Cervical Carcinoma and Sexual Behavior: Collaborative Reanalysis of Individual Data on 15,461 Women with Cervical Carcinoma and 29,164 Women without Cervical Carcinoma from 21 Epidemiological Studies

International Collaboration of Epidemiological Studies of Cervical Cancer

Abstract

High-risk human papillomavirus (HPV) types cause most cervical carcinomas and are sexually transmitted. Sexual behavior therefore affects HPV exposure and its cancer sequelae. The International Collaboration of Epidemiological Studies of Cervical Cancer has combined data on lifetime number of sexual partners and age at first sexual intercourse from 21 studies, or groups of studies, including 10,773 women with invasive cervical carcinoma, 4,688 women with cervical intraepithelial neoplasia grade 3 (CIN3)/carcinoma *in situ*, and 29,164 women without cervical carcinoma. Relative risks for invasive cancer and CIN3 were estimated by conditional logistic regression. Risk of invasive cervical carcinoma increased with lifetime number of sexual partners (*P* for linear trend <0.001). The relative risk for ≥6 versus 1 partner, conditioned on age, study, and age at first intercourse, was 2.27 [95% confidence interval (95% CI), 1.98-2.61] and increased to 2.78 (95% CI, 2.22-3.47) after additional conditioning on reproductive factors. The risk of invasive cervical carcinoma increased with earlier age at first intercourse (*P* for linear trend <0.001). The relative risk for age at first intercourse ≤14 versus ≥25 years, conditioned on age, study, and lifetime number of sexual partners was 3.52 (95% CI, 3.04-4.08), which decreased to 2.05 (95% CI, 1.54-2.73) after additional conditioning on reproductive factors. CIN3/carcinoma *in situ* showed a similar association with lifetime number of sexual partners; however, the association with age at first intercourse was weaker than for invasive carcinoma. Results should be interpreted with caution given the strong correlation between sexual and reproductive factors and the limited information on HPV status. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1060–9)

Introduction

The association of cervical carcinoma with sexually transmitted infection has long been suggested by demographic and epidemiologic data (1, 2). A woman's lifetime number of sexual partners, becoming sexually active at an early age (3), and multiple sexual partners of a woman's husband have all been found to be consistent risk factors for cervical carcinoma (4). High-risk types of human papillomavirus (HPV), which are sexually transmitted, were first associated with cervical carcinoma worldwide in the 1990s (5, 6) and are now considered a necessary cause of cervical cancer.

The International Collaboration of Epidemiological Studies of Cervical Cancer was set up in 2003 to bring together, reanalyze, and publish the worldwide data on hormonal contraceptive use and cervical cancer risk (7). The collaboration has also published reports on the role of smoking and reproductive factors (8-10). The present report concerns the role played by a woman's lifetime number of sexual partners and age at first sexual intercourse. Unlike the risk factors previously studied by the collaboration, sexual behavior is intimately connected to the acquisition of HPV, which causes cervical cancer. Our goal in collating the available data is to analyze sexual behavior in more detail than previously possible.

Materials and Methods

Identification of Studies and Collection of Data. The methods of study identification and data verification, collection, and correction have been described elsewhere (8, 9). Briefly, cohort (prospective) studies were eligible if they included at least 30 cases of invasive cervical carcinoma (ICC) or cervical intraepithelial neoplasia grade 3 (CIN3)/carcinoma *in situ*; case-control studies were eligible if they had at least 100 ICC cases or 200

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CIN3/carcinoma *in situ* cases. When invasive and *in situ* carcinoma were both present, the carcinoma was classed as invasive. Cohort studies were analyzed as nested case-control studies with up to four randomly selected controls per case matched by age at diagnosis and date of entry into the study.

Analyses were restricted to women between 16 and 89 years of age. Controls who had undergone a hysterectomy were excluded, as were women who reported no previous sexual partners (27 cases and 2,324 controls).

Statistical Methods and Presentation of Data. We refer to individual studies included in the analysis by the names found in the first column of Table 1. Some studies collected information on lifetime number of sexual partners as aggregated categories. All but one study (Male Factor) had information that allowed categorization as 1, 2-5, and ≥6 sexual partners and hence we used these groups for most analyses. A more detailed classification (1, 2, 3, 4, 5-10, and ≥11) was also done; however, this entailed the exclusion of 604 ICC cases, 477 CIN3/carcinoma *in situ* cases, and 916 and 951 controls, respectively, from seven studies (Brinton US, Male Factor, Daling Seattle, WHO, IARC Colombia, IARC Paraguay, IARC Spain) that did not allow for unambiguous classification into one of these groups. One study (Johannesburg) had information on lifetime number of sexual partners, but not age at first intercourse, and therefore contributed only to analyses that did not require the latter variable. Age at first intercourse was recorded in single years in all other studies save one (Male Factor).

Conditional logistic regression was used to calculate odds ratio (OR) estimates, which approximate to relative risk (RR) estimates, and 95% confidence intervals (95% CI). When more than two groups were compared, the method of floating absolute risk (11, 12) was used to calculate floating SEs for the log-relative risk. For the figures, floating confidence intervals were calculated from the floating SEs to represent the dose-response relationship in a way that is independent of the choice of reference category.

Heterogeneity tests were carried out by calculating the likelihood ratio between two models: one in which the effect of the risk factor of interest was allowed to vary between strata and another where it was constrained to be the same across strata. Tests for trend were carried out using lifetime number of sexual partners and age at first intercourse as continuous variables.

