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The Section of Infections (INF) has two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The research activities of both Groups aim to evaluate the role of infectious agents in human cancers through biological and epidemiological studies.

The functional studies of ICB during the 2020–2021 biennium were focused on the characterization of the biological properties of oncoproteins from several human viruses, in particular cutaneous beta human papillomavirus (HPV) types (Gupta et al., 2020a; Minoni et al., 2020; Romero-Medina et al., 2020; Magnotti et al., 2021). With regard to epidemiological studies, ICB developed a highly sensitive diagnostic assay for a large number of infectious agents, with the final aim of (i) evaluating the contribution of infections to human carcinogenesis; and (ii) identifying novel algorithms for early diagnosis of human cancers driven by infections (Amorrortu et al., 2020, 2021; Galati et al., 2020a, 2021; Tagliabue et al., 2020; Rollison et al., 2021; Simoens et al., 2021).

The overall strategy of ICE is to improve the epidemiological evidence base with respect to prevention of infection-attributable cancer. This strategy relies on obtaining both high-quality data and biological samples from populations that have been well characterized epidemiologically. Although the strategy of ICE is global, work is naturally focused on low- and middle-income countries (LMICs), which have a disproportionate burden of infection-attributable cancers, and particularly on countries in Africa and Asia. There are currently 11 infectious agents that are classified as carcinogenic by the IARC Monographs, and they are at different stages along the pathway from discovery to public health intervention. Correspondingly, ICE research includes a wide portfolio of study designs that are tailored to specific infectious agents across a spectrum of epidemiological research, from etiology or natural history through global burden assessment to evaluation and modelling of the impact of interventions and/or policy.

ICB and ICE are also participating in several collaborative studies to assess the impact of HPV vaccine in LMICs and to characterize the role of mucosal high-risk (HR) HPV infection in the etiology of head and neck cancer.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, INF became part of the newly created Early Detection, Prevention, and Infections Branch.

Gastric cancer prevention in the Republic of Korea: the HELPER study

Helicobacter pylori is the most important infectious cause of cancer worldwide. In 2013, IARC and the National Cancer Center of Korea launched the HELPER study, a multicentre double-blind randomized controlled trial in the Republic of Korea, to assess the effect of *H. pylori* eradication in gastric cancer prevention. HELPER has recruited about 12 000 middle-aged participants from the general population, including 5269 *H. pylori*-positive participants, who were subsequently randomized to eradication with bismuth quadruple therapy or placebo. Biennial endoscopic follow-up is continuing within the Korean National Cancer Screening Programme, and an interim analysis is planned for 2026.

HELPER Investigators' Workshop, Seoul, Republic of Korea. © IARC.

