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CENTRE

# **Human Papillomavirus and Related Diseases Report**

## **SAN MARINO**

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## Executive summary

Human papillomavirus (HPV) infection is now a well-established cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) as well as head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide. HPV vaccines that prevent HPV 16 and 18 infections are now available and have the potential to reduce the incidence of cervical and other anogenital cancers.

This report provides key information for San Marino on: cervical cancer; other anogenital cancers and head and neck cancers; HPV-related statistics; factors contributing to cervical cancer; cervical cancer screening practices; HPV vaccine introduction; and other relevant immunisation indicators. The report is intended to strengthen the guidance for health policy implementation of primary and secondary cervical cancer prevention strategies in the country.

Table 1: Key Statistics

<b>Population</b>		
Women at risk for cervical cancer (Female population aged >=15 years)		14907
<b>Burden of cervical cancer and other HPV-related cancers</b>		
Annual number of cervical cancer cases		-
Annual number of cervical cancer deaths		-
Crude incidence rates per 100,000 and year:		
	Male	Female
Cervical cancer	-	-
Anal cancer ‡	-	-
Vulvar cancer ‡	-	-
Vaginal cancer ‡	-	-
Penile cancer ‡	-	-
Pharynx cancer (excluding nasopharynx)	-	-
<b>Burden of cervical HPV infection</b>		
Prevalence (%) of HPV 16 and/or HPV 18 among women with:		
	Normal cytology	3.2 <sup>†</sup>
	Low-grade cervical lesions (LSIL/CIN-1)	25.4 <sup>†</sup>
	High-grade cervical lesions (HSIL/CIN-2/CIN-3/CIS)	53.2 <sup>†</sup>
	Cervical cancer	68.0 <sup>†</sup>
<b>Other factors contributing to cervical cancer</b>		
Smoking prevalence (%), women		-
Total fertility rate (live births per women)		NA
Oral contraceptive use (%) among women		-
HIV prevalence (%), adults (15-49 years)		-
<b>Sexual behaviour</b>		
Percentage of 15-year-old who have had sexual intercourse (men/women)		- / -
Range of median age at first sexual intercourse (men/women)		- / -
<b>Cervical screening practices and recommendations</b>		
Cervical cancer screening coverage, % (age and screening interval, reference)	76.0% (All women aged 20-65, Health Plan 2015-2017 San Marino)	
Screening ages (years)	25-30 (cytology), 30-65 (HPV test)	
Screening interval (years) or frequency of screens	3 years (cytology), 5 years (HPV test)	
<b>HPV vaccine</b>		
HPV vaccine introduction		
	HPV vaccination programme	National program
	Date of HPV vaccination routine immunization programme start	2008

‡Please see the specific sections for more information.

<sup>†</sup> The data is the subregion Southern Europe

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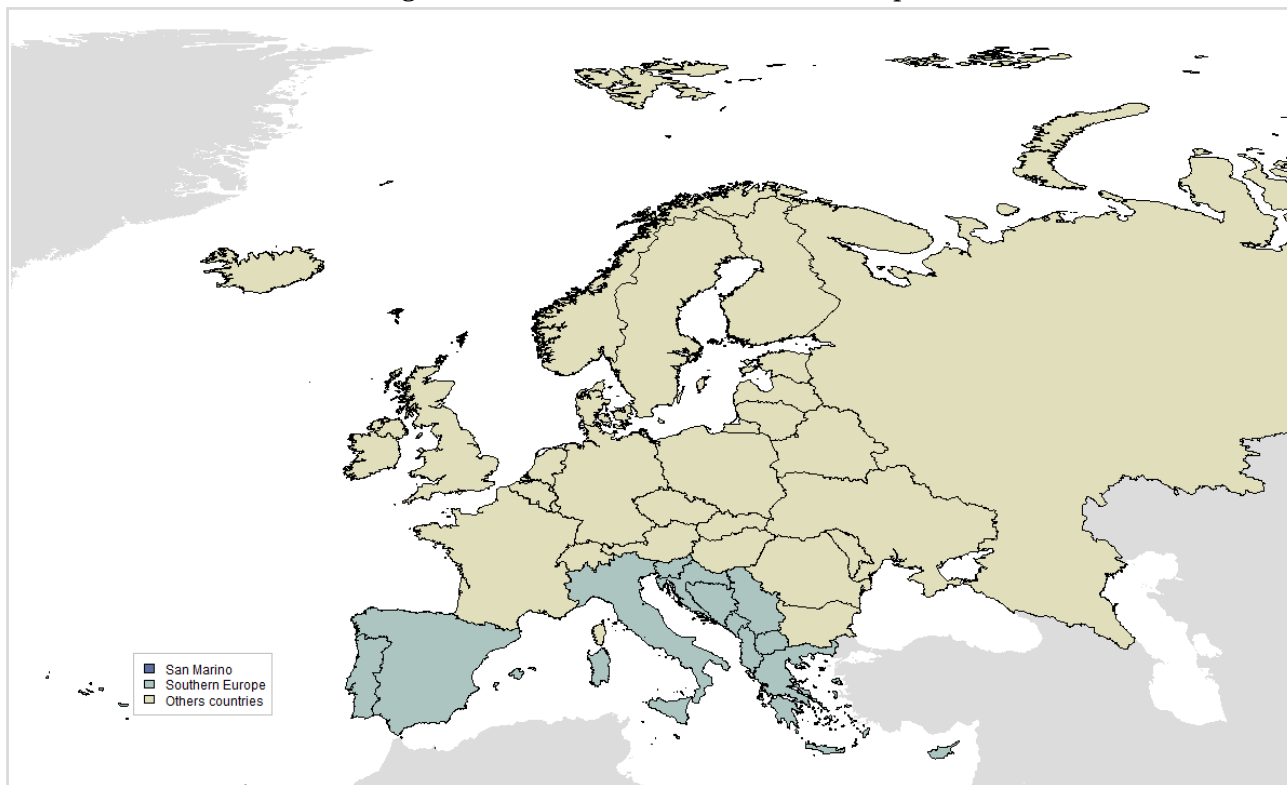
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# 1 Introduction

Figure 1: San Marino and Southern Europe



The HPV Information Centre aims to compile and centralise updated data and statistics on human papillomavirus (HPV) and related cancers. This report aims to summarise the data available to fully evaluate the burden of disease in San Marino and to facilitate stakeholders and relevant bodies of decision makers to formulate recommendations on cervical cancer prevention. Data include relevant cancer statistic estimates, epidemiological determinants of cervical cancer such as demographics, socioeconomic factors, risk factors, burden of HPV infection, screening and immunisation. The report is structured into the following sections:

**Section 2, Demographic and socioeconomic factors.** This section summarises the socio-demographic profile of country. For analytical purposes, San Marino is classified in the geographical region of Southern Europe (Figure 1, lighter blue), which is composed of the following countries: Albania, Andorra, Bosnia & Herzegovina, Cyprus, Spain, Gibraltar, Greece, Croatia, Italy, Macedonia, Malta, Montenegro, Portugal, San Marino, Serbia, Slovenia, Holy See. Throughout the report, San Marino estimates will be complemented with corresponding regional estimates.

**Section 3, Burden of HPV related cancers.** This section describes the current burden of invasive cervical cancer and other HPV-related cancers in San Marino and the Southern Europe region with estimates of prevalence, incidence, and mortality rates.

**Section 4, HPV related statistics.** This section reports on prevalence of HPV and HPV type-specific distribution in San Marino, in women with normal cytology, precancerous lesions and invasive cervical cancer. In addition, the burden of HPV in other anogenital cancers (anus, vulva, vagina, and penis) and men are presented.

**Section 5, Factors contributing to cervical cancer.** This section describes factors that can modify the natural history of HPV and cervical carcinogenesis such as smoking, parity, oral contraceptive use,



and co-infection with HIV.

**Section 6, Sexual and reproductive health behaviour indicators.** This section presents sexual and reproductive behaviour indicators that may be used as proxy measures of risk for HPV infection and anogenital cancers.

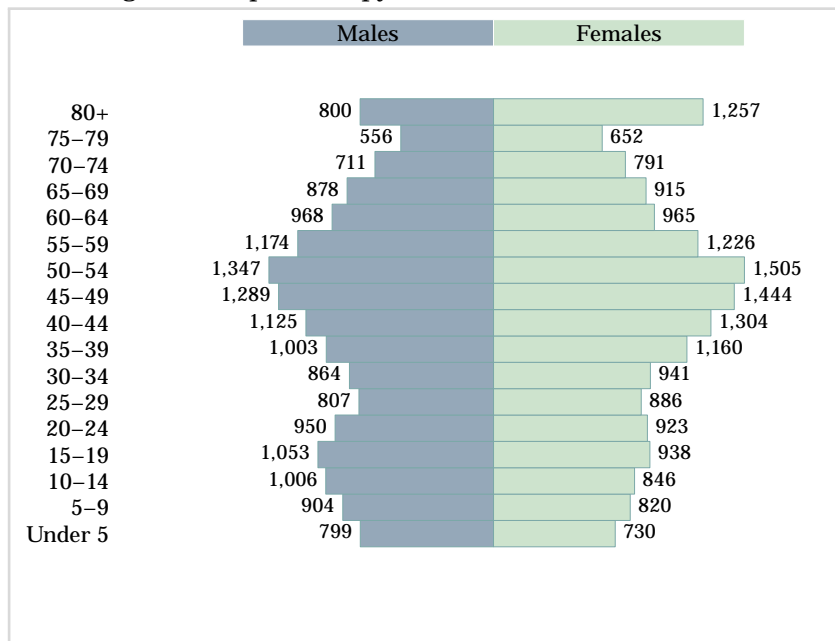
**Section 7, HPV preventive strategies.** This section presents preventive strategies that include basic characteristics and performance of cervical cancer screening status, status of HPV vaccine licensure introduction, and recommendations in national immunisation programmes.

**Section 8, Protective factors for cervical cancer.** This section presents the prevalence of male circumcision and condom use.

**Section 9, Indicators related to immunisation practices other than HPV vaccines.** This section presents data on immunisation coverage and practices for selected vaccines. This information will be relevant for assessing the country's capacity to introduce and implement the new vaccines. The data are periodically updated and posted on the WHO immunisation surveillance, assessment and monitoring website at [http://www.who.int/immunization\\_monitoring/en/](http://www.who.int/immunization_monitoring/en/).

## 2 Demographic and socioeconomic factors

Figure 2: Population pyramid of San Marino for 2017



Data accessed on 27 Mar 2017.

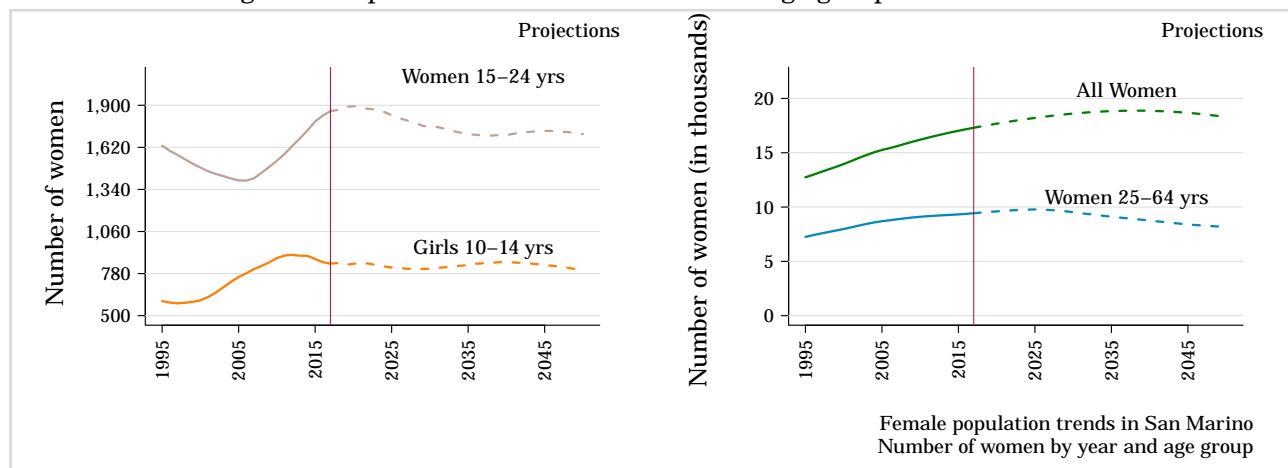
Please refer to original source for methods of estimation.

Year of estimate: 2017;

Data sources:

International Programs Center for Demographic and Economic Studies, Population Division, U.S. Census Bureau. International Database. Available at <http://www.census.gov/population/international/data/idb/informationGateway.php>. [Accessed on March 21, 2017].

Figure 3: Population trends in four selected age groups in San Marino



Data accessed on 27 Mar 2017.

Please refer to original source for methods of estimation.

Year of estimate: 2017;

Data sources:

International Programs Center for Demographic and Economic Studies, Population Division, U.S. Census Bureau. International Database. Available at <http://www.census.gov/population/international/data/idb/informationGateway.php>. [Accessed on March 21, 2017].

Table 2: Sociodemographic indicators in San Marino

Indicator	Male	Female	Total
Population in thousands <sup>1,±</sup>	16.2	17.3	33.5
Population growth rate (%) <sup>2,∓</sup>	-	-	0.7
Median age of the population (in years) <sup>2</sup>	-	-	-
Population living in urban areas (%) <sup>3,*</sup>	-	-	94.2
Crude birth rate (births per 1,000) <sup>1,±</sup>	-	-	9
Crude death rate (deaths per 1,000) <sup>1,±</sup>	-	-	9
Life expectancy at birth (in years) <sup>4,a,b</sup>	-	-	-
Adult mortality rate (probability of dying between 15 and 60 years old per 1,000) <sup>5</sup>	-	-	-
Maternal mortality ratio (per 100,000 live births) <sup>4,c</sup>	-	-	-
Under age five mortality rate (per 1,000 live births) <sup>4,d,*</sup>	-	-	2.9
Density of physicians (per 1,000 population) <sup>6,e,*</sup>	-	-	6.362
Gross national income per capita (PPP current international \$) <sup>7,f</sup>	-	-	-
Adult literacy rate (%) (aged 15 and older) <sup>8</sup>	-	-	-
Youth literacy rate (%) (aged 15-24 years) <sup>8</sup>	-	-	-
Net primary school enrollment ratio <sup>8,g,°</sup>	93.1	92.3	92.7
Net secondary school enrollment ratio <sup>8</sup>	-	-	-

**Data accessed on 27 Mar 2017.**

Please refer to original source for methods of estimation.

<sup>a</sup>World Population Prospects, the 2015 revision (WPP2015). New York (NY): United Nations DESA, Population Division.<sup>b</sup>WHO annual life tables for 1985–2015 based on the WPP2015, on the data held in the WHO Mortality Database and on HIV mortality estimates prepared by UNAIDS. WHO Member States with a population of less than 90 000 in 2015 were not included in the analysis.<sup>c</sup>WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2015 (<http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2015/en/>, accessed 25 March 2016). WHO Member States with a population of less than 100 000 in 2015 were not included in the analysis.<sup>d</sup>Levels & Trends in Child Mortality. Report 2015. Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. New York (NY), Geneva and Washington (DC): United Nations Children's Fund, World Health Organization, World Bank and United Nations; 2015 ([http://www.unicef.org/publications/files/Child\\_Mortality\\_Report\\_2015\\_Web\\_9\\_Sept\\_15.pdf](http://www.unicef.org/publications/files/Child_Mortality_Report_2015_Web_9_Sept_15.pdf), accessed 26 March 2016).<sup>e</sup>Number of medical doctors (physicians), including generalist and specialist medical practitioners, per 1 000 population.<sup>f</sup>GNI per capita based on purchasing power parity (PPP). PPP GNI is gross national income (GNI) converted to international dollars using purchasing power parity rates. An international dollar has the same purchasing power over GNI as a U.S. dollar has in the United States. GNI is the sum of value added by all resident producers plus any product taxes (less subsidies) not included in the valuation of output plus net receipts of primary income (compensation of employees and property income) from abroad. Data are in current international dollars based on the 2011 ICP round.<sup>g</sup>National Estimation

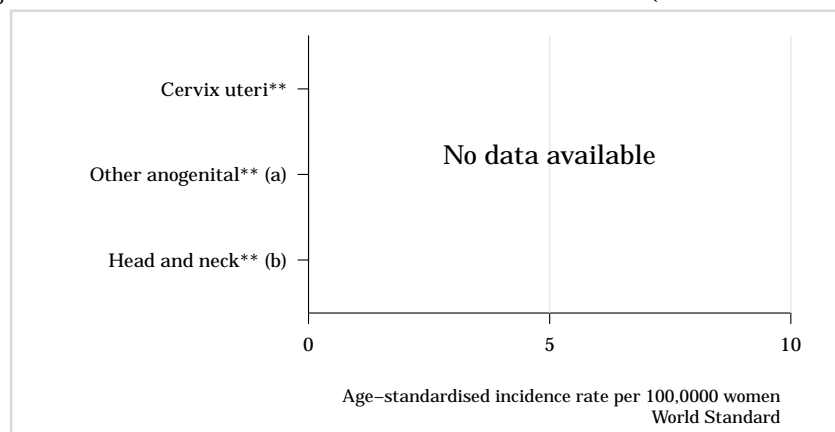
Year of estimate: ± 2017; ∓ 2010-2015; \* 2015; \* 2014; ° 2012;

**Data sources:**<sup>1</sup>International Programs Center for Demographic and Economic Studies, Population Division, U.S. Census Bureau. International Database. Available at <http://www.census.gov/population/international/data/idb/informationGateway.php>. [Accessed on March 21, 2017].<sup>2</sup>United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision, DVD Edition. Available at: <https://esa.un.org/unpd/wpp/Download/Standard/Population/>. [Accessed on March 21, 2017].<sup>3</sup>United Nations, Department of Economic and Social Affairs, Population Division (2014). World Urbanization Prospects: The 2014 Revision, CD-ROM Edition. Available at: <https://esa.un.org/unpd/wup/CD-ROM/>. [Accessed on March 21, 2017].<sup>4</sup>World Health Statistics 2016. Geneva, World Health Organization, 2016. Available at: [http://who.int/entity/gho/publications/world\\_health\\_statistics/2016/en/index.html](http://who.int/entity/gho/publications/world_health_statistics/2016/en/index.html). [Accessed on March 21, 2017].<sup>5</sup>World Health Organization. Global Health Observatory data repository. Available at: <http://apps.who.int/gho/data/view.main.1360?lang=en>. [Accessed on March 21, 2017].<sup>6</sup>The 2016 update, Global Health Workforce Statistics, World Health Organization, Geneva (<http://www.who.int/hrh/statistics/hwfstats/>). [Accessed on March 21, 2017].<sup>7</sup>World Bank, World Development Indicators Database. Washington, DC. International Comparison Program database. Available at: <http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators#>. [Accessed on March 21, 2017].<sup>8</sup>UNESCO Institute for Statistics Data Centre [online database]. Montreal, UNESCO Institute for Statistics. Available at: <http://stats.uis.unesco.org> [Accessed on March 21, 2017].

### 3 Burden of HPV related cancers

HPV is the cause of almost all cervical cancer cases and is responsible for an important fraction of other anogenital and head and neck cancer. Here, we present the most recent estimations on the burden of HPV-associated cancer.

Figure 4: HPV-related cancer incidence in San Marino (estimates for 2012)



\*\* No rates are available.

**Data accessed on 08 May 2017.**

<sup>a</sup>Other anogenital cancer cases (vulvar, vaginal, anal, and penile).

<sup>b</sup>Head and neck cancer cases (oropharynx, oral cavity and larynx).

ASR: Age-standardized rate, rates per 100,000 per year.

Please refer to original source for methods.

Data sources:

de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017

#### 3.1 Cervical cancer

Cancer of the cervix uteri is the 4th most common cancer among women worldwide, with an estimated 527,624 new cases and 265,672 deaths in 2012 (GLOBOCAN). The majority of cases are squamous cell carcinoma followed by adenocarcinomas. (*Vaccine 2006, Vol. 24, Suppl 3; Vaccine 2008, Vol. 26, Suppl 10; Vaccine 2012, Vol. 30, Suppl 5; IARC Monographs 2007, Vol. 90*)

This section describes the current burden of invasive cervical cancer in San Marino and in comparison to geographic region, including estimates of the annual number of new cases, deaths, incidence, and mortality rates.

##### 3.1.1 Cervical cancer incidence in San Marino

Table 3: Cervical cancer incidence in San Marino (estimates for 2012)

Indicator	San Marino	Southern Europe	World
Annual number of new cancer cases	-	9,285	527,624
Crude incidence rate <sup>a</sup>	-	11.6	15.1
Age-standardized incidence rate <sup>a</sup>	-	8.5	14.0
Cumulative risk (%) at 75 years old <sup>b</sup>	-	0.8	1.4

**Data accessed on 15 Nov 2015.**

<sup>a</sup>Rates per 100,000 women per year.

