original article

Worldwide burden of cervical cancer in 2008

M. Arbyn[1,2,3]*, X. Castellsagué[3,4,5], S. de Sanjosé[3,4,5], L. Bruni[3,4,5], M. Saraiya[6], F. Bray[7] &
J. Ferlay[7]

[1]Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium; [2]European Cooperation on Development and Implementation of Cancer Screening and Prevention Guidelines, International Agency for Research on Cancer, Lyon, France; [3]Health-Economic Modelling of Prevention Strategies for HPV-Related Diseases in European Countries, Free University of Amsterdam, Amsterdam, The Netherlands; [4]Unit of Infections and Cancer, Catalonian Institute of Oncology, Barcelona; [5]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Barcelona, Spain; [6]Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, USA; [7]Section of Cancer Information, International Agency for Research on Cancer, Lyon, France

Background: The knowledge that persistent human papillomavirus infection is the main cause of cervical cancer has resulted in the development of assays that detect nucleic acids of the virus and prophylactic vaccines. Up-to-date and reliable data are needed to assess impact of existing preventive measures and to define priorities for the future.

Materials and methods: Best estimates on cervical cancer incidence and mortality are presented using recently compiled data from cancer and mortality registries for the year 2008.

Results: There were an estimated 530 000 cases of cervical cancer and 275 000 deaths from the disease in 2008. It is the third most common female cancer ranking after breast (1.38 million cases) and colorectal cancer (0.57 million cases). The incidence of cervical cancer varies widely among countries with world age-standardised rates ranging from <1 to >50 per 100 000. Cervical cancer is the leading cause of cancer-related death among women in Eastern, Western and Middle Africa; Central America; South-Central Asia and Melanesia. The highest incidence rate is observed in Guinea, with ~6.5% of women developing cervical cancer before the age of 75 years. India is the country with the highest disease frequency with 134 000 cases and 73 000 deaths. Cervical cancer, more than the other major cancers, affects women <45 years.

Conclusions: In spite of effective screening methods, cervical cancer continues to be a major public health problem. New methodologies of cervical cancer prevention should be made available and accessible for women of all countries through well-organised programmes.

Key words: cervical cancer, global estimates, HPV, human papillomavirus, incidence, mortality

introduction

At the turn of the millennium, cervical cancer ranked as the second most common cancer among women worldwide and in many low-income countries, it was the most common female cancer [1]. Compared with other cancers, screening for cervical cancer is the most effective [2]. However, cytology-based cervical cancer screening requires having an infrastructure, skilled human resources, and quality assurance in place [3]. Now that it is established that virtually all cases of cervical cancer follow from an infection by oncogenic human papillomavirus (HPV) types, screening opportunities using alternative HPV-based strategies give further hope to expanding and simplifying screening strategies, pending availability of low-cost tests [4, 5]. Additionally, there are two HPV vaccines available that can prevent human papillomavirus type 16 and human papillomavirus type 18 infections, which jointly cause 70%–75% of all cervical cancers and 40%–60% of its precursors [6, 7]. Currently, the countries with the highest

burden are not able to implement HPV vaccination due to its high costs [8, 9]. Now more than ever, effective cervical cancer control planning requires having access to the most accurate statistics. According to the World Health Organization (WHO), one of the fundamental steps in the action plan for non-communicable diseases is to establish a high-quality surveillance and monitoring system that should provide, as minimum standards, reliable population-based mortality statistics and standardised data on non-communicable diseases [10]. Using the 2008 estimates of the worldwide cancer burden compiled by the International Agency for Research on Cancer (IARC), Lyon, France, we describe the current patterns of incidence, mortality of cervical cancer alongside corresponding HPV prevalence data for a more comprehensive assessment of the global cervical cancer burden [11].

materials and methods

The estimated number of diagnosed cancers and deaths from cancer of the cervix uteri [International Classification of Diseases (ICD)-10 = C53] together with the female population data for 182 countries in the year 2008

Correspondence to: Dr M. Arbyn, Unit of Cancer Epidemiology, Scientific Institute of Public Health, J. Wytsmanstreet 14, B-1050 Brussels, Belgium. Tel: +32-2-642-50-21; Fax: +32-2-642-54-10; E-mail: marc.arbyn@wiv-isp.be

Table 1. Burden of cervical cancer incidence and mortality in 2008, aggregated for the whole world, more and less developed countries and by continent: female population size, world ASIR and ASMR; SIR and SMR; cumulative rate of developing cervical cancer (CIR) or dying from cervical cancer (CMR) before the age of 75 years; % of all female cancer cases or deaths originating from the cervix uteri and ranking of cervical cancer among all female cancer sites

Area	Total female population[a]	No. of cases	ASIR[b]	SIR	CIR (%)	% of all cancers	Rank (all ages)	Rank (15–44 years)	No. of deaths	ASMR[b]	SMR	CMR (%)	% of all cancers	Rank (all ages)	Rank (15–44 years)
World	3357	529 512	15.2	100	1.6	8.8	3	2	274 967	7.8	100	0.9	8.2	4	2
More developed countries	632	76 480	9.0	56	0.9	3.0	10	3	33 149	3.2	41	0.3	2.7	10	2
Developing countries	2724	453 032	17.7	116	1.9	13.1	2	2	241 818	9.7	125	1.1	11.4	2	2
Eastern Africa	156	31 482	34.5	207	3.9	14.9	1	1	21 625	25.3	308	3.1	11.3	1	2
Middle Africa	62	8209	23.0	140	2.5	22.0	2	2	5697	17.0	210	1.9	20.7	1	3
Northern Africa	102	5278	6.6	40	0.7	6.4	2	6	3101	4.0	49	0.5	5.6	4	8
Southern Africa	29	6500	26.8	167	3.0	16.9	2	1	3467	14.8	184	1.7	13.6	2	2
Western Africa	145	28 903	33.7	198	3.9	25.9	2	2	19 412	24.0	289	2.9	24.9	1	2
Caribbean	20	4592	20.8	141	2.1	13.0	2	1	2177	9.4	128	1.0	10.4	4	2
Central America	76	15 606	22.2	150	2.3	16.9	2	1	7631	11.1	147	1.2	13.7	1	1
South America	195	47 888	24.1	160	2.6	14.4	2	2	21 837	10.8	143	1.2	11.8	2	1
Northern America	175	12 488	5.7	35	0.5	1.6	13	4	4413	1.7	22	0.2	1.4	15	3
Eastern Asia	762	90 768	9.6	64	0.9	5.7	7	2	39 726	3.9	53	0.4	4.3	7	6
South-Eastern Asia	289	44 351	15.8	103	1.7	11.4	2	2	22 473	8.3	106	0.9	9.3	3	2
South-Central Asia	845	174 129	24.5	156	2.6	22.5	1	2	95 984	14.0	178	1.6	19.8	1	1
Western Asia	104	3454	4.2	26	0.5	3.8	9	6	1562	2.0	25	0.2	2.8	12	10
Eastern Europe	156	31 012	14.5	90	1.4	6.3	4	2	15 817	6.3	79	0.7	5.6	6	2
Northern Europe	50	5325	8.3	50	0.8	2.3	9	3	2085	2.4	33	0.2	1.8	16	3
Southern Europe	78	8645	8.0	50	0.8	2.7	10	3	3396	2.5	33	0.3	2.2	13	3
Western Europe	96	9318	6.9	43	0.7	2.0	14	4	3794	2.0	29	0.2	1.9	15	4
Australia/New Zealand	13	798	5.0	31	0.5	1.4	14	5	294	1.4	20	0.2	1.4	17	7
Melanesia	4	724	23.7	156	2.3	19.5	1	1	463	16.6	219	1.7	18.7	1	1
Micronesia/Polynesia	0.3	42	14.6	96	1.5	7.7	4	2	13	4.8	59	0.6	6.1	4	2

