Why the time is right to tackle breast and cervical cancer in low-resource settings

Vivien Davis Tsu, Jose Jeronimo & Benjamin O Anderson

Abstract The health concerns of women in their mid-adult years – when the prime age of reproduction has passed – have been traditionally given little or no attention by health systems and donors, despite the heavy burden that diseases such as breast and cervical cancer impose on women and their families. The risk of sexually transmitted infections that accompanies sexual relations and the risk of death and morbidity associated with pregnancy have long been recognized and have stimulated major control efforts that are finally yielding positive results. Much less attention has been focused, however, on how experiences in early life can affect women’s health in adulthood.

Breast and cervical cancers kill more women than any other types of cancer in all parts of the developing world. In most of Asia and Latin America and some African countries, deaths from these two forms of cancer now outnumber pregnancy-related deaths. There are five compelling reasons for focusing on these cancers now to try to reverse these epidemiologic trends: (i) the burden of breast and cervical cancer is large and is growing; (ii) effective screening and treatment are available; (iii) research is generating new knowledge; (iv) there are opportunities for synergy with other health programmes; and (v) noncommunicable diseases are the focus of much current interest.

Introduction

It has been recognized for decades that women in low-resource settings suffer a crushing burden of morbidity and mortality associated with the universal life experience of reproduction. Since the clarion call from Allan Rosenfield and Deborah Maine in 1985 and the first Safe Motherhood meeting, which was held in Nairobi in 1987, there has been a dedicated movement to reduce this toll – an effort that is finally showing good results. Much attention has been paid to women in their teens and twenties because of the risks associated with sexuality and pregnancy – namely, infection with the human immunodeficiency virus (HIV) and other sexually transmitted infections, unwanted pregnancy and associated unsafe abortion, and obstetric complications. Much less attention has been focused by governments and donors on how these earlier life experiences affect the health of women when they reach their thirties, forties and fifties – those ill-defined middle years between youth and old age.

Cancers of the breast and cervix kill more women than any other forms of cancer in all parts of the developing world. While in the past maternal deaths dominated reproductive mortality in low and middle-income countries, in most countries of Asia and Latin America and some countries of Africa, deaths due to the complications of pregnancy are now outnumbered by deaths from breast or cervical cancer (Fig. 1). The causes of breast and cervical cancer are related, at least in part, to a woman’s sexual and reproductive choices and other exposures in early life – i.e. history of infection with the human papillomavirus (HPV), age at first pregnancy and number of pregnancies, breastfeeding history, diet and physical activity. However, the same reproductive factors that protect against one form of cancer increase the risk of the other form. Women who have early and frequent pregnancies and who breastfeed their children have a lower risk of getting breast cancer but are at increased risk of developing cervical cancer. In low- and middle-income countries, where acute, infectious diseases and pregnancy-related morbidity and death are common, health care has understandably been designed primarily around these areas. However, there is a growing recognition in these countries that new epidemiologic patterns are emerging because of lifestyle changes and gains in life expectancy and that noncommunicable diseases, including cancer, are becoming an increasingly important part of the health landscape.

The time is right to focus on breast and cervical cancer and to support critical interventions for reducing the incidence of these two diseases and their case-fatality rates. Thanks to a concerted global effort, in many places maternal mortality is no longer the leading cause of death among adult females. With similar effort, comparable strides can be made towards reducing the morbidity and mortality linked to breast and cervical cancer. This paper presents five compelling reasons for marshalling our resources and taking action now, a time during which need and opportunity are converging.

Burden is high, growing and inequitable

In “less developed countries”, as defined by GLOBOCAN, 690,000 new cases of breast cancer and 450,000 new cases of cervical cancer occurred in 2008. Unless action is taken to reverse epidemiologic trends, by 2030 incident cases of breast and cervical cancer will have increased to 1.1 million and 730,000, respectively – figures that represent an increase of more than 60% in disease incidence over a period of just over 20 years. The gap between more and less developed regions is expected to widen (Fig. 2) as the proportion of global deaths from cervical cancer and breast cancer that occur in less developed parts of the world rises from the current 88% to 99% and from 59% to 63%, respectively. Despite the common misconception that breast cancer is primarily a problem of high-income countries, in 2010 the majority of the world’s 425,000 deaths from breast cancer occurred in developing...
countries (as defined by Forouzanfar et al.)). Of the breast cancer deaths that occurred in developing countries, 68,000 were in women less than 50 years old.

