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Bevacizumab in Advanced Cervical Cancer: Issues and Challenges for Low- and Middle-Income Countries

Bevacizumab became the first molecular antibody to show survival benefit in advanced cervical cancer. In the GOG-0240 (Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer) trial, it improved overall survival by a significant 3.7 months over platinum doublet chemotherapy alone. However, this discovery is not likely to improve the status of global cervical cancer because more than 85% of patients with cervical cancer live in low- and middle-income countries and cannot afford bevacizumab. This commentary looks at the options by which this drug can be made more affordable and cost-effective for patients in low- and middle-income countries. We also discuss other important questions related to its affordability and cost issues such as the optimal number of cycles and personalizing the treatment. Finally, we emphasize that although the unaffordability of bevacizumab in cervical cancer seems to be a very important issue, the best cost-effective strategy against cervical cancer is prevention with screening and vaccination.

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Perceptions and Barriers of Survivorship Care in Asia: Perceptions From Asian Breast Cancer Survivors

**Purpose** With the long-term goal to optimize post-treatment cancer care in Asia, we conducted a qualitative study to gather in-depth descriptions from multiethnic Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up.

**Methods** Twenty-four breast cancer survivors in Singapore participated in six structured focus group discussions. The focus group discussions were voice recorded, transcribed verbatim, and analyzed by thematic analysis.

**Results** Breast cancer survivors were unfamiliar with and disliked the term “survivorship,” because it implies that survivors had undergone hardship during their treatment. Cognitive impairment and peripheral neuropathy were physical symptoms that bothered survivors the most, and many indicated that they experienced emotional distress during survivorship, for which they turned to religion and peers as coping strategies. Survivors indicated lack of consultation time and fear of unplanned hospitalization as main barriers to optimal survivorship care. Furthermore, survivors indicated that they preferred receipt of survivorship care at the specialty cancer center.

**Conclusion** Budding survivorship programs in Asia must take survivor perspectives into consideration to ensure that survivorship care is fully optimized within the community.
Breast Cancer Downstaging Practices and Breast Health Messaging Preferences Among a Community Sample of Urban and Rural Ugandan Women

**Purpose** Among a community sample of Ugandan women, we provide information about breast cancer downstaging practices (breast self-examination, clinical breast examination [CBE]) and breast health messaging preferences across sociodemographic, health care access, and prior breast cancer exposure factors.

**Methods** Convenience-based sampling was conducted to recruit Ugandan women age 25 years and older to assess breast cancer downstaging practices as well as breast health messaging preferences to present early for a CBE in the theoretical scenario of self-detection of a palpable lump (breast health messaging preferences).

**Results** The 401 Ugandan women who participated in this survey were mostly poor with less than a primary school education. Of these women, 27% had engaged in breast self-examination, and 15% had undergone a CBE. Greater breast cancer downstaging practices were associated with an urban location, higher education, having a health center as a regular source of care, and receiving breast cancer education ($P < .05$). Women indicated a greater breast health messaging preference from their provider (66%). This preference was associated with a rural location, having a health center as a regular source of care, and receiving breast cancer education ($P < .05$).

**Conclusion** Most Ugandan women do not participate in breast cancer downstaging practices despite receipt of breast cancer education. However, such education increases downstaging practices and preference for messaging from their providers. Therefore, efforts to downstage breast cancer in Uganda should simultaneously raise awareness in providers and support improved education efforts in the community.

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South African Breast Cancer and HIV Outcomes Study: Methods and Baseline Assessment

**Purpose** In low- and middle-income, HIV-endemic regions of sub-Saharan Africa, morbidity and mortality from the common epithelial cancers of the developed world are rising. Even among HIV-infected individuals, access to antiretroviral therapy has enhanced life expectancy, shifting the distribution of cancer diagnoses toward non–AIDS-defining malignancies, including breast cancer. Building on our prior research, we recently initiated the South African Breast Cancer and HIV Outcomes study.

**Methods** We will recruit a cohort of 3,000 women newly diagnosed with breast cancer at hospitals in high (average, 20%) HIV prevalence areas, in Johannesburg, Durban, Pietermaritzburg, and Empangeni. At baseline, we will collect information on demographic, behavioral, clinical, and other factors related to access to health care. Every 3 months in year 1 and every 6 months thereafter, we will collect interview and chart data on treatment, symptoms, cancer progression, comorbidities, and other factors.

We will compare survival rates of HIV-infected and uninfected women with newly diagnosed breast cancer and their likelihood of receiving suboptimal anticancer therapy. We will identify determinants of suboptimal therapy and context-specific modifiable factors that future interventions can target to improve outcomes. We will explore molecular mechanisms underlying potentially aggressive breast cancer in both HIV-infected and uninfected patients, as well as the roles of pathogens, states of immune activation, and inflammation in disease progression.

**Conclusion** Our goals are to contribute to development of evidence-based guidelines for the management of breast cancer in HIV-positive women and to improve outcomes for all patients with breast cancer in resource-constrained settings.

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Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa

**Purpose** Breast cancer is the most common cause of cancer in women in South Africa, and often patients present late. There is little understanding of the psychosocial stresses affecting women with breast cancer in Africa.

**Methods** A questionnaire was distributed to 263 patients with breast cancer at two sites (one government and one private facility) in Johannesburg. Self-reported levels of fear were recorded on summative scales and their relationship to demographic variables assessed through univariable and multivariable modified Poisson regression.

**Results** Fears related to treatments and prognosis, particularly radiation, loss of hair, and loss of breast, were far stronger than those related to socioeconomic barriers. Relative risk (RR) of most fears was higher in women younger than age 40 years, including treatment affordability (RR, 1.80; 95% CI, 1.26 to 2.56), hair loss (RR, 1.48; 95% CI, 1.12 to 2.95), and surgery (RR, 1.31; 95% CI, 1.02 to 1.68). Difficulty taking time off work predicted fear of job loss (RR, 2.59; 95% CI, 1.59 to 4.21) and missing appointments because of transport (RR, 2.46; 95% CI, 1.52 to 3.96) or family commitments (RR, 2.46; 95% CI, 1.52 to 3.96). Women with dependents and black women were more afraid of dying (RR, 1.73; 95% CI, 1.03 to 2.90; and RR, 1.79; 95% CI, 1.33 to 2.24, respectively); however, socioeconomic status in this sample was a strong confounder of race and explained most of the racial differences in levels of fear.

**Conclusion** The most significant fears around breast cancer were related to treatment modalities and adverse effects rather than transport, financial, or work concerns. Young age and job insecurity were predictive of increased fears. Education about treatments has a key role to play in improving access to breast cancer care in South Africa.

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Second Primary Cancers After Primary Breast Cancer Diagnosis in Israeli Women, 1992 to 2006

**Purpose** Improvements in early detection and treatment have resulted in improved long-term survival from breast cancer, which increases the likelihood of the occurrence of second primary cancers. We calculated the risk of second primary cancers among Israeli women receiving a first primary breast cancer diagnosis.

**Methods** By using data from the Israel National Cancer Registry, we identified 46,090 women with invasive breast cancer diagnosed between 1990 and 2006 and non-breast primary cancers diagnosed subsequent to breast cancer diagnosis. We used life table analysis to calculate the risk of a second primary cancer and calculated standardized incidence ratios (SIRs) by using age-specific cancer risk in the general population of Israeli women as the standard and stratifying by diagnosis period (1992 to 1996, 1997 to 2001, 2002 to 2006) and age at diagnosis (< 50 and ≥ 50 years).

**Results** The probability of a second malignancy was 3.6% within 5 years, 8.2% within 10 years, and 13.9% within 15 years. The SIR for any second non-breast primary cancer was 1.26 (95% CI, 1.23 to 1.30). Significantly increased risks of colorectal, uterine, lung, ovarian, and thyroid cancer and leukemia were observed for the full follow-up period, which persisted after excluding the first 6 months after index diagnosis, although increased leukemia and colorectal cancer risks were no longer statistically significant. Women younger than age 50 years at initial diagnosis had a greater excess risk than women age 50 years and older (SIR, 1.77 [95% CI, 1.63 to 1.91] and 1.20 [95% CI, 1.15 to 1.24], respectively).

**Conclusion** The findings likely reflect a combination of personal risk factors (genetics, hormonal therapy, environmental exposures) as well as the effects of the initial cancer treatment and are unlikely to be explained by enhanced surveillance alone.

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Challenges of Treating Childhood Medulloblastoma in a Country With Limited Resources: 20 Years of Experience at a Single Tertiary Center in Malaysia

**Purpose** Pediatric medulloblastoma (MB) treatment has evolved over the past few decades; however, treating children in countries with limited resources remains challenging. Until now, the literature regarding childhood MB in Malaysia has been nonexistent. Our objectives were to review the demographics and outcome of pediatric MB treated at the University Malaya Medical Center between January 1994 and December 2013 and describe the challenges encountered.

**Methods** Fifty-one patients with childhood MB were seen at University Malaya Medical Center. Data from 43 patients were analyzed; eight patients were excluded because their families refused treatment after surgery.

**Results** Headache and vomiting were the most common presenting symptoms, and the mean interval between symptom onset and diagnosis was 4 weeks. Fourteen patients presented with metastatic disease. Five-year progression-free survival (± SE) for patients ≥3 years old was 41.7% ± 14.2% (95% CI, 21.3% to 81.4%) in the high-risk group and 68.6% ± 18.6% (95% CI, 40.3% to 100%) in the average-risk group, and 5-year overall survival (± SE) in these two groups was 41.7% ± 14.2% (95% CI, 21.3% to 81.4%) and 58.3% ± 18.6% (95% CI, 31.3% to 100%), respectively. Children younger than 3 years old had 5-year progression-free and overall survival rates (± SE) of 47.6% ± 12.1% (95% CI, 28.9% to 78.4%) and 45.6% ± 11.7% (95% CI, 27.6% to 75.5%), respectively. Time to relapse ranged from 4 to 132 months. Most patients who experienced relapse died within 1 year. Febrile neutropenia, hearing loss, and endocrinopathy were the most common treatment-related complications.

**Conclusion** The survival rate of childhood MB in Malaysia is inferior to that usually reported in the literature. We postulate that the following factors contribute to this difference: lack of a multidisciplinary neuro-oncology team, limited health care facilities, inconsistent risk assessment, insufficient data in the National Cancer Registry and pathology reports, inadequate long-term follow-up, and cultural beliefs leading to treatment abandonment.

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Surgery for CNS Tumors in the Brazilian National Health Care System

Purpose Resource limitations in low- and middle-income countries make the management of CNS tumors challenging, particularly in Brazil, a country with major disparities in socioeconomic status and access to health care. We aimed to evaluate cancer-related neurosurgical procedures in the public health care system.

Methods On the basis of Brazil’s public health system database, we collected data for neurosurgical procedures related to CNS tumors performed between January 2008 and November 2013. Information about the number of procedures, costs, length of stay, and number of inpatient deaths were analyzed for each state and then correlated to the state-specific population, gross domestic product per capita, and number of procedures.

Results In all, 57,361 procedures were performed, the majority of them in the Southeast region. The mean length of hospital stay was 14.4 days, but longer hospital stay was reported for patients treated in the North. The inpatient mortality rate was 7.11%. Mortality rates decreased as the number of procedures ($P < .001$), gross domestic product per capita ($P < .001$), or state population increased ($P < .001$). On multivariate analysis, only the number of procedures (odds ratio, 0.93; 95% CI, 0.91 to 0.96; $P < .001$) and state population (odds ratio, 1.25; 95% CI, 1.13 to 1.38; $P < .001$) had an independent association with mortality.

Conclusion To the best of our knowledge, this is the first study to evaluate disparities in CNS tumor surgery in a middle-income country, confirming that regional disparities exist and that clinical and economic outcomes correlate with income level, number of procedures, and state population.

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continued
Surgical Management of Breast Cancer in Africa: A Continent-Wide Review of Intervention Practices, Barriers to Care, and Adjuvant Therapy

Breast cancer has emerged as a leading cancer among women in Africa, necessitating improved understanding of its management across the continent. Although previous studies have described regional trends in therapy, this review aims to summarize continent-wide management and focus specifically on surgical interventions. Current literature shows that the rates of surgery, chemotherapy, and radiation therapy vary across different countries and institutions, indicating the need for greater use of standardized cancer treatment guidelines. Surgery, primarily modified radical mastectomy, is the most common form of therapy described. When chemotherapy is offered, the limited availability and cost of treatment lead to high rates of interruption and premature termination of cycles. Few patients have access to radiation or hormonal therapy because these treatments are not available in many countries. Significant delays in seeking treatment are common and contribute to patients presenting with advanced disease. Although limited infrastructure favors surgical management, interventions to improve early detection behavior, provide timely referrals to medical care, and initiate early treatment with access to clinically justified neo-adjuvant and adjuvant therapy are key to improving prognosis.

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Innovative Breast Cancer Awareness and Advocacy Campaign

Breast cancer is a major disease in Nigeria; in 2012, 27,304 new occurrences were diagnosed, and the number of mortalities was 13,960. Greater than 70% of patients present with advanced disease, which has a poor survival outcome. The mortality rates are high mainly because of a lack of awareness about breast health, screening guidelines, and treatment centers, and because of sociocultural barriers. In Nigeria, health care professionals remain the backbone for the provision of medical information to the public. This is a study of the innovative ways that breast health and cancer awareness were promoted across communities and institutions in Lagos State, Nigeria, in 2015. Several community awareness campaigns were carried out in the forms of health talks, breast cancer screenings, radio and television interviews, and campaigns on social media. Anomalies noticed during the screenings were promptly referred to appropriate hospitals for additional treatment. The campaign culminated in the #12KLLP, or 12,000 people light Lagos pink, which was a Guinness World Record attempt for the largest human awareness ribbon formed for breast cancer. There was a total reach of 28,774,812 people across platforms: 285,318 were on social media, 3,620 were in communities, 7,466,276 were on the website, 20 million were through media events, 12,000 were through publications, 7,598 were verified participants at the Guinness World Record, and approximately 1 million were through blogs. Eighty partnerships were made with various private and government institutions to facilitate different aspects of the campaign. The community members were able to learn about the need for early detection and awareness; volunteerism and corporate social responsibility were promoted among individuals and corporate institutions.

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Bevacizumab became the first molecular antibody to show survival benefit in advanced cervical cancer. In the GOG-0240 (Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer) trial, it improved overall survival by a significant 3.7 months over platinum doublet chemotherapy alone. However, this discovery is not likely to improve the status of global cervical cancer because more than 85% of patients with cervical cancer live in low- and middle-income countries and cannot afford bevacizumab. This commentary looks at the options by which this drug can be made more affordable and cost-effective for patients in low- and middle-income countries. We also discuss other important questions related to its affordability and cost issues such as the optimal number of cycles and personalizing the treatment. Finally, we emphasize that although the unaffordability of bevacizumab in cervical cancer seems to be a very important issue, the best cost-effective strategy against cervical cancer is prevention with screening and vaccination.

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Cisplatin-paclitaxel combination therapy has remained the standard of care for advanced cervical cancer for many years. This combination improves survival by only a few months compared with placebo, and we have been unable to make any progress in treating this disease. The demonstration of survival advantage with bevacizumab, therefore, is a milestone—the first positive trial in many years and the first antibody therapy to be approved for cervical cancer. The GOG-0240 (Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer) trial showed a significant survival benefit of 3.7 months (17.0 v 13.3 months; hazard ratio, 0.71; P = .004) with the use of bevacizumab plus chemotherapy compared with chemotherapy alone. Adding bevacizumab also significantly improved the response rates compared with chemotherapy alone (48% v 36%; P = .008). This finding has the potential to significantly improve the prognosis of nearly a half million patients with cervical cancer across the globe annually.

In this commentary, we discuss some important issues regarding the applicability of this important study to the majority of patients with cervical cancer who live in low- and middle-income countries (LMICs).

Is Bevacizumab Really Expensive?

Whether a particular commodity is expensive depends on the purchasing capacity of the consumers. More than 85% of cervical cancers occur in LMICs, with a mortality rate more than three times that in developed countries. A study showed that treatment with bevacizumab will incur an expense of nearly $21,083 per month of added life and $24,597 per quality-adjusted life month. To put this into perspective, the gross national income (GNI) per capita of an LMIC is $2,037 according to World Bank data. It is quite paradoxical that a month of treatment costs more than ten times the annual GNI per capita. Cervical cancer is a disease we stage using the International Federation of Gynecology and Obstetrics (FIGO) staging system, which does not include computed tomography (CT) or magnetic resonance imaging (MRI) because CT and MRI are out of reach of many patients in LMICs. Surely, patients who cannot afford CT or MRI could never afford bevacizumab.

Furthermore, the high cost of bevacizumab and the resulting financial toxicity to the patient, society, and the entire health care system has been a matter of much concern, even for high-income countries (HICs). This high cost has rendered...
bevacizumab cost-ineffective, even for cancers in which it has shown survival gains such as colorectal cancer and cervical cancer. When bevacizumab is considered cost-ineffective for HICs, no one would argue that it is unaffordable and beyond the reach of most patients with cervical cancer living in LMICs. It is striking to note that even if the price of bevacizumab were reduced by 75%, it would still cost $6,737 per quality-adjusted life month, which is still three times the annual per capita GNI of someone living in an LMIC. Thus, despite the promising results from the GOG-0240 trial, the global cervical cancer survival rate in the post-bevacizumab era is not likely to improve appreciably.

Can Bevacizumab Be Made Affordable for Patients Living in LMICs?

At the moment, this is the most pressing question bothering both oncologists and patients living in LMICs, and some solutions have already been proposed. The authors of the GOG-0240 trial acknowledge that bevacizumab is out of reach for people living in LMICs and speculate that it will take many years before this option becomes accessible to them. The major hope lies in the introduction of biosimilars in the future that will reduce the incremental cost-effectiveness ratio significantly. However, introduction of biosimilars will take considerable time. Furthermore, bevacizumab is considered to be an especially challenging product for producing biosimilars. The biosimilars should then undergo an equivalence study before we can confidently put our trust in them.

Besides waiting for biosimilars, it is high time we demanded that the pharmaceutical industry truthfully acknowledge its corporate social responsibility and provide the drug for free (preferably) or at a large discount to patients living in LMICs. Surely the cost incurred in the development of bevacizumab has already been replenished a thousandfold, given its use against a wide variety of cancers, including glioblastoma and lung, breast, kidney, colorectal, and ovarian cancer, for a long time. Thus, it is not entirely unrealistic to demand free bevacizumab for poor patients living in LMICs in collaboration with other nonprofit organizations. The Glivec International Patient Assistance Program that provides free imatinib to eligible patients living in developing countries serves as a testimony for the feasibility of this approach.

Unfortunately though, this optimism seems unrealistic when looking at recent developments. India, an LMIC in South Asia that has recently been taking proactive steps to combat cancer, has taken a liberal policy in allowing development of biosimilars of many cancer drugs to promote competition and lower pricing. However, as of May 17, 2016, Roche—the manufacturer of bevacizumab—is known to have sued the Drug Controller General of India in Delhi High Court over the approval of biosimilars of bevacizumab. We, echoing the voices of all oncologists and patients from LMICs, strongly appeal to Roche to instead follow the lead taken by industry members such as GlaxoSmithKline, which has recently announced that it will not patent cancer drugs in LMICs.

Dose, Schedule, and Duration of Bevacizumab

The pivotal trial establishing the role of bevacizumab in cervical cancer used bevacizumab at a dose of 15 mg/kg once every 3 weeks. The earlier phase II trial decided upon this dose and schedule on the basis of the ease of combining it with chemotheraphy agents. Thus, there is no strong rationale for strictly adhering to this dose and schedule. A cost-effectiveness analysis of bevacizumab in cervical cancer has shown that the cost of chemotherapy decreased from $49,831 to $26,472 when bevacizumab dose was reduced to 7.5 mg/kg from 15 mg/kg. Although this is still quite expensive for patients in LMICs, it does represent a significant cost reduction. Clinical studies comparing various doses and schedules of bevacizumab would settle this question, but such trials are unlikely to be funded by the industry. Hence, LMICs—with assistance from international nonprofit organizations and institutions—should take the initiative and conduct and/or participate in the trials comparing different doses and schedules of bevacizumab for cervical cancer. That trial in itself would provide an opportunity for many patients with cancer to receive bevacizumab and validate the efficacy of lower doses of bevacizumab. HICs would be equally interested in such studies because bevacizumab has been shown to be cost-ineffective, even for HICs, at the current price and dosing levels. Thus, collaboration between LMICs and HICs is highly desired in the conduct of such trials and is of global importance. We have already shown that it is much cheaper and easier to conduct clinical trials in LMICs compared with HICs, although some unique challenges need to be addressed.

Another important issue with bevacizumab is the uncertainty regarding the optimal number of cycles for administration. In the GOG-0240 trial, it was given once every 21 days until disease progression. The median number of cycles was seven (range, zero to 36), the most common reason for
stopping treatment being disease progression.\textsuperscript{2} For patients and physicians working in LMICs, it is important to ascertain whether the administration of a limited number of cycles of bevacizumab, say two or three, is equally efficacious. This question is important because we sometimes encounter patients who can afford only one or two cycles of bevacizumab, but not more. We have no guidelines regarding whether using two cycles of bevacizumab is better than not using it at all. Because anti-VEGF stress induces tumors to develop alternative mechanisms of angiogenesis-independent tumor vasculature, there are concerns that bevacizumab withdrawal could cause the tumor to become more aggressive.\textsuperscript{18} The authors of a recent cost-effectiveness analysis of bevacizumab in cervical cancer reported that “if a payer is able or willing to pay $21,083 for one more additional life month before death, then chemotherapy plus bevacizumab should be administered.”\textsuperscript{5(p493)} But we are concerned that for a patient who can afford only $21,083 but not more, one cycle of bevacizumab might not provide an additional month of life, and at worst, it could even make the disease more aggressive. A subgroup analysis of the GOG-0240 trial according to the number of bevacizumab cycles (eg, one to three or more than three) would provide some useful insights.

Can We Personalize Treatment With Bevacizumab?

In the era of such expensive treatment, personalizing treatment is the most cost-effective method available. Unfortunately, we do not yet have validated predictive factors for bevacizumab. However, using Moore criteria in the GOG-0240 trial, the hazard ratios for death in low-risk, mid-risk, and high-risk patients were 0.96, 0.673, and 0.536, respectively. The lack of statistically significant benefit among low-risk patients means that bevacizumab should be reserved for mid- and high-risk patients only.\textsuperscript{11} In addition, preliminary reports suggest the decrease in circulating tumor cells could be used as a predictor and prognostic biomarker.\textsuperscript{19} Further validation of this finding would help realize the dream of personalizing bevacizumab treatment in cervical cancer.

Are LMICs Going to Lose the Battle Against Cervical Cancer Without Bevacizumab?

Although bevacizumab is the most recent and attractive option, the most effective weapon we have in the battle against cervical cancer is prevention. More than 99% of cervical cancers are associated with human papillomavirus (HPV) infection, and effective vaccines are now available that can help make this disease preventable. Although nine-valent vaccines are now available for HICs, if the LMICs can incorporate quadrivalent or bivalent vaccines into their routine vaccination program, that would prevent more than 70% of cervical cancer cases.\textsuperscript{20} With support from the GAVI Alliance, HPV vaccination in developing countries is slowly gaining coverage and the poorest countries now have access to a sustainable supply of HPV vaccines for as little as $4.50 per dose compared with $100 for the same in HICs.\textsuperscript{21} Therefore, the governments of LMICs should be focused on increasing the coverage of HPV vaccination rather than the affordability of bevacizumab. Because smoking is another important risk factor for cervical cancer, another focus for the governments of LMICs should be to conduct effective anti-smoking campaigns. If we can control HPV infection through vaccination and smoking control campaigns, we can control a significant percentage of advanced cervical cancer cases.

Cervical cancer passes through sequential pre-cancerous stages that allow us to intervene for early detection. It is known that invasive cervical malignancy typically develops in those who are unscreened or underscreened.\textsuperscript{22} Thus, early detection represents a very important area of intervention. Fortunately, several studies regarding cost-effective modalities for screening have provided options useful for low-resource settings. A single round of HPV testing significantly reduced advanced cervical cancer incidence and mortality in rural India.\textsuperscript{23} Screening that uses visual inspection with acetic acid in one or two visits is found to be a cost-effective alternative to three-visit cytology-based screening for resource-limited settings.\textsuperscript{24} Another important study showed that this type of screening can be conducted effectively by primary health workers and can significantly reduce mortality.\textsuperscript{25} Thus, effective screening by using cost-effective methods represents the best solution. With concentrated efforts toward vaccination coverage and screening, we can envision a future in which the number of patients that present with advanced-stage cervical cancer can be significantly reduced so that the affordability of bevacizumab becomes less of a social problem.
AUTHOR CONTRIBUTIONS
Administrative support: Bishal Gyawali
Provision of study materials or patients: Bishal Gyawali
Manuscript writing: All authors
Final approval of manuscript: All authors

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Bishal Gyawali
No relationship to disclose

Mahesh Iddawela
No relationship to disclose

REFERENCES


Perceptions and Barriers of Survivorship Care in Asia: Perceptions From Asian Breast Cancer Survivors

Purpose With the long-term goal to optimize post-treatment cancer care in Asia, we conducted a qualitative study to gather in-depth descriptions from multiethnic Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up.

Methods Twenty-four breast cancer survivors in Singapore participated in six structured focus group discussions. The focus group discussions were voice recorded, transcribed verbatim, and analyzed by thematic analysis.

Results Breast cancer survivors were unfamiliar with and disliked the term “survivorship,” because it implies that survivors had undergone hardship during their treatment. Cognitive impairment and peripheral neuropathy were physical symptoms that bothered survivors the most, and many indicated that they experienced emotional distress during survivorship, for which they turned to religion and peers as coping strategies. Survivors indicated lack of consultation time and fear of unplanned hospitalization as main barriers to optimal survivorship care. Furthermore, survivors indicated that they preferred receipt of survivorship care at the specialty cancer center.

Conclusion Budding survivorship programs in Asia must take survivor perspectives into consideration to ensure that survivorship care is fully optimized within the community.

INTRODUCTION

Cancer survivorship care is still in its infancy in Asia. The majority of the institutions lack formal and standardized survivorship programs for cancer survivors. Yet, numerous challenges exist in the management of post-treatment complications within Asia. An observational study showed that cancer survivors in Asia suffer significant post-treatment–related symptoms, including anxiety, fatigue, and cognitive disturbances, and that these treatment-related complications are likely to have a major effect on health-related quality of life during cancer recovery. In addition, greater than 60% of the Southeast Asian oncology practitioners from numerous countries suggested that patient-specific barriers are the main barriers to follow-up care among the survivors they routinely treat. Because the success of survivorship care also depends greatly on the cooperation and participation of the survivors, it would be prudent to fully understand cancer survivorship from the end user perspective. Much of what is known about survivorship care and the issues faced by cancer survivors originates from studies that were conducted in the West, so ethnocultural differences may contribute to the delivery and experience of survivorship care among Asian cancer survivors.

With the long-term goal to optimize post-treatment care in breast cancer survivors in Asia, we conducted a qualitative study to gather in-depth descriptions from Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up.

METHODS

Design and Participants

As part of a study to evaluate the performance of group psychoeducation to improve survivorship in breast cancer survivors, a qualitative study was conducted at the National Cancer Centre Singapore (NCCS) that involved focus group discussions. NCCS is a leading regional center for cancer research and treatment in Southeast Asia, and it serves approximately 70% of all adult patients with cancer in Singapore.
The participants recruited for the focus group discussions fulfilled the following inclusion criteria: age older than 21 years, ability to read and understand English, diagnosis of early-stage breast cancer made by a medical oncologist, and completion of primary chemotherapy for early-stage breast cancer. This study was approved by the SingHealth Centralized Institutional Review Board, and informed consent was obtained from all of the participants.

Procedures
Six English-speaking structured focus groups were conducted over 2 separate days. Four to six participants were included in each focus group, and grouping of the participants was based on the type of cancer treatment they had received. Each focus group discussion was designed to be 60 to 90 minutes long and was coordinated by trained facilitators. These facilitators were medical social workers, and each facilitator was assisted by one of the investigators as a note taker. The discussions used an open-ended approach that proceeded from a general question to more specific questions, which thus reduced the influence of probing by the facilitators. Two training sessions were held before the focus group discussions to ensure consistency in the facilitation of the groups.

In each discussion, the facilitator would first understand the participant definitions and perception of the term survivorship and then gather information on the physical, emotional, social, and spiritual effects of cancer treatment on the survivor. Subsequently, the participants were asked to state the obstacles and factors that might deter them from joining survivorship programs (if offered; Table 1).

Data Analysis
The focus group discussions were voice-recorded, transcribed verbatim, and analyzed by thematic analysis. The open-ended discussion guide and data-driven analytical methods used in this study were adopted from certain elements of the grounded theory. Codes that described similar manifestations were grouped into themes. Two coders (L.Z.K. and A.C.) first familiarized themselves with the transcripts and generated initial codes independently. They then met to discuss and reach a consensus on the codes. Discrepancies were resolved with a consensus method.

RESULTS
Demographics
Twenty-four survivors participated in the six different focus groups. The mean (standard deviation) age was 56.4 years (± 7.0 years). Most of the survivors were Chinese (87.5%), were married (70.8%), and were diagnosed with stage II breast cancer (58.3%; Table 2).

Open codes were created and categorized into five broad themes: understanding the terminology: who is a cancer survivor, physical issues, psychological issues, barriers to follow-up care, and how can the health care system address participants' needs.