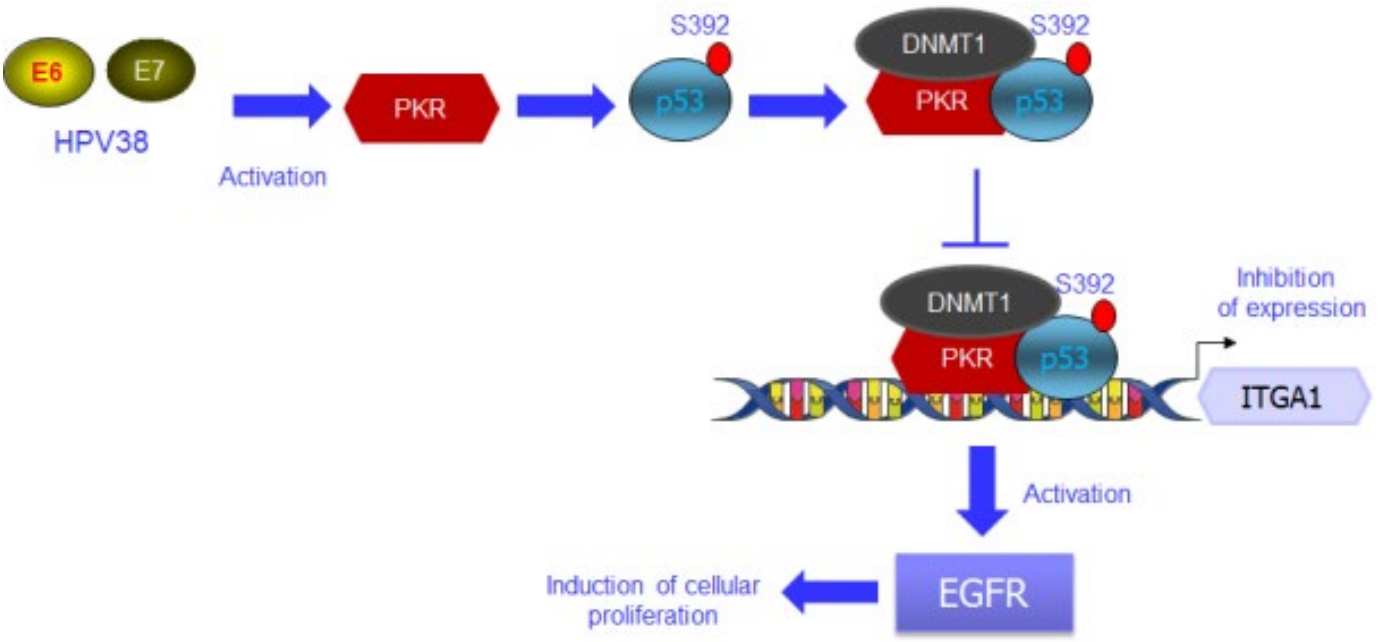
This trial is expected to determine to what extent *H. pylori* eradication reduces the risk of gastric cancer in the general population, while also providing important data on how to optimize the allocation of the resources devoted to gastric cancer control in the Republic of Korea. Globally, the study will have major public health implications by providing leads for gastric cancer prevention in populations with elevated rates of gastric cancer, particularly in Asian countries.

Role of beta HPV types in the development of cutaneous squamous cell carcinoma

A large number of HPV types have been isolated and fully characterized so far. They are subdivided into genera and species in the HPV phylogenetic tree according to the DNA genome sequence. A subgroup genus alpha, referred to as mucosal HR HPV types, infect the epithelia of the anogenital tract as well as the upper respiratory tract; these HR HPV types have been clearly associated with a broad spectrum of human cancers, including cervical and oropharyngeal cancers. In addition to the HR HPV types, cutaneous beta HPV types also appear to be implicated in carcinogenesis, although by different mechanisms. Using in vitro and in vivo experimental models, studies by ICB and other groups have highlighted the transforming properties of E6 and E7 from several cutaneous beta HPV types. In a recent study, ICB characterized a novel mechanism of virus-mediated p53 inactivation. Beta HPV38 E6 and E7 promote accumulation of a wild-type p53 form in human keratinocytes, promoting cellular proliferation. Inactivation of p53 by different means strongly decreases the proliferation of HPV38 E6 and E7 human keratinocytes. This p53 form is phosphorylated at S392 by the double-stranded RNA-dependent protein kinase PKR, which is highly activated by HPV38. PKR-mediated S392 p53 phosphorylation promotes the formation of a p53–DNMT1 complex, which inhibits expression of integrin alpha 1 (ITGA1), a repressor of epidermal growth factor receptor (EGFR) signalling (Romero-Medina et al., 2020) (Figure 1). These findings reveal the existence of a specific wild-type p53 form that displays pro-proliferation properties and are in agreement with a model in which beta HPV E6 and E7 proteins and ultraviolet (UV) radiation intimately cooperate in promoting skin carcinogenesis (Figure 2). A recent study by ICB showed that UV irradiation per se increases the beta HPV positivity in the skin, most likely because of its inhibitory activity on the immune system. In turn, by targeting key cellular pathways, beta HPV types act as facilitators of HPV UV-induced DNA mutations. However, after the accumulation of DNA mutations and the development of skin lesions, the expression of the HPV38 E6 and E7 genes is dispensable for the maintenance of the malignant phenotype of skin cancer cells (Lambert et al., 2020a).