All the analyses were conditioned on single year of age and on study, or study center in the case of multicentric studies (WHO, Brinton Latin America, IARC). Conditioning on other variables was also done as reported in Results. When conditioning on sexual factors (i.e., lifetime number of sexual partners, age at first intercourse), the broad classification of 1, 2-5, and ≥6 was used for lifetime number of sexual partners, and single years were used for age at first intercourse in the range 15 to 24 years, with additional categories of ≤14 years and ≥25 years for women outside of this range. When conditioning on reproductive factors [i.e., number of full-term pregnancies (FTP) and age at first FTP], the number of FTPs was categorized as 0, 1-2, 3-4, and ≥5, and age at first FTP was categorized as <17, 17-19, 20-24, ≥25 years, and nulliparous. FTP was defined as a pregnancy lasting ≥26 weeks. Subjects with missing data in any conditioning variable were dropped from the corresponding analysis.

Presentation of Results. Results in the text are presented as RRs and their appropriate CIs. Where results are presented in the form of plots, RRs are represented by squares and their corresponding CIs/floating CIs by horizontal lines. The position of the square indicates the point estimate of the RR, and the area of the square is inversely proportional to the variance of the logarithm of the RR estimate, thus providing an indication of the amount of statistical information available for that particular estimate. Where summary RRs have been calculated, they are shown as open diamonds.

Results

Study Population. Thirty-six eligible studies were identified. Data could not be retrieved for 10 (13-23) and one research group declined to take part in the collaboration (24). Four of the 25 studies that joined the collaboration did not have information on sexual behavior (25-28), leaving 21 studies available for the present reanalysis (29-63).

Table 1 shows the studies included in the analysis, ordered by study design and, within studies of the same design, by median year of diagnosis of the cases. Three multicentric studies (WHO, Brinton Latin America, IARC) were counted as single studies, even when results from individual centers had been published separately. Likewise, two studies on invasive and *in situ* carcinoma in Milan were considered as two arms of a single study. Table 1 thus shows data on 21 studies in total, of which 16 separate studies or groups of studies included data on ICC and 15 studies included data on CIN3/carcinoma *in situ*. The combined study population included 10,773 ICC cases, 4,688 cases of CIN3/carcinoma *in situ*, and 29,164 women without carcinoma of the cervix. When a study included both invasive and *in situ* cases, the same controls were used (n = 19,121) for both outcomes. The median year at diagnosis by study ranged between 1980 and 1999, and the median age at diagnosis ranged between 26 and 55 years. Among control women, the proportion reporting ≥2 sexual partners ranged between 1% and 94% and the median age at first intercourse varied between 15 and 23 years. Table 1 also shows the studies that included assessment of HPV infection in both cases and controls. Five studies of ICC included HPV testing by PCR.

Table 2 shows the associations between sexual factors and potential confounding variables among controls. The associations are quantified by the ORs for having ≥2 versus 1 sexual partner and for having first intercourse at age <19 years versus ≥19 years. There was a strong association between the two sexual behavior variables: women with first intercourse at age <17 years were more likely to have more than one sexual partner than women with first intercourse at age ≥25 years (OR, 8.75; 95% CI, 7.63-10.03). Women with ≥3 FTPs were less likely to have more than one sexual partner than nulliparous women (OR, 0.24; 95% CI, 0.20-0.28) and more likely to have first intercourse before age 19 years (OR, 7.65; 95% CI, 6.74-8.68). Women with earlier first FTP were less likely to have more than one sexual partner. Among parous women, there was a strong correlation between age at first intercourse and age at first FTP, because, in many of

