

# A review of the global inequalities in the management of gynaecological cancers

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## ABSTRACT

### KEY CONTENT

- The burden of gynaecological cancers is growing rapidly globally. Low-resource countries are disproportionately affected with high rates of premature deaths from gynaecological cancers. This represents an epidemiological shift in these regions, which have historically been burdened with communicable diseases.
- Despite cervical cancer being a largely preventable disease, over 300,000 women die annually from the disease. Most of these deaths occur in low-resource countries making this a disease of inequity. Initiatives such as the WHO cervical cancer elimination strategy demonstrates awareness of the problem, but considerable obstacles hinder attainment of their goals.
- Closing the gynaecological cancer care gap between high-resource and low-resource countries requires a multifaceted approach. Work must be done to increase public awareness of gynaecological cancers and dispel stigma and myths. Investment into healthcare infrastructure, workforce and research in low-resource settings is

needed, and strategies to reduce the negative impacts of poverty such as universal health coverage deserve consideration.

### Learning objectives

- To understand the global impact of gynaecological cancers.
- To understand the barriers to closing the gynaecological cancer gap between high-resource and low-resource countries.
- To understand how collaboration, research and implementation can be used to improve gynaecological cancer outcomes globally.

### Ethical issues

- Significant geographical disparities exist in gynaecological cancer outcomes, with the majority of deaths occurring in low-resource countries.
- Addressing this disparity requires a multifaceted approach that thoughtfully examines all contributing factors and offers practical, actionable solutions.

**Keywords:** cancer disparities / cervical cancer / global women's cancer / global women's health / gynaecological cancer / gynaecological surgery

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## Introduction

Gynaecological cancers are a leading cause of premature morbidity and mortality worldwide. Huge geographical variations exist in the incidence and mortality from gynaecological cancers. In high-income countries (HICs) such as the United Kingdom, effective cancer control strategies have led to survival improvements from gynaecological cancers, whereas in low-income and lower middle-income countries (LLMICs), these strategies have not been as effective due to underinvestment, sociocultural barriers and resource constraints. Thus, a cancer equity gap

has formed between HICs and LLMICs, and the rising global incidence of gynaecological cancers due to increased life expectancy and risk factor exposure is causing this gap to rapidly widen.

The global health focus in LLMICs has historically been on communicable diseases such as malaria, human immunodeficiency virus (HIV) and tuberculosis.<sup>1</sup> As a result, these diseases have attracted significant attention and investment globally, resulting in improvements in control. In global women's health, the focus has additionally been on reproductive and maternal health.<sup>2</sup> There has been a recent epidemiological shift in disease burden in LLMICs from

infectious diseases to chronic, non-communicable diseases including cancers. Cancer is rapidly becoming a leading cause of death in many LLMICs, and women are particularly affected. Premature mortality from non-communicable diseases refers to death between ages 30 and 70 and negatively impacts economies due to loss of productivity.<sup>3</sup> Seventy-two per cent of the cancer deaths in women in LLMICs are premature, compared to 36% in HICs.<sup>2</sup> Globally, 2.3 million women die prematurely from cancer each year and it is estimated that 1.5 million of these deaths could be averted.<sup>2</sup> Each premature cancer death in women in LLMICs has far-reaching consequences for orphaned children left behind, for families and more broadly, for societies.<sup>1</sup>

Recent data show that LLMICs have the highest combined age-standardised mortality from genital tract cancers—cervical, ovarian, uterine, vulval and vaginal cancers<sup>4</sup> (Figure 1). However, cervical cancer is the leading gynaecological cancer in LLMICs, second in incidence and mortality to breast cancer. Nearly 350 000 women died from cervical cancer in 2022, of which 90% of these deaths occurred in LLMICs, particularly in sub-Saharan Africa.<sup>4</sup> With the recognition that cervical cancer is largely a preventable disease, the World Health Organization (WHO) in 2020 launched a global strategy to eliminate cervical cancer as a public health problem.<sup>5</sup> For a country to be considered as having eliminated cervical cancer, the strategy defines an annual incidence of below 4 per 100 000 women. In many sub-Saharan African countries, the incidence of cervical cancer is approximately 40 per 100 000 women.<sup>6</sup> A concerted, international effort is required to reduce the incidence of cervical cancer in these regions and prevent the huge number of resultant premature deaths.

