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Annie Young, University of Warwick, Coventry, UK
Purpose The nonprofit Project Medishare launched a breast cancer treatment program in Port-au-Prince in July 2013 to address the demand for breast cancer care in Haiti. We outline the development of the program, highlight specific challenges, and discuss key considerations for others working in global oncology.

Methods We reflected on our experiences in the key areas of developing partnerships, building laboratory capacity, conducting medical training, using treatment algorithms, and ensuring access to safe, low-cost chemotherapy drugs. We also critically reviewed our costs and quality measures.

Results The program has treated a total of 139 patients with breast cancer with strong adherence to treatment regimens in 85% of patients. In 273 chemotherapy administrations, no serious exposure or adverse safety events were reported by staff. The mortality rate for 94 patients for whom we have complete data was 24% with a median survival time of 53 months. Our outcome data were likely influenced by stage at presentation, with more than half of patients presenting more than 12 months after first noticing a tumor. Future efforts will therefore focus on continuing to improve the level of care, while working with local partners to spread awareness, increase screening, and get more women into care earlier in the course of their disease.

Conclusion Our experiences may inform others working to implement protocol-based cancer treatment programs in resource-poor settings and can provide valuable lessons learned for future global oncology efforts.
Impact of the *Bim* Deletion Polymorphism on Survival Among Patients With Completely Resected Non–Small-Cell Lung Carcinoma

**Purpose** A deletion polymorphism of the *Bim* gene has been reported to be a prognostic factor for patients with non–small-cell lung cancer (NSCLC) treated with epidermal growth factor receptor-tyrosine kinase inhibitors in the Asian population. We investigated the impact of the *Bim* deletion polymorphism on survival among patients with completely resected NSCLC.

**Patients and Methods** The *Bim* polymorphism was detected by polymerase chain reaction analysis. We measured overall survival (OS) and recurrence-free survival rates in 411 patients and postrecurrence survival (PRS) in 94 patients who experienced recurrence and received additional anticancer therapy.

**Results** The *Bim* deletion polymorphism was detected in 61 patients (14.8%). OS rates were significantly lower for patients with the *Bim* deletion polymorphism than for those with the wild-type sequence. On multivariable analysis, the *Bim* deletion polymorphism was identified as an independent prognostic factor for OS (hazard ratio, 1.98; 95% CI, 1.17 to 3.36; *P* = .011). Among the 94 patients who experienced recurrence and were treated with anticancer therapy, patients with the *Bim* deletion polymorphism showed significantly poorer PRS than those with the wild-type sequence (median, 9.8 months vs 26.9 months, respectively; *P* < .001). Multivariable analysis revealed that the *Bim* deletion polymorphism was an independent predictor of PRS (hazard ratio, 3.36; 95% CI, 1.75 to 6.47; *P* < .001). This trend remained apparent in subgroup analyses stratified by EGFR status, histology, and therapeutic modality.

**Conclusion** The *Bim* deletion polymorphism is a novel indicator of shortened PRS among patients with recurrent NSCLC treated with anticancer therapy in the Asian population.
Tuberculosis Diagnosis Delaying Treatment of Cancer: Experience From a New Oncology Unit in Blantyre, Malawi

**Purpose** Malawi is a low-income country in sub-Saharan Africa with limited health care infrastructure and high prevalence of HIV and tuberculosis. This study aims to determine the characteristics of patients presenting to Queen Elizabeth Central Hospital Oncology Unit, Blantyre, Malawi, who had been treated for tuberculosis before they were diagnosed with cancer.

**Methods** Clinical data on all patients presenting to the oncology unit at Queen Elizabeth Central Hospital from 2010 to 2014 after a prior diagnosis of tuberculosis were prospectively recorded, and a descriptive analysis was undertaken.

**Results** Thirty-four patients who had been treated for tuberculosis before being diagnosed with cancer were identified between 2010 and 2014, which represents approximately 1% of new referrals to the oncology unit. Forty-one percent of patients were HIV positive. Mean duration of tuberculosis treatment before presentation to the oncology unit was 3.6 months. The most common clinical presentation was a neck mass or generalized lymphadenopathy. Lymphoma was the most common malignancy that was subsequently diagnosed in 23 patients.

**Conclusion** Misdiagnosis of cancer as tuberculosis is a significant clinical problem in Malawi. This study underlines the importance of closely monitoring the response to tuberculosis treatment, being aware of the possibility of a cancer diagnosis, and seeking a biopsy early if cancer is suspected.

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*continued*
Lung Cancer Survival Among Chinese Americans, 2000 to 2010

Purpose Despite being the leading cause of cancer death, no prior studies have characterized survival patterns among Chinese Americans diagnosed with lung cancer. This study was conducted to identify factors associated with survival after lung cancer in a contemporary cohort of Chinese patients with lung cancer.

Methods The study design is a prospective descriptive analysis of population-based California Cancer Registry data. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) for overall mortality. Participants were Chinese American residents diagnosed with first primary invasive lung cancer from 2000 to 2010 (2,216 men and 1,616 women).

Results Among Chinese men, decreased mortality was associated with care at a National Cancer Institute cancer center (HR, 0.85; 95% CI, 0.73 to 0.99) and adenocarcinoma versus small-cell carcinoma (HR, 0.78; 95% CI, 0.65 to 0.92). Women had better survival compared with men (HR, 0.82; 95% CI, 0.75 to 0.89), with mortality associated with never married versus currently married status (HR, 1.36; 95% CI, 1.11 to 1.66), lower versus higher neighborhood socioeconomic status (HR, 1.38; 95% CI, 1.10 to 1.72 comparing lowest to highest quintile), care at a cancer center (HR, 0.80; 95% CI, 0.67 to 0.96), and squamous cell relative to small-cell carcinoma (HR, 1.60; 95% CI, 1.04 to 2.48).

Conclusion Focusing on factors associated with marital status, community socioeconomic status, and characteristics unique to National Cancer Institute–designated cancer centers may help to identify potential strategies for improving the length of survival for Chinese Americans.

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Increasing Access to Oral Anticancer Medicines in Middle-Income Countries: A Case Study of Private Health Insurance Coverage in Brazil

The World Health Organization estimates that approximately 60% of the world’s new annual cancer cases occur in Asia, Africa, and Central and South America, and that 70% of cancer deaths occur in these regions. Although oral chemotherapy is a promising intervention for cancer treatment, given its high cost, it is usually unavailable in middle-income countries. In 2013, after strong lobbying from civil society, Brazil’s Congress passed legislation mandating that all private health insurance companies provide access to oral antineoplastic treatment. The decision to scale up the provision of oral chemotherapy was a watershed event in the regulation of private health insurance in Brazil. Until then, private insurers, which cover 25% of the population, were exempted from the provision of pharmaceutical drugs for home care treatments. This article explores the political process involved in regulating the provision of oral chemotherapy medicines by private health insurers. Elements of this successful advocacy case included investment in strategic communication, specialized knowledge of regulatory policy, and the ability to act via democratic channels of political representation. In turn, the receptiveness of government branches such as the Congress and regulating bodies, as well as the Cancer Awareness Month campaign, opened a window of opportunity. However, prospects for expanded access to such medicines in the public health system are bleak in the short term because of the ongoing political and economic crisis.

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Cervical cancer is the leading cause of cancer-related mortality in the developing world, where HIV and *Mycobacterium tuberculosis* (TB) infection are also endemic. HIV infection is independently associated with increased morbidity and mortality among women with cervical cancer. TB is believed to increase the risk of malignancies and could cause chronic inflammation in the gynecologic tract. However, the relationship between cervical cancer and TB in settings hyperendemic for HIV is unknown. We found that 18 (10%) of a cohort of 180 women with cervical cancer in Botswana had a history of TB disease. Age and HIV infection were also associated with a history of TB disease. Our data show that prior TB disease is highly prevalent among patients with cervical cancer infected with HIV. The coexistence of cervical cancer, HIV infection, and prior TB infection might be higher than expected in the general population. Prospective studies are needed to better determine the impact of the collision of these three world health epidemics.
Randomized clinical trials in cancer medicine are increasingly conducted in low- and middle-income countries (LMICs). The proper way to conduct such studies is complex and the subject of much debate.1 Two key questions outline the debate. First, what is the appropriate control arm for such studies? For example, when can trials use placebo or some control less than global best practice? Second, what obligations do trial sponsors have toward host nations and communities?

These key questions were first debated more than a decade ago in the context of clinical trials in Africa, which tested shorter, cheaper courses of zidovudine against placebo to prevent perinatal transmission of AIDS. Critics argued that these placebo-controlled trials were unethical and that control participants should have access to the longer, full course of zidovudine used elsewhere in the world. Proponents countered that only placebo-controlled trials could answer the relevant question: whether an affordable course of therapy is better than the actual practice of doing nothing, and not the ideal, but unrealistic question: whether a shorter course is noninferior to a longer course. In recent months, these questions have regained relevance as recent trials recapitulate these tensions.

Citing recent examples in cancer medicine, we argue that placebo-controlled trials may be ethical but only if the intervention being tested has a reasonable chance of being implemented in the host community.

WHAT IS THE APPROPRIATE CONTROL ARM FOR TRIALS IN LOW-RESOURCE SETTINGS?

Advanced cervical cancer, now infrequently encountered in developed nations, carries a substantial global burden.2 Unfortunately, universal screening programs that use cytology-based techniques that have been credited with transforming outcomes have been deemed impractical or unaffordable in low-resource settings.3 For this reason, several randomized controlled trials have tested whether a low-cost cervical cancer screening program can improve outcomes. In a recent large, randomized trial conducted in India, Shastri et al3 tested whether four successive biennial visual inspections with acetic acid (VIAs) performed by public health workers could reduce cervical cancer mortality. VIAs involve a process in which a trained health care worker uses a speculum and applies dilute acetic acid (vinegar) to the cervix and is able to directly visualize abnormal preneoplastic tissue that turns white. The results of the Shastri study were positive and showed 31% relative risk reduction in cause-specific death. As a result, this intervention has been hailed as a realistic, affordable cervical cancer screening program with the potential of saving 22,000 lives per year. But because the study used a control arm that received the local standard of care (no screening), it has been criticized as unethical.4,5 However, India had already deemed a screening program with cytology impractical and, in practice, it is seldom performed. We believe the study is ethical and meets the standard for such trials in low-resource settings. We support this because in India, there is no universal cervical cancer screening, and the burden of disease is high. Furthermore, the study by Shastri et al was reviewed by the US National Cancer Institute before funding, was approved by a local institutional review board, and was reviewed annually by the institutional review board and a data safety and monitoring committee.

Discouraging studies like that of Shastri et al8 would limit the ability of individual nations to set
their own research agenda and conduct trials they deem important. Furthermore, diffuse criticism of screening studies in LMICs diverts attention from truly unethical trials, which explore questions that will not benefit the country in which the trials are conducted. The study by ShastrI et al provided the highest level of evidence that VIAs save lives and can be reasonably expected to benefit the host population in India and other LMICs with high burdens of cervical cancer and no cytology-based universal screening programs.

IS THERE A REASONABLE EXPECTATION OF BENEFIT FOR THE HOST POPULATION FROM CLINICAL TRIALS?

Some have argued that sponsors must not only provide benefit to the individual patients on trials but must also provide health-related resources to the host community and help with infrastructure development. Others submit that sponsors and investigators should ensure that participation in such trials is voluntary, that individual participants are provided fair benefits for their participation, and that this is the sole requirement for ethical research.1

We take a middle position. Sponsors and investigators should not be expected to provide health-related resources and infrastructure to the host community in which they conduct clinical trials. Conducting clinical trials is expensive, and in today’s economic environment, an expectation to provide additional, post-trial services could be prohibitive and discourage sponsors from supporting rational trials. We do believe, however, that when trials in low-resource settings reach positive conclusions regarding an intervention’s benefit, that intervention should be reasonably likely to be implemented by the community in which the trials are conducted.

This tension is best illustrated in two recent examples. The first is that of afatinib (Boehringer Ingelheim, Ingelheim, Germany), a next-in-class epidermal growth factor receptor (EGFR) inhibitor in patients with lung cancer harboring EGFR mutations. The IPASS (First Line IRESSA Versus Carboplatin/Paclitaxel in Asia) trial published in 2009 found that patients with non–small-cell lung cancer (NSCLC) and activating mutations in EGFR had a marked progression-free survival benefit (9.5 vs 6.3 months) and improvement in the quality of their life when treated with gefitinib (AstraZeneca, London, United Kingdom), an anti-EGFR–targeted drug, compared with standard chemotherapy.6 These results led the European Medicines Agency to approve gefitinib for this indication on June 24, 2009, and in turn led to an international best practice of using targeted agents as the initial therapy in patients whose tumors harbor EGFR mutations. Yet from August 2009 to November 2011, LUX-Lung 3 (BIBW 2992 [Afatinib] Versus Chemotherapy as First Line Treatment in NSCLC With EGFR Mutation) and then LUX-Lung 6 (LUX-Lung 6: A Randomized, Open-label, Phase III Study of BIBW 2992 Versus Chemotherapy as First-line Treatment for Patients With Stage IIIIB or IV Adenocarcinoma of the Lung Harbouring an EGFR Activating Mutation) randomly assigned more than 1,200 and 910 patients, respectively, with NSCLC harboring EGFR mutations to either afatinib or cytotoxic chemotherapy.7,8 Both studies were performed largely in LMICs and, in effect, addressed the question previously answered by the 2009 IPASS study: Is there value in using an EGFR-targeted agent over conventional chemotherapy? From our perspective, the ethics of these trials hinged on whether afatinib was somehow more affordable or feasible for use in the nations where the trial was conducted. But unfortunately at a cost of $79,000 per year of treatment, afatinib could not be seen as affordable in nations that could not afford the $25,000 cost of gefitinib (all prices are from the most recent edition of the Redbook). Instead, the results of LUX-Lung 3 and LUX-Lung 6 were used to petition the US Food and Drug Administration for an approval that was granted in 2013.

Another trial had a similar pattern. Traztuzumab (Genentech, San Francisco, CA) added to chemotherapy has been the standard of care in the initial treatment of human epidermal growth factor 2 (HER2)–positive metastatic breast cancer since 2001. A recent study sought to determine whether lapatinib (GlaxoSmithKline, London, United Kingdom), a different HER2-targeted drug, also had efficacy in this indication.9 From 2006 to 2009, more than 400 Chinese women were randomly assigned to lapatinib or placebo added to chemotherapy. However, because the majority of patients in China cannot afford traztuzumab ($66,000 for 1 year of treatment), it is not clear that lapatinib ($67,000 for 1 year of treatment) represents a realistic alternative. It is worth noting that these trials would not have succeeded in enrolling patients in the United States, because most oncologists would not have allowed their patients to have a 50% chance of being randomly assigned to a treatment deemed inferior by previous studies.

Under what circumstances placebo-controlled research is ethical in low-resource settings is still a
contested matter. Few would criticize our position that such research is clearly unethical when the question addressed cannot realistically benefit the nation in which the trial is performed. We propose the following decision aid to help determine which clinical trials are warranted. First, in accordance with the seventh Declaration of Helsinki (2013), “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.” Thus, for any proposed trial, investigators should postulate the following: If the results were positive, what changes could realistically be expected in the host nation, as well as the world? and the same question if the trial were negative. Ultimately, the decision will require weighing these potential benefits to the society against the risks to participants.

Placebo-controlled trials of anticancer drugs with prices similar to those of proven alternatives benefit only the sponsoring companies. Instead, trials seeking to identify interventions that can realistically be implemented by developing nations are justified. They are desperately needed to inform pressing policy decisions facing the leaders of these nations. Condemning these studies is a perverse form of first-world paternalism. The need for clarity regarding the ethical conduct of trials in the developing world is great, because recent criticism has been misplaced, a disservice to citizens around the world.

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Vinay Prasad
No relationship to disclose
Hemanth Kumar
No relationship to disclose
Sham Mailankody
No relationship to disclose

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REFERENCES
Breast cancer burden is high in low-resource countries. From 1980 to 2010, new breast cancer cases increased by more than 50% worldwide. Disease burden increased even more rapidly in low- and middle-income countries (LMICs), where more than half of breast cancer cases now occur. Moreover, breast cancer disproportionately affects young women in LMICs, such that 23% of new breast cancer cases occur among women age 15 to 49 years in LMICs versus 10% in high-income countries.

Breast cancer mortality is also higher in LMICs compared with high-income countries, and reasons for this are multifactorial. One contributing factor is a lack of breast cancer awareness and early detection in LMICs. For example, more than 90% of women with newly diagnosed breast cancer in the United States have locoregional disease, whereas more than half of women with newly diagnosed breast cancers in LMICs have stage III or IV disease. According to an analysis from the 2003 World Health Survey, only 2.2% of women age 40 to 69 years in LMICs had received any breast cancer screening. In addition to insufficient early detection, other factors contributing to delayed diagnosis include poverty, cultural and religious beliefs, misconceptions about the disease, and fear of mastectomy. Women’s autonomy in health care decision making may also be limited in some cultures.

The WHO, along with many national cancer control programs, recommends population-based screening mammography for detection of early-stage breast cancer in high-income countries, even though there continues to be honest and sometimes heated debate regarding this recommendation. It is worthwhile to consider the possible benefits versus harms of breast cancer screening in LMICs, which have received far less attention. In this commentary, we discuss breast cancer screening and early detection in LMICs with a particular focus on Malawi. We highlight areas of uncertainty and suggest pragmatic strategies for moving forward in light of current evidence gaps.

