

Breast cancer in South Africa: developing an affordable and achievable plan to improve detection and survival

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It is projected that by 2030, more than 70% of the world's cancer burden will be in low- and middle-income countries (LMICs), such as South Africa, where breast cancer is the most commonly diagnosed cancer among women. South Africa is committed to the Sustainable Development Goals, which call for universal access to reproductive health services and a one-third reduction in premature deaths due to non-communicable diseases, including cancer, by 2030.

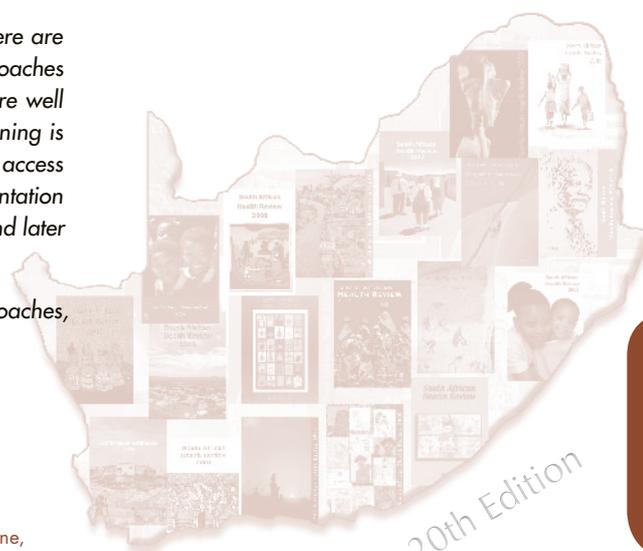
The South African National Department of Health is currently drafting the country's first national policy on breast cancer diagnosis and management. This chapter explores the pathways available in South Africa for achieving universal access to breast cancer-related services under the new policy. The chapter also discusses barriers to the implementation of equitable access, and highlights health-delivery models that could help achieve South Africa's goals.

The chapter begins with a description of successes in breast-cancer treatment, both globally and within South Africa, over the last 20 years as access to better diagnostic and treatment options has improved and awareness regarding the importance of early screening and treatment has grown. This description includes a summary of South Africa's current environment regarding breast cancer-related care.

Significant challenges remain in terms of access and quality of care. Yet, there are few data from or guidance for LMICs regarding the most cost-effective approaches for breast-cancer management. The benefits of mammographic screening are well documented, although the cost-effectiveness of routine mammographic screening is contested. An argument is presented for South Africa to approach universal access to breast care in a step-wise fashion, first reducing widespread late presentation and late-stage disease through provider-based population-level screening, and later moving (if possible) to more costly, technologically dependent approaches.

Finally, recommendations are made regarding optimal service-delivery approaches, recognising South Africa's integrated primary health care model.

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Introduction

Cancer is a leading cause of mortality globally.¹ As the world's population grows and ages, the global burden of non-communicable diseases (NCDs), including cancer, is expected to rise.² This is particularly true for low- and middle-income countries (LMICs). Without significant intervention, it is projected that by 2030 more than 70% of the world's cancer burden will be in LMICs.³

Breast cancer is the mostly commonly diagnosed cancer among women globally. In 2012, 1.67 million women were diagnosed with breast cancer, and more than half a million women died from the disease.⁴ LMICs were disproportionately burdened. While 53% of diagnoses occurred in LMICs in 2012, 62% of breast cancer deaths occurred in these countries.⁴ Without significant advances in screening and treatment efforts in the near future, the number of women dying from breast cancer annually is predicted to increase. Based on current trends, Ginsburg et al. estimate that by 2030 the number of women diagnosed globally with breast cancer will increase to almost 3.2 million per year,⁵ nearly double the incidence in 2012.

According to South Africa's National Cancer Registry, breast cancer was the most commonly diagnosed cancer among women in 2011, with an age-adjusted incidence rate of 31.4 per 100 000 women and a lifetime risk of 1 in 29.⁶ In 2012, 9 815 women were diagnosed with breast cancer, and 3 848 died from the disease.⁷ The Sustainable Development Goals (SDGs), to which South Africa is committed, call for universal access to reproductive health services and one-third reduction in premature deaths caused by non-communicable diseases, including cancer, by 2030.⁸ However, without significant shifts in the funding and advocacy for women's cancers, these goals may go unmet in South Africa and elsewhere.⁵ Globally, just 5% of spending on cancer benefits LMICs, where the highest burden exists.⁹

Fortunately, in South Africa activities are under way that could impact significantly on the magnitude of morbidity and mortality associated with breast cancer in coming years. The South African National Department of Health (NDoH) is currently drafting the country's first national policy on breast-cancer diagnosis and management. This chapter explores the pathways available in South Africa for achieving universal access to breast cancer-related services under a new policy. To mark this 20th anniversary of the *South African Health Review*, a summary is provided of progress in breast-cancer screening and treatment globally and in South Africa over the past 20 years. This includes a summary of South Africa's current environment regarding breast cancer-related care. Barriers to the implementation of equitable access – including perceived costs – are discussed, and health-delivery models are suggested that could help achieve South Africa's goals.

