Epidemiology of HPV-associated cancers past, present and future: towards prevention and elimination

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Abstract

Cervical cancer is the first cancer deemed amenable to elimination through prevention, and thus lessons from the epidemiology and prevention of this cancer type can provide information on strategies to manage other cancers. Infection with the human papillomavirus (HPV) causes virtually all cervical cancers, and an important proportion of oropharyngeal, anal and genital cancers. Whereas 20th century prevention efforts were dominated by cytology-based screening, the present and future of HPV-associated cancer prevention relies mostly on HPV vaccination and molecular screening tests. In this Review, we provide an overview of the epidemiology of HPV-associated cancers, their disease burden, how past and contemporary preventive interventions have shaped their incidence and mortality, and the potential for elimination. We particularly focus on the cofactors that could have the greatest effect on prevention efforts, such as parity and human immunodeficiency virus infection, as well as on social determinants of health. Given that the incidence of and mortality from HPV-associated cancers remain strongly associated with the socioeconomic status of individuals and the human development index of countries, elimination efforts are unlikely to succeed unless prevention efforts focus on health equity, with a commitment to both primary and secondary prevention.

Key points

- Human papillomavirus (HPV) infection is a necessary cause for virtually all cervical cancers and an attributable cause for variable proportions of anal, oropharyngeal, vaginal, vulvar and penile cancers worldwide.
- Cervical cancer screening led to substantial declines in cervical cancer incidence and mortality in many countries during the 20th century.
- The advent of HPV vaccines and screening approaches has created the opportunity to eliminate cervical cancer, a recognized public health problem, by the end of the 21st century.
- HPV vaccination programmes will probably prevent HPV-associated cancers other than cervical cancer, although research into the optimal screening approaches for these cancers is still ongoing.
- Parity, tobacco use and human immunodeficiency virus infections are major cofactors that influence the epidemiology of HPV-associated cancers.
- Cervical cancer elimination will require combined primary and secondary prevention approaches as well as a focus on reducing health inequities within and between countries.

Introduction

The dream of a world without cancer is not new; it has now been over 50 years since US President Nixon declared a "war on cancer" through the National Cancer Act of 1971[1]. Although tremendous advances in our biological understanding and the treatment of cancers have been made since then, researchers have long argued that the only way to eliminate cancer is through further research and investment in cancer prevention[1,2,3]. Cervical cancer is the first cancer that researchers believe can be eliminated with public-health approaches such as prevention, and the first one to have a global health strategy for its elimination[4]. The case for elimination arose from decades of research that confirmed human papillomavirus (HPV) infection as the necessary cause of all cervical cancers[5,6,7], which created the impetus for the subsequent development of extremely effective HPV vaccines[8]. HPV infection has been widely recognized as a necessary cause of cervical cancer for over 20 years, meaning that all cervical cancers are believed to be caused by an underlying HPV infection[6]. Although a minority of cervical cancers are considered HPV-negative upon testing, further investigation suggests that in most situations these are false-negative results or misdiagnosed cancers of other origins (such as B cell lymphomas), and thus true HPV-negative cervical cancers are extremely rare[9,10]. In 2020, the WHO presented a global strategy to eliminate cervical cancer as a public health problem, with goals referred to as the 90–70–90 targets: vaccinating 90% of girls against HPV by 15 years of age, screening 70% of women with a high-performance test at 35 and 45 years of age, and treating 90% of women with cervical disease (precancerous lesions or invasive cancer)[4]. Meeting these predefined targets could enable the vast majority of countries to reach an 'elimination threshold' annual incidence of fewer than 4 cancers per 100,000 women by the end of the 21st century[11]. Importantly, this strategy depends strongly on primary and secondary cancer prevention, and thus the main objective is the reduction of incidence, not just mortality.

Thus far, elimination efforts have focused solely on cervical cancer, although they are expected to substantially influence the incidence of other HPV-associated cancers. In addition to being a necessary cause of all cervical cancers, HPV also causes 88% of anal, 31% of oropharyngeal, 78% of vaginal, 25% of vulvar and 50% of penile cancers worldwide[12]. Even if these cancers are not explicitly addressed in the WHO Cervical Cancer Elimination Initiative, their associated public-health burden has led to extensive research into their prevention, and the technological developments and lessons learned from cervical cancer elimination strategies will serve as a blueprint for the future approach to elimination of these and other cancers.

In this Review, we provide an overview of the epidemiology of cervical and other HPV-associated cancers worldwide, and discuss how past and current prevention approaches have shaped the course of these diseases and the potential for their elimination. We also pay particular attention to cofactors that can hamper prevention efforts, as well as the social determinants of health that must be considered to achieve elimination of these preventable cancers.

Temporal and geographical trends

Cervical cancer

In the mid-20th century, cervical cancer was one of the most frequently diagnosed cancer types worldwide and, together with breast, colorectal and stomach cancers, was among those with the greatest incidence in women[13]. However, many high-income countries (HICs) in North America and Europe saw steady declines in cervical cancer incidence and mortality rates over the second half of the 20th century, to the point where cervical cancer is now rare in many of these countries[14,15,16,17,18,19,20] (Fig. 1). A large part of this decline is undoubtedly attributable to the

introduction of cervical cancer screening with the Papanicolaou cytology-based test, which started between the late 1950s and the 1970s in many HICs, where incidence subsequently decreased[14,15,16,17,18]. These declines have been mostly observed for cancers in women ≥30 years of age and for squamous cell carcinomas (SCCs), suggesting that screening is most effective at preventing these cancers[18,21,22,23,24]. Nonetheless, declines in incidence and mortality occurred in some of these countries years before the widespread adoption of cervical cancer screening[25,26,27,28], suggesting that concurrent changes in the prevalence of other risk factors for this disease (such as reduced parity) were already influencing epidemiological trends. In the 1960s, sexual behaviours changed considerably in many North American and European countries and evidence suggests that this so-called sexual revolution led to a substantial increase in the prevalence of HPV infection[29,30,31]. Age–period–cohort analyses have concluded that the introduction of screening in many countries is likely to have prevented a resurgence in cervical cancer incidence that would have occurred after changes in sexual behaviour[14,16,32]. Increases in cervical cancer incidence rates in some countries over the past 10–20 years might be attributable to these cohort effects, which are starting to reverse the long-term observed decreases[33]. Moreover, the incidence of adenocarcinomas of the cervix has notably increased in many of the countries in which that of SCCs has declined, especially in younger cohorts[22,34,35,36,37]. This effect might have been a result of both the lower sensitivity of cytology screening against cervical adenocarcinomas relative to SCCs[38] and to changes in sexual behaviour leading to higher HPV prevalence in younger birth cohorts.

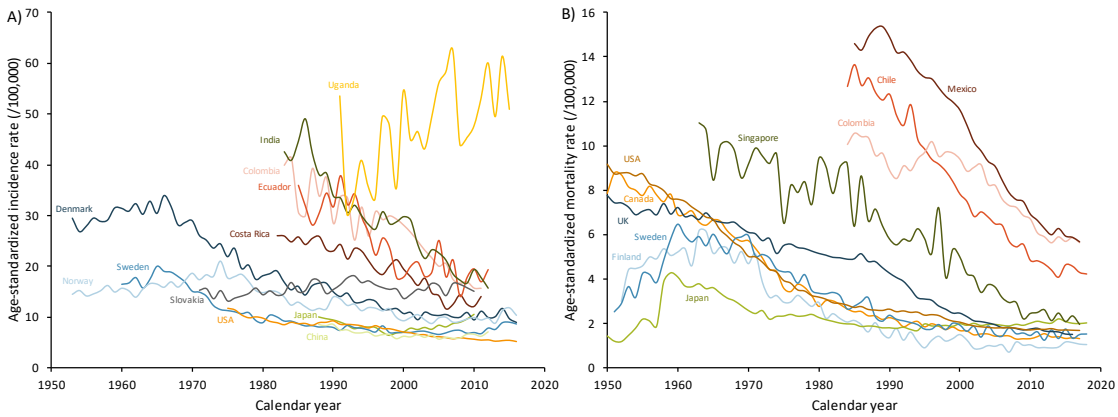

Fig. 1: Age-standardized incidence and mortality from cervical cancer in women. *Incidence (part **a**) and mortality (part **b**) rates for selected countries with high-quality population-based cancer registries and established mortality surveillance. Data were obtained from GLOBOCAN[20]. Rates are age-standardized according to the Segi–Doll World Standard Population definition[294].*

In many countries, the declines observed in incidence have resulted in declines in cervical cancer mortality (Fig. 1). Over the second half of the 20th century and before the advent of cisplatin plus radiotherapy in 1999, improvements in cervical cancer survival were moderate at best[39,40,41]. This trend suggests that improvements in treatment only had a minor contribution to the reductions in mortality over this time period, most of which can be attributed to declining incidence through prevention, earlier detection and concurrent changes in other oncogenic cofactors.

