Health, equity, and women's cancers 2

Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries

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Breast and cervical cancers are the commonest cancers diagnosed in women living in low-income and middle-income countries (LMICs), where opportunities for prevention, early detection, or both, are few. Yet several cost-effective interventions could be used to reduce the burden of these two cancers in resource-limited environments. Population-wide vaccination against human papillomavirus (HPV) linked to cervical screening, at least once, for adult women has the potential to reduce the incidence of cervical cancer substantially. Strategies such as visual inspection with acetic acid and testing for oncogenic HPV types could make prevention of cervical cancer programmatically feasible. These two cancers need not be viewed as inevitably fatal, and can be cured, particularly if detected and treated at an early stage. Investing in the health of girls and women is an investment in the development of nations and their futures. Here we explore ways to lessen the divide between LMICs and high-income countries for breast and cervical cancers.

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This is the second in a Series of three papers about health, equity, and women's cancers

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Introduction

Despite the complexity of diagnosing and treating cancer, there are many cost-effective interventions that do not rely on tertiary care or specialised cancer health care. Just over 14·9 million new cancer cases worldwide were diagnosed in 2013, and 8·2 million deaths were recorded.[1] Of these, 8·0 million new cases and 5·3 million deaths occurred in low-income and middle-income countries (LMICs). Among women worldwide, breast cancer was the commonest cancer, with roughly 1·7 million incident cases and 0·5 million deaths, followed by colorectal, lung, and cervical cancers. Cervical cancer alone accounted for 0·5 million incident cases and 260 000 deaths.[1] More than 85% of new cases and deaths for cervical cancer were in LMICs. In sub-Saharan Africa, despite a slightly lower incidence of cervical cancer than breast cancer (just over 93 000 *vs* just over 94 000 new cases per year) there were more deaths among women with cervical cancer than among those with breast cancer.[1]

The differences in access to care, quality of care, and diagnosis for these two cancers differs strikingly between high-income countries (HICs) and LMICs. The variance in burden is especially evident when Gavi-eligible countries (ie, those with average incomes per person of <US$1 per day, according to World Bank estimates) are compared with HICs (figure). The burden of disease, measured as incidence rate ratios, increases from age 40 years up to age 60 years. Additionally, incidence is

Search strategy and selection criteria

We searched MEDLINE (OVID), Scopus, and Embase for articles published in English between Jan 1, 2005, and Dec 15, 2015, using the search terms "breast cancer", "cervical cancer", "screening", "prevention", "low income country", "middle income country", and "developing country". We largely selected publications from the past 5 years, but did not exclude widely referenced and highly regarded publications from 2005 onwards. We also manually searched the reference lists of retrieved articles.

Key messages

- Cervical cancer incidence and mortality have declined sharply in the past 40 years in many high-income countries due to widespread screening, treatment of precancerous lesions and invasive cancer, and improved socioeconomic status.
- Cervical cancer is highly preventable, and universal HPV vaccination of all girls at age 12 years could avert 690 000 cases and 420 000 deaths worldwide over their lifetime.
- While cytology-based screening programmes are unsuitable for LMICs, studies of VIA screening and treatment programmes suggest reductions in incidence of high-grade lesions and cervical cancer, but scaling up and sustaining programmes in routine health services is challenging.
- HPV testing shows great promise, but is prohibitively expensive for most LMICs.
- Breast cancer mortality has decreased in many high-income countries over the past 25 years due to a combination of awareness, early detection, and effective treatments.
- Despite controversy, mammography is supported as a way to reduce breast cancer mortality among women aged 50–74 years, but is recommended only in high-resource settings or limited-resource settings where it is proven that health systems can meet the conditions for implementation, including good programmatic quality control.
- Screening by clinical breast examination is a promising approach because evidence suggests that it lowers stage distribution at detection, although whether breast cancer mortality is reduced remains unclear.
- Management of breast cancer and invasive cervical cancer requires pathology, imaging, and laboratory services, cancer surgery, radiotherapy, chemotherapy, and hormone therapy, provided by adequately trained doctors, nurses, and other support staff; initial high vertical investments to develop facilities and resources would yield long-term benefits for millions of women.

HPV=human papillomavirus. LMICs=low-income and middle-income countries. VIA=visual inspection with acetic acid.