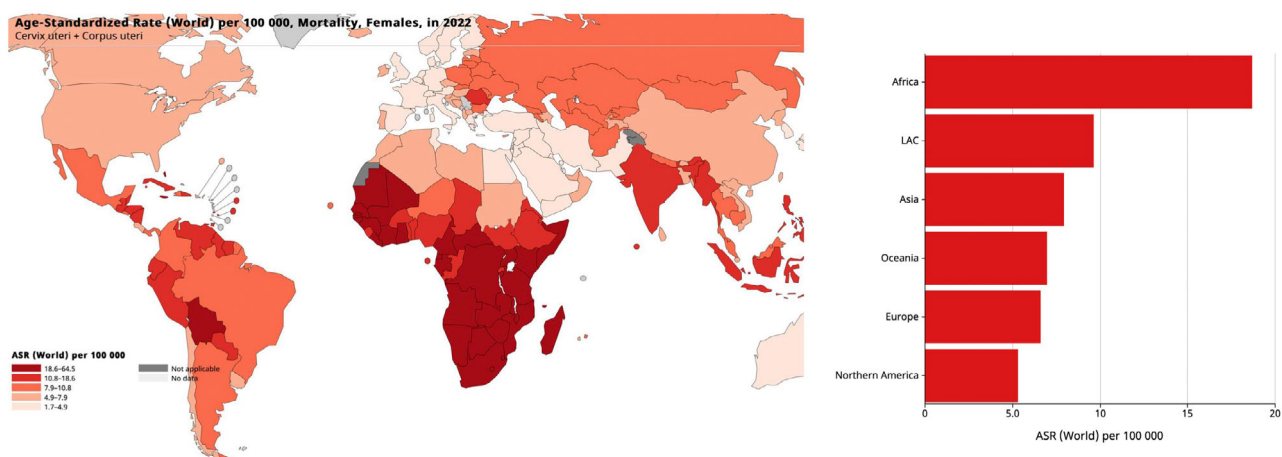
Disparities in gynaecological cancers span the entire cancer care continuum, including cancer screening, diagnosis,

treatment and survival. Thus, frequent calls have been made to 'close the cancer gap'. To achieve this, it is important to recognise the barriers to closing the cancer gap, particularly in gynaecological cancers which have been neglected for some time.<sup>7</sup> As we find ourselves in an era of rapidly rising cancer mortality in women, it is imperative to understand the challenges faced in the control of gynaecological cancers globally in a bid to stimulate engagement from the international community to drive solutions and progress in the field.

The Global Cancer Framework developed by the WHO set out a strategy to reduce the global burden of cancer.<sup>8</sup> The framework promotes the implementation of effective national cancer control plans which consider cancer prevention, early detection, diagnosis and treatment, palliative care, health system strengthening, surveillance and research.<sup>8</sup> This global cancer framework aligns with the United Nations Development Programme (UNDP) sustainable development goal of reducing premature mortality from non-communicable diseases, including cancer, by one-third by 2030.<sup>9</sup> In this article, we will review the global challenges faced in implementing these strategies in controlling gynaecological cancers.