Health care systems in LMICs may face strong incentives and pressure to adopt health care interventions such as screening mammography that are well established in high-resource settings, with implicit assumptions that benefits demonstrated in more developed countries will generalize to less developed countries. Such assumptions are inherently problematic and unrealistic in settings of severe resource scarcity. For example, there are compelling reasons to believe that breast cancer screening would perform differently in LMICs than in high-income countries. Factors that could reduce efficacy of breast cancer screening in LMICs include a younger population with lower breast cancer incidence, shorter life expectancy, more prevalent competing causes of death, and higher prevalence of biologically aggressive subtypes for which patient outcomes are less likely to be affected by screening. Conversely, breast cancer screening could have greater impact in LMICs if it increases breast cancer awareness and early detection of symptomatic disease. For example, there may be more diffuse effects than would be expected in resource-rich settings where strong health care systems and higher levels of awareness narrow the scope of breast cancer screening principally to detection of asymptomatic disease. Indeed, for weak health care systems, it is plausible that effects beyond breast cancer may be realized and may extend to cancer more generally or to women’s health. Investments in HIV programs have similarly had far-reaching effects beyond providing antiretroviral therapy, and antiretroviral therapy clinics are now established vehicles for effective delivery of many other essential health care services.
services. In Malawi, commonly piggybacked health services in HIV clinics now include cervical cancer screening, Kaposi sarcoma treatment, nutritional supplementation, and reproductive health and mother-child wellness initiatives, all of which seek to maximize impacts from initial investments for HIV.

Despite recent controversies about screening mammography in high-income countries and a scarcity of high-quality data for this approach in LMICs, it is often assumed that wherever mammography is available, it must benefit women. This may be the case, even when screening is available only in the private sector without clearly defined eligibility guidelines, quality control measures, or follow-up procedures. Examples of this exist in Malawi, where a major intersection in Lilongwe (the capital) features a billboard advertising screening mammography in a private clinic promoted by a famous young Malawian breast-cancer survivor. However, the cost of a screening mammogram in Lilongwe is approximately US$90 in a country with an annual gross domestic product per capita of US$253. Moreover, screening is often directly marketed to and used for women who can pay for it, without clear eligibility criteria accounting for age, comorbidities, or projected life expectancy. In Lilongwe, mammography sponsors have distributed coupons for discounted screening mammography at public breast cancer awareness events to unselected audiences of women primarily in their 20s and 30s. Benefits of screening mammography have not been clearly demonstrated for average-risk women in these age groups anywhere in the world, nor is it recommended for them in consensus guidelines.

In addition, LMICs often lack the necessary infrastructure to ensure high-quality mammography and subsequent follow-up care. Operating a mammography unit continuously requires a consistent supply of electricity and x-ray films, as well as engineers, technicians, and radiologists, all of which may be lacking in many LMICs. Four mammography units were donated to Malawi in 2012, one to each tertiary referral hospital, with the intent to provide the first publicly available mammography services in the country, but these units have yet to become operational. Mammography screening programs have also been estimated to cost US$16,000 to US$37,000 per life saved, which exceeds per capita health care budgets in many LMICs by a significant margin. International guidelines recommend clinical breast examination (CBE) as a preferred approach to screening in settings in which mammography screening is not available. Even in high-resource settings, there is some evidence that annual CBE might be as effective as screening mammography in lowering breast cancer mortality. Relative advantages for mammography versus CBE with respect to implementation are detailed in Table 1.

In LMICs, two clinical trials in Egypt found that CBE conducted by physicians was effective and cost-effective in rural and urban areas. In Malaysia, training rural nurses to perform CBE resulted in significant breast cancer downstaging (77% vs 37% late-stage diagnoses). In an ongoing cluster-randomized trial in India, CBE performed by female community health care workers detected more early-stage (I to IIA) cancers (18.8 vs 8.1 per 100,000 women) in intervention versus control villages; no differences were observed for stage IIB and higher-stage cancers. A cross-sectional study in Nepal comparing CBE performed by female community health care workers with examinations by surgeons reported interobserver agreement of 64% for lump detection, with 70% sensitivity and 95% specificity. Moreover, modeling studies have suggested that CBE is cost-effective in low-resource settings.

In addition to health care workers, lay volunteers can also be trained to perform CBE. A study in rural Sudan screened approximately 10,000 women age 18 years or older by using this approach. Seventeen of those screened had carcinoma in situ or breast cancer, including eight with carcinoma in situ and four with early-stage breast cancer. In control villages, only four women self-referred for

### Table 1. – Relative Advantages of Mammography Versus Clinical Breast Examination as Screening Approaches in Low- and Middle-Income Countries

<table>
<thead>
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<th>Relative Advantages</th>
<th>Mammography</th>
<th>Clinical Breast Examination</th>
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<tr>
<td>More proven method (at least in resource-rich settings)</td>
<td>Typically accessed in settings where follow-up diagnostic services are readily available and travel distances for follow-up are short</td>
<td>Lower cost</td>
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breast symptoms, three of whom had advanced-stage breast cancer. In Tanzania, laypersons in villages were trained to provide screening for a variety of cancers by using basic history and physical examination. After 3 years, breast cancer downstaging was one of the most significant results of the program, evidenced by a 74% increase in stage I to II breast tumors.

In LMICs where health care systems are significantly weakened by limited resources and human capacity, it is worth emphasizing that anticipated impacts of widespread breast cancer screening would not be limited to detecting asymptomatic disease. For example, in Malawi, 47% of women with pathologically confirmed breast cancer at the tertiary referral hospital in Lilongwe had symptom durations greater than 12 months, and only 44% of randomly selected women from rural and urban areas in the Lilongwe district were aware of breast cancer as a disease. Therefore, if CBE were effectively scaled up throughout Malawi in a manner that engages communities with effective downstream referral, anticipated benefits might be large with respect to improved cancer awareness and earlier identification of unaddressed, prevalent, symptomatic disease. In addition, there may be collateral effects on other public health problems apart from breast cancer, including promotion of healthier lifestyles among women as well as increased cancer awareness and destigmatization. These off-target effects of breast cancer screening are no less important simply because they are harder to define and measure than the number of early-stage breast cancers diagnosed.

Classical cancer screening paradigms and messaging must be adapted to the LMIC context. The HIV implementation science field now champions pragmatic scale-up of proven multicomponent interventions to maximize population-level outcomes in LMICs. Similar approaches may be attractive for cancer screening as well. We are currently conducting a pilot breast cancer education and CBE screening intervention in Lilongwe among women attending diverse health clinics. The major objectives are to assess uptake and feasibility of packaging CBE with other health services, performance characteristics of CBE performed by trained lay breast health promoters, and completion rates for referrals among women with detected abnormalities. These preliminary data will help inform wider scale-up of breast cancer awareness and screening efforts throughout Malawi.

Even as the screening mammography debate evolves in resource-rich settings, mammography is being actively promoted and implemented in many resource-limited countries in the world, including Malawi. We believe there is agreement within the global health community that high breast cancer burden and mortality in LMICs require an urgent response, but competing health needs and local realities require that available resources be optimally used to provide the best value for populations overall. This may be particularly true, given that several breast cancer screening approaches are available that can be packaged together in varying combinations. We believe more evidence is needed to guide large-scale breast cancer screening approaches in LMICs under varying socioeconomic and cultural conditions, and we emphasize that although CBE has been shown to result in cancer downstaging in LMIC settings, effects on breast cancer–specific mortality remain unclear. Limited cancer diagnosis, treatment, and registration throughout LMICs also limit the impact of screening interventions as well as metrics for their evaluation and must be simultaneously strengthened. We eagerly await results of ongoing studies, including our own work, to define optimal approaches in Malawi, with the expectation that successful strategies here may be quite different from those in other LMIC settings.
Blandina Khondowe
Employment: Center for Medical Diagnostics, Lilongwe
No relationship to disclose

Agnes Moses
No relationship to disclose

Racquel E. Kohler
No relationship to disclose

Lisa A. Carey
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No relationship to disclose

Satish Gopal
No relationship to disclose

AFFILIATIONS
Lily A. Gutnik, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY; Lily A. Gutnik, Blandina Khondowe, Agnes Moses, and Satish Gopal, UNC[en]Project Malawi; Beatrice Matanje-Mwagomba, Malawi Ministry of Health; Vanessa Msosa and Suzgo Mzumara, Kamuzu Central Hospital, Lilongwe; Suzgo Mzumara and Agnes Moses, University of Malawi College of Medicine, Blantyre, Malawi; Racquel E. Kohler, Gillings School of Global Public Health; Lisa A. Carey, Clara N. Lee, and Satish Gopal, Lineberger Comprehensive Cancer Center; and Satish Gopal, Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC.

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REFERENCES


Development of a Breast Cancer Treatment Program in Port-au-Prince, Haiti: Experiences From the Field

**Purpose** The nonprofit Project Medishare launched a breast cancer treatment program in Port-au-Prince in July 2013 to address the demand for breast cancer care in Haiti. We outline the development of the program, highlight specific challenges, and discuss key considerations for others working in global oncology.

**Methods** We reflected on our experiences in the key areas of developing partnerships, building laboratory capacity, conducting medical training, using treatment algorithms, and ensuring access to safe, low-cost chemotherapy drugs. We also critically reviewed our costs and quality measures.

**Results** The program has treated a total of 139 patients with breast cancer with strong adherence to treatment regimens in 85% of patients. In 273 chemotherapy administrations, no serious exposure or adverse safety events were reported by staff. The mortality rate for 94 patients for whom we have complete data was 24% with a median survival time of 53 months. Our outcome data were likely influenced by stage at presentation, with more than half of patients presenting more than 12 months after first noticing a tumor. Future efforts will therefore focus on continuing to improve the level of care, while working with local partners to spread awareness, increase screening, and get more women into care earlier in the course of their disease.

**Conclusion** Our experiences may inform others working to implement protocol-based cancer treatment programs in resource-poor settings and can provide valuable lessons learned for future global oncology efforts.
trauma and critical care services, making the location an ideal place to implement a program involving chemotherapy. Before the implementation of this program, neither Project Medishare nor Hospital Bernard Mevs provided any kind of breast cancer care apart from mastectomies. The program has also helped provide the necessary infrastructure to begin collecting data on the epidemiologic profile and tumor biology of breast cancer in Haiti.7

In this article, we outline the key steps in the implementation of Project Medishare’s breast cancer treatment program: building and maintaining partnerships with the local oncology community; securing laboratory services abroad while building local laboratory capacity; using experts in oncology, nursing, and research to establish treatment algorithms and train local staff; and purchasing and importing safe, effective, low-cost chemotherapy and hormone therapy. We also discuss costs and other practical barriers to treatment, and we critically reflect on our own objective performance as a program.

METHODS

Building Partnerships

Project Medishare’s breast cancer treatment program focused on developing strong local partnerships, which were crucial for the program to gain acceptance in the local medical community. Before launching the project, Project Medishare physicians and organizers met with clinicians and administrators from the Haitian Ministry of Health and the oncology program at the University Hospital of Haiti to discuss the scope of the program and request their input. Project directors asked them to review and approve all of the program’s initial patient staging and treatment protocols before they were submitted to the Haitian Ministry of Health for governmental approval. Project Medishare also sent patients to local health care providers for verification of the clinical staging in an effort to ensure quality control in the new program.

In addition, Project Medishare partnered with the Support Group Against Cancer to offer counseling and social services to the program’s patients and help raise awareness of the program through local television and radio campaigns. This partnership increased the program’s credibility in Port-au-Prince among both patients and providers and helped reach more patients than would otherwise have been possible.

Pathology and Laboratory Capacity

The challenge of limited pathology services in Haiti is being addressed via a step-wise approach. Because the immunohistochemical studies for estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 biomarkers cannot currently be performed at any laboratory in Haiti, it was necessary to turn to international pathology laboratories. As an initial stopgap measure, tissues from breast biopsy and excision specimens were placed in formalin and sent directly to partner laboratories in the United States for processing, paraffin embedding, and staining. The specimens were hand carried at regular intervals via travelers from Port-au-Prince to Florida, which requires no special importation documentation.

Specimens were previously collected via open biopsy, but core needle biopsies were implemented as part of the program launch. Four Haitian doctors were trained in obtaining samples via three passes with core needle biopsy, typically using 16- to 20-gauge needles. After finding a high false-negative rate in tumors that were clinically apparent cancer, the program switched to six quality samples with the core needle and increased the needle gauge to 14 or 16.

To set up a permanent and reliable system for ascertaining the pathology, Project Medishare partnered with a local pathology laboratory in Haiti to process the formalin-fixed specimens into paraffin-embedded blocks. All samples were then evaluated by breast pathologists in the United States, and all invasive carcinomas were graded according to the Nottingham Histologic Score system. Electronic copies of pathology reports were sent to the treating physicians by e-mail. All specimens with ductal carcinoma in situ or invasive carcinoma of the breast were assayed for ER, progesterone receptor, and human epidermal growth factor receptor 2.8

In conjunction with the Haitian Ministry of Health and several US universities, a reference laboratory will soon be established in Port-au-Prince that can perform immunohistochemistry for ER status for all specimens originating in Haiti, and two new pathology laboratories distributed geographically throughout Haiti will open in the next 12 months.

Clinical Training and Treatment Algorithms

Another critical step in the development of the program was training clinicians in cancer care. At the inception of the program, there were only two
trained subspecialty hematologists in Haiti and no medical oncologists. Chemotherapy options for postmastectomy patients in Port-au-Prince at that time were limited to private clinics and University Hospital of Haiti, where patients had to purchase chemotherapy at high prices and often received substandard chemotherapy regimens such as cyclophosphamide/doxorubicin/fluorouracil. By using educational models similar to those developed for addressing the HIV/AIDS epidemic in sub-Saharan Africa, local health care providers were trained to use curative chemotherapy and palliative care. Training at the Project Medishare oncology program was initiated by a US board-certified internist who had previous international experience helping to develop the national cancer treatment program in Rwanda.

Because gynecologists in Haiti were typically the first medical interface for patients with breast cancer, they were selected as the clinicians for the Project Medishare breast cancer treatment program. They received 40 hours of intensive classroom education on breast cancer pathophysiology, presentation, diagnosis, and treatment. In addition, they were trained to use chemotherapy treatment algorithms and were required to discuss all patients individually with the program director for the first 6 weeks of clinical application.

The development and use of treatment algorithms was a crucial part of the oncology training. As mentioned previously, the Project Medishare team worked in conjunction with oncologists from the University of Florida and the University of Miami to develop treatment protocols specifically for Haiti. The protocols included basic staging guidelines, timing of surgical interventions, chemotherapy regimens, hormonal therapy, and radiotherapy recommendations. The two intravenous chemotherapy regimens are four to six cycles of docetaxel/cyclophosphamide or four cycles of doxorubicin/cyclophosphamide followed by four cycles of paclitaxel given once every 3 weeks. These regimens are standard regimens in the United States and do not require growth factor support. Of note, dose-dense scheduling of chemotherapy is not possible in Haiti because of the unavailability of growth factor support, and weekly dosing with paclitaxel is impractical because of significant issues with transportation. Trastuzumab is also not available because of its prohibitive cost. Tamoxifen and letrozole are available and were used by the program in the neoadjuvant, adjuvant, and metastatic settings. The exact algorithm changed depending on the stage, degree of lymphatic invasion, and hormone sensitivity. Mastectomies and other surgeries, such as bilateral salpingo-oophorectomies for premenopausal women with ER-positive, advanced-stage tumors, were performed by surgeons at Hospital Bernard Mevs. Surgical and anesthesia capacity are less frequently barriers to basic breast cancer care in urban hospitals in developing countries than chemotherapy and other medical treatments. Nevertheless, it is important to note that existing surgical capacity at Hospital Bernard Mevs was key to the rapid scaling up of the Project Medishare breast cancer treatment program.

Unfortunately, radiotherapy is not available in Haiti, making it impossible to offer breast conservation for those without the resources to pay $2,000 for private treatment in the neighboring Dominican Republic. Moreover, 80% of the women treated by the program in the first 2 years were not candidates for breast conservation therapy because of tumor size, chest wall invasion, skin ulcerations, or the presence of metastasis. Nonetheless, radiotherapy was recommended as part of the treatment algorithm for all women with stage IIB to IIIC disease after chemotherapy and mastectomy. Going forward, the Haitian government has articulated a long-term plan to build a radiotherapy center in Haiti, and Project Medishare continues to rely on close contacts in Dominican Republic radiotherapy centers to help direct clinical care decisions for qualifying patients.

For breast cancer cases that fall outside the established treatment algorithms, breast oncologists from the University of Florida advise the team on the ground via e-mail and telephone. Roughly 10% of patients required consultation from these oncologists, with the remainder being managed by the Haitian gynecologists alone. Discussion regarding these patients and consistent communication with the University of Florida breast oncologists provided Haitian clinicians with an ongoing education in cancer care.

Nursing protocols were developed for mixing and administering chemotherapy. Nurses in Project Medishare were trained in chemotherapy mixing, administration, and extravasation protocols by Haitian pharmacologists and Haitian-American chemotherapy infusion nurses from Miami. The Haitian compounding pharmacist provided oversight in mixing the chemotherapy to ensure staff and patient safety. After the initial week-long training, the nurses received continued training on a regular basis from visiting infusion nurses who confirmed that the quality of care remained at a consistently high level. All staff wear personal protective equipment when mixing and administering
chemotherapy, ensuring a safe environment for the nurses, pharmacists, and patients.

After 12 months of experience, the Project Medishare nurses designed and implemented an in-service training program for the chemotherapy nurses at the public University Hospital of Haiti to raise the level of care and improve patient and staff safety at the country’s largest public hospital. With trained nurses at the two sites, the “train the trainer” model has proved useful in the Haitian context, although periodic quality control by US-based nurses still occurs at present.