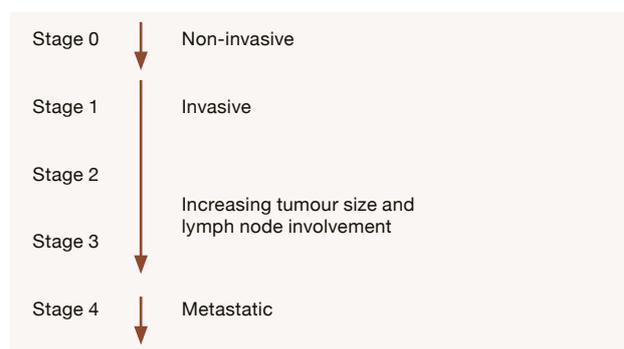
Twenty years of progress – then and now

Access to care

Historically in South Africa, access to breast-cancer screening and treatment services has been characterised by regional and socio-economic disparities. These disparities, compounded by relatively low levels of knowledge of the disease and how to detect it early, have tended to result in late presentation at health facilities. In

2001, Vorobiof et al. described the presentation of breast cancer in Johannesburg. A disproportionate number of black patients presented with locally advanced and metastatic disease (stage 3 or 4), and just 23.3% presented with early-stage disease (stage 1 or 2) (Figure 1).¹⁰ In the intervening years, a change in awareness and access to care has doubled the percentage of women presenting with stage 2 cancer or lower to 46%.¹¹ However, large disparities and barriers to accessing care persist, and there is still room for improvement. In comparison, in the USA, over 82% of women are diagnosed with stage 2 cancer or lower.¹²

Figure 1: Breast cancer staging



It has been noted that delay in access to healthcare services is both patient- and provider-driven. Globally in the last two decades, understanding of barriers to breast care has shifted from patient (mis)beliefs and cultural factors to recognition that an interplay of biological, economic, geographical and psychosocial influences are important in delayed patient presentation.¹³⁻¹⁵

'Provider delay' is defined as the structural or provider-dependent factors that impact negatively on the time from first presentation to a healthcare practitioner to receiving primary treatment, be that surgical or non-surgical.¹⁶ In 2016, Moodley et al. noted that limitations of the South African healthcare system and service-delivery mechanisms prevent optimal timing and access to breast-disease management and cancer treatment.¹⁷ These delays impact negatively on patient survival.^{16,18,19} In patients presenting with advanced disease, a delay of more than 60 days from tissue diagnosis to primary treatment was found to have an adverse impact on mortality.²⁰ Also, a recent meta-analysis studying delay from surgery to adjuvant therapy found that a delay of more than four weeks to chemotherapy and any delay to radiation adversely affected patient outcomes.²¹

Service-delivery models

Little has been written about breast-cancer services in South Africa; however, changes in the last 20 years have resulted in fundamental improvements to clinical care in some settings. To illustrate, according to local experts in breast-care services, historically in most areas and currently in areas without specialist care, women with breast masses would present to a primary care nurse and be referred to the surgical outpatient clinic or emergency department of the nearest hospital. The woman would likely be seen by a junior doctor. The most common route for diagnosis would be aspiration of the breast mass/masses using clinical palpation only. The specimen would be sent to

the nearest laboratory, and results could be expected a minimum of six weeks later. An inadequate specimen would necessitate repeat aspiration or surgical biopsy, which could be delayed, if performed at all. An alternative route would be surgical excision of the mass/masses or mastectomy without confirmatory diagnosis. Both approaches would provide quicker initial treatment, but at a cost of potential patient disfigurement or unnecessary or inadequate excision that could potentially compromise later oncological care.

Fortunately, service delivery has progressed considerably in some areas. In many public-sector settings, diagnosis now includes the global gold standard of triple assessment (i.e. clinical breast examination, imaging using ultrasound or mammography or both, and biopsy) performed by multi-disciplinary teams. In fact, a number of specialist breast-cancer centres have been developed in South Africa, usually by interested clinicians and receptive hospitals. Although access is still limited mostly to urban centres, where available these services receive patients from primary health care facilities, district hospitals, and in some cases, as walk-in, or 'self-referred' patients. These facilities usually feature multi-disciplinary breast-cancer teams including medical and radiation oncologists, surgeons, radiologists, pathologists, nurses and counsellors. Collaboration within multi-disciplinary teams facilitates expedient diagnosis and expert care. It can also improve the navigation of patients through diagnosis and treatment processes. In some instances, breast-cancer advocates, representing survivors and other interested parties, form a part of the team and contribute assistance with transportation, translation, and overall education

for patients on the disease-management process. Advocates also assist in raising awareness on survivorship issues such as prosthesis following surgery, psychosocial support, and access to grants and social welfare, which may not be addressed routinely by the medical team.