## Infectious agents

Despite the decreasing burden of communicable diseases in LLMICs, there remains a significant impact of infectious diseases on cancer incidence and mortality. Persistent infection with human papillomavirus (HPV) is responsible for most cervical cancers.<sup>10</sup> Many LLMICs, particularly in sub-Saharan Africa, have a higher burden of chronic HPV infection which contributes to high incidence and mortality from cervical cancer.<sup>11</sup> HIV is endemic in many of these



**Figure 1.** Age-standardised mortality from uterine cancer and cervical cancer worldwide in 2022. Data from International Agency for Research on Cancer, Cancer Today.<sup>4</sup>

regions, and this worsens the cervical cancer burden. Cervical cancer is six times more common in women living with HIV, due to a higher probability of HPV persistence,<sup>12</sup> as immune pathways are impaired in this population. Furthermore, HIV infection is associated with reduced survival from cervical cancer, despite antiretroviral use.<sup>13</sup>

In high-resource settings, both primary and secondary cervical cancer prevention measures are centred on HPV. The HPV vaccination, through eradication of oncogenic HPV subtypes, has the potential to virtually eliminate cervical cancer. High HPV vaccination coverage has been attained in many HICs, such as the United Kingdom, where the vaccine has been highly efficacious and effective at reducing the incidence of cervical cancer.<sup>10</sup> In LLMICs, barriers including vaccine cost, supply issues, cold-chain requirement and vaccine hesitancy have significantly slowed HPV vaccine uptake, and global coverage remains low at 21% as of 2022.<sup>14</sup>

## Population awareness

Increased population awareness unsurprisingly improves healthcare outcomes. Public awareness of cancer in many LLMICs is low.<sup>15</sup> In particular, genital tract cancers have been a taboo subject, and many patients present with advanced cancer.<sup>16</sup> The concept of seeing a clinician when asymptomatic, that is, screening, can be absurd to many. Where symptoms do not interfere with daily life, their significance can be overlooked, leading to delays in seeking help.

Of all genital tract cancers, cervical cancer by far has the highest incidence and mortality in LLMICs.<sup>4</sup> Globally, 90% of the burden of cervical cancer is carried by LLMICs. Consequently, most gynaecological cancer awareness campaigns in LLMICs have targeted cervical cancer awareness and screening. HPV vaccination uptake and cervical cancer screening coverage remain low in these areas,<sup>17</sup> suggesting a modest effect of these campaigns, although other factors likely contribute to this.

Endometrial cancer is the most common gynaecological cancer in most HICs and the third most common in many LLMICs.<sup>4</sup> As patterns of risk factor exposure change and LLMICs adopt more 'western' lifestyles such as dietary and behavioural patterns, the burden of endometrial cancer is likely to increase in LLMICs.<sup>18</sup> In the United Kingdom and United States, endometrial cancer mortality is much higher in women belonging to Black ethnic groups compared to women of other ethnicities. This is in part due to reduced public awareness on abnormal bleeding patterns, which is the commonest symptom of endometrial cancer.<sup>19</sup> There is a culture of silence regarding vaginal bleeding in LLMICs,<sup>20</sup> and there is minimal information regarding awareness campaigns on recognition of abnormal vaginal bleeding in these regions. It may be assumed that public awareness on

endometrial cancer and its symptoms is lacking in LLMICs given this culture of silence around abnormal vaginal bleeding.

In addition to reduced public awareness of gynaecological cancers and their symptoms, there is also a reduced awareness of the availability of health services such as cervical cancer screening in LLMICs.<sup>21</sup> In HICs, information about local and national health services is readily available from primary care facilities, community pharmacies and through online resources. This information can be hard to obtain in LLMICs, where geographical differences in service availability also play an important role.

## Societal and cultural factors

In many LLMICs, there is a strong stigma associated with a diagnosis of cancer, and patients may withhold diagnosis from their family members and communities.<sup>22</sup> Gynaecological cancers are especially stigmatised because they involve the genital tract organs. Some believe that genital tract disease is associated with sexual promiscuity. This is especially true of HPV given its sexual mode of transmission.<sup>23</sup> Women often feel shame and embarrassment when discussing gynaecological symptoms, and many fear pelvic examinations.<sup>24</sup>

Cultural, religious and social barriers exist globally, but are most prevalent in Africa and Asia.<sup>25</sup> Where religious beliefs are predominant, fatalism can feature significantly, that is, the belief that events are predestined and inevitable. This feeds into a cycle of hopelessness and fear and can hinder individuals from accessing health services. Late presentation resulting in poorer cancer outcomes further fuels fear and cancer stigmatisation.