Table 1. Characteristics of cases and controls by type of study design

Study name	Country (substudy)	Cases		Controls	Diagnosis		Among controls		HPV detection method
		Invasive	CIN3/*in situ*		Median year	Median age	≥2 sexual partners	Median age at first intercourse	
Cohort									
Sweden (29)	Sweden	0	378	378	1987	34	81%	17	PCR
Manchester (30)	UK	0	199	181	1989	32	78%	18	PCR
Portland Kaiser (31)	USA	0	69	263	1992	30	70%	18	PCR
Copenhagen (32)	Denmark	0	190	754	1992	26	94%	16	PCR
Guanacaste (33)	Costa Rica	42	129	683	1993	38	41%	18	PCR
Total		42	965	2,259					
Population case-control									
Los Angeles squamous (34)	USA	200	0	198	1981	44	46%	19	None
Brinton US (35)	USA	477	291	791	1983	41	62%	18	None
Male Factor (36)	Denmark	59	586	607	1985	31	89%	18	None
London CIN (37)	UK	0	224	528	1985	29	83%	18	None
UK case-control (38)	UK	578	0	928	1986	35	55%	18	Serology
Los Angeles adeno (39)	USA	141	53	373	1986	37	74%	18	None
IARC (40)	Colombia (invasive)	218	0	177	1987	45	41%	18	PCR
	Spain (invasive)	248	0	231	1987	53	9%	23	PCR
North Thames invasive (41)	UK	119	0	242	1988	34	71%	18	None
Daling Seattle (42, 43)	USA	673	190	1,421	1992	40	70%	18	Serology
US adeno (44)	USA	184	80	299	1993	37	63%	18	PCR
Latvia (45)	Latvia	219	0	237	1999	55	69%	20	PCR
Total		3,116	1,424	6,032					
Hospital case-control									
WHO (46)	Australia	37	42	647	1980	35	38%	19	None
	Nigeria	27	0	149	1980	40	30%	19	None
	Philippines	154	9	733	1981	42	5%	20	None
	Kenya	113	3	681	1982	39	81%	16	None
	Chile	136	154	1,051	1982	39	33%	19	None
	Israel	78	32	1,929	1982	37	23%	19	None
	Colombia	27	32	194	1982	39	28%	18	None
	Mexico	277	153	1,467	1983	41	19%	18	None
	Thailand (Siriraj)	761	504	2,613	1984	41	11%	20	None
	Thailand (Chulalongkorn)	591	365	2,357	1984	41	21%	20	None
	Thailand (Chiang Mai)	800	203	2,514	1985	44	20%	19	None
Milan (47, 48)	Italy (invasive)	781	0	878	1985	52	17%	22	None
	Italy (*in situ*)	0	270	303	1985	40	25%	20	None
Bangkok (49, 50)	Thailand	289	76	761	1992	42	7%	21	PCR
Brinton Latin America (51)	Colombia	212	0	407	1986	47	44%	18	FISH
	Costa Rica	191	0	366	1986	44	40%	18	FISH
	Mexico	155	0	291	1986	45	31%	19	FISH
	Panama	192	0	307	1986	48	58%	18	FISH
IARC (52-61)	Colombia (CIN3)	0	234	269	1986	37	41%	18	PCR
	Spain (CIN3)	0	222	241	1987	34	19%	21	PCR
	Paraguay	116	0	101	1989	48	24%	19	PCR
	Brazil	199	0	225	1990	50	33%	19	PCR
	Thailand	386	0	354	1991	49	18%	20	PCR
	Mali	82	0	97	1992	45	52%	15	Serology
	Philippines	387	0	386	1992	47	10%	21	PCR
	Morocco	214	0	203	1993	49	20%	18	PCR
	Peru	198	0	196	1996	48	57%	18	PCR
	Algeria	198	0	202	1998	53	28%	18	PCR
	India	205	0	213	1998	47	1%	18	PCR
Johannesburg (62, 63)	South Africa	809	0	738	1997	52	78%	NA	Serology
Total		7,615	2,299	20,873					
Grand total		10,773	4,688	29,164					

Abbreviations: NA, not applicable; FISH, fluorescence *in situ* hybridization.

the study populations, first FTP occurred shortly after first intercourse.

The effect on the RR estimates of conditioning on different confounding variables was examined in a subset of 5,383 cases and 9,500 control women for whom data on all potential confounders were available. Of the many potential confounding factors considered, age at first intercourse reduced the effect of lifetime number of

sexual partners (Table 3). The converse was also true. Conditioning on reproductive factors did not strongly affect the RR estimate for lifetime number of sexual partners, but the RR estimate for age at first intercourse was strongly attenuated and the width of the CI greatly increased so that the effect of age at first intercourse was no longer significant in this subset. Conditioning on other factors such as education, tobacco smoking, hormonal contraceptive use, and history of Pap smear did not materially change the RRs or the CIs. Due to the strong effect of number of FTPs and age at first FTP on the RR estimates, it was decided to control for these reproductive factors in all further analyses. However, because the strong association between age at first intercourse and age at first FTP may result in overadjustment, results are also presented without controlling for reproductive factors.

Invasive Cervical Carcinoma. Figure 1 shows the RR of ICC by lifetime number of sexual partners. The RR for ≥6 partners versus 1 was 2.27 (95% CI, 1.98-2.61) conditioned on age at first intercourse and increased to 2.78 (95% CI, 2.22-3.47) when additionally conditioned on reproductive factors. The fully adjusted RR for ≥11 sexual partners versus 1 in the studies that allowed finer classification was 3.15 (95% CI, 2.19-4.52).

Figure 2 shows the RR of ICC by age at first intercourse. The risk increased steadily with decreasing age at first intercourse, but the RRs conditioned on lifetime number of sexual partners were substantially reduced after additional conditioning on reproductive factors. The RR for age at first intercourse ≤14 versus ≥25 years was 3.52 (95% CI, 3.04-4.08) conditioning on lifetime number of sexual partners and 2.05 (95% CI, 1.54-2.73) after additional conditioning on reproductive factors.

Table 2. ORs and 95% CIs for having >1 sexual partner versus 1, and for age at first sexual intercourse less than 19 y versus 19 y or older among women without cervical cancer, by factors potentially relevant to risk of cervical cancer