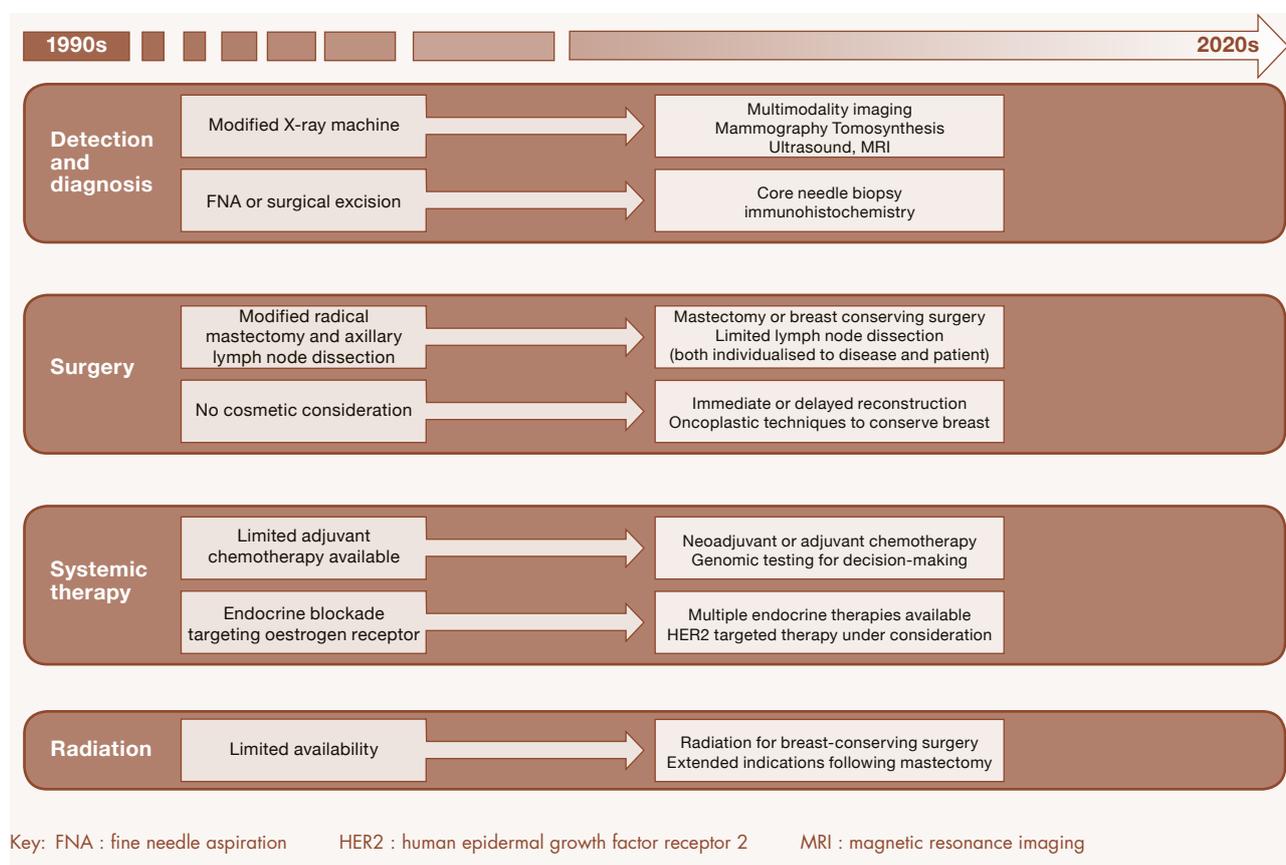
After diagnosis, cancer management and treatment in South Africa (breast and other cancers) are generally offered in centralised oncology units in select facilities, for example, regional or teaching hospitals. Access to these units requires formal referral, a common delivery model for specialist care globally. However, as a result of significant provider-driven delays in the diagnosis process, women with breast cancer frequently experience significant delays and unnecessary progression of disease prior to treatment initiation.

Advances in diagnosis and treatment

In addition to improved service-delivery models globally and in South Africa today, there has been a shift in understanding the pathogenesis of breast cancer and advances in care and treatment since the 1990s.^{22,23} Many of the changes that have affected breast-cancer detection and treatment worldwide have also become influential in South Africa.

