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)

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.

We tested the heterogeneity of the association between two age groups (< 35 and ≥35 years) and across centers by comparing the difference between the −2*log likelihood of the model estimating a common OR and of the model estimating a group-specific OR using the χ^2 distribution, with degrees of freedom given by the number of groups minus one.

3. Results

Table 1 shows the distribution of the cases and controls included in our analysis by country, age at interview, and sexual habit indicators including sexual partnerships for which Adiff was available. Controls are additionally shown separately by HPV-positivity. The majority of enrolled women were 35 years of age or older (89%) and reported only one lifetime sexual partner (70%). Among controls HPV-positivity was 17% (range: 9% in the Philippines and 28% in India) and was similar in different age groups. Both CC risk and HPV-positivity were positively associated with the number of sexual partners and negatively associated with age at first sexual intercourse but only CC risk was associated with male partner's extramarital relationship. In total, we had information on Adiff for 1755 sexual partnerships for CC cases and 1501 for controls. First and current partnerships involved the same partner in 808 cases and 962 controls (Table 1).

Table 2 shows the ORs for CC overall and by age group according to the Adiff between the man and the woman and type of partnership. Adiff for both first and current partnership was positively associated with CC risk (OR for ≥10 vs ≤2 year-difference=2.00, 95%CI: 1.62–2.48; and 1.99, 95% CI: 1.55–2.55, respectively). These findings were consistent in women below age 35 and in older women and were not heterogeneous across centers (p=0.28 and 0.31, for first and current partnership, respectively).

Table 3 shows the risk of being HPV-positive among controls overall and by age group according to Adiff and type of partnership.

Adiff in first sexual partnership was not associated with HPV-positivity (OR for ≥10 vs ≤2 year-difference=0.74, 95% CI: 0.48–1.14) whereas the Adiff in the current sexual partnership was negatively associated (OR for ≤2 vs ≥10 year-difference=0.60, 95% CI: 0.36–0.98; p for trend=0.03). These findings were consistent in women below age 35 and in older women, and were not heterogeneous across centers (p=0.25 and 0.24 for first and current partnership, respectively).

Table 4 shows the effects of adjustment for various confounding factors on the ORs for CC and HPV-positivity according to Adiff. For a-priori reasons (see Section 4) first partnership and current partnership were selected, respectively, in the assessment of risk of CC and HPV-positivity risk and Adiff was dichotomized (≥3 vs ≤2 years) to avoid dealing with small subgroups. For CC, the country- and age-adjusted OR for Adiff was not modified by additional adjustment for number of lifetime sexual partners and partner's extra-marital relationships but the positive association was eliminated by adjustment for woman's age at first sexual intercourse (OR=1.03; 95% CI: 0.86–1.24). Table A.1 shows the strong negative relationship (p-value < 0.0001) between Adiff in the first partnership and a woman's age at first intercourse. The average age of first sexual intercourse in women was 21.66 years if Adiff was 2 years or less but 17.32 years if it was 10 years or more. The effect of Adiff in the current partnership on risk of HPV-positivity was not significantly modified by any of the three additional adjustment variables and the OR after complete adjustment was 0.59 (95% CI: 0.39–0.85) (Table 4).

Fig. 1 shows that the relationship between Adiff in the current sexual partnership and the age- and country-adjusted OR of HPV positivity steeply decreases until approximately 5 years of Adiff, whereas for larger Adiff the risk of HPV positivity remains virtually unchanged. In Fig. A.1, we confirm that Adiff (up to 15 years) in the first sexual partnership does not significantly affect the OR of CC adjusted by age, country, and woman's age at first sexual intercourse.

Table 2

Risk of cervical cancer by age difference between man and woman and type of sexual partnership. IARC multicentric case-control study, 1985–1999.