Characteristics	Lifetime number of sexual partners			Age at first sexual intercourse		
	n		OR* (95% CI)	*n*		OR† (95% CI)
	≥2	1		<19	≥19‡	
All controls	11,711	18,698		14,204	15,370	
Lifetime number of sexual partners						
1				6,604	11,870	1.00
2-5				5,218	2,902	2.74 (2.57-2.92)
≥6				2,382	598	5.77 (5.09-6.53)
Age at first sexual intercourse (y)						
≥25	366	3,157	1.00			
20-24	2,031	6,748	2.05 (1.79-2.34)			
17-19	4,574	5,963	4.50 (3.95-5.13)			
<17	4,129	2,606	8.75 (7.63-10.03)			
Full-term pregnancies						
Nulliparous	2,640	1,649	1.00	2,141	2,148	1.00
<3	4,036	6,606	0.37 (0.32-0.43)	4,387	6,255	2.58 (2.29-2.90)
≥3	4,416	10,211	0.24 (0.20-0.28)	7,667	6,960	7.65 (6.74-8.68)
Age at first full-term pregnancy (y)						
Nulliparous	2,640	1,649	1.00	2,141	2,148	1.00
≥25	1,926	4,606	0.60 (0.51-0.71)	1,076	5,456	0.71 (0.62-0.82)
19-24	3,747	8,640	0.23 (0.19-0.27)	4,906	7,481	3.61 (3.18-4.10)
<19	2,327	3,193	0.15 (0.13-0.19)	5,520	0	—
Study location						
Developing countries	5,226	13,681	1.00	8,778	10,129	1.00
Developed countries	5,874	4,793	1.42 (1.26-1.59)	5,426	5,241	0.81 (0.73-0.89)
Years of full-time education						
<10	4,859	11,920	1.00	8,641	8,138	1.00
≥10	5,997	5,604	1.36 (1.21-1.53)	5,289	6,312	0.26 (0.24-0.28)
Hormonal contraceptive use						
Never	4,207	10,571	1.00	6,387	8,391	1.00
Ever	6,893	7,903	1.19 (1.09-1.30)	7,817	6,979	1.05 (0.99-1.12)
Condom use						
Never	5,932	14,011	1.00	8,891	11,052	1.00
Ever	3,527	3,034	1.02 (0.91-1.14)	3,398	3,163	0.75 (0.69-0.81)
Tobacco smoking						
Never	5,116	9,646	1.00	6,549	8,213	1.00
Past	1,357	745	1.76 (1.48-2.09)	1,242	860	1.45 (1.28-1.64)
Current	2,448	1,208	2.22 (1.92-2.56)	2,432	1,224	1.77 (1.60-1.97)
History of Pap smear						
0	2,789	8,828	1.00	5,125	6,492	1.00
≥1	7,093	9,020	0.98 (0.89-1.09)	7,855	8,258	0.88 (0.82-0.95)

NOTE: Overall there were 30,409 controls; however, information was not available from all studies for all variables.
* Conditioned on age, study, and age at first sexual intercourse.
† Conditioned on age, study, and lifetime number of sexual partners.
‡ Median age at first sexual intercourse among controls is 19 y.

Table 3. Effect of additional adjustment by potential confounding factors on the RR and 95% CI of invasive cervical cancer in relation to lifetime number of sexual partners or age at first intercourse in a subset of 5,383 cases and 9,500 controls who had complete information on all variables

Adjustment variables	RR (95% CI)	
	Lifetime number of sexual partners (≥2 vs 1)	5-y decrease in age at first intercourse
Age + study	2.21 (2.03-2.41)	2.02 (1.89-2.15)
Age + study + lifetime number of sexual partners or age at first intercourse	1.86 (1.65-2.10)	1.78 (1.66-1.91)
As above +		
Number of full-term pregnancies	1.91 (1.57-2.33)	1.51 (1.36-1.67)
Age at first full-term pregnancy	1.93 (1.59-2.35)	1.22 (0.95-1.55)
Education	2.00 (1.69-2.38)	1.49 (1.35-1.63)
Tobacco smoking	1.72 (1.50-1.98)	1.73 (1.60-1.87)
Hormonal contraceptive use	1.74 (1.53-1.99)	1.82 (1.69-1.97)
Condom use	1.81 (1.59-2.06)	1.74 (1.62-1.88)
History of Pap smear	1.65 (1.41-1.95)	1.69 (1.55-1.85)
Number of and age at first full-term pregnancy	1.75 (1.21-2.53)	1.18 (0.78-1.78)

Lifetime number of sexual partners and age at first intercourse were examined in combination (Fig. 3). The RR for women who reported both ≥2 sexual partners and age at first intercourse <17 years compared with those who reported both 1 partner and an age at first intercourse of ≥25 years was 5.94 (95% CI, 5.24-6.74). This RR decreased to 3.60 (95% CI, 2.95-4.38) after additional conditioning on reproductive factors. A relation between age at first intercourse and ICC risk was also seen among nulliparous women (RR for age at first intercourse <17 versus ≥25, 2.28; 95% CI, 1.62-3.19) and in different strata of age at first FTP (Fig. 4).

The consistency of the associations between ICC and lifetime number of sexual partners or age at first intercourse across individual studies and by study design is shown in Supplementary Fig. S1 and S2. The RR for ≥2 sexual partners versus 1, conditioned on age at first intercourse and reproductive factors, showed significant heterogeneity between individual studies and was lower in case-control studies with hospital controls (1.47; 95% CI, 1.29-1.67) than studies with population controls (RR, 2.89; 95% CI, 2.25-3.71; Supplementary Fig. S1). However, women with ≥2 sexual partners reported a much lower median lifetime number of sexual partners (2 for both cases and controls) in hospital-based case-control studies than the corresponding women in population-based case-control studies (four among cases and five among controls; Supplementary Fig. S1). Only one cohort study (Guanacaste) could be included and had too few cases to estimate the RR controlling for all the variables in the model.