Understanding the Terminology: Who Is a Cancer Survivor?
A number of survivors understood the term survivorship as its literal meaning. However, two poles were observed through the discussions in terms of the definition of survivorship. Some survivors agreed that the connotation of survivorship is positive, but others viewed survivorship as a pessimistic description of their condition.

“Survivorship brings [me] a different kind of hope.”
“I am not sure do you need to wait for 5 years to be called a cancer survivor, or is it immediately now when you finished all your treatment [...] Don’t really understand.”

Some survivors viewed survivorship as a negative reflection of their condition, and being tagged with the term survivor caused them emotional discomfort. The Chinese translation of the term survivorship implies that the survivors had undergone hardship during their treatment, and this is a term that was not favored by the survivors.

“Personally when I heard the word ‘survivor,’ it makes me go into sadness. I don’t like the term because it somehow [has] this connotation of [...] barely getting by.”

Physical Symptoms
Cancer treatment brought about numerous physical adverse effects that affected the quality of life and personal relationships of survivors. Cognitive impairment, peripheral neuropathy, and fatigue were highlighted by most survivors. Hair loss, nausea, constipation, and mouth ulcers were other physical effects of cancer treatment that were experienced by numerous survivors during treatment.

Cognitive impairment. A number of survivors indicated that their memory loss had affected their daily functioning, and they became dependent on others around them for daily living. This group of survivors was saddened by their memory loss, which indirectly affected their self-esteem.
“Last time I do work very independent[ly] […] I can guide people, but now I cannot. I still have to ask.”

These survivors overcame memory loss mainly through physical self-reminders by note-taking and by using certain tools to aid in memory recall. A small number of them turned to alternative medical therapies, such as traditional Chinese medicine and meditation, to improve their memory.

Peripheral neuropathy. The majority of the survivors claimed that the numbness that resulted from chemotherapy manifested as physical pain that caused disruptions to their daily living. Because neuropathy interferes with their daily living, the survivors were afraid that this effect would be permanent, and they were skeptical about recovering from the adverse effects.

“It is painful [that] you couldn’t open the [bottle] cap, […] you couldn’t do so many things. I remembered […] at one stage, splashing water on my face is also painful.”

“I am not that confident […] the nerves take time to recover.”

This resulted in some survivors turning to alternative medical therapies to overcome this adverse effect, and a small number of them attempted to massage the areas of numbness.

“The therapist that I went to, she does a mixture […] of […] Western, […] Japanese, [and] a little bit [of] traditional Chinese medicine.”

Fatigue. Most of the survivors also complained that they experienced fatigue, especially after chemotherapy. They admitted that chemotherapy made them tired and very sleepy. However, they also acknowledged that this effect might not be significant, because healthy individuals can also get tired. Some survivors claimed that they had to find ways, such as taking afternoon naps, to keep themselves alert, and one survivor mentioned consuming coffee to stay awake.

Emotional, Social, and Spiritual Effects of Cancer Treatment

Fear and sadness were common among survivors. Some survivors were not optimistic about their prognosis, and this negative mindset led them to experience depression and anxiety.

Fear, sadness (uncertainty), and stress. The fear and uncertainty of the future resulted in a negative outlook on life for many survivors. As they suffered from the adverse effects of chemotherapy and the symptoms of breast cancer, the optimistic survivors grew to accept their fate and lost much hope in life.

"Table 1. Guiding Questions That Were Used in the Focus Group Discussions"

<table>
<thead>
<tr>
<th>Theme</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitions and perceptions of the term survivorship</td>
<td>Do you understand the term “survivor” of breast cancer? What does the term mean to you? Has any health care professional mentioned this term to you?</td>
</tr>
<tr>
<td>Gather information on the survivors’ physical effects of cancer treatment</td>
<td>What physical effects of cancer treatment bothered you the most during treatment and may continue to pose as problems/difficulties for you after treatment? How do you manage these side effects? What kind of role does your family and peers play in the management of these side effects?</td>
</tr>
<tr>
<td>Gather information on the survivors’ emotional, social, and spiritual concerns.</td>
<td>What were the emotional, social, and spiritual concerns that you faced during cancer treatment and may continue to pose as problems/difficulties for you after treatment? How do you manage these side effects? What kind of role does your family and peers play in the management of these concerns?</td>
</tr>
<tr>
<td>Discuss the obstacles and factors that might deter them from joining survivorship programs.</td>
<td>What are some barriers to follow-up care after completion of active treatment? Why?</td>
</tr>
<tr>
<td>Discuss the opportunities that the public health system could improve post-treatment care.</td>
<td>What should the public health system do to address your needs after cancer treatment? Why?</td>
</tr>
</tbody>
</table>
When you first started, you live from cycle to cycle, you can survive cycle to cycle, but then subsequently when it gets worse, you start living from day to day, then from day to day, it becomes meal to meal.

The majority of the survivors agreed that they were constantly under stress and did not have time to relax. One of the common concerns that arose from the various discussions was the fear of recurrence of their cancer.

Difficult in coping with distress. With the variations in advice that they received, many survivors agreed that they were confused about whom to trust, and they had minimal avenues by which they could cope with this emotional distress. Controlling their emotions posed a great challenge to the survivors.

“Initially [my husband kept] telling me […] to stay positive and things like that. I keep on telling him, you are not me, you don’t know how I feel, can you let me [vent] out my feelings or not?”

Religious beliefs and support of family and friends. The majority of the survivors agreed that support from family and friends was important during their treatment and battle with cancer. For those survivors who did not know how to cope with emotional distress, they turned to religious support; many of them went to healing rooms or turned to prayer in churches or temples.

Post-Treatment Follow-Up: Patient-Related Barriers

Through the discussions, we aimed to establish the factors that might deter survivors from continuation of their treatment or participation in any post-actively treatment programs.

Lack of consultation time with specialists. One common barrier reflected by the majority of the survivors was the issue of time spent with their oncologists. The survivors agreed that most of their questions were left unanswered because of the short consultation time with the oncologists.

“Sometimes [during] the consultation, we do not have that much time to […] talk to the doctor.”

Although lack of time is a concern, many survivors also agreed that generally this was not a significant barrier to their follow-up care, because there were other allied health care professionals to turn to who could answer their queries.

“I find that when I talk to the oncologist and the doctor, I am a bit rush, but I find talking to the pharmacist, the time that I don’t have to see the doctor right, I go and see the pharmacist just before the chemo, and I think that talking to the pharmacist, I have more time.”

Unplanned hospitalization. Some survivors also mentioned the fear of unplanned hospitalization during their follow-up care. Some expressed their fear of diagnostic tests, including blood tests, because these tests may detect other health problems.

“I don’t like to be hospitalized […] because I already have very bad insomnia, even in my house at night I have difficulties sleeping. But if I have this condition, I find it harder to cope.”

Table 2. Sociodemographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Patients (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>56.4 ± 7.0</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Pre-university</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Graduate/postgraduate</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>21 (87.5)</td>
</tr>
<tr>
<td>Malay</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Married</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Divorced</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Currently working</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Not working</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Retired</td>
<td>2 (8.2)</td>
</tr>
<tr>
<td>On long-term medical leave</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>2</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>3</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy received</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
for me to sleep […] If [I] need to be hospitalized, [I don’t have] to sleep [already].”

Post-Treatment Follow-Up: Health Care System–Related Barriers
Almost all of the survivors expressed their desire to continue their follow-up at the specialized cancer center. These survivors perceived the health care professionals at the cancer center as more knowledgeable in cancer treatment, and they thought that maintenance of treatment records at the cancer center was important. This confidence arose mainly as a result of prior experience with the center and was boosted by the services they received during active treatment.

Generally, the survivors were not confident with community cancer care, especially follow-up care with the community general practitioners (GPs). They perceived the GPs as not adequately knowledgeable about cancer treatment, and some of the survivors reflected that they were turned away by GPs when they approached the community clinic for consultation. Thus, many survivors preferred to continue follow-up at the specialized cancer center, even for simple procedures, such as vaccinations.

“I go to the GP, he doesn’t know how to do it […]. They actually turn you off, they say ‘No, I don’t do things like that.’ They turn you all away.”

DISCUSSION
This qualitative study was conducted to gain an in-depth understanding of the health concerns identified by breast cancer survivors in Asia and the barriers that would hinder them from optimal care during survivorship. Although much of the perspectives carry similarities with known literature, this study has identified a number of unique perspectives, particularly with the way survivors in Asia manage and cope with survivorship issues.

Survivors were overwhelmed by symptoms, including cognitive impairment, fatigue, and peripheral neuropathy, and they expressed concerns that these toxicities would become permanent over time. Although neurologic complications (both peripheral neuropathy and cognitive impairment) are significant after cancer treatment, it is clear to us that the survivors are not aware of strategies for coping with the physical effects of these complications. Thus, many of them resorted to complementary and alternative medicine (CAM). CAM is believed to have positive effects on psychological relief. One study found that Asian survivors believe that ginkgo biloba may have beneficial effects to reverse cancer-related cognitive toxicity. There is minimal evidence of the effectiveness of such CAM treatments to provide psychological symptom relief in cancer survivors. Yet, our participants expressed their eagerness and willingness to try these unconventional therapies to attain relief. These findings highlight the importance of conducting studies to evaluate specific CAM therapies that could resolve cancer-related symptoms.

Asians are generally influenced by culture and beliefs, and it is apparent that peers and family play a major role in the road of cancer recovery among Asians. This finding is consistent with a number of studies conducted among Asian survivors who observe the importance of adequate family support on the road to cancer recovery. Previous studies have shown that Asians uphold family values and remain conservative and dependent upon the support of friends and family members during critical illnesses. This is in contrast to a group of young breast cancer survivors in the United States, of whom most stated that they had lost family support or even interaction with their family members. Although the current guidelines from the Institute of Medicine on the cancer survivorship care plan do not address how family and peer support should be incorporated into a patient’s care plan, it is essential that survivorship programs implemented in Asia ensure sufficient involvement from family and peers. Such cultural differences between the Asian and Western societies should not be ignored.

We have also identified several patient- and health care–related barriers that are specific to Asian breast cancer survivors who participate in survivor care programs. Patient-related barriers were mainly personal in nature, such as the fear of unplanned hospitalizations or the receipt of inappropriate treatments. These barriers could be explained in part by the poor health literacy of our survivors. Past studies have also suggested that Asian survivors who have migrated to the Western world suffer from cultural barriers that lead to poorer outcomes in survivorship care. This highlights the importance of taking into account cultural sensitivity when survivorship programs for Asian breast cancer survivors are designed.

ASCO has recently provided recommendations to guide the management of breast cancer survivorship, which emphasize the role of a primary care provider to deliver survivorship care. Given the wide disparity of health care resources among different Asian countries, the ASCO standards must be carefully tailored and adopted, particularly in resource-limited countries. In Asia,
confidence remained an issue in this context; many of the breast cancer survivors noted that primary care clinicians were not adequately trained to handle the complexity of their conditions. This issue has also been greatly discussed in the literature within the Western context.17 As the breast cancer burden in Asia increases, it might not be feasible to solely depend on the specialized cancer center to adequately meet the needs of these survivors. A few strategies could be implemented to improve the seamless transition of care between the specialized cancer center and the GPs: greater use of electronic resources, such as web-based survivorship care plans, to ensure that care plans are accessible by GPs; improvement in the knowledge and confidence of GPs about care of cancer survivors by using different platforms, including didactic workshops, certification courses, and distance learning; and safe distribution of some services to a multidisciplinary team that comprises primary care providers and allied health professionals, such as nurses, pharmacists, and medical social workers (under a shared model) to provide holistic care for Asian cancer survivors. Currently, a randomized controlled trial is ongoing to evaluate the effectiveness of a standardized multidisciplinary survivorship program that is culturally adapted for Asian breast cancer survivors who have completed chemotherapy.3 The results from this study will drive the directions of survivorship care and provide insights into how such a structured program might be implemented on a larger scale and on a national level.

There are a few limitations to this qualitative study. Given that all of the participants of the focus group discussions were breast cancer survivors, findings of this study may not be generalizable to other cancer populations. Furthermore, participants of these focus groups were relatively highly educated; hence, their perspectives may not represent women who are less educated.

In conclusion, with the increase of cancer survivors in the next few decades, cancer survivorship is recognized as an important issue on a global scale. As interest in cancer survivorship grows in Asia, a more comprehensive understanding of Asian breast cancer survivors is needed to create transitional programs that suit their needs. Our data suggest that breast cancer survivors in Asia are still unfamiliar with the term survivorship and have a multitude of physical health and psychological issues to address to allow the transition to normalcy. Budding survivorship programs in Asia must take survivor perspectives into consideration to ensure that survivorship care is more fully optimized within the community.

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AUTHOR CONTRIBUTIONS
Conception and design: Alexandre Chan, Terence Ng, Yee Pin Tan, Gilbert Fan
Collection and assembly of data: Alexandre Chan, Zheng Kang Lum, Terence Ng, Tewodros Eyob, Xiao Jun Wang, Jung-woo Chae, Sreemanee Dorajoo, Maung Shwe, Yan Xiang Gan, Yee Pin Tan, Gilbert Fan
Data analysis and interpretation: Alexandre Chan, Zheng Kang Lum, Terence Ng, Rose Fok, Kiley Wei-Jen Loh, Yee Pin Tan, Gilbert Fan
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Alexandre Chan
Honoraria: Merck Sharp & Dohme
Consulting or Advisory Role: Merck Sharp & Dohme
Speakers’ Bureau: Merck Sharp & Dohme
Travel, Accommodations, Expenses: Merck Sharp & Dohme

Zheng Kang Lum
No relationship to disclose

Terence Ng
No relationship to disclose

Tewodros Eyob
No relationship to disclose

Xiao Jun Wang
No relationship to disclose

Jung-woo Chae
No relationship to disclose

Sreemanee Dorajoo
No relationship to disclose

Maung Shwe
No relationship to disclose

Yan Xiang Gan
No relationship to disclose

Rose Fok
No relationship to disclose

Kiley Wei-Jen Loh
No relationship to disclose

Yee Pin Tan
No relationship to disclose

Gilbert Fan
No relationship to disclose

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Affiliations
Alexandre Chan, Zheng Kang Lum, Terence Ng, Tewodros Eyob, Xiao Jun Wang, Jung-woo Chae, Sreemanee Dorajoo, Maung Shwe, Yan Xiang Gan, National University of Singapore; Alexandre Chan, Terence Ng, Tewodros Eyob, Xiao Jun Wang, Jung-woo Chae, Sreemanee Dorajoo, Maung Shwe, Yan Xiang Gan, Rose Fok, Kiley Wei-Jen Loh, Yee Pin Tan, and Gilbert Fan, National Cancer Centre Singapore; and Alexandre Chan, Duke–National University of Singapore Medical School Singapore, Singapore

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Breast Cancer Downstaging Practices and Breast Health Messaging Preferences Among a Community Sample of Urban and Rural Ugandan Women

**Purpose** Among a community sample of Ugandan women, we provide information about breast cancer downstaging practices (breast self-examination, clinical breast examination [CBE]) and breast health messaging preferences across sociodemographic, health care access, and prior breast cancer exposure factors.

**Methods** Convenience-based sampling was conducted to recruit Ugandan women age 25 years and older to assess breast cancer downstaging practices as well as breast health messaging preferences to present early for a CBE in the theoretical scenario of self-detection of a palpable lump (breast health messaging preferences).

**Results** The 401 Ugandan women who participated in this survey were mostly poor with less than a primary school education. Of these women, 27% had engaged in breast self-examination, and 15% had undergone a CBE. Greater breast cancer downstaging practices were associated with an urban location, higher education, having a health center as a regular source of care, and receiving breast cancer education ($P<.05$). Women indicated a greater breast health messaging preference from their provider (66%). This preference was associated with a rural location, having a health center as a regular source of care, and receiving breast cancer education ($P<.05$).

**Conclusion** Most Ugandan women do not participate in breast cancer downstaging practices despite receipt of breast cancer education. However, such education increases downstaging practices and preference for messaging from their providers. Therefore, efforts to downstage breast cancer in Uganda should simultaneously raise awareness in providers and support improved education efforts in the community.

**INTRODUCTION**

Breast cancer incidence in Uganda, like many other low- and middle-income countries (LMICs) in sub-Saharan Africa (SSA), has been increasing by a staggering 5.2% per year for the past 15 years. Unlike most SSA countries, Uganda offers cancer treatment, including surgery, radiation, and chemotherapy, at no cost through the Ugandan Cancer Institute (UCI) and a collaborative arrangement with the Ugandan Ministry of Health, the US National Cancer Institute, and the Fred Hutchinson Cancer Research Center. Nonetheless, late-stage presentation is a primary obstacle to improving breast cancer outcomes in Uganda, where > 77% of women are given a diagnosis of advanced-stage disease, including 26% with metastatic stage IV cancer at initial presentation. In a recent analysis of patients with breast cancer treated at UCI, 187 presented with stage III or IV disease and had a $< 40\%$ chance of surviving 5 years; by contrast, no deaths occurred at 5 years for the 22 patients who presented initially with stage I or II disease. Thus, an understanding of the systems-based factors that contribute to late-stage presentation and may promote breast cancer downstaging is important to improving outcomes in Uganda and potentially other SSA countries where breast cancer treatment can be available.

In LMICs where population-based screening is neither practical nor affordable, early breast cancer detection requires active participation by both...
levels.6,7,9 Thus, the measurement of BSE and breast diagnosis in health settings at all economic thickenings and is a basic-level resource for nostic evaluation of clinically detectable masses staging.12 Similarly, CBE is necessary for diag-

Improved breast cancer early detection and down-

With increased self-reported BSE and may link to breast cancer awareness education is associated
downstaging. Work in rural Ghana has shown that factors that contribute to or defeat breast cancer causation (CBE) has been demonstrated in a screening setting to independently reduce breast cancer mortality.10,11 Nonetheless, for countries like Uganda where women commonly first present with visually obvious breast masses or ulcerated tumors that have been present for many months or years, the assessment of BSE and CBE practices can serve as surrogate measures for essential factors that contribute to or defeat breast cancer downstaging. Work in rural Ghana has shown that breast cancer awareness education is associated with increased self-detected BSE and may link to improved breast cancer early detection and downstaging.12 Similarly, CBE is necessary for diagnostic evaluation of clinically detectable masses and thickenings and is a basic-level resource for breast diagnosis in health settings at all economic levels.6,7,9 Thus, the measurement of BSE and CBE practices is a relevant proxy for patient-
determined (BSE) and clinic-determined (CBE) breast cancer downstaging practices in an LMIC where breast cancer screening is unavailable. Furthermore, understanding how breast health messaging preferences related to these factors vary across sociodemographic, health care access, and prior breast cancer exposure factors can inform future approaches and programs to better target downstaging among women who have access to treatment.

The objectives of the current study were to pro-

The objectives of the current study were to pro-
due information about downstaging practices and breast health messaging preferences among Ugandan women 25 to 65 years old and to examine downstaging practices and breast health messaging preferences across sociodemographic, health care access, and prior breast cancer exposure factors.

METHODS

Procedure

This study was conducted between January and July 2014 in close collaboration with the Ugandan Women’s Cancer Support Organization (UWOCASO), a local group of breast cancer survivors. These Ugandan women are familiar with Ugandan culture and have experience with administering survey instruments and providing breast cancer education. After the development of the survey through multiple iterations and its translation from English (primary language of Uganda) to Luganda (common local language), we piloted the survey among a group of UWOCASO workers.

This study was exempt from Ugandan and US institutional review board review. Local guides and UWOCASO workers recruited women from the community for this study. We included asymptomatic women age 25 years and older with no personal history of breast cancer. Trained UWOCASO members interviewed eligible women individually in a semiprivate area. Participating women received a small financial incentive for their time and effort in accordance with local recommendations.

Participants and Setting

We collected survey data from 401 participants as follows: 100 from the capital city and largest urban center Kampala (Kamwonkya [n = 50] and Namuwongo [n = 50] communities) and 301 from rural villages and communities in south central Uganda (Rakai District: Kakuuto County, Ssanje Community [n = 100] and Mannya Parish [n = 100]; Kooki County, Lwanda Parish [n = 100]. The population densities were 24,423 people/square mile for the urban centers and ranged from < 50 people/square mile (Kakuuto County) to 251 to 500 people/square mile (Kooki County) for the rural centers.13

Measures

Sociodemographic, Health Care Access, and Prior Breast Cancer Exposure Factors. Sociodemographic information included geographic region (urban, rural), age (25 to 39, 40 to 49, and 50 to 74 years), ethnicity (Bantu, other), religion (Christian, other), intimate partner status (marital/living with partner, other), education (primary or less [= 7 years], more than primary [> 7 years]), and income (<= 500,000 shillings, > 500,000 shillings). The annual income question was recategorized into
a bivariate response because few participants reported income greater than the poverty level (approximately 1.5 million shillings/year).\textsuperscript{14,15} For health care access factors, women reported their regular source of care (health center, other [eg, self-care at home, traditional healer]) and their usual form of payment for care (self-pay, charity care, other [eg, private health insurance]). For prior breast cancer exposure, women self-reported whether they had a family history of breast cancer (no, yes) and whether they had ever received breast cancer education (no, yes).

**Breast Cancer Downstaging Practices.** Women reported their lifetime history of examining or observing their own breasts for palpable lumps (BSE: never, ever) and whether they had undergone a CBE by a health provider in the past year (no, yes).

**Breast Health Messaging Preferences.** Women indicated whose advice would most influence them in presenting early for a CBE in the theoretical scenario of self-detection of a palpable lump. Response categories were health providers, family/friends, and societal sources (advertisement by the government, television, or radio). Women were also asked where they would choose to go for a CBE (local health clinic, regional referral hospital, or other [eg, no preference, abroad]).

**Data Collection and Analysis**

The Collaborative Data Services at the Fred Hutchinson Cancer Research Center entered the questionnaire data by using the DatStat Illume software package (Seattle, WA). We produced descriptive information about downstaging practices and breast health messaging preferences. We conducted \(\chi^2\) tests to examine the relationships of downstaging practices and health care messaging preferences across sociodemographic, health care access, and prior breast cancer exposure factors. All statistical analyses were performed with SPSS software (IBM Corporation, Chicago, IL).

**RESULTS**

Table 1 summarizes sociodemographic factors and health care factors. The median age for the 401 women surveyed was 38 years (25 to 74 years). Most were married or living with a partner (62%), had a primary education or less (66%), and had an annual household income below the 33% poverty line (50%). Most participants reported receipt of medical care from a health center (61%) and self-pay for their care (67%). For prior breast cancer exposure, 14% reported a family history of breast cancer, and 47% self-reported receipt of previous breast cancer education.

<p>| Table 1. Overall Sample Characteristics (N = 401) |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic factor</td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>100 (25)</td>
</tr>
<tr>
<td>Rural</td>
<td>301 (75)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>25-39</td>
<td>215 (54)</td>
</tr>
<tr>
<td>40-49</td>
<td>107 (27)</td>
</tr>
<tr>
<td>50-74</td>
<td>77 (19)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Bantu</td>
<td>355 (88)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (11)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>336 (84)</td>
</tr>
<tr>
<td>Other</td>
<td>65 (16)</td>
</tr>
<tr>
<td>Intimate partner status</td>
<td></td>
</tr>
<tr>
<td>Married/living with partner</td>
<td>247 (62)</td>
</tr>
<tr>
<td>Other</td>
<td>148 (37)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Primary or lower</td>
<td>265 (66)</td>
</tr>
<tr>
<td>Higher than primary</td>
<td>116 (29)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
</tr>
<tr>
<td>(\leq 500,000) shillings</td>
<td>150 (50)</td>
</tr>
<tr>
<td>(&gt; 500,000) shillings</td>
<td>147 (50)</td>
</tr>
<tr>
<td>Health care access factors</td>
<td></td>
</tr>
<tr>
<td>Regular source of care</td>
<td></td>
</tr>
<tr>
<td>Health center</td>
<td>245 (61)</td>
</tr>
<tr>
<td>Other (eg, self-care at home, traditional healer)</td>
<td>151 (38)</td>
</tr>
<tr>
<td>Usual form of payment for care</td>
<td></td>
</tr>
<tr>
<td>Self-pay</td>
<td>267 (67)</td>
</tr>
<tr>
<td>Charity care</td>
<td>102 (25)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Prior breast cancer exposure</td>
<td></td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (14)</td>
</tr>
<tr>
<td>No</td>
<td>327 (86)</td>
</tr>
<tr>
<td>Received breast cancer education</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>181 (47)</td>
</tr>
<tr>
<td>No</td>
<td>204 (53)</td>
</tr>
</tbody>
</table>
Frequency of Downstaging Practices and Health Care Preferences

Table 2 depicts information about downstaging practices and breast health messaging preferences. Overall, the sample had low levels of downstaging practices: 27% had performed a BSE at least once in their lifetime and 15% had received a CBE in the past 12 months. Variability was found with regard to breast health messaging preferences: Women reported the greatest preference for breast health messaging by their health provider (66%) followed by friends/family (23%). Women preferred receipt of a CBE at a regional referral hospital (51%) to a local health clinic (12%).

Variation of Downstaging Practices and Breast Health Messaging Preferences Across Sociodemographic, Health Care Access, and Prior Breast Cancer Exposure Factors

We next analyzed the distribution of downstaging practices across sociodemographic, health care access factors, and prior breast cancer exposure factors (Table 3). On the basis of geographic region, urban participants were significantly more likely to report on performing BSE (46% vs. 20%, \( P < .001 \)) and having a CBE in the past 12 months (34% vs. 9%, \( P < .001 \)) than their rural counterparts. Participants with more than a primary school education were more likely to perform BSE (39% vs. 21%, \( P < .001 \)). Women who received regular care at the health center also were more likely to receive a CBE in the past 12 months (20% vs. 9%, \( P = .004 \)). Women who received previous breast cancer education showed significantly higher downstaging practices for both BSE (37% vs. 18%, \( P < .001 \)) and CBE (27% vs. 5%, \( P < .001 \)). No significant difference was found in downstaging practices related to age, marital status, income, usual pay, and family history.

We also analyzed breast health messaging preference across sociodemographic, health care access, and prior breast cancer exposure factors (Table 4). Relative to urban counterparts, a greater proportion of rural women indicated that they preferred breast health messaging from their health provider (69% vs. 56%, \( P < .001 \)). Conversely, urban women showed a greater preference for breast health messages from societal factors after self-detection of a palpable lump (24% vs. 7%, \( P < .001 \)). With regard to health care access factors, women who reported health centers as the regular source of health care showed a greater preference for breast health messaging from their health providers (72% vs. 57%, \( P < .005 \)). Women who self-paid for health care showed less preference for breast health messaging from their health providers compared with those who paid by other means (62% vs. 71% to 75%, \( P < .048 \)) and a greater preference for breast health messaging from family/friends (28% vs. 9% to 16%, \( P < .048 \)). Women who reported having received breast cancer education showed a greater preference for breast health messages from their health providers compared with those who reported no breast cancer education (70% vs. 58%, \( P < .021 \)) and less preference from family/friends (18% vs. 30%, \( P < .021 \)).

DISCUSSION

Breast cancer is a growing problem in SSA and has the potential to overwhelm limited resources.\(^{16,17}\) The increasing incidence of breast cancer in LMICs places an enormous burden on individuals and their families in an already taxed health care system.\(^{18,19}\) For these reasons, the World Health Organization is leading efforts to reduce this avoidable late disease burden by 2025.\(^{20}\) Breast cancer treatment is available in Uganda, but these efforts are thwarted by late-stage presentation when 75% to 90% of such women receive a diagnosis of locally advanced (stage III) or metastatic (stage IV)
Even in the United States, where the latest treatment options are available, such late stages are associated with more costly and technically demanding treatment and poorer survival; therefore, efforts should focus on detecting breast cancer at an earlier stage (downstaging).

### Table 3. Variation in Breast Cancer Downstaging Practices

<table>
<thead>
<tr>
<th>Downstaging Practice, No. (%)</th>
<th>Performed BSE</th>
<th>Received CBE ≤ 12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>46</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>20</td>
<td>&lt; .001</td>
<td>9</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or lower</td>
<td>21</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Higher than primary</td>
<td>39</td>
<td>&lt; .001</td>
<td>19</td>
</tr>
<tr>
<td><strong>Health care access factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular source of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health center</td>
<td>27</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Other (eg, self-care at home, traditional healer)</td>
<td>27</td>
<td>.540</td>
<td>9</td>
</tr>
<tr>
<td><strong>Prior breast cancer exposure factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received breast cancer education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>&lt; .001</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination.

### Table 4. Variations in Breast Health Messaging Preferences

<table>
<thead>
<tr>
<th>Who Would Most Influence You to Present Early for a CBE?* (%)</th>
<th>Health Provider</th>
<th>Family/Friend</th>
<th>Societal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>56</td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>69</td>
<td>24</td>
<td>7</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Health care access factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular source of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health center</td>
<td>72</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>57</td>
<td>32</td>
<td>11</td>
<td>.005</td>
</tr>
<tr>
<td>Usual form of payment for care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-pay</td>
<td>62</td>
<td>28</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Charity care</td>
<td>71</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>75</td>
<td>9</td>
<td>16</td>
<td>.048</td>
</tr>
<tr>
<td><strong>Prior breast cancer exposure factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received breast cancer education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58</td>
<td>30</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>18</td>
<td>12</td>
<td>.021</td>
</tr>
</tbody>
</table>

Abbreviation: CBE, clinical breast examination.