[a]In millions; [b]per 100 000.

ASIR, age-standardised incidence rate; ASMR, age-standardised mortality rate; SIR, standardised incidence ratio; SMR, standardised mortality ratio; CIR, cumulative incidence rate; CMR, cumulative mortality rate.

were extracted from the GLOBOCAN 2008 database, as published by the IARC [12, 13]. Data were aggregated by 5-year age groups, except for the youngest groups, which were collapsed into age groups comprising 0–14 and 15–39 years, and the oldest group comprising women of ≥75 years. In the current paper, the age groups 15–44 years were merged to assess occurrence of cervical cancer in young women. Data sources and methods of estimation have been described previously [1, 12] and are summarised below.

population data

Population data were derived from the Population Division of the United Nations (UN; http://www.un.org/) [14]. Countries were grouped into 21 subcontinents as defined by the UN, with the exception of Cyprus and Chinese Taipei (Taiwan), which were reallocated to Southern Europe and Eastern Asia, respectively. In this paper, Micronesia and Polynesia were aggregated to comprise one subcontinental region. More and less developed countries were distinguished with the former encompassing Europe, Northern America, Japan, Australia and New Zealand and the latter the remaining countries globally.

projection of rates to 2008

Rates for 2008 were estimated using (i) a linear regression when the available national incidence or mortality data covered 5–10 years with at least 50 cases per year or (ii) an age-period-cohort model for longer data series containing at least 100 cases per 5-year period. Otherwise, the most recent reported rates were accepted.

sources used for estimation of incidence rates

For incidence of cervical cancer, the following sources were used: (i) national cancer registries; (ii) national mortality data with estimation of incidence using regression models, specific for site and age, derived from sub-national or regional cancer registry data; (iii) regional incidence data from one or more cancer registries within the country together with some weighting proportions; (iv) frequency data, when only data on the relative frequency of different cancers (by sex, site and age groups) are available; the proportions are applied to estimates of the 'all cancers' incidence rates for the country, derived from cancer registry data in the same region; (v) in the absence of available data, observed or estimated rates from neighbouring countries in the same region were used.

sources used for estimation of mortality rates

The WHO mortality database (http://www.who.int/whosis/mort/download/en/) was used as a source for the numbers of deaths caused by cancer where available, with the figures adjusted for incomplete registration and corrected for ill-defined cause of deaths. Studying cervical cancer mortality is particularly difficult since the certified cause of death often does not indicate the anatomical origin [cervix (CVX) or corpus uteri (CRP)] with sufficient precision but rather is indicated as a death from uterine cancer. In GLOBOCAN 2008, it was assumed that the death certification 'uterus cancer not otherwise specified (NOS)' was allocated at random within age groups (i) and the corrected number of cervical cancer deaths was computed using the following reallocation rule: $corCVX_i = CVX_i + NOS_i \times CVX_i / (CVX_i + CRP_i)$ [15]. For a few countries with reliable national cancer registries and survival statistics, $corCVX_i$ was estimated from age-specific incidence and the 5-year relative survival probability.

In certain countries including China, locally available cause of death statistics were used to partition the overall cancer mortality as provided by WHO [12, 16].

For most developing countries, where no vital statistics were available, mortality/incidence ratios were applied to the estimated incidence (as
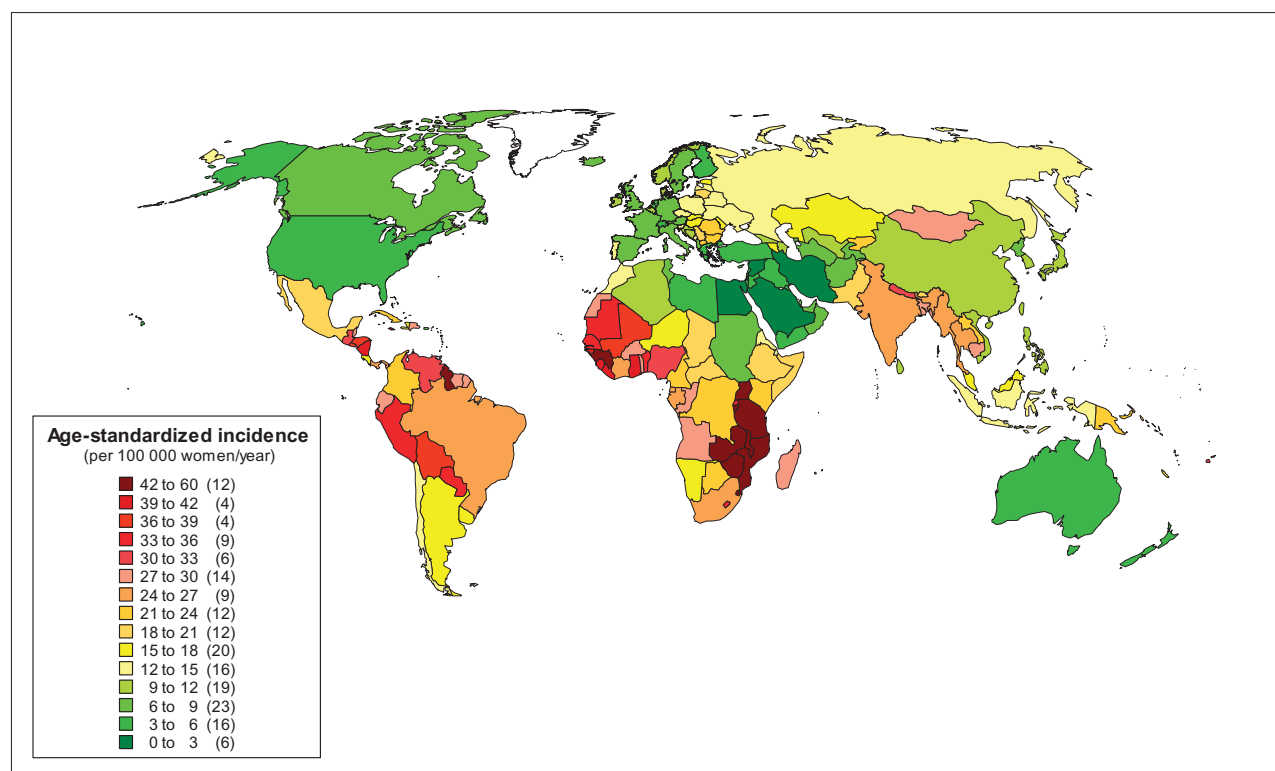