Age difference between partners	First partnership[a]						Current partnership[a]					
	Control		Cases				Control		Cases			
	N	(%)	N	(%)	OR[b]	(95% CI)	N	(%)	N	(%)	OR[b]	(95% CI)
All women												
≤2	507	(37.6)	439	(29.7)	Ref. Cat.		465	(41.8)	385	(35.5)	Ref. Cat.	
3–6	390	(28.9)	435	(29.4)	1.34	(1.11–1.63)	311	(27.9)	294	(27.1)	1.21	(0.97–1.50)
7–9	187	(13.9)	184	(12.4)	1.19	(0.93–1.52)	140	(12.6)	130	(12.0)	1.21	(0.91–1.59)
≥10	266	(19.7)	421	(28.4)	2.00	(1.62–2.48)	197	(17.7)	275	(25.4)	1.99	(1.55–2.55)
Chi-square for trends (1 df)					p=0.000						p=0.000	
≥3 vs ≤2 years					1.49	(1.26–1.75)					1.40	(1.16–1.69)
Women aged < 35												
≤2	64	(34.8)	42	(33.6)	Ref. Cat.		66	(37.5)	43	(40.2)	Ref. Cat.	
3–6	60	(32.6)	43	(34.4)			52	(29.5)	30	(28.0)		
7–9	26	(14.1)	18	(14.4)	1.46	(0.87–2.46)	24	(13.6)	11	(10.3)	1.25	(0.73–2.15)
≥10	34	(18.5)	22	(17.6)			34	(19.3)	23	(21.5)		
Women aged ≥35												
≤2	443	(38.0)	397	(29.3)	Ref. Cat.		399	(42.6)	342	(35.0)	Ref. Cat.	
3–6	330	(28.3)	392	(28.9)			259	(27.6)	264	(27.0)		
7–9	161	(13.8)	166	(12.3)	1.51	(1.26–1.80)	116	(12.4)	119	(12.2)	1.45	(1.19–1.77)
≥10	232	(19.9)	399	(29.5)			163	(17.4)	252	(25.8)		

CI, confidence interval; df, degrees of freedom; 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] Adjusted by country and age of the woman at interview.

Table 3

Risk of HPV-positivity by age difference between man and woman and type of sexual partnership. IARC multicentric case-control study, years, 1985–1999.

Age difference between partners	First Partnership[a]						Current Partnership[a]					
	HPV+		HPV-				HPV+		HPV-			
	N	(%)	N	(%)	OR[b]	(95% CI)	N	(%)	N	(%)	OR[b]	(95% CI)
All women												
≤2	82	(36.8)	425	(37.7)	Ref. Cat.		81	(43.8)	384	(41.4)	Ref. Cat.	
3 – 6	64	(28.7)	326	(28.9)	0.74	(0.51–1.09)	49	(26.5)	262	(28.2)	0.61	(0.40–0.94)
7 – 9	31	(13.9)	156	(13.8)	0.74	(0.46–1.20)	21	(11.4)	119	(12.8)	0.55	(0.32–0.96)
≥10	46	(20.6)	220	(19.5)	0.74	(0.48–1.14)	34	(18.4)	163	(17.6)	0.60	(0.36–0.98)
Chi-square for trends (1 df)					p=0.173						p=0.027	
≥3 vs ≤2 years					0.74	(0.54–1.03)					0.59	(0.41–0.86)
Women aged < 35												
≤2	9	(33.3)	55	(35.0)	Ref. Cat.		9	(36.0)	57	(37.7)	Ref. Cat.	
3–6	8	(29.6)	52	(33.1)			6	(24.0)	46	(30.5)		
7–9	4	(14.8)	22	(14.0)	0.76	(0.27–2.11)	3	(12.0)	21	(13.9)	0.72	(0.25–2.05)
≥10	6	(22.2)	28	(17.8)			7	(28.0)	27	(17.9)		
Women aged ≥35												
≤2	73	(37.2)	370	(38.1)	Ref. Cat.		72	(45.0)	327	(42.1)	Ref. Cat.	
3–6	56	(28.6)	274	(28.2)			43	(26.9)	216	(27.8)		
7–9	27	(13.8)	134	(13.8)	0.74	(0.52–1.05)	18	(11.3)	98	(12.6)	0.58	(0.39–0.86)
≥10	40	(20.4)	192	(19.8)			27	(16.9)	136	(17.5)		

CI, confidence interval; df, degrees of freedom; 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] Adjusted by country and age of woman at interview.

