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Cancer an Emerging Healthcare Crisis in Kerala

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Management of cancer remains one of the most rapidly progressing fields in medicine and has witnessed several novel developments in the recent years including immunotherapy, molecular targeted therapeutics and precision medicine. Over the past 40 years U.S government (National Institutes of Health) and many major global economies have invested heavily into basic research to understand the pathogenesis of cancer. This led to intense translational efforts by pharmaceutical companies and Universities and resulted in many ground breaking changes in cancer treatment globally. United States (US), being a leader in the cancer research witnessed a fivefold increase in immunotherapeutics in the past decade and tripling of cancer types that can be treated by at least one immunotherapeutic agent [1]. Another breakthrough has been the successful laboratory to clinical translation of chimeric antigen receptor T-cell therapies (CAR T-cell) where patient's cells are genetically engineered to attack the cancer cells [1]. Targeted therapies based on cell specific molecules has unfolded the paradigm of precision medicine in cancer. Just last year, eleven molecularly targeted therapeutic agents were approved by the US Food and Drug Administration (FDA) [2]. The precision medicine and next generation sequence were extended to the selection process of novel therapeutic options such as immunotherapy, PI3K inhibitors, PARP inhibitors and EGFR inhibitors [2]. Concurrent with these developments, progress in cancer mortality was also achieved with a 29% decline in the last 3 decades that includes the largest single-year drop happening in 2017 [3]. The patterns in improvement reflect underlying epidemiological transitions as well. For instance, decline in lung cancer incidence paralleled the trends in tobacco cessation while increase in obesity and decrease in fertility paralleled increasing incidence of breast and uterine cancers [3]. But in the future, unfortunately 70% of the mortality due to cancer will happen in low and middle income countries such as India, China and countries in Africa. In the following sections we discuss cancer as an emerging challenge in Kerala, examine the recent progress in various cancer subtypes in terms of prevention and treatment, and outline some of the implications for health care providers and policy makers.

Cancer incidence in Kerala

Kerala has historically been known for great strides in health care with health care indices that are at par with developed countries and much better compared to that of rest of India [4]. The

improvement in health care while promising a longer life expectancy, does also bring with it new challenges in the form of epidemiologic transition [5]. As a result, cancer has emerged as the second most common cause of death following cardiovascular diseases. As of 2013, there were an estimated 100,000 cancer patients in the state with an annual incidence rate of 135.3 per 100 000 people [6]. While this is the highest in the country, it is not surprising given the life expectancy and efficient tracking process of the regional registries that is lacking in other parts of the country [7]. In attempting to discuss the challenges and implications of rising cancer incidence, it may be prudent to begin the process by examining the risk factors for cancer and strategies for risk reduction and early detection.

Prevention by Risk Reduction of Common Cancers

Table 1 outlines the incidence rates and mortality for common cancer types in Kerala in comparison to national and global data. This has been stratified by the risk factors strongly associated with cancer. As in the United States where 40% of cancer cases are caused by modifiable risk factors (2014 data), these patterns are reflected in Kerala as well [8]. **Figure 1** is a graphical representation of the contributions of various risk factors to cancer deaths in India and could be extrapolated to Kerala. Tobacco in the form of cigarettes and chewing products continues to be the leading cause of cancer [9]. This has been linked to 18 different types of cancer – predominantly lung cancer, oral cavity cancer and laryngeal cancer [8]. An important fact with respect to tobacco and its health effects is that quitting at any age reduces the health risks immediately and specifically reduces the risk of cancer by 50 percent at 10 years [8]. The impact can be noticed at a population level as well. For instance, it is estimated that tobacco control programs implemented in the US saved 800,000 lives between 1975 and 2000 [10]. In Kerala, massive public health campaigns succeeded in banning smokeless tobacco products and public smoking but more needs to be done [9]. We need to do more research to inform appropriate strategies [11]. Seventeen states in the US passed legislation recently raising the legal age of smoking to 21 based on the finding that nearly 95 percent of adult smokers tried their first cigarette before the age of 21. It is estimated that this would prevent 223,000 deaths overall including 50,000 deaths from lung cancer [8].