All providers and staff were trained to document clinical encounters on an electronic record system that was principally online but that could be used offline during the frequent power outages. Wireless USB jump drive modems provided Internet via mobile networks. In addition to adapting the treatment protocols to local resources, Project Medishare also adapted consent forms, including those for biopsy and receiving chemotherapy treatments, to adhere to local standards.

Chemotherapy Supply

A critical challenge to the development of the Project Medishare oncology program in Haiti was the inadequate supply of chemotherapy drugs. Project Medishare initially attempted to source chemotherapy drugs locally from each of three pharmacies in Port-au-Prince, but the prices were prohibitively high, selection was small, and quantities were limited and subject to frequent stock outages. Generic drugs were purchased from a manufacturer (Angel Biogenics, Gujarat, India) that had WHO approval. Oncologists from the University of Florida and the University of Miami, in consultation with the team in Haiti, selected drug regimens that were easy to administer, did not require growth factor support, and required the fewest patient visits possible. We estimated the quantities of each drug needed through demand forecasting from partners, based on the local population needs and the financial resources available.

As often happens in countries with poor infrastructure, the imported medications were significantly delayed in customs. The maximum customs delay was 6 weeks, which delayed patients receiving chemotherapy by as much as 1 month. During this time, Project Medishare was again unsuccessful in its attempt to purchase drugs locally. The nursing staff implemented an intensive inventory system at Project Medishare to track usage of the different drugs and ensure timely reordering with the par level set at 3 months, allowing for a buffer of 1 month for customs delays. The local design and ownership of the inventory tracking by the nursing staff contributed to the success of the system and helped avoid stockouts of medications in the second year of the program.

A significant proportion of patients with breast cancer in Haiti do not finish their prescribed chemotherapy sessions because of drug costs, and many more are forced to delay treatment while saving money for future sessions.12 Because Project Medishare purchased generic drugs in bulk, our patients’ costs were considerably lower than the costs for patients at the University Hospital of Haiti, who purchased drugs individually from private pharmacies. Project Medishare now partners with the University Hospital of Haiti and the Support Group Against Cancer (Groupe de Support Contre le Cancer) to offer chemotherapy to the poorer patients on a sliding scale according to means, thereby increasing access to care. Patients are able to receive the generic drugs from the Project Medishare program, occasionally with financial assistance from Support Group Against Cancer, and bring those drugs to the public University Hospital to be infused. Through this partnership, the University Hospital of Haiti has continued to treat patients, demonstrating the capacity of the public health care system to effectively treat patients when the necessary resources are available.

Costs

The average cost of treatment per patient was initially calculated to be $1,500 per patient: $550 for mastectomy, $450 for chemotherapy, and $500 for the combined cost of pathology, laboratory, radiology, and operating costs. In practice, the cost per patient to Project Medishare was approximately $750 when dividing the total amount of money spent by the total number of patients treated. The cost was lower because of less care given per patient as a result of advanced disease or untimely death. Mastectomy was performed in only 70% of patients (DeGennaro et al, manuscript submitted for publication). The remaining 30% of patients presented after they had already had a mastectomy at another institution or with stage IV disease, which did not clinically warrant a mastectomy. In addition, the curative chemotherapy regimens included more expensive drugs such as docetaxel and paclitaxel than the palliative regimens, which consisted of monotherapy with less expensive agents such as doxorubicin or cyclophosphamide. We plan to calculate the cost-effectiveness of the program as we go forward.
RESULTS

The program has enrolled 139 patients and offers care at an average cost of $750 per patient. However, outcome data are limited and are strongly influenced by poor predictors at time of presentation. For example, the initial data from the first year of our program show that 80% of patients presented with stage III to IV disease, and 50% had a tumor in their breast for 12 months at the time of presentation. The mortality rate for the 94 patients for whom we have complete data, including those who had been diagnosed before the start of the program, was 24% with median survival time of 53 months. Barriers to seeking clinical diagnosis and treatment for breast cancer in LMICs and in Haiti specifically have previously been investigated. Failure to recognize that a lump in the breast might signal illness and fear of the cost of treatment were found to be the most significant contributors to delays in seeking care.12,13

For women receiving intravenous chemotherapy, adherence to 21-day administration intervals for the entire four- to eight-cycle regimen is recommended to all patients.14,15 Traditionally, this has been difficult in Haiti. In efforts to achieve the best possible outcomes, clinic staff were taught to emphasize the importance of timely administration of chemotherapy cycles, and patients were provided with social services, including transportation costs and nutritional support. A retrospective review of our data shows that more than 77% of chemotherapy cycles were delivered on time and 85% were delivered within 1 day of the desired treatment date. All women who received either curative or palliative intravenous chemotherapy and had completed at least two cycles at the time of the investigation were included. Results can be seen in Table 1.

The reasons for treatment delay were reviewed in hopes of finding modifiable factors. Medical reasons for delaying chemotherapy included fever, hemoglobin below 7 g/dL, and an absolute neutrophil count below 1,000. Patients who presented with these adverse events were given treatment for the symptoms, and chemotherapy was resumed as soon as it was safe to do so. Supply-chain delays in importing chemotherapy drugs and/or procuring chemotherapy drugs locally led to more significant delays.

A safety review showed that in 273 chemotherapy administrations, there were no instances of extravasation. There were three instances of chemotherapy drugs being spilled on the floor, which were addressed with preapproved clean-up protocols. There were seven allergic reactions, all to docetaxel, and those quickly went to zero after implementing prednisone pretreatment and administering dexamethasone no more than 1 hour before chemotherapy initiation.

CONCLUSION

Strong local partnerships, significant commitment by the staff of Project Medishare, collaboration with oncology institutions and laboratories abroad, and lessons learned from similar initiatives all helped to make the breast cancer treatment program possible. Despite these efforts, there is significant room for improvement. Most importantly, an increase in cancer awareness nationally is needed to create a shift in cancer stage at presentation and an increase in the cure rate.7 Project Medishare is working with the Haitian Ministry of Health to expand access to pathology, surgery, and chemotherapy for breast cancer nationally by using these same techniques. Project Medishare staff are hopeful that this cancer treatment program will demonstrate new possibilities for hospitals in resource-poor settings and that our lessons learned highlight important considerations and solutions for advancing cancer care in the developing world.

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Table 1 – Rates of Treatment Schedule Adherence

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>No. of IV Chemotherapy Doses Administered (%) (N = 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given every 21 days exactly</td>
<td>211 (77.3)</td>
</tr>
<tr>
<td>Given every 21 days ± 1 day</td>
<td>234 (85.8)</td>
</tr>
</tbody>
</table>

NOTE. Total No. of patients for this analysis was 58.
Abbreviation: IV, intravenous.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Vincent DeGennaro Jr
No relationship to disclose

Rachel Libby
No relationship to disclose

Elizabeth Patberg
No relationship to disclose

Dieudina Gabriel
No relationship to disclose

Samer Al-Quran
No relationship to disclose

Matthew Kasher
No relationship to disclose

Coy Heldermon
No relationship to disclose

Karen Daily
No relationship to disclose

Joseph R. Auguste
No relationship to disclose

Valery C. Suprien
No relationship to disclose

Judith Hurley
No relationship to disclose

AFFILIATIONS
Vincent DeGennaro Jr, Samer Al-Quran, Coy Heldermon, and Karen Daily, University of Florida College of Medicine, Gainesville; Rachel Libby and Judith Hurley, University of Miami Miller School of Medicine, Miami, FL; Elizabeth Patberg, Emory University School of Medicine, Atlanta, GA; Vincent DeGennaro Jr, Dieudina Gabriel, Joseph R. Auguste, and Valery C. Suprien, Project Medishare, Port-au-Prince, Haiti; and Matthew Kasher, University of North Carolina School of Medicine, Chapel Hill, NC.

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7. Reference deleted
Impact of the *Bim* Deletion Polymorphism on Survival Among Patients With Completely Resected Non–Small-Cell Lung Carcinoma

**Abstract**

**Purpose** A deletion polymorphism of the *Bim* gene has been reported to be a prognostic factor for patients with non–small-cell lung cancer (NSCLC) treated with epidermal growth factor receptor-tyrosine kinase inhibitors in the Asian population. We investigated the impact of the *Bim* deletion polymorphism on survival among patients with completely resected NSCLC.

**Patients and Methods** The *Bim* polymorphism was detected by polymerase chain reaction analysis. We measured overall survival (OS) and recurrence-free survival rates in 411 patients and postrecurrence survival (PRS) in 94 patients who experienced recurrence and received additional anticancer therapy.

**Results** The *Bim* deletion polymorphism was detected in 61 patients (14.8%). OS rates were significantly lower for patients with the *Bim* deletion polymorphism than for those with the wild-type sequence. On multivariable analysis, the *Bim* deletion polymorphism was identified as an independent prognostic factor for OS (hazard ratio, 1.98; 95% CI, 1.17 to 3.36; *P* = .011). Among the 94 patients who experienced recurrence and were treated with anticancer therapy, patients with the *Bim* deletion polymorphism showed significantly poorer PRS than those with the wild-type sequence (median, 9.8 months vs 26.9 months, respectively; *P* < .001). Multivariable analysis revealed that the *Bim* deletion polymorphism was an independent predictor of PRS (hazard ratio, 3.36; 95% CI, 1.75 to 6.47; *P* < .001). This trend remained apparent in subgroup analyses stratified by *EGFR* status, histology, and therapeutic modality.

**Conclusion** The *Bim* deletion polymorphism is a novel indicator of shortened PRS among patients with recurrent NSCLC treated with anticancer therapy in the Asian population.

**INTRODUCTION**

Lung cancer is the leading cause of cancer death worldwide. Even after radical surgery in patients with early-stage non–small-cell lung cancer (NSCLC), 30% to 40% of patients experience recurrence within 5 years. Postoperative recurrent disease is usually treated as metastatic NSCLC. Although molecule-targeted drug therapies such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have produced considerable survival benefits in patients with both advanced disease and postoperative recurrence of *EGFR*-mutated NSCLC, the majority of patients eventually become refractory to these therapies.

B-cell chronic lymphatic leukemia lymphoma 2-like 11 (BCL2L11), or BIM, is a proapoptotic member of the Bcl-2 protein family and is a key modulator of EGFR-TKI–induced apoptosis in NSCLC cell lines. Ng et al reported a common intronic deletion with a 2,903-base pair (bp) polymorphism in the gene encoding BIM. This deletion polymorphism leads to impaired expression of BH3-containing BIM isoforms, resulting in resistance to EGFR-TKIs in patients with NSCLC who have *EGFR* mutations. Interestingly, this deletion polymorphism was observed only in East Asian populations. Several clinical studies of East Asian populations have indicated that the *Bim* deletion polymorphism is an independent prognostic factor for progression-free survival in advanced *EGFR*-mutated NSCLC treated with EGFR-TKIs and cytotoxic chemotherapy. The *Bim* deletion polymorphism is expected to...
be a novel biomarker in anticancer therapy against inoperable NSCLC, especially adenocarcinoma. Patients with NSCLC who have recurrence after curative surgery have a more favorable prognosis than those with advanced-stage disease at initial presentation, because patients with NSCLC who have postoperative recurrence have different characteristics from those with stage IV disease. However, there have been no studies regarding the prognostic power of the Bim deletion polymorphism in postoperative patients with lung cancer, including those with non-adenocarcinoma histology, or the influence of the polymorphism on postrecurrence treatment.

We hypothesized that the Bim deletion polymorphism affects survival among patients with postoperative recurrent NSCLC. In this study, we investigated the impact of the Bim deletion polymorphism on the outcomes of patients with completely resected NSCLC.

PATIENTS AND METHODS

Patients and data collection

A total of 565 patients with NSCLC who underwent pulmonary resection at Gunma University Hospital between June 2003 and December 2013 were identified in our database. Among these patients, 481 underwent complete resection (lobectomy or greater with systematic lymph node dissection) without induction chemotherapy or radiotherapy. We excluded patients with residual lesions (macroscopically or microscopically apparent), as well as those with pathologic stage IV disease and those without adequate documentation. Consequently, 411 patients were eligible for inclusion in this study. Histologic diagnoses were made on the basis of WHO criteria, and disease stage was determined according to the TNM Classification of Malignant Tumors, 7th edition. This study was approved by the ethics committee of Gunma University Hospital. Informed consent for a global genome analysis of samples was obtained from each patient before inclusion in the study. Institutional review board approval for the study was obtained for the analysis of Bim and other genes in those samples.

Diagnosis of Recurrence and Survival Analysis

Patients were followed at 3-month intervals for the first 2 years and at 6-month intervals thereafter on an outpatient basis. Follow-up evaluation included a physical examination, chest radiography, and blood analysis, including analysis of pertinent tumor markers. Computed tomography of the chest and abdomen or positron emission tomography-computed tomography was performed annually. When symptoms or signs of recurrence were detected, further evaluations were performed. Recurrence was diagnosed based on compatible physical examination and diagnostic imaging findings, and the diagnosis was confirmed histologically when clinically feasible. The date of recurrence was defined as the date of histologic confirmation, or in patients whose diagnosis was based on clinical evidence, the date of recognition of recurrent disease by the attending physician. Local recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemithorax, or mediastinum. Distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum.

The overall survival (OS) period was defined as the time between the date of surgery and the date of death as a result of any cause. Patients who were lost to follow-up were censored from analysis at the time of the last negative follow-up. For the patients who developed recurrent disease during follow-up, postrecurrence survival (PRS) was measured from the date of initial recurrence to the date of death as a result of any cause or the date on which the patient was last known to be alive. Recurrence-free survival (RFS) was measured from the date of surgery to the date of initial recurrence.

DNA Extraction and Gene Analysis

After surgical removal of the tumor, a portion of each sample was immediately frozen and stored at −80°C before DNA extraction. Genomic DNA was extracted from a 3- to 5-mm cube of tumor tissue by using DNA Mini Kits (QIAGEN, Hilden, Germany) and was subsequently diluted to a concentration of 20 ng/μL. EGFR mutations in lung cancer tissue were analyzed by peptide nucleic acid–enriched sequencing, as described previously. Presence of the Bim deletion polymorphism was analyzed by first extracting DNA from peripheral blood mononuclear cells by using a QIAamp DNA Blood Mini Kit (QIAGEN, Venlo, the Netherlands) followed by polymerase chain reaction assay as described previously.

Statistical Analysis

Statistical analyses were conducted by using SPSS software for Windows, version 12.0 (SPSS, Chicago, IL) and Power and Sample Size Calculation software, version 3.1.2 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). All categorical variables were analyzed by using the χ² test. Continuous variables were compared by
using the independent samples t test. Survival was analyzed by using the Kaplan-Meier method, and statistical analysis was performed by using the log-rank test. Prognostic groups were assessed by using Cox proportional hazards regression analysis. Variables significantly associated with OS and PRS on univariable analysis were tested by multivariable analysis using a Cox proportional hazards regression model. A two-tailed P value of less than .05 was taken to indicate statistical significance. On the basis of previous reports, we assumed that 13.7% of Japanese patients had the Bim deletion polymorphism and an OS of 24.8 and 16.8 months, respectively, for patients with advanced NSCLC who received anticancer therapy in the Bim wild-type and Bim deletion groups. Under these assumptions, with a two-tailed α of .05 and power at 0.8, 64 patients with the Bim deletion polymorphism and 403 patients with the wild-type sequence were required to evaluate the effect of the Bim deletion polymorphism on PRS for anticancer therapy.

RESULTS

Clinicopathologic Characteristics

Patient characteristics are presented in Table 1. All patients were Japanese. The median age at the

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 411)</th>
<th>Wild Type (n = 349)</th>
<th>Deletion Polymorphism (n = 61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>67.6</td>
<td>67.9</td>
<td>66.5</td>
<td>.294</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>.483</td>
</tr>
<tr>
<td>Female</td>
<td>175</td>
<td>152 (86.9)</td>
<td>23 (13.1)</td>
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<tr>
<td>Male</td>
<td>236</td>
<td>198 (83.9)</td>
<td>38 (16.1)</td>
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<tr>
<td>Smoking status</td>
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<td></td>
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<tr>
<td>Never smoker</td>
<td>157</td>
<td>140 (89.2)</td>
<td>17 (10.8)</td>
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<tr>
<td>Ever smoker</td>
<td>254</td>
<td>210 (82.7)</td>
<td>44 (17.3)</td>
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<tr>
<td>Histology</td>
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<td></td>
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<td>259 (87.2)</td>
<td>38 (12.8)</td>
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<td>74 (79.6)</td>
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<td>21</td>
<td>17 (81.0)</td>
<td>4 (19.0)</td>
<td></td>
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<tr>
<td>Tumor size, cm</td>
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<td></td>
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<tr>
<td>≤ 3</td>
<td>248</td>
<td>215 (86.7)</td>
<td>33 (13.3)</td>
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<tr>
<td>&gt; 3</td>
<td>163</td>
<td>135 (82.8)</td>
<td>28 (17.2)</td>
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<tr>
<td>Node metastases</td>
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<td></td>
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<tr>
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<tr>
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<tr>
<td>Negative</td>
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<td>223 (87.1)</td>
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<td>Positive</td>
<td>155</td>
<td>127 (81.9)</td>
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<td>Lymphatic invasion</td>
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<td>II or III</td>
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<td>104 (76.5)</td>
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<tr>
<td>EGFR gene</td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Wild type</td>
<td>276</td>
<td>235 (85.1)</td>
<td>41 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>135</td>
<td>115 (85.2)</td>
<td>20 (14.8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADC, adenocarcinoma; EGFR, epidermal growth factor receptor; SQC, squamous cell carcinoma.