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five times higher and mortality seven times higher in the least-developed than in the most-developed countries.[2,3] In some LMICs, regular screening is already recommended for a high proportion of women, but no effect on the incidence of cervical cancer has been reported.[4] Good-quality control, population coverage of the appropriate target age group, and effective treatment after screening are needed to yield an effect, as was well illustrated in the Nordic countries in the 1960s when large national cervical cancer programmes were instituted. These programmes showed clearly that high coverage of the appropriate target population and adherence to the programme steps provided a very high level of protection to women at individual and population levels, and resulted in a substantial reduction in the cumulative incidence of cervical cancer.[5–7] Poorly organised programmes have not had such positive effects.[8]

The incidence of cervical cancer is declining in many LMICs, except those in sub-Saharan Africa, at an annual percentage change of –1·0% to –3·5%. For instance, in India, annual percentage changes in the past three decades have been –1·1% in Bhopal and –3·4% in Chennai.[9] In fact, in the latter the age-standardised incidence dropped from 44·5 per 100 000 women in 1982–86 to 17·8 per 100 000 in 2007–11.[10]

Among women in the population-based cancer registry of Dindigul District, Tamil Nadu, India, the incidence of cervical cancer reduced by 68% in 2003–06 for those with 12 or more years of education compared with those with no education.[11] Falling incidence of cervical cancer in successive generations from 1976 to 2005 in the cancer registry for the Mumbai population was partly attributed to improved education and socioeconomic status, increased age at marriage and at having the first child, and lowered parity.[12]

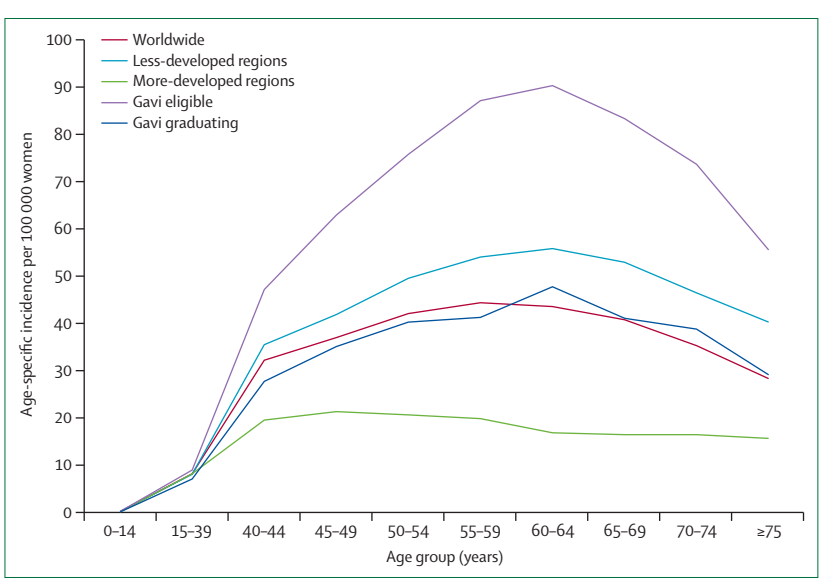

Figure: **Estimated age-specific incidence of cervical cancer according to country development status and Gavi eligibility**

In LMICs, cervical cancer is more advanced at presentation, access to care is more difficult, and case fatality rate is higher than those in HICs, representing substantial global health inequity. This situation results from a multitude of factors.[3] Cultural norms and local traditions might contribute to poor access to appropriate cancer care, which is often linked to low levels of education and lack of trust of western medicine approaches to health care. Up to 80% of people in sub-Saharan Africa are thought to seek remedies from a traditional healer before accessing western health-care systems.[13] In this second paper in *The Lancet*'s Series on women's cancers, we explore interventions and innovations that have helped to reduce the cancer divide between HICs and LMICs for breast and cervical cancers. It is beyond the scope of this article to address treatment of cervical cancer in detail; however, appropriate management of invasive disease is best done within a multidisciplinary setting, with radiation oncologists, gynaecological oncologists, and pathologists at a minimum.