Table 1: Comparing Global, Indian National and Kerala State Statistics on the Burden of Cancer in terms of Incidence and Mortality when stratified by the Risk Factors^a

Risk Group	Cancer Site	Age-standardized Incidence rate/100,000 (25–27)			Age-standardized Mortality rate/100,000 (25,26,28)			
		Global (2018)	India (2018)	Kerala (2016)	Global (2018)	India (2018)	Kerala Men (2014)	Kerala Women (2014)
Overall		197.9	89.4	125.4	101.1	61.4	84.8	87.9
Tobacco								
	Lung	22.5	5.4	11	18.6	5	10.3	2.6
	Oral cavity	4	9.1	12.9	2	5.6	6.8	2.5
	Larynx	2	2.3	3.3	1	1.4	2.0	
Alcohol								
	Liver	9.3	2.2	3.5	8.5	2	2.7	0.6
	Stomach	11.1	4.5	4.3	8.2	4.1	2.8	1.3
	Esophagus	6.3	4.2	2.8	5.5	3.7	2.3	0.5
Life style and Diet								
	Colon-Rectum	19.7	4.4	8.1	8.9	3.4	3.2	2.4
	Breast	46.3	24.7	18.4	13.0	13.3	-	9
	Prostate	29.3	4.4	5.1	7.6		2.2	-
	Cervix	13.1	14.7	5.3	6.9	9.2	-	3

^aPlease note that although most data is from 2018, the incidence and mortality data for Kerala are from a different year as data corresponding to the same year was not available. The mortality data for Kerala was obtained from a single cancer registry from Trivandrum and is available only as separate for men and women.

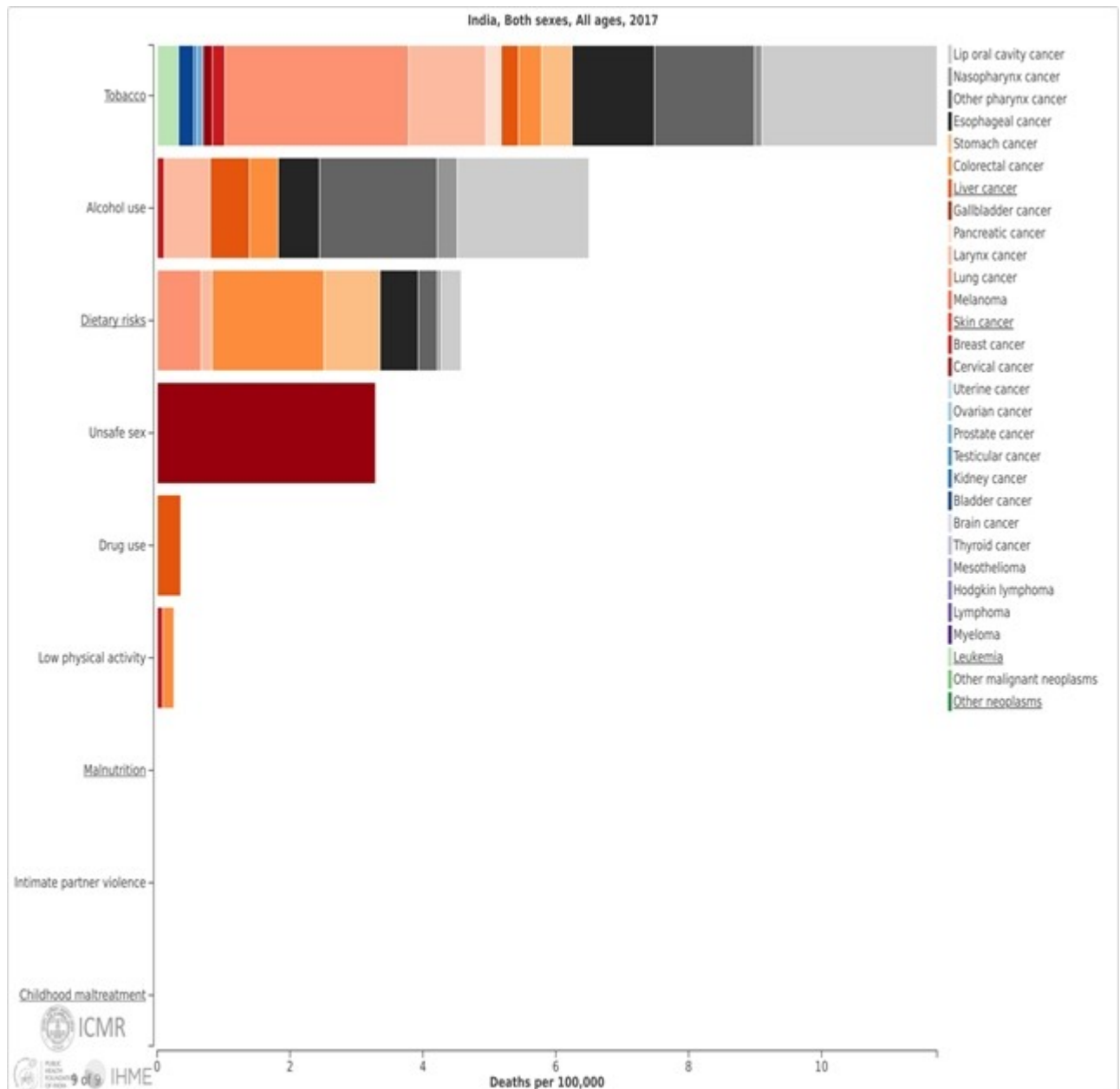


Figure 1: Risk Factors Contributing to Cancer Deaths in India, 2017 [29]