Disparities in morbidity and mortality rates reflect the influence not only of biological and environmental factors, but also of social and cultural determinants linked to the question of fairness and social justice. Equity is an important aspect to consider in control efforts, which should be guided by special consideration for those who are more vulnerable to illness or less able to access health-care services because of social, economic or demographic factors beyond their control. The “cancer divide” between rich and poor countries is further exacerbated by gender discrimination. Because of a combination of gender-related social and economic factors, in some countries women have traditionally had less access to health-care services than men. Cancers of the breast and cervix most often strike women in theirforties and fifties, when they are still raising families. In addition to the suffering this brings to women, the accompanying illness and death are detrimental to their children and other dependants in the family and deprive communities of their contribution to society as experienced health workers, teachers and food producers.

Cervical cancer is largely preventable with effective screening and treatment of precancerous lesions, and breast cancer survival rates are greatly reduced through early detection and treatment. Hence, much of the disparity in disease burden is rooted in inequitable access to care. This becomes even more evident when the number of deaths is divided by the number of incident cases to obtain an approximation of case-fatality rates. Many more women die of their cancers in African countries than in industrialized countries. In the United States of America, the ratio of the number of cervical cancer deaths to the number of new cases was 0.27 in 2008, whereas in less developed regions it was 0.53 and in sub-Saharan Africa it was 0.67. Similarly, the ratio of breast cancer deaths to new cases was just 0.22 in the United States, whereas in less developed regions it was 0.39 and in sub-Saharan Africa it was 0.54. Rates of screening for breast and cervical cancer are very low in low-income countries. According to data from the World Health Survey of 2003, 4.1% of women between the ages of 18 and 69 years had been screened for cervical cancer in the previous three years and 2.2% of women between the ages of 40 and 69 years had had a mammogram in the previous five years. Living in a poor household, in a rural area and in a country with low government expenditure on health were the primary determinants of reported low rates of cervical cancer screening.

**Availability of proven interventions**

Two myths that deter women from getting screened for cervical and breast cancer are that effective interventions against these diseases are not available or not affordable. For cervical cancer and, to a lesser extent, breast cancer, effective control measures are available and affordable.
Cervical cancer

Cervical cancer can be largely prevented through vaccination against HPV infection and by screening for and treating precancerous lesions. The two HPV vaccines in use are extremely safe and efficacious. In addition, experience has shown that well-designed immunization programmes can achieve high coverage among young adolescent girls in low- and middle-income countries. High vaccine costs, an important barrier for many governments, have come down steadily in low- and middle-income countries and in 2012 the GAVI Alliance accepted applications from eligible countries for subsidized HPV vaccine. Although the vaccine has only been in use for a few years and any impact on cervical cancer rates will not be appreciable for another 25 to 30 years, there is already preliminary evidence of an effect on the prevalence of HPV infection and cervical abnormalities.

Advances in screening have also been made. New screening tests have been developed and new screening programme models have been validated. Visual inspection with acetic acid (VIA) and new tests for the detection of HPV DNA, which became commercially available in China and India in 2013, provide low- and middle-income countries with cheaper and less cumbersome alternatives to the traditional Papanicolaou (Pap) smear. Although screening based on the Pap smear ushered in the decline in cervical cancer rates in the second half of the 20th century in industrial countries, it has proved difficult to establish and sustain in low- and middle-income countries. As of December 2012, 24 countries had selected VIA as their national screening strategy and 29 others had piloted VIA screening. “Screen and treat” approaches, in which VIA or HPV testing is followed by treatment of precancerous lesions with cryotherapy without further confirmatory diagnostic testing, have led to reductions in cervical cancer incidence and mortality. Tests for the detection of HPV DNA have the added advantage that a woman can obtain her own vaginal sample and take it for testing to a nearby laboratory. Recent studies in India, Nicaragua and Uganda, which have strikingly different cultures, have shown that self-collection of vaginal specimens for testing with a low-cost HPV DNA test designed for low-resource settings was highly acceptable to women. In addition, the test showed higher sensitivity in detecting high-grade cervical lesions than Pap smears or VIA, despite good specificity.