*ADC v SQC and other.
time of surgery was 67.6 years (range, 36 to 90 years), and the study population consisted of 175 females and 236 males. On the basis of the histology of the lesions, the study population included 297 adenocarcinomas, 93 squamous cell carcinomas, 12 large-cell neuroendocrine carcinomas, seven large-cell carcinomas, and two adenosquamous cell carcinomas. With regard to diagnosis, 275 patients were classified as pathologic stage I, and 136 patients were classified as stage II or III. EGFR mutation was detected in 135 tumors (32.8%) consisting of 133 adenocarcinomas and two squamous cell carcinomas. The Bim deletion polymorphism was detected in 61 patients (14.8%). The percentage of patients according to sex, smoking history, histology, and EGFR mutational status did not differ significantly between the wild-type and Bim deletion polymorphism groups, although the percentage of lymph node metastases, positive lymphatic invasion, and advanced stage in the patients with Bim deletion polymorphism was significantly higher than in those with the wild-type Bim sequence (Table 1).

Prognostic Impact of Bim Polymorphism on OS and RFS

Factors associated with OS and RFS, as revealed through univariable analysis, included sex, smoking status, histology, vascular invasion, lymphatic invasion, pathologic stage, EGFR gene status, and Bim polymorphism. In the multivariable analysis, pathologic stage, EGFR gene mutation, and the Bim deletion polymorphism were independent factors associated with OS, and pathologic stage and lymphatic invasion were independent factors associated only with poor RFS (Table 2). The Bim deletion polymorphism was independently associated with OS but not RFS in 411 patients. The 5-year OS rate was significantly lower for patients with the Bim deletion polymorphism compared with those with wild-type Bim (58.8% v 78.9%, respectively; P < .001; Fig 1A). To eliminate bias, we analyzed survival by using propensity score matching (Data Supplement). The 5-year OS in the propensity score–matched analysis was also significantly poorer in patients with Bim deletion than in those with wild-type Bim (58.8% v 80.3%, respectively; P = .036; Fig 1B).

In addition, we investigated RFS among patients who developed recurrence. As of October 2014, 109 patients had experienced recurrence. Patient characteristics are shown in the Data Supplement. In the univariable analysis, the variables associated with RFS in patients with recurrence were vascular invasion and Bim deletion polymorphism, and these remained as independent factors in the multivariable analysis (Data Supplement). Furthermore, patients with the Bim deletion polymorphism showed significantly shortened RFS compared with those with wild-type Bim (median, 9.8 v 13.9 months, respectively; P = .003; Fig 2A).

Prognostic Impact of Bim Polymorphism on PRS

To determine the impact of the Bim deletion polymorphism on outcome after recurrence, we investigated 94 (86%) of 109 patients with recurrent disease who received additional anticancer therapy, including cytotoxic chemotherapy, EGFR-TKIs, or radiotherapy with curative intent. The characteristics of the 94 patients who received anticancer therapies are summarized in Table 3. The median time to follow-up was 16.4 months (range, 2.0 to 91.8 months), median age at recurrence was 68.6 years (range, 37 to 80 years), and the patients consisted of 38 females and 56 males. There were 65 patients with adenocarcinoma and 29 with non-adenocarcinomas (23 squamous cell carcinomas, four large-cell neuroendocrine carcinomas, and two large-cell carcinomas). Sixteen patients (17%) harbored the Bim deletion polymorphism, and 29 patients (31%) harbored

---

**Table 2 – Multivariable Analysis of Predictors of OS and RFS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS HR (95% CI)</th>
<th>P</th>
<th>RFS HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.008 (0.456 to 2.229)</td>
<td>.985</td>
<td>1.056 (0.562 to 1.985)</td>
<td>.866</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>0.817 (0.330 to 2.020)</td>
<td>.662</td>
<td>0.974 (0.487 to 1.945)</td>
<td>.940</td>
</tr>
<tr>
<td>ADC histology</td>
<td>0.656 (0.375 to 1.147)</td>
<td>.139</td>
<td>0.776 (0.495 to 1.218)</td>
<td>.271</td>
</tr>
<tr>
<td>Positive vascular invasion</td>
<td>1.211 (0.704 to 2.084)</td>
<td>.489</td>
<td>1.039 (0.675 to 1.601)</td>
<td>.861</td>
</tr>
<tr>
<td>Positive lymphatic invasion</td>
<td>1.210 (0.674 to 2.171)</td>
<td>.524</td>
<td>1.673 (1.032 to 2.711)</td>
<td>.037</td>
</tr>
<tr>
<td>Pathologic stage II or III</td>
<td>5.213 (2.913 to 9.327)</td>
<td>&lt; .001</td>
<td>4.738 (2.994 to 7.498)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EGFR mutated</td>
<td>0.358 (0.172 to 0.743)</td>
<td>.006</td>
<td>0.762 (0.466 to 1.245)</td>
<td>.277</td>
</tr>
<tr>
<td>Bim deletion polymorphism</td>
<td>1.979 (1.166 to 3.357)</td>
<td>.011</td>
<td>1.231 (0.781 to 1.939)</td>
<td>.370</td>
</tr>
</tbody>
</table>

Abbreviations: ADC, adenocarcinoma; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.
EGFR-mutated tumors. Thirty-seven patients (39%) showed local recurrence only, and 59 patients (61%) showed distant recurrence. Recurrence in multiple foci was detected in 65 patients (69%). Treatment for recurrence consisted of platinum-based chemotherapy in 43 patients (46%), radiotherapy in 43 patients (46%), and EGFR-TKIs in 33 patients (35%). No significant differences in age, sex, tumor histology, smoking status, pathologic stage, site of recurrence, number of recurrent foci, EGFR gene status, or therapeutic modality were observed between patients with the Bim deletion polymorphism and those with wild-type Bim (Table 3).

Univariable analysis indicated that RFS shorter than 12 months, EGFR gene status, and Bim polymorphism influenced PRS, all of which remained as independent prognostic factors for PRS in the multivariable analysis (Table 4). Median PRS was 26.9 months among those with wild-type Bim and 11.4 months among those with the Bim deletion polymorphism (P < .001; Fig 2). Subset analysis of PRS showed that patients with wild-type Bim consistently showed prolonged survival compared with those with the deletion polymorphism when stratified by EGFR gene status (mutated: median, 61.0 v 23.2 months; P < .001; Fig 3A; wild-type: median, 19.7 v 9.8 months; P = .001; Fig 3B) or tumor histology (adenocarcinoma: median, 33.9 v 11.4 months; P = .009; Fig 3C; non-adenocarcinoma: median, 19.7 v 9.8 months; P = .013; Fig 3D). When analyzed according to therapeutic modality, the median PRS was significantly shorter in patients with the Bim deletion polymorphism compared with those with the wild-type Bim or EGFR-mutated NSCLC treated with EGFR-TKIs (median, 38.1 v 23.2 months, respectively; P = .007; Fig 4A), those treated with cytotoxic chemotherapy alone (median, 18.5 v 6.2 months, respectively; P = .003; Fig 4B), and those treated with radiotherapy alone (median, 26.9 v 11.4 months, respectively; P = .046; Fig 4C). No bias was observed in the distribution of the Bim deletion polymorphism in terms of platinum or taxane use among the 23 patients who received cytotoxic chemotherapy. Similarly, there was no significant difference in the distribution of the Bim deletion polymorphism according to the radiotherapy method (conventional or cyberknife) or total...
DISCUSSION

The Bim deletion polymorphism has been investigated in inoperable advanced NSCLC and identified as a heritable factor conferring resistance to EGFR-TKIs and chemotherapy in the Asian population. However, only one report has examined the impact of the Bim deletion polymorphism on survival in patients with resectable NSCLC. In this study, we demonstrated the impact of the Bim deletion polymorphism on NSCLC outcomes (survival) after complete tumor resection. The Bim deletion polymorphism was an independent unfavorable prognostic factor of OS in all patients with NSCLC who received complete resection, which was the result of shorter RFS and PRS associated with the Bim deletion polymorphism among those who developed recurrent disease. Furthermore, the PRS trend was consistent in subgroup analyses stratified by EGFR mutation status, histology, and therapeutic modality. On the basis of the results of this study, we suggest that the Bim deletion polymorphism has a positive impact on early emergence of metastasis and a negative impact on anticancer treatment in recurrent NSCLC.

There have been few studies regarding the biologic characteristics associated with Bim deletion polymorphism, but several basic studies demonstrated that the BIM protein is essential for anticancer therapy-induced apoptosis. EGFR-TKI–induced apoptosis requires BIM protein expression in EGFR-mutated NSCLC cell lines, and clinical studies have focused on the relationship between the Bim deletion polymorphism or Bim messenger RNA expression and EGFR-mutated NSCLC treated with EGFR-TKIs. Our results support the notion that the Bim deletion polymorphism is an indicator of significantly poorer outcomes for EGFR-TKI therapy against EGFR-mutated NSCLC (Fig 4A). In terms of cytotoxic chemotherapy, BIM protein was shown to mediate apoptosis induced by paclitaxel in NSCLC cells and to be a major determinant in the response of tumors to paclitaxel. Wang et al reported that BIM plays a
critical role in cisplatin resistance, demonstrating that BIM protein is degenerated in cisplatin-resistant but not in cisplatin-sensitive cells, and inhibition of BIM degeneration can effectively induce cancer cell death. Because expression of the proapoptotic BH3 domain in BIM is suppressed in individuals with the Bim deletion polymorphism,10 sensitivity to cytotoxic chemotherapy may be low in such patients. Consequently, as demonstrated here and in a previous study,13 patients with the Bim deletion polymorphism tend to have shorter survival periods than those with wild-type Bim after cytotoxic chemotherapy (Fig 4B).

With regard to radiotherapy-induced apoptosis, it has been reported that radiation increases FOXO3a protein expression, leading to upregulation of BIM expression and apoptotic induction, a reaction that is downstream of the PI3K/AKT signaling pathway and independent of the p53 pathway.24,25 The PI3K/AKT pathway, which regulates BIM expression, is expected to contribute to radiotherapy resistance, and blockade of the pathway may enhance cancer cell radiotherapy sensitivity.25,26 Our results indicate that the Bim deletion polymorphism is an indicator of poorer radiotherapy outcomes in recurrent NSCLC after complete resection (Fig 4C). Taken together, these findings suggest that the Bim deletion polymorphism confers resistance against treatment with EGFR-TKIs, chemotherapy, and radiotherapy.

The relationship between BIM and tumor development has been investigated in several solid tumors. Comparison of BIM levels in primary and metastatic tumors revealed progressive decreases in BIM expression in melanoma,27 renal cell carcinoma,28 and colon carcinoma cells.29 In NSCLC cells, low BIM expression was observed more frequently in cases of advanced pathologic stage, poorer differentiation, and squamous histology, although no impact on survival was observed.30 These studies support the suggestion that BIM protein plays an important role in suppressing tumor development. Merino et al31 recently reported that Bim loss does not affect proliferation or the expression of epithelial-mesenchymal transition markers but does increase the number of lung metastases in breast cancers. They suggested that the loss of Bim may be responsible for dissemination of tumor cells and their colonization of distant
To the best of our knowledge, this is the first investigation of the impact of Bim deletion polymorphism on PRS in patients with NSCLC. Previous studies\(^{10-12,14}\) demonstrated that the Bim deletion polymorphism is a prognostic factor for progression-free survival in patients with stage IIIIB or IV NSCLC who received EGFR-TKIs and chemotherapy, although all but one study\(^{13}\) showed no obvious impact on OS. The reasons underlying these inconsistencies regarding the impact of the Bim deletion polymorphism in this and previous studies are unclear. However, previous studies indicated that patients with NSCLC who had recurrence after curative surgery had a favorable prognosis compared with those with advanced-stage disease at initial presentation.\(^{15,32}\) These results suggest that although both patient groups can be classified as advanced NSCLC, biologic characteristics, such as EGFR-TKI and/or chemotherapy treatment outcome, may be distinct.

The Bim polymorphism may be a novel germline biomarker for therapy resistance in patients with advanced NSCLC. The presence of the Bim deletion polymorphism may be a negative indication for standard therapies, with the exception of surgery, because such patients are at risk of developing aggressive cancer refractory to EGFR-TKI, chemotherapy, and radiotherapy. Thus, patients with unresectable or recurrent NSCLC who harbor the Bim deletion may benefit from treatment with a BH3-mimetic drug\(^{3,10}\) or histone deacetylase inhibitor\(^{19}\) to overcome therapy resistance.

This study had several limitations. The first and most important one was the small sample size. The survival analysis included heterogeneous patient backgrounds. Because the subset analyses according to histology or therapy modality were performed by using small sample sizes, this study lacked statistical power, and further investigation is required with a larger sample. Second, this was a retrospective study. Although the indications and therapeutic strategies for recurrent disease were reviewed by the cancer board of our department, not all patients received treatment according to the

Table 5 – Therapeutic Background of Patients Who Received Cytotoxic Chemotherapy or Radiotherapy Alone

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Wild Type No. (%)</th>
<th>Deletion Polymorphism No. (%)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>19</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (75.0)</td>
<td>4 (25.0)</td>
<td>.273</td>
</tr>
<tr>
<td>No</td>
<td>7 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Taxane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>No</td>
<td>16 (84.2)</td>
<td>3 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Radiation*</td>
<td>17</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>15 (88.2)</td>
<td>4 (11.8)</td>
<td>.637</td>
</tr>
<tr>
<td>Cyberknife</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

\*Total dose average: patients with wild-type sequence, 66.0 Gy (range, 39-100 Gy); patients with deletion polymorphism, 52.0 Gy (range, 30-104 Gy); \(P = .217\).
same standard. A prospective multicenter study is required to determine the clinical significance of the \textit{Bim} deletion polymorphism with regard to therapy for advanced and recurrent NSCLC. Finally, this polymorphism is observed only in Asian populations. Even if the significance of the \textit{Bim} deletion polymorphism is validated, the results would not provide any benefit to non-Asian patients with NSCLC.

In conclusion, the \textit{Bim} deletion polymorphism was an indicator of poor RFS and PRS in patients with recurrence after complete resection and is consequently an independent unfavorable prognostic factor for OS in all patients with NSCLC who received complete resection. The polymorphism was associated with tumor aggressiveness and therapy resistance in metastatic disease. If validated, these results suggest that the \textit{Bim} polymorphism may be a biomarker of poor outcome for multimodal therapies in treating recurrent or advanced NSCLC in the Asian population.

\textbf{AUTHOR CONTRIBUTIONS}

Conception and design: Kimihiro Shimizu  
Collection and assembly of data: Jun Atsumi, Yoichi Ohtaki, Seiichi Kakegawa, Toshiteru Nagashima, Yasuaki Enokida, Kai Obayashi, Yoshiaki Takase, Osamu Kawashima, Mitsuhiro Kamiyoshihara, Masayuki Sugano, Takashi Ibe, Hitoshi Igai, Izumi Takeyoshi  
Data analysis and interpretation: Jun Atsumi, Kimihiro Shimizu, Yoichi Ohtaki, Kyoichi Kaira, Seshiru Nakazawa  
Manuscript writing: All authors  
Final approval of manuscript: All authors

\textbf{AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST}

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to \url{www.asco.org/rwc} or \url{jco.ascopubs.org/site/ifc}.

Jun Atsumi  
No relationship to disclose  
Kimihiro Shimizu  
No relationship to disclose  
Yoichi Ohtaki  
No relationship to disclose  
Kyoichi Kaira  
No relationship to disclose  
Seiichi Kakegawa  
No relationship to disclose

Toshiteru Nagashima  
No relationship to disclose  
Yasuaki Enokida  
No relationship to disclose  
Seshiru Nakazawa  
No relationship to disclose  
Kai Obayashi  
No relationship to disclose  
Yoshiaki Takase  
No relationship to disclose  
Osamu Kawashima  
No relationship to disclose  
Mitsuhiro Kamiyoshihara  
No relationship to disclose  
Masayuki Sugano  
No relationship to disclose  
Takashi Ibe  
No relationship to disclose  
Hitoshi Igai  
No relationship to disclose  
Izumi Takeyoshi  
No relationship to disclose

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\textbf{AFFILIATIONS}

Jun Atsumi, Kimihiro Shimizu, Yoichi Ohtaki, Kyoichi Kaira, Toshiteru Nagashima, Yasuaki Enokida, Seshiru Nakazawa, Kai Obayashi, Yoshiaki Takase, Masayuki Sugano, and Izumi Takeyoshi, Gunma University Graduate School of Medicine, Maebashi, Gunma; Seiichi Kakegawa and Osamu Kawashima, National Hospital Organization Nishi-Gunma Hospital, Shibukawa, Gunma; and Mitsuhiro Kamiyoshihara, Takashi Ibe, and Hitoshi Igai, Maebashi Red Cross Hospital, Maebashi, Gunma, Japan

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Tuberculosis Diagnosis Delaying Treatment of Cancer: Experience From a New Oncology Unit in Blantyre, Malawi

Leo Peter Lockie Masamba
Yankho Jere
Ewan Russell Stewart Brown
Dermot Robert Gorman

INTRODUCTION

Malawi is a low-income country within sub-Saharan Africa and thus has a low number of trained medical personnel. Outside the main government central hospitals, most health care is delivered by nursing and clinical officer staff. Resources are scarce, and there are high levels of HIV, with a national seroprevalence rate of 10.0% in adults age 15 to 49 years (2014 data). Although the country has mounted an effective scale-up program of antiretroviral therapy, the rates of tuberculosis (156 per 100,000) and AIDS-related cancers, particularly lymphomas, are high. Cancer incidence in Malawi is estimated at 55.5 per 100,000 in males and 68.8 per 100,000 in females (age-standardized rates), and the most common cancer sites are Kaposi’s sarcoma, esophageal cancer, non-Hodgkin lymphoma, cervical cancer, and breast cancer. Age-standardized incidence of non-Hodgkin lymphoma is reported at 2.3 per 100,000 in males and 1.9 per 100,000 in females, considerably lower than the incidence of tuberculosis. Since the oncology unit at Queen Elizabeth Central Hospital (QECH) opened in 2010, it has registered more than 4,000 new patients with cancer, with diagnoses reflecting the distribution of cancer in Malawi. Several of the cancers are AIDS defining, the proportion of patients with cancer who are HIV positive is high (44% of new patients at the oncology unit were recorded as HIV positive in 2013 and 2014 combined), and some are co-infected with tuberculosis. Although tuberculosis rates in Malawi are reported by WHO to be lower than in some surrounding countries and are definitely dropping, they remain high, with tuberculosis treatment often based on clinical diagnosis alone.