Cervical cancer

Screening

Cytology

Cervical cytology screening programmes with wide coverage, call, and recall systems, the capacity to treat women with cervical disease, and in-built quality assurance have achieved substantial (50–80%) reductions in cervical cancer incidence and mortality in HICs.[14,15] Before the implementation of large-scale, population-based cytology screening, age-standardised cervical cancer incidence (27–38 per 100 000 women) and age-specific incidence curves (peak incidence exceeding 80 per 100 000 women) in HICs, such as Canada, Denmark, Germany, and the USA, were similar to those now seen in LMICs.[16] Frequent cytology screening and treatment of cervical cancer precursors have led to substantial declines in incidence among women aged 30–70 years, and particularly among those aged 45–55 years where good coverage was obtained.[17]

Cytology-based screening programmes have not been successfully implemented nor are they feasible in most developing countries because they need complex human, financial, and bricks-and-mortar infrastructures to start and be sustained. Additional factors are multiple competing health needs, such as malaria, tuberculosis, AIDS, and maternal mortality, along with poor governance, and inadequate investment in health. Much of the existing cytology screening is opportunistic or sporadic and has low population coverage, usually including only young women in urban areas who have access to health insurance. The result, therefore, is minimum or no reduction in cervical cancer incidence or mortality.[4]

Visual inspection with acetic acid

Alternative cervical screening tests have been explored in LMICs, such as visual inspection with acetic acid (VIA)

and human papillomavirus (HPV) testing (table). Management paradigms, such as the single-visit approach, in which women are screened and treated at the same visit, have been investigated in clinical trials. The realistic sensitivity and specificity of VIA in detecting high-grade cervical intraepithelial neoplasia grade 2 and 3 lesions are around 50% and 85%, respectively.[18] The feasibility, safety, and acceptability of a single-visit approach with VIA and cryotherapy have been shown in Thailand and several sub-Saharan African countries.[19–21,27]

In randomised trials, a single-visit approach with VIA has been associated with reductions in the incidence of high-grade lesions and cervical cancer mortality.[22–24] In a cluster-randomised controlled trial in Dindigul District, India, one round of screening was associated with 25% reduction in the incidence of cervical cancer and 35% reduction in mortality (incidence hazard ratio 0·75, 95% CI 0·55–0·95 and mortality hazard ratio 0·65, 0·47–0·89) at 7 years of follow-up.[23] After 12 years of follow-up in another cluster-randomised controlled trial in Mumbai, India, involving around 151500 women aged 35–64 years at recruitment, Shastri and colleagues[24] reported a 31% reduction in cervical cancer mortality (risk ratio 0·69, 95% CI 0·54–0·88, p=0·003) after four rounds of VIA screening with 2-year intervals, when compared with routine care, which in this setting was no programmatic screening.

Scaling up and sustaining VIA screening programmes can be challenging, given the subjective nature of the test, which leads to high variability in the performance of providers, frequent false-positive results, low to moderate sensitivity, low specificity, overtreatment, and poor performance in post-menopausal women. There are also no validated quality assurance methods. Despite these challenges, large-scale systematic scaling up of VIA screening is being attempted in various settings in LMICs.

At best, VIA screening offers an interim approach to establishing a screening culture and infrastructure in low-resource settings until affordable HPV testing can be introduced. Inherent in any screening strategy are the trade-offs between the characteristics of the test (ie, sensitivity to maximise detection of precursors and specificity to minimise overtreatment) and programmatic issues, such as population coverage and the necessary diagnostic and treatment procedures, costs, and quality control. Campos and colleagues[25] investigated health and economic trade-offs between the sensitivity and coverage of the screening test and loss to follow-up of women with positive screening results to identify the most beneficial programme investments. They concluded that setting-specific data on achievable test sensitivity, coverage, follow-up rates, and programmatic costs are all needed to guide decision making for cervical cancer screening.

An aspect of the single-visit approach that has not been well assessed is point-of-care testing and treatment at the primary care level. The single-visit approach does not obviate the need for counselling or careful explanation about the need for follow-up, and adds work to already overloaded health-care workers and fragile health systems. How to integrate this approach into other women's and general health interventions, therefore, needs careful investigation and planning.

