PART 3.

TACKLING SOCIAL INEQUALITIES IN CANCER

CHAPTER 16.

Low-cost approaches to reducing social inequalities in cancer in low- and middle-income countries and disadvantaged populations

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Introduction

Cancer control has received significantly less attention compared with other public health issues from governments in many low- and middle-income countries (LMICs) despite a significant and increasing disease burden. The striking inequalities in cancer burden and outcomes between high-income countries (HICs) and LMICs are exemplified by the fact that, although 60% of the estimated 14 million new cases and 75% of the estimated 8.8 million cancer deaths per year occur in LMICs, only 5% of global spending on cancer is directed at these countries; most LMICs spend less than 2% of their gross domestic product on health (Prager et al., 2018). Given these realities, it is not surprising that substantial inequalities exist between countries in terms of cancer occurrence, care, and outcomes.

The health systems in LMICs and in disadvantaged population must be reoriented to adopt proven and cost-effective low-cost technologies and approaches to reduce and eliminate the inequalities in cancer outcomes. Some of the low-cost technologies and approaches that have the potential to reduce inequalities if implemented correctly are discussed in this chapter.

Eliminating cervical cancer

Cervical cancer is a very rare long-term outcome of persistent infection of the lower genital tract with one of the high-risk human papillomavirus (HPV) types, particularly HPV16 and HPV18 (Bosch et al., 2002; IARC 2007). HPV vaccination and screening for precancerous lesions are two major and highly effective interventions to prevent invasive cervical cancer.

It is possible to eventually eliminate cervical cancer, and to achieve a drastic reduction or elimination in cervical cancer incidence in successive age-specific cohorts, in the foreseeable future if the currently available prevention and early detection interventions are implemented with high coverage and quality assurance.

Of the estimated 528 000 new cervical cancer cases and 266 000 deaths per year, more than 85%

occur, disproportionately, in LMICs. Low-cost technologies and approaches that may be used in LMICs to minimize inequalities in cervical cancer outcomes are listed in Table 16.1.

Vaccination

HPV vaccination is a highly effective primary prevention intervention, which is becoming more affordable for governments to introduce as part of national immunization programmes. The reasons for its increasing affordability include: falling vaccine prices; the scope for negotiated pricing; the possibility of obtaining assistance from donor agencies and Gavi, the Vaccine Alliance, for eligible countries; and the de-escalation from three doses to two doses for the primary target group of girls and boys aged 9–14 years. For girls and boys aged 9–14 years a two-dose schedule is now recommended by the World Health Organization, which has been adapted by several countries (WHO, 2017). For those older than 15 years, three doses are recommended. HPV vaccination at the population level in different national programme settings has consistently been found to be associated with a reduction in the prevalence of vaccine-targeted high-risk HPV types, cross-protection, no HPV type-replacement, and a reduction in the prevalence of anogenital warts, Pap smear abnormalities, and high-grade cervical neoplasia among young vaccinated women; these findings, together with excellent safety indicators, confirm that HPV vaccination can substantially reduce inequalities in cervical cancer risk globally (Drolet et al., 2015; Garland et al., 2016; Saccucci et al., 2018).

Recent results from observational studies indicate that even a single dose of HPV vaccine is immunogenic and has similar effectiveness in preventing vaccine-targeted high-risk HPV as two or three doses of HPV vaccine (Kreimer et al., 2018;

Table 16.1. Strategic low-cost approaches to reducing inequalities in cervical cancer prevention and elimination

