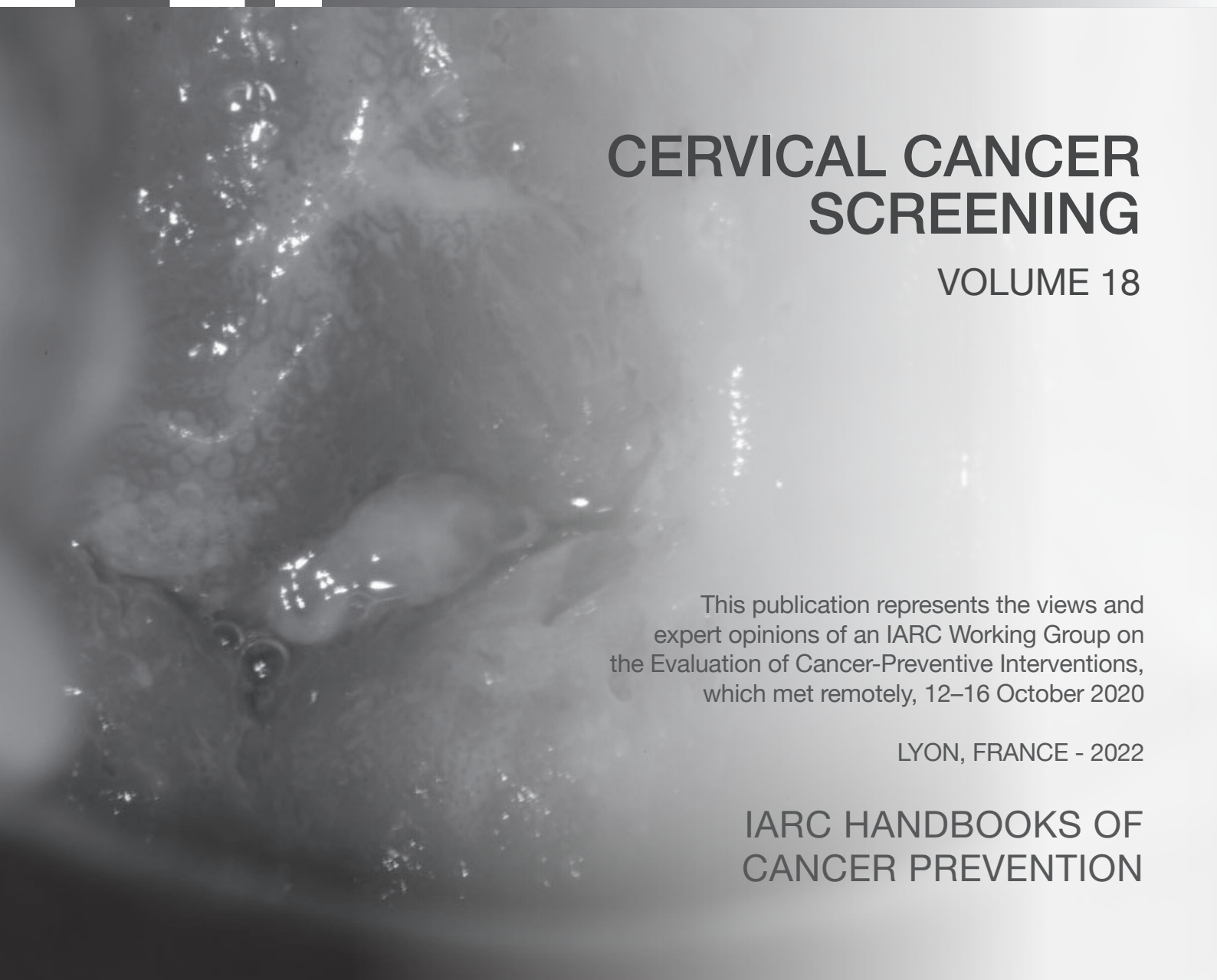
IARC HANDBOOKS



CERVICAL CANCER SCREENING

VOLUME 18

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely, 12–16 October 2020

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

1. CERVICAL CANCER

1.1 Global cervical cancer burden

1.1.1 Incidence

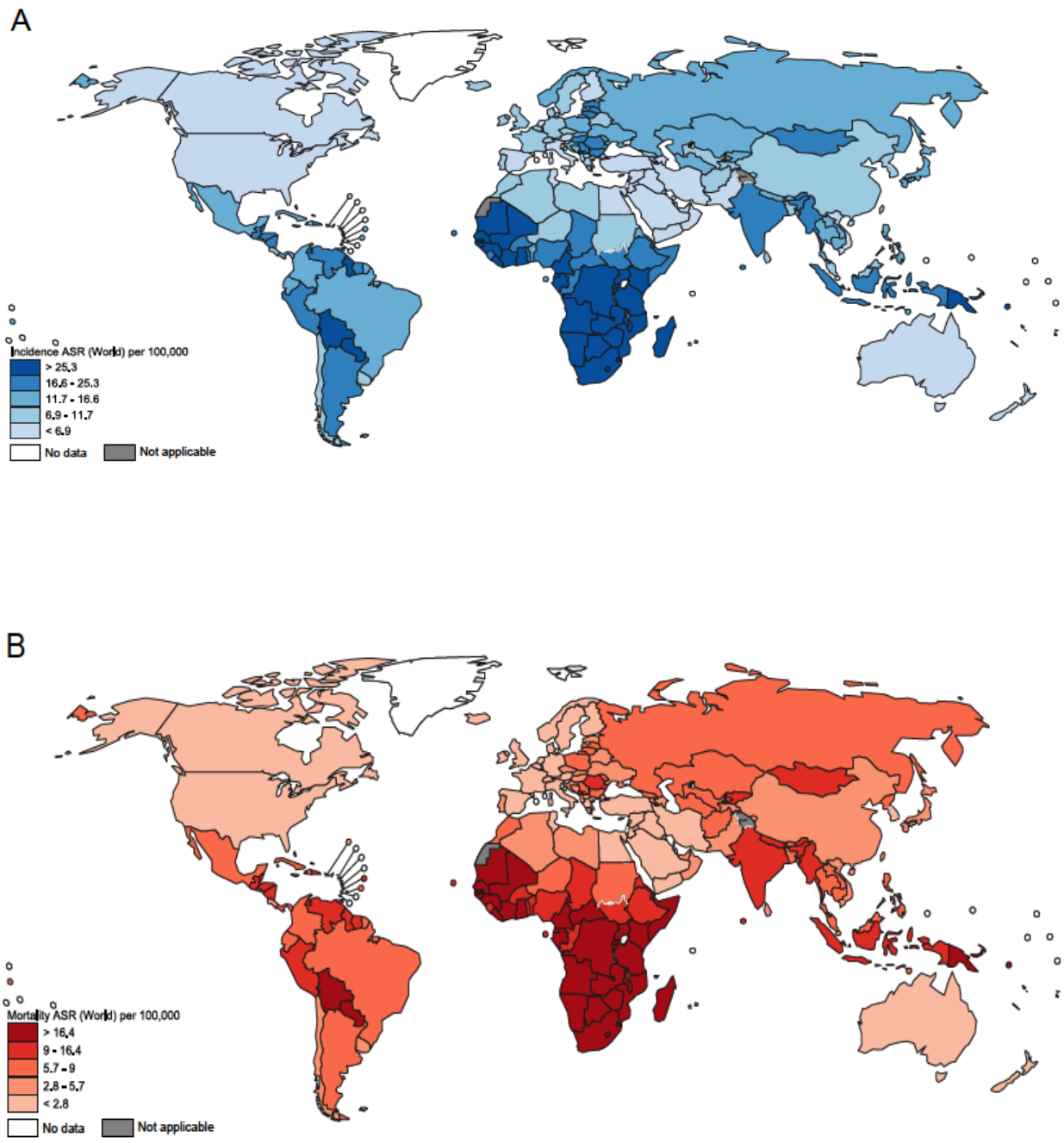
Cervical cancer (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code, C53 – Malignant neoplasm of cervix uteri) is the fourth most commonly diagnosed cancer type in women of all ages worldwide (Sung et al., 2021). In women of reproductive age (15–44 years), it is the second most common cancer type; cervical cancer is the most common cancer in 23 countries, most of which are in sub-Saharan Africa (Ferlay et al., 2020). In 2020, there were an estimated 604 000 new cases worldwide, and cervical cancer represented about 6.5% of the global cancer burden in women; the proportions were higher for only breast cancer (24.2%), colorectal cancer (9.4%), and lung cancer (8.4%). The highest proportion of new cases occurred in Asia (58.2%), followed by Africa (19.4%), Latin America and the Caribbean (9.8%), Europe (9.6%), Northern America (2.5%), and Oceania (0.4%) (Ferlay et al., 2020; Sung et al., 2021).

In 2020, the global age-standardized incidence rate (ASIR) of cervical cancer was 13.3 per 100 000 women worldwide (Ferlay et al., 2020). The incidence rates of cervical cancer vary markedly across the world, with a 10-fold variation between the highest and lowest rates (Fig. 1.1 and Fig. 1.2). The estimated incidence rates (ASIR, per 100 000 women) are highest in Eastern Africa (40.1), Southern Africa (36.4), Middle Africa (31.6), Melanesia (28.3), and Western Africa (22.9), followed by the Federated States of Micronesia (18.7), South-Eastern Asia (17.8), South America (15.4), and South-Central Asia (15.3), and lowest in Western Asia (4.1) and Australia and New Zealand (5.6) (Ferlay et al., 2020; Sung et al., 2021). The incidence rates of cervical cancer are higher in countries that have a high prevalence of HIV infection and/or lack sustained cervical cancer screening programmes (Rohner et al., 2020).

1.1.2 Mortality

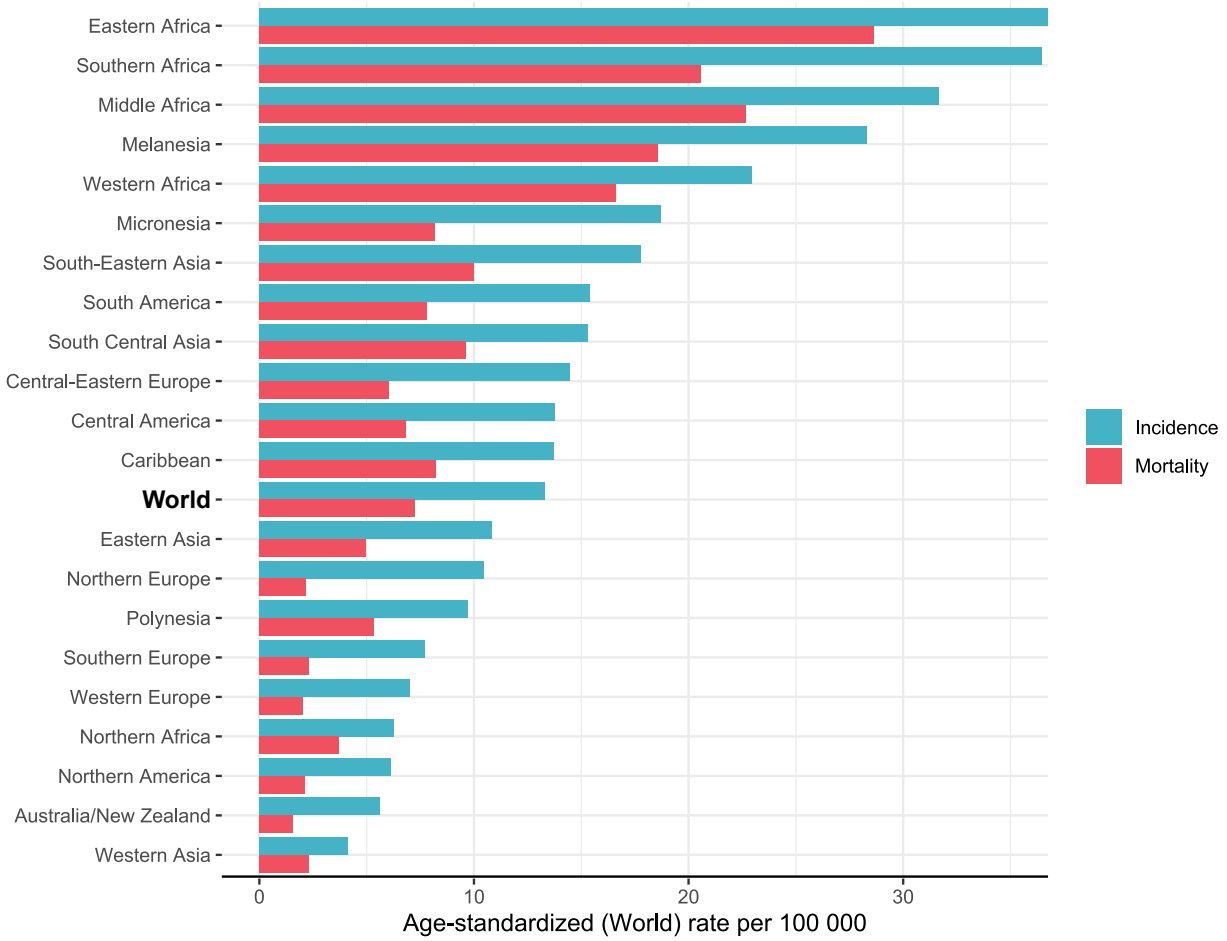
Cervical cancer is the fourth most common cause of cancer death in women of all ages, after breast cancer, lung cancer, and colorectal cancer. In women of reproductive age (15–44 years), it is the second most common cause of cancer death (Arbyn et al., 2020). In 2020, there were an estimated 342 000 deaths worldwide due to cervical cancer; the proportion of deaths was highest in Asia (58.5%) and Africa (22.5%), followed by Latin America and the Caribbean (9.2%) and Europe (7.6%), and lowest in Northern America (1.9%) and Oceania (0.4%) (Ferlay et al., 2020; Sung et al., 2021).

Fig. 1.1 Global distribution of estimated age-standardized (World) incidence rates (A) and mortality rates (B) per 100 000 for cervical cancer, 2020



Adapted from Ferlay et al. (2020). Courtesy of Jérôme Vignat.

Fig. 1.2 Estimated age-standardized (World) incidence and mortality rates per 100 000 for cervical cancer, by large world regions, 2020

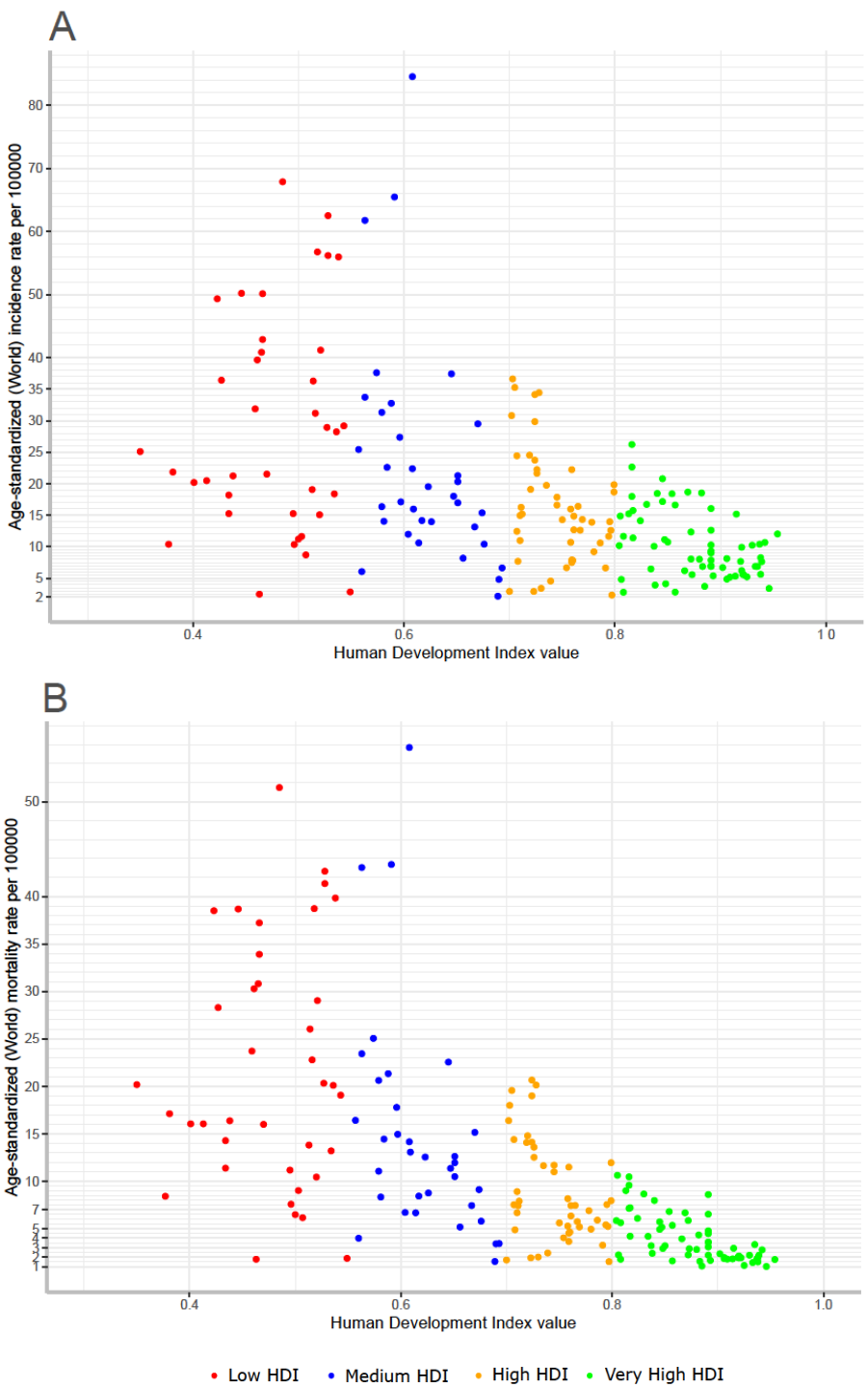


Adapted from Ferlay et al. (2020). Courtesy of Jérôme Vignat.