<sup>b</sup> Cumulative risk (incidence) is the probability or risk of individuals getting from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to develop from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Table 4: Cervical cancer incidence in San Marino by cancer registry

Cancer registry	Period	N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>
No Data Available	-	-	-	-

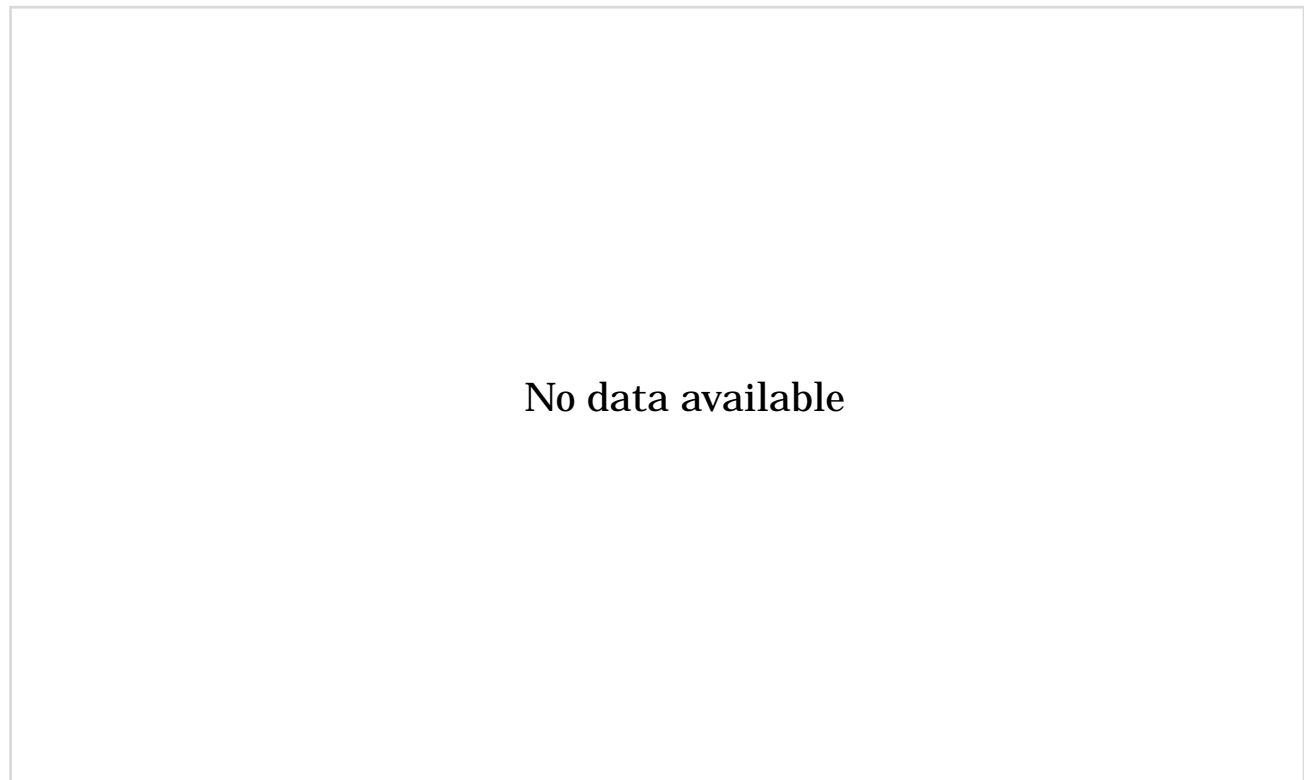
**Data accessed on 05 May 2015.**

ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference; Please refer to original source (available at <http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm>)

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

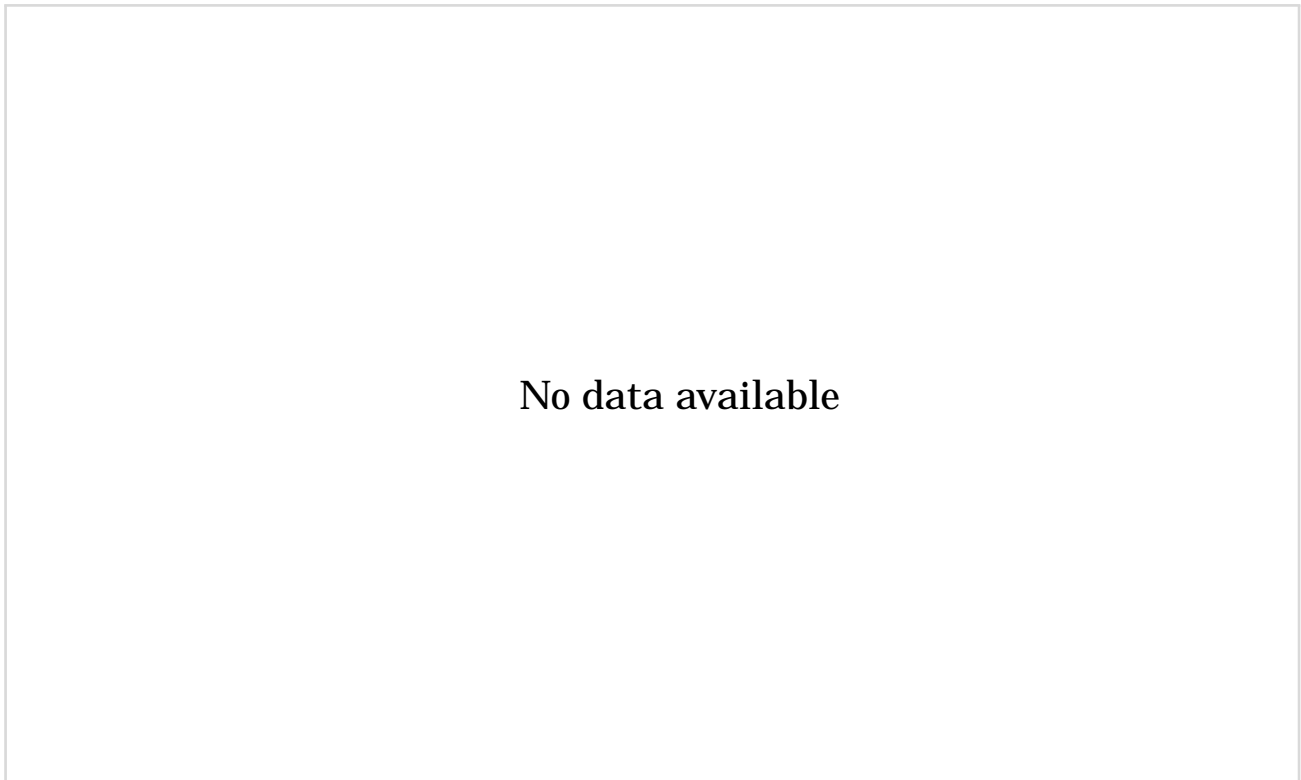
<sup>b</sup>Rates per 100,000 women per year.

Figure 5: Comparison of cervical cancer incidence to other cancers in women of all ages in San Marino (estimates for 2012)

**Data accessed on 15 Nov 2015.**Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 6: Comparison of age-specific cervical cancer to age-specific incidence of other cancers among women 15-44 years of age in San Marino (estimates for 2012)

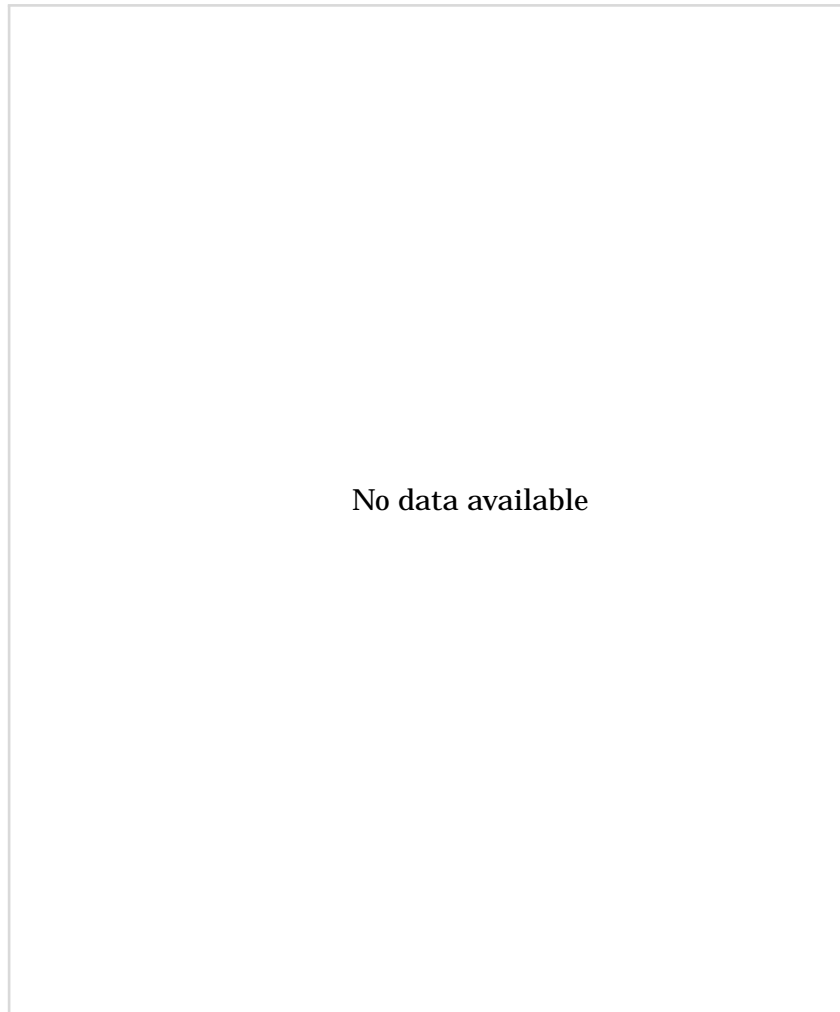


**Data accessed on 15 Nov 2015.**

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 7: Annual number of cases and age-specific incidence rates of cervical cancer in San Marino (estimates for 2012)



**Data accessed on 15 Nov 2015.**

Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

### 3.1.2 Cervical cancer incidence by histology in San Marino

Table 5: Age-standardised incidence rates of cervical cancer in San Marino by histological type and cancer registry

Cancer registry	Period	Carcinoma			
		Squamous	Adeno	Other	Unspec.
No data available	-	-	-	-	-

**Data accessed on 24 Jul 2015.**

Adeno: adenocarcinoma; Other: Other carcinoma; Squamous: Squamous cell carcinoma; Unspec: Unspecified carcinoma;

Standardised rates have been estimated using the direct method and the World population as the references.

Rates per 100,000 women per year.

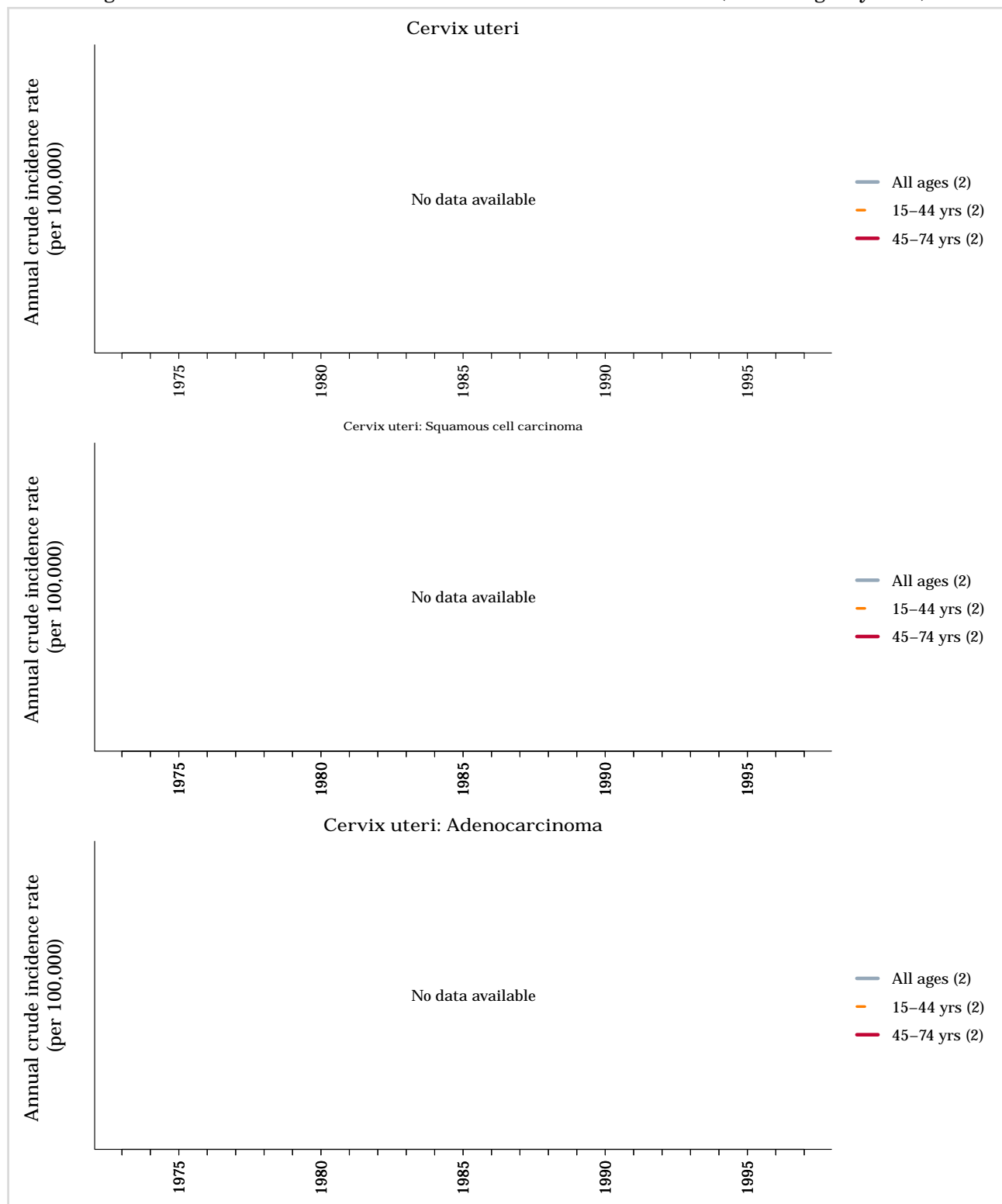
Standardized rates have been estimated using the direct method and the World population as the references.

Data sources:

Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J eds (2013). Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. <http://ci5.iarc.fr>



Figure 8: Time trends in cervical cancer incidence in San Marino (cancer registry data)



Data accessed on 27 Apr 2015.

<sup>a</sup> Estimated annual percentage change based on the trend variable from the net drift for the most recent two 5-year periods.

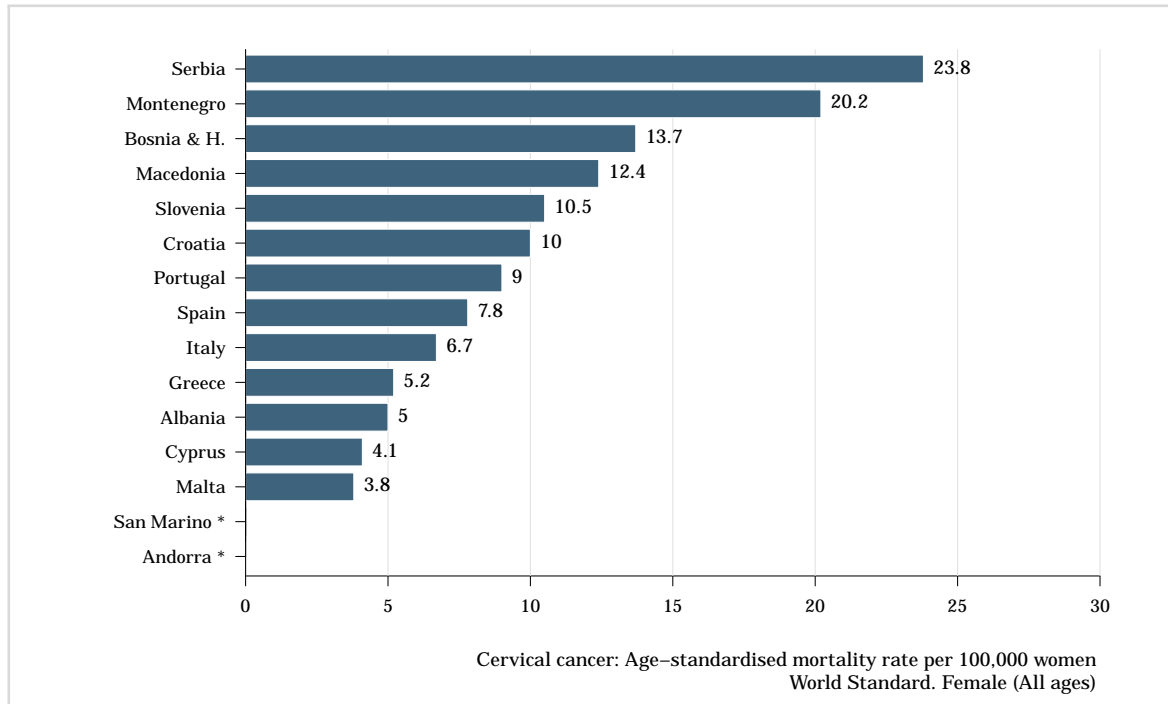
Data sources:

<sup>1</sup> Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors. *eur J Cancer* 2013;49:3262-73.

<sup>2</sup> Ferlay J, Bray F, Steliarova-Foucher E and Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: <http://ci5.iarc.fr>

### 3.1.3 Cervical cancer incidence in San Marino across Southern Europe

Figure 9: Age-standardised incidence rates of cervical cancer of San Marino (estimates for 2012)



\* No rates are available.

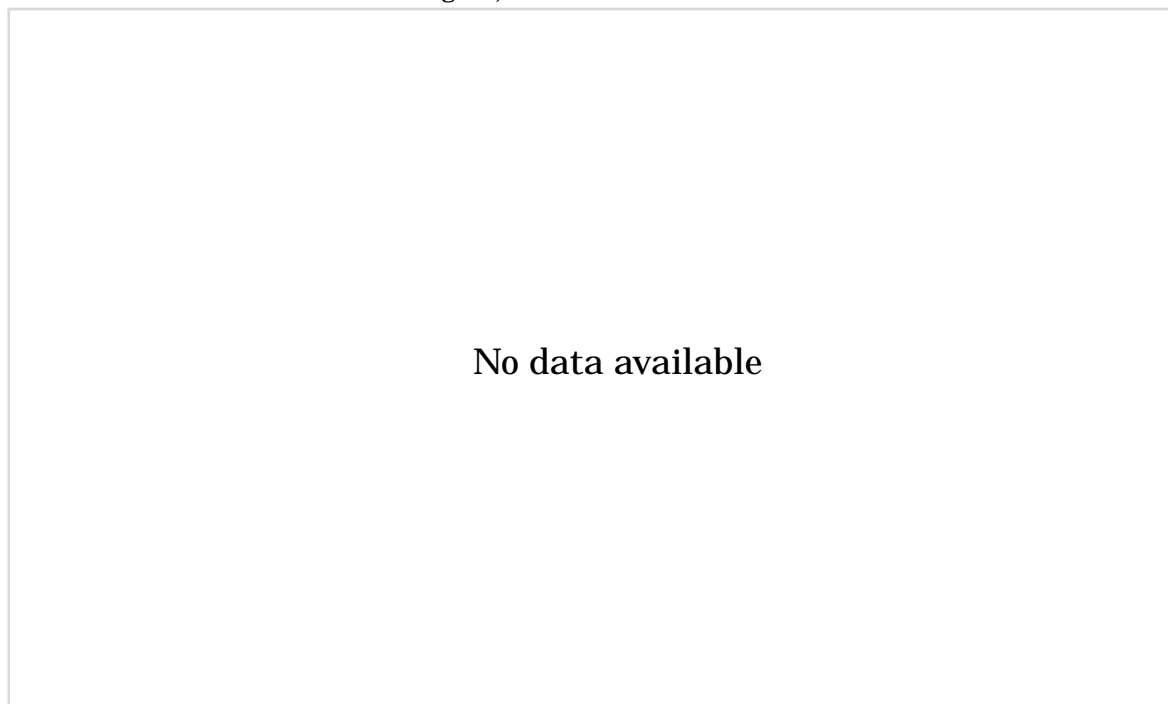
**Data accessed on 15 Nov 2015.**

Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 10: Comparison of age-specific cervical cancer incidence rates in San Marino, within the region, and the rest of world



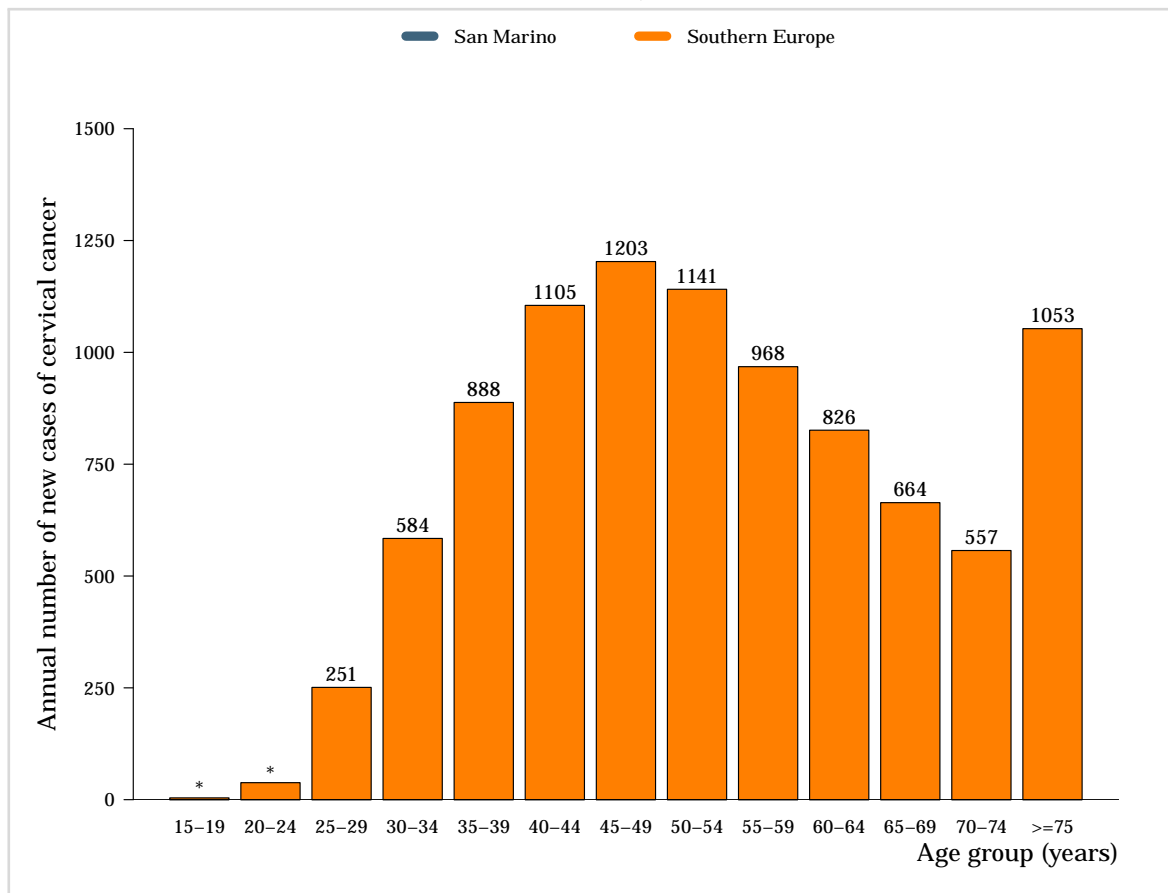
**Data accessed on 15 Nov 2015.**

Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 11: Annual number of new cases of cervical cancer by age group in San Marino (estimates for 2012)



\*0 cases for San Marino and 4 cases for Southern Europe in the 15-19 age group. 0 cases for San Marino and 38 cases for Southern Europe in the 20-24 age group.

**Data accessed on 15 Nov 2015.**

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

### 3.1.4 Cervical cancer mortality in San Marino

Table 6: Cervical cancer mortality in San Marino (estimates for 2012)

Indicator	San Marino	Southern Europe	World
Annual number of deaths	-	3,526	265,672
Crude mortality rate <sup>a</sup>	-	4.4	7.6
Age-standardized mortality rate <sup>a</sup>	-	2.4	6.8
Cumulative risk (%) at 75 years old <sup>b</sup>	-	0.2	0.8

Data accessed on 15 Nov 2015.