Most of the decline in cervical cancer incidence and mortality in North American and European countries in the 20th century is attributable to improvements in screening; however, many

countries in Asia and Latin America also saw declines in cervical cancer incidence during this time period despite low screening coverage[21]. Experts have speculated that this trend might have been partly driven by a long-term trend of decreasing parity in many countries[42]. An age–period–cohort analysis of data from India for the period 1976–2005 supports the notion that declines in cervical cancer incidence are probably attributable to socioeconomic development, which has led to later ages at marriage and fewer children per woman[43]. Conversely, increases in cervical cancer incidence in China during the period 1990–2019 have been attributed to changes in sexual behaviour leading to rising HPV transmission, such as increasing numbers of partners and younger age at the onset of sexual activity[33,44].

Data on temporal trends in sub-Saharan Africa are limited owing to a paucity of long-term quality data from cancer registries, but the available data suggest that the incidence of cervical cancer has increased in many of these countries since the 1990s[45,46]. This trend is probably the result of a high HPV prevalence combined with the human immunodeficiency virus (HIV) epidemic and low screening coverage in many countries[46]. Although part of the variations in cervical cancer incidence worldwide can be attributed to differences in HPV prevalence[47] and its cofactors, screening coverage remains the strongest driver of disparities between countries. Nowadays, the incidence of cervical cancer incidence remains highest in low-income and middle-income countries (LMICs), which have low levels of implementation and limited effective coverage of cervical cancer screening[48].

Oropharyngeal cancers

Here we mostly focus on oropharyngeal cancers, which have the highest HPV-attributable percentage worldwide (31%) of head and neck cancers[12]. The incidence of oropharyngeal cancer has been increasing in most countries with long-term cancer registry data available[49], with more marked increases in younger cohorts[50,51,52] (Fig. 2). Nonetheless, epidemiological trends in oropharyngeal cancer are more difficult to directly attribute to HPV owing to the major independent aetiological roles of tobacco and alcohol use in this disease.

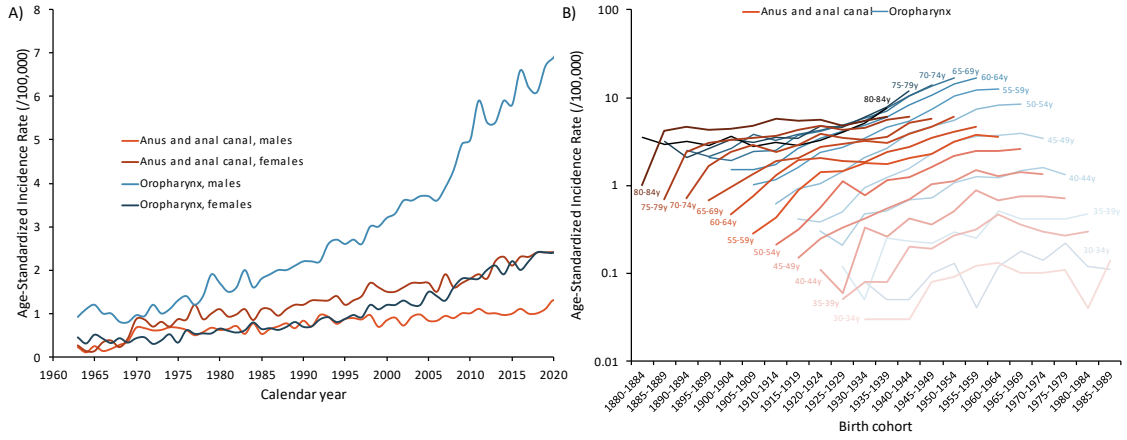

Fig. 2: Incidence of oropharyngeal and anal cancer in Nordic countries. *Charts include data for Denmark, Finland, Iceland, Norway and Sweden (excluding the Faroe Islands and Greenland) age-standardized by sex over time (part **a**) and by age and cohort (part **b**). Data were obtained from NORDCAN[52]. In part **a**, rates are age-standardized to the Nordic age standard[52]. In part **b**, the y-axis is on a logarithmic scale and the values shown next to the plotted lines refer to age in years.*

The best evidence that the incidence of HPV-associated oropharyngeal cancer is increasing comes from studies that examined either HPV positivity, ideally via detection of transcripts for the viral oncogenes E6 and E7, or immunohistochemical detection of cyclin-dependent kinase 4 inhibitor A (commonly referred to as p16-INK4A or p16), a cellular protein encoded by *CDKN2A*, which is overexpressed in HPV-associated oropharyngeal cancers[53]. Evidence suggests that the proportion of HPV^+ and $p16^+$ oropharyngeal SCCs is increasing in many countries[54,55,56,57]. Although data on HPV status in patients with oropharyngeal cancer are not available for all countries, the contrasting trends of a decreasing incidence of lung cancer and an increasing incidence of oropharyngeal cancer incidence in most countries strongly support the view that the latter trend is attributable to HPV infection rather than tobacco use[49]. The average age at diagnosis of HPV^+ oropharyngeal SCC is also increasing[56,58], suggesting that the rising incidence of this cancer type is also the result of a cohort effect[49,59]. Both the incidence of HPV-associated oropharyngeal cancers and the proportion attributable to HPV are highest in HICs in North America and Europe[12,60]. The incidence of oropharyngeal and oral cavity cancers is also very high in South Asia, although in this region a high proportion of these malignancies are caused by tobacco consumption and betel quid chewing rather than HPV infection[61]. Whether the high proportion of oropharyngeal cancers attributable to HPV in North America and Europe results from a higher prevalence of oral HPV infection or other cofactors is unclear owing to the limited availability of large population-based studies of oral HPV infection, which would enable comparisons between countries. A meta-analysis with results published in 2018 concluded that the prevalence of oral HPV infection was highest in studies conducted in South America and lowest in those from Asia[62], but these results must be interpreted with caution because most studies of oral HPV infection did not involve representative populations.

Anal and genital cancers

Similar to cervical cancer and oropharyngeal cancer, the incidence of anal and vulvar cancer has been increasing over the past decades and in successive birth cohorts in several countries[63,64,65] (Fig. 2). Temporal trends for penile cancer incidence have been less consistent worldwide[66], although a few European countries have reported long-term increases in incidence probably attributable to HPV infection[67,68]. Most anal cancers worldwide are attributable to HPV (88%)[12], and thus epidemiological trends are likely to be driven either by changes in HPV prevalence or its cofactors. Anal SCCs, the histological subtype most commonly caused by HPV infection, account for most of the increasing incidence, thus supporting the view that the epidemiological trends of the past decades are driven by HPV-attributable cancers[69]. In many countries, the incidence of anal cancer is higher in women than in men[52,70,71,72]; however, the subpopulations at highest risk of anal cancer are men who have sex with men and individuals living with HIV[73]. A study has provided evidence that the HIV epidemic contributed to increases in anal cancer incidence in men but not in women in the USA[74], although incidence rates were rising in many countries prior to 1980 (Fig. 2). Therefore, the HIV epidemic is probably only one of the factors explaining the increasing incidence of anal cancer. Although no longitudinal data on the prevalence of anal HPV infection over time are available, this trend could be partly attributable to an increasing prevalence of anal HPV infections, which share many risk factors with cervical HPV infection[75].