	Overall evidence base	Cost-effectiveness in LMICs	Feasibility
Cervical cancer			
VIA[18–26]	Randomised trials, cross-sectional studies, modelling studies	Very cost-effective if used as part of a screening and treatment approach	Feasible
Digital photography or digital cervicography VIA[27,28]	Cross-sectional studies	Not available	Feasible
HPV testing[22,25,26,29–37]	Randomised trials, cohort studies, cross-sectional studies, modelling studies	Very cost-effective if high treatment rates of women with positive screening findings can be achieved	Feasible
HPV vaccination[38–48]	Randomised trials, cohort studies, post-vaccination observational studies, modelling studies	Very cost-effective if cost per vaccinated girl is low (preferably US$10–25 but up to $50) and vaccine efficacy is high and long lasting	Feasible
Diagnosis and treatment of pre-cancerous lesions[19–23,26,27,29,28]	Randomised trials, cross-sectional studies, cohort studies	Not available	Feasible
Diagnosis and treatment of early-stage disease[49,50]	Observational studies of survival outcomes	Not available	Feasible
Diagnosis and treatment of advanced-stage disease[49–51]	Observational studies of survival outcomes	Not available	Not feasible in some low-income countries, especially those in sub-Saharan Africa
Breast cancer			
Mammography screening[51–59]	Randomised trials, cohort studies, cross-sectional studies, assessments of service screening programmes, modelling studies	Not cost-effective	Not feasible
Clinical breast examination screening[55–57,60,61]	Randomised trials, cross-sectional studies, modelling studies	Cost-effective	Feasible
Breast awareness[49,50,55,57,62,63]	Observational studies, modelling studies	Cost-effective	Feasible
Diagnosis and treatment of early-stage disease[49,50,51,58,59]	Observational studies of survival outcome, reviews	Not available	Feasible
Diagnosis and treatment of advanced-stage disease[49,50,51,58,59]	Observational studies of survival outcome, reviews	Not available	Not feasible

LMICs=low-income and middle-income countries. VIA=visual inspection with acetic acid. HPV=human papillomavirus.

Table: **Summary of potential interventions for breast cancer and cervical cancer control in LMICs**

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HPV testing

HPV testing is objective and reproducible and screens for the causative agent of cervical cancer (table). This method is more sensitive (30–40% gain) than cytology but 3–5% less specific. Randomised controlled trials

have shown that HPV testing increases detection of cervical intraepithelial neoplasia grade 2 and 3 lesions at first screening and substantially reduces the number of such lesions in subsequent rounds of screening, leading to a 70% reduction in invasive cancer overall.[29] A randomised controlled trial in India reported a 50% reduction in mortality associated with invasive cervical cancer with one round of HPV testing when compared with routine care.[30]

Despite its promising performance, the costs, logistics, and technology requirements for successful implementation of HPV testing are challenging for under-resourced health systems in LMICs. Newer technologies, such as GeneXpert, a PCR-based test that has been extensively used for diagnosis of tuberculosis in sub-Saharan Africa, including South Africa, gives a result on the detection of 15 high-risk types of HPV within 1 h and can be used in very resource-restricted environments.[64] Although expensive, this is the closest that modern technology has come to creating a point-of-care HPV test, and it might make the single-visit approach feasible, which could change the future of HPV testing.[31,32]

Use of self-collection samples for detection of high-risk HPV identified women at risk of grade 2 or higher cervical intraepithelial neoplasia in a large study in Mexico (relative risk 15·7 for detection).[33] Self-sampling is acceptable and effective and can dramatically increase coverage in various settings,[34,35] particularly for hard-to-reach populations, but its use in the context of screening programmes needs to be defined.

The data on VIA and HPV testing programmes have been growing since the landmark study on cost-effectiveness of HPV testing by Goldie and colleagues.[26] These show that, head to head, one screen with VIA remains cheaper than one with HPV testing, but that VIA screening must be done more frequently to achieve the same health benefit as with HPV testing. Thus, the total cost of the two approaches is similar overall.[36,37] When wide ranges of assumptions and scenarios are considered, health economists have shown robustly that a screening programme with HPV testing would be more cost-effective than programmes using either VIA or cytology testing.

