Novel Methods for Measuring Global Cancer Burden
Implications for Global Cancer Control

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International organizations and agencies have recognized the need to broaden their focus from infectious diseases to address the rising impact of noncommunicable diseases (NCDs) on global health in low- and middle-income countries. The United Nations (UN) held a historic high-level meeting on September 19, 2011, to consider the prevention and control of NCDs with the aim to adopt a concise, action-oriented outcome document that will shape the global agendas for generations to come.1 New attention is being directed toward heart disease, lung disease, diabetes, and cancer as problems to address in countries at all economic levels. However, specific cancer control recommendations by the UN and the World Health Organization (WHO) have been largely limited to prevention strategies and only superficially address cancer diagnosis and treatment strategies. The NCD political declaration mentions cancer generally and promotes “increased access to cost-effective cancer screening programmes, as determined by national situations”1(p7) but otherwise gives little or no guidance about how diagnosed cancers should be managed. To improve cancer care, it is critical to have good assessments of the global burden of cancer to provide an actionable framework for health policy makers, particularly in low- and middle-income countries, where health resources are limited and competing health demands are great.

Cancer Registration Methodology for Estimating Global Cancer Burden

Cause-specific cancer incidence and mortality statistics are essential to the development of appropriately targeted cancer plans. Ideally, international cancer statistics would be provided through high-quality population-based cancer registries strategically located around the globe. Unfortunately, such registries do not exist in much of the world, especially in low- and middle-income countries. The International Agency for Research on Cancer (IARC) publishes the Cancer Incidence in Five Continents (CI5) series, now in its 10th volume,2 which is the world’s compendium of high-quality population-based cancer registries. Only 14% of the world’s population is covered by population-based cancer registries that fulfill the CI5 inclusion criteria, with even less coverage in Asia (5%) and Africa (2%). Alternate methods to assessing cancer incidence, mortality, and other vital statistics are necessary and important. In response to this imperative, IARC created the GLOBOCAN model, now in its fifth iteration (GLOBOCAN 2012),3 to provide statistical estimates for cancer incidence and mortality based on best-available data for cancer incidence and mortality at the national level in assembling regional and global profiles. In this most recent iteration, IARC introduced an alphanumeric scoring system that provides information on the availability and quality of cancer incidence and mortality sources at the country level.

Global Burden of Disease Methodology for Assessing Global Cancer Burden

From a health policy perspective, disease management has to be adjusted according to overall health needs of a population, rather than be based on one specific disease or group of diseases. While cancer incidence, mortality, and other vital statistics are important, they need to be assessed in a broader context of general health needs. In their global burden of disease (GBD) study, the Institute for Health Metrics and Evaluation (IHME), led by Murray and colleagues,4 developed a unique systematic analysis approach to assess global and regional causes of death, years of life lost, and disability from disease and injury for countries around the world at all economic levels.5-7 These mathematically rigorous and elegant methods provide insights to disease burden that previously could only loosely be approximated. In this issue of JAMA Oncology, the Global Burden of Disease Cancer Collaboration8 presents the first GBD analysis by IHME of overall global cancer burden. Key questions that arise are (1) How do the outcomes of GBD analysis for cancer compare with cancer registry methodology developed by IARC, heretofore considered by most to be the gold standard? and (2) What new information might be gleaned to inform policy makers attempting to make headway in limiting avoidable, premature death and decreasing individual disability related to cancer?