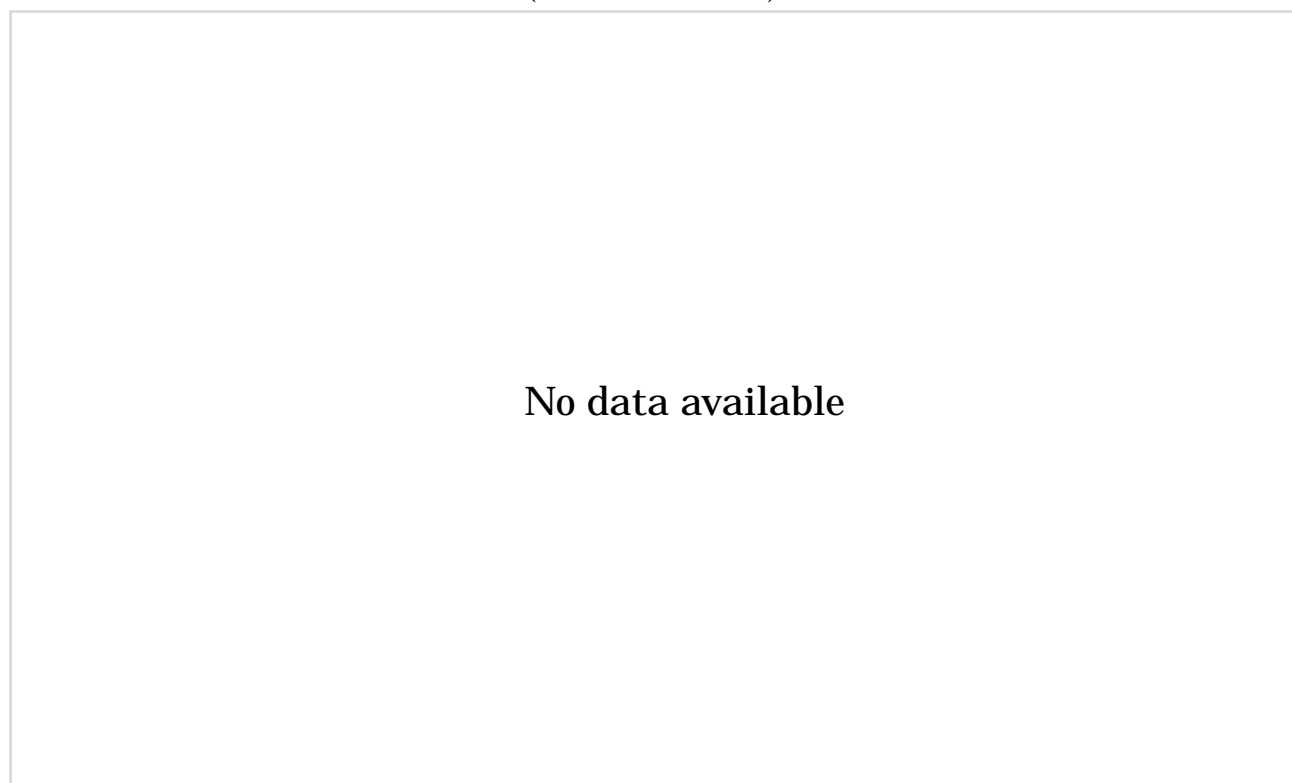
<sup>a</sup>Rates per 100,000 women per year.

<sup>b</sup>Cumulative risk (mortality) is the probability or risk of individuals dying from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to die from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 12: Comparison of cervical cancer mortality to other cancers in women of all ages in San Marino (estimates for 2012)

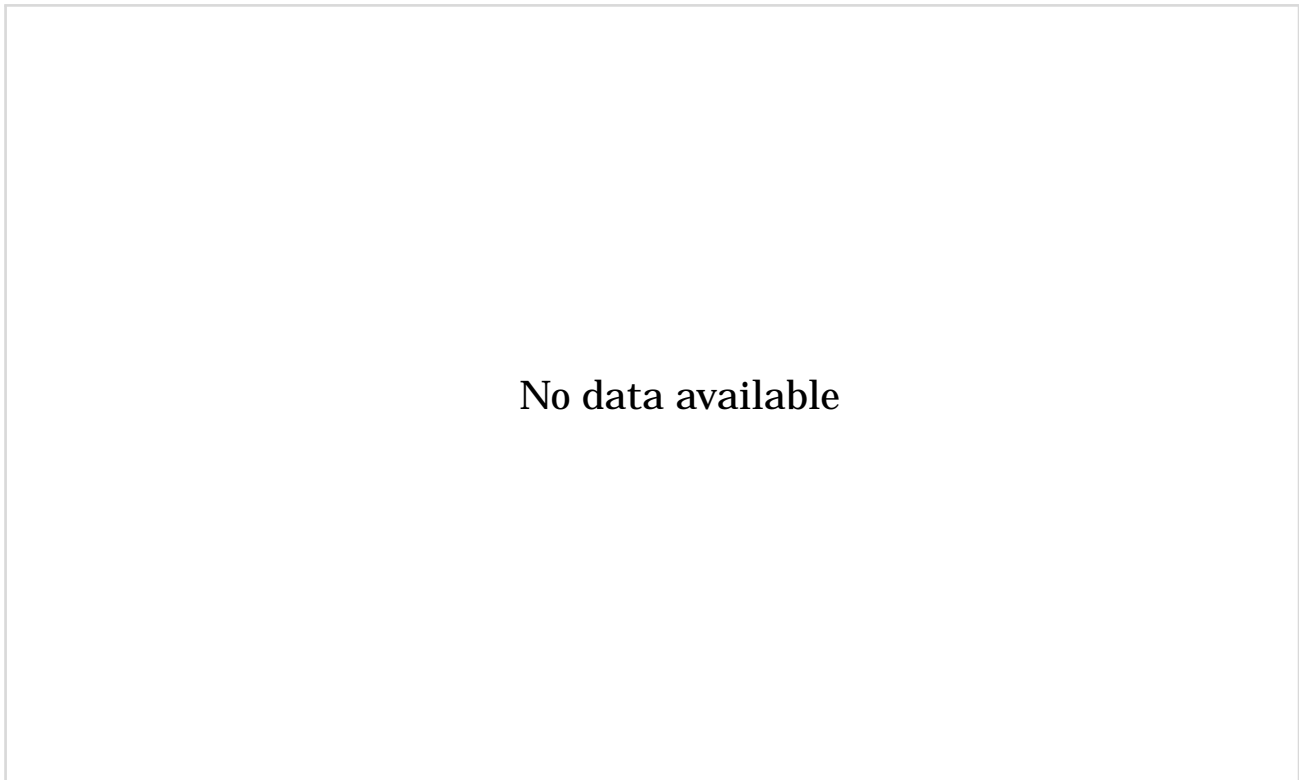


Data accessed on 15 Nov 2015.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 13: Comparison of age-specific mortality rates of cervical cancer to other cancers among women 15-44 years of age in San Marino (estimates for 2012)

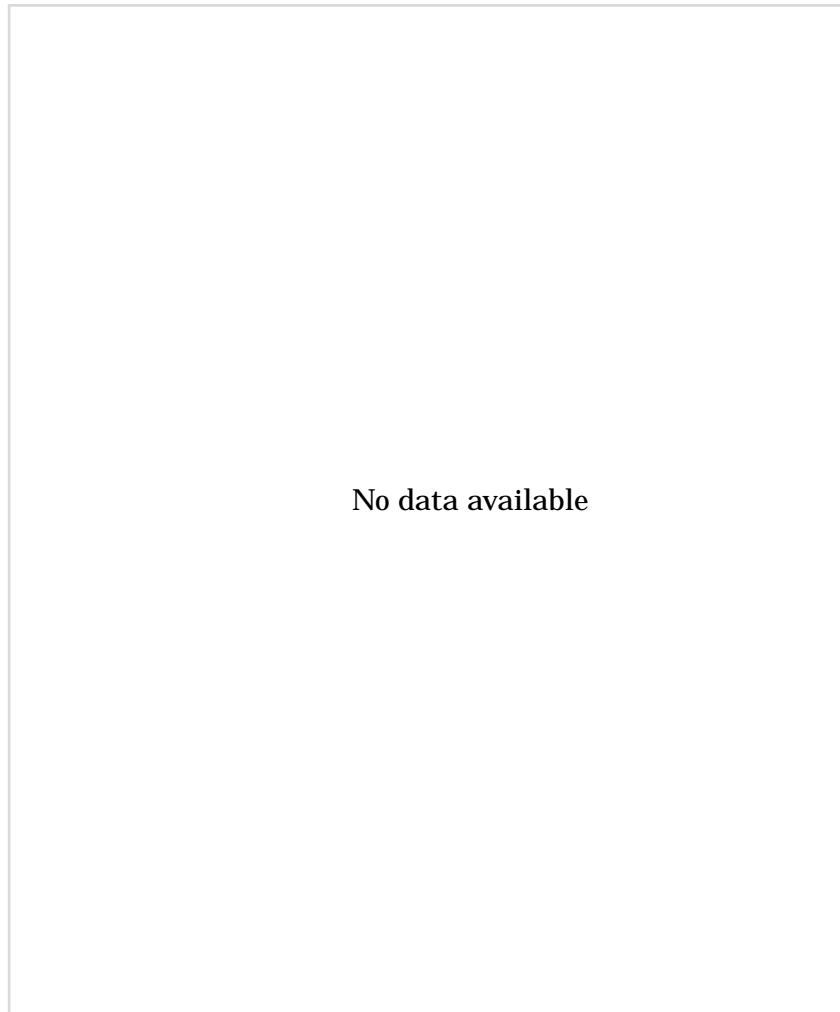


**Data accessed on 15 Nov 2015.**

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 14: Annual number of deaths and age-specific mortality rates of cervical cancer in San Marino (estimates for 2012)



**Data accessed on 15 Nov 2015.**

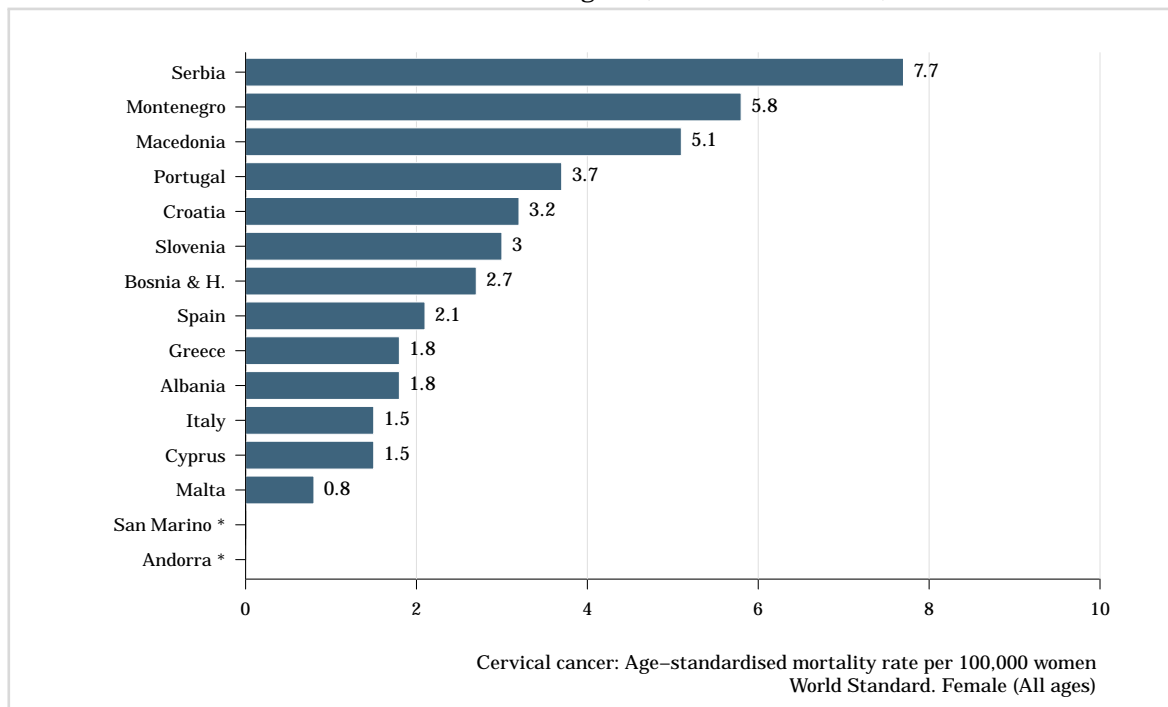
Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

### 3.1.5 Cervical cancer mortality in San Marino across Southern Europe

Figure 15: Comparison of age-standardised cervical cancer mortality rates in San Marino and countries within the region (estimates for 2012)



\* No rates are available.

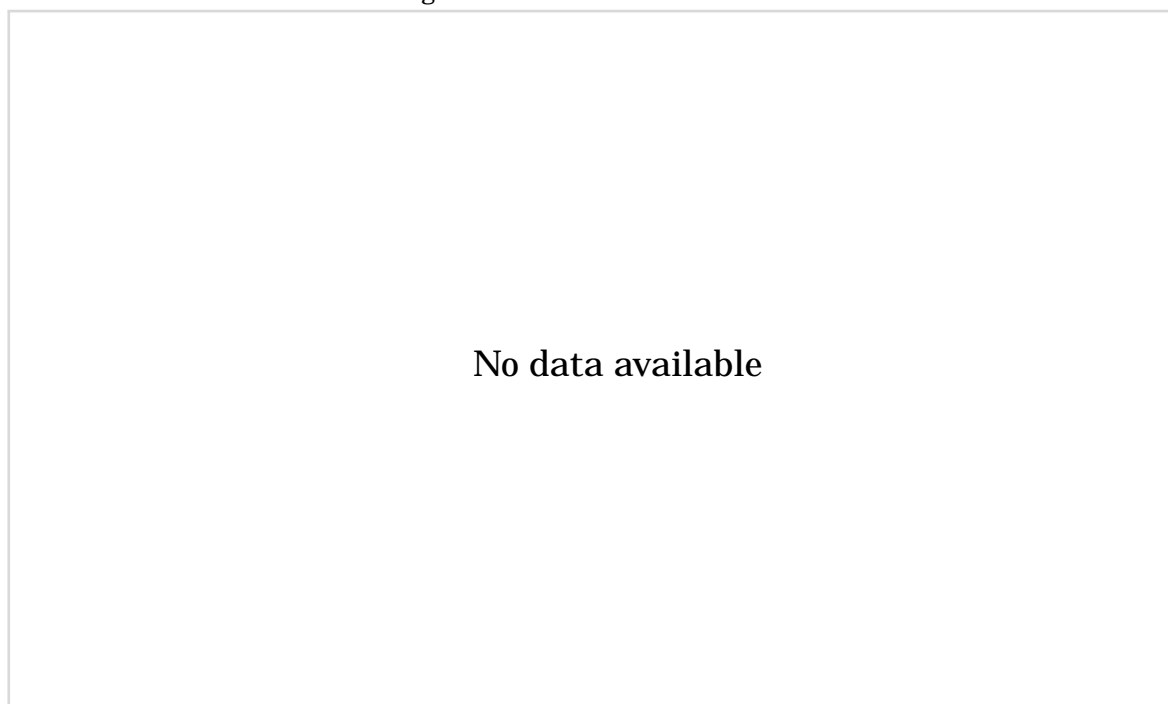
**Data accessed on 15 Nov 2015.**

Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 16: Comparison of age-specific cervical cancer mortality rates in San Marino, within its region and the rest of the world



**Data accessed on 15 Nov 2015.**

Rates per 100,000 women per year.

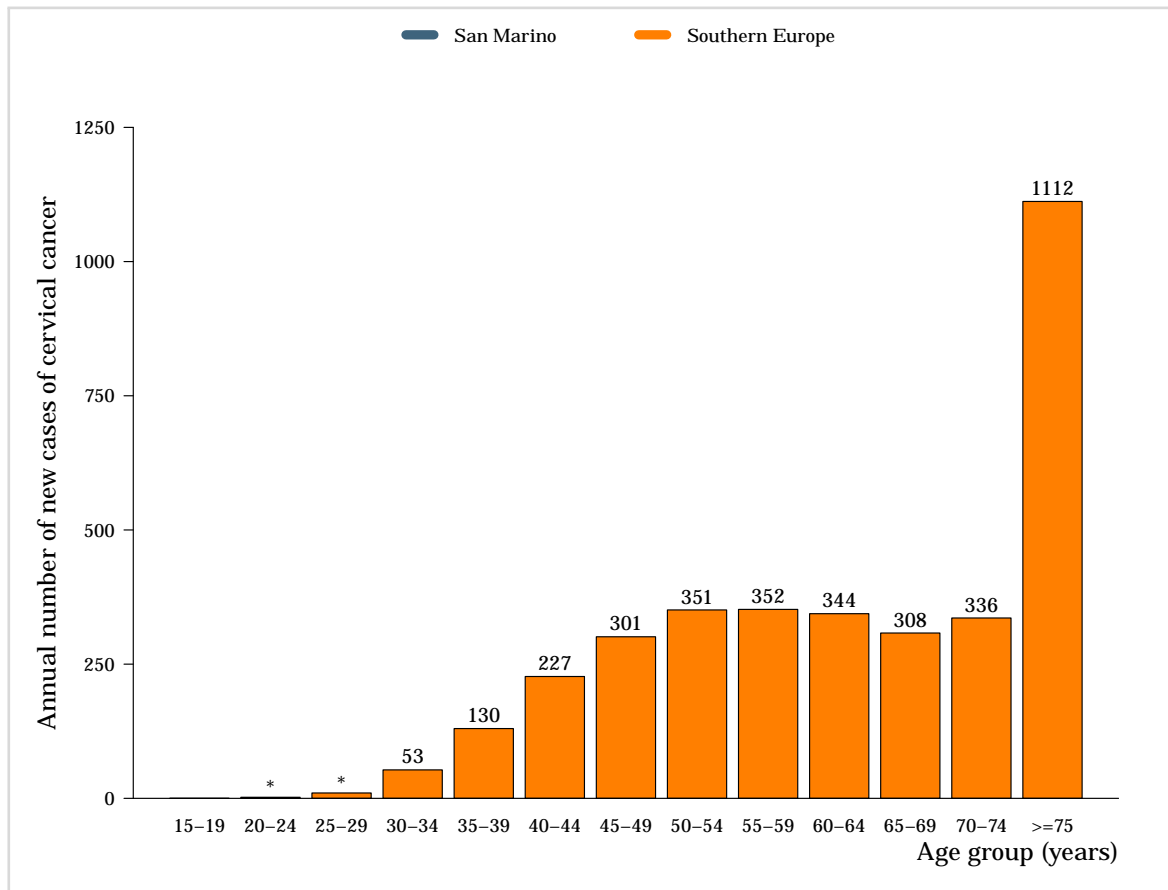
(Continued on next page)

(Figure 16 – continued from previous page)

**Data sources:**

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Figure 17: Annual deaths number of cervical cancer by age group in San Marino (estimates for 2012)



\*0 cases for San Marino and 0 cases for Southern Europe in the 15-19 age group. 0 cases for San Marino and 2 cases for Southern Europe in the 20-24 age group. 0 cases for San Marino and 10 cases for Southern Europe in the 25-29 age group.

**Data accessed on 15 Nov 2015.**

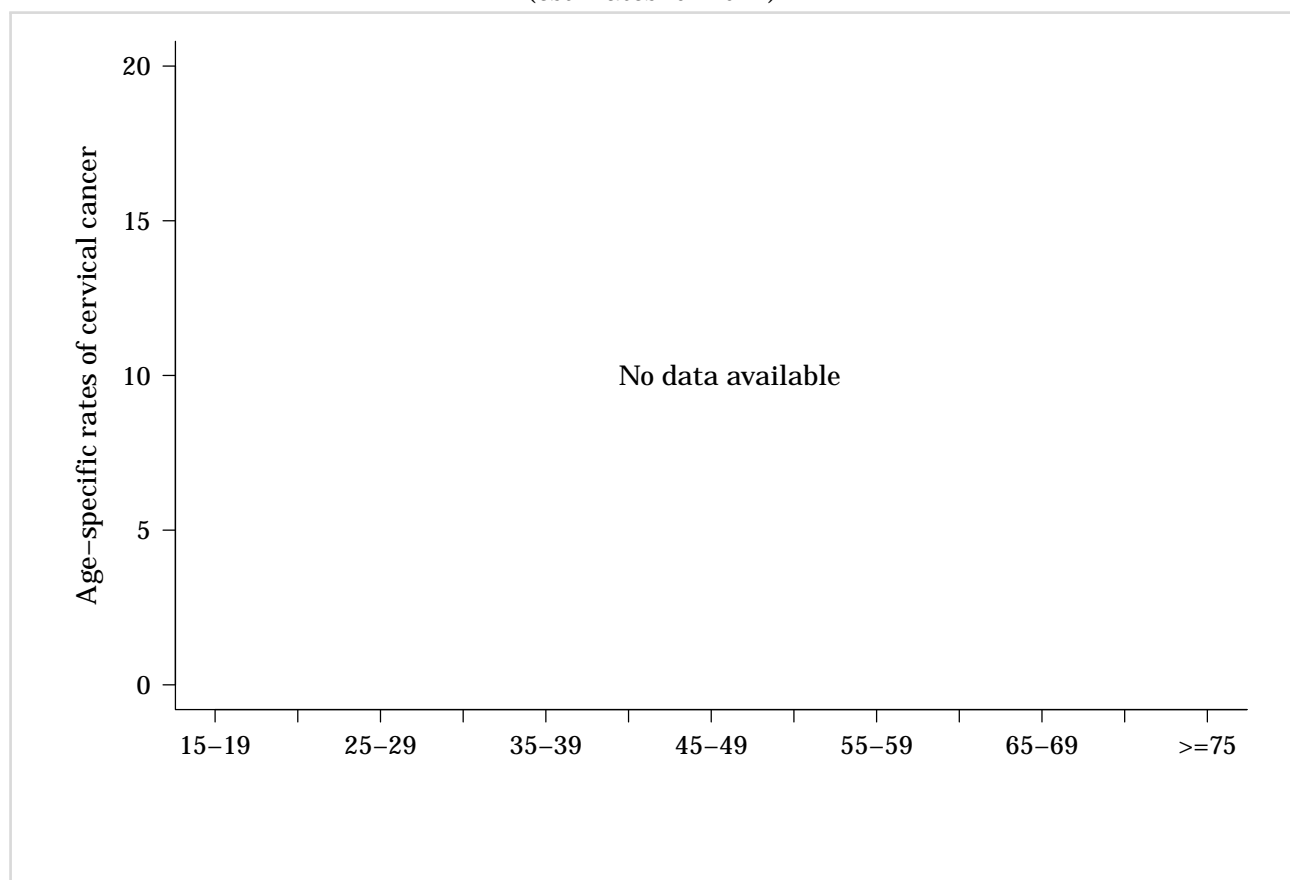
**Data sources:**

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.



### 3.1.6 Cervical cancer incidence and mortality comparison, Premature deaths and disability in San Marino

Figure 18: Comparison of age-specific cervical cancer incidence and mortality rates in San Marino (estimates for 2012)



Data accessed on 15 Nov 2015.

Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Table 7: Premature deaths and disability from cervical cancer in San Marino, Southern Europe and the rest of the world (estimates for 2008)

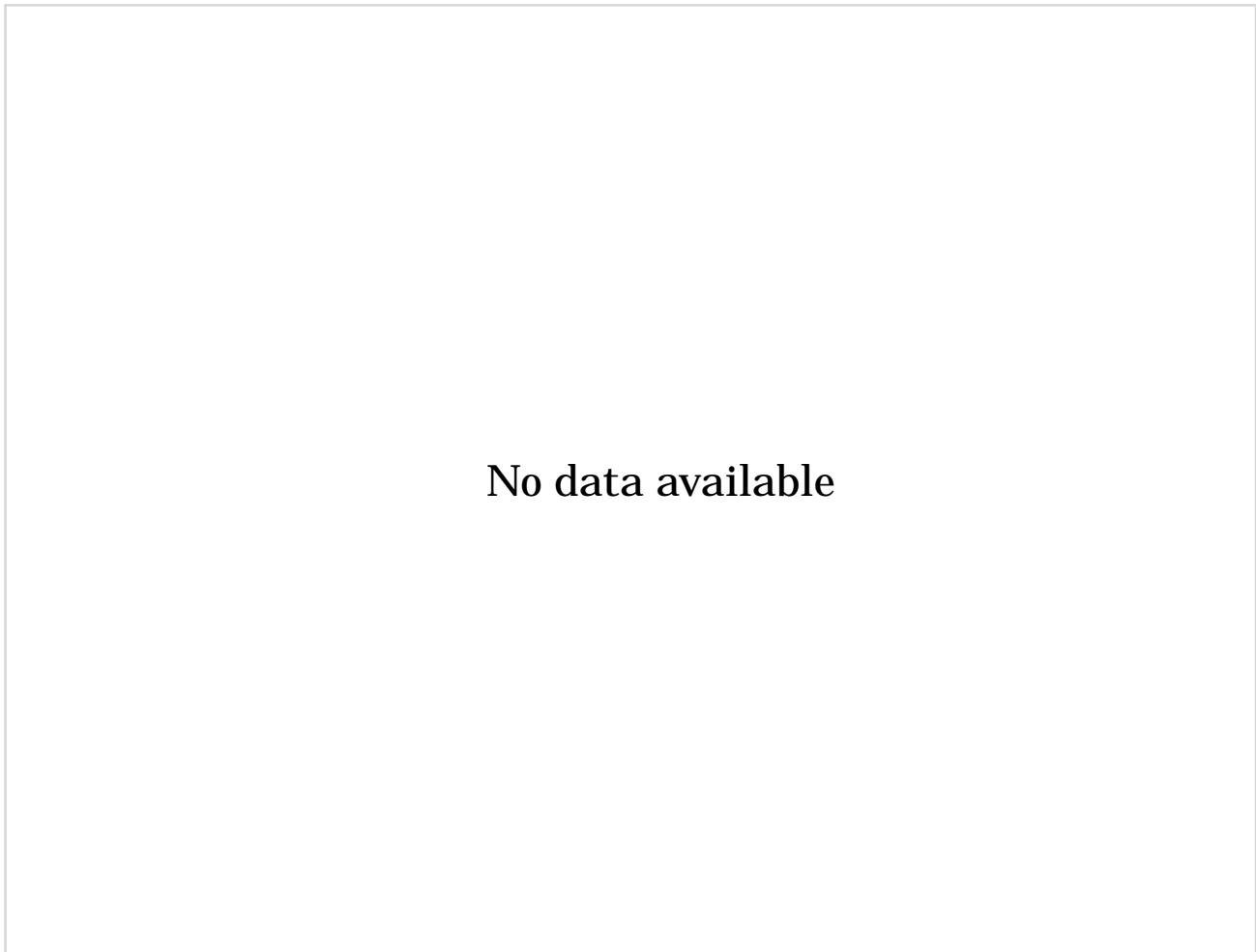
Indicator	San Marino		Southern Europe		World	
	Number	ASR (W)	Number	ASR (W)	Number	ASR (W)
Estimated disability-adjusted life years (DALYs)	-	-	98,923	96	8,738,004	293
Years of life lost (YLLs)	-	-	80,996	75	7,788,282	264
Years lived with disability (YLDs)	-	-	17,927	21	949,722	28

Data accessed on 04 Nov 2013.

Data sources:

Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, Bray F. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*. 2012 Nov 24;380(9856):1840-50.

Figure 19: Comparison of annual premature deaths and disability from cervical cancer in San Marino to other cancers among women (estimates for 2008)



**Data accessed on 04 Nov 2013.**

CNS: Central Nervous System; YLDs: years lived with disability; YLLs: Years of life lost;

Data sources:

Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, Bray F. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*. 2012 Nov 24;380(9856):1840-50.

## 3.2 Anogenital cancers other than the cervix

Data on HPV role in anogenital cancers other than cervix are limited, but there is an increasing body of evidence strongly linking HPV DNA with cancers of anus, vulva, vagina, and penis. Although these cancers are much less frequent compared to cervical cancer, their association with HPV make them potentially preventable and subject to similar preventative strategies as those for cervical cancer. (*Vaccine 2006, Vol. 24, Suppl 3; Vaccine 2008, Vol. 26, Suppl 10; Vaccine 2012, Vol. 30, Suppl 5; IARC Monographs 2007, Vol. 90*).

### 3.2.1 Anal cancer

Anal cancer is rare in the general population with an average worldwide incidence of 1 per 100,000, but is reported to be increasing in more developed regions. Globally, there are an estimated 27,000 new cases every year (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Women have higher incidences of anal cancer than men. Incidence is particularly high among populations of men who have sex with men (MSM), women with history of cervical or vulvar cancer, and immunosuppressed populations, including those who are HIV-infected and patients with a history of organ transplantation. These cancers are predominantly squamous cell carcinoma, adenocarcinomas, or basaloid and cloacogenic carcinomas.

Table 8: Anal cancer incidence in San Marino by cancer registry and sex

Cancer registry	Period	MALE			FEMALE		
		N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>	N cases <sup>a</sup>	Crude rate <sup>c</sup>	ASR <sup>c</sup>
No Data Available	-	-	-	-	-	-	-

Data accessed on 05 May 2015.

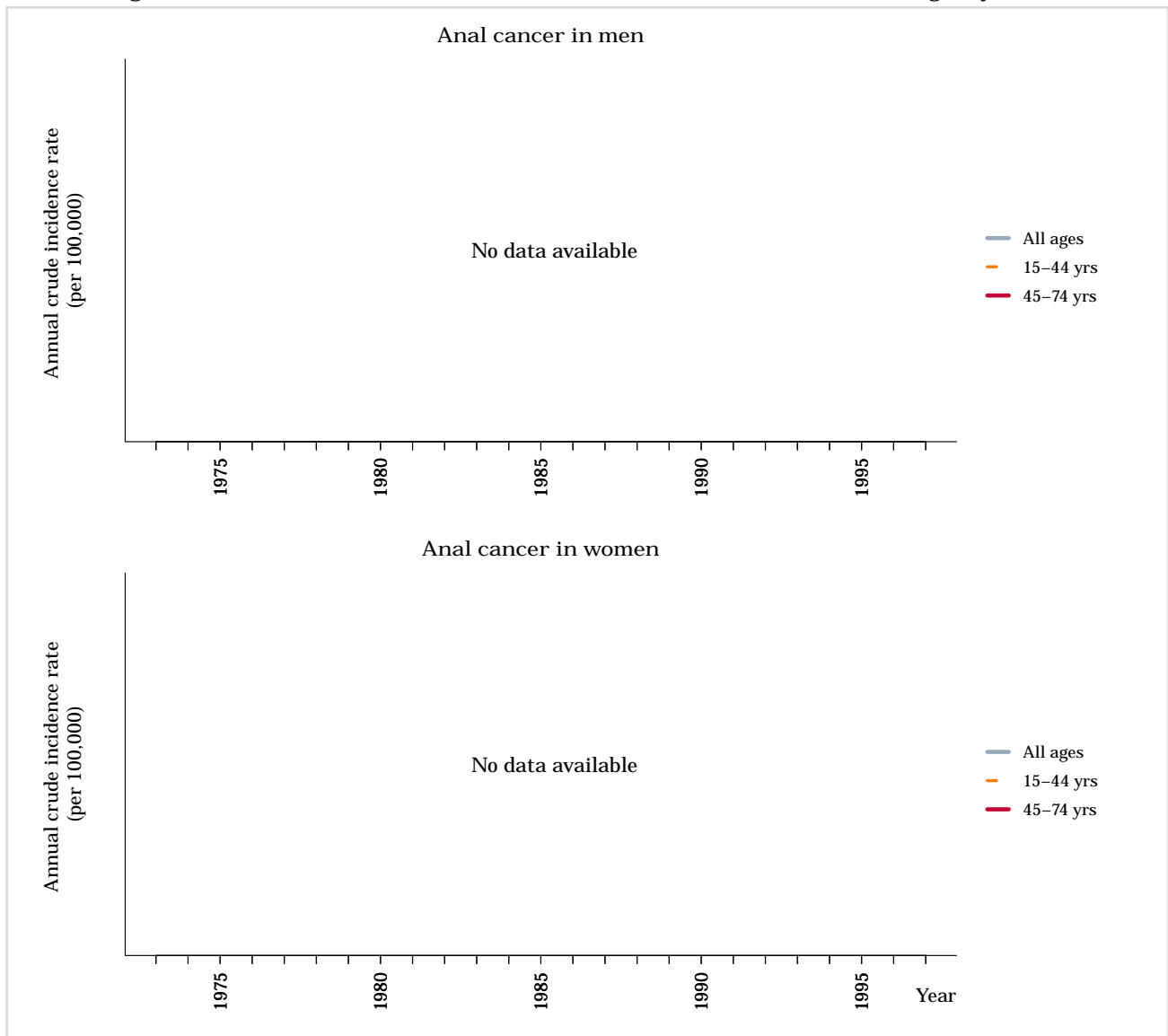
ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference; Please refer to original source (available at <http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm>)

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

<sup>b</sup>Rates per 100,000 men per year.

<sup>c</sup>Rates per 100,000 women per year.

Figure 20: Time trends in anal cancer incidence in San Marino (cancer registry data)



Data accessed on 27 Apr 2015.

Data sources:

Ferlay J, Bray F, Steliarova-Foucher E and Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: <http://ci5.iarc.fr>

### 3.2.2 Vulvar cancer

Cancer of the vulva is rare among women worldwide, with an estimated 27,000 new cases in 2008, representing 4% of all gynaecologic cancers (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Worldwide, about 60% of all vulvar cancer cases occur in more developed countries. Vulvar cancer has two distinct histological patterns with two different risk factor profiles: (1) basaloid/warty types (2) keratinising types. Basaloid/warty lesions are more common in young women, are very often associated with HPV DNA detection (75-100%), and have a similar risk factor profile as cervical cancer. Keratinising vulvar carcinomas represent the majority of the vulvar lesions (>60%), they occur more often in older women and are more rarely associated with HPV (*IARC Monograph Vol 100B*).

Table 9: Vulvar cancer incidence in San Marino by cancer registry

Cancer registry	Period	N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>
No Data Available	-	-	-	-

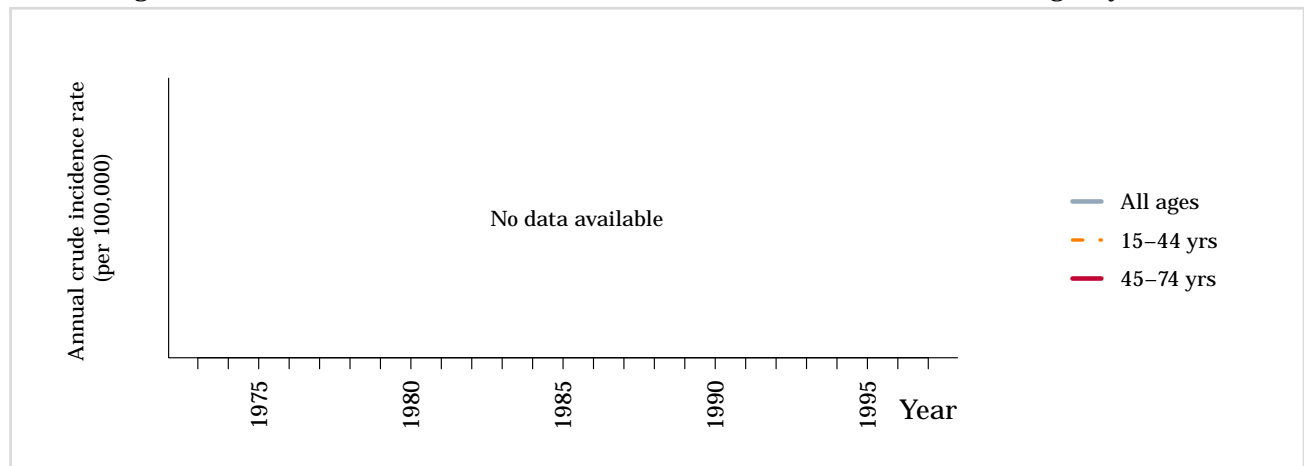
Data accessed on 05 May 2015.

ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference;

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

<sup>b</sup>Rates per 100,000 women per year.

Figure 21: Time trends in vulvar cancer incidence in San Marino (cancer registry data)



Data accessed on 27 Apr 2015.

Data sources:

Ferlay J, Bray F, Steliarova-Foucher E and Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: <http://ci5.iarc.fr>

### 3.2.3 Vaginal cancer

Cancer of the vagina is a rare cancer, with an estimated 13,000 new cases in 2008, representing 2% of all gynaecologic cancers (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Similar to cervical cancer, the majority of vaginal cancer cases (68%) occur in less developed countries. Most vaginal cancers are squamous cell carcinoma (90%) generally attributable to HPV, followed by clear cell adenocarcinomas and melanoma. Vaginal cancers are primarily reported in developed countries. Metastatic cervical cancer can be misclassified as cancer of the vagina. Invasive vaginal cancer is diagnosed primarily in old women ( $\geq 65$  years) and the diagnosis is rare in women under 45 years whereas the peak incidence of carcinoma in situ is observed between ages 55 and 70 (*Vaccine 2008, Vol. 26, Suppl 10*).

Table 10: Vaginal cancer incidence in San Marino by cancer registry

Cancer registry	Period	N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>
No Data Available	-	-	-	-

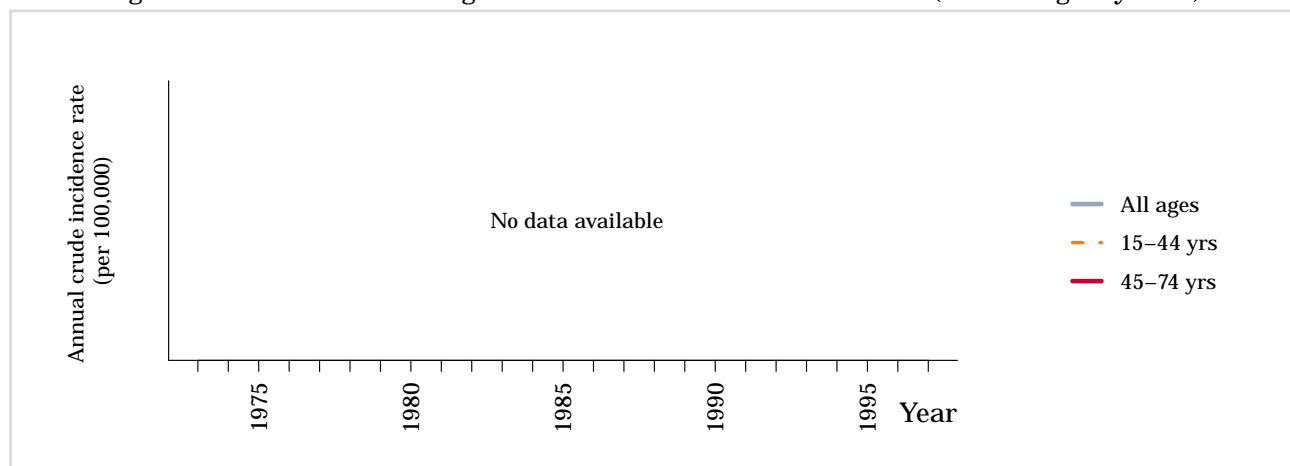
Data accessed on 05 May 2015.

ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference; Please refer to original source (available at <http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm>)

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

<sup>b</sup>Rates per 100,000 women per year.

Figure 22: Time trends in vaginal cancer incidence in San Marino (cancer registry data)



Data accessed on 27 Apr 2015.

Data sources:

Ferlay J, Bray F, Steliarova-Foucher E and Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: <http://ci5.iarc.fr>

### 3.2.4 Penile cancer

The annual burden of penile cancer has been estimated to be 22,000 cases worldwide with incidence rates strongly correlating with those of cervical cancer (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Penile cancer is rare and most commonly affects men aged 50-70 years. Incidence rates are higher in less developed countries than in more developed countries, accounting for up to 10% of male cancers in some parts of Africa, South America and Asia. Precursor cancerous penile lesions (PeIN) are rare.

Cancers of the penis are primarily of squamous cell carcinomas (SCC) (95%) and the most common penile SCC histologic sub-types are keratinising (49%), mixed warty-basaloid (17%), verrucous (8%) warty (6%), and basaloid (4%). HPV is most commonly detected in basaloid and warty tumours but is less common in keratinising and verrucous tumours. Approximately 60-100% of PeIN lesions are HPV DNA positive.

Table 11: Penile cancer incidence in San Marino by cancer registry

Cancer registry	Period	N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>
No Data Available	-	-	-	-

Data accessed on 05 May 2015.

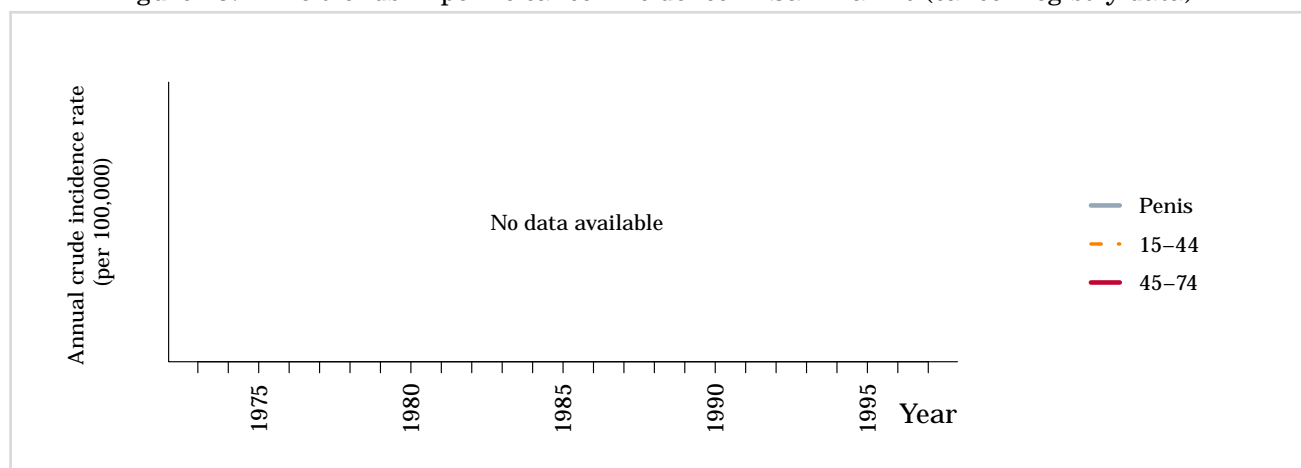
ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference;

Please refer to original source (available at <http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm>)

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

<sup>b</sup>Rates per 100,000 men per year.

Figure 23: Time trends in penile cancer incidence in San Marino (cancer registry data)



Data accessed on 27 Apr 2015.

Data sources:

Ferlay J, Bray F, Steliarova-Foucher E and Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: <http://ci5.iarc.fr>

### 3.3 Head and neck cancers

The majority of head and neck cancers are associated with high tobacco and alcohol consumption. However, increasing trends in the incidence at specific sites suggest that other aetiological factors are involved, and infection by certain high-risk types of HPV (i.e. HPV16) have been reported to be associated with head and neck cancers, in particular with oropharyngeal cancer. Current evidence suggests that HPV16 is associated with tonsil cancer (including Waldeyer ring cancer), base of tongue cancer and other oropharyngeal cancer sites. Associations with other head and neck cancer sites such as oral cancer are neither strong nor consistent when compared to molecular-epidemiological data on HPV and oropharyngeal cancer. Association with laryngeal cancer is still unclear (*IARC Monograph Vol 100B*).

#### 3.3.1 Pharyngeal cancer (excluding nasopharynx)

Table 12: Incidence and mortality of cancer of the pharynx (excluding nasopharynx) in San Marino, Southern Europe and the rest of the world by sex (estimates for 2012). Includes ICD-10 codes: C09-10,C12-14

Indicator	MALE			FEMALE		
	San Marino	Southern Europe	World	San Marino	Southern Europe	World
<b>INCIDENCE</b>						
Annual number of new cancer cases	-	4,137	115,131	-	731	27,256
Crude incidence rate <sup>a</sup>	-	5.3	3.2	-	0.9	0.8
Age-standardized incidence rate <sup>a</sup>	-	3.4	3.2	-	0.5	0.7
Cumulative risk (%) at 75 years old <sup>b</sup>	-	0.4	0.4	-	0.1	0.1
<b>MORTALITY</b>						
Annual number of deaths	-	2,342	77,585	-	430	18,505
Crude mortality rate <sup>a</sup>	-	3.0	2.2	-	0.5	0.5
Age-standardized mortality rate <sup>a</sup>	-	1.8	2.2	-	0.3	0.5
Cumulative risk (%) at 75 years old <sup>c</sup>	-	0.2	0.3	-	0.0	0.1

**Data accessed on 15 Nov 2015.**

<sup>a</sup>Male: Rates per 100,000 men per year. Female: Rates per 100,000 women per year.