Breast cancer

In the case of breast cancer, evidence surrounding the effectiveness of primary prevention is less straightforward. Nonetheless, low- and middle-income countries present opportunities for action. Interventions that promote changes in lifestyle, including reduced alcohol consumption, reduced fat intake and the practice of regular physical activity, can lower the risk of developing the disease and will have additional benefits by also lowering the risk of developing other noncommunicable diseases. The highest impact on mortality, though, will come from earlier detection, accurate diagnosis and more widely available basic treatment. Although screening mammography has been shown to reduce breast cancer mortality in high-income countries, it is generally neither affordable nor appropriate for detecting tumours in the advanced stages usually seen in low-resource settings, where women often present with tumours that are easily palpable, visible or ulcerated through the skin.

Interventions that promote clinical breast examination and increase community awareness of the symptoms of breast cancer and of the importance of screening can greatly increase the fraction of tumours that are detected at an earlier stage, before they become readily palpable or visible, as shown by Mittra et al. and Sankaranarayanan et al.

The role of screening mammography is still being debated. Opinions differ on the age when it should be initiated and how often it should be performed. In most high- and upper-middle-income countries in Europe, Latin America and North America where mammography screening is practised, the established age of initiation is generally 50 years and subsequent mammograms are performed every two years, as recommended in 2009 by the United States Preventive Services Task Force. As important as these debates may be for wealthy countries, they are largely irrelevant for low- and lower-middle-income countries, where the per capita cost of mammographic screening surpasses what the government can afford to pay. However, women in these same countries usually present to health services with advanced disease and poor quality of life. In such cases, the cure rate is low and case management, except for palliative care, becomes resource-intensive and costly. Educational interventions and basic clinical tools, such as regular breast examinations by a well-trained health-care professional, can result in early detection and lead more women to receive basic treatment at an affordable cost.

The optimal age to start screening with clinical breast examination has not been determined because data from randomized clinical trials are not yet available regarding the method’s impact on stage at diagnosis and on breast cancer mortality in low- and middle-income countries. In high-income countries, population-based screening mammography is not routinely performed before the age of 40 – or in many cases 50 years – but in the United States clinical breast examination is recommended instead of mammography every one to three years during routine wellness visits in women between the ages of 20 and 40 years. This generates many false-positive results that need to be verified by means of expensive and invasive tests and has a relatively low yield in terms of the number of cancers detected, given the low rate of cancer in this age group. In low- and middle-income countries, the average age in which breast cancer is diagnosed is in the early forties. Since clinical breast examination does not require any technology, routine screening with this method can be initiated at the age of 35 years, as in Mumbai, India, or at the age of 40 years in settings with more limited resources with which to perform diagnostic evaluations.

In Peru, an innovative, community-based breast cancer screening model is being tested. It spans the continuum from community education and clinical breast examination at the primary care level to diagnostic triage at the community hospital level and referral of women with breast cancer to a regional cancer centre for treatment. PATH, an international non-profit organization, is working with Peru’s National Cancer Institute and Ministry of Health and with the Regional Cancer Institute in the northern region of La Libertad to offer screening services to rural women. Community health promoters hold educational sessions with women to explain to them about breast cancer awareness.
and the eight key signs and symptoms of the disease and to encourage women between the ages of 40 and 64 years to undergo annual clinical breast examinations at their local health centres. Midwives have been trained to perform such examinations and to counsel women and refer them to appropriate services, and local physicians have been trained to obtain a fine needle aspiration biopsy and examine the specimen for adequacy before sending it for analysis by a pathologist trained in breast cytology. Women with positive biopsies are referred for full evaluation and treatment. More than 3000 women were screened in the first 18 months of the programme and six cases of cancer were diagnosed. As a next step, two components will be added to the care model: (i) to perform an ultrasound for more thorough evaluation before obtaining a biopsy, and (ii) to offer women community support during and after treatment. The competency-based curricula for promoters, midwives and physicians have been coordinated to ensure consistent messages at all levels. In Mexico, breast cancer screening and treatment has been incorporated into the national health insurance scheme. In Brazil, a group has developed an urban mammography-based screening programme.37,38