In agreement with this working model, a prospective study showed that baseline beta HPV detection significantly predicted the development of cutaneous squamous cell carcinoma (Rollison et al., 2021).

Figure 1. HPV38 alters wild-type p53 activity to promote cell proliferation via the downregulation of integrin alpha 1 (ITGA1) expression. EGFR, epidermal growth factor receptor. © IARC.



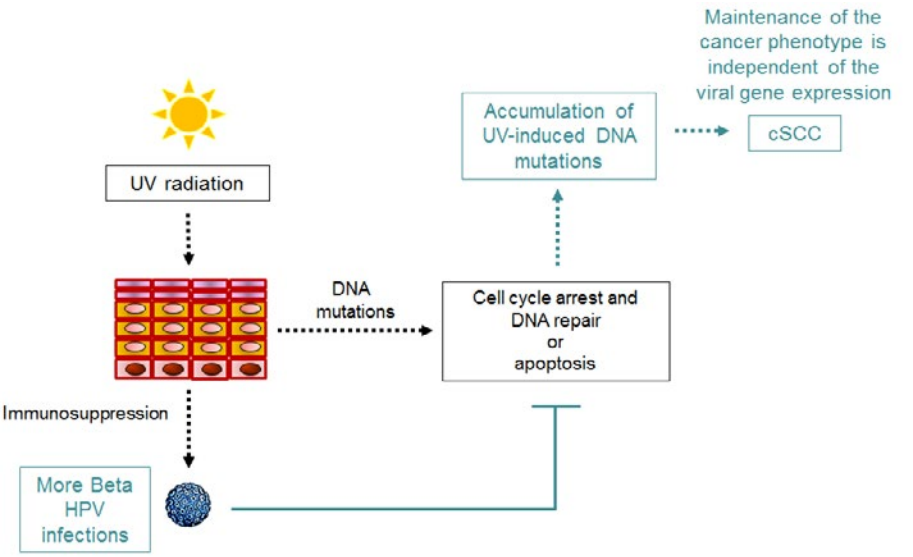


Figure 2. Model for cooperation between some beta human papillomavirus (HPV) types and ultraviolet (UV) radiation in promoting cutaneous squamous cell carcinoma (cSCC). Under physiological conditions, UV irradiation of the skin induces DNA mutations in keratinocytes and immunosuppression. The UV-induced damage results in (i) cell-cycle arrest and repair of DNA mutations or (ii) apoptosis if the DNA damage is unrepairable. Beta HPV early proteins, E6 and E7, can alter the cellular response to UV-induced stress, maintaining alive DNA-damaged cells that have a high risk of evolving into cancer cells. After accumulation of mutations in oncogenic driver genes (e.g. cellular tumour suppressor genes or oncogenes), the expression of the viral genes becomes dispensable. Reproduced from Lambert et al. (2020a). Copyright © 2020, The Authors, under exclusive licence to Springer Nature Limited.

Infections and Cancer Epidemiology Group (ICE)