Advances in breast disease and cancer care (Figure 2) have been primarily via two routes: global advances in the diagnosis and treatment of cancer generally, and in the case of breast disease, the introduction in many settings of population-level mammographic screening.^{22,23}

Figure 2: Chronological advances in detection and diagnosis of breast disease and oncological care



Advances in the understanding of cancer have led to progress in oncological care and a more holistic approach to patient management. The 'War on Cancer', initiated in 1971 with the signing of the National Cancer Act in the USA by then-President, Richard Nixon,²² made funding available for randomised trials and the development of systemic therapies, such as chemotherapy. Globally, over the last 50 years, more precise laboratory-based diagnostics have become available.²² Imaging services have also improved, facilitating better staging and more appropriate treatment of disease. Therapy options now include improved chemotherapy regimens, hormone therapy, immunotherapy, and targeted therapy, which allows for reduced damage to healthy cells during the treatment process.²² In South Africa, improved chemotherapy and hormone therapy are available broadly, while targeted therapy is available in private practice only, and immunotherapy is not available for breast cancer (but is available for other cancers).

Surgical services have also advanced. The US-based National Surgical Adjuvant Breast Project Study Protocol 04, conducted in the early 1970s and evaluated with 25 years of follow-up, demonstrated that breast-conserving surgery plus radiation has equivalent outcomes to complete breast removal (i.e. mastectomy).²⁴ Subsequently, breast-conserving surgery has become the gold standard where available. In South Africa, breast surgery has evolved from an under-resourced section of general surgery to a well-developed, if not yet fully recognised, sub-speciality.

In tandem with increased global availability of funding for cancer research, the international feminist movement of the 1970s and 1980s compelled surgeons to discuss diagnostic and operative strategies with their breast-cancer patients. Newly formed breast-cancer patient advocacy groups included breast-cancer survivors or families of women with cancer. These groups facilitated education of women on their options, and led to greater accountability and more patient-centred care globally.

In South Africa, access to new or improved diagnostic, treatment and surgical services is not homogeneous. Late-stage presentation of disease continues to prohibit certain management approaches, and a lack of treatment facilities and specialist capacity to perform these procedures in the public sector also significantly limits access for many women.

Mammography and other screening options

The second major global innovation that has influenced the management of breast cancer is the initiation of mammographic breast-cancer screening in many settings. Mammography uses low-dose X-ray to screen for changes in breast tissue, and can identify such changes before they can be felt by the woman or a healthcare practitioner.²⁵

Use of mammography increased substantially throughout the 1980s and early 1990s in the USA and other areas worldwide.²⁶ Subsequently, population-level screening with mammography has been credited with an increase in the detection of breast cancer, particularly early-stage disease.²⁶ Early detection of breast cancer followed by timely management is the most effective approach in improving survival. This is due to the staged progression of cancer, with earlier and more localised disease being more amenable to complete removal and long-term survival.^{27,28}

Despite the seeming successes of mammographic screening where it has been implemented, there is controversy as to whether the reported increase in breast cancer detected is truly 'new' detection, or simply 'over-diagnosis' of very early disease, particularly not-yet-invasive disease that otherwise would not have progressed or impacted on survival.^{26,29,30} There is also research showing that population-level screening has had only marginal impact on the diagnosis of late-stage disease.²⁶ However, despite the controversy surrounding population-level mammographic screening, advocacy groups have developed a powerful voice in advocating for increased, or at least sustained, availability of the service.

In South Africa there is currently no population-level mammographic screening programme, and there are significant questions as to whether initiating a new service would be feasible or cost-effective in improving health outcomes. Population-level mammographic screening is not recommended for very low-resource settings.³¹ In such settings, the recommendations are to improve awareness of the importance of early detection, and to strengthen and scale up treatment for clinically detectable cancer.³² However, South Africa is not a 'very low-resource setting'. Technically, South Africa is classified as an upper middle-income country.³³ South Africa also has strong advocacy groups calling for greater access to mammographic screening.

The lure of arguments for mammographic population-level screening is understandable, including from an economic perspective. Much of the literature exploring the cost-effectiveness of mammography concludes that it is a cost-effective or even 'highly cost-effective' healthcare intervention. However, such literature can be easily misinterpreted. Cost-effectiveness analysis outcomes are highly dependent on the data sources and service-delivery models studied, and as a result may not be readily applicable across regions, countries or even service-delivery settings. The 'mammography cost' literature tends to focus on high-income settings and comparisons of screening for different age groups or different screening intervals. This work may not be applicable in a country like South Africa where no population-level screening currently exists. Further, decisions as to whether or not an intervention is cost-effective are often based on older World Health Organization (WHO) threshold guidance that indicates that an intervention is cost-effective when it produces a "healthy year of life" for less than the equivalent of three times the country's gross domestic product (GDP).³⁴ This approach may seem straightforward; however, the threshold approach for determining cost-effectiveness has been strongly criticised, with opponents pointing out the relatively arbitrary nature of the WHO threshold, complications in highly inequitable countries like South Africa where per capita GDP may be high and poorly reflect actual societal willingness to pay, and the complete lack of consideration of affordability.^{35,36}