An important tool for the detection and management of breast cancer is a set of guidelines that cover the whole spectrum of breast care and that are stratified by resource level. The Breast Health Global Initiative (BHGI), established in 2002, applied a consensus panel process to develop evidence-based, resource-sensitive guidelines for breast cancer early detection, diagnosis and treatment and for improving health-care delivery systems for women with breast cancer in low- and middle-income countries.9 Under the BHGI framework, a four-tiered system of resource allotment is used to establish prioritization schemes based on the level of existing resources (basic, limited, enhanced and maximal) and the stage of disease at diagnosis. In the past, health ministries and other decision-making bodies have lacked the tools needed to perform internal analyses to determine the suitability of the existing infrastructure for breast cancer screening, diagnosis and treatment, the areas that would need to be improved and the cost of improving them at the basic level. The BHGI framework provides a useful tool for objective and rational decision-making based upon verifiable local and global evidence.

Where available, basic surgery, low-cost generic drugs and radiation therapy are the cornerstones of breast cancer treatment.40 Modified radical mastectomy is the mainstay of locoregional treatment at the basic level. Endocrine therapy with generic (low-cost) drugs such as tamoxifen provides effective post-surgical treatment for tumours that are positive for estrogen receptors (ERs), or binding sites. Unlike systemic chemotherapy, which requires complex systems for dose determination, infusion and monitoring, endocrine therapy is oral and can be dispensed from a pharmacy. However, a tumour’s ER status must be known before the drug can be used. For estrogen-receptor-negative cancers, systemic cytotoxic chemotherapy is effective but needs to be administered in a safe, sterile environment and requires monitoring for drug toxicity in the form of periodic blood chemistry profiles and complete blood counts. Some older cytotoxic drugs are effective and affordable and efforts are under way to include them in essential medicine lists. Radiation therapy allows for breast-sparing surgery and is used for chest wall irradiation after mastectomy and for the palliation of painful or symptomatic metastases. It is not sufficiently available yet, but the International Atomic Energy Agency is working with countries to increase its availability.41

Partnerships between industrialized and developing countries to build specialist capacity or to provide access to specialist care while local staff are in training have been quite successful. A collaborative training programme between a pathology department in Tromsø, Norway, and the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana, provides an example of how pathology diagnostic services can be made available to patients in low-income settings.42 Problems observed in the Ghana laboratory, such as poor specimen quality and inadequate descriptions of macroscopic specimens, led to the development of new onsite guidelines for tissue fixation procedures, macroscopic examination and tissue block selection. Telepathology can also enhance training in some settings and has been used by doctors in the United Republic of Tanzania and other countries to consult with North American and European colleagues on challenging cases.43

Research to fill knowledge gaps

Cryotherapy is generally used to treat precancerous cervical lesions because it can be easily taught to mid-level care providers, the initial equipment purchase price is lower than for alternative therapeutic methods, and the level of infrastructure needed, such as electricity, is less. However, it requires a reliable supply of gas (nitrous oxide or carbon dioxide), which has proven difficult to secure in some rural settings. The International Agency for Research on Cancer is evaluating the feasibility and effectiveness of cold coagulation as an alternative treatment and several private companies are also developing alternative treatment modalities, including pharmacological methods.

Appropriate breast cancer treatment depends on an accurate pathology diagnosis, which in turn requires the availability of tissue sampling procedures. Fine-needle aspiration biopsy is the most cost-effective procedure and has a short turnaround time. However, the choice of sampling procedure – fine needle aspiration biopsy, core needle biopsy or excisional biopsy – should be based on the relative availability of cytologists or pathologists in each medical community and on the availability and cost of the required equipment and supplies. In Peru, for example, the cost of large-bore needles for core biopsy (about 60 United States dollars per unit) was prohibitive. One of the authors (JJ) is working with PATH’s technology development group to investigate less expensive sources and alternative designs for core-needle devices and components.