*In the theoretical scenario of self-detecting a lump.
To inform interventions to improve outcomes, we surveyed Ugandan women to assess their baseline downstaging practices and breast health messaging preferences and to examine variations in these across sociodemographic, health care access, and prior breast cancer exposure factors. Uganda was chosen as the study site because the UCI offers breast cancer treatment at no cost to the patient. Unfortunately, improved access to treatment is not as effective against late-stage breast cancer as it is in early-stage breast cancer. Therefore, downstaging is a prerequisite to improve breast cancer outcomes in a limited resource setting.23,25,26

Before designing interventions, it is valuable to understand the populations’ baseline experiences with the downstaging practices and health messaging preferences (eg, providers, family/friends) that are likely to be effective.27,28 Two previous studies suggested that the majority of Ugandan women performed a BSE at least once and almost one half received a CBE in the past year.29,30 Both these studies were limited in their generalizability to the Ugandan population, with one focusing on breast cancer survivors and the other on patients who already accessed health care at the largest hospital in Uganda. An understanding of these downstaging practices and breast health messaging preferences in the general population would better inform interventions.

Before the present study, little was known about the variation in downstaging practices and breast health messaging preferences across sociodemographic, health care access, and prior breast cancer exposure factors in Uganda. Health care access factors in Uganda, such as where a woman receives her routine medical care and how medical care is usually paid for, are influenced by sociodemographic variables, including geographic region (rural or urban), education, and income.14,31-33 Although prior breast cancer exposure (positive family history and breast cancer education) could influence downstaging practices,34-37 this question had not been evaluated. The present study confirms that downstaging practices and breast health messaging preferences vary by sociodemographic, health care access, and prior breast cancer exposure factors. We found that few Ugandan women participate in downstaging practices (BSE, 27%; CBE, 15%), despite what previous research has suggested (BSE, 60%; CBE, 40%).29 These differences may be related to our community-based sample compared with the sample used by Elsie et al29 that had already accessed the health care system. Within the present sample, we similarly noted that women who received their health care at a health clinic, and therefore accessed the health care system, were twice as likely to have a recent CBE. Although 54% reported having received prior breast cancer education and did not participate in downstaging practices, we simultaneously observed that women who received previous breast cancer education were twice as likely to have performed a BSE and more than five times more likely to have had a CBE than women who had not received breast cancer education. Such findings provide some support for the positive impacts of breast cancer education promoted by advocacy groups for improving practices in LMICs.12,38 These findings also emphasize the challenges facing downstaging efforts in LMICs and suggest that some barriers are not being addressed with current education efforts.

Our second objective was to identify sources of information most likely to be effective in communicating breast health information. We found in the present sample that 66% of women prefer breast health messaging from their health provider. These findings support previous studies that have shown the patient-provider relationship as the most important influence on health practices in Uganda.39,40 We also found that breast cancer education significantly increased preference for breast health messages from health providers. These findings suggest that education that targets providers may boost current efforts led by village health teams and nongovernmental organizations.

Although an improvement on prior survey studies, the convenience-based sampling used in the present study may limit its generalizability. Specifically, the urban and rural centers surveyed were mostly poor, and their residents had less than a primary school education. The middle class in SSA is growing, but still >67% of Ugandans are poor or vulnerable to poverty and have little education.15,31 Thus, we believe that the present study population provides a reasonable estimate of most Ugandan women. We also acknowledge that other social factors and beliefs beyond those considered here may adversely affect the stage of diagnosis, such as the role of traditional healers in delaying presentation to the hospital. These factors go beyond the scope of the current analysis but warrant investigation, especially once standard early detection and diagnosis systems are established and functioning.
In summary, we conclude that knowledge of the variations in downstaging practices and breast health messaging preferences across various sociodemographic, health care access, and prior breast cancer exposure factors can help to inform future basic interventions. The findings suggest that by providing education to both health providers and women downstaging practices will improve, and this combined approach may be more effective in encouraging women to present early after self-detection of a lump.

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AUTHOR CONTRIBUTIONS
Conception and design: John R. Scheel, Donald L. Patrick, Gertrude Nakigudde, Constance D. Lehman, Beti Thompson
Financial support: Beti Thompson
Administrative support: Beti Thompson
Collection and assembly of data: John R. Scheel, Donald L. Patrick, Constance D. Lehman
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Breast Cancer Downstaging Practices and Breast Health Messaging Preferences Among a Community Sample of Urban and Rural Ugandan Women
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John R. Scheel
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Yamile Molina
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Donald L. Patrick
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Benjamin O. Anderson
Research Funding: Pfizer, Roche

Gertrude Nakigudde
No relationship to disclose

Constance D. Lehman
Honoraria: GE Health Care
Research Funding: GE Health Care
Travel, Accommodations, Expenses: GE Health Care

Beti Thompson
Honoraria: General Electric
Consulting or Advisory Role: General Electric
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Affiliations
John R. Scheel, Donald L. Patrick, and Benjamin O. Anderson, University of Washington; John R. Scheel, Seattle Cancer Care Alliance; Benjamin O. Anderson and Beti Thompson, Fred Hutchinson Cancer Research Center, Seattle, WA; Yamile Molina, University of Illinois at Chicago, Chicago, IL; Gertrude Nakigudde, Uganda Women’s Cancer Support Organization, Kampala, Uganda; and Constance D. Lehman, Massachusetts General Hospital, Boston, MA.

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South African Breast Cancer and HIV Outcomes Study: Methods and Baseline Assessment

**Purpose** In low- and middle-income, HIV-endemic regions of sub-Saharan Africa, morbidity and mortality from the common epithelial cancers of the developed world are rising. Even among HIV-infected individuals, access to antiretroviral therapy has enhanced life expectancy, shifting the distribution of cancer diagnoses toward non–AIDS-defining malignancies, including breast cancer. Building on our prior research, we recently initiated the South African Breast Cancer and HIV Outcomes study.

**Methods** We will recruit a cohort of 3,000 women newly diagnosed with breast cancer at hospitals in high (average, 20%) HIV prevalence areas, in Johannesburg, Durban, Pietermaritzburg, and Empangeni. At baseline, we will collect information on demographic, behavioral, clinical, and other factors related to access to health care. Every 3 months in year 1 and every 6 months thereafter, we will collect interview and chart data on treatment, symptoms, cancer progression, comorbidities, and other factors.

We will compare survival rates of HIV-infected and uninfected women with newly diagnosed breast cancer and their likelihood of receiving suboptimal anticancer therapy. We will identify determinants of suboptimal therapy and context-specific modifiable factors that future interventions can target to improve outcomes. We will explore molecular mechanisms underlying potentially aggressive breast cancer in both HIV-infected and uninfected patients, as well as the roles of pathogens, states of immune activation, and inflammation in disease progression.

**Conclusion** Our goals are to contribute to development of evidence-based guidelines for the management of breast cancer in HIV-positive women and to improve outcomes for all patients with breast cancer in resource-constrained settings.

**INTRODUCTION**

Until recently, most malignancies in low- and middle-income, HIV-endemic regions of sub-Saharan Africa were related to infectious agents, such as Epstein-Barr virus and human papillomavirus. In the past decade, increases in longevity as a result of Westernization and the rollout of antiretroviral therapy (ART) have increased cancer incidence and shifted the spectrum of cancer diagnoses toward the epithelial malignancies that are typical of developed countries.3

Little is known about breast cancer (BC) outcomes in HIV-positive patients.4,5 In developed countries, BC may be slightly less common among HIV-infected than HIV-uninfected women or the general population because reproductive factors associated with HIV infection, such as young age at first pregnancy and multiple pregnancies, are associated with reduced risk of BC. In southern Africa, however, HIV may be associated with lower parity.11 If HIV-infected women have fewer children at an older age and breastfeed less than uninfected women, they may have higher risks of BC. HIV-related CD8+ T-cell dysfunction may affect cancer prognosis because CD8+ T cells can develop cytotoxic responses to tumor cell surface proteins. Although ART seems to mitigate the adverse effects of HIV on survival in certain cancers, its effects on breast cancer outcomes are unknown.

In a retrospective cohort of 220 BC cases in Uganda, where more than 80% had stage III or IV disease and 11% were HIV positive,27 HIV-infected patients had twice the 1-year mortality of uninfected patients. However, this study included only 24 HIV-positive patients with BC and lacked detailed information on their CD4 counts, viral loads, and ART use.

Herbert Cubasch
Paul Ruff
Maureen Joffe
Shane Norris
Tobias Chirwa
Sarah Nietz
Vinay Sharma
Raquel Duarte
Ines Buccimazza
Sharon Čačala
Laura W. Stopforth
Wei-Yann Tsai
Eliezer Stavsky
Katherine D. Crew
Judith S. Jacobson
Alfred I. Neugut

Author affiliations appear at the end of this article.
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**Corresponding author:** Alfred I. Neugut, MD, PhD, Division of Medical Oncology, Columbia University Medical Center, 722 W 168th St, Room 725, New York, NY 10032; e-mail: ain1@columbia.edu.
In 2010, South Africa had an age-standardized BC incidence rate of 25.86 per 100,000 women, but rates varied by ethnicity (Table 1). As of 2013, HIV prevalence among adults in South Africa was estimated to be 19.1% overall, but varied by age group, ethnicity, region, and sex; the highest HIV prevalence among sex and age groups in the general population was in women 30 to 34 years old (36%), but prevalence in female sex workers was nearly 60%.

Although HIV prevalence and ART availability are similar in several sub-Saharan African countries, in most such countries, > 75% of BC is diagnosed at stage III or IV. In addition, receptor testing is not routinely available and treatment, where available, is often not affordable. Few countries have cancer registries or systems for reporting mortality data or detailed clinical and pathologic data of patients with cancer at diagnosis.

South Africa has a pathology-based registry that reports incident cases and annual incidence rates overall and is stratified by population subgroup. The registry does not break down incident cases by clinical categories, such as stage or molecular subtype, nor does it report mortality data. In 2011, new legislation made cancer a notifiable condition, and the staffing of the registry was strengthened. Since then, the collection of public and private pathology data has been reliable and consistent. The registry is currently piloting a population-based cancer reporting system in a district east of Johannesburg, with a population of 3 million. However, rapid progression of disease, poor access to the health system, and rare diagnoses remain barriers to case finding.

In South Africa, cancer surgery, chemotherapy, radiotherapy, and hormonal therapies are available in tertiary referral hospitals; treatment costs to patients in the public sector are low or can be waived depending on patient resources; and social support mechanisms (eg, Cancer Association of South Africa care homes, hospital transport) may facilitate repeat hospital visits during treatment. Routine diagnostic work-ups include imaging; histologic confirmation conducted by the National Health Laboratory Service; immunohistochemistry (IHC) classification by estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status; and Ki-67 proliferation index staining on pretreatment biopsy or resection specimens.

In a US cohort of patients with BC, triple-negative breast cancer (TNBC), characterized by a lack of ER, PR, and HER2 receptors, was found in 10% to 20% of newly diagnosed patients and was associated with poor outcomes. African patients with BC have been reported to be two to three times more likely to have TNBC than patients of European ancestry. However, in our recent Soweto (Johannesburg, South Africa) study, only 20.7% of black women had TNBC. Large-scale molecular subtyping studies of BC have been conducted, but mainly in US populations.

Increasing evidence indicates that patients with BC who receive the full course of prescribed chemotherapy or hormonal therapy fare better than those who receive incomplete therapy. HIV-infected patients may have fewer financial resources, less social support, and lower baseline WBC counts than uninfected patients. HIV-infected patients receiving chemotherapy may also have higher risk of myelosuppression as a result of poor bone marrow reserve, opportunistic infections, and interactions with ART. Such patients may receive insufficient anticancer treatment.

South Africa’s unique combination of high HIV prevalence, widely available ART, and advanced facilities for BC diagnosis and treatment in the public sector has motivated us to undertake the South African Breast Cancer and HIV Outcomes (SABCHO) study.

### Preliminary Data

In 2006, the Surgical Breast Unit at Chris Hani Baragwanath Academic Hospital in Soweto established a clinical database that now includes almost 2,000 patients. Baseline characteristics of the patients diagnosed before 2013 have been described. All patients are offered HIV testing during their diagnostic work-up, and women who test positive for HIV are referred to the specialist HIV unit so that they can begin ART before cancer treatment.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No.</th>
<th>ASR Per 100,000</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>322</td>
<td>46.04</td>
<td>5.3</td>
</tr>
<tr>
<td>Black</td>
<td>2,997</td>
<td>18.33</td>
<td>48.9</td>
</tr>
<tr>
<td>Coloured</td>
<td>776</td>
<td>37.35</td>
<td>12.7</td>
</tr>
<tr>
<td>White</td>
<td>1,735</td>
<td>83.72</td>
<td>28.3</td>
</tr>
<tr>
<td>Unknown</td>
<td>295</td>
<td>NA</td>
<td>4.8</td>
</tr>
<tr>
<td>Total</td>
<td>6,125</td>
<td>25.86</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Abbreviations: ASR, age-standardized rate; NA, not available.
Of 1,092 consecutive patients with BC enrolled between 2006 and 2012, 765 (70%) were tested for HIV; 151 (19.7%) tested positive (including one-third of patients, 50 years old) and 37 (24.5%) had CD4 cell counts < 200 cells/L (median CD4 count, 316 cells/L).38 More than half of the patients were diagnosed with stage III or IV disease. Older age and residence farther from the hospital were associated with later-stage disease at diagnosis.47 HIV-positive patients with BC were younger than their HIV-negative counterparts, reflecting the age distribution of the HIV-positive population in the region, but did not differ in tumor characteristics.38

These findings raised questions about the pathways by which patients arrived at their BC diagnoses, the adjuvant treatment they received, and their ability, especially given HIV and other comorbidities, to tolerate chemotherapy and radiotherapy to the extent that they received it.

METHODS

Overall Study Design

For the SABCHO prospective cohort study, we will recruit 3,000 women with newly diagnosed BC at five hospital sites that serve populations with high HIV prevalence (Fig 1) over a 3-year period and follow them for at least 2 years. The study has been approved by the ethical review committees of the participating institutions.

Study Sites

The key characteristics of each hospital are summarized in Table 2. Each site is the main public tertiary hospital and sees most women diagnosed with BC in its catchment area. Most sites primarily serve low- to middle-income black African populations with limited or no health insurance. The five sites diagnose up to 1,200 patients per year with BC; approximately 20% may be infected with HIV.47a

Study Population

Subject eligibility. Female patients of any ethnicity and HIV status are eligible for study participation if they are ≥ 18 years of age, newly diagnosed with primary invasive BC at one of the participating hospitals, have no significant cognitive deficit, and have no previous cancer diagnosis other than nonmelanoma skin cancer or in situ cervical cancer.

As part of their routine diagnostic work-up, all patients are offered and almost all consent to HIV testing. Those who test positive are referred to the HIV unit so that they can initiate ART according to The South African Antiretroviral Treatment Guidelines 201348 before cancer treatment. Patients may refuse HIV testing but consent to participate in our study; they will be categorized in analyses as HIV status unknown.

Recruitment. At each participating hospital, a dedicated study nurse approaches every patient being seen for suspected BC, and obtains her demographic data and contact information. At the diagnostic confirmation visit, or by telephone if the patient does not return, the study nurse invites the patient to participate. If the patient agrees, a study nurse interviews her immediately or as soon as is feasible, before initiation of systemic or local therapy.

Study Procedures

Baseline visit. At the baseline interview (Table 3), the patient provides written informed consent for the study procedures, including administration of baseline and follow-up questionnaires, collection of a blood specimen, and use of the biopsy specimen and data from medical records. The patient may sign a separate consent for use of HIV-related data. Our validated Barriers to Care questionnaire (available on request) includes questions on BC knowledge and attitudes, social support, entry into the health care system, sources of delay in obtaining care, and facilitators of access to care. The study nurse obtains data on age, reproductive history, smoking, alcohol use, family history of breast and other cancers, and prior medical conditions from the baseline interview questionnaire and medical records. From the routine diagnostic work-up database, the nurse obtains the clinical stage; volume and grade of tumor; specimen margins; IHC data on ER, PR, and HER2 status (with fluorescence in situ hybridization reports for IHC 2+ results); and Ki-67 proliferation index, measured by the National Health Laboratory Service, Johannesburg, South Africa.

For consenting patients who have HIV, the study nurse ascertains the stage of HIV infection (acute infection, clinical latency, or AIDS [CD4 count < 200 cells/μL]), as well as ART use, pre- and post-ART viral load (if applicable), and diagnoses and treatment of opportunistic infections.

Follow-up interviews. Follow-up interviews will be conducted at 3, 6, 12, 18, and 24 months and every 6 months thereafter. The follow-up interview questionnaire (adapted from the Memorial...
Symptom Assessment\textsuperscript{49} will cover self-assessed health status and treatment-related adverse effects. After 24 months, the follow-up interview will involve a clinical examination for signs of recurrence and will focus on performance status and vital status. If the patient has died, the next of kin will be asked for the date of death, the likely cause of death (on the basis of the 2012 WHO verbal autopsy instrument), and the impact of the patient’s death on the family.

Medical record reviews will be used to obtain data on the patient’s surgery type (breast conserving, mastectomy, axillary lymph node dissection) and timing (primary or adjuvant), as well as chemotherapeutic, hormonal, and radiotherapy dates, doses, toxicities, and compliance. Routine laboratory tests

Table 2. Characteristics of Study Sites Participating in the South African Breast Cancer and HIV Outcomes Study

<table>
<thead>
<tr>
<th>Site</th>
<th>Catchment Area (population in millions)</th>
<th>HIV Prevalence, %\textsuperscript{47a}</th>
<th>Ethnic Composition</th>
<th>No. of New Breast Cancer Cases Per Year</th>
<th>Expected No. of HIV-Positive Diagnoses Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chris Hani Baragwanath</td>
<td>Soweto (3)</td>
<td>16</td>
<td>90% black (isiXhosa, Sesotho, isiZulu, Setswana speaking)</td>
<td>300</td>
<td>48</td>
</tr>
<tr>
<td>Charlotte Maxeke</td>
<td>Johannesburg (1.5)</td>
<td>14</td>
<td>80% black</td>
<td>250</td>
<td>35</td>
</tr>
<tr>
<td>Inkosi Albert Luthuli</td>
<td>Durban metropolitan (3.5)</td>
<td>26</td>
<td>Indian and black (isiZulu speaking)</td>
<td>300</td>
<td>78</td>
</tr>
<tr>
<td>Gray’s, Pietermaritzburg</td>
<td>Western KwaZulu/Natal (3.5)</td>
<td>26</td>
<td>Black (isiZulu speaking) and Indian</td>
<td>300</td>
<td>78</td>
</tr>
<tr>
<td>Ngwelezana, Empangeni</td>
<td>Uthungulu, Umkhananyakude, KwaZulu/Natal (3)</td>
<td>26</td>
<td>95% black (isiZulu speaking)</td>
<td>50</td>
<td>13</td>
</tr>
</tbody>
</table>
Biomarker assays. We will obtain 10-μM tissue sections from 400 well-annotated BC cases (200 HIV positive and 200 HIV negative). From each tumor block, our pathologists will obtain a hematoxylin and eosin–stained slide to verify tissue morphology and tumor volume, and to guide macrodissection of the tumor to avoid normal tissue contamination, before mRNA extraction for the PAM50 gene test using a NanoString assay.

The genomic NanoString assay has been found comparable to real-time reverse transcriptase polymerase chain reaction and DNA/RNA microarrays in its ability to profile hundreds of DNA and RNA samples with high sensitivity and precision. It requires fewer steps and is relatively easy to analyze and interpret. The protocol eliminates enzymatic reactions that introduce bias into the results. Therefore, it reduces human error and provides more accurate data on gene expression from mRNA extracted from formalin-fixed paraffin-embedded (FFPE) tumor samples. We will use the PAM50 NanoString assay, as customized...
by Perou et al., for intrinsic subtyping and risk of recurrence analyses by PAM50 and IHC4 methods. We have acquired the resources to conduct these assays at the University of the Witwatersrand.

Breast tumor development involves complex interactions among many cell types. Cytokines and chemokines secreted by tumor cells can promote or inhibit tumor progression. We will use blood samples collected from the patients to profile cytokine and chemokine expression using a multianalyte screening strategy by Luminex (Bio-Plex Pro cytokine assay, Bio-Rad, Hercules, CA).

**Analytic Approach**

We will use a classic bio-psychosocial theoretical model to elucidate how system-level factors (access to early diagnostics and appropriate treatment), individual-level factors (socioeconomic status, psychosocial factors, lifestyle factors, comorbidities), and clinical factors (tumor characteristics, treatment, comorbidities) influence our primary and secondary end points among HIV-infected and uninfected patients with BC.

**End points.** The primary end point is overall survival; secondary end points are BC-specific and disease-free survival, treatment-related adverse events, and health status (for the > 90% of women with stages I to III BC). Survival time will be calculated both from confirmed diagnosis and, as a sensitivity analysis, from the date of first presentation to a health care provider for a breast problem that is subsequently confirmed as BC to the date of death. Additional outcomes (Table 3) will be adherence to cancer (chemo-, radiation, and hormonal) and HIV therapy, as well as toxicities.

**Statistical analyses.** The baseline data will be analyzed after recruitment is complete. We will compare HIV-infected and uninfected patients with respect to socioeconomic status, psychosocial factors, lifestyle factors, comorbidities, tumor characteristics, and surgical procedures, using t tests for continuous variables and χ² tests for categorical variables to evaluate statistical significance.

For survival analyses, we will use statistical methods described by Swaminathan and Brenner, including specific methods for estimating cancer survival in limited-resource settings where follow-up through electronic registries is often not possible. We will use similar approaches to analyze all time-to-event outcomes, including time between BC diagnosis and death; first clinical presentation and diagnosis; diagnosis and first treatment (any); surgery and systemic therapy; and diagnosis and BC recurrence. We will use medians and interquartile ranges to summarize the data. We will generate Kaplan-Meier estimates, with the log-rank test at the 5% significance level, to compare overall, BC-specific, and disease-free survival by HIV status.

We will then develop Cox proportional hazards models to investigate factors associated with the

---

**Fig 2.** Causal pathways under investigation within the South African Breast Cancer and HIV Outcomes study for breast cancer survival among HIV-positive and HIV-negative women. ART, antiretroviral therapy.
These analyses will involve univariate assessment of each factor for association with survival outcome at a conservative 20% significance level and forward multiple regression modeling, in which all factors significant at the univariate level will be considered for significance at the 5% level. We will subdivide HIV-positive patients on the basis of CD4 count (≥500, 200 to 499, and <200 cells/L) and prior HIV infection and receipt of ART at the time of cancer diagnosis.

We will also investigate determinants of optimal therapy for BC among HIV-positive and HIV-negative women, seeking modifiable reasons for disparities in cancer care and clinical outcomes.

Figure 3 depicts our four-state stochastic process, where $\lambda_1(t;x)$ and $\lambda_2(s,t;z)$ are, respectively, the hazard rate from state 1 to state 2 and from state 2 to state 3; $x$ and $z$ are covariates that may be time dependent. State 1 is diagnosis. The time origin is the date of BC diagnosis. State 2 is cancer therapy (chemotherapy, radiotherapy, or hormonal therapy), and $t$ is the date of the patient’s first cancer therapy. State 3 is the dropout state, and $s$ is the dropout date. Patients who complete optimal therapy will be censored at the completion date. Patients who do not initiate optimal therapy within 6 months after diagnosis will be in state 4, which is noninitiation of optimal therapy. We will use logistic regression to analyze the association of HIV and covariates with noninitiation of therapy. We will also relate HIV and covariates to initiation time and dropout time using Cox proportional hazards models.

Using our NanoString data, we will classify each patient as luminal A, luminal B, HER2-enriched, basal-like, or normal-like, and as low, intermediate, or high risk. We will then compare the proportions of cases in each category in the HIV-positive and HIV-negative groups using $\chi^2$ tests. We will also generate a risk of recurrence (ROR) score from the PAM50 test, which is derived from the gene expression profile (with special weighting of proliferation-associated genes) and accounts for tumor size. Two-sample $t$ tests (or non-parametric analogs) will be used to compare mean ROR scores by HIV status. Results will be compared with those obtained from the cost-effective IHC4 ROR algorithm.

We will use the Kruskal-Wallis analysis of variance by ranks method to compare cytokine expression levels of the intrinsic subtypes in the context of HIV infection, and we will conduct multiple-comparison two-tailed post hoc tests to home in on differences between groups by the Kruskal-Wallis test. We will use hierarchical clustering methods to show the cytokine associations within each subtype and to generate dendograms, using the unweighted pair-group average and evaluating Euclidean distance to indicate similarities.

RESULTS

Recruitment for the SABCHO study began in October 2015 and is in progress.

DISCUSSION

This study expands on our previous data collection efforts by including long-term follow-up for survival, assessing detailed treatment-specific adherence and toxicities, and collecting similar data at five institutions in South Africa. In addition, it includes more rigorous phenotyping with the PAM50 genomic assay.

The few genomic studies of breast tumors in African women have mainly used FFPE tissues and existing multigene tests to identify gene expression signatures on the basis of microarrays and real-time reverse transcriptase polymerase chain reaction applied to frozen tissue. These assays are technically complex, and their results may not be reproducible. Instead, we are using the nanotechnology-based nCounter digital gene expression platform, which has highly reproducible results with FFPE RNA samples. The system automatically applies a series of quality control metrics to each sample during analysis to determine whether results fall within expected values. We expect to measure gene expression in FFPE tumors accurately and to identify different spectra and frequencies of RNA transcripts.

In conclusion, the complex problem of HIV and cancer in resource-constrained settings calls for the prospective, integrated, multidisciplinary approach we will use in the SABCHO study. Our data will provide a basis for assessing health care system responses to patient needs and for the development of interventions to improve survival.
rates in South Africa and potentially other sub-Saharan African countries.

The strengths of our study include its focus on a region of sub-Saharan Africa with a high prevalence of HIV, a multiethnic population with poor BC outcomes, and facilities for efficacious diagnosis and treatment. To our knowledge, this is also one of the first large-scale studies of tumor molecular profiling among African patients with BC, using gene expression signatures with known prognostic significance and correlating them with HIV status. Our intention is that this multicenter study will help identify context-specific, modifiable factors that can be targeted in future interventions to improve BC outcomes in South and sub-Saharan Africa.

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AUTHOR CONTRIBUTIONS
Conception and design: Herbert Cubasch, Paul Ruff, Maureen Joffe, Raquel Duarte, Katherine D. Crew, Judith S. Jacobson, Alfred I. Neugut
Financial support: Paul Ruff, Maureen Joffe, Alfred I. Neugut
Administrative support: Paul Ruff, Maureen Joffe
 Provision of study materials or patients: Sarah Nietz, Vinay Sharma, Ines Buccimazza, Sharon Čačala, Laura W. Stopforth
Collection and assembly of data: Herbert Cubasch, Maureen Joffe, Sarah Nietz, Vinay Sharma, Ines Buccimazza, Sharon Čačala, Laura W. Stopforth
Data analysis and interpretation: Herbert Cubasch, Paul Ruff, Shane Norris, Tobias Chirwa, Sarah Nietz, Wei-Yann Tsai, Eliezer Stavsky, Judith S. Jacobson, Alfred I. Neugut
Manuscript writing: All authors
Final approval of manuscript: All authors

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 www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Herbert Cubasch
No relationship to disclose

Paul Ruff
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Maureen Joffe
No relationship to disclose

Shane Norris
No relationship to disclose

Tobias Chirwa
No relationship to disclose

Sarah Nietz
No relationship to disclose

Vinay Sharma
No relationship to disclose

Raquel Duarte
No relationship to disclose

Ines Buccimazza
No relationship to disclose

Sharon Čačala
No relationship to disclose

Laura W. Stopforth
No relationship to disclose

Wei-Yann Tsai
No relationship to disclose

Eliezer Stavsky
No relationship to disclose

Katherine D. Crew
No relationship to disclose

Judith S. Jacobson
No relationship to disclose

Alfred I. Neugut
Stock or Other Ownership: Stemline Therapeutics
Consulting or Advisory Role: Pfizer, Teva, Otsuka, UBC, EHE International

Affiliations
Herbert Cubasch, Sarah Nietz, Paul Ruff, Maureen Joffe, Shane Norris, Tobias Chirwa, Vinay Sharma, and Raquel Duarte, University of the Witwatersrand; Sarah Nietz, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg; Herbert Cubasch and Vinay Sharma, Chris Hani Baragwanath Academic Hospital, Soweto; Ines Buccimazza, University of KwaZulu-Natal; Ines Buccimazza, Inkosi Albert Luthuli Central Hospital, Durban; Sharon Čačala and Laura W. Stopforth, Grey’s Hospital, Pietermaritzburg, South Africa; and Wei-Yann Tsai, Eliezer Stavsky, Katherine D. Crew, Judith S. Jacobson, and Alfred I. Neugut, Columbia University, New York, NY.
REFERENCES


Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa

Abstract

Purpose Breast cancer is the most common cause of cancer in women in South Africa, and often patients present late. There is little understanding of the psychosocial stresses affecting women with breast cancer in Africa.

Methods A questionnaire was distributed to 263 patients with breast cancer at two sites (one government and one private facility) in Johannesburg. Self-reported levels of fear were recorded on summative scales and their relationship to demographic variables assessed through univariable and multivariable modified Poisson regression.

Results Fears related to treatments and prognosis, particularly radiation, loss of hair, and loss of breast, were far stronger than those related to socioeconomic barriers. Relative risk (RR) of most fears was higher in women younger than age 40 years, including treatment affordability (RR, 1.80; 95% CI, 1.26 to 2.56), hair loss (RR, 1.48; 95% CI, 1.12 to 2.95), and surgery (RR, 1.31; 95% CI, 1.02 to 1.68). Difficulty taking time off work predicted fear of job loss (RR, 2.59; 95% CI, 1.59 to 4.21) and missing appointments because of transport (RR, 2.46; 95% CI, 1.52 to 3.96) or family commitments (RR, 2.46; 95% CI, 1.52 to 3.96). Women with dependents and black women were more afraid of dying (RR, 1.73; 95% CI, 1.03 to 2.90; and RR, 1.79; 95% CI, 1.33 to 2.24, respectively); however, socioeconomic status in this sample was a strong confounder of race and explained most of the racial differences in levels of fear.