The oncology team has been aware of some patients presenting with malignancy who have been erroneously diagnosed and treated for tuberculosis, thus delaying cancer care. The unit has been prospectively recording information about such instances, and we report on this.

METHODS

All patients presenting to the oncology unit at QECH from 2010 to 2014 were assessed by either a clinical officer (Y.J.), a consultant oncologist (L.P.L.M.), or both. Patients who had an erroneous tuberculosis diagnosis that delayed their cancer diagnosis were
identified, and clinical data that included age, HIV status, clinical presentation, and type of malignancy were prospectively recorded and entered onto an Excel spreadsheet. A descriptive analysis of the data was undertaken. Ethics approval was gained through the Malawi Health Sciences Research Board.

RESULTS

Thirty-four patients who had been treated for tuberculosis before being diagnosed with cancer were identified between 2010 and 2014 (seven in 2010, nine in 2011, 11 in 2012, five in 2013, two from January through March 2014; Table 1). Forty-one percent of patients were HIV positive.

Mean duration of tuberculosis treatment before oncology presentation was 3.6 months. The mean resultant delay in cancer diagnosis was 5.4 months. This was slightly longer for men (5.9 months) than for women (4.5 months).

Many patients had a constellation of signs and symptoms on presentation, including prominent neck masses, fever, malaise, weight loss, cough, and abdominal pain (Table 2). Mean hemoglobin was 9.2 g/dl.

Misdiagnoses of tuberculosis were predominantly clinical (17 instances) but were often supported by chest x-ray (seven), other x-ray (two), ultrasound scan (one), fine-needle aspirate (one), magnetic resonance imaging (one), and cerebrospinal fluid analysis (one). The most common site for misdiagnosis of tuberculosis was lymph nodes (Table 3).

The eventual cancer diagnosis was confirmed by histology or cytology in 33 of the 34 patients. The single patient with Kaposi’s sarcoma had a clinical diagnosis. The most common diagnosis was non-Hodgkin lymphoma followed by Hodgkin lymphoma (Table 4).

DISCUSSION

This study confirms that delay in diagnosing cancer caused by previous incorrect diagnosis and treatment of tuberculosis is an important clinical problem in Malawi. Our figure of 34 misdiagnosed patients since 2010 represents approximately 1% of the oncology patients that presented to the QECH Oncology Unit. This misdiagnosis is well understood in the literature, notably in lymphomas5 and the lungs.6 In our series, the most common malignancies that were misdiagnosed were lymphoma followed by lung cancer. The delay in treatment in this series was 5.4 months, and this study reinforces the concerns raised about inappropriate tuberculosis care leading to delayed cancer diagnosis in a second Malawian central hospital.7 Therefore, cancer treatment for our patients often started at a later clinical stage in which outcomes may have been compromised.

Malawi has a large number of patients and few staff, particularly in rural areas with limited investigative capacity; as a consequence, the diagnosis of tuberculosis is sometimes made on clinical grounds alone. This contributed to misdiagnosis.

Table 1 – Demographic Characteristics and HIV Status of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (n = 23)</th>
<th>Female (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. % Age (years)</td>
<td>No. % Age (years)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>32.7*</td>
<td>36.8</td>
</tr>
<tr>
<td>HIV positive</td>
<td>6 (26)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>HIV negative</td>
<td>16 (69)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>HIV status unknown</td>
<td>1 (53)</td>
<td>1 (23)</td>
</tr>
</tbody>
</table>

*Mean

Table 2 – Symptoms Reported on Presentation to Queen Elizabeth Central Hospital Oncology Unit

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Instances in Which Sign or Symptom Was Noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck masses</td>
<td>8</td>
</tr>
<tr>
<td>Plus respiratory</td>
<td>4</td>
</tr>
<tr>
<td>Plus abdominal</td>
<td>2</td>
</tr>
<tr>
<td>Generalized lymphadenopathy</td>
<td>6</td>
</tr>
<tr>
<td>Primarily respiratory or chest</td>
<td>4</td>
</tr>
<tr>
<td>Primarily neurologic</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Lower limb weakness</td>
<td>1</td>
</tr>
<tr>
<td>Headaches</td>
<td>1</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3</td>
</tr>
<tr>
<td>Detail missing</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 – Site of Misdiagnosed Tuberculosis

<table>
<thead>
<tr>
<th>Site of Misdiagnosed Tuberculosis</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis lymph nodes</td>
<td>16</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>9</td>
</tr>
<tr>
<td>Spinal</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 4 – Cancer Diagnoses in Patients Treated as Having Tuberculosis (No. HIV positive)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma/carcinoma</td>
<td>1 (1)</td>
<td>2 (0)</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 (0)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>0</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0</td>
<td>1 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3 (0)</td>
<td>7 (0)</td>
<td>10</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5 (5)</td>
<td>6 (2)</td>
<td>11</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>0</td>
<td>2 (1)</td>
<td>2</td>
</tr>
</tbody>
</table>

in 17 of 35 patients and is a common challenge for health care services in low-income countries, particularly for cancers that share features of presentation with tuberculosis.5

The majority of symptoms and signs described are common between tuberculosis and malignancy, especially the lymphomas. Given the limited investigative capacity and the common presentation of tuberculosis, the misdiagnoses are not unexpected, and similar findings have been found and similar explanations for the problem have been given in South Africa and elsewhere in Malawi.5,7

The empirical treatment of tuberculosis is common in Malawi, but when this is undertaken for extrapulmonary or smear-negative tuberculosis, close monitoring for response is important. Patients presenting with lymphadenopathy should be considered for biopsy referral because there is a high likelihood of cancer diagnosis: 53% and 35% in two Malawian series.7,8 Where biopsy and histopathologic facilities are available, a clinical diagnosis of tuberculosis for lymphadenopathy should be discouraged.

Follow-up of patients with tuberculosis in a resource-poor setting is notoriously difficult. Here, although the treatment was incorrect, this sample of patients often had complete or almost complete courses of tuberculosis treatment over several months under some form of clinical supervision, mostly by nursing and clinical officer staff. This creates an opportunity to intervene and offer training to health care staff and also provides an opportunity for health care institutions to improve their monitoring of response to tuberculosis treatment. Our findings raise the concern that patients with potentially treatable cancers may miss the opportunity to have access to cancer treatment because of misdiagnosis and emphasize the importance of more cancer awareness training for all health care staff.

Ensuring the microbiologic diagnosis of tuberculosis, promoting biopsies of patients with lymphadenopathy, and being more alert to the possibility of a cancer diagnosis in people who were originally diagnosed as having tuberculosis but who do not improve with treatment are all key to improving care for this group of patients. When the diagnosis is reviewed and cancer is correctly diagnosed and then treated promptly, a successful outcome for the patient is more likely. We recommend that health care workers have a low threshold for referring patients for investigation for malignancy if empirical tuberculosis treatment does not lead to a clinical response within 4 weeks. The Malawian Ministry of Health National Action Plan for Prevention and Management of Non-Communicable Disease in Malawi 2012-20169 plans initiatives to improve cancer knowledge in the general population and improve cancer education for health care providers. We hope that these and other initiatives will help improve outcomes for patients with cancer in Malawi.

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AUTHOR CONTRIBUTIONS
Conception and design: Leo Peter Lockie Masamba, Yankho Jere, Dermot Robert Gorman
Collection and assembly of data: Leo Peter Lockie Masamba, Yankho Jere, Ewan Russell Stewart Brown
Data analysis and interpretation: Leo Peter Lockie Masamba, Ewan Russell Stewart Brown, Dermot Robert Gorman
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Tuberculosis Diagnosis Delaying Treatment of Cancer: Experience From a New Oncology Unit in Blantyre, Malawi
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Leo Peter Lockie Masamba
No relationship to disclose

Yankho Jere
No relationship to disclose

Ewan Russell Stewart Brown
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Dermot Robert Gorman
No relationship to disclose
REFERENCES


Lung Cancer Survival Among Chinese Americans, 2000 to 2010

Purpose Despite being the leading cause of cancer death, no prior studies have characterized survival patterns among Chinese Americans diagnosed with lung cancer. This study was conducted to identify factors associated with survival after lung cancer in a contemporary cohort of Chinese patients with lung cancer.

Methods The study design is a prospective descriptive analysis of population-based California Cancer Registry data. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) for overall mortality. Participants were Chinese American residents diagnosed with first primary invasive lung cancer from 2000 to 2010 (2,216 men and 1,616 women).

Results Among Chinese men, decreased mortality was associated with care at a National Cancer Institute cancer center (HR, 0.85; 95% CI, 0.73 to 0.99) and adenocarcinoma versus small-cell carcinoma (HR, 0.78; 95% CI, 0.65 to 0.92). Women had better survival compared with men (HR, 0.82; 95% CI, 0.75 to 0.89), with mortality associated with never married versus currently married status (HR, 1.36; 95% CI, 1.11 to 1.66), lower versus higher neighborhood socioeconomic status (HR, 1.38; 95% CI, 1.10 to 1.72 comparing lowest to highest quintile), care at a cancer center (HR, 0.80; 95% CI, 0.67 to 0.96), and squamous cell relative to small-cell carcinoma (HR, 1.60; 95% CI, 1.04 to 2.48).

Conclusion Focusing on factors associated with marital status, community socioeconomic status, and characteristics unique to National Cancer Institute–designated cancer centers may help to identify potential strategies for improving the length of survival for Chinese Americans.

INTRODUCTION

Chinese Americans are the largest Asian group in the United States, with 4.0 million Chinese Americans counted in the 2010 Census. In California, the most populous US state for Chinese Americans, this population increased 30% over a decade from 2000 to 2010, numbering nearly 1.5 million. Lung cancer is the second most common cause of cancer death for Chinese men and women, respectively, and the most common cause of cancer death for both men and women, followed by prostate and colorectal cancers for men and breast and colorectal cancer for women. We previously documented differences across multiple Asian American ethnic groups in survival after lung cancer among patients in the California Cancer Registry (CCR) and among a series of female never-smoker patients. However, no prior studies, to our knowledge, have characterized the survival patterns specific for Chinese Americans, particularly as the biology of the disease may be unique among this population, with a higher incidence of epidermal growth factor receptor (EGFR) tyrosine kinase domain–activating mutations and, among Chinese women, a majority of lung cancers presenting among never-smokers. Considering the high burden of disease in Chinese Americans, an examination of survival patterns and prognostic factors, with attention to both clinicopathologic and sociodemographic factors, may inform strategies to improve survival and potentially early detection by identifying subgroups with poor survival who may benefit from targeted screening efforts.

To provide insight into the prognostic factors for lung cancer among the growing Chinese American population, we used population-based CCR data enhanced with information regarding immigrant status and neighborhood-level information on socioeconomic status (SES) and residence in ethnic enclaves to examine patterns in lung cancer survival among Chinese persons in California, the US state with the largest Chinese population (one third of the US Chinese population).
METHODS

Case Selection

We obtained data for all first primary invasive lung cancers (International Classification of Diseases [ICD] for Oncology, third edition, site codes, C34.0 to C34.9, excluding histologic codes 9050 to 9055, 9140, and 9590 to 9992) among Chinese American residents of California during the period between January 1, 2000, and December 31, 2010, from the CCR (comprised of four registries [San Francisco Bay Area, San Jose/Monterey, Los Angeles, and Greater California] within the National Cancer Institute [NCI] SEER program; n = 4,537). We excluded patients diagnosed without microscopic confirmation (n = 390), those diagnosed at autopsy or via death certificate (n = 59), and patients with survival time less than 30 days who did not undergo any first course of treatment (n = 256). The final study cohort included 2,216 male and 1,616 female patients with lung cancer (total, N = 3,832). Other patient and clinical characteristics obtained from CCR data include age and year of diagnosis, birthplace, sex, residential address and stage at diagnosis, histologic subtype (coded using ICD for Oncology, third edition, histology codes as follows: small-cell carcinoma, 8041 to 8045 and 8246; squamous cell carcinoma, 8051, 8052, 8070 to 8078, 8083, and 8084; adenocarcinoma, 8050, 8140 to 8147, 8201, 8230, 8250 to 8255, 8260, 8263, 8290, 8310, 8320, 8323, 8220, 8350, 8441, 8460, 8470, 8471, 8480, 8481, 8490, 8500, 8503, 8507, 8550, and 8570 to 8576; large-cell carcinoma, 8011 to 8015, 8082, and 8123; and non–small-cell lung cancer [NSCLC], not otherwise specified, 8010, 8020 to 8022, 8030 to 8035, 8046, 8094, 8120, 8130, 8170, 8200, 8240 to 8249, 8340, 8430, 8525, 8551, 8560, 8562, 8580, 8940, 8972, and 8980), and first course of treatment (extent of surgical resection, chemotherapy [yes/no], and radiation [yes/no]). All data used in this analysis came from the CCR. Smoking status is not collected by the cancer registry.

Information on patient race and ethnicity from cancer registry data is primarily based on information abstracted from hospital records and usually self-reported by patients,9 but for a small proportion of patients, race and ethnicity may be based on assumptions or inferences by hospital personnel from other patient data including maiden name, surname, birthplace, or death records. Chinese ethnicity in cancer registry data includes Taiwanese. Because our previous studies have shown that Asian patients in the CCR with unknown registry birthplace are more likely to be US born,10,11 random imputation of nativity (US or foreign born) for patients with unknown birthplace would thus lead to an underestimate of US-born patients. To more accurately impute nativity, we applied a statistical imputation method based on the age at issue of Social Security number (SSN), using a crosswalk file provided by the Social Security Administration that indicates the year of issuance for each SSN sequence. By comparing the age of SSN issue with self-reported birthplace in previously interviewed cancer patients (n = 1,836) and based on maximization of the area under the receiver operating characteristic curve and confirmation with logistic regression modeling, patients receiving an SSN before age 25 years were considered US born, and those who had received an SSN at or after age 25 years were considered foreign born. This age cut point resulted in 84% sensitivity and 80% specificity for assigning foreign-born status across the Asian populations.12 For our study, registry-based birthplace data were available for 93% of the Chinese patients (72% from hospital records and 21% from death certificates). Nativity was imputed using the method described earlier for approximately 7% of patients without registry birthplace information. For the remaining less than 1% of patients for whom SSNs were missing or invalid, we randomly assigned nativity based on the overall sample’s joint distributions of race/ethnicity, sex, and age.

Patient residential address at diagnosis was geocoded and assigned to a census block group, which was then linked to block group–level census measures. Neighborhood SES is a composite index developed previously from principal component analysis, incorporating information on education, occupation, employment, household income, poverty, and rent and house values from the Census 2000 Summary File (for patients diagnosed from 2000 to 2005) and American Community Survey (ACS) 2007 to 2011 data (applied to patients diagnosed from 2006 to 2010 because ACS replaced the decennial census long form after 2000).13,14 Ethnic enclave is defined as a neighborhood that maintains more Asian ethnic mores and norms and/or is ethnically distinct from its surrounding area. It is characterized using a composite index based on the following four census indicator variables: percentage of recent immigrants, percentage of Asian/Pacific Islander (API) language–speaking households that were linguistically isolated, percentage of API language speakers with limited English proficiency, and percentage of API population.15 For patients...
diagnosed during the period from 2000 to 2005, this information was derived from the summary files of Census 2000; for patients diagnosed from 2006 to 2010, we used the Census 2000 data because the component variables are lacking or unreliable in the ACS. Both neighborhood SES and ethnic enclave measures were classified into quintiles based on distributions across California block groups.

**Determination of Follow-Up and Vital Status**

CCR routinely collects information on patients with cancer through active and passive follow-up until confirmation of their death using linkages to data from the diagnosing hospital, state and national vital statistics databases, and other data sources. Underlying causes of death, coded by ICD, 10th edition (used in the CCR for deaths starting in 1999), were obtained from death certificates, and deaths assigned codes C34.0 to C34.9 (ICD, 10th edition) were identified as being a result of lung cancer. Follow-up time for overall mortality was computed as the number of days between the date of diagnosis and the first occurrence of the following dates: date of death, date of last known contact, or end date of follow up (December 31, 2012).

