Esophageal Cancer in Tanzania: A Welcome Stimulus in Primary Prevention Research

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ABSTRACT

In this issue, Mmbaga and colleagues present results of a case–control study to investigate environmental and lifestyle risk factors for esophageal cancer in Tanzania, East Africa. The results contribute to the early stage of a growing evidence base aimed to inform primary prevention of a major poor prognosis cancer in East Africa. In this commentary, we first discuss considerations needed to evaluate causality of associations, a feature needed for primary prevention. There is a need for further studies across the African esophageal cancer corridor, for more refined exposure assessment and a careful consideration of potential epidemiologic biases within study designs for real-life situations in the setting. This study also forms a prime example of the broader research needs for cancer in low- and middle-income countries and in Sub-Saharan Africa, a setting with distinct and underresearched cancers and exposure patterns. While this etiologic research is challenging, it is an essential component of the ground-shot approach to global health research needed to inform primary prevention.

See related article by Mmbaga et al., p. 305

Introduction

The United Nations' blueprint aimed to achieve a sustainable future with better health and life for all is structured around specific Sustainable Development Goals (SDG). SDG target 3.4 is for a one-third reduction by 2030, relative to 2015 levels, in the risk of death at ages 30–70 years from four major noncommunicable diseases (1). Cancer is one of these four. Achieving this goal requires primary and secondary prevention measures for cancer, however, in many settings globally, even for the most common cancers, we are still not armed with solid evidence on the major attributable modifiable factors. Designing setting-specific cancer control plans and achieving reductions in cancer incidence rates in the absence of such knowledge is far from optimal. Indeed, region-specific cancer prevention recommendations, or "codes," are needed (2). In sub-Saharan Africa, the importance of cancer primary prevention is further elevated, due to health systems' demands. Notably, the specialized diagnostic and treatment facilities for cancer are already overstretched, yet the cancer burden will near double in the next two decades.

Esophageal cancer in Tanzania, and along the African esophageal cancer corridor more generally (3), provides one such example of cancer research needs for primary prevention in low- and middle-income countries (LMIC). This cancer was documented as having relatively high incidence and mortality rates for as long as cancer records exist. Notably, *The Lancet* highlighted incidence of the disease in Kenya in 1935 (4), yet substantial etiologic studies only followed this century (5, 6). East Africa, stretching from Ethiopia down to the eastern Cape of South Africa, has the highest incidence, while the cancer is extremely rare in West Africa (**Fig. 1**; ref. 7). The disease, which is predominantly esophageal squamous cell carcinoma (ESCC), has poor prognosis and patients suffer a particularly painful death. Severe dysphagia drastically reduces their quality of life.

Study findings

It is within this context that the current study of the aetiology of ESCC in Tanzania was undertaken. ESCC was documented in this country in 1976 in an impressive body of work by Hiza on all malignancies (8). He documented cancers diagnosed during 1969–73 at the Tanzanian Cancer Registry, and among the large number of cancers of the alimentary system, the most common were liver, mouth, stomach and, in fourth rank, oesophagus. Incredibly since then, to our knowledge, there have been no sizeable studies of the aetiology of esophageal cancer, other than a study of thermal injury as a likely contributor (9). This long-overdue research by Mmbaga and colleagues must thus be applauded and, in the future, expanded (10). The team conducted a case–control study of ESCC based at Dar-es-Salaam's the Muhimbili National Hospital (Salaam, Tanzania) and cancer treatment centre. Almost 500 cases and 500 age- and sex-matched controls were recruited over a 3-year period. The case profile was 70% male, median age almost 60 years, yet with a considerable (11%) number of very young patients (in their 30s, those under 30 were not included). This relatively high proportion of such young patients is a unique feature of ESCC in Africa (11). The broad groups of risk factors identified were low socioeconomic status, former smoking, household smoke, residence in the central, northern/lake and southern zones, and regular consumption of chilies and salted food. Protective factors included consumption of fruits, vegetables, and smoked fish.

Identifying causal risk factors

These results form an excellent base upon which to build further investigations to inform primary prevention. Notably, this and future investigations need to consider in-depth exposure assessments and the effects of potential biases. While lower socioeconomic status was identified as a risk factor, this must be a proxy of other causal risk factors that need to be identified if targeted prevention strategies are to be implemented.