Conclusion The most significant fears around breast cancer were related to treatment modalities and adverse effects rather than transport, financial, or work concerns. Young age and job insecurity were predictive of increased fears. Education about treatments has a key role to play in improving access to breast cancer care in South Africa.

Sarah Rayne
Kathryn Schnippel
Cynthia Finnhaber
Kathryn Wright
Deirdre Kruger
Carol-Ann Benn

INTRODUCTION

Breast cancer is the most common form of cancer to affect women in South Africa and in 2013 was responsible for 20.8% of female cancers and more than 10% of the entire cancer burden.1 The National Cancer Registry (most recent report, 2009) reports an age-adjusted incidence of 27.6 per 100,000, equating to a lifetime risk of 1 in 33 women.1

In developed countries, advances in the management of breast cancer over the last 50 years, including screening and early detection programs, have led to an increase in survival rates. Early-stage breast cancer has a survival of > 95%;2 however, late-stage disease continues to be responsible for most cancer deaths, through metastatic progression.

Optimal treatment of breast cancer and increased survival rely not just on early detection but on early and continued presentation at a center capable of treating the disease. Thus, health care disparities will affect a patient’s outcome.3 In trying to understand these disparities and their effect on outcome, studies often look to socioeconomic factors, including education, health insurance status, work, and transportation.4,5 These factors may provide physical barriers in accessing adequate health care. Physical barriers can also become a source of psychosocial stress for the patient, causing fears that can also affect timely presentation, treatment, and patient choices about their breast cancer care.6 In addition to physical barriers to access of care and fears
related to sociodemographic factors, further stress can be associated with knowledge (or lack of knowledge) of treatment modalities and their associations and adverse effects.

Understanding the fears associated with breast cancer in South Africa is important in improving care and enabling and encouraging all women to access treatment earlier. By interviewing women accessing services in both government and private facilities in Johannesburg, we sought to determine the fears experienced by all women with a diagnosis of breast cancer, allowing identification of important universal areas for education and improved care provision.

METHODS

This dual-center study included patients with and without medical aid in Johannesburg, South Africa. Medical aid is the system of health insurance in South Africa bought by the end-user that allows access to private facilities. Patients without medical aid or with poor coverage are seen in government-funded facilities at low or no cost. The government clinic is based within a provincial government tertiary hospital and manages approximately 350 new breast cancer diagnoses each year. Only 6% of these patients have medical insurance (unpublished local data). The private facility sees private- or medical insurance (unpublished local data). The private facility sees private- or medical insurance-funded patients and manages approximately 400 new breast cancer cases per year.

From November 2011 to May 2013, patients undergoing treatment of breast cancer in each center were recruited to complete a questionnaire. The questionnaire was distributed to consenting patients attending for diagnosis, operation, or follow-up over a 21-month period. Each patient was offered the choice to complete the questionnaire alone or with the aid of an assistant, who could translate into the patient’s preferred language. The study received ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand (M111121).

The first part of the questionnaire included sections on demographics, socioeconomic status, educational background, work, transport, and religious affiliations. The second part of the questionnaire used a summative scale of 0 (no fear) through 5 (fear under control) to 10 (very fearful) to determine the patients’ feelings of fear and concern at diagnosis about issues related to their care, social circumstances, or prognosis.

Patient characteristics were described using frequencies and proportions. Age was categorized as age 40 years and younger or age 41 years and older. Having dependents was compared with not having dependents. Social status was categorized as being married or unmarried, the latter of which included women who were single, divorced, or widowed. Women who were employed by others or considered themselves self-employed were compared with women who were unemployed or retired. Education was grouped according to highest level of formal schooling completed: primary, secondary, or tertiary. Reported race was collapsed into black and nonblack categories, including women who indicated white, Indian (Asian), colored, and mixed races. Women who indicated that they sometimes or always had difficulty with transport or taking time off from work were compared with women who indicated they seldom or never had those difficulties. Two-sided differences of proportions were compared using Pearson’s $\chi^2$ test. A $P$ value < .05 was considered statistically significant.

Patients who did not have a confirmed diagnosis of cancer were excluded from the analysis of fears ($n = 4$). Responses were categorized as fearful (score $>5$) or not fearful. Modified Poisson regression with robust error estimation was applied to the data to estimate the relative risk (RR) of being fearful according to patient characteristics; RRs and a 95% CIs are presented. Univariable and multivariable results adjusted for the patient characteristics described above are presented. All statistical analyses were done in Stata v13.1 (College Station, TX).

RESULTS

A convenience sample of 263 patients was included. Patient age ranged from 18 to 86 years, with a median of 52 years (interquartile range, 44 to 62), with 41 patients who were age 40 years or younger at diagnosis (16%). Table 1 lists patient characteristics grouped as either private hospital or government hospital and shows that government patients were more likely to be black ($P < .001$), single, and living with others. They were less likely to be employed when compared with private facility patients (52% vs 73%; $P = .001$). Significantly more private facility patients had a tertiary education (53% vs 13%, $P < .001$), and 36% of government patients attained primary education only compared with 6% from the private facility. Access to cell phones was extremely high in both groups (97% private facility, 95% government), but computer and internet usage was significantly higher in private patients (87% vs 39%, $P < .001$).
Figure 1 illustrates how many patients with a confirmed cancer diagnosis (n = 259) were fearful (score > 5) for each domain included in the questionnaire. The overall pattern demonstrates that fears related to treatments and prognosis were far stronger than those related to socioeconomic barriers. The most common treatment-related fears were related to chemotherapy adverse effects (65.4%), followed by radiation and surgery (59.7% and 53.9%, respectively). Although some patients feared both surgery and breast loss, the differences between the women who feared surgery and those who feared breast loss was statistically significant (P < .001), as were women who feared surgery and women who feared radiation (P < .001), using the Pearson’s χ² test. Concerns over ability to attend appointments for reasons including transport and work were the lowest.

Relative Risks of Different Fears

The RRs of fearfulness for women younger than age 40 years were uniformly higher than for older women (Fig 2). This was most pronounced in their worry over affording all appointments and treatments (RR, 1.80; 95% CI, 1.26 to 2.56). Young women also had an increased likelihood of treatment-related fears, significantly in fear of hair loss (RR, 1.48; 95% CI, 1.12 to 2.95) and fear of surgery (RR, 1.31; 95% CI, 1.02 to 1.68).

In women of all ages, difficulty with taking time off work (a relative measure of job insecurity) had increased likelihood of fear about job loss (RR, 2.59; 95% CI, 1.59 to 4.21), and women were more likely to fear missing appointments either because of transport (RR, 2.46; 95% CI, 1.52 to 3.96) or because of family commitments (RR,

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Private Hospital (n = 93; 35%)</th>
<th>Government Hospital (n = 171; 65%)</th>
<th>Total (n = 264)</th>
<th>P</th>
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<td>Age</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;= 40 years</td>
<td>15 (16)</td>
<td>34 (21)</td>
<td>207 (81)</td>
<td>.388</td>
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<tr>
<td>&gt; 41 years</td>
<td>77 (84)</td>
<td>130 (79)</td>
<td>49 (19)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7 (8)</td>
<td>78 (48)</td>
<td>85 (33)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Nonblack</td>
<td>85 (92)</td>
<td>85 (52)</td>
<td>170 (67)</td>
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<td>Marital status</td>
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<tr>
<td>Married</td>
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<td>70 (47)</td>
<td>120 (51)</td>
<td>.081</td>
</tr>
<tr>
<td>Not married</td>
<td>35 (41)</td>
<td>79 (53)</td>
<td>114 (49)</td>
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<tr>
<td>Formal education</td>
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<tr>
<td>Primary</td>
<td>5 (6)</td>
<td>56 (36)</td>
<td>61 (25)</td>
<td>&lt; .001</td>
</tr>
<tr>
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<td>80 (51)</td>
<td>117 (48)</td>
<td></td>
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<tr>
<td>Tertiary</td>
<td>48 (53)</td>
<td>20 (13)</td>
<td>68 (28)</td>
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<td>Dependents</td>
<td></td>
<td></td>
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<td></td>
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<td>23 (15)</td>
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<td>.297</td>
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<td>132 (85)</td>
<td>204 (83)</td>
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<td>98 (97)</td>
<td>147 (95)</td>
<td>265 (96)</td>
<td>.484</td>
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<td>Use computer</td>
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<tr>
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<td>79 (87)</td>
<td>62 (39)</td>
<td>141 (56)</td>
<td>&lt; .001</td>
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<tr>
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<td>67 (73)</td>
<td>83 (52)</td>
<td>150 (60)</td>
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<td>Time off for appointments difficult</td>
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<td></td>
<td></td>
</tr>
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<td>12 (13)</td>
<td>32 (24)</td>
<td>44 (20)</td>
<td>.039</td>
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<tr>
<td>Transport for appointments difficult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (9)</td>
<td>58 (36)</td>
<td>66 (26)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Data presented as No. (%).
They also feared the adverse effects of chemotherapy more (RR, 1.30; 95% CI, 1.07 to 1.58). A tertiary education was protective against fear of job loss (RR, 0.46; 95% CI, 0.24 to 0.92) and not attending appointments because of transport and family (RR, 0.20; 95% CI, 0.07 to 0.58; and RR, 0.33; 95% CI, 0.14 to 0.75, respectively).

The RR of fear of dying had a median of 5 and the widest spread of any of the fears, with an interquartile range of 1 to 9; 47.7% of participants indicated they were fearful of dying (a score > 5). Women with dependents were 1.73 times more likely to be afraid of dying (95% CI, 1.03 to 2.90), as were black women (RR, 1.79; 95% CI, 1.33 to 2.24). Figure 3 shows that black women experience much more fear toward the physical barriers to care: they were much more afraid of missing appointments because of transport problems (RR, 4.11; 95% CI, 1.42 to 8.12) or because of family commitments (RR, 2.56; 95% CI, 1.42 to 4.62) and worried they could not afford to get cancer (RR, 1.66; 95% CI, 1.17 to 2.37). These results are similar to those experienced by women in the public hospital (Fig 4).

In adjusted regression, where patient characteristics were held constant (Fig 5), black race remained a significant predictor of fear of dying (adjusted RR, 1.73; 95% CI, 1.13 to 2.64). Socioeconomic characteristics such as employment, use of the government hospital, and computer use were not statistically significant predictors of fear of dying. Although being young, black, in a government hospital, or with transport difficulties increased the fear of affordability of treatments, none remained significant in the multivariable adjusted model.

**DISCUSSION**

In women with a diagnosis of breast cancer, this study found that breast cancer treatment and its adverse effects, including the universal fears of cancer and dying, were associated with increased fear at diagnosis, but socioeconomic factors, including transport, work, and financial issues, were not. Affordability of cancer treatment was the only socioeconomic factor that was associated with an increased level of concern.

Studies have found that fear can be important in determining delay to treatment. How patients are treated also seems to influence if they continue to attend for care, whether by their physicians or because of adverse effects. However, the relative contribution of these factors to fear...
associated with a diagnosis has not been determined. The new findings from this study suggest that physical obstacles may represent less of a barrier to care than psychological fears associated with treatments in our urban South African setting.

Within this sample, different populations emerged, each with unique combinations of concerns. Like many other studies, we found a significant relationship between younger age and higher cosmetic fears around hair loss, although not loss of the breast. This lack of fear around mastectomy may reflect the options of reconstruction and breast-conserving surgery. Younger women also face increased fears over affordability of treatment, having surgery, and job insecurities. These differences reflect the pressures these women face in maintaining income after a diagnosis. The loss of hair could also be concerning in this light, as it would publicize cancer therapy to employers and colleagues. Studies that have looked at the psychological needs of young women have found that younger patients viewed themselves as different from older patients, with problematic work and relationship issues, fertility decisions, and poor support when transitioning into survivorship. Our findings are consistent with this and highlight the distinctive support needs of this young group.

In addition, this study highlighted other groups with less psychological resilience around breast cancer treatments, including those with job insecurities (increased fear of job loss) and those with dependents (fear of dying), whose additional supportive needs may be overlooked. The near-universal fear of cancer, with all its negative connotations, was present in increasing measure in those with dependents. In an economic center such as Johannesburg, members of the working population are often held responsible for household dependents in addition to supporting an extended family and homesteads in rural areas. It is possible that the demands of close caregiving to family, the economic demands of dependents near and far, and the unexpected nature of cancer can add significant psychological stress to such patients.

The highest-scoring fear was in relation to possible radiation treatment. This mirrors other studies that show women have a nonspecific fear of radiation and possibly fear its relationship to causing cancer. These findings highlight the important role of education of the presymptomatic woman (essentially every woman) in how breast cancer is not just diagnosed but also treated. Education has been shown to reduce fears and improve attendance in diverse global populations, including recent successes of HIV/AIDS community education in sub-Saharan Africa, where radio and television soap operas have...
been used to highlight diseases such as HIV/AIDS with measurable effect.24 The contribution of recent high-profile breast cancer survivors in South Africa can also be used as an opportunity to introduce public discussion of treatment options and successes in breast cancer care.25

The current study indicated an extremely high ownership of mobile phones in the population studied (89%). This, coupled with the increasing use of internet through smartphone connectivity, allows eHealth (using communication technology for health) and mHealth (using mobile

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**Fig 3.** The relative risk (RR) of fears in women of black race shown relative to all other women in the study.

**Fig 4.** The relative risk (RR) of fears in women at public sector hospital shown relative to women at private sector hospital.
communication technology to deliver health care) strategies to be used for education. Already, young patients in South Africa access health information for themselves and family through smartphone internet access, and this has been shown to modify health behavior, if not knowledge, in a South African patient population. These forms of education can complement more traditional mass-education initiatives, which have been used in breast cancer awareness in low-income, low-awareness areas of the world and in South Africa, with layering of messages of education through multimedia. This new finding that breast cancer treatments are a source of fear and potential barrier to care means that introducing management options and expectations into the dialogue of breast cancer awareness and screening should be a practical application after this study for cancer care in South Africa.

The fear of dying in black women was moderated by attendance at a government hospital. This may be a reflection of good social support, closer ties to community, and in particular the presence of survivor-navigators in the government hospital, funded by a nongovernmental organization. Other studies have also found that having counsellors or navigators present reassures patients and helps them negotiate the complex medical system, and they are then likely to receive recommended standard treatment. In addition, navigators are able to identify and resolve intrapersonal (defined as beliefs, knowledge, attitudes, and socioeconomic) barriers that affect patients. Securing funding to maintain and increase the number of available navigators is a challenging undertaking in our resource-limited environment; however, the potential future outcome of improved patient care highlights the necessity.

Previous studies have shown strong relationships between disparities of access and response to breast cancer care for different races internationally and in South Africa. Studies from Africa or of African migrants often rely on using cultural beliefs and fears to explain these barriers to care, whereas in this study we found that although there were differences between races in their levels of fear, these were related to inherent socioeconomic disparities rather than cultural responses. Black women were more likely to fear hair or breast loss and more likely to experience concerns over socioeconomic obstacles. However, because of the legacy of previous economic/political policies in the country, there remains a significant association between race and socioeconomic status. These socioeconomic factors were strong confounders of race in this study and, on multivariable analysis, most of the race-fear relationships weakened, demonstrating
few inherent racial differences but inherent strong educational and economic drivers of fear. These data provide preliminary support for questioning the existence of culturally bound reasons for delay and failure in breast cancer treatment and point to more holistic concerns shared by women of all races in all countries.

In all countries, but particularly in post-apartheid South Africa, relying on factors such as race to predict fears, attitudes, and access is problematic. These data confirm the questioning of the influence race alone has on fears around breast cancer and receptiveness to treatment and, in fact, whether universal concerns over welfare and fear around treatment and death transcend race or culture. Health surveys among other seemingly homogeneous groups show great diversity of language, education, diet, and health behaviors, and therefore assuming help-seeking behavior or barriers will be standardized in a racial group should be treated with caution.

For practical reasons, an opt-in invitation method was used in this study, and no information is available for those who declined to complete the questionnaire. Although translation was available, there may be a selection bias toward English-speaking patients of all races, and this may confound some of the variables, particularly around education and employment. Therefore, the extent to which this can be generalized to all patients with breast cancer is unknown. An additional consideration and scope for further work is that the study was purely quantitative in its approach. Examination of the full scope of fears and attitudes of patients through interviews would increase the range of our understanding of the patient’s experience.

The study was cross-sectional in nature, and although women were asked to recall the fear experienced at diagnosis, in recollection some of these fears may have been moderated or increased for women who had already started treatment. In addition, a further limitation as with many studies of breast cancer in sub-Saharan Africa is that this sample is taken from patients attending an urban specialist center. Although they would have vital and valid responses for this study, particularly regarding access and barriers to care, it is impossible to target patients with breast cancer who fail or refuse to present to medical services at any point in their care. However, many of the patients in this study would be presenting in the later stages of the disease for final palliative care of fungating wounds or terminal disease symptoms. More studies are required to relate medical details, including staging at presentation, to psychosocial and socioeconomic characteristics.

In conclusion, studies on barriers to cancer care in underserved populations have often focused on the physical barriers that prevent patients from accessing care. Our results show that women are far less fearful of how they will negotiate life during treatment (including work, finances, and family commitments) than they are of the planned treatments. Young patients are particularly vulnerable to increased fear when approaching treatment of breast cancer, and this group should be targeted with specific support. For all women, the public message of breast awareness should include education about breast cancer treatment and emphasize the importance of treatment for survival.

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AUTHOR CONTRIBUTIONS
Conception and design: Sarah Rayne, Carol-Ann Benn
Collection and assembly of data: Sarah Rayne, Kathryn Schnippel, Kathryne Wright
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Sarah Rayne
Consulting or Advisory Role: AstraZeneca

Kathryn Schnippel
No relationship to disclose

Cynthia Firnhaber
Research Funding: Merck (Inst)

Kathryne Wright
No relationship to disclose

Deirdre Kruger
No relationship to disclose

Carol-Ann Benn
Employment: International SOS (I)
Consulting or Advisory Role: Netcare Hospital Group (Inst)
Travel, Accommodations, Expenses: Novartis
REFERENCES


Second Primary Cancers After Primary Breast Cancer Diagnosis in Israeli Women, 1992 to 2006

Barbara G. Silverman, Irena Lipshitz, and Lital Keinan-Boker

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in Israeli women and constitutes approximately one third of all newly diagnosed tumors in both Jewish and Arab women every year. Improvements in early detection and treatment have resulted in increased long-term survival of breast cancer, which increases the likelihood of the occurrence of second primary cancers. Estimates from population-based studies of the increased risk of a second non–breast primary cancer after a breast cancer diagnosis range from 1% to 40%. Primary cancer diagnoses for which a significantly increased risk has been observed in women with a history of breast cancer include endometrial, ovarian, and colon cancer as well as sites associated with previous radiotherapy. In most studies, women given a diagnosis of first primary breast cancer before the age of 50 years had a greater excess risk of a second primary cancer than those given a diagnosis at age 50 and older. The identification of factors associated with subsequent cancer diagnoses in women with breast cancer can guide long-term follow-up and screening of these patients. The aim of the current study was to characterize the factors associated with subsequent diagnoses of any type of cancer in a cohort of Israeli women who received a diagnosis of breast cancer from 1992 to 2006.

METHODS

The Israel National Cancer Registry (INCR) was founded in 1960. Cancer reporting by hospitals, pathology and cytology laboratories, and other health care providers has been mandatory since 1982. The INCR covers the entire Israeli population (approximately 8 million), of which the ethnic distribution is as follows: 75% Jewish, 20% Arab, and 5% other ethnic groups. The following groups...
of diagnoses are recorded in the registry: all malignant neoplasms, excluding basal cell and squamous cell carcinoma of the skin; carcinoma in situ; high-grade (grade 3) intraepithelial neoplasias; and benign neoplasms of the brain and nervous system.

The registry currently includes information on approximately 800,000 people; 30,000 new cases are entered per year. Sources of information include pathology reports, hospital discharge summaries, death certificates, and patient listings from cancer centers. Registry staff review all documents submitted to the registry and assign site and morphology codes according to the International Classification of Diseases for Oncology, Third Edition. Completeness of ascertainment has been estimated at 94% for solid tumors.

Stage of disease at the time of diagnosis is determined on the basis of criteria established by the Middle East Cancer Consortium, of which INCR is a member. Middle East Cancer Consortium staging is primarily based on the criteria of the SEER Summary Staging Manual—2000. Demographic data and information on vital status are derived from the Central Population Registry of the Ministry of the Interior and updated at least annually. For purposes of disease surveillance, the Israeli population is divided, on the basis of data from the Ministry of Interior, into three ethnic subpopulations: Jewish, Arab, and other. Because previous work has shown that age-standardized cancer incidence in the Arab subpopulation is considerably lower than that in the Jewish or other subpopulations, we aggregated the Jewish and other subjects into a single group for the purpose of analysis.

The study cohort consisted of women who met the following criteria: diagnosed with invasive cancer of the breast (International Classification of Diseases for Oncology topography codes 50.0 to 50.9) between 1990 and 2006, excluding breast lymphomas; and no cancer diagnosis recorded before the date of breast cancer diagnosis.

For all the women in the study cohort, we identified all cancers diagnosed at another site after the date of the first breast cancer diagnosis. We did not consider subsequent breast cancer diagnoses as secondary primary cancers for the purpose of this study. We considered two follow-up periods. The first period was calculated from the date of breast cancer diagnosis through the end of the observation period (defined as the earliest of the following: date of the first subsequent non-breast cancer diagnosis; date of death; or December 31, 2011).

The second follow-up time was calculated from 6 months after the initial diagnosis through the end of the observation period. Subjects with more than one cancer during the follow-up period were censored after the first subsequent cancer diagnosis.

To allow for examination of the effects of changes in treatment strategies over time, we divided the cohort into three groups according to year of diagnosis: 1992 to 1996, 1997 to 2001, and 2002 to 2006.

Crude incidence of subsequent cancers (overall and for selected sites) was calculated as the number of cases per 1,000 person-years of follow-up from time 0 (diagnosis of first primary invasive breast cancer) and from 6 months after time 0. Cumulative rates of second primary cancers within 5 years of breast cancer diagnosis, by period of diagnosis and age at diagnosis, were calculated by life table analysis. Expected numbers of cancer cases (overall and for selected sites) were calculated by using age-specific incidence data for Jewish Israeli women derived from the INCR database. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cases for several follow-up times (1, 5, 10, and 15 years). We based the expected number of cases on the rates in the Jewish population for two reasons: The majority of the women in the study population were Jewish, and the cancer rates are considerably higher in Jewish than in Arab women. Therefore, use of these rates resulted in a more-conservative estimate of the risk of second primary cancers in a population of women with breast cancer. Ninety-five percent CIs were calculated for SIRs that assumed a Poisson distribution. All data analyses were performed with SAS version 9.12 software (SAS Institute, Cary, NC).

RESULTS

A total of 46,090 Israeli women with no previous cancer history were given a diagnosis of invasive breast cancer between 1990 and 2006 (42,355 Jewish; 2,296 Arab; 1,439 other ethnicity). Overall, 92% of cases were diagnosed in Jewish women, although the proportion of cases occurring in women in the Arab and other population groups increased with year of diagnosis (Table 1).

Of women with breast cancer between 1992 and 2006, 3,980 (8.6%) were given a diagnosis of a second non-breast primary cancer during the follow-up period. Ninety-five percent of these cases (3,773) were among Jewish women, 3% among Arab women, and 2% among women of other ethnic backgrounds (Table 2). When the first
6 months after breast cancer diagnosis were excluded from the follow-up period, 3,619 second non–breast primary cancers were identified, with a distribution of ethnic backgrounds almost identical to that of cases identified during the full follow-up period. Twenty-five percent of index cases were diagnosed in women younger than age 50 years; of these women, 5.7% experienced a second non–breast primary cancer compared with 12.1% of those age 50 years and older at the time of the index diagnosis. Crude incidence of second non–breast primary cancers in this population was 10.6 per 1,000 person-years for the full follow-up period and 10.3 per 1,000 person-years for the shortened follow-up period.

The relatively small number of second primary cancers in the Arab population precluded stratification by age-group and cancer type. Therefore, all subsequent analyses, including calculation of SIR overall and for specific cancer types, focused on the Jewish and other subpopulations (43,794 women; 3,866 second non–breast primary cancers). This group contributed 363,333 person-years of follow-up beginning on the date of breast cancer diagnosis and 343,462 person-years when follow-up was assumed to begin 6 months after the breast cancer diagnosis. Mean available follow-up time per patient was 8.3 years (1992 to 1996, 10.6 years; 1997 to 2001, 8.9 years; 2002 to 2006, 6.1 years).

The most commonly diagnosed second primary cancers were colorectal, uterine, lung, ovarian, non-Hodgkin lymphoma, brain, malignant melanoma, thyroid, and leukemia (Table 3). During the more-conservative follow-up period, the most commonly occurring cancer types were consistent with those observed for the longer follow-up period but at slightly lower crude rates.

The SIR for a second non–breast primary cancer in women with a previous breast cancer diagnosis was 1.26 (95% CI, 1.23 to 1.30). The corresponding SIR for follow-up that commenced at 6 months after breast cancer diagnosis was 1.21 (95% CI, 1.16 to 1.25). Significantly increased risks of colorectal, uterine, lung, ovarian, and thyroid cancer and leukemia were observed for the full follow-up period. When follow-up excluded the first 6 months after breast cancer diagnosis, the increased risk of these cancers persisted, although for colorectal cancer and leukemia, this finding was no longer statistically significant (Table 4).

Stratification by age at diagnosis demonstrated greater excess risk for a second cancer among women given a diagnosis of breast cancer before age 50 years than in those age 50 years and older. Both groups, however, had a risk that was significantly higher than that for the general population of women the same age (SIR, 1.77 [95% CI, 1.63 to 1.91] and 1.20 [95% CI, 1.15 to 1.24], respectively).

Life table analysis indicated a cumulative probability of a second malignancy of 4.4% within 5 years, 9.3% within 10 years, and 15.3% within 15 years of the first breast cancer diagnosis. Probability of a second malignancy within 5 years of initial diagnosis did not vary significantly with period of first breast cancer diagnosis (1992 to 1996, 1997 to 2001, or 2002 to 2006); the number of patients remaining for analysis at 10 years for the group diagnosed between 2002 and 2006 was insufficient to allow for a comparison among all periods (Table 5). Women who were younger than 50 years of age at the time of index breast cancer diagnosis were less likely to receive a diagnosis of a second cancer within 5 years of follow-up than women age 50 and older at the time of index breast cancer diagnosis. The number of patients younger than age 50 years at that time of diagnosis who remained for analysis at 10 years was insufficient to allow for between-age comparison at that point in follow-up (Table 6).

**Table 1.** Distribution of Breast Cancer Cases in Israeli Women by Period of Diagnosis and Population Group, 1992 to 2006

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
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<td>12,018</td>
<td>94.4</td>
<td>14,972</td>
<td>92.1</td>
</tr>
<tr>
<td>Arab</td>
<td>463</td>
<td>3.6</td>
<td>768</td>
<td>4.7</td>
</tr>
<tr>
<td>Other</td>
<td>247</td>
<td>1.9</td>
<td>514</td>
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<td>12,728</td>
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<td>16,254</td>
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**Table 2.** Distribution of Second Non–Breast Primary Cancer Cases in Israeli Women by Period of Diagnosis and Population Group, 1992 to 2011

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Jewish</td>
<td>1,385</td>
<td>96.2</td>
<td>1,455</td>
<td>94.5</td>
</tr>
<tr>
<td>Arab</td>
<td>31</td>
<td>2.2</td>
<td>48</td>
<td>3.1</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
<td>1.6</td>
<td>36</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>1,439</td>
<td>100.0</td>
<td>1,539</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In a cohort of women with a first primary breast cancer diagnosed between 1992 and 2006, we observed a 25% increased risk of second non–breast cancers during follow-up compared with the risk in the general population, adjusted for age.
Overall, the cumulative risk of a second non-breast primary cancer was 4.4% after 5 years of follow-up and 9.3% after 10 years.

A recent meta-analysis of 15 population- and hospital-based studies from Europe, Asia, and North America resulted in a pooled estimate of the increased risk of second cancers among patients with breast cancer of 1.17 (95% CI, 1.10 to 1.25) and found that the excess risk of a second primary cancer after breast cancer decreases with age at diagnosis of the index cancer (women age < 50 years: SIR, 1.51; 95% CI, 1.35 to 1.70; women age ≥ 50 years: SIR, 1.11; 95% CI, 1.02 to 1.21). Our estimate of the overall risk of a second cancer among patients with breast cancer is consistent with that analysis. As in previous studies, we found that although all women with breast cancer experience an increased risk of second primary cancer, younger women have a greater excess risk for a second primary cancer than the general population of women of the same age. As has been reported in other studies, the most pronounced excess risks in the current study population were for cancers of the uterus, ovary, and thyroid.

Several potential explanations exist for an increased risk of subsequent cancers in breast cancer survivors, including the effects of radiotherapy and hormone therapy, environmental factors, health behaviors, and genetics. Hormonal and radiation treatment of cancer carry an increased risk for the development of cancer. Duration of use of tamoxifen (but not the daily dose) has been associated with an increased risk of uterine cancer. Cancers most likely to be related to radiotherapy for breast cancer include leukemia and cancers of organs close to the breast, such as esophagus, lung and pleura, thyroid gland, stomach, and soft tissue sarcomas of thorax and upper limb.