Global burden of cancer attributable to infectious agents

Given the amenability of infections to prevention, estimates of infection-attributable cancer burden are key public health indicators. ICE updated estimates of infection-attributable cancer burden at the country, regional, and global level with the most pertinent exposure assessment tools and the latest global cancer incidence data for 11 infectious carcinogens (viruses, bacteria, and parasites) (de Martel et al., 2020) (Figure 3). This work estimated that in 2018, 2.2 million infection-attributable cancer cases were diagnosed worldwide, corresponding to an age-standardized incidence rate (ASIR) of 25.0 cases per 100 000 person-years. Primary causes were *H. pylori* (810 000 cases; ASIR, 8.7), HPV (690 000 cases; ASIR, 8.0), hepatitis B virus (360 000 cases; ASIR, 4.1), and hepatitis C virus (160 000 cases; ASIR, 1.7). The infection-attributable ASIR was highest in eastern Asia (37.9) and sub-Saharan Africa (33.1) and lowest in northern Europe (13.6) and western Asia (13.8) (de Martel et al., 2020) (Figure 3). China accounted for one third of global cancer cases attributable to infection, driven by the high ASIR of *H. pylori* (15.6) and hepatitis B virus (11.7) infections. HPV-attributable cancer incidence showed the strongest relationship with income level, from ASIR of 6.9 in high-income countries to ASIR of 16.1 in low-income countries. Follow-up analyses focused on the global burden of cervical cancer attributable to HIV infection (Stelzle et al., 2021) and on the HPV-related cancer burden in China (Duan et al., 2020). These findings are important to raise awareness for the control of oncogenic infections, particularly in an era where global cancer prevention is seen within the context of noncommunicable diseases.

Anal cancer epidemiology and prevention

Understanding the burden and natural history of HPV-related anal squamous cell carcinoma (ASCC) is needed to raise awareness and inform prevention initiatives. Globally every year, an estimated 29 000 people, predominantly women, are diagnosed with ASCC (de Martel et al., 2020). An ASCC risk scale was developed, based on a meta-analysis of anal cancer incidence, to help prioritize high-risk groups for anal cancer prevention programmes, most notably people living with HIV, men who have sex with men, women diagnosed with HPV-related gynaecological precancerous lesions or cancer, and recipients of solid organ transplants (Clifford et al., 2021) (Figure 4). A collaborative re-analysis of individual-level data of almost 30 000 men from 64 studies comprehensively described the age-specific epidemiology of anal HPV infection and high-grade

Figure 3. Global burden of cancer attributable to infections in 2018: 2.2 million cases (13% of all cancers). HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus. Reproduced from de Martel et al. (2020). © 2019 International Agency for Research on Cancer; licensee Elsevier.