Mmbaga and colleagues' observation of an unexplained higher incidence in zones beyond the coast is intriguing and appears to mirror Hiza's findings in the aforementioned 1976 publication of

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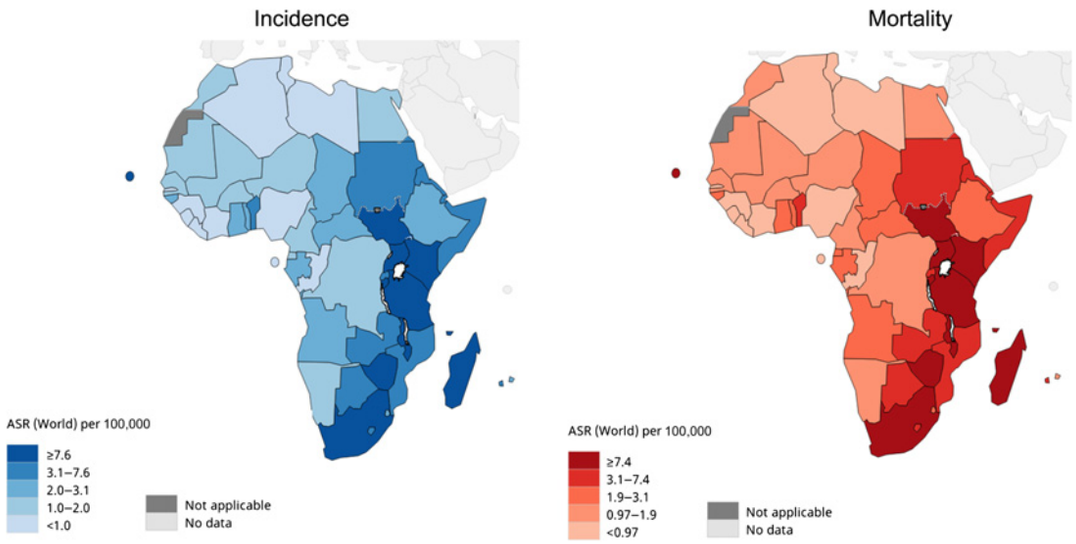

Figure 1.
2018 Globocan estimates of age-standardized rates of esophageal cancer in Africa, both sexes, all ages.

disease excess in the Kilimanjaro and Tanga regions. We reprint Hiza's map in **Fig. 2** (8). This northern excess appears to be real but poses considerable challenges in deciphering the etiologic factors for the excess. As the recent article, and Hiza, acknowledged, the case profile in major city hospitals serving nationwide populations are influenced both by true spatial variations in incidence rates, but also by variations (by geography, sex, socioeconomic and ultimately unknown factors) in referral patterns, that is, what proportion and whom of the countryside cases reach the major city hospitals for diagnosis and/or treatment? The factors that drive referral and are correlated with the region of origin may turn out as "statistical" risk factors in an analysis comparing cases with controls who have different drivers of referral and subregional cultures. Explicitly, in the Northern (23% of cases), Central (13%), and Southern highland (11%) zones, where a cumulative 47% of cases originated but only 19% of controls, there may be cultural habits of cases that are unrelated to ESCC disease risk had the study been conducted in local districts, but will differ to controls who are recruited predominantly from other districts (even after adjusting for broad zones). These inherent problems of cancer case–control studies are challenges around the world, but are more critical in many LMICs where hospital cases of diseases needing specialized treatment are likely to be a highly selective group. Selective effects may also apply to hospital controls. Matching on district, on the other hand, may potentially mask associations if exposure contrasts between districts are stronger than within districts. Recruitment in smaller disease hotspots, that is, lower down the referral pathway, is likely to reduce risks of bias but may require larger logistical efforts. At present, innovative approaches are encouraged, for example, using multiple control groups recruited in different ways, to enhance our understanding of the optimal local setup, as no "master" solution from other settings appears to be easy to implement.