4. Discussion

Our multi-country study shows that a large Adiff between heterosexual partners is associated with a reduced risk of HPV-positivity among CC-free women (controls). On account of the predominance of monogamous women in our study, the first sexual partner was frequently also the current one creating a strong collinearity between Adiff in first and current partnership. However well-established knowledge on the natural history of HPV infection and CC allowed us to focus on either of the two partnerships depending on disease outcome.

On account of the decade-long latency of CC, the positive association between Adiff and CC risk is expected to refer to the first partnership, and we clearly show that the influence of Adiff is nearly completely explained by the strong negative correlation between Adiff

and a woman's age at first sexual intercourse, i.e. a strong CC risk factor independent from other sexual habits and other CC risk factors [20,21]. We had already proposed that early age at first intercourse is a reasonable proxy for early age at first HPV cervical infection since in most world regions the infection is common and women show a very sharp rise in HPV-positivity in the year after the beginning of sexual activity [22]. An early age at first HPV infection is, therefore, associated with a longer-duration infection and higher CC risk since cancer probability increases as a power of time exposure to the relevant carcinogen [22].

Conversely, the negative association observed between Adiff and HPV-positivity among controls should refer to the current partnership and be attributable to the combination of HPV clearance (in a woman) and the sexual behavior of male partners. Most (~80%) newly acquired

Table 4

Effects of adjustment by various confounding factors on the country- and age-adjusted odds ratio for cervical cancer and HPV-positivity by age difference between man and woman and type of sexual partnership. IARC multicentric case-control study, 1985–1999.

Adjustment variables	Age difference ≥3 vs ≤2 years in first partnership		Age difference ≥3 vs ≤2 years in current partnership	
	OR of cervical cancer	(95% CI)	OR of HPV infection	(95% CI)
Country and age of woman at interview	1.49	(1.26–1.75)	0.59	(0.41–0.86)
As above +				
Lifetime sexual partners	1.51	(1.28–1.79)	0.60	(0.41–0.86)
Partner's[a] extramarital sexual relationships	1.49	(1.26–1.75)	0.60	(0.41–0.86)
Age at first sexual intercourse	1.03	(0.86–1.24)	0.58	(0.39–0.83)
All the above	1.05	(0.88–1.26)	0.59	(0.39–0.85)

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

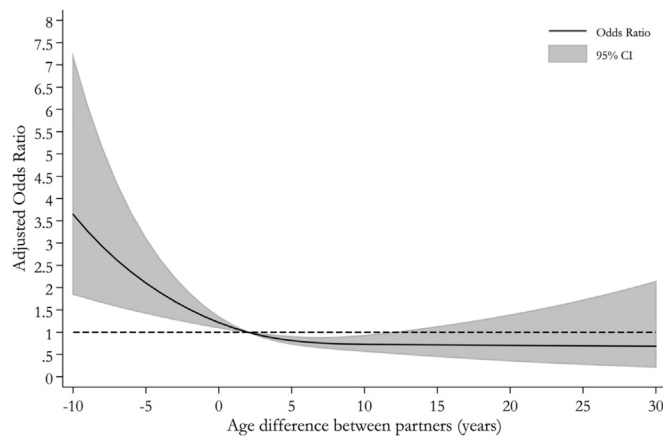[a] First partner for cervical cancer, current partner for HPV infection.

Fig. 1. Odds ratio of HPV positivity adjusted by age and country, by age difference between man and woman in current sexual partnership.