Primary prevention

Education, empowerment and awareness, access to reproductive health interventions and family planning practices, and general socioeconomic improvement constitute the so-called social vaccination that is probably responsible for the decline in cervical cancer incidence, albeit slow, in many LMICs that do not have screening or those without substantial population coverage. Primary prevention can be substantially augmented by implementing HPV vaccination as part of national immunisation programmes in LMICs (table). Whereas implementation of even low-intensity screening based on few lifetime tests and low-level technology can be challenging, HPV vaccination might be easier to implement because of the availability of national immunisation programmes. Compared with screening, HPV vaccination is likely to provide long-term protection, requires few visits (two doses 6 or 12 months apart for girls younger than 14 years or three doses within 12 months for girls older than 14 years), can generate herd immunity (non-vaccinated people are partly protected by interrupting HPV transmission in the population), and protects against persistent HPV16 and HPV18 infections and cervical pre-cancerous lesions.[38–42]

Several model-based analyses have been done to assess the health and economic effects of HPV vaccination in LMICs. One indicated that 690 000 incident cervical cancers and 420 000 cervical cancer deaths would be prevented during the lifetime of a cohort of 58 million girls who received HPV vaccination at age 12 years in 179 countries, most of which would be LMICs. The cost of such vaccination was estimated to be $4 billion.[43] Goldie and colleagues[44] also concluded that HPV vaccination is likely to be very cost-effective in the poorest countries of the world. Additional analyses that have assessed HPV vaccination with screening in LMICs have shown that vaccination of preadolescent girls followed by HPV testing up to three times per lifetime in adulthood could be cost-effective, highlighting the synergies of primary and secondary prevention even in settings that are highly resource constrained.

Breast cancer

Early detection and treatment in LMICs

Breast cancer is the most frequent cancer among women worldwide and is the leading cause of cancer death in LMICs, except in sub-Saharan Africa where more women die from cervical cancer. The prognosis for women in LMICs is often poor because they frequently present with advanced disease and have no or limited access to early diagnosis, treatment, or both.[49,50] The combination of early detection and prompt, adequate treatment is the most effective strategy for breast cancer control, since primary prevention is neither available nor feasible (eg, chemoprevention with tamoxifen or other oestrogen-receptor modulators) in the public health context.

Although the incidence of breast cancer has stabilised or even decreased in some HICs, in most Asian and other LMICs it continues to escalate. In Colombia, an upper-middle-income country, a cluster-randomised pragmatic trial of opportunistic mammographic screening in Bogota showed downstaging of disease and improvement in the proportion of patients who had early-stage cancers at diagnosis. In turn, breast-conservation therapy rather than mastectomy was increasingly successful for definitive locoregional control.[65] Thus, although opportunistic screening might be a helpful adjunct for establishing early detection strategies, particularly in countries with improving

health-care systems and infrastructures, broad-coverage, population-based, early detection programmes are generally agreed to be necessary if the goal is to have favourable effects on breast cancer mortality at the national level.

Screening

Mammography

Mammography screening in asymptomatic women is the only population-based method that has been associated with reductions in breast cancer mortality in HICs. It was introduced on the basis of results from multiple randomised controlled trials, and has been the subject of many reviews and meta-analyses, including by an International Agency for Research on Cancer (IARC) expert panel.[52] Although the IARC working group concluded that there is sufficient evidence to show a reduction in breast cancer mortality among screened women aged 50–74 years, the interpretation of the evidence on the relative benefits and harms of mammography screening differs widely between experts, particularly in the context of improvements in breast cancer treatment.

The extent of overdiagnosis, which age groups to target for screening, and logistics of implementing and maintaining quality-assured breast cancer screening programmes remain uncertain. The relevance of randomised controlled trials done more than two decades ago might be less than that of later trials, given the advances in mammography techniques and treatment. Evidence from cohort studies based on health service mammography screening programmes in HICs indicates a 23% reduction in breast cancer mortality overall in women aged 50–69 years invited to screening, and a 40% reduction in those who attend.[52] A reduction in risk for women aged 40–49 years, however, is less evident.[52] The rate of false-positive results is higher in this age group than in the older age group, probably because of greater breast density, which is an important factor in LMICs, where the average age at diagnosis of breast cancer is 45 years. Another small risk with mammography is radiation-induced cancer.[52]

Despite extensive reanalyses of the available evidence on the benefits and harms of mammographic screening, lively debate continues about its use, especially in HICs. A report by the Independent UK Panel on Breast Cancer Screening,[53] issued in 2012, showed that for every 10 000 UK women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented, and recommended continuation of the breast screening programme in the UK. In a focused rebuttal, Baum[66] refuted the conclusions of this analysis and estimated that an additional one to three deaths would occur per breast cancer death avoided. Mammography screening requires substantial investments in equipment, histopathology, and treatment services, committed radiologists and technicians, and a large organisation because screening is needed every 1–2 years. Such programmes, therefore, are simply out of reach for most LMICs (table) and are unlikely to be feasible or cost-effective in those with weak health systems.

