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Variations in the age-specific curves of human papillomavirus prevalence in women worldwide

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An inverse relationship between age and human papillomavirus (HPV) prevalence has been reported in many developed countries, but information on this relationship is scarce in many other parts of the world. We carried out a cross-sectional study of sexually active women from the general population of 15 areas in 4 continents. Similar standardised protocols for women's enrolment, cervical specimen collection and PCR-based assays for HPV testing were used. HPV prevalence in different age groups was compared by study area. 18,498 women aged 15–74 years were included. Age-standardised HPV prevalence varied more than 10-fold between populations, as did the shape of age-specific curves. HPV prevalence peaked below age 25 or 35, and declined with age in Italy, the Netherlands, Spain, Argentina, Korea and in Lampang, Thailand and Ho Chi Minh, Vietnam. This was not the case in Songkla, Thailand nor Hanoi, Vietnam, where HPV prevalence was low in all age groups. In Chile, Colombia and Mexico, a second peak of HPV prevalence was detected among older women. In the poorest study areas in Asia (Shanxi, China and Dindigul, India), and in Nigeria, HPV prevalence was high across all age groups. The substantial differences observed in age-specific curves of HPV prevalence between populations may have a variety of explanations. These differences, however, underline that great caution should be used in inferring the natural history of HPV from age-specific prevalences.

Key words: human papillomavirus; prevalence; age-specific curves; sexual habits

Studies of cervical human papillomavirus (HPV) infection in large series of women without cervical cancer, predominantly from North America[1–3] and Northern Europe[4,5] showed marked declines in prevalence with age, with a nearly 10-fold higher HPV prevalence in women younger than 25 years compared with those 45 years or older. Young women who had recently become sexually active, again from North America and Northern Europe, showed a very high cumulative incidence of HPV infection (*e.g.*, approximately 50% in 3 years[6,7]). Hence, it was suggested that the vast majority of HPV infections were acquired in the first few years after sexual debut and that HPV prevalence steadily declined thereafter on account of spontaneous clearance of prevalent infection,[8] with little acquisition of new ones in middle age.[3]

However, a few studies, notably 2 cohort studies from Costa Rica and Colombia, showed a second peak in HPV prevalence[9–11] and, to a lesser extent, HPV incidence[12,13] in women 55 years or older. This raised the possibility that the age distribution of HPV infection may vary from one population to another.

In the present study, we aimed to use the findings of the International Agency for Research on Cancer (IARC) HPV Prevalence Surveys[14] to compare HPV prevalence by age in representative samples of women from 15 areas in Latin America, Europe, Asia and sub-Saharan Africa.

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Material and methods

Study participants

Similar protocols were developed for each of 13 areas in 11 countries, chosen to represent regions of low, intermediate and high incidence of cervical cancer. Complete population-sampling methods of participating women have been previously described for the individual areas: Spain, Barcelona[15]; Argentina, Concordia[16]; Chile, Santiago[17]; Colombia, Bogota[10]; Mexico, Morelos[18]; Korea, Busan[19]; Thailand, Lampang and Songkla[20]; Vietnam, Hanoi and Ho Chi Minh[21]; China, Shanxi[22]; India, Dindigul[23] and Nigeria, Ibadan.[24] Surveys were carried out between 1993 (Colombia) and 2004 (China).

Briefly, in each area attempts were made to obtain a population-based, age-stratified random sample that included at least 100 women in each 5-year age group from 15–19, to 55 years and older, or 65 years and older. Participation ranged from 48% to 70% in Spain, Argentina, Korea, Thailand, Songkla, China and Nigeria; 70%–90% in Chile; Thailand, Lampang, Vietnam, Ho Chi Minh and India; and >90% in Colombia, Mexico and Vietnam, Hanoi. The main cause for lack of participation was not women's refusal, but the impossibility of finding women due to inaccuracies in the population lists available, which were not completely up-to-date in many areas. More women in the youngest and oldest age groups refused to undergo gynaecological examination than middle-aged women, and so were under-represented in most areas. To compensate for the relative lack of information on women below age 25, an additional source was used for the recruitment of young women in Colombia (adolescent contraceptive counselling clinic[10]).

To expand the information on Europe, in 2 additional areas (*i.e.*, Italy, Turin[25] and the Netherlands, Amsterdam[26]) exfoliated cervical cells were derived from cytological samples collected within the framework of 2 high-quality organised screening programmes (*i.e.*, programmes with active call/recall of eligible women and high compliance[25,26]). As a consequence of age groups targeted by organised screening programmes, women below the age of 25 years were either absent (Italy[25]) or under-represented (the Netherlands[26]).

Very few women who reported being a virgin underwent gynaecological examination; therefore the following analyses were restricted to women who reported being sexually active. Only 8.7% of women had never been married, the percent being lowest (0.1%) in Asian substudies. Other exclusion criteria were pregnancy at the time of recruitment, previous hysterectomy or cervical conisation, and mental or physical incompetence. Very few women reported a history of cervical conisation on account of lack, or low intensity, of screening in most study areas. All participants were interviewed about their lifestyle, reproductive history and, except for Italy and the Netherlands, sexual habits, and they signed informed consent forms according to the recommendations of the IARC and local ethical review committees, which approved the study.

On the basis of population density and predominant activities, most study areas can be considered urban or peri-urban except those in China and India, which were rural areas. Study areas varied greatly in respect to socioeconomic level, and per capita income in 2000 for the 15 studied countries was derived from the World Bank website (www.worldbank.org).

