# COURSE: Evidence-Based Approaches to HPV Screening implementation

## Module 1. Natural history of HPV and cervical cancer


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# INTRODUCTION AND LEARNING OBJECTIVES

A significant understanding of the natural history of cervical cancer, particularly over recent years, has contributed to the success and improvement of cervical cancer prevention. It has facilitated the development of vaccines for primary prevention and enabled targeting of precancerous lesions and the development of novel molecular screening technologies.

This module covers the natural history of HPV infections and the carcinogenic process, and how this relates to cervical cancer prevention.

At the conclusion of this course, participants will be able to:

- Examine the HPV virus life cycle and the process of carcinogenesis.
- Interpret the role of the HPV types in cancer risk stratification.
- Examine the epidemiology of HPV infections and precancerous lesions.
- Interpret the current classification of precancerous lesions and its implications for screening.
- Assess the burden and attributable fractions of HPV-related cancer.

# UNIT 1. HUMAN PAPILLOMAVIRUS

## 1.1 What is HPV?

HPV, or human papillomavirus, does not refer to a single virus but to a group of over 200 different viral types from the papillomaviridae family which are able to infect humans. All these types share the same genome structure and organisation: a circular double-stranded DNA genome that contains the following 3 regions:

- The **control region** or LCR regulates viral replication.
- The **early region** encodes seven proteins. E1 and E2 are involved in viral replication while E4, E5, E6 and E7 drive cell cycle entry, immune evasion, and viral release.
- The **late region** encodes the L1 and L2 proteins involved in the formation of the capsid or external membrane of the virus (viral packaging).

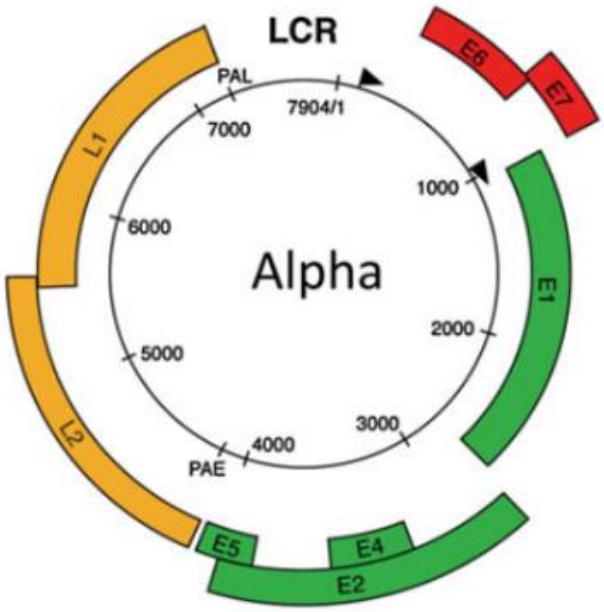



**Figure 1. HPV genome structure.** Adapted from Doorbar et al., 2015

**Did you know?**

L1 proteins can self-assemble to form the capsid or external membrane of the virus. When produced in the laboratory, these self-assembled molecules lack viral DNA. These empty structures, called *virus-like particles* or VLPs, are used in current HPV vaccines. When inoculated into humans, VLPs trigger an immune system response with no risk of developing a productive HPV infection because of the absence of viral DNA.

Human papillomaviruses have specific survival strategies and are phylogenetically classified in five genera –Alpha, Beta, Gamma, Mu and Nu– based on their DNA sequence and their tropism to human tissue (mucosal or cutaneous):

- **Alpha**: These HPV types mainly infect anogenital mucocutaneous surfaces and the upper aerodigestive tract mucosa. This genus includes HPV types that can cause no apparent pathology as well as highly productive warts and those with carcinogenic potential.
- **Beta and Gamma**. Many of these HPV types are associated with non-apparent skin infections acquired in early childhood. They can persist and produce virus particles at low levels over years or decades.
- **Mu and Nu**: These genera include very few HPV types. These infect cutaneous tissue causing benign skin lesions such as cutaneous papillomas or warts that are typically cleared by a cell-mediated immune response after months or years.

**Did you know?**

When the DNA sequences of two viruses differ by more than 10%, they are classified as different types. When the difference is less than 10%, they are classified as variants or isolates within the same HPV type. These variants or isolates have been linked to the natural history of HPV infections and related outcomes.

***Oncogenic HPV types are not only responsible for cervical cancer but also contribute to some head and neck cancers as well as other anogenital cancers such as vulvar, vaginal, penile, and anal.***

**Did you know?**

Time to disease differs significantly based on the outcome under study. These differences have been used to measure the impact or the effectiveness of HPV vaccines over the short (anogenital warts), medium (precancerous lesions) and long term (cervical cancer).

For more information, please refer to **MODULE 6**.

Based predominantly on cervical cancer, a total of 12 HPV types are established carcinogens and were classified by the International Agency for Research on Cancer (IARC) / World Health Organization (WHO) in 2012 as Class 1 carcinogens (commonly called ***high risk HPV types - hrHPV***). These are: HPV16, HPV31, HPV33, HPV35, HPV52 and HPV58 (in Alpha-9); HPV18, HPV39, HPV45 and HPV59 (Alpha-7); HPV51 (Alpha-5); and HPV56 (Alpha-6).

HPV68 (Alpha-7) is a probable carcinogen or Class 2A in the IARC classification. Several others are possibly carcinogenic in extremely rare circumstances. These include HPV types 5, 8, 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 and 97, classified as Class 2B .However, among these, a recent systematic analysis of the global literature led by the IARC including more than 100,000 cervical cancer cases only considered attributable HPV types 26, 69, 73 and 82 although very weakly carcinogenic (Wei et al., 2024 **RISCC**).

## *The HPV types detected by current HPV tests used in screening are under discussion*

Most HPV screening tests target the 12 high-risk types as well as HPV types 68 and sometimes 66. However, the risk of progression to cervical cancer differs significantly by HPV type. Identification of highly prevalent HPV types with a very low risk of progression can result in a substantial number of women receiving unnecessary treatment and follow-up.

***NOTE:*** *For more information on the use of genotyping in screening, please see* ***MODULE 3****.*

## 1.2 How is HPV acquired?

Anogenital HPV is mainly transmitted through contact with anogenital and oral mucosa (i.e vaginal or anal intercourse or oral sex). The following therefore carry a higher risk of contracting HPV:

- Earlier initiation of sexual activity.
- An increasing number of lifetime sexual partners.
- Factors concerning the sexual contacts of partners.

The average pattern of these three characteristics is key in determining the average age-specific prevalence of HPV infection in a given population.

Other forms of non-penetrative transmission have been occasionally reported, such as skin-on-skin genital contact (e.g. penile-vulvar or vulvar-vulvar) and mother-to-child transmission, though are not major routes of infection. HPVs have also been isolated from surfaces but their ability to transmit and cause productive infection has yet to be established.

## 1.3 Is HPV common?

Cervical HPV is one of the most common sexually transmitted infections worldwide in both sexes. An estimated 80% of sexually active individuals will become infected with HPV at some point in their lives, though 90% of these infections are asymptomatic and transient.

The *HPV prevalence* in the cervix by age largely depends on the sexual behaviour of a given population. Prevalence begins at the average age of sexual debut (adolescence), peaks at ages when the number of sexual partners is highest and starts to decline at increasing age as the number of sexual partners diminishes (around late-20s) and a natural immune response facilitates clearance.

