Short Communication

International Correlation between Human Papillomavirus Prevalence and Cervical Cancer Incidence

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Abstract

Data from population-based human papillomavirus (HPV) surveys in regions of low, intermediate, and high cervical cancer incidence were used to study the ecologic correlation between high-risk HPV prevalence and cervical cancer incidence. All the surveys were conducted by the IARC according to a standardized protocol for the collection of female population samples and detection of HPV DNA using PCR assay in a central laboratory. Cervical cancer incidence data were extracted, when available, from a cancer registry covering the surrounding or nearby area of the prevalence survey. Thirteen areas were included in this analysis. The relation between high-risk HPV prevalence and cervical cancer incidence was investigated within 10-year age groups from age 25 to 65 years. A Poisson regression model was used to predict cervical cancer incidence from HPV prevalence, and the strength of the correlation was assessed using Spearman's rank correlation coefficient. The rank correlation was weakest in women ages 25 to 34 years and strongest in women ages 55 to 64 years. In addition, the prevalence of high-risk HPV was not able to predict cervical cancer incidence accurately in every country. Nevertheless, our data raise a concern about the cervical cancer burden in areas where reliable cervical cancer statistics do not exist but where the prevalence of high-risk HPV in women over age 45 is high. (Cancer Epidemiol Biomarkers Prev 2008;17(3):717–20)

Introduction

Persistent infection with 1 of 15 high-risk types of human papillomavirus (HPV) is considered a necessary cause of cervical cancer (1). Between 1993 and 2006, the IARC carried out a series of population-based HPV prevalence surveys in regions of low, intermediate, and high cervical cancer incidence (2-16). These surveys were carried out in 18 areas in Latin America, Europe, Asia, and sub-Saharan Africa using a standardized protocol. The results of these surveys reveal a >10-fold between variation in overall HPV prevalence in these populations as well as distinct patterns of age-specific HPV prevalence (17). The purpose of this article is to investigate the strength of the international correlation between age-specific HPV prevalence and cervical cancer incidence by combining HPV prevalence data from the IARC HPV Prevalence Surveys with routinely collected cancer incidence data in the same populations.

Materials and Methods

The studies included in the IARC HPV Prevalence Surveys are described in detail elsewhere (2-16). Briefly, in each area, attempts were made to obtain a random age-stratified sample that included at least 100 women in 5-year age groups from 15 to 19 to ≥55 years or, in some centers, ≥65 years. After signing an informed consent form, subjects underwent a pelvic examination, done by a gynecologist or trained nurse, which included collection of exfoliated cervical cells. HPV DNA was detected in cervical cell samples using a GP5+/6+-based PCR assay detecting at least 36 types. The following HPV types were defined as high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Refusal to undergo gynecologic examination was more frequent in women in the youngest and oldest age groups. In these age groups, it cannot be assumed that the study subjects were representative of the general population. We therefore restricted the analysis to women aged 25 to 64 years.

Age-specific cervical cancer incidence rates were extracted when possible from *Cancer Incidence in Five Continents, Volume VIII* (18), which covers cancer

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Note: In addition to the aforementioned, collaborators of the IARC HPV Prevalence Surveys Study Group include, in alphabetical order by country, Argentina (L. Herrera, D. Loria, E. Matos, and M.A. Prince), Colombia (M. Molano, N. Muñoz, H. Posso, and M. Ronderos), France (A. Arslan, G. Clifford, M. Dai, and S. Vaccarella), India (J. Cherian, deceased), Italy (V. Ghisetti, A. Gillio-Tos, S. Gallus, G. Ronco, and N. Segnan), Korea (H.R. Shin and D-H. Lee), Nigeria (I. Ajayi, K. Ojemakinde, A. Omigbodum, and J.O. Thomas), Poland (A. Bardin and W. Zatonski), Spain (X.F. Bosch, R. Font, and S. de Sanjosé), Thailand (A. Deechaisate, V. Kaenploy, V. Kesararat, S. Kongchuchuy, T. Kornsilp, S. Sukrivach, S. Tunsakul, and P. Yingseri), The Netherlands (C.J.L.M. Meijer, P.J.F. Snijders, and M. Jacobs), and Vietnam (P.T.H. Anh and N.T. Hieu).