Comparisons and Outcomes

In developing GBD methodology, IHME has created unique methods for assessing disease burden from broad data sets. The massive data crunching is systematic and comprehensive, but at the same time considers lower-level data than what is seen in high-quality population-based cancer registries. In the current GBD cancer study,8 37% of the data comes from registries, but only half met high-quality eligibility criteria for CI5. This implies that 80% of GBD data comes from “other sources” and lower-quality cancer registries, which, even with postcollection quality-improvement data processing, could limit primary data precision, especially in performing subset analysis, where analytic data errors can become amplified.
In oncology, diagnostic accuracy is a critical issue for developing cancer treatment strategies. Cancer registries are linked to surgical pathology assessments. While some cancers may be amenable to accurate diagnosis through clinical evaluation or simple diagnostic testing, most cancers can be difficult to specify in the absence of tissue diagnosis. The GBD investigators provide estimates of years of life lost for different cancers, some of which showed little change in ranking over the study years (eg, lung, colon, breast, esophagus, ovarian, uterine, melanoma), whereas others had marked variation in rank order (eg, pancreatic, bladder, gall bladder, Hodgkin lymphoma, myeloma). These variations in the latter group could reflect differences in cancer prevalence, biology, and/or treatment but may alternatively relate to diagnostic inaccuracy, because all of the cancers with variations in rank order require higher-quality imaging studies and/or pathology assessment for definitive diagnosis. Histologically different cancers that present in adjacent anatomic locations and/or with similar signs and symptoms could easily be confused. Without histologic evidence confirming malignant tissue diagnosis, mortality causation assessment tools cannot reliably differentiate between primary liver cancer, gall bladder cancer, pancreatic cancer, and cancer metastatic to liver, all of which have similar clinical presentations. Because accurate tissue diagnosis is fundamental to cancer registry methodology but is not required in GBD analysis, the GBD approach developed by IHME seems unlikely to achieve the diagnostic precision of a pure cancer registry-based method. These findings highlight the importance for strengthening global pathology and imaging services in conjunction with expanding cancer registration data systems throughout the world, which could benefit both GLOBOCAN and GBD estimates.

While GBD estimates of global cancer burden are unlikely to displace or replace CI5 and GLOBOCAN statistics, the profound benefits of GBD methodology should not be overlooked or undervalued in the oncology community. When IHME published their results regarding breast and cervical cancer in 2011,10 their study was promptly criticized for having findings that varied from those of cancer registry data in general and GLOBOCAN in specific.10,11 Certainly, when GBD outcomes vary considerably from GLOBOCAN, the reasons for these differences are worthy of evaluation. In low- and middle-income countries, cancer patients may go uncounted in cancer registries, because they die of advanced disease before interfacing with the health care system. As a result, GBD can correctly identify cancer mortality in populations that CI5 and GLOBOCAN will miss. It may be that in some circumstances, GBD estimates may be more accurate in reflecting overall cancer impact.

Conclusions
The oncology community would be unwise to interpret GLOBOCAN and GBD methodologies as competitive or mutually exclusive. The most important outcome for all of this work is to provide a framework for improving cancer care delivery. For the first time, GBD offers a powerful methodology that permits a direct comparison between cancer and other diseases and provides estimates for both disease prevalence and trends over time, which are essential in determining overall health burden to society. This comparative perspective is critical for communicating with health care and finance ministers, who are required to allocate scarce health care resources and may in the past have overlooked cancer as being “too expensive” or invariably fatal, without a complete evaluation of what could be done with limited health care resources to realistically improve outcomes at the systems level.

Because cancer can occur in young people and creates significant disability prior to death, the social impact as measured by disability-adjusted life-years (DALYs) is staggering. The current GBD findings inform us that of the more than 14 million new cancer cases and more than 8 million cancer deaths in 2013, 56% of new cancer cases, 62% of cancer deaths, and 69% of cancer-caused DALYs occurred in developing countries. Global burden of disease methodology suggests that cancer caused an astonishing 196.3 million DALYs in 2013 alone. Key decision makers and funding authorities may be increasingly persuaded by this big picture presentation on the burden of cancer in the developing world and could feel compelled to allocate resources to support effective cancer treatment strategies that in the past were unfunded. Seen from this perspective, the findings of GBD 20134 and GLOBOCAN 20122 should be seen as complementary and synergistic, particularly as we look at methods for improving cancer control at the global level. The data matters most when it causes us to act.