WHO suggests considering an organised, population-based mammography screening programme for women aged 50–69 years only if the conditions for implementation can be met by the health-care system.[54] Large-scale opportunistic mammography screening in some Latin American countries (eg, Argentina, Brazil, Chile, Colombia, Peru, and Uruguay) and east Asian countries (eg, Malaysia and Thailand) have so far had very little effect on breast cancer mortality.[51,61,62] Possibly, however, it is too early to expect any appreciable change in mortality, as data from HICs showed delays between implementation and decreases in population-based mortality. For instance, in the USA the availability of screening began to increase in the early 1980s as a result of the Health Insurance Plan trials,[67] but mortality did not start to drop until 1991.[68]

Clinical breast examination and breast self-examination

Clinical breast examination as a method of screening asymptomatic women by health workers, nurses, and primary care doctors is being assessed for breast cancer control in LMICs. In randomised controlled trials of clinical breast examination versus no screening, cancers detected at baseline and in the early years of the trials were generally of smaller size and earlier stages in the group allocated to clinical examination than in the control group.[60,61]

Screening by clinical breast examination seems to be a promising approach (table), with sufficient evidence that it lowers stage distribution at detection,[52,60,61] but evidence from studies of routine population-based screening on whether breast cancer mortality is reduced and programmes are cost-effective is awaited. In general, the extent of treatment required decreases with earlier stages of breast cancer at diagnosis, but whether the downstaging associated with clinical breast cancer screening is associated with reduced need for treatment resources in LMICs has not yet been assessed. Additionally, detection of a lump by this method is insufficient for diagnosis, meaning that clinical breast examination is, ultimately, part of a package of care. Further diagnostic tests will include mammography or ultrasonography imaging and needle sampling (fine-needle aspiration cytology or core-needle biopsy).

By contrast with clinical breast examination, results from two randomised controlled trials have shown no reductions in mortality after systematic teaching or practising of breast self-examination.[62,69] Whether it would be feasible to ensure that a large proportion of women in the population would frequently and systematically practise breast self-examination has also been questioned. Most evidence for the efficacy of breast self-examination comes from two randomised controlled

trials, one from Saint Petersburg, Russia,[69] and the other from Shanghai, China.[62] In these two trials, women were randomised to receive instruction on performing and periodic reminders to do breast self-examination or to receive no education or formal breast cancer screening. Breast cancer mortality was unchanged by breast self-examination in both studies. These negative findings might, however, not be relevant in other LMICs, where women commonly first present with large (>4 cm) cancers.[70] Of note, although breast cancer downstaging might be a necessary prerequisite to improving breast cancer outcomes and quality of life, alone it would be unlikely to reduce mortality since the benefits of early detection can only be realised if it is followed by prompt diagnosis and effective multimodal treatment.[71]

In a study in rural Jakarta, Indonesia, done in 2007–08, the efficacy of screening mammography plus clinical breast examination by trained midwives was assessed.[72] 1179 previously unscreened women (mean age 46·4 years, 67% premenopausal) received clinical breast examination and mammography. The two methods showed similar efficacy in detecting prevalent breast cancers. Of the 14 breast cancers diagnosed in the study, all had abnormal findings on mammography and 13 on clinical breast examination. Unfortunately, only six (42·8%) of women returned for treatment after receiving a diagnosis of cancer, which obviated the purpose of screening; failure to treat screen-detected disease is an exercise in futility. Furthermore, whether the breast mass was detected by clinical breast examination or mammography, the full diagnostic assessment did not differ and, therefore, there was no cost saving.