Women treated with radiation after mastectomy have been shown to have an increased risk for lung cancer, although radiation after lumpectomy does not carry this risk. Both radiation treatment and chemotherapy are associated with an increased risk of leukemia in patients with breast cancer; the risk of leukemia in this population has been shown to increase with the intensity of treatment. SEER data indicate that the increased risk of a subsequent cancer associated with chemotherapy and radiation therapy is most pronounced in children and young adults and is not seen in older adults. This finding is consistent with the bulk of the literature that indicates that the excess risk of second primary cancers after breast cancer is most pronounced among younger women.

### Table 3. Most Commonly Occurring Second Non–Breast Primary Cancer Cases in Israeli Women by Follow-up Period After Index Breast Cancer Diagnosis, 1992 to 2006

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>No. of Cases</th>
<th>Crude Rate/1,000 Person-Years</th>
<th>Cancer Type</th>
<th>No. of cases</th>
<th>Crude Rate/1,000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>530</td>
<td>1.5</td>
<td>Colon</td>
<td>485</td>
<td>1.4</td>
</tr>
<tr>
<td>Uterus</td>
<td>511</td>
<td>1.4</td>
<td>Uterus</td>
<td>481</td>
<td>1.4</td>
</tr>
<tr>
<td>Lung</td>
<td>282</td>
<td>0.8</td>
<td>Lung</td>
<td>261</td>
<td>0.8</td>
</tr>
<tr>
<td>Ovary</td>
<td>224</td>
<td>0.6</td>
<td>Ovary</td>
<td>192</td>
<td>0.6</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>220</td>
<td>0.6</td>
<td>Non-Hodgkin lymphoma</td>
<td>188</td>
<td>0.5</td>
</tr>
<tr>
<td>Rectum</td>
<td>180</td>
<td>0.5</td>
<td>Rectum</td>
<td>168</td>
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</tr>
<tr>
<td>Brain</td>
<td>179</td>
<td>0.5</td>
<td>Brain</td>
<td>161</td>
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<tr>
<td>Melanoma, invasive</td>
<td>173</td>
<td>0.5</td>
<td>Melanoma, invasive</td>
<td>159</td>
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<tr>
<td>Thyroid</td>
<td>155</td>
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<td>Thyroid</td>
<td>141</td>
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<tr>
<td>Leukemia</td>
<td>130</td>
<td>0.4</td>
<td>Pancreas</td>
<td>123</td>
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<td>Stomach</td>
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<td>Kidney</td>
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<td>Leukemia</td>
<td>114</td>
<td>0.3</td>
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<tr>
<td>Pancreas</td>
<td>134</td>
<td>0.4</td>
<td>Bladder</td>
<td>114</td>
<td>0.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>129</td>
<td>0.3</td>
<td>Kidney</td>
<td>112</td>
<td>0.3</td>
</tr>
<tr>
<td>Melanoma, in situ</td>
<td>62</td>
<td>0.2</td>
<td>Melanoma, in situ</td>
<td>60</td>
<td>0.2</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>61</td>
<td>0.2</td>
<td>Multiple myeloma</td>
<td>56</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Jewish and other population groups.*
Another possible explanation for the increase in diagnoses of subsequent cancers in women with a history of breast cancer is that these women are under more intensive surveillance after treatment and therefore have a higher likelihood of subclinical lesions being detected. Sadetzki et al.\(^2\) reported an increased risk of thyroid cancers in Israeli women previously treated for breast cancer and concluded that enhanced surveillance, common risk factors, and genetic predisposition were the likely causes for this finding. Mellemkjær et al.\(^3\) reached a similar conclusion that although patients with breast cancer had an increased risk for subsequent thyroid cancer, this risk did not increase with latency and was accompanied by an increased risk of breast cancer occurring after thyroid cancer. Van Fossen et al.\(^2\) noted a bi-directional association between breast and thyroid cancer, which suggests the existence of common risk factors for the two illnesses. We found that the exclusion of the first 6 months after breast cancer diagnosis from follow-up had little effect on the risk of subsequent thyroid cancer, which suggests that an increase in diagnoses of existing thyroid tumors

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Observed</th>
<th>No. Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up from date of breast cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers</td>
<td>3,866</td>
<td>3,071</td>
<td>1.26</td>
<td>1.22 to 1.30</td>
</tr>
<tr>
<td>Colorectal</td>
<td>710</td>
<td>634</td>
<td>1.12</td>
<td>1.04 to 1.20</td>
</tr>
<tr>
<td>Uterus</td>
<td>511</td>
<td>203</td>
<td>2.58</td>
<td>2.30 to 2.72</td>
</tr>
<tr>
<td>Lung</td>
<td>282</td>
<td>232</td>
<td>1.22</td>
<td>1.08 to 1.35</td>
</tr>
<tr>
<td>Ovary</td>
<td>224</td>
<td>124</td>
<td>1.80</td>
<td>1.59 to 2.02</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>218</td>
<td>193</td>
<td>1.13</td>
<td>0.98 to 1.28</td>
</tr>
<tr>
<td>Brain</td>
<td>179</td>
<td>166</td>
<td>1.08</td>
<td>0.92 to 1.24</td>
</tr>
<tr>
<td>Melanoma, invasive</td>
<td>173</td>
<td>120</td>
<td>1.44</td>
<td>1.23 to 1.66</td>
</tr>
<tr>
<td>Thyroid</td>
<td>155</td>
<td>102</td>
<td>1.58</td>
<td>1.29 to 1.74</td>
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<tr>
<td>Leukemia</td>
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<td>104</td>
<td>1.31</td>
<td>1.05 to 1.45</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>85</td>
<td>81</td>
<td>1.03</td>
<td>0.84 to 1.27</td>
</tr>
<tr>
<td>Follow-up from 6 months after date of breast cancer diagnosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers</td>
<td>3,534</td>
<td>2,927</td>
<td>1.21</td>
<td>1.17 to 1.25</td>
</tr>
<tr>
<td>Colorectal</td>
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<td>606</td>
<td>1.08</td>
<td>0.99 to 1.16</td>
</tr>
<tr>
<td>Uterus</td>
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<td>194</td>
<td>2.48</td>
<td>2.26 to 2.71</td>
</tr>
<tr>
<td>Lung</td>
<td>261</td>
<td>221</td>
<td>1.18</td>
<td>1.03 to 1.33</td>
</tr>
<tr>
<td>Ovary</td>
<td>192</td>
<td>118</td>
<td>1.63</td>
<td>1.38 to 1.88</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>188</td>
<td>184</td>
<td>1.02</td>
<td>0.88 to 1.17</td>
</tr>
<tr>
<td>Brain</td>
<td>161</td>
<td>158</td>
<td>1.02</td>
<td>0.86 to 1.18</td>
</tr>
<tr>
<td>Melanoma, invasive</td>
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<td>114</td>
<td>1.40</td>
<td>1.18 to 1.61</td>
</tr>
<tr>
<td>Thyroid</td>
<td>141</td>
<td>99</td>
<td>1.46</td>
<td>1.20 to 1.71</td>
</tr>
<tr>
<td>Leukemia</td>
<td>114</td>
<td>102</td>
<td>1.15</td>
<td>0.92 to 1.37</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>78</td>
<td>80</td>
<td>1.03</td>
<td>0.79 to 1.27</td>
</tr>
</tbody>
</table>

Abbreviation: SIR, standardized incidence ratio.
*Jewish and other population groups. Boldface indicates a 95% CI for the SIR that does not include 1.0 and is therefore considered to be indicative of significantly increased risk.

Table 5. Life Table Analysis: Cumulative Rate of Second Non–Breast Primary Cancer Among Israeli* Women With Breast Cancer by Period of Diagnosis

<table>
<thead>
<tr>
<th>Period of Diagnosis</th>
<th>Cumulative Risk by 5 Years, %</th>
<th>95% CI</th>
<th>Cumulative Risk by 10 Years, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-1996</td>
<td>4.7</td>
<td>4.3 to 5.1</td>
<td>9.0</td>
<td>8.4 to 9.6</td>
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<tr>
<td>1997-2001</td>
<td>4.2</td>
<td>3.9 to 4.6</td>
<td>9.2</td>
<td>8.7 to 9.7</td>
</tr>
<tr>
<td>2002-2006</td>
<td>4.3</td>
<td>4.0 to 4.6</td>
<td>††</td>
<td>††</td>
</tr>
</tbody>
</table>

*Jewish and other population groups.
†Fewer than 30 patients remaining for analysis at this point in follow-up.
Table 6. Life Table Analysis: Cumulative Rate of Second Non–Breast Primary Cancer Among Israeli* Women With Breast Cancer by Age at Diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Cumulative Risk by 5 Years, %</th>
<th>95% CI</th>
<th>Cumulative Risk by 10 Years, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>2.2</td>
<td>1.9 to 2.5</td>
<td>5.1</td>
<td>4.8 to 5.3</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>5.1</td>
<td>4.8 to 5.3</td>
<td>10.9</td>
<td>10.4 to 11.3</td>
</tr>
</tbody>
</table>

*Jewish and other population groups.
†Fewer than 30 patients remaining for analysis at this point in follow-up.

at the time of breast cancer diagnosis is insufficient to explain the increased risk observed.

We used data from a large population-based national cancer registry to estimate the risk of second primary cancers a cohort of 46,090 Israeli women with a first diagnosis of breast cancer. The use of data from a well-established cancer registry for observational epidemiology research offers certain strengths. The INCR receives reports of cancer cases from all Israeli hospitals and pathology laboratories, thus the likelihood that cases of breast cancer and subsequent cancers diagnosed during the period of the study were excluded from the study cohort is minimal. All cases are reported by using a unique national identifier that allows for elimination of duplicate cases reported to the registry from different facilities. We focused on cases diagnosed between 1992 and 2006 to allow for an average follow-up time of 8.3 years. Population data available from the Israel Bureau of Statistics allowed us to calculated expected cancer rates in the general population for the purpose of calculating SIRs. Vital status information in the registry is supplemented with Israel Bureau of Statistics data to allow the censoring of patients who died during the follow-up period.

The INCR receives a limited amount of clinical data for patients with cancer. For this reason, we were unable to study the association of various types of breast cancer treatment on the occurrence of second cancers. No information on family history, personal risk factors (obesity, diet, or other health behaviors), or genetic testing is available for the patients in the cancer registry; therefore, these factors could not be taken into consideration in estimating second cancer risk. Genetic predisposition to cancer is an important consideration in the Israeli population. Between 2.0% and 2.5% of Ashkenazi Jewish women carry one or more of the founding mutations in the BRCA1 and BRCA2 genes.26 The cumulative risk at age 70 years of breast cancer in Ashkenazi women who are carriers of the BRCA1 and BRCA2 mutations has been estimated at 46% and 26%, respectively.27 Because mutations of the BRCA1 or BRCA2 genes contribute to an increased risk for cancers in other sites, such as the ovaries, cervix, uterus, pancreas, and colon, their high prevalence in the Israeli female population may limit the generalizability of the current data to populations with a low prevalence of BRCA1/2 mutations.

Over the past 20 years, survival after breast cancer diagnosis has improved throughout the developed world, including Israel.28 With prolonged survival, however, comes an increased likelihood that patients treated for breast cancer in the past will be receive a diagnosis of additional primary cancers as a result of underlying genetic and other risk factors related to the primary breast cancer and to treatment of the original illness. Breast cancer survivors tend to be more intensive users of medical services than other women their age.29 Specialist and primary care providers must take advantage of this continued contact to educate patients about their risk for second cancers and implement appropriate preventive and screening procedures tailored to their patients’ individual risks.

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REFERENCES


Challenges of Treating Childhood Medulloblastoma in a Country With Limited Resources: 20 Years of Experience at a Single Tertiary Center in Malaysia

**Purpose** Pediatric medulloblastoma (MB) treatment has evolved over the past few decades; however, treating children in countries with limited resources remains challenging. Until now, the literature regarding childhood MB in Malaysia has been nonexistent. Our objectives were to review the demographics and outcome of pediatric MB treated at the University Malaya Medical Center between January 1994 and December 2013 and describe the challenges encountered.

**Methods** Fifty-one patients with childhood MB were seen at University Malaya Medical Center. Data from 43 patients were analyzed; eight patients were excluded because their families refused treatment after surgery.

**Results** Headache and vomiting were the most common presenting symptoms, and the mean interval between symptom onset and diagnosis was 4 weeks. Fourteen patients presented with metastatic disease. Five-year progression-free survival (± SE) for patients ≥3 years old was 41.7% ± 14.2% (95% CI, 21.3% to 81.4%) in the high-risk group and 68.6% ± 16.8% (95% CI, 40.3% to 100%) in the average-risk group, and 5-year overall survival (± SE) in these two groups was 41.7% ± 14.2% (95% CI, 21.3% to 81.4%) and 58.3% ± 18.6% (95% CI, 31.3% to 100%), respectively. Children younger than 3 years old had 5-year progression-free and overall survival rates (± SE) of 47.6% ± 12.1% (95% CI, 28.9% to 78.4%) and 45.6% ± 11.7% (95% CI, 27.6% to 75.5%), respectively. Time to relapse ranged from 4 to 132 months. Most patients who experienced relapse died within 1 year. Febrile neutropenia, hearing loss, and endocrinopathy were the most common treatment-related complications.

**Conclusion** The survival rate of childhood MB in Malaysia is inferior to that usually reported in the literature. We postulate that the following factors contribute to this difference: lack of a multidisciplinary neuro-oncology team, limited health care facilities, inconsistent risk assessment, insufficient data in the National Cancer Registry and pathology reports, inadequate long-term follow-up, and cultural beliefs leading to treatment abandonment.

**INTRODUCTION**

Malaysia is a limited-resource country that consists of two large territories, Peninsular Malaysia and East Malaysia. This multiethnic, multicultural country has a population of 30.3 million (2015 estimate), such that 29% of which is younger than 14 years. Malaysian public health care services are provided by the government at subsidized rates, irrespective of income or insurance status.

With improvement in socioeconomic conditions, implementation of a national immunization program, and optimal treatment of diarrheal diseases and respiratory infections, cancer has emerged as the main cause of childhood deaths in Malaysia. The National Cancer Registry was initiated in 2002, and reports are based on epidemiologic data from hospitals in Peninsular Malaysia. Statistics from East Malaysia and private practices are unavailable. A Malaysian childhood cancer survey from 2010 to 2012 found that CNS tumors are the second most common childhood malignancy (11.4%) after leukemia (46.8%). The overall incidence of CNS tumors is 9.9 per million per year (unpublished data). This
rate seems to be low as a result of under-reporting of benign or non–histologically confirmed tumors, death before diagnosis, and low contribution from nonacademic institutions.

The Pediatric Hematology-Oncology Division (PHOD) at the University of Malaya Medical Center (UMMC; Kuala Lumpur, Malaysia) is a referral center for childhood cancer. The PHOD sees approximately 100 new oncology patients every year, accounting for 13% of childhood cancer diagnoses in the country annually. PHOD does not have a designated pediatric neuro-oncology team, and the number of staff members fluctuates unpredictably.

Before 1997, patients requiring radiation therapy (RT) were referred elsewhere, which delayed their treatment. In 1997, UMMC launched a radiation oncology service with two clinical radiation oncologists, and a linear accelerator was used to deliver RT. In 2002, the center implemented a radiation oncology postgraduate program and recruited seven radiation oncologists in 2013, including two with pediatric subspecialization. Conformal RT for craniospinal irradiation (CSI) was initiated in 2002, and the selection of patients was influenced by the limited number of machines available.

From 1994 to 2001, CNS tumors in Malaysia were most likely under-reported as a result of patients being transferred to other centers for surgical intervention. In 2001, UMMC established a general neurosurgical unit, followed by a pediatric neurosurgical unit in 2008. Currently, three pediatric neurosurgeons are practicing in Malaysia. Weekly multidisciplinary team discussions involving pediatric and adult neuro-oncology staffs were implemented in 2013. The objectives of this retrospective analysis were to review the demographic data, survival outcome, prognostic factors, challenges, and limitations in the clinical management of childhood medulloblastoma (MB) at UMMC.

METHODS

Patients

Medical records of patients with MB treated at PHOD from January 1994 to December 2013 were retrospectively reviewed. Age, sex, ethnicity, prediagnosis symptoms, presenting signs, place and type of surgery, postoperative residual tumor, radiologic imaging, histopathology results, chemotherapy regimen, CSI dose, and outcome and treatment-related complications were recorded. The extent of surgical resection was categorized into the following four groups: gross total resection (GTR), no visible tumor remaining in the surgical field; near-total resection (NTR), removal of more than 95% but less than 100% of tumor; subtotal resection (STR), removal of more than 50% to less than 95% of tumor; and partial resection (PR), less than 50% excision of tumor. Patients with residual tumors greater than 1.5 cm², metastatic disease, and/or age less than 3 years were classified as having high-risk (HR) MB. Evaluation of metastatic disease was based on the Chang classification system.3

Treatment

The PHOD has used the Children’s Cancer Group (CCG) 9892 protocol since 1994 to treat children ≥ 3 years old.4 The protocol was designed to give reduced-dose CSI with 23.4 Gy in 13 fractions (daily fraction, 1.8 Gy) with a posterior fossa boost to patients with average-risk (AR) disease; those with HR disease received a CSI dose of 36 Gy in 20 fractions on the neuraxis. Eight weekly injections of vincristine (VCR; 1.5 mg/m²; maximum dose, 2 mg) were administered during CSI and followed by eight cycles of intravenous cisplatin (75 mg/m²) on day 1; VCR (1.5 mg/m²; maximum, 2 mg) on days 1, 7, and 14; and oral lomustine (75 mg/m²) on day 1 at 6-week intervals. Ideally, RT should be commenced within 4 weeks and no later than 7 weeks after surgery.

For patients younger than 3 years old, several protocols were used during different periods, as follows: United Kingdom Children’s Cancer Study Group (UKCCSG) 9204 (1994 to 1996),5 Head Start (HS) I (1997 to 2002),6,7 and HS II (from 2003 onward).7,8 These changes coincided with the availability of an autologous stem-cell transplantation (ASCT) service at UMMC.

At UMMC, ASCT is considered a treatment option for not only MB, but also metastatic Ewing sarcoma, HR neuroblastoma, relapsed extracranial germ cell tumor, and infant primitive neuroectodermal tumor. General Hospital Kuala Lumpur, UMMC, and Sime Darby Medical Center are the three pediatric oncology centers with autologous and allogeneic stem-cell or marrow transplantation programs in Malaysia.

Statistical Methods

SPSS (version 20; SPSS, Chicago, IL) software and R statistical environment 3.2.3 (https://www.r-project.org/) were used to calculate progression-free survival (PFS) and overall survival (OS), with censoring at the time of last contact.9 PFS is defined as the time elapsed between treatment initiation
and tumor progression. OS was calculated from the date of diagnosis to that of last follow-up or death by any cause.

RESULTS
Patient Demographics and Clinical Characteristics
Fifty-one patients with MB were admitted to UMMC during the study period. Eight patients’ families declined treatment after surgery and were excluded from the study. Thus, 43 patients were studied. The median age at diagnosis was 3.5 years (range, 3 months to 15 years), and the male-to-female ratio was 1.4:1. Headache (43%) and vomiting (57%) were the most common presenting symptoms. The mean interval between onset of symptoms and diagnosis was 4 weeks (range, 1 to 20 weeks). Nineteen patients (44%) were younger than 3 years old. Ten patients had M3 disease; three had M2 disease; and one had M1 disease (Fig 1).

Surgery and Risk Groups
All patients underwent surgical excision of the primary tumor. Twenty-two patients (51.1%) underwent GTR, two (4.7%) NTR, 17 (39.5%) subtotal resection, and two (4.7%) partial resection.Extent of resection was determined by postoperative magnetic resonance imaging (MRI) or computed tomography scans. An external ventricular drain was inserted in 11 patients, and three patients underwent ventriculostomy before definitive surgery. However, these results might be under-reported as a result of a lack of consistent data from referring institutions. Seven patients had second-look surgery, and 30 patients (69.8%) received a ventriculoperitoneal (VP) shunt (Fig 1).
Twenty-six patients (60.5%) underwent surgical resection at another institution before being referred to UMMC, including 12 patients who had residual tumor greater than 1.5 cm². Seventeen patients underwent surgical resection at UMMC, seven of whom had residual tumor greater than 1.5 cm². Surgery was performed by general neurosurgeons in most cases. Metastasis was infrequently investigated. CSF cytology was not investigated in 10 patients, and reports were missing for four additional patients who underwent a diagnostic lumbar puncture. Spinal MRI was not performed in two patients, and MRI reports were irretrievable for four patients. In 22 patients (51.2%), postoperative scans were performed after 72 hours (range, 4 to 30 days after surgery). Thus, risk group stratification was based on best available results for each patient at the time of diagnosis and treatment. Upon pathology review, one diagnosis was revised to MB from ependymoma after tumor recurrence. This patient was treatment naïve before relapse, so the patient was subsequently managed as having a newly diagnosed HR MB. Histology subclass was reported as desmoplastic in five patients; the remaining 38 patients had no record of histology subclass (Fig 1).

Treatment of Patients Age 3 Years or Older: RT and Chemotherapy

Of the children age ≥ 3 years, three patients were enrolled onto the HS protocol because their families refused RT. The patients were 4, 5, and 6 years old. Two of these patients discontinued treatment after one course of chemotherapy and subsequently died of progressive disease. The other patient received five courses of chemotherapy; local and leptomeningeal recurrence was then detected before ASCT, and the patient received palliative RT (Table 1). The remaining patients received CSI at a median time of 5 weeks after surgery (range, 2 to 9 weeks). CSI was delayed in eight patients, one of whom received a first course of CGG 9892 chemotherapy (Table 1). After CSI, 15 patients received CGG 9892 chemotherapy (Table 1). The families of two patients refused chemotherapy after the first course, one of whom experienced local recurrence 10 years later and underwent complete excision that was complicated by severe neurologic impairment requiring tracheostomy; no salvage chemotherapy was given. One patient remains in complete remission despite refusing chemotherapy after two courses. Among three patients who received six cycles of chemotherapy, two suffered local and leptomeningeal recurrence after the sixth course and received palliative oral etoposide. Nine patients completed eight cycles of chemotherapy, three of whom experienced local and leptomeningeal recurrence (Table 1).

Treatment of Patients Younger Than 3 Years Old: Chemotherapy Only

Of the 19 patients younger than age 3 years, one died of a postoperative complication, and 18 received chemotherapy (Fig 1 and Table 2). One family refused CSI after completion of UKCCSG chemotherapy, and that patient is still in complete remission. The other two patients treated on the UKCCSG protocol experienced tumor recurrence after the second and third cycles of chemotherapy, respectively. One patient received CSI (35.2 Gy with boost) followed by two courses of CGG 9892 chemotherapy, but treatment failed. Two patients on the HS I protocol did not undergo ASCT; one of these patients died of Candida sepsis after the second course of chemotherapy, and the other died of disease recurrence after the fifth course without salvage treatment. Nine patients were treated per the HS II protocol, but four of these patients did not receive ASCT. Three patients experienced tumor recurrence after the second, third, and fourth courses, respectively, and none received salvage treatment. One family refused ASCT and opted for traditional medicine. This child experienced MB recurrence after 2 months and was referred to palliative care. Only nine infants received myeloablative chemotherapy with ASCT (Table 2).

Outcome

The median follow-up time of survivors was 12 years (range, 5.75 to 19.17 years). MB recurred in 19 patients, including six who discontinued treatment. The sites of relapse were local (n = 7) and local with spinal dissemination (n = 12). Median time to relapse was 12 months (range, 4 to 132 months), and most patients died within 1 year of relapse.

The 5-year PFS rates (± SE) for older children in the HR group, patients in the AR group, and younger children in the HR group were 41.7% ± 14.2% (95% CI, 21.3% to 81.4%), 68.6% ± 18.6% (95% CI, 40.3% to 100%), and 47.6% ± 12.1% (95% CI, 28.9% to 78.4%), respectively. The 5-year OS rates (± SE) were 41.7% ± 14.2% (95% CI, 21.3% to 81.4%) in older patients in the HR group, 58.3% ± 18.6% (95% CI, 31.3% to 100%) in patients in the AR group, and 45.6% ± 11.7% (95% CI, 27.6% to 75.5%) for children younger than age 3 years (Figs 2 and 3). In this study, age less than 3 years did not influence the outcome. In addition, it is difficult to...
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/ Sex</th>
<th>YOD</th>
<th>PSI (weeks)</th>
<th>Surgery</th>
<th>M+</th>
<th>HPE MB Subclass</th>
<th>RTI* (weeks)</th>
<th>Chemotherapy</th>
<th>Time to Relapse (years)</th>
<th>Site of Relapse</th>
<th>Duration of Survival (years)</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11/F</td>
<td>1996</td>
<td>4</td>
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<td>0</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>7/M</td>
<td>2000</td>
<td>3</td>
<td>NTR</td>
<td>0</td>
<td>NS</td>
<td>4</td>
<td>CCG 9892; 8 courses; no dose reduction</td>
<td>-</td>
<td>-</td>
<td>14.14+</td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
<td>10/M</td>
<td>2001</td>
<td>NI</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>3</td>
<td>Refused chemotherapy</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>4</td>
<td>3.9/M</td>
<td>2001</td>
<td>4</td>
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<td>0</td>
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<td>3</td>
<td>CCG 9892; 8 courses; 50% CDDP dose reduction during sixth to eighth courses</td>
<td>1.37</td>
<td>Local and spine</td>
<td>1.43</td>
<td>DOD</td>
</tr>
<tr>
<td>5</td>
<td>15/F</td>
<td>2002</td>
<td>2</td>
<td>NTR</td>
<td>0</td>
<td>Desmoplastic</td>
<td>7</td>
<td>CCG 9892; 8 courses; no dose reduction</td>
<td>-</td>
<td>-</td>
<td>12.74+</td>
<td>NED</td>
</tr>
<tr>
<td>6</td>
<td>14/M</td>
<td>2002</td>
<td>12</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>9</td>
<td>CCG 9892; 8 courses; 50% CDDP dose reduction during fourth to eighth courses</td>
<td>-</td>
<td>-</td>
<td>12.09+</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>10/M</td>
<td>2003</td>
<td>NI</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>5</td>
<td>Transferred to OTH for chemotherapy</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>8</td>
<td>12/M</td>
<td>2005</td>
<td>2</td>
<td>GTR</td>
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<td>2005</td>
<td>8</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>7</td>
<td>CCG 9892; 8 courses; 50% CDDP dose reduction during fifth course, sixth to eighth courses substituted with carboplatin</td>
<td>-</td>
<td>-</td>
<td>6.92+</td>
<td>NED</td>
</tr>
<tr>
<td>10</td>
<td>6/M</td>
<td>2008</td>
<td>1</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>Refused RT after surgery</td>
<td>HS II; 5 courses; no dose reduction</td>
<td>0.5</td>
<td>Local and spine</td>
<td>1.06</td>
<td>DOD</td>
</tr>
<tr>
<td>11</td>
<td>12/M</td>
<td>2012</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>Desmoplastic</td>
<td>4</td>
<td>CCG 9892; defaulted after first course</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
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<td>High risk</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>5/M</td>
<td>1995</td>
<td>3</td>
<td>PR; STR second-look surgery</td>
<td>3</td>
<td>NS</td>
<td>7</td>
<td>CCG 9892; 8 courses; no dose reduction</td>
<td>1.39</td>
<td>Local and spine</td>
<td>2</td>
<td>DOD</td>
</tr>
<tr>
<td>13</td>
<td>9/F</td>
<td>1996</td>
<td>3</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>3</td>
<td>Refused chemotherapy</td>
<td>5.09</td>
<td>Local</td>
<td>5.27</td>
<td>DOD</td>
</tr>
<tr>
<td>14</td>
<td>5/M</td>
<td>1999</td>
<td>8</td>
<td>GTR</td>
<td>1</td>
<td>NS</td>
<td>4</td>
<td>CCG 9892; 8 courses; no dose reduction</td>
<td>1.58</td>
<td>Local and spine</td>
<td>2.0</td>
<td>DOD</td>
</tr>
<tr>
<td>15</td>
<td>10/F</td>
<td>1999</td>
<td>1.4</td>
<td>GTR</td>
<td>2</td>
<td>NS</td>
<td>7</td>
<td>CCG 9892; refused chemotherapy after 2 courses; no dose reduction</td>
<td>-</td>
<td>-</td>
<td>14.42+</td>
<td>NED</td>
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</table>

(Continued on following page)
Table 1. Characteristics of 24 Patients Who Were ≥ 3 Years Old at Time of Medulloblastoma Diagnosis (Continued)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/Sex</th>
<th>YOD</th>
<th>PSI (weeks)</th>
<th>Surgery</th>
<th>M+</th>
<th>HPE MB Subclass</th>
<th>RTI* (weeks)</th>
<th>Chemotherapy</th>
<th>Time to Relapse (years)</th>
<th>Site of Relapse</th>
<th>Duration of Survival (years)</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>5/F</td>
<td>2001</td>
<td>3</td>
<td>STR; GTR second-look surgery</td>
<td>3</td>
<td>NS</td>
<td>Refused RT; 5 after PD</td>
<td>HS I defaulted after first course; switched to CCG 9892 during PD (local and spinal metastasis) for 8 courses; 50% CDDP reduction during seventh and eighth courses</td>
<td>First: 0.48; second: 2.64</td>
<td>Local and spine</td>
<td>3.02</td>
<td>DOD</td>
</tr>
<tr>
<td>17</td>
<td>3/M</td>
<td>2002</td>
<td>4</td>
<td>STR</td>
<td>3</td>
<td>NS</td>
<td>9</td>
<td>CCG 9892; 8 courses; 50% CDDP reduction during fourth to eighth courses</td>
<td>1.37</td>
<td>Local and spine</td>
<td>1.63</td>
<td>DOD</td>
</tr>
<tr>
<td>18</td>
<td>3.5/M</td>
<td>2003</td>
<td>4</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>7</td>
<td>CCG 9892 defaulted after first course</td>
<td>10.86</td>
<td>Local</td>
<td>11.31</td>
<td>DOD</td>
</tr>
<tr>
<td>19</td>
<td>8/F</td>
<td>2003</td>
<td>0.4</td>
<td>STR; GTR second-look surgery</td>
<td>3</td>
<td>NS</td>
<td>8</td>
<td>CCG 9892; completed only 6 courses as a result of recurrence; no dose reduction</td>
<td>1.08</td>
<td>Local and spine</td>
<td>3.08</td>
<td>DOD</td>
</tr>
<tr>
<td>20</td>
<td>4/F</td>
<td>2004</td>
<td>4</td>
<td>STR; GTR second-look surgery</td>
<td>2</td>
<td>NS</td>
<td>5</td>
<td>CCG 9892; 8 courses; omitted CDDP during fourth to eighth courses</td>
<td>—</td>
<td>—</td>
<td>9.82+</td>
<td>NED</td>
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<tr>
<td>21</td>
<td>8/M</td>
<td>2005</td>
<td>NI</td>
<td>GTR; GTR</td>
<td>0</td>
<td>NS</td>
<td>5</td>
<td>CCG 9892; refused chemotherapy after sixth course; no dose reduction</td>
<td>—</td>
<td>—</td>
<td>9.15+</td>
<td>NED</td>
</tr>
<tr>
<td>22</td>
<td>5/M</td>
<td>2005</td>
<td>1</td>
<td>STR</td>
<td>3</td>
<td>NS</td>
<td>2</td>
<td>CCG 9892; completed only 6 courses due to recurrence; 50% CDDP dose reduction during first to sixth courses</td>
<td>1.0</td>
<td>Local and spine</td>
<td>1.95</td>
<td>DOD</td>
</tr>
<tr>
<td>23</td>
<td>11/M</td>
<td>2006</td>
<td>0.6</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>—</td>
<td>NTR; transferred to OTH for treatment</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
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<td>24</td>
<td>4/M</td>
<td>2008</td>
<td>20</td>
<td>STR</td>
<td>3</td>
<td>NS</td>
<td>Refused RT</td>
<td>HS II; defaulted after first course</td>
<td>0.34</td>
<td>Local</td>
<td>0.70</td>
<td>DOD</td>
</tr>
</tbody>
</table>

Abbreviations: CCG, Children’s Cancer Group; CDDP, cisplatin; DOC, died of complication; DOD, died of disease; F, female; GTR, gross total resection; HPE, histopathologic examination; HS, Head Start; M, male; M+, metastasis; M0, no dissemination; M1, tumor cells in lumbar CSF; M2, cerebral meningeal thickening; M3, spinal meningeal dissemination; M4, extraneural metastases; MB, medulloblastoma; NED, no evidence of disease; NI, no information; NS, no specific comment; NTR, near-total resection; OTH, other tertiary hospital; PD, progressive disease; PR, partial resection; PSI, prediagnosis symptoms interval; RT, radiotherapy; RTI, radiotherapy interval after surgery; STR, subtotal resection; YOD, year of diagnosis.