***[Definition HPV PREVALENCE]*** *HPV prevalence, i.e. how many people are infected with HPV at a certain point in time, is a combined measure of newly acquired transient infections and the persistence/clearance of previously acquired infections in the absence of preventive measures.*

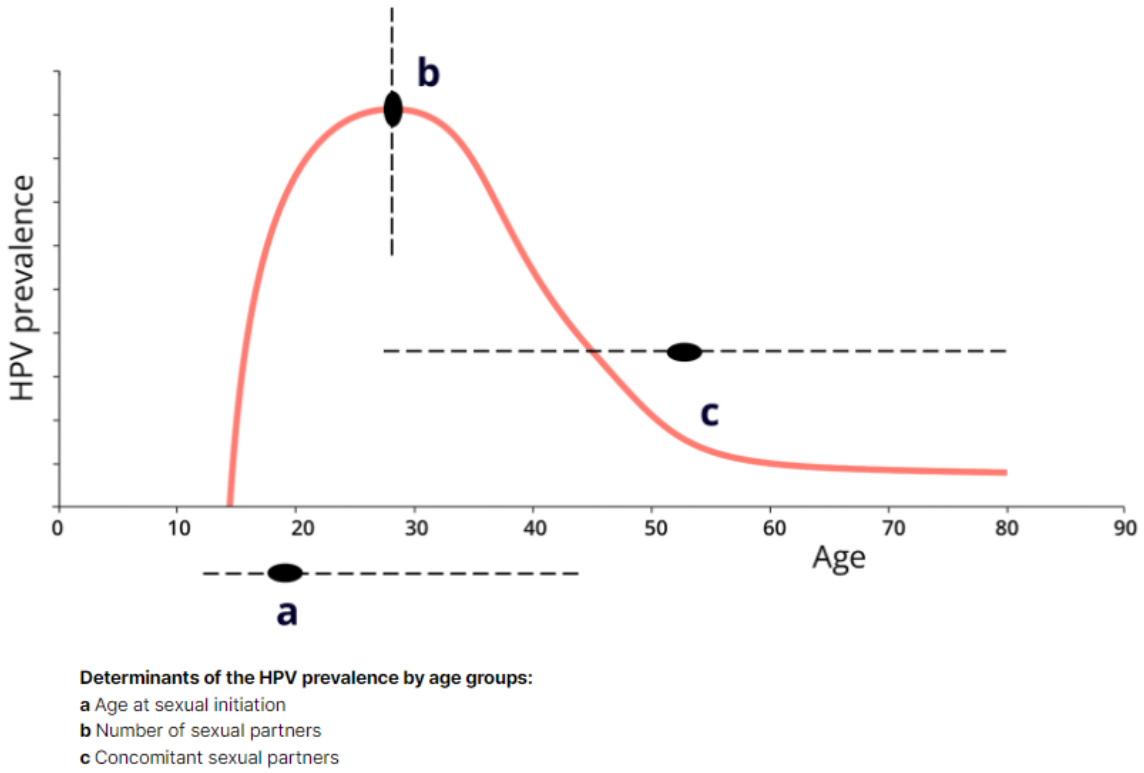



**Figure 2. Conceptual pattern of cervical HPV DNA prevalence by age.** Adapted from (de Sanjosé, Brotons, et al., 2018)

HPV prevalence stabilises at middle age, though some populations experience a second peak around menopause. The cause has not been fully established but is suspected to be associated with either newly acquired infections from new sexual partners or the reactivation of latent infections.

The presence of viral DNA does not necessarily imply a productive infection, whereas the presence of mRNA and viral proteins are likely expressing HPV activity in the host cell. However, in terms of clinical use, no clear distinction has been made for the use of DNA or RNA based tests.

**Did you know?**

An HPV test can be positive for different reasons: a new infection, reinfection, reactivation, a hidden low-level infection, autoinoculation, or just viral deposition after sex. The last one doesn't mean real infection or replication.

## 1.4 Are Women with a previous HPV infection protected from new ones?

The immune response to HPV may be insufficient in some women:

- Not all people seroconvert, i.e. they do not produce antibodies, as if they were never infected.
- Immune responses are type-specific, i.e. they may protect partially or fully against new infections with the same HPV type but not others.
- The risk of reinfection depends on antibody levels. Women with higher levels are less likely to be reinfected with the same HPV type than those with lower levels; the immune response may be slow and weak. Additionally, among women living with HIV, in many instances, immunity is impaired.

***Women who have cleared an HPV infection are still at risk of reinfection with other HPV types and/or potential reactivation of previously acquired infections currently in a latent state.***

**ACTIVITY**

Read the following statements and decide if they are TRUE or FALSE.

1. HPV refers to human papillomavirus, a single virus.
2. HPV established carcinogen types, called High risk HPV types, are: HPV16, HPV31, HPV33, HPV35, HPV52 and HPV58; HPV18, HPV39, HPV45 and HPV59; HPV51; and HPV56.
3. Oncogenic HPV types are responsible for cervical cancer, and some head and neck cancers, vulval, vaginal, penile and anal cancers.
4. A high number of sexual lifetime partners is an example of a sexual behaviour associated with increased risk of anogenital HPV.
5. Overall, the highest prevalence of HPV infection occurs during early adolescence, immediately after the first sexual relationships.
6. Women who have cleared a naturally acquired HPV infection are still at risk of reinfection with other HPV types.

The correct answers are:

1 False, 2 True, 3 True, 4 True, 5 False, 6 True.

# UNIT 2. FROM HPV INFECTION TO CERVICAL CANCER

## 2.1 HPV persistence

Only a minority of women infected with high-risk HPV types will develop precancerous lesions and cancer.

Most HPV infections, irrespective of HPV type, are transient and clear within a few months (i.e, no differences in clearance time by HPV type). Among those that *persist*, the clearance rate will be lower and type-dependent (for example, a lower proportion of HPV16 persitent infections will clear in comparison to those HPV58 persistent infections that will clear) but still, 80% of infections will not be detected two years following acquisition.

***[Definition HPV persistence]*** *Persistence is the detection of the same HPV type on two or more time-spaced tests. Rates of persistent infection depend on the time interval between tests. Although there is no clear biological threshold for time of infection to be considered persistent, there is a general agreement to suspect persistence if the infection has been detected for over 2 years.*

When infection persists –between 5% and 10% of infected women overall, and up to 20% in some circumstances such as the presence of a concomitant HIV infection – there is a high risk of developing precancerous lesions on the cervix that can progress to invasive cervical cancer.

**Did you know?**

Lack of detection can either be attributed to the absence of the virus in the tissue, or situations in which the virus is present but under immune system control resulting in very low activity that cannot be detected by DNA tests (i.e. a latent infection). Current tests cannot distinguish between these two states.

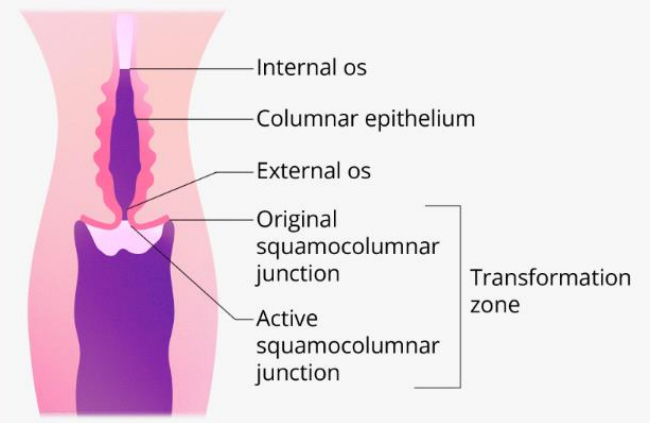
## 2.2 Carcinogenesis: How does It unfold?

Invasive cervical cancer includes several histological subtypes but the most common is squamous cell carcinoma, the HPV-related natural history of which is well understood.

In a productive infection, the virus life cycle most often begins when microtraumas or wounds in the cervical squamous epithelium enable the virus to reach and infect the epithelial basal stem cells. As the infected stem cells differentiate across the epithelial layers, the virus first expresses the E proteins for viral replication and, as it gets closer to the epithelium surface, produces the structural L proteins for virus assembly and release. Most recently, a potential role in cervical carcinogenesis is also attributed to reserve cells. These are pluripotential cells that are distributed underneath the columnar epithelium of the endocervical canal and the crypts.

**Did you know?**

In the cervix, most neoplastic lesions caused by HPV infections are detected in the cervical squamo-columnar junction of the cervical transformation zone, i.e, the point in which the squamous and columnar epithelium of the cervix meet. It is the existence of the metaplasic cells in the cervical junction and the transformation zone that could explain the higher incidence of cervical intraepithelial lesions and cervical cancer in comparison with nearby sites such as the vagina and vulva. The exact mechanism to explain why there is such increased susceptibility is still the subject of research.




In some cases, HPV induces cell proliferation in the basal and parabasal layers which is not compatible with a productive infection. It is thought that this process is mainly triggered by the increased activity and expression of the E6 and E7 viral proteins from high-risk HPV types. This persistent deregulated expression, and the accumulation of additional genetic errors, can eventually lead to cancer.