<sup>b</sup> Cumulative risk (incidence) is the probability or risk of individuals getting from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to develop from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

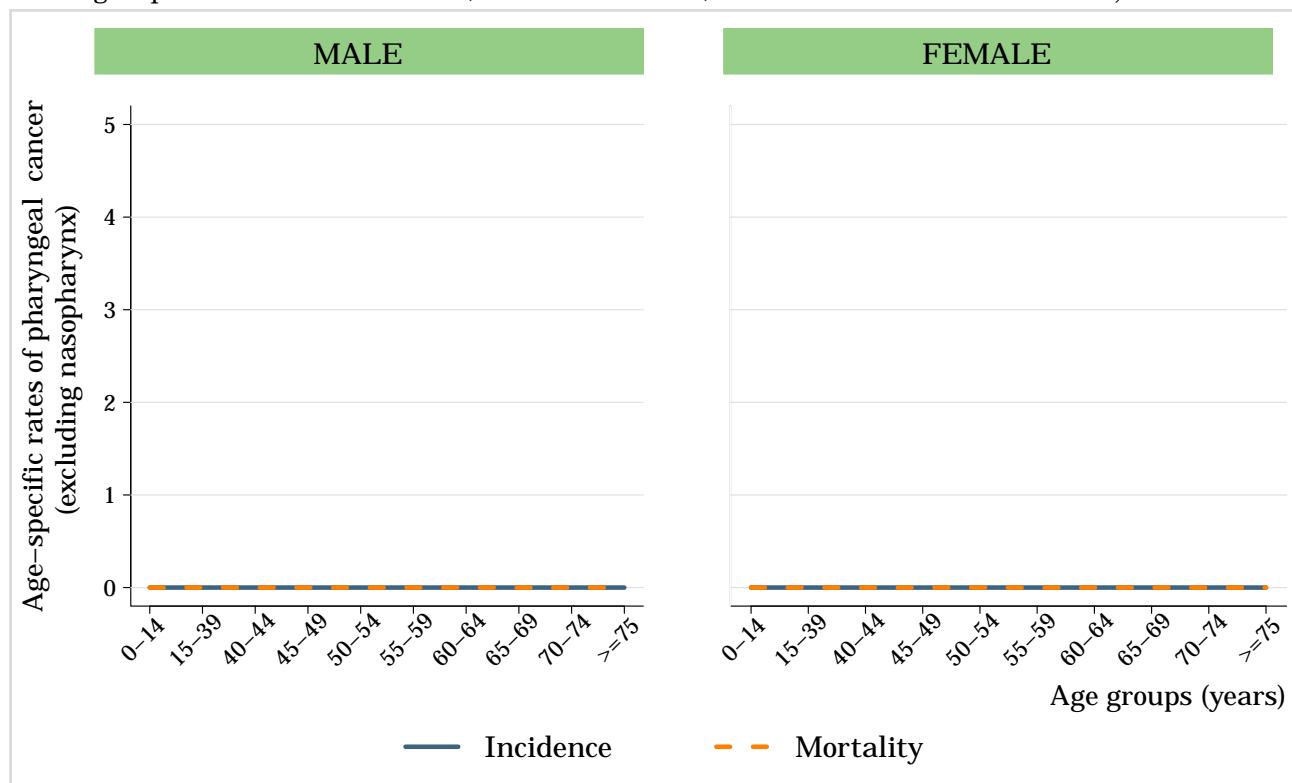
<sup>c</sup> Cumulative risk (mortality) is the probability or risk of individuals dying from the disease during ages 0-74 years. For cancer, it is expressed as the % of new born children who would be expected to die from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.

**Data sources:**

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.



Figure 24: Comparison of incidence and mortality rates of the pharynx (excluding nasopharynx) by age group and sex in San Marino (estimates for 2012). Includes ICD-10 codes: C09-10,C12-14



Data accessed on 15 Nov 2015.

Male: Rates per 100,000 men per year. Female: Rates per 100,000 women per year.

Data sources:

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>.

Table 13: Incidence of oropharyngeal cancer in San Marino by cancer registry and sex

Cancer registry	Period	MALE			FEMALE		
		N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>	N cases <sup>a</sup>	Crude rate <sup>b</sup>	ASR <sup>b</sup>
<b>Base of tongue (ICD-10 code: C01)</b>							
-	-	-	-	-	-	-	-
<b>Tonsillar cancer (ICD-10 code: C09)</b>							
-	-	-	-	-	-	-	-
<b>Cancer of the oropharynx (excludes tonsil) (ICD-10 code: C10)</b>							
-	-	-	-	-	-	-	-

**Data accessed on 05 May 2015.**

ASR: Age-standardised rate. Standardised rates have been estimated using the direct method and the World population as the reference.

Please refer to original source (available at <http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm>)

<sup>a</sup>Accumulated number of cases during the period in the population covered by the corresponding registry.

<sup>b</sup>Male: Rates per 100,000 men per year. Female: Rates per 100,000 women per year.

## 4 HPV related statistics

HPV infection is commonly found in the anogenital tract of men and women with and without clinical lesions. The aetiological role of HPV infection among women with cervical cancer is well-established, and there is growing evidence of its central role in other anogenital sites. HPV is also responsible for other diseases such as recurrent juvenile respiratory papillomatosis and genital warts, both mainly caused by HPV types 6 and 11 (*Lacey CJ, Vaccine 2006; 24(S3):35*). For this section, the methodologies used to compile the information on HPV burden are derived from systematic reviews and meta-analyses of the literature. Due to the limitations of HPV DNA detection methods and study designs used, these data should be interpreted with caution and used only as a guide to assess the burden of HPV infection within the population. (*Vaccine 2006, Vol. 24, Suppl 3; Vaccine 2008, Vol. 26, Suppl 10; Vaccine 2012, Vol. 30, Suppl 5; IARC Monographs 2007, Vol. 90*).

### 4.1 HPV burden in women with normal cervical cytology, cervical precancerous lesions or invasive cervical cancer

The statistics shown in this section focus on HPV infection in the cervix uteri. HPV cervical infection results in cervical morphological lesions ranging from normalcy (cytologically normal women) to different stages of precancerous lesions (CIN-1, CIN-2, CIN-3/CIS) and invasive cervical cancer. HPV infection is measured by HPV DNA detection in cervical cells (fresh tissue, paraffin embedded or exfoliated cells).

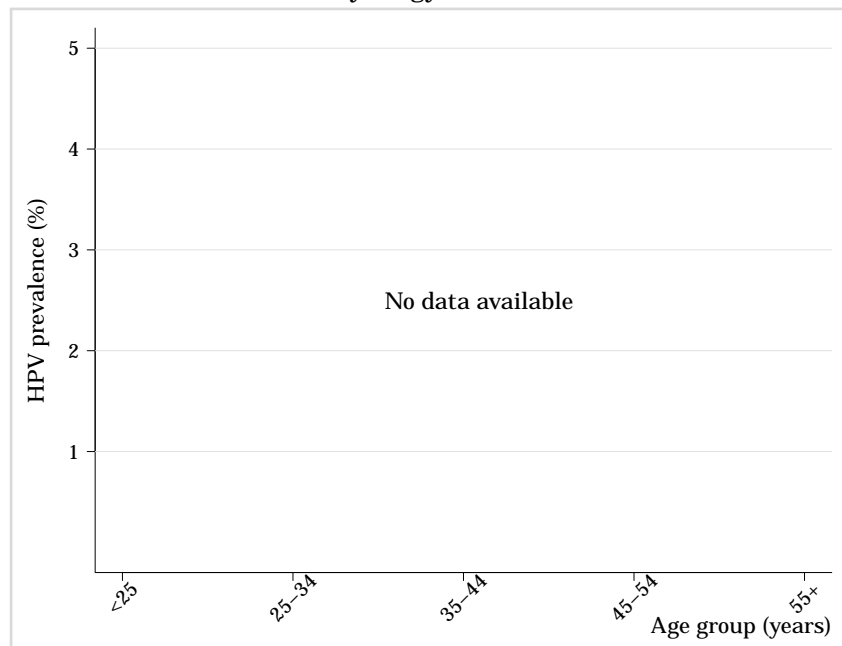
The prevalence of HPV increases with lesion severity. HPV causes virtually 100% of cervical cancer cases, and an underestimation of HPV prevalence in cervical cancer is most likely due to the limitations of study methodologies. Worldwide, HPV16 and 18 (the two vaccine-preventable types) contribute to over 70% of all cervical cancer cases, between 41% and 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions. After HPV16/18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58; these account for an additional 20% of cervical cancers worldwide (*Clifford G, Vaccine 2006;24(S3):26*).

#### **Methods: Prevalence and type distribution of human papillomavirus in cervical carcinoma, low-grade cervical lesions, high-grade cervical lesions and normal cytology: systematic review and meta-analysis**

A systematic review of the literature was conducted regarding the worldwide HPV-prevalence and type distribution for cervical carcinoma, low-grade cervical lesions, high-grade cervical lesions and normal cytology from 1990 to 'data as of' indicated in each section. The search terms for the review were 'HPV AND cerv\*' using Pubmed. There were no limits in publication language. References cited in selected articles were also investigated. Inclusion criteria were: HPV DNA detection by means of PCR or HC2, a minimum of 20 cases for cervical carcinoma, 20 cases for low-grade cervical lesions, 20 cases for high-grade cervical lesions and 100 cases for normal cytology and a detailed description of HPV DNA detection and genotyping techniques used. The number of cases tested and HPV positive extracted for each study were pooled to estimate the prevalence of HPV DNA and the HPV type distribution globally and by geographical region. Binomial 95% confidence intervals were calculated for each HPV prevalence. For more details refer to the methods document.

#### 4.1.1 HPV prevalence in women with normal cervical cytology

Figure 25: Crude age-specific HPV prevalence (%) and 95% confidence interval in women with normal cervical cytology in San Marino



Data updated on 15 Dec 2016 (data as of 30 Jun 2015).

Data sources:

Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bruni L, J Infect Dis 2010; 202: 1789. 2) De Sanjosé S, Lancet Infect Dis 2007; 7: 453

Figure 26: HPV prevalence among women with normal cervical cytology in San Marino, by study

Study	Age	N
No data available		

Data updated on 15 Dec 2016 (data as of 30 Jun 2015).

95% CI: 95% Confidence Interval; N: number of women tested;

The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

#### 4.1.2 HPV type distribution among women with normal cervical cytology, precancerous cervical lesions and cervical cancer

Table 14: Prevalence of HPV16 and HPV18 by cytology in San Marino

	No. tested	HPV 16/18 Prevalence	
		%	(95% CI)
Normal cytology <sup>1</sup>	-	--	
Low-grade lesions <sup>2</sup>	-	--	
High-grade lesions <sup>3</sup>	-	--	
Cervical cancer <sup>4</sup>	-	--	

Data updated on 19 May 2017 (data as of 30 Jun 2015 / 30 Jun 2015).

95% CI: 95% Confidence Interval; High-grade lesions: CIN-2, CIN-3, CIS or HSIL; Low-grade lesions: LSIL or CIN-1;

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells)

Data sources:

(Continued on next page)

( Table 14 – continued from previous page)

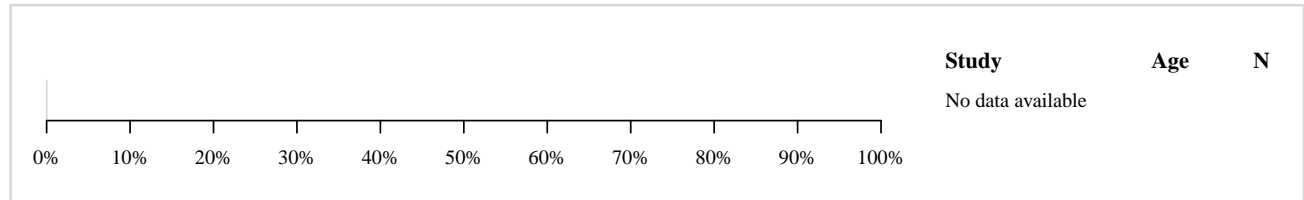
<sup>1</sup>Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Bruni L, J Infect Dis 2010; 202: 1789. 2) De Sanjosé S, Lancet Infect Dis 2007; 7: 453

<sup>2</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Clifford GM, Cancer Epidemiol Biomarkers Prev 2005;14:1157

<sup>3</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Smith JS, Int J Cancer 2007;121:621 3) Clifford GM, Br J Cancer 2003;89:101.

<sup>4</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.

Figure 27: HPV 16 prevalence among women with normal cervical cytology in San Marino, by study



**Data updated on 15 Dec 2016 (data as of 30 Jun 2015).**

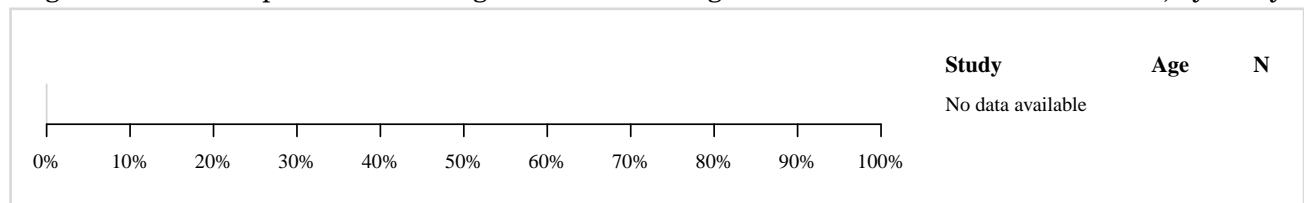
95% CI: 95% Confidence Interval; N: number of women tested;

The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

Data sources:

Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Bruni L, J Infect Dis 2010; 202: 1789. 2) De Sanjosé S, Lancet Infect Dis 2007; 7: 453

Figure 28: HPV 16 prevalence among women with low-grade cervical lesions in San Marino, by study



**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

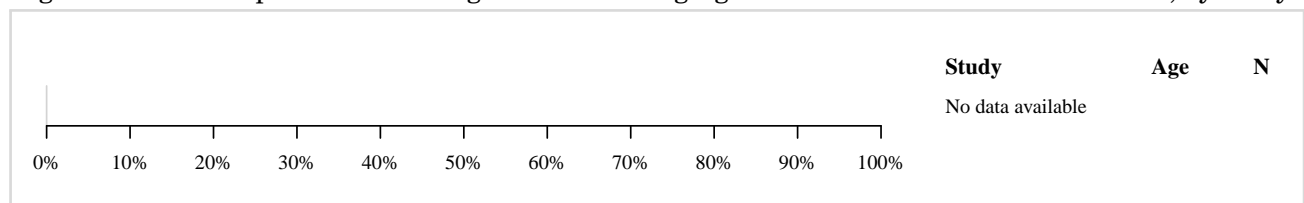
95% CI: 95% Confidence Interval; Low-grade lesions: LSIL or CIN-1; N: number of women tested;

The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

Data sources:

Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Clifford GM, Cancer Epidemiol Biomarkers Prev 2005;14:1157

Figure 29: HPV 16 prevalence among women with high-grade cervical lesions in San Marino, by study



**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

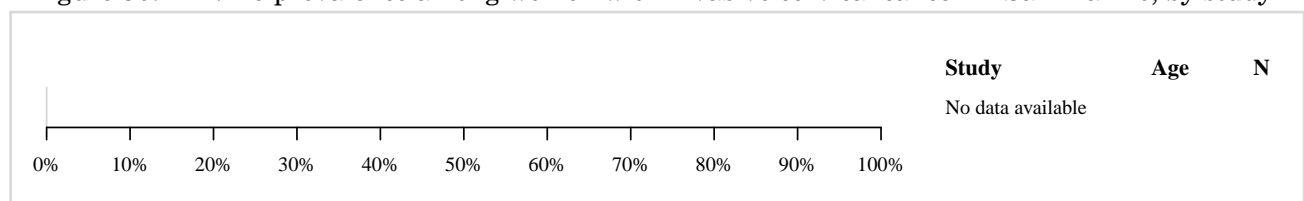
95% CI: 95% Confidence Interval; High-grade lesions: CIN-2, CIN-3, CIS or HSIL; N: number of women tested;

The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

Data sources:

Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Smith JS, Int J Cancer 2007;121:621 3) Clifford GM, Br J Cancer 2003;89:101.

Figure 30: HPV 16 prevalence among women with invasive cervical cancer in San Marino, by study



**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

(Continued on next page)

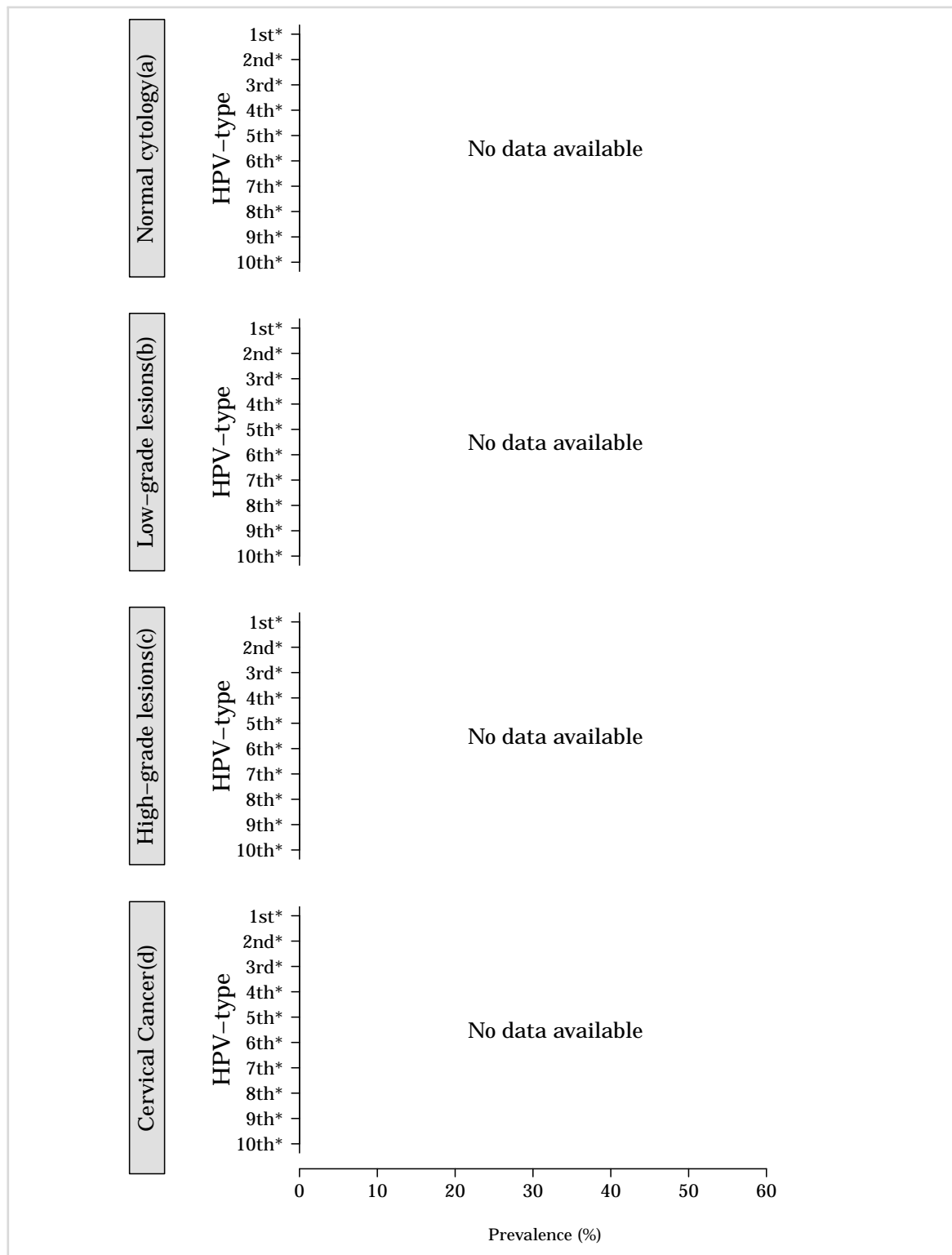
( Figure 30 – continued from previous page)

95% CI: 95% Confidence Interval; N: number of women tested;  
The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

Data sources:

Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.

Figure 31: Comparison of the ten most frequent HPV oncogenic types in San Marino among women with and without cervical lesions



\*No data available. No more types than shown were tested or were positive.

**Data updated on 19 May 2017 (data as of 30 Jun 2015 / 30 Jun 2015).**

(Continued on next page)

(Figure 31 – continued from previous page)

High-grade lesions: CIN-2, CIN-3, CIS or HSIL; Low-grade lesions: LSIL or CIN-1;  
The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).

**Data sources:**

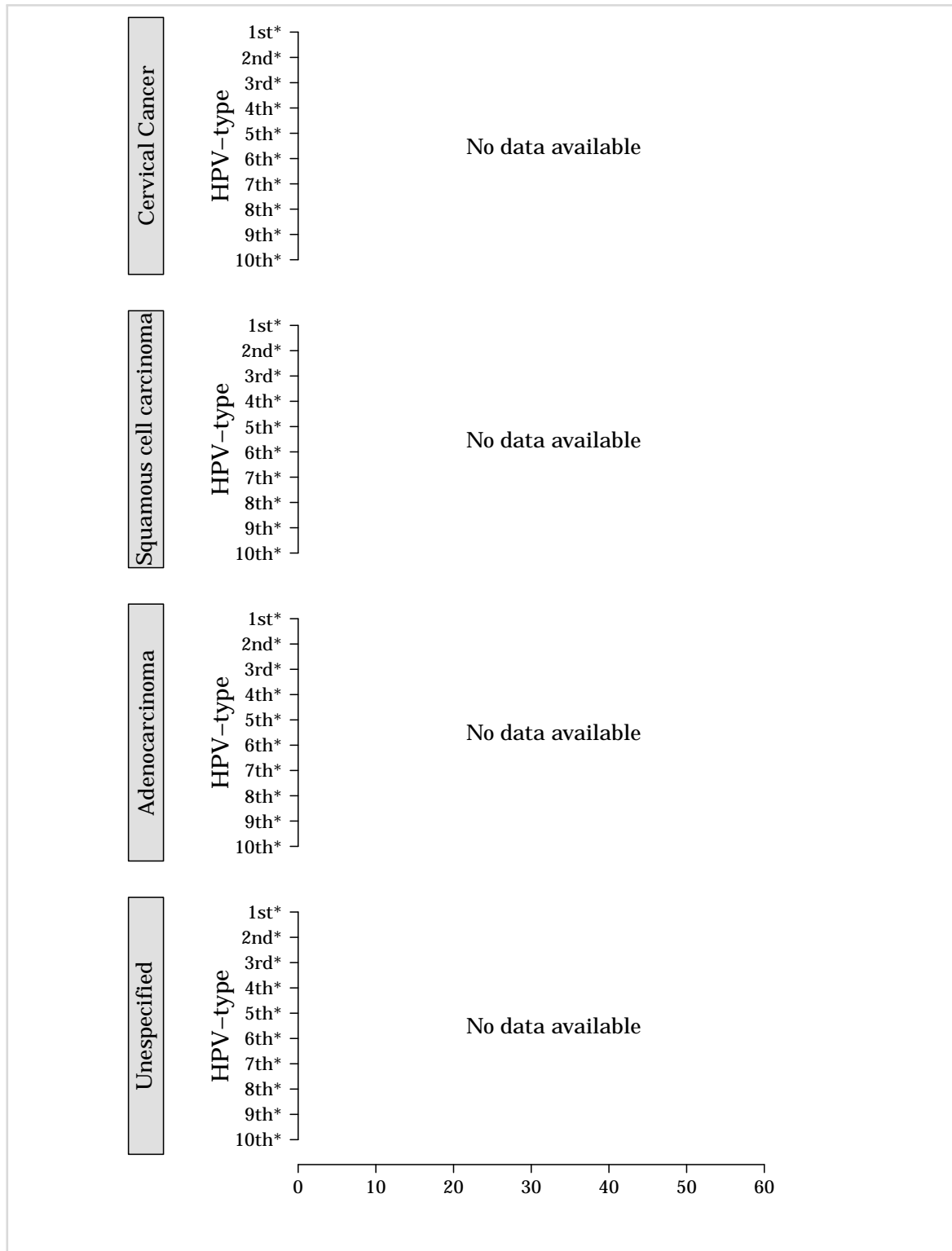
<sup>a</sup>Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Bruni L, J Infect Dis 2010; 202: 1789. 2) De Sanjosé S, Lancet Infect Dis 2007; 7: 453

<sup>b</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Clifford GM, Cancer Epidemiol Biomarkers Prev 2005;14:1157

<sup>c</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Smith JS, Int J Cancer 2007;121:621 3) Clifford GM, Br J Cancer 2003;89:101.