The overall RR of ICC per 5-year decrease in age at first intercourse was 1.31 (95% CI, 1.21-1.41), conditioned on lifetime number of sexual partners and reproductive factors (Supplementary Fig. S2). RRs by age at first intercourse did not show significant heterogeneity by study or by study design (Supplementary Fig. S2).

Data on stage were available on 5,395 ICC cases from eight studies. A subgroup analysis of these subjects found no evidence of heterogeneity by stage for either age at first intercourse or lifetime number of sexual partners (data not shown).

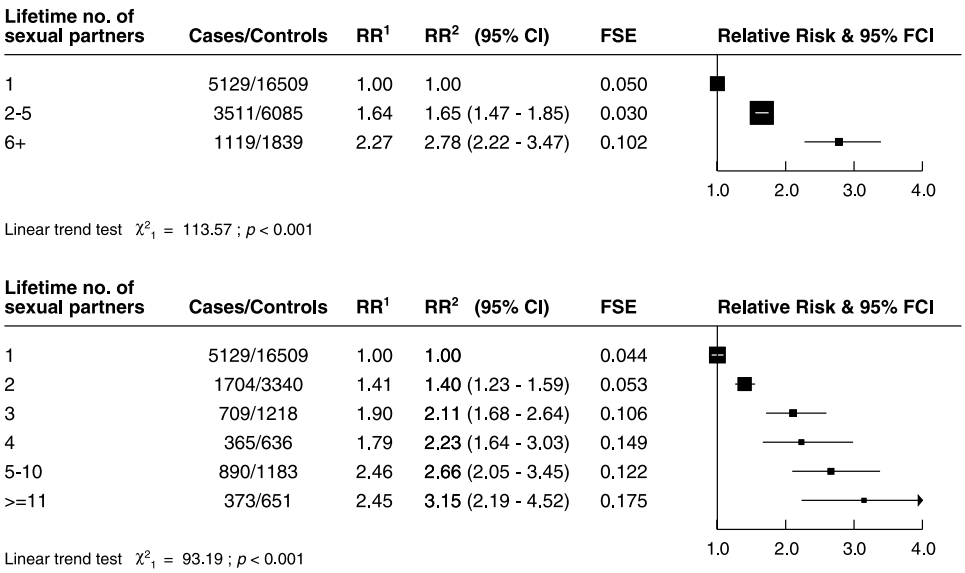
CIN3/Carcinoma *in situ*. Figures 5 and 6 show results analogous to Figs. 1 and 2 for the 15 studies that included cases of CIN3/carcinoma *in situ*. The pattern of risk by lifetime number of sexual partners was very similar to that for ICC in both shape and magnitude (Fig. 5). The RR for ≥6 versus 1 sexual partner was 2.51 (95% CI, 2.13-2.97) conditioning on age at first intercourse and 2.31 (95% CI, 1.83-2.92) after additionally conditioning on reproductive factors. The risk of CIN3/carcinoma *in situ* increased with decreasing age at first intercourse, as observed for ICC. The RR of CIN3/carcinoma *in situ* for age at first intercourse ≤14 versus ≥25 years was 2.33 (95% CI, 1.88-2.91) conditioning on lifetime number of sexual partners and decreased to 2.03 (95% CI, 1.41-2.91) after additional conditioning on reproductive factors.

Supplementary Figs. S3 and S4 show the consistency of the relationship between lifetime number of sexual partners and age at first intercourse and risk of CIN3/carcinoma *in situ* across different studies and study designs. As for ICC (Supplementary Fig. S1), the fully adjusted RR for ≥2 versus 1 sexual partner was higher in population-based case-control studies (RR, 3.23; 95% CI, 2.10-4.96) than in hospital-based case-control studies (RR, 1.51; 95% CI, 1.24-1.85). In cohort studies, it was 2.10 (95% CI, 1.12-3.93). Heterogeneity was significant across individual studies and study designs. This may be attributable to the higher lifetime number of sexual partners reported by women in cohort and population-based case-control studies than in hospital-based case-control studies (Supplementary Fig. S3).

The inverse association between CIN3/carcinoma *in situ* and age at first intercourse, conditioned on lifetime number of sexual partners and reproductive factors (RR per 5-year decrease in age at first intercourse, 1.32; 95% CI, 1.16-1.50) showed no significant heterogeneity between individual studies nor by study design (Supplementary Fig. S4).

Discussion

This collaborative reanalysis of individual data from more than 15,000 women with ICC or CIN3/carcinoma



[1] *Conditioned on age, study or study centre and age at first sexual intercourse.*

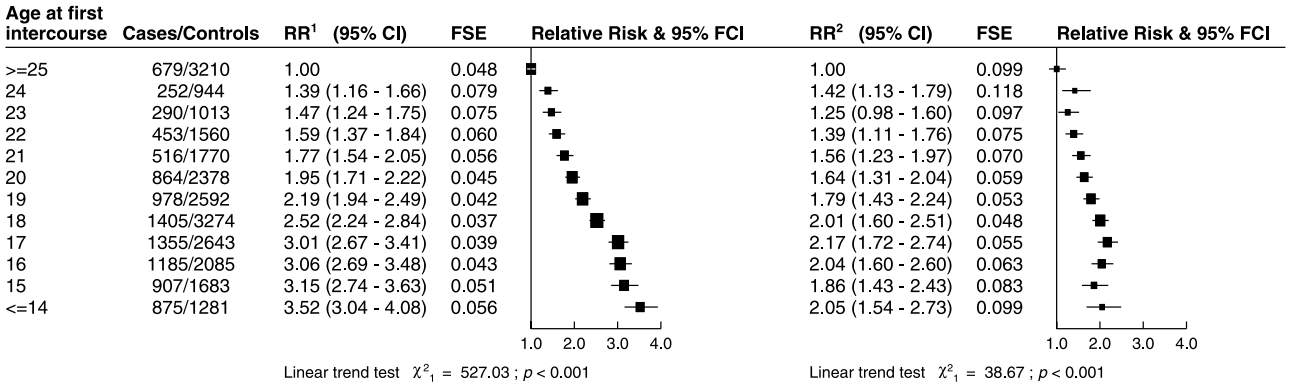
[2] *As above, and additionally conditioned on number of full-term pregnancies and age at first full-term pregnancy.*

