

# Uniting Latin America Through Research: How Regional Research Can Strengthen Local Policies, Networking, and Outcomes for Patients With Lung Cancer

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OVERVIEW

Lung cancer represents a considerable global health threat, leading the list in terms of cancer-related deaths worldwide. An important proportion of lung cancer cases occur within Latin America, and current projections show that over the next decade, the number of deaths due to lung cancer will double in the region, underscoring the need to implement evidence-based interventions to improve outcomes. Several challenges have limited the progress in lung cancer research in Latin America for many years, though recently the surge of multidisciplinary, transnational, and transcultural research groups have overcome many of these limitations. The increase in region-specific knowledge has improved cancer care in the area, providing clinicians with a specific demographic and molecular profile for Hispanic patients with lung cancer; as a result, the implementation of precision oncology has benefited from a profound knowledge of the patient profile. Nonetheless, there are still challenges to improve research in Latin America, including stabilizing funding sources to continue independent research, supporting mentoring programs and an early immersion in clinical research for early career fellows, and overcoming barriers for publishing.

Lung cancer, a heterogeneous group of neoplasms affecting the lung, represents a global public health threat, consistently leading the list of cancer-related deaths over several decades in diverse countries worldwide, including developed and developing nations.<sup>1,2</sup> Although the tobacco epidemic—the principal risk factor associated with this disease—began mainly among men in several high-income countries, more than half of incident and mortality cases currently occur in low- and middle-income areas.<sup>2,3</sup> In Latin America, epidemiologic data have consistently shown the magnitude of the problem encompassed by lung cancer. Approximately 16% of the global deaths caused by lung cancer occur in the Americas region. Although the issue is as pressing as it is, it has been estimated that by 2035, this number will double, causing more than 500,000 deaths.<sup>4</sup>

Despite its epidemiologic relevance, lung cancer is often an overlooked disease, a reality that stems from many factors, including lack of screening programs in most areas, the poor prognosis from previous chemotherapy-based treatment schemes, and the considerable stigma associated with tobacco use and the incidence of lung

cancer.<sup>5,6</sup> Even though several screening trials have shown the benefit for individuals at high risk for lung cancer, these do not consider specific regional determinants, including the incidence of tuberculosis, the high rate of patients without a smoking history, and the exposure to other risk factors such as wood smoke or air pollution.<sup>7,8</sup> In addition, the disease presentation and characteristics of the population of Latin America have been difficult to assess because of the lack of research in the region before the last decade, when this situation was reversed by concrete efforts by cooperative groups. A simple PubMed search using the terms “lung cancer” and “Latin America” will show that from 1979 to 2011, the number of articles published yearly with these critical terms averaged 1.6; when considering publications from 2012 to 2022, this figure increases to 8.9. There are several factors implicated in this considerable increase in regional research. In this paper, we discuss the impact of regional research through strong cooperative groups within the Latin American region, mainly focusing on the role of CLICaP (Latin American Consortium for the Investigation of Lung Cancer), which originated in 2011.

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## PRACTICAL APPLICATIONS

- Despite the considerable burden of lung cancer in Latin America, regional research pertaining to this disease has been scant until recently.
- Cooperative transnational and transcultural research groups can overcome the diverse limitations in performing applicable, high-impact research in Latin America.
- The increased knowledge regarding lung cancer in patients living in Latin America has led to improvements in precision oncology for patients with specific sociodemographic determinants.
- Several challenges must be tackled to continue reaping benefits from regional research, including stabilizing funding sources, supporting mentoring programs, and overcoming barriers to publishing.