REFERENCES
Advances in immune therapy for the treatment of melanoma have resulted in unprecedented responses and survival rates for patients with unresectable and metastatic disease. The recent regulatory approvals of the PD-1 blocking agents nivolumab and pembrolizumab represent the great potential of immune-directed therapy to have an impact on the care of patients with advanced cancer.

Given the availability of several new active therapies, the identification of subsets of patients who may be more or less likely to benefit from any agent or class of agents is important for clinical decision making. In this issue of JAMA Oncology, Larkin et al examine the activity of nivolumab in the subsets of patients with and without a BRAF V600-activating mutation. In a retrospective analysis of 4 clinical trials including 334 patients with BRAF wild-type melanoma and 106 who were positive for the BRAF V600 mutation, the authors suggest that there are no differences in adverse events, objective response rates, time to response, or duration of responses to nivolumab in patients with advanced melanoma, with or without the BRAF mutation. The objective response rate was 34.6% for patients with wild-type BRAF melanoma and 29.7% for those with mutant BRAF melanoma, suggesting that nivolumab had similar efficacy and safety outcomes regardless of BRAF mutation status in the study population.

This retrospective analysis included 440 patients who received treatment with nivolumab as a single agent while enrolled in 1 of 4 clinical trials. Most of the patients included in the analysis (approximately 75%) did not have an activating BRAF V600 mutation, whereas the incidence of BRAF V600 mutant melanoma is approximately 50% in the overall population of patients with advanced melanoma. The smaller proportion of patients with BRAF mutant melanoma in the study is likely owing in part to the availability of competing BRAF-directed clinical trials and treatment options for these patients.

In addition, most of the study patients with BRAF-mutant melanoma had received prior BRAF inhibitor therapy; therefore, the BRAF-mutant patients included in the analysis were limited to those patients who remained eligible, with a good performance status and organ function, following prior BRAF-directed therapy. Therefore, trial eligibility criteria possibly also account for the smaller percentage of BRAF-mutant patients included. That is, it is possible that patients treated with prior BRAF inhibitor therapy may have developed a clinical decline owing to disease progression and therefore were not eligible for the clinical trials of nivolumab included in this analysis.

Apart from the lower percentage of patients with BRAF-mutant melanoma, the patient population was representative of the overall population of patients with advanced melanoma, with balanced demographics between the BRAF-mutant and nonmutant comparison groups. Both groups had a majority of patients who had received prior ipilimumab and who had stage IV disease.

The results suggest a similar rate of adverse events in patients with and without BRAF-mutant melanoma treated with nivolumab; 6.0% and 11.3% of patients discontinued nivolumab therapy owing to any grade of treatment-related adverse events in those with BRAF nonmutant and BRAF-mutant melanoma, respectively. Overall, nivolumab is very well tolerated by all patients, with a very small incidence of grade 3 to 4 treatment-related adverse events observed across all single-agent studies to date.

Objective response rates were similar among the BRAF-mutant and nonmutant patient comparison groups, with complete responses observed in both groups. Furthermore, although based on a much smaller number of patients, there was no clear difference in response rates among patients with BRAF-mutant melanoma who had received a prior BRAF inhibitor (11 of 37 patients [29.7%]) vs those patients with BRAF-mutant melanoma who had not received a prior BRAF inhibitor (5 of 17 patients [29.4%]) among the overall study population included in this analysis.

Of note, 1 of the 4 studies included, the randomized phase 3 study of nivolumab vs chemotherapy (the CheckMate 037 trial), which comprised approximately 60% of the patients included in the analysis, required all patients with a BRAF mutation to have received prior BRAF inhibitor therapy. An exploratory analysis of response by BRAF mutation status in that study alone identified an objective response rate of 34% in non-BRAF-mutant patients vs 23.1% in BRAF-mutant patients treated with nivolumab, all of whom would have received prior BRAF therapy as well. Given that all of the patients with BRAF-mutant melanoma in that study were uniformly required to have received prior BRAF inhibitor therapy, it is possible that there may be a small effect of prior treatment with BRAF inhibition (as opposed to BRAF mu-