Current prevention approaches

Primary prevention: HPV vaccination

The development of HPV vaccines began in the early 1990s after substantial epidemiology research demonstrated that HPV infection is the necessary causative agent of cervical cancer[8].

The first HPV vaccine was licensed in 2006, and currently six HPV vaccines are licensed worldwide for the prevention of HPV-related diseases[76]. The first vaccines (Gardasil and Cervarix) were both licensed in the USA and Europe, and subsequent vaccines were developed in China (Cecolin and Walrinvax) and India (Cervavac), a remarkable advance in the context of increasing the global supply and reducing the cost of vaccines[77,78]. All vaccines protect against infection with HPV16 and HPV18, which account for 71% of cervical cancers[12,79,80]. Gardasil and Cervavac are quadrivalent vaccines that additionally protect against infection with HPV6 and HPV11, which cause anogenital warts. Randomized controlled trials have shown that bivalent and quadrivalent vaccines have extremely high prophylactic efficacy against persistent infection and precancerous lesions[81,82,83]. Finally, Gardasil 9 is a nonavalent vaccine that also protects against oncogenic types HPV31, HPV33, HPV45, HPV52 and HPV58, which account for 19% of cervical cancers[12,84,85]. Studies have shown that bivalent and quadrivalent vaccines can also provide a certain degree of cross-protection against infection with phylogenetically related non-vaccine HPV types[86,87]. As of 2022, 125 countries (64%) have introduced HPV vaccination in their national immunization programme for girls, and 47 countries (24%) also include boys aged 9–15 years[76]. Global vaccination coverage with at least one dose in girls by 15 years of age was estimated to be 21% as of 2022 (ref. [88]). The WHO recommends administering HPV vaccines before the onset of sexual activity to maximize their prophylactic efficacy[4,76].

The incidence of high-grade squamous intraepithelial lesions (HSIL) of the cervix, which include the previously used terms cervical intraepithelial neoplasia grades 2 and 3 (ref. [89]), is an important early outcome for measuring vaccine effectiveness as these are precancerous lesions caused by HPV that have a high risk of progressing to cervical cancer. Marked declines in the prevalence of genital infection with vaccine-type HPV and high-grade cervical lesions have been reported in vaccine-eligible cohorts from many countries worldwide[90,91,92,93,94,95,96,97]. Owing to the decades-long time lag between primary prevention and reduction in cancer incidence, HPV vaccines have not yet substantially affected the incidence of HPV-associated cancers in most countries. However, the countries that were early adopters of HPV vaccination programmes and achieved moderate to high vaccination coverage (>50%) in the late 2000s, such as the UK[98,99], Sweden[100] and Denmark[101], are now (15–20 years later) starting to observe declines in cervical cancer incidence among young adult women who were vaccinated as pre-adolescents. These studies have shown considerably higher vaccine effectiveness against cancer in women who were vaccinated during pre-adolescence or early adolescence than among those who were vaccinated in late adolescence or as adults. The higher effectiveness of HPV vaccination when immunization occurs at younger ages was expected based on the known epidemiology of HPV infections. Randomized controlled trials have shown that HPV vaccines have high prophylactic efficacy (>95%) in adults with no prior evidence of infection[81,82,83]. However, the population of susceptible individuals in which vaccines are effective diminishes with age, and ~75% of infections causing cervical cancer are expected to have been already acquired by the age of 30 years[102]. This observation highlights the importance of early vaccination, before exposure to HPV infection through sexual activity.

At the time of writing, declines in the incidence of HPV-associated cancers attributable to vaccination programmes have not yet been documented for cancers other than cervical cancer, such as anal and oropharyngeal cancers, which are generally diagnosed at older ages than cervical cancer. Randomized controlled trials have provided evidence that HPV vaccines are effective against oral HPV infections, and reduce the incidence of vulvar, vaginal and anal precancerous lesions[103,104,105,106]. Women who were vaccinated in a trial as young girls had less than half the

oral prevalence of HPV16 and HPV18 infections relative to unvaccinated women[103], and the incidence of anal precancerous lesions caused by vaccine HPV types was 77–84% lower in the vaccinated versus unvaccinated arm in per-protocol analyses of trials testing vaccines[104,105]. Thus, we expect vaccination to eventually reduce the incidence of these cancers as well. Registry data from Denmark have shown a 70% reduction in the rate of anal HSIL or worse in women who were vaccinated before the age of 17 years relative to unvaccinated women, confirming the earlier results seen in trials[107]. The prevalence of oral infection with vaccine-type HPV has also declined since 2012 among men in the USA, most probably as a result of herd immunity from women vaccinated during this time period[108]. Nevertheless, a complete understanding of the effect of vaccination on the incidence of other HPV-associated cancers might take a few decades. Long-term follow-up data (11 years) from a cluster-randomized trial in Finland have encouragingly shown no occurrence of vulvar, vaginal or oropharyngeal cancers in vaccinated women thus far (compared with 0.1% of individuals in the control cohort)[109], although these numbers are currently too low to reliably measure vaccine effectiveness against these cancers.

Secondary prevention: screening and management of precancerous lesions

HPV testing for cervical cancer screening

Despite the major effect that cytology-based screening has had on reducing cervical cancer incidence in many HICs, the cytology test is a far from perfect screening test, with suboptimal sensitivity, ranging from as low as 30% to 87% in different settings[110]. Cytology-based screening requires substantial infrastructure, trained personnel and quality assurance, which makes it difficult to implement in many LMICs[111,112]. Similarly to HPV vaccines, interest in using HPV-based testing for cervical cancer screening started in the 1990s. Many studies over subsequent years confirmed that HPV testing with the first available clinical HPV assays (Hybrid Capture II, consensus PCR with GP5+ and GP6+ primers) had superior average sensitivity than cytology (96% versus 53%), albeit with lower specificity (91% versus 96%) for detection of high-grade precancerous lesions[113]. Much of the HPV research over the past 20 years has gone into developing new HPV assays enabling reliable point-of-care or high-throughput testing for use in screening. In 2003, the Hybrid Capture II HPV test was the first screening test approved by the FDA for use in conjunction with cytology-based testing, and in 2014 the cobas HPV test was the first one approved for use as a fully primary HPV screening test[114]. However, not all HPV assays are clinically validated for screening; the list of available HPV assays has exploded into the hundreds, but 60% of currently marketed HPV tests do not have a single peer-reviewed publication to support their use in evidence-based practice[115]. As of 2020, only 11 HPV DNA assays meet the international validation guidelines for cervical cancer screening (briefly, that they should be at least 90% as sensitive and 98% as specific as the Hybrid Capture II or GP5+/GP6+ PCR assays for detection of high-grade cervical lesions)[116]. In 2021, the WHO recommended HPV DNA detection as the primary cervical cancer screening test in all countries[117]. Although they do not recommend any particular assay, they note the importance of selecting a test based on information about its clinical validation for screening.