Figure 1. Geographic distribution of the world ASIR of cervical cancer, by country, estimated for 2008 (per 100 000 women-years). The counts in brackets in the legend correspond to the number of countries in each ASIR range. ASIR, age-standardised incidence rate.
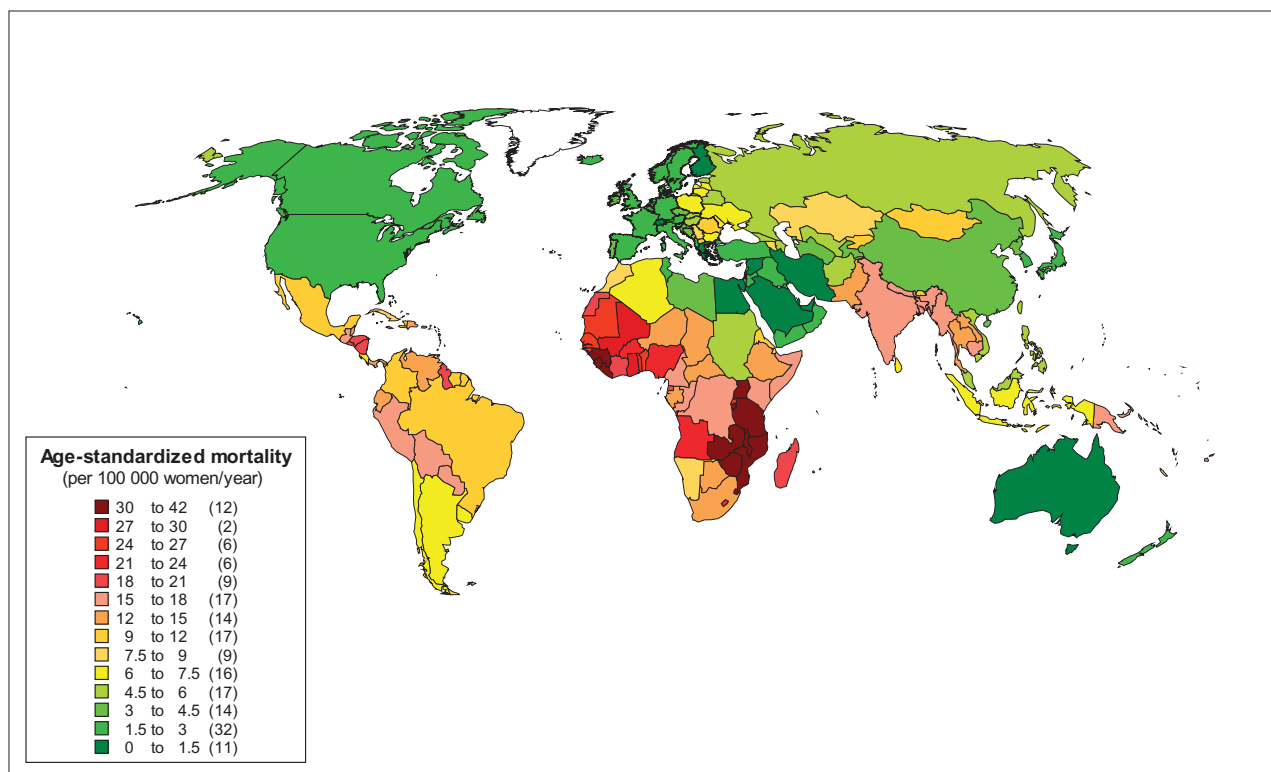
Figure 2. Geographic distribution of the world ASMR of cervical cancer, by country, estimated for 2008 (per 100 000 women-years). The counts in brackets in the legend correspond to the number of countries in each ASMR range. ASMR, age-standardised mortality rate.

described above), using survival probabilities from established registries extrapolated to other countries using gross domestic product [1, 17].

computed parameters

The numbers of cases of and deaths from cervical cancer were calculated by applying the estimated age- and country-specific rates for 2008 with the size of the corresponding population strata. The directly age-standardised incidence rate (ASIR) and age-standardised mortality rate (ASMR) were calculated using the world standard population as the reference [18]. The indirectly standardised incidence ratio (SIR) and standardised mortality ratio (SMR) were derived from the ratio of $\Sigma O_i / \Sigma E_i$, where O_i corresponds with the observed number of cases or deaths and E_i with their expected number, being the product of $a_{wi} \times N_{ci}$ [world age-specific rates × number of women in the corresponding age stratum (i) of each country (c)]. The cumulative rates were computed by summing the products of the age-specific rates (a_i) multiplied by the width of the corresponding age groups (ΔT_i) up to the age of 74 years (complete response=$\Sigma a_i \times \Delta T_i$) [19].

role of funding agencies

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

results

In 2008, an estimated 530 000 women developed cervical cancer and 275 000 women died of it, corresponding to standardised incidence and mortality rates of 15 and 8 per 100 000, respectively (see Table 1). Worldwide, cervical cancer was the third most common cancer ranking after breast (1.38 million cases) and colorectal cancer (0.57 million cases) and the fourth

most common cause of cancer death ranking below breast (458 000 deaths), lung (427 000 deaths) and colorectal cancer (288 000 deaths). Eighty-six percent of all cervical cancers and 88% of all deaths caused by cervical cancer occurred within developing countries. The ASIR and ASMR were 18 and 10 per 100 000, respectively, in developing countries and 9 and 3 per 100 000, respectively, in more developed countries. In developing countries, 1.9% of women developed cervical cancer and 1.1% died of the disease, before the age of 75 years, in the absence of competing causes of death. Correspondingly, in more developed countries, the respective cumulative rates of cervical cancer incidence and mortality of 0.9% and 0.3% were two to three times lower.