**Statistical Analysis**

To describe overall survival time after lung cancer diagnosis among Chinese Americans in California, we estimated median all-cause survival among patients, overall and by demographic, neighborhood, and tumor factors by sex. To assess the independent influence of patient, tumor, or treatment characteristics on survival and identify possible prognostic factors, we conducted Cox proportional hazards multivariable regression by sex. We tested the proportional hazards assumption based on correlation test of time versus scaled Schoenfeld residuals. The assumption of proportional hazards was violated for chemotherapy, and 95% CIs were computed using stratified Cox models, with stratification on chemotherapy and SEER summary stage, which allowed the baseline hazards within each model to vary by the strata variable(s). All of the independent variables of interest in Table 1 that were statistically significant at $P < 0.10$ in unadjusted models were included in the multivariable model, and covariates included in the final models included year of diagnosis, age, marital status, nativity, neighborhood SES, neighborhood ethnic enclave, urban or rural region, surgery type, radiation, cancer center, and histologic subtype. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). All statistical tests were two-sided with an $\alpha = 0.05$.

**RESULTS**

**Patient Characteristics**

Among Chinese American men in California diagnosed with lung cancer between 2000 and 2010, more than half (55.8%) were age 70 years or older at diagnosis (Table 1). The vast majority (90.5%) were foreign born (66.2% born in China, 6.1% born in Taiwan, and 4.3% born in Hong Kong). Most were married (80.4%), were insured on public insurance (45% on Medicaid, military, or other public insurance), lived in the highest two statewide SES quintiles (23.5% in SES quintile 4 and 26.9% in quintile 5), and lived in the most Asian ethnic neighborhoods (73.9% in quintile 5). A small proportion of patients (11.7%) were reported by an NCI cancer center (includes comprehensive and noncomprehensive designation). Most male patients (60.8%) were diagnosed with distant disease, and nearly half (46.5%) were diagnosed with adenocarcinomas, although a relatively high proportion (23.4%) had NSCLC, not otherwise specified. Twenty-two percent of patients received any surgery, 38.9% received radiation, and 49.3% received chemotherapy.

Among Chinese American female patients, slightly more than half were diagnosed at age 70 years or older, and nearly 90% were foreign born. Relative to Chinese American men, a considerably lower proportion of women (58.4%) were married at diagnosis, whereas nearly one third (30.8%) were previously married (separated, divorced, or widowed). The distributions of primary health insurance, neighborhood SES, and ethnic enclave were similar to those for men. A small proportion of female patients (12.9%) received care at an NCI-designated cancer center. Although a slightly higher proportion of female patients, relative to male patients, were diagnosed at local stage (14.7% vs. 13.6%, respectively), women also had a slightly higher rate of distant disease compared with men (63.3% vs. 60.8%, respectively). Of note, a considerably higher proportion of tumors were adenocarcinomas in women versus men (65.5% vs. 46.5%, respectively), whereas women had lower rates of small-cell and squamous cell histologies.

**Survival**

Table 2 lists the median survival time and adjusted HRs for overall (all-cause) mortality after diagnosis
with lung cancer. Among Chinese American men, the median survival time was 13.0 months (95% CI, 12.0 to 14.2 months) overall, with minor differences between US-born patients (median, 12.5 months; 95% CI, 10.5 to 17.7 months) and foreign-born patients (median, 13.0 months; 95% CI, 12.0 to 14.2 months). In multivariable hazard models, independent associations with better overall survival were found for receiving care at an NCI-designated cancer center and specific histologies including adenocarcinoma and large-cell carcinoma (although the latter association was of borderline statistical significance). Married men had somewhat lower mortality than unmarried men, but this association was not statistically significant (HR, 1.22; 95% CI, 0.98 to 1.51).

Among Chinese American women, overall median survival was higher than for men (18.7 months; 95% CI, 17.1 to 20.6 months) overall. In a multivariable model including both men and women, the HR comparing risk of death among women to men was 0.82 (95% CI, 0.75 to 0.89; data not shown), suggesting that the female survival benefit was not explained by other variables. In the multivariable hazard model, higher mortality was independently associated with never being married, living in lower SES neighborhoods, receiving care from facilities other than NCI-designated cancer centers, and having squamous cell histology (relative to small-cell histology).

**DISCUSSION**

In this analysis of survival among all Chinese American patients with lung cancer in California from 2000 to 2010, we found that social factors such as birthplace, marital status, and SES were important prognostic factors for women but less so for men. Among Chinese American women, median survival varied substantially, by as much as 12 months among those living in the highest and lowest socioeconomic groups. We also found significantly higher survival among Chinese American women compared with Chinese American men, with a 5-month difference in median survival. Although we did not have data on smoking status among the patients with cancer, prior studies in Chinese Americans have shown that the majority of female patients are never-smokers (eg, 70% in one study), whereas the majority of male patients are current or former smokers (eg, 86% in the same study). These major discrepancies in smoking history by sex suggest either that the survival differences we observed may be in part

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of Patients</th>
<th>x² Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong> (n = 2,216)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
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<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>20.2</td>
<td>.01</td>
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<tr>
<td>60-69</td>
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<td>70+</td>
<td>55.8</td>
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<td>.09</td>
</tr>
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<tr>
<td>Foreign born</td>
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<tr>
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<tr>
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<tr>
<td>2</td>
<td>16.9</td>
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</tr>
<tr>
<td>3</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>23.5</td>
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<tr>
<td>5 (high SES)</td>
<td>26.9</td>
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<tr>
<td>Neighborhood ethnic enclave, quintile</td>
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<tr>
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</tr>
<tr>
<td>3</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13.0</td>
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<tr>
<td>5 (most ethnic)</td>
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<tr>
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<tr>
<td>Distant</td>
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<td>Unknown</td>
<td>5.1</td>
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</table>

(Continued on following page)
attributable to our inability to measure smoking as a prognostic factor and/or that lung cancer among smokers is a different, perhaps more aggressive disease entity than lung cancer among never-smokers. The improved survival among women compared with men has been consistently observed and is thought to indicate sex as an independent prognostic factor that may be related to differences in tumor molecular or biologic profile, drug metabolism, and/or DNA damage susceptibility and repair capacity. Social factors are suggested from the results to be potentially important prognostic factors after lung cancer diagnosis, although more so for Chinese women than for Chinese men. Improved survival among patients who are married compared with those who are unmarried has been well documented across multiple cancer sites, other health outcomes, and overall mortality. This association is often suggested to be attributed to greater social support among patients with cancer who are married. However, we do not observe a difference in survival when comparing married patients with those who were previously married (ie, separated, divorced, widowed), suggesting that additional factors may be responsible for the higher mortality among never-married patients that is distinct from previously married patients. The successively higher mortality with lower neighborhood SES suggests mechanisms related to access to health care and other resources. Although we were able to account for health insurance and other tumor and treatment characteristics, we were not able to account for quality of care, detailed treatment, comorbidities, use of palliative care, and other factors that may mediate the association between SES and survival.

We found that among both male and female Chinese American patients, the small proportion of patients receiving care at an NCI-designated cancer center had improved survival compared with those receiving care at non–cancer center facilities. NCI-designated cancer centers are academic centers that are characterized by their cancer research, but with relevance to cancer care, they may also provide more state-of-the-art cancer care, integrated care and tumor boards, and access to clinical trials. We cannot discount that unmeasured sociodemographic or clinical patient characteristics may confound these survival patterns; for example, patients with EGFR mutations may more likely be referred to an NCI cancer center for treatment.

Interestingly, because we included small-cell lung cancers in our analysis, we were able to compare survival for NSCLC histologic subtypes with survival for small-cell lung cancer, and we found that, as expected, mortality for adenocarcinoma was lower than that for small-cell cancer among Chinese American men; however, we did not find a comparable mortality difference among Chinese women. In contrast, we found markedly worse survival for squamous cell lung cancer than small-cell lung cancer among women. These results should be interpreted with caution, however,
Table 2 – Median Survival and Adjusted HRs for All-Cause Mortality Among Chinese Americans Diagnosed With Lung Cancer by Sex, California, 2000 to 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Survival, Months (95% CI)</th>
<th>HR (95% CI)</th>
<th>Median Survival, Months (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>13.0 (12.0 to 14.2)</td>
<td>—</td>
<td>18.7 (17.1 to 20.6)</td>
<td>—</td>
</tr>
<tr>
<td>Nativity</td>
<td></td>
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<tr>
<td>US born</td>
<td>12.5 (10.5 to 17.7)</td>
<td>1.05 (0.89 to 1.25)</td>
<td>23.4 (16.2 to 37.3)</td>
<td>0.92 (0.74 to 1.14)</td>
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<td>Foreign born</td>
<td>13.0 (12.0 to 14.2)</td>
<td>1.0</td>
<td>18.4 (16.7 to 20.4)</td>
<td>1.0</td>
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<td>14.0 (12.7 to 15.3)</td>
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<td>21.8 (18.8 to 24.3)</td>
<td>1.0</td>
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<td>Never married</td>
<td>8.7 (6.6 to 10.8)</td>
<td>1.22 (0.98 to 1.51)</td>
<td>18.7 (13.0 to 23.0)</td>
<td>1.36* (1.11 to 1.66)</td>
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<tr>
<td>Separated/divorced/widowed</td>
<td>10.1 (7.7 to 13.4)</td>
<td>1.10 (0.93 to 1.29)</td>
<td>14.3 (11.9 to 16.5)</td>
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<td>Unknown</td>
<td>12.7 (8.4 to 22.3)</td>
<td>0.82 (0.58 to 1.15)</td>
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<td>10.5 (6.4 to 23.8)</td>
<td>1.10 (0.72 to 1.69)</td>
<td>16.4 (4.2 to 39.5)</td>
<td>1.04 (0.62 to 1.74)</td>
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<tr>
<td>Private</td>
<td>14.7 (12.9 to 16.8)</td>
<td>1.0</td>
<td>23.9 (20.1 to 27.3)</td>
<td>1.0</td>
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<td>Public/Medicaid</td>
<td>11.8 (10.8 to 13.2)</td>
<td>0.94 (0.84 to 1.06)</td>
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<td>Medicare</td>
<td>12.9 (9.1 to 16.9)</td>
<td>0.96 (0.82 to 1.13)</td>
<td>16.2 (11.9 to 18.8)</td>
<td>0.91 (0.73 to 1.12)</td>
</tr>
<tr>
<td>Military</td>
<td>13.7 (4.5 to 26.2)</td>
<td>1.72 (0.91 to 3.23)</td>
<td>—</td>
<td>0.44* (0.31 to 0.62)</td>
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<td>Unknown</td>
<td>12.5 (4.4 to 18.3)</td>
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<td>Neighborhood SES, quintile</td>
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<tr>
<td>1 (low SES)</td>
<td>10.4 (8.3 to 13.3)</td>
<td>1.16 (0.98 to 1.38)</td>
<td>10.9 (8.4 to 15.1)</td>
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<td>2</td>
<td>11.0 (8.9 to 13.2)</td>
<td>1.12 (0.95 to 1.32)</td>
<td>17.3 (13.1 to 21.7)</td>
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<td>3</td>
<td>13.3 (11.2 to 16.9)</td>
<td>1.11 (0.95 to 1.28)</td>
<td>17.3 (13.5 to 23.4)</td>
<td>1.18 (0.94 to 1.41)</td>
</tr>
<tr>
<td>4</td>
<td>13.9 (11.7 to 16.2)</td>
<td>1.06 (0.93 to 1.22)</td>
<td>19.8 (16.7 to 22.9)</td>
<td>0.97 (0.82 to 1.15)</td>
</tr>
<tr>
<td>5 (high SES)</td>
<td>15.2 (12.8 to 17.9)</td>
<td>1.0</td>
<td>23.0 (19.7 to 26.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ethnic enclave, quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (least ethnic)</td>
<td>12.8 (4.8 to 31.9)</td>
<td>1.0</td>
<td>22.4 (5.7 to 72.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>15.7 (11.0 to 25.8)</td>
<td>0.92 (0.59 to 1.47)</td>
<td>19.6 (11.8 to 35.2)</td>
<td>1.03 (0.56 to 1.91)</td>
</tr>
<tr>
<td>3</td>
<td>14.1 (11.3 to 17.1)</td>
<td>1.14 (0.77 to 1.71)</td>
<td>19.0 (15.2 to 24.3)</td>
<td>1.12 (0.63 to 2.00)</td>
</tr>
<tr>
<td>4</td>
<td>14.3 (11.3 to 19.6)</td>
<td>1.11 (0.75 to 1.63)</td>
<td>17.9 (14.7 to 23.7)</td>
<td>1.22 (0.69 to 2.15)</td>
</tr>
<tr>
<td>5 (most ethnic)</td>
<td>12.6 (11.3 to 14.0)</td>
<td>1.13 (0.78 to 1.64)</td>
<td>18.2 (16.3 to 20.5)</td>
<td>1.01 (0.58 to 1.77)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10.5 (5.9 to 27.5)</td>
<td>2.42 (0.91 to 6.43)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Care at NCI-designated cancer center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22.4 (18.3 to 25.9)</td>
<td>0.85* (0.73 to 0.99)</td>
<td>34.2 (22.8 to 39.8)</td>
<td>0.80* (0.67 to 0.96)</td>
</tr>
<tr>
<td>No</td>
<td>12.1 (11.2 to 13.1)</td>
<td>1.0</td>
<td>17.6 (16.0 to 19.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>64.0 (44.5 to 88.6)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Regional</td>
<td>27.1 (23.8 to 32.1)</td>
<td>52.3 (42.0 to 59.8)</td>
<td>11.5 (10.2 to 12.9)</td>
<td>16.0 (13.3 to 26.0)</td>
</tr>
<tr>
<td>Distant</td>
<td>8.0 (7.1 to 8.7)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unknown</td>
<td>16.2 (12.7 to 21.3)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>9.7 (8.0 to 11.0)</td>
<td>1.0</td>
<td>12.0 (9.1 to 16.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>13.5 (11.4 to 15.3)</td>
<td>0.91 (0.74 to 1.11)</td>
<td>10.6 (6.0 to 14.2)</td>
<td>1.60* (1.04 to 2.48)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19.2 (16.7 to 21.2)</td>
<td>0.78* (0.65 to 0.92)</td>
<td>25.0 (22.5 to 28.9)</td>
<td>1.00 (0.69 to 1.45)</td>
</tr>
</tbody>
</table>

(Continued on following page)
considering the high proportion of tumors classified here as NSCLC, not otherwise specified (23% among men and 20% among women). The proportion of NSCLCs diagnosed with histology not otherwise specified has steadily declined over time\(^\text{19}\) as a result of the availability of targeted therapies for specific lung cancer histologies; the majority of these are likely adenocarcinomas.

The primary limitation in our study involves the absence of cancer registry data on potentially important prognostic factors for lung cancer, including specific treatments, tumor genetic markers (such as \(\text{EGFR}\) and \(\text{ALK}\) mutation status), smoking history, and comorbid conditions that affect treatment decisions and survival time. Sex differences in \(\text{EGFR}\) mutations may well explain the survival differences between Chinese men and women; however, it is unlikely that \(\text{EGFR}\) mutations would confound the associations between marital status and SES with survival. Although it is possible that our study results are biased as a result of misclassification of race or ethnicity, prior research shows minimal misclassification of Chinese ethnicity in cancer registry data.\(^\text{20}\)

In summary, despite generally poor survival for lung cancer, our study did identify several non-clinical factors associated with lung cancer survival among Chinese Americans, including sex, marital status, and SES. Focusing on factors that differ between female married and unmarried patients (eg, greater social and/or instrumental support or improved economic resources) and patients who live in low versus high SES communities (eg, greater socioeconomic resources, ability to access and pay for treatments), as well as characteristics unique to NCI-designated cancer centers (eg, presence of tumor boards, access to clinical trials), may help to identify potential strategies for improving the length and quality of survival for Chinese Americans after diagnosis of lung cancer.

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**Table 2** – Median Survival and Adjusted HRs for All-Cause Mortality Among Chinese Americans Diagnosed With Lung Cancer by Sex, California, 2000 to 2010 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Survival, Months (95% CI)</th>
<th>HR (95% CI)</th>
<th>Median Survival, Months (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large cell</td>
<td>11.8 (8.4 to 19.2)</td>
<td>0.76 (0.55 to 1.04)</td>
<td>12.7 (9.6 to 19.9)</td>
<td>0.98 (0.60 to 1.58)</td>
</tr>
<tr>
<td>NSCLC, NOS</td>
<td>8.9 (7.4 to 10.6)</td>
<td>0.92 (0.76 to 1.10)</td>
<td>11.4 (8.7 to 13.1)</td>
<td>1.21 (0.82 to 1.78)</td>
</tr>
<tr>
<td>Other lung cancer</td>
<td>12.4 (8.9 to 17.6)</td>
<td>0.60 (0.37 to 0.97)</td>
<td>10.9 (5.7 to 23.9)</td>
<td>0.97 (0.47 to 2.01)</td>
</tr>
</tbody>
</table>

NOTE. HRs computed via multivariable Cox proportional hazards models stratified by SEER summary stage and chemotherapy, and adjusted for all factors shown in the table in addition to age at diagnosis, year of diagnosis, urbanicity, surgery type, and radiation. —, Not estimated.

Abbreviations: HR, hazard ratio; NCI, National Cancer Institute; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; SES, socioeconomic status.