The following short video provides a visual representation of the process (1m28s): https://www.youtube.com/watch?v=7dyKKjIhwBM&feature=emb_logo

**Figure 3. Conceptual representation of viral carcinogenesis** (Jamie Doorbar, 2020)

***An overall understanding of the virus life cycle, and its carcinogenic process leading to cervical cancer, is crucial to correctly interpreting the results of screening and triage tests***

Viral DNA detection does not enable differentiation between a transient or a productive infection. Morphologic *tests*, like cytology, provide us with information on the severity of the cellular changes produced by the viral infection, though are affected by subjective evaluation. Molecular tests such as methylation, on the other hand, aim to discriminate progressive high-grade lesions that might require treatment from non progressive lesions.

***NOTE:*** *For more detailed information on the carcinogenic process, see the reviews from Burk et al., 2009, Doorbar et al., 2015 and Schiffman et al., 2016.*

## 2.3 Why do some infections progress to cancer?

The reasons why some infections progress to cancer are unknown, but some factors or cofactors, whether related to HPV infection or not, may play a role in the natural history of cervical cancer:

- **Viral factors**

These include the HPV type, variants and sublineages within type (Nelson & Mirabello, 2023), and the viral load (i.e. the amount of virus). The HPV type is the most important factor for persistence and progression to precancerous lesions, though is not the only one.

***The unparalleled carcinogenicity of HPV16 compared with other high-risk HPV types makes it one of the most important human carcinogens. In some screening programmes using HPV testing, genotyping allows to prioritize the management of women based on their risk of progression by HPV type.***

***NOTE:*** *For more information on the use of genotyping in screening, please see* ***MODULE 3****.*

- **Host cofactors**

These include endogenous hormones, genetic factors and other factors related to immune response, such as the immunosuppression associated with HIV infection, treatment of an autoimmune disease or an organ transplant.

***Women living with HIV have a higher prevalence of HPV infections and an increased risk of progression to cervical cancer. Therefore, these women usually require more exhaustive screening.***

***NOTE:*** *For more information on the link between HIV and HPV, please see* ***MODULE 7****.*

- **Environmental or exogenous factors**

These include long-term tobacco use, long-term use of oral contraceptives and high parity. Women with persistent HPV infections and any of these risk factors may be candidates for closer monitoring.

***Ideally, candidate environmental factors should be assessed in prospective studies to properly evaluate causality and the strength of the association. Nevertheless, adopting a 'wait and see' approach, delaying intervention until progression when prevention and treatment options are available, raises ethical concerns. Therefore, the association with smoking and high parity has been consistently observed only in cross-sectional studies.***

EXAMPLE

Using retrospective data from a cohort study with an average follow-up of 9 years, women with more than 3 full-term pregnancies had a two-fold increase in risk of developing severe precancerous lesions in comparison with women who had never been pregnant (Roura et al., 2016).

**Did you know?**

There is ongoing research on the cervicovaginal microbiota, which may play a role in HPV prevalence, persistence and progression by either acting as a barrier to HPV infection or modulating the innate and adaptive responses at mucosal and cutaneous surfaces. However, its impact remains uncertain.

## 2.4 The epidemiology of cervical intraepithelial lesions

The process of carcinogenesis has historically been considered as a continuum of disease that ranges from mild dysplasia to squamous cervical cancer over 5 to 15 years if not detected and treated. Multiple classifications have been in place trying to describe the process. However, our preferred approach, based on comprehensive scientific evidence (Lycke et al., 2025), is to describe the HPV carcinogenesis as the following few necessary stages (**Figure 4**):

1) *Infection* with a specific oncogenic or high-risk HPV type, which may or may not be detectable by molecular testing.
2) *Precancer*, defined as a persistent, transforming HPV infection associated with lesions and high likelihood of invasion if left untreated.
3) Invasive cervical cancer.

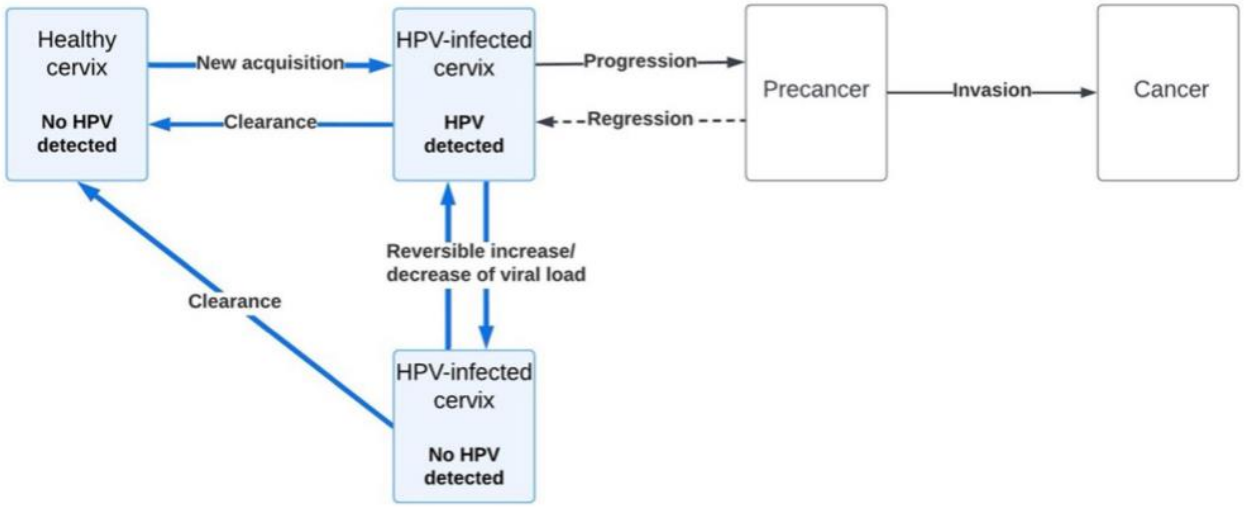



**Figure 4. Universal natural history of cervical carcinogenesis for health decisions in cervical cancer screening** (Lycke et al., 2025)

Cervical tissue in which no high-risk HPV is detected by DNA or RNA testing are included in the **Normal** step.

The **HPV infection** phase may also manifest as low-grade intraepithelial lesions **(LSIL)** or cervical intraepithelial neoplasia grade 1 **(CIN1)**. These lesions constitute a productive HPV infection that should not be considered a precancerous lesion per se. Their diagnosis is observer-dependent and there is a high likelihood of clearance. Many HPV types may be involved in these lesions, most of which do not have oncogenic potential. It should also be noted that HPV detection by molecular tests depends on the viral load; therefore, a negative result following a previous positive test could indicate either clearance or a transient period of undetectable infection.
Grade 2 intraepithelial lesions or CIN2 lesions may be induced by oncogenic or non oncogenic HPV types. Consequently, the assessment of a CIN2 lesion is enhanced when the HPV genotype is identified.

**Precancer** includes high-grade intraepithelial lesions **(HSIL),** CIN2 lesions induced by oncogenic HPV types and all CIN3, i.e a cancer precursor with a very high probability of invasion if untreated. Though many of these lesions will regress on their own, the difficulty in understanding which ones will progress mean that all are considered treatable to prevent potential invasion. Ongoing research is exploring the use of biomarkers to identify those CIN2 and CIN3 lesions with higher risk of progression.

EXAMPLE

A meta-analysis of follow-up data for women with untreated CIN2 lesions (Tainio et al., 2018) found that 2 years after the diagnosis:

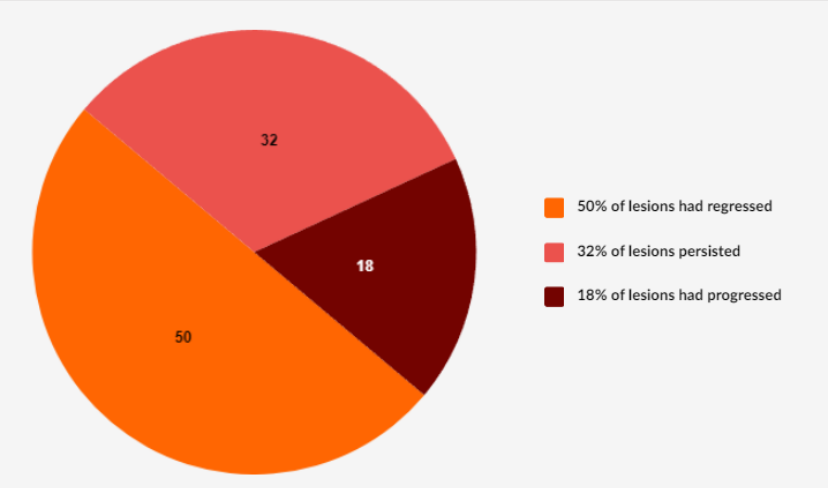



Figure 5. 2-year outcome of untreated CIN2+ lesions

**Did you know?**

Because of the heterogeneity of CIN2 lesions, the use of HPV genotyping is becoming a potential discriminator in defining a precancer status and therefore determining the need for treatment (Perkins et al., 2020).