The accurate determination of a tumour’s ER status spares women with ER-negative breast cancer from the side-effects and expense of endocrine treatment. The use of immunohistochemistry to determine a tumour’s ER status requires substantial resources. The development of a low-cost technology for assessing ER status in the field would reduce this problem.44 PATH’s diagnostic development group is exploring alternative approaches for rapid, point-of-care tests based on nucleic acid amplification.

Two models of care that have long been studied in India may prove to be viable and effective. Mittra et al. are conducting joint breast and cervical cancer
screening in Mumbai using VIA and clinical breast examination.\textsuperscript{32} In Trivandrum, where clinical breast examination and community education about breast cancer’s warning signs and symptoms are being taught, as recommended by the World Health Organization, long-term follow-up will reveal whether education without screening but linked to diagnosis and adequate treatment can lead to the detection of breast cancer at an earlier stage.\textsuperscript{33}

Opportunities for synergy

With a coordinated approach to breast and cervical cancer screening, opportunities for synergy exist at several levels. At the primary care level, midwives and nurses frequently have skills that enable them to conduct cervical examination. Both midwives and nurses are trusted by women in the community, who often consult them when they develop problems with their breasts in the postnatal period. More formal training about normal and abnormal breast tissue would improve these health workers’ ability to detect breast cancer early.

The prevention and early detection of breast and cervical cancer have some features in common and involve a similar audience. For example, women need to get screened even if they feel well. Some age stratification is needed since cervical screening should start when women are in their thirties and breast cancer screening when they are in their forties. The frequency of screening may also differ, with clinical breast exams performed annually, usually starting at the age of 40 years,\textsuperscript{34} and cervical cancer screening at least once or twice in a woman’s lifetime (and more often only after high coverage with a single screening has been attained).\textsuperscript{35}

Although a relatively small proportion of cervical abnormalities need specialty care, all breast cancers detected through screening or case-finding have to be treated by physicians with specialized training. Regional and national referral services are needed for both breast and cervical cancer and who benefit patients with other types of cancer. Strengthening pathology services, ensuring the capacity to perform basic surgery and administer chemotherapy, establishing at least one source of radiotherapy in the country and developing appropriate palliative care policies and services can start with breast and cervical cancer and then become the foundation for other cancer care. Success with these two forms of cancer, which are amenable to prevention or early detection, can help reverse the prevailing myth that cancer is uniformly fatal in low- and middle-income countries.

There is momentum now

The 2011 high-level meeting of the United Nations General Assembly on the prevention and control of NCDs led to heightened awareness of the importance of leading killers such as cancer, heart disease, diabetes and chronic respiratory disease. The ensuing political declaration by the United Nations explicitly mentions cervical cancer and promotes “increased access to cost-effective cancer screening programmes, as determined by national situations.”\textsuperscript{36} After a consultation with its Member States, WHO recommended the inclusion of indicators related to palliative care, cervical cancer screening and HPV vaccine in the monitoring framework. This is indicative of the growing recognition of the importance of cervical cancer, but breast cancer is not mentioned in the political declaration.\textsuperscript{37} In fairness, it is difficult at this time to select a single specific breast cancer metric to recommend universally to countries, given the limited availability of baseline data and the difficulty of collecting reliable routine data in resource-constrained settings. A useful initial metric would be, for example, a marker of disease stage at diagnosis, such as tumour size, since the frequency of late-stage presentation and diagnosis will drive outcomes.

The synergies and momentum created by the recent international focus on non communicable diseases will have varying impact depending on the region, local resources and competing demands. By themselves they are not enough to create the opportunity for change, but they can enhance such an opportunity when combined with the availability of proven interventions and the results from ongoing research.