Lower-cost methods of breast disease detection, which are easily available, include breast self-examination and clinical breast examination (i.e. a breast exam performed by a healthcare provider).³⁷⁻³⁹ Research is still preliminary in this area; however, screening programmes based on clinical breast examination have been recommended as a 'promising technique' for the early detection of breast cancer in LMICs.^{40,41} The highest burden of disease in LMICs is clinically detectable (i.e. palpable on clinical exam) and does not require mammography for detection.⁴² In a cluster-randomised trial done in India, age-standardised incidence of advanced-stage breast

cancer was found to be lower among clinically screened women than unscreened women,⁴³ and economic models suggest that clinical breast examination performed annually from 40 to 60 years of age may be nearly as effective as mammography every two years in reducing mortality in resource-limited areas.⁴⁴

Similar trends may be attributed to breast self-examination in some settings. The US Preventative Taskforce has concluded that breast self-examination does not contribute additional benefits in terms of preventing breast cancer mortality in settings where prevention using routine mammographic screening is commonplace.⁴⁵ A large randomised trial in China showed that breast self-examination did not reduce breast-cancer mortality among female factory workers.⁴⁶ However, in some low-income settings where population-level mammographic screening is not available, breast self-examination may have a role to play. In an Egyptian study, women who practised breast self-examination presented earlier and with smaller tumours than women who did not practise self-examination.⁴⁷

In addition to the potential benefits of self-detection of breast cancer among women in low-resource settings, teaching breast self-examination also promotes breast awareness and supports general health-education efforts. Instruction on self-examination normally includes the signs of breast cancer and information on where to receive care. Broader awareness-raising campaigns can complement individual-level interventions. Campaigns promote greater awareness of breast conditions, including cancer, and availability of care, and reduce the stigmatisation of cancer among women.⁴⁰

In addition to self-examination and clinical breast exams, ultrasound of the breast can be used to explore the characteristics of palpable and some impalpable breast lesions, particularly in dense and young breasts. It is used to guide breast biopsies for diagnostic purposes. Ultrasound has been shown to be as good as mammography in detecting invasive cancer, albeit with more false-positives.⁴⁸ However, it is not sensitive in determining calcification in the breast, which is indicative of pre-invasive cancer,⁴⁹ and it is therefore not recommended as a population-level method of screening for very early-stage disease.⁵⁰ Ultrasound of the breast is also highly dependent on the skill of the individual performing the service and can be resource-intensive. Because ultrasound can be used for multiple purposes, including screening of the liver and for gynaecological assessments, the availability of ultrasound may be greater than that of other imaging technologies⁵¹ and it remains an important alternative for breast screening.

Strategies for achieving universal access

South Africa currently has no national-level policy on breast-cancer screening and treatment. However, a policy is currently being drafted by the NDoH, and with it comes an opportunity to establish national guidance. Current provider-dependent delays, which lead to poor survival outcomes, could be reduced through increased availability of multi-disciplinary teams in specialist breast-cancer centres. If not located in oncology treatment units, such teams should be closely linked to these units in order to facilitate rapid bi-directional referral, transfer of patient information, and more timely access to treatment. Such specialist breast-cancer centres should also liaise with local primary health clinics and district hospitals and could contribute to training of staff in those facilities. Advocate and counsellor members

in the multi-disciplinary teams could co-ordinate community-based education and patient-support activities (e.g. through support groups) from diagnosis, through to treatment and follow-up, or link patients with palliative care where appropriate.

Currently many women in South Africa are unaware of their breast-cancer risk. Those who do recognise the need for assistance may travel long distances to access high-quality breast-care services.⁵² Current inefficiencies in patient management and referral often result in patients making repeated visits to health facilities. Planning of specialist breast-cancer centres should include community outreach and involve careful consideration of the geographic spread of services and patient transport systems.

Globally, there is a false belief that it is too expensive to screen and treat cancers in LMICs.⁴⁰ However, cost-effective interventions for reducing breast-cancer mortality do exist.⁴⁰ Given the large proportion of women in South Africa who present with clinically detectable later-stage cancer, a low-cost option for population-level screening in the near term is clinical breast examinations conducted in primary health care clinics; this would be for all symptomatic and asymptomatic women aged over 35 years. Through a hub-and-spoke service-delivery model, trained primary care nurses could immediately refer women with abnormalities to specialist centres where diagnostic mammography and/or ultrasound and biopsy could be performed as needed. If walk-in access was prioritised at specialist centres, women could also initiate their diagnosis process at the specialist centres directly, thus reducing appointments and patient costs. Regardless, quick, co-ordinated referral would contribute to reduced delays in treatment initiation.