<sup>d</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.

**Figure 32: Comparison of the ten most frequent HPV oncogenic types in San Marino among women with invasive cervical cancer by histology**



**Data updated on 19 May 2017 (data as of 30 Jun 2015).**

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells). The ranking of the ten most frequent HPV types may present less than ten types because only a limited number of types were tested or were HPV-positive.

Data sources:

Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.



Table 15: Type-specific HPV prevalence in women with normal cervical cytology, precancerous cervical lesions and invasive cervical cancer in San Marino

HPV Type	Normal cytology <sup>1</sup>		Low-grade lesions <sup>2</sup>		High-grade lesions <sup>3</sup>		Cervical cancer <sup>4</sup>	
	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)
<b>ONCOGENIC HPV TYPES</b>								
<b>High-risk HPV types</b>								
16	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-
31	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-
35	-	-	-	-	-	-	-	-
39	-	-	-	-	-	-	-	-
45	-	-	-	-	-	-	-	-
51	-	-	-	-	-	-	-	-
52	-	-	-	-	-	-	-	-
56	-	-	-	-	-	-	-	-
58	-	-	-	-	-	-	-	-
59	-	-	-	-	-	-	-	-
<b>Probable/possible carcinogen</b>								
26	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-
34	-	-	-	-	-	-	-	-
53	-	-	-	-	-	-	-	-
66	-	-	-	-	-	-	-	-
67	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-
70	-	-	-	-	-	-	-	-
73	-	-	-	-	-	-	-	-
82	-	-	-	-	-	-	-	-
85	-	-	-	-	-	-	-	-
97	-	-	-	-	-	-	-	-
<b>NON-ONCOGENIC HPV TYPES</b>								
6	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-
32	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-
42	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	-
54	-	-	-	-	-	-	-	-
55	-	-	-	-	-	-	-	-
57	-	-	-	-	-	-	-	-
61	-	-	-	-	-	-	-	-
62	-	-	-	-	-	-	-	-
64	-	-	-	-	-	-	-	-
71	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-
74	-	-	-	-	-	-	-	-
81	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-
84	-	-	-	-	-	-	-	-
86	-	-	-	-	-	-	-	-
87	-	-	-	-	-	-	-	-
89	-	-	-	-	-	-	-	-
90	-	-	-	-	-	-	-	-
91	-	-	-	-	-	-	-	-

**Data updated on 19 May 2017 (data as of 30 Jun 2015 / 30 Jun 2015).**

95% CI: 95% Confidence Interval; High-grade lesions: CIN-2, CIN-3, CIS or HSIL; Low-grade lesions: LSIL or CIN-1;

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).

**Data sources:**

<sup>1</sup>Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Bruni L, J Infect Dis 2010; 202: 1789. 2) De Sanjosé S, Lancet Infect Dis 2007; 7: 453

<sup>2</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Clifford GM, Cancer Epidemiol Biomarkers Prev 2005;14:1157

<sup>3</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Smith JS, Int J Cancer 2007;121:621 3) Clifford GM, Br J Cancer 2003;89:101.

<sup>4</sup>Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.



Table 16: Type-specific HPV prevalence among invasive cervical cancer cases in San Marino by histology

HPV Type	Any Histology		Squamous cell carcinoma		Adenocarcinoma		Unspecified	
	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)	No. tested	HPV Prev % (95% CI)
<b>ONCOGENIC HPV TYPES</b>								
<b>High-risk HPV types</b>								
16	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-
31	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-
35	-	-	-	-	-	-	-	-
39	-	-	-	-	-	-	-	-
45	-	-	-	-	-	-	-	-
51	-	-	-	-	-	-	-	-
52	-	-	-	-	-	-	-	-
56	-	-	-	-	-	-	-	-
58	-	-	-	-	-	-	-	-
59	-	-	-	-	-	-	-	-
<b>Probable/possible carcinogen</b>								
26	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-
34	-	-	-	-	-	-	-	-
53	-	-	-	-	-	-	-	-
66	-	-	-	-	-	-	-	-
67	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-
70	-	-	-	-	-	-	-	-
73	-	-	-	-	-	-	-	-
82	-	-	-	-	-	-	-	-
85	-	-	-	-	-	-	-	-
97	-	-	-	-	-	-	-	-
<b>NON-ONCOGENIC HPV TYPES</b>								
6	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-
32	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-
42	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	-
54	-	-	-	-	-	-	-	-
55	-	-	-	-	-	-	-	-
57	-	-	-	-	-	-	-	-
60	-	-	-	-	-	-	-	-
61	-	-	-	-	-	-	-	-
62	-	-	-	-	-	-	-	-
64	-	-	-	-	-	-	-	-
71	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-
74	-	-	-	-	-	-	-	-
76	-	-	-	-	-	-	-	-
81	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-
84	-	-	-	-	-	-	-	-
86	-	-	-	-	-	-	-	-
87	-	-	-	-	-	-	-	-
89	-	-	-	-	-	-	-	-
90	-	-	-	-	-	-	-	-
91	-	-	-	-	-	-	-	-
No Data Available	-	--	-	--	-	--	-	--

Data updated on 19 May 2017 (data as of 30 Jun 2015).

95% CI: 95% Confidence Interval;

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).

Data sources:

Based on meta-analysis performed by IARC's Infections and Cancer Epidemiology Group up to November 2011, the ICO HPV Information Centre has updated data until June 2014. Reference publications: 1) Guan P, Int J Cancer 2012;131:2349 2) Li N, Int J Cancer 2011;128:927 3) Smith JS, Int J Cancer 2007;121:621 4) Clifford GM, Br J Cancer 2003;88:63 5) Clifford GM, Br J Cancer 2003;89:101.

### 4.1.3 HPV type distribution among HIV+ women with normal cervical cytology

Table 17: Studies on HPV prevalence among HIV women with normal cytology in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

**Data updated on 31 Jul 2013 (data as of 31 Dec 2011). Only for European countries.**

95% CI: 95% Confidence Interval;

Data sources:

Systematic review and meta-analysis were performed by the ICO HPV Information Centre up to December 2011. Selected studies had to include at least 20 HIV positive women who had both normal cervical cytology and HPV test results (PCR or HC2).

#### 4.1.4 Terminology

##### **Cytologically normal women**

No abnormal cells are observed on the surface of their cervix upon cytology.

##### **Cervical Intraepithelial Neoplasia (CIN) / Squamous Intraepithelial Lesions (SIL)**

SIL and CIN are two commonly used terms to describe precancerous lesions or the abnormal growth of squamous cells observed in the cervix. SIL is an abnormal result derived from cervical cytological screening or Pap smear testing. CIN is a histological diagnosis made upon analysis of cervical tissue obtained by biopsy or surgical excision. The condition is graded as CIN 1, 2 or 3, according to the thickness of the abnormal epithelium (1/3, 2/3 or the entire thickness).

##### **Low-grade cervical lesions (LSIL/CIN-1)**

Low-grade cervical lesions are defined by early changes in size, shape, and number of abnormal cells formed on the surface of the cervix and may be referred to as mild dysplasia, LSIL, or CIN-1.

##### **High-grade cervical lesions (HSIL/ CIN-2 / CIN-3 / CIS)**

High-grade cervical lesions are defined by a large number of precancerous cells on the surface of the cervix that are distinctly different from normal cells. They have the potential to become cancerous cells and invade deeper tissues of the cervix. These lesions may be referred to as moderate or severe dysplasia, HSIL, CIN-2, CIN-3 or cervical carcinoma in situ (CIS).

##### **Carcinoma in situ (CIS)**

Preinvasive malignancy limited to the epithelium without invasion of the basement membrane. CIN 3 encompasses the squamous carcinoma in situ.

##### **Invasive cervical cancer (ICC) / Cervical cancer**

If the high-grade precancerous cells invade the basement membrane is called ICC. ICC stages range from stage I (cancer is in the cervix or uterus only) to stage IV (the cancer has spread to distant organs, such as the liver).

##### **Invasive squamous cell carcinoma**

Invasive carcinoma composed of cells resembling those of squamous epithelium.

##### **Adenocarcinoma**

Invasive tumour with glandular and squamous elements intermingled.

## 4.2 HPV burden in anogenital cancers other than cervix

### Methods: Prevalence and type distribution of human papillomavirus in carcinoma of the vulva, vagina, anus and penis: systematic review and meta-analysis

A systematic review of the literature was conducted on the worldwide HPV-prevalence and type distribution for anogenital carcinomas other than cervix from January 1986 to 'data as of' indicated in each section. The search terms for the review were 'HPV' AND (anus OR anal) OR (penile) OR vagin\* OR vulv\* using Pubmed. There were no limits in publication language. References cited in selected articles were also investigated. Inclusion criteria were: HPV DNA detection by means of PCR, a minimum of 10 cases by lesion and a detailed description of HPV DNA detection and genotyping techniques used. The number of cases tested and HPV positive cases were extracted for each study to estimate the prevalence of HPV DNA and the HPV type distribution. Binomial 95% confidence intervals were calculated for each HPV prevalence.

#### 4.2.1 Anal cancer and precancerous anal lesions

Anal cancer is similar to cervical cancer with respect to overall HPV DNA positivity, with approximately 88% of cases associated with HPV infection worldwide (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). HPV16 is the most common type detected, representing 73% of all HPV-positive tumours. HPV18 is the second most common type detected and is found in approximately 5% of cases. HPV DNA is also detected in the majority of precancerous anal lesions (AIN) (91.5% in AIN1 and 93.9% in AIN2/3) (*De Vuyst H et al. Int J Cancer 2009; 124: 1626-36*). In this section, the burden of HPV among cases of anal cancers and precancerous anal lesions in San Marino are presented.

Table 18: Studies on HPV prevalence among anal cancer cases in San Marino (male and female)

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

Data updated on 17 Jul 2017 (data as of 30 Jun 2015).

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Table 19: Studies on HPV prevalence among cases of AIN2/3 in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

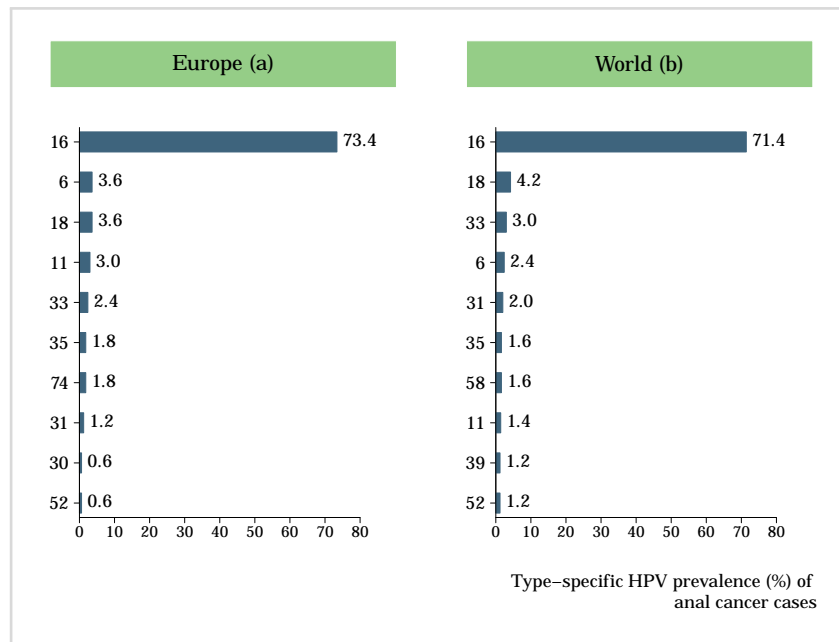
Data updated on 17 Jul 2017 (data as of 30 Jun 2015).

95% CI: 95% Confidence Interval; AIN 2/3: Anal intraepithelial neoplasia of grade 2/3;

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Figure 33: Comparison of the ten most frequent HPV types in anal cancer cases in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

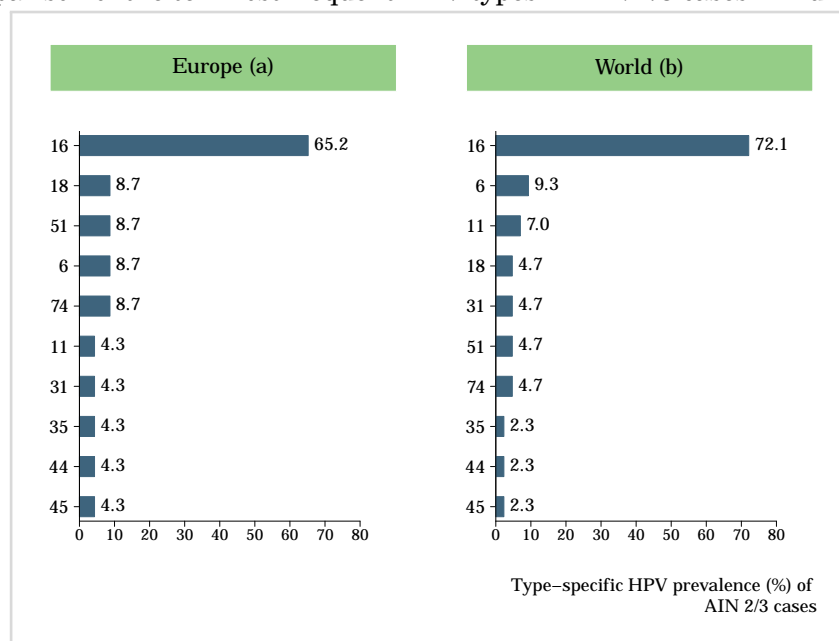
<sup>a</sup>Includes cases from Bosnia-Herzegovina, Czech Republic, France, Germany, Poland, Portugal, Slovenia, Spain and United Kingdom.

<sup>b</sup>Includes cases from Europe (Bosnia-Herzegovina, Czech Republic, France, Germany, Poland, Portugal, Slovenia, Spain and United Kingdom); America (Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay and United States); Africa (Mali, Nigeria and Senegal); Asia (Bangladesh, India and South Korea)

Data sources:

Data from Alemany L, Int J Cancer 2015; 136: 98. This study has gathered the largest international series of anal cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

Figure 34: Comparison of the ten most frequent HPV types in AIN 2/3 cases in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

AIN 2/3: Anal intraepithelial neoplasia of grade 2/3;

<sup>a</sup>Includes cases from Bosnia-Herzegovina, Czech Republic, France, Germany, Poland, Portugal, Slovenia, Spain and United Kingdom

<sup>b</sup>Includes cases from Europe (Bosnia-Herzegovina, Czech Republic, France, Germany, Poland, Portugal, Slovenia, Spain and United Kingdom); America (Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay)

Data sources:

Data from Alemany L, Int J Cancer 2015; 136: 98. This study has gathered the largest international series of anal cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

### 4.2.2 Vulvar cancer and precancerous vulvar lesions

HPV attribution for vulvar cancer is 43% worldwide (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Vulvar cancer has two distinct histological patterns with two different risk factor profiles: (1) basaloid/warty types (2) keratinising types. Basaloid/warty lesions are more common in young women, are frequently found adjacent to VIN, are very often associated with HPV DNA detection (86%), and have a similar risk factor profile as cervical cancer. Keratinising vulvar carcinomas represent the majority of the vulvar lesions (>60%). These lesions develop from non HPV-related chronic vulvar dermatoses, especially lichen sclerosus and/or squamous hyperplasia, their immediate cancer precursor lesion is differentiated VIN, they occur more often in older women, and are rarely associated with HPV (6%) or with any of the other risk factors typical of cervical cancer. HPV prevalence is frequently detected among cases of high-grade VIN (VIN2/3) (85.3%). HPV 16 is the most common type detected followed by HPV 33 (*De Vuyst H et al. Int J Cancer 2009; 124: 1626-36*). In this section, the HPV burden among cases of vulvar cancer cases and precancerous vulvar lesions in San Marino are presented.

Table 20: Studies on HPV prevalence among vulvar cancer cases in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

Data updated on 17 Jul 2017 (data as of 30 Jun 2015).

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Table 21: Studies on HPV prevalence among VIN 2/3 cases in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

Data updated on 17 Jul 2017 (data as of 30 Jun 2015).

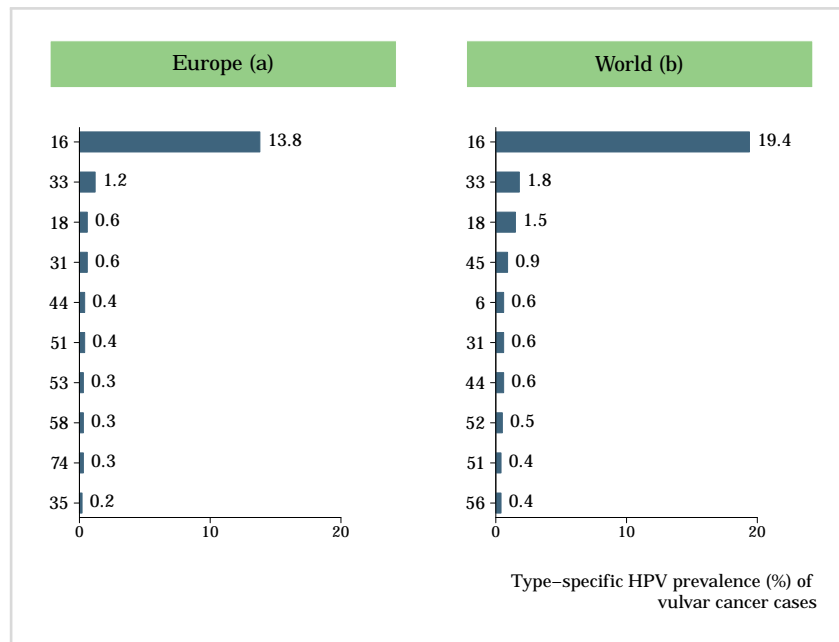
95% CI: 95% Confidence Interval; VIN 2/3: Vulvar intraepithelial neoplasia of grade 2/3;

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626



Figure 35: Comparison of the ten most frequent HPV types in cases of vulvar cancer in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

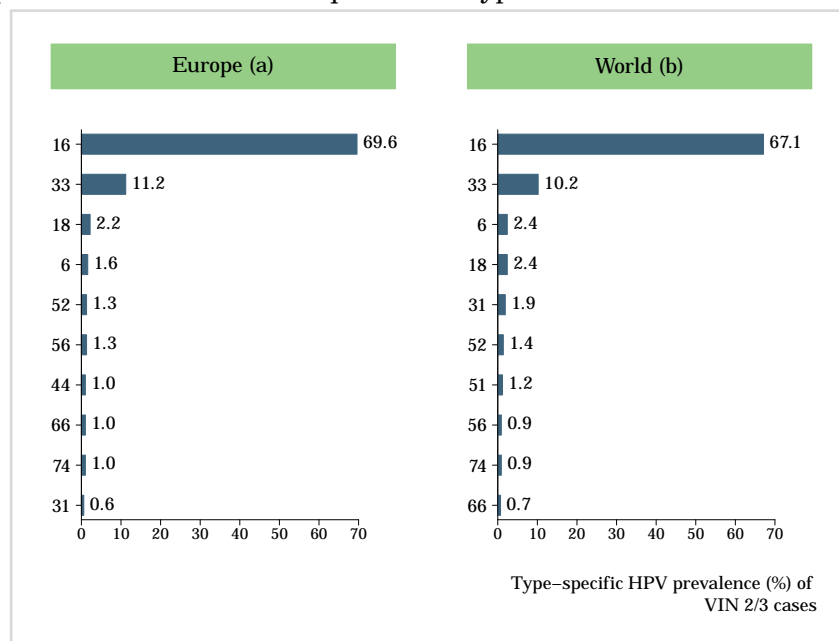
<sup>a</sup>Includes cases from Austria, Belarus, Bosnia-Herzegovina, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain and United Kingdom.

<sup>b</sup>Includes cases from America (Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Uruguay, United States of America and Venezuela); Africa (Mali, Mozambique, Nigeria, and Senegal); Oceania (Australia and New Zealand); Europe (Austria, Belarus, Bosnia-Herzegovina, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain and United Kingdom); and in Asia (Bangladesh, India, Israel, South Korea, Kuwait, Lebanon, Philippines, Taiwan and Turkey)

Data sources:

Data from de Sanjosé S, Eur J Cancer 2013; 49: 3450. This study has gathered the largest international series of vulva cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

Figure 36: Comparison of the ten most frequent HPV types in VIN 2/3 cases in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

<sup>a</sup>Includes cases from Austria, Belarus, Bosnia-Herzegovina, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain and United Kingdom.

<sup>b</sup>Includes cases from America (Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Uruguay and Venezuela); Oceania (Australia and New Zealand); Europe (Austria, Belarus, Bosnia-Herzegovina, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain and United Kingdom); and in Asia (Bangladesh, India, Israel, South Korea, Kuwait, Lebanon, Philippines, Taiwan and Turkey)

Data sources:

Data from de Sanjosé S, Eur J Cancer 2013; 49: 3450. This study has gathered the largest international series of vulva cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

### 4.2.3 Vaginal cancer and precancerous vaginal lesions

Vaginal and cervical cancers share similar risk factors and it is generally accepted that both carcinomas share the same aetiology of HPV infection although there is limited evidence available. Women with vaginal cancer are more likely to have a history of other ano-genital cancers, particularly of the cervix, and these two carcinomas are frequently diagnosed simultaneously. HPV DNA is detected among 70% of invasive vaginal carcinomas and 91% of high-grade vaginal neoplasias (VaIN2/3). HPV16 is the most common type in high-grade vaginal neoplasias and it is detected in at least 70% of HPV-positive carcinomas (*de Martel C et al. Lancet Oncol 2012;13(6):607-15; De Vuyst H et al. Int J Cancer 2009; 124:1626-36*). In this section, the HPV burden among cases of vaginal cancer cases and precancerous vaginal lesions in San Marino are presented.