Breast ultrasonography

Breast ultrasonography has an important role in breast cancer diagnosis. This method is seen as a standard tool for assessment of palpable masses or thickenings found on clinical breast examination or to provide diagnostic information about focal densities or asymmetries seen on screening mammography.[73–75] However, the role of ultrasonography in breast screening, where the entire breast is examined for abnormalities, is less clear. The ACRIN 6666 study,[76] which included women at heightened risk of breast cancer, showed that screening mammography and ultrasonography identified similar numbers of cancers, although ultrasonography led to significantly more false-positive results than mammography, which calls into question its usefulness in average-risk populations. Similar screening studies in Japan are underway and are showing promising early results.[77]

Breast awareness

Breast awareness is a universally feasible approach to improve early detection of breast cancer, and has the potential to lessen the differences in outcomes between HICs and LMICs (table). Early diagnosis was mainly responsible for the advances in breast cancer control in HICs before the introduction of mammography screening programmes, although it is important not to minimise the positive effect of adjuvant therapy in the management of breast cancer.[63] To increase the likelihood of early diagnosis, public information or education campaigns are needed to improve breast awareness and shorten patients' delays in seeking medical attention after discovering a breast symptom or sign. In-service orientation is also needed to improve the awareness and skills of health-care professionals in recognising signs and symptoms of breast cancer, providing diagnostic clinical breast examination, and referring patients.

Eliciting thorough histories from patients is important in the clinical assessment of breast symptoms and signs and other associated illnesses that could have a bearing on treatment decisions. Availability of health-care providers in primary health services who are proficient in clinical breast examination is fundamental for the assessment of women with breast symptoms. Fine-needle aspiration cytology rather than surgical excision is the preferred option for initial assessment of suspected breast lumps and lesions, as core-needle biopsy is generally unaffordable in LMICs. Histopathology of tissue samples provides the definitive diagnosis of breast cancer. Diagnostic mammography, ultrasonography, or both if available, substantially contribute to the diagnostic assessment of breast lumps and facilitate image-guided fine-needle aspiration.

Among the predictive biomarkers, testing for oestrogen receptors is helpful to guide whether hormonal treatments will be useful in disease management. Tamoxifen is low cost and widely accessible in most settings.

Unfortunately, diagnostic imaging, fine-needle aspiration cytology, quality-assured histopathology, and immunohistochemistry services are not widely developed and accessible in many low-income countries, particularly those in sub-Saharan Africa. Improving access to better-than-basic diagnostic services (ie, clinical breast examination, diagnostic imaging, and tissue diagnosis, collectively called triple assessment) in health systems in LMICs is crucial to investigation and early diagnosis of breast cancer in symptomatic women.

Treatment

Breast cancer outcomes in all settings correlate with the proportion of cancers detected at an early stage, especially with access to timely, affordable, high-quality care, including multimodal treatment if needed.[78–80] Management requires accurate staging and tumour-marker assessment to guide treatment decisions, including those for surgery, radiotherapy, and systemic chemotherapy, hormone therapy, or both. Trastuzumab is a humanised monoclonal antibody that interferes with the HER2 (also known as ERBB2)/neu receptor and has been efficacious in the treatment of HER2/neu-positive cancers. This drug has now been added to the WHO essential medicines list, increasing the importance of

including targeted therapies in the treatment packages offered to patients.[81] Despite the good efficacy of new treatments, affordability remains an important barrier to the use of some. In addition, the absence of radiation therapy in many LMICs could significantly disadvantage women, particularly those who present with late-stage disease.

Future challenges

Going forward, important elements to the provision of prevention, early detection, or both, of breast and cervical cancers include understanding the social determinants of health, human rights, community involvement and mobilisation, empowerment of women and the health systems that serve them, political will, and awareness. Cancer health services in many LMICs are understaffed, poorly equipped, and inadequate, and are still evolving. The infrastructure and human resources of national immunisation programmes have been developed further than for most other health services in many LMICs. These provide suitable platforms for integrating HPV vaccination to prevent cervical cancer without affecting other vaccination campaigns or health services, as has been shown in various LMICs.[82] By contrast, high-intensity cancer screening for breast and cervical cancer with frequent use of complex tests, such as mammography or HPV testing, and targeting a wide age range of women is impossible to integrate into health systems in LMICs unless additional resources are provided.

The pathology, imaging, laboratory services, cancer surgery, radiotherapy, radiation physics, chemotherapy, and hormone therapy needed to optimise management of breast and invasive cervical cancer require adequately trained doctors, nurses, and other support staff. Initially high vertical investments to develop facilities and resources in secondary and tertiary care will eventually provide services for a long time. Most LMICs spend less than 4% of gross domestic product on health care, and in many the share has remained constant or declined over time. In HICs, health-care expenditure is much higher, and reaches an average of 12·3% of the gross domestic product.[83] Substantial financial investment by increasing the proportion of gross domestic product spent on cancer care is essential to make cancer treatments available and accessible in LMICs.

