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Effect of age-difference between heterosexual partners on risk of cervical cancer and human papillomavirus infection

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ABSTRACT

Background: Age difference (Adiff) within a heterosexual couple may influence a woman's risk of being HPV-positive and developing cervical cancer (CC).
Methods: We assessed the relationship between Adiff within the first and current sexual partnership and risk of CC and HPV infection in 1495 cases and 1358 control women from 6 countries included in IARC's multicentric case-control study (median age: 48 years).
Results: Large Adiff within the first partnerships was associated with increased CC risk (OR≥3 vs. ≤2 years=1.49, CI: 1.26–1.75); this association disappeared after correction for age at first sexual intercourse (OR=1.03, 0.86–1.24). The relationship between Adiff within the current partnership and HPV-positivity was opposite (OR≥3 vs. ≤2 years=0.59, 0.41–0.86) and not affected by adjustment for sexual confounding. The influences of Adiff on CC risk and HPV-positivity were consistent across age groups and countries.
Conclusion: The association between CC risk and large Adiff in the first sexual partnership is mostly explained by young age at first intercourse. Conversely, the negative association between Adiff in current partnership and HPV-positivity is probably related to decreased infectiousness of the male partner with age. The study of Adiff in sexual partnerships helps elucidate HPV circulation in different populations.

1. Introduction

Cervical cancer (CC) is caused by sexually transmitted high-risk (HR) types of human papillomavirus (HPV) [1]. A woman's risk of HPV infection and CC is therefore governed by her sexual behavior and the sexual behavior of her partner(s) [2,3]. Characteristics including age at first sexual intercourse and lifetime number of sexual partners have been consistently associated with a rise in HPV [4] and invasive CC risk [5], but other aspects such as a population's sexual habits, e.g., age difference (hereafter referred to as "Adiff") within heterosexual couples, have seldom been studied [6]. Adiff is largely determined by social norms [7,8] and, especially with respect to married couples, is often measured in demographic and health-related surveys.

Studies on HIV in sub-Saharan Africa in the pre-HAART era suggested that Adiff between heterosexual partners was positively associated with the risk of HIV infection and could explain the different age-specific distribution of the infection between genders [8–12]. The effect of Adiff on the risk of HIV within selected populations has been suggested by mathematical models [8] but not shown in longitudinal studies on the topic [13].

We have recently illustrated, using a dynamic model of HPV infection, the way in which sexual preferences, such as Adiff age-specific rates of sexual activity in each gender, influence the age-specific distribution of HPV infection among women in different populations and may also have an impact on HPV vaccination effectiveness [14]. However, empirical evidence of the association between Adiff and HPV infection is sparse [6] and absent for CC. In the present study, we use data from the International Agency for Research on Cancer (IARC)

Abbreviations: Adiff, age difference; CC, cervical cancer; CI, confidence interval; HPV, human papillomavirus; HR, high-risk; IARC, International Agency for Research on Cancer; OR, odds ratio

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multicentric case-control study [15,16], to assess the role of Adiff as a risk factor for CC and for HPV infection among CC-free control women.

2. Material and methods

We assessed records from the IARC international case-control study [15,17,18] that included detailed information about the sexual history of participating women, including the Adiff between a woman and her first and current sexual partner (including her husband or cohabiting partner at time of interview) [16]. Study populations, data collection, and laboratory methods of the IARC international case-control study are described in detail elsewhere [15,16]. Below, we provide a brief summary of the study methods and describe the data subset used for the present report.

2.1. Study populations and data

Studies were conducted in six countries where the effect of screening programs has been small, if present at all, and showing substantial variability in CC incidence i.e., high-risk populations in Africa (Morocco), Asia (India) and South America (Brazil, Peru), and intermediate-risk populations in Asia (Thailand and the Philippines). Eligible cases were residents in predefined study areas who had been admitted to local hospital(s) with incident, histologically confirmed CC. Controls were cytologically normal women who had been admitted to the same hospitals as CC cases. They were frequency-matched to cases by 5-year age group. Patients with gynecological diseases and other diseases potentially related to known risk factors for CC were not eligible as controls.

Face-to-face interviews were conducted in the hospital by trained interviewers using a standardized questionnaire. For each woman, we included the following information: country of enrollment, age and HPV status (i.e. positive or negative) at interview, age at first sexual intercourse, lifetime number of sexual partners, and woman's reported extramarital relationships of first and of current partner. We also extracted the age of the partners engaged in the current and the first sexual partnerships of each woman and calculated the Adiff in each partnership. All women for whom we could calculate Adiff of the first and of the current sexual partnership were included in the present report, i.e. 1495 invasive CC cases and 1358 controls.