Factors contributing to inequalities	Strategic low-cost approaches
Inability to access HPV vaccine because of high costs	Introduce HPV vaccination, targeting girls aged 10–11 years, in national immunization programmes
Misinformation on safety and efficacy of HPV vaccination	Continuous, focused education of the public and stakeholders; prompt documentation and management of adverse events, if any; vaccine delivery supported by efficient cold-chain infrastructure
No access to cervical cytology or HPV screening	Offer VIA screening by nurses or midwives
Loss to follow-up for diagnosis and treatment of precancerous lesions	Use single-visit approach of screening and treating using VIA and cryotherapy and/or thermocoagulation
Erratic cryotherapy service; erratic refrigerant supply chain	Use thermocoagulation for treatment of precancerous lesions
Limited financial resources for screening	Offer screening to women aged 30–39 years
Inability to provide catch-up vaccination to extended age groups (e.g. 13–18 years) and organized screening every 5 years to women aged 30–64 years	Provide HPV vaccination to girls aged 11–12 years and offer a single lifetime screen at age 35–39 years
Lack of radiotherapy services	Offer surgery for early-stage cancer; advocate, lobby, and catalyse national engagement in improving access to surgical care and in establishing radiotherapy infrastructure
Lack of any cancer treatment facilities and/or services	Offer palliative care; advocate, lobby, and catalyse national engagement in establishing and improving access to treatment infrastructure
Insufficient financing of prevention, early detection, and treatment interventions	Advocate, lobby, and obtain national budgetary commitment

HPV, human papillomavirus; VIA, visual inspection with acetic acid

Sankaranarayanan et al., 2018). Further long-term follow-up and evaluation of those receiving a single dose, whether by default in national programmes or in planned studies, in terms of lasting immunity and prevention of persistent infection and of high-grade cervical intraepithelial neoplasia (CIN), is a top research priority to reduce disparities in vaccination coverage and cervical cancer prevention. Another research priority is investigating the value of two doses of HPV vaccine for cervical cancer prevention in those aged 15–18 years. If resources permit additional vaccination of this age group as part of catch-up vaccination, substantial cervical cancer prevention benefits can be obtained. A recent study in India reported similar efficacy of two and three doses in girls aged 15–18 years in generating antibodies and in preventing persistent HPV16 and HPV18 infections (Bhatla et al., 2018). Dosage de-escalation to one dose or two doses for older girls will lead to substantial cost savings, improved vaccine coverage, and significant logistical advantages in vaccine delivery, thereby ultimately reducing inequalities in primary prevention initiatives for cervical cancer. Although sex-neutral vaccination of boys and the use of polyvalent vaccine for both boys and girls are attractive options, these are not recommended in many countries because they are not cost-effective in LMICs.

Screening

Even with the advent of HPV vaccination, screening will be an important complementary intervention for cervical cancer prevention for several years to come. The primary objective of cervical cancer screening is to detect high-grade (grades 2 and 3) CIN, the precursor lesion of the common squamous cell carcinoma, and adenocarcinoma in situ, the precursor of adenocarcinoma, sufficiently early that they can be treated to prevent the development of cancer. Effective cervical screening tests include conventional cytology (Pap smear), liquid-based cytology, HPV testing, and visual inspection with acetic acid (VIA). Because the risk of HPV16 and HPV18 infections is substantially reduced in vaccinated populations, the approach to cervical cancer screening will be re-evaluated so that the harms and costs associated with screening can be reduced and an optimal screening approach can be developed that is integrated with HPV vaccination.

Although the Pap smear is still the main method of screening and is associated with substantial declines in cervical cancer risk in HICs, it is a challenging and resource-intensive technology and is not feasible in LMICs, where cervical cancer risk is high (Vaccarella, 2016). Cytology-based screening programmes in some middle-income countries have been associated with suboptimal outcomes in reducing the cervical cancer burden because of poor organization, poor coverage, a lack of quality assurance, and inadequate health systems. Cost–effectiveness studies have indicated that cytology-based screening is the least cost-effective screening method (Mezei et al., 2017). Any LMICs without current screening programmes planning to invest in cervical cancer screening should consider screening with HPV testing at prolonged intervals (e.g. 7 or 10 years) rather than cytology-based screening, because HPV testing is a more objective and accurate test than cytology-based screening and has a high negative predictive value. HPV screening, particularly self-collected HPV testing, linked with treatment has enormous potential to reduce inequalities and is highly cost-effective (Mezei et al., 2017). The average costs of the different screening approaches were calculated (in 2005 dollars) as US$ 13.3 for provider-collected HPV testing, US$ 7.5 for self-collected HPV testing, US$ 6.6 for cytology-based screening, and US$ 2.1 for VIA (Mezei et al., 2017). In the context of declining rates of HPV infection after the introduction of HPV vaccines, HPV testing will be the screening test of choice in the future.