Additional interventions that might present opportunities to improve programmes of care for breast and cervical cancers are telemedicine programmes, such as the WHO mHealth initiative that capitalises on the use of smartphones (panel 1), but further assessment is needed. The urgent priority of achieving universal health coverage including control of women's cancers and the policy landscape in which global cancer control is now situated owing to the adoption of the Sustainable Development Goals, is explored further in the third paper of this Series.[87]

Panel 1: WHO mHealth initiative and cervical cancer

In 2012, WHO launched a mobile health initiative (mHealth) to combat non-communicable diseases (eg, hypertension, diabetes, cardiovascular disease, and some cancers). It uses mobile phone applications and text messaging to improve disease prevention, detection, management, and control.[84] mHealth could improve control of cervical cancer control in low-income countries, where smartphones have high uptake and reasonably low costs.

Many cervical cancer screening programmes based on visual inspection with acetic acid struggle with quality assurance because the duration of face-to-face training of providers is short, retention of providers is poor, and retraining is expensive. To improve performance and retention of trained personnel, newly trained providers actively screening in clinics can obtain cervical images with smartphone cameras and transfer them to expert mentors, even in other districts or regions, who can quickly provide feedback in a text-message-based closed-user-group platform. A programme in northern Tanzania has shown that such a programme is feasible and is effective in providing mentorship and rapidly increasing the skills of cervical cancer screening providers.[85]

Follow-up of patients and treatment can be improved in other ways with mHealth approaches in low-income and middle-income countries. For instance, in a study in Bangladesh, Ginsburg and colleagues[86] showed that community health workers guided by a smartphone application were more efficient and effective in promoting breast health and encouraging women with abnormal breast examination findings to adhere to advice regarding clinic attendance than community health workers who did not use the application.

Panel 2: Recommendations

- Governments need to recognise the importance of cancer control to their health and development agendas, and to allocate adequate resources to improve equitable access to high-quality cancer services; rapid improvements in breast and cervical cancer control would be a good starting point.
- The public and health-care professionals need to be better educated about breast and cervical cancer, opportunities for prevention and early detection, and warning signs, which will help to destigmatise these diseases and cancer overall.
- Some elements of breast and cervical cancer control, such as advocacy, prevention, early detection, pain and symptom management, and effective therapies (eg, ablative treatments for preinvasive cervical lesions), should be integrated and managed through existing health-care platforms, by leveraging existing resources where possible.
- Training of community health workers (eg, in clinical breast examination) and nurses in cervical screening by visual inspection with acetic acid are low-cost, feasible interventions that may be readily incorporated into reproductive health, HIV prevention, and AIDS control or primary care programmes, optimise constrained human resources in many settings, and will strengthen the health system overall.
- The myth that cancer is inevitably fatal must be dispelled to empower cancer survivors to help reduce stigma, dispel other myths, break down barriers preventing access to care, and encourage women to seek care early in the disease course.

Conclusions

More than 2 million women worldwide have breast or cervical cancer. Despite evidence that cervical cancer is declining in certain regions of the world and that survival in women with breast cancer has improved, far too many women die from these two very common cancers. Interventions that do not require massive capital

investment are available and need to be explored in low-resource settings, where access to early detection and cancer care is generally limited. There are great disparities in many situations worldwide, but they are particularly evident in health. Access to care is limited for communicable diseases, maternal and neonatal morbidity and mortality, and non-communicable diseases. We hope to enlighten decision makers about possible alternative strategies that could improve the lives of women with breast and cervical cancer, destigmatise these diseases in communities, and ensure that they remain on the health-care agenda (panel 2).

Contributors

LD and RS searched the literature and drafted and amended the paper. All authors were responsible for drafting key messages and approving the final draft of the paper. OG led the Series.

Declaration of interests

LD has participated in various speaker forums on vaccination against human papillomavirus for and received research support from GlaxoSmithKline and Merck. SdS has received travel grants from Merck to attend scientific meetings, and her institution receives unrestricted grants from Merck SD. SdS is involved in a trial on a human papillomavirus therapeutic vaccine sponsored by Genticel. The other authors declare no competing interests.

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