In 2020, the age-standardized mortality rate (ASMR) for cervical cancer was 7.3 per 100 000 in women worldwide (Ferlay et al., 2020; Sung et al., 2021). The mortality rates of cervical cancer have a global pattern similar to that for the incidence rates, with a more than 15-fold variation between the highest and lowest rates (Fig. 1.1 and Fig. 1.2). The estimated mortality rates (ASMR, per 100 000 women) are highest in Eastern Africa (28.6), Middle Africa (22.7), Southern Africa (20.6), Melanesia (18.6), Western Africa (16.6), South-Eastern Asia (10.0), and South-Central Asia (9.6), and lowest in Australia and New Zealand (1.6) and Western Europe (2.0) (Ferlay et al., 2020; Sung et al., 2021).

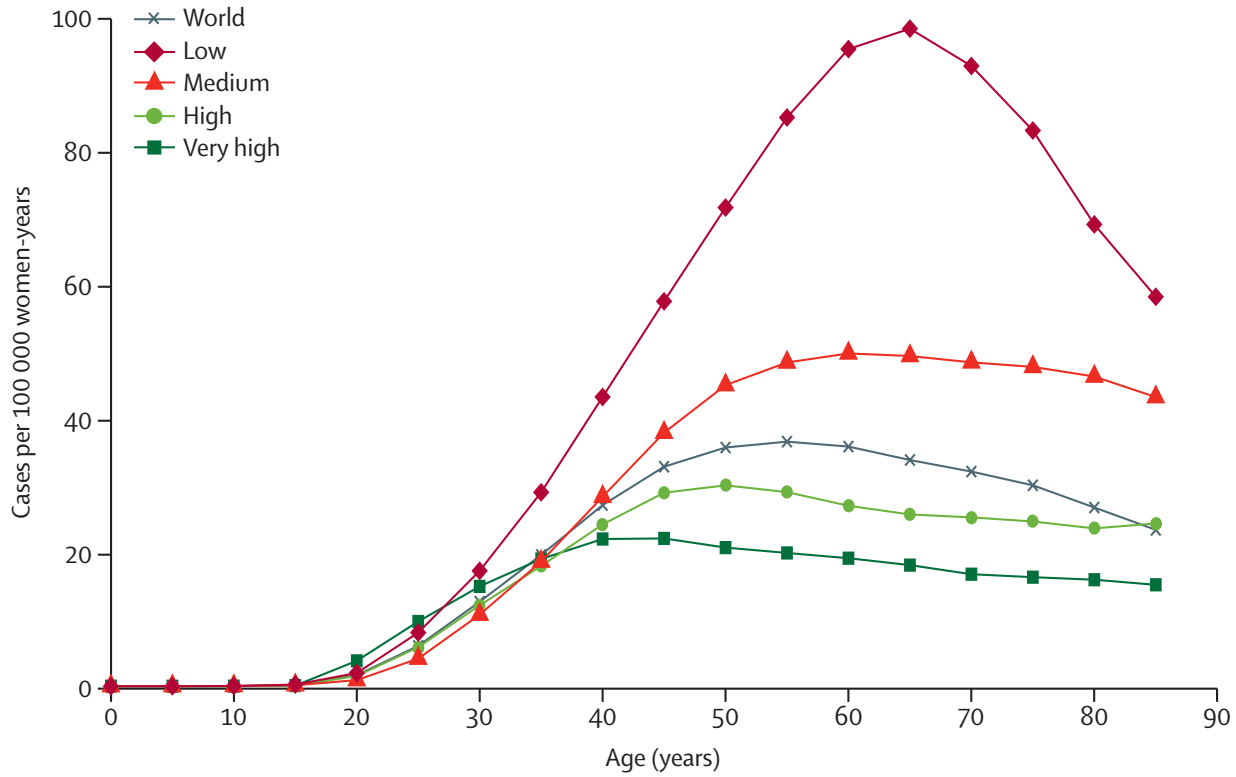
The highest cervical cancer incidence and mortality rates are generally observed in countries with the lowest levels of the Human Development Index (HDI) (Ginsburg et al., 2017) (Fig. 1.3). In countries with lower HDI, the incidence and mortality rates span a wider range, suggesting that other factors besides HDI may account for the variability, such as exposure to human papillomavirus (HPV) or other cofactors

Fig. 1.3 Correlation between estimated age-standardized (World) cervical cancer incidence rates (A) and mortality rates (B) per 100 000 and Human Development Index (HDI), 2020



The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Created using data from Ferlay et al. (2020) and UNDP (2020). Courtesy of Jérôme Vignat.

Fig. 1.4 Age-specific incidence of cervical cancer worldwide and in terms of the four-tier Human Development Index (HDI), 2018



The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Reproduced from Arbyn et al. (2020).

or the coverage and type of screening (opportunistic vs organized). In those countries with the highest HDI, both incidence rates and mortality rates are in a narrow range despite similar prevalences of HPV infection or other cofactors. The age-specific incidence rates of cervical cancer are presented in Fig. 1.4. Cervical cancer incidence rates start rising after age 25 years worldwide, but in countries with high and very high HDI, the peak of incidence is reached at about age 40 years, whereas in countries with medium and low HDI, the rate continues to rise until age 55–69 years (Arbyn et al., 2020).

1.1.3 Trends in incidence

An analysis of trends in age-standardized cervical cancer incidence rates over time using the *Cancer Incidence in Five Continents* database (Ferlay et al., 2018) revealed variability in trends across countries and showed how these trends are influenced by a country's context of policy, programmes, practice, and culture. Fig. 1.5 shows overall trends and trends in women younger than 40 years by country in all registries that provided data for the longest period. Trends for women older than 40 years are not presented, because they tend to be very similar to the overall trends. Also, trends in the registries that provided data for the longest period may not represent trends in the whole country. Three patterns emerge

Fig. 1.5 Trends in age-standardized (World) incidence rates for cervical cancer by country

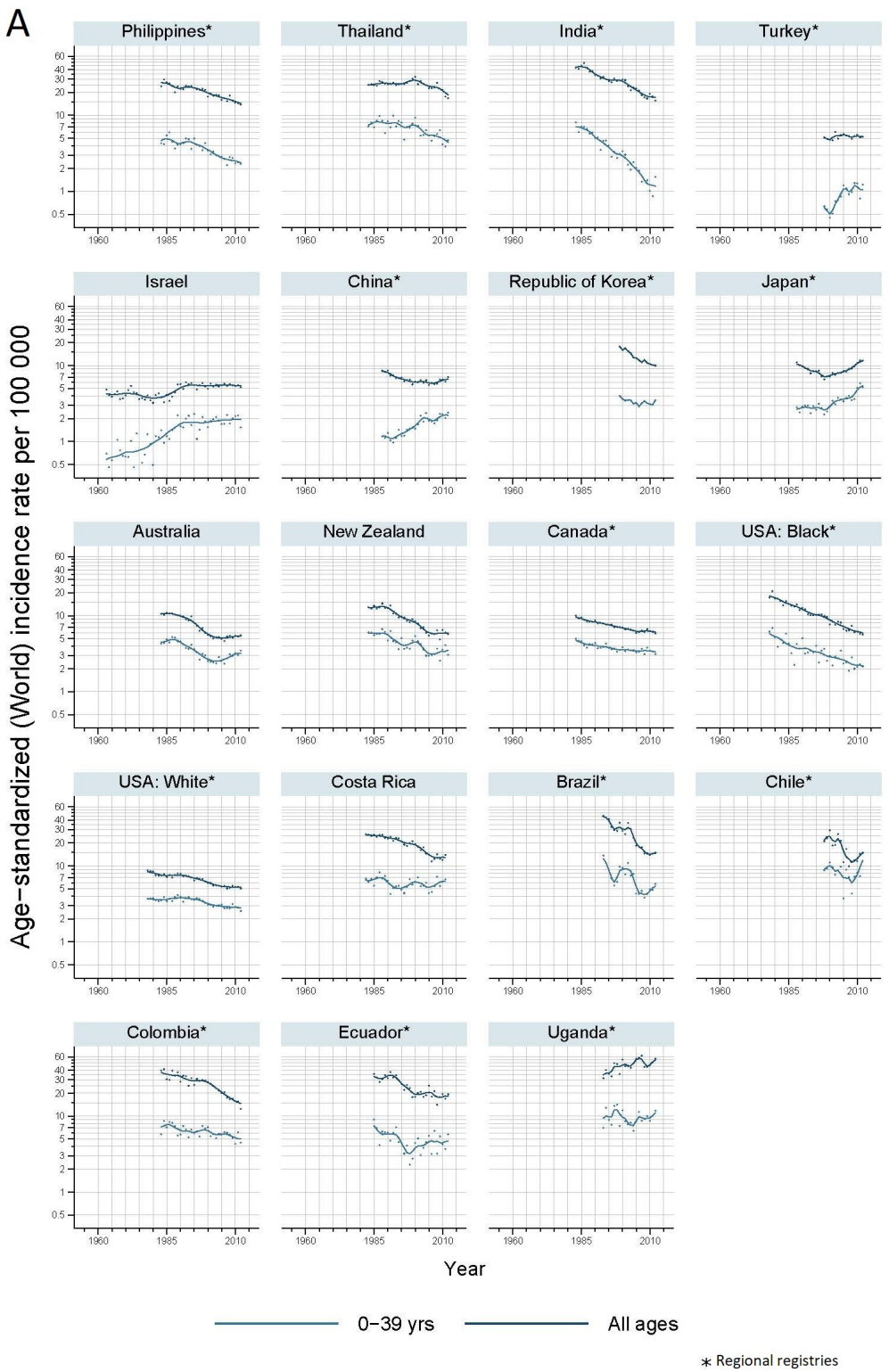
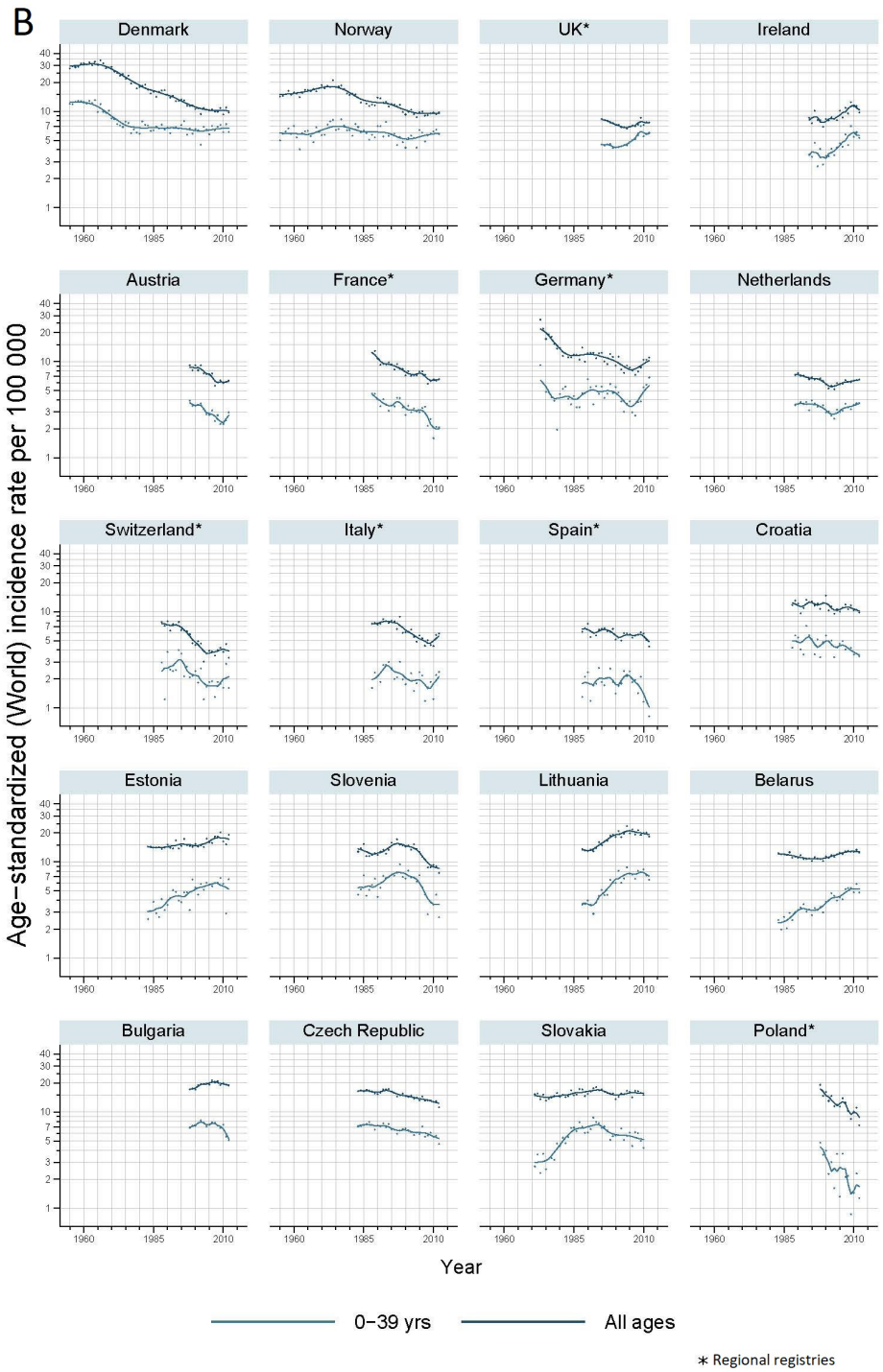


Fig. 1.5 (continued)



(A) For World, countries with fewer than 500 cases have been excluded (Bahrain and Kuwait).
(B) For Europe, countries with fewer than 1000 cases have been excluded (Cyprus, Iceland, and Malta).
Created using data from Ferlay et al. (2018). Courtesy of Jérôme Vignat.

from these trends: (i) a decrease in rates over the years, (ii) an increase in overall rates, and (iii) an increase in rates in the younger age groups.

In most countries, cervical cancer incidence rates have been decreasing over the past decades, although the magnitude of the decrease may vary. In many of these countries, the decrease can be attributed to sustained population-based screening programmes; for example, in Denmark, Finland, Norway, and Sweden, the introduction of screening programmes in the 1960s and 1970s resulted in an almost 50% reduction in cervical cancer incidence. In countries where there is no population-based screening, as for example in India, the decrease in cervical cancer incidence may reflect improved conditions, such as better education for girls and women, which lead to reduced exposure to HPV, among other factors (Dhillon et al., 2011).