Figure 1. RRs of invasive cervical carcinoma and corresponding 95% CIs by lifetime number of sexual partners.

in situ confirms the relationship between major indicators of sexual behavior and the risk of cervical carcinoma. On account of the large number of women involved, this reanalysis allowed the examination of the joint effect of two closely correlated sexual variables: lifetime number of sexual partners and age at first intercourse.

Various aspects of sexual behavior are related to the acquisition of HPV infection, the primary cause of cervical cancer. The probability of HPV transmission per sexual act with an infected partner is unknown, but available evidence suggests that it is higher than other viral sexually transmitted diseases (64). Furthermore, the prevalence of HPV infection increases rapidly among young women after they become sexually active (65). Hence, first exposure to HPV probably occurs soon after first intercourse in many women (66).

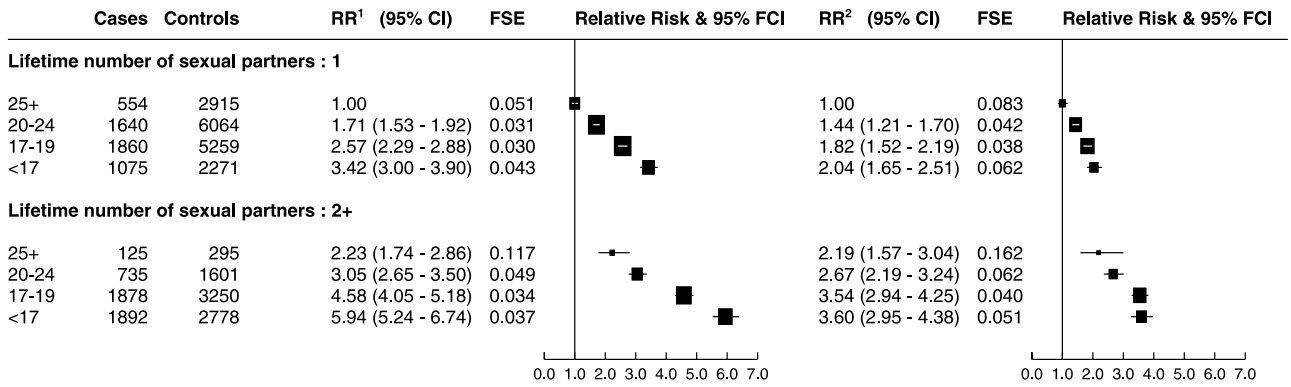
The majority of HPV infections become undetectable within 1 to 2 years of exposure, although it is unclear whether they resolve completely or remain in a latent state in the basal cell epithelium of the cervix (66). The onset of microscopically detectable precancer (e.g., CIN3) may occur rapidly after infection, possibly within 5 years (66). The rate at which CIN3 progresses to invasive cancer is not known precisely. The unique study in which CIN3 was left untreated by design showed a cumulative incidence of invasive cancer of ~30% over 30 years (67). This is consistent with an earlier estimate, based on modeling of cancer mortality data in the United Kingdom, that 40% of untreated CIN3 will eventually progress to invasive cancer (68). This natural history of HPV infection can be interrupted if CIN3 is detected by screening (68) and is treated (67), but this is unlikely to



[1] *Conditioned on age, study or study centre and lifetime number of sexual partners.*

[2] *As above, and additionally conditioned on number of full-term pregnancies and age at first full-term pregnancy.*

Figure 2. RRs of invasive cervical carcinoma and corresponding 95% CIs by age at first sexual intercourse.



[1] *Conditioned on age and study or study centre.*
[2] *As above, and additionally conditioned on number of full-term pregnancies and age at first full-term pregnancy.*