***Data from various studies worldwide have identified that the key factors of progression are HPV type and the time passed since the infection has been detected.***

A critical aspect in the estimations of the prevalence of lesions is the age. Using data from the Swedish population-based screening programme from 2017, the highest burden of precancerous lesions occurs at young ages (**Figure 6**). While LSIL lesions are more frequent in the early-20s, HSIL lesions or worse are most prevalent in the late-20s and early 30s depending on societal average age of first sexual intercourse (leading to HPV infections).

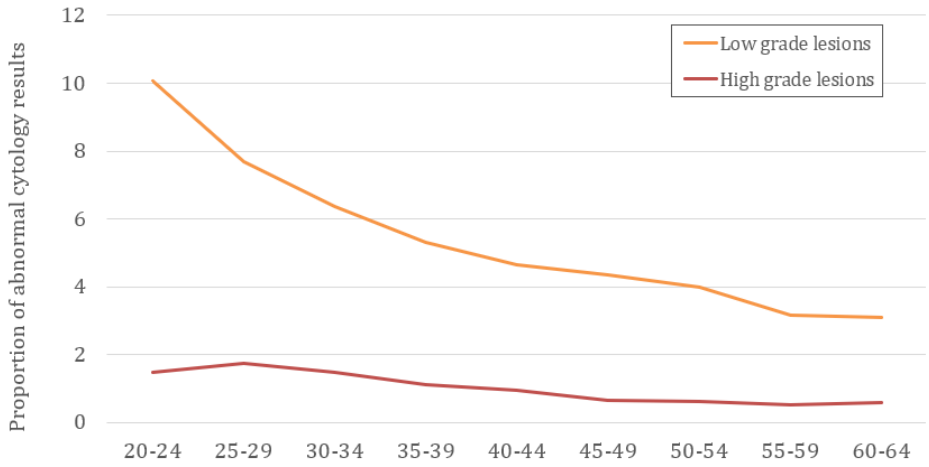



**Figure 6. Prevalence of precancerous lesions detected by cytology**, based on data from Sweden from 2017 available at the Nordscreen website (https://nordscreen.org/analysis/)

These prevalence values and age-related trends are likely to differ by country due to the country-specific background HPV prevalence. Furthermore, the existence of a screening programme may affect the detection of lesions as the screening process per se ´cleans´prevalent infections if the program is effective and has high coverage.

## 2.5 HPV detection in precancerous lesions

Although low- and high-risk HPV types can be detected in the cervix, detection of overall and specific HPV oncogenic types vary with increasing severity of lesions (**Figure 7**).

As described before, in women with no detected abnormalites, the detection of hrHPV will vary by age, region and prevalence of HIV. Accordingly, in screened women aged 30-50 years the prevalence can range from 5% to 20% although 70% can be reached in populations with a high prevalence of HIV. Women with acute infection with low grade morphological changes may have up to 50% detectable hrHPV, while the proportion will increase to 70-90% of women with precancerous lesions (CIN2/CIN3) and virtually all cases of cervical cancer will harbour an HPV infection (<5% of HPV-negative cases).

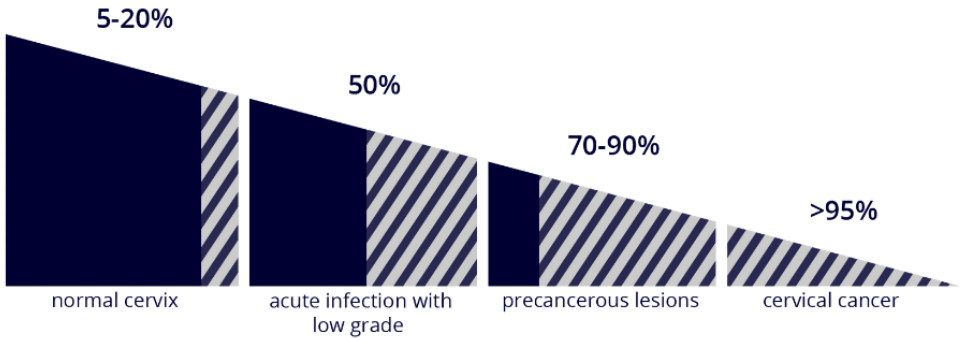



**Figure 7. HPV prevalence at the different stages of cervical cancer development**

***HPV is considered to be the necessary cause of the two main histological subtypes of cervical cancer, squamous cell carcinoma and adenocarcinoma.***

The absence of HPV detection in fewer than 5% of cervical cancer cases has been associated to slow progressing tumors that lose the viral markers over time and to mislabelled diagnosis of endometrial tumors (Pirog et al., 2014). The quality of the

specimen and the sensitivity of the HPV test used can also explain false negative results.

EXAMPLE

A recent study in Sweden (Arroyo Mühr et al., 2020) conducted redetermination of HPV using a more sensitive method and detected HPV in 169 out of 392 cervical cancer samples where HPV had not been detected previously.

Besides the increasing HPV prevalence, the relative relevance of each HPV oncogenic type also varies in the different carcinogenic steps from normal to cancer. At an increasing severity of **precancerous lesions**, especially HPV type 16, but also types 31 and 33 are present in a higher proportion of women with lesions than those with normal cytology (**Figure 8**).

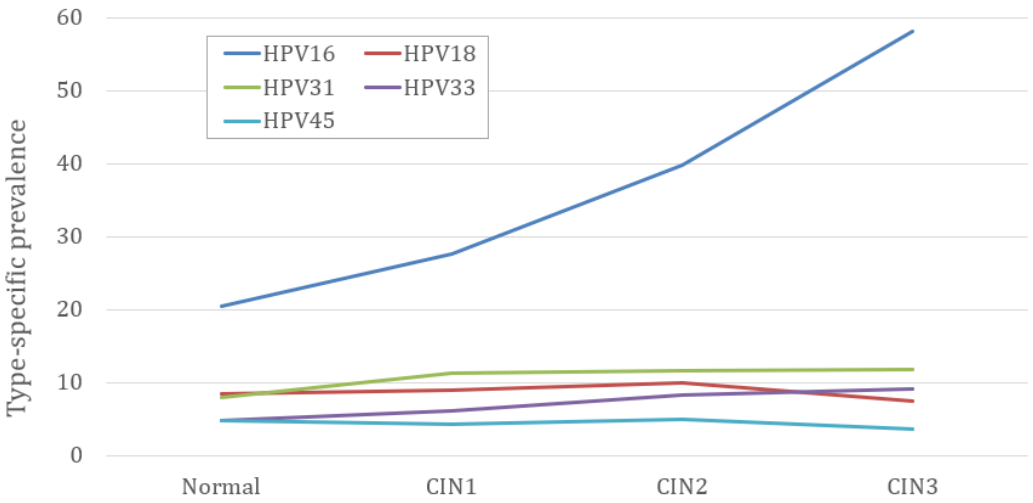



**Figure 8. Distribution of HPV type-specific prevalence in HPV-positive normal cervix and precancerous lesions** (Guan et al., 2012).

For ***cervical cancer***, the three most common and carcinogenic viruses are HPV types 16, 18 and 45 (**Table 1**). Over 90% of adenocarcinomas are due to HPV16,18 and 45.

**Table 1. HPV type-specific attributable fractions**. Table from IARC, 2022, updated with data from Wei et al., 2024 **RISCC**.

| | Attributable fraction (%) | IARC carcinogenic group |
|---|---|---|
| HPV16 | 61.3 | Group 1 |
| HPV18 | 15.7 | Group 1 |
| HPV45 | 5 | Group 1 |
| HPV33 | 3.8 | Group 1 |
| HPV58 | 3.6 | Group 1 |
| HPV31 | 2.8 | Group 1 |
| HPV52 | 2.4 | Group 1 |
| HPV35 | 1.7 | Group 1 |
| HPV59 | 0.9 | Group 1 |
| HPV39 | 0.7 | Group 1 |
| HPV56 | 0.6 | Group 1 |
| HPV68 | 0.3 | Group 2A |
| HPV51 | 0.3 | Group 1 |
| HPV73 | 0.4 | Group 2B |

**Did you know?**

HPV types with a higher prevalence in precancerous lesions and cervical cancer (HPV16, 18, 31, 33, 35, 45, 52 and 58) are included in the current nonavalent vaccine except for HPV35, which is especially important among women of African descent and that can explain about 10% of cancers in this population.