Globally, women are less likely than men to have the power to make cancer-related decisions.<sup>2</sup> In communities where men hold the decision-making power, women and girls in their families have limited access to the healthcare resources that they need.<sup>25</sup> In such patriarchal communities in LLMICs, it is not unusual to hear of husbands not permitting wives to take up cervical cancer screening<sup>26,27</sup> because they do not understand its importance, or because they associate it with sexual promiscuity.<sup>24</sup>

## Economic inequality

Poverty remains one of the most significant barriers to accessing high-quality cancer care globally. Most poor individuals reside in LLMICs and are simply unable to afford healthcare services. Poverty is a major risk factor for the development of cancers and can itself be referred to as a carcinogen.<sup>28</sup> Unlike the United Kingdom, many LLMICs do not have a publicly funded healthcare system. With much of the population living below the poverty line, the direct costs

of all aspects of cancer care—screening, imaging, histology, surgery, chemotherapy and radiotherapy—are unaffordable to most. These out-of-pocket expenditures for health care are higher for cancer compared to many other health conditions. Indirect costs such as transport costs to healthcare facilities and loss of earnings for time spent not working leave many patients who seek cancer care impoverished.<sup>21,29</sup> The lack of affordability can result in delays in health seeking and interruptions to treatment while patients raise funds. This is a significant contributor to advanced cancer stages in women in LLMICs and consequent increased mortality. The cycle of poverty is exacerbated by the disability and premature death that results from these cancers, as a result of disruption to families and impact on national economies.<sup>1</sup>

Additionally, poverty is associated with malnourishment and poor living conditions. This predisposes individuals to other illnesses, which can further deplete their finances and impair cancer treatment response.<sup>28</sup> The alleviation of poverty in all its forms is one of the UNDP 2030 sustainable development goals, as it is recognised to be one of the biggest challenges to humanity.<sup>9</sup>

By definition, LLMICs are economically poorer than HICs. Cancer care is often not prioritised within national budgets, and there is insufficient allocation of gross national incomes to strengthening cancer care.<sup>30</sup> Many LLMICs rely on foreign aid to fund cancer care; however, this is neither sufficient nor sustainable.<sup>31</sup> The implementation of national cancer control plans in these regions will help focus cancer priorities and distribute resources to where they are needed most.<sup>32</sup> Lessons can be learned from Rwanda, which has been able to develop and implement a national cancer programme that prioritises cancer screening and early detection, and a community-based health insurance scheme which covers several cancer services.<sup>33</sup> Despite being an LLMIC, prioritisation of cancer care by the Rwanda government has yielded these positive outcomes.

## Workforce capacity

The management of gynaecological cancers requires multidisciplinary input from a diverse workforce. At a basic level, this requires skilled pathologists, radiologists, gynaecologists, surgeons, nurses, and oncologists. A more comprehensive workforce additionally includes palliative care specialists and allied healthcare professionals such as dietitians and physiotherapists. There is huge variability in the availability of these human resources globally, with gaps in many LLMICs. The few available specialists have high workloads, indicating a likely human resource gap.<sup>34</sup>

### Gynaecological cancer surgery

In low-resource settings, under 5% of patients currently have access to safe, affordable and timely cancer surgery.<sup>35</sup>