Table 22: Studies on HPV prevalence among vaginal cancer cases in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Table 23: Studies on HPV prevalence among VaIN 2/3 cases in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

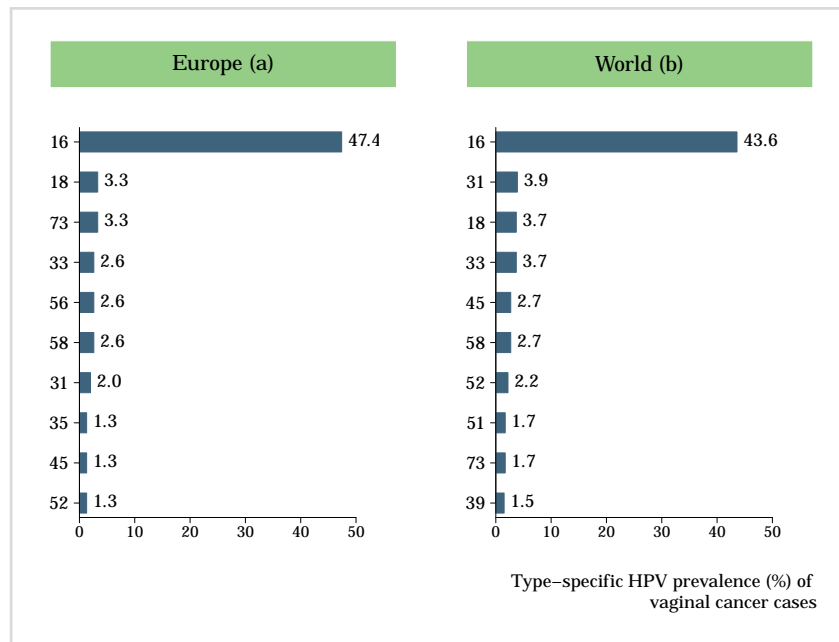
95% CI: 95% Confidence Interval; VaIN 2/3: Vaginal intraepithelial neoplasia of grade 2/3;

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Data sources:

Based on systematic reviews (up to 2008) performed by ICO for the IARC Monograph on the Evaluation of Carcinogenic Risks to Humans volume 100B and IARC's Infections and Cancer Epidemiology Group. The ICO HPV Information Centre has updated data until June 2015. Reference publications: 1) Bouvard V, Lancet Oncol 2009;10:321 2) De Vuyst H, Int J Cancer 2009;124:1626

Figure 37: Comparison of the ten most frequent HPV types in cases of vaginal cancer in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

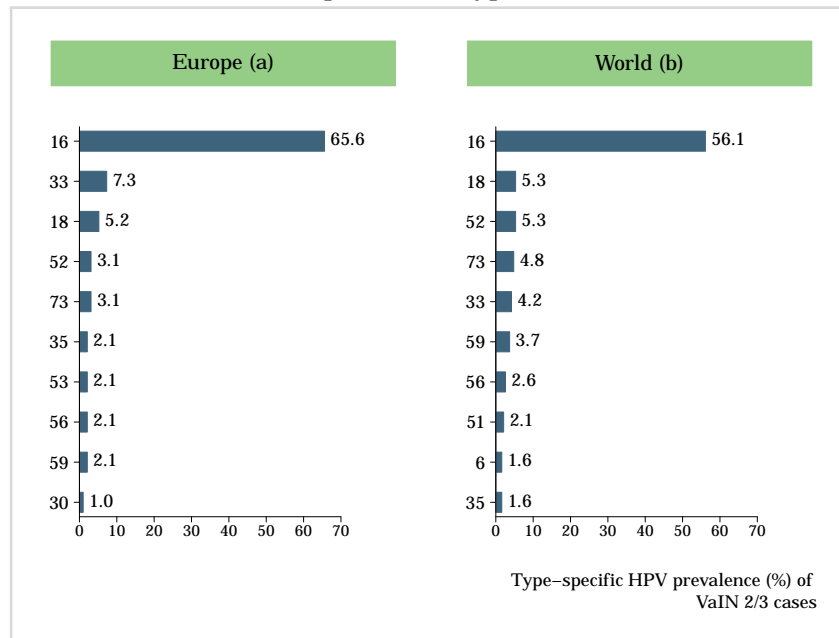
<sup>a</sup>Includes cases from Austria, Belarus, Czech Republic, France, Germany, Greece, Poland, Spain and United Kingdom.

<sup>b</sup>Includes cases from Europe (Austria, Belarus, Czech Republic, France, Germany, Greece, Poland, Spain and United Kingdom); America (Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Paraguay, Uruguay, United states of America and Venezuela); Africa (Mozambique, Nigeria); Asia (Bangladesh, India, Israel, South Korea, Kuwait, Philippines, Taiwan and Turkey); and Oceania (Australia)

Data sources:

Data from Alemany L, Eur J Cancer 2014; 50: 2846. This study has gathered the largest international series of vaginal cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

Figure 38: Comparison of the ten most frequent HPV types in VaIN 2/3 cases in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2014).

VAIN 2/3: Vaginal intraepithelial neoplasia of grade 2/3;

<sup>a</sup>Includes cases from Austria, Belarus, Czech Republic, France, Germany, Greece, Poland, Spain and United Kingdom.

<sup>b</sup>Includes cases from Europe (Austria, Belarus, Czech Republic, France, Germany, Greece, Poland, Spain and United Kingdom); America (Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Paraguay, Uruguay, United states of America and Venezuela); Asia (Bangladesh, India, Israel, South Korea, Kuwait, Philippines, Taiwan and Turkey); and Oceania (Australia)

Data sources:

Data from Alemany L, Eur J Cancer 2014; 50: 2846. This study has gathered the largest international series of vaginal cancer cases and precancerous lesions worldwide using a standard protocol with a highly sensitive HPV DNA detection assay.

#### 4.2.4 Penile cancer and precancerous penile lesions

HPV DNA is detectable in approximately 50% of all penile cancers (*de Martel C et al. Lancet Oncol 2012;13(6):607-15*). Among HPV-related penile tumours, HPV16 is the most common type detected, followed by HPV18 and HPV types 6/11 (*Miralles C et al. J Clin Pathol 2009;62:870-8*). Over 95% of invasive penile cancers are SCC and the most common penile SCC histologic sub-types are keratinising (49%), mixed warty-basaloid (17%), verrucous (8%), warty (6%), and basaloid (4%). HPV is commonly detected in basaloid and warty tumours but is less common in keratinising and verrucous tumours. In this section, the HPV burden among cases of penile cancer cases and precancerous penile lesions in San Marino are presented.

Table 24: Studies on HPV prevalence among penile cancer cases in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

95% CI: 95% Confidence Interval;

Data sources:

The ICO HPV Information Centre has updated data until June 2015. Reference publications (up to 2008): 1) Bouvard V, Lancet Oncol 2009;10:321 2) Miralles-Guri C, J Clin Pathol 2009;62:870

Table 25: Studies on HPV prevalence among PeIN 2/3 cases in San Marino

Study	HPV detection method and targeted Method	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
No Data Available	-	-	-	-	-

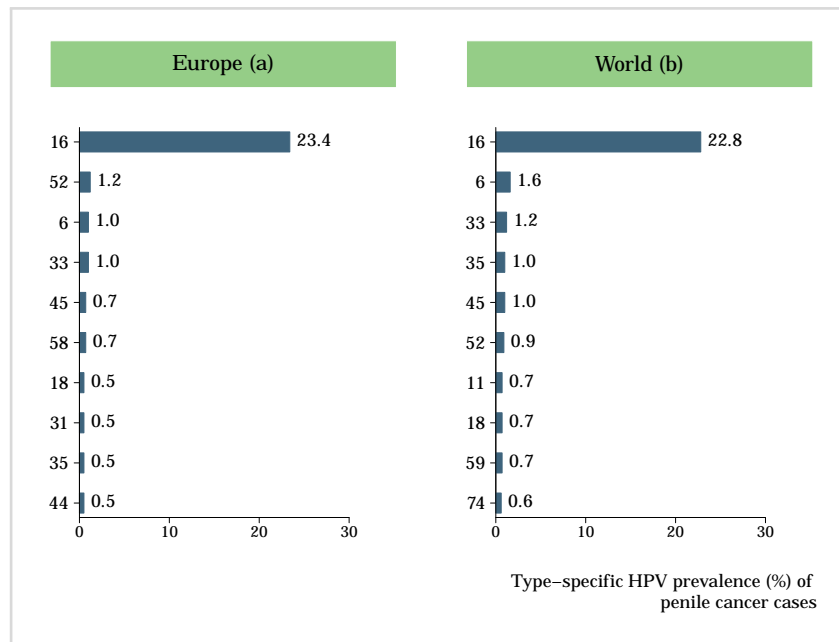
**Data updated on 17 Jul 2017 (data as of 30 Jun 2015).**

95% CI: 95% Confidence Interval; PeIN 2/3: Penile intraepithelial neoplasia of grade 2/3;

Data sources:

The ICO HPV Information Centre has updated data until June 2014. Reference publication (up to 2008): Bouvard V, Lancet Oncol 2009;10:321

Figure 39: Comparison of the ten most frequent HPV types in cases of penile cancer in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2015).

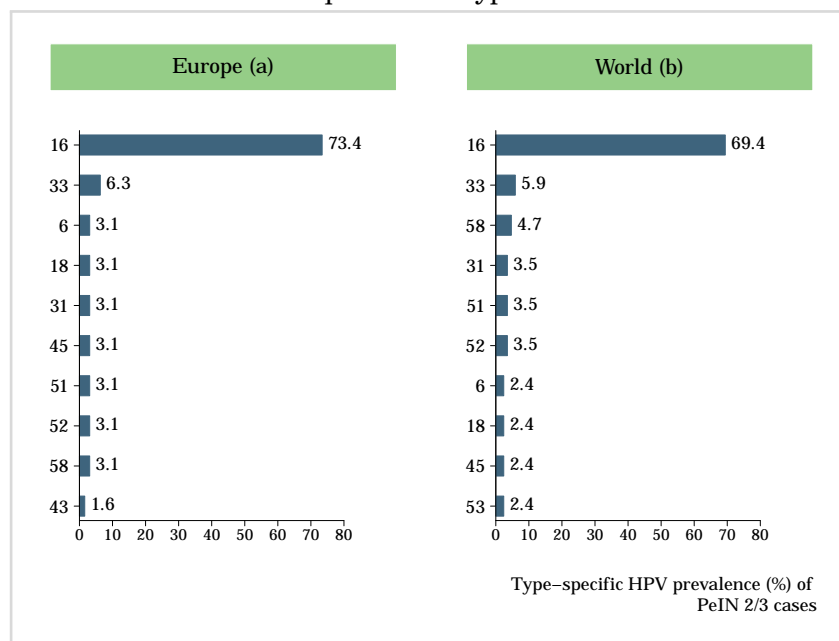
<sup>a</sup>Includes cases from Czech Republic, France, Greece, Poland, Portugal, Spain and United Kingdom

<sup>b</sup>Includes cases from Australia, Bangladesh, India, South Korea, Lebanon, Philippines, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Venezuela and United States, Mozambique, Nigeria, Senegal, Czech Republic, France, Greece, Poland, Portugal, Spain and United Kingdom.

Data sources:

Alemanly L, Eur Urol 2016; 69: 953

Figure 40: Comparison of the ten most frequent HPV types in PeIN 2/3 cases in Europe and the World



Data updated on 09 Feb 2017 (data as of 30 Jun 2015).

<sup>a</sup>Includes cases from Czech Republic, France, Greece, Poland, Portugal, Spain and United Kingdom

<sup>b</sup>Includes cases from Australia, Bangladesh, India, South Korea, Lebanon, Philippines, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Venezuela, Mozambique, Nigeria, Senegal, Czech Republic, France, Greece, Poland, Portugal, Spain and United Kingdom.

Data sources:

Alemanly L, Eur Urol 2016; 69: 953

### 4.3 HPV burden in men

The information to date regarding anogenital HPV infection is primarily derived from cross-sectional studies of selected populations such as general population, university students, military recruits, and studies that examined husbands of control women, as well as from prospective studies. Special subgroups include mainly studies that examined STD (sexually transmitted diseases) clinic attendees, MSM (men who have sex with men), HIV positive men, and partners of women with HPV lesions, CIN (cervical intraepithelial neoplasia), cervical cancer or cervical carcinoma in situ. Globally, prevalence of external genital HPV infection in men is higher than cervical HPV infection in women, but persistence is less likely. As with genital HPV prevalence, high numbers of sexual partners increase the acquisition of oncogenic HPV infections (Vaccine 2012, Vol. 30, Suppl 5). In this section, the HPV burden among men in San Marino is presented.

#### Methods

HPV burden in men was based on published systematic reviews and meta-analyses (Dunne EF, J Infect Dis 2006; 194: 1044, Smith JS, J Adolesc Health 2011; 48: 540, Olesen TB, Sex Transm Infect 2014; 90: 455, and Hebnes JB, J Sex Med 2014; 11: 2630) up to October 31, 2015. The search terms for the review were human papillomavirus, men, polymerase chain reaction (PCR), hybrid capture (HC), and viral DNA. References cited in selected articles were also investigated. Inclusion criteria were: HPV DNA detection by means of PCR or HC (ISH if data are not available for the country), and a detailed description of HPV DNA detection and genotyping techniques used. The number of cases tested and HPV positive cases were extracted for each study to estimate the anogenital prevalence of HPV DNA. Binomial 95% confidence intervals were calculated for each anogenital HPV prevalence.

Table 26: Studies on HPV prevalence among men in San Marino

Study	Anatomic sites samples	HPV detection method	Population	Age (years)	HPV prevalence		
					No	%	(95% CI)
No Data Available	-	-	-	-	-	-	--

Data updated on 17 Jul 2017 (data as of 31 Oct 2015).

95% CI: 95% Confidence Interval;

Data sources:

Based on published systematic reviews, the ICO HPV Information Centre has updated data until October 2015. Reference publications: 1) Dunne EF, J Infect Dis 2006; 194: 1044 2) Smith JS, J Adolesc Health 2011; 48: 540 3) Olesen TB, Sex Transm Infect 2014; 90: 455 4) Hebnes JB, J Sex Med 2014; 11: 2630.

Table 27: Studies on HPV prevalence among men from special subgroups in San Marino

Study	Anatomic sites samples	HPV detection method	Population	Age (years)	HPV prevalence		
					No	%	(95% CI)
No Data Available	-	-	-	-	-	-	--

Data updated on 17 Jul 2017 (data as of 31 Oct 2015).

95% CI: 95% Confidence Interval;

Data sources:

Based on published systematic reviews, the ICO HPV Information Centre has updated data until October 2015. Reference publications: 1) Dunne EF, J Infect Dis 2006; 194: 1044 2) Smith JS, J Adolesc Health 2011; 48: 540 3) Olesen TB, Sex Transm Infect 2014; 90: 455 4) Hebnes JB, J Sex Med 2014; 11: 2630.

## 4.4 HPV burden in the head and neck

The last evaluation of the International Agency for Research in Cancer (IARC) on the carcinogenicity of HPV in humans concluded that (a) there is enough evidence for the carcinogenicity of HPV type 16 in the oral cavity, oropharynx (including tonsil cancer, base of tongue cancer and other oropharyngeal cancer sites), and (b) limited evidence for laryngeal cancer (*IARC Monograph Vol 100B*). There is increasing evidence that HPV-related oropharyngeal cancers constitute an epidemiological, molecular and clinical distinct form as compared to non HPV-related ones. Some studies indicate that the most likely explanation for the origin of this distinct form of head and neck cancers associated with HPV is a sexually acquired oral HPV infection that is not cleared, persists and evolves into a neoplastic lesion. The most recent figures estimate that 25.6% of all oropharyngeal cancers are attributable to HPV infection with HPV16 being the most frequent type (*de Martel C. Lancet Oncol. 2012;13(6):607*). *In this section, the HPV burden in the head and neck in San Marino is presented..*

### 4.4.1 Burden of oral HPV infection in healthy population

Table 28: Studies on oral HPV prevalence among healthy in San Marino

Study	Method specimen collection and anatomic site	HPV detection method and targeted HPV types	Population	Age (years)	No. Tested	HPV prevalence		Prev. of 5 most frequent HPV types (%)
						%	(95% CI)	
<b>MEN</b>								
No Data Available	-	-	-	-	-	-	-	-
<b>WOMEN</b>								
No Data Available	-	-	-	-	-	-	-	-
<b>BOTH OR UNSPECIFIED</b>								
No Data Available	-	-	-	-	-	-	-	-

Data as of 29 feb. 2012. Only for European countries.

95% CI: 95% Confidence Interval;

Data sources:

Systematic review and meta-analysis was performed by ICO HPV Information Centre until July 2012. Pubmed was searched using the keywords oral and papillomavirus. Inclusion criteria: studies reporting oral HPV prevalence in healthy population in Europe; n > 50. Exclusion criteria: focused only in children or immunosuppressed population; not written in English; case-control studies; commentaries and systematic reviews and studies that did not use HPV DNA detection methods.

### 4.4.2 HPV burden in head and neck cancers

Table 29: Studies on HPV prevalence among cases of oral cavity cancer in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPV types (%)
			%	(95% CI)	
<b>MEN</b>					
No Data Available	-	-	-	-	-
<b>WOMEN</b>					
No Data Available	-	-	-	-	-
<b>BOTH OR UNSPECIFIED</b>					
No Data Available	-	-	-	-	-

Data as of 31 dic. 2015. Only for European countries.

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews and meta-analysis performed by ICO. Reference publications: 1) Ndiaye C, Lancet Oncol 2014; 15: 1319 2) Kreimer AR, Cancer Epidemiol Biomarkers Prev 2005; 14: 467

Table 30: Studies on HPV prevalence among cases of oropharyngeal cancer in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
<b>MEN</b>					
No Data Available	-	-	-	-	-
<b>WOMEN</b>					
No Data Available	-	-	-	-	-
<b>BOTH OR UNSPECIFIED</b>					
No Data Available	-	-	-	-	-

**Data as of 31 dic. 2015. Only for European countries.**

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews and meta-analysis performed by ICO. Reference publications: 1) Ndiaye C, Lancet Oncol 2014; 15: 1319 2) Kreimer AR, Cancer Epidemiol Biomarkers Prev 2005; 14: 467

Table 31: Studies on HPV prevalence among cases of hypopharyngeal or laryngeal cancer in San Marino

Study	HPV detection method and targeted HPV types	No. Tested	HPV prevalence		Prevalence of 5 most frequent HPVs HPV type (%)
			%	(95% CI)	
<b>MEN</b>					
No Data Available	-	-	-	-	-
<b>WOMEN</b>					
No Data Available	-	-	-	-	-
<b>BOTH OR UNSPECIFIED</b>					
No Data Available	-	-	-	-	-

**Data as of 31 dic. 2015. Only for European countries.**

95% CI: 95% Confidence Interval;

Data sources:

Based on systematic reviews and meta-analysis performed by ICO. Reference publications: 1) Ndiaye C, Lancet Oncol 2014; 15: 1319 2) Kreimer AR, Cancer Epidemiol Biomarkers Prev 2005; 14: 467



## 5 Factors contributing to cervical cancer

HPV is a necessary cause of cervical cancer, but it is not a sufficient cause. Other cofactors are necessary for progression from cervical HPV infection to cancer. Tobacco smoking, high parity, long-term hormonal contraceptive use, and co-infection with HIV have been identified as established cofactors. Co-infection with Chlamydia trachomatis and herpes simplex virus type-2, immunosuppression, and certain dietary deficiencies are other probable cofactors. Genetic and immunological host factors and viral factors other than type, such as variants of type, viral load and viral integration, are likely to be important but have not been clearly identified. (Muñoz N, Vaccine 2006; 24(S3): 1-10). In this section, the prevalence of smoking, parity (fertility), oral contraceptive use, and HIV in San Marino are presented.

Table 32: Factors contributing to cervical carcinogenesis (cofactors) in San Marino

INDICATOR <sup>a</sup>		MALE	FEMALE	TOTAL
<b>Smoking</b>				
Smoking of any tobacco adjusted prevalence (%) [95% CI]	Current <sup>1,b,c</sup>	-	-	-
	Daily <sup>1,b,d</sup>	-	-	-
Cigarette smoking adjusted prevalence (%) [95% CI]	Current <sup>1,b,c</sup>	-	-	-
	Daily <sup>1,b,d</sup>	-	-	-
<b>Parity</b>				
Total fertility rate per woman		-	-	-
	15-19 years	-	NA	-
Age-specific fertility rate (per 1000 women)	20-24 years	-	NA	-
	25-29 years	-	NA	-
	30-34 years	-	NA	-
	35-39 years	-	NA	-
	40-44 years	-	NA	-
	45-49 years	-	NA	-
<b>Hormonal contraception</b>				
Oral contraceptive use (%) among women who are married or in union <sup>2</sup>		-	-	-
Hormonal contraception use (%) (pill, injectable or implant), among women who are married or in union <sup>2,e</sup>		-	-	-
<b>HIV</b>				
Estimated percent of adults aged 15-49 who are living with HIV [low estimate - high estimate] <sup>3,f</sup>		-	-	-
Estimated percent of young adults aged 15-24 who are living with HIV [low estimate - high estimate] <sup>3,f</sup>		-	-	-
HIV prevalence (%) among female sex workers in the capital city <sup>3,g</sup>		-	-	-
HIV prevalence (%) among men who have sex with men in the capital city <sup>3</sup>		-	-	-
Estimated number of adults (15+ years) living with HIV [low estimate - high estimate] <sup>3,h</sup>		-	-	-
Estimated number of adults and children living with HIV [low estimate - high estimate] <sup>3,h</sup>		-	-	-
Estimated number of AIDS deaths in adults and children [low estimate - high estimate] <sup>3,i</sup>		-	-	-

### Data accessed on 22 Mar 2017.

<sup>a</sup>Please refer to original source for methods of estimation of the following indicators.

<sup>b</sup>Adjusted and age-standardized prevalence estimates of tobacco use by country, for the year 2013. These rates are constructed solely for the purpose of comparing tobacco use prevalence estimates across countries, and should not be used to estimate the number of smokers in the population.

<sup>c</sup>"Current" means smoking at the time of the survey, including daily and non-daily smoking. "Tobacco smoking" means smoking any form of tobacco, including cigarettes, cigars, pipes, hookah, shisha, water-pipe, etc. and excluding smokeless tobacco.

<sup>d</sup>"Daily" means smoking every day at the time of the survey. "Tobacco smoking" means smoking any form of tobacco, including cigarettes, cigars, pipes, hookah, shisha, water-pipe, etc. and excluding smokeless tobacco.

<sup>e</sup>Proportion (%) of women using hormonal contraception (pill, injectable or implant), among those of reproductive age who are married or in union.

<sup>f</sup>Estimates include all people with HIV infection, regardless of whether they have developed symptoms of AIDS.

<sup>g</sup>Data on key populations at higher risk from country progress reports typically derive from surveys in capital cities and are not representative of the entire country. In particular, surveys in capital cities are likely to overestimate national HIV prevalence and service coverage.