The second emerging pattern is a continued increase in incidence rates. In some countries (e.g. Belarus, Estonia, and Lithuania), incidence rates are increasing despite the introduction of screening programmes; this trend reflects weak opportunistic screening, poor coverage of screening, and poor quality (Vaccarella et al., 2016; Ojamaa et al., 2018). In Uganda, which has one of the longest-standing high-quality registries, there has been a continued increase in cervical cancer incidence rates. In a recent analysis of 10 African registries with 10–25 years of data, a similar pattern was seen and was attributed to a high prevalence of HPV infection, a high prevalence of HIV infection, and a lack of well-attended population-based screening programmes (Jedy-Agba et al., 2020).

In the third pattern, the overall trend is decreasing but incidence rates in women younger than 40 years are increasing. Such a pattern has been observed in China, most likely reflecting increased exposure to HPV in the youngest cohort of women (Li et al., 2017).

Trends by histology cannot be provided at a global level, given the lack of histology data in many cancer registries. However, in selected countries the examination of incidence rates by histology provides insights into the impact of prevention strategies. For example, the reduction in the incidence of cervical cancer seen in the USA from the introduction of the Pap test in the 1960s until the early 2000s has been driven by reductions in the incidence rates of squamous cell carcinoma (SCC) of the cervix (Wang et al., 2004). In the past two decades, incidence rates of cervical SCC have stabilized in the USA (Islami et al., 2019), whereas incidence rates of cervical adenocarcinoma have increased both in the USA (especially in White women aged 40–60 years) (Islami et al., 2019) and in Europe (Bray et al., 2005). This trend may reflect changing sexual behaviours over time (Ryser et al., 2017), as well as an inability to detect cervical adenocarcinoma through cytology-based screening programmes (Castle et al., 2017).

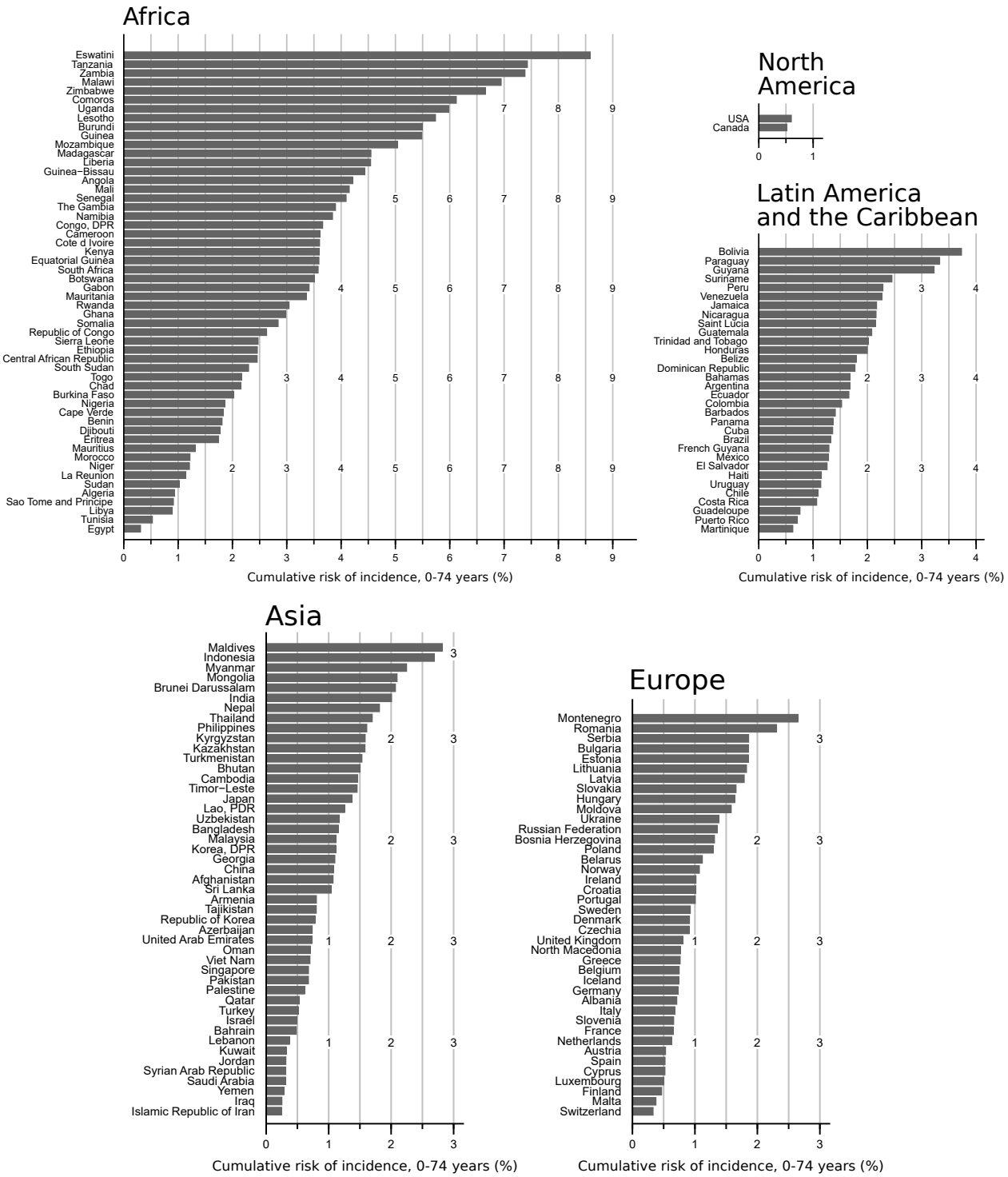
1.1.4 Lifetime risk of cervical cancer

The lifetime cumulative risk of cervical cancer for women aged 0–74 years is presented by region in Fig. 1.6. In Africa, the lifetime risk varies from 8.6% in Eswatini to 0.3% in Egypt. In Latin America and the Caribbean, women in the Plurinational State of Bolivia and in Guyana have a lifetime risk of 3.7%, whereas those in Martinique, France, have a lifetime risk of 0.6%. In Asia, the lifetime risk is highest in Maldives, Indonesia, and Mongolia and lowest in Iraq. Women in eastern Europe have consistently higher lifetime risk than those in western Europe (Ferlay et al., 2020; Sung et al., 2021).

1.1.5 Survival

At the end of 2020, there were an estimated 1.5 million women alive who had been diagnosed with cervical cancer during the previous 5 years,

Fig. 1.6 Estimated cumulative risk (ages 0–74 years) of cervical cancer incidence by world region and country or territory, 2020



Adapted from Ferlay et al. (2020). Courtesy of Mathieu Laversanne.

representing about 5.8% of all people who were diagnosed with cancer within the previous 5 years (Ferlay et al., 2020).

The third cycle of the CONCORD programme for global surveillance of cancer survival trends (CONCORD-3) included data for 660 744 women diagnosed with cervical cancer in 2000–2014 from 295 population-based cancer registries in 64 countries or territories. Population-based survival is estimated from data provided by population-based cancer registries that record all diagnoses of malignancy in the population of the country or region that they cover. It is a key measure of the overall effectiveness of the health system in managing cancer in a given country or region (Allemani, 2017; Allemani et al., 2018).

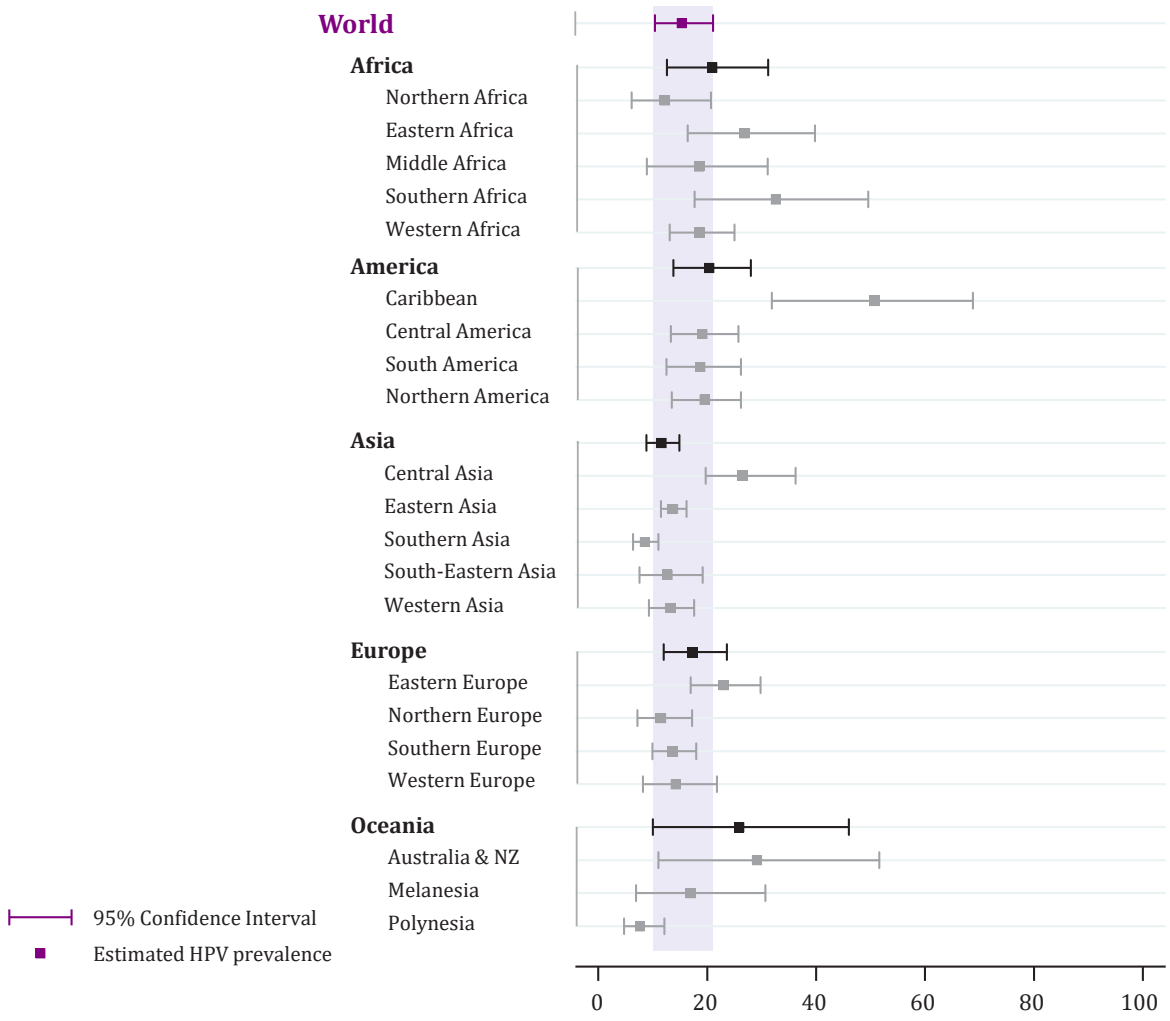
Population-based survival is a measure of the average survival of all patients with cancer. Population-based survival is usually presented as net survival (Perme et al., 2012), which is the probability of patients with cancer surviving until a given time since diagnosis, typically 5 years, after controlling for competing causes of death (background mortality).

The global range in 5-year age-standardized net survival for cervical cancer was wide (50–70%) in all three calendar periods (2000–2004, 2005–2009, 2010–2014), reflecting inequity in access to diagnostic facilities and optimal treatment (Allemani et al., 2018). For women diagnosed in 2010–2014, 5-year age-standardized net survival was 70% or higher in seven countries or territories (Cuba; Denmark; Japan; Norway; the Republic of Korea; Switzerland; and Taiwan, China), most of which have high HDI. Survival was in the range 60–69% in 29 countries or territories: Canada and the USA; Brazil and Puerto Rico; 5 countries or territories in Asia (China, Hong Kong Special Administrative Region, Israel, Singapore, and Turkey); 18 countries in Europe; and Australia and New Zealand. Survival was in the range 50–59% in 5 countries or territories in Central and South America (Argentina; Ecuador; Martinique, France; Peru; and Uruguay) and in 6 countries in Europe (Bulgaria, Latvia, Lithuania, Malta, Poland, and the Russian Federation), most of which have low or medium HDI. Between 2000 and 2014, 5-year survival increased by 4–6% in Japan and in 11 European countries and by 10% in India. In China, it increased from 53% for women diagnosed in 2000–2004 to 68% for those diagnosed in 2010–2014. Survival trends could not be systematically assessed in Africa, because the data were incomplete (Allemani et al., 2018).

1.1.6 Prevalence of HPV infection in women

Cervical cancer incidence often reflects exposure to HPV, which is the central cause of cervical cancer (see Sections 1.2.1 and 1.2.2). A meta-analysis evaluated more than 500 studies that tested for HPV infection in 2.4 million women aged 15 years and older with normal cytology (Bruni et al., 2016), including population-based studies, screening studies, and representative control series in case–control studies. The global pooled prevalence was 15.3% for any HPV infection, 70% of which were with carcinogenic types. The age-standardized overall prevalence of HPV infection by world region is presented in Fig. 1.7. The Caribbean has the highest prevalence (50.7%), and Southern Asia has the lowest (8.5%). [Some estimates may be unstable for regions with few studies or with studies in subpopulations.] The age-specific analysis (Fig. 1.8) shows that the prevalence of HPV infection is highest in younger women and lower in older women, and that the pattern appears flatter for Asia than for other regions. For some regions, such as Northern and Western Africa and Central America, there is a modest second peak of HPV prevalence in women older than 40 years. In studies with specific information on HPV type distribution, HPV16 was the most common type in all regions (standardized prevalence, 3.5%); HPV18 (1.3%), HPV52 (1.3%), HPV58 (1.0%), and HPV31 (0.9%)

Fig. 1.7 Standardized prevalence of human papillomavirus (HPV) infection by world region



Squares represent the estimated adjusted HPV prevalence from the random-effects models for each corresponding region.
Courtesy of Laia Bruni, Bruni et al. (2016).

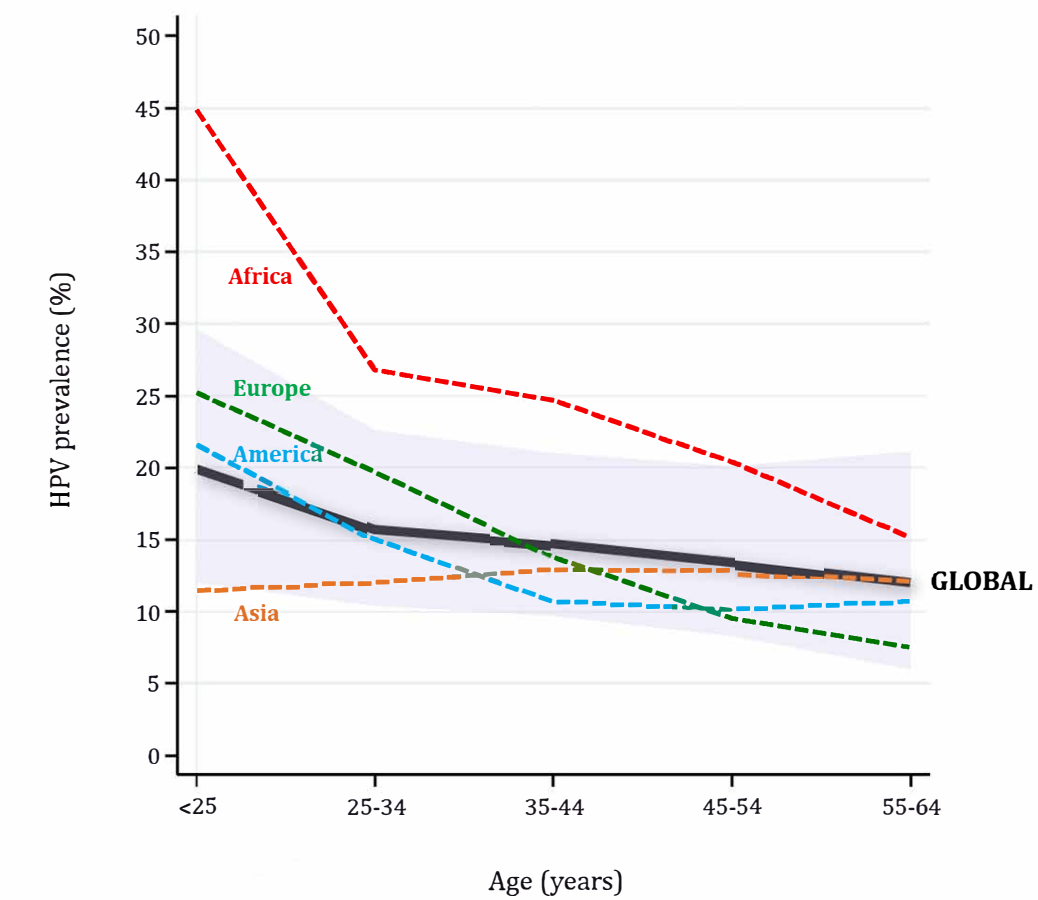
were the other most common carcinogenic HPV types (Bruni et al., 2016).