Alcohol – another risk factor for cancer, has been linked to six different cancer types [8]. These include liver cancer, gastric cancer, esophageal cancer and breast cancer. Kerala, being among the highest alcohol consuming states in the country also has high incidence of liver diseases and alcohol related cancers. As a consequence, approximately 150-200 liver transplants take place in the state a year – also a high figure nationally [12]. In order to curtail the impact of alcohol abuse, more efforts at policy interventions such as regulation of prices and taxes are needed along with public health campaigns. Unhealthy diet, physical inactivity and obesity that are byproducts of economic prosperity also contribute to increasing incidence of liver diseases in the form of non-alcoholic fatty liver disease as well as different cancers [12]. Being overweight or obese as an adult increases a person’s risk for 15 types of cancer and globally, excess body weight is responsible for about 4 percent of all cancer cases [8]. According to the National Family Health Survey, the prevalence of obesity increased in Kerala from 28% (Women) and 18% (Men) in 2005-06 to 32% and 29% respectively in 2015-16 [13]. It is imperative that policies are implemented to promote healthy dietary habits and facilitate physical activity.

Lifestyle interventions such as exercise, weight management and diet may reduce the risk of breast

cancer. Safe sex practices, could potentially reduce the incidence of cervical cancer. Lastly, policy efforts to reduce environmental pollution are also important as environmental risk factors contribute to nearly 20 percent of all global cancer burden most of which occur in low- and middle-income countries [8].

Prevention by Screening and Early Detection of Common Cancers

The future of cancer prevention will incorporate a risk based strategy. For instance lung and oral cancer screening among tobacco users or cervical cancer screening in those infected with HPV. Significant research is also being done to identify genomic and biological markers to permit risk-based screening [14]. Vaccines targeted against Human Papilloma Virus (HPV), have demonstrated efficacy in the prevention of cervical cancer and efficacy of Hepatitis B vaccination for prevention of Hepatocellular cancer is being studied [14]. However, the cost-effectiveness and feasibility of these strategies in Kerala or India need to be explored further. This is because of the population size and the fact that customs and treatment seeking behaviors drive the outcomes of these programs to a large extend.

To its credit, Kerala was the first state in the India to formulate a state-wide cancer control program and did so in 1988 as a 10-year action plan with notable success [15,16]. We will need to continue to improvise the strategies and adapt them in the context of Kerala’s society. For instance, while developed countries have gotten away with the breast self-exam as a screening tool, this may be a useful strategy in Kerala where stigma and gender disparities continues to influence health seeking behaviors. The utility of once in lifetime massive screening for certain age groups or at risk populations could also be investigated.

Recent Advances in Cancer Treatment

We will give a brief overview of recent advances in 4 most common cancers in Kerala.

Lung cancer

Screening for lung cancer using low dose helical CT scan has shown to decrease mortality in high risk population in the U.S. In the past 5-10 years, we have come to understand that there are many types of lung cancer based on molecular and genomic profiling. Better understanding of these molecular subtypes of lung cancer has allowed us to develop targeted therapies to specific subtypes. A major focus of research has been introduction of immunotherapy agents such as pembrolizumab, nivolumab and atezolizumab for lung cancer. Treatments that target tumor mutations (targeted therapies) have transformed lung cancer treatment – Anaplastic Lymphoma Kinase inhibitors (ALK inhibitors such as alectinib, crizotinib, certinib, brigatinib and lorlatinib), Epidermal Growth Factor Receptor (EGFR inhibitors, such as osimertinib, gefitinib, erlotinib and afatinib), BRAF inhibitors (dabrafenib and trametinib) to name a few [17]. It is hoped that with these newer agents outcomes for recurrent and advanced cancer patients will improve.

Colon cancer

Like breast cancer, colon cancer is a preventable cancer. In the western countries, colon cancer screening is routinely recommended for men and women older than 50 years of age. Screening modality includes, Fecal Occult Blood Test, Fecal Immunochemical based (FIT), sigmoidoscopy and Colonoscopy. Surgery remains a corner stone of treatment of early stage colon cancer. Novel treatment options in colorectal cancer includes anti-VEGF agents (bevacizumab, ramucirumab and aflibercept) and monoclonal antibody against EGFR (cetuximab, panitumumab) [18]. Many studies are looking at blood tests involving circulating tumor DNAs or liquid biopsy in the management of colon cancer [18].