<sup>h</sup>The number of people with HIV infection, whether or not they have developed symptoms of AIDS, estimated to be alive at the end of a specific year.

<sup>i</sup>The estimated number of adults and children that have died due to HIV/AIDS in a specific year.

### Data sources:

<sup>1</sup>WHO report on the global tobacco epidemic, 2015: The MPOWER package. Geneva, World Health Organization, 2015. Available at [http://www.who.int/tobacco/global\\_report/2015/en/index.html](http://www.who.int/tobacco/global_report/2015/en/index.html)

<sup>2</sup>United Nations, Department of Economic and Social Affairs, Population Division (2016). World Contraceptive Use 2016 (POP/DB/CP/Rev2016). <http://www.un.org/en/development/desa/population/publications/dataset/contraception/wcu2016.shtml>. Available at: [Accessed on March 22, 2017].

<sup>3</sup>UNAIDS database [internet]. Available at: <http://aidsinfo.unaids.org/> [Accessed on March 22, 2017]

## 6 Sexual and reproductive health behaviour indicators

Sexual intercourse is the primary route of transmission of genital HPV infection. Information about sexual and reproductive health behaviours is essential to the design of effective preventive strategies against anogenital cancers. In this section, we describe sexual and reproductive health indicators that may be used as proxy measures of risk for HPV infection and anogenital cancers. Several studies have reported that earlier sexual debut is a risk factor for HPV infection, although the reason for this relationship is still unclear. In this section, information on sexual and reproductive health behaviour in San Marino are presented.

Table 33: Percentage of 15-year-olds who have had sexual intercourse in San Marino

Indicator	Male	Female
Percentage of 15-year-old subjects who report sexual intercourse	-	-

**Data accessed on 16 Mar 2017.**

Please refer to original source for methods of estimation

Table 34: Marriage patterns in San Marino

Indicator		Male	Female
Average age at first marriage <sup>1</sup>		33.5	30.7
Age-specific % of ever married <sup>2</sup>	15-19 years	0.0	0.0
	20-24 years	2.03	4.6
	25-29 years	15.5	31.3
	30-34 years	42.8	60.8
	35-39 years	63.6	74.5
	40-44 years	79.0	82.3
	45-49 years	85.9	87.4

**Data accessed on 16 Mar 2017.**

Year of estimate: 2014;

Please refer to original source for methods of estimation.

**Data sources:**

<sup>1</sup>The world bank: health nutrition and population statistics. Updated 16-Dec-2016. Accessed on March 16 2017. Available at <http://data.worldbank.org/data-catalog/health-nutrition-and-population-statistics>

<sup>2</sup>United Nations, Department of Economic and Social Affairs, Population Division (2015). World Marriage Data 2015 (POP/DB/Marr/Rev2015). Available at: <http://www.un.org/en/development/desa/population/theme/marriage-unions/WMD2015.shtml> Accessed on April 3, 2017.

## 7 HPV preventive strategies

It is established that well-organised cervical screening programmes or widespread good quality cytology can reduce cervical cancer incidence and mortality. The introduction of HPV vaccination could also effectively reduce the burden of cervical cancer in the coming decades. This section presents indicators on basic characteristics and performance of cervical cancer screening, status of HPV vaccine licensure and introduction in San Marino.

### 7.1 Cervical cancer screening practices

Screening strategies differ between countries. Some countries have population-based programmes, where in each round of screening women in the target population are individually identified and invited to attend screening. This type of programme can be implemented nationwide or only in specific regions of the country. In opportunistic screening, invitations depend on the individual's decision or on encounters with health-care providers. The most frequent method for cervical cancer screening is cytology, and there are alternative methods such as HPV DNA tests and visual inspection with acetic acid (VIA). VIA is an alternative to cytology-based screening in low-resource settings (the 'see and treat' approach). HPV DNA testing is being introduced into some countries as an adjunct to cytology screening ('co-testing') or as the primary screening test to be followed by a secondary, more specific test, such as cytology.

Table 35: Main characteristics of cervical cancer screening in San Marino

Availability of a cervical cancer screening programme <sup>α</sup>	Yes
Quality assurance structure and mandate to supervise and to monitor the screening process <sup>β</sup>	-
Active invitation to screening <sup>γ</sup>	Yes
Main screening test used for primary screening	Cytology/HPV test
Undergoing demonstration projects	
Screening ages (years)	25-30 (cytology), 30-65 (HPV test)
Screening interval or frequency of screenings	3 years (cytology), 5 years (HPV test)

#### Data accessed on 31 Dec 2016.

Screening program since 1968.

<sup>α</sup>Public national cervical cancer screening program in place (Cytology/VIA/HPV testing). Countries may have clinical guidelines or protocols, and cervical cancer screening services in a private sector but without a public national program. Publicly mandated programmes have a law, official regulation, decision, directive or recommendation that provides the public mandate to implement the programme with an authorised screening test, examination interval, target group and funding and co-payment determined.

<sup>β</sup>Self-reported quality assurance: Organised programmes provide for a national or regional team responsible for implementation and require providers to follow guidelines, rules, or standard operating procedures. They also define a quality assurance structure and mandate supervision and monitoring of the screening process. To evaluate impact, organised programmes also require ascertainment of the population disease burden. Quality assurance consists of the management and coordination of the programme throughout all levels of the screening process (invitation, testing, diagnosis and follow-up of screen-positives) to assure that the programme performs adequately and provides services that are effective and in-line with programme standards. The quality assurance structure is self-reported as part of the national cancer programs or plans.

<sup>γ</sup>Self-reported active invitation or recruitment, as organised population-based programmes, identify and personally invite each eligible person in the target population to attend a given round of screening.

#### Data sources:

Istituto per la Sicurezza Sociale. Screening prevenzione. Available at: <http://www.iss.sm/on-line/home/menudestra/screening-prevenzione.html>

Table 36: Estimated coverage of cervical cancer screening in San Marino

Reference <sup>1</sup>	Year	Population	Urban vs rural or both (all)	N Women	Age range	Within the last year(s)	Coverage (%) <sup>a</sup>
Health Plan 2015-2017 San Marino	2013	General female population	All	-	20-65	-	76

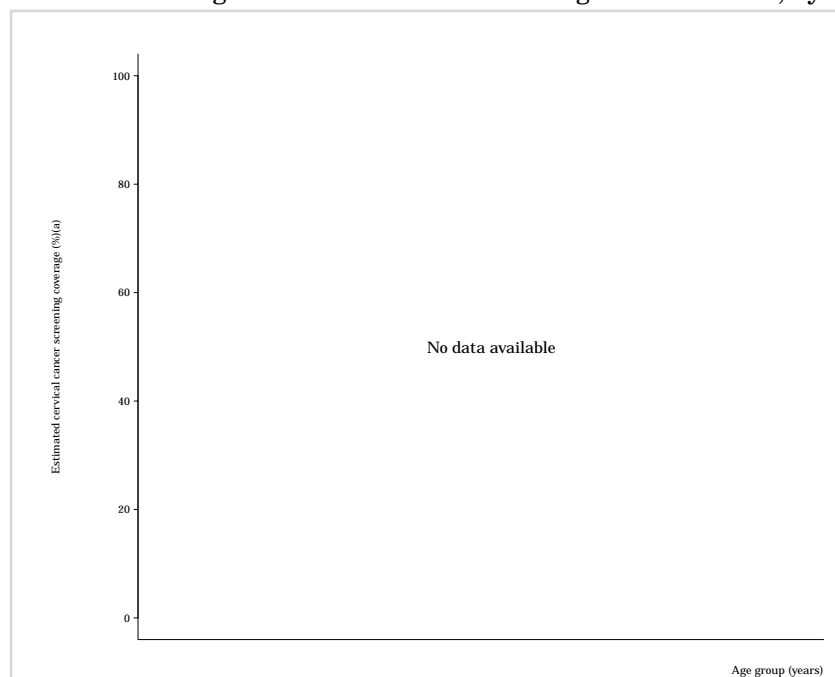
**Data accessed on 31 Dec 2016.**

<sup>a</sup>Proportion of women in the total sample of the mentioned age range in the country or region that reported having a Pap smear during a given time period (e.g., last year, last 2, 3, 5 years or ever).

**Data sources:**

<sup>1</sup>Segretaria di Stato per la Sanità e Sicurezza Sociale, Famiglia, Previdenza e Programmazione Economica; Authority per l'Autorizzazione, l'Accreditamento e la Qualità dei Servizi Sanitari, Socio-sanitari e Socio-educativi. Piano Sanitario e Socio-sanitario della Repubblica di San Marino 2015-2017 [Health Plan of the Republic of San Marino 2015-2017].

Figure 41: Estimated coverage of cervical cancer screening in San Marino, by age and study

**Data accessed on 31 Dec 2016.**

<sup>a</sup>Proportion of women in the total sample of the mentioned age range in the country or region that reported having a Pap smear during a given time period (e.g., last year, last 2, 3, 5 years or ever).

**Data sources:**

ICO Information Centre on HPV and Cancer. Country-specific references identified in each country-specific report as general recommendation from relevant scientific organizations and/or publications.

Table 37: Estimated coverage of cervical cancer screening in San Marino, by region

Region	N Women	Age range	LY <sup>a</sup>	Population	Coverage (%) <sup>b</sup>	Year(s) studied	Reference
-	-	-	-	-	-	-	-

**Data accessed on 31 Dec 2016.**

<sup>a</sup>LY: Within the last year(s).

<sup>b</sup>Proportion of women in the total sample of the mentioned age range in the country or region that reported having a Pap smear during a given time period (e.g., last year, last 2, 3, 5 years or ever).

## 7.2 HPV vaccination

Table 38: National HPV Immunization programme in San Marino

	Female	Male
Year of introduction	2008	-
Primary target age (years)	11	-
Organized catch-up age (years)	-	-
Opportunistic catch-up age (years)	-	-
Strategy	Health C.	-
Schedule <sup>a,b</sup>	3 doses standard	-

**Data updated on 11 Jul 2017 (data as of 31 Dec 2016)**

<sup>a</sup> 2 doses: 0-6m if not otherwise stated. Since 2014, based on clinical trials results several agencies responsible for the scientific evaluation of medicines, like the European Medicines Agency, approved a two-dose schedule for girls aged less than 15 or 14 depending on the vaccine (Cervarix or Gardasil).

<sup>b</sup> 3-doses standard: administration of three doses following the standard vaccination schedule as 0-2-6 months for the quadrivalent vaccine or 0-1-6 months for the bivalent vaccine.

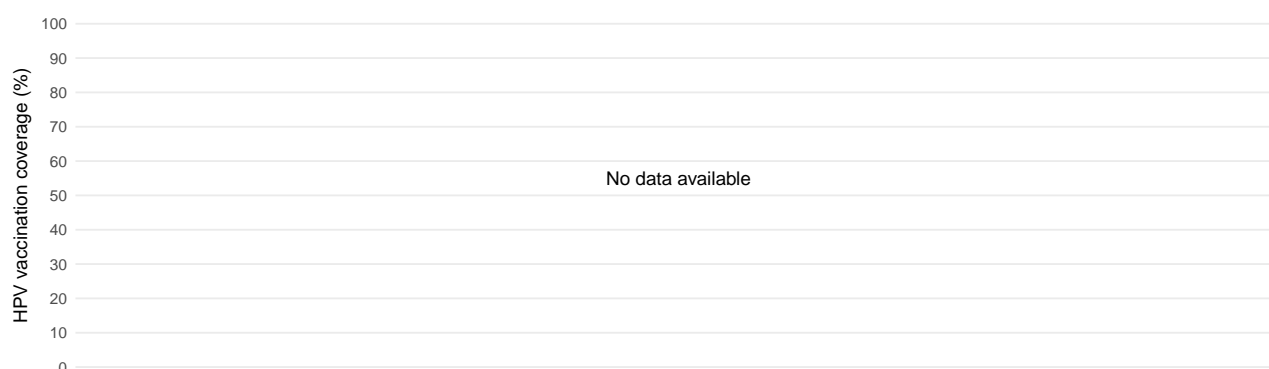
Data sources:

<sup>1</sup> Adapted from Bruni et al 2016 Lancet Global Health (data up to October 2014).

**Specifically, data from San Marino was extracted from:**

<sup>2</sup> Istituto Sicurezza Sociale Repubblica di San Marino. Vaccino contro l'HPV: San Marino si allinea all'Europa [Internet]. 2008. Available from: <http://www.iss.sm/on-line/home/notizie-dalla-sanita/articolo3000451.html?comeback=/on-line/home/artCatnotizie-dalla-sanita.3000175.1.10.2.1.html>

Figure 42: Reported HPV vaccination coverage in females by birth cohort in National HPV Immunization programme in San Marino



**Data updated on 11 Jul 2017 (data as of 31 Oct 2014)**

Data sources:

<sup>1</sup> Adapted from Bruni et al 2016 Lancet Global Health (data up to October 2014).

## 8 Protective factors for cervical cancer

Male circumcision and the use of condoms have shown a significant protective effect against HPV transmission.

Table 39: Prevalence of male circumcision in San Marino

Reference	Prevalence % (95% CI)	Methods
No Data Available	-	-

**Data accessed on 31 Aug 2015.**

95% CI: 95% Confidence Interval;

Please refer to country-specific reference(s) for full methodologies.

**Data sources:**

Based on systematic reviews and meta-analysis performed by ICO. The ICO HPV Information Centre has updated data until August 2015. Reference publication: Albero G, Sex Transm Dis. 2012 Feb;39(2):104-13.

Table 40: Prevalence of condom use in San Marino

Indicator	Year of estimate	Prevalence % <sup>a</sup>
Condom use	-	-

**Data accessed on 21 Mar 2017.**

Please refer to original source for methods of estimation.

<sup>a</sup> Condom use: Proportion of male partners who are using condoms with their female partners of reproductive age (15-49 years) to whom they are married or in union by country.**Data sources:**United Nations, Department of Economic and Social Affairs, Population Division (2016). World Contraceptive Use 2016 (POP/DB/CP/Rev2016). <http://www.un.org/en/development/desa/population/publications/dataset/contraception/wcu2016.shtml>. Available at: [Accessed on March 22, 2017].

## 9 Indicators related to immunisation practices other than HPV vaccines

This section presents data on immunisation coverage and practices for selected vaccines. This information will be relevant for assessing the country's capacity to introduce and implement the new HPV vaccines. The data are periodically updated and posted on the WHO Immunisation surveillance, assessment and monitoring website at [http://who.int/immunization\\_monitoring/en/](http://who.int/immunization_monitoring/en/).

### 9.1 Immunisation schedule

Table 41: General immunization schedule in San Marino

Vaccine	Schedule	Coverage <sup>a</sup>	Comment
Hexavalent diphtheria, tetanus toxoid with acellular pertussis, Hib, hepatitis B and IPV vaccine	2-3, 4-5, 11-12 months;	entire	-
Diphtheria and tetanus toxoid with acellular pertussis, and IPV vaccine	5-6 years;	entire	-
Human Papillomavirus vaccine	11 years;	entire	-
Influenza adult dose vaccine	-	entire	and adults with chronic illness, and health care workers
Influenza pediatric dose vaccine	-	entire	children with chronic diseases
Measles mumps and rubella vaccine	15 months; 9-10 years;	entire	-
Tetanus and diphtheria toxoid for older children / adults vaccine	15-16 years;	entire	-
Tetanus and diphtheria toxoids and acellular pertussis vaccine	7 years;	entire	-
Tetanus toxoid vaccine	18 years;	entire	-

Data accessed on 27 Jan 2017.

The schedules are the country official reported figures

<sup>a</sup>Entire:introduced in the entire country. Part:partially introduced.

Data sources:

Annual WHO/UNICEF Joint Reporting Form (Update of 2015/July/15). Geneva, Immunization, Vaccines and Biologicals (IVB), World Health Organization. Available at: [http://www.who.int/immunization/monitoring\\_surveillance/en/](http://www.who.int/immunization/monitoring_surveillance/en/)

### 9.2 Immunisation coverage estimates

Table 42: Immunization coverage estimates in San Marino

Indicator	Year of estimation	Coverage (%)
Third dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine	2015	76
Third dose of hepatitis B vaccine administered to infants	2015	75
Third dose of Haemophilus influenzae type B vaccine	2015	-
Measles-containing vaccine	2015	53
Third dose of polio vaccine	2015	76

Data accessed on 27 Jan 2017.

The coverage figures (%) are the country official reported figures. Immunization coverage levels are presented as a percentage of a target population that has been vaccinated.

Data sources:

Annual WHO/UNICEF Joint Reporting Form and WHO Regional offices reports (Update of 2015/July/16). Geneva, Immunization, Vaccines and Biologicals (IVB), World Health Organization. Available at: [http://www.who.int/immunization/monitoring\\_surveillance/en/](http://www.who.int/immunization/monitoring_surveillance/en/)

## 10 Glossary

Table 43: Glossary

Term	Definition
Incidence	Incidence is the number of new cases arising in a given period in a specified population. This information is collected routinely by cancer registries. It can be expressed as an absolute number of cases per year or as a rate per 100,000 persons per year (see Crude rate and ASR below). The rate provides an approximation of the average risk of developing a cancer.
Mortality	Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year.
Prevalence	The prevalence of a particular cancer can be defined as the number of persons in a defined population who have been diagnosed with that type of cancer, and who are still alive at the end of a given year, the survivors. Complete prevalence represents the number of persons alive at certain point in time who previously had a diagnosis of the disease, regardless of how long ago the diagnosis was, or if the patient is still under treatment or is considered cured. Partial prevalence, which limits the number of patients to those diagnosed during a fixed time in the past, is a particularly useful measure of cancer burden. Prevalence of cancers based on cases diagnosed within one, three and five years are presented as they are likely to be of relevance to the different stages of cancer therapy, namely, initial treatment (one year), clinical follow-up (three years) and cure (five years). Patients who are still alive five years after diagnosis are usually considered cured since the death rates of such patients are similar to those in the general population. There are exceptions, particularly breast cancer. Prevalence is presented for the adult population only (ages 15 and over), and is available both as numbers and as proportions per 100,000 persons.
Crude rate	Data on incidence or mortality are often presented as rates. For a specific tumour and population, a crude rate is calculated simply by dividing the number of new cancers or cancer deaths observed during a given time period by the corresponding number of person years in the population at risk. For cancer, the result is usually expressed as an annual rate per 100,000 persons at risk.
ASR (age-standardised rate)	An age-standardised rate (ASR) is a summary measure of the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer. The ASR is a weighted mean of the age-specific rates; the weights are taken from population distribution of the standard population. The most frequently used standard population is the World Standard Population. The calculated incidence or mortality rate is then called age-standardised incidence or mortality rate (world). It is also expressed per 100,000. The world standard population used in GLOBOCAN is as proposed by Segi [1] and modified by Doll and al. [2]. The age-standardised rate is calculated using 10 age-groups. The result may be slightly different from that computed using the same data categorised using the traditional 5 year age bands.
Cumulative risk	Cumulative incidence/mortality is the probability or risk of individuals getting/dying from the disease during a specified period. For cancer, it is expressed as the number of new born children (out of 100, or 1000) who would be expected to develop/die from a particular cancer before the age of 75 if they had the rates of cancer observed in the period in the absence of competing causes.
Cytologically normal women	No abnormal cells are observed on the surface of their cervix upon cytology.

(Continued)



Table 43 – Continued

<b>Term</b>	<b>Definition</b>
Cervical Intraepithelial Neoplasia (CIN) / Squamous Intraepithelial Lesions (SIL)	SIL and CIN are two commonly used terms to describe precancerous lesions or the abnormal growth of squamous cells observed in the cervix. SIL is an abnormal result derived from cervical cytological screening or Pap smear testing. CIN is a histological diagnosis made upon analysis of cervical tissue obtained by biopsy or surgical excision. The condition is graded as CIN 1, 2 or 3, according to the thickness of the abnormal epithelium (1/3, 2/3 or the entire thickness).
Low-grade cervical lesions (LSIL/CIN-1)	Low-grade cervical lesions are defined by early changes in size, shape, and number of ab-normal cells formed on the surface of the cervix and may be referred to as mild dysplasia, LSIL, or CIN-1.
High-grade cervical lesions (HSIL / CIN-2 / CIN-3 / CIS)	High-grade cervical lesions are defined by a large number of precancerous cells on the sur-face of the cervix that are distinctly different from normal cells. They have the potential to become cancerous cells and invade deeper tissues of the cervix. These lesions may be referred to as moderate or severe dysplasia, HSIL, CIN-2, CIN-3 or cervical carcinoma in situ (CIS).
Carcinoma in situ (CIS)	Preinvasive malignancy limited to the epithelium without invasion of the basement membrane. CIN 3 encompasses the squamous carcinoma in situ.
Invasive cervical cancer (ICC) / Cervical cancer	If the high-grade precancerous cells invade the basement membrane is called ICC. ICC stages range from stage I (cancer is in the cervix or uterus only) to stage IV (the cancer has spread to distant organs, such as the liver).
Invasive squamous cell carcinoma	Invasive carcinoma composed of cells resembling those of squamous epithelium
Adenocarcinoma	Invasive tumour with glandular and squamous elements intermingled.
Eastern Europe	References included in Belarus, Bulgaria, Czech Republic, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, and Ukraine.
Northern Europe	References included in Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, and United Kingdom of Great Britain and Northern Ireland.
Southern Europe	References included in Albania, Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Montenegro, Portugal, Serbia, Slovenia, Spain, The former Yugoslav Republic of Macedonia.
Western Europe	References included in Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Netherlands, and Switzerland.
Europe PREHDICT	References included in Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Turkey, Ukraine, and United Kingdom of Great Britain and Northern Ireland.

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### **Institut Català d'Oncologia (ICO), in alphabetic order**

Albero G, Barrionuevo-Rosas L, Bosch FX, Bruni L, de Sanjosé S, Gómez D, Mena M, Muñoz J, Serrano B.

**7th Framework Programme grant PREHDICT project:** health-economic modelling of PREvention strategies for Hpv-related Diseases in European CounTries. Coordinated by Drs. Johannes Berkhof and Chris Meijer at VUMC, Vereniging Voor Christelijk Hoger Onderwijs Wetenschappelijk Onderzoek En Patientenzorg, the Netherlands.

([http://cordis.europa.eu/projects/rcn/94423\\_en.html](http://cordis.europa.eu/projects/rcn/94423_en.html))

**7th Framework Programme grant HPV AHEAD project:** Role of human papillomavirus infection and other co-factors in the aetiology of head and neck cancer in India and Europe. Coordinated by Dr. Massimo Tommasino at IARC, International Agency of Research on Cancer, Lyon, France.

([http://cordis.europa.eu/project/rcn/100268\\_en.html](http://cordis.europa.eu/project/rcn/100268_en.html))

### **International Agency for Research on Cancer (IARC)**

## Note to the reader

Anyone who is aware of relevant published data that may not have been included in the present report is encouraged to contact the HPV Information Centre for potential contributions.

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