*RT was considered delayed if it was administered more than 6 weeks after surgery.
†Outcome data were obtained at a median follow-up time of 24 months (range, 0.25 to 230 months).
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)/Sex</th>
<th>YOD</th>
<th>PSI (weeks)</th>
<th>Surgery</th>
<th>M+</th>
<th>HPE MB Subclass</th>
<th>Chemotherapy/RT</th>
<th>ASCT</th>
<th>RT</th>
<th>Time to Relapse (years)</th>
<th>Site of Relapse</th>
<th>Duration of Survival (years)</th>
<th>Outcome*</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2/F</td>
<td>1995</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>UKCCSG; 7 cycles, no dose reduction; refused RT</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>19.17+</td>
<td>NED</td>
</tr>
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<td>2</td>
<td>2.5/F</td>
<td>1996</td>
<td>2</td>
<td>GTR</td>
<td>3</td>
<td>NS</td>
<td>UKCCSG; completed only 3 courses as a result of recurrence</td>
<td>—</td>
<td>Yes</td>
<td>0.55</td>
<td>Local and spine</td>
<td>1.06</td>
<td>DOD</td>
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<td>0.9/M</td>
<td>1996</td>
<td>4</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>UKCCSG; defaulted after 2 courses</td>
<td>—</td>
<td>No</td>
<td>1.79</td>
<td>Local and spine</td>
<td>1.81</td>
<td>DOD</td>
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<td>4</td>
<td>1/M</td>
<td>1996</td>
<td>16</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>HS I; 5 courses of induction, no dose reduction</td>
<td>Yes</td>
<td>No</td>
<td>1.17</td>
<td>Local</td>
<td>1.20</td>
<td>DOD</td>
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<tr>
<td>5</td>
<td>2.9/F</td>
<td>1997</td>
<td>4</td>
<td>GTR</td>
<td>3</td>
<td>NS</td>
<td>HS I; 5 courses of induction, no dose reduction</td>
<td>No</td>
<td>No</td>
<td>0.45</td>
<td>Local and spine</td>
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<td>4</td>
<td>STR</td>
<td>2</td>
<td>NS</td>
<td>HS I; 5 courses of induction, no dose reduction</td>
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<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>HS I; 5 courses of induction, no dose reduction</td>
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<td>14.16+</td>
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<td>8</td>
<td>2/F</td>
<td>2000</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>Desmoplastic</td>
<td>HS I; 5 courses of induction, no dose reduction</td>
<td>Yes</td>
<td>No</td>
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<td>—</td>
<td>13.33+</td>
<td>NED</td>
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<td>9</td>
<td>1/F</td>
<td>2002</td>
<td>12</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>HS I; 4 courses of induction, no dose reduction</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>0.40</td>
<td>DOC</td>
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<tr>
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<td>1.8/M</td>
<td>2003</td>
<td>1</td>
<td>STR</td>
<td>3</td>
<td>NS</td>
<td>HS II; completed only 2 courses as a result of recurrence; no dose reduction</td>
<td>No</td>
<td>No</td>
<td>0.33</td>
<td>Local and spine</td>
<td>0.35</td>
<td>DOD</td>
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<td>11</td>
<td>1/M</td>
<td>2005</td>
<td>4</td>
<td>GTR</td>
<td>0</td>
<td>Desmoplastic</td>
<td>HS II; 5 courses of induction, 20% CDDP dose reduction during fourth and fifth courses</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>7.78+</td>
<td>NED</td>
</tr>
<tr>
<td>12</td>
<td>2/M</td>
<td>2006</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>HS II; 5 courses + ASCT, no dose reduction</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>6.60+</td>
<td>NED</td>
</tr>
<tr>
<td>13</td>
<td>1/F</td>
<td>2006</td>
<td>4</td>
<td>STR; GTR second-look surgery</td>
<td>0</td>
<td>NS</td>
<td>HS II; 5 courses + ASCT, no dose reduction</td>
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<td>No</td>
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<td>—</td>
<td>7.40+</td>
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<td>1/F</td>
<td>2007</td>
<td>12</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>HS II; 5 courses + ASCT, no dose reduction</td>
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<td>No</td>
<td>—</td>
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<td>5.58+</td>
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(Continued on following page)
Table 2. Characteristics of 19 High-Risk Patients Younger Than 3 Years Old at Time of Medulloblastoma Diagnosis (Continued)

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<th>Patient No.</th>
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<th>YOD</th>
<th>PSI (weeks)</th>
<th>Surgery</th>
<th>M+</th>
<th>HPE MB Subclass</th>
<th>Chemotherapy/RT</th>
<th>ASCT</th>
<th>RT</th>
<th>Time to Relapse (years)</th>
<th>Site of Relapse</th>
<th>Duration of Survival (years)</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>2.7/F</td>
<td>2008</td>
<td>1</td>
<td>STR; GTR second-look surgery</td>
<td>3</td>
<td>NS</td>
<td>HS II; 5 courses with MTX intensification, no dose reduction</td>
<td>Yes</td>
<td>Yes</td>
<td>1.0</td>
<td>Local</td>
<td>1.96</td>
<td>DOD</td>
</tr>
<tr>
<td>16</td>
<td>1.4/F</td>
<td>2008</td>
<td>4</td>
<td>PR</td>
<td>0</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.02</td>
<td>DOC</td>
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<td>17</td>
<td>1/F</td>
<td>2009</td>
<td>NI</td>
<td>STR</td>
<td>0</td>
<td>NS</td>
<td>HS II; completed only 4 courses as a result of recurrence; 50% CDDP dose reduction during fourth course</td>
<td>No</td>
<td>No</td>
<td>0.35</td>
<td>Local</td>
<td>0.43</td>
<td>DOD</td>
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<td>18</td>
<td>0.25/M</td>
<td>2010</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>HS II; completed 3 courses as a result of recurrence; 10% CDDP dose reduction</td>
<td>No</td>
<td>No</td>
<td>0.39</td>
<td>Local</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>19</td>
<td>3/M</td>
<td>2012</td>
<td>2</td>
<td>GTR</td>
<td>0</td>
<td>NS</td>
<td>HS II; defaulted after 5 courses, no dose reduction</td>
<td>Local</td>
<td>No</td>
<td>0.5</td>
<td>Local</td>
<td>0.60</td>
<td>DOD</td>
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</table>

Abbreviations: ASCT, autologous stem-cell transplantation; CCG, Children’s Cancer Group; CDDP, cisplatin; DOC, died of complication; DOD, died of disease; F, female; GTR, gross total resection; HPE, histopathologic examination; HS, Head Start; M, male; M+, metastasis; M0, no dissemination; M1, tumor cells in lumbar CSF; M2, cerebral meningeal thickening; M3, spinal meningeal dissemination; M4, extraneural metastases; MB, medulloblastoma; MTX, methotrexate; NED, no evidence of disease; NI, no information; NS, no specific comment; NTR, near-total resection; OTH, other tertiary hospital; PD, progressive disease; PR, partial resection; PSI, prediagnosis symptoms interval; RT, radiotherapy; RTI, radiotherapy interval after surgery; STR, subtotal resection; UKCCSG, United Kingdom Childhood Cancer Study Group; YOD, year of diagnosis.

*Outcome data were obtained at a median follow-up time of 24 months (range, 0.25 to 230 months).
conclude the role of residual tumor greater than 1.5 cm² and distant metastasis in relation to prognosis as a result of inconsistent risk assessments among patients. Fifteen survivors are still being followed, including seven patients from the older age group and eight patients from the younger age group, including one patient with M2 disease. None of the eight survivors in the younger group required RT.

Treatment-Related Complications
In the group of older children, the most common treatment-related complication was high-frequency sensorineural hearing loss. Hearing tests were performed routinely in all patients before commencement of treatment. Eleven patients had evidence of moderate to severe hearing loss during treatment surveillance, and seven patients required cisplatin dose adjustment. No records were available on hearing aid usage. One patient had pre-existing hearing loss before the first course of chemotherapy. In patients who received chemotherapy on the CCG 9892 protocol, hearing loss occurred as early as after the second course of chemotherapy (median time to hearing loss, fourth course). We did not find any correlation between the location of the tumor (midline or lateral) and the occurrence of hearing loss. Two patients suffered reversible VCR-induced neuropathy with paralytic ileus and ptosis. VCR was then omitted from the regimen until full recovery of the clinical signs. The incidence of neutropenic fever was low in the older children. Three episodes of sterile febrile neutropenia (FN), two episodes of *Pseudomonas* pneumonia, and one episode each of *Escherichia coli* urinary tract infection and methicillin-resistant *Staphylococcus epidermidis* meningitis were observed. One patient died during CSI secondary to *Acinetobacter baumannii* infection of a VP shunt.

Thirty-six episodes of FN were seen in 15 younger children on the HS protocols; three of these patients were admitted for a single FN episode, and 12 experienced two to four episodes. Most FN episodes (52.8%) had a positive blood culture, and the documented organisms included methicillin-resistant *S. epidermidis*, *Candida albicans*, *E. coli*, methicillin-sensitive *Staphylococcus aureus*, *A. baumannii*, extended-spectrum 𝛽-lactamases, *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Streptococcus mitis*, and *Pseudomonas aeruginosa*. One patient recovered from *S. mitis* infective endocarditis, and two patients required admission to the pediatric intensive care unit for hemodynamic instability as a result of methicillin-sensitive *S. aureus* and *P. aeruginosa* infection, respectively. One death occurred secondary to disseminated *Candida* infection. All patients required blood transfusions, especially platelet support during chemotherapy. Severe myelotoxicity (eg, neutropenia, thrombocytopenia) was observed during the HS I and II protocols, despite prophylactic administration of granulocyte colony-stimulating factor. Five infants with midline tumors suffered moderate to severe high-frequency sensorineural hearing loss, and two required cisplatin dose adjustment.

Endocrine insufficiency was the most common long-term sequela in older patients. Six (85%) of seven survivors and one patient with relapsed MB had endocrine insufficiencies. Full-panel endocrine tests were performed every 6 months after completion of treatment, and hypothyroidism was the first finding in these patients. All of these patients required thyroxine replacement after 18 months of CSI. Neuropsychology and cognitive testing were not performed because no psychologist was available. Neurocognitive assessments were based on academic performance during outpatient follow-up. Poor academic performance and short attention span were noted in four older patients and two younger patients.

**DISCUSSION**
Survival of childhood MB has dramatically improved over the past few decades as a result of the adoption of a multimodal treatment approach. Recent clinical trials in high-income countries have shown that patients with AR MB who receive reduced-dose CSI and adjuvant chemotherapy experience 5-year event-free survival (EFS) greater than 80%.
than 80%, and those with HR MB who receive standard-dose CSI and adjuvant chemotherapy experience 5-year EFS of 66% to 70%. The outcome of MB in low-income countries varies based on the availability of health care resources and choice of chemotherapy regimens. At UMMC, the 5-year OS rates for older patients with HR and AR disease were 41.7% and 58.3%, respectively; in younger patients, this rate was 45.6%. These rates are low compared with those in high-income countries (Table 3), and several reasons may explain this difference.

Until the early 2000s, most patients with MB treated at UMMC underwent their initial surgical intervention elsewhere because of the lack of pediatric neurosurgical support at UMMC, and most of those interventions were performed by general neurosurgeons. As a result, only 55.8% of pediatric patients had GTR or NTR, and 70% required VP shunt insertion. Our GTR + NTR rate was inferior to that in other developing countries. Menon et al reported a GTR + NTR rate of 75% in India, and only 29% of their patients required a VP shunt.

The timing of imaging examinations after surgery is important for assessing residual disease and leptomeningeal dissemination. Postoperative imaging of children is often delayed because general anesthesia may be required to obtain MRIs, and longer imaging time is needed for brain and spine pre- and postcontrast sequences. In addition, inconsistent assessments (eg, absence of spinal MRIs and/or CSF analysis) may have resulted in incorrect risk stratification.

Besides risk assessment, the lack of neuropathology expertise was a limitation as evidenced by the absence of tumor histology subclass in most reports. Diffuse anaplasia indicates poor prognosis, and patients with that histology subtype may benefit from more intensive treatment. Similarly, infants with desmoplastic MB and MB with extensive nodularity experience excellent outcome with chemotherapy alone. Recently, several molecular and genetic tests have been developed that may improve risk stratification. The UMMC Biobank started tumor tissue banking in 2012, which will be useful for future molecular and genetic studies.

Chemotherapy approaches for children younger than 3 years old varied, and the numbers were too small to compare across protocols. The 5-year OS and EFS rates were acceptable when compared with those of other developing countries, but this response might not reflect long-term disease control. This group received definitive surgery and chemotherapy without delay. More intensive chemotherapy with ASCT and better supportive care during the mid- to late 2000s may have contributed to these promising results. Treatment of the older children on CCG 9892 varied by dose and the number of courses. Therefore, some patients may have received suboptimal treatment.

A literature review showed that MB survivors have multiple long-term morbidities (eg, physical disability, endocrinopathy, hearing loss, visual impairment). The majority of our survivors (85%) have experienced endocrine insufficiency and required hormonal replacement. Apart from treating endocrinopathy, no formal long-term follow-up was scheduled at UMMC.
### Table 3. Comparison of the Childhood Medulloblastoma Survival Rates in the Current Study and High-Income Countries

<table>
<thead>
<tr>
<th>Risk Group and Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>RT (Gy)</th>
<th>5-Year EFS/PFS (%)</th>
<th>5-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AR, ≥ 3 years old</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>2016</td>
<td>11</td>
<td>Weekly VCR during RT followed by 8 cycles of VCR, CCNU, and CDDP</td>
<td>23.4</td>
<td>54-55.8</td>
<td>68.6</td>
</tr>
<tr>
<td>Lannering et al</td>
<td>2012</td>
<td>340</td>
<td>Hyperfractionated RT followed by 8 cycles of CDDP, CCNU, and VCR</td>
<td>36</td>
<td>60 (total dose to tumor bed, 68)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard fractionated RT followed by 8 cycles of CDDP, CCNU, and VCR</td>
<td>23.4</td>
<td>54</td>
<td>77</td>
</tr>
<tr>
<td>Gajjar et al</td>
<td>2006</td>
<td>86</td>
<td>Reduced-dose RT followed by 4 cycles of high-dose chemotherapy (VCR, CDDP, and cyclo) with ASCT</td>
<td>23.4</td>
<td>55.8</td>
<td>83</td>
</tr>
<tr>
<td>Packer et al</td>
<td>2006</td>
<td>383</td>
<td>Weekly VCR during RT followed by CCNU, CDDP, and VCR</td>
<td>23.4</td>
<td>55.8</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly VCR during RT followed by cyclo, CDDP, and VCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, ≥ 3 years old</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>2016</td>
<td>13</td>
<td>Weekly VCR during RT followed by 8 cycles of VCR, CCNU, and CDDP</td>
<td>36</td>
<td>54-55.8</td>
<td>41.7</td>
</tr>
<tr>
<td>Tarbell et al</td>
<td>2013</td>
<td>224</td>
<td>3 cycles of CDDP and Eto, followed by RT, and then 7 cycles of cyclo and VCR</td>
<td>35.2-44.0</td>
<td>53.2-54.4</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT, followed by 3 cycles of CDDP and Eto, and then 7 cycles of cyclo and VCR</td>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Gajjar et al</td>
<td>2006</td>
<td>48</td>
<td>Topotecan pre-RT followed by 4 cycles of high-dose chemotherapy (VCR, CDDP, and cyclo) with ASCT</td>
<td>36-39.6</td>
<td>55.8</td>
<td>70</td>
</tr>
<tr>
<td>Packer et al</td>
<td>1994</td>
<td>56</td>
<td>Weekly VCR during RT followed by 8 cycles of VCR, CCNU, and CDDP (patients &gt; 18 months old included in the analyses)</td>
<td>36</td>
<td>55.8</td>
<td>85</td>
</tr>
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<td><strong>HR, &lt; 3 years old</strong></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Current study</td>
<td>2016</td>
<td>19</td>
<td>UKCCSG/Head Start I/Head Start II (patients &lt; 5 years old included in the analyses)</td>
<td>—</td>
<td>—</td>
<td>47.6</td>
</tr>
<tr>
<td>Rutkowski et al</td>
<td>2010</td>
<td>270</td>
<td>UKCCSG/HIT-SKK 87/HIT-SKK 92/BBSFOP/AIEOP/Head Start (patients &lt; 5 years old included in the analyses)</td>
<td>Radiotherapy based on local preference</td>
<td>55 (8-year EFS)</td>
<td>76</td>
</tr>
<tr>
<td>Dhali et al</td>
<td>2008</td>
<td>21</td>
<td>Head Start I and II</td>
<td>—</td>
<td>—</td>
<td>52</td>
</tr>
</tbody>
</table>

Abbreviations: AR, average risk; ASCT, autologous stem-cell transplantation; AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; BBSFOP, Baby Brain French Society of Pediatric Oncology; CCNU, lomustine; CDDP, cisplatin; CSI, craniospinal irradiation; cyclo, cyclophosphamide; EFS, event-free survival; Eto, etoposide; HIT-SKK, Therapieprotokoll fur Sauglinge und Kleinkinder mit Hirntumoren; HR, high-risk; PF, posterior fossa; PFS, progression-free survival; RT, radiotherapy; UKCCSG, United Kingdom Children’s Cancer Study Group; VCR, vincristine.
Cultural barriers and a lack of parental awareness influence treatment adherence in Malaysia. Reasons for treatment abandonment were intolerance to chemotherapy adverse effects, sepsis, poor social support during prolonged hospitalization, lack of housing facilities for families from distant areas, and cultural beliefs that traditional medicine is superior. In our series, eight patients declined treatment after surgery, three were lost to follow-up, and seven refused further treatment in the midst of chemotherapy. One Malaysian study found that 25% of parents sought help from traditional healers while their children were receiving cancer treatment in the hospital. The patients were given cactus juice, blessed water from holy places, horse milk, and ginseng.\textsuperscript{22} Financial issues were not a major factor in treatment refusal because the health care services are subsidized by the government. Since 2013, most families have received free accommodations at UMMC to reduce the burden of traveling and facilitate treatment without interruption.

Pediatric neuro-oncology is still an evolving subspecialty in Malaysia. Several steps to overcome the gaps and challenges must be addressed to improve the outcome of children with MB. Coordinated multidisciplinary pediatric neuro-oncology teams with better health care facilities, standardized treatment protocols, accurate disease staging and risk stratification, detailed pathology reports, formal assessment of long-term morbidity, and implementation of a national cancer registry require further attention from pediatric hematology-oncology units. Furthermore, a twinning program and research collaborations with developed countries should be considered to improve the outcome of childhood MB in the future. Such initiatives have shown excellent outcomes in childhood leukemia at UMMC through the Malaysia-Singapore 2003 research collaboration,\textsuperscript{23} and this approach has significantly improved the survival of patients with MB in Jordan.\textsuperscript{10}

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AUTHOR CONTRIBUTIONS
Conception and design: Revathi Rajagopal, Wan Ariffin Abdullah
Collection and assembly of data: Revathi Rajagopal, Vida Jawin, Su Han Lum, Tsiao Yi Yap
Data analysis and interpretation: Revathi Rajagopal, Sayyidatul Abd-Ghafar, Dharmendra Ganesan, Anita Zarina Bustam Mainudin, Kum Thong Wong, Norlisah Ramli, Eric Bouffet, Ibrahim Qaddoumi, Shekhar Krishnan, Hany Ariffin, Wan Ariffin Abdullah
Manuscript writing: All authors
Final approval of manuscript: All authors

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Revathi Rajagopal
No relationship to disclose
Sayyidatul Abd-Ghafar
No relationship to disclose
Dharmendra Ganesan
No relationship to disclose
Anita Zarina Bustam Mainudin
Travel, Accommodations, Expenses: MSD Oncology

Kum Thong Wong
No relationship to disclose
Norlisah Ramli
No relationship to disclose
Vida Jawin
No relationship to disclose
Su Han Lum
No relationship to disclose
Tsiao Yi Yap
No relationship to disclose
Eric Bouffet
Research Funding: Genentech

Ibrahim Qaddoumi
No relationship to disclose
Shekhar Krishnan
Travel, Accommodations, Expenses: Sigma-Tau

Hany Ariffin
No relationship to disclose
Wan Ariffin Abdullah
No relationship to disclose

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Surgery for CNS Tumors in the Brazilian National Health Care System

Luciola Pontes
Maryam Nemati Shafaee
Benjamin Haaland
Gilberto Lopes

INTRODUCTION

Brain malignancies are among the highest-cost cancers in the United States. The mainstay of therapy for the majority of CNS tumors is surgery, which is often followed by radiation therapy. Many factors have been reported to affect the outcome of surgical management for CNS tumors. These factors generally fall under the two broad categories of patient-related factors and hospital-related factors. More favorable outcomes have been reported in patients with active health insurance status and fewer comorbid conditions. Hospital-related positive predictors of improved outcomes include a hospital infrastructure geared towards high-volume neurosurgical procedures and high socioeconomic status of the patient population served by the hospital. In addition, racial and ethnic disparities in access to high-volume neuro-oncologic care and final health outcomes have been reported to disproportionately affect the African American and Hispanic patient population in the United States. African American patients are reported to present with more advanced disease, undergo neurosurgical procedures in low-volume centers, experience more procedure-related mortality, and experience poorer discharge conditions after craniotomy compared with white patients. Geographic maldistribution of oncologic specialty care centers has also been associated with unfavorable outcomes, and addressing the variation in regional resources has been suggested as a way to narrow the disparity gap in neuro-oncologic care in the United States.

On a global scale, in low- and middle-income countries where availability of resources, or lack thereof, directly dictates lower investment on diagnostics and treatments, management of CNS tumors may pose different challenges. The annual incidence rate of primary CNS tumors globally is reported to be higher for males compared with females (3.7 v 2.6 per 100,000 person-years) and higher in developed countries compared with developing countries. According to a recent report on global status of cancer in 2013 by the Institute
for Health Metrics and Evaluation, 3.6% of cancers in developing countries are primary tumors of the CNS.\textsuperscript{11} There is no uniform approach to how different developing countries allocate resources for management of primary CNS tumors. In this article, we aim to provide a country-wide picture of the state of surgical management for primary brain tumors in Brazil. The fifth largest and fifth most populous country in the world, Brazil is riddled with socioeconomic inequalities, which consequently translates into palpable disparities across all aspects of cancer care.\textsuperscript{12} The country is geopolitically subdivided into five regions: North, Northeast, South, Southeast, and Midwest. Each of these regions is investigated separately for frequency of neurosurgical operations for CNS tumors. Here we attempt to identify opportunities for developing cost-effective approaches to address the burden of primary CNS tumors and improve their surgical management.

**METHODS**

The Brazilian public health system database (DATASUS) was reviewed for data collected between January 2008 and November 2013. All neurosurgical procedures related to primary CNS tumors were identified. Detailed information, including number of procedures, costs of each procedure and cost as a whole, length of inpatient hospital stay, and incidence of inpatient mortality were extracted for each state, and then they were associated with state-specific population, gross domestic product (GDP) per capita, and number of procedures.

Relationships among state-specific potential predictive variables such as population, number of procedures, and GDP per capita were summarized in terms of Spearman’s rank correlation. The relationships between state-specific respective outcomes, mortality, cost, length of inpatient hospitalization, and predictive variables were assessed in the context of univariate and multivariate generalized linear models, with a logit link.
for mortality, identity links for cost and length of hospitalization, and state-specific observations weighted by number of procedures.

**RESULTS**

Between January 2008 and November 2013, a total of 57,361 procedures pertaining to management of primary CNS tumors were identified on retrospective review of procedures logged in Brazil’s public health system records. Regional population was strongly associated with number of procedures (Spearman’s rank correlation, 0.91; \( P < .001 \)). There was no strong evidence that either population or number of procedures was related to GDP per capita (Spearman’s rank correlations were 0.17 \( P = .404 \) and 0.33 \( P = .090 \), respectively).

The highest number of neurosurgical procedures (46%) was performed in the Southeast region, followed by 22% in the South, 18% in the Northeast, 9% in the Midwest, and 5% in the North (Fig 1). The mean length of inpatient hospital stay was 14.4 days (95% CI, 13.1 to 15.7 days).

The duration of hospitalization was significantly longer for patients treated in the North region (20 days) and shortest in the South and Midwest regions (13 days), as seen in Figure 2. On univariate analysis, there was no association between the number of days of hospitalization and number of procedures, GDP per capita, or regional population. On multivariate analysis, number of procedures, GDP per capita, and the regional population each had an independent association with number of days of hospitalization. For fixed GDP per capita and population, days of hospitalization tended to decrease as number of procedures increased. For a fixed number of procedures and population, days of hospitalization tended to increase as GDP per capita increased, and for a fixed number of procedures and GDP per capita, days of hospitalization tended to increase as population increased.

A total of 4,079 inpatient deaths were reported, translating into an inpatient mortality rate of 7.11%. Highest rates were seen in the North (13%). South and Midwest regions had the lowest procedure related mortality rate, 6% each (Fig 3). On univariate analysis, an inverse relationship was found between the mortality rates and number of procedures \( (P < .001) \), GDP per capita \( (P < .001) \), and state population \( (P < .001) \). On multivariate analysis, number of procedures (odds ratio \( OR \), 0.93; 95% CI, 0.91 to 0.96; \( P < .001 \)) and population (\( OR \), 1.25; 95% CI, 1.13 to 1.38; \( P < .001 \)) were found to have an independent association with inpatient mortality.

Total cost for the 57,361 procedures performed was calculated at US$108,363,802. Average cost per admission was US$1,889. For this calculation, the currency rate of 1 US$ = 2.40 Brazilian Real (R$) was used. The rate stands at 1 US$ = 4 R$ at this time. For a fixed number of procedures and population, the average cost per state tended to decrease as GDP per capita increased (US$250 decrease per US$10,000 per capita GDP; 95% CI, US$100 to US$400; \( P = .001 \)). The North region was again found to stand out as having the highest cost per hospitalization and the lowest number of reimbursements to health care professionals per hospitalization event (Fig 4).

**DISCUSSION**

Disparities in cancer care are a matter of public health concern worldwide. Socioeconomic disparities exist not only in different regions of the globe, but also in different regions of a single country.13 This means that when devising health policies, resource allocation needs to be made with areas of highest disparity in mind. This signifies the importance of careful assessment of the magnitude of disparities and their determinants before investing in remedial work.