Procedures

Study participants underwent a pelvic examination performed by a gynaecologist or trained nurse. In all areas, samples of exfoliated cells were collected from the ectocervix using 2 wooden Ayre spatulas, and from the endocervix with one or more cytobrushes. After preparation of a conventional cytology specimen, spatulas and brushes were placed in buffer and stored on ice. Cells were spun in a vortex and subsequently centrifuged at 3,000*g* for 10 min. Resulting cell pellets were diluted in buffer and frozen between −20°C and −80°C until they were shipped to IARC in dry ice. Cervical cells were stored in cytoRich (Tripath Imaging, Burlington, NC, USA) medium in Italy and China, and in preservCyt (Cytyc Corporation, Boxborough, MA, USA) medium in India. Liquid-based cytology was performed in Italy, China and India.

Conventional or liquid-based cytology smears were stained and read by local cytopathologists and classified according to the Bethesda[27] or equivalent system. All analyses in the present study included women with or without cervical abnormalities.

Cervical specimens were screened by PCR with β-globin gene-specific primers, and β-globin-negative samples were excluded from all analyses. A first screening was done to determine the overall presence of HPV DNA using a general primer GP5+/6+-mediated PCR.[26] HPV positivity was assessed by enzyme immunoassay (EIA) with an HPV oligoprobe cocktail to detect the following 36 HPV types: HPV6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 66, 68, 70, 71 (equivalent to CP8061), 72, 73 (equivalent to MM9), 81 (equivalent to CP8304), 82 (IS39 and MM4 subtypes), 83 (equivalent to MM7), 84 (equivalent to MM8) and cand89 (equivalent to CP6108). Additionally, HPV positivity was assessed by low-stringency Southern blot analysis of PCR products with a cocktail probe of HPV-specific fragments. PCR products of HPV-positive samples were subsequently subjected to further typing with EIA of reverse line blot hybridisation[28] for the aforementioned types. Samples that were GP5+/6+-positive by low-stringency Southern blot analysis or EIA, but did not reveal positivity in the typing assays, were judged to be uncharacterised HPV types (HPV X).

HPV testing was performed differently in Mexico[18]: biotinylated MY09/11 consensus primers and genotyping by a single-hybridisation, reverse-line blot detection method were used at the Department of Molecular Microbiology and Immunology, John Hopkins University School of Public Health (Baltimore, MD) and the National Institute of Public Health (Cuernavaca, Morelos, Mexico[29]). Probes for 27 HPV types were included: HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–59, 66, 68, 73, 82, 83 and 84. Good comparability of findings from GP5+/GP6+ and MY09/11-based PCR has been reported.[30]

HPV types considered high-risk for this study were HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82.[31] All other types, including HPV X, were considered to be low-risk.

Statistical analysis

To take into account differences in age distribution across study areas, we calculated age-standardised HPV prevalence by applying age-specific prevalence estimates for age groups 15–24, 25–34, 35–44, 45–54, 55–64 and 65–74 years to the world standard population reported by Doll and colleagues.[32] Where no data existed for the oldest or youngest age groups, age-standardised prevalence represents the truncated value for women aged 15–59 (China and India) and 25–74 years (Italy), respectively.

HPV-positive women were classified according to the type(s) detected (*i.e.*, HPV16 or 18; other high-risk types; low-risk types). Women with multiple-type infections were classified hierarchically as positive for (i) HPV16 or 18, if one or both of these types were present; (ii) other high-risk types, if any such types had been detected; or (iii) low-risk types only, if no high-risk HPV types had been found. Age-specific prevalence was also evaluated separately for high- and low-risk HPV types (data available upon request), but this analysis is not shown as it was not materially different from the hierarchical classification described above.

Age profiles in each area were classified into 3 groups by fitting a logistic regression model with both linear and quadratic terms for age (classified into 8 five-year age groups from <25 to ≥55 years). Areas with a significant ($p < 0.05$) quadratic term were classified as "nonlinear". For the remaining areas, a simpler model was fitted with only a linear age term, and the significance of this term was used to classify areas as having a "flat age profile" ($p \geq 0.05$) or "linear trend with age" ($p < 0.05$).

Probabilities of being infected with high-risk HPV types in HPV-positive women below age 35 and those aged 35 years or

TABLE I – PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) BY AGE GROUP AND AGE-STANDARDISED OVERALL PREVALENCE IN DIFFERENT AREAS (IARC HPV PREVALENCE SURVEYS, 1993–2004)