Modelling studies project a 57% increase in the number of cancer cases that will require surgical management by 2040, with the largest increases happening in LLMICs.<sup>36</sup> Many of these will be gynaecological cancers. The workforce in LLMICs is unable to meet these needs, with a 383% gap in the surgical workforce and a 550% gap in the anaesthetic workforce.<sup>37</sup> At present, in many LLMICs, surgical procedures and anaesthesia are sometimes carried out by minimally trained non-physicians, and cancer surgery is often performed by general surgeons.<sup>38</sup> Gynaecological oncology subspecialty training is lacking in most LLMICs, and where doctors sometimes emigrate for specialist training abroad, only a proportion return to practice in their country of origin.<sup>39</sup>

### Pathology services

Pathology services are crucial to comprehensive gynaecological cancer care. Pathologists are required for the interpretation of cervical cancer screening tests, cancer diagnosis and therefore treatment, and are also essential for appropriate surgical management of cancers. There is a severe shortage of pathologists in many LLMICs. In sub-Saharan Africa, there is <1 pathologist per 500 000 people, compared to one pathologist per 15 000–20 000 people in the United Kingdom.<sup>40</sup> This deficiency in LLMICs results in pathology services being run by non-pathology staff, with huge variation in standards of pathology reporting.<sup>40</sup>

These capacity challenges exist across the entire cancer workforce in LLMICs. The ratio of clinical oncologist per 100 000 population in LLMICs is 0.03 versus 0.88 in HICs. For medical oncologists, this ratio is 0.09 in LLMICs versus 1.6 in HICs.<sup>41</sup> To compound these capacity challenges, healthcare providers who work in governmental facilities are inadequately compensated financially in many LLMICs. Those who do not emigrate resort to dividing their time between governmental work and private work to make ends meet.<sup>42</sup> This culture detracts from the efficiency of the governmental healthcare facilities, where there can be severe delays in obtaining a clinical review due to limited availability.

Given these challenges, many clinicians in LLMICs choose to emigrate to other parts of the world, seeking economic and career stability. Nigeria, the most populous country in Africa, has been significantly affected by this 'brain-drain' which has left the healthcare system extremely strained with a very low doctor-to-population ratio.<sup>43</sup> In a recent statement, the Nigerian Minister of Health highlighted the strain caused by the exodus of Nigerian healthcare professionals to the United Kingdom, stating that 'the NHS would struggle to deliver essential care' without their services.<sup>44</sup> Healthcare professional emigration propagates cancer control challenges in these populations, resulting in worse cancer outcomes.

## Health infrastructure and access to cancer services

Health infrastructure refers to the physical structures and supportive services such as information technology, electricity and water, which enable health services to be delivered to a population. Although these systems and services vary significantly globally, they are largely underdeveloped and underfunded in many LLMICs. Health infrastructure must also consider the factors which affect the ability of the population to utilise health services, for example, transportation and communication systems. In general, health systems in LLMICs are poorly structured and services are uncoordinated. Primary and secondary health facilities have collapsed, placing a strain on the tertiary workforce and facilities.<sup>31</sup>

### Cancer screening and diagnosis

Cervical cancer is the only gynaecological cancer with established screening tests, which in combination with HPV vaccination, has been successful at controlling the disease in many HICs. The WHO global strategy for the elimination of cervical cancer aims for 90% of girls to be vaccinated with the HPV vaccine by age 14; 70% of women to be screened with a high-quality test by age 35 and 45; and 90% of women with cervical disease to receive treatment.<sup>5</sup> Unfortunately, cervical cancer screening remains challenging in many LLMICs with only 9% of women in LLMICs having ever been screened for cervical cancer.<sup>45</sup>

National cervical cancer screening programmes have been difficult to establish in LLMICs where a robust health infrastructure is lacking. In most LLMICs, clear cervical cancer screening and management guidelines are absent.<sup>24</sup> Cervical screening efforts are haphazard, and non-governmental organisations lead outreach programmes to increase screening coverage. Screening centres are often located far from rural communities, and a lack of access to cervical screening has been identified as a key barrier to screening as patients must travel long distances using poor transport networks.<sup>24,37</sup> There are challenges with the follow-up of screen-positive patients, and there is a shortage of screening equipment and consumables.<sup>24</sup> The cost to patients, lack of national cervical cancer screening programs, reduced the availability of facilities for screening, and lack of sufficient workforce for test interpretation are barriers to achieving higher screening coverage in LLMICs.