VIA involves detection of acetowhite lesions on the cervix 1 minute after the application of freshly prepared 3–5% acetic acid. Its feasibility of being rapidly introduced in public health services with the least infrastructure means that VIA has been widely implemented in opportunistic settings in many low-income countries in sub-Saharan Africa and in Bangladesh. A single-visit approach (SVA) for screening with rapid diagnosis and treatment improves coverage for all elements of screening, eliminates the need for follow-up visits, and makes screening more time- and cost-efficient in low-resource settings (Parham et al., 2015; Msyamboza et al., 2016; Shiferaw et al., 2016).

Both VIA and HPV testing have been associated with a reduction in high-grade CIN and a reduced incidence of and mortality from cervical cancer in randomized trials, and this evidence provides a solid basis for the introduction of HPV- and VIA-based screening programmes (Denny et al., 2005; Sankaranarayanan et al., 2007, 2009; Ronco et al., 2010; Shastri et al., 2014). However, the infrastructure requirements and

affordability of HPV testing and the subjective nature of VIA testing are major limitations of these screening methods.

VIA screening is particularly suitable for SVA, and WHO has issued guidelines for implementing SVA in public health settings (WHO, 2013). Whether provider-collected HPV testing or VIA is a more efficient alternative depends on the cost of the HPV test, loss to follow-up, and VIA test performance. Self-collected HPV testing is cost-effective when it yields population coverage gains over other screening methods. Major research priorities are how to triage HPV-positive women (both vaccinated and unvaccinated women) and the potential role of VIA in the triage of HPV-positive women in LMICs.

In summary, VIA screening is feasible, simple, safe, accurate, acceptable, and easily accessible to the women at highest risk. Its introduction in health services helps to establish a screening culture and infrastructure that can be used to implement more accurate HPV testing in the future, when affordable, simple, and point-of-care HPV tests become available. In the short term, although it is less optimal relative to HPV testing, VIA screening has the most potential to reduce screening-related disparities. Although it is unlikely that a single screening modality will be appropriate worldwide, with the current knowledge it is possible to adapt a cost-effective means of cervical cancer screening to each country to reduce disparities. A judicious combination of HPV vaccination and screening with HPV testing or VIA has enormous potential to eliminate cervical cancer and substantially reduce inequalities, a potential that remains largely unexploited in many high-risk countries (Sankaranarayanan et al., 2015; Denny et al., 2017).

Reducing breast cancer disparities

Despite extraordinary progress in basic, translational, and clinical research that has yielded better biological categorization of disease and more effective new treatments, significant disparities exist in breast cancer awareness, early detection, uptake of screening where it is available, diagnosis and treatment, and survival outcomes between HICs and LMICs, between urban and rural populations, and between different ethnicities within countries (Iqbal et al., 2015; Pace et al., 2015; Jedy-Agba et al., 2016; Pace and Shulman, 2016). In recent years there has been substantial progress in early detection and treatment; more than 90% of patients with early-stage breast cancer are cured, provided they are adequately treated. However, this progress has not percolated uniformly between different countries and different populations in the same country, as exemplified by the fact that only 12% of breast cancer patients diagnosed in The Gambia survive beyond 5 years (Sankaranarayanan et al., 2010). Patients with low socioeconomic status (SES) and in LMICs are more likely to be diagnosed with breast cancer at late clinical stages, to experience delays in treatment, and to die from the disease.