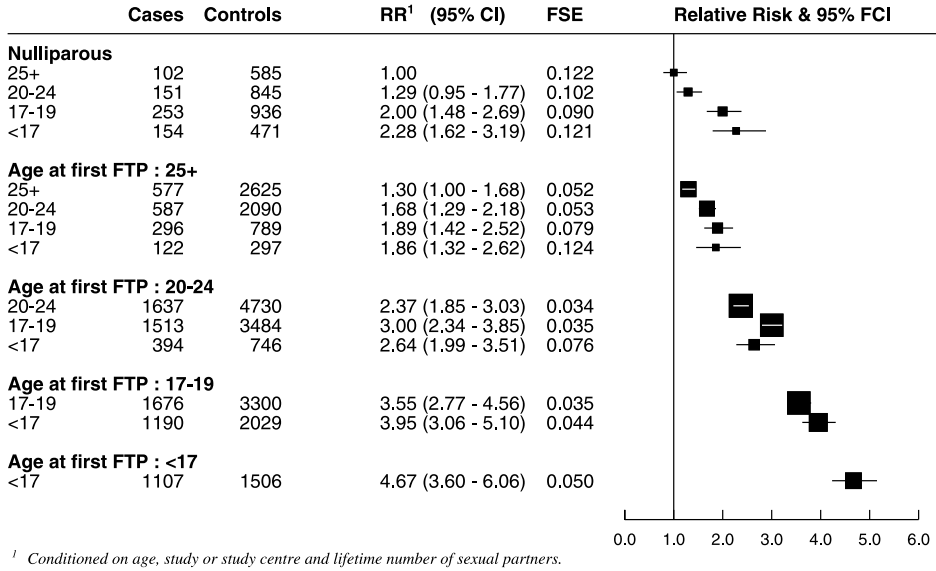
Figure 3. RRs of invasive cervical carcinoma and corresponding 95% CIs by age at first sexual intercourse and lifetime number of sexual partners.

have consistently occurred in most of the study populations included in this reanalysis, where screening was suboptimal or nonexistent during the study period.

With this understanding of the natural history of HPV infection, we interpret the increasing risk of both ICC and CIN3/carcinoma *in situ* with lifetime number of sexual partners as an effect of increased exposure to HPV infection. As might be expected, lifetime number of sexual partners has been found to be associated with HPV prevalence among women without cervical carcinoma (69).

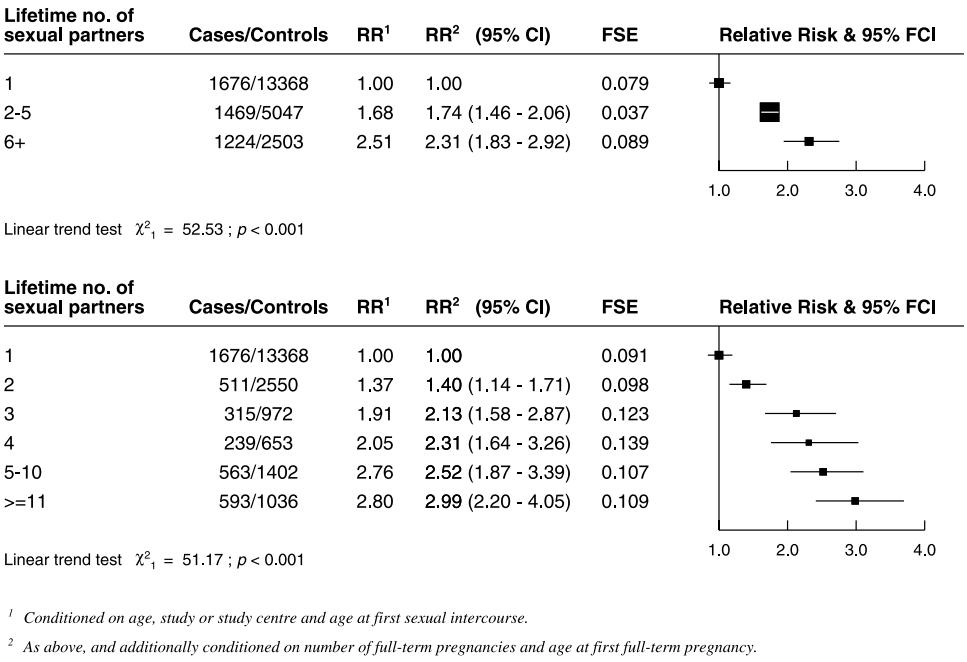
The results on age at first intercourse are more difficult to interpret. One interpretation is in terms of confounding by reproductive factors. Age at first FTP and number of FTPs have previously been found to be strongly associated with ICC risk in our collaborative reanalysis (9). The strength of the association between age at first intercourse and ICC risk was substantially attenuated after controlling for age at first FTP, and a further influence of residual confounding cannot be ruled out. Nevertheless, an association between cervical carcinoma and age at first intercourse was found even among nulliparous women. Moreover, because first intercourse was shortly followed by first FTP in many of the study populations, controlling for reproductive factors may have resulted in overadjustment when examining the effect of age at first intercourse.

It is also conceivable that age at first intercourse is related to ICC risk through HPV acquisition. One possibility is that cervical cancer risk may increase with duration of HPV infection (47). As noted above, it is likely that women who have earlier first sexual intercourse are also exposed to HPV earlier. Therefore, among women of the same age, as our cases and controls were by design, those who had earlier first intercourse might have a longer duration of infection. A second possibility is that early first intercourse is a marker of high-risk behavior for HPV exposure. This would be consistent with the high incidence of HPV infection in young women shortly after the first sexual intercourse (65). A third possibility is that younger women are more



[1] *Conditioned on age, study or study centre and lifetime number of sexual partners.*

Figure 4. RRs of invasive cervical carcinoma and corresponding 95% CIs by age at first sexual intercourse and age at first FTP.