Most HPV prevalence surveys have been conducted in women, and very few population-based data exist for men.

1.1.7 Projections of global burden

Table 1.1 shows the estimated global burden of cervical cancer incidence and mortality in 2020 and projected to 2040, overall and by HDI category. Overall, a 32.0% increase in the estimated number of new cases and a 40.8% increase in the number of deaths are projected by 2040. Numbers of deaths are projected to increase more rapidly in countries with lower HDI, and relatively large increases are projected in countries with medium and high HDI. These projections take into account only global demographic changes in population structure and growth according to United Nations estimates. The risk of developing or dying from cervical cancer is assumed to remain constant, and no allowance

Fig. 1.8 Age-specific standardized prevalence of human papillomavirus (HPV) infection by world region



The shaded area represents the 95% confidence interval for the global HPV prevalence.
Courtesy of Laia Bruni, Bruni et al. (2016).

is made for changes in increased detection or improvements in survival. Modelling studies have also projected that the number of new cases per year will increase from 600 000 in 2020 to 1.3 million in 2069; these projections also take into account changes in underlying demographics and exposure to risk factors (Simms et al., 2019). Widespread coverage of both HPV vaccination and screening has the potential to decrease the incidence of cervical cancer in the future (Brisson et al., 2020).

1.2 Cervical neoplasia

1.2.1 Biology of HPV and of the cervix relevant to carcinogenesis and screening

HPVs are a group of circular, double-stranded DNA viruses of about 8000 base pairs that infect human skin and mucosal epithelia. The group includes more than 200 different genotypes, which are numbered in order of discovery and characterization. The small genomes of the HPV types that cause cervical cancer consist of an upstream regulatory region and six early (E)

Table 1.1 Global burden of cervical cancer: estimated annual numbers of incident cases and deaths, by HDI category and overall, in 2020 and projected to 2040

HDI category[a]	Population in 2020		Number of new cases (thousands)		Increase	Number of deaths (thousands)		Increase
	(millions)	(%)	2020	2040	(%)	2020	2040	(%)
Low HDI	494	12.8	82	162	97.3	56	112	99.9
Medium HDI	1136	29.4	183	292	59.6	113	189	66.8
High HDI	1442	37.3	240	297	23.5	129	182	40.6
Very high HDI	791	20.5	99	105	6.1	43	51	18.0
World	3863	100	604	798	32.0	342	481	40.8

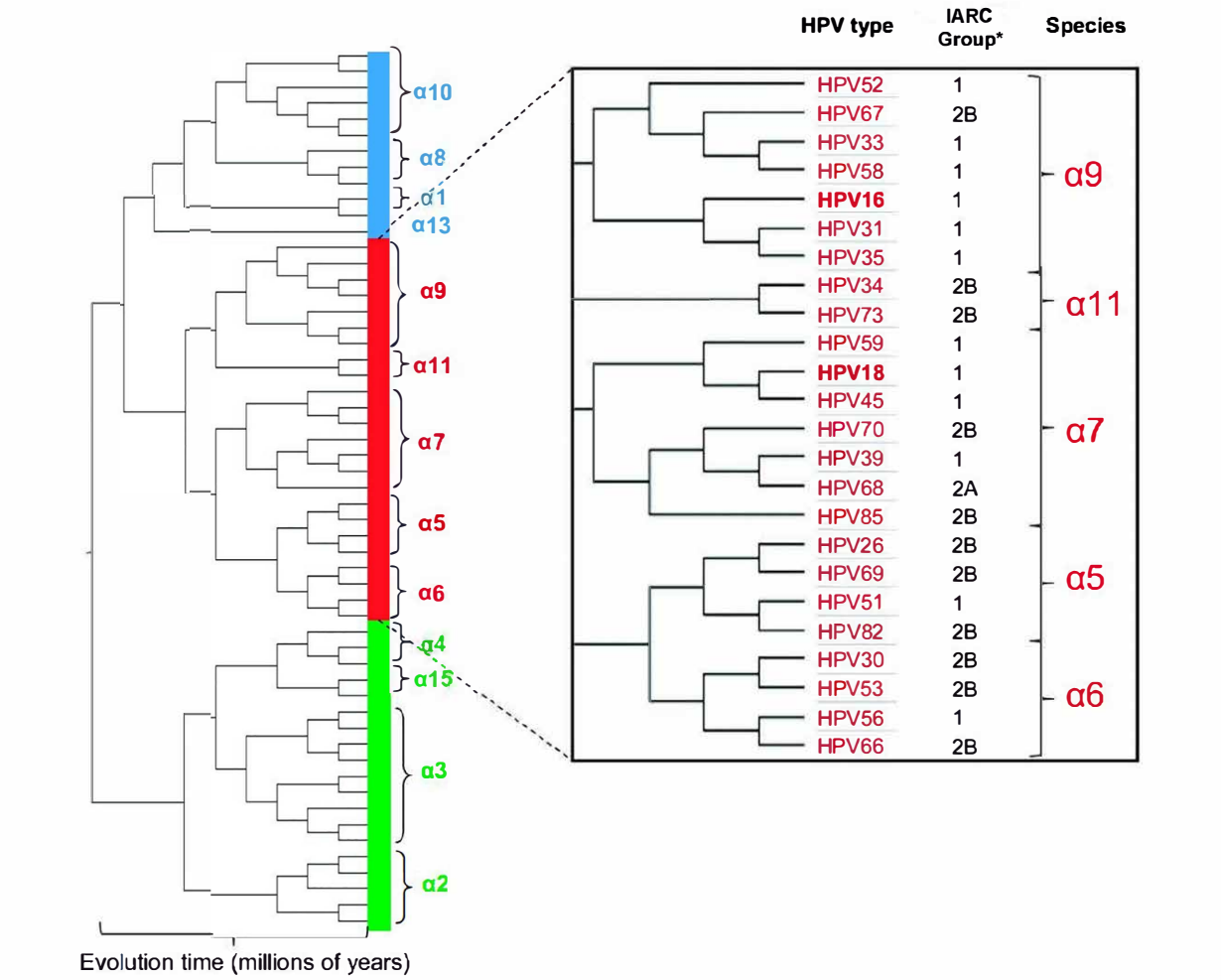
HDI, Human Development Index.
[a] The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Created using data from Ferlay et al. (2020) and UNDP (2020). Courtesy of Jérôme Vignat.

and two late (L) genes on the positive coding strand. The early genes are involved in viral replication and maintenance within the host cell; L1 and L2 encode the self-assembling major and minor capsid proteins, respectively (Schiffman et al., 2016).

Evolutionary taxonomy predicts the cells that specific HPV types infect and their carcinogenicity (Schiffman et al., 2005). The stable HPV genome has evolved very slowly in parallel with human evolution. The alpha genus contains 14 species, including more than 50 mucocutaneous types (Bzhalava et al., 2015); a single evolutionary branch includes the four species that contain the dozen or so HPV types that cause almost all cervical cancers (Fig. 1.9). The 12 types classified by IARC as carcinogenic to humans (Group 1) are HPV16, HPV31, HPV33, HPV35, HPV52, and HPV58 in alpha-9; HPV18, HPV39, HPV45, and HPV59 in alpha-7; HPV51 in alpha-5; and HPV56 in alpha-6 (Bouvard et al., 2009). In addition, HPV68 in alpha-7 is classified as probably carcinogenic to humans (Group 2A). The IARC classification refers to the carcinogenic potential based on prevalence in cervical cancers, not potency. Rarely, cervical cancers are found that contain only HPV types that are classified as possibly carcinogenic to humans (Group 2B), such as HPV73, but the attributable fraction and absolute risk are very low (Schiffman et al., 2009; de Sanjose et al., 2010) (Fig. 1.10).

There is great variation in cervical carcinogenicity between the 12 HPV types that are classified by IARC in Group 1, and the importance of specific carcinogenic types may differ, depending upon the specific geographical population (Guan et al., 2012; de Martel et al., 2017; de Sanjosé et al., 2018; Demarco et al., 2020). The etiological fractions of the types can best be determined by analysing cervical cancer case series, which now include tens of thousands of cases of (mainly squamous) invasive cancer (Fig. 1.10) (Combes et al., 2015). Five categories can be distinguished on the basis of cancer risk: HPV16 (in the alpha-9 species) is singularly carcinogenic and causes about 60% of cases of SCC. HPV18 and HPV45 (in the alpha-7 species) cause 15% and 5% of SCC cases, respectively. Other closely related alpha-9 types (HPV31, HPV33, HPV35, HPV52, and HPV58) together account, with some regional variation, for 15% of SCC cases. The remaining carcinogenic types (HPV39 and HPV59 in alpha-7, HPV51 in alpha-5, and HPV56 in alpha-6) are much less carcinogenic and together cause about 5% of SCC cases. HPV-associated cases of adenocarcinoma, which are an uncommon histological group globally, are caused half by variants

Fig. 1.9 Phylogeny of the alpha human papillomavirus (HPV) types, with species groups and IARC classifications of the branch that contains carcinogenic types



Note that almost all alpha-9 types (HPV16-associated) are carcinogenic. The other most important carcinogens are HPV18-associated, in alpha-7. There is no absolute division between carcinogenic and not carcinogenic; several of the types in this branch are classified as possibly carcinogenic to humans (Group 2B), because of genetic relatedness and because they have very rarely been associated with cancer cases.
* Carcinogenic to humans (Group 1); probably carcinogenic to humans (Group 2A); possibly carcinogenic to humans (Group 2B) (IARC, 2012).
Reprinted from Schiffman et al. (2005). Copyright 2005, with permission from Elsevier.

of HPV16 and half by HPV18 or HPV45 (and only uncommonly by other types, particularly in alpha-7) (Guan et al., 2013).

This grouping is supported by a recent prospective study of large numbers of type-specific HPV infections and the absolute risk of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) (Demarco et al., 2020).

To optimize cervical screening using HPV testing requires knowledge of the relative importance of the carcinogenic HPV types in a specific region. For the purposes of screening and vaccination, each type can be considered as a single invariant virus. Nonetheless, for deeper understanding, epidemiological study, and possible future applications, each HPV type can be further divided phylogenetically into several

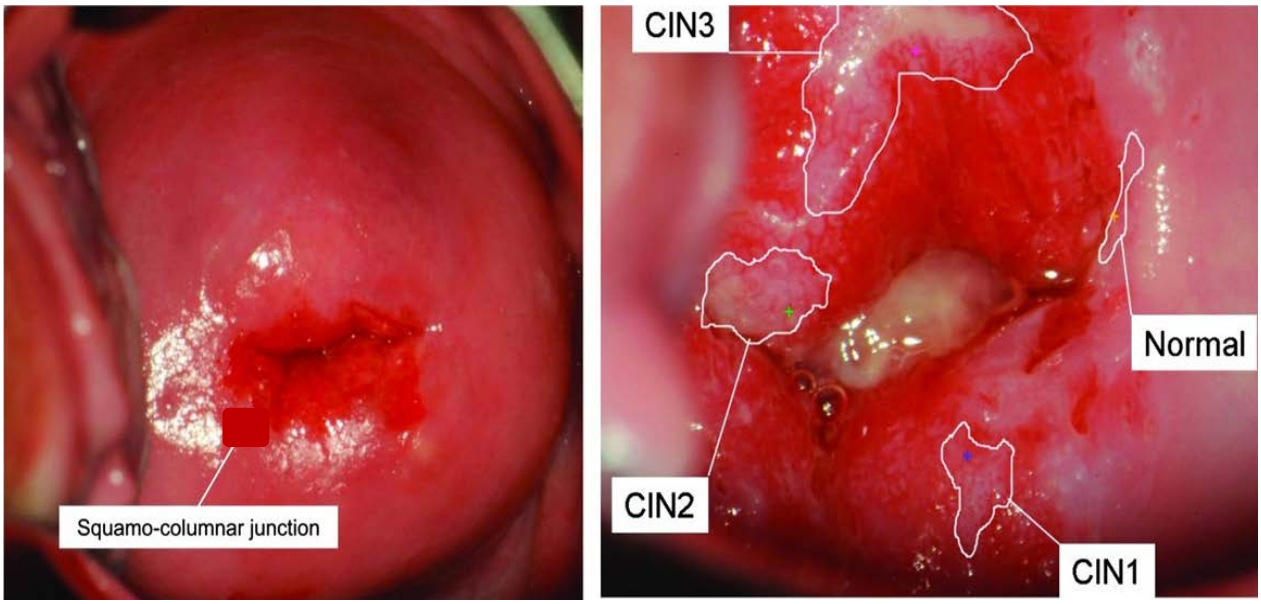
Fig. 1.10 Relative importance of the carcinogenic human papillomavirus (HPV) types

HPV type	HPV species	IARC Group[a]	% HPV type prevalence in cancer	% HPV type prevalence in normal	Odds ratio	% Attributable (etiological) fraction
HPV16	**α-9**	**Group 1**	**55.8**	**2.6**	**47.6**	**62.4**
HPV18	**α-7**	**Group 1**	**14.3**	**1**	**15.7**	**15.3**
HPV45	**α-7**	**Group 1**	**4.8**	**0.6**	**8.3**	**4.8**
HPV33	**α-9**	**Group 1**	**4**	**0.6**	**7.1**	**3.9**
HPV58	**α-9**	**Group 1**	**4**	**0.8**	**5.1**	**3.7**
HPV31	**α-9**	**Group 1**	**3.5**	**1**	**3.7**	**2.9**
HPV52	**α-9**	**Group 1**	**3.2**	**1**	**3.3**	**2.6**
HPV35	**α-9**	**Group 1**	**1.6**	**0.4**	**3.9**	**1.4**
HPV59	**α-7**	**Group 1**	**1.2**	**0.4**	**2.9**	**0.9**
HPV39	**α-7**	**Group 1**	**1.3**	**0.6**	**2.0**	**0.8**
HPV68	**α-7**	**Group 2A**	**0.6**	**0.4**	**1.5**	**0.2**
HPV51	**α-5**	**Group 1**	**1**	**0.9**	**1.2**	**0.2**
HPV56	**α-6**	**Group 1**	**0.8**	**0.6**	**1.3**	**0.2**
HPV73	α-11	Group 2B	0.5	0.3	1.8	0.2
HPV26	α-5	Group 2B	0.2	0.1	4.1	0.2
HPV30	α-6	Group 2B	0.2	0.1	2.6	0.1
HPV69	α-5	Group 2B	0.2	0.1	1.4	0.1
HPV67	α-9	Group 2B	0.3	0.2	1.2	< 0.1
HPV82	α-5	Group 2B	0.2	0.1	1.2	< 0.1
HPV34	α-11	Group 2B	0.1	0.1	1.0	Not attributable
HPV66	**α-6**	**Group 2B**	**0.3**	**0.6**	**0.4**	**Not attributable**
HPV70	α-7	Group 2B	0.2	0.8	0.3	Not attributable
HPV53	α-6	Group 2B	0.5	1.1	0.4	Not attributable

There is substantial variability in carcinogenicity between HPV types, including those classified by IARC in Group 1. However, for clinical use, commercial HPV screening assays often detect a pool of carcinogenic (or high-risk) HPV types; the 14 types most commonly included in current HPV tests are shown in bold here.
The attributable fraction is the percentage of cancer caused by that type. For each type, a relative risk can be estimated by the odds ratio of positivity in invasive cervical cancer compared with cytologically normal controls. A worldwide pooled analysis of invasive cancers (n = 13 763–40 706 cases, depending on type) and normal controls (n = 26 599–263 971, depending on type) reveals a five-level natural grouping in attributable fraction, shown by colour bands. (Attributable fractions are weighted to sum to 100%.) HPV16 is uniquely carcinogenic (red). HPV18 and HPV45 are relatively important for cancers (orange), especially adenocarcinomas, rather than precancers. Then follow other alpha-9 types related to HPV16 (yellow) and a group of less carcinogenic types (dark green), all classified by IARC in Group 1 or Group 2A. Last, there are types classified by IARC in Group 2B (light green), some of which contribute very small attributable fractions and some of which cannot be attributed at all. [For HPV66, which is more prevalent in normal cytology than in invasive cervical cancer and is sometimes mistakenly included in HPV screening tests, the attributable fraction is zero.]
[a] Carcinogenic to humans (Group 1); probably carcinogenic to humans (Group 2A); possibly carcinogenic to humans (Group 2B) (IARC, 2012).
Created by the Working Group using data from Combes et al. (2015). Courtesy of Gary Clifford.

variants and subvariants, which in turn consist of many subtly varying genomes (Burk et al., 2013; Chen et al., 2018). These individual genome differences inform our understanding of evolution (García-Vallvé et al., 2005; Van Doorslaer & Burk, 2010), fine differences in carcinogenicity (Cullen et al., 2015), and racial differences in response to specific HPV types (e.g. the prevalence of particular variants of HPV35 explains the higher percentage of cancers in women of African ancestry) (Pinheiro et al., 2020).