Many HICs utilise a 'test, triage and treat' cervical cancer screening approach using HPV testing. Testing cervical samples for HPV DNA or HPV oncoprotein mRNA testing has consistently demonstrated high sensitivity, which far exceeds traditional cervical cytology.<sup>46</sup> The main drawback of HPV testing is its poor specificity. Most women will be

infected with HPV at one point in their lives; the vast majority will clear this infection without intervention. HPV-based screening methods detect these transient infections, resulting in high recall rates and overtreatment. In LLMICs, underdeveloped infrastructure and additional costs make HPV-based screening less appealing. Inferior screening methods such as visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI) and traditional cytology are more commonly used. However, even these are under-utilised. Attaining the screening coverage recommended by the WHO global strategy will require significant investments to ensure laboratory facilities are adequate, the workforce is available and trained, and there are adequate resources to manage screen-positive women. Following implementation, ongoing investments will be necessary to maintain these screening programmes.

Similar infrastructural challenges limit the diagnosis of cervical and other gynaecological cancers. Facilities for investigations such as hysteroscopy, aspiration cytology and tissue biopsy are necessary to obtain histological diagnosis. Adequate laboratory services and imaging facilities are also vital for cancer diagnostic services. There is a deficiency of these services in LLMICs due to underinvestment and workforce capacity challenges. Consequently, the majority of the population does not have access to quality diagnostic services, resulting in misdiagnoses.<sup>7</sup>

### Cancer treatment

The major pillars of gynaecological cancer management are surgery, chemotherapy, radiotherapy and palliation. Gynaecological cancer surgery ranges in complexity and can be done for preventive, diagnostic, curative, supportive, palliative or reconstructive reasons.<sup>35</sup> Underinvestment and de-prioritisation of cancer surgery in national cancer control plans has left the majority of LLMIC populations who are unable to access safe cancer surgery.<sup>35</sup> Safe cancer surgery requires well-equipped facilities with a reliable source of electricity and water; surgical equipment and technology such as laparoscopes and hysteroscopes; supportive services such as preoperative care, anaesthetic services and equipment; and availability of blood and post-operative care including intensive care units. These services and infrastructure are poorly developed in LLMICs and post-operative outcomes are poor.<sup>47,48</sup>

Radiotherapy is fundamental to the management of gynaecological cancers. As a result of insufficient cancer surgery services, more patients in LLMICs require radiotherapy compared to HICs.<sup>38</sup> There are significant disparities in access to radiotherapy services globally, with Asia and Africa having the largest challenges with access.<sup>49</sup> In Africa, only 52% and 31% of countries, respectively, have access to external beam radiotherapy and brachytherapy<sup>50</sup>; less than half of the radiotherapy centres in Nigeria have

functional equipment.<sup>51</sup> The maintenance of radiotherapy machines is expensive, and machines often break down.<sup>51</sup> These disparities in access to radiotherapy machines are well described, as are the significant benefits of increasing investment in radiotherapy.<sup>50,52</sup>

## Research and implementation

In HICs, cancer research has been critical to improving cancer-specific mortality, improving the quality of clinical care and developing an effective learning environment.<sup>16</sup> Minimal cancer research is conducted in LLMICs, and most utilised cancer control strategies have arisen from research conducted in HICs and translated to LLMICs, with the expectation of similar successes. Allocation of funds for cancer research is skewed, with only 0.5% of research funding globally allocated to LLMICs.<sup>53</sup> This imbalance in research raises several issues. Research priorities in HICs and LLMICs are different; research and innovation in HICs does not address the cancers that burden LLMICs and does not consider the unique challenges faced by LLMICs such as health system capacities, availability of treatment options and sociocultural factors. Furthermore, there may be biological ethnic variations unaccounted for in research undertaken in HICs only.<sup>16</sup> It is imperative that LLMICs conduct their own research which prioritises local problems with realistic, implementable and cost-effective solutions.