The variations in rates are more striking when the focus is on subcontinents. Overall, the lowest burden was noted in Australia/New Zealand (ASIR = 5.0/100 000 and ASMR = 1.4/100 000), Northern America (ASIR = 5.7/100 000 and ASMR = 1.7/100 000) and Western Europe (ASIR = 6.9/100 000 and ASMR = 2.0/100 000), whereas the highest burden was found in Eastern Africa (ASIR = 34.5/100 000 and ASMR = 25.3/100 000), Western Africa (ASIR = 33.7/100 000 and ASMR = 24.0/100 000), Southern Africa (ASIR = 26.8/100 000 and ASMR = 14.8/100 000), South-Central Asia (ASIR = 24.5/100 000 and ASMR = 14.0/100 000), South America (ASIR = 24.1/100 000 and ASMR = 10.8/100 000) and Melanesia (ASIR = 23.7/100 000 and ASMR = 16.6/100 000) (Table 1). Cervical cancer was the predominant cancer among women in Eastern Africa, South-Eastern Asia and Melanesia, whereas it was the most common cause of cancer death in
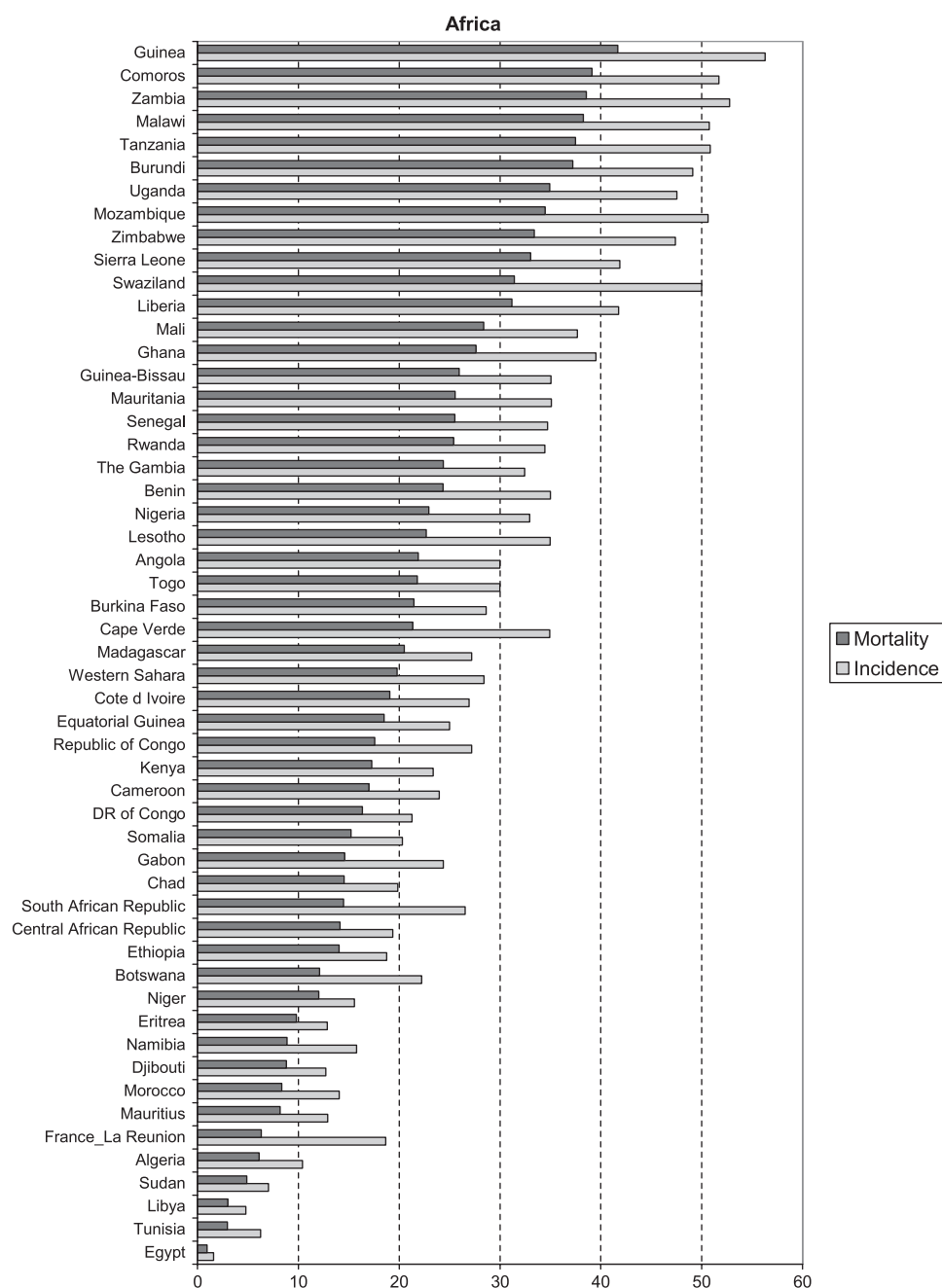
Figure 3. (A–E) World age-standardised rates of incidence of and mortality from cervical cancer (per 100 000 women-years) in 182 countries, estimates for 2008, ordered by continent and ranked by increasing mortality from bottom to top (direct standardisation using the world reference population). (A) Africa; (B) America; (C) Asia; (D) Europe; (E) Oceania.

Eastern, Middle and Western Africa; Central America; South-Central Asia and Melanesia.

Supplemental Table S1 (available at *Annals of Oncology* online) shows cervical cancer incidence and mortality statistics for 182 countries worldwide. The geographical distribution of the standardised incidence and mortality rates is displayed in Figures 1 and 2, respectively, using 15 categories of increasing rates in steps of 3 per 100 000, over a green–yellow–red–brown gradient. The lower ASMR categories in Figure 2 increase in steps of 1.5 per 100 000 to distinguish differences among