Fig. 1.11 Topology of human papillomavirus (HPV) infection of the cervix



Most cervical cancers arise in a zone of uniquely susceptible tissue at the dynamic squamocolumnar junction. Multiple concurrent and asynchronous infections can cause clonal lesions of varying severity, which are difficult to distinguish visually. The cervical intraepithelial neoplasia (CIN) scale is found to be difficult to replicate either visually or microscopically. The available evidence suggests that a more reliable distinction can be made between signs of HPV infection and high-grade precursor lesions (precancer).
From Schiffman et al. (2011).

Another area of biology that affects screening strategies is the adequate definition of the cervix from a screening perspective. Anatomically, the cervix is defined as the terminal part of the uterus extending into the anterior aspect of the vagina, and it is composed of fibrous connective tissue, scant smooth muscle, and overlying epithelial components. However, from the perspective of carcinogenesis and screening, the cervix can be viewed as a ring of epithelium positioned at the junction between the glandular endocervix and the adjoining squamous ectocervix (Doorbar & Griffin, 2019). Multiple HPV infections and related clonal lesions of differing severity can be observed concurrently by cervical microdissection studies (Fig. 1.11) (Quint et al., 2001; Wentzensen et al., 2009; van der Marel et al., 2014; Venetianer et al., 2020). Cervical lesions can collide and seemingly merge, but each clone contains a single driving HPV infection.

Cervical cancers typically arise adjacent to the squamocolumnar junction (SCJ), which is subject to lifelong squamous metaplasia, the inward-moving gradual replacement of single-cell-thick columnar or glandular epithelium by the thicker squamous epithelium. Thus, the position of the SCJ moves centrally throughout a woman's life, from its distal origin on the ectocervix or vagina into the endocervical canal, until it has gradually moved out of the visible area in most older women. The ring of tissue between the early and eventual late SCJ positions, called the transformation zone (TZ), contains a compartment of immortal cells, which have an elevated risk of HPV-induced cervical cancer compared with the flanking tissues of the vagina or the deeper endocervix (Doorbar & Griffin,

2019). Cell sample collection and destruction of the TZ are the basis of secondary prevention of cervical cancer (see Section 1.2.5). Depending on the position of the SCJ, the cells collected during cervical screening will be mainly glandular cells, a mixture of TZ cell types, or mature squamous cells (Castle et al., 2006).

1.2.2 Transmission and natural history of HPV infection and multistage cervical carcinogenesis

Each individual case of cervical cancer arises from persistent infection with a specific carcinogenic HPV genome (Schiffman et al., 2016). Although it is well researched, cervical carcinogenesis has an unpredictable quality, because a woman may successfully control a large number of concurrent or asynchronous HPV infections but fail, for reasons that are still unexplained, to control the causal one. The whole process typically takes decades from acquisition of HPV infection to cancer diagnosis, although more rapid transitions are sometimes seen.

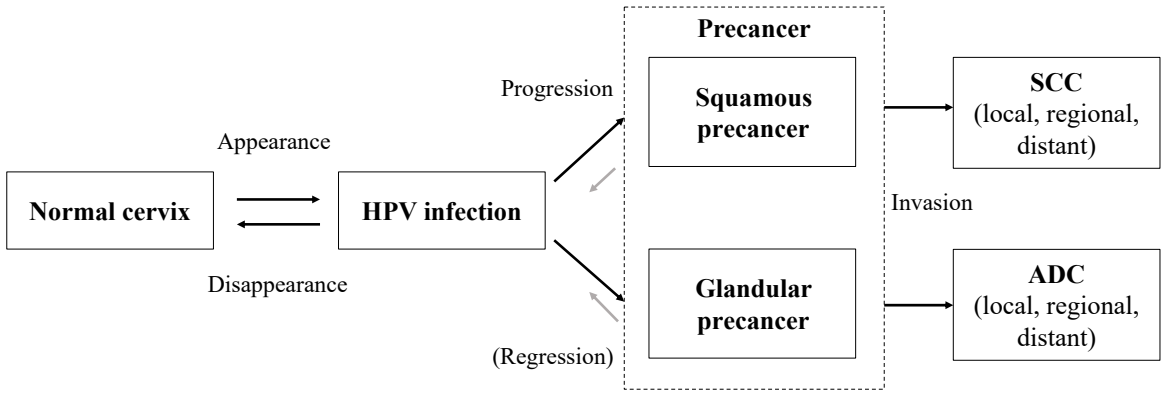
There is a well-established set of necessary health states and transitions leading from the normal cervix to invasive cancer (Fig. 1.12) (Campos et al., 2021). The schema presents the necessary transition states that are currently measurable with reasonable international reproducibility by a combination of HPV typing and expert gynaecological pathology: normal cervix (uninfected), HPV infection (type-specific carcinogenic), precancer, and cancer. The transition between normal cervix and HPV infection can be called appearance and disappearance of HPV detection, to acknowledge the limitations of existing measurement assays and the potential for reactivation of latent infections. The transitions between infection and precancer are described as progression to and regression of precancer. Invasion is considered a typically irreversible transition when HPV-associated cells cross the basement membrane. Precancers and cancers are subdivided into the predominant squamous pathway and the uncommon glandular pathway, not only because the histological types vary clinically but also because the observed transition probabilities from infection to precancer to cancer seem to differ (Schiffman et al., 2016). Fig. 1.13 shows the parallel between HPV infection and cervical carcinogenesis at the levels of molecular pathogenesis and clinical microscopic or visual diagnoses.

As shown in Fig. 1.12, the cervix uninfected by carcinogenic HPV is considered normal from the point of view of cervical cancer risk, i.e. at extraordinarily low risk of prevalent or near-term incident cancer. Vertical transmission is not known to be an important factor in cervical carcinogenesis (Zahreddine et al., 2020). Anogenital HPV infections are very readily transmitted through direct physical, i.e. sexual (not necessarily intromissive), contact (Malagón et al., 2019). The average age at the start of sexual activity in a population determines the average starting time point of cervical carcinogenesis (Kjaer et al., 1992).

For any given infection, the moment of acquisition is not precisely known. Detection (i.e. appearance) of HPV can represent primary acquisition or reappearance after one or more episodes of disappearance (the two are, in practical terms, indistinguishable) (González et al., 2010). The closer a woman is in age to the start of her sexual activity, the more likely it is that appearance represents a truly new acquisition (Ho et al., 1998; Maucort-Boulch et al., 2010).

Following the general epidemiological principle, the prevalence odds of HPV infection = incidence × duration (i.e. persistence); when prevalence is low, the equation reduces to prevalence = incidence × duration. In women without evidence of prevalent precancer, the HPV types most commonly found on screening (i.e. prevalent infections) are also the most likely to appear during follow-up (i.e. incident infections). The strong correlation between HPV

Fig. 1.12 Human papillomavirus (HPV) infection and multistage development of cervical cancer



Each box in the figure represents a necessary stage, or health state, on the path to cervical cancer. The arrows represent forward and backward transitions between health states. The transitional probabilities form a basis of epidemiological research and health decision models.
ADC, adenocarcinoma; SCC, squamous cell carcinoma.
Reproduced with permission from Campos et al. (2021).

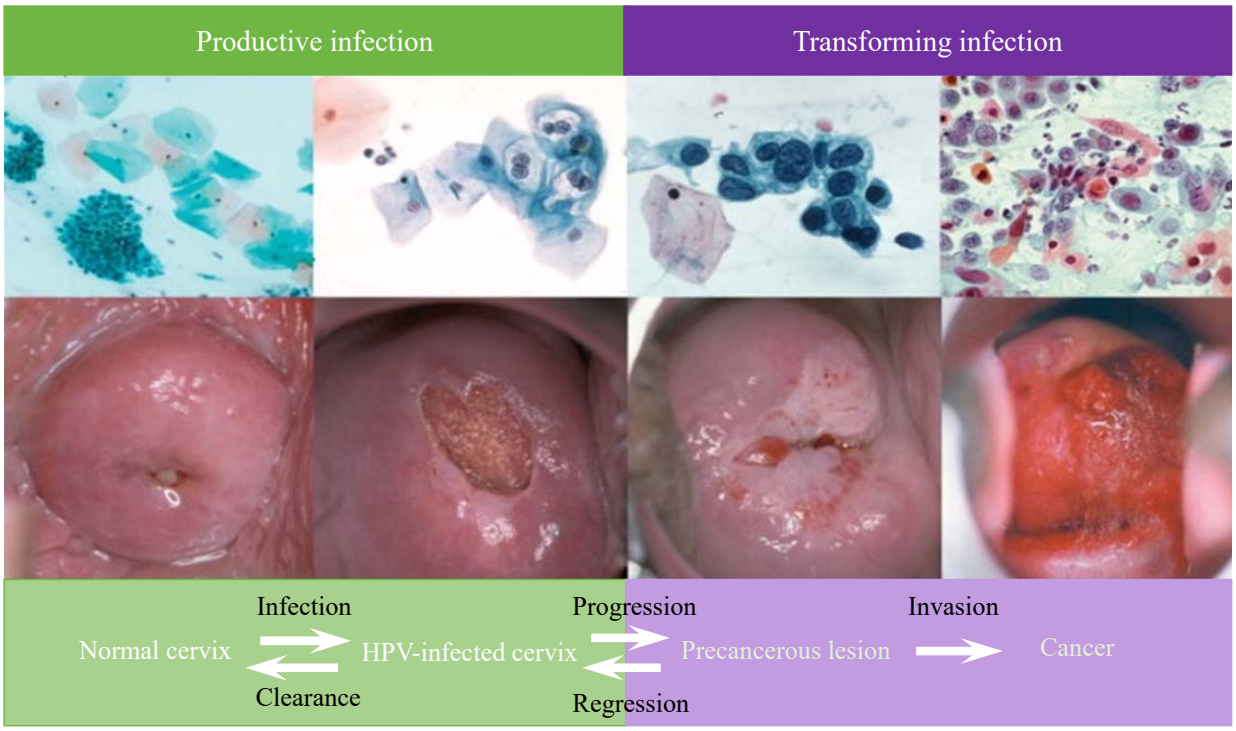
appearance and prevalence, which is seen in all age groups, holds because the pattern of disappearance (often called clearance) is nearly the same for all HPV types (including non-carcinogenic types) in immunocompetent women, irrespective of age (Plummer et al., 2007; Demarco et al., 2020). The clearance curve is very distinct, with extremely rapid disappearance of a high proportion of infections in the initial months, leading to median clearance by about 1 year in most screen-detected infections, with a large fraction undetectable within 2–3 years. Only a very small proportion of carcinogenic HPV infections are detectable for more than 5 years (without progression to precancer) (Ho et al. 1998; Demarco et al., 2020).

The disappearance of HPV can indicate immune control (resulting in latent infections, which replicate in the basal epithelial layer without a complete life-cycle and full virion production) or complete eradication from the cervix (Doorbar, 2018). The distinction cannot currently be measured; in any case, only persistently apparent infections, detectable for years by HPV DNA assays, confer risk of precancer.

Progression to precancer is a function of HPV type and time of persistence (Fig. 1.14) (Schiffman et al., 2005; Rodríguez et al., 2010). Compared with these major influences, progression is increased only slightly by etiological cofactors such as smoking, multiparity, or use of hormonal contraceptives (Perkins et al., 2020). Whereas viral clearance follows a curve that is initially very fast and then slows, progression is a more linear product of time spent as persistently detectable. HPV16 has the highest progression rate per time (Demarco et al., 2020). The lowest-risk carcinogenic types have considerably lower progression rates.

The prevalence of HPV in adult women in a population is a critical determinant of cervical screening and triage strategies, because most infections are acquired in young adulthood and resolve; prevalently detected HPV infections in mid-adult and older women are more likely to be persistent infections that have not resolved. In screening, point prevalent infections are observed; if prevalence is high, it becomes impractical to treat all infected women by use of currently available destructive or excisional

Fig. 1.13 Major steps in the development of cervical cancer

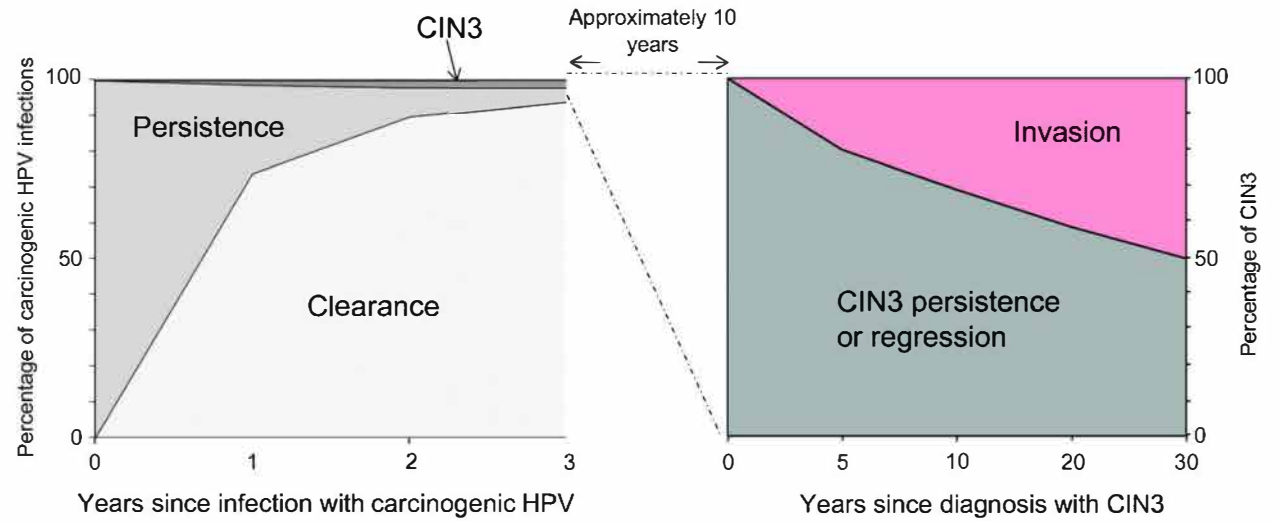


Reprinted from Schiffman et al. (2007). Copyright 2007, with permission from Elsevier. Adapted from Schiffman & Castle (2005).

methods. International studies of prevalence of carcinogenic HPV types indicate that low prevalence in mid-adulthood is characteristic of immunocompetent, frequently screened populations (Fig. 1.15) (Bruni et al., 2010). However, a high prevalence throughout adulthood is observed in some important regions, such as sub-Saharan Africa, and may be linked to partial immunodeficiency (or, alternatively, to some unknown behavioural difference combined with lack of screening). The partial immunodeficiency hypothesis suggests that there is a tolerant immune response secondary to chronic parasitoses or gut helminth prevalence (Petry et al., 2003; Gravitt et al., 2016). Women living with HIV are an important special population; they have a high HPV prevalence, and screening and management require separate consideration (see Section 5.2.1).