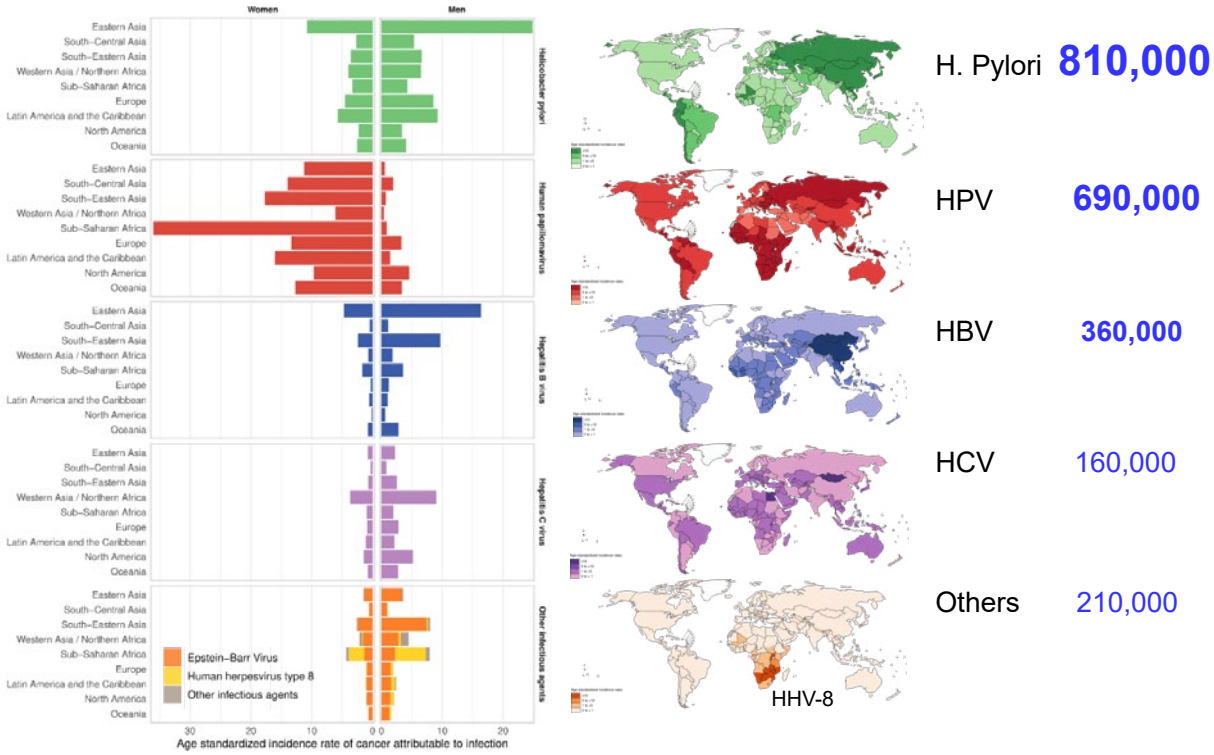
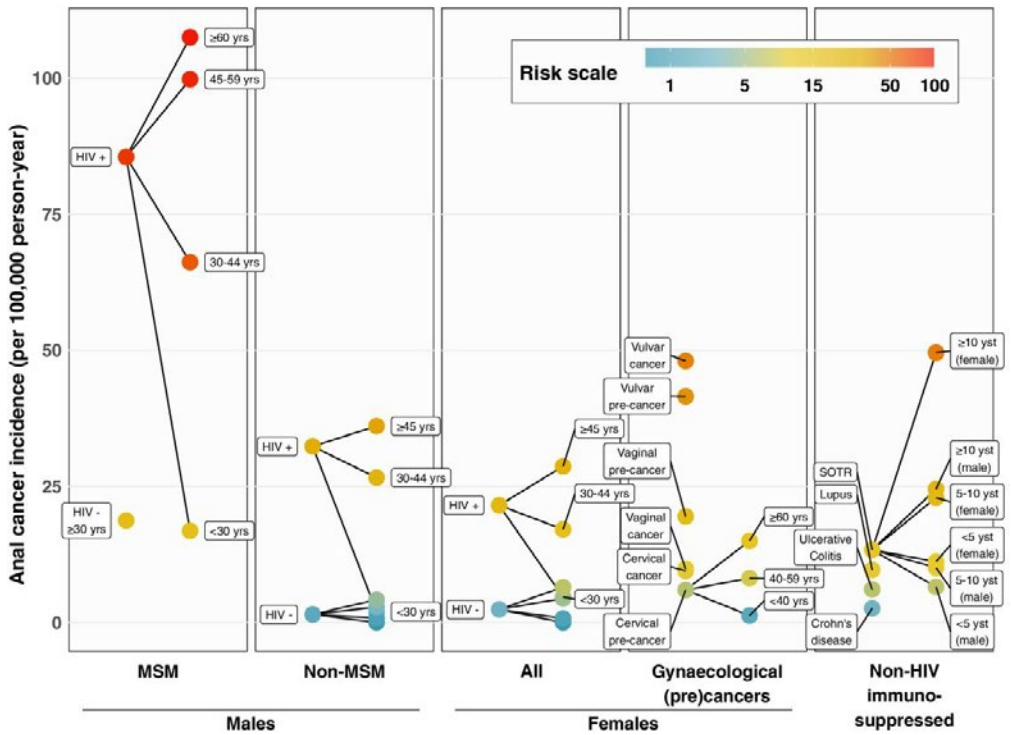


