and high node positivity.

Cervix uteri: Incidence of cervical cancer was the highest in Papumpare district (AAR–27.7), Aizawl district (AAR–27.4) and Pasighat (AAR–20.3). In this study, cervix uteri was found to be the leading site of cancer among women in Arunachal Pradesh, Tripura, Mizoram and Nagaland and second leading site in Meghalaya and Sikkim. Persistent infection with HPV-16 and HPV-18 has been identified as an important risk factor in the aetiology of cervical cancer⁵³. However, despite being detected in almost 100 per cent of the cases, HPV may not be sufficient to induce cervical cancer and a multifactorial aetiology is more likely⁵⁴. The number of cancer-treating hospitals in the NE region was inadequate to meet the need for cancer services, as shown in Table III. Nagaland with a population of 1,978,502 had six cancer treating hospitals, while Manipur (2,855,794) and Tripura (3,673,917)⁵⁵ with higher populations had only one cancer treating hospital each. There were scant radiotherapy facilities in the region, while cancer patient welfare schemes only existed in Assam and Mizoram¹¹. The proportion of patients seeking care outside NE region was particularly high in Sikkim (98.3%), Nagaland (78.7%) and Manipur (62.4%)¹¹.

Discussion

The NE region has a predominantly rural population (81.64%)⁵⁵. There is tribal majority in Mizoram (94.5%), Nagaland (89.1%), Meghalaya (85.9%) and Arunachal Pradesh (64.2%)⁵⁵. In addition to the high incidence in the region, the prognosis and survival for cancers were also found to be worse in these States and the proportion of cases exhibiting distant metastasis at diagnosis was found to be higher¹¹. This finding, however, needs to be corroborated in the PBCR data and is open to further research. Due to low coverage in some of the States such as Assam and Nagaland, the pattern and incidence rates from PBCR data may not be generalized to the entire State.

A high prevalence of tobacco use, both smoked and smokeless, is noted in the NE region²³. Fifty seven per cent of all cancers in men and 28 per cent of all cancers in women in this region are tobacco related¹¹. The second round of the GATS found that while overall tobacco use had declined in India from 34.8 to 28.6 per cent between 2009-2010 and 2016-2017, there was a rise in tobacco use in Assam (from 39.3% in 2009-2010 to 48.2% in 2016-2017), Tripura (from 55.9% in 2009-2010 to 64.5% in 2016-2017) and Manipur (from 54.1% in 2009-2010 to 55.1% in 2016-2017)²³. While the other States in the region showed a decline in the prevalence of tobacco use, the rates continued to be higher than the Indian average. Current tobacco use in Tripura (64.5%), Mizoram (58.7%) and Manipur (55.1%) was found to be more than 50 per cent. The age of initiation for tobacco use also declined in the three States of Arunachal Pradesh, Nagaland and Sikkim, from 17.5 in 2009 to 15.9 in 2016-2017²³.

Lack of adequate healthcare facilities for providing cancer services was a major factor influencing cancer

outcomes. The proportion of women who had been examined at least once for cervical and breast cancer was found to be much lower in NE states, according to data from the fourth round of the NFHS²². Among the NE states, Assam (5.2%) and Tripura (5.1%) had the lowest proportion of women who reported having a cervical examination. Tripura (1.3%) and Nagaland (2.0%) had the lowest proportion of women who reported having had a breast examination done at least once²². Since the NFHS questionnaire did not specifically ask about cancer screening, the actual proportion of women screened for cancer of the cervix and breast is unknown and expected to be much lower. Lack of adequate trained staff at the primary and secondary health centres to provide risk factor identification, screening and referral services and lack of accurate data on specialized healthcare staff were major obstacles to the organization of adequate cancer control in the region⁵⁶. Sikkim and Mizoram had no specialists in community health centres against the requirement of 8 and 36 specialists, respectively. Arunachal Pradesh had only four specialists in position at community health centres against the required 252 specialists⁵⁷.

Key research areas: There is a need to lay out a prioritized research agenda which should enable short-term resolution and also long-term redressal of the problem. The major areas for research include in depth aetiological research, health system research, operational research, research for developing cancer programmes, and programme for implementation and monitoring of research.

It is crucial to have a comprehensive and coherent approach in planning and implementing programmes targeting specific regionally prevalent cancers. If emphasized, inclusion of community in planning and development of programmes and services will have long-term benefits by enhancing acceptability of socio-behavioural interventions such as tobacco cessation, dietary modifications and lifestyle changes.

The NCRP 2020 report⁶ and the report on cancer burden in NE States¹¹ provided data on the cancer incidence and common types prevalent in the NE region of India. The data also underscored the heterogeneity in incidence rates and cancer trends of various cancer types within the NE region. When addressing cancer in this region, the efforts should focus on those cancers showing the highest AARs and contributing the highest disability-adjusted life years in this region,

such as cancers of the head and neck, oesophagus, stomach, lung, breast and cervix. Through strategies for addressing the knowledge gap, strengthening infrastructure, supporting human resources in local health facilities, spreading awareness and promoting community-based approaches, it would be possible to target specific cancers at the local, State and regional level for North-East India.

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