Finally, patients experiencing life-threatening and terminal illnesses of all kinds require palliative care, an inherently multi-disciplinary service, often including pain management and psychological and spiritual counselling and support.⁵³ Palliative care is currently available in South Africa, often through community- and home-based structures, but access varies geographically, and linkages between tertiary-care facilities and palliative-care services could be strengthened. Rising cancer incidence and improvements in screening and treatment will continue to increase the number of patients requiring long-term follow-up and lifelong surveillance for cancer recurrence. These women require careful tracking and follow-up within the health system, including annual mammography, gynaecological assessments, and routine monitoring of bone density.⁵⁴ Many cancer survivors in South Africa also contend with co-morbidities such as HIV, tuberculosis and other NCDs. This is important to keep in mind in efforts to strengthen cancer care in the country, as integration of services is critical to meet the needs of the population comprehensively.

Conclusions and recommendations

A special series on women's cancers, published in *The Lancet* in 2016, called for "all women who develop breast cancer to have an equal opportunity for early diagnosis and timely access to potentially curative treatment".⁴⁰ Currently in South Africa, access to high-quality cancer care is variable. The private sector offers high-quality, yet costly, care that is unaffordable for many South Africans. In the public sector, where more than 80% of South Africans seek health care,⁵⁵ high-quality breast-cancer services are available, but in limited supply. Survival rates are often dependent on patients'

awareness of breast health and knowledge of and access to quality screening services and specialty diagnostic and treatment centres.

Below is a list of recommendations towards addressing South Africa's current challenges in breast-cancer screening and treatment. It must be noted that these recommendations are made based on limited literature and reports detailing the current state of affairs in South Africa. The list is not exhaustive. Nonetheless, it is known that cancer diagnosis and treatment will be increasingly in demand in the coming decades. Fortunately, the public-health system in South Africa is changing, and service delivery should improve due to several efforts. A breast-cancer diagnosis and treatment policy is being drafted. Planning for and piloting of National Health Insurance is under way,⁵⁶ and primary health care re-engineering has engendered renewed focus on community-level service delivery. On a global scale, South Africa has committed to achieving the new SDGs by 2030. Breast-care advocacy groups in the country will have to focus actively on breast care as these larger changes occur; however, progress over the past 20 years demonstrates commitment on the part of health professionals and government alike to improve care and treatment in order to save women's lives.

Recommendations

- Incorporate breast-health education and awareness-raising, the early signs of breast cancer, and breast self-examination into existing health-education and outreach activities.
- Increase the number of specialist breast centres nationwide and ensure that they are staffed with multi-disciplinary teams.
- As a first step towards population-level screening, re-train primary health care nurses on how to perform clinical breast examinations and begin screening of asymptomatic women above 35 years of age (in addition to offering screening for all symptomatic women).
- Strengthen existing referral systems, including through facilitated patient-transport systems.
- Maximise the use of mammography and ultrasound for diagnosis by ensuring that the machines are placed in specialist breast centres with trained personnel.
- Increase support for and links to patient advocates and counsellors in communities and within specialist breast centres to ensure comprehensive, full-spectrum care.
- Establish strong monitoring and evaluation systems to track access to and utilisation of screening, diagnostic and treatment services nationwide.
- Support and lead clinical, social and economic research on breast cancer and breast-disease management in the country in order to address the current dearth of available information.