All women consented to study participation in writing and the IARC and local ethics and research committees approved study protocols.

2.2. Laboratory methods

Exfoliated cells were collected with a wooden spatula and an endocervical brush. After the preparation of a Papanicolaou smear to confirm cervical diagnosis, remaining cells were eluted in phosphate-buffered saline, pelleted, and kept at −70 °C. HPV DNA testing was performed centrally in the Department of Pathology, VU Medical Center, Amsterdam, The Netherlands by PCR amplification of a small fragment of the L1 gene using GP5+/6+ primers. DNA quality was assessed with β-globin primers. PCR products were assessed for HPV-positivity by low-stringency Southern blot hybridization with a cocktail of HPV-specific probes for 33 HPV types [19]. In a second step, E7 primers for 14 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cells or tissue biopsies were tested in all cases that were positive for GP5+/6+ primers.

2.3. Statistical analysis

We conducted distinct analyses considering the risk of CC (among cases and controls) and the risk of HPV-positivity (among controls only) as separate outcomes and Adiff in the current and first sexual partnership as separate exposures. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were computed using unconditional logistic regression models and adjusted for design variables, i.e., country and age of the woman at interview, and other potential confounders, as reported. Tests for linear trend in the OR were done, giving an increasing score for each level of categorized variable and fitting these into the model as continuous variables. To model non-linear dose-response relationships between Adiff in the current and first sexual partnership and the risk HPV-positivity and CC, respectively, we fitted restricted cubic splines with three knots (at percentiles 25%, 50%, 75% of Adiff) in adjusted logistic regressions.

Table 1
Distribution of cervical cancer cases and controls and HPV-positivity (controls only) by selected characteristics. IARC multicentric case-control study, 1985–1999.

Characteristic	Cases		Controls		Controls only			
					HPV+		HPV-	
	N	(%)	N	(%)	N	(%)	N	(%)
Country								
Brazil	184	(12.3)	189	(13.9)	31	(13.8)	158	(13.9)
Morocco	188	(12.6)	173	(12.7)	37	(16.4)	136	(12.0)
Philippines	363	(24.3)	380	(28.0)	35	(15.5)	345	(30.5)
Thailand	376	(25.1)	258	(19.0)	40	(17.8)	218	(19.2)
Peru	196	(13.1)	175	(12.9)	31	(13.8)	144	(12.7)
India	188	(12.6)	183	(13.5)	51	(22.7)	132	(11.7)
Age at interview								
< 35	127	(8.5)	185	(13.6)	27	(12.0)	158	(13.9)
35–44	418	(28.0)	388	(28.6)	70	(31.1)	318	(28.1)
45–54	451	(30.1)	380	(28.0)	59	(26.2)	321	(28.3)
≥55	499	(33.4)	405	(29.8)	69	(30.7)	336	(29.7)
Lifetime sexual partners								
1	955	(63.9)	1033	(76.1)	162	(72.0)	871	(76.9)
2	434	(29.0)	233	(17.2)	42	(18.7)	191	(16.9)
≥3	106	(7.1)	92	(6.8)	21	(9.3)	71	(6.3)
Age at first sexual intercourse								
< 17	518	(34.6)	281	(20.7)	59	(26.2)	222	(19.6)
17–19	525	(35.1)	417	(30.7)	68	(30.2)	349	(30.8)
20–22	319	(21.3)	374	(27.5)	59	(26.2)	315	(27.8)
≥23	133	(8.9)	286	(21.1)	39	(17.3)	247	(21.8)
Type of partnership[a]								
First and Not Current	671	(38.2)	388	(25.8)	67	(26.6)	321	(25.7)
First and Current	808	(46.0)	962	(64.1)	156	(61.9)	806	(64.5)
Current and Not First	276	(15.7)	151	(10.1)	29	(11.5)	122	(9.8)
Male partner's extra-marital relationship in first partnership[b]								
No	509	(34.4)	700	(51.9)	112	(50.2)	588	(52.2)
Yes or Unknown	969	(65.6)	650	(48.1)	111	(49.8)	539	(47.8)
Male partner's extra-marital relationship in current partnership								
No	405	(37.4)	620	(55.7)	102	(55.1)	518	(55.8)
Yes or Unknown	679	(62.6)	493	(44.3)	83	(44.9)	410	(44.2)
Total	1495	(52.4)	1358	(47.6)	225	(16.6)	1133	(83.4)

CI, confidence interval; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; OR, odds ratio.

[a] First and current partnerships involved the same partner in 808 cases and 962 controls.

[b] One woman with missing data.