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Table 1. Age-specific cervical cancer incidence rates and contemporary high-risk HPV prevalence

Location	*n*	Prevalence (%)					Incidence rate per 100,000			
		Year	Age group (y)				Year	Age group (y)			
			25-34	35-44	45-54	55-64		25-34	35-44	45-54	55-64
Turin, Italy	911	2002	11.1	7.9	3.9	3.5	1993-1997	3.7	14.6	15.1	17.5
Barcelona, Spain	634	1998	1.9	1.7	0.6	0.0	1993-1997	8.8	22.5	22.0	18.6
Warsaw, Poland	570	2005-2006	18.8	11.3	7.9	4.3	1998-2002	4.9	24.6	36.4	38.2
Amsterdam, The Netherlands	3,260	1995-1998	8.3	2.0	2.3	1.4	1993-1997	9.3	16.3	12.7	11.2
Concordia, Argentina	802	1998	16.2	11.0	6.2	6.3	1993-1997	32.1	64.9	92.4	59.3
Bogota, Colombia	1,490	1993-1995	11.5	7.6	1.8	8.5	1992-1996	12.8	40.1	68.0	85.7
Busan, Korea	830	1999-2000	9.9	3.9	5.1	6.2	1996-1997	8.6	33.2	35.4	43.6
Lampang, Thailand	711	1997-1998	7.8	7.9	5.4	5.3	1993-1996	13.6	48.1	71.7	61.5
Songkla, Thailand	518	1997-1999	4.3	0.0	2.3	0.7	1993-1997	8.2	37.9	37.1	50.5
Hanoi, Vietnam	755	1997	2.8	0.5	1.8	0.5	1993-1997	2.1	12.3	18.8	17.6
Ho Chi Min City, Vietnam	678	1997	5.8	7.0	4.5	6.0	1995-1998	3.4	27.0	72.4	128.4
Dindigul, India	1,601	2003	11.2	14.1	11.7	10.8	1998-2002	16.9	98.4	224.2	231.5
Ibadan, Nigeria	812	1999-2000	14.3	18.7	16.8	20.2	1998-2001	8.7	48.2	127.7	175.4

incidence for the period 1993 to 1997. For HPV surveys conducted after this period, we requested the corresponding data from the cancer registries concerned or, in the case of India, from a published source (19). As no cancer registry data were available for the study area in Colombia (4), cancer incidence data were taken from a nearby registry. Cancer registry data were lacking for the study areas in Chile (5) and Mexico (6). In addition, none of the three Chinese study areas (13, 15, 16) could be included as Shanxi Province and Shenyang City were lacking cancer registry data, and (16) Shenzhen City is unsuitable for ecologic analysis given its rapidly changing demographic structure mainly due to migration.

Statistical Methods. The association between high-risk HPV prevalence and cervical cancer incidence was studied within 10-year age groups (25-34, 35-44, 45-54, and 55-64). A Poisson regression model was fitted to the aggregate data from the 13 centers using high-risk HPV prevalence in each center to predict the cervical cancer incidence rate. The regression model was fitted without an intercept term to satisfy the constraint that cervical cancer rates should be zero if the HPV prevalence is zero.