	Per capita national income in 2000 (US$)[1]	N (% HPV+) in each age group					Age-standardised[2] HPV prevalence (95%CI) per 100 women
		15–24	25–34	35–44	45–54	≥55	
Europe							
Italy, Turin	20,160	0	225 (13.3)	228 (12.7)	229 (5.7)	331 (5.1)	9.4 (7.5–11.2)
The Netherlands, Amsterdam	25,210	26 (15.4)	432 (10.9)	994 (3.4)	1138 (3.6)	709 (2.8)	7.7 (4.0–11.4)
Spain, Barcelona	14,790	160 (6.3)	158 (2.5)	173 (2.9)	160 (0.6)	257 (1.2)	2.9 (1.7–4.1)
Latin America							
Argentina, Concordia	7,490	151 (25.2)	197 (21.3)	201 (16.4)	193 (11.9)	166 (10.2)	17.7 (15.1–20.3)
Chile, Santiago	4,780	136 (21.3)	189 (11.6)	218 (8.3)	170 (10.0)	258 (14.0)	13.7 (11.3–16.1)
Colombia, Bogota	2,050	441 (27.2)	783 (16.2)	526 (10.1)	110 (3.6)	121 (14.0)	15.5 (13.6–17.4)
Mexico, Morelos	5,110	276 (16.7)	280 (8.9)	269 (3.7)	179 (12.3)	336 (19.3)	12.4 (10.6–14.2)
Asia							
Korea, Busan	9,790	7 (28.6)	152 (13.2)	280 (8.9)	236 (11.0)	195 (8.7)	14.8 (5.8–23.8)
Thailand, Lampang	2,010	129 (14.0)	179 (10.6)	177 (8.5)	167 (8.4)	372 (4.6)	9.6 (7.5–11.7)
Thailand, Songkla	2,010	70 (4.3)	116 (6.9)	124 (0.0)	133 (3.0)	273 (4.4)	3.8 (2.1–5.5)
Vietnam, Hanoi	380	124 (0.8)	182 (2.7)	187 (2.1)	171 (1.8)	343 (0.9)	1.6 (0.8–2.4)
Vietnam, Ho Chi Minh	380	158 (21.5)	172 (9.9)	185 (7.6)	155 (7.1)	248 (6.9)	11.4 (9.1–13.6)
China, Shanxi	840	46 (13.0)	176 (7.4)	177 (20.3)	180 (16.7)	91 (14.3)	14.0 (10.5–17.4)
India, Dindigul	450	339 (16.8)	863 (16.1)	462 (18.4)	239 (16.3)	37 (16.2)	16.8 (14.9–18.8)
Africa							
Nigeria, Ibadan	260	120 (30.8)	189 (25.4)	134 (26.9)	196 (26.0)	294 (24.8)	27.0 (23.9–30.2)

CI, confidence interval.
[1]From the World Bank Web site (www.worldbank.org).–[2]Based on world standard population aged 15–74 (aged 25–74 in Italy; aged 15–59 in China and India).

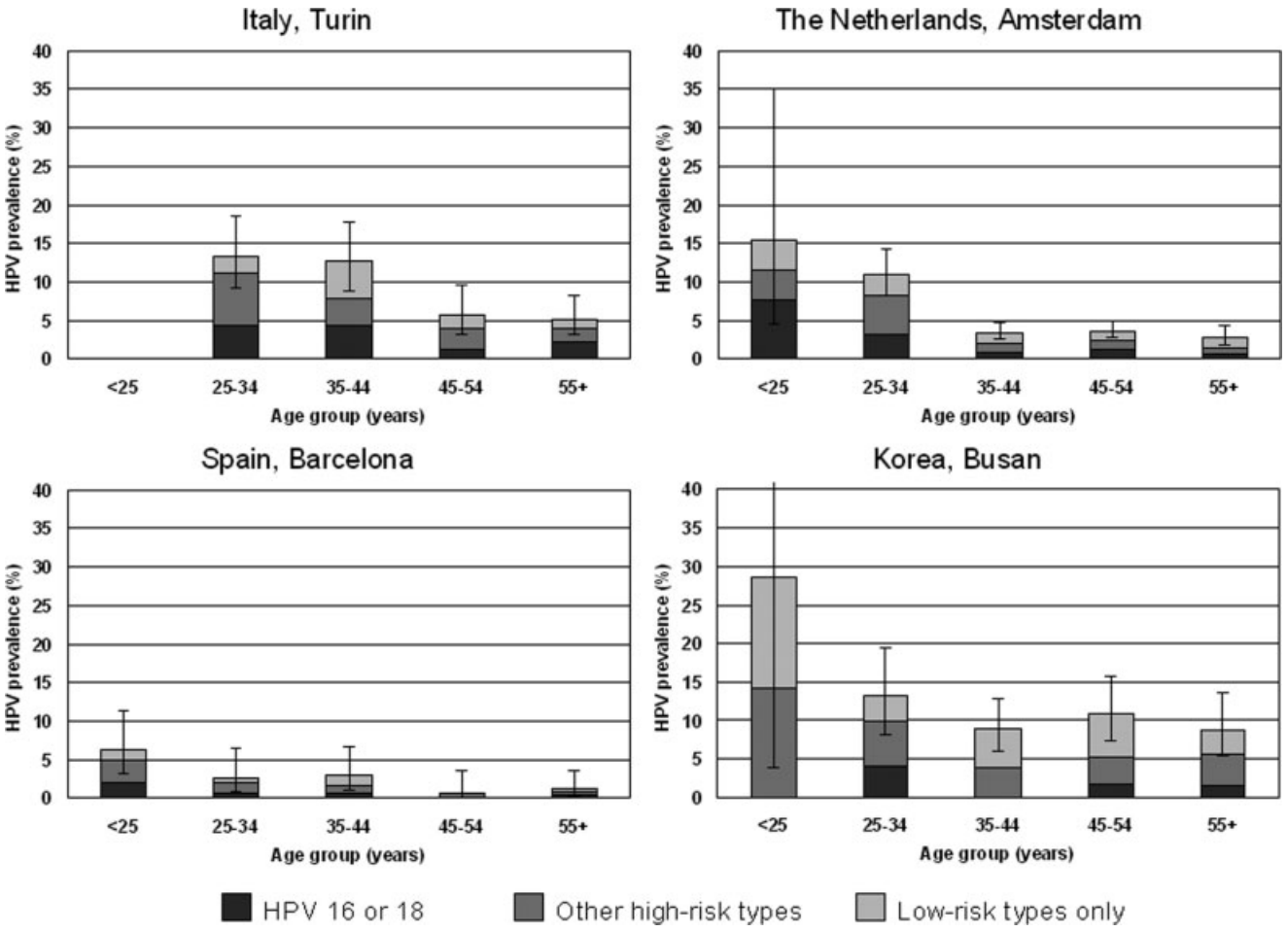

FIGURE 1 – Prevalence of human papillomavirus (HPV) and corresponding 95% confidence intervals by age group in 3 areas in Europe and Korea. IARC HPV Prevalence Surveys, 1993–2004.