Figure 4. Anal cancer risk scale, showing estimates for people living with HIV, men who have sex with men (MSM), women diagnosed with HPV-related gynaecological precancerous lesions or cancer for different age groups, and solid organ transplant recipients (SOTR) for different periods since transplant; yrs, years; yst, years since transplant. Reproduced from Clifford et al. (2021). © 2020 International Agency for Research on Cancer (IARC/WHO); licensed by John Wiley & Sons Ltd on behalf of Union for International Cancer Control.



precancerous lesions according to the main known determinants of male ASCC risk, namely HIV status and sexuality (Wei et al., 2021a). Another meta-analysis focused on describing anal HPV, anal lesions, and cancer in recipients of solid organ transplants (Albuquerque et al., 2020). Clinical studies also continue to provide information about natural history in these high-risk groups, including anal HPV prevalence in HIV-positive women in China, the utility of HPV16 E6 antibodies to stratify people living with HIV for risk of anal cancer in the Swiss HIV Cohort Study (Combes et al., 2020), and a longitudinal study of anal HPV16 and HPV18 incidence and clearance in the APACHES study of 500 HIV-positive men who have sex with men in France (Alberts et al., 2020a).

HPV vaccination impact in LMICs: public health decision modelling

Effective prophylactic vaccines against HR HPV types have shown high safety and efficacy, and vaccination programmes are cost-effective in high-income countries. However, the introduction of HPV vaccination in LMICs remains challenging and requires the long-lasting commitment of local public health authorities. To support HPV vaccination in LMICs, ICE is conducting field studies to monitor the local impact of HPV vaccination and is developing predictive algorithms to project, at a global scale, the expected reduction in cervical cancer incidence as a result of vaccination. In Rwanda and Bhutan, ICE has demonstrated HPV vaccination effectiveness through urine-based HPV prevalence surveys in schools (Baussano et al., 2021) and cytology-based surveys in the general population (Baussano et al., 2020a) (Figure 5). In Rwanda, ICE has concomitantly assessed the nationwide cohort-specific coverage of vaccination (Sayinzoga et al., 2020). Meanwhile, to support the introduction of HPV vaccination at a global scale, ICE has estimated expected and preventable cervical cancers among women born between 2005 and 2014 in 185 countries (Bonjour et al., 2021; Piñeros et al., 2021b) (Table 1). To assess the local burden of cervical cancer in settings where cancer registry data are not available, ICE has also developed a procedure to estimate cervical cancer incidence from population-based HPV prevalence data. Finally, in collaboration with colleagues from other leading institutions worldwide, ICE has assessed optimal HPV vaccination strategies to prevent cervical cancer in limited-resource settings (Drolet et al., 2021). These studies support the WHO global initiative to eliminate cervical cancer as a public health problem.

Figure 5. Type- and age-specific HPV prevalence in baseline and repeated surveys in Bhutan. Vaccine types are HPV6, HPV11, HPV16, and HPV18; non-vaccine types are 42 types detected by GP5+/6+, excluding the 4 vaccine types. Error bars represent 95% confidence intervals. From Baussano et al. (2020a). Copyright © 2020 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