The Netherlands was the first country to fully replace cytology testing with HPV testing as the primary screening modality in 2017 (ref. [118]). As of 2022, an estimated 48 of 139 countries with cervical cancer screening programmes (35%) recommend HPV testing as the primary screening test[48], although most of these countries are still transitioning from cytology-based screening and have not yet fully implemented HPV-based screening. Consequently, the population-level effects of HPV-based primary screening can only be measured in a handful of countries. The general observation is that HPV-based primary screening improves the detection of high-grade cervical

lesions albeit with higher colposcopy referral rates than with cytology screening, at least within the first few years of implementation[119,120,121]. Of note, the effect of HPV-based primary screening on colposcopy referral rates clearly depends on a country's screening management algorithm and on how stringent the referral criteria are for HPV testing compared with cytology testing[122]. Consequently, unnecessary colposcopy referral rates could be reduced by refining triage strategies for women with HPV^+ findings[123,124,125]. Ongoing research is addressing the performance of additional molecular tests to triage and better risk-stratify HPV test results, including extended genotyping, host and viral methylation markers, E6 and E7 oncoprotein expression, viral load and mRNA testing[126,127,128]. The identification of appropriate triage tests is becoming increasingly urgent owing to the accumulating evidence that the performance of cervical cancer screening programmes is declining in vaccinated cohorts[129,130,131]. For example, the positive predictive value of cytology for detection of HSIL has been reported to be 17% lower in women in Scotland who were vaccinated before the age of 17 years relative to unvaccinated women in Scotland[129]. This decline in screening performance in vaccinated cohorts was predicted when HPV vaccination started being implemented[132,133].

In countries that have successfully transitioned to primary HPV-based testing, the future of cervical cancer screening is likely to increasingly rely on HPV self-sampling by women rather than sample collection by health-care providers. This prediction is based on the fact that self-sampling has numerous advantages, including the potential to reach marginalized populations, comparable performance with provider-collected sampling and high public acceptability[134,135]. At the time of writing, at least nine countries worldwide have introduced HPV self-sampling as the primary approach for cervical cancer screening, and this number is expected to increase[136,137]. Many of these are LMICs that introduced HPV primary screening simultaneously with self-sampling.

The third target of the WHO Cervical Cancer Elimination Initiative, treating 90% of women with cervical disease (precancerous lesions or cancer), is no less important for cervical cancer elimination[138]. Discussing cervical cancer treatment in detail is beyond the scope of this Review; these aspects are comprehensively discussed in clinical guidelines and other reviews[139,140]. However, the management and treatment of precancerous lesions is an essential component of secondary prevention without which cervical cancer screening would be ineffective. Certainly, one of the greatest challenges in achieving treatment targets has been loss to follow-up of women in whom additional clinical management is warranted based on their screening test results, especially those of low socioeconomic status and in lower resource settings[141,142]. Although triage of HPV test results helps to avoid overtreatment and over-referral, the WHO also recommends the alternative strategy of a 'screen-and-treat' approach in which treatment is provided immediately or soon after a positive HPV screening test result to reduce loss to follow-up[117]. Artificial intelligence-based screening and triage solutions could eventually improve upon current screening methods, although these options are an ongoing topic of research that still face many challenges[143].

Screening for other HPV-associated cancers

After cervical cancer, anal cancer is the HPV-associated cancer with the most evidence supporting potential benefits from screening. Anal cancer is biologically similar to cervical cancer, with most cases attributable to HPV infection (88%), and with anal HSILs having a high risk of progression to cancer[144,145]. Several subpopulations have a clear higher risk and can be thus prioritized for screening: a meta-analysis found that anal cancer incidence rates are highest

among HIV-seropositive men who have sex with men (85 per 100,000 person-years), and are also very high among HIV-seronegative men who have sex with men (19 per 100,000 person-years), HIV-seropositive women (22 per 100,000 person-years) and solid organ transplant recipients (13 per 100,000 person-years) compared with lower rates seen in HIV-negative men and women from the general population (≤6 per 100,000 person-years)[73]. In 2022, a randomized controlled trial testing ablative procedures for anal HSIL demonstrated a 57% lower risk of progression to anal cancer among treated individuals relative to those untreated, establishing the efficacy of anal precancerous lesion management in cancer prevention[146]. Nonetheless, substantial logistical issues remain that need be resolved before implementing population-level anal cancer screening. For example, the specificity of HPV-based screening tests for this cancer type is low (42%) owing to the high (>50%) prevalence of high-risk anal HPV infection in populations at the highest risk of anal cancer[147]. Anal cytology-based screening also has only moderate sensitivity (81%) and specificity (62%), and would result in many referrals for further investigation using high-resolution anoscopy with directed biopsy[147,148]. Such an approach is resource-intensive and requires a high level of training, leading to issues of scalability even in high-resource settings[149,150,151]. Other biomarkers for risk stratification and identification of individuals at the highest risk of high-grade anal precancerous lesions, such as dual staining for p16 and Ki-67, host and viral DNA methylation, and HPV E6 and E7 mRNA testing are ongoing research topics[149,152]. Owing to the aforementioned scalability issues, some experts have advocated for less resource-intensive anal cancer screening programmes using digital rectal examination, with the aim of early cancer detection rather than prevention[153]. The latest guidelines from the International Anal Neoplasia Society recommend screening for anal precancerous lesions in high-risk populations in settings with adequate capacity for high-resolution anoscopy[154]. However, given that such capacity is limited in most regions worldwide, they also recommend digital anal rectal examination for earlier detection of anal cancer in the absence of high-resolution anoscopy[154].

Screening for oropharyngeal cancers is becoming increasingly attractive in regions with a high percentage of HPV-attributable malignancies such as North America and Europe, although several logistical challenges remain that have made such screening approaches unfeasible[155,156]. To date, no recognized treatable oropharyngeal precancerous lesions have been identified, and thus the objective of a putative screening programme would be early detection rather than prevention. Furthermore, the potential population-level effects would be more modest than those from cervical cancer screening, and more akin to those of breast or lung cancer screening programmes, which aim to reduce mortality and morbidity rather than incidence. Thus far, most attention has focused on screening with either oral rinse HPV DNA tests or blood tests for antibodies against HPV16 oncoproteins, namely HPV16 E6. Both of these biomarkers are strongly associated with the risk of oropharyngeal cancer, and have moderate to high sensitivity (≥45% for oral HPV and ≥90% for HPV16 E6 seropositivity) and high specificity (≥90%) for detection of HPV-associated oropharyngeal cancer[157,158,159,160]. However, even with their high specificity these tests could lead to very high rates of false-positive results if they were used for screening in the general population[155,156]. Early detection of HPV-associated oropharyngeal cancer is made more difficult by the occult nature of early lesions in palatine and lingual tonsils, which are difficult to inspect[161]. Therefore, performing targeted screening of high-risk individuals who are more likely to benefit is the desired approach. Unlike anal cancer, however, a suitable high-risk target population has not yet been clearly defined. Owing to these issues, no prospective randomized controlled trial has evaluated the effectiveness of any test for oropharyngeal cancer screening.

The current evidence supporting screening for genital HPV-associated cancers is at best tenuous. Given that the incidence of vulvar, vaginal and penile cancers is very low, these malignancies do not meet the conventional criteria for experts to recommend screening, which would potentially have limited benefits and high harms[162]. Pelvic examinations have long held a prominent place in women's health in many countries; however, no evidence supports their role in reducing mortality from non-cervical gynaecological cancers, and some organizations, such as the American College of Physicians and the Canadian Task Force on Preventive Health Care, no longer recommend using them for screening asymptomatic women[163,164]. Although vulvar precancerous lesions could be targeted for screening purposes, insufficient data currently support using cytology or self-examination to detect these lesions. Moreover, excisional treatments are associated with high psychosocial morbidities, another negative consequence from potential overdiagnosis[165,166].

HPV oncogenic cofactors

Cervical cancer

Nearly all cervical cancers are caused by HPV[5]. However, as 85% of women are expected to be infected with HPV in their lifetimes[167] but the lifetime risk of cervical cancer is <2%[168], only a minority of women infected with this virus ever develop cervical cancer. Therefore, understanding the cofactors that influence progression from HPV infection to cervical cancer is an active area of research. Cervical cancer screening with subsequent treatment of precancerous lesions is an important opportunity to interrupt this progression; however, other cofactors can also influence global trends in cervical cancer incidence[46,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185] (Box 1). We believe that the following cofactors are the main contributors to worldwide trends.