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References

- 1 International Agency for Research on Cancer. World Cancer Report 2014. Lyon: IARC; 2014.
- 2 Bloom D, Cafiero E, Jane-Llopis E, et al. The Global Economic Burden of Non-communicable Diseases. Geneva: World Economic Forum; 2011.
- 3 International Agency for Research on Cancer. World Cancer Report 2008. Geneva: World Health Organization; 2008.
- 4 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2014;136:E359–86.
- 5 Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. *Lancet*. 2016; Nov 1. doi:10.1016/S0140-6736(16)31392-7.
- 6 National Health Laboratory Service. National Cancer Registry: Summary statistics 2011. Johannesburg: National Health Laboratory Service; 2011.
- 7 International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 (South Africa) 2012. [Internet] [cited 19 May 2016]. URL: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx
- 8 United Nations Department of Economic and Social Affairs. Sustainable Development Goals. Sustainable Development Knowledge Platform 2015. [Internet] [cited 26 November 2015]. URL: <https://sustainabledevelopment.un.org/topics>
- 9 The Lancet. Breast cancer in developing countries. *Lancet*. 2009;374:1567. doi:10.1016/S0140-6736(09)61930-9.
- 10 Vorobiof D, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. *J Clin Oncol*. 2001;19:125S–7S.
- 11 Dickens C, Joffe M, Jacobson J, et al. Stage at breast cancer diagnosis and distance from diagnostic hospital in a periurban setting: A South African public hospital case series of over 1,000 women. *Int J Cancer*. 2014;135:2173–82. doi:10.1002/ijc.28861.
- 12 Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. *JAMA*. 2015;313:165–73. doi:10.1001/jama.2014.17322.
- 13 Rayne S, Schnippel K, Firnhaber C, Wright K, Kruger D, Benn C-A. Fear of Treatments Surpasses Demographic and Socioeconomic Factors in Affecting Patients With Breast Cancer in Urban South Africa. *J Glob Oncol*. 2016; doi:10.1200/JGO.2015.002691.
- 14 Ukwenya AY, Yusufu LM, Nmadu PT, Garba ES, Ahmed A. Delayed treatment of symptomatic breast cancer: the experience from Kaduna, Nigeria. *S Afr J Surg*. 2008;46:106–10.
- 15 Oluwatosin O. Rural women's perception of breast cancer and its early-detection measures in Ibadan, Nigeria. *Cancer Nurs*. 2006;29:461–6. doi:10.1097/00002820-200611000-00006.
- 16 Otieno E, Micheni J, Kimende S, Mutai K. Provider delay in the diagnosis and initiation of definitive treatment for breast cancer patients. *East Afr Med J*. 2010;87:143–6. doi:10.4314/eamj.v87i4.62201.
- 17 Moodley J, Cairncross L, Naiker T, Momberg M. Understanding pathways to breast cancer diagnosis among women in the Western Cape Province, South Africa: a qualitative study. *BMJ Open*. 2016;6:e009905. doi:10.1136/bmjopen-2015-009905.
- 18 De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev*. 2008;17:545–54. doi:10.1097/CEJ.0b013e3282f75ea1.
- 19 McLaughlin J, Anderson R, Ferketich A, Seiber E, Balkrishnan R, Paskett E. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. *Journal of Clinical Oncology*. 2012 Nov 19;30(36):4493-500. doi:10.1200/JCO.2012.39.7695.
- 20 Ramirez A, Westcombe A, Burgess C, Sutton S, Littlejohns P, Richards M. Factors predicting delayed presentation of symptomatic breast cancer: A systematic review. *Lancet*. 1999;353:1127–31. doi:10.1016/S0140-6736(99)02142-X.
- 21 Gupta S, King WD, Korzeniowski M, Wallace DL, Mackillop WJ. The Effect of Waiting Times for Postoperative Radiotherapy on Outcomes for Women Receiving Partial Mastectomy for Breast Cancer: A Systematic Review and Meta-Analysis. *Clin Oncol*. 2016;28:739–49. doi:10.1016/j.clon.2016.07.010.
- 22 Melmed G. The war on cancer: a report from the front lines. *Proc (Bayl Univ Med Cent)* 2006;19:323–34.
- 23 Tiwari AK, Roy HK. Progress against cancer (1971–2011): How far have we come? *J Intern Med*. 2012;271:392–9. doi:10.1111/j.1365-2796.2011.02462.x.
- 24 Fisher B, Jeong J-H, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347:567–75. doi:10.1056/NEJMoa020128.
- 25 American Cancer Society. Mammogram Basics 2016. [Internet]. [cited 8 February 2017]. URL: <https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/mammograms/mammogram-basics.html>
- 26 Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*. 2012;367:1998–2005. doi:10.1056/NEJMoa1206809.
- 27 Bleiche R, Ruth K, Sigurdson E, et al. Time to surgery and breast cancer survival in the United States. *JAMA Oncol*. 2016;2:330–9. doi:10.1001/jamaoncol.2015.4508.
- 28 Jedy-Agba E, McCormack V, Adebamowo C, dos-Santos-Silva I. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health*. 2016;4:e923–35. doi:10.1016/S2214-109X(16)30259-5.
- 29 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet*. 2012;380:1778–86. doi:10.1016/S0140-6736(12)61611-0.
- 30 Groen EJ, Elshof LE, Visser LL, et al. Finding the balance between over- and under-treatment of ductal carcinoma in situ (DCIS). *Breast*. 2016;31:274–83. doi:10.1016/j.breast.2016.09.001.
- 31 Anderson BO, Shyyan R, Eniu A, et al. Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J*. 2006;12 Suppl 1:S3–15. doi:10.1111/j.1075-122X.2006.00199.x.