The implementation of research findings into policies and clinical practice is a crucial part of any translational research. The science of implementation requires buy-in from governments and policymakers.<sup>42</sup> In LLMICs with political unrest, this buy-in can be difficult to secure. National guidelines and cancer care policies are absent in many LLMICs, which instead rely on international guidelines from HICs such as the European Society of Gynaecological Oncology and National Comprehensive Cancer Network guidelines. Management plans recommended by such guidelines are often not applicable in LLMICs. This can result in significant inconsistencies in the management of cancers within countries. Implementation challenges are secondary to underinvestment; although many LLMICs have introduced cancer control plans in the last decade, the resources to fund implementation are lacking.<sup>34</sup> The national and regional gynaecological cancer societies in LLMICs, where they exist, have an important role to play in the development of cancer control plans and lobbying for increased political investment.

## Cancer surveillance

High-quality cancer data from national and subnational databases are essential to assess the burden of cancers and as a means of evaluating the effectiveness of interventions. The

International Agency for Research on Cancer (IARC) through the GLOBOCAN project provides the interval estimate of the incidence, mortality and prevalence of 36 cancer types across 185 countries.<sup>4</sup> The agency has supported capacity building for cancer registration through initiatives such as the Global Initiative for Cancer Registry Development partnership<sup>54</sup>; however, the quality of national and subnational cancer data remains poor in many LLMICs. Civil and death registration systems are unavailable or unreliable in many LLMICs.<sup>55</sup> This is a major challenge faced in global oncology, as the absence of site-specific cancer data on incidence, mortality and disease stage can hinder the development of effective cancer control strategies.