Few studies of type-specific regression of precancer have been conducted, because of the ethical requirement for prompt treatment. However, it is well established that HPV type is a key determinant of the precancerous state and the risk of progression. The carcinogenic and non-carcinogenic HPV types found in precancers, even when stringently defined as CIN3 or AIS, are more numerous (specifically for CIN3) than the types found in invasive cancer (Guan et al., 2012) (Fig. 1.10). This shows that current clinical definitions of precancer are not perfect surrogates of cancer risk. HPV31 and HPV51 are examples of HPV types whose role in causing precancers may lead to an exaggerated view of their importance for cancers. Similarly, HPV53

Fig. 1.14 Average clearance, persistence, and progression of carcinogenic human papillomavirus (HPV) infections

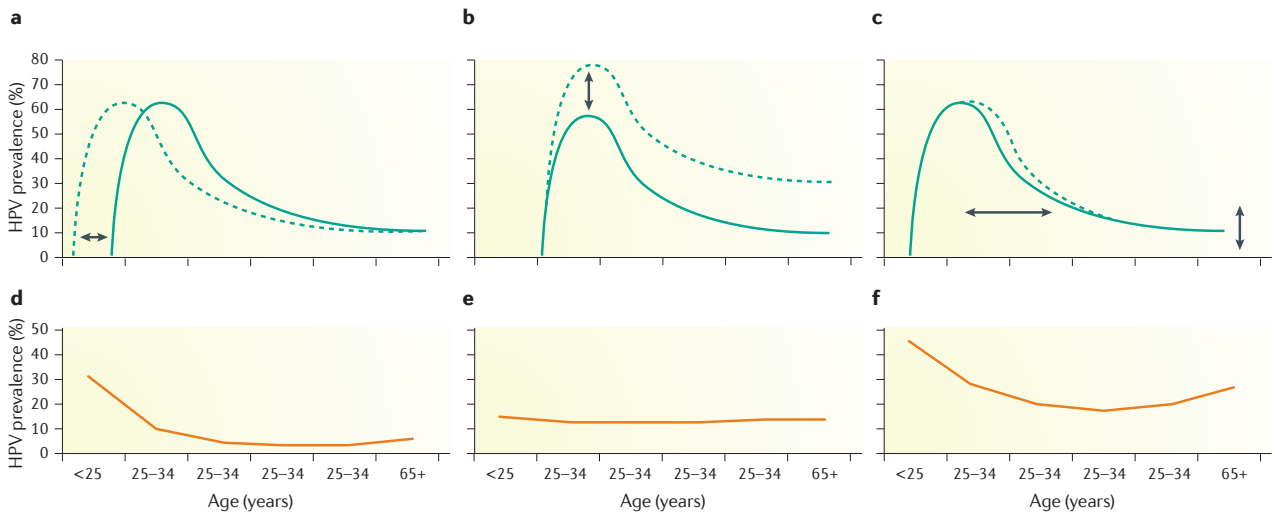


This figure combines the early natural history of rapid clearance of HPV infection with slower progression to precancers, which can, in turn, eventually invade, as described by McCredie et al. (2008).
CIN3, cervical intraepithelial neoplasia grade 3.
Reproduced from Schiffman et al. (2011).

and HPV66, two types that are possibly carcinogenic to humans (Group 2B), are frequent causes of precancer but almost never cause cancer (Schiffman & de Sanjose, 2019). Type-specific transition probabilities of invasion cannot be directly observed ethically (McCredie et al., 2008); however, they can be crudely ranked by the relative proportions of the individual types in cancers versus precancers in a given population (Guan et al., 2012) (Fig. 1.10). A higher relative proportion in cancers suggests an association with invasive potential, as exemplified by the predominance of HPV16 in invasive cancers.

The epidemiology of HPV natural history and multistage cervical carcinogenesis can also be viewed in molecular terms describing type-specific viral carcinogenicity. Viral genomes persist at low levels in the undifferentiated cells in the lowest layers of the epithelium, typically with only low (and regulated) levels of viral gene expression. This is the reservoir of infection that underlies viral latent persistence. As cells from this layer differentiate and migrate towards the epithelial surface, a pattern of gene expression is initiated, which leads to the production of virus particles; these are eventually shed from the epithelial surface (Doorbar, 2018). The cellular immune system, a combination of intraepithelial and stromal cellular surveillance and destruction of infected cell clones, plays an important role in controlling HPV infections in cervical tissue (Stanley et al., 1994). Sometimes, if cellular immune control weakens (e.g. due to immune senescence), infections persisting in a latent, non-infectious state may be reactivated and resume a full viral life-cycle, leading to virion production and release (Schiffman et al., 2016). The risk of subsequent precancer after reappearance is equal to or lower than the risk after first acquisition (Rodríguez et al., 2012; Gage et al., 2014).

Fig. 1.15 Factors that influence age-specific human papillomavirus (HPV) prevalence in women, and three patterns of HPV prevalence



The prevalence of HPV and associated cellular and visual changes in mid-adulthood is a critical determinant of screening and management strategies. Prevalence patterns by age vary widely between settings, because of behavioural and immunological variables. Examples are given in (a), (b), and (c). (a) Age at first sexual intercourse determines the beginning of the curve. (b) Sequential and concurrent multiple sexual partnership (both sexes) determines the height. (c) Partner stability and/or immune response shape the curve descent, and cervical cancer screening practices determine the height at older ages. Three illustrative examples of age-specific HPV prevalence are given in (d), (e), and (f): (d) more-developed regions, (e) India, and (f) Africa.
Adapted from Schiffman et al. (2016).

The difference between productive HPV infection and precancer has been studied comprehensively at the molecular level, and there are important changes in both viral and cellular biology. HPV infections are very common, and even infections with carcinogenic types are usually benign. However, when they are persistent, infections with carcinogenic types may shift from the usual and common productive state (i.e. the complete life-cycle designed to produce new virus particles). Instead, the virus can enter an abortive or transforming state characteristic of precancer. This occurs when the viral proteins used for cellular adaptation in the successful vegetative life-cycle disrupt cell differentiation and, as an unintended consequence, are no longer able to generate infectious virus. The correlated visual, microscopic, and molecular signs or biomarkers of the shift from productive infection to transforming infection underlie almost all cervical screening, triage, and diagnostic tests designed to detect precancer.

At the molecular level, viral gene expression changes from a productive infection characterized by expression of the E4, L2, and L1 viral genes to a strongly increased expression of the viral oncogenes E6 and E7 (Doorbar et al., 2012; Griffin et al., 2015). This deregulated expression of E6 and E7 in replicating basal cells leads to disturbances of cell-cycle regulation, disrupted differentiation and cell density regulation, and abrogation of apoptosis. The changes include disruption of the retinoblastoma protein (pRB) family regulatory pathway by E7, which results in accumulation of p16; detection by p16/Ki-67 dual staining provides accurate cytological and histological markers of precancer (Wentzensen et al., 2007, 2019). Deregulated expression of E6

Table 1.2 Summary of the current WHO classification of tumours of the uterine cervix

Squamous cell tumours and precursors	*Germ cell tumours*
Squamous intraepithelial lesions	*Neuroendocrine neoplasia*
Squamous cell carcinoma, HPV-associated	Neuroendocrine tumour
Squamous cell carcinoma, HPV-independent	Neuroendocrine carcinoma
Squamous cell carcinoma NOS	Small cell neuroendocrine carcinoma
Glandular tumours and precursors	Large cell neuroendocrine carcinoma
Adenocarcinoma in situ, HPV-associated	Mixed neuroendocrine–non-neuroendocrine neoplasms
Adenocarcinoma, HPV-associated	Carcinoma admixed with neuroendocrine carcinoma
Adenocarcinoma in situ, HPV-independent	*Mesenchymal tumours of the lower genital tract*
Adenocarcinoma, HPV-independent, gastric type	Adipocytic tumours
Adenocarcinoma, HPV-independent, clear cell type	Fibroblastic and myofibroblastic tumours
Adenocarcinoma, HPV-independent, mesonephric type	Vascular tumours
Other adenocarcinomas of the uterine cervix	Smooth muscle tumours
Other epithelial tumours	Skeletal muscle tumours
Carcinosarcoma	Peripheral nerve sheath tumours
Adenosquamous and mucoepidermoid carcinomas	Tumours of uncertain differentiation
Adenoid basal carcinoma	Undifferentiated small round cell sarcomas
Carcinoma, unclassifiable	*Melanocytic lesions*
Mixed epithelial and mesenchymal tumours	Naevi
Adenomyoma	Melanoma
Adenosarcoma	*Metastasis*

HPV, human papillomavirus; NOS, not otherwise specified.
Adapted from WHO Classification of Tumours Editorial Board (2020).

and E7 oncoproteins also affects DNA methylation; in transformed cells, HPV genomes are highly methylated throughout CpG sites, especially in the capsid encoding the L1 and L2 genes (yielding a biomarker predictive of precancer) (Lorincz et al., 2013; von Knebel Doeberitz & Prigge, 2019; see also Section 4.6).

1.2.3 Terminology for pathological classification

This section provides an overview of the classification and pathology of cervical cancer. The current WHO classification is summarized in Table 1.2, and the text below focuses on the most common cervical cancer types: SCC and adenocarcinoma, which typically arise in the TZ. These two tumour types account for more than 95% of all cervical cancers. SCC is considerably more common than adenocarcinoma, which accounts for about 5% of all cervical carcinomas in non-screened populations, although more recently a higher proportion (10–25%) has been reported in screened populations (Smith et al., 2000; Adegoke et al., 2012). Other tumour types are rare, but screening programmes do identify appreciable numbers of them (Lei et al., 2019). The WHO classification of tumours of female genital tumours provides detailed information on all of the tumours and tumour-like lesions that arise in the uterine cervix (WHO Classification of Tumours Editorial Board, 2020).

Most cervical cancers are HPV-associated carcinomas, but a small percentage of tumours are not associated with HPV infection. Moreover, there is accumulating evidence that HPV-independent cervical carcinomas are more aggressive than their HPV-associated counterparts (Nicolás et al., 2019; Stolnicu et al., 2019). To reflect this, the classification of cervical

carcinomas has changed in the latest edition of the WHO classification, to separate tumours associated with HPV infection from those that arise independently of HPV (WHO Classification of Tumours Editorial Board, 2020).

(a) Etiology and pathogenesis

The etiology and pathogenesis of epithelial tumours of the cervix are dominated by HPV infection, as discussed in detail in Sections 1.2.1 and 1.2.2.

An important consequence of our improved understanding of the relationship between HPV infection and cervical cancer is that it has enabled reconsideration of the terminology of precursor lesions. HPV infections occur in two forms: productive and transforming. Productive HPV infection cannot occur in glandular epithelium, because it is tightly linked to squamous differentiation. However, transforming infection can occur in glandular epithelium, and this leads to the development of HPV-associated AIS, the precursor of HPV-associated adenocarcinoma. This has led to increasing use of a two-tier classification for HPV-associated squamous precursor lesions (Table 1.2).

(b) Epithelial tumours

(i) Precursors of squamous cell carcinoma

The histopathological classification of precursors of cervical SCC has changed over time (Fig. 1.16). Until the 1960s, non-invasive lesions were subdivided into carcinoma in situ and dysplasias, which were in turn subdivided into three grades (mild, moderate, and severe) of increasing cytological abnormality (Reagan et al., 1953). In 1967, Richart proposed the term cervical intraepithelial neoplasia (CIN) to encompass the spectrum of changes encountered in intraepithelial lesions of squamous epithelium (Richart, 1967). CIN lesions are identified on the basis of full-thickness nuclear abnormality, with the grades (CIN1, CIN2, and CIN3) determined traditionally by the position in the epithelium, in thirds, at which cytoplasmic maturation occurs; these features correlate with increasing risk of progression to invasive disease (Östör, 1993; Cantor et al., 2005). Initially, carcinoma in situ (CIS) was separated from CIN3, but reproducible separation was problematic, and CIS was subsequently incorporated into the CIN3 category. The CIN system has been used widely, both for the diagnosis of cervical disease and, since the 1980s, in screening programmes, particularly in Europe (Fox et al., 1999; Hirschowitz et al., 2012). The alternative two-tier system (Lower Anogenital Squamous Terminology [LAST]), which recognizes low-grade and high-grade squamous intraepithelial lesions (SILs), has its origins in the Bethesda system for reporting cytopathology, in the late 1980s (Solomon, 1989), and has been translated into histopathological use, particularly in North America (Tabbara et al., 1992; Stoler et al., 2001). Broadly, low-grade SIL corresponds to a combination of the categories of CIN1 and HPV-associated changes without CIN; and high-grade SIL corresponds to a combination of CIN2 and CIN3. A detailed review of classification systems, together with considerations of HPV biology, led to the recommendation in 2012 that the SIL terminology be used (Darragh et al., 2012); this was endorsed in 2014 in the WHO classification (Kurman et al., 2014) and has been retained in the 2020 classification (WHO Classification of Tumours Editorial Board, 2020). Both LAST and WHO recommend that the appropriate CIN term is provided in parentheses after the SIL designation, for example "high-grade SIL (CIN2)". In cases where there is diagnostic uncertainty, p16 immunostaining, when available, is helpful (Darragh et al., 2012; Castle et al., 2020).

For cytology, the Bethesda (SIL) system is widely used, but the Pap and WHO systems are also used in some areas. This variation is also true for histopathology; both the CIN and LAST (SIL) systems are used in different geographical

Fig. 1.16 Classification systems currently used for squamous lesions of the cervix

Histology		Cytology			Molecular
CIN	LAST	Pap	WHO	Bethesda	
Normal	Normal	I	Negative	NILM	Normal cervix
		II	Squamous atypia	ASC-US	
CIN1	LSIL	III	Mild	LSIL	HPV infection
		IIID			
CIN2	HSIL		Moderate	HSIL	Precancer
CIN3		IV	Severe		
Cancer	Cancer	V	Cancer	Cancer	Cancer

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LAST, Lower Anogenital Squamous Terminology; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion and malignancy; Pap, Papanicolaou; WHO, World Health Organization.
Adapted from Schiffman et al. (2016).

regions. The relationship between the systems currently in use is shown in Fig. 1.16. This discussion relates to HPV-associated squamous precursor lesions. There are no validated reports of HPV-independent squamous precursor lesions, which are therefore not included in the WHO classification (WHO Classification of Tumours Editorial Board, 2020).

(ii) Squamous cell carcinoma

SCC is the most common type of cervical cancer, constituting 80–90% of cases (de Sanjose et al., 2010). SCC can be defined as a malignant tumour comprising invasive epithelium exhibiting squamous differentiation. This tumour can show several different histological patterns, for example keratinizing, non-keratinizing, basaloid, or papillary. These patterns aid diagnosis but do not influence clinical management. Most cervical SCCs (an estimated 93–95%) are HPV-associated (de Sanjose et al., 2010; Rodríguez-Carunchio et al., 2015; Nicolás et al., 2019). The presence of HPV can be determined by molecular testing, but p16 immunohistochemistry is an effective surrogate marker of HPV in most cases (Klaes et al., 2001, 2002; Darragh et al., 2012). Immunohistochemistry for p16 is available in many, but not all, diagnostic laboratories, and therefore the WHO classification allows for a diagnosis of SCC not otherwise specified (NOS), in settings where the distinction between HPV-associated and HPV-independent tumours cannot be made by either p16 immunostaining or HPV testing (WHO Classification of Tumours Editorial Board, 2020).

(iii) Precursors of adenocarcinoma

In contrast to SILs, both HPV-associated and HPV-independent precursor lesions are recognized for adenocarcinomas of the cervix. The HPV-associated lesions, termed AIS, constitute the majority of cases and can generally be identified by their typical morphological features and diffuse positivity for p16 (Kurman et al., 2014; Stolnicu et al., 2018, 2019). The HPV-independent lesions have been increasingly recognized in

recent years, particularly as precursor lesions for HPV-independent adenocarcinoma of gastric type, which have been referred to historically as lobular endocervical glandular hyperplasia (LEGH) and atypical LEGH (Kawauchi et al., 2008; McCluggage, 2016; Mikami, 2020). Mesonephric remnant hyperplasia may be a precursor lesion for HPV-independent adenocarcinoma of mesonephric type (McCluggage, 2016).