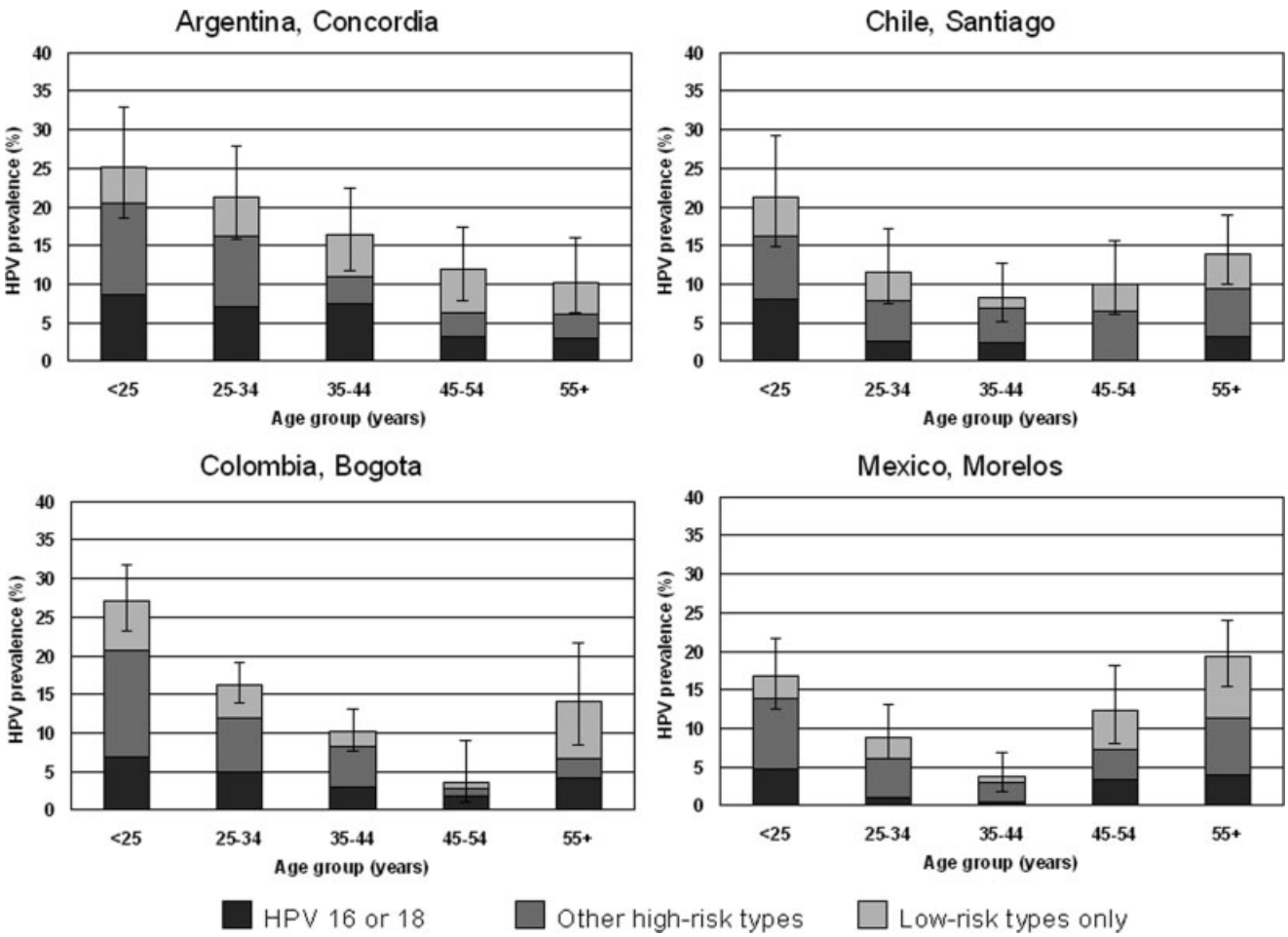

FIGURE 2 – Prevalence of human papillomavirus (HPV) and corresponding 95% confidence intervals by age group in 4 areas in Latin America. IARC HPV Prevalence Surveys, 1993–2004.

older were compared by use of odds ratios (ORs) and corresponding 95% confidence intervals (CIs) computed by unconditional logistic regression. Age 35 was chosen as a cut-off because it allowed us to constitute 2 large groups and also to distinguish relatively young women from middle-aged and old ones.

Results

Table I shows the distribution of 18,498 study women and the percentage of HPV-positive women by age group and study area. Per capita income in 2000 ranged between less than 1,000 US dollars in Vietnam, China, India and Nigeria to over 20,000 US dollars in Italy and the Netherlands. Age-standardised HPV prevalence varied greatly by study area, between 1.6% in Vietnam, Hanoi and 27.0% in Nigeria. Large differences were also found in the age-specific prevalence, *e.g.*, 38-fold variation between the areas of lowest and highest prevalence among women younger than 25 years (range: 0.8%–30.8%), 13-fold among women 35–44 years (range: 2.1%–26.9%), and 28-fold among women older than 55 years (range: 0.9%–24.8%).