HPV infections in women of any age group are cleared within approximately 30 months [23] and, therefore, any prevalent HPV infection is most probably acquired from a recent partner. In the middle-aged women included in our study, a large Adiff corresponded to a relatively old age, and possibly less active sexual behavior of the current partner compared to those for whom the Adiff was smaller. The OR trend presented in Fig. 1 indicates that the risk of HPV infection steadily increased with the younger age of the woman's partner. Younger partners of middle-aged women are closer to their sexual activity peak and therefore more likely to acquire and transmit sexually transmitted infections such as HPV. This finding is consistent with a recently published model-based hypothesis that the risk of HPV infection among women below age 35 years is stronger in populations in whom Adiff is small and genders have similar age-specific sexual activity rates, because the peak of early sexual activity in young and HPV-susceptible women and men nearly coincide, and the spread of HPV is more rapid and efficient due to higher HPV infection reproductive rates [14]. By contrast, based on the same model, we have proposed that in traditional populations, in which genders have different age-specific sexual activity rates and a large Adiff of spouses or cohabiting sexual partners, the spread of HPV is less rapid and efficient due to lower infection reproductive rates. Thus a large Adiff increases the herd immunity effect of vaccination programs and is favorable for the introduction of HPV prophylactic vaccination and of ambitious catch-up programs [14]. Our current study suggests a similar association between small Adiff and the spread of HPV infection in middle-aged couples and corroborates our previous indications.

Our study has strengths and weaknesses. Strengths include the availability of high-quality information on HPV-positivity and the sexual history of women and their sexual partners. More detailed information on male sexual partner(s) would have allowed us to challenge the effect of Adiff on HPV-positivity by better adjustment

for sexual indicators. The consistency of our findings on Adiff across multiple countries is also important. A possible limitation of the present study is represented by the inclusion of mainly monogamous middle-aged women and, therefore, nearly super-imposable Adiff for first and current partnership. We think however that our interpretation is unambiguous; it is not plausible that a recently acquired HPV infection in women may be causally related to CC risk or that an HPV infection acquired at first sexual intercourse would be detectable decades later in cytologically normal women.

5. Conclusions

We demonstrate for the first time that a link exists between large Adiff in the first sexual partnership and CC but this depends on the strong negative correlation of Adiff with a woman's age at first sexual intercourse. Conversely, the negative association between large Adiff in current partnership and HPV-positivity is likely to be related to a decreased infectiousness of the male partner, as he grows older. The study of Adiff in sexual partnerships may help elucidate HPV circulation in different populations.

Conflict of interest

The authors have no conflict of interest to disclose.

Author contributions

NM, SdS, FXB, and SF provided data from the IARC's multicentric case-control study. ST, MD, and IB analyzed the data. IB and SF drafted the manuscript. All authors contributed to conception and design of the study, contributed to the interpretation of data, revised the manuscript for important intellectual content and approved the final manuscript.

All authors read and approved the final manuscript.

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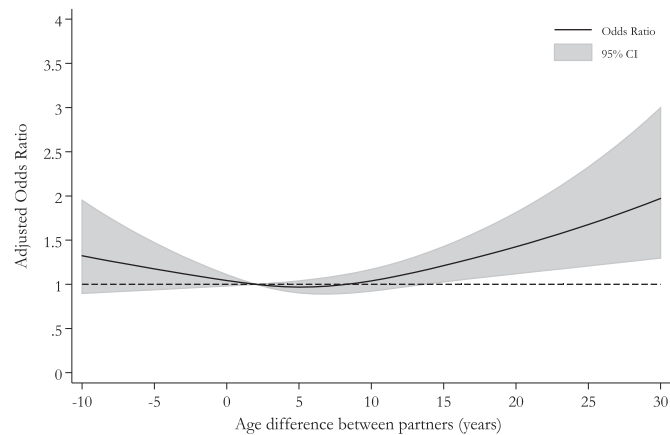
Appendix

see Fig. A.1 and Table A.1.

Fig. A.1. Odds ratio of cervical cancer adjusted by age, country, and woman's age at first sexual intercourse, adjusted by age difference between man and woman in first sexual partnership.

Table A.1
Woman's average age at first sexual intercourse by age-difference with her first male sexual partner.
IARC multicentric case-control study, 1985–1999.

Age difference between partners (years)	Age at first sex (years)		
	N	Average Age[a]	Standard deviation
≤2	946	21.66	4.87
3–6	825	18.46	3.60
7–9	371	17.95	3.70
≥10	687	17.32	3.67

[a] P-value for linear regression < 0.0001.

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