Box 1 Cofactors associated with risk of progression from HPV infection to cancer

Cervical cancer

Environmental and exogenous cofactors

- ***Tobacco use****. Smoking has been associated with an increased risk of squamous cell carcinoma, with a dose–response effect, among HPV-positive women, and smoking cessation has been associated with regression of precancerous lesions[169,170,171,173,175,177].*
- ***HIV infection****. HIV infection induces chronic inflammation and affects the host's capacity to clear HPV infections, which increases the risk of developing cervical cancer[46,172,173,174,177,178].*
- ***Hormonal contraceptive use****. The evidence on the association between use of oral hormonal contraceptives and increased cervical cancer risk is not consistent[169,171,173,175,177]. Some of the associations described could be confounded by sexual activity, parity and use of barrier contraceptive methods.*
- ***Sexually transmitted infections****. Some studies have found associations between infection with Chlamydia trachomatis or herpes simplex virus type 2 and increased risk of cervical cancer among HPV-positive women, potentially through the induction of cervical inflammation[171,176]. Some of these associations could be confounded by sexual activity, parity and use of barrier contraceptive methods.*
- ***Immunosuppressive drugs****. Long-term users of immunosuppressive drugs, such as transplant recipients, are at a higher risk of cervical cancer owing to of their inability to clear HPV infection effectively[185].*
- ***Diet****. Low intake of certain micronutrients (including carotenoids and vitamin E) has been associated with increased risk of cervical cancer[169,180,185].*

Viral cofactors

- ***HPV type***. *Among different HPV types, HPV16 has the greatest oncogenic risk, followed by HPV18 (ref. [184]).*
- ***HPV variants***. *Within HPV types, some variants might be associated with a higher risk of cervical cancer. Infections with non-European HPV variants tend to be the most persistent, increasing the risk of precancerous lesions and cervical cancer*[171,176,179].
- ***Viral genome integration***. *Analysis of cervical cancer-derived samples often shows integration of high-risk HPV DNA into the host cell genome and could be associated with disease progression. Viral integration causes host genomic instability and promotes several pathways leading to carcinogenesis*[179].

Host cofactors

- ***HLA gene polymorphism***. *These genes are involved in modulating the immune response and can affect clearance of HPV infection, increasing the risk of cervical lesions*[176].
- ***Age at infection***. *Early age at first intercourse, first marriage and first full-term pregnancy have been inconsistently associated with higher risk of cervical cancer across studies*[173,182,183]. *Hypothetical explanations for these associations include a biological predisposition to infection of the immature cervix at younger ages, or an immature immune system. Nevertheless, this association could be confounded by lifetime number of sexual partners and parity.*
- ***Parity***. *An increasing number of full-term pregnancies increases exposure of the exocervix to HPV and causes immunological changes that could affect clearance and reactivation of HPV infections*[169,171,175].

Other HPV-associated cancers

- ***Tobacco use***. *Tobacco smoking is associated with increased incidence of vaginal, vulvar and anal cancer*[214]. *Evidence suggests that tobacco is not a cofactor in HPV-associated head and neck cancers*[213].
- ***HIV infection***. *High incidence of HIV infection is associated with increased incidence of and mortality from anal cancer as well as increased risk of cancer of the oropharynx, vagina, vulva and penis*[189,212].
- ***Immunosuppressive drugs***. *Individuals with autoimmune conditions or solid organ transplant recipients receiving immunosuppressive treatment have an increased risk of anal cancer relative to the general population*[222].

Parity

An increasing number of full-term pregnancies has been linked to an increased risk of precancerous lesions and cervical cancer in HPV-positive women[42,169,175,186]. Pregnancy is associated with cervical ectopy, which involves migration of the transformation zone (the area where the endocervix joins the exocervix, where most squamous cell cervical cancers develop) to the exocervix. This process might increase exposure of cells in the transformation zone to HPV[169,171]. Many studies have observed rising cancer risk with increasing number of full-term pregnancies, with the risk being highest in women with seven or more full-term pregnancies who have an odds ratio for cervical SCC of 3.8 compared with nulliparous women, and of 2.3 compared with women with one or two full-term pregnancies[42]. In 2021, countries in sub-Saharan Africa had the highest fertility rate (4.6 births per women), more than twice that reported in other regions. Fertility rates have decreased over the past 60 years, especially in Latin America and the Caribbean and in the East Asia and Pacific regions (68% and 67% decrease, respectively). The

declining incidence of cervical cancer observed in Latin America might be partially explained by these decreases in fertility[187,188].

HIV infection

HIV infection substantially increases the incidence of and mortality from cervical cancer[178,189]. HIV infection compromises the host's ability to clear HPV infection and induces chronic inflammation, which has a crucial role in promoting carcinogenesis[173,174,179]. Women living with HIV face a sixfold higher risk of developing cervical cancer relative to uninfected women[46]. An estimated 4.9% cervical cancers worldwide are attributable to coinfection with HIV and HPV, with the highest burden in Africa (21%)[46]. The country-level incidences of cervical cancer and HIV infection in adults tend to be strongly correlated[190,191] (Fig. 3). Most regions worldwide have concentrated HIV epidemics (defined as a prevalence <1%), except for Africa (where the prevalence was 3.3% in individuals aged 15–49 years in 2021)[192]. Although the incidence of HIV infection is declining in many regions[193], the effect of this reduction on HPV carcinogenesis might take some time to become evident because trends in cancer epidemiology are more likely to be influenced by HIV prevalence than incidence. Africa is the region with the highest burden of HIV infection and cervical cancer, but also the only region with a relevant reduction in HIV prevalence during the period 1995–2021 (4.2% to 3.3%). In other regions, HIV prevalence has not changed or has slightly increased over the same period of time[192]. HIV prevention and control should be considered as a core component of cervical cancer elimination[194]. The early initiation of antiretroviral therapy has been shown to reduce the incidence and progression of high-grade precancerous lesions to cervical cancer[172,195].

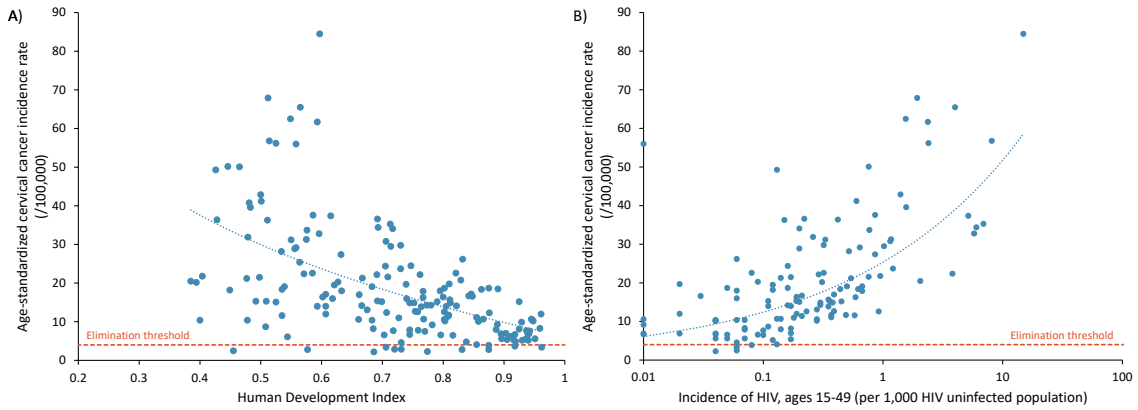

Fig. 3: Age-standardized incidence of cervical cancer in 2020. *Incidence rates plotted against each country's human development index in 2021 (part **a**) and estimated new infections with human immunodeficiency virus (HIV) in individuals aged 15–49 per 1,000 uninfected individuals in 2021 (part **b**). Data were obtained from GLOBOCAN[191], the United Nations Development Programme[228] and the World Bank[190]. Cervical cancer incidence rates are age-standardized according to the Segi–Doll World Standard Population definition[294]. In part **b**, HIV incidence is presented on a logarithmic scale. Blue dotted lines show trendlines fitted assuming a logarithmic relationship for human development index and a power relationship for incidence of HIV.*