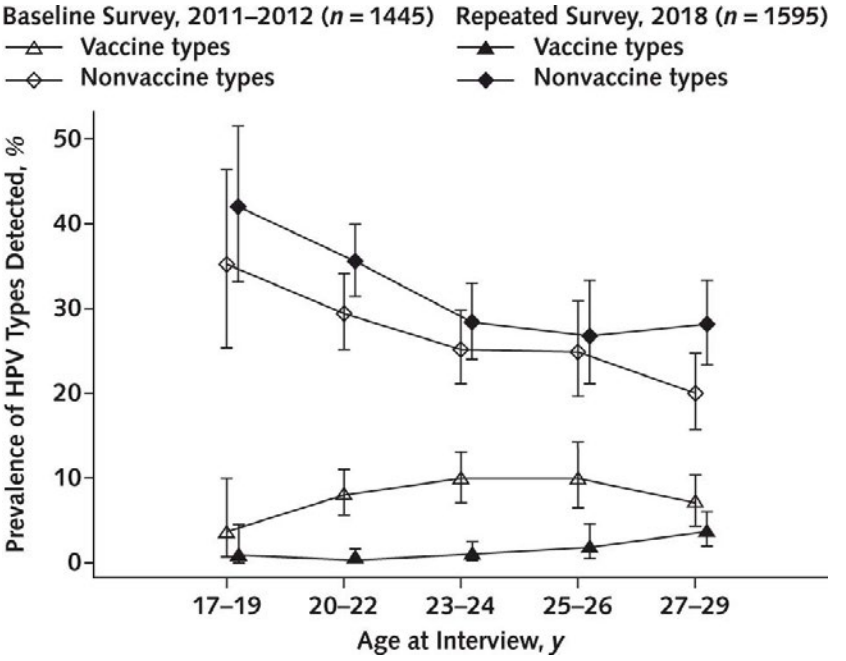


Table 1. Number of women at risk and number of expected and preventable cervical cancer cases among women born between 2005 and 2014 by continent, cervical cancer burden category, and 2018 Human Development Index

	Number of women at risk	Cases expected in the absence of vaccination		Cases preventable through vaccination	
		Number (95% UI)	Percentage of total cases in each category	Number (95% UI)	Percentage of total cases in each category
Continent					
Africa	165 606 523	5 648 149 (5 428 370–6 021 112)	48.7	4 162 782 (4 000 569–4 437 821)	73.7
Asia	344 978 554	4 486 109 (4 372 716–4 643 003)	38.7	3 480 802 (3 380 678–3 608 856)	77.6
Europe	38 508 937	416 241 (410 384–423 343)	3.6	332 124 (327 352–337 944)	79.8
Latin America	52 222 051	863 532 (835 639–919 393)	7.4	605 918 (586 145–644 957)	70.2
North America	22 124 133	140 961 (137 550–144 461)	1.2	111 009 (107 869–114 330)	78.8
Oceania	3 061 127	42 855 (39 073–47 384)	0.4	35 485 (32 318–39 271)	82.8
Cervical cancer burden[a]					
Very high	292 719 493	5 949 749 (5 745 857–6 186 696)	51.3	4 568 726 (4 405 526–4 755 927)	76.8
High	136 428 165	2 808 840 (2 671 891–3 045 844)	24.2	2 062 358 (1 961 833–2 236 491)	73.4
Medium	77 561 473	1 697 817 (1 597 925–1 890 372)	14.6	1 231 586 (1 158 349–1 372 443)	72.5
Low	106 942 955	1 027 948 (992 516–1 118 556)	8.9	778 124 (752 326–844 285)	75.7
Very low	12 849 239	113 492 (109 602–120 963)	1.0	87 326 (84 360–93 058)	76.9
Human Development Index[b]					
Low–middle	352 464 260	8 025 880 (7 794 459–8 447 380)	69.2	6 117 421 (5 939 136–6 430 904)	76.2
High	186 108 791	2 775 193 (2 720 782–2 837 271)	23.9	1 994 697 (1 954 640–2 039 514)	71.9
Very high	87 928 274	796 774 (786 593–810 166)	6.9	616 002 (607 835–626 440)	77.3
Total	626 501 325	11 597 847 (11 366 107–12 027 739)	100.0	8 728 120 (8 549 700–9 049 217)	75.3

UI, uncertainty interval.
[a] Individual countries were sorted according to the expected number of cervical cancer cases, then grouped into the following categories: very high burden (8 countries accounting for up to 50% of all cases worldwide), high burden (17 countries accounting for the next 25% of all cases), medium burden (25 countries accounting for the next 15%), low burden (68 countries accounting for the next 9%), and very low burden (67 countries accounting for the remaining 1%).
[b] Low–middle, < 0.70; high, 0.70–0.79; very high, ≥ 0.80.
Source: Reproduced from Bonjour et al. (2021). © 2021 World Health Organization; licensee Elsevier.