(iv) Adenocarcinoma

Adenocarcinomas are defined as malignant tumours comprising invasive epithelium exhibiting glandular differentiation. They are also separated into HPV-associated and HPV-independent tumours (Stolnicu et al., 2018). Most cervical adenocarcinomas (75–90%) are HPV-associated, and typical cases of usual-type adenocarcinoma can be identified on the basis of haematoxylin and eosin morphology. p16 immunostaining and/or high-risk HPV testing can be helpful in confirming the diagnosis (Stolnicu et al., 2018). HPV-independent adenocarcinomas are less common and include gastric-type adenocarcinomas (incorporating adenoma malignum) (Nishio et al., 2019; Mikami, 2020), clear cell carcinoma, and mesonephric carcinoma. Gastric-type adenocarcinomas comprise 10–15% of all cervical adenocarcinomas worldwide (Stolnicu et al., 2018; Hodgson et al., 2019) and 20–25% of cervical adenocarcinomas in Japan (Kojima et al., 2007; Kusanagi et al., 2010; Wada et al., 2017). There is accumulating evidence that HPV-independent cervical carcinomas, particularly gastric-type adenocarcinomas, behave more aggressively than their HPV-associated counterparts (Nicolás et al., 2019; Stolnicu et al., 2019).

[It is important to recognize that screening programmes traditionally are not as effective for the identification of adenocarcinomas or their precursors; however, HPV-associated AIS and adenocarcinomas are identified more effectively by HPV testing than by cytology.]

(v) Neuroendocrine tumours

Low-grade neuroendocrine tumours (carcinoid and atypical carcinoids) are very rare in the cervix. High-grade neuroendocrine carcinomas of small cell and large cell type occur much more frequently, are typically HPV-associated (small cell, 85%; large cell, 88%; Castle et al., 2018), and may be accompanied by an HPV-associated adenocarcinoma component. These tumours tend to present at an advanced stage and behave aggressively (Gibbs et al., 2019).

(vi) Other epithelial tumours

This category includes adenosquamous carcinoma, in which there is a mixture of both adenocarcinoma and SCC, and rare tumour types such as adenoid cystic carcinoma and adenoid basal carcinoma. True adenoid cystic carcinoma must be distinguished from an HPV-associated carcinoma with an adenoid cystic growth pattern. Carcinosarcomas occur as primary cervical tumours and are considered metaplastic carcinomas (WHO Classification of Tumours Editorial Board, 2020).

(c) Non-epithelial tumours

Malignant non-epithelial tumours are rare in the cervix. An important tumour in this category is embryonal rhabdomyosarcoma, which typically occurs in young children and may be associated with *DICER1* syndrome, where it is associated with other syndromic tumours such as cystic nephroma, pleuropulmonary blastoma, and thyroid tumours (WHO Classification of Tumours Editorial Board, 2020).

1.2.4 Stage at diagnosis and survival

Tumour staging assesses the extent of tumour spread, and for many tumours it is the most important determinant of clinical management, largely because it is strongly associated with patient outcome. Staging assesses spread within the organ of origin, spread to local structures,

and spread to lymph nodes and distant sites; this forms the basis of the tumour–node–metastasis (TNM) staging system, which assigns separate categories to the tumour (T), lymph nodes (N), and metastases to distant sites (M) (Fig. 1.17).

Gynaecological tumours are typically also staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system, which, for cervical carcinomas, is traditionally based on the extent of local spread and is designed to be clinically (rather than pathologically or radiologically) assessable. Most of the recent literature is based on the 2009 FIGO classification, which separates clinically visible disease from microscopically detected disease and assesses spread on the basis of involvement of other pelvic structures (Pecorelli et al., 2009; Brierley et al., 2017). In 2018, the FIGO staging system was modified to include lymph node metastasis, based on either radiological or pathological assessment (Table 1.3) (Bhatla et al., 2018, 2019; Anonymous, 2019). Patients with tumours confined to the cervix but with lymph node metastasis are now considered to have stage III rather than stage I disease. A second significant change in the 2018 system was the removal of lesion width assessment from the microinvasive disease categories. Thus, stage IA and microscopic stage IB disease are defined solely on the basis of depth of invasion.

A comparison of the 2009 and 2018 FIGO staging systems in a study of 1282 patients at a centre in the USA demonstrated upward stage migration in more than 50% of patients, largely because of the inclusion of lymph node metastasis in the 2018 system. This resulted in improved stratification of outcome, but heterogeneity remained, particularly for patients with stage III disease. Overall, progression-free survival at 5 years by the 2009 FIGO system versus the 2018 FIGO system was: stage I, 80% versus 87% ($P = 0.02$); stage II, 59% versus 71% ($P = 0.002$); stage III, 35% versus 55% ($P < 0.001$); and stage IV, 20% versus 16% ($P = 0.41$) (Grigsby et al., 2020). The differences for stages I, II, and III were statistically significant.

Improved discrimination of survival groups was also shown in a study focusing on stage IB and stage III disease using retrospective data from the Surveillance, Epidemiology, and End Results (SEER) Program (Matsuo et al., 2019). These are early data after these significant changes to the FIGO staging system, but there does appear to be improved patient stratification using the 2018 system.

Data from studies describing stage at diagnosis and stage-related survival are given in Table 1.4, Table 1.5, Table 1.6, and Table 1.7.

1.2.5 Treatment of cervical cancer and of precancerous lesions

The successful reduction of cervical cancer incidence or mortality requires appropriate follow-up and treatment of screen-positive women. Women with precancerous lesions are treated in order to prevent invasive cervical cancer. Treatment of precancer can be carried out by biopsies performed during colposcopy or as part of a screen-and-treat approach. Two main categories of treatment techniques are available: destructive and excisional. These aim to effectively eradicate precancerous lesions of the cervix, with minimal associated morbidity. For cervical cancer, treatment options rely mainly on radical surgery and radiotherapy. This section gives a short overview of the treatment options and refers mostly to the recent comprehensive IARC review (Prendiville & Sankaranarayanan, 2017) and WHO reports (WHO, 2014, 2019, 2020).

(a) Treatment of squamous precancerous lesions

Comprehensive colposcopic examination before the treatment enables the provider to determine the type and size of the TZ of the cervix and to recognize or rule out cancer, microinvasive disease, or precancer (see Section 4.5). The

Table 1.3 Staging of cervical carcinoma according to the 2018 FIGO staging system[a]

FIGO stage (2018)	Definition
I	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm (all macroscopically visible lesions, even those with superficial invasion, are stage IB)
IA1	Measured stromal invasion < 3 mm in depth
IA2	Measured stromal invasion ≥ 3 mm and < 5 mm in depth
IB	Clinically visible lesion confined to the cervix or invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter[b]
IB1	Invasive carcinoma ≥ 5 mm depth of stromal invasion, and < 2 cm in greatest dimension
IB2	Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension
IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	The carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma < 4 cm in greatest dimension
IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases),[c] irrespective of tumour size and extent (with r and p notations)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (bullous oedema alone does not indicate stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings.

[b] The involvement of vascular or lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c] Isolated tumour cells do not change the stage, but their presence should be recorded.

[d] Add the notation r (imaging) or p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r, and if confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique should always be documented. When in doubt, the lower stage should be assigned.

Compiled from Bhatla et al. (2018, 2019) and Anonymous (2019).

Fig. 1.17 Tumour–node–metastasis (TNM) staging of tumours of the cervix uteri

(ICD-O-3 C53)

The definitions of the T and M categories correspond to the FIGO stages. Both systems are included for comparison.

Rules for Classification

The classification applies only to carcinomas. There should be histological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories	Clinical examination and imaging*
N categories	Clinical examination and imaging
M categories	Clinical examination and imaging

Note

* The use of diagnostic imaging techniques to assess the size of the primary tumour is encouraged but is not mandatory. Other investigations, e.g., examination under anaesthesia, cystoscopy, sigmoidoscopy, intravenous pyelography, are optional and no longer mandatory.

The FIGO stages are based on clinical staging. For some Stage I subdivisions (IA–IB1) are mainly pathological, including the histological examination of the cervix. (TNM stages are based on clinical and/or pathological classification.)

Anatomical Subsites

1. Endocervix (C53.0)
2. Exocervix (C53.1)

Regional Lymph Nodes

The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, lateral sacral nodes, and para-aortic nodes.*

Note

* In the 7th edition the para-aortic nodes were considered to be distant metastatic but to be consistent with advice from FIGO the para-aortic nodes are now classified as regional.

TNM Clinical Classification

T – Primary Tumour

TNM Categories	FIGO Stages	Definition
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumour confined to the cervix[a]
	T1a[b,c]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[d]
	T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
	T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
	T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
	T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
	T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2		II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
	T2a	IIA	Tumour without parametrial invasion
	T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
	T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
	T2b	IIB	Tumour with parametrial invasion
T3		III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non functioning kidney
	T3a	IIIA	Tumour involves lower third of vagina
	T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non functioning kidney
T4		IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]

Notes

[a] Extension to corpus uteri should be disregarded.

[b] The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion.

[c] All macroscopically visible lesions even with superficial invasion are T1b/IB.

[d] Vascular space involvement, venous or lymphatic, does not affect classification.

[e] Bullous oedema is not sufficient to classify a tumour as T4.

Fig. 1.17 (continued)

N – Regional Lymph Nodes*
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Note
* No FIGO equivalent.

M – Distant Metastasis
M0 No distant metastasis
M1 Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa, and adnexa

pTNM Pathological Classification
The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pM – Distant Metastasis*
pM1 Distant metastasis microscopically confirmed

Note
* pM0 and pMX are not valid categories.

Stage			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1,T2,T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

FIGO, International Federation of Gynecology and Obstetrics.
Reproduced from Brierley et al. (2017).

TZ varies in its size and its precise position on the cervix, and it may lie partially or completely in the endocervical canal. Determining whether the TZ is fully visible and where it is situated will enable determination of the TZ type (Fig. 1.18). A fully visible ectocervical and small TZ (type 1 TZ) is both easy to assess and simple to treat, either by destruction or by simple excision. In contrast, a large type 3 TZ cannot be assessed completely, and treatment will be associated with greater difficulty, a higher risk of morbidity (Khalid et al., 2011), and an increased risk of failure (Ghaem-Maghami et al., 2007).

Because the TZ is where cervical SCC originates, treatment aims to accomplish eradication of the entire TZ and not only the lesion. Independently of the technique used, ablation to a depth of 7 mm is considered optimal (Shafi et al., 2006); this gives a sufficient degree of safety, because gland crypts containing CIN can be as deep as 4 mm (Anderson & Hartley, 1980).

The choice of the technique to be used depends on the TZ type, the severity and nature of the cervical lesion, the local circumstances, the equipment and training available, and whether general anaesthesia is accessible. Table 1.8 summarizes the treatment options, and the different excision types are illustrated in Fig. 1.18.

(i) Destructive or ablative methods

With ablative techniques, the TZ epithelium is destroyed rather than preserved, thereby negating the opportunity for histopathological examination; these techniques should not be performed when suspicion of malignancy is high. The most common techniques currently used are cryosurgery (also known as cryocautery, cryotherapy, or cryo) and thermal coagulation (also called thermal ablation or misnamed as cold coagulation). Two other destructive methods are not presented here: radical diathermy, which is no longer used, and laser ablation, which is currently less often used (Monaghan, 1995).

Table 1.4 Stage distribution of cervical cancer using FIGO staging at diagnosis, by country or region and period

Country (territory or region)	Data source	Period of diagnosis	FIGO stage at diagnosis (%)					Reference
			I	II	III	IV	Unknown	
Brazil	Hospital-based cancer registry	2005–2014	21.2	30.7	39.9	8.2	–	Vale et al. (2019)
Canada (Ontario)	Population-based cancer registry	2005–2009	39.8	16.6	14.5	7.0	22	Liu et al. (2016)
Colombia	Hospital-based cancer registry	2007–2012	24.3	21.0	35.2	4.5	15	Pardo & de Vries (2018)
Ethiopia	Hospital or oncology centre	2014–2016	9.9	24.9	40.2	24.9	–	Wassie et al. (2019)
France (Martinique)	Population-based cancer registry	2002–2011	66.7		33.3		–	Melan et al. (2017)
India (Mumbai)	Hospital	2010	13.0	32.0	33.5	6.0	14	Chopra et al. (2018)
Russian Federation (Arkhangelsk)	Population-based cancer registry	2005–2016	39.1	26.1	22.7	12.0	–	Roik et al. (2017)

FIGO, International Federation of Gynecology and Obstetrics.

In the past decade, **cryosurgery** has become very popular as part of a screen-and-treat approach in many low- and middle-income countries (LMICs), but difficulties with maintaining a cheap and reliable supply of carbon dioxide (CO_2) have limited its popularity. Cryosurgery destroys tissue by freezing to below –20 °C, using a metal probe held in close contact with the TZ epithelium. When the method is used for type 1 TZs that are small enough to be completely covered by the probe, success rates are likely to be high. Failure rates are high for lesions that extend to four quadrants of the TZ.

Unlike cryosurgery, which uses cold temperatures to destroy tissue, **thermal coagulation** uses heat. The probe is heated electrically and reaches temperatures of 100–120 °C, which causes intracellular boiling and cell necrosis. It achieves tissue destruction to a depth of 4–7 mm (Haddad et al., 1988). Thermal coagulation has success rates similar to those of cryosurgery, is quicker to perform, has low complication rates, and does not require refrigerated gas. The procedure takes less than 2 minutes to complete and is usually performed without either general or local anaesthesia; it appears to be well tolerated. Newer thermal coagulation units are battery-operated and can provide sufficient battery power for 30 procedures before recharging is necessary (Pinder et al., 2020). Subsequent pregnancy and fertility rates do not appear to be affected by thermal coagulation.

(ii) Excisional methods

There are several ways of excising the TZ. These include hysterectomy, cold-knife excision (also known as cold-knife cone biopsy or cold-knife conization), laser cone biopsy, and large loop excision of the transformation zone (LLETZ)/loop electrosurgical excision procedure (LEEP).

Hysterectomy has been widely used to treat suspected or proven cervical precancer. However, hysterectomy should not be used as a treatment of CIN. For women with precancerous lesions, hysterectomy offers no advantage over local excision of the lesion, and for women in whom unsuspected invasive disease is revealed at hysterectomy, the patient will have been poorly served.

Table 1.5 Stage distribution of cervical cancer using three-tiered staging at diagnosis, by country or region and period

Country (region or city)	Data source	Period of diagnosis	Stage at diagnosis (%)[a]				Reference
			Localized	Regional	Distant	Unknown	
Australia (New South Wales)	Population-based cancer registry	2003–2012	41.5, 47.2[b]	34.2, 27.8[b]	17.1, 8.3[b]	7.3, 16.7[b]	Diaz et al. (2018)
Austria	Population-based cancer registry (EUROCARE5)	2000–2007	56	21	7	17	Minicozzi et al. (2017)
Costa Rica	Population-based cancer registry	1995–2000	22.4	40.5	4	33.1	Sankaranarayanan et al. (2011)
Cuba	Population-based cancer registry	1994–1995	41.3	34.3	1.7	22.7	Sankaranarayanan et al. (2011)
Czechia	Population-based cancer registry (EUROCARE5)	2000–2007	61	19	8	12	Minicozzi et al. (2017)
Estonia	Population-based cancer registry (EUROCARE5)	2000–2007	60	26	8	6	Minicozzi et al. (2017)
Finland	Population-based cancer registry (EUROCARE5)	2000–2007	43	5	24	28	Minicozzi et al. (2017)
India (Bhopal)	Population-based cancer registry	1991–1995	28.3	70.5	0.3	0.9	Sankaranarayanan et al. (2011)
India (Chennai)	Population-based cancer registry	1990–1999	6.4	86.0	3.7	3.9	Sankaranarayanan et al. (2011)
India (Karunagappally)	Population-based cancer registry	1991–1997	15.3	60.6	8.8	15.3	Sankaranarayanan et al. (2011)
India (Mumbai)	Population-based cancer registry	1992–1999	27.9	56.8	8.6	6.7	Sankaranarayanan et al. (2011)
Japan (Osaka)	Population-based cancer registry	1976–2012	53	7, 10[c]	10	20	Yagi et al. (2019)
Kuwait	Population-based cancer registry	2000–2013	24.5	36.2	6.1	33.1	Alawadhi et al. (2019)
Norway	Population-based cancer registry	1990–2014	59.6	29.6	8.9	1.9	Thøgersen et al. (2017)
Philippines (Manila)	Population-based cancer registry	1994–1995	21.5	30.5	10.3	37.7	Sankaranarayanan et al. (2011)
Republic of Korea	Nationwide, hospital-based cancer registry	2006–2010	56.4	25.2	6.1	12.4	Jung et al. (2013)
Singapore	Population-based cancer registry	1993–1997	45.5	5.7	5.0	43.8	Sankaranarayanan et al. (2011)
Spain (Basque Country)	Population-based cancer registry (EUROCARE5)	2000–2007	57	30	8	5	Minicozzi et al. (2017)
Spain (Cuenca)	Population-based cancer registry (EUROCARE5)	2000–2007	66	11	20	3	Minicozzi et al. (2017)
Switzerland (St Gallen)	Population-based cancer registry (EUROCARE5)	2000–2007	63	18	12	8	Minicozzi et al. (2017)
Thailand (Chiang Mai)	Population-based cancer registry	1993–1997	26.1	69.7	3.7	0.5	Sankaranarayanan et al. (2011)
Thailand (Chang Mai)	Population-based cancer registry	2008–2012	48	46	5	1	Sripan et al. (2019)

Table 1.5 (continued)

Country (region or city)	Data source	Period of diagnosis	Stage at diagnosis (%)[a]				Reference
			Localized	Regional	Distant	Unknown	
Thailand (Khon Kaen)	Population-based cancer registry	1993–1997	17.3	53.8	6.3	22.6	Sankaranarayanan et al. (2011)
Thailand (Lampang)	Population-based cancer registry	1990–2000	31.2	53.9	5.8	9.2	Sankaranarayanan et al. (2011)
Thailand (Songkhla)	Population-based cancer registry	1990–1999	22.3	54.6	5.8	17.3	Sankaranarayanan et al. (2011)
Turkey (Izmir)	Population-based cancer registry	1995–1997	28.9	41.8	6.1	23.2	Sankaranarayanan et al. (2011)
USA	Population-based cancer registry (SEER)	2004–2009	44.7	35.5	11.5	8.4	Benard et al. (2017)
USA	Population-based cancer registry (SEER)	2014–2016	42	36	17	5	Benard et al. (2019)

EUROCARE, European Cancer Registry-Based Study on Survival and Care of Cancer Patients; SEER, Surveillance, Epidemiology, and End Results Program.