Breast cancer

Early detection and effective treatments in breast cancer has resulted in 40% decrease mortality. Breast cancer screening with mammogram is routinely recommended for women older than 45 years and a risk based approach is recommended for screening. More than 70% of the patients in the western countries undergo lumpectomy and sentinel node biopsy, due to the early stage of diagnosis. After the introduction of Genomic testing such as OncotypeDX or MammaPrint, utilization of adjuvant chemotherapy has decreased by 30%. Breast cancer was one of the first cancers to have targeted therapies in the form of anti-estrogen and anti-Her-2 based treatments. Targeted non chemotherapy options include a number of hormonal therapies (tamoxifen, anastrozole, letrozole), Her-2 targeted agents (trastuzumab, pertuzumab, TDM1, neratinib, tucatinib and DS8201), novel CDK 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) and immunotherapy (atezolizumab and pembrolizumab). Introduction of genomic based assays have transformed the risk based approach for early breast cancer.

Prostate cancer

Prostate cancer screening with PSA is a controversial topic. Median age of prostate cancer is about 66 years. Prostate cancer can be cured when it is a local disease with surgery and radiation. Many of the patients with early stage prostate cancer will die from other diseases than prostate cancer. So in asymptomatic older patients with comorbid conditions, it is reasonable to do watchful waiting or active surveillance. Prostate cancer can be controlled even when it is metastatic with anti-hormonal treatment and other novel treatments. Hormonal therapy include abiraterone, luprolide, goserelin, flutamide and bicalutamide. Clinical trials are looking at the role of immunotherapy and development of vaccines for prostate cancer [19].

Implications for Health Care Providers

Keeping the above discussion in mind, the key role of physicians as leaders in the treatment and preventive efforts for cancer cannot be understated. Unfortunately, statistics indicate a dearth of Oncologists with an estimate of 180 physicians according to report by National Centre for Disease Informatics and Research (NCDIR) and Indian Council of Medical Research (ICMR) [20]. Recognizing this as an unmet need would be the first step towards solving the problem. The practice of Oncology is a multidisciplinary one and multidisciplinary tumor boards play a crucial role in making evidence based treatment decisions. In circumstances where a physical meeting cannot be established, remote meeting through video calls or tele-conferencing could be considered. A challenge faced by the physicians is the high prevalence of prejudice against modern medicine or “chemophobia” despite the high literacy rates. Programs for educating the public and removing misconceptions are needed while selectively integrating alternate practices to modern medicine without compromising the principles of scientific medicine. To address these issues and to find solutions, the state needs academic oncologists who would be willing to invest time in research – both in terms of clinical trials and assessing real world outcomes [11]. It is also important to realize that the workforce for management of cancer is not limited to clinical oncologists (such as surgeons, medical oncologists and radiation oncologists) but consist of pathologists, specialized nurses, pharmacists, physical and community health workers.

Palliative care

A discussion on management of cancer patients cannot be concluded without discussing palliative care. Fortunately for Kerala, community-based palliative care programs through the leadership of Institute of Palliative Medicine in Calicut is globally recognized for its achievements in providing accessible palliative care to the society [21,22]. While the misconception of equating palliative care

to end of life care is prevalent, fact remains that palliative care teams do play an important role in this transition for patients with terminal illnesses and making it least uncomfortable as possible. Majority of patients with cancer present with advanced stage disease at the time of diagnosis and constitute a significant proportion of the patients utilizing palliative care services in India [16,23]. Luckily, the relatives and neighbors continue to be an integral part of life in Kerala even as the families are progressively becoming nuclear and isolated. This is something to be cherished and promoted [24]. Continued expansion of the palliative care services through institutional and community based settings should remain an integral part of the evolving cancer management plans.

Kerala in Leadership role

Disease burden data from India and predictions based on this data show that the more populous and currently less economically developed states will start to undergo transition similar to Kerala in the coming decades [9]. These states have already accumulated huge gaps in cancer care and therefore tremendous efforts will be needed in the future to improve their outcomes [9]. By virtue of having experienced the transformation first, Kerala could use the knowledge gained to serve as a leader for rest of India if only we are able to address our own challenges first.

Conclusions

With its rapidly aging population and increase in life expectancy, Kerala is in a unique position to be a leader in defining the cancer care priorities. This should include prevention, early detection and effective treatments. It is important to train more health care providers, including nurses, technicians, social workers and various cancer specialists, including pathologists, radiologists, surgeons, medical oncologists, and radiation oncologists at our medical colleges and regional cancer centers. Kerala has one of the best palliative care infrastructures in the world, and it is important to enhance and sustain it. Financial toxicity of cancer care has to be addressed by private and public partnerships. Cancer care will improve only through research, education and global collaboration.

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