Moving from populations, we turn to exposure and outcome data. The inclusion of multiple investigated factors by Mmbaga and colleagues was a prudent approach. We look forward to results that delve deeper into more granular exposure assessment and dose–response analyses, especially for factors expected to be associated at certain high levels of exposure, for example, excessive alcohol consumption as found in neighboring Kenya (5), and types and intensity of tobacco. Furthermore, most data are self-reported, so underreporting and recall bias cannot be ruled out and may be differential by case/control status. Even in case-only analyses or in the search for tumor mutation signatures linked to specific exposures, the quality of exposure data may have an impact. Independent exposure assessments need to be considered, via other reports in the same or external studies. For example, in Tanzania, underreporting of tobacco smoking is a concern in women (12). Biomarker-based exposures that are not subject to reverse causality in the case–control setup of advanced stage cancers will also be insightful.

To identify environmental risk factors, it is the environment that needs to be measured but this is challenging in the case–control study design. Methods need to be developed for this design and in this region, for example, through household visits, by confirming that contemporary measurements sufficiently represent past exposures, and through collaborative approaches to integrate geospatially indexed exposure measurements in environmental and water quality surveys. In this way, such surveys could be utilized not only for detection of contaminations but also with the aim to develop exposure maps.

Outcome misclassification of ESCC is less of a concern due to its specific symptoms but will be a consideration in studies of other cancer types to establish malignant status and histologic subtype. Nevertheless, even when we can be reasonably confident of a clinical diagnosis, ideally tumor biopsies will be stored for future tumor genomic investigations.

Study implementation

Study implementation is challenging in a single site setup, and more so in a multiple site setup, often optimal for inclusive case recruitment. More rural settings will, as expected, have more basic health care services, as endoscopy and pathology are typically only available in central locations. At times, research funds must reserve substantial costs to set up these essential services for cancer diagnosis. In turn, this may hinder the conduct of more granular study as resources are spent on service provision. A related challenge is availability of trained

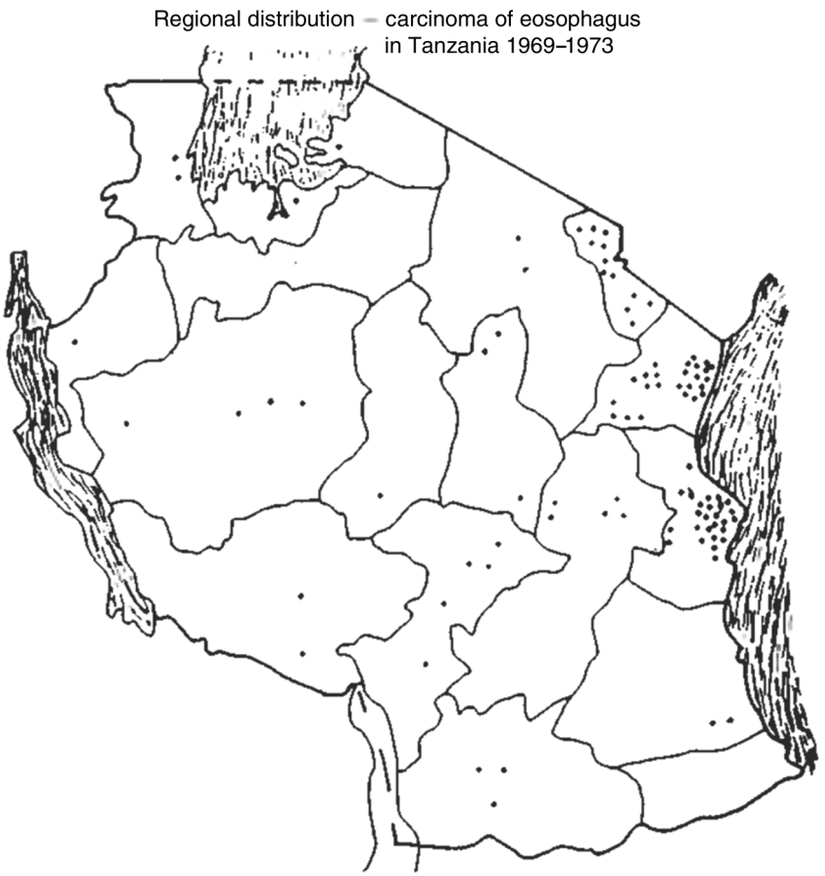

Figure 2.
Residential location of patients with esophageal cancer in Tanzania 1969–73, as published in 1976 in Figure 6 of Hiza (8). Striking similarities in high-incidence areas are found today by Mmbaga and colleagues.