A lack of breast cancer awareness, poor availability of and access to public health services, and low participation in mammography screening programmes, where they exist, all lead to delays in diagnosis and treatment, which are responsible for the late-stage diagnoses and poor outcomes in groups with low SES in HICs and in populations of LMICs in general.

Improving breast cancer awareness among women, increasing the skills of primary care physicians to promptly refer women with suspected breast cancer, and increasing access to timely early-stage diagnosis and to comprehensive, good-quality health-care coverage and treatment are important to minimize inequalities in breast cancer outcomes. The approaches that can be used to address inequalities in breast cancer control are outlined in Table 16.2. Whereas measures to improve the participation of women in screening programmes, where they exist, are vital for early detection in HICs, systematic mammography screening or ultrasound screening (USS) of asymptomatic women is not feasible in LMICs because of the inadequacy or even paucity of infrastructure, trained human resources, and health-care funding.

USS with a breast probe is used mostly as a supplementary screening tool to mammography to assess lesions not visible by mammography, such as in dense breasts with a lot of connective and glandular tissue. USS is relatively more affordable, is well tolerated, and does not require intravenous contrast or ionizing radiation. However, a highly experienced provider is required, and USS has less specificity than mammography. USS may be valuable as a potential screening tool for those with dense breasts (Geisel et al., 2018), but it is not widely available in LMICs.

There is sufficient evidence from randomized trials that breast cancer can be diagnosed in its early stages after a clinical breast examination (CBE) (Mittra et al., 2010; Sankaranarayanan et al., 2011; Lauby-Secretan et al., 2015). However, even a CBE-based screening programme will require resources to investigate

Table 16.2. Strategic low-cost approaches to reducing inequalities in breast cancer control

Factors contributing to inequalities	Strategic low-cost approaches
Patients with breast cancer present at advanced clinical stages	Improve breast cancer awareness; increase participation in screening, where such programmes are available; improve access to early diagnosis using CBE, basic imaging, and FNAC for symptomatic women (triple testing)
Mammography screening is not feasible	Improve breast cancer awareness among women; promote opportunistic CBE among asymptomatic women; use triple testing to triage women found to have abnormalities on CBE
Diagnostic mammography is not feasible because of lack of equipment and human resources	Provide ultrasound imaging
Any form of imaging is not feasible	Provide CBE and FNAC; advocate and ensure national commitment to improve infrastructure and human resources
Core biopsy is unaffordable	Offer FNAC
Testing for all three receptors (estrogen receptor, progesterone receptor, and HER2/Neu) is not feasible	At the least, test for estrogen receptor; advocate and ensure national commitment to introduce immunohistochemistry to test for estrogen receptor and progesterone receptor
Radiotherapy services are lacking, and anti-cancer drugs are not available	Offer modified radical mastectomy for early-stage and locally advanced-stage cancer; advocate and ensure national commitment to improve infrastructure and human resources; catalyse national engagement in improving access to anti-cancer drugs and in establishing radiotherapy infrastructure
Branded drugs are not available	Use generic drugs
Providing antiestrogen and/or estrogen receptor modulators is not feasible	Offer bilateral prophylactic salpingo-oophorectomy by surgery or radiotherapy
Cancer treatment facilities and/or services are lacking	Offer palliative care; advocate, lobby, and catalyse national engagement in establishing and improving access to early diagnosis and treatment infrastructure
Patients do not accept treatment or abandon treatment before its completion	Improve awareness of the importance of completing treatment to be cured; improve treatment access and affordability by appropriate health-care financing mechanisms
Financing of prevention, early detection, and treatment interventions is insufficient	Advocate, lobby, and obtain national budgetary commitment

CBE, clinical breast examination; FNAC, fine-needle aspiration cytology; HER2, human epidermal growth factor receptor 2

and treat screen-positive women and follow them up. Although CBE is widely used in the early detection of breast cancer, there are no formal health service programmes that are based on CBE alone; it is therefore difficult to quantify the proportional contribution of CBE in the early detection of breast cancer. Compared with screening, early diagnosis of breast cancer linked with adequate treatment of symptomatic women therefore seems to be a more feasible approach to reducing disparities in breast cancer outcomes.