Histograms in Figures 1–4 show the HPV prevalence in 5 age groups in the 15 study areas. Each bar further distinguishes the prevalence of HPV16 or 18, other high-risk types and low-risk types only.

The age distribution of HPV positivity in the 3 European study areas and Korea, the highest-income Asian country in our study, is shown in Figure 1. Although HPV prevalence varied greatly between areas, the highest prevalence was found consistently in the youngest women. In Italy, where women below age 25 were not included, relatively high prevalence also emerged in the 25–34 and 35–44 year age groups.

Figure 2 includes 4 Latin American countries. Except for Argentina, where the prevalence of HPV steeply declined with age, a more or less marked U-shaped curve was found. However, the second increase in HPV prevalence started earlier (45–54 years) in Chile and Mexico than in Colombia, where it was seen only among women 55 years or older.

Four Asian areas are shown in Figure 3. Vietnam, Ho Chi Minh and, to a lesser extent, Thailand, Lampang, showed an age-specific distribution of HPV similar to that seen in high-income countries (Fig. 1). HPV prevalence in any age group was low in Thailand, Songkla; and very low in Vietnam, Hanoi; and did not show a clear decline in HPV prevalence across age groups.

Figure 4 shows the age distribution of HPV prevalence in China, India and Nigeria (the only area from sub-Saharan Africa). In India and Nigeria the 5 age groups considered showed similar levels of HPV positivity, whereas in China HPV prevalence was lower in the 25–34 year age group than among older women. The age patterns in Figures 1–4 were not modified by the elimination of women with abnormal cytological findings.

With respect to age-specific HPV prevalence, 5 areas were classified as having a nonlinear age profile, with a highly significant ($p < 0.01$ for each area) quadratic term: Chile, Colombia and Mexico, for which a U-shaped age profile was observed (Fig. 2); and the Netherlands (Fig. 1) and Vietnam, Ho Chi Minh (Fig. 3), for which the prevalence was much higher in younger women