Tobacco use

HPV-positive women who smoke have a twofold higher risk of cervical SCC and high-grade lesions relative to HPV-positive women who have never smoked[169,171,175]. Moreover, in an interventional study involving 82 women with low-grade cervical intraepithelial neoplasia,

reductions in lesion size of ≥20% or 4 mm^2 occurred in 82% of those who stopped smoking for at least 6 months compared with 28% of those who continued to smoke[196]. The pathophysiology of tobacco smoke in HPV-mediated carcinogenesis seems to be a multifactorial process that remains not completely understood[175,197]. Tobacco promotes viral and host-related alterations involved in epithelial carcinogenesis, including HPV replication, expression of HPV E6 and E7 and DNA damage, as well as changes in innate and adaptive immunity that decrease the ability of the immune system to clear HPV infection in the cervix[169,170,175,177]. Although substantial evidence supports tobacco smoking as an oncogenic cofactor for cervical cancer, the strength of its contribution to geographical differences relative to other factors (such as parity and HIV infection) and screening coverage remains unclear. In 2020, Europe and North America had the highest prevalence of women who smoke (23.7% and 16.8%, respectively)[84], yet the incidence of cervical cancer remains lowest in these regions owing the high coverage of screening programmes. Latin America and the Caribbean have seen large decreases in tobacco consumption in the past 20 years (49%)[84] that could have contributed to the decreases in cervical cancer incidence observed in these regions.

HPV types

Oncogenicity varies across HPV types, with HPV16, HPV18 or HPV45 infection conferring greater risks of cervical cancer progression than other HPV types[198,199]. Distribution of the HPV types most commonly found in cervical cancer (HPV16, HPV18, HPV31, HPV33, HPV35, HPV45, HPV52 and HPV58) is widely consistent across continents, with minor geographical variations[79,200]. As discussed previously, these combined types account for 91% of cervical cancers worldwide, with the largest proportion (71%) resulting from HPV16 and HPV18 infection[80].

HPV variants

The advent of high-throughput next-generation sequencing has revealed that, even within HPV types, different variants might have differing levels of oncogenic potential[201,202]. HPV16, the most oncogenic type, has five established variants: European, Asian–American, Asian, African-1 and African-2, with different prevalences across geographies and ethnicities that reflect the co-evolution of HPV and humans[85,203]. Non-European variants have been found to be associated with a twofold to fourfold increased risk of persistent infection, precancerous lesions and cervical cancer in some studies[176,202,204,205]. Potential explanations for this increased risk include enhanced transcriptional activity, the ability to promote cellular immortalization, migration, invasiveness and transformation to resilient phenotypes, and activation of certain oncogenic pathways in high-risk variants relative to low-risk variants[171,176,179]. Nevertheless, the association between non-European variants and higher risk of cervical disease has not been observed across all populations, and some researchers have hypothesized that differences across populations reflect host–gene interactions[176,179,206]. Therefore, although different variant prevalences might contribute to geographical differences in cervical cancer incidence, their clinical utility for screening remains elusive and requires further research[201].

Cofactors for other HPV-associated cancers

HPV cofactors in HPV-associated cancers other than cervical cancer remain to be well characterized. Infection with HPV16 accounts for a higher proportion of anal and oropharyngeal cancers (83% each) than cervical cancers (61%)[207,208]. To the best of our knowledge, most studies of non-cervical cancers did not control for HPV status or restrict their analysis to HPV^+ cancers only. Consequently, differentiating between factors increasing the risk of HPV infection and

cofactors interacting with HPV to promote carcinogenesis is difficult. Herein, we limit our discussion to HIV infection, immunosuppression and tobacco consumption, for which the evidence is most robust[145,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,189,209,210,211,212,213,214] (Box 1).

HIV infection

People living with HIV and acquired immunodeficiency syndrome (AIDS) have a greater risk of anal high-grade intraepithelial lesions and HPV-related cancers relative to the general population[189,211,212,215,216,217]. Moreover, people living with HIV, and especially those with AIDS, develop HPV-related cancers at younger ages than HIV-seronegative individuals[211,215]. A systematic review of data from 64 studies involving 29,900 men found an increased risk of anal HSIL associated with HIV in HPV16-positive men who have sex with men (adjusted prevalence ratio 1.19)[216]. Analysis of data from the French Hospital Database on HIV found that people living with HIV had standardized incidence ratios for invasive anal SCC of 109.8 in men who have sex with men, 49.2 in heterosexual men, and 13.1 in women, relative to the general population[218]. Highly active antiretroviral therapy (ART) has reduced the risk of virus-related cancers in people living with HIV, although these individuals remain at increased risk of HPV-related cancers relative to the general population: the standardized incidence ratio of anal cancer in HIV-infected individuals in the USA declined from 22.1 in the period 1996–1999 to 14.8 in the period 2009–2012; declines were also observed for cervical cancer, but not for vaginal, vulvar, penile and HPV-related oropharyngeal cancers over the same time period[219]. A meta-analysis found that although ART use is associated with a 35% lower odds of high-risk anal HPV prevalence but not with a lower risk of anal cancer incidence, ART use with sustained undetectable HIV viral load is associated with a 44% lower rate of anal cancer[220]. Therefore, although the benefits of ART for reducing anal cancer risk remain controversial[221], the evidence suggests a potentially low to moderate benefit of ART for anal cancer risk reduction.

Immunosuppression

In individuals living with HIV, immunosuppression (characterized by a low $CD4^+$ T cell count) is associated with increased risk of progression of low-grade to high-grade squamous anal intraepithelial lesions, and increased incidences of high-grade squamous anal intraepithelial lesions and invasive anal cancer, with a relative risk of 1.34 for the latter in men[189,212]. Similarly, patients with autoimmune diseases such as lupus, Crohn's disease and psoriasis who receive immunosuppressive treatments and solid organ transplant recipients have standardized anal cancer incidence ratios of 1.3–1.6 for combined autoimmune diseases and 14.4 for solid organ transplant recipients relative to the general population, although the effect varies by specific autoimmune disease[73,222].

Tobacco use

Tobacco smoking has been associated with increased risk of vaginal, vulvar and anal cancer owing to an increased risk of persistent HPV infection[214]. Women treated for vulvar or vaginal precancerous lesions and who smoke are 1.61–2.97 times more likely to have recurrence or progression to cancer than those who do not smoke[223]. Although tobacco consumption is also a major risk factor for head and neck cancers, biological and epidemiological evidence supports the notion that HPV-associated oropharyngeal cancers and tobacco-associated oropharyngeal cancers have separate aetiologies[210,213]. Given that oropharyngeal cancers caused by tobacco can occur in individuals who test positive for HPV and HPV-associated oropharyngeal cancers can occur in individuals who smoke, whether the molecular and cellular mechanisms affected by tobacco use

and HPV infection interact to increase oropharyngeal cancer risk remains unclear. To disentangle these associations, researchers need to perform formal tests of interaction to determine whether the risk of oropharyngeal cancer departs from additive risks expected from exposure to both HPV and tobacco. Such studies have generally not revealed synergistic interactions between the two risk factors, and instead have consistently shown either no interactions or no effect of tobacco use among HPV-positive individuals[224,225,226,227]. Therefore, although ample evidence supports the notion that HPV infection and tobacco consumption are independent risk factors for oropharyngeal cancer, the currently available evidence suggests that smoking is not a cofactor in HPV-associated oropharyngeal cancers.

Social inequalities

Although virtually all individuals get infected with HPV during their lifetime[167], demographic and socioeconomic factors strongly influence the burden of HPV-associated cancers. The incidence of HPV-associated cancers is substantially higher in women than in men, mainly owing the contribution of cervical cancer[12]. Socioeconomic factors are also important determinants of outcomes from HPV-associated cancers.