**ACTIVITY**

Read the following statements and decide if they are TRUE or FALSE.

1. Not all HPV types are oncogenic, but most women infected with high-risk HPV types will eventually develop precancerous lesions and/or cancer.
2. Morphologic tests, like cytology, provide us with information on the severity of the cellular changes produced by the viral infection, though are affected by subjective evaluation.

3. Tobacco use, genetic factors, HPV type or immune response capacity are all factors that seem to play a role in the progress of HPV infection to cancer.
4. The HPV type is the most important cofactor for persistence and progression to precancerous lesions. The unparalleled carcinogenicity of HPV16 compared with other high-risk HPV types makes it one of the most important human carcinogens.
5. The current understanding of cervical carcinogenesis includes the following stages/states: Infection, precancer and invasive cervical cancer.
6. All CIN2+ lesions, irrespective of the HPV type that has caused it, are to be considered in the precancer stage of the cervical carcinogenesis and therefore require treatment.
7. Among women with cervical disease (from acute infection to cervical cancer), the prevalence of HPV infection increases as the severity of disease increases.
8. The three most common viruses detected in cervical cancer are HPV types 31, 33 and 35.

The correct answers are:

1 False, 2 True, 3 True, 4 True, 5 True, 6 False, 7 True, 8 False.

# UNIT 3. THE BURDEN OF HPV-RELATED DISEASES

***NOTE:*** *Available burden data for 2022 is available at* ***Global Cancer Observatory: Cancer Today 2022****. Yet, the burden associated to HPV can not be estimated using these data. The current unit provides the 2020 data for comparison purposes.*

## 3.1 Cervical cancer

In 2020, around 604,000 new cases of cervical cancer were estimated worldwide, which represents 6.5% of all cancer cases and the fourth most common cancer in women of all ages. Yet, cervical cancer is the second most common cancer in women under 70 years old, constituting 8.6% of all cancer cases in this age group.

If we compare age-standardised incidence rates worldwide (number of new cases of cervical cancer per 100,000 women), we observe a wide range of incidences (1.9 in Iran to 80.2 in Eswatini). The lowest rates occur in developed and Middle-East countries and the highest rates in Sub-Saharian countries and Pacific islands (**Figure 9**).

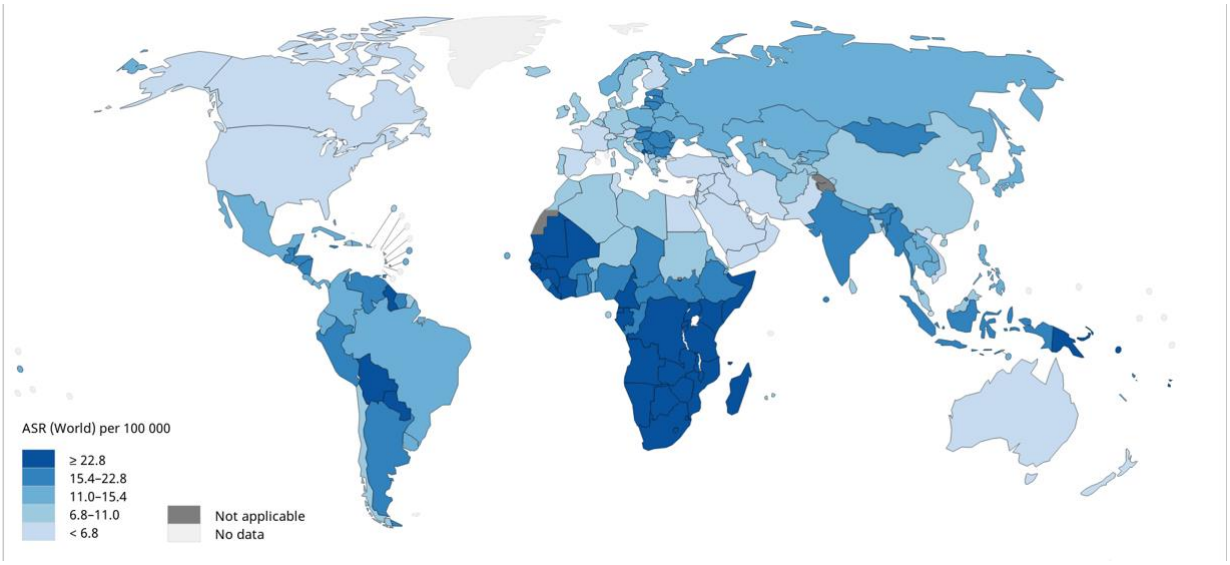
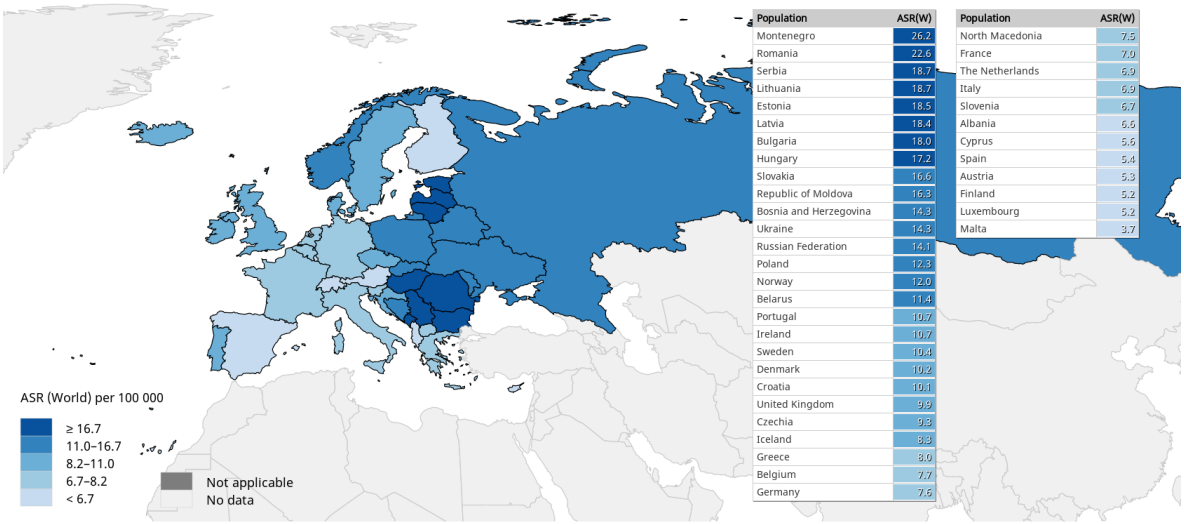



**Figure 9. Global estimated age-standardised incidence rates for cervical cancer among women aged 0-69 years in 2020**. Ref: Global Cancer Observatory: Cancer Today 2020 (Ferlay et al., 2020)

Within Europe, the highest incidences (>17 cervical cancer cases per 100,000 women) are observed in Eastern European countries, with Russia and Ukraine accounting for the 41.1% of the 58,000 cases of cervical cancer in Europe in 2020 (**Figure 10**).




| Population | ASR(W) |
|---|---|
| Montenegro | 26.2 |
| Romania | 22.6 |
| Serbia | 18.7 |
| Lithuania | 18.7 |
| Estonia | 18.5 |
| Latvia | 18.4 |
| Bulgaria | 18.0 |
| Hungary | 17.2 |
| Slovakia | 16.6 |
| Republic of Moldova | 16.3 |
| Bosnia and Herzegovina | 14.3 |
| Ukraine | 14.3 |
| Russian Federation | 14.1 |
| Poland | 12.3 |
| Norway | 12.0 |
| Belarus | 11.4 |
| Portugal | 10.7 |
| Ireland | 10.7 |
| Sweden | 10.4 |
| Denmark | 10.2 |
| Croatia | 10.1 |
| United Kingdom | 9.9 |
| Czechia | 9.8 |
| Iceland | 8.8 |
| Greece | 8.0 |
| Belgium | 7.7 |
| Germany | 7.5 |

| Population | ASR(W) |
|---|---|
| North Macedonia | 7.5 |
| France | 7.0 |
| The Netherlands | 6.9 |
| Italy | 6.9 |
| Slovenia | 6.7 |
| Albania | 6.6 |
| Cyprus | 5.6 |
| Spain | 5.4 |
| Austria | 5.3 |
| Finland | 5.2 |
| Luxembourg | 5.2 |
| Malta | 3.7 |