\(*)\text{Statistically significant at } P < .05.\)

**AUTHOR CONTRIBUTIONS**

**Conception and design:** Scarlett Lin Gomez, Shih-Wen Lin, Margaret McCusker, Christina A. Clarke

**Financial support:** Scarlett Lin Gomez, Shih-Wen Lin, Margaret McCusker, Christina A. Clarke

**Administrative support:** Scarlett Lin Gomez

**Provision of study materials or patients:** Scarlett Lin Gomez, Christina A. Clarke

**Collection and assembly of data:** Scarlett Lin Gomez, Juan Yang, Christina A. Clarke

**Data analysis and interpretation:** Scarlett Lin Gomez, Juan Yang, Alan Sandler, Manali Patel, Iona Cheng, Heather A. Wakelee, Christina A. Clarke

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Lung Cancer Survival Among Chinese Americans, 2000 to 2010**

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Scarlett Lin Gomez

**Employment:** Eurofin (I), Boehringer Ingelheim (I)

**Stock or Other Ownership:** Amgen (I)

**Research Funding:** Genentech

**Travel, Accommodations, Expenses:** Genentech

Juan Yang

No relationship to disclose
Shih-Wen Lin
Employment: Genentech
Stock or Other Ownership: Genentech
Travel, Accommodations, Expenses: Genentech

Margaret McCusker
Employment: Genentech
Stock or Other Ownership: Roche
Travel, Accommodations, Expenses: Genentech

Alan Sandler
Employment: Genentech
Stock or Other Ownership: Roche

Manali Patel
No relationship to disclose

Iona Cheng
No relationship to disclose

Heather A. Wakelee
Consulting or Advisory Role: Peregrine Pharmaceuticals, Acea, Pfizer
Research Funding: Genentech, Pfizer, Xcovery, Celgene, Bristol-Myers Squibb, Novartis, Clovis, Gilead Sciences, AstraZeneca/MedImmune, Exelixis
Travel, Accommodations, Expenses: Pfizer, Genentech, Clovis Oncology, Acea

Christina A. Clarke
Leadership: Healthline
Stock or Other Ownership: Healthline, Tonic Health Solutions
Research Funding: Genentech
Travel, Accommodations, Expenses: Genentech

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REFERENCES


Increasing Access to Oral Anticancer Medicines in Middle-Income Countries: A Case Study of Private Health Insurance Coverage in Brazil

The World Health Organization estimates that approximately 60% of the world’s new annual cancer cases occur in Asia, Africa, and Central and South America, and that 70% of cancer deaths occur in these regions. Although oral chemotherapy is a promising intervention for cancer treatment, given its high cost, it is usually unavailable in middle-income countries. In 2013, after strong lobbying from civil society, Brazil’s Congress passed legislation mandating that all private health insurance companies provide access to oral antineoplastic treatment. The decision to scale up the provision of oral chemotherapy was a watershed event in the regulation of private health insurance in Brazil. Until then, private insurers, which cover 25% of the population, were exempted from the provision of pharmaceutical drugs for home care treatments. This article explores the political process involved in regulating the provision of oral chemotherapy medicines by private health insurers. Elements of this successful advocacy case included investment in strategic communication, specialized knowledge of regulatory policy, and the ability to act via democratic channels of political representation. In turn, the receptiveness of government branches such as the Congress and regulating bodies, as well as the Cancer Awareness Month campaign, opened a window of opportunity. However, prospects for expanded access to such medicines in the public health system are bleak in the short term because of the ongoing political and economic crisis.

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INTRODUCTION

Cancer is a leading cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012. More than 60% of the world’s total new annual cases occur in Asia, Africa, and Central and South America, and these areas account for 70% of the world’s cancer deaths. Since the 1990s, oncology treatment has advanced from intravenous chemotherapy to include only orally administered antineoplastic agents, which are more convenient to administer and often have fewer adverse effects than do their older parenteral counterparts. Oral drugs may also lead to lower costs through savings related to decreased hospitalization times, for instance, and better quality of life. Usually, newer technologies such as oral antineoplastics put pressure on health care budgets and are incorporated infrequently by health systems in middle-income countries because of their added direct cost.

Brazil is well known for offering free and universal access to antiretroviral drugs, which are delivered exclusively through its public dispensing units. However, far less is known and has been published about the country’s experience with other, noncommunicable diseases that require high-cost treatments, such as cancer. Unlike drugs for AIDS, cancer medicines have been provided within the public health care system, purchased out of pocket at pharmacies by individuals and families, or purchased/reimbursed by private insurance companies. This article focuses on the recent developments in oral anticancer drug coverage through the supplemental (private) health insurance system.

After a new parenterally administered anticancer drug is approved by ANVISA, the Brazilian regulatory agency, it gains coverage automatically in the private health care system after a price is set by an interministerial commission. Historically, however, oral drugs were not covered. In 2013, after
strong lobbying from civil society, Congress approved legislation mandating that all private health insurance companies provide access to oral antineoplastic treatment (Brazilian Federation Law 12880/2013). At the same time, the National Regulatory Agency for Private Health Insurance (ANS) issued a resolution mandating private health insurance companies to cover 37 orally administered oncology drugs for home cancer treatment (ANS Resolution 388/2013). Between January 2013 and December 2014, the number of requests for oral antineoplastic treatment increased by almost 90% in the private health insurance sector.7

The decision to scale up the provision of oral chemotherapy was a watershed event in the regulation of private health insurance in Brazil, which was until then exempted from the provision of pharmaceuticals drugs for home care treatment. In addition, it is particularly important to highlight that this case builds evidence for the role of civil society in advocating access to cancer treatment within a middle-income country. Although much has been said regarding the relevance of civil groups to cancer policy advocacy,8 we know little about the processes by which they affected change in regulatory policies. This article aims to explore the political process involved in regulating the provision of oral chemotherapy medicines by private health insurance companies for cancer home care treatment in Brazil.

BACKGROUND

The Brazilian National Cancer Institute estimates that there will be 576,000 new cases of cancer, including nonmelanoma skin cancer, in the country in 2015. Among men, prostate cancer represents 22.8% of incident cases, whereas among women, breast cancer represents 20.8% of all cases.9 Breast cancer has been one of the leading causes of death from cancer among Brazilian women, whereas lung and prostate cancer have been among the leading causes of death in men.10

Oncology treatment in public health care in Brazil is provided by 278 accredited establishments.11 It is the responsibility of the reference service to purchase and provide chemotherapy, which is reimbursed by the state government with resources transferred from the Ministry of Health and funded through general taxation.12 Between 2006 and 2011, a commission was established in the Ministry of Health to assess the inclusion of new technologies into the National Health Service (SUS); before that, health technology assessment was not commonly performed in Brazil. During this period, only two oral antineoplastic medicines (nilotinib and dasatinib) were incorporated into the SUS (public list).

Parallel to the SUS, which covers all Brazilian citizens and foreigners who are physically present in the country (including illegal aliens), private health insurance companies are also responsible for providing oncology treatment to their clients. Although Brazil has one of the largest public health systems in the world, approximately 25% of the population is also enrolled in private health insurance.13 The majority of private health insurance plans are collective plans (approximately 80%) obtained through work or cooperatives, and a small and declining percentage are individual plans (approximately 20%). The Private Health Insurance Act (Law 9656/1998) regulates private insurance in Brazil. According to this act, insurance companies are required to cover only medicines used during periods of hospitalization and during ambulatory visits (article 12) and not during home care treatment (article 10). Therefore, oral antineoplastic medicines for home care were excluded from the list of procedures covered by private insurance. These two scenarios led to an increase in the number of lawsuits over access to cancer medicines.14

The 2013 National Health Survey, a household-based nationwide study, suggested that 49 million people are covered by private health insurance in Brazil. Among these, approximately 17% do not pay for their medicines because they have free access to medicines through their governmental programs or employer’s insurance program; 60.9% had to pay for medications out of pocket, 16.1% paid for a percentage of the medicines needed, and 6% were not able to afford the medicines prescribed. As such, it is clear that among those people who hold private health insurance, a large proportion pay for 100% of their medicines themselves.

In 2011, three parallel events paved the way for the inclusion of oral cancer treatments in private health insurance coverage; they are divided here for clarity. Table 1 provides a chronologic list of these events.

Revision of the Minimal List of Procedures Covered by Private Health Insurance

Every 2 years, the ANS revises the minimal list of procedures with mandated coverage by private health insurance companies, and this process is open to different segments of society through public consultation. In May 2011, the regulatory
**Table 1 – List of Events Preceding Approval of Law 12.880/2013**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Publishing of the ANS Regulatory Agenda for 2011-2012</td>
<td>Inclusion of the question of pharmaceutical assistance as a core issue for discussion in the ANS</td>
</tr>
<tr>
<td>Apr 15, 2011 to May 21, 2011</td>
<td>ANS Public Consultation No. 40</td>
<td>Different segments of society given the opportunity to comment on the revision of the list of procedures covered by private health insurance</td>
</tr>
<tr>
<td>May 2, 2011 to May 20, 2011</td>
<td>Instituto Oncoguia mobilizes other civil society organizations and begins a mass media campaign for the inclusion of oral chemotherapy in private health insurance plans</td>
<td>Signatures supporting the campaign submitted to the ANS, distribution of folders informing the population about oral chemotherapy</td>
</tr>
<tr>
<td>May 11, 2011</td>
<td>Seminar in Congress to discuss the rights of people living with cancer</td>
<td>The Instituto Oncoguia and the ANS invited to give speeches</td>
</tr>
<tr>
<td>Jun 22, 2011</td>
<td>Presentation of Bill 352/2011</td>
<td>Senator Ana Amélia presents Bill 325/2011 to Senate</td>
</tr>
<tr>
<td>Aug 1, 2011</td>
<td>ANS Resolution 262</td>
<td>Updated list of procedures mandatory for inclusion in health insurance plans; oral chemotherapy is not among them</td>
</tr>
<tr>
<td>Aug 18, 2011</td>
<td>Oncoguia meets with the minister of health</td>
<td>The minister endorses the campaign on oral chemotherapy, which receives inclusion in the ANS list of procedures</td>
</tr>
<tr>
<td>Sep 29, 2011</td>
<td>First meeting of the WGPA at the ANS</td>
<td>Presentation of successful cases of pharmaceutical care packages offered by nonprofit, private insurance companies</td>
</tr>
<tr>
<td>Dec 15, 2011</td>
<td>Congress Hearing on Bill 352/2011</td>
<td>Different stakeholders express their positions</td>
</tr>
<tr>
<td>Mar 27, 2012</td>
<td>Second meeting of the WGPA at the ANS</td>
<td>One of the directors of the ANS, Maurício Ceschin, opens the meeting stating the relevance of this issue; different stakeholders express their positions</td>
</tr>
<tr>
<td>Apr 28, 2012</td>
<td>Senate approval of Bill 352/2011</td>
<td>Bill 352/2011 is submitted to the Chamber of Deputies</td>
</tr>
<tr>
<td>Apr 30, 2012</td>
<td>Third meeting of the WGPA at the ANS</td>
<td>Discussions to provide input regarding a resolution to regulate a voluntary pharmaceutical care package that would include oral chemotherapy in private health insurance plans</td>
</tr>
<tr>
<td>Sep 4, 2012 to Oct 6, 2012</td>
<td>ANS Public Consultation No. 49</td>
<td>Different segments of society invited to comment on the regulation of the pharmaceutical care package</td>
</tr>
<tr>
<td>Oct 30, 2012</td>
<td>Resolution 310</td>
<td>Regulation of voluntary pharmaceutical care packages offered by private health insurance companies</td>
</tr>
<tr>
<td>Nov 30, 2012</td>
<td>Fourth meeting of the WGPA at the ANS</td>
<td>Presentation of ANS Resolution 310</td>
</tr>
<tr>
<td>Aug 27, 2013</td>
<td>Bill 3.998/2012* is approved by the CCJC of the Chamber of Deputies</td>
<td>The CCJC acknowledges the importance of the mobilization of civil society in the approval of this proposal</td>
</tr>
<tr>
<td>Oct 21, 2013</td>
<td>The ANS issues Resolution 338</td>
<td>Update to list of procedures covered by private insurance plans; this time, the list includes oral chemotherapy</td>
</tr>
<tr>
<td>Oct 22, 2013</td>
<td>Senate approves the amendment proposed by the Chamber of Deputies</td>
<td>Legislation submitted to President Dilma Rousseff for ratification</td>
</tr>
<tr>
<td>Nov 12, 2013</td>
<td>President Dilma Rousseff enacts Law 12.880/2013</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANS, National Regulatory Agency for Private Health Insurance; CCJC, Commission on Constitution, Justice and Citizenship; WGPA, Working Group on Pharmaceutical Assistance.

*Bill 352/2011 and 3.998/2012 are the same. The bill number was modified once submitted to Congress.
A group called Instituto Oncoguia, which represents people living with cancer, saw this as an opportunity to submit a much-sought-after claim for these patients, that is, that insurance companies should cover the cost of oral antineoplastic medicines. A number of patients reported to Oncoguia that their insurance plans did not cover oral antineoplastic drugs and that they were also denied access to these medicines in the public sector, forcing them to file lawsuits to obtain treatment. The institute, a nonprofit organization, was formed in 2009 by health professionals working with people living with cancer in the state of São Paulo. This civil society organization is sponsored by pharmaceutical industries and other private sector companies such as Google Grants, Asics, and others. In addition, the American Cancer Society has provided training on strategic political advocacy and technical assistance to cancer nongovernmental organizations (NGOs), including Oncoguia and the Brazilian Federation of Philanthropic Breast Health Institutions.15,16

Between May 2 and May 20, 2011, the Instituto Oncoguia launched a large mass media campaign called the “Campaign for Inclusion of Oral Chemo” to put pressure on the government to include oral antineoplastic medicines on the mandated list of ANS procedures. For the duration of this campaign, Oncoguia coordinated a group of more than 17 associations including medical and professional societies and AIDS and hepatitis NGOs that were sympathetic to this demand, as well as specific groups of patients with cancer, such as those representing individuals with lymphoma and others. According to their records, the social media campaign received more than 900 citations, 2,500 informative folders were distributed to inform the population about their demands, and a petition was submitted to the ANS after collecting 18,000 signatures. Despite these efforts, the ANS initially denied their claim for the inclusion of oral chemotherapy drugs in the new list of procedures covered by insurance (Resolution 262/2011). The ANS argued that this inclusion was not allowed under the Private Health Insurance Act.16a However, after this decision, the agency created a Working Group of Pharmaceutical Assistance (WGPA) to discuss avenues for pharmaceutical care within private health insurance in Brazil. Instituto Oncoguia not only participated in this working group, but also coordinated, in tandem with a group of other NGOs, a campaign in Congress to amend the Private Health Insurance Act, which we discuss in the next section.

Working Group of Pharmaceutical Assistance

The ANS noted that the theme of pharmaceutical care was a main concern of the “Regulatory Agenda for 2011/2012,” which is the planning instrument that set the priority goals for the agency in the biennium. As a consequence, in September 2011, the WGPA was created that included representation from private insurance companies, consumers, health professionals, and regulators. The motivation for the creation of the WGPA was twofold. First, the agency was aware that a large proportion of consumers were paying out of pocket for medicines not covered by insurance plans. Second, the ANS was concerned that the regulatory framework for private health insurance in Brazil was encouraging a health care model strongly focused on hospital and ambulatory care, with little focus on home care coverage.17

During the first WGPA meeting, the ANS invited some private health insurance companies that provided a pharmaceutical care package, in addition to their regular coverage, to share their experiences. However, these were nonprofit health care plans (ie, self-managed by the company or a third party responsible for the social benefit),18 and therefore, other insurance companies questioned the viability of applying their experience to for-profit insurance plan models.

One of the opponents to the idea of including pharmaceutical care coverage in insurance plans was the Institute of Studies of Supplementary Health Care, a think tank that produces analyses for the sector, which prepared a technical note discussing cases of pharmaceutical coverage by private health insurance in several countries.19 They argued, mostly on the basis of the United States Medicare model, that there was no evidence to suggest that pharmaceutical coverage reduces health care expenditure, but that in contrast, there was evidence to indicate that new medicines increase cost and that there is an increased use of medicines among healthy people after enrolling in such insurance coverage (ie, it would increase moral hazard). Although their study did not provide a comprehensive discussion of the methodologic procedures necessary to draw such conclusions, it was widely used by private insurance representatives as evidence against the idea of regulating the inclusion of pharmaceuticals in insurance plans (personal communication,
October 24, 2014). However, civil society groups such as the Otimismo Group, which represents patients living with viral hepatitis B and C, and Oncoguia also participated in the WGPA discussions. These civil society groups demanded that the ANS request a more effective response from private health insurance companies regarding the provision of pharmaceutical care.

Given the strong conflicting positions, the coordinator of the WGPA consulted the attorney general for the ANS and requested a legal opinion on this matter. The interpretation was that because article 10 of the Private Health Insurance Regulatory Act exempted private health insurances from covering medicines for home care treatment, the ANS would be entitled to regulate only complementary, voluntary packages of pharmaceutical care.20

The WGPA was therefore able to discuss a draft resolution for pharmaceutical care packages that could be offered as additional, voluntary products to willing private health insurance plans. A draft resolution was then submitted for public consultation (Public Consultation No. 49/2012). The final document, approved in 2012 (Resolution 310/2012), established that pharmaceutical care is a voluntary and supplementary product to health insurance plans, similar to products such as air ambulance services. Therefore, civil society groups were once more left with just one avenue for action: the Private Health Insurance Act would have to be amended to allow access to home pharmaceutical care in private insurance plans. This would require a political debate in Congress.