## THE IMPORTANCE OF INDEPENDENT RESEARCH IN LATIN AMERICA

Undoubtedly, scientific research represents the most critical strategy for improving outcomes in patients with oncologic diseases. However, despite its transcendence, the implementation of concrete scientific efforts focused on patients with lung cancer in Latin America has, for many years, lagged behind that in other world regions. Globally, the pharmaceutical industry absorbs most of the staggering costs associated with clinical research, although this often entails a dissociation between the areas of interest and priorities in terms of public health and the actual studies conducted.<sup>9</sup>

Although pharmaceuticals have played a very positive role in the advancement of care for patients with cancer, the absence of most Latin American countries, and therefore patients, from pivotal clinical trials is evident.<sup>10–12</sup> As such, many of the most relevant advances in the characterization, diagnosis, and treatment of lung cancer have been performed in high-income settings, including North America, Europe, and some regions of Asia. In a globalized context, though, this implies that patients from other areas will settle for extrapolated data, and many studies have shown the vast limitations that accompany these assumptions. For example, a previous phase II study evaluated toxicity outcomes in patients from Latin America treated with tyrosine kinase inhibitor afatinib; the results showed a considerably higher rate of grade 3 and 4 adverse events with standard-dose treatment than in the pivotal LUX-

LUNG1 study, which did not recruit patients from Latin America.<sup>13,14</sup> Interestingly, in this study, patients who required a dose reduction had progression-free survival similar to that of patients who did not require dose reductions, highlighting the potential benefit of dose selection within specific demographic groups, including the regional setting. This concept has previously been established in the treatment of advanced non-small cell lung cancer with *ALK* rearrangements; in this scenario, alectinib, a second-generation inhibitor, has been used successfully at a dose of 600 mg twice daily in the United States and 300 mg twice daily in Japan,<sup>12,15,16</sup> with regional differences in demographic characteristics such as body composition cited for the discrepancy.<sup>16</sup> In this regard, dosing schemes, toxicity profiles, and efficacy evaluations regularly stem from studies in which Latin American patients are not well represented in the study population, leading to insufficient knowledge of such parameters within this major patient subgroup.

## CURRENT CHALLENGES

It is estimated that global expenditure for research and development has tripled since 2000, from \$677 billion to \$2.2 trillion in 2019.<sup>17</sup> In terms of health-related research, this research and development area seeks to advance knowledge for the benefit of society, identify tools to better prevent and treat diseases, and improve global health.<sup>18</sup> However, achievement of an improvement in global health would entail a global effort, and this is unfortunately not the case. Most of the research and development expenditure is funded by the United States, with China ranked second. In fact, almost 85% of the global expenditure for research and development is funded by 10 countries, none of which are in Latin America.<sup>17</sup> Nonetheless, the current globalized context that seeks to tackle global health problems should approach research and development in a transnational and transcultural manner to truly seek an improvement in health-related outcomes for patients worldwide, achieving the sustainable development goals pertaining to health care.<sup>19</sup>

Research in Latin America in lung cancer has advanced considerably in the past decade, as previously stated. However, challenges to improve the development of studies in the area are varied and complex. For instance, performing novel and impactful lung cancer research requires highly specialized physicians and treatment centers to adequately identify opportunity areas, design protocols through a multidisciplinary approach, and recruit patients who meet criteria and are homogeneously treated and followed. In many Latin American countries, most institutions have generalized oncology centers, and it is rare to have a team, especially in the public care setting, dedicated exclusively to a specific neoplastic disease. Through this approach, the health care system seeks to satisfy the operational needs of each clinic,

but it renders it incredibly difficult to perform cutting-edge research in complex diseases such as lung cancer.

Other challenges include economic and curricular incentives to undertake research activities by health care staff. A strong research culture must be promoted in order to develop conditions that encourage research. In this sense, potential researchers in low- and middle-income countries are usually overburdened with high demands from clinical practice,<sup>20</sup> which include dozens of daily consults for oncologists working in a public health care setting in Latin America. Moreover, a scant presence of role models for young trainees is also a major setback. In Latin America, as in many low- and middle-income regions, mentorship in research for health science students is rare at most. As renowned physicians many times favor their private clinical practice, the interest in the field of medical research is inadvertently discouraged.<sup>20</sup> Highly specialized training centers such as MD Anderson Cancer Center in the United States include a comprehensive rotation and complete immersion during 6 to 12 months in research for residents in the field of oncology, whereas in Latin America, residents will rarely leave their clinical duties, and after graduating, they are many times hired by the same institutions in which they prepared. In this sense, a very low salary in public hospitals implies that most physicians will seek to breach this with additional income from a part-time private practice. Because research activities in most instances do not generate meaningful additional income for interested and talented potential researchers, a brain flux effect occurs in favor of economic goals that are achieved otherwise.<sup>20</sup>