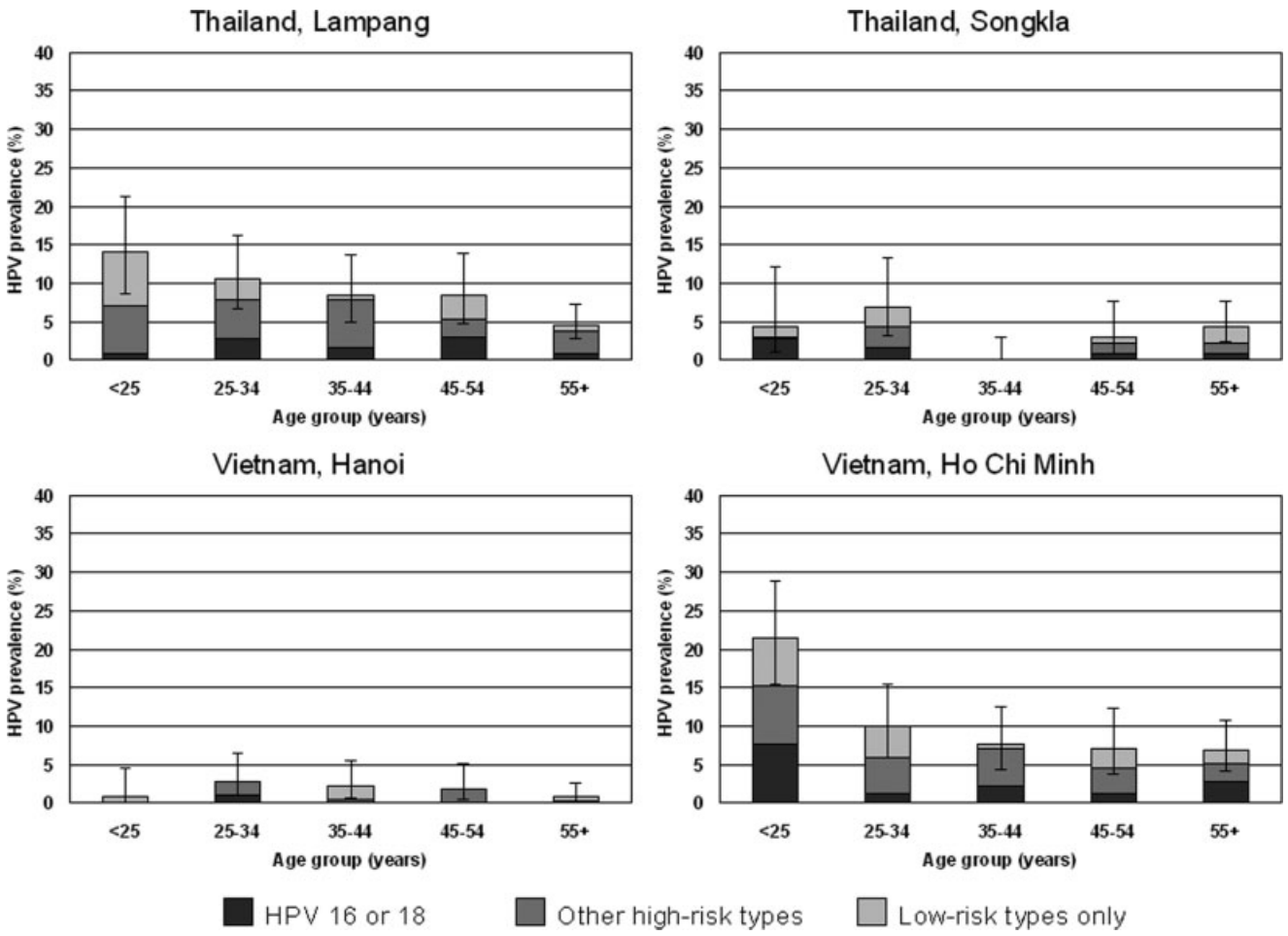

FIGURE 3 – Prevalence of human papillomavirus (HPV) and corresponding 95% confidence intervals by age group in 4 areas in Asia. IARC HPV Prevalence Surveys, 1993–2004.

(<35 or <25 years of age, respectively) than older women. Among the remaining areas, linear decline was significant ($p < 0.05$ in each area) in Italy and Spain (Fig. 1); Argentina (Fig. 2); and Thailand, Lampang (Fig. 3). No significant linear trend by age emerged for Korea (Fig. 1), Thailand, Songkla and Vietnam, Hanoi (Fig. 3), nor for China, India and Nigeria ($p > 0.20$ in all areas except for China, for which the p value was 0.06 with borderline evidence of an upward trend, Fig. 4).

Table II shows the ORs of HPV-positive women to be infected with high-risk HPV types by 2 age groups and area. In the majority of study areas, HPV-positive women below age 35 were more often infected with high-risk HPV types than women aged 35 years or older. In the Netherlands, Argentina and Mexico, the difference by age group was statistically significant. Using different cut-offs (*i.e.*, 25 or 45), findings were consistent with those reported in Table II except for Colombia, where a significant excess of high-risk infections was observed in women in all age groups under 45 years, compared with those aged 45 or older. Comparisons were also made among HPV-positive women of the proportion infected by HPV16 or 18 and multiple types below age 35 and above. No significant difference was detected (data not shown).

Two indicators of sexual behaviour (*i.e.*, age at first sexual intercourse, and the proportion of women who reported ≥2 lifetime sexual partners) are shown in Table III in order to evaluate whether any substantial difference existed in each study area between women younger than 25 and women aged 45 years or older. This information was not available for Italy and the Netherlands and was not included for Korea, where only 7 women were below 25 years of age. Women below 25 years of age reported a significantly earlier sexual debut than women 45 or older in all study areas except China and India. Significantly more women under 25 years than 45 years and older reported 2 or more lifetime sexual partners in Spain and Vietnam, Ho Chi Minh, but the reverse was found in Thailand, Lampang; Vietnam, Hanoi; and Nigeria. Elsewhere the proportion of women who reported 2 or more lifetime sexual partners was similar in the 2 age groups considered.

Discussion

The present overview of the distribution of HPV prevalence in representative samples of women from 15 areas in 4 continents revealed substantial variation in the shape of age-specific curves of HPV prevalence. In agreement with many similar studies in the United States[1–3] and Northern Europe,[4,5] steady declines in HPV prevalence were observed with increasing age in the highest-income countries included in the IARC HPV Prevalence Surveys. Three areas in Latin America (Chile, Colombia and Mexico) are examples of the U-shaped curve of age-specific prevalence[9] or incidence[12,13] already observed in some parts of the world. A clear peak of HPV positivity in women younger than 25 years of age was also found in urban (Vietnam, Ho Chi Minh) or peri-urban (Thailand, Lampang) settings in Asia. Very few women below age 25 could be included in our population-based survey in Korea, but we also found elevated HPV prevalence (38.8%) among 217 sexually active female university students in the same study area.[33]