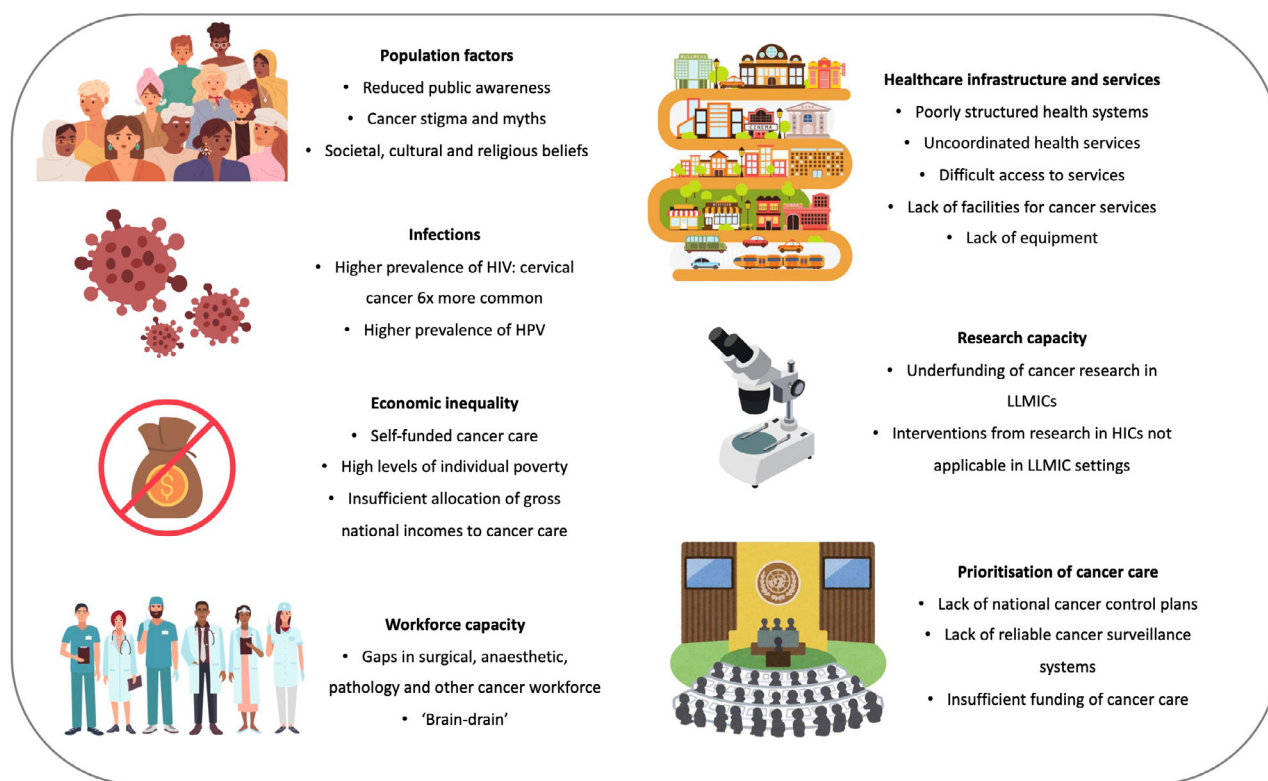
## Conclusion: changing the narrative

There are huge disparities in gynaecological cancer mortality globally. In LLMICs, women are dying at alarming rates from cancers which are potentially preventable and/or curable. These deaths result in significant societal impact, given the multiple roles women play in their communities. Access to high-quality cancer care for women globally must be prioritised, as it is unacceptable for geographical location, socioeconomic status or ethnicity to contribute so significantly to mortality. Much of this inequity arises from poverty, which can begin to be addressed using the universal health coverage system which will enable all women to access high-quality cancer services without financial hardship.<sup>21</sup>

Increasing public awareness on gynaecological cancer symptoms, screening and treatment is a priority. Empowering patients with knowledge of these cancers can help eliminate the associated stigmatisation, myths and fears. Ideally, this education should start at an early stage and take on a life course approach.

The cancer workforce capacity is insufficient in most LLMICs, and this requires investment into training cancer specialists able to provide comprehensive cancer care. International training fellowships may be beneficial, but the workforce must be incentivised to return to their home countries. While this capacity is being built, technology can be leveraged to improve cancer control through telemedicine, artificial intelligence and machine learning for pathology and radiology.<sup>7</sup> Digital platforms may be used to foster collaborative working akin to an international multidisciplinary team, to fill gaps in expertise.

The creation of reliable population-based cancer registries in LLMICs will ensure that cancer control plans and their outcomes are adequately monitored. This will help determine the research priorities relevant to LLMICs. Increased investment into gynaecological cancer research in these areas will help improve outcomes by generating implementable solutions. Researchers and clinicians in



**Figure 2.** Summary of the challenges faced in gynaecological cancer control in LLMICs. HIV, human immunodeficiency virus; HPV, human papilloma virus; LLMIC, low-income and lower middle-income countries.

HICs such as the United Kingdom can form research collaborations founded on partnership and trust, and thus contribute towards the elimination of disparate outcomes from gynaecological cancers.

Addressing disparities in gynaecological cancer in LLMICs requires coordinated efforts across multiple sectors (Figure 2). By (1) enhancing healthcare infrastructure, (2) increasing access to education and prevention, (3) prioritising early detection and screening, (4) making treatment more accessible and affordable, (5) supporting research and cancer surveillance and (6) advocating for supportive strategies, strides can be made to reduce these disparities and improve outcomes for women globally.

## Conflict of interest statement

There are no conflicts of interest.

## Author contributions

AO instigated the article. OI researched and wrote the article. IM-B and AO critically revised the article. All authors approved the final version.

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