Last, it is essential to state the part played by the publishing industry in discouragement from performing research in low- and middle-income countries, including Latin America. An important incentive for performing relevant research despite all the limitations mentioned previously is the motivation for the generated knowledge to be recognized and distributed so that it will be useful for clinicians practicing under similar conditions, conditions that are many times limited in terms of access to latest-generation treatments and equipment, which becomes a major limiting factor.<sup>5,21,22</sup> When, despite the barriers, clinicians perform studies that are highly relevant to their regional setting, they are usually met with negative feedback from high-impact journals, which usually respond that the research is irrelevant to the current standard of care (in their privileged high-income country) or that it does not interest their readers, because novel data stem from a Latin American population. This elitist approach to publications and research distribution further widens the gap between what is considered relevant research, even though many times it is not applicable (because of accessibility or availability issues) to a considerable proportion, or even the majority, of patients with lung cancer worldwide, half of

whom, as mentioned earlier, reside in developing nations and lack access to novel therapeutics. In Latin America, for example, access to the third-generation tyrosine kinase inhibitor osimertinib is extremely limited in several countries; therefore, strategies to prevent brain metastases in patients treated with agents without brain activity are urgently needed. Trials that address this unmet need have been performed with encouraging outcomes and adequate safety profiles, but they are many times widely criticized by peers who struggle to see past their own privilege to the unmet needs.<sup>23,24</sup>

### COOPERATIVE GROUPS AND THE SEARCH FOR MULTIDISCIPLINARY APPROACHES

Although strong single-center research groups have emerged in Latin American countries in the past 2 decades, it has been action by cooperative groups that has unified the efforts within the region to improve care for patients diagnosed with lung cancer. One such example is CLICaP, a consortium funded in 2011 that has been working consistently to improve lung cancer research in Latin America. As of 2021, CLICaP includes more than 75 lung cancer researchers from most Latin American countries, who perform cutting-edge research to address regional needs in areas including medical oncology, surgical oncology, radiotherapy, pulmonology, nutrition, rehabilitation, palliative care, access, and public policy, among others. The group has produced 41 articles published in indexed journals with a mean impact factor of 6.2, as well as a series of training courses for continuing medical education in the field of thoracic oncology.

The considerable efforts performed by members of CLICaP have resulted in the characterization of the disease within the region, fueling novel hypotheses to explore for patients in Latin America. These include studies regarding the molecular epidemiology of several genetic drivers, many of them druggable, which showcase the differences of the Latino population compared with the White or Asian populations. In the initial genotyping effort published in 2011, a total of 1,150 biopsies from four Latin American countries were assessed for *EGFR* and *KRAS* mutations, with results showing frequencies of 33.2% and 16.6%, respectively. The study also showed positive outcomes for treatment of actionable mutations with *EGFR* tyrosine kinase inhibitors, which resulted in programs to grant access to these agents for patients with economic limitations.<sup>25</sup> A follow-up study in 2015 included 5,738 samples from six different Latin American countries, and the results showcased the heterogeneity of molecular drivers within the Latin American populations, with *EGFR* mutation frequencies ranging from 14.4% to 51.1% in Argentina and Peru.<sup>26</sup> The results later led to a strong collaboration with the Dana-Farber Cancer Institute to better understand the genomic ancestry of lung

cancer in Latin America, revealing striking associations between Native American ancestry, which is marked in several countries, and somatic landscape, including mutations in *EGFR*. The results would suggest that genetics plays an important role in the disparities observed, and this in turn could be further explored to better understand cancer development and even suggest novel therapeutic targets.<sup>27</sup>