countries with lower burden and to allow comparisons with earlier publications [20, 21]. The standardised incidence and mortality rates are also shown in bar charts by continent and ranked according to ASMR in Figure 3A–E. The highest incidence rates (ASIR > 43/100 000) are all found in Eastern, Southern or Western Africa [Guinea (ASMR = 56/100 000)]; Zambia (53/100 000); Comoros (52/100 000); Tanzania (51/100 000); Malawi (51/100 000); Mozambique (51/100 000); Swaziland (50/100 000); Burundi (49/100 000); Uganda (48/100 000); Zimbabwe (47/100 000); the Caribbean [Jamaica
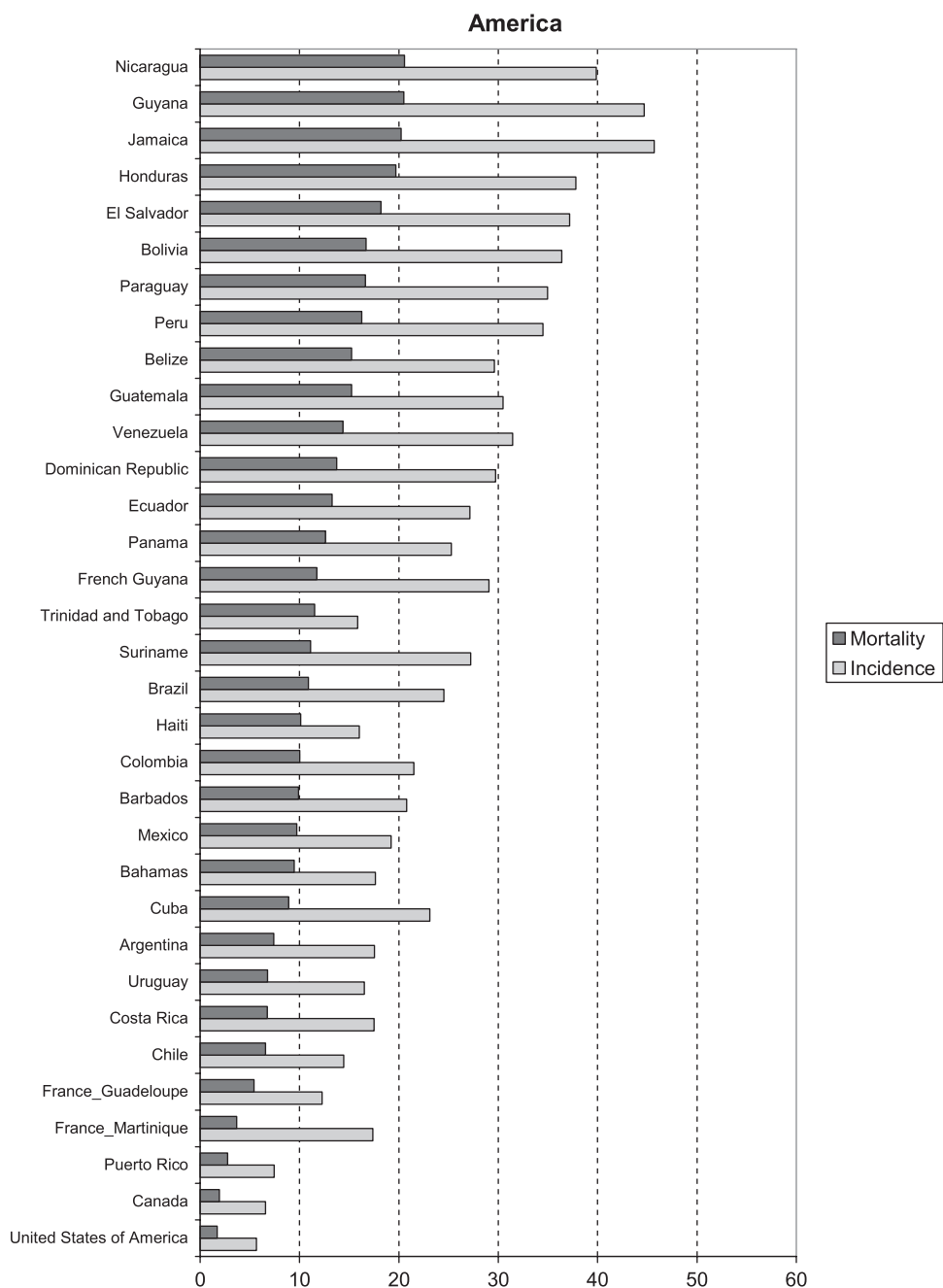
Figure 3B.

(46/100 000)] or South America [Guyana (45/100 000)]. India is the country with the highest number of cases (134 000) and deaths (73 000 deaths), representing one-quarter of the cervix cancer burden globally.

The lowest ASIR values (<5/100 000, dark green in Figure 1) were observed in nine countries in Western or South-Central Asia [Gaza and West Bank (ASIR < 1), Syrian Arab Republic (2.0/100 000), Saudi Arabia (2.1/100 000), Islamic Republic of Iran (2.2/100 000), Yemen (3.0/100 000), Iraq (3.1/100 000), Jordan (3.6/100 000), Lebanon (3.8/100 000), Turkey (4.2/100 000)], two countries in North Africa [Egypt (1.6/100 000) and Libya (4.8/100 000)], three countries in Southern Europe

[Malta (2.1/100 000), Greece (3.8/100 000), and Cyprus (4.5/100 000)], and further in Finland (3.7/100 000), Switzerland (4.0/100 000) and Australia (4.9/100 000). The ASMR was highly correlated with ASIR (Pearson's correlation coefficient $\rho = 0.95$) resulting in a very similar geographic distribution (Figure 2). However, the range of variation was wider for mortality (SMR ranging from 3 to 514) than for incidence (SIR ranging from 3 to 344). This can be attributed to lower survival [approximated by the compliment of the mortality/incidence ratio $(1 - M/I)$] in countries with higher incidence [Pearson's correlation coefficient $(\rho) = -0.49$].
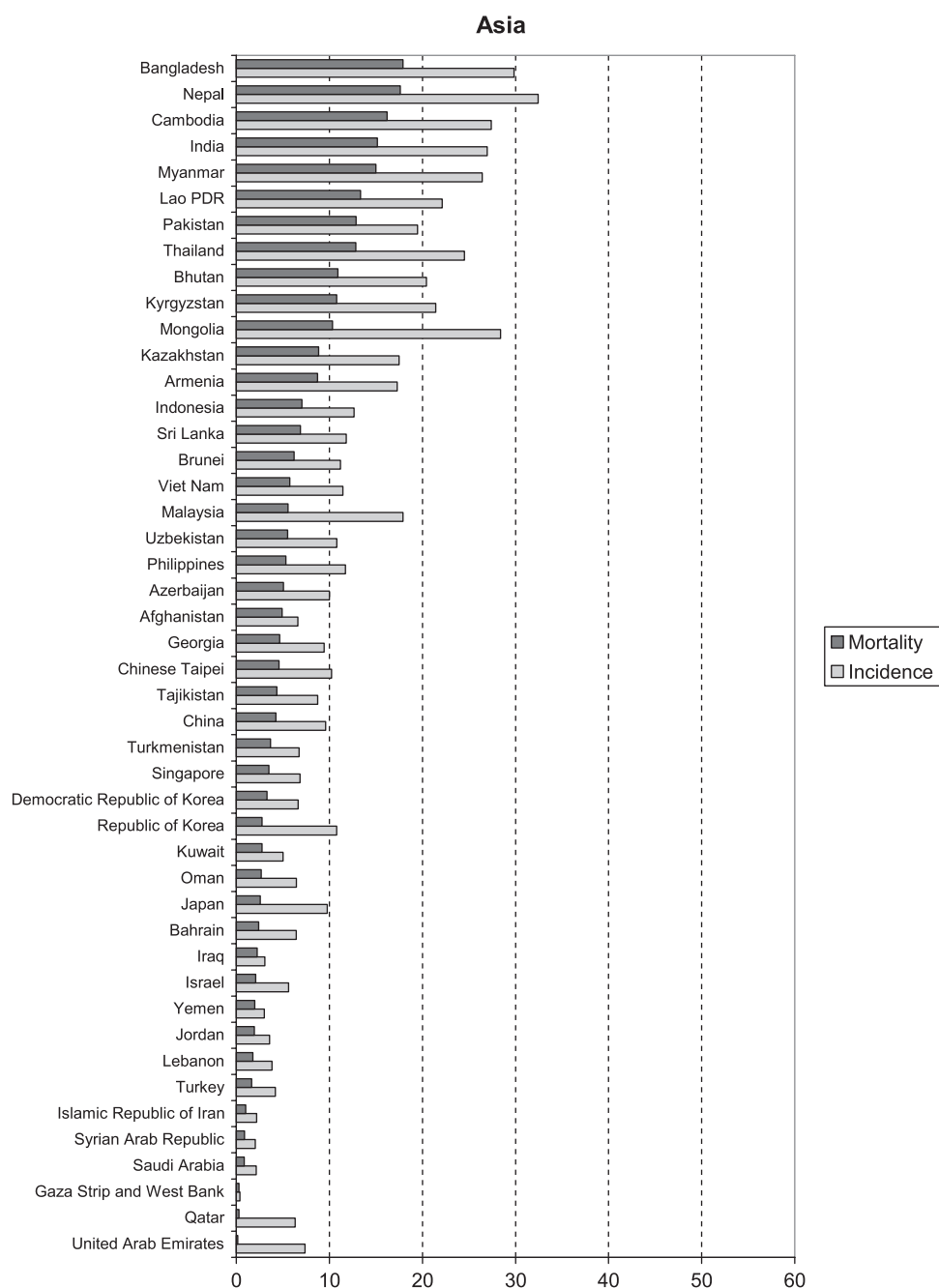
Figure 3C.