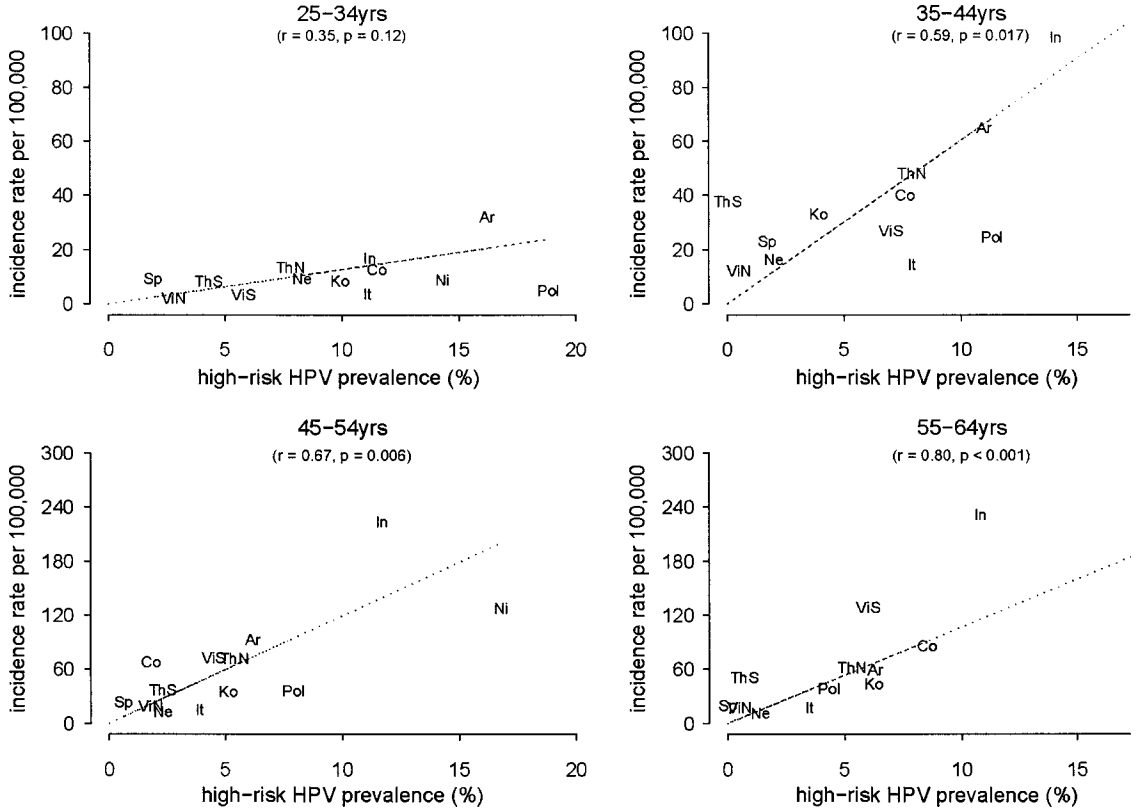

Figure 1. International correlation between cervical cancer incidence and high-risk HPV prevalence by age group.

The model was adjusted for measurement error in the HPV prevalence estimates.

The strength of the international correlation between high-risk HPV prevalence and cervical cancer incidence rates was also assessed using the Spearman rank correlation coefficient.

Results

Table 1 summarizes cervical cancer incidence rates and high-risk HPV prevalence within 10-year age groups. Figure 1 presents the same data in graphical form, plotting incidence rates against HPV prevalence. The dotted line represents the fitted Poisson model. Different scales are used for the *Y* axis in each age group to adjust for the increasing incidence of cervical cancer with age.

As expected, prevalence of high-risk HPV was correlated with cervical cancer incidence at the population level. The Spearman rank correlation was 0.35 in age group 25 to 34, 0.59 in age group 35 to 44, 0.67 in age group 45 to 54, and 0.80 in age group 55 to 64. The corresponding *P* values were 0.12, 0.02, 0.006, and 0.001, respectively. Thus, the strength of the correlation steadily increased with age. However, several inconsistencies emerged for the correlation between high-risk HPV prevalence and cervical cancer incidence. Poland and Argentina, for instance, had comparable high-risk HPV prevalence at all ages, but the cervical cancer incidence rates were substantially higher in Argentina in all age groups, except for women ages 55 to 64 years.

Discussion

This study showed, as expected, a substantial correlation between the population prevalence of high-risk HPV infection and cervical cancer incidence, especially among middle-aged and elderly women. The correlation coefficient was, however, low among women below age 35 years, and in every age group, several countries did not fit the predicted cervical cancer incidence well. Hence, this analysis highlights some of the limitations of ecologic inference, in which aggregate measures of exposure and disease are compared between populations.

Despite the existence of a known causal relationship between HPV infection and cervical cancer, the ecologic correlation was attenuated by several factors, which may be classified into three groups: data quality, measurement error, and confounding. Data quality issues concern the difficulty of accurately enumerating the population for calculation of cancer incidence rates, which is a problem in many low-resource settings, and the difficulty of ensuring a representative sample of the population for the assessment of HPV prevalence. Although this study has used the highest-quality data currently available on both incidence and prevalence, it was not possible to eliminate these problems. Measurement error also concerns the difficulty, in a cross-sectional survey, of distinguishing between persistent and transient HPV infections (20). Only women with persistent high-risk HPV infection are at risk for cervical cancer. The weaker correlation observed among younger women may be explained by a higher proportion of transient infections in this age group and by the still low rates of cervical cancer incidence below age 35 years.

Although HPV is considered a necessary cause of cervical cancer, it has been shown that various lifestyle and behavioral aspects, such as reproductive behavior factors, hormonal contraceptive use, and smoking, are cofactors for cervical cancer risk (21-23). Systematic differences in these cofactors between populations may confound the ecologic relationship between HPV prevalence and cervical cancer. At a population level, the most important confounding factor is cervical cancer screening. Screening reduces cancer incidence, and treatment of precancerous cervical lesions discovered by screening eliminates HPV infection. Screening was known to be taking place, either opportunistically or as part of an organized program, in survey areas in Argentina (3), The Netherlands (14), Spain (2), Italy (11), Poland,[5] and Korea (7). Notably, cervical cancer incidence rates in Poland[5] and Italy (11) were substantially lower than the prediction from the Poisson regression model. However, a sensitivity analysis comparing never- and ever-screened women in the IARC HPV Prevalence Surveys found no difference in HPV prevalence (17).

Despite the overall weakness of the international correlation, the analysis of HPV prevalence in women ages >45 years identified the two populations with high-risk HPV prevalence more than 10% as being the two highest-risk populations for cervical cancer [India (10) and Nigeria (12)]. Although this observation cannot be extended to a quantitative risk prediction, it raises concerns over the cervical cancer burden in some parts of the world (e.g., many provinces in China; refs. 13, 15, 16) where reliable cervical cancer statistics do not exist but HPV prevalence has been shown to be elevated in middle-aged and older women.

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