Other achievements by CLICaP include the characterization of lung cancer in young patients,<sup>28</sup> treatment outcomes in Hispanic patients and potential biomarkers for response,<sup>29,30</sup> mechanisms of resistance to treatment with first-generation tyrosine kinase inhibitors,<sup>31</sup> molecular epidemiology of *ALK* rearrangements,<sup>32</sup> *EGFR* exon 20 insertions,<sup>33</sup> *EGFR* amplifications,<sup>34</sup> *KRAS* mutations,<sup>35</sup> patterns of progression to treatment with tyrosine kinase inhibitors,<sup>36</sup> outcomes of immunotherapy in Hispanic individuals,<sup>37</sup> characteristics of small cell lung cancer,<sup>38</sup> mesothelioma,<sup>39</sup> thymomas,<sup>40</sup> squamous cell carcinoma,<sup>41</sup> and real-world data from Hispanic individuals treated with novel agents.<sup>42</sup> Furthermore, CLICaP started a mentoring program that seeks to offer effective networking and mentoring opportunities for talented oncologists and investigators from Latin America to promote leadership and address current limitations within the regional setting.<sup>43</sup>

#### HOW REGIONAL RESEARCH HAS RESHAPED THE OUTLOOK FOR PATIENTS WITH LUNG CANCER IN LATIN AMERICA

There are many implications of the knowledge gap regarding lung cancer presentation, treatment, and outcomes in Latin America, which should underscore the relevance of strengthening research programs within the region as a means of advancing development goals. In fact, investment in research has been shown to improve many aspects of social well-being, including economic performance.<sup>44</sup> In Latin America, research can unite and improve diverse determinants of well-being for patients with oncological diseases. Region-specific studies address priority issues that are many times not shared by other areas; for example, risk factors in Latin America for the development of lung cancer include wood smoke exposure,<sup>45–49</sup> as well as elevated concentrations of arsenic.<sup>7,50</sup> Importantly, the different risk factors can cause diversity in disease presentation; for example, patients with wood smoke exposure are predominantly women without a history of tobacco use, and up to 55% present with activating mutations in the *EGFR* gene, which consequently makes them susceptible to treatment with *EGFR* tyrosine kinase inhibitors.<sup>51</sup> This helped drive public policy in Mexico to offer access to these drugs to low-resource patients who would otherwise be treated, at best, with platinum-based chemotherapy, hindering their quality of life and survival.

In line with the information reported above, regional research can also provide valuable information regarding epidemiologic data specific to the Latin American setting. For many years, and even now to some extent, much of the epidemiologic data used in Latin America originated in different geographic areas, populations with diverse ethnic backgrounds, and other socioeconomic determinants. Generating population-specific knowledge is highly valued in high-income countries and is a key component behind generating treatment algorithms and public health interventions. For example, cancer clinical practice guidelines in the United Kingdom include up to 19.1% of references from studies performed in the United Kingdom<sup>52</sup>; meanwhile, cancer clinical practice guidelines in Mexico include 1% to 4% of references from studies in Mexican patients.<sup>53</sup>

In the past decade, the successful implementation of research strategies has been instrumental in providing improved care for patients with lung cancer in Latin America. Furthermore, the efforts have been driven forward by the establishment of strong research networks with other established groups in North America and Europe. A previous study that evaluated cancer-related Latin American publications identified that the region experienced a 9% growth in the number of publications between 2000 and 2018. Factors associated with high productivity included the number of authors in a collaboration network and invested gross domestic product; the results also highlighted the relevance of multiple-country (regional) publications to achieve strong collaborative networks.<sup>54</sup>

#### CONCLUSION

Latin America faces a considerable and growing lung cancer burden; nonetheless, regional research on this disease remained mostly neglected until the late 2000s. Although considerable efforts have been put forward to improve research in Hispanic individuals, several challenges still hinder the optimization of strategies, including unstable and often agenda-driven funding sources, few research and mentoring opportunities for young trainees, and barriers to publishing results from relevant regional studies. Nonetheless, concrete efforts by cooperative groups have been instrumental in improving research in the region, and continued support to strengthen research networks can prospectively help meet the current and future challenges to optimize care for patients with lung cancer in Latin America.

Because of continued political instability and skepticism over their scientific capabilities, many Latin American countries have few or highly fluctuating research policies, ultimately affecting cancer research and treatment. There are budgetary delays and sometimes massive reductions, which make sustainable planning and implementation difficult, except in the state of São Paulo, Brazil.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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