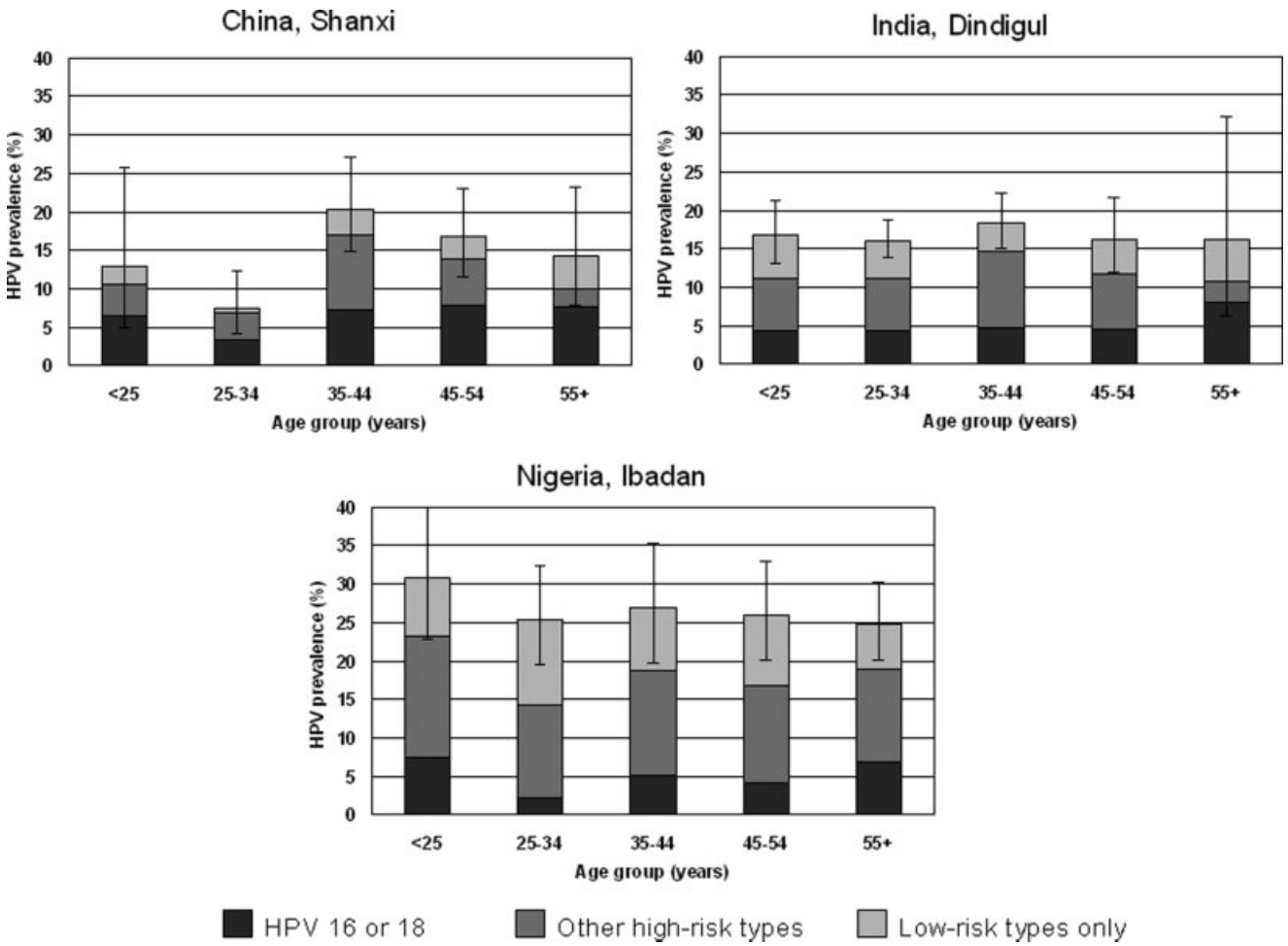

FIGURE 4 – Prevalence of human papillomavirus (HPV) and corresponding 95% confidence intervals by age group in China, India and Nigeria. IARC HPV Prevalence Surveys, 1993–2004.

TABLE II – ODDS RATIO (OR) AND 95% CONFIDENCE INTERVAL (CI) OF BEING INFECTED WITH HIGH-RISK HUMAN PAPILLOMAVIRUS (HPV) TYPES IN HPV-POSITIVE WOMEN AGED <35 *VS* ≥35 (IARC HPV PREVALENCE SURVEYS, 1993–2004)

	High-risk HPV types (pos/neg)		OR (95% CI)
	<35	≥35	
Europe			
Italy, Turin	25/5	40/19	1.4 (0.8–7.2)
The Netherlands, Amsterdam	39/12	56/39	2.3 (1.1–4.9)
Spain, Barcelona	11/3	6/3	1.8 (0.3–12.1)
Latin America			
Argentina, Concordia	63/17	44/29	2.4 (1.2–5.0)
Chile, Santiago	37/14	50/21	1.1 (0.5–2.5)
Colombia, Bogota	185/62	54/20	1.1 (0.6–2.0)
Mexico, Morelos	55/16	59/38	2.2 (1.1–4.4)
Asia			
Korea, Busan	16/6	34/34	2.7 (0.9–7.6)
Thailand, Lampang	23/14	37/9	0.4 (0.1–1.1)
Thailand, Songkla	7/4	9/7	1.4 (0.3–6.6)
Vietnam, Hanoi	5/1	5/5	5.0 (0.4–59.7)
Vietnam, Ho Chi Minh	34/17	33/9	0.5 (0.2–1.4)
China, Shanxi	17/2	64/15	2.0 (0.4–9.6)
India, Dindigul	135/61	97/33	0.8 (0.5–1.2)
Africa			
Nigeria, Ibadan	55/30	114/46	0.7 (0.4–1.3)

The most interesting age pattern that the overview of IARC HPV Prevalence Surveys disclosed, however, is the flat age curve observed in the lowest-income areas of Asia and in Nigeria, where HPV prevalence was similar across age groups. Of the 3 areas that showed high HPV prevalence and no decline in older age groups, all have high[34] or very high[35] rates of cervical cancer incidence and mortality, and very low income levels. The studies in China and India, in particular, were performed in isolated rural communities that have been seldom assessed with respect to HPV prevalence.[36,37] Although HPV prevalence is consistently high, the age-specific curve may differ across sub-Saharan African regions (reviewed in Clifford and Franceschi[38]). In studies from South Africa, Tanzania, the Gambia and Senegal, HPV prevalence remained high, or even increased, in middle and old age.[38] Similarly elevated HPV prevalence across all age groups is also typically seen in studies of HPV among HIV-positive women in different continents.[39,40] In our present study, the vast majority of women can be assumed to be HIV-negative, including those from Nigeria where the proportion of HIV-positive women should not exceed 3%.[24]

Some between-area differences were also found with respect to the relative contribution of high-risk and low-risk types to the burden of HPV infection in different age groups. A significant excess of high-risk types among women below age 35 was present in the Netherlands, Argentina and Mexico. Elsewhere, the proportion of HPV-positive women infected by high-risk types was not significantly different in women under 35 years of age and those 35 or older.