**Legislative Actions to Amend the Private Health Insurance Act**

Parallel to the discussions at the ANS, Oncoguia, together with other civil society organizations, coordinated a campaign to amend the Private Health Insurance Act in Congress. The first step was taken in May 2011 after a meeting with Senator Ana Amélia Lemos (Progressive Party, Rio Grande do Sul State), who organized a seminar to discuss the rights of people living with cancer. During this event, a main discussion point was the denied coverage of oral antineoplastics by private health insurance providers.20 As a consequence, Senator Ana Amélia, sensitive to issues related to cancer control, tabled a bill in Congress (Bill 352/2011) that would mandate that all private health insurance plans include oral cancer treatment as a mandatory procedure. Oncoguia also appealed to the minister of health for support of Bill 352/2011.21

In December 2011, a public hearing was held in Congress to discuss the different positions around this bill.22 Several stakeholders took part, including representatives from the ANS; representatives of a reference cancer hospital; a representative from the Brazilian Association of Group Medicine (Abramge); a representative from the Brazilian Medical Association; and Oncoguia, representing the interests of civil society. During this event, Abramge, with Arlindo de Almeida representing private health insurance companies, argued that there is a lack of governmental funds to support cancer care treatment and that oral antineoplastic medicines should be the responsibility of the federal government. Abramge also mentioned that there was a reorganization of private health insurance companies, with more than 1,100 companies exiting the market since the creation of the ANS in 1998. Finally, he stated that annual margins for the private health insurance sector were less than 1%. The arguments used by private insurance companies to emphasize the cost of providing oral antineoplastics, and the effects of the bill on the private insurance sector, were not well received in Congress.22 On the other hand, the argument for supporting the needs of people living with cancer resonated more widely in the Senate and Chamber of Deputies (the two houses that form the Brazilian Congress). Access to cancer treatment is an argument that is hard to counter when elections are around the corner.

Records of Oncoguia’s and its partners’ activities are publicly available online22a and suggest that these groups constantly lobbied members of the commissions responsible for the bill. They also identified other civil society organizations that could help them in the advocacy process. For instance, in August 2013, the bill was approved by the Commission of the Constitution, Justice and Citizenship, which received more than 250 messages of support for this proposal.22b The final step in approving the legislation was the endorsement of the Senate. The Brazilian Congress joined the international Breast Cancer Awareness Month campaign in October and, as a consequence, the president of the Senate agreed to make all bills related to cancer care a voting priority. In this context, the bill was finally approved. In November 2013, President Dilma Rousseff enacted Law 12.880/2013.

Interestingly, a day before the Senate approved the bill, the ANS, foreseeing the decision, also decided to include 37 oral antineoplastic drugs in the new revision of the list of procedures covered by
insurance plans (Resolution 338/2013). Together, the ANS resolution and Law 12.880/2013 ensure that all consumers of private health insurance in Brazil are eligible to receive the 37 oral antineoplastic medicines, if needed.

Using as an example the experience of Brazil in covering oral antineoplastic medicines through private health insurance plans, it is possible to draw some conclusions regarding regulatory policy.

Civil Society Advocacy on Pharmaceutical Care

We know a great deal about the role of civil society in advocating for antiretroviral medicines in Brazil and other developing countries and about the necessity of empowering cancer advocacy groups in developing countries. Findings from this study suggest that civil society, coordinated by the Instituto Oncoguia, played a crucial role in Brazil’s regulation of oral antineoplastic coverage under private health insurance. On the other hand, there were several institutional channels, including public consultations, congressional hearings, and a meeting with the minister of health, through which these advocacy groups could voice their concerns. The process described here suggests a democratic, pluralist process of policy making.

Persuading Decision Makers

Studies of HIV/AIDS advocacy have long called attention to the policy frame and strategic use of ideas, that is, the use of normative values and information to influence policy debates. In the process discussed here, medicines can save lives or extend the lives of people living with cancer, arguments that are persuasive and hard to deconstruct. Therefore, the second explanatory element for the successful campaign on oral chemotherapy was the ability of civil society to frame their demands and publicize their position in different political arenas.

Policy Context

The third important element in the case of oral antineoplastic medicines refers to the context in which this proposal was formulated. Scholars of policy argue that it is crucial to understand the historical circumstances through which public policies are designed and implemented. The ANS was sensitive to the discussion of pharmaceutical care presented by private health insurance companies. Although the initial outcome was unsatisfactory because it proposed voluntary coverage only, the ANS ended up including oral antineoplastic treatment in the minimum coverage list of procedures. In addition, given the strong support of civil society, Congress was mobilized to endorse an amendment in the Private Health Insurance Act. Finally, the recognition and marking of Breast Cancer Awareness Month created a window of opportunity to finally approve the bill in Congress.

Few studies have detailed the consequences of this change in regulatory policy on the private health insurance sector and on the treatment of people living with cancer; however, the available data suggest an important increase in the percentage of requests for oral chemotherapy in private health insurance between 2013 and 2014 (approximately 90%), and the authors are currently working with data from Intercontinental Marketing Services Health to quantify the increase to access that has occurred since January 2014 when the coverage became official. In the current context of political and economic crisis, it is unlikely that such innovations could be incorporated into Brazil’s public health system, already affected by dramatic cuts of 70 billion reais (nearly 20 billion dollars) in 2015. In any case, the successful reform of private health insurance plans may pave the way for future changes in the public sphere.

In summary, this Brazil case study suggests that civil society played a crucial role in the regulatory process. The main elements leading to this successful intervention were (1) the investment in strategic communication, (2) the possession of specialized knowledge of regulatory policy, and (3) the ability to act via democratic channels of political representation, such as public consultations. In turn, the receptiveness of government branches such as Congress and the ANS, and the Cancer Awareness Month campaign, opened a window of opportunity for the change desired by these groups. The impact of civil society was less a result of their material resources and more a result of their capacity to persuade decision makers, despite the strong and resourceful lobbying of the private health insurance sector.

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Collection and assembly of data: Elize Massard da Fonseca, Francisco Inácio Bastos
Data analysis and interpretation: All authors
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Increasing Access to Oral Anticancer Medicines in Middle-Income Countries: A Case Study of Private Health Insurance Coverage in Brazil

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Elize Massard da Fonseca
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Francisco Inácio Bastos
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Gilberto Lopes
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Expert Testimony: Sanofi
Board Member: Instituto Oncoguia scientific board

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Nicola M. Zetola
Surbhi Grover
Chawangwa Modongo
Sebathu P. Chiyapo
Memory
Nsingo-Bvochora
Mohan
Narasimhamurthy
Lile L. Lin
Joseph Jarvis
Sanghyuk S. Shin
Erle Robertson

Cervical cancer is the leading cause of cancer-related mortality in the developing world, where HIV and Mycobacterium tuberculosis (TB) infection are also endemic. HIV infection is independently associated with increased morbidity and mortality among women with cervical cancer. TB is believed to increase the risk of malignancies and could cause chronic inflammation in the gynecologic tract. However, the relationship between cervical cancer and TB in settings hyperendemic for HIV is unknown. We found that 18 (10%) of a cohort of 180 women with cervical cancer in Botswana had a history of TB disease. Age and HIV infection were also associated with a history of TB disease. Our data show that prior TB disease is highly prevalent among patients with cervical cancer infected with HIV. The coexistence of cervical cancer, HIV infection, and prior TB infection might be higher than expected in the general population. Prospective studies are needed to better determine the impact of the collision of these three world health epidemics.

INTRODUCTION

Cervical cancer is the third most common malignancy in women worldwide and the leading cause of cancer-related death for women in developing countries. Globally, it is estimated that approximately half a million women are diagnosed with cervical cancer every year, and approximately 275,000 women die of the disease, 85% of whom live in low- and middle-income countries.1 In Botswana, cervical cancer is the most common gynecologic cancer and the leading cause of cancer death.2,3

HIV infection accelerates the progression toward cervical cancer and likely is associated with worse clinical outcomes.4 In Botswana, 60% of patients diagnosed with cervical cancer are also infected with HIV.2,5 With cervical cancer rates rising in developing countries where HIV is endemic, identifying and understanding the factors leading to increased morbidity and mortality in these populations should be a priority.6

The devastating impact of the colliding HIV and tuberculosis (TB) pandemics in resource-limited settings has been long recognized.7 HIV infection is one of the most important risk factors for progression to active TB disease. Furthermore, TB is the number one killer of people living with HIV in the world.5 Importantly, the impact of these pandemics is more severe in countries with more challenging health care systems, where TB and HIV are less controlled, and patients may have more advanced disease states compared with the developed world. Botswana has one of the highest TB prevalence rates in the world, and it is estimated that 60% to 75% of people diagnosed with TB are coinfected with HIV.8

An association between malignancies and TB was previously established.9 TB has been implicated in the pathogenesis of malignancies and may interfere with their diagnosis. TB and cancer frequently coexist, and the relative immunosuppression caused by cancer or its treatment may lead to reactivation of latent TB infections, leading to increased morbidity and mortality.9 However, data on the association between cervical cancer and TB are scarce.10

Despite the magnitude of the cervical cancer, HIV, and TB epidemics coexisting in many resource-limited settings, their associations and the potential interactions among all three pandemics have not been documented previously, although, as previously mentioned, those between HIV and cervical cancer as well as between HIV and TB have been explored. However, there is limited information on the impact of TB or the
combination of TB and HIV on cervical carcinomas. In this study, we examined the association between cervical cancer and a prior history of TB by HIV serostatus in a prospective cohort of patients with cervical cancer in Botswana.

METHODS

Cervical cancer diagnosis and treatment in Botswana is centralized at Princess Marina Hospital, the largest referral hospital in the country, located in the capital, Gaborone. Approximately 95% of all patients diagnosed with any cancer in public hospitals from all over the country are referred there for confirmation of diagnosis and treatment. In this study, we enrolled consecutive patients referred to Princess Marina Hospital for the treatment of cervical cancer between July 2013 and January 2015. We collected demographic characteristics and cancer- and TB-specific information prospectively through patient interviews and medical record reviews. All data were collected before cancer treatment initiation. Prior TB disease was defined as an episode of clinically or microbiologically diagnosed TB requiring initiation of TB treatment at any point in the past. HIV testing was performed on all patients in accordance with Botswana’s national guidelines. Radiologic information was unavailable in most cases, and it was not analyzed in this study.

We first described the characteristics of patients with cervical cancer when stratified by history of active TB and cervical cancer. Associations were determined using $\chi^2$, $t$ test, and Mann-Whitney testing as appropriate. A logistical regression model was developed to describe correlates of prior TB disease. Variables for the model were identified a priori on the basis of their conceptual importance and included age at diagnosis of cervical cancer, age of first sexual encounter, smoking history, and presence of HIV infection. A separate model was developed to determine the association of CD4 cell count categories using HIV-negative patients as referents. Odds ratios and 95% CI were calculated. Data processing and analyses were performed using Stata software (STATA, College Station, TX). This study was approved by the institutional review boards at the University of Pennsylvania, University of Botswana, and Botswana Ministry of Health. All patients provided informed consent.

RESULTS

We enrolled 180 women during the study period, of whom 117 (65%) were infected with HIV at the time of their cervical cancer diagnosis. Overall, 18 (10%) patients with cervical cancer had a history of TB disease, and 16 (89%) of them were coinfected with HIV. All patients with TB were treated for their disease. All HIV-positive patients were either already receiving antiretroviral treatment or had started on antiretroviral treatment at the time of cancer diagnosis. The main demographic and clinical characteristics of the sample stratified by history of TB infection are listed in Table 1. Our bivariate analyses showed a significantly higher prevalence of HIV infection among patients with cervical cancer with a history of TB compared with those without a history of TB (16 [89.8%] of 18 patients vs 101 [62.3%] of 162 patients; $P = .02$). As listed in Table 2, this difference remained significant in multivariable analysis (adjusted odds ratio [AOR], 21.5; 95% CI, 2.16 to 214.52; $P < .01$). Increasing age was also found to be significantly associated with prior TB disease after accounting for confounders (AOR, 1.1; 95% CI, 1.01 to 1.11; $P = .02$). In a separate multivariable model, we found that CD4 counts less than 350 cells/µL (AOR, 57.3; 95% CI, 4.44 to 740.8) and greater than 500 cells/µm$^3$ (AOR, 39.0; 95% CI, 3.15 to 483.89) were associated with prior TB disease compared with no HIV infection.

DISCUSSION

In this study, we found that prior TB disease was common in our sample of patients with cervical cancer in Botswana. HIV infection was also highly prevalent among patients with cervical cancer who had TB disease before their diagnosis of cervical cancer. Our findings are not surprising, given the well-known association between HIV and TB. Nevertheless, they highlight an underappreciated overlap of three of the most devastating epidemics in developing countries: cervical cancer, HIV, and TB.

Our study design does not allow any inference regarding the role of TB in the causal pathway of cervical cancer, the temporal nature of events, or the presence of interactions between TB, HIV, and cervical cancer that may alter the natural course of any of those diseases. However, our results indicate that the coexistence of prior TB disease, HIV infection, and cervical cancer is common, suggesting that potential interactions between two or more of those conditions might be common as well. Disseminated (gynecologic) TB has the potential to lead to delays in cervical cancer diagnosis and an increase in morbidity and mortality during cancer treatment. Conversely, cervical cancer diagnosis may delay the diagnosis and treatment initiation of coexisting TB. Although TB has
not been associated with the development of cervical cancer, chronic TB infection and inflammation in the gynecologic tract is an important cause of infertility in the developing world. Thus, the chronic inflammation due to chronic gynecologic TB infection might be a contributing factor in the progression toward cervical cancer.\textsuperscript{11,13,14} HIV infection is associated with a higher incidence, as well as increased morbidity and mortality, of both TB and cervical cancer, independently. Whether HIV infection modifies the relationship between TB and cervical cancer remains to be determined.

We acknowledge the limitations of our study. Multiple sources of bias could have confounded our findings. Our study was performed on a convenience sample of all consecutive patients with cervical cancer referred to the only cancer treatment center in Botswana, and we did not have a comparison group from the general population. Therefore, we are unable to determine whether the overall prevalence of prior TB infection was higher than what would be expected from the general population with or without stratifying it by HIV status. Our inability to prospectively determine the extent of active TB disease after cancer diagnosis severely limits any inference regarding the true burden of TB in our population. Prospective TB-attributable morbidity and mortality data are highly needed.

Despite these limitations, we believe that these results highlight the critical need to better understand the imminent collision of three of the most important pandemics of our time: HIV, TB, and cancer. Although data remain scant, HIV is a leading factor increasing the incidence of both AIDS-defining and non–AIDS-defining cancers in southern Africa. In Botswana, 43% of all cancers and an even greater proportion of cancer deaths are attributable to HIV. Future studies are needed to determine the extent of the interactions among these highly prevalent conditions worldwide.

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### Table 1 – Characteristics of Cervical Cancer Patients by History of Prior Tuberculosis in Botswana

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of Prior Tuberculosis (n = 18)</th>
<th>No History of Prior Tuberculosis (n = 162)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>47.3 (41.1-57.8)</td>
<td>47.8 (39.2-56.2)</td>
<td>.78</td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td></td>
<td></td>
<td>.24</td>
</tr>
<tr>
<td>Single</td>
<td>13 (86.7)</td>
<td>90 (67.7)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>2 (13.3)</td>
<td>41 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Divorced or widowed</td>
<td>0</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Age of first sexual activity, median (IQR)</td>
<td>18 (17-19)</td>
<td>18 (16-20)</td>
<td>.39</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>1 (5.6)</td>
<td>4 (2.5)</td>
<td>.49</td>
</tr>
<tr>
<td>HIV infection, No. (%)</td>
<td>16 (88.9)</td>
<td>101 (62.3)</td>
<td>.02</td>
</tr>
<tr>
<td>CD4 cell count, median (IQR)*</td>
<td>367 (261-592)</td>
<td>474 (343-579)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, cells/µL, No. (%)*</td>
<td></td>
<td></td>
<td>.51</td>
</tr>
<tr>
<td>&lt; 350</td>
<td>6 (37.5)</td>
<td>22 (25.3)</td>
<td></td>
</tr>
<tr>
<td>351-500</td>
<td>3 (18.8)</td>
<td>26 (29.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 500</td>
<td>7 (43.8)</td>
<td>39 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Taking ART, No. (%)†</td>
<td>16 (100)</td>
<td>95 (101)</td>
<td>.18</td>
</tr>
<tr>
<td>Viral load undetectable, No. (%)</td>
<td>16/16 (100)</td>
<td>63/66 (95.5)</td>
<td></td>
</tr>
<tr>
<td>Cancer type, No. (%)</td>
<td></td>
<td></td>
<td>.53</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>150 (93.2)</td>
<td>16 (88.9)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>11 (6.8)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ART, HIV antiretroviral treatment; IQR, interquartile range.

*CD4 cell count at the time of cervical cancer diagnosis.
†Only available results presented. One case of papillary serous carcinoma excluded from the analyses.

### Table 2 – Multivariate Analyses to Determine Factors Associated With Prior History of Tuberculosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.01 to 1.11</td>
<td>.023</td>
</tr>
<tr>
<td>HIV</td>
<td>21.5</td>
<td>2.16 to 214.52</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Smoking</td>
<td>4.8</td>
<td>3.89 to 61.91</td>
<td>.227</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV negative</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 350</td>
<td>57.3</td>
<td>4.44 to 740.8</td>
<td>.002</td>
</tr>
<tr>
<td>351-500</td>
<td>14.9</td>
<td>0.96 to 232.78</td>
<td>.054</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>39.0</td>
<td>3.15 to 483.89</td>
<td>.004</td>
</tr>
</tbody>
</table>

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References


Affiliations

Nicola M. Zetola, Surbhi Grover, Lilib L. Lin, and Erle Robertson, University of Pennsylvania, Philadelphia, PA; Nicola M. Zetola, Surbhi Grover, and Mohan Narasimhamurthy, University of Botswana; Chawangwa Modongo, Botswana-University of Pennsylvania Partnership; Sebathu P. Chiyapo, Princess Marina Hospital; Memory Nsingo-Bvochora, Gaborone Private Hospital, Gaborone, Botswana; Joseph Jarvis, London School of Hygiene and Tropical Medicine, London, United Kingdom; and Sanghyuk S. Shin, University of California–Los Angeles, Los Angeles, CA.