Late-stage presentation of breast cancer is attributed largely to modifiable factors; strategies to improve breast cancer awareness in women and in the health system could be highly conducive to reducing inequalities (McKenzie et al., 2018). Improving awareness of breast cancer and access to triple diagnosis – expert CBE, diagnostic imaging by USS or mammography or both, and tissue diagnosis in the form of fine-needle aspiration cytology (FNAC) or excision biopsy – have been associated with early diagnosis of breast cancer (Gadgil et al., 2017). The combination of mobile health (m-Health, the use of mobile devices in public health practice) to improve awareness and the use of CBE, USS, and FNAC to examine women suspected to have

breast cancer provides an attractive package of low-cost diagnostic interventions for LMICs. It is likely that most of the gains observed in breast cancer survival before the introduction of widespread mammography screening and adjuvant chemotherapy and hormone therapy in developed countries were due to (i) improved awareness of breast cancer symptoms and signs and (ii) the value of locoregional treatment in improving survival outcomes of women with clinically detected early-stage breast cancer (Sankaranarayanan et al., 2010).

To benefit from early-detection initiatives to reduce inequalities in breast cancer outcomes, it is critical that diagnosis of early-stage breast cancer is followed by adequate treatment (Denny et al., 2017). The third edition of the Disease Control Priorities project, a global initiative funded by the Bill & Melinda Gates Foundation, has identified treatment of early-stage breast cancer as part of essential cancer interventions for LMICs that could be "effective, cost-effective, affordable, and feasible", along with tobacco control, HPV and hepatitis B virus vaccinations, cervical cancer screening, and treatment of certain childhood cancers, in reducing inequalities in cancer outcomes in LMICs (Gelband et al., 2016). Guidelines to develop affordable and effective breast cancer treatment programmes tailored to existing resources in LMICs have been proposed by the Breast Health Global Initiative (Anderson et al., 2011). These guidelines may be adapted by LMICs to improve survival outcomes from breast cancer. It is the responsibility of the governments in such countries to strengthen health systems to improve awareness, early diagnosis, and adequate treatment to eliminate current disparities in breast cancer outcomes.

Reducing oral cancer inequalities and improving outcomes

In LMICs where the risk of oral cancer is high, such as Bangladesh, India, Nepal, Pakistan, and Sri Lanka, most patients with oral cancer present at advanced clinical stages. When the disease has spread to the regional lymph nodes and surrounding tissues, 5-year survival rates are less than 30%, even with the most aggressive treatments. Advanced oral cancers contribute to the poor overall cancer outcomes in LMICs compared with HICs. Whereas tobacco and alcohol control measures are of paramount importance in preventing oral cancer, early detection at stage I or II and adequate single-modality treatment, such as surgery or radiotherapy, improves prognosis considerably, with 5-year survival rates exceeding 90%. It has been well documented in a randomized trial that oral visual screening was associated with a significant reduction in oral cancer incidence and mortality among people who use tobacco and/or consume alcohol (Sankaranarayanan et al., 2005, 2013). An atlas for the early detection of oral cancer published by IARC is a useful manual for primary care practitioners to perform oral visual screening and correctly diagnose precancerous lesions and early-stage asymptomatic invasive cancer, enabling the prompt referral of the patient (Ramadas et al., 2008). Because oral cancers are preceded by oral precancerous lesions, such as leukoplakia, erythroplakia, and oral submucous fibrosis, interventions to change habits in such individuals have the potential to prevent oral cancer.