TABLE III – COMPARISON OF AGE AT FIRST SEXUAL INTERCOURSE AND PERCENTAGE OF WOMEN WHO REPORTED ≥2 SEXUAL PARTNERS BETWEEN WOMEN <25 AND ≥45 YEARS OF AGE IN DIFFERENT AREAS[1] (IARC HPV PREVALENCE SURVEYS, 1993–2004)

	Mean age at first sexual intercourse (years)		≥2 sexual partners (%)	
	<25	≥45	<25	≥45
Europe				
Spain, Barcelona	17.1	23.1[2]	36.9	12.5[2]
Latin America				
Argentina, Concordia	16.5	21.0[2]	41.1	32.9
Chile, Santiago	16.0	19.6[2]	39.0	42.5
Colombia, Bogota	15.8	19.6[2]	41.0	43.8
Mexico, Morelos	16.4	17.8[2]	18.8	23.5
Asia				
Thailand, Lampang	17.8	20.4[2]	7.8	19.1[2]
Thailand, Songkla	17.4	20.7[2]	8.6	13.1
Vietnam, Hanoi	18.3	20.3[2]	0.0	7.8[2]
Vietnam, Ho Chi Minh	18.9	22.2[2]	12.0	6.5[3]
China, Shanxi	19.4	19.0	19.6	21.8
India, Dindigul	17.7	17.8	–	–
Africa				
Nigeria, Ibadan	16.8	20.3[2]	36.7	49.9[2]

[1]The comparison was not possible in Italy, Korea and the Netherlands.–[2]$p < 0.01$ for the difference between women <25 vs. ≥45 at Student's t test (age at first sexual intercourse) or χ^2_1 test.–[3]$p < 0.05$ for the difference between women <25 vs. ≥45 at Student's t test (age at first sexual intercourse) or χ^2_1 test.

Marked variation in the age-specific curve of HPV prevalence across different populations may have different explanations.[41] Before considering them, however, it is worth bearing in mind that gynaecological examination of women who report to be virgins is seldom possible. Consequently our present study, as well as most previous investigations,[11] had to be restricted to the proportion of women who admitted to being sexually active and were in the vast majority married women. Selection bias may also derive from HPV studies based on college students[6,33] or young women attending family planning clinics for contraception[7,10,42] by preferential participation of the most sexually active women in the corresponding age groups. Although the comparison of HPV prevalence in young women across different studies requires great caution, it is unlikely that the several-fold variation in the ratio between HPV prevalence in women below 25 years and those 45 years or older that we have found in the IARC HPV Prevalence Surveys is completely reliant on chance or bias.

Participation in high-quality cervical screening programmes may lower the prevalence of HPV infection, notably high-risk types in middle-aged women, through treatment of detected HPV-associated cervical lesions. In our study, the majority of women in Latin America (≥70%) and Europe (≥80%) reported to have had at least 1 cytological smear, but only study areas in Italy and the Netherlands had active high-quality population-based screening programmes in place for some years.[43] In Asia, the percentage of women who had ever had a cytological smear was only found to be consequential in Korea (72%) and Thailand (49%). Less than 10% of women in Vietnam and China, and virtually no women in India and Nigeria, had ever been screened for cervical cancer. Nevertheless, where numbers allowed for comparison of age-specific curves of HPV prevalence in never- and ever-screened women (*i.e.*, Argentina, Colombia, Korea, Thailand, both areas, and Vietnam, Ho Chi Minh), no evidence of lower HPV prevalence in ever-screened middle-aged women emerged (data not shown).

Viral prevalence is the product of incidence (acquisition of new infection) and persistence (duration) of infection. Thus, in some countries young women may be much more exposed to new HPV infections than older women, whereas in countries where HPV prevalence does not decline, or where it increases again at a certain age, younger women may have no more new infections than older women. Large cohort studies in Colombia[13] and Costa Rica[12] have indeed shown that new HPV infections in middle-aged women, especially with high-risk types, are relatively frequent. As a majority of women in our study reported only one lifetime sexual partner, a large proportion of such new HPV infection at any age is likely to be related to the husband's extramarital sexual relationships, which were significantly associated with an excess of HPV positivity in the IARC HPV Prevalence Surveys.[44] Castle *et al.*,[12] however, suggested a stronger role for viral persistence than for acquisition of new infections in women 45 years or older in Costa Rica.

Finally, changes in sexual behaviour have led to rises in seroprevalence[45] of, and cervical infection with high-risk HPV types[46] among young women throughout the 1980s and 1990s in various countries. In our study, we also observed some evidence of changes in sexual behaviour, *i.e.*, a significant anticipation in the age at sexual debut in women younger than 25 years compared with those 45 or older in all study areas where this information was available, except China and India.

Regardless of the reasons for the observed variations, the substantial differences between age-specific curves of HPV prevalence worldwide are a strong reminder that great caution must be exerted in inferring the natural history of HPV infection from cross-sectional HPV prevalence studies. From a practical viewpoint, the differences we observed help to estimate the burden of HPV infection overall and in different age groups in various parts of the world. This information can help to identify which age groups might still benefit from prophylactic vaccines against HPV and where a catch-up programme of nonadolescent women can be forseen. It also gives us an idea of the proportion of women who would test HPV-positive in different countries, where HPV test-based screening may be implemented in the future.

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