In the United States, racial disparities in disease outcomes, not immediately explainable by differences in disease biology, are well documented. Race is noted to represent a crude measure of many other factors influencing the risks and treatment of disease. The US Department of Health and Human Services has officially acknowledged these disparities as well as actions taken by the government agencies in addressing them.14
Our study attempted to identify areas of disparity with regard to surgical management of CNS tumors in the middle-income country of Brazil. We found significant differences in the frequency of procedures and inpatient mortality rates between different regions. Duration of inpatient stay and mortality rates were highest in the North. This region was also significant for having the lowest number of procedures compared with the other four regions. The North is notable for having the largest land mass and lowest GDP of the five regions. Demographically, this area is home to only 6% of the country’s population, which includes the largest community of Native Amerindians. The lower GDP, higher land mass, and smaller population density in this region compared with the other regions in the country could influence the lower rates of surgical management of CNS tumors through potential lack of access, lower number of hospitals per population, greater distances to travel, fewer health care professionals, and fewer training facilities.

The Southeast region, which is home to 38% of the population and which has the highest GDP per capita, predictably experiences the highest number of neurosurgical procedures. The other three regions of the country fall on a spectrum with little variability in terms of hospital stay, mortality rates, and cost.

Average inpatient mortality rate postsurgery for CNS tumors in the United States is reported to be between 1.28% and 2.8%, depending on the insurance status of the patient. The rate in Brazil is considerably higher, at an average of 7.11%, with wide variation in the five different geopolitical areas.

Further studies are warranted to elucidate the causes of the high mortality from primary CNS tumors seen in Brazil as a whole. An area of future endeavor could be evaluating access to radiation therapy after surgical resection of CNS tumors.

In summary, this is the first study, to the best of our knowledge, to evaluate disparities in CNS tumor surgery in a middle-income country, confirming that regional disparities exist within a country under single governance. This study confirms that clinical and economic outcomes correlate with income level, number of procedures, and regional population.

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Luciola Pontes
No relationship to disclose

Maryam Nemati Shafaee
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Benjamin Haaland
No relationship to disclose

Gilberto Lopes
Honoraria: AstraZeneca, Genentech, Merck Serono, Merck Sharp & Dohme, Fresenius Kabi, Novartis, Bristol-Myers Squibb, Janssen-Cilag
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Expert Testimony: Sanofi

REFERENCES

Fig 4. Cost per admission according to region. Used with permission. © 2014 American Society of Clinical Oncology. All rights reserved.
Surgical Management of Breast Cancer in Africa: A Continent-Wide Review of Intervention Practices, Barriers to Care, and Adjuvant Therapy

Breast cancer has emerged as a leading cancer among women in Africa, necessitating improved understanding of its management across the continent. Although previous studies have described regional trends in therapy, this review aims to summarize continent-wide management and focus specifically on surgical interventions. Current literature shows that the rates of surgery, chemotherapy, and radiation therapy vary across different countries and institutions, indicating the need for greater use of standardized cancer treatment guidelines. Surgery, primarily modified radical mastectomy, is the most common form of therapy described. When chemotherapy is offered, the limited availability and cost of treatment lead to high rates of interruption and premature termination of cycles. Few patients have access to radiation or hormonal therapy because these treatments are not available in many countries. Significant delays in seeking treatment are common and contribute to patients presenting with advanced disease. Although limited infrastructure favors surgical management, interventions to improve early detection behavior, provide timely referrals to medical care, and initiate early treatment with access to clinically justified neo-adjuvant and adjuvant therapy are key to improving prognosis.

INTRODUCTION

Breast cancer is a paramount concern to women’s health. It is the most common invasive cancer in the world; more than 1.4 million women receive the diagnosis of breast cancer every year. Management of this disease among Western health care systems has led to remarkable improvements in outcome in the past 40 years. In the United States, the spike in breast cancer incidence in the 1980s corresponded with a decrease in mortality because the widespread use of mammography as a screening tool detected more cases of cancer at an earlier stage of disease. As a result, the overall 5-year survival in the United States is now almost 92% and continues to rise.

These improvements in breast cancer management do not reflect the current situation throughout the African continent, where women suffer a particular burden of disease and lack resources for detection and treatment. Estimates of cancer statistics released in 2012 for 26 African countries indicated that breast cancer has become a leading cancer among women. Of special concern, patients present late with advanced disease, treatment is often unavailable, delayed, or prohibitively expensive, and survival rates are low. Early research suggests that breast cancer among African women is more aggressive, with a greater proportion of patients presenting at an earlier age and with high-grade and receptor-negative tumors. A literature search was conducted using search terms “breast cancer” and “Africa.” Whereas other studies have described regional variation of the occurrence of breast cancer in Africa, the focus of this review is to summarize the current management of breast cancer throughout the entire continent of Africa, specifically attempting to investigate surgical procedure rates and barriers to surgical care.

EARLY DETECTION AND SCREENING

Although the current literature does not provide consistent detailed information regarding surgical management of breast cancer in various African countries, common trends are apparent that may make surgery a secondary concern to ministries of...
health. Screening is lacking in all the countries with published literature in this area. As noted in other articles, most recently in an article by Kantelhardt et al., screening via mammography and the appropriate resources for proper follow-up of any results are not widely available in Africa. Thus, patients may present at a late stage, when palliative chemotherapy is of more use than surgery. Surgery may be used for palliative management only when the resources needed to provide sufficient chemotherapy are lacking or unavailable.

From studies in Ghana, Nigeria, South Africa, Cameroon, Eritrea, Rwanda, Tanzania, and Uganda, only three countries report the main form of breast cancer detection, which is self-examination: Ghana (62.2%), Nigeria (92%, Ile-Ife; 73.3%, Enugu), and Cameroon (92.9%). Only the Eritrea study notes the use of radiology in screening, and this is for only 29% of patients. When an abnormality was detected via self-examination, a significant delay between detection and presentation for health care was reported. Of the 10 studies that note delay time, more than half of all patients waited 3 months or more to seek medical advice, with some averages approaching a year or more. As a result, totals from 13 different studies show that more than 75% of patients presented in stages III to IV. On the basis of this information alone, it is apparent that initiating programs that emphasize self-examination techniques and early access to care would be a major first step in making a proper place for the use of surgery and improving outcomes overall.

The main causes of delay are attributed to the patients not understanding the severity of their disease and seeking treatment with alternative healers before presenting for medical attention. Patients commonly said that they were unaware of the implication of their disease or believed that it would disappear without treatment. Studies from Ghana, Eritrea, and Nigeria found that between 12.2% and 38.4% of patients initially sought treatment with an alternative practitioner, including traditional healers, prayer homes, and herbal specialists. Seeing an alternative practitioner was significantly associated with a delay of more than 3 months. Considering the relative scarcity of health care providers, this preference for traditional medicine is not surprising, because traditional healers are more affordable, are easily accessible, provide less invasive treatment, and offer a more intimate relationship. Therefore, it has been suggested that natural healers could be integrated into the medical framework and could provide patient referrals to hospitals, which would allow traditional and medical approaches to be implemented in parallel.

Table 1. Screening for Breast Cancer in African Countries by Detection Method

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>Hospital</th>
<th>Years of Data Collection</th>
<th>No. of Patients</th>
<th>Detection Method</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>Douala</td>
<td>DGH</td>
<td>06-09</td>
<td>42</td>
<td>Self</td>
<td>92.9</td>
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<td>Eritrea</td>
<td>Orrota, Halibet, Sembel</td>
<td></td>
<td>07-08</td>
<td>82</td>
<td>Radiologic</td>
<td>29</td>
</tr>
<tr>
<td>Ghana</td>
<td>Kumasi</td>
<td>KATH</td>
<td>08-10</td>
<td>597</td>
<td>Self</td>
<td>62.2</td>
</tr>
<tr>
<td>Malawi</td>
<td>Kamuzu</td>
<td>KCH</td>
<td>04-07</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Calabar</td>
<td>UCTH</td>
<td>80-84</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Enugu</td>
<td>UNTHE</td>
<td>99-05</td>
<td>164</td>
<td>ND</td>
<td>Self</td>
<td>73.3</td>
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<tr>
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<td>UCH</td>
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<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Ile-Ife</td>
<td>OAUTHC</td>
<td>96-03</td>
<td>212</td>
<td>ND</td>
<td>Self</td>
<td>92</td>
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<tr>
<td>Kaduna</td>
<td>ABUTH</td>
<td>03-05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
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<td>LUTH</td>
<td>84-89</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Lagos</td>
<td>LSUTH</td>
<td>09-10</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nnewi</td>
<td>NAUTH</td>
<td>04-08</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Rwanda</td>
<td>Butaire, Kigali, King Faisal</td>
<td>07-11</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>South Africa</td>
<td>Private center</td>
<td></td>
<td>00-08</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Mwanza</td>
<td>BMC</td>
<td>02-10</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Uganda</td>
<td>Kampala, Mulago</td>
<td>96-00</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND, no data.
study showing delayed or no referrals for treatment, erroneous advice from initial health care providers, delays in biopsy analysis, and infrastructural insufficiencies affecting 46.2% of patients.9 Finally, lack of funds is also cited as a barrier to seeking initial treatment, with approximately 3% of patients reporting this as the cause of their delay; however, prohibitive cost seems to be a greater factor in the interruption and discontinuation of treatment later in the course of breast cancer care.11,14,15

SURGERY

Surgical intervention is the primary focus of treatment in Africa.6 Because tumor staging is rare in this region, most of the studies included in this review do not report treatment as guided by disease stage. Instead, therapy choice seems to be dictated by the local availability of resources; surgery represents the most popular option when access to chemotherapy and radiotherapy is limited. A need for more detailed record keeping throughout the continent is essential to understanding treatment decision making and the associated outcomes.

The rates of surgical treatment vary greatly across the different countries in Africa, ranging from 35.2% in Nigeria to 100% in Cameroon; the majority of countries report surgical rates between 48% and 75%6,7,10,14-16 (Table 2). This divergence in surgical treatment popularity seems to be dependent on both patient preference and country-specific resources. In Nigeria, for example, the comparatively low breast cancer surgery rate was attributable to inoperable advanced tumors, inability to pay for treatment, and patient unwillingness to have a mastectomy.16 In Eritrea, 80 of the 82 women who were observed received surgical intervention as their only treatment because there are no chemotherapy or radiotherapy options available nationally.12 Nguefack et al10 in Cameroon observed 42 women for breast cancer over a 3-year period, and nearly all were treated with some form of surgery (92.9%), despite the majority of patients presenting with stage III disease; 79% of patients received neoadjuvant chemotherapy to downstage tumors and therefore allow surgical excision and closure to occur.10 This suggests a possible regional difference in approach to multidisciplinary breast cancer care, as well as a chasm in cultural attitudes toward surgical options, because very few women in Eritrea and Cameroon are refusing mastectomies in comparison with their counterparts in Nigeria.

When surgical options are pursued, the most common procedure is a mastectomy, with all institutions surveyed reporting a rate of well above 50%, with many above 90%.7,10,16,17 Modified radical mastectomy is most frequently performed, which consists of removing the whole breast tissue along with the axillary tail and complete clearance of axillary lymph nodes and connective tissue.15,16 Breast-conserving surgeries and lumpectomies remain rare in this region, because the majority of patients present with advanced stages (III and IV) of invasive cancer, which limits the options for conservative surgery in the absence of neoadjuvant chemotherapy.6,8,15,17 Furthermore, the ability to assess surgical margins for tumor-free tissue is often not feasible, and postoperative follow-up is low.12,16

Despite a shortage of other treatment options, many African women report fear of mastectomy, which may contribute to the delay in seeking surgical evaluation.7,9,13,18 Ajekigbe et al18 report that the most prevalent cause of delay among Nigerian women is fear of mastectomy; 44.7% of women surveyed acknowledged that they were aware that their ailment could be cancer, but they delayed treatment because of fear of mastectomy. This fear was a consistent cause of delay across age and educational background groups. Similar studies found that patients refuse mastectomy because they do not want their bodies to be disfigured and fear the effect of mastectomy on their relationship with their partners.13 A reason cited for treatment refusal is that family members believe that hospital treatment could result in an escalation of the disease.13 This fear of surgery and delay in treatment creates a cycle that may result in overall poor outcomes for the African region: when patients have a fear of mastectomy, they delay their treatment and seek alternative therapies, only presenting to the hospital when the disease has escalated to an advanced stage. At advanced stages, aggressive treatment is necessary and the prognosis is poor. This may lead to an association of the hospital with poor outcomes and a belief that treatment will escalate the disease.14

ADJUVANT THERAPY

As previously mentioned, with patients presenting at late stages, the role of surgery as a curative measure is significantly diminished. With locally advanced or metastatic disease, chemotherapy becomes ideal for treatment and palliation, yet the proper resources for its use are lacking, and its availability varies greatly across country and
Whereas patients in the West currently receive chemotherapy to downstage locally advanced tumors or treat node-positive and metastatic disease, adoption of this practice remains limited and varied on the African continent. Hospitals in South Africa, Nigeria, and Cameroon report that more than 85% of their patients receive chemotherapy compared with 28% in Rwanda and 1.2% in Eritrea (Table 3). This disparity in chemotherapy rates reflects heavily on the available medical resources of the country. Rwanda has a shortage of health care providers who are equipped to treat patients with breast cancer, with only 15 general surgeons and no oncologists in the country. Women in Eritrea have few alternatives to surgical management, because the country has no permanent center for chemotherapy treatment. Without the facilities or personnel trained to provide chemotherapy, these options are inaccessible for many patients. Treatment is skewed toward surgical options because of country-specific resource limitations, even when chemotherapy is recommended.

When chemotherapy is available, the majority of patients are not able to complete the recommended regimen, and treatment interruptions are common. A study from Uganda reports that only 29% of patients completed the six recommended cycles of chemotherapy, and fewer than 20% in Nigeria completed six to 12 cycles. The vast majority of patients (86.4%) report obstacles that interrupted or completely ended chemotherapy treatment. Financial cost of treatment represents the most prohibitive factor in continuing care. A course of chemotherapy costs approximately US$250, which most people are unable to pay. Further, patients need to seek additional funds to pay for transportation to the hospital and for laboratory costs. Patients also report that they discontinue treatment because of a lack of space in the hospital and because they do not have a relative to care for them.

Radiation therapy is indicated to destroy localized breast cancer cells and reduce the rate of recurrence after surgical resection of the tumor. However, radiation therapy is not easily accessible, because only 23 of 52 African countries are equipped with radiation facilities. Rates for use of radiation therapy greatly differ among countries; 0% in Eritrea, 1% in Rwanda, 33.2% in Nigeria, and 5% in South Africa (Table 2).

### Table 2. Surgery Rates for African Patients With Breast Cancer by Type of Surgery

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>Hospital</th>
<th>Years of Data Collection</th>
<th>No. of Patients</th>
<th>Patients Treated Surgically (%)</th>
<th>Type of Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mastectomy Lumpectomy Other/ Combined Unknown</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Douala</td>
<td>DGH</td>
<td>06-09</td>
<td>42</td>
<td>100</td>
<td>92.9</td>
</tr>
<tr>
<td>Eritrea</td>
<td>Orrota, Halibet, Sembel</td>
<td>07-08</td>
<td>82</td>
<td>98.8</td>
<td>80.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Ghana</td>
<td>Kumasi</td>
<td>KATH</td>
<td>08-10</td>
<td>597</td>
<td>48.2</td>
<td>53.1</td>
</tr>
<tr>
<td>Malawi</td>
<td>Kamuzu</td>
<td>KCH</td>
<td>04-07</td>
<td>49</td>
<td>NR</td>
<td>48.9</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Calabar</td>
<td>UCTH</td>
<td>80-84</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Enugu</td>
<td>UNTH-E</td>
<td>99-05</td>
<td>49</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Ibadan</td>
<td>UCH</td>
<td>99-09</td>
<td>354</td>
<td>35.2</td>
<td>96.7</td>
</tr>
<tr>
<td></td>
<td>Ille-Ife</td>
<td>OAUTHC</td>
<td>96-03</td>
<td>212</td>
<td>87.3</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Kaduna</td>
<td>ABUTH</td>
<td>03-05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Lagos</td>
<td>LUTh</td>
<td>84-89</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Lagos</td>
<td>LSUTH</td>
<td>09-10</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Nnewi</td>
<td>NAUTH</td>
<td>04-08</td>
<td>275</td>
<td>42.2</td>
<td>97.3</td>
</tr>
<tr>
<td>Rwanda</td>
<td>Butoire, Kigali, King Faisal</td>
<td>07-11</td>
<td>145</td>
<td>71</td>
<td>71.8</td>
<td>28.1</td>
</tr>
<tr>
<td>South</td>
<td>Private center</td>
<td>00-08</td>
<td>141*</td>
<td>91</td>
<td>87.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>Mwanza</td>
<td>BMC</td>
<td>02-10</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Uganda</td>
<td>Kampala, Mulago</td>
<td>96-00</td>
<td>297</td>
<td>75</td>
<td>93.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Abbreviations: ND, no data; NR, not reported.
*Younger than age 35 years.
<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>Hospital</th>
<th>Years of Data Collection</th>
<th>No.</th>
<th>Chemotherapy (%)</th>
<th>Hormonal Therapy (%)</th>
<th>Radiation (%)</th>
<th>Declined Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>Douala</td>
<td>DGH</td>
<td>06-09</td>
<td>42</td>
<td>NR</td>
<td>78.6</td>
<td>92.9</td>
<td>92.9</td>
</tr>
<tr>
<td>Eritrea</td>
<td>Orrota, Halibet, Sembel</td>
<td></td>
<td>07-08</td>
<td>82</td>
<td>1.2</td>
<td></td>
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</tr>
<tr>
<td>Ghana</td>
<td>Kumasi</td>
<td>KATH</td>
<td>08-10</td>
<td>597</td>
<td>48</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>Kamuzu</td>
<td>CH</td>
<td>04-07</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Calabar</td>
<td>UCTH</td>
<td>80-84</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Enugu</td>
<td>UNTHE</td>
<td>99-05</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Ibadan</td>
<td>UCH</td>
<td>99-09</td>
<td>354</td>
<td>89</td>
<td>49.1</td>
<td>35.9</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Ile-Ife</td>
<td>OAUTHC</td>
<td>96-03</td>
<td>212</td>
<td>NR</td>
<td>30.6</td>
<td>84 (less than 20 completed)</td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td>Buari, Kigali, King Faisal</td>
<td></td>
<td>07-11</td>
<td>145</td>
<td>28</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>South Africa</td>
<td>Private center</td>
<td></td>
<td>00-08</td>
<td>141*</td>
<td>86.5</td>
<td>41.1</td>
<td>58.9</td>
<td>48.1</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Mwanza</td>
<td>BMC</td>
<td>02-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>Kampala, Mulago</td>
<td></td>
<td>96-00</td>
<td>29 completed (40 offered, 11 dropped out)</td>
<td>60</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ND, no data; NR, not reported.
*Younger than age 35 years.
In countries in which radiation therapy exists, the facilities often attempt service beyond their capabilities, so the facilities become overcrowded with long wait times. Radiotherapy is often localized to private or tertiary hospitals, which limits its accessibility to many segments of the population.

In the absence of focused studies, tumor marker analysis is rarely possible in resource-poor countries. However, recent studies have suggested that the proportion of estrogen receptor–positive tumors in Africa is higher than previously reported (63% compared with 24%) and warrants further investigation. In the literature reviewed, only three studies reported the rate of hormone therapy use in their patients. Tamoxifen was used in 37.7% of patients in Nigeria, 48.1% in South Africa, 60% in Uganda, and 92.9% in Cameroon. Because hormone receptor status remains predominantly unknown, tamoxifen is currently prescribed blindly. Nevertheless, tamoxifen is cost prohibitive for most patients on the African continent, and newer classes of anti-estrogen aromatase inhibitors appropriate for postmenopausal women are not available or affordable in Africa.

FOLLOW-UP

Follow-up is poor among African patients with breast cancer, which hinders accurate assessment of the efficacy of treatment paths. Uganda and Cameroon report comparatively high follow-up rates: 28% of patients receive follow-up at the end of a 5-year period in Uganda, and 58.5% receive follow-up at 3 years in Cameroon. Studies from Nigeria show a more significant proportion of patients to be lost to follow-up, with only 37.9% of patients attending outpatient clinics 18 months after mastectomy; the percentage continued to decline until most patients were lost to follow-up by 30 months. The vast majority of patients are lost to follow-up within the first year of diagnosis, suggesting that interventions to improve follow-up should be implemented during the initial appointments.

Survival rates are similarly poor, reflecting the advanced nature of the tumors at presentation and the numerous barriers to treatment. In South Africa and Nigeria, the 5-year survival rates are 20% and 14%, respectively. The prognosis predictably varies, depending on disease stage at presentation; 2-year survival in South Africa for those diagnosed as stage 0 to III is 56% compared with 16% for those in stage IV. Approximately 91.4% of deaths occur within the first year of diagnosis. Overall, studies generally assess the long-term outcomes of only those patients who completed treatment and, as a result, the survival rates are likely even worse than currently reported because they do not capture patients lost to follow-up or patients who did not complete treatment. The survival rate could be improved if interventions brought patients to clinical attention at earlier disease stages. Improvements in patient education and screening, including self-examination, that raise the awareness of breast cancer, the significance of breast lumps, and increased trust in the medical establishment could increase survival prognosis.

In conclusion, the goal of this review was to provide insight into the current management of breast cancer across the continent of Africa, focusing on surgical interventions. The literature shows that the rates of surgery, chemotherapy, and radiation therapy vary across different countries and institutions, emphasizing the need for a greater use of standardized cancer treatment guidelines. Surgery is the most commonly implemented therapy, but the intention of surgery remains consistently unclear, because treatment choice and disease stage do not correlate in regional studies. It seems that surgery is used as a treatment even in advanced disease because of the inaccessibility and expense of adjuvant chemotherapy and radiation therapy, and the high rates of patients lost to follow-up care.

To better understand the clinical reasoning for specific treatments and the efficacy of treatment options, it is necessary that medical records consistently include description of the disease and therapy. Improvements to follow-up monitoring would provide the much needed information on patient prognosis after treatment. Interventions to improve awareness of breast cancer and encourage self-examination, clinical breast examination, and prompt medical attention may improve survival. Adopting a minimum standard of care, including mastectomy, axillary clearance, and adjuvant therapy in resource-limited countries would be ideal.

To this end, it would be most ideal if African women underwent resource-appropriate early detection examinations so they could present for surgical evaluation with resectable disease or have access to neoadjuvant chemotherapy to downstage locally advanced tumors and facilitate complete resection and closure.

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AUTHOR CONTRIBUTIONS
Conception and design: Deo Darius Balumuka, Katrina B. Mitchell
Collection and assembly of data: Stephanie A. Sutter, Aaron Slinker, Katrina B. Mitchell
Data analysis and interpretation: Stephanie A. Sutter, Katrina B. Mitchell
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF
POTENTIAL CONFLICTS OF INTEREST
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Stephanie A. Sutter
No relationship to disclose
Aaron Slinker
No relationship to disclose
Deo Darius Balumuka
No relationship to disclose
Katrina B. Mitchell
No relationship to disclose

REFERENCES
INTRODUCTION

Cancer refers to any one of a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer cells are abnormal because they divide uncontrollably. A life-threatening characteristic of these cells is their ability to spread to distant vital organs such as the lungs, liver, brain, and bone.

Worldwide, cancer is a leading cause of morbidity and mortality; there were approximately 14 million new occurrences and 8.2 million cancer-related deaths in 2012.² On average, in Nigeria, cancer has an annual incidence of 102,100 per year and a mortality rate of 71,600.³ In 2012, Nigeria recorded an incidence of 27,304 breast cancer occurrences and a mortality rate of 13,960.⁴ It has been estimated that 52,728 new occurrences will be recorded by the year 2035.⁴

The majority of patients with breast cancer present with stages III or IV disease, which is associated with lower survival rates. Some of the factors that account for late presentations include lack of awareness and information about basic symptoms of cancer as well as poor access to early screening and treatment.⁵

Breast cancer is a major disease in Nigeria; in 2012, 27,304 new occurrences were diagnosed, and the number of mortalities was 13,960. Greater than 70% of patients present with advanced disease, which has a poor survival outcome. The mortality rates are high mainly because of a lack of awareness about breast health, screening guidelines, and treatment centers, and because of sociocultural barriers. In Nigeria, health care professionals remain the backbone for the provision of medical information to the public. This is a study of the innovative ways that breast health and cancer awareness were promoted across communities and institutions in Lagos State, Nigeria, in 2015. Several community awareness campaigns were carried out in the forms of health talks, breast cancer screenings, radio and television interviews, and campaigns on social media. Anomalies noticed during the screenings were promptly referred to appropriate hospitals for additional treatment. The campaign culminated in the #12KLLP, or 12,000 people light Lagos pink, which was a Guinness World Record attempt for the largest human awareness ribbon formed for breast cancer. There was a total reach of 28,774,812 people across platforms: 285,318 were on social media, 3,620 were in communities, 7,466,276 were on the website, 20 million were through media events, 12,000 were through publications, 7,598 were verified participants at the Guinness World Record, and approximately 1 million were through blogs. Eighty partnerships were made with various private and government institutions to facilitate different aspects of the campaign. The community members were able to learn about the need for early detection and awareness; volunteerism and corporate social responsibility were promoted among individuals and corporate institutions.

To address the lack of awareness and to improve information about cancer screening services, Sebeccly Cancer Care, a national breast cancer charity, implemented an innovative public awareness program called the #12KLLP (12,000 people light Lagos pink). The overall goal of the #12KLLP campaign was to promote awareness of breast cancer and of the availability of breast cancer screening services. The #12KLLP was a Guinness World Record (GWR) attempt to form the largest human pink ribbon made up of 12,000 people. The awareness program was a 10-month-long event that began in February 2015 and ended in November 2015. During the preparatory phase, a local organizing committee was formed to give strategic direction
and planning. The #12KLLP featured community awareness programs, social media campaigns, and radio and television interviews, and it culminated with the GWR attempt on October 10, 2015. The campaign attracted people of all social classes and walks of life.

The existing record that the #12KLLP attempted to break stood at 6,487 individuals and was held on April 2, 2014, at the New Grain Market in Karnal, India. Other GWR attempts for awareness about breast cancer include a largest shirt record in Brazil for breast cancer awareness. Previous awareness campaigns at Sebeccly Cancer Care included the light Lagos pink campaign in 2014, in which various notable landmarks and buildings in Lagos were illuminated pink to raise awareness of breast cancer.

The objectives of this effort were to address the lack of awareness about cancer screening services and to improve information about cancer screening services.

PRE-CAMPAIGN STRATEGY

Awareness Before the Campaign

In preparation for the world breast cancer month of 2015, it was decided that a program to increase awareness of breast cancer should be carried out. The local organizing committee was set up to decide on a strategy that was based on innovation and that increased community involvement. The option of breaking a GWR and reaching women through the ensuing publicity was suggested and agreed upon. Partnership and endorsement was sought from the Lagos State government and the Nigeria police force to host and secure the campaign.

Major components of the campaign were community mobilization (in charge of recruitment and provision of information to the participants, who were corporate representatives, individuals, and volunteers), project management (in charge of overseeing the different aspects of the planning of the campaign), operations (in charge of procurement and logistics, including transportation, feeding, miscellaneous needs), administration, fundraising (in charge of sourcing funds, in-kind gifts, and technical support from donors and partners), and the medical unit and media (who were in charge of providing medical information and screenings and who attended media interviews and public relations). Publicity for the campaign was carried out by social media, television and radio interviews, electronic and print media, flyers, publications, community events, and word of mouth.

Training. Training on social media management, fundraising, and project management was carried out in June 2015 by Niidasat Technologies and Sebeccly. Seven team staff members were recruited, of whom five were on contract and two were volunteers, in addition to three full-time staff. The training by Niidasat Technologies lasted 4 days, and the training by Sebeccly was held in 1 day.

Recruitment of team captains was done with the snowballing technique, in which a volunteer, upon hearing about the event, would tell and invite other volunteers to join. Criteria for inclusion as the team captain was age older than 18 years, commitment, place of work/residence, and capacity to mobilize at a community level. Volunteers were also recruited with the snowballing technique on the basis of their place of work/residence, commitment to work in selected units of their choice, and age older than 18 years. Several meetings were held to ascertain the volume of participants expected on the day of the record attempt and to prepare logistics of transport to the venue, food, security, and promotional materials, as well as media considerations (photography, videography, press releases, and social media platforms). Attendance records at the meetings were used to track the number of volunteers. Community awareness campaigns were carried out before the event to sensitize the communities in Surulere, Shomolu, Iganmu, Iyi-Araba, Eti-Osa, Ikeja, Akoka, Yaba, and other areas.

Field work and visits had been conducted by the surveyor and security personnel at the chosen venue before the event. The chosen venue was the Teslim Balogun Stadium which is a 24,360-seater stadium of international standards; its turf dimensions are 120 meters by 80 meters. The stadium is located in Surulere, Lagos, opposite the National Stadium. The outline of the ribbon was marked out in chalk by the surveyor 2 days before the event, and calculations and projections on the population expected were made. In October 2015, the Sebeccly office moved to the Teslim Balogun Stadium for closer proximity and ease of logistics. Several high-level meetings were held with the stakeholders of the event, such as the heads of security agencies, Lagos State government officials, volunteers, medical services personnel, and members of the Sebeccly team. Letters and emails were sent to popular blogs in Lagos State to partner with Sebeccly Cancer Care in spreading the word online.