Figure 4 displays the ranking that cervical cancer takes in each country among all female cancer sites, in terms of number of cases and deaths, for all ages and young women (aged 15–44 years), respectively. In 61% and 53% of all countries, cervical cancer was noted among the three most frequent cancers or causes of cancer deaths in females of all ages. However, in young women, these percentages were, respectively, 85% and 75%.

discussion

With more than half a million new cases and 275 000 deaths per year, cervical cancer continues to constitute a major public health problem, respectively ranking as the third and the fourth most common cause of cancer incidence and mortality in women worldwide. Moreover, on the basis of the age-standardised rates, cervical cancer ranks second after breast cancer in terms of incidence (ASIR = 39.0, 15.2 and 14.6/100 000 for breast, cervix uteri and colorectal cancers, respectively) and third place for mortality (ASMR = 12.5, 11.0 and 7.8/100 000 for breast, lung and cervix uteri cancers, respectively). This partly relates to the fact that cervical cancer occurs at a relatively young age, resulting in proportionally more life-years lost, compared with other major cancers [22]. Age-specific analyses clearly indicate that cervical cancer
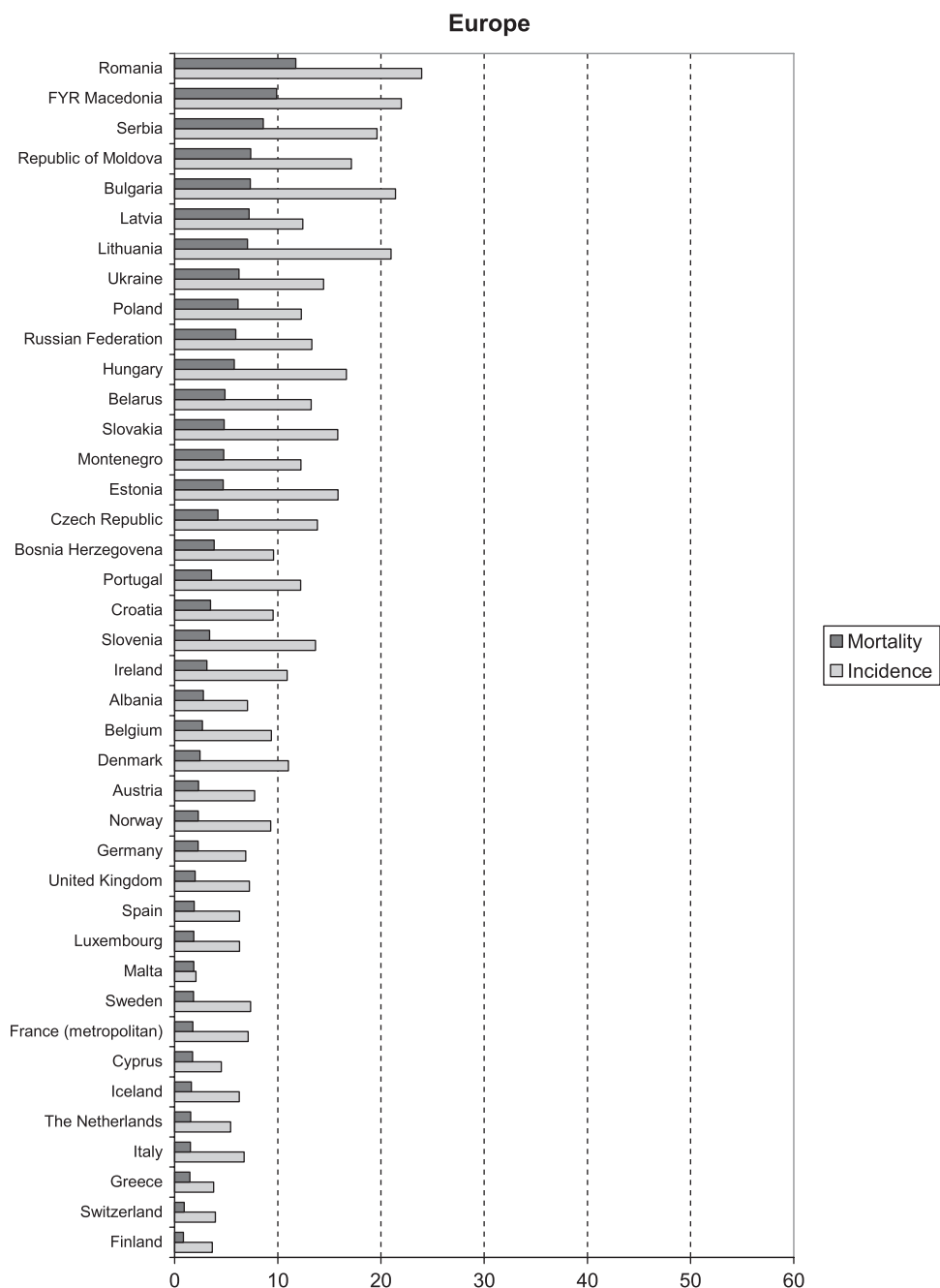
Europe

Figure 3D.

primarily affects young adult women who are actively involved in their careers or caring for their families.