**Figure 10. European estimated age-standardised incidence rates for cervical cancer among women of all ages in 2020.** Ref: Global Cancer Observatory: Cancer Today 2020 (Ferlay et al., 2020)

***NOTE:*** *To properly assess the burden of cervical cancer in a specific setting, it is important to estimate different measures:*

- *If we divide the number of cases by the total number of inhabitants, we obtain the* ***crude incidence rate****. The fact that this rate depends on the country age structure hinders comparison between countries. Crude rates are therefore usually translated into a specific age structure to enable comparison (i.e.* ***age-standardised rates****). Crude rates show the real burden whereas age-standardised rates allow for comparison between settings.*
- *Low incidence rates can provide us with a false sense of security. In large populations, low rates can result in a substantial burden in* ***absolute numbers****: China and India have crude incidence rates of 10.7 and 18.0 but because of the large populations in these countries they account for 38.7% of total new cervical cancer cases worldwide and 39.9% of cervical cancer deaths observed in 2020.*

In 2020, around 342,000 women died of cervical cancer worldwide, constituting 7.7% of all cancer deaths and the fourth most common cause of cancer death in women of

all ages. Cervical cancer is the second most common cause of cancer death (12.4%) in women under 65 years old.

If we compare age-standardised mortality rates worldwide (number of deaths due to cervical cancer per 100,000 inhabitants), we observe a wide range of rates (1.0 in Switzerland to 54.5 in Malawi). The lowest rates are observed in high-income countries and the highest rates in resource-constrained countries, mainly in Sub-Saharan Africa (**Figure 11**).

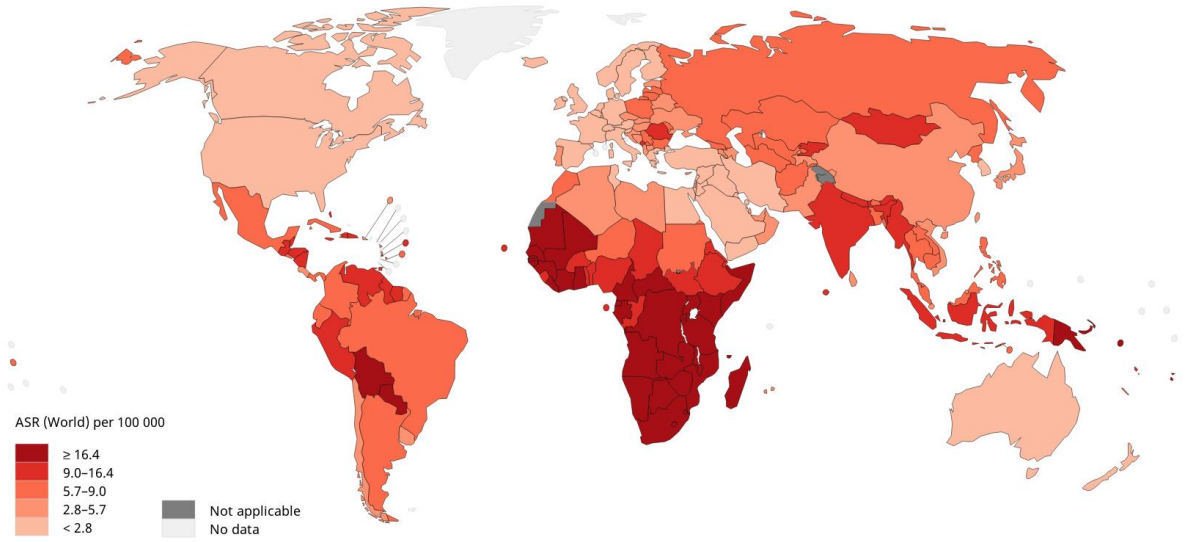



**Figure 11. Global estimated age-standardised mortality rates for cervical cancer among women of all ages in 2020.** Ref: Global Cancer Observatory: Cancer Today 2020 (Ferlay et al., 2020)

Within Europe, the highest mortality rates (>6 cervical cancer cases per 100,000 women) are observed once again in Eastern European countries, with Russia and Ukraine accounting for 38.7% of the 26,000 cervical cancer deaths in Europe in 2020 (**Figure 12**).

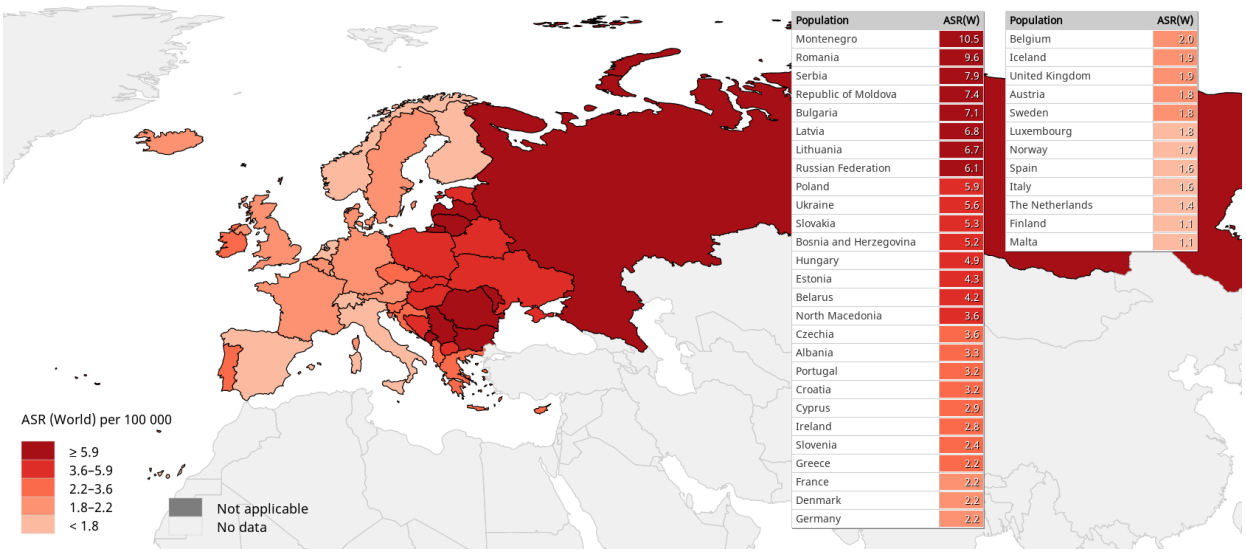



**Figure 12. European estimated age-standardised mortality rates for cervical cancer among women of all ages in 2020**. Ref: Global Cancer Observatory: Cancer Today 2020 (Ferlay et al., 2020)

Cervical cancer death rates are generally much lower than incidence rates. However, cervical cancer affects relatively young women and is therefore a major cause of potential years of life lost (i.e. premature death), a phenomenon exacerbated in resource-constrained countries where cervical cancer is the leading individual cause of premature death.

By age, the peak in the incidence rates varies largely by country from 30-34 years to over 65 years. In countries with a high screening coverage, cervical cancer incidence is the highest at age 35 years and remains more or less stable at relatively low levels. However, in countries with sporadic or no screening programmes, the incidence increases with age peaking at around age 55–64 years (Singh et al., 2022 **RISCC**).

## 3.2 Other HPV-related cancers

HPV infections have been detected and are suspected to be responsible (i.e. HPV-attributable fraction) in other anogenital and some head and neck cancers although in variable proportions (**Figure 13**). These proportions indicate the proportion of cases that could have been averted if HPV infections were prevented or treated before they caused cancer.