[1] *Conditioned on age, study or study centre and age at first sexual intercourse.*

[2] *As above, and additionally conditioned on number of full-term pregnancies and age at first full-term pregnancy.*

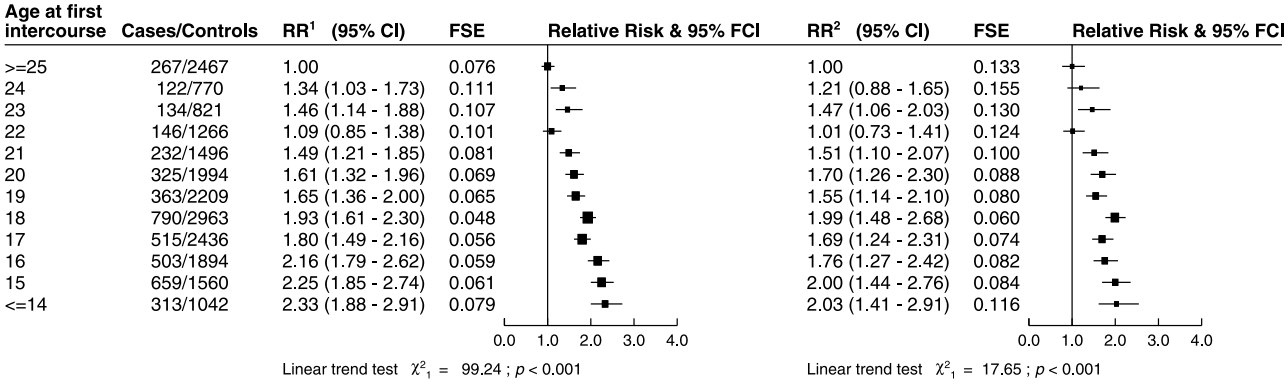
Figure 5. RRs of CIN3/carcinoma *in situ* and corresponding 95% CIs by lifetime number of sexual partners.

susceptible to HPV infection (1, 2). Although this possibility cannot be ruled out, it is unlikely to involve a specific vulnerability of the cervix to HPV infections in the interval shortly after menarche because we observed a steady increase in ICC risk with decreasing age at first intercourse across the age range considered and not exclusively in the ages surrounding menarche. This conclusion is also supported by a prospective study of HPV infection risk in the first years after menarche (70).

Further interpretation of the effect of lifetime number of sexual partners and age at first intercourse on cervical cancer risk is made difficult by the fact that these variables do not fully describe a woman's risk profile for HPV infection. In many of the study populations, most women reported only one sexual partner. For these women, the risk of exposure to HPV, and consequently of developing cervical cancer, chiefly depends on the lifetime number of sexual partners of their husband (69). With few exceptions, we did not have data on husbands' sexual behavior or other data relevant to HPV transmission, such as condom use. Differences in these unmeasured variables may contribute to the heterogeneity between studies.

In addition to these problems of interpretation, there are the usual epidemiologic concerns over misclassification, bias, and confounding. The acceptability and reliability of questions on sexual behavior have always been of great concern (3) and data on the accuracy of self-reports of sexual behavior are scant (71). The data on sexual behavior were also incomplete. Among studies that contributed to the present collaborative reanalysis, four cohort studies did not include information on sexual behavior (25-28). Findings on sexual behavior have been published from eight studies that were not included and were consistent with our present results (14, 16-23).

The fact that the evidence on sexual behavior in the present study derives, in large part, from case-control studies raises the possibility of recall bias. The RR for



[1] *Conditioned on age, study or study centre and lifetime number of sexual partners.*

[2] *As above, and additionally conditioned on number of full-term pregnancies and age at first full-term pregnancy.*

Figure 6. RRs of CIN3/carcinoma *in situ* and corresponding 95% CIs by age at first sexual intercourse.

each additional sexual partner was lower in hospital-based than in population-based case-control studies and in studies carried out in developing countries. This suggests a possible variation in the quality of the information available.

With respect to potential confounding factors other than reproductive factors, the strength of the associations we found between risk of cervical carcinoma and sexual factors was not materially affected by tobacco smoking, use of hormonal contraceptives and condoms, or history of Pap smear.

The consistency of the association between ICC and sexual behavior by histologic type has previously been investigated as part of a review of all risk factors considered by the collaboration (10). No evidence was found for a difference in between squamous cell carcinoma and adenocarcinoma for either age at first intercourse or lifetime number of sexual partners.

Previous publications by this collaboration on tobacco, reproductive factors, and hormonal contraceptives have included analyses restricted to HPV-positive women in the studies that used PCR-based detection of HPV (8-10). Supplementary Fig. S5 shows this subgroup analysis for lifetime number of sexual partners and age at first intercourse. Both associations were attenuated by restriction to HPV-positive women. Further control for reproductive factors rendered the relative risk estimates unstable and neither association was statistically significant. There are good reasons, however, for skepticism over the utility of this analysis, primarily due to the asymmetrical interpretation of HPV-positive findings in cases and controls. A current HPV infection in a case is almost certainly a long-term infection, possibly acquired at a much younger age, whereas a current infection in a control may be a recently acquired transient infection. Restriction to HPV-positive women does not, therefore, yield a subset of cases and controls with similar age at infection. The existence of a current HPV infection in a middle-aged woman gives little information about lifetime infection history, which is the information required to fully interpret the findings on sexual behavior.

Future prospective studies, including current trials of prophylactic vaccines against HPV16 and HPV18 (72), should shed further light on the natural history of HPV infection; however, they will seldom include lesions more severe than CIN3. Therefore, our present collaborative reanalysis represents an overview of the majority of information that has been, and probably ever will be, collected on sexual behavior and ICC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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