Reducing colorectal cancer inequalities and improving outcomes

Colorectal cancer incidence rates are increasing in most LMICs where long-term incidence data are available. Screening with faecal occult blood tests, most commonly with faecal immunochemical tests, and triaging screen-positive people with colonoscopy are the most widely used prevention and control approaches. Screening for early-stage colorectal cancer and its precursors is highly effective in reducing mortality rates. Although many HICs have initiated population-based screening programmes with faecal occult blood tests and colonoscopy triage, participation in such programmes is low and is highly variable between groups with different levels of education or SES; these differences in screening participation contribute to inequalities in outcomes (Honein-AbouHaidar et al., 2013; Decker and Singh, 2014; Kim and Hwang 2016; Basu et al., 2018). Colorectal cancer screening programmes are still evolving; interventions to raise awareness and increase participation among population subgroups with low participation are needed to reduce disparities in uptake rates. Recently, Thailand introduced faecal immunochemical test screening for colorectal cancer through primary care clinics in public health services in Lampang Province, demonstrating the feasibility of introducing such organized programmes in middle-income countries. The pilot project was associated with increased diagnosis of early-stage colorectal cancer and its precursors (Khuhaprema et al., 2014). As a result of this experience, colorectal cancer screening is being scaled up in phases in Thailand.

Other low-cost approaches to reduce cancer disparities

Strengthening cold-chain infrastructure and delivery systems in national immunization programmes can substantially improve the coverage and efficiency of cancer-preventive vaccination programmes, such as hepatitis B virus and HPV vaccination. Telepathology networks have the potential to substantially improve diagnostic accuracy, patient care, and professional education. Given the substantial penetration rates of mobile phones in LMICs, using m-Health applications can: enhance awareness for the public, patient, and provider; provide health education and promote healthy behaviours; improve early diagnosis; enable better monitoring and evaluation of healthcare interventions; and improve adherence to treatment and follow-up care (Eskandar et al., 2015). Health system reforms to improve breast cancer awareness and introduce cervical cancer screening, CBE, oral visual screening, and faecal immunochemical tests, and the shifting of follow-up of treated cancer patients to the primary health care level, have immense potential to reduce disparities. Many LMICs, particularly in sub-Saharan Africa and Central America, will benefit substantially by systematically investing in basic cancer diagnostic tools (e.g. histopathology, FNAC, and basic immunohistochemistry such as estrogen receptor, basic imaging, and tumour markers), treatment infrastructure (e.g. investing in radiotherapy and clinical oncology services, augmenting surgical capacity, and improving the supply chain for essential drugs), and monitoring and evaluation systems (e.g. medical records and population-based cancer registries) in a timely manner. LMICs have the worst cancer outcomes, and such investments can substantially reduce disparities in cancer outcomes.

Conclusions

The disparities in access to cancer care and outcomes between HICs and LMICs, and between population subgroups within countries, are staggering. The reasons for these disparities include fragmented and poorly financed and organized health-care systems, a lack of suitable healthcare financing mechanisms, inadequate infrastructure and trained human resources, the poor affordability and accessibility of care for many patients, and a lack of awareness among both the public and medical communities. Addressing these multiple deficiencies at the same time is impossible; however, tackling disparities resulting from major cancer types with low-cost, low-technology methods offers the most pragmatic approach in addressing the inequalities in cancer outcomes in LMICs.

Key points

- A pragmatic approach to reducing social inequalities in cancer is to focus on addressing inequalities in the outcomes of major cancer types.
- A judicious combination of human papillomavirus (HPV) vaccination and screening with HPV testing or visual inspection with acetic acid has enormous potential to eliminate cervical cancer and substantially reduce inequalities.
- Improving breast cancer awareness and access to triple diagnosis, consisting of expert clinical breast examination, diagnostic imaging, and tissue sampling, and improving access to treatment have enormous potential to reduce inequalities in breast cancer outcomes.
- Introducing oral visual screening in public health settings in high-risk countries can improve oral cancer outcomes.
- Systematically introducing faecal immunochemical testing and improving access to colonoscopy triage have large potential to reduce disparities in colorectal cancer outcomes.
- Systematically investing in mobile health, primary health care, and basic cancer care infrastructure has substantial potential to reduce disparities in cancer outcomes.

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