Wide variations exist between high- and low-burden countries, with incidence rates ranging from <3 to >50 per 100 000. These contrasts are believed to reflect both differences in exposure to risk factors and protection from screening. Sexually transmitted infection with high-risk HPV types is the main etiological factor for cervical cancer [23, 24]. Recently, international data were pooled from studies that had assessed HPV prevalence in >1 million women with a normal cervical cytology result. The scatter plot (Figure 5) clearly shows the

positive correlation between the HPV prevalence and the ASIR by subcontinent (ρ = 0.68) [25]. The increased frequency of other cofactors such as smoking, oral contraception, and certain sexually transmittable infections [human immunodeficiency virus (HIV) and *Chlamydia trachomatis*] may have contributed as well to the recent rise in cervical cancer incidence among young cohorts [26–30].

The deeply green-coloured countries (in Western Asia and the Mediterranean zone) correspond with low prevalence of HPV, most plausibly explained by societal disapproval of extramarital sexual contacts [31]. On the contrary, the high-risk
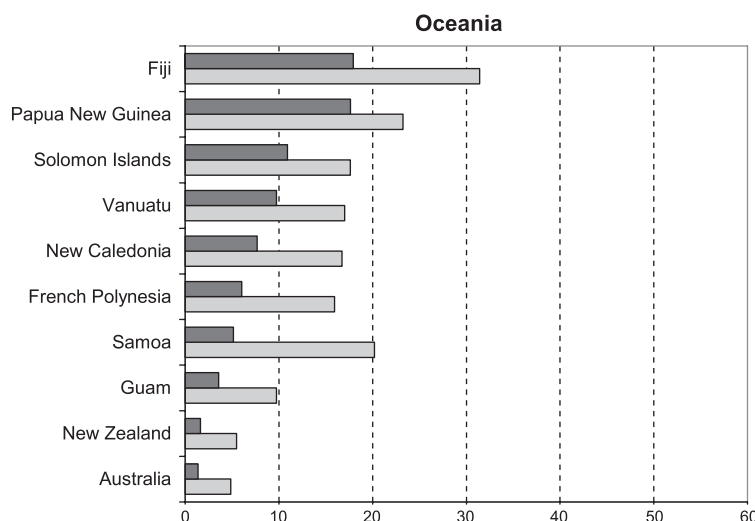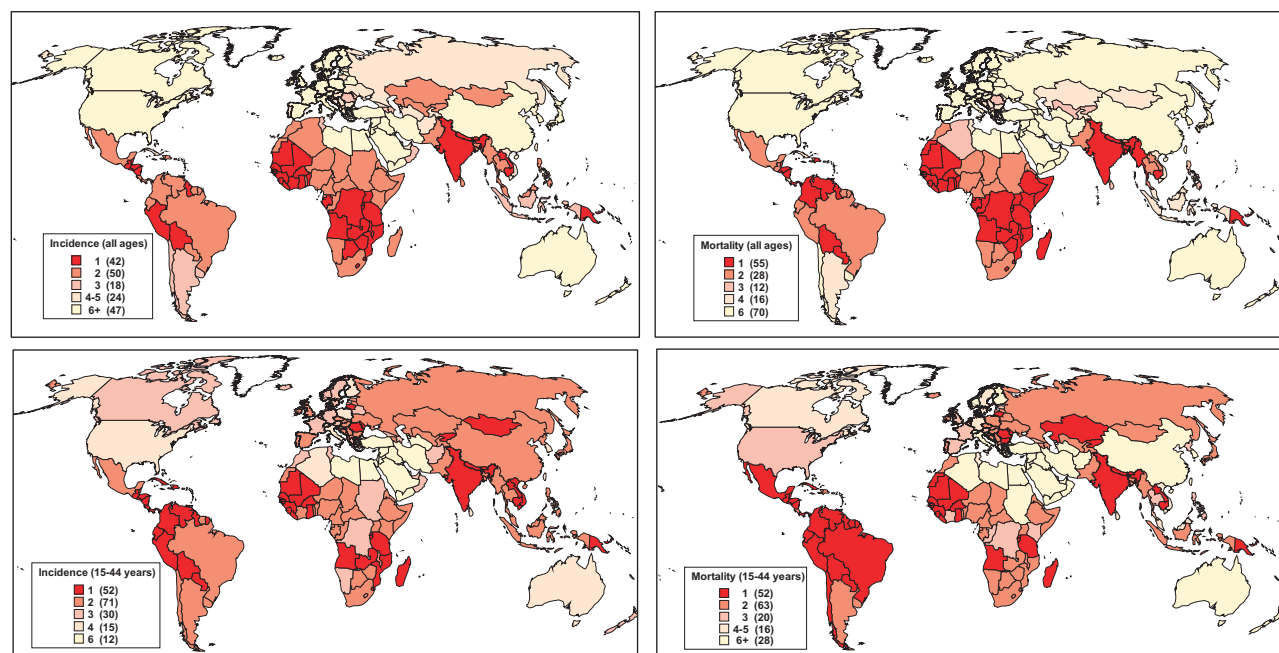
Figure 3E.

Figure 4. Rank of cervical cancer incidence (left) or mortality (right) among all female cancer sites for all ages (top) or for young women aged 14–44 years (bottom).

areas in sub-Saharan Africa, Latin America and South Asia likely reflect an elevated background risk explained by high rates of HPV and HIV transmission [32]. The low rates of cervical cancer observed in North America, Northern and Western Europe, Australia and New Zealand are probably the result of successful cytological screening [15, 33–37]. Along with established screening programmes, a number of these countries have observed an increased exposure to risk factors among generations born after 1940, as can be discerned from age-cohort-period analyses [35] or from HPV prevalence surveys in archived bio-specimens [38]. Where screening coverage is low or of poor quality, these cohort effects result in rising or stable trends, as observed in Ireland, as well as in several East-European countries, where the burden of cervical cancer is the highest on the European continent [39, 40].

data quality

The GLOBOCAN 2008 estimations are considered the best possible given the data available at the present time; but they should of course be interpreted with some caution since their reliability is determined by the quality and completeness of cancer incidence and death registrations, as well as the appropriateness of external data used to derive unavailable data [12]. In particular, the proportion of deaths from uterine cancer without specification of exact topographic origin compromises the accuracy of cause of death certification. Figure 6 reveals that countries with extreme burden often coincide with areas where local data are either sparse or unavailable (mainly in Africa). Nevertheless, independently obtained HPV prevalence data seem to corroborate roughly the estimates of incidence and mortality [25].