personnel to conduct the research in more rural settings. Most research personnel tend to live in cities and are reluctant to work in settings which are largely rural and lack career advancement opportunities and basic public services. As such, it is difficult to conduct multiyear community-based research in these settings without using considerably higher budgets than if similar work was conducted in cities. Continuity of study recruitment can be challenging when relying on imported and expensive equipment, such as endoscopy scopes which may break down and severely disrupt recruitment schedules.

In summary, Mmbaga and colleagues' results form a valuable contribution to ESCC etiologic research in Tanzania. Initial research findings need further investigation, independent validation, and complementary mechanistic studies. The research forms part of the African Esophageal Cancer Consortium which was set up in recent years to bring together researchers and clinicians interested in research and patient care to improve the ESCC situation across Africa (13). Similar setting-specific studies on other common cancers with curious patterns in sub-Saharan Africa will lead not only to better understanding and prevention at a local level but also to an understanding of carcinogenesis with global relevance. This approach forms part of the essential "cancer ground-shot" real-world epidemiologic research needed globally (14).

Authors' Disclosures

No disclosures were reported.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of these organizations.

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References

1. NCD Countdown 2030 Collaborators. NCD countdown 2030: pathways to achieving sustainable development goal target 3.4. Lancet 2020;396:918–34.
2. Espina C, Herrero R, Sankaranarayanan R, Krug E, Wild CP, Schuz J. Toward the world code against cancer. J Glob Oncol 2018;4:1–8.
3. McCormack VA, Menya D, Munishi MO, Dzamalala C, Gasmelseed N, Leon Roux M, et al. Informing etiologic research priorities for squamous cell esophageal cancer in Africa: a review of setting-specific exposures to known and putative risk factors. Int J Cancer 2017;140:259–71.
4. Vint F. Malignant disease in the natives of Kenya. Lancet 1935;226:628–30.
5. Menya D, Kigen N, Oduor M, Maina SK, Some F, Chumba D, et al. Traditional and commercial alcohols and esophageal cancer risk in Kenya. Int J Cancer 2019;144:459–69.

6. Menya D, Oduor M, Kigen N, Maina SK, Some F, Kibosia C, et al. Cancer epidemiology fieldwork in a resource-limited setting: experience from the western Kenya ESCCAPE esophageal cancer case-control pilot study. Cancer Epidemiol 2018;57:45–52.
7. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
8. Hiza PR. Malignant disease in Tanzania. East Afr Med J 1976;53:82–95.
9. Munishi MO, Hanisch R, Mapunda O, Ndyetabura T, Ndaro A, Schuz J, et al. Africa's oesophageal cancer corridor: do hot beverages contribute?. Cancer Causes Control 2015;26:1477–86.
10. Mmbaga E, Mushi B, Deardorff K, Mgisha W, Akoko L, Paciorek A, et al. A Case-control study to evaluate environmental and lifestyle risk factors for esophageal cancer in Tanzania. Cancer Epidemiol Biomarkers Prev 2021;30:305–16.
11. Dawsey SP, Tonui S, Parker RK, Fitzwater JW, Dawsey SM, White RE, et al. Esophageal cancer in young people: a case series of 109 cases and review of the literature. PLoS One 2010;5:e14080.
12. Jagoe K, Edwards R, Mugusi F, Whiting D, Unwin N. Tobacco smoking in Tanzania, East Africa: population based smoking prevalence using expired alveolar carbon monoxide as a validation tool. Tob Control 2002;11:210–4.
13. Van Loon K, Mwachiro MM, Abnet CC, Akoko L, Assefa M, Burgert SL, et al. The African esophageal cancer consortium: a call to action. J Glob Oncol 2018;4:1–9.
14. Gyawali B, Sullivan R, Booth CM. Cancer groundshot: going global before going to the moon. Lancet Oncol 2018;19:288–90.