[a] Localized, confined to the cervix and uterus; regional, spread beyond the cervix and uterus to nearby lymph nodes; distant, spread to nearby organs (e.g. bladder or rectum) or distant sites (e.g. lung or bone) (ACS, 2020).

[b] Data are shown for Indigenous and non-Indigenous populations, respectively.

[c] For regional lymph nodes reported separately from adjacent organs.

Table 1.6 Stage-related survival of cervical cancer using FIGO staging at diagnosis, by country or region and period

Country (territory or region)	Data source	Period of diagnosis	FIGO stage at diagnosis (%)					Follow-up	Reference
			I	II	III	IV	Unknown		
India (Mumbai)	Hospital	2010	–	62	45	4	–	5-yr disease-free survival (3-yr for stage IV)	Chopra et al. (2018)
Ethiopia	Hospital or oncology centre	2014–2016	81.04	67.94	23.33	20.03	–	5-yr survival	Wassie et al. (2019)
Colombia	Hospital-based cancer registry	2007–2012	90.3	75.6	47.6	22.6	50.6	2-yr survival	Pardo & de Vries (2018)
France (Martinique)	Population-based cancer registry	2002–2011	71		23		–	5-yr survival	Melan et al. (2017)
Sub-Saharan Africa (excluding Mauritius and Kampala)	Population-based African Cancer Registry Network member registries	2008–2014 (varies between countries)	50.3		20.5		–	5-yr survival	Sengayi-Muchengeti et al. (2020)

FIGO, International Federation of Gynecology and Obstetrics; yr, year.

Table 1.7 Stage-related survival of cervical cancer using three-tiered staging at diagnosis, by country or region and period[a]

Country (region or city)	Period of diagnosis	Stage at diagnosis (%)				Follow-up	Reference
		Localized	Regional	Distant	Unknown		
Costa Rica	1995–2000	89.5	43.1	11.3	43.2	5-yr absolute survival	Sankaranarayanan et al. (2011)
Cuba	1994–1995	73.9	41.5	33.3	45.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Bhopal)	1991–1995	60.6	22.7	0.0	0.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Chennai)	1990–1999	69.1	55.3	12.4	43.4	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Karunagappally)	1991–1997	72.1	43.5	23.1	44.3	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Mumbai)	1992–1999	68.3	35.7	2.4	40.7	5-yr absolute survival	Sankaranarayanan et al. (2011)
Japan (Osaka)	2003–2010	90.4	50.3, 59.6[b]	6.9	–	5-yr relative survival	Yagi et al. (2019)
Kuwait	2005–2009	88.4	68.3	–	72.9	5-yr unstandardized net survival	Alawadhi et al. (2019)
Philippines (Manila)	1994–1995	63.1	29.9	7.1	28.2	5-yr absolute survival	Sankaranarayanan et al. (2011)
Republic of Korea[c]	2006–2010	91.1	70.9	25.8	75.1	5-yr survival	Jung et al. (2013)
Singapore	1993–1997	69.7	48.0	20.4	55.7	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Chiang Mai)	1993–1997	81.2	52.7	12.2	75.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Khon Kaen)	1993–1997	65.1	48.7	30.6	57.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Lampang)	1990–2000	78.7	57.9	6.5	70.6	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Songkhla)	1990–1999	81.2	56.3	15.4	61.3	5-yr absolute survival	Sankaranarayanan et al. (2011)
Turkey (Izmir)	1995–1997	67.7	54.6	9.3	69.1	5-yr absolute survival	Sankaranarayanan et al. (2011)
USA[d]	2004–2009	85.9	55.8	16.3	56.2	5-yr relative survival	Benard et al. (2017)

yr, year.

[a] Unless otherwise specified, data are from population-based cancer registries.

[b] For regional lymph nodes reported separately from adjacent organs.

[c] Nationwide, hospital-based cancer registry.

[d] Surveillance, Epidemiology, and End Results Program (SEER).

Table 1.8 Treatment options for precancerous lesions of the cervix

Severity and nature of lesion	Treatment options		
	Type 1 TZ	Type 2 TZ	Type 3 TZ
No visible lesion[a]	Ablation	LLETZ Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal	Type 3 excision by LLETZ
Low-grade or high-grade squamous lesions[b]	Ablation (preferred in a screen-and-treat setting or for low-grade lesions) LLETZ	LLETZ Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal	Type 3 excision by LLETZ using a sufficiently long loop, or top-hat excision, SWETZ, or NETZ; CKC (only if the electrosurgical techniques are not feasible)
Glandular lesions[c]	Type 3 excision with CKC, SWETZ or NETZ, followed by endocervical curetting LLETZ with a sufficiently long loop, if the other techniques are not feasible		
Microinvasive cancer[d]	Type 3 excision with CKC, SWETZ, or NETZ, followed by endocervical curetting		

CKC, cold-knife conization; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LLETZ, large loop excision of the transformation zone; NETZ, needle excision of the transformation zone; SWETZ, straight wire excision of the transformation zone; TZ, transformation zone; VIA, visual inspection with acetic acid.

[a] HPV-positive women in a screen-and-treat setting; cytology suspecting HSIL or glandular abnormalities.

[b] Abnormal VIA in a screen-and-treat setting, colposcopically suspected or histopathologically proved.

[c] Cytology suspecting glandular lesion, suspicion of glandular abnormalities on colposcopy, or adenocarcinoma in situ confirmed on histopathology.

[d] Early invasive cancer suspected on colposcopy although histopathology shows less severe abnormality; microinvasive cancer confirmed on histopathology.

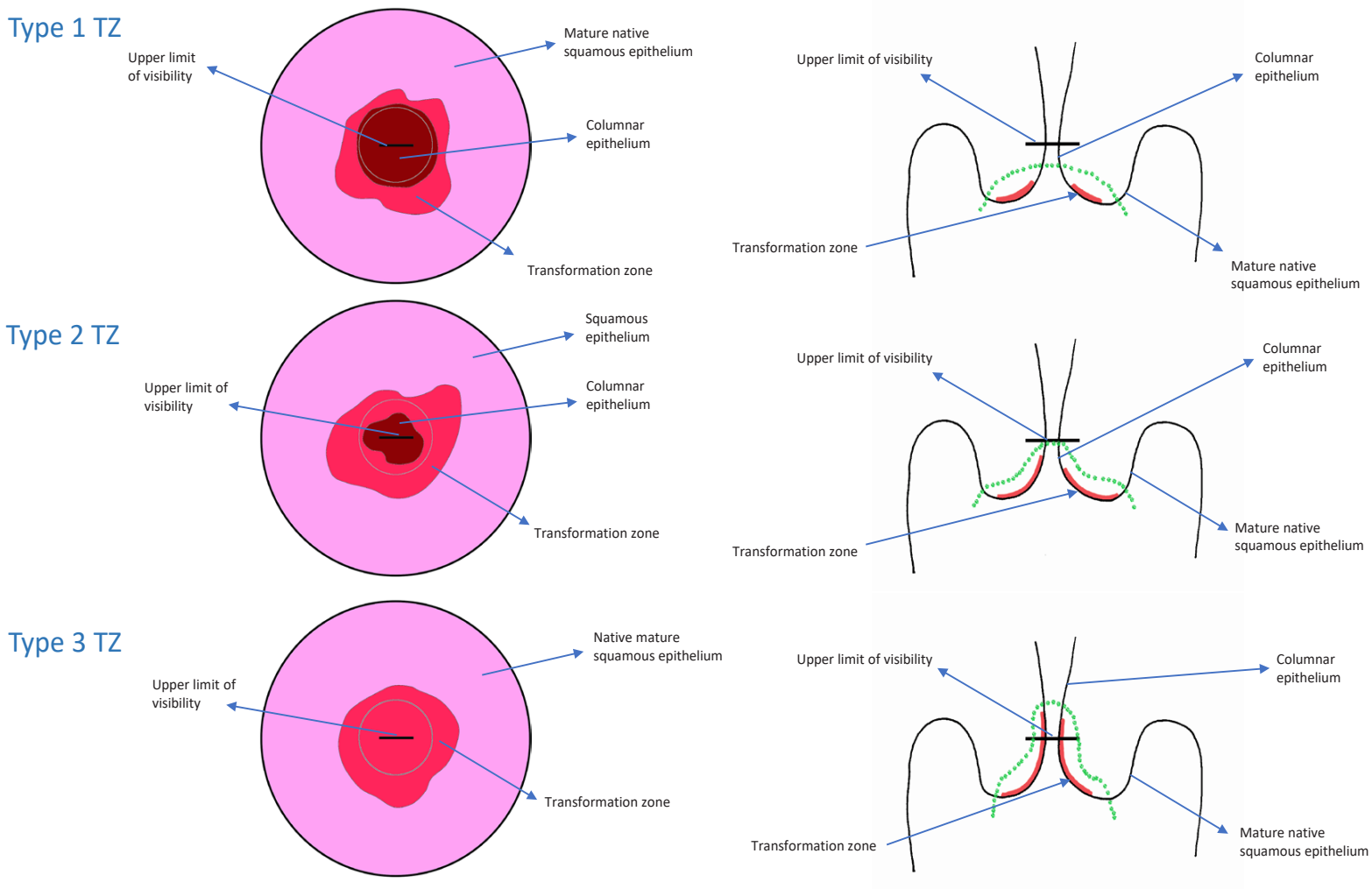
After a simple hysterectomy, it is not possible to offer the appropriate radiotherapy regime, and radical hysterectomy is also not possible.

Cold-knife conization, the oldest method of local excision, is still widely used, especially where colposcopy facilities and/or expertise are not available. The technique leaves a relatively large cervical defect and often removes more tissue than is necessary. The procedure is usually performed under general anaesthesia. A suture or sutures are often used to achieve post-excision haemostasis. Cold-knife conization is associated with well-recognized short- and long-term complications, including primary and secondary haemorrhage, cervical stenosis, and cervical incompetence. It may be selected for glandular or microinvasive disease, but otherwise cold-knife conization has no advantages over LLETZ/LEEP or laser excision and is associated with greater morbidity and long-term pregnancy-related complications (Jones et al., 1979; Kristensen et al., 1993; Arbyn et al., 2008).

LLETZ/LEEP involves excision of the TZ using a low-voltage diathermy loop of thin wire, usually with blended diathermy under local anaesthesia. This technique is used for a type 1 excision (Fig. 1.18) and is appropriate for most women with CIN (i.e. for a small or medium-sized type 1 TZ). It leads to the excision of the entire TZ and only the TZ, to a depth of about 5–7 mm, and the diathermy artefactual damage of the loop will cause necrosis for a further 2–3 mm. Short-term complications after LLETZ include light vaginal bleeding, mild discomfort, and a little discharge.

Alternative electrosurgery techniques for an endocervical TZ. Although type 3 excisions, especially large ones, are known to be associated with an increase in the risk of subsequent pregnancy-related complications (primarily premature delivery) (Khalid et al., 2012), a type 3

Fig. 1.18 Determination of the transformation zone (TZ) types of the cervix, and TZ excision types



A type 1 TZ is completely ectocervical, is fully visible, and may be small or large. A type 2 TZ has an endocervical component but is still fully visible. The ectocervical component may be small or large. A type 3 TZ has an endocervical component, and the upper limit is not fully visible. The ectocervical component, if present, may be small or large.
The dotted green lines represent the TZ excision types. Type 1 and type 2 excisions relate exactly to the corresponding TZ types. In contrast, a type 3 excision may also be used in several circumstances not dictated purely by the TZ type (e.g. for glandular lesions) (see Table 1.8).
Courtesy of Walter Prendiville, with permission. Adapted from Prendiville & Sankaranarayanan (2017).

excision is sometimes necessary, for example for a type 3 TZ with suspected high-grade SIL, glandular disease, or even suspected microinvasion. A type 3 excision may require general anaesthesia, depending on how large and how long the excision needs to be, access to the cervix, and patient compliance. Alternative techniques to LLETZ use a straight wire (SWETZ; Russomano et al., 2015) or a needle (NETZ). Top-hat LEEP involves two steps of loop excision: a conventional LEEP followed by a second excision of the residual endocervix using a smaller-diameter loop. Given the greater extent of endocervical excision compared with conventional LEEP, top-hat LEEP may reduce the risk of incomplete endocervical excision in women with a type 3 TZ (Kietpeerakool et al., 2010).

(iii) Follow-up after treatment of squamous precancerous lesions

Because treatment methods are not associated with a 100% success rate, it is important to establish a follow-up protocol to identify the small percentage (< 10%) of women treated who will have residual CIN. Women who have been treated for cervical precancer are much more likely to develop cervical cancer. This increased risk has been quantified as being 2–5 times the background risk, and much of it is a result of poor long-term follow-up (Soutter et al., 1997; Strander et al., 2007). Several case series of cervical cancer have demonstrated that more than 50% of cancers occur in women who are lost to follow-up (Ghaem-Maghami et al., 2007) and that this increase in risk lasts for 20 years or more.

(b) Treatment of adenocarcinoma in situ

AIS is a precursor of invasive adenocarcinoma. Colposcopic assessment of glandular dysplasia is less reliable than that of squamous disease. Most glandular disease has an endocervical component, and it is often not possible to determine the extent of endocervical involvement of dysplastic epithelium in the endocervical canal. Therefore, destructive techniques are contraindicated. The definitive management of glandular dysplasia is excision of the TZ and a proportion of full-thickness endocervical canal epithelium. It is crucial that the pathologist has sufficient undamaged tissue with which to make a diagnosis and assess margin involvement. A cylindrical type 3 excision should be performed using a straight wire, cold knife, or laser. Such conservative management of AIS is justified in a young woman who is assured of adequate follow-up until she has completed her family, when hysterectomy should be considered.

(c) Treatment of invasive cervical cancer

In general, early cervical cancer (SCC or adenocarcinoma) is treated using surgical excision with simple or radical hysterectomy and pelvic lymph node evaluation, whereas advanced cervical cancer is treated with concurrent chemotherapy and radiation. Fertility-sparing surgical procedures such as conization or trachelectomy can also be offered to women who have not completed their family. Detailed information can be found elsewhere (e.g. WHO, 2014; Buchanan et al., 2017; Prendiville & Sankaranarayanan, 2017; Cancer Research UK, 2020; Nica et al., 2021).

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