Conclusion

The health concerns of women in their mid-adult years have long been given little or no attention in most low-resource settings, despite the heavy burden of suffering that diseases such as breast and cervical cancer impose on women and their families.

The time has come to tackle these two cancers. There are numerous opportunities to prevent cervical cancer and to improve survival in women with cancer of the breast or cervix. It will take time to build the necessary human capacity, establish programmes, change community attitudes of fatalism and stigma and see the benefits of these measures become apparent. Further delay in taking up the opportunities that are now available will harm another generation of women.

Competing interests: None declared.

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لذا الوقت مناسب للتعامل مع سرطان الثدي وسرطان عنق الرحم في المواقع المنخفضة الموارد

عادة ما تؤدي النظام الصحي والأجهزة المانحة الدعم إلى تحفيز جهود الوقاية والعلاج المبكر ورفع مستوى الوعي في المجتمعات. وتتضمن التدابير التالية:

- زيادة الوعي الصحية للنساء في مرحلة أواسط العمر، مثل توزيع الوثائق التعليمية التي تรวดيج عادات الحياة الصحية من خلال وسائل الإعلام والمواقع الإلكترونية.
- تدريب وتشجيع النساء على تجنب المخاطر المرتبطة بالحمل، مثل تجنب التدخين أثناء الحمل، وتشجيعهن على ممارسةعزامة الصيام أثناء الحمل، وتوفير الدعم النفسي والاجتماعي للنساء المكتسبات.
- تشجيع النساء على ممارسة الرياضة والطعام الصحي، وتعزيز الواحة الصحية للنساء، وتشجيعهن على التباعد عن المخاطر المرتبطة بالحمل، مثل تجنب المخاطر المرتبطة بالحمل، وتوفير الدعم النفسي والاجتماعي للنساء المكتسبات.

النتيجة:

يتطلب التعامل مع سرطان الثدي وسرطان عنق الرحم في المواقع المنخفضة الموارد تدخلات متعددة من الجوانب، بما في ذلك التعليم الصحي، والتشجيع على النمط الصحية الصحي، والتشجيع على الممارسات الصحية المناسبة، والتوفير الدعم النفسي والاجتماعي للنساء المكتسبات.

ملخص

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- تشجيع النساء على ممارسة رياضة الطعام الصحي، وتوفير الدعم النفسي والاجتماعي للنساء المكتسبات.

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Resumen

Por qué es el momento adecuado para hacer frente al cáncer de mama y de cuello uterino en entornos con recursos escasos

Los problemas de salud de las mujeres de mediana edad, una vez que han pasado la plenitud de la edad reproductora, han recibido tradicionalmente poca o ninguna atención por parte de los sistemas sanitarios y donantes, a pesar de la gran carga que enfermedades como el cáncer de mama o de cuello uterino representan para las mujeres y sus familias. El riesgo de enfermedades de transmisión sexual a través de relaciones sexuales, y el riesgo de muerte y enfermedad asociados con el embarazo han sido reconocidos y se han impulsado esfuerzos de control a gran escala que al fin están dando resultados positivos. Sin embargo, se ha prestado mucha menos atención a cómo las experiencias en las grandes escala que al fin están dando resultados positivos. Sin embargo, se ha prestado mucha menos atención a cómo las experiencias en estas últimas etapas de la vida pueden afectar la salud de las mujeres en la vida adulta.

En el mundo desarrollado, los cánceres de mama y de cuello uterino matan a más mujeres que ningún otro tipo de cáncer. En la mayor parte de Asia y América Latina y algunos países africanos, las muertes por estos dos tipos de cáncer superan en número a las muertes relacionadas con el embarazo. Hay cinco razones de peso para centrar la atención en estos tipos de cáncer con objeto de intentar revertir estas tendencias epidemiológicas: (i) la carga de los cánceres de mama y de cuello uterino es muy elevada, y sigue creciendo; (ii) existen controles y tratamientos eficaces; (iii) la investigación está proporcionando conocimientos nuevos; (iv) existen oportunidades de sinergia con otros programas sanitarios y (v) las enfermedades no transmisibles reciben gran parte de la atención actual.

Referencias