recent breakthroughs

A major breakthrough in cervical cancer control was the development of an effective prophylactic vaccine against the two main carcinogenic HPV types [41–43]. However, very high costs precluded the introduction of HPV vaccination in developing countries. Another landmark finding was the demonstration, in a large randomised study conducted in India, that screening with a high-risk HPV DNA assay once in a lifetime results in a reduction of the incidence of advanced cervical cancer as well as the cause-specific mortality by about

Figure 5. Age-standardised incidence (computed using the world reference population) of cervical cancer as a function of the weighted prevalence (in %) of high-risk HPV infection in women with a normal Pap smear, by continent. Prevalence of hrHPV estimates derived from Bruni et al. [25]. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; EAf, Eastern Africa; NAf, Northern Africa; SAf, Southern Africa; CAm, Central America; Car, Carribean; NAm, Northern America; SAm, Southern America; EAs, Eastern Asia; SCAs, South-Central Asia; SEAs, South-Eastern Asia; WAs, Western Asia; EEu, Eastern Europe; NEu, Northern Europe; SEu: Southern Europe; WEu, Western Europe).

one-half [44]. In Europe, four randomised trials consistently showed, in the second screening round, a significant reduction of CIN3+ (cervical intraepithelial neoplasia of grade III or worse) by screening with a validated HPV assay compared with cytology [45], and one trial showed even a significant reduction in the cumulative incidence of invasive cervical cancer [46]. In China, a rapid and low-cost HPV assay, easily applicable in field conditions, demonstrated an accuracy for cancer precursors that was similar to the clinically validated Hybrid Capture-2 assay (Qiagen, Hilden, Germany) [4]. These findings should now be translated into effective prevention strategies, applicable in developing countries [47]. These include one or two HPV tests, in a lifetime followed by visual inspection and cryotherapy of eligible lesions among HPV-positive women for generations already sexually active and completed with immunisation of young girls with an affordable prophylactic HPV vaccine [48]. Many of these interventions are being introduced in Africa, a continent with a low number of cancer registries. If these major breakthroughs are successfully implemented, careful thought and consideration should be given to the investment in adequate monitoring systems and developing cancer registries in target areas to measure the impact on incidence and mortality of cervical cancer [49].
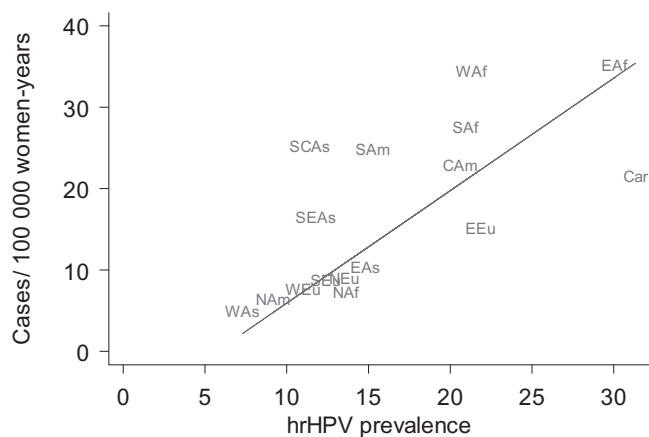
conclusions

Cervical cancer continues to be a major public health problem that kills approximately a quarter of million women every year and affects developing countries and young women in particular. New effective preventive strategies are currently available that offer the potential to reduce the morbidity and mortality from this cancer in low- and medium-, as well as high-income countries.

Surveillance, including high-quality cancer registries, linked to screening and vaccination registries is essential to
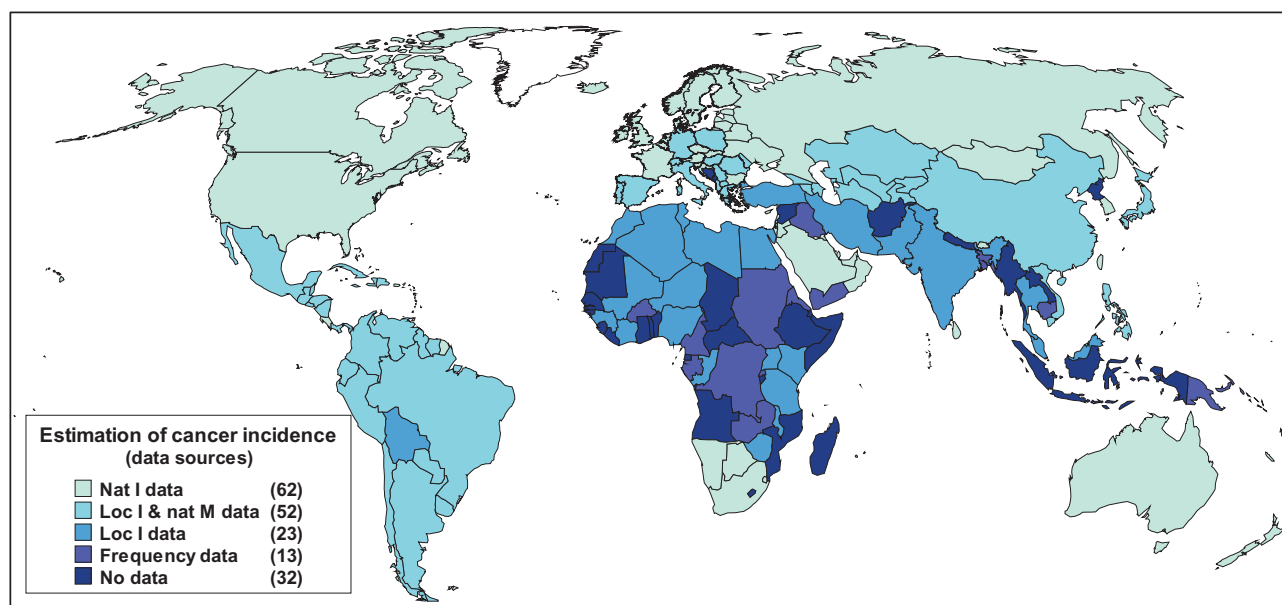
Figure 6. Availability of data per country to estimate cervical cancer incidence. Nat I, national incidence; Nat M, national mortality; Loc I, local incidence; loc M, local mortality.

track the impact of these prevention strategies and to provide the foundation for advocacy, national policy and global action.

disclosure

MA had membership in the Belgian advisory board up to 2008 [Cervarix and Cervarix, produced by Glaxo-Smith-Kline (GSK)], Eurogin Conference, Monaco 2010 (subscription and travel costs were sponsored by organisers); XC provided consultancy in GSK and SPMSD (Sanofi-Pasteur/Merck, Sharpe & Dome); SdS received travel support from SPMSD and Qiagen; LB received travel support from SPMSD and GSK. The authors MS, FB, and JF declare no conflict of interests.

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