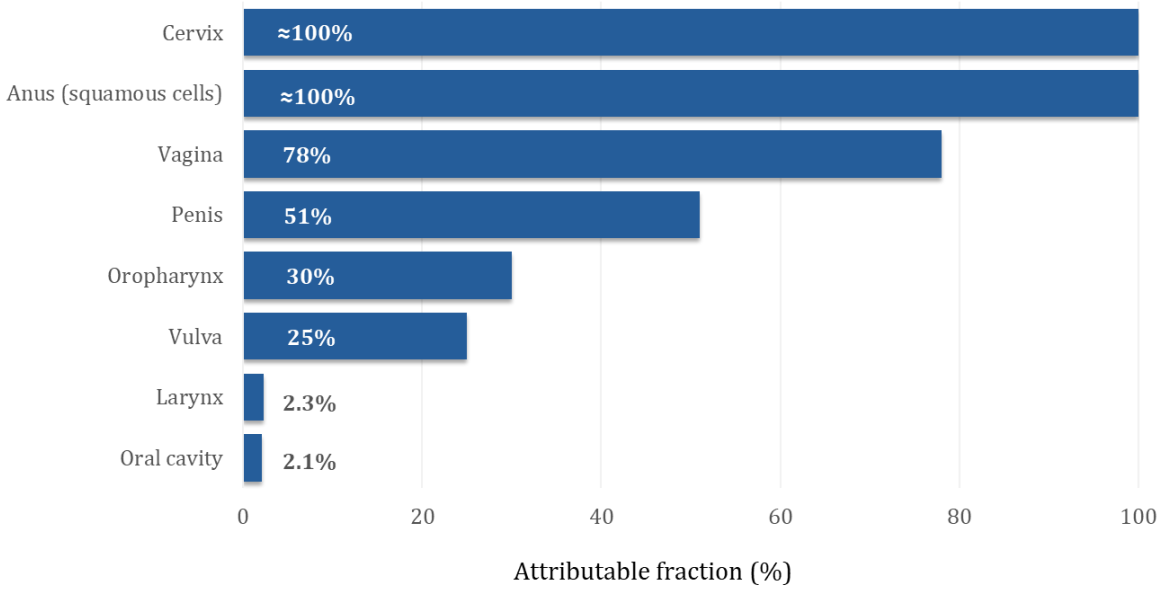



**Figure 13. HPV attributable fractions in HPV-related cases.** Adapted from de Martel et al., 2020.

Based on the above attributable fractions, in 2020, there were an estimated 126,000 diagnosed HPV-related cancer cases at sites other than the cervix (Global Cancer Observatory: Cancer Today 2020). When stratified by anatomical site, despite a smaller attributable fraction of 30%, the highest number of non-cervical HPV-related cancer than can be prevented are those in the oropharynx (**Figure 14**).

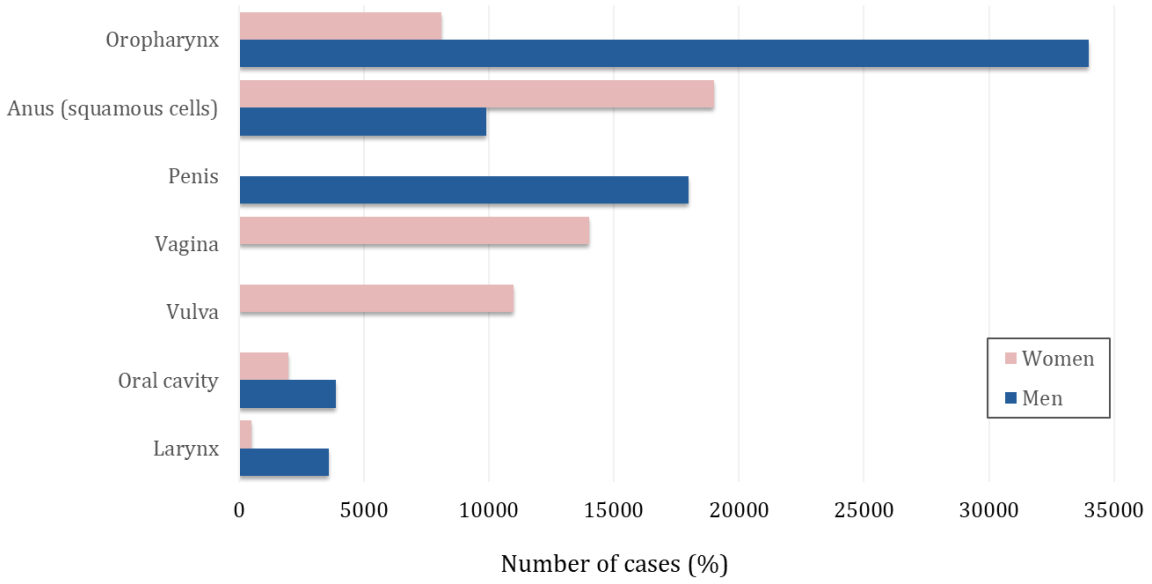



**Figure 14. Estimated number of non-cervical HPV-related cancers in 2018, by anatomical site and sex.** Adapted from de Martel et al., 2020.

***In 2020, there were an estimated total of 730,000 HPV-related cancer cases.***

As with cervical cancer, most of these tumours are caused by HPV16 although in different distributions (range: 44.4% in larynx to 90.9% in oral cavity). Accordingly, the contribution of the additional 6 HPV types included in the nonavalent vaccine (HPV18, 31, 33, 45, 52 and 58) ranges from 1.8% in oral cavity to 30.5% in laryngeal cancers (**Figure 15**).

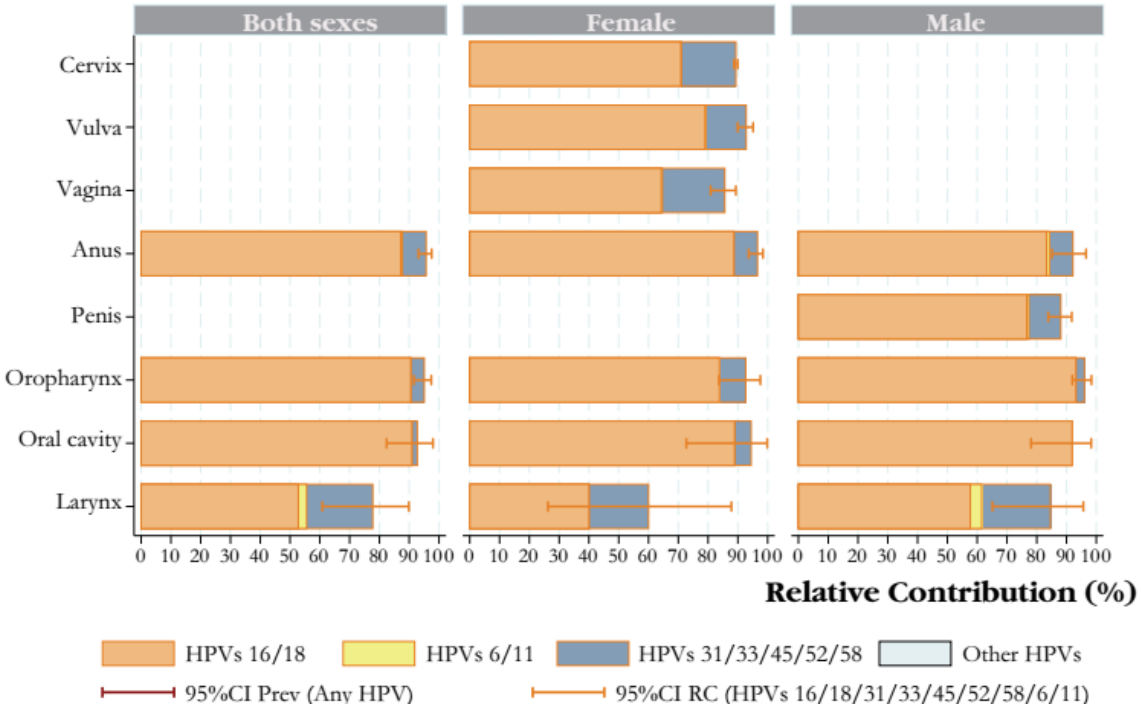



**Figure 15. Relative contribution of HPV types targeted by the HPV vaccines in HPV-related cancers** (de Sanjosé, Serrano, et al., 2018)

## 3.3 Cervical cancer prevention strategies

There are two main types of cervical cancer prevention strategies: primary prevention through ***HPV vaccination*** provided as part of the routine immunisation programme or via catch-up campaigns, and secondary prevention or ***screening*** usually between the ages of 25 and 65 years (**Figure 16**).