Cervical cancer

Disparity between countries

The considerable worldwide geographical disparities in incidence of and mortality from cervical cancer (40-fold to 50-fold variation in national incidence rates) are closely related to the average human development of each country[188]. In particular, the incidence and mortality rates of cervical cancer are highest in countries with low human development (defined as a low human development index (HDI))[228], and decrease sharply with increasing HDI levels (Fig. 3). Accordingly, the burden of cervical cancer is very high in countries in Africa, Latin America and Asia, and relatively low in countries in northern and western Europe, and North America.

Disparity within countries

Consistent with socioeconomic development being a good predictor of the national incidences of cervical cancer, the individual socioeconomic status of women within each region is associated with the distribution of cervical cancer in that population. Indeed, several studies in both HICs and LMICs have documented that women with low socioeconomic status are more likely to develop and die from cervical cancer relative to their more affluent fellow citizens[229,230,231]. A study with results published in 2023 compared the social gradient in cervical cancer mortality across several countries in Europe[232]. In agreement with other studies, inequalities in cervical cancer mortality attributable to level of education were observed in every country in Europe: mortality was higher in women with lower education levels relative to those with intermediate and especially high levels of education. The study also showed that the magnitude of these inequalities varies greatly across countries, being smaller in those with a higher HDI (northern and western Europe) and larger in those with lower HDI (Baltic countries and eastern Europe) (Fig. 4). An important novel observation from this study is that women with a high level of educational attainment have similarly low mortality from cervical cancer regardless of where they live in Europe but, conversely, mortality rates among those with lower levels of education vary depending on the country of residence. Although similar comparative studies do not exist outside Europe, some general conclusions can be drawn. At the individual level, these data suggest that women with a high socioeconomic status might be able to ‘protect’ themselves from cervical cancer to a great extent regardless of where they live. Conversely, the risk of dying from cervical cancer among those of low socioeconomic status strongly depends on the country in which they

live, and that country's health-care system. At the population level, these results imply that differences in national incidence and mortality rates from cervical cancer are driven by differences among women of low socioeconomic status.

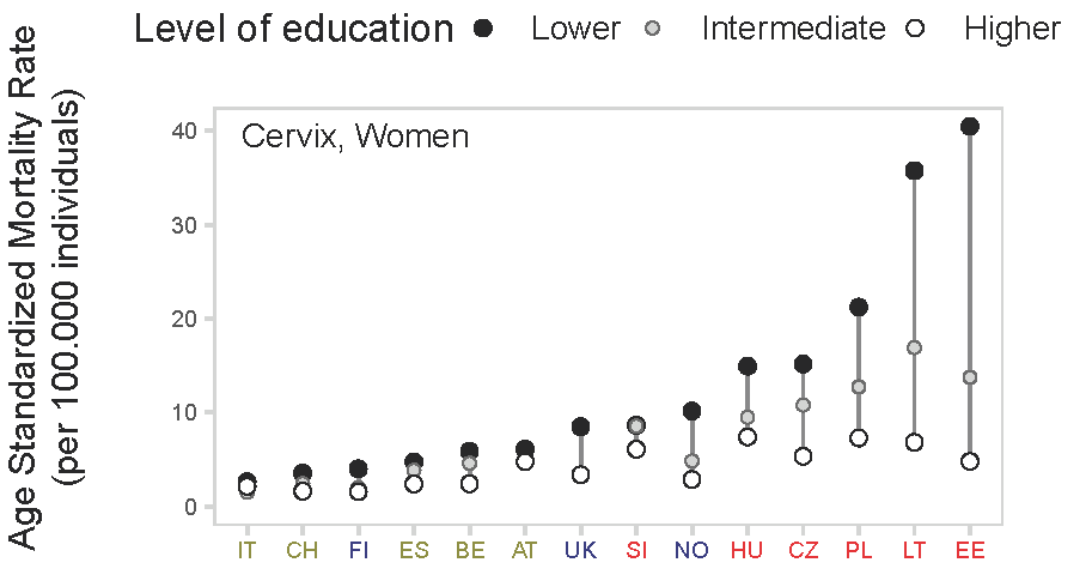

Fig. 4: Correlation between cervical cancer mortality and level of education attainment across European countries. *Cervical cancer mortality rates are age-standardized according to the European Standard Population 2013 revision[295]. Lower, intermediate and higher education levels correspond to the 1997 International Standard Classification of Education (ISCED) categories 0–2, 3–4 and 5–6, respectively[296]. Adapted with permission from ref. [232], Elsevier.*

Causes of the social gradient

Socioeconomic inequalities in the incidence of and mortality from cervical cancer between and within countries predominantly stem from a combination of several factors, the most important of which is the unequal availability and access to effective screening. Despite the general declines in cervical cancer incidence observed in the past decades in most regions worldwide (Fig. 1), further improvement is unlikely to be observed within the next few decades without the implementation and scaling up of screening and vaccination initiatives. Even countries with cervical cancer screening programmes have a social gradient in participation rates[233,234,235,236,237,238,239], which is particularly pronounced in countries in which screening programmes are not well organized[240]. Countries with effective screening programmes in place, with a high level of coverage across all societal segments of the population, and where testing is followed by proper diagnosis, follow-up and management of women with positive results, are more likely to show smaller inequalities in cervical cancer mortality; consequently, their average national burden is low[48]. Some studies have also found social gradients in HPV infection prevalence[241,242], albeit other studies have not found such differences[243], and thus the correlation between socioeconomic status and HPV prevalence is not as consistent worldwide as that between socioeconomic status and screening coverage. Inequalities in the distribution of the cofactors discussed in this Review — especially multiparity, which is strongly related to the socioeconomic status of women and their country of residence — could also contribute to the observed inequalities in the burden of cervical cancer[244]. Unequal

uptake of HPV vaccination could also eventually affect the cancer social gradient[245,246,247,248,249]. Nevertheless, the full effect of this gradient on cervical cancer incidence has not yet been observed although, interestingly, a study conducted in Scotland with results published in 2024 has shown that declines in cancer incidence attributable to vaccination are largest among women living in the most deprived areas[99].

Implications for cancer elimination

The strong association between socioeconomic status and cervical cancer has implications for the control of this malignancy and for achieving the WHO Cervical Cancer Elimination Initiative targets. In 172 out of 185 countries or territories, incidence rates still exceed the set elimination threshold, often by a considerable margin[188] (Fig. 3). Effective approaches to achieving cervical cancer elimination within the next century need to be designed with consideration of the individuals and social groups in which disease burden is highest, in order to achieve the 90–70–90 targets in the most disadvantaged populations. The implications for other HPV-related cancers and other malignancies are that, even when effective preventive measures are sustained for extended periods of time, reducing the burden of disease without addressing socioeconomic inequalities is not possible. Implementing policies and interventions specifically designed to increase health equity is needed. For example, substantial evidence indicates that providing free HPV vaccination primarily through a universal schooling system reduces barriers to vaccination and increases vaccination equity[246,250]. HPV self-sampling tests are widely viewed as another intervention that could help to reduce barriers to cervical cancer screening for many women[251]; indeed, a randomized intervention in the USA showed that direct mailing of HPV self-collection kits with scheduling assistance increases uptake of cervical cancer screening among under-screened women[252].

Other HPV-associated cancers

Evidence on the role of socioeconomic inequalities in the burden of HPV-associated cancers other than cervical cancer remains less robust than that for cervical cancer. Given that most studies do not distinguish between cancers attributable or not to HPV, whether documented inequalities are caused by the distribution of HPV and its cofactors, or by the distribution of other aetiological factors (such as tobacco and alcohol consumption), is not always clear.

Oropharyngeal cancer

The incidence of oropharyngeal cancer is higher in men than in women worldwide, with a male to female rate ratio of 4.8 (refs. [61,213]). This incidence varies substantially across countries worldwide, with a difference of >20-fold among men and >50-fold among women between the countries with the highest and the lowest incidence[49,191]. In contrast to cervical cancer, incidence rates of oropharyngeal cancer are higher in countries with higher HDI[49]. Regarding the role of social factors within countries, a large global consortium-led study of pooled data from 31 studies found that a lower level of educational attainment is associated with a higher risk of developing most subtypes of head and neck cancers worldwide[253]. Although part of the association between level of education and risk of oropharyngeal cancer results from differences in smoking and alcohol consumption, the study found that two-thirds of differences attributed to education level could not be explained by these behaviours. This result suggests a potential role for HPV and its cofactors in the social gradient in oropharyngeal cancer incidence.