- 32 Anderson BO, Braun S, Carlson RW, et al. Overview of breast health care guidelines for countries with limited resources. *Breast J.* 2003;9:42–51. doi:10.1046/j.1524-4741.9.s2.3.x.
- 33 World Bank. Country and Lending Groups 2015. [Internet]. [cited 11 February 2017]. URL: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.
- 34 World Health Organization Commission on Macro Economics and Health. *Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health.* Geneva: WHO; 2001.
- 35 Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ.* 2015;93:118–24.
- 36 Bertram MY, Lauer JA, De Joncheere K, et al. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ.* 2016;94:925–30. doi:http://dx.doi.org/10.2471/BLT.15.164418.
- 37 Gadgil A, Sauvaget C, Roy N, et al. Cancer early detection program based on awareness and clinical breast examination: Interim results from an urban community in Mumbai, India. *Breast.* 2017;31:85–9. doi:10.1016/j.breast.2016.10.025.
- 38 Gözümlü S, Karayurt O, Kav S, Platin N. Effectiveness of peer education for breast cancer screening and health beliefs in eastern Turkey. *Cancer Nurs.* 2010;33:213–20. doi:10.1097/NCC.0b013e3181cb40a8.
- 39 World Health Organization. *Breast cancer: prevention and control.* 2017 n.d. [Internet]. [cited 9 February 2017]. URL: <http://www.who.int/cancer/detection/breastcancer/en/index3.html>
- 40 Samarasekera U, Horton R. Women’s cancers: shining a light on a neglected health inequity. *Lancet.* 2016;389:771–3. doi:10.1016/S0140-6736(16)31798-6.
- 41 Kardinah D, Anderson BO, Duggan C, Ali IA, Thomas DB. Short report: Limited effectiveness of screening mammography in addition to clinical breast examination by trained nurse midwives in rural Jakarta, Indonesia. *Int J Cancer.* 2014;134:1250–5. doi:10.1002/ijc.28442.
- 42 Cubasch H, Joffe M, Hanisch R, et al. Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa. *Breast Cancer Res Treat.* 2013;140:177–86. doi:10.1007/s10549-013-2606-y.
- 43 Sankaranarayanan R, Ramadas K, Thara S, et al. Clinical breast examination: Preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst.* 2011;103:1476–80. doi:10.1093/jnci/djr304.
- 44 Okonkwo QL, Draisma G, der Kinderen A, Brown ML, de Koning HJ. Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. *J Natl Cancer Inst.* 2008;100:1290–300. doi:10.1093/jnci/djn292.
- 45 United States Preventative Services Taskforce. *Screening for Breast Cancer – Questions and Answers 2014.* [Internet]. [cited 8 February 2017]. URL: <https://www.uspreventiveservicestaskforce.org/Page/Name/screening-for-breast-cancer-questions-and-answers>.
- 46 Thomas D, Gao D, Ray R, et al. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst.* 2002;94:1445–57.
- 47 Abdel-Fattah M, Zaki A, Bassili A, El-Shazly M, Tognoni G. Breast self-examination practice and its impact on breast cancer diagnosis in Alexandria, Egypt. *East Mediterr Health J.* 2000;6:34–40.
- 48 Berg WA, Bandos AI, Mendelson EB, Lehrer D, Jong RA, Pisano ED. Ultrasound as the primary screening test for breast cancer: Analysis from ACRIN 6666. *J Natl Cancer Inst.* 2016;108:1–8. doi:10.1093/jnci/djv367.
- 49 Tang XY, Yamashita T, Hara M, Kumaki N, Tokuda Y, Masuda S. Histopathological characteristics of breast ductal carcinoma in situ and association with imaging findings. *Breast Cancer.* 2016;23:491–8. doi:10.1007/s12282-015-0592-0.
- 50 Gartlehner G, Thaler KJ, Chapman A, et al. Adjunct ultrasonography for breast cancer screening in women at average risk: a systematic review. *Int J Evid Based Healthc.* 2013;11:87–93. doi:10.1111/1744-1609.12022.
- 51 Groen RS, Leow JJ, Sadasivam V, Kushner AL. Review: indications for ultrasound use in low- and middle-income countries. *Trop Med Int Health.* 2011;16:1525–35. doi:10.1111/j.1365-3156.2011.02868.x.
- 52 Rayne S, Lince-Deroche N, Hendrickson C, et al. Characterizing breast conditions at an open-access breast clinic in South Africa: a model that is more than cancer care for a resource-limited setting. *BMC Health Serv Res.* 2017;17:63. doi:10.1186/s12913-016-1959-4.
- 53 World Health Organization. *Palliative Care (Fact sheet number 402).* 2015 n.d. [Internet]. [cited 10 February 2017]. URL: <http://www.who.int/mediacentre/factsheets/fs402/en/>.
- 54 American Cancer Society. *Follow up care after breast cancer treatment.* 2016 n.d. [Internet]. [cited 10 February 2017]. URL: <https://www.cancer.org/cancer/breast-cancer/living-as-a-breast-cancer-survivor/follow-up-care-after-breast-cancer-treatment.html>
- 55 Health Systems Trust. *Medical scheme coverage (%) 1995–2014 n.d.* [Internet]. [cited 30 June 2016]. URL: <http://indicators.hst.org.za/healthstats/77/data>
- 56 South African National Department of Health. *National Health Insurance: The First Eighteen Months.* Pretoria: NDoH; 2013.