**Figure 16. Conceptual illustration of cervical cancer prevention strategies by age**

***In 2020, the WHO launched a global initiative to eliminate cervical cancer as a public health problem in the 21st century (WHO, 2020).***

Cervical cancer elimination is expected to be achieved through the achievement of the following objectivs by the year 2030:

- 90% of girls are vaccinated against HPV before age 15.
- 70% of women screened with a high-performance cervical cancer test at least twice by age 35 and again by age 45.
- 90% of women with cervical cancer or precancerous lesions treated or managed appropriately.

Cervical cancer will be considered eliminated as a public health problem when there are fewer than 4 cases per 100,000 women-years (elimination threshold).
With the WHO Elimination Campain, awareness of cervical cancer burden has increased, and many projects have been launched, particularly in low-resource settings, to reduce it. It is unlikely that by 2030 the world will have reached the three main pillars of the strategy (90,70,90). It is however expected that new or updated strategies in vaccination, screening and treatment will be in place in many settings to accelerate cervical cancer control.

***NOTE:*** *For more information on the WHO strategy, see https://www.youtube.com/watch?v=rTViRKW4PIU.*

## HPV vaccination

HPV vaccination as a primary intervention aims to prevent the acquisition of HPV infections. As of 2024, there are six licensed vaccines and further more under development (Kuter et al., 2021; World Health Organization, 2022). The main differences between these vaccines lie in the HPV types included in them:

- Bivalent vaccines (Cervarix® by GSK, Cecolin® by Xiamen Innovax and Walrinvax® by Walvax): HPV types 16 and 18
- Quadrivalent vaccine (Gardasil® by MSD and Cervavac by the Serum Institute of India): HPV types 16, 18, 6 and 11.
- Nonavalent vaccine (Gardasil 9® by MSD): HPV types 16, 18, 31, 33, 45, 52, 58, 6 and 11.

**ACTIVITY**

Given their proven high efficacy and safety, and based on the relative contribution of the HPV types included in the vaccines to HPV-related cancers, how many HPV-related cancers do you think could have been prevented if men and women alike had been vaccinated?

a) 0-50%

b) 50-70%

c) 70-90%

d) 90-100%

The correct answer is C.

The preventable fraction for each cancer corresponds to the type-specific prevalence of the HPV types included in each vaccine. If we apply these preventable fractions to the number of cases attributed to HPV in each specific HPV-related cancer, we obtain the number of cancers that could have been prevented.

Using burden data from 2018, the sum of the cancers that could have been prevented divided by the total number of HPV-related cancers equates to 73% of cancers prevented by

the bivalent and quadrivalent vaccines (HPV types 16/18) and 89% by the nonavalent vaccine (HPV types 16/18/31/33/45/52/58).

However, the vaccination coverage is too low to observe a substantial reduction in the global HPV-related burden. Worldwide, only 21% of girls and 6% of boys received a single dose in 2022 (World Health Organization, 2023). This is related to the following barriers:

- HPV vaccination has predominantly been introduced in developed countries. As of 2024, there are still many countries, particularly in Africa and Asia, without an HPV vaccination programme.
- In developing countries in particular, HPV vaccination has mainly targeted one or a few cohorts of adolescent girls. It will take around 20 years for a decrease in cervical cancer incidence to be observed (i.e. once vaccinated girls reach their early 30s).
- Routine gender-neutral vaccination (including both men and women) has been implemented in only 58 countries, primarily high-income countries (**Figure 17**).

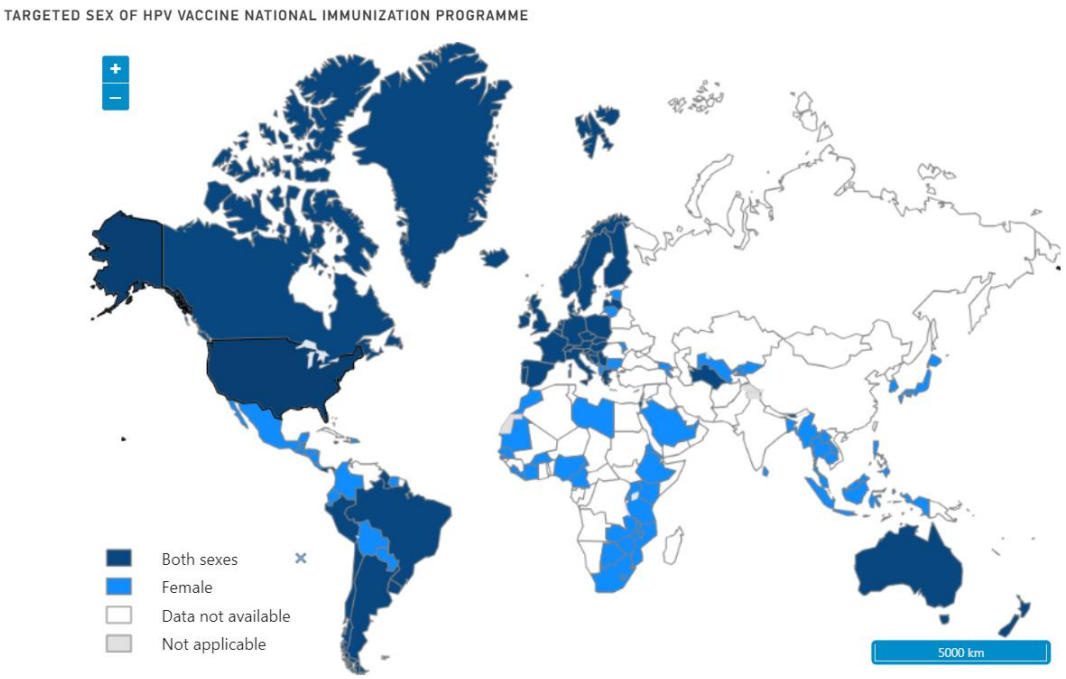



**Figure 17. Worldwide map of HPV vaccine introduction by targeted sex as of 2023** (World Health Organization, 2023)

## Cervical cancer screening

***Despite the availability of HPV vaccines, they do not include all HPV types and screening will remain necessary and the main preventive intervention in many settings for unvaccinated women.***

Screening is not just an initial test but a series of steps until diagnosis. When performed, it must be followed by effective treatment to be worthwhile. We'll dive into more details in the subsequent modules:

- On **MODULE 2** we will review the basic concepts to understand and assess the performance of screening tests and procedures as well as screening programs as a whole.
- On **MODULE 3** we will evaluate the options for primary screening in the asymptomatic population.
- On **MODULE 4** we will detail the options for triage tests for screenning-positive women together with diagnostic tests and managements options for precancerous lesions.
- On **MODULE 5** we will learn abou the use of self-sampling devices to increase primary screening coverage.
- On **MODULE 6** we will discuss the possible need of adaptation os screening in vaccinated women.
- On **MODULE 7** we will discuss why immunocompromised women, particularly those with HIV, require more intensive screening strategies.
- On **MODULE 8** we will define a series of aspects that need to be taken into account to implement a successful screening programme.

**ACTIVITY**

Read the following statements and decide if they are TRUE or FALSE.

1. Cervical cancer is the third most common cancer in women under 70 years old worldwide, with its burden similarly distributed around the world.
2. In 2022, cervical cancer was the fourth most common cancer in women of all ages.
3. The main strategy to prevent cervical cancer is HPV vaccination. Only in contexts where HPV vaccination is not available, screening for cervical cancer is necessary.
4. HPV infection is only known to be related to cervical cancer.
5. Screening is not just understood as a test, but rather a series of steps until diagnosis which must be followed by effective treatment to be worthwhile.

The correct answers are:

1 False, 2 True, 3 False, 4 False, 5 True.

# SUMMARY

- HPV is a common infection that causes cervical cancer, though only a very small proportion of infections caused by high-risk HPV types will progress to cancer.
- The main determinant of progression is the persistence and HPV type. HPV16 is the most prevalent type and when persistent the most carcinogenic (higher rate of progression).
- HPV can be detected in precancerous lesions, which allows for HPV screening. However, 5-20% of women with a normal cervix will test positive due to a prevalent HPV infection and most will rarely progress, leading to the need of a triage test to avoid overtreatment.
- The highest burden of cervical cancer occurs in low-resource settings due to higher incidence rates or a large at-risk population both coupled with poor screening uptake.
- HPV also causes other anogenital and head-and-neck cancers. Around 126,000 such cancers were caused by HPV in 2020.
- Cervical cancer can be prevented via HPV vaccination and screening

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