Anal cancer

In 2020, the incidences of anal cancer in women and in men were similar worldwide[254]; however, the gender ratio can vary substantially between countries and many HICs have reported higher

incidence among women than among men[52,71,72]. Social inequalities affect the risk of developing and dying from anal cancer, as observed for individuals with lower socioeconomic status and for individuals of African American ethnicity in the USA[255,256,257]. HIV seropositivity and smoking are important cofactors that could drive the observed social inequalities observed for this disease[258].

Penile cancer

The incidence of and mortality from penile cancer is heterogeneous across countries worldwide, with a particularly high burden in Africa and Latin America[66,191]. The relationship between incidence and country-level HDI is less strong for penile cancer than for other HPV-associated cancers[66]. Within countries, however, lower socioeconomic status is correlated with higher incidence and mortality because this cancer type is particularly common among men with low income and low levels of education, and in those living in socioeconomically deprived areas[259,260,261,262].

Vaginal and vulvar cancer

Vaginal and vulvar cancers have a low incidence worldwide; therefore, available evidence on socioeconomic disparities is more limited. However, studies from England and Denmark indicate that women living in the most economically deprived areas are nearly twice as likely to be diagnosed with and die from these two cancer types than those living in the most affluent areas[259,260].

Lessons from cervical cancer

Cervical cancer is the first tumour type with an established elimination strategy, and thus many lessons from this malignancy can guide approaches to control other cancer types. Many issues relating to implementation, including political and economic aspects, need to be addressed to achieve the present targets and have been described in detail elsewhere[263,264]; herein we focus on the two that are most related to the major themes presented in this Review.

The first and most important lesson is that no single preventive intervention is sufficient to achieve cancer elimination. Although having HPV as a necessary cause of cervical cancer makes its primary prevention perhaps more straightforward than that of other malignancies, vaccination alone is highly likely to be insufficient to eliminate cervical cancer, and action on screening, treatment and HIV control are also important[4,265]. Theoretically, a sustained high level of vaccination coverage of >90% alone can lead to a long-term reduction in the incidence of cervical cancer below the elimination threshold[11,266]; however, whether many countries will be able to achieve, let alone maintain, this target is unclear. As of 2020, only five countries worldwide have been able to reach >90% vaccination coverage in adolescent girls owing to numerous challenges[267]. Vaccine hesitancy continues to plague many countries and periodically leads to reductions in HPV vaccination coverage in both LMICs and HICs[268,269,270,271,272,273]. Public confidence crises are therefore not the exception, but rather the rule, and need to be effectively managed to prevent long-term erosion of vaccination coverage. Crises, such as the COVID-19 pandemic, political instability and/or financial crises, can also lead to declines in vaccination coverage and missed prevention opportunities[274,275,276]. Given that HPV vaccination is a prophylactic approach, benefits can only be observed several decades after the start of a vaccination programme. This limitation means that in the next few decades a substantial proportion of cervical and other HPV-associated cancers will not be prevented by vaccination. Secondary prevention through screening remains highly important, both to prevent cervical cancer in women who are too old to benefit from HPV vaccination, and to act as a safeguard for

the predictable periodic drops in vaccine coverage. Although vaccinated women will eventually need fewer screening investigations in their lifetime than those who are not vaccinated, most studies suggest that these women could still benefit from two to five lifetime screenings to maintain a low risk of cervical cancer, with the optimal number varying between countries[277,278,279]. The need for concerted primary, secondary and tertiary prevention is not unique to cervical cancer, and thus, despite the availability of HPV vaccines, developing screening methods for HPV-associated cancers such as anal and oropharyngeal cancers is an active area of research[146,149,156,280,281,282].

The second aspect learned from the experience with cervical cancer is the need to consider social determinants of health and health equity to achieve cancer elimination. The global Cervical Cancer Elimination Strategy focuses on a country-level elimination threshold of four cancers per 100,000 women[4]. Even if countries could achieve this target as a national average, cervical cancer rates would probably remain higher in less-advantaged women as well as in specific subpopulations owing to the highly unequal distribution of cervical cancer within countries. For example, although Australia is poised to be among the first countries to reach the cervical cancer elimination target at the national level[283], incidence rates remain two to three times higher in Indigenous Australian women relative to non-Indigenous women[284], and thus the elimination target might not be met in all subpopulations. In the USA, projections indicate that highly economically deprived counties will need substantially longer time to reach elimination targets than less deprived ones[285]. We argue, as others have[286,287], that achieving cervical cancer elimination requires not only national strategies, but also a focus on the social determinants of health and on achieving the elimination threshold in the most deprived and in equity-deserving subpopulations at highest risk of cancer. Elimination will not be a reality if it cannot be achieved for all.

The WHO Cervical Cancer Elimination Initiative mentions the need for approaches tailored to vulnerable and under-served populations, as well as equity-oriented targets[4], but does not identify any specific populations or socioeconomic groups of interest, leaving individual countries to interpret how this recommendation applies to their local situation. Although the subpopulations at high risk of cancer can differ between countries, they are likely to be characterized by socioeconomic disadvantages or affected by discriminatory social and institutional power structures such as systemic racism, colonialism and class structures. Achieving elimination of cervical cancer in these groups is therefore complex, and cancer control action plans should involve community engagement to identify the most appropriate strategies. Building infrastructure for disaggregated data collection is also important for equitable surveillance, monitoring and evaluation. For example, the action plan for the elimination of cervical cancer in Canada includes action points to improve data collection on sociodemographic factors correlated with HPV vaccination coverage, and to engage with communities to identify cervical cancer prevention strategies that take into account the self-determined priorities of Indigenous populations[288]. New technologies, such as HPV self-sampling tests, are unlikely to reduce health inequalities unless they are combined with outreach efforts for under-screened populations, such as direct mailing of test kits[289]. Cervical cancer is far from the only cancer with striking socioeconomic gradients in incidence within countries[290,291,292]. Solutions for data collection and disaggregation, and community engagement initiatives developed for elimination of cervical cancer can therefore serve as a framework to reduce health inequalities for other cancers.

Conclusions

In this Review, we provide an overview of worldwide long-term trends in the burden of several HPV-associated cancers, addressing cofactors and social determinants of health that influence epidemiological trends. Although technological advances have provided tools that can be used in primary and secondary prevention of HPV-associated cancers, the more difficult task of implementing these tools lies ahead. Models predict that, even if the 90–70–90 WHO targets are met by 2030, most countries might only be able to achieve the elimination threshold for cervical cancer by the second half of the 21st century owing to the long-term effects of vaccination[11,266]. Therefore, focusing on mortality reduction in the short to medium term through the implementation and scaling up of cancer screening and treatment is crucial[138]. Cervical cancer is far from the only cancer with a long time between prevention and reduction in incidence; over 50 years of tobacco control were necessary to lead to sizeable reductions in lung cancer incidence, and control approaches will still be needed in the long term[293]. In conclusion, even more than science, cancer elimination requires leadership, vision and a commitment to the next generations.

Contributions

R.T. and S.V. researched data for the article. T.M. and E.L.F. contributed substantially to discussion of the content. All authors wrote, reviewed and/or edited the manuscript before submission.

Competing interests

T.M. is a board member of the International Papillomavirus Society. E.L.F. has received personal fees from Merck, and holds a patent related to the discovery of DNA methylation markers for the early detection of cervical cancer, which is registered at the Office of Innovation and Partnerships, McGill University, Montreal, Quebec, Canada. R.T. and S.V. declare no competing interests.

Additional information

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