Selection and recruitment of ambassadors and witnesses. Criteria for selection of witnesses and ambassadors included the size of the social media
following, willingness to partner, interest, and commitment. In line with the rules and regulations of the GWR, witnesses were chosen on the basis of their willingness to function at the campaign without any form of remuneration from Sebeccly Cancer Care and by their occupations. Only occupations such as accountants, attorneys or judges, and senior police officers could be recruited to function as witnesses. Gbenga Badejo & Co, an auditing firm, was the independent auditor for the event. Witnesses were employees from other auditing and accounting firms in Lagos who voluntarily agreed to witness the record attempt, free of charge. An independent auditing firm was randomly selected from a list of firms that had been approached to partner with the effort. The witnesses and the auditing firm were all provided with the GWR guidelines for the record attempt in advance of the event.

The ambassadors were selected on the basis of the above-mentioned criteria. There were 10 ambassadors. Three ambassadors were entrepreneurs, two were media personnel (publishers in newspapers), and the remaining five were actresses in Nigeria (Nollywood). Awareness began in approximately May 2015; some of the venues where events occurred are listed in Table 1.

RESULTS

There were a total of 70 team captains who helped to speak to and gather the participants at the event, and there were 400 volunteers who were involved in different areas of organization, like transport, registration, and ushering.

There were approximately 9,000 participants present at the event; 7,598 were registered participants, and greater than 1,000 were unregistered. This number was verified by independent witnesses and an independent auditing firm (Gbenga Badejo & Co).

Sixteen meetings were held with the volunteers and team captains between February and October 2015. A total of 890 volunteers and staff were present during the meetings.

Areas of Innovation

The innovative nature of the campaign was apparent in the use of social media to recruit participants and disseminate information and in the use of a GWR attempt to generate interest and raise awareness about breast cancer. In addition, this was the first GWR attempt of its size in Nigeria and West Africa; it was the first largest human pink ribbon GWR attempt in Africa; and it was the first time that community members showed up in such numbers to support breast cancer awareness and explain the need to reduce stigmatization. Also, we had partnerships with 49 corporate bodies to help cut costs, and we had the ability to gather a crowd and educate them by leveraging good will. Last, it was the first campaign to have a robust network of cancer stakeholders, and this also helped us cut costs and leverage resources of our partners.

How Awareness Was Raised

Existing social media accounts for Sebeccly Cancer Care were used to raise awareness. During the 2015 campaign, the total reach on Twitter was 217,395, and it was 67,923 on Facebook (Fig 1). Twenty community events held prior to the #12KLLP campaign raised awareness through distribution of breast health publications and conduct of breast cancer screenings and health talks. When abnormalities were detected in patients, appropriate referrals were made. There was a total community reach of 3,620, as recorded by the attendance taken at the events.

The website had 7,466,276 views in the year 2015 (between February and November). Views increased as the awareness for the program started and increased (Fig 2).

More than 50 media events promoted awareness; these included media interviews, press releases, press conferences, and advertisements granted by TV and radio houses and published in newspapers and magazines. The total reach estimated from the media events is about 20 million people from about 500,000 people reached per media interview.

A total of 5,000 copies of various publications about breast awareness and the #12KLLP were made. Through publications, short message service (SMS), and blog topics, there was an estimated reach of 12,000 people from the events where the publications were shared.

At the #12KLLP event, a record of 7,598 verified participants, as validated by the independent auditors and witnesses, was achieved. Health talks were given by a radiation oncologist, a survivor, and a representative of the Lagos State Ministry of Health.

Details of the event and breast awareness promotions were sent online on a weekly basis to subscribers of a #12KLLP e-newsletter. Short text messages (bulk SMS) were sent on a weekly basis from September to November 2015 to disseminate information about the campaign, such as the instructions for participants at the
venue and the directions to the venue. The text messages were funded by Sebecly Cancer Care. The campaign was featured on five popular blogs that had national coverage. Each of the blogs had an estimated reach of 200,000 in Lagos, so an estimated total of 1 million people were reached by blogs.

The total estimated reach for the awareness campaign in 2015 was 28,774,812 people.

**Partnerships**

Partnerships in the form of technical, mobilization, media, and financial sponsorships were secured with several stakeholders. The partnerships were sources of funds, kind gifts, and services. Fundraising was done through crowdfunding, corporate donations, and sale of merchandise to generate funds from the event (exhibition booths and advertisements).

A total of 20 corporate organizations (Fig 3) financially sponsored the logistics and planning of the #12KLLP. Ten product sponsors partnered with Sebecly Cancer Care to provide products for

---

**Table 1. List of Advocacy Activities in 2015 at Sebecly Cancer Care**

<table>
<thead>
<tr>
<th>Date</th>
<th>Type of Event</th>
<th>Venue</th>
<th>Estimated Reach (No. of people)</th>
<th>No. Screened</th>
<th>No. of Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 16, 2015</td>
<td>Health talk and breast cancer screening</td>
<td>CAC Church, Ileri St, Ogba, Lagos</td>
<td>20</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>June 6, 2015</td>
<td>Health talk only</td>
<td>Kingdom Pentecostal Church Assembly</td>
<td>50</td>
<td>NA*</td>
<td>NA</td>
</tr>
<tr>
<td>July 1, 2015</td>
<td>Breast cancer screening, health talk</td>
<td>News Agency of Nigeria</td>
<td>30</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>July 9, 2015</td>
<td>Health talk, breast cancer screening</td>
<td>University of Lagos, main auditorium</td>
<td>1000</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>August 4, 2015</td>
<td>Health talk only</td>
<td>Meiran Model College Hall</td>
<td>300</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>August 7, 2015</td>
<td>Health talk only</td>
<td>Yusuf Grillo Hall, Yabatech</td>
<td>200</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>August 15, 2015</td>
<td>Health talk</td>
<td>The Palms, Lekki, entrance 2</td>
<td>200</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>August 20 and</td>
<td>Health talk</td>
<td>Nigerian Legion, Ikoyi office</td>
<td>300</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>September 3, 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>August 26, 2015</td>
<td>Health talk</td>
<td>Yaba College of Technology, Yaba</td>
<td>500</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>August 27, 2015</td>
<td>Breast cancer screening and cancer information stand</td>
<td>Nigerian Union of Journalists</td>
<td>100</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>August 29, 2015</td>
<td>Clinical breast cancer screening and cancer information stand</td>
<td>University of Lagos sports center</td>
<td>500</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>September 1, 2015</td>
<td>Breast cancer screening and cancer information stand</td>
<td>University of Lagos</td>
<td>100</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>September 27, 2015</td>
<td>Health talk</td>
<td>Fountain of Life Church</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>October 2, 2015</td>
<td>Health talk</td>
<td>Leadway Assurance</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>October 6, 2015</td>
<td>Health talk</td>
<td>JNCI office</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>October 17, 2015</td>
<td>Health talk and breast cancer screening</td>
<td>Oriade local council hall</td>
<td>20</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>3,620</td>
<td>234</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*NA indicates that only a health talk was given.

---

**Fig 1. Online reach across social media and the Web site #12KLLP, 12,000 people light Lagos pink.**
the campaign. Media consideration was provided through the services of 19 media outfits that part-
nered with Sebeccly Cancer Care in areas of grant-
ing interviews, advertising the campaign, and
broadcasting radio and television jingles. We had
ambassadors who were prominent citizens to
lend the #12KLLP their community followership
and public image. The ambassador role was
to influence the general public about cancer
awareness. We had 10 ambassadors at the
campaign, and we had a representative of the
first lady of Lagos State.

After inclusion of technical and mobilization part-
ers, the total number of partnerships, in addition
to 10 ambassadors, was greater than 80.

Technical Partners
Our technical and mobilization partners ranged
from government agencies to local partners. They
are listed in Table 2.

DISCUSSION
Social media is now an important tool to dissemin-
ate information about cancer prevention and
screening.9 As seen from the results of our cam-
paign, and as reflected by the number of people
who accessed and shared details on cancer on the
website and on the social media pages, the aware-
ess of the Lagos population about breast cancer
was increased.10 The increase is seen graphically
in Figures 1 and 2: the number of people who
viewed the information increased steadily through-
out the campaign. With a reach of greater than 28
million people, the information about cancer risk
factors and treatment options available in Nigeria
reached a substantial amount of the population.11

At Sebeccly Cancer Care, there is a history that
spans many years of helping patients who have
cancer with their health care by sourcing funds for
their drugs and treatment.12 A workforce that con-
sists of doctors, dedicated office staff, and volun-
teers work toward provision of services that will
increase cancer awareness and help patients.12

The opportunity for members of the public as well
as office staff to give voluntarily and generously to
the cause of helping patients with cancer was made
available by enabling various means of giving through
the account, the website, and online payment path-
ways.12 Subsidies provided at some hospitals for
some cancer treatment procedures were an innova-
tive means of handling financial obstacles. This, with
the support of the hospitals, goes a long way to re-
duce the financial load on the patient and the group.12

Perseverance and professionalism are our traits seen
by our partners and patients, who have come to
appreciate these attributes in their dealings with us in
preparation for our campaigns and for patient care.12
There are some limitations to this campaign. The political landscape was unpredictable because of the 2015 election period and was unstable because of the time taken to appoint government officials by the new government. Also, threats of insurgency in gatherings and minimal manpower were added obstacles that were overcome by the security personnel on ground.

The impact of the effort was broad. Through various speakers, including a survivor, we educated greater than 7,500 participants on breast cancer at the event venue and more than 20 million on social media platforms and in communities, with activities like community-awareness campaigns and trends on social media. The #12KLLP campaign promoted and encouraged community social responsibility; team captains were members of the communities where they recruited participants.

Team captains and volunteers gave individuals the opportunity to give back to the community. The #12KLLP campaign promoted corporate social responsibility by fostering partnerships among 49 companies. We collaborated with up to 49 companies to aid in different aspects of the campaign, including provision of food, security of the venue, event security, marking out the ribbon, and ensuring the event ran smoothly. We helped promote volunteerism in Nigeria: greater than 400 volunteers participated in the campaign, and countless others volunteered in the planning but were unavoidably absent at the event. The campaign promoted awareness about the need for the community to support cancer management. Partnerships were formed with the Lagos State government in a bid to influence cancer policies and to help facilitate any future cancer awareness events.

Many lessons were learned in this campaign. The road to reduction of the cancer burden is not an easy one. There is a need for more collaboration between well-meaning citizens and institutions to help increase the availability of screening services and treatment options available. This need is especially apparent in developing countries. Volunteers are an important aspect of any campaign. As such, they should be effectively trained for their responsibilities. This is important when such responsibilities include health information dissemination and screening. Social media is a major agent of connection in the world and has been used for countless campaigns in many places. Nongovernmental organizations and other institutions that provide cancer care can use social media to share details about early access to screening services and treatment options. This will help to reduce the overall burden.

In conclusion, there is a need to present cancer information through an engaging platform, to promote awareness and empower the community to actively fight cancer by early presentation and initiation of treatment. To this end, the #12KLLP breast cancer awareness campaign was able to disseminate information and raise awareness effectively by the community events and the GWR attempt, in which approximately 9,000 individuals gathered together for the cause.

The need to access cancer screening was communicated effectively by doctors, cancer survivors, and celebrities at the event and at the awareness campaigns throughout the year. However, there is much to be done. There needs to be greater cooperation among the government agencies, private institutions, nongovernmental organizations, and individuals to spread information about cancer. This will go a long way in reduction of the overall burden on the populace.

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Table 2. List of Technical and Mobilization Partners for #12KLLP

<table>
<thead>
<tr>
<th>Technical Partner</th>
<th>Mobilization Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagos State Ministry of Health</td>
<td>Lagos State local government and chiefancy affairs</td>
</tr>
<tr>
<td>Lagos State Sports Commission</td>
<td>National youth service corps</td>
</tr>
<tr>
<td>Lagos State Ministry of the Environment</td>
<td>Boys Brigade</td>
</tr>
<tr>
<td>Lagos State Traffic Maintenance Agency</td>
<td>National Orientation Agency</td>
</tr>
<tr>
<td>Lagos State Waste Management Agency</td>
<td>Team Medilag</td>
</tr>
<tr>
<td>Lagos State Public Service Office</td>
<td>Team Uniag</td>
</tr>
<tr>
<td>Lagos State Ambulance Service</td>
<td>Team Yabatech</td>
</tr>
<tr>
<td>Lagbus Asset Management</td>
<td>Eva Adelaja Girls Secondary Grammar School</td>
</tr>
<tr>
<td>Lagos State Signage and Advertisement Agency</td>
<td>Soroptimist International</td>
</tr>
<tr>
<td>Fountain of Life Church</td>
<td>Other</td>
</tr>
<tr>
<td>Gbenga Badejo &amp; Co</td>
<td></td>
</tr>
<tr>
<td>Walsher Design and Build</td>
<td></td>
</tr>
<tr>
<td>Nigerian Red Cross (Lagos chapter)</td>
<td></td>
</tr>
<tr>
<td>Nigeria Police Force</td>
<td></td>
</tr>
<tr>
<td>Kick Against Indiscipline</td>
<td></td>
</tr>
<tr>
<td>Megascreen</td>
<td></td>
</tr>
<tr>
<td>Red Care HMO</td>
<td></td>
</tr>
<tr>
<td>War Against Indiscipline</td>
<td></td>
</tr>
<tr>
<td>Niidasat</td>
<td></td>
</tr>
<tr>
<td>Sage Photography</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HMO, health maintenance organization.
AUTHOR CONTRIBUTIONS

Financial support: Omolola Salako
Administrative support: Omolola Salako, Alero A. Roberts, Victor I. Isibor, Oluwatimiliehin Babatunde
Provision of study materials or patients: Omolola Salako
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Omolola Salako
Employment: St Nicholas Hospital Lagos
Travel, Accommodations, Expenses: AstraZeneca
Alero A. Roberts
Employment: Royal Cross Medical Centre (I)
Leadership: Royal Cross Medical Centre (I)
Stock or Other Ownership: Royal Cross Medical Centre (I)
Honoraria: Royal Cross Medical Centre (I)
Consulting or Advisory Role: Royal Cross Medical Centre (I)
Victor I. Isibor
No relationship to disclose
Oluwatimiliehin Babatunde
No relationship to disclose

Omolora Fatiregun
Speakers’ Bureau: AstraZeneca

Chukwumere N. Nwogu
Leadership: Lakeshore Cancer Center
Stock or Other Ownership: Lakeshore Cancer Clinic
Travel, Accommodations, Expenses: Lakeshore Cancer Center

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REFERENCES


CASE REPORT
A 40-year-old man presented with a 6-month history of insidious and gradual onset of progressive pain in right shoulder and neck. He also noted progressive weakness of his right upper and lower limb. A magnetic resonance imaging (MRI) of his brain and spine was performed that revealed an intradural extramedullary lesion at the cervicomedullary junction (CMJ), for which he underwent surgery in February 2009. The histopathological diagnosis was melanocytic neoplasm of intermediate-grade malignancy. The symptoms reoccurred in October 2012, and a repeat MRI of the cervical spine was performed that revealed recurrent lesions at the CMJ. The patient was referred to our tertiary center for further management. Figure 1 shows the images obtained before the second surgery (2012), and Figure 2 displays the follow-up images obtained after the second surgery (2014). MRI showed well-defined intradural extramedullary lesions at the CMJ. On plain T1-weighted sagittal views (Figs 1A and 2A), the mass was hyperintense (white arrows); on plain T2-weighted sagittal views (Figs 1B and 2B), it showed hypointense signal intensity (arrowheads). Postcontrast T1-weighted coronal views (Figs 1C and 2C) showed intense postcontrast enhancement (yellow arrows). The imaging findings described were diagnostic for melanoma.

DISCUSSION
Primary CNS melanoma is a rare entity, accounting for 1% of all melanoma cases and 0.06% to 0.1% of all CNS malignancies. Primary spinal cord malignant melanoma is even rarer, with most of the cases reported in the mid or lower thoracic spinal cord. Other pigmented CNS malignancies include meningeal melanocytoma, melanoic schwannoma, and blue nevus tumor of the CNS. Knowledge of the hallmark neuroimaging pattern is critical for appropriate and timely management.

MRI is the imaging modality of choice for characterizing tumors of the spinal cord; however, differentiation of the tumors on the basis of the morphology and signal-intensity pattern on MRI sometimes poses a diagnostic dilemma. The paramagnetic properties of melanin and intraleisional hemorrhages in melanotic lesions lead to bright signal on T1-weighted and dark signal on T2-weighted imaging, which is described as the classic melanotic pattern. However, this characteristic appearance on imaging is not homogeneous and universal; rather, it is seen to depend on the percentage of melanocytes and prior hemorrhages. Lesions with > 10% melanin-containing cells tend to show this diagnostic imaging pattern, and the ones with < 10% tend to exhibit an amelanotic pattern (compared with cortex, hypointense on T1-weighted images, and hyper- or iso-intense on T2-weighted images).

Two more patterns have been described in literature; these are indeterminate or mixed pattern and hematoma pattern (in these patterns, the MR signal characteristics do not conform to either melanotic or amelanotic pattern). Also, it is important to note that on the basis of the MRI patterns, melanin cannot be completely distinguished from methemoglobin, and both have overlapping imaging morphology. This could be one of the possible explanations for hemorrhagic tumors masquerading as melanomas.

Primary CNS melanomas are aggressive tumors and have grave prognoses. Surgery is the mainstay of treatment; complete resection has a better prognosis. Incompletely resected tumors have been found to benefit from temozolomide therapy. Immunotherapy, such as high-dose interferon beta or interferon alfa-2b, has been shown to improve disease control and survival; however, the toxicities related to the dosage of these drugs remain disputed. Our patient underwent complete excision of the tumor in 2009 and had recurrent disease in 2012, for which he had surgery twice. A centimeter-sized tumor (residual disease) on the left side was treated with external-beam radiotherapy (50.4 Gy in 28 fractions), followed by 12 cycles of temozolomide. The last follow-up was...
in April 2016, and interval MRI showed stable residual tumor.

To conclude, the MRI imaging characteristics described in our case highlight the typical radiologic findings in cases of primary CNS melanocytic tumors. Awareness of this imaging pattern aids in timely and appropriate diagnosis. Caution should be exercised in scenarios such as hemorrhagic cord tumors and melanotic schwannomas that may masquerade the typical MRI pattern of melanocytic tumor and may pose a diagnostic challenge to the radiologist.

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**AUTHOR CONTRIBUTIONS**

Provision of study materials or patients: Abhishek Mahajan
Manuscript writing: All authors
Final approval of manuscript: All authors

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

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Abhishek Mahajan
No relationship to disclose

Rakesh Jalali
No relationship to disclose

**Fig 1.** Images obtained before the second surgery (2012). Magnetic resonance imaging showed well-defined intradural extramedullary lesions at the cervicomedullary junction. On the plain T1-weighted sagittal view (A), the mass was hyperintense (white arrows); on the plain T2-weighted sagittal view (B), it showed hypo-intense signal intensity (arrowheads). The postcontrast T1-weighted coronal view (C) showed intense postcontrast enhancement (yellow arrows). The imaging findings described were diagnostic for melanoma.

**Fig 2.** Follow-up images obtained after the second surgery (2014). Magnetic resonance imaging showed well-defined intradural extramedullary lesion at the cervicomedullary junction. On the plain T1-weighted sagittal view (A), the mass was hyperintense (white arrow); on the plain T2-weighted sagittal view (B), it showed hypo-intense signal intensity (arrowhead). The postcontrast T1-weighted coronal view (C) showed intense postcontrast enhancement (yellow arrow). The imaging findings described were diagnostic for melanoma and represented residual disease after the second surgery.
REFERENCES

TO THE EDITOR:

The meta-analysis of breast cancer demographics in Indian patients by Sandhu et al.1 highlights significant variability in estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2) status and presenting age reported by various authors and then pools the data to ascertain the rate of triple-negative breast cancer (TNBC) to be around 31%. We feel that such a report may overlook a few important issues, which we would like to outline. The authors rightly highlight that local, environmental, and physical factors may contribute to the heterogeneity but have not explored some of them. Of the studies included, only four centers reported an average of over 20 patients per month. Small series, such as that by Akhtar et al.,2 are likely to be unrepresentative of the regional population and could present a selection bias. However, the referral patterns for high-volume tertiary care centers may also contribute significantly to the selection bias, which is reflected in the younger age in some of these series. In addition, some studies, such as those by Nandi et al.3 and Ambroise et al.4 reported immunohistochemistry (IHC) only on patients receiving curative therapy, in contrast to others, who reported on all patients who presented to the hospital. This could also contribute to the heterogeneity reported.

Some technical issues also need to be highlighted. The majority of these studies have used manual methods to determine IHC status, whereas automated methods using adequately fixed and processed tissue standardizes the technique with fewer testing variations compared with manual methods.5 In addition, many of the studies did not report the antibodies used or whether they followed optimal preanalytic requirements, such as cold ischemia time and adequate fixation. In most of the studies included in the analysis, IHC was performed on lumpectomies or mastectomies rather than on core biopsies; this itself may lead to a 9% false-negative ER result.6 Core biopsies are better specimens because of less cold ischemia time and quick formalin infiltration, resulting in uniform and consistent fixation.7 In addition, with the advent of robust rabbit monoclonal antibodies with improved sensitivity and specificity, such as SP1 for ER and 1E2 for PR, low levels of ER and PR are being detected, possibly reducing the number of triple-negative patients.8

We recently published the IHC status of unselected patients receiving curative therapy in a tertiary care center in eastern India between June 2011 and December 2013.9 Our overall rates of TNBC were 12.5%, with 15.5% for those with locally advanced tumors. Following the meta-analysis by Sandhu et al.,1 we looked at our more recent data for 2014 and 2015, which showed persistent TNBC rates of 11.9% and 11.3%, respectively, with a further 5.1% and 4.4% for ER-negative/PR-negative HER2 2+ disease, where fluorescent in situ hybridization evaluation of HER2 positivity was not available. For all patients in our series, IHC was tested on mostly core biopsies using automated, approved, and peer-reviewed methods, with appropriate internal and formal external quality assurance.

The heterogeneity in the reported prevalence of TNBC and, in general, the prevalence of various...
luminal tumor types are likely to be multifactorial as mentioned previously. A pooled meta-analysis with the Indian-patient tag may be simplistic and may not be the actual representation, which a prospective population-based study of breast cancer with appropriate quality assurance will provide.

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Sanjoy Chatterjee
No relationship to disclose

Indu Arun
No relationship to disclose

Sanjit Agrawal
No relationship to disclose

Moses Arunsingh
No relationship to disclose

Indranil Mallick
Employment: Mylan (I)

Rosina Ahmed
No relationship to disclose

REFERENCES


TO THE EDITOR:

The recent article by Gulia et al1 in Journal of Global Oncology proposed a model for chemotherapy delivery in India that effectively uses district health centers, medical colleges, and apex hospitals in hierarchical chemotherapy delivery according to the complexity of treatment and ease of administration. We believe that this model, although ideal, is more of theoretical interest because previously, a three-tier system for rural health miserably failed in India.2 As reported recently by Sharma et al,3 in community health centers (ie, the third tier in the rural health system) a huge deficit of physician-surgeons (83%), obstetricians and gynecologists (76%), physicians (83%), and pediatricians (82%) exists. These shocking statistics provoke ire among health professionals but still have not drawn any intervention or immediate actions by the government. Although these authors have proposed involvement of district hospitals, this seems difficult for various reasons. First, district hospitals and community health centers do not deliver the services they are supposed to, and the current quality of care is pathetic, with almost nonexistent services for basic medicine, surgery, gynecology, and pediatrics. In a nationally representative spatial analysis, Dare et al4 showed that approximately two thirds of deaths from acute abdominal conditions in India could have been averted by improvement in human and physical resources at existing district hospitals. The addition of medical oncology would be a burden too difficult to manage in the absence of basic resources. The lack of trained specialists in district hospitals is not because of the lack of trained professionals but because of the lack of government incentives, as reported recently in a district hospital in Meerut (second-tier city in India) where all specialist positions in the district hospital are vacant.5 Second, the administration of various modalities in different hospitals (eg, chemotherapy in district hospitals and radiation therapy in higher-volume centers) would be difficult on patients. Third, hardly any chemotherapy regimen in district hospital practice currently meets the criteria specified by Gulia et al2 because most of the regimens for breast cancer, lung cancer, and head and neck cancer cannot be administered in district hospitals for various reasons, such as extravasation and the need for premedication, hydration, and concurrent radiotherapy.6 Furthermore, patients might also prefer to go to specialized centers with expertise in multimodality treatment. Thus, before embarking on low-quality, erratic services in district hospitals, we believe it better to strengthen the already-crumbling health system of medical colleges and apex centers in India.

Even if this model or its modification is implemented, some ideas need clarification, first and foremost of which is the difficulties in coordination among all levels of care. In other words, the first step in implementing such a system is the improvement of outdated and virtually nonexistent information technology. Such improvements would help to track patient history and make quick referrals for various modalities and complications. This type of integrated health system would avoid duplication of duties and use personnel and the infrastructure optimally. Besides this, the largely unregulated private sector should be made accountable to use information technology and to properly document treatments given and cost regulation. As of now, the government sector caters only to a fraction of patients, and the majority of patients are treated in the private sector, so it is imperative to improve both systems simultaneously because the two are intertwined. Another thing that is of immense concern in this hierarchical system is the treatment of complex diseases, like sarcoma. There is plenty of literature that suggests that patients with sarcoma treated at
higher-volume centers have better outcomes as compared to those treated at low-volume centres.\textsuperscript{6} Thus, we believe that it is not only the difficulty and administration of chemotherapy that governs the choice of center, but also the type of disease and complexity of diagnosis. Beyond this model, we believe that the government of India has confused priorities, as shown by the dip in the overall health budget,\textsuperscript{7} but yet the funds allotment to the ministry of ayurveda, yoga and naturopathy, unani, siddha, and homeopathy (traditional Indian medicines) was increased.\textsuperscript{8} Although we appreciate the earnest effort by Gulia et,\textsuperscript{1} we believe that the implementation of this model is difficult and impractical. However, we concede that such a model may be a harbinger for the evolution of the ideal model. Furthermore, the government of India should wake up to the call of the formidable opponent known as cancer and take immediate initiatives for the larger good of its people.

\textbf{REFERENCES}


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Sameer Rastogi
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Aditi Aggarwal
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For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.
We thank Rastogi and Aggarwal for their interest in our recent article that proposes a framework for organization of chemotherapy and systemic therapy services in India. They have highlighted some relevant practical difficulties in integrating oncology services into the health care infrastructure of India. However, we disagree with their contention that oncology care cannot be integrated within existing public sector health care facilities. Several indications in India’s health indices, affected by the same health care system, have shown steady improvement. A consistent decline in the infant mortality rate (IMR) has been seen in India, from 165 per 1,000 live births in 1960 to 38 per 1,000 in 2015. The maternal mortality rate (MMR) has been reduced from 556 per 100,000 live births in 1990 to 174 per 100,000 in 2015. The reduction in IMR and MMR strongly reflects the overall effectiveness of the health care system in India. Rastogi and Aggarwal contend that the rural health program in India has miserably failed, which is not true. Since the launch of the National Rural Health Mission in 2005, > 157,000 personnel have been used in the health sector, the Janani Suraksha Yojana has been successful in ensuring peripartum care of > 150 million women in government facilities, and > 600,000 newborns receive care in neonatal units in district hospitals every year. Furthermore, by using the same health care infrastructure, Kerala (one of the Indian states) attained an IMR and MMR (12 in 1,000 and 66 in 100,000, respectively) comparable with that of developed countries. Recently, the health sector in India has seen considerable improvement in human resource availability. Various strategies, such as compulsory rural service, linkage of rural service to postgraduate education, and provision of monetary incentives, have been instituted to increase the availability of physicians in underserved rural areas. A substantial increase in number of undergraduate and postgraduate seats in medical colleges across India has occurred. Furthermore, financial support is provided to states under the National Rural Health Mission to strengthen the health system, including engagement of nurses, physicians, and specialists.

The most effective health care models around the world have not created separate verticals for every disease, and this is unlikely to be a viable strategy in the long run. In keeping with this experience from other countries, we have proposed maximal use of the existing public sector health care delivery system in India to undertake safe and effective delivery of chemotherapy to patients with cancer. Recently, our institution has partnered with the Government of Maharashtra to initiate the delivery of chemotherapy for breast, cervical, and oral cancers at five district hospitals, which will be extended to 24 districts in the next 3 years. Of note, a gap analysis of infrastructure and human resources within this venture has used elements of our proposal. We do not believe, unlike Rastogi and Aggarwal, that the need for premedication, hydration, and potential problems like extravasation are insurmountable challenges in initiating chemotherapy services in district hospitals, and our confidence is shared by many partners in public and private health care domains.

Perhaps the biggest challenge in India is the disparity in human development indices and level of infrastructure among various regions and states. Therefore, we have proposed human resource and infrastructure recommendations at each health care level to guide the allocation of resources for safe delivery of chemotherapy in various scenarios. In this context, we agree with Rastogi and Aggarwal that the innovative use of modern information technology and efficient record keeping are important to the integration of oncology health care delivery at various levels.

Although several constraints exist, with hope, optimism, and careful, cost-effective, hierarchical planning, India will improve its health care (including oncology) delivery mechanisms. An overly pessimistic attitude is unlikely to facilitate meaningful change in the long run.

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Seema Gulia
Sudeep Gupta

Seema Gulia and Sudeep Gupta, Tata Memorial Centre, Mumbai, India
Corresponding author: Sudeep Gupta, MD, Tata Memorial Hospital, Homi Bhabha Block, Room 1109, Mumbai 400012, India; e-